Efficient Preparation of Cyclic Poly(methyl acrylate)-*block*-poly(styrene) by Combination of Atom Transfer Radical Polymerization and Click Cyclization

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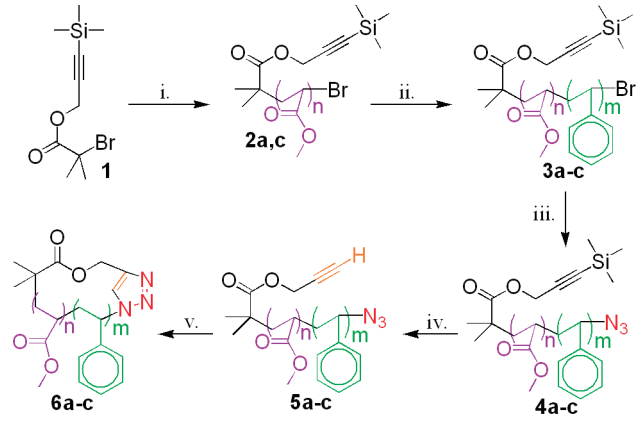
Introduction. Diblock copolymers demonstrate a unique ability to self-assemble into complex nanoscale morphologies resulting from the phase segregation of contrasting blocks. Extensive research has been devoted to studying how linear diblocks segregate in bulk to yield a diverse range of nanoscale symmetries,[1,2] including lamellae, hexagonally packed cylinders, bicontinuous gyroids, and body-centered-cubic arrays of spheres. Diblock copolymers also demonstrate the ability to self-assemble in solution to yield micellar aggregates which can be used to encapsulate guests and can be stabilized via cross-links to afford more robust nanoscale carriers.[3] With the development of synthetic techniques to prepare more architecturally complex block copolymers including star block polymers,[4] ABC triblocks,[5–7] ABCD tetrablocks,[8,9] and miktoarm stars,[10–12] the relationship between the block copolymer architecture and the resultant self-assembly is being explored. In the case of triblock copolymers the addition of the third block leads to a vastly increased set of complex morphologies.[13] Cyclic block copolymers belong to a unique polymer topological that is expected to exhibit characteristic changes in both solution and bulk properties.[14,15] However, exploration of these materials has been very limited,[16,17] largely because of the technical difficulties in preparing and purifying well-defined cyclic block copolymers. Recently, cyclic block copolymers have been prepared using the ^{60}Co γ-ray-induced polymerization from cyclic dithioester initiators, though this technique has not seen widespread use.[18] The most common synthetic route has been the end-group coupling of telechelic ABA triblock copolymers prepared using anionic polymerization, including poly(dimethylsiloxane)-*block*-poly(styrene)-*block*-poly(dimethylsiloxane),[16,19,20] poly(2-vinylpyridine)-*block*-poly(styrene)-*block*-poly(2-vinylpyridine),[16] poly(styrene)-*block*-poly(butadiene)-*block*-poly(styrene),[17,21] and poly(styrene)-*block*-poly(isoprene)-*block*-poly(styrene),[22] which were cyclized with difunctional coupling agents such as dichlorodimethylsilane or di(bromomethyl)benzene. While anionic polymerization techniques can yield very narrow polydispersity (PDI) linear precursors, the nonspecific coupling chemistry between two bifunctional reagents results in significant quantities of linear oligomers from multiple intermolecular coupling events, in addition to unreacted linear precursors. The anionic preparation of block copolymers with complementary amine and carboxylic acid end groups[23] provides a more specific functional group coupling via their dicyclohexylcarbodiimide (DCC) coupling to form an amide linkage, but the low efficiency of the DCC coupling requires extensive purification. Among the reported anionic techniques for preparing cyclic diblocks, the isolation of reasonably pure cyclics requires tedious and repetitive fractionation to remove acyclic impurities. For physical studies of block copolymer self-assembly as well as exploration of these materials for biomedical applications, narrow polydispersity and high cyclic purity are critical for providing meaningful and reproducible data. Therefore, a more efficient route toward well-defined cyclic block copolymers with diverse side chain functional groups would be invaluable.

