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Facile Strategy to Well-Defined Water-Soluble Boronic Acid (Co)polymers

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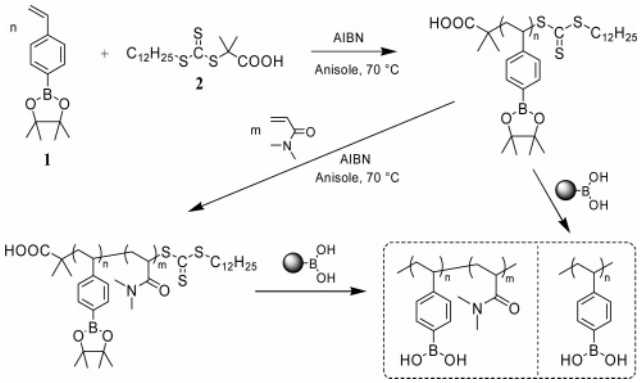
Organoboron polymers are important precursors to materials with potential utility in catalysis, separations, and sensing applications. Recent reports detail boron-containing polymers serving as electrolyte materials for batteries, blue emissive polymers, self-healing materials, and precursors for functional polyolefins.[1] These polymers have demonstrated promise in biological applications as well, which is especially evidenced by water-soluble boronic acid-containing polymers having garnered a great deal of attention for glucose or RNA sensing, diabetes treatment therapies, and as supramolecular materials.[2] To more fully realize the potential of boronic acid containing macromolecules in sensing and delivery applications, it is vital to expand the capability to prepare such polymers with precise control over topology, molecular weight, and composition. Herein, we report the first, to our knowledge, successful synthesis of well-defined water-soluble boronic acid copolymers from stable and easily manipulated boron-containing monomers.

A variety of polymerization techniques have been considered for the synthesis of polymers with pendant boron functionality, with conventional radical polymerizations arguably being most successful due to facile experimental setup and lack of significant side reactions.[3] Controlled radical polymerization techniques facilitate the preparation of (co)polymers with predetermined molecular weights, narrow molecular weight distributions, and high degrees of chain-end functionalization, the latter of which facilitate the preparation of complex macromolecular architectures that lead to self-assembly and other advanced materials applications.[4] Jäkle et al. pioneered the efficient synthesis of organoboron vinyl (co)-polymers via atom transfer radical polymerization (ATRP),[5] either from silylated precursors that were subsequently borylated[6] or from the polymerization of organoboron monomers.[7] We are primarily interested in the synthesis and aqueous solution behavior of amphiphilic organoboron block copolymers, especially those with acrylamido hydrophilic blocks. While the success of ATRP for the polymerization of most acrylamido monomers has drastically improved over the past few years, reversible addition−fragmentation chain transfer (RAFT) polymerization[8] has proven excellent for the synthesis of a range of polyacrylamides.[9] RAFT can be conducted under relatively mild conditions, is applicable to nearly any monomer susceptible to radical polymerization, and has been employed to prepare a range of well-defined complex macromolecular topologies. The plethora of stimuli-responsive and water-soluble acrylamido polymers, coupled with the potential biological applications of controlled architecture boron-containing polymers, suggests significant value in developing synthetic capabilities to prepare such block copolymers.

We prepared homopolymers of selected molecular weights and block copolymers with poly(*N*,*N*-dimethylacrylamide) (PDMA). While there have been reports of uncontrolled random copolymers of acrylamido and boron-containing monomers being prepared by conventional radical polymerization,[10] this is the first example of block copolymers with organoboron and acrylamido segments. Polymeric boronic acids tend to be extremely hygroscopic and are challenging to characterize by gel permeation chromatography (GPC). Therefore, we polymerized the pinacol ester of 4-vinylphenylboronic acid and subsequently deprotected utilizing a mild and convenient strategy to obtain the boronic acid (co)polymers. A previous successful route to well-defined polymeric boronic acids proceeded via ATRP and postpolymerization modification of silylated precursors with toxic and air-sensitive BBr_3.[7]

Scheme 1. Synthesis of Boronic Ester and Boronic Acid Homopolymers and Block Copolymers by RAFT Polymerization



We polymerized 4-pinacolatoborylstyrene (pBSt) (**1**) with 2-dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionic acid (**2**) as the chain transfer agent (CTA) and 2,2′-azobisisobutyronitrile (AIBN) as the initiator (Scheme 1). Polymerizations were conducted at 70 °C in anisole with a monomer concentration of 50 vol %. Reaction stoichiometry ([monomer]/[CTA]/[initiator]) was varied, and the agreement between theoretical and experimental molecular weights was excellent over the course of the polymerizations (Figure 1). Kinetics followed the expected dependence on the ratio of [CTA]/[AIBN]. Increasing the amount of initiator relative to the CTA resulted in somewhat faster rates, and with the exception of a slight inhibition period being observed at low initiator concentrations, pseudo-first-order kinetics were observed up to relatively high conversions. As further evidence of polymerization control, poly(4-pinacolatoborylstyrene) (PpBSt) homopolymers were employed as macro-chain transfer agents to synthesize block copolymers with DMA. Successful chain extension confirmed end group retention indicative of polymerization control, while simultaneously allowing the preparation of amphiphilic diblock copolymers (Table 1). Indeed, $PpBSt_{145}$-*b*-$PDMA_{273}$ (M_n = 60800 g/mol, M_w/M_n = 1.09) formed micelles with an average hydrodynamic diameter of approximately 98 nm in water, as determined by dynamic light scattering (Figure 1).

