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Synthesis of Macrocyclic Polymers Formed via Intramolecular Radical Trap-Assisted Atom Transfer Radical Coupling

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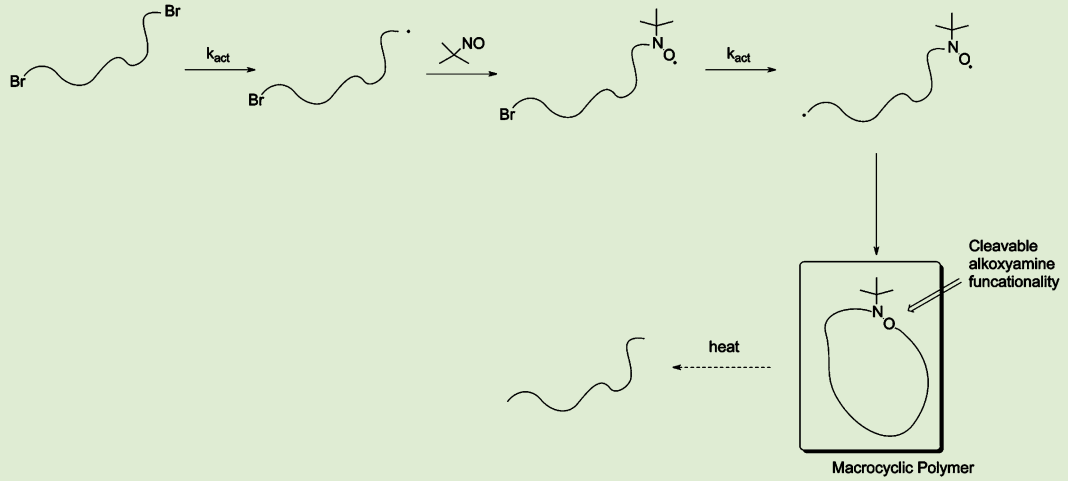
Supporting Information



ABSTRACT: The synthesis of cyclic polystyrene (PSt) with an alkoxyamine functionality has been accomplished by intramolecular radical coupling in the presence of a nitroso radical trap. Linear α,ω-dibrominated polystyrene, produced by the atom transfer radical polymerization (ATRP) of styrene using a dibrominated initiator, was subjected to chain-end activation via the atom transfer radical coupling (ATRC) process under pseudodilute conditions in the presence of 2-methyl-2-nitrosopropane (MNP). This radical trap-assisted, intramolecular ATRC (RTA-ATRC) produced cyclic polymers in greater than 90% yields, possessing $\langle G \rangle$ values in the 0.8−0.9 range as determined by gel permeation chromatography (GPC). Thermal-induced opening of the cycles, made possible by the incorporated alkoxyamine, resulted in a return to the original apparent molecular weight, further supporting the formation of cyclic polymers in the RTA-ATRC reaction. Liquid chromatography−mass spectrometry (LC-MS) provided direct confirmation of the cyclic architecture and the incorporation of the nitroso group into the macrocycle. RTA-ATRC cyclizations carried out with faster rates of polymer addition into the redox active solution and/or in the presence of a much larger excess of MNP (up to a 250:1 ratio of MNP:C−Br chain end) still yielded cyclic polymers that contained alkoxyamine functionality.

Cyclic polymers present not only a synthetic challenge for polymer chemists but also offer a set of properties that often differ substantially from linear polymers.[1,2] The most well-known differences include reduced hydrodynamic radii,[3,4] increased glass transition temperatures,[5−7] and advantageous spatial orientations of pendent groups in terms of energy transfer applications.[8−11] Very recently, it has also been reported that macrocycles may be potentially useful as drug delivery vehicles, owing to increased circulation times and greater accumulation into tumors compared to otherwise identical linear polymers.[12−14] While cyclic polymers have been produced by both ring closing[15−17] and ring expansion methods,[18−20] there remains substantial interest in both new routes and improving existing methods of their production. Controlled radical polymerization techniques have found their way into synthetic routes of several macromolecular architectures,[21−25] and macrocycles are no exception. For example, a linear precursor polymer can be produced by atom transfer radical polymerization (ATRP) and then subjected to intramolecular ring closure once the chain ends have been appropriately modified to be compatibly reactive.[26,27]

