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An Efficient Route to Well-Defined Macrocyclic Polymers via "Click" Cyclization

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Because the properties of polymers are intimately related to their molecular structure, diverse polymer architectures have been explored over the last few decades. Recently, many investigators have developed synthetic methods to control polymer architecture and tailor a material's properties for a specific application. Examples include hyperbranched perfluorinated/hydrophilic block copolymers for antifouling coatings,[1] branched and dendritic structures for targeted drug delivery,[2] globular polymers for use in the microelectronics industry,[3] dendrimers for light harvesting applications,[4] and a variety of polymer architectures as scaffolds for catalysis.[5]

Synthetic routes for the preparation of macrocyclic polymers have long been a goal for polymer chemists, owing to their unique topology and physical properties.[6] While numerous methods have been explored for the preparation of these compounds, most involve the cyclization of linear precursors that typically suffer from poor yields and competing reactions, requiring tedious purification to isolate pure macrocycles.[7] Deffieux and Schappacher[8] have improved the purity of the cyclic polymers by employing a high yielding coupling reaction and using extreme dilution during their synthesis. More recently, the inefficiencies of cyclization have been addressed by techniques, such as lactone ring expansion,[9] polyhomologation of cyclic boranes,[10] electrostatic self-assembly,[11] and ring opening metathesis polymerization from a cyclic ruthenium catalyst.[12]

However, the existing techniques do not offer the same control over molecular weight, narrow polydispersity, and functional group tolerance demonstrated by controlled radical polymerization techniques, such as atom transfer radical polymerization (ATRP), nitroxide-mediated polymerization (NMP), and reversible addition fragmentation transfer polymerization (RAFT). ATRP is a particularly attractive approach for making macrocyclic precursors because of the ability to modify the terminal end group in reasonable yields.[13] Therefore, a synthetic route was sought to efficiently cyclize polymers prepared by ATRP.

"Click" chemistry has been used extensively since its introduction, due to the high efficiency and technical simplicity of the reaction.[14] Perhaps the most popular "click" reaction has been the copper-catalyzed Huisgen dipolar cycloaddition of a terminal alkyne and an azide to form a 1,4-disubstituted 1,2,3-triazole.[15] Its value has been particularly useful in polymer chemistry,[16] where less efficient transformations often suffer from incomplete reactions as a result of the steric inaccessibility of reactive sites within the polymer structure. Herein we report the first nearly quantitative preparation of macrocyclic polymers via the "click" cyclization of linear polymers.

The main challenge in preparing macrocyclic polymers using a "click" cyclization was finding a polymer that was amenable to efficient end-group modification. A styrenic backbone prepared by ATRP was selected because the terminal benzylic bromide represents an ideal substrate for a nucleophilic displacement with an azide. Incorporation of an alkyne within the initiator would then provide the requisite functional groups at opposite ends of the polymer chain for a "click" cyclization.

The linear poly(styrene) (*l*-PS) precursors were prepared using the standard ATRP techniques developed by Matyjaszewski and co-workers.[13] Propargyl 2-bromoisobutyrate was used as initiator with Cu(I)Br and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) as catalyst. The reaction was carried out in bulk with a [styrene]/[initiator]/[CuBr]/[$CuBr_2$]/[PMDETA] ratio of 60/1/1/0.05/1.3 to consistently yield polymers with a polydispersity of less than 1.2. The bromine-terminated product (*l*-PS-Br) was purified by extraction from water into CH_2Cl_2 and precipitation into methanol. Azidation of the end group was carried out in DMF with sodium azide (Scheme 1).[17]

The concentration of the polymer is the primary factor in determining whether an α,ω-functionalized polymer will prefer cyclization or condensation. During the "click" step growth condensation of polystyrene, Tsarevsky et al. reported an unreacted low molecular weight impurity, likely the result of cyclization.[16c] In our study, using Cu(I) catalyst (3.6 mM) in THF/water, concentrations of polymer above 0.1 mM favored condensation, while dilution below that concentration favored intramolecular cyclization. Because the dilution required to afford high purity macrocycle would be prohibitively excessive, a continuous addition technique was utilized[3] to ensure an infinitesimal concentration of unreacted linear polymer during the course of the reaction. Using a syringe pump, 5 mL of a 2 mM solution of the *l*-PS-N_3 in DMF was added over 25 h into a 115 mL volume of warm DMF solution containing Cu(I)Br and bipyridine. After 1 additional hour, the product, *c*-PS, was isolated by extraction and precipitation. The cyclization reaction was successfully carried out on *l*-PS-N_3 with an M_n of 2200 and 4200 as well as poly(*p*-acetoxystyrene) with an M_n of 2700.

