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Synthesis of Copolymers from Phenylboronic Acid-Installed Cyclic Carbonates

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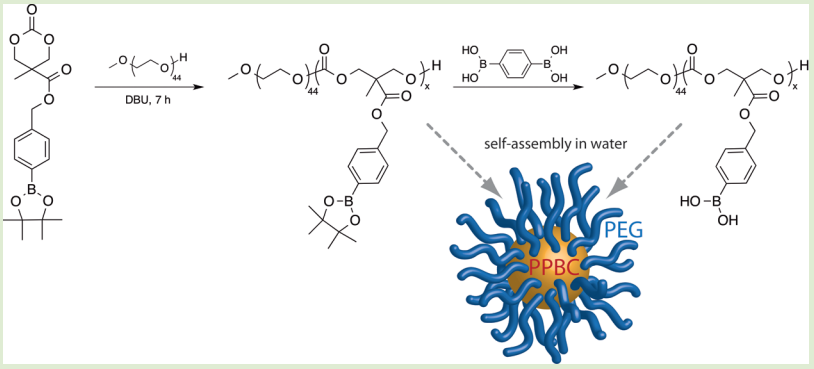
Supporting Information



ABSTRACT: Organoboron polymers play important roles in biomedical applications. An ample number of monomers bearing boronic acid derivatives have been synthesized, particularly focusing on controlled free radical polymerization methods. Organoboron polymers synthesized by ring-opening polymerization (ROP) routes are far less explored. We report on the ROP of boronic acid-installed cyclic carbonates, catalyzed by DBU from a poly(ethylene glycol) macroinitiator. Controlled polymerization proceeded to relatively high conversions (~70%) with low polydispersity. Deprotection of the copolymer to generate the boronic acid pendant group was readily achieved by displacement of the protecting group with free diboronic acid. The resulting amphiphilic copolymers self-assembled in water into spherical nanoparticles or vesicles, depending on hydrophilic/hydrophobic ratio. We envision these functional carbonates finding direct applications for core stabilization of biodegradable amphiphilic assemblies or in drug and protein encapsulation.

Organoboron polymers are important in biomedical applications enabling triggered drug delivery, as biosensing elements, in targeted delivery, and for the construction of supramolecular materials.[1−12] Their attraction results from their capacity to reversibly bind to 1,2- or 1,3-diols and catechol-containing molecules, reactivity toward H_2O_2, and the delicate effect of molecular structure on boronic acid pK_a. A number of monomers bearing boronic acid derivatives have been synthesized, particularly targeting controlled free radical polymerization methods. The most common are boronate ester-functionalized acrylamides, acrylates, and styrenes polymerizable by RAFT, ATRP, and nitroxide-mediated routes.[13−21]

Biodegradable derivatives of organoboron polymers synthesized by ring-opening polymerization (ROP) routes are far less explored. We are interested in functional derivatives of polycarbonates (PCs). Aside from nonacidic degradation products and good mechanical properties,[22−25] installation of functional groups onto PC backbones will influence their degradation kinetics and mechanism and serve to optimize sustained release profiles.[26−31] Functional aliphatic PCs are generally synthesized by ROP of cyclic carbonates by a coordination/insertion route, catalyzed by metal-based Lewis acids or organic catalysts from neutral bases.[29,32−34] Polymerization proceeds with great control provided the functional groups do not interfere with ROP conditions.[35−38] This strategy is common for the synthesis of PCs with amine, carboxylic acids, and hydroxyls, mediated by the use of appropriate protecting groups that are removed postpolymerization to yield the desired functionality.[29,39−42]

Herein, we report on the controlled polymerization of boronic acid-installed cyclic carbonates, catalyzed by 1,8-diazabicycloundec-7-ene (DBU) from a poly(ethylene glycol) macroinitiator. To the best of our knowledge, this is the first example of a boronic acid polymer synthesized by ROP. Installation of a boronic acid derivative onto ROP monomers could potentially allow for drug binding and release by competitive displacement or upon reaction with H_2O_2, influence micelle stability by core cross-linking, or prompt amphiphile self-assembly in aqueous environments through diol