Our group recently introduced a relatively simple method for producing cyclic polymers via a pseudodilute, intramolecular atom transfer radical coupling (ATRC) reaction of an α,ω-dibrominated precursor produced by ATRP using a dibrominated initiator (Scheme 1, bottom).[28] While this cyclization pathway could be adjusted to obtain near-quantitative yields of macrocycles, this closure reaction was necessarily carried out by the very slow addition of the linear precursor into a redox active solution, the principle reason being a ring closing ATRC

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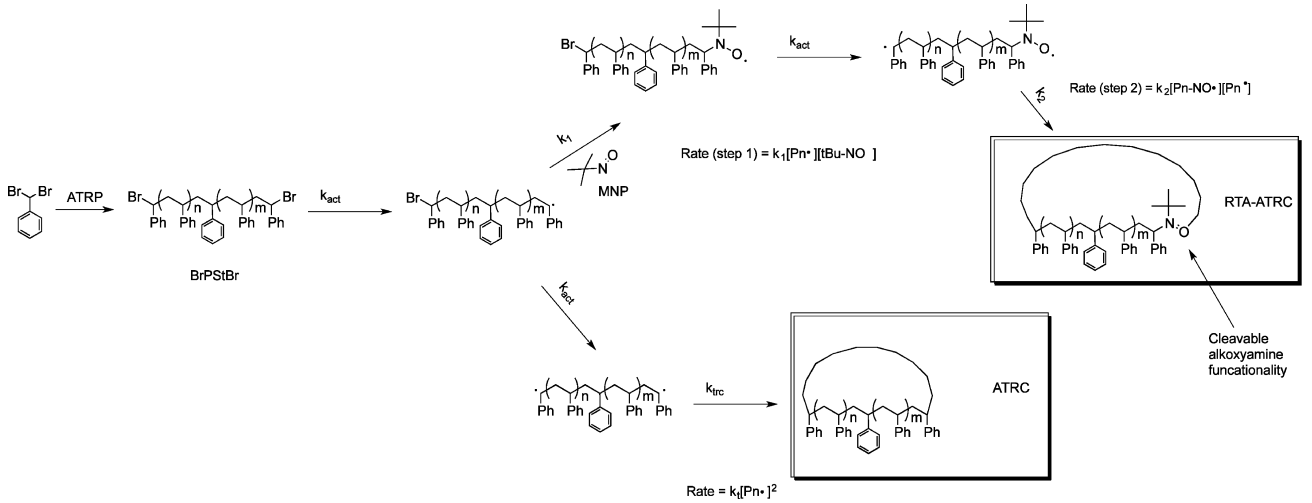
Scheme 1. Comparison of the Mechanistic Steps and Rate Equations of Radical Trap-Assisted Atom Transfer Radical Coupling (RTA-ATRC, top) to Intramolecular ATRC (bottom)[a]



[a]In both cases cyclic polymer is formed, yet the RTA-ATRC route produces cycles with a cleavable alkoxyamine functionality.

Table 1. Results of Radical Trap Assisted-Atom Transfer Radical Coupling (RTA-ATRC) of Linear α,ω-Dibrominated Polystyrene Precursor[a]

		precursor[b]						
trial	[PStBr]/[MNP][c]	M_p[d]	PDI[e]	rate[f] (nmol/h)	M_p[d]	PDI[e]	cyclic (%)[g]	⟨G⟩[h]
1	no MNP	2725	1.11	81	5050[i]	1.24		
2	1:10	2300	1.09	81	2050	1.11	~80	0.88
3	1:20	2300	1.09	81	2075	1.11	>90	0.87
4	1:25	2725	1.11	81	2425	1.05	>90	0.89
5	1:25	4275	1.14	81	3475	1.29	>90	0.81
6	1:250	2725	1.11	81	2250	1.07	>90	0.83
7	1:25	2725	1.11	112	2400	1.06	>90	0.88
8	1:25	2725	1.11	169	2350	1.08	>90	0.86
9	1:25	2725	1.11	337	2400	1.11	~90	0.88
10	1:35	2725	1.11	253	2325	1.06	>90	0.85
11	1:45	2725	1.11	253	2425	1.11	>90	0.89

