Macromolecules **2007,** *40,* 8518−8520

Communications to the Editor

A Facile Method for the Synthesis of Cleavable Block Copolymers from ATRP-Based Homopolymers

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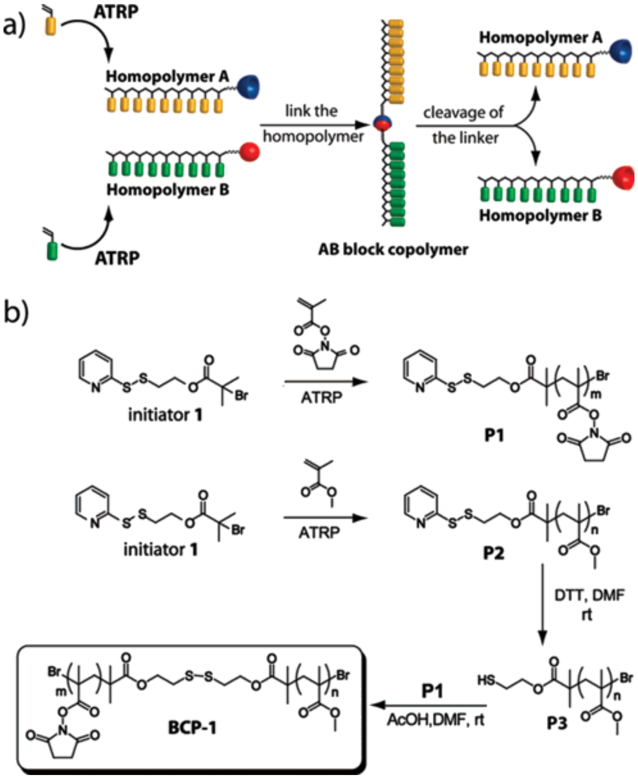
Received August 16, 2007
Revised Manuscript Received October 2, 2007

Block copolymers continue to garner significant interest due to their propensity to form self-assembled nanostructures, the morphologies of which are determined by the mutual compatibility and the volume fractions of the constituent blocks.[1] If one were to create nanoporous structures from these, it is necessary that one of the blocks is selectively degraded after the assembly. Most commonly used techniques to achieve such structures involve rather harsh conditions and/or are limited to a few classes of polymers.[2] Recently, a synthetic methodology has been reported in which acid-catalyzed cleavage of PS−PEO block copolymers can be achieved under mild conditions,[3] which has been used subsequently to generate nanoporous thin films.[4] We have been interested in developing a general synthetic methodology that provides access to a wide variety of block copolymers that are cleaved under mild conditions. We also stipulated that the syntheses of both blocks should be achieved with significant control in polydispersity, as this could impact the long-term interests in obtaining well-defined nanoporous structures.[5] Here, we describe a versatile synthetic methodology that provides such an access to a broad class of cleavable block copolymers.

Controlled radical polymerization methods, such as ATRP, have emerged as a popular approach to achieve polymers with narrow polydispersity.[6,7] ATRP has been achieved with initiators that allow for post-polymerization manipulations.[8] This has been utilized mainly in achieving protein−polymer conjugates.[8,9] However, we do not know of any work that utilizes such functionalized initiators to achieve cleavable block copolymers. One of the reported ATRP initiators involved the use of pyridyldisulfide functionality, where the thiol-based entities could be installed in the last steps of the synthesis through a disulfide exchange. We envisaged the possibility of synthesizing cleavable diblock copolymers very simply from the constituent homopolymers using the pyridyldisulfide functionality as the handle. The resultant block copolymer will be linked through a disulfide functionality as the cleavable linker (Scheme 1a). Disulfides can be readily cleaved using a reducing agent such as dithiothreitol (DTT) or glutathione.[10]

Scheme 1. (a) Schematic of the Synthetic Approach toward Cleavable Block Copolymers from the Homopolymers and (b) Synthesis of BCP1 from Its Homopolymers



Heterosubstituted disulfides can be obtained in high yields, when a molecule containing a free thiol functionality is treated with another molecule containing the pyridyldisulfide moiety. Therefore, to obtain the targeted AB block copolymer linked by a disulfide functionality, it is necessary that one of the homopolymer chains contain a pyridyldisulfide functionality while the other chain contains a free thiol unit. It is interesting that the thiol functionality can be introduced into the polymer chain by initially introducing it as a pyridyldisufide and then reducing it in a post-polymerization step.

We illustrate our approach with the synthesis of poly(*N*-hydroxysuccinimidyl methacrylate-*b*-methyl methacrylate) (**BCP1**, P-NHSMA-*b*-MMA), as shown in Scheme 1b. The reasons for choosing these particular monomers to demonstrate the methodology are the following; (i) NHS esters allow for post-polymerization functionalizations and (ii) methyl methacrylate is a commonly used monomer for synthesizing various block copolymers, where the phase separation is well studied.