Scheme 1. Polymerization and Cyclization of Poly(methyl acrylate (MA))-*b*-poly(styrene (S)): (a) $n \approx 26$, $m \approx 38$; (b) $n \approx 26$, $m \approx 56$; (c) $n \approx 30$, $m \approx 23$[a]



(i) methyl acrylate, Cu(I)Br, N,N,N',N',N''-pentamethyldiethylene triamine (PMDETA), in bulk 50°C; (ii) styrene, Cu(I)Br, PMDETA, anisole, 90°C; (iii) NaN_3, dimethylformamide; (iv) $(C_4H_9)_4NF$, tetrahydrofuran; (v) Cu(I)Br, PMDETA, dimethylformamide, N_2 120°C

[a] The degree of polymerization for PMA and PS blocks was calculated from the average of the number-average molecular weight (M_n) values measured by gel permeation chromatography (GPC) and matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF MS).

Herein, an alternative cyclization approach is investigated that promises to provide access to a diverse range of high-purity cyclic block copolymers. Laurent and Grayson[24] recently demonstrated that the functional group tolerance, facile end-group modification, and well-controlled polymerizations offered by atom transfer radical polymerization (ATRP)[25] can be paired with the Huisgen 1,3-dipolar cycloaddition "click" coupling[26–28] to yield high-purity cyclic polystyrene without excess quantities of solvent or time-consuming fractionation methods to purify the product. Because of the functional group tolerance of both ATRP and the click reaction, this procedure can provide an efficient route to prepare a broad range of homopolymers. In addition, because ATRP has demonstrated high efficiency in reinitiating macroinitiators,[29,30] this procedure should be equally well-suited to preparing diverse cyclic block copolymers. The application of this technique toward the preparation of well-defined cyclic block copolymers of methyl acrylate and styrene (Scheme 1) is reported below.

Results and Discussion. Using a previously reported alkyne initiator,[31] **1**, methyl acrylate (MA) was polymerized in bulk using Cu(I)Br catalyst with *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) ligand at 50 °C after a series of freeze−pump−thaw cycles to remove oxygen from the reaction environment. The resulting trimethylsilyl (TMS)-alkyne-terminated poly(methyl acrylate) (TMS−C≡C−PMA−Br) homopolymers **2a**,**c** were purified by washing their methylene chloride solution with water, passing the organic layer through

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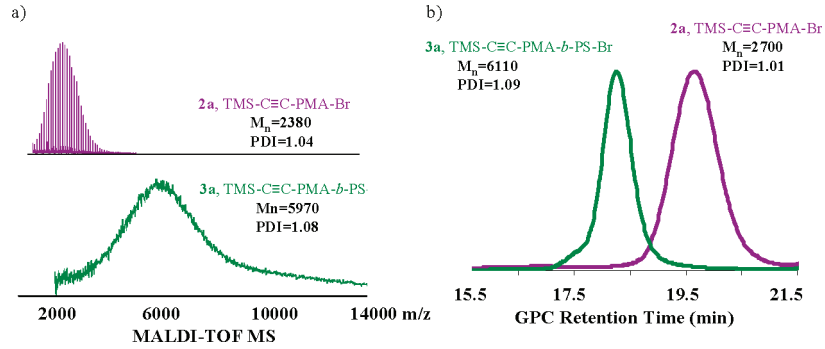

Figure 1. Characterization data for the block copolymerization: trimethylsilyl (TMS)-alkyne-terminated poly(methyl acrylate) homopolymer, TMS−C≡C−PMA−Br (**2a**), and the poly(methyl acrylate)-*block*-poly(styrene) copolymer, TMS−C≡C−PMA-*b*-PS−Br (**3a**) as observed by matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF MS) (a) and gel permeation chromatography (GPC) (b).