[a]RTA-ATRC products were formed by the pseudodilute addition of a 25 mL THF solution of the precursor to a 40 mM THF solution of Cu^0, CuBr, and PMDETA at the rate indicated in the fifth column. [b]The precursor is α,ω-dibrominated polystyrene produced from the atom transfer radical polymerization of benzal bromide. Precursor polymer was passed through an alumina column and thrice precipitated in MeOH prior to coupling. [c]Ratio of brominated chain ends to 2-methyl-2-nitrosopropane (MNP). [d]Peak molecular weight (M_p) was determined by gel permeation chromatography (GPC). [e]The polydispersity index (PDI) was determined by GPC. [f]Rate at which BrPStBr was added into the redox-active THF solution. [g]The percentage of cyclic product was estimated from the areas under the RI traces of the gel permeation chromatogram. [h]The ratio of the M_p of the RTA-ATRC product and precursor. [i]A substantial peak matching the linear precursor was seen in the GPC trace product. See Supporting Information, Figure S1 for the GPC trace of this trial along with the linear precursor.

reaction in which both chain ends must be activated simultaneously for the cyclization to occur. However, we[29] and others[30,31] have demonstrated that ATRC may be carried out in the presence of a radical trap, such as a nitrone or a nitroso. The simultaneous activation of two specified chain ends are no longer a requirement in the resulting intramolecular, radical trap-assisted ATRC (RTA-ATRC), with each reaction step involving polymeric radicals being first order with respect to the radical (Scheme 1, top).[31,32] In this scenario, k_1 is much less than k_2, and intuitively, the addition of the initially formed chain-end radical into the nitroso compound (step 1) occurs at slower rate than a radical−radical reaction (step 2).[32]

In traditional, intermolecular ATRC, this mechanistic alteration may not be so vital, as the reaction and ultimate coupling fate of one polymer radical is not tied solely to the activation of another singly specific C−X bond but can conceivably react with any other polymer radical in the system. However, in intramolecular ATRC reactions applied to the synthesis of cyclic polymers (Scheme 1, bottom), shifting from ring closing reactions that are second order with respect to polymer radicals—as in the case of RTA-ATRC, k_{trc}—to those that are first order could offer substantial benefits. In addition to faster cyclization times, more leniency may be achieved in the specific choice of metal−ligand catalyst (our initial demonstration of intramoleculer ATRC was only successful with the highly active tris[2-(dimethylamino)ethyl]amine (Me_6TREN) ligand,[28] and was unsuccessful with the less expensive, yet less active, *N*,*N*,*N*′,*N*′,*N*′′-pentamethyldiethylenetriamine (PMDETA)). Furthermore, the cycle is expected to contain a thermally degradable alkoxyamine unit, allowing the cycle to be transformed back to a linear form and offer

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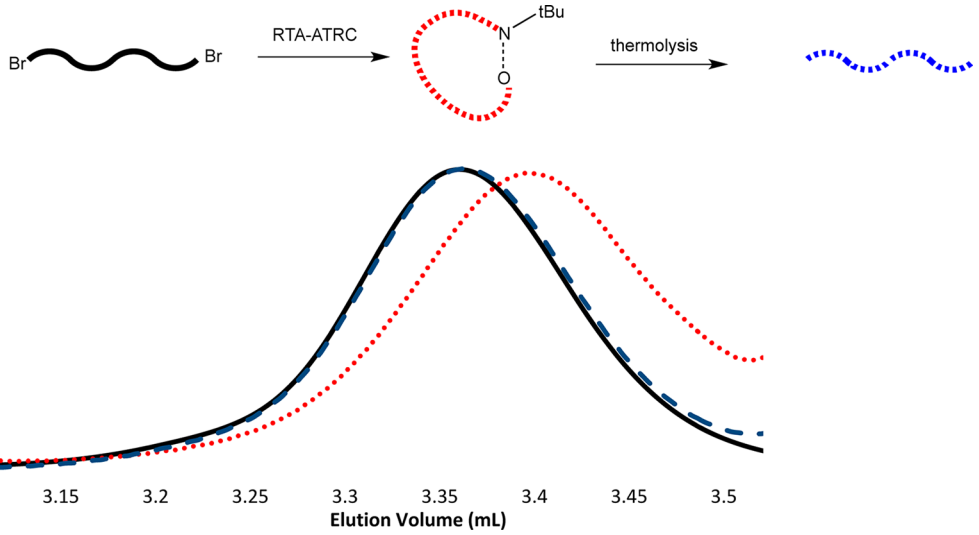