The homopolymers (PNHSMA (**P1**) and PMMA (**P2**)) were synthesized using the initiator **1** under ATRP conditions (Scheme 1b). Both polymers were obtained with low polydispersity values (1.28 and 1.21, respectively).[11] Since the initiator contains an aromatic chromophore, its presence can be examined by UV−visible spectroscopy. The intense peak at 280 nm is due to the presence of the pyridyldisulfide moiety.[11] As mentioned above, one of the homopolymer functionalities should contain a free thiol unit to achieve the targeted cleavable block

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10.1021/ma071852n CCC: $37.00

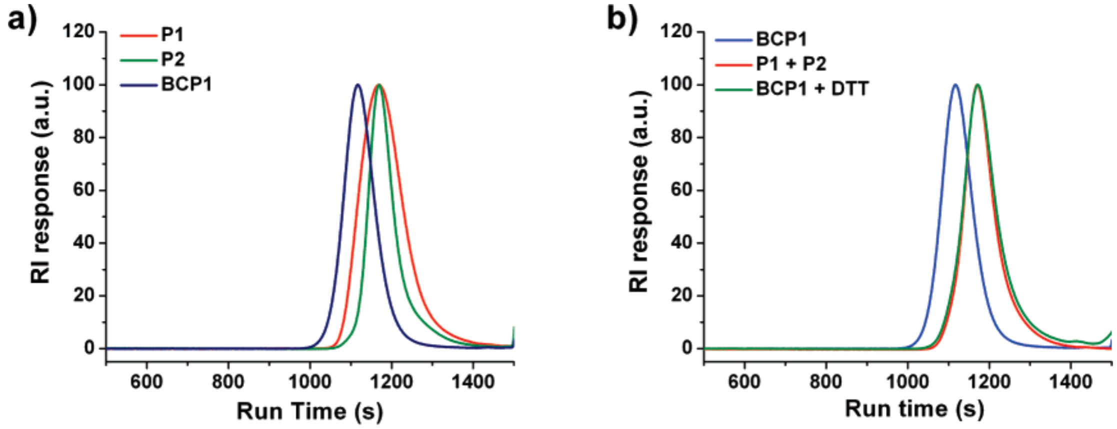
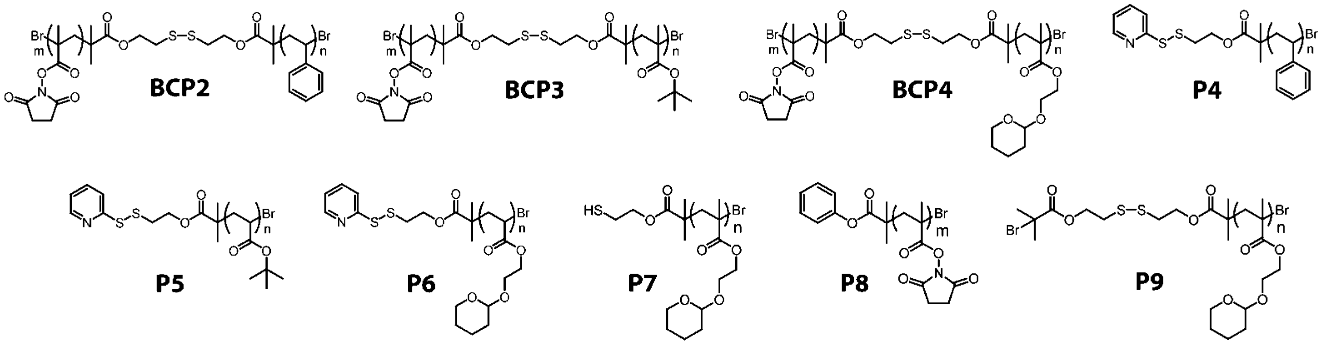


Figure 1. (a) GPC profile of block copolymer **BCP1** compared with **P1** and **P2**. (b) GPC profile of the cleavage of block copolymer **BCP1** by DTT compared with a physical mixture of **P1** and **P2**. Although there are two polymers both in the physical mixture and in the DTT-cleaved reaction mixture, only one peak is observed as the molecular weight and the PDI of the two polymers are almost identical.

Scheme 2. Structure of Polymers P5−P9 and Block Copolymers BCP2−BCP4



copolymer. For this purpose, the disulfide moiety in polymer **P2** was reduced to the thiol using dithiothreitol (DTT). This reaction can be easily monitored using UV−visible absorption spectroscopy, since the byproduct of this reaction is pyridothione, which has a distinct absorption with a λ_{max} at 375 nm. The evolution of this peak with time was monitored and the reaction was stopped when the peak intensity did not increase further, suggesting the completion of the reaction. The resulting polymer **P3** was precipitated out and the UV−visible spectra was checked again. The absence of any peak at 280 nm confirmed the conversion of the pyridine disulfide functionality to the free thiol.

