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Strategy for Rapid and High-Purity Monocyclic Polymers by CuAAC "Click" Reactions

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ABSTRACT: Cyclization of linear polymers by coupling end-groups together to form monocyclic polymers using the very fast Cu-catalyzed azide/alkyne cycloaddition (CuAAC) "click" reaction has been used for many polymer systems. However, the strategy based on the CuAAC methodology has not been guided by theory and relies on the very slow feed of polymer into a highly dilute reaction mixture of solvent and Cu catalyst. This leads to the production of monocyclic polymer in very low concentrations over long periods of time (> 10 h) and at high temperatures (> 100 °C). In this work we use the Jacobson−Stockmayer theory to predict the % monocyclic polystyrene (c-PSTY) in a one-pot reaction at 25 °C and find from an empirical relationship based on experimental diffusion-controlled rate coefficients for cyclization and condensation of α,ω-polymer chains that the Jacobson−Stockmayer theory is applicable for the CuAAC reaction. This means the % monocyclic can be predicted from theory and is independent of reaction rate parameters (such as catalytic concentration and temperature) and only dependent on polymer concentration. Given this quantitative knowledge, we investigated the effect of l-PSTY concentration, temperature, feed rate, Cu(I)Br concentration, and linear-PSTY molecular weight to find the optimum conditions for the synthesis of monocyclic polymers. It was found that for feed rates greater than or equal to the reaction rate high % monocyclic polymers could be formed. Our strategy allowed us to produce c-PSTY (with 51 monomer units) with high purity (> 95%) at a concentration of 1.85×10^{-3} M in less than 9 min at 25 °C. This is the highest concentration, shortest time, and lowest temperature, to our knowledge, that anyone has used to obtain macrocycles in high purity by the CuAAC methodology. It also allowed us to develop strategies to produce high % monocyclic from parent l-PSTY with higher molecular weights.

Introduction

"Living" radical polymerization techniques, such as atom transfer radical polymerization (ATRP),[1] nitroxide-mediated polymerization (NMP),[2] and reversible addition−fragmentation chain transfer polymerization (RAFT)[3] not only offer control over molecular weight and molecular weight distribution (MWD) but also provide a means to obtain functional chain end-groups.[4] Lepoittevin et al.[5] were the first group to utilize NMP to prepare linear precursor for cyclization of polystyrene. A difunctional RAFT agent was used in the polymerization of styrene with subsequent conversion of the dithioester groups to thiols, in which monocyclic polymers were produced under dilute conditions in high yields through the oxidation reaction to form disulfide linkages.[6] Tsarevsky et al.[7] prepared narrow polystyrene samples by ATRP, converted the Br end-group to an azide (see Scheme 1), and made multiblocks with a small amount of monocyclic structure via the Cu-catalyzed azide/alkyne cycloaddition (CuAAC) "click" reaction. Laurent and Grayson[4] realized that through a feed process of linear polystyrene (l-PSTY) the CuAAC methodology could be used to produce near-quantitative yields of monocyclic polystyrene (c-PSTY). Their strategy relied on the CuAAC reaction taking place under very dilute conditions, at 100 times mole excess of Cu(I)Br and ligand to l-PSTY and at a very high temperature of 120 °C.

This synthetic methodology and strategy utilized by Laurent and Grayson[4] has become widely used to produce monocyclic polymers, ranging from polystyrene,[4,8,9] poly(*N*-isopropylacrylamide) (PNIPAM),[10,11] poly(methyl acrylate)-*block*-poly(styrene)[12] to poly(ε-caprolactone).[13] Can this strategy be optimized to produce monocyclic polymers efficiently, rapidly at low temperatures, and under more concentrated conditions? The aim of this work is to develop with the aid of theory the optimum conditions for the CuAAC cyclization reaction of α,ω-polystyrene. Such a study should provide a guide in the experimental design for the cyclization of other polymer systems and for scale-up processes. Herein, we report the cyclization of azide−alkyne α,ω-heterocyclic linear polystyrene polymers (n = 51, 104, and 136) with polydispersity indexes (PDIs) less than 1.1 (Scheme 1). The higher molecular weight polymers were fractionated to obtain these narrow molecular weight distributions for accurate data analysis and comparison to theory. Our study showed that the synthetic strategy could be optimized to produce monocyclic PSTY in high yields at 25 °C in less than 9 min.

Experimental Section

Materials. The following chemicals, solvents, initiators, and ligands were used as received, unless otherwise stated: alumina, activated basic (Aldrich: Brockmann I, standard grade, ~150 mesh, 58 Å), sodium azide (NaN_3: Aldrich, ≥99.5%), dichloromethane (DCM: Labscan, AR grade), anhydrous methanol (MeOH: Mallinckrodt, 99.9%, HPLC grade), tetrahydrofuran (THF: Lichrosolv, HPLC grade), toluene (HPLC grade, Labscan, 99.8%), Milli-Q water (Biolab, 18.2 MΩ m), *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (PMDETA: Aldrich, 99%), copper(I) bromide (Cu(I)Br: Aldrich, 99.999%), copper(II)

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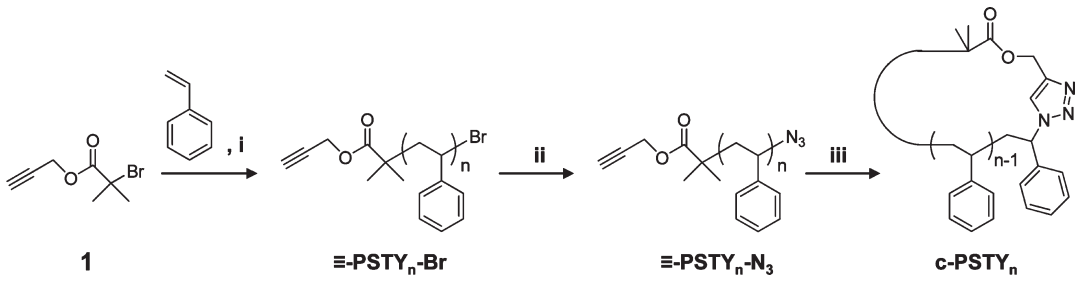
Scheme 1. Synthetic Route for the Preparation of Monocyclic Polystyrene via the Combination of ATRP and CuAAC Click Coupling for Three Different Chain Lengths:[a] (a) n = 51, (b) n = 104, and (c) n = 136



[a] Reactants and conditions: (i) CuBr, PMDETA, $CuBr_2$/PMDETA in toluene or bulk at 80 °C; (ii) NaN_3 in DMF for 24 h at RT; and (iii) CuBr, PMDETA in toluene.

bromide (Cu(II)Br_2: Aldrich, 99%); prop-2-ynyl 2-bromo-2-methylpropanoate (**1**) was synthesized according to the method of Luedtke et al. and is well documented.[14] Styrene (STY, Aldrich, >99%) was purified from inhibitor prior to use by passing through a basic alumina column.