Figure 1. Typical gel permeation chromatography trace of linear α,ω-dibrominated polystyrene (Table 1, trial 4: solid line; peak molecular weight (M_p) = 2300; polydispersity index (PDI) = 1.09) and the cyclic product formed by the radical trap assisted-atom transfer radical coupling (dotted line; M_p = 2100; PDI = 1.11) and thermally cleaved cycle (dashed line; M_p = 2300; PDI = 1.06).

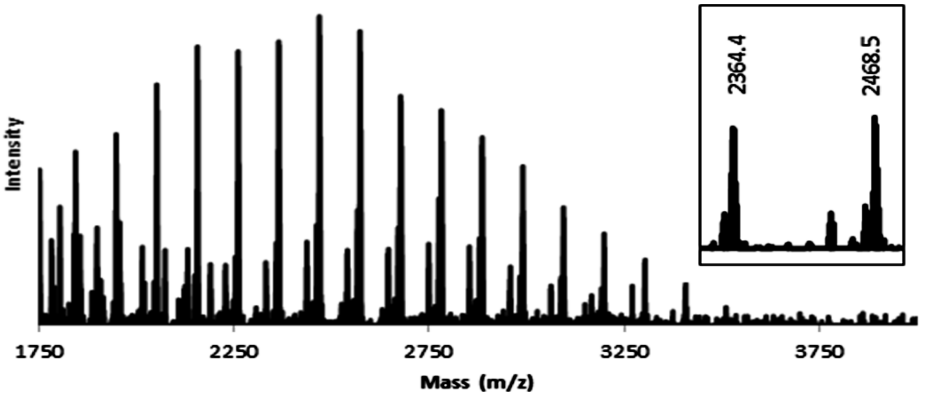

Figure 2. LC-MS mass spectrum of the product of the radical trap assisted-atom transfer radical coupling of linear α,ω-dibrominated polystyrene in the presence of 25 equiv of 2-methyl-2-nitrosopropane.[38] Calculated values of peaks shown in inset: 2364 Da (21 monomer units); 2468 Da (22 monomer units).

convincing evidence of both the formation of the cycle and the mechanistic pathway in which it was formed.

Intramolecular RTA-ATRC in the presence of the radical trap MNP (Scheme 1, top) was performed on dibrominated polystyrene (BrPStBr, formed by ATRP[33]), and the results are tabulated in Table 1. In all cases, a THF solution of BrPStBr precursor—with (trials 2−11) or without (trial 1) MNP in this solution—was added dropwise into a redox-active, THF solution of PMDETA and CuBr to create pseudohigh dilution conditions with the intention of favoring intramolecular radical coupling. Initially, a coupling reaction was performed in the absence of MNP (trial 1), resulting in no observable cyclic product, and showed coupled product formed by an intermolecular "step" ATRC reaction and a substantial portion of linear precursor remaining after the reaction. In this case, cycles would have had to be formed by traditional, intramolecular ATRC (Scheme 1, bottom), requiring the simultaneous generation and coupling of chain-end radicals on single polymer chains, which expectedly could not occur under these conditions (PMDETA as the ligand, 81 nmol/h addition rate of the BrPStBr into the redox-active solution). The low concentration of polymer chain ends in the reaction mixture, coupled with the use of this weaker ligand in this study apparently created a scenario where very few chains were activated at any given moment. Thus, bimolecular termination reactions that required two chain end radicals to occur, even if intermolecularly, were not favored, and most chains remained unreacted. See Figure S1 in the Supporting Information for GPC traces of trial 1. Subsequent reactions were performed in an otherwise identical manner, but with increasing equivalents of MNP present in the ATRC reaction, and the coupled products were compared to the original BrPStBr linear precursors (trials 2−6). In this case, when a chain-end C−Br bond was activated, the presence of the nitroso group allowed for trapping the active radical and "holding" it as a persistent, chain-end alkoxide that will readily react with a second chain-end radical (Scheme 1). GPC analysis of the RTA-ATRC products demonstrated a shift to lower apparent molecular weights in all cases, compared to the BrPStBr precursor from which they were derived, characteristic of the formation of cyclic polymers.[34−36] The $\langle G \rangle$ values, defined as the ratio of the peak molecular weight of the cyclic product and linear precursor, were between 0.81 and 0.89,[37] consistent with cyclic formation in all cases despite the extreme variation in the