Postpolymerization modification of silylated precursors prepared by ATRP can successfully lead to polymeric boronic acids,[7] but deprotection of the stable and conveniently manipulated polymeric pinacol esters has yet to be reported. Rather harsh conditions are generally required to deprotect hindered boronic esters. Transesterification with another boronic acid followed by hydrolysis is an attractive approach, but the requirement of an excess of this second

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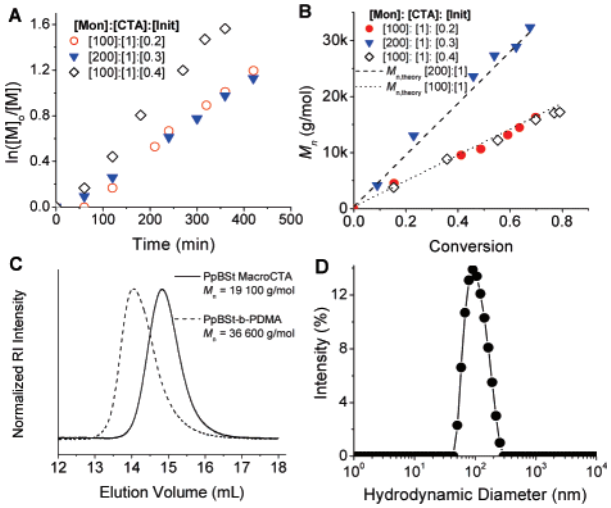

Figure 1. (A) Pseudo-first-order kinetic plot and (B) M_n versus conversion for RAFT polymerization of 4-pinacolatoborylstyrene (pBSt) with various ratios of monomer (Mon), chain transfer agent (CTA), initiator (Init); (C) GPC traces for a PpBSt homopolymer and block copolymer with poly(*N*,*N*-dimethylacrylamide) (PDMA); (D) hydrodynamic diameter distribution for $PpBSt_{145}$-*b*-$PDMA_{273}$ in water.

Table 1. Results from Synthesis of Poly(4-pinacolatoborylstyrene) (PpBSt) and PpBSt-*b*-Poly(*N*,*N*-dimethylacrylamide) (PDMA)

polymer	[M]/[CTA]/[I][a]	time min	conversion[b] %	M_n[c] g/mol	M_w/M_n[c]
PpBSt	[100]/[1]/[0.15]	518	74	16 900	1.16
PpBSt	[100]/[1]/[0.20]	420	70	16 300	1.13
PpBSt	[200]/[1]/[0.30]	420	68	32 400	1.11
PpBSt	[100]/[1]/[0.40]	360	79	17 200	1.15
PpBSt-b-PDMA	[150]/[1]/[0.40]	360	99	36 600	1.08
PpBSt-b-PDMA	[250]/[1]/[0.40]	300	99	60 800	1.09

[a] Stoichiometric ratio of monomer/chain transfer agent/initiator. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GPC.

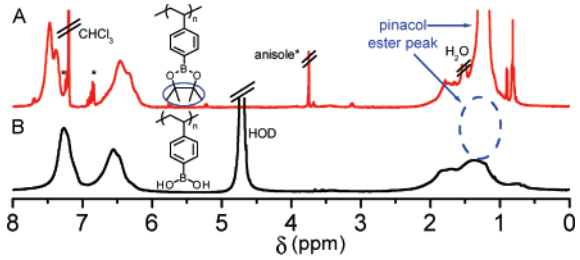

Figure 2. ^{1}H NMR spectra for (A) poly(4-pinacolatoborylstyrene) ($CDCl_3$) and (B) deprotected poly(4-vinylphenylboronic acid) (D_2O/NaOD).

free boronic acid significantly complicates purification and separation. This problem was conveniently avoided by transesterification of the PpBSt units in acetonitrile/2% trifluoroacetic acid with excess boronic acid immobilized on an insoluble support.[11] Purification was greatly simplified, and the efficiency of pinacol removal was essentially quantitative, as determined via ^{1}H NMR spectroscopy by the disappearance of the pinacol ester methyl protons of the PpBSt units ($\delta = 1.23$ pm) (Figure 2). Conversion to boronic acid functionality was sufficient to induce solubility of the PpBSt in basic aqueous media, as expected because of the formation of anionic polyelectrolyte boronates at high pH. On the other hand, the polymeric ester precursors were insoluble under these conditions, and thus the change in solubility serves as further evidence of successful deprotection to the free boronic acid moieties. For the block copolymers with PDMA, deprotection was sufficiently mild to proceed without degradation of the acrylamido units.

This facile route leads to well-defined polymeric boronic acids via RAFT polymerization of their stable pinacol esters. This is the first example of boronic acid/ester block copolymers being prepared by RAFT polymerization and the first time a block copolymer containing organoboron and acrylamido segments has been prepared by any polymerization method. The self-assembly potential of organoboron amphiphilic copolymers was demonstrated by formation of polymeric micelles of PpBSt-*b*-PDMA in water. The versatility of acrylamido polymers in applications requiring water-solubility or stimuli-responsive behavior, combined with the anticipated biological and catalytic utility of controlled architecture boron-containing polymers, suggests significant promise in the development of synthetic strategies toward water-soluble boronic acid-containing macromolecules. Future studies will investigate the responsive behavior of boronic acid block copolymers as a function of specific small molecule organics.

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Supporting Information Available: Detailed experimental and analytical details, and additional GPC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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