Instruments and Measurements. *Size Exclusion Chromatography* (*SEC*). All polymer samples were dried prior to analysis in a vacuum oven for 2 days at 25 °C. The dried polymer was dissolved in tetrahydrofuran (THF) to a concentration of 1 mg/mL and then filtered through a 0.45 μm PTFE syringe filter. Analysis of the molecular weight distributions of the polymers was accomplished using a Waters 2695 separations module, fitted with a Waters 410 refractive index detector maintained at 35 °C, a Waters 996 photodiode array detector, and two Ultrastyragel linear columns (7.8 × 300 mm) arranged in series. These columns were maintained at 40 °C for all analyses and are capable of separating polymers in the molecular weight range of 500−4 million g/mol with high resolution. All samples were eluted at a flow rate of 1.0 mL/min. Calibration was performed using narrow molecular weight PSTY standards (PDI ≤ 1.1) ranging from 500 to 2 million g/mol. Data acquisition was performed using Empower software, and molecular weights were calculated relative to polystyrene standards.

Absolute Molecular Weight Determination by Triple Detection-SEC. Absolute molecular weights of polymers were determined using a Polymer Laboratories GPC50 Plus equipped with dual angle laser light scattering detector, viscometer, and differential refractive index detector. HPLC grade tetrahydrofuran was used as the eluent at a flow rate of 1.0 mL/min. Separations were achieved using two PLGel Mixed C (7.8 × 300 mm) SEC columns connected in series and held at a constant temperature of 40 °C. The triple detection system was calibrated using a 2 mg/mL PSTY Standard (Polymer Laboratories: M_{wt} = 110 K, dn/dc = 0.185, and IV = 0.4872 mL/g). Polymer samples of known concentration were freshly prepared in THF and passed through a 0.45 μm PTFE syringe filter just prior to injection. The absolute molecular weights and dn/dc values were determined using Polymer Laboratories Multi-Cirrus software. The dn/dc values determined by the quantitative mass recovery technique using the Cirrus software were in good agreement with theory.

Preparative Size Exclusion Chromatography (*Prep-SEC*). Linear PSTY was purified using a Varian ProStar preparative SEC system equipped with a manual injector, differential refractive index detector, and single wavelength ultraviolet−visible detector. HPLC grade tetrahydrofuran was used as the eluent at flow rate of 10 mL/min. Separations were achieved using a PLGel 10 μm 10E3 Å, 300 × 25 mm preparative SEC column held at 25 °C. The dried impure polymer was dissolved in THF to give a concentration of 100 mg/mL. This solution was filtered through a 0.45 μm PTFE syringe filter prior to injection. Fractions were collected manually, and the composition of each was determined using the Polymer Laboratories GPC50 Plus equipped with triple detection as described above.

^{1}H Nuclear Magnetic Resonance (*NMR*). All NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer using an external lock ($CDCl_3$) and referenced to the residual non-deuterated solvent ($CHCl_3$).

Attenuated Total Reflectance Fourier Transform Spectroscopy (*ATR-FTIR*). ATR-FTIR spectra were obtained using a horizontal, single bounce, diamond ATR accessory on a Nicolet Nexus 870 FT-IR. Spectra were recorded between 4000 and 500 cm^{-1} for 64 scans at 4 cm^{-1} resolution with an OPD velocity of 0.6289 cm/s. Solids were pressed directly onto the diamond internal reflection element of the ATR without further sample preparation.

Matrix-Assisted Laser Desorption Ionization−Time-of-Flight (*MALDI-ToF*) *Mass Spectrometry*. MALDI-ToF MS spectra were obtained using a Bruker MALDI-ToF autoflex III smartbeam equipped with a nitrogen laser (337 nm, 200 Hz maximum firing rate) with a mass range of 600−400 000 Da. All spectra were recorded in reflectron mode (1500−4500 Da). *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-propenylidene]malononitrile (DCTB; 20 mg/mL in THF) was used as the matrix and Ag(CF_3COO) (2 mg/mL in THF) as the cation source. Samples were prepared by cospotting the matrix (20 μL), Ag(CF_3COO) (2 μL), and polymer (20 μL, 1 mg/mL in THF) solutions on the target plate.

Synthesis of $CuBr_2$/PMDETA Complex. Cu(II)Br_2 (2.05 g, 9.18×10^{-3} mol) was stirred in MeOH (200 mL) until complete dissolution was achieved. To this stirred solution PMDETA (1.55 g, 8.94×10^{-3} mol) was added dropwise and stirred for a further 30 min at RT. The solution was then gravity filtered, the MeOH was removed by rotary evaporator, and the complex was dried in vacuo for 17 h at 25 °C.

Synthesis of ≡-$PSTY_{51}$-Br. Styrene (5 g, 0.05 mol), PMDETA (0.07 mL, 3.57×10^{-4} mol), $CuBr_2$/PMDETA (0.03 g, 7.14×10^{-5} mol), and initiator (0.07 g, 3.57×10^{-4} mol) were added to a 10 mL Schlenk flask equipped with a magnetic stirrer and sparged with argon for 15 min to remove oxygen. Cu(I)Br (0.05 g, 3.57×10^{-4} mol) was then carefully added to the solution under an argon blanket. The reaction mixture was further degassed for 5 min and then placed into a temperature-controlled oil bath at 80 °C for 6 h. The reaction was quenched by cooling the reaction mixture to 0 °C, exposure to air, and dilution with DCM (ca. 3-fold to the reaction mixture volume). The copper salts were removed by passage through an activated basic alumina column. The solution was concentrated by airflow and the polymer was recovered by precipitation into large volume of MeOH (20-fold excess to polymer solution), and the polymer was recovered by vacuum filtration. The polymer was dried in vacuo for 24 h at 25 °C and characterized by SEC (M_n = 5100, PDI = 1.10) and triple detection-SEC (M_n = 5300, PDI = 1.10).

Polymers ≡-$PSTY_{104}$-Br and ≡-$PSTY_{136}$-Br were synthesized following a similar procedure with slight variations in concentrations of the reactants and polymerization time (Table S1; available from Supporting Information).

Table 1. Molecular Weight Distribution Data of Starting Linear Polystyrene Polymers

	before fractionation		after fractionation					
	PSTY calibration curve[a]		PSTY calibration curve[a]			absolute triple detection[b]		
polymer	M_n	PDI	M_n	M_P	PDI	M_n	M_P	PDI
≡-PSTY$_{51}$-Br	5 100	1.10	5 100	5 400	1.10	5 300	5 600	1.10
≡-PSTY$_{104}$-Br	11 300	1.08	10 600	10 900	1.07	10 800	11 000	1.05
≡-PSTY$_{136}$-Br	14 900	1.11	14 000	14 400	1.07	14 200	14 500	1.05

[a] The data were acquired using SEC based on a polystyrene calibration curve. [b] The data were acquired using triple detection SEC.

Synthesis of ≡-PSTY$_{51}$-N$_3$. Polymer ≡-PSTY$_{51}$-Br (3.6 g, 7.00×10^{-4} mol) was dissolved in 20 mL of DMF in a 50 mL reaction vessel equipped with magnetic stirrer. To this solution NaN_3 (0.46 g, 7.00×10^{-3} mol) was added, and the mixture stirred for 24 h at RT. The polymer was precipitated into MeOH, recovered by vacuum filtration, and washed exhaustively with water and MeOH. The polymer was dried in vacuo for 48 h at 25 °C.

