Telechelic Aminooxy Polystyrene Synthesized by ATRP and ATR Coupling

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ABSTRACT: Aminooxy α- and α,ω-end-functionalized polystyrene were synthesized via atom transfer radical polymerization (ATRP) and atom transfer radical (ATR) coupling. A 1-bromoethylphenyl initiator possessing an *N*-hydroxyphthalimide group was used for copper-mediated ATRP of styrene. The polymerization kinetics indicated good control with high initiator efficiency, and the resulting polymers had polydispersity indices (PDIs) as low as 1.12. *N*-Hydroxyphthalimide−polystyrene was then dimerized using Cu(0)-mediated ATR coupling, and GPC results indicated high coupling efficiency. Hydrazine deprotection of both the α and α,ω-end-functionalized polystyrene to the aminooxy groups was confirmed by ^{1}H NMR spectroscopy. End-group reactivity was verified by reaction with 4-bromobenzaldehyde to form the oxime linkages.

Introduction

The synthesis of well-defined polymers possessing unique end-group reactivity is an important target that has received considerable attention, particularly for researchers employing controlled radical polymerizations (CRPs).[1−5] End-group control is one essential element for successful incorporation of synthetic polymers into biomolecule conjugates, for stable surface coatings, and to make materials that exhibit intricate self-assembled structures.[6−12] Thus, the use of CRPs to synthesize end-functionalized polymers for applications in nanotechnology, biotechnology, and medicine is increasing.[1,13−17]

Atom transfer radical polymerization (ATRP) is a useful CRP methodology for producing well-defined polymers and from a synthetic standpoint has the benefit of being tolerant to a wide range of functional groups.[18,19] There are two main methods that have been employed to prepare polymers with a designed functional group at one end by ATRP.[1] The first approach takes advantage of the fact that polymers synthesized by ATRP contain a halogen chain end. This feature has been exploited to create many monofunctional polymers, since the chain end can be subsequently modified into other functional groups. For example, Matyjaszewski and co-workers have investigated the transformation of halogen-terminated polystyrene to an azide.[20] This affords end-groups that can be employed in Huisgen 1,3-dipolar cycloaddition "click" reactions between azides and alkynes.[21−24] Alternatively, the azides are readily reduced to amines.[20] The second approach exploits the functional group tolerance of ATRP and employs designed initiators in the reaction. This route has been widely exploited to incorporate functional groups such as alcohols[1,25] or carboxylic acids.[26] Additionally, "latent" functional groups, such as pyridyl disulfide,[27] protected thiols,[28] or a phthalimide,[29−31] have been used. The latter are deprotected under mild conditions to afford amines.

Polymers that have functional groups at both ends are equally interesting. These types of polymers have been shown to be useful as precursors to multiblock polymers, surface immobilizers, and tethering agents.[32] A typical method for the generation of these so-called telechelic polymers via ATRP employs bis-functional initiators, followed by transformation of the halogen chain ends.[1] More recently, polystyrene synthesized via ATRP has been demonstrated to undergo a highly efficient coupling reaction at the halogenated chain end known as atom transfer radical (ATR) coupling to afford a polymeric dimer.[33,34] In contrast to the low radical concentration sought in ATRP, in ATR coupling, Cu(0) is introduced into the reaction. This process yields a higher polymeric radical concentration that in the absence of monomer increases the probability of termination events. Thus, utilizing a functional ATRP initiator to produce the polymer and coupling of the halogen chain ends is an alternate pathway to telechelic polystyrene (Figure 1). Several reports have employed this technique to fashion dimeric polymers with a variety of functional groups including alcohols, carboxylic acid, and aldehydes.[35−37]

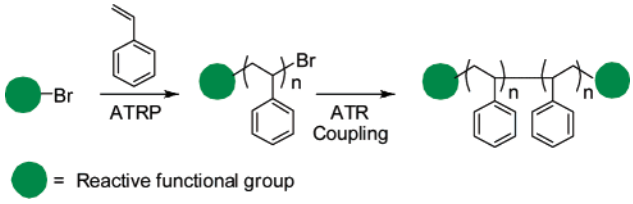