It is well-known that thiols are susceptible to air oxidation, which could cause the homodimerization of the polymer chain. In order to confirm that this did not occur in the process of isolation, the GPC of **P3** was monitored and no change in the MW was observed (compared to polymer **P2**). Polymer **P3** was then reacted with polymer **P1** to achieve the block copolymer **BCP1** (Scheme 1b). Here again, the formation of the block copolymer was monitored using absorption spectroscopy.[11] Upon completion of the reaction, when the peak intensity at 375 nm remained constant, the resulting polymer was precipitated out. The GPC profile of the product block copolymer **BCP1** was compared with that of **P1** and **P2** (Figure 1a). The GPC of **BCP1** is shifted toward a higher molecular weight compared to **P1** and **P2**, suggesting that the targeted block copolymer has been achieved. Also, the PDI of **BCP1** is lower than the two lower MW constituents, which is taken to be another indication of the formation of the block copolymer. These conclusions are further supported by ^{1}H NMR.[11]

In order to test the broader applicability of our methodology, three other block copolymers **BCP2−BCP4** were synthesized (Scheme 2 and Table 1). There are several supporting pieces of evidence to show that the block copolymers are indeed synthesized from the corresponding homopolymers using this methodology.[11] For example, the block copolymers MWs are nearly equal to the sum of the parent homopolymers (Table 1). Similarly, when the ^{1}H NMR of the block copolymers were examined, peaks for both the blocks were clearly visible as expected.[11] Also, the solubility parameters were consistent with the formation of block copolymers. For instance, the **BCP1** is soluble in acetone while **P1** is not. Also, **BCP1** is precipitated from ether, in which homopolymer **P2** is soluble.

The block copolymers **BCP1−BCP4** contain NHSMA as one of the blocks, which is an activated form of the carboxylic acid functionality. It is necessary then to show that the reaction of the thiol is indeed selective to the pyridyldisulfide functionality. To ascertain this, we carried out a control experiment in which we treated polymer **P7** with a mixture of the initiator **1** and the polymer **P8**. Polymer **P8** contains all the functionalities present in **P1** except for the disulfide initiator. The product of this reaction provided only a reaction of **1** with **P7**. There is no evidence of any cross−polymer reaction, as confirmed by GPC.[11]

Finally, the key objective of this work is to demonstrate that the block copolymers that we achieved are cleavable under mild conditions. If the block copolymer is indeed formed through a disulfide bond, then we should be able to cleave the block copolymer to the constituent blocks by treating it with a mild reducing agent such as DTT. In order to examine this possibility, we treated **BCP1** with DTT and monitored the GPC profile of the reaction mixture. We show the GPC of the reaction mixture along with that of **BCP1** and the physical mixture of **P1** and **P2** in Figure 1b. The GPC of the reaction mixture matches with that of the physical mixture of the two constituent polymers indicating the cleavage of the block copolymer.[12] This was

Table 1. Molecular Weights and Polydispersities of the Block Copolymers BCP1−BCP4

block copolymer	polymer (A + B)				M_n (block copolymer)	PDI
	polymer A	M_n	polymer B	M_n		
BCP1	P1	9940^a	P3	9640^a	18 181^a	1.18
BCP2^c	P1	9940^a	P4	5130^b	16 540^b	1.16
BCP3^c	P1	9940^a	P5	4900^a	14 094^a	1.22
BCP4^c	P1	10 640^a	P6	9870^a	21 240^a	1.28

[a] Estimated using PMMA standards. [b] Estimated using PS standards. [c] See Supporting Information for details

consistently the case with all the block copolymers **BCP1−BCP4**, which clearly demonstrates the versatility of our strategy.

In summary, we have shown the following: (i) A variety of cleavable block copolymers can be synthesized by a simple combination of the homopolymers synthesized by ATRP. (ii) Complementary reactive functionalities can be incorporated in these block copolymers that allow for incorporation of additional functionalities in a post-polymerization step. (iii) The disuflide-containing block copolymers can be cleaved into its constituent blocks under mild reductive conditions. The methodology developed here will potentially impact a variety of areas. For example, we have synthesized the block copolymers without utilizing the active chain ends here. This opens up the possibility of further utilizing the active chain ends to achieve tetrablock and triblock copolymers, where the cleavable unit could be strategically placed. Another example of the impact of this work is the generation of microphase-separated nanostructures, which can then be used for achieving nanoporous structures in which the interfaces are decorated with highly reactive thiol functionalities. Such nanostructures can be utilized to achieve a variety of composite structures with implications in materials and biology.

Acknowledgment. We thank the NSF−Fueling the Future Center (Chemical Bonding Center, CHE-0739227) for partial support of this work.

Supporting Information Available: Text giving synthetic and other experimental details, including a table giving details of the polymerization, figures showing absorption spectra, ^{1}H NMR spectra, GPC profiles, thermographic analyses, and the stability of disulfide, and schemes showing the reactions used. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) See Supporting Information for details.

(12) The molecular weights of **P1** and **P2** from **BCP1** are similar. Therefore, the distinct presence of two homopolymers is not seen clearly in Figure 5. However, these are clear in other block copolymers.[11]

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