The above synthetic and purification procedures were repeated to produce polymers ≡-PSTY$_{104}$-N$_3$ and ≡-PSTY$_{136}$-N$_3$.

Cyclization of Polymers by CuAAC Chemistry. *Synthesis of c-PSTY: A Typical Synthetic Procedure* (*c-PSTY$_{51}$, Experiment 17 in Table S2*). A solution of ≡-PSTY$_{51}$-N$_3$ (0.02 g, 4.00×10^{-6} mol) in toluene (1 mL) was sparged with argon for 15 min to remove oxygen. This polymer solution was added via syringe pump, at a flow rate of 0.124 mL/min, to a deoxygenated solution of Cu(I)Br (0.03 g, 2.00×10^{-4} mol) and PMDETA (0.04 mL, 2.00×10^{-4} mol) in toluene (1 mL) at 25 °C. After the addition of the polymer solution, which in this case was 8 min, the reaction mixture was further stirred for 3 h and the polymer then analyzed. It should be noted that for all cyclization experiments in Table S2 the reactions were stopped 3 h after all the linear polymer solution was fed into the reaction mixture. At the end of this period (i.e., feed time plus an additional 3 h) the reaction was diluted with DCM (ca. 3-fold to the reaction mixture volume). The copper salts were removed by passage through activated basic alumina column, the solution concentrated by airflow, and the polymer recovered by precipitation into MeOH (10-fold excess to polymer solution) and then by filtration. The polymer was dried in vacuo for 24 h at 25 °C. The experimental details for cyclization of ≡-PSTY$_{51}$-N$_3$ are given in Table S2 and for ≡-PSTY$_{104}$-N$_3$ and ≡-PSTY$_{136}$-N$_3$ in Table S3.

Coupling of Linear Polymers by CuAAC "Click" Chemistry. *Synthesis of PSTY$_{42}$-N$_3$ and PSTY$_{42}$-≡.* The synthesis of these polymers and subsequent end-group modifications were done by previously described procedures.[15]

Coupling of PSTY$_{42}$-N$_3$ with PSTY$_{42}$-≡. A solution of PSTY$_{42}$-N$_3$ (0.02 g, 4.58×10^{-6} mol) and PSTY$_{42}$-≡ (0.021 g, 4.75×10^{-6}) in toluene (1 mL) was sparged with argon for 25 min to remove oxygen. This polymer solution was added via syringe pump, at a flow rate of 0.124 mL/min, to a deoxygenated solution of Cu(I)Br (0.068 g, 4.75×10^{-4} mol) and PMDETA (0.098 mL, 4.75×10^{-4} mol) in toluene (1 mL) at 25 °C. After the addition of the polymer solution, which in this case was 8 min, a sample was taken for SEC analysis, and the reaction mixture was further stirred for 3 h with another sample taken for SEC analysis.

The above coupling procedure was repeated with 50×, 25×, 10×, and 1× molar excess of CuBr and PMDETA to the polymer.

Results and Discussion

Synthesis of α,ω-Functionalized Linear Precursors. Atom transfer radical polymerization was used to prepare three ≡-PSTY$_n$-Br with narrow molecular weight distributions. Polydispersities of the three polymers were lower than 1.2. However, ≡-PSTY$_{104}$-Br and ≡-PSTY$_{136}$-Br showed a small distribution at double the M_n, most probably formed through bimolecular radical termination and/or oxidative coupling of the alkyne terminal end-groups in the presence of Cu catalyst.[16] We therefore used preparative SEC (Prep-SEC) to fractionate out this high molecular weight polymer. Further analysis of the polymers by absolute triple detection SEC gave PDI's < 1.11 and M_n's as follows: 5300 (≡-PSTY$_{51}$-Br), 10 800 (≡-PSTY$_{104}$-Br), and 14 200 (≡-PSTY$_{136}$-Br) (Table 1). The bromine end-groups were converted to azides with NaN_3 in DMF to form ≡-PSTY$_n$-N$_3$. Figure 1 shows the ^{1}H NMR spectra of the starting compound ≡-PSTY$_{51}$-N$_3$ (Figure 1A,B) and the conversion from bromine to azide (Figure 1C). Loss of the protons (H$_g$) at 4.5 ppm adjacent to the Br (Figure 1B) and its relocation to a lower chemical shift (3.9 ppm in Figure 1C) shows near-quantitative formation of azide end-groups. These chemical shifts correspond well to literature assignments.[7] Confirming the presence of the desired azide and alkyne end-groups, ATR-FTIR spectra (Figure S2C) showed the characteristic azide and alkyne stretches at 2095 and 3295 cm^{-1}, respectively.

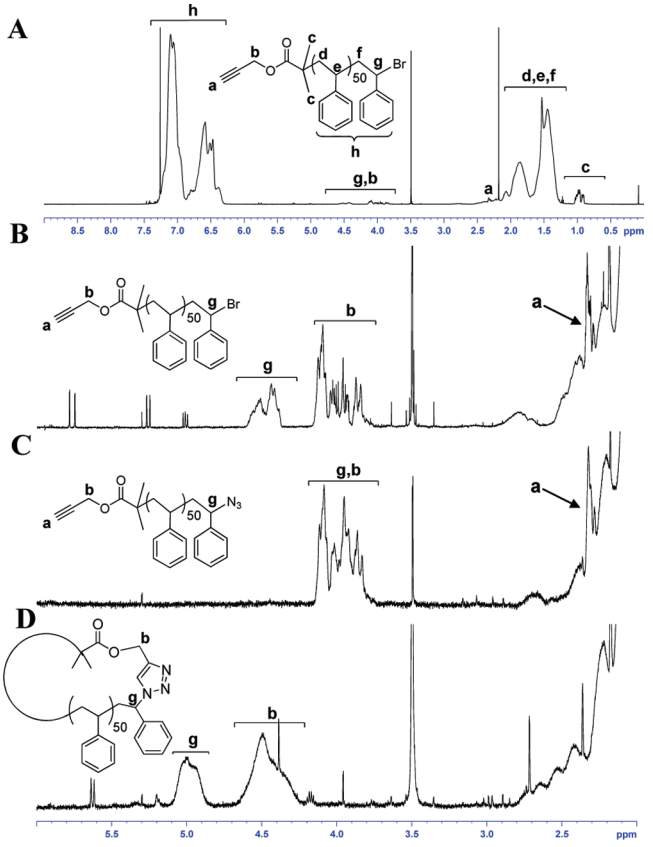


Figure 1. 500 MHz ^{1}H NMR analysis of l-PSTY (M_n = 5300, PDI = 1.10) chain-end modification and cyclization. (A) Full spectrum of ≡-PSTY$_{51}$-Br. (B) Expanded spectrum of ≡-PSTY$_{51}$-Br. (C) Expanded spectrum of ≡-PSTY$_{51}$-N$_3$. (D) Expanded spectrum of c-PSTY$_{51}$ cyclized at a feed rate of 0.003 mL/min with Cu(I)Br and PMDETA (100× molar excess to PSTY) at 80 °C: Refer to Table S2 (entry 1).