Table 1. Number-Average Molecular Weight (M_n) and Polydispersity Index (PDI = M_w/M_n) Data for Block Copolymers As Calculated by Gel Permeation Chromatography (GPC), Matrix-Assisted Laser Desorption Ionization (MALDI) Mass Spectroscopy, and ^{1}H NMR Spectroscopy of Polymers 2−6[a]

	M_n			PDI	
polymer	GPC	NMR	MALDI	GPC	MALDI
2a	2700	2800	2380	1.01	1.04
3a	6110	5600	5970	1.09	1.08
4a	5740	5800	6160	1.08	1.07
5a	5660	5800	5920	1.10	1.07
6a	4150	6400	5890	1.13	1.07
2a	2700	2800	2380	1.01	1.04
3b	8300	8500	8270	1.11	1.05
4b	7980	9100	8420	1.09	1.05
5b	8140	8900	8220	1.11	1.05
6b	6140	9000	8120	1.14	1.06
2c	2820	2600	2880	1.06	1.02
3c	5130	5600	5400	1.11	1.10
4c	5510	5100	5840	1.08	1.03
5c	5700	5400	5650	1.28	1.08
6c	4600	5400	5640	1.39	1.07

[a] The structures of polymers **2**−**6** are defined in Scheme 1.

a silica plug to remove the copper salts, and removing unreacted monomer *in vacuo*. The isolated PMA samples were characterized by matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF MS) (Figure 1a), gel permeation chromatography (GPC) (Figure 1b), and ^{1}H NMR spectroscopy and could be prepared reproducibly with number-average molecular weights (M_n) ranging between 2000 and 3000 with very narrow polydispersities (PDI < 1.06) (Table 1). The M_n of the PMA samples was determined via ^{1}H NMR spectroscopy by integrating the methyl protons (3.5 ppm) of the acrylate methyl ester with respect to the nine methyl protons (0.1 ppm) of the TMS-protecting group on the initiator.

Polystyrene (PS) blocks were prepared from the PMA homopolymers by reintroduction of Cu(I)Br catalyst in a degassed solution of styrene and the TMS−C≡C−PMA−Br macroinitiators in anisole at 90 °C. The PMA-*block*-PS copolymers, **3a**−**c**, were purified and isolated by extraction, filtration through a plug of silica gel, and precipitation into methanol. Block copolymers **3a,b** were both prepared from PMA homopolymer **2a**, whereas block copolymer **3c** was prepared from **2c**. The resultant TMS−C≡C−PMA-*b*-PS−Br copolymers were characterized by MALDI-TOF MS (Figure 1a), GPC (Figure 1b), and ^{1}H NMR spectroscopy with M_n ranging between 5000 and 9000 with a narrow polydispersity (PDI < 1.12) (Table 1). The technical simplicity and high efficiency of click chemistry have led to its widespread use for macromolecular couplings,[32,33] and it was employed for these reasons to effect cyclization. Because the benzyl bromide end group of TMS−C≡C−PMA-*b*-PS−Br is very susceptible to nucleophilic displacement, it can be transformed to the azide TMS−C≡C−PMA-*b*-PS−N_3 (**4a**−**c**) in nearly quantitative yields using sodium azide as a nucleophile.[34,35] To provide the complementary functional groups to enable the Huisgen cycloaddition, the initiator can be deprotected using tetrabutylammonium fluoride to yield the terminal alkyne, H−C≡C−PMA-*b*-PS−N_3 (**5a**−**c**). Both of these end-group transformations can be monitored using ^{1}H NMR spectroscopy by visualizing the loss of the benzylic bromide resonance at 5.0 ppm and the loss of the methyl resonances of the TMS group at 0.1 ppm. The M_n of the block copolymers was determined via ^{1}H NMR spectroscopy by integrating the methyl protons (3.5 ppm) of the methyl ester on the acrylate repeat units, the aromatic protons (6.2−7.2 ppm) of the styrene repeat units with respect to the nine methyl protons