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equivalents of MNP present in the cyclization. The ⟨G⟩ values observed using this RTA-ATRC sequence were slightly larger than those we reported with intramolecular ATRC (which ranged from 0.80 to 0.84).[28] In this case, the cycle incorporates an alkoxyamine unit (Scheme 1), adding size to the product and potentially causing a less dramatic shift to lower apparent molecular weights. Typical GPC traces of a BrPStBr precursor along with the cycle formed by RTA-ATRC are shown in Figure 1.

The cyclic products were heated at 150 °C for 20 h in dimethylformamide (DMF) to induce cleavage of the C−O bond predicted to be incorporated in cycles prepared by the RTA-ATRC method. This resulted in a near quantitative shift to shorter elution volumes with a corresponding increase in the apparent molecular weight (Figure 1). The successful return to the original apparent molecular weight of the linear precursor upon ring-opening by thermolysis provided strong confirmation of formation of the cyclic architecture, along with the GPC data listed in Table 1. The cyclic products formed by RTA-ATRC were also analyzed by liquid chromatography−mass spectrometry (LC-MS), and the m/z of major series was found to be identical to the m/z predicted for the MNP containing cycles (Figure 2, and Supporting Information, Table S1), offering direct evidence of the cyclic structure and consistent with the mechanism of its formation outlined in Scheme 1. The presence of minor peaks on the LC/MS may be due to small amounts of linear contamination, which could partially account for the ⟨G⟩ values being larger in cycles formed by RTA-ATRC compared to intramolecular ATRC or anionic methods. However, based on the clear shift in GPC elution volumes, the shift back to the original elution volume upon thermolysis, and the major series LC/MS experimental data matching calculated values, cyclization is clearly the dominant pathway.

Surprisingly, the addition of a huge excess of MNP equivalents (trial 6) still led to the creation of cycles, as opposed to simply end-capping each chain end with a nitroso group. This is consistent with k_2 being much greater than k_1 in Scheme 1, and the second chain end radical formed having a strong preference for ring closure by radical−radical trapping, while the first chain end radical was trapped with the nitroso group by default.

The possibility of carrying out the RTA-ATRC reaction more quickly—while still forming cyclic product—was explored by increasing the rate of the addition of the BrPStBr precursor (initially held at 81 nM of BrPStBr/h) into the reaction mixture while holding the number of eq of MNP at 25 (compared the C−Br chain ends). Interestingly, cycles were still formed in all cases under increasingly faster rates of addition (Table 1, trial 5 vs 7−9). When both amounts of the MNP were ramped up and the addition of BrPStBr was still at a relatively high rate (253 nmol/h, trials 10 and 11), cyclic polymers were still formed. These results again point to very effective, intramolecular trapping of the second chain end radical (step 2) by the nitroxide radical formed in step 1.

In conclusion, the inclusion of a nitroso radical trap in the pseudodilute ATRC reaction of α,ω-dibrominated polystyrene allows for the formation of cyclic polymers, while otherwise identical reactions in its absence form largely higher molecular weight polymers as a result of intermolecular coupling. The RTA-ATRC reactions presented in this paper can be performed more quickly and with weaker, more common ligands than traditional, intramolecular ATRC reactions. Furthermore, the cycles formed in this process contain alkoxyamine functionality that allows them to be thermally cleaved back to its linear form, providing a useful and convenient tool to substantiate the formation of the cyclic material.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(38) GPC characteristics of cyclic polymer: M_p = 3480, PDI = 1.29, $\langle G \rangle$ = 0.81, [MNP]:[C−Br] = 25:1. See Table 1 and Supporting Information for experimental details.