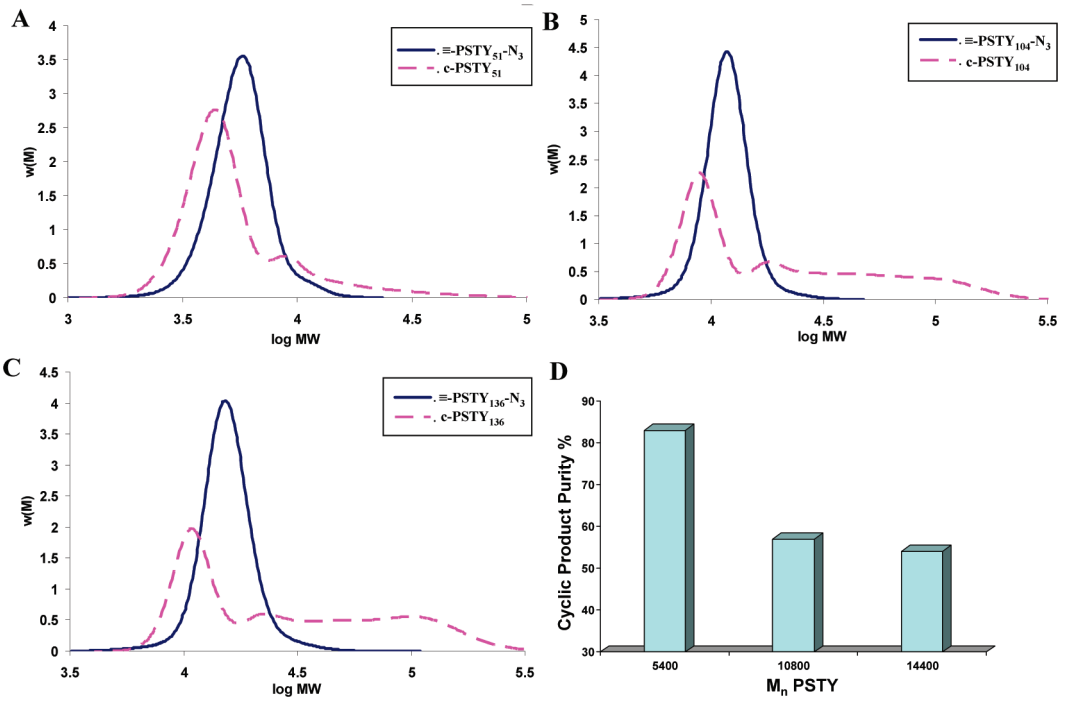
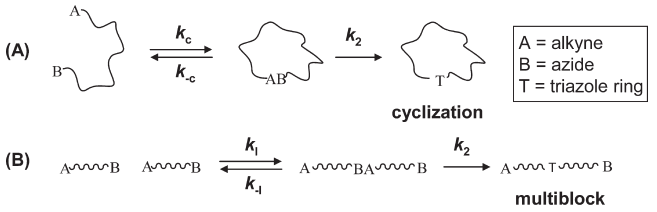


Figure 2. One-pot cyclization reactions performed by reacting 20 mg of ≡-PSTY$_n$-N$_3$, Cu(I)Br, and PMDETA (50× molar excess to l-PSTY) in toluene (2 mL) at 25 °C (refer to Table S2, entry 18 and Table S3, entries 21 and 29). (A) SEC traces of ≡-PSTY$_{51}$-N$_3$ before and after cyclization. (B) SEC traces of ≡-PSTY$_{104}$-N$_3$ before and after cyclization. (C) SEC traces of ≡-PSTY$_{136}$-N$_3$ before and after cyclization. (D) % purity of monocyclic products determined from SEC.

Scheme 2. Encounter Pair Model for a Chemical Reaction



CuAAC Cyclization of ≡-PSTY$_n$-N$_3$ in a One-Pot Reaction. One-pot cyclization reactions of ≡-PSTY$_n$-N$_3$ (20 mg in 2 mL of toluene) were performed using a 50× molar excess of Cu(I)Br and PMDETA to polymer at 25 °C for 4 h (Figure 2). The formation of c-PSTY$_n$ was evident from a shift to a lower molecular weight distribution to that of the starting l-PSTY$_n$. Such a reduction in hydrodynamic volume is typical for c-PSTY chains due to their more compact topology[17,18] (where $M_{ring}^{SEC} = 0.71 M_{ring}^{abs}$).[18] Characterization of the monocyclic species was carried out on the reactions in which the purity was greater than 90% (see below for details). The purity for these one-pot reactions decreased from 83% (c-PSTY$_{51}$) to 54% (c-PSTY$_{136}$), showing a distinct molecular weight dependence on cyclization.

Cyclization of a single polymer chain depends on the chain end-to-end distance between the reactive groups on either end of its random coil. When the chain ends diffuse to be within a capture radius (or volume) with rate coefficient k_c, a covalent bond can form through a chemical reaction at k_2, or the chain ends can diffuse apart at k_{-c} (Scheme 2A). Such an "encounter-controlled" or "diffusion-controlled" process allows the equilibrium cyclization probability to be determined following the derivation by Jacobson and Stockmayer[19] only when $k_{-c} \gg k_2$. Since the rate of chemical reaction, k_2, to form a monocyclic species via an intramolecular process is the same as that for an intermolecular process (Scheme 2), the fraction of monocyclic species will depend only on the probability of a chain end being within the capture volume, v_s, with its other chain end (P_c) over that of another chain end (P_L). The relative probabilities follow that of Jacobson and Stockmayer[19] for a case II type condensation are

$$P_c = \left(\frac{3}{2\pi}\right)^{3/2} \frac{v_s}{\langle r^2\rangle^{3/2}} \quad (1)$$

$$P_L = 2N\frac{v_s}{V} = \frac{2N_A c}{M} v_s \quad (2)$$

where $\langle r^2\rangle$ is the mean-square end-to-end distance of the chain, N is the total number of polymer molecules in total volume V, N_A is Avogadro's number, M is the molecular weight of the polymer, and c is the concentration of polymer in g mL^{-1}. The ratio between monocyclic and other condensed species is given by[20]

$$\frac{P_c}{P_L} = \left(\frac{3}{2\pi\langle r^2\rangle}\right)^{3/2} \frac{2000}{N_A[P]} = \frac{k_c}{k_1[P]} \quad (3)$$

such that

$$\frac{k_c}{k_1} = \left(\frac{3}{2\pi\langle r^2\rangle}\right)^{3/2} \frac{2000}{N_A} \quad (4)$$

and therefore the theoretical percent monocyclic is given by

$$\%\ \text{cyclic} = \frac{P_c}{P_c + P_L} \times 100 \quad (5)$$

where [P] is the concentration (mol L^{-1}) of starting linear polymer in solution.

For polystyrene, Roovers[21] found in a good solvent that $\langle r^2\rangle = 6.88 \times (1.66 \times 10^{-18}\ M^{-1.17})$, where excluded volume effects play a dominant role resulting in a more open random coil structure.