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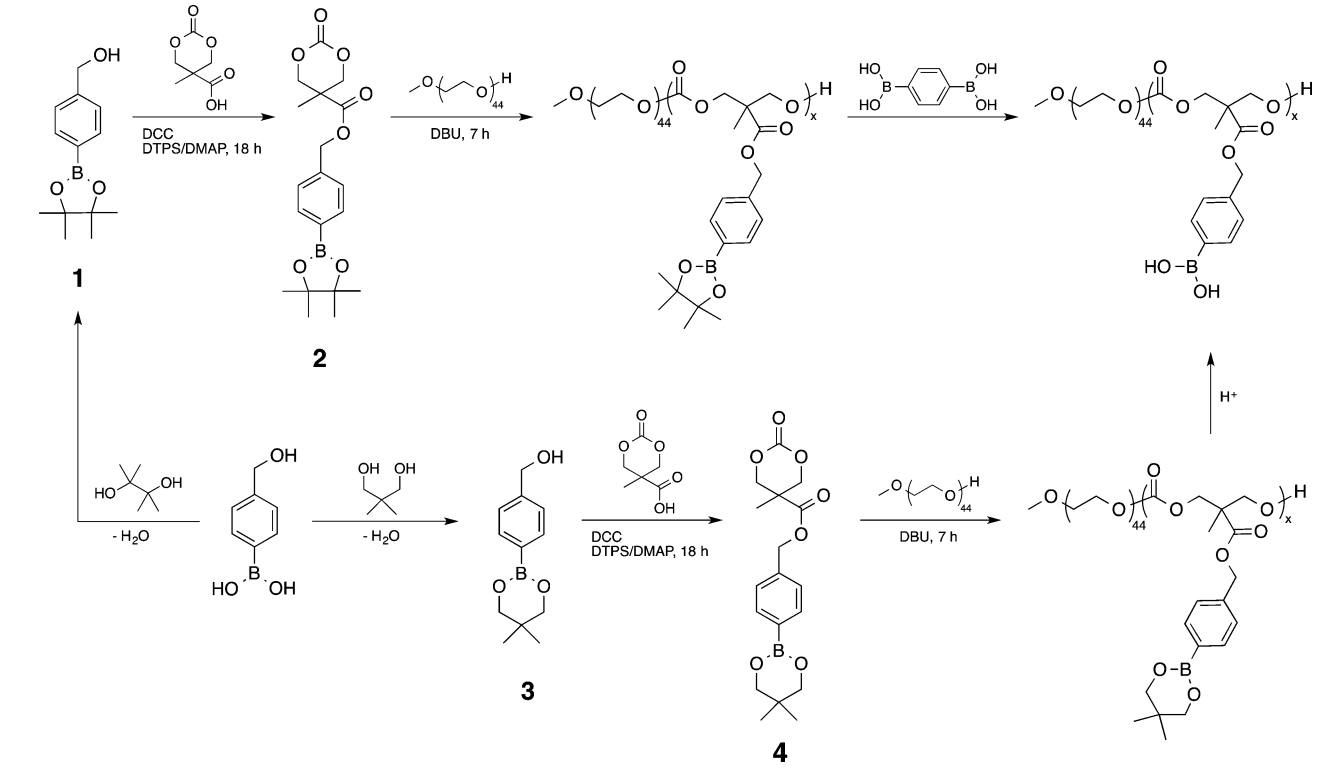
Scheme 1. Synthesis of Phenylboronic Acid Carbonate-Based Amphiphiles from the Ring-Opening Polymerization of Boronic Acid-Installed Cyclic Carbonates Using mPEG as Macroinitiator