The key methods for verifying the successful cyclization were SEC, MALDI-TOF MS, NMR, and FTIR. The MALDI TOF mass spectra verified that the molecular weight of the polymer samples remained unchanged after "click" cyclization (Figure 1); however, because the cyclization leads to a more compact polymer structure, the macrocyclic polymers exhibit a longer size exclusion retention time than the parent linear polymer (Figure 2). The presence of higher MW impurities, such as macrocyclic dimers or catenanes, was not observed in the mass spectral data.[18]

NMR was used to verify the chemical transformations of the end groups. As described by Tsarevsky et al.,[16c] the ^{1}H NMR resonances could be used to verify the transformation from the benzylic azide (resonances overlapping with the propynyl ester from 4 to 4.5 ppm) to the 1,2,3-triazole (4.3−4.8 and 5.3−5.7 ppm). As the SEC data exclude the possibility of condensation, nearly quantitative formation of the triazole confirms conversion to the macrocycle. Further evidence for the formation of the triazole could be seen in the FTIR spectra, by monitoring the disappearance of the azide (2090 cm^{-1}) and terminal alkyne (3300 cm^{-1}) peaks

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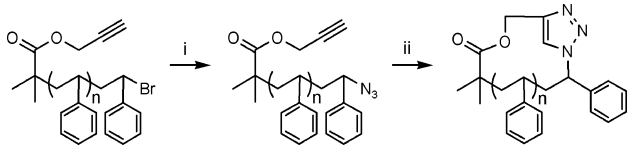
Scheme 1. The Terminal Azidation (i) and "Click" Cyclization (ii) of Polystyrene Prepared via ATRP[a]



[a] (i) NaN_3 in DMF, 25 °C; (ii) CuBr/Bipy, in degassed DMF, 120 °C.

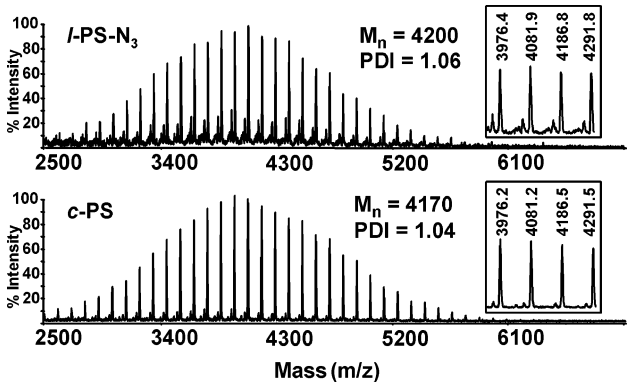


Figure 1. MALDI-TOF mass spectra for precursor, *l*-PS4200-N_3, and the cyclic polymer, *c*-PS4200.

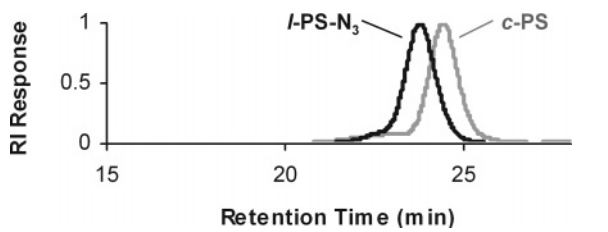


Figure 2. Overlay of SEC traces for precursor, *l*-PS4200-N_3, and the cyclic polymer, *c*-PS4200.

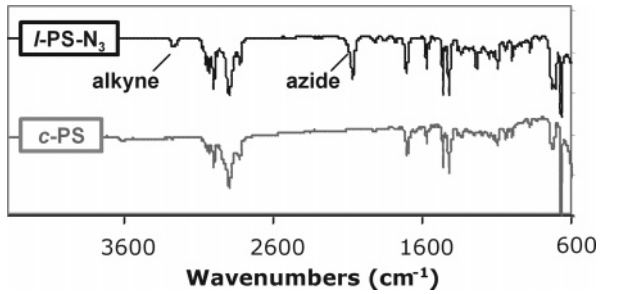


Figure 3. IR spectra of the linear precursor, *l*-PS2200-N_3, and the cyclic polymer, *c*-PS2200, verifying the loss of the azide (2090 cm^{-1}) and terminal alkyne (3300 cm^{-1}) functionalities.

(Figure 3). Initial attempts to hydrolyze the lactone using KOH in H_2O/DMF failed to open the macrocycle, as judged by SEC, MALDI, and NMR.

In conclusion, the high efficiency of the "click" reaction enables the cyclization of styrenic polymers prepared by ATRP polymerization. Both the end-group modification and the cyclization of *l*-PS appear to be nearly quantitative, preventing the need for fractionation or preparative SEC for obtaining macrocycles. The described cyclization technique is expected to be particularly useful, owing to the excellent molecular weight control and functional group tolerance of ATRP. While cyclization has been demonstrated with 2200 and 4200 MW PS and poly(acetoxystyrene) of similar size, the ability to cyclize significantly larger polymers has yet to be demonstrated and is presently under investigation. In addition, the use of functional monomers and nonstyrenic monomers will also be explored.

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Supporting Information Available: Full characterization data of representative polymer samples, and specific acknowledgments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The full range of the MALDI mass spectra of both PS samples are included in the Supporting Information. The detection limit of higher molecular weight impurities is approximated to be <1%.

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