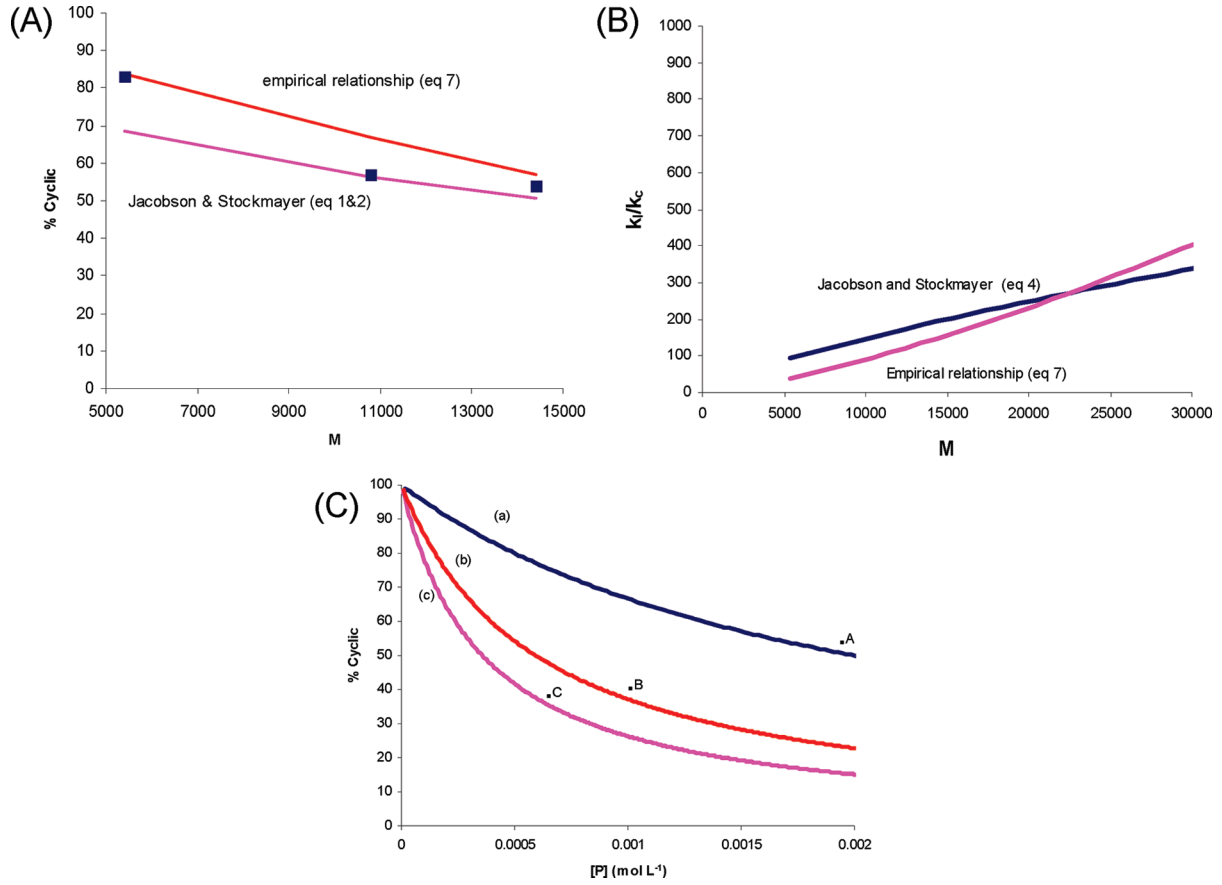


Figure 3. (A) Jacobson−Stockmayer theory (eqs 1 and 2) and empirical relationship (eq 7) determined from experimental diffusion coefficients for styrene. Squares are experimental values. (B) Comparison of k_l/k_c determined by eq 4 vs eq 7. (C) Effect of polymer concentration, P mol L^{-1}, on M from Jacobson−Stockmayer theory: (a) $M = 5400$, $n = 51$; (b) $M = 10\,800$, $n = 104$; (c) $M = 14\,400$, $n = 136$.

The theoretical % monocyclic based on eqs 3 and 5 as a function of molecular weight is given in Figure 3A, where the value of [P] was set equal to $[P]_0/2$. An increase in M gave a decrease in the % monocyclic, which was in good agreement with experiment especially at the higher molecular weights. This good correlation strongly suggests that cyclization was under diffusion control. To test that the system is actually controlled by diffusion, we calculated the molecular weight dependence empirically from diffusion-controlled rate coefficient data for two ends of the same chain to meet or ends from different chains to diffuse to each other. Winnik and co-workers[22] used pyrene fluorescence to determine k_c over a molecular weight range from 3900 to 27 000 and found the following relationship: $\log k_c = 11.97 - 1.52 \log M$. The rate coefficient, k_l, is equivalent to the free-radical bimolecular termination rate coefficient, $k_t^{n,n}$, for chains of the same length n (where $n = M/MW_{mon}$), since k_2 for this termination reaction is much greater than k_{-1} (Scheme 2). Therefore, k_l can be determined for different molecular weights in dilute solutions below the chain overlap concentration, c^*, according to[23]

$$k_t^{n,n} = k_t^0 n_{SL}^{(\alpha_L - \alpha_S)} n^{-\alpha_L} \quad (6)$$

where for polystyrene[23] $\log k_t^0 = 8.7$, $\alpha_S = 0.53$, $n_{SL} = 15$, and $\alpha_L = 0.15$, leading to the empirical relationship

$$\frac{k_l}{k_c} = \frac{k_t^0 n_{SL}^{(\alpha_L - \alpha_S)} n^{-\alpha_L}}{10^{(11.97 - 1.52 \log M)}} \quad (7)$$

This empirical relationship when used in eq 5 was plotted as a function of M (Figure 3A), and the percent monocyclic was found to be slightly greater than that predicted from the Jacobson−Stockmayer equations. At the lowest molecular weight the empirical relationship was in close agreement with experiment most probably due to the fact that the Jacobson and Stockmayer equations do not hold for chain lengths where Gaussian chain statistics do not apply. This occurs for chain lengths < 15 due to short-range interactions and steric effects. The difference between the Jacobson and Stockmayer equations and our empirical relationship can be seen more clearly in Figure 3B. Our empirical relationship shows slightly lower k_l/k_c values than that of Jacobson and Stockmayer in the molecular weight range from 3000 to 22 000. It was satisfying to see that our relationship was in such good agreement with theory, again strongly supporting that $k_{-1} \gg k_2$ for our CuAAC reaction.