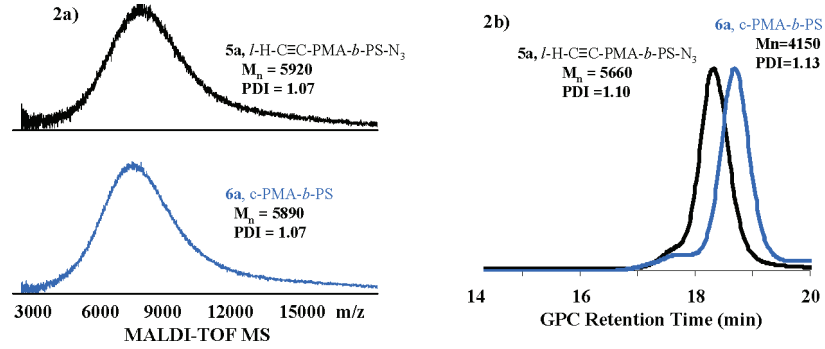

Figure 2. Characterization data for the click cyclization: linear azide-terminated poly(methyl acrylate)-*b*-poly(styrene), *l*-H−C≡C−PMA-*b*-PS−N_3 (**5a**), and cyclic poly(methyl acrylate)-*b*-poly(styrene), *c*-PMA-*b*-PS (**6a**), via matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF MS) (a) and gel permeation chromatography (GPC) (b).

(0.1 ppm) of the TMS-protecting group on the initiator for **3** and **4**, and the two methylene protons (4.2 ppm) adjacent to the alkyne of the initiator for **5**.

The continuous addition "click" polymer cyclization technique[24] was then utilized to efficiently produce the desired cyclic polymers (**6a**−**c**) with negligible formation of oligomers or other byproducts, but without using vast quantities of solvent. This technique takes into account that an α,ω-functionalized polymer will favor intramolecular cyclization under dilute Ruggli−Ziegler conditions.[36,37] In order to circumvent the need for large volumes of solvent, the linear precursor is added dropwise to the copper catalyst solution using a continuous addition technique[38] to ensure an infinitesimally small concentration of unreacted linear polymer in the reaction vessel throughout the course of the reaction. The rates of addition were determined empirically (0.22 mM at 2 mL/h) such that each drop of linear precursor added would be diluted in the copper catalyst solution and would be cyclized before the next drop was added. Cyclization of the block copolymer is verified by a shift in the GPC to longer retention times relative to the linear precursor (Figure 2b), while simultaneously maintaining the molecular weight of the precursor, as measured by MALDI-TOF MS (Figure 2a). This shift in the GPC retention time results from the reduction in the hydrodynamic radius due to the more compact conformation of the block copolymer upon cyclization. An advantage of the living polymerization route is that each of the intermediates and the cyclic product can be isolated by relatively simple filtrations through a silica plug and precipitations, yielding narrow polydispersity cyclic polymers without any fractionation or complex chromatographic purification. A trace of a high molecular weight impurity is observed in the GPC, which likely is a result from either the formation of cyclic dimers or the loss of one of the end groups from the linear precursor, thereby preventing cyclization. This impurity, however, is negligible compared to the previously reported cyclization methods using anionic routes, and its structure and mechanism of formation are being studied presently to enable further optimization of the click approach in preparing cyclic polymers.

Conclusion. The synthesis of well-defined cyclic diblock copolymers is made possible by combining a controlled radical polymerization technique, ATRP, with click coupling to cyclize α,ω-difunctional linear block copolymers. ATRP is ideal for preparing the linear precursors because the functional group tolerance and molecular weight control provide low-polydispersity polymers with a wide range of monomer functionality. The use of click chemistry to cyclize the linear precursor is particularly valuable because slow dropwise addition of the linear precursor to copper catalyst leads to a near-quantitative conversion to the cyclic polymer, circumventing the need for time-consuming purification. The versatility of this approach is presently being explored to prepare a broad diversity of cyclic block copolymers with a range of monomer functionalities.

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Supporting Information Available: Experimental details and full characterization for all of the reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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