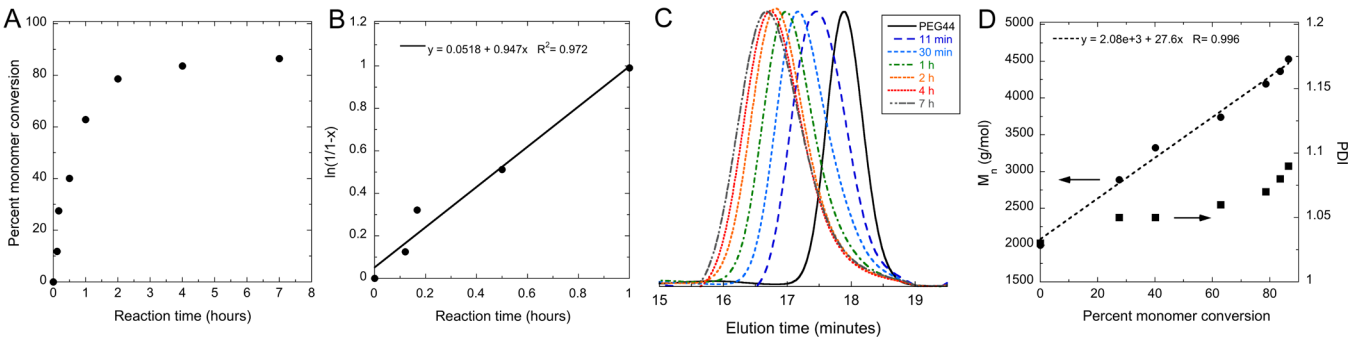


Figure 1. Polymerization of **2**, initiated by $mPEG_{44}$–OH and catalyzed by DBU. Polymerization was carried out at 20 °C in dichloromethane with molar ratios of [**2**]/[OH]/[DBU] = 12.7:1:0.67. (A) Polymerization kinetics monitored by ^1H NMR showing a plateau at ∼2 h. (B) Polymerization kinetics for the first hour of reaction showing the controlled character of the reaction and a linear dependence of conversion on time. (C) Chromatograms of the reaction mixture showing the increase in copolymer molecular weight, and slight broadening of the distribution, over 7 h. (D) Linear dependence of molecular weight on conversion and PDI values.

binding, as observed for linear diblock copolymers based on boronic acid-derived acrylates.

As shown in Scheme 1, phenylboronic acid carbonate (BC) monomers **2** and **4** were prepared in two steps: (*i*) boronic acid hydroxyl groups were selectively protected using either pinacol (**2**) or 2,2-dimethyl-1,3-propane diol (acetonide, **4**), followed by (*ii*) direct coupling of the protected hydroxyl phenyl boronic ester to an acid functional carbonate, MTC–OH, using DCC chemistry in the presence of DMAP (10% mol) and DTPS (25% mol). Boronic acid hydroxyl protection was necessary to preclude undesired side reactions that would interfere with ring-opening polymerization. Both monomers were purified by column chromatography and subsequent recrystallization from hexane/ethyl acetate (80:20 v/v) and were isolated in ∼60% yield. Successful syntheses of monomers **2** and **4** were confirmed by ^1H and ^{13}C NMR, as observed by the downfield shift of the resonances of methylene protons (CH_2–O) and the appearance of the corresponding carbonyl peak (147.35 ppm) in ^{13}C NMR spectra (Figures S2 and S3).

ROP of monomer **2**, to generate the pinacol-protected polymer PPBC, was carried out through an initiator chain-end activation mechanism using the superbase DBU as organocatalyst. DBU is a proven versatile organocatalyst that offers excellent control over the polymerization of numerous cyclic carbonates, yielding polymers with well-defined properties and high end-group fidelity. ROP kinetics of **2** was studied at room temperature using methoxypoly(ethylene glycol) ($mPEG_{44}$–OH) as a macroinitiator and a monomer/initiator ratio of 30. Monomer conversion as a function of time was determined by ^1H NMR, comparing the resonance signal of PEG methyl

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protons with CH_2O protons of the polymer, which appear as a broad peak in the range between 4.1 to 4.4 ppm, or by simply monitoring the disappearance of the doublet at 4.7 ppm indicative of monomer CH_2O protons (Figure S4).