How do we use this knowledge to optimize the experimental conditions in the CuAAC click reactions? The curves in Figure 3C, determined from the Jacobson−Stockmayer equations, show that as [P] decreased, the percent monocyclic increased up to 100%. Starting concentrations of P used in our one-pot reactions were denoted on the graph by A for $n = 51$, B for $n = 104$, and C for $n = 136$. In a one-pot reaction, it is clear that with increasing conversion of end-groups the % monocyclic increases. Another way to reach high percentages of monocyclic (i.e., greater than 90%) would be through a feed of ≡-$PSTY_n$-N_3 into a solution already containing the CuBr catalyst. The feed rate must be slow enough such that the instantaneous concentrations of P in the reaction mixture are less than 2.2×10^{-4} mol L^{-1} (for $n = 51$), 6.48×10^{-5} mol L^{-1} (for $n = 104$), and 4.17×10^{-5} mol L^{-1} (for $n = 136$) to meet the minimum requirement of 90% monocyclic. Lower instantaneous [P] will result in

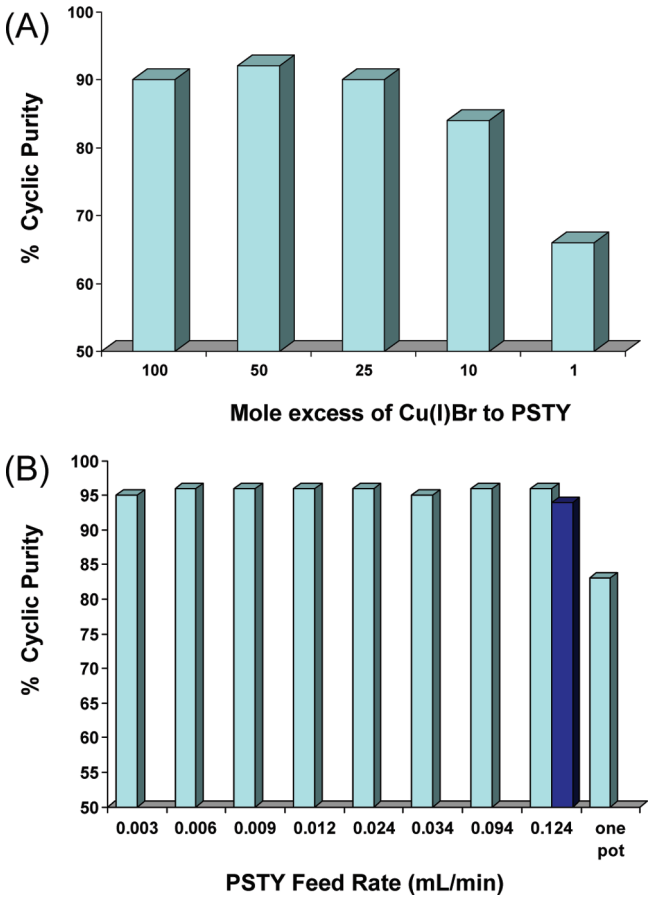


Figure 4. Cyclization of ≡-$PSTY_{51}$-N_3 at 25 °C using feed conditions; 1 mL (20 mg of ≡-$PSTY_{51}$-N_3 in toluene) was fed into a reaction vessel containing 1 mL of toluene, CuBr, and PMDETA. (A) Effect of CuBr mole excess on % monocyclic at a feed rate of 0.003 mL min^{-1} and (B) effect of feed rate at a 50 molar excess of CuBr to polymer on % monocyclic.

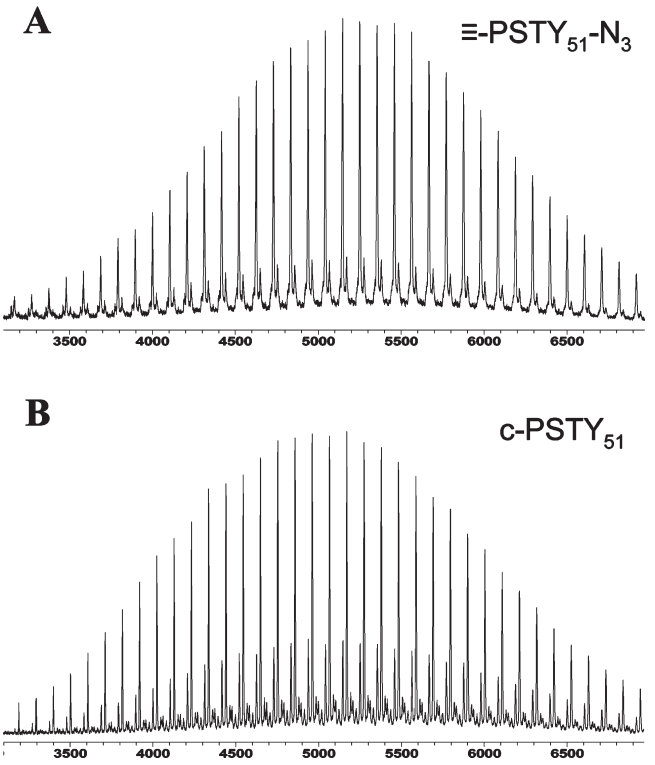


Figure 5. MALDI-ToF mass spectra acquired in reflectron mode with Ag salt as cationization agent and DCTB matrix. The full molecular weight distributions correspond to (A) ≡-$PSTY_{51}$-N_3 and (B) c-$PSTY_{51}$, cyclized by feeding 20 mg of ≡-PSTY51-N3 in 1 mL of toluene into a reaction vessel containing 50 mL of toluene, Cu(I)Br, and PMDETA (100× molar excess to PSTY) at a feed rate of 0.003 mL/min and temperature of 80 °C.

higher % monocyclic. Therefore, the rate of reaction must be close to or greater than the feed rate.

CuAAC Cyclization of ≡-$PSTY_n$-N_3 by Feed. In the CuAAC reaction, the rate of reaction can be increased by increasing the CuBr catalyst concentration. In a one-pot reaction (vide supra), increasing the rate of reaction, through an increase in either catalyst concentration or temperature, will not affect the % monocyclic but only the time to reach complete conversion. Figure 4A shows the % monocyclic as a function of the molar excess of CuBr to ≡-$PSTY_{51}$-N_3 with a feed rate of 0.003 mL min^{-1} at 25 °C. In these reactions, 1 mL of 20 mg ≡-$PSTY_{51}$-N_3 in toluene was fed into a reactor containing 1 mL of toluene, PMDETA, and CuBr. As the molar excess of CuBr decreased from 100 to 25, no obvious change in the % monocyclic was observed. Decreasing the CuBr excess further to 10 or 1 decreased the % monocyclic to 84 and 66%, respectively, suggesting that the rate of feed was now greater than the rate of the CuAAC reaction. Since the 25 mol excess of CuBr was on the borderline in which the feed rate was close to the reaction rate, we chose to use a 50× molar excess and increase the feed rate from 0.003 to 0.124 mL min^{-1} (Figure 4B). The results show that we can increase the feed rate up to 0.124 mL min^{-1} (in which all polymer was fed into the reactor in 8 min) without compromising the % monocyclic (~95%). When the % monocyclic was determined immediately after the feed was completed, the % monocyclic was 93%, suggesting that the feed rate was lower than the CuAAC reaction rate. For the higher molecular weight polymers ≡-$PSTY_{104}$-N_3 and ≡-$PSTY_{136}$-N_3, the feed rate of 0.012 mL min^{-1} was much greater than the reaction rate using 50 molar excess of CuBr at 25 °C, resulting in less than 90% monocyclic. The % monocyclic was increased by carrying out the reaction at 80 °C, reaching greater than 90% (see Table S3, entries 22, 23, 32, and 33).

Characterization of Monocyclic PSTY. The monocyclic product was confirmed by MALDI-ToF acquired in reflectron mode. Full molecular weight distributions of the linear polymer ≡-$PSTY_{51}$-N_3 (Figure 5A) and that of >95% monocyclic (Figure 5B) were near identical. In agreement with this finding, SEC analysis using a PSTY calibration curve showed that the MWD shifted to a lower molecular weight indicative of monocyclic polymer and when analyzed by absolute triple detection method also gave a MWD that was identical to the starting ≡-$PSTY_{51}$-N_3 (see Figure S1). Analysis of the MALDI-ToF between 4200 and 4250 m/z for the monocyclic showed two peaks, each exhibiting isotopic resolution (Figure 6). The major peak at 4232.48 correlated to the theoretical value for the c-PSTY + Ag, and the minor peak at 4209.06 could not be assigned to known fragmentation patterns of the azide end-group by the laser. It did fit with cleavage of an alkyne which is surprising as there is no literature evidence for such a fragmentation. Interestingly, this peak decreased with reaction temperature, suggesting it or its parent species formed during the CuAAC reaction. The formation of c-$PSTY_{51}$ was further confirmed by ^{1}H NMR in Figure 1D. Compared to the l-PSTY precursor, a new resonance peak at ~5 ppm characteristic of protons adjacent to the triazole ring (i.e., H_g) was observed. This together with the disappearance of the protons on the methylene group adjacent to the C≡C (H_b) suggested that nearly all starting l-PSTY was

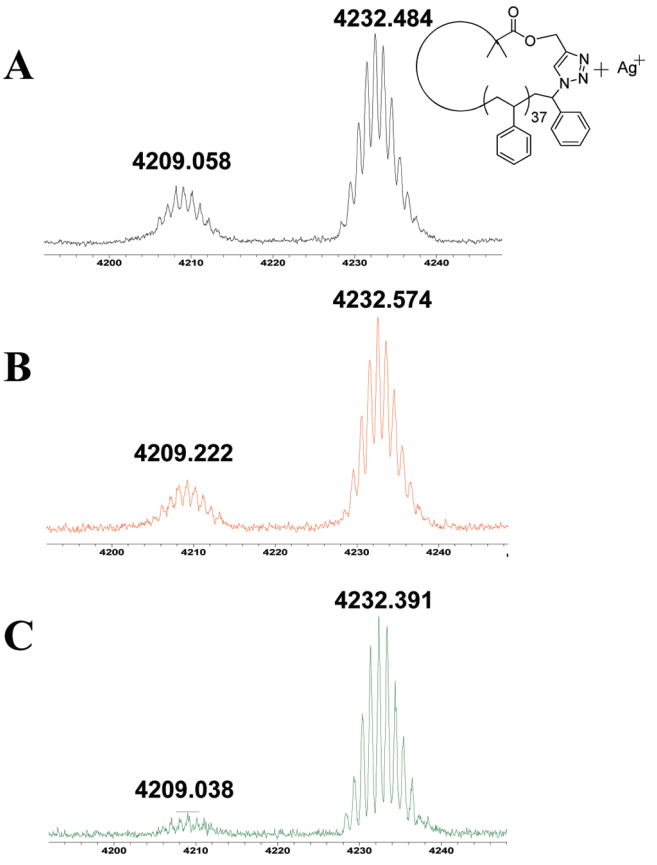


Figure 6. MALDI-ToF expanded mass spectra of c-PSTY$_{51}$, cyclized at (A) 80, (B) 50, and (C) 25 °C. All cyclizations were performed by feeding 20 mg of ≡-PSTY$_{51}$−N$_3$ in 1 mL of toluene into a reaction vessel containing 50 mL of toluene, Cu(I)Br, and PMDETA (100× molar excess to PSTY) at a feed rate of 0.003 mL/min. The major peak at 4232 correlates to the theoretical value for the c-PSTY + Ag, and the minor peak at 4209 could not be assigned to known fragmentation structures for azide moieties.

consumed due to the formation of a triazole ring. ATR-FTIR spectra provided further evidence of consumption of the end-groups of ≡-PSTY$_{51}$-N$_3$ (Figure S2D). After the CuAAC "click" reaction the signals attributed to azide and alkyne stretches at 2095 and 3295 cm^{-1}, respectively, disappeared.

To show that little or no staring linear polymer is left after the CuAAC "click" reactions, we ran the ^{1}H NMR of a cyclization reaction using the fastest feed rate of 0.372 mL/min (equates to 0.124 mL/min for 1 mL polymer solution into 1 mL CuBr solution) of 3 mL of polymer solution into 3 mL of CuBr/PMDETA solution at 25 °C using 50× excess CuBr to alkyne end-groups, in which all the linear starting polymer is fed into the reaction mixture within 8 min and left for a further 3 h to react. Figure 7 (spectrum a) shows the ^{1}H NMR after only 8 min with a very small amount of nonreacted azide groups ($\delta \sim 4$ ppm), and after a further 3 h of reaction there was little or no azide end-groups. To quantify the amount of azides and thus the amount of linear polymer, we spiked the 3 h sample with varying percentages of starting linear ≡-PSTY$_{51}$-N$_3$, ranging from 2.5 to 10 wt %. Therefore, the amount of linear polymer after 8 min is less than 2.5 wt %, which does not change the % cyclic determined in this work. It should also be noted that the linear species in 8 min and 3 h samples include high molecular weight multiblock species.

The speed of the CuAAC reaction under our conditions was tested using a model system by coupling PSTY$_{42}$-N$_3$ and PSTY$_{42}$-≡ through the fastest feed process of 0.124 mL/min at 25 °C using varying amounts of CuBr (Figure 8). At 100× CuBr excess, the reaction is found to be nearly complete after the polymer has been fed (8 min), and there is no change after a further 3 h reaction time (Figure 8A). Near identical SEC traces are observed for all CuBr amounts, even when 1× CuBr is used (Figure 8D). This strongly suggests that the reaction is very fast under our conditions, and there is a negligible effect of side reactions even at high Cu catalyst amounts (e.g., 100× excess). If side reactions (e.g., alkyne−alkyne oxidative coupling) dominate, then we should expect high amounts of starting PSTY-N$_3$ remaining. Since this is