Conversion of **2** varied linearly with time until ~70% (Figure 1A), corresponding to a polymerization time between 1 and 1.5 h. After, the polymerization became sluggish, reaching a limiting conversion of 85% at ~7 h. The decrease in polymerization rate can be attributed to ROP-chain growth equilibration or possible steric impediments. We have previously shown that the polymerization of highly sterically hindered cyclic carbonates is facilitated by the incorporation of less bulky monomers, such as D,L-lactide.[43] ROP of **2**, within the limited conversion regime, shows a good fit for a linear relationship between monomer consumption ($\ln(1/1 - x)$) and reaction time, indicating that the reaction obeys pseudo first-order kinetics. The apparent reaction rate coefficient was $k_{app} = 0.95\ h^{-1}$ (Figure 1B). The DBU-catalyzed polymerization of **2** is considerably faster than that of 9-phenyl-2,4,8,10-tetraoxaspiro[5,5]undecan-3-one ($k_{app} = 0.16\ h^{-1}$), a diol-functionalized carbonate,[43] but slower than 5,5-bis-(azidomethyl)-1,3-dioxan-2-one ($k_{app} = 5.04\ h^{-1}$),[38] evidencing the steric limitations hampering the polymerization of trimethylene carbonate derivatives with bulky rigid substituents.

Evolution of the number-average molecular weight was assessed by gel permeation chromatography. GPC analysis showed monomodal distributions for all reaction times with a slight broadening toward higher elution times for longer polymerizations (Figure 1C), possibly suggesting the occurrence of undesirable side-reactions such as transesterification. Unreacted macroinitiator, however, was not observed. Nevertheless, molecular weight showed an excellent linear dependence on monomer conversion (Figure 1D). Furthermore, polydispersity exhibited relatively low values throughout the reaction (PDI < 1.1), particularly during the first hour of polymerization, where its value did not exceed 1.05.

We further examined the controlled nature of the polymerization of **2** by varying monomer/initiator molar feed ratios (M/I), to afford a series of copolymers with varying PBC lengths (Table 1 and Figure 2). Having optimized the conditions for the polymerization of **2**, we limited reaction time to 1 h. As shown in Figure 2, an excellent linear relationship was observed between molecular weight (determined by ^{1}H NMR) and M/I. In addition, experimental average molecular weights were very close to predicted ones in all cases, and monomodal distributions, with PDI values below 1.12, were observed for the three ratios examined. Taken together, these results suggest that the ROP of **2** proceeded with excellent control, resulting in polymers with well-defined molecular weights and low PDI values.

Table 1. Characterization of mPEG-*b*-PPBC with Variable Hydrophobic Block Lengths

polymer	M/I (feed)	M_n[a]	M_w[a]	$Đ_M$[a]	M_n[b]	conv.[b] (%)
$mPEG_{44}$-*b*-$PPBC_{11}$	13	5006	5581	1.11	6138	85
$mPEG_{44}$-*b*-$PPBC_{26}$	30	8022	8924	1.11	11782	86
$mPEG_{44}$-*b*-$PPBC_{42}$	50	8537	9568	1.12	17800	84

[a]Determined by GPC. [b]Molecular weight and conversion (conv.) were estimated by ^{1}H NMR, referencing PEG methyl protons (δ = 3.35 ppm) with those of the CH_2O protons of the polymer, which appear as a broad peak in the range between 4.1 to 4.4 ppm.

The sensitivity of polycarbonates to hydrolytic degradation complicates the selection of an appropriate catalyst for removal of the pinacol protecting group. Catalytic displacement of this protecting group has been achieved using a combination of TFA/boronic acid-functionalized polystyrene beads (BA-PSB) at elevated temperatures (80 °C),[13] or by successive washings with a concentrated solution of HCl for nonhydrolyzable polymer backbones.[18] The use of such harsh conditions for the deprotection of our boronic acid-derived polycarbonates could potentially lead to degradation of the backbone.

Indeed, the use of TFA (2% v/v)/BA-PSB mixture at 40 °C resulted in polymer degradation. The use of a resin (Dowex) at elevated temperatures or for extended periods also resulted in uncontrollable extents of deprotection (Table S1). Although hydrolytic degradation of carbonate linkages is favored under alkaline conditions, we believe that water formation during pinacol transesterification can possibly accelerate the degradation process under the conditions examined.

The successful deprotection of pinacol-protected boronic acid-derived polycarbonates was achieved under mild temperature (40 °C) by simply using an excess of 1,4-diboronic acid. The extent of deprotection could be controlled according to reaction time, as shown in Table S1. The byproducts resulting from this transesterification reaction, and the excess of 1,4-diboronic acid, were readily removed by dialysis against methanol. The efficiency of pinacol removal was nearly quantitative, as shown by the disappearance of the pinacol ester methyl protons (δ = 1.25 ppm). Furthermore, deprotection was sufficiently mild to proceed without noticeable degradation of the carbonate backbone, as assessed by ^{1}H NMR (Figure S4). To confirm the stability of the polycarbonate backbone under the conditions used for deprotection, we carried out the esterification of boronic acids with pinacol (Figure 2C). The resultant polymer was characterized by ^{1}H NMR (Figure S6) and GPC. The similarity of the chromatograms (i.e., peak position and distribution in Figure 2D) before and after esterification suggest that degradation of the polycarbonate backbone did not occur during deprotection.

Because of the challenges posed by deprotection of the pinacol-derived PPBC, we synthesized monomers containing other protecting groups that could lead to a more amenable deprotection route. Of these, 2,2-dimethyl-1,3-propanediol, is a good candidate as it can be readily displaced under mild acidic conditions. We synthesized the acetonide-protected monomer (**4**), following a similar strategy to that described for **2**. Polymerization of **4**, like **2**, proceeded to high conversions (~90%) after 7 h, also yielding copolymers with low polydispersity (<1.09, Table S2 and Figure S7).

Indeed, deprotection of the acetonide-protected derivative, PEG_{44}-*b*-$PABC_{12}$ was achieved under more tractable conditions than those previously described for the pinacol-protected polymer, by simply using an ion-exchange resin at room temperature. Nearly 95% deprotection was achieved in the first 12 h of reaction without noticeable degradation of the polymer backbone (Figure S5).

The self-assembly of the amphiphilic polymers mentioned above was then examined. Aggregates from PEG-*b*-PPBC copolymers were formed by a rapid change in solvent quality using a multi-inlet vortex mixer (MIVM). This mixing method

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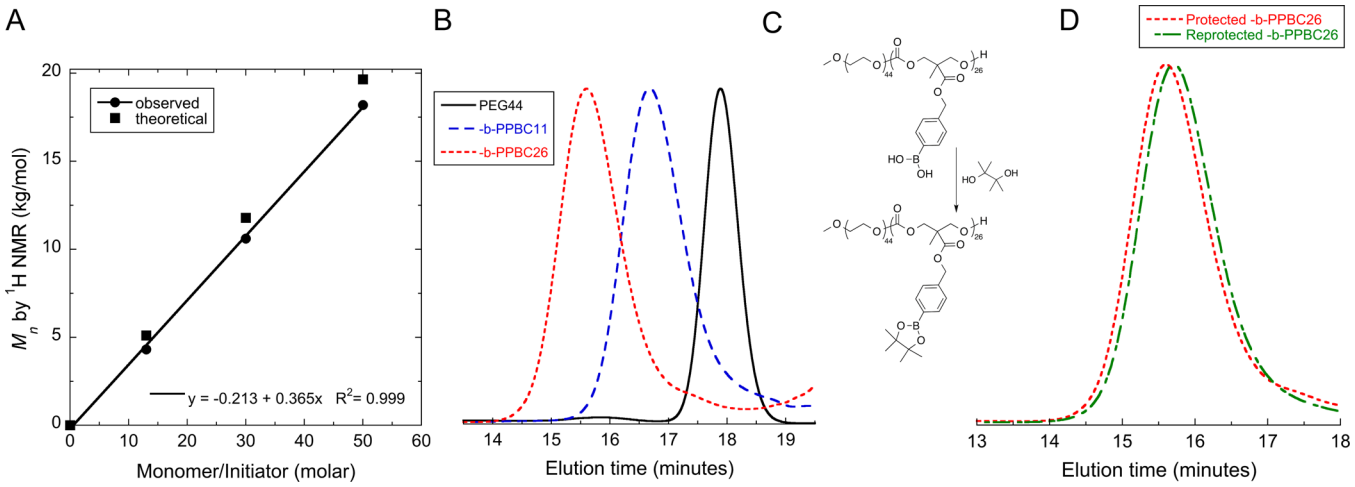

Figure 2. PEG-*b*-PBC with different hydrophobic block lengths. Copolymerizations were limited to 1 h. (A) Linear dependence of hydrophobic block molecular weight with initiator concentration showing the similarity between observed and predicted values, and the controlled variation in molecular weight of the boronic acid-containing block with initiator concentration. (B) Copolymer molecular weight distributions. (C) Reprotection of deprotected polymer with pinacol, and gel permeation chromatograms of protected and reprotected copolymers (D). The similarity of the distributions shows degradation of the backbone did not take place during the exchange reaction with free boronic acid.

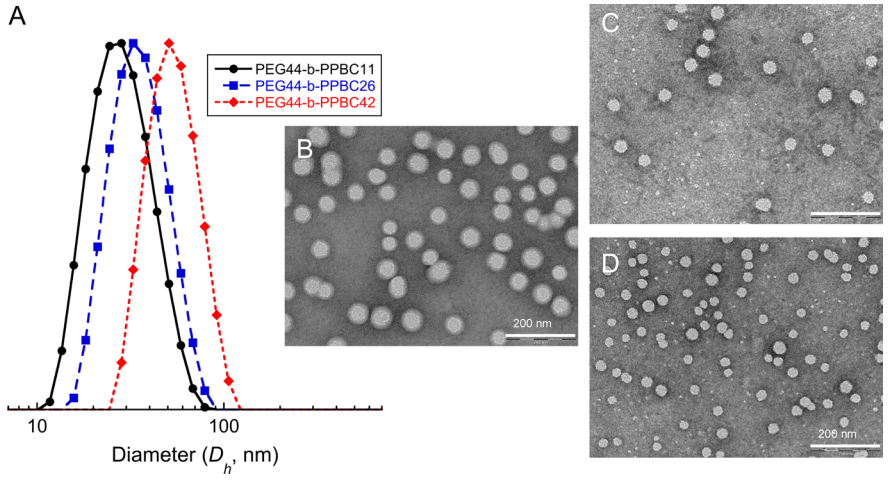

Figure 3. Aggregates from the self-assembly in water of PEG-*b*-PPBC of variable hydrophobic block lengths. (A) Regardless of their morphology, aggregates showed relatively narrow size distributions, as determined by DLS. (B–D) TEM images of vesicle-like aggregates from PEG_{44}-*b*-$PPBC_{42}$ (B) and spherical aggregates from PEG_{44}-*b*-$PPBC_{26}$ (C) and PEG_{44}-*b*-$PPBC_{11}$ (D).

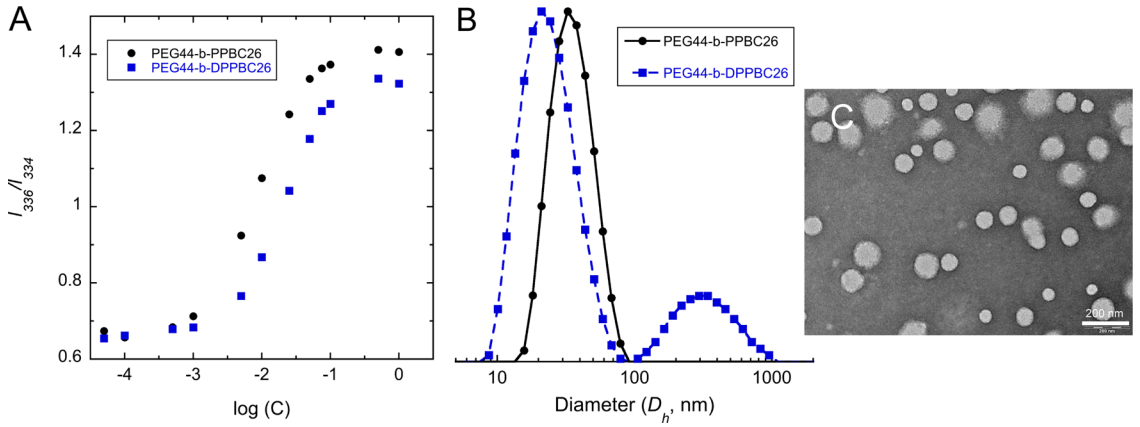

Figure 4. Aggregates from the protected and deprotected forms of PEG_{44}-*b*-$PPBC_{26}$. (A) Fluorescence spectroscopy data to determine critical micelle concentrations. (B) Particle size distributions of protected and deprotected polymers, measured by DLS. (C) TEM images of deprotected polymer self-assemblies.

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ensures high mass transfer so as to achieve spatially homogeneous superstation and rapid supersaturation rates.[44−46] Amphiphile concentration was kept at 5 mg/mL in the organic phase (THF), and the mixing ratio used was 1:9 (v_{water}/v_{THF}), resulting in 0.5% w_p/w suspensions. Aggregate morphology is shown in Figure 3B−D. In all cases, size distributions showed single narrow peaks. Both size and morphology varied with hydrophobic block length, as expected.[47] Smaller, spherical aggregates were formed from the amphiphiles with shorter PPBC lengths (C, D), while vesicle-like aggregates were observed for the copolymer with the longest PPBC block (B). To further confirm the structure of these aggregates, static light scattering measurements were performed. The ρ-parameter (R_g/R_h), which provides information regarding the inner density profile of the micellar structure, was determined for PEG_{44}-*b*-$PPBC_{26}$ and PEG_{44}-*b*-$PPBC_{42}$ (Table S3). Their values are 0.78 and 0.98, respectively. These results clearly indicate that the amphiphile with the shorter PPBC block exhibits a core−shell structure, while the one with the long hydrophobic block self-assembles into a hollow vesicle.

Deprotection increases the hydrophilicity of the phenylboronic acid carbonate block, as reflected in the C_{CMC} values of PEG_{44}-*b*-$PPBC_{26}$ (Figure 4); at 100% deprotection the C_{CMC} increases from 1.45 to 3.64 μg/mL. Aggregates from the deprotected polymer are quite distinct from the protected analog. DLS analysis shows a bimodal distribution with an average particle size of 25.68 nm and a distribution of 0.335; this is in contrast to the protected polymer, the distribution of which is considerably narrower (for this polymer, diameter and distribution are 34.73 and 0.199, respectively). More information regarding morphology can be obtained from TEM, where the coexistence of aggregates of different sizes is observed. Aside from the smaller spherical particles with a diameter ranging from 25 to 50 nm, we also observe the presence of larger aggregates, with a diameter of >200 nm, exhibiting diffuse interfaces. Together, these results suggest that the assembly of block copolymers exhibiting a lesser amphiphilic character, under the rapid conditions used herein, result in a more diffuse interface between the hydrophobic core and the hydrophilic corona, possibly leading to the physical inclusion of PEG chains in the core. Similar observations have been made of nanoparticles from a copolymer with a stronger amphiphilic character than ours (PEG-*b*-PLGA), in which case thermal analysis pointed to an incomplete phase segregation of both blocks.[48]

The widespread use of boronic acids in biomedical applications requires the development of methods for the functionalization of biologically relevant polymers. Herein, we examined the ring-opening polymerization of boronic acid-installed cyclic carbonates, catalyzed by DBU. This is, to the best of our knowledge, the first example of this class of materials. Controlled polymerization proceeded to relatively high conversions (~70%) within less than 1.5 h, yielding polymers with low polydispersity. Organoboron polymer length was readily tuned by varying monomer/initiator ratio. While the carbonate backbone is susceptible to cleavage under extreme pH, displacement of the protecting group through competitive displacement resulted in boronic acid-functionalized polycarbonates. Polymer self-assembly, induced by a change in solvent quality, was also studied. Spherical nanoparticles or vesicle-like aggregates were observed, depending on the hydrophilic/hydrophobic ratio of the polymer. These polymers are expected to finding direct applications for core stabilization of biodegradable amphiphilic assemblies or in drug and protein encapsulation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental section including materials, characterization, methods and experimental procedures, as well as additional figures including NMR spectra and conditions for deprotection. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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