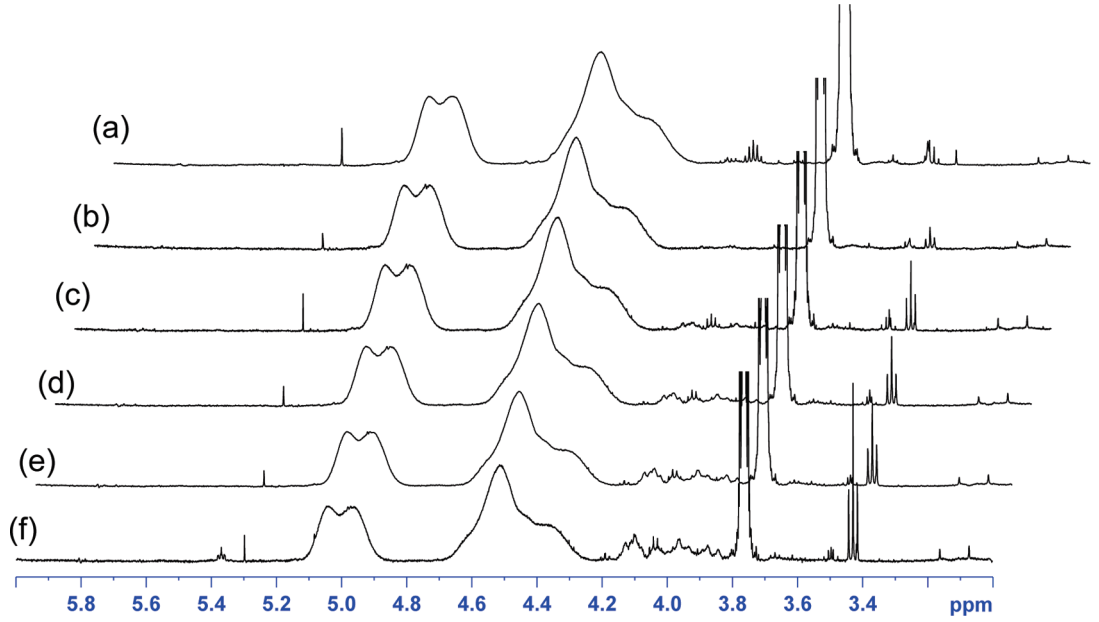


Figure 7. 500 MHz ^{1}H NMR analysis of c-PSTY$_{51}$ cyclized by feeding 60 mg of of ≡-PSTY$_{51}$-N$_3$ in 3 mL of toluene, at a feed rate of 0.372 mL/min into a reaction vessel containing 3 mL of toluene, Cu(I)Br, and PMDETA (50× molar excess to polymer) at 25 °C. (a) Sample taken right after the feed was finished (8 min). (b) Sample taken after an additional 3 h. (c) Sample b doped with 2.5 wt % of ≡-PSTY$_{51}$-N$_3$. (d) Sample b doped with 5 wt % of ≡-PSTY$_{51}$-N$_3$. (e) Sample b doped with 7.5 wt % of ≡-PSTY$_{51}$-N$_3$. (f) Sample b doped with 10 wt % of ≡-PSTY$_{51}$-N$_3$.

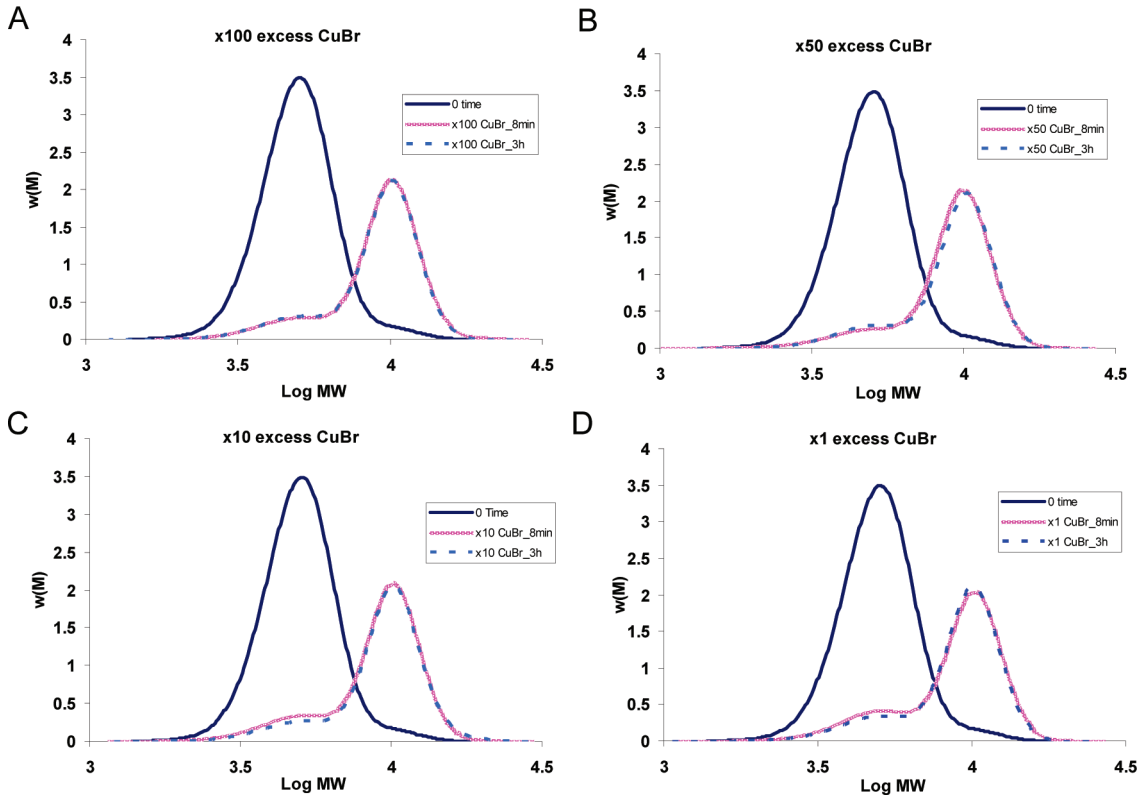


Figure 8. SEC chromatograms of coupling reactions performed by feeding $PSTY_{42}$-N_3 (20 mg) and $PSTY_{42}$-≡ (21 mg) in 1 mL of toluene at a feed rate of 0.124 mL/min and temperature of 25 °C to a solution of toluene (1 mL) containing CuBr and PMDETA: (A) 100×, (B) 50×, (C) 10×, and (D) 1× molar excess to PSTY. All chromatograms are based on PSTY calibration curve, and all plots were normalized by weight.

not the case, we can strongly suggest that these side reactions play a negligible part in the CuAAC reaction under our conditions. The residual starting polymer can be prescribed to be nonfunctionalized polymer chains and is consistent with previous results.[24]

Conclusion

The CuAAC methodology for the production of monocyclic polymers has become widespread. However, the strategy has not yet been guided by theory for this reaction. In this work we use the Jacobson−Stockmayer theory to predict the % monocyclic PSTY in a one-pot reaction and find from an empirical relationship based on experimentally found diffusion-controlled rate coefficients for cyclization and condensation of α,ω-polymer chains that the Jacobson−Stockmayer theory is applicable for the very fast CuAAC reactions. Therefore, the % monocyclic will always follow theory and is independent of reaction rate parameters (such as catalytic concentration and temperature) and only dependent on polymer concentration. This means that when carrying out condensation reactions to make multiblock (i.e., higher molecular weights) polymer, the concentration and molecular weight of the starting polymer should be chosen by first evaluating the Jacobson−Stockmayer equations. We investigated the effect of l-PSTY concentration, temperature, feed rate, Cu(I)Br concentration, and l-PSTY molecular weight to find the optimum conditions for the synthesis of monocyclic polymers. It was found that for feed rates greater than or equal to the reaction rate high % monocyclic polymers could be formed. Our strategy allowed us to produce c-PSTY with high purity (>95%) at a concentration of 1.85×10^{-3} M in less than 9 min at 25 °C. This is the highest concentration, shortest time, and lowest temperature, to our knowledge, that anyone has used to obtain macrocycles in high purity by the CuAAC methodology.

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Supporting Information Available: SEC traces, experimental conditions for cyclic reactions, MALDI-ToF, ^{1}H NMR, and ATR-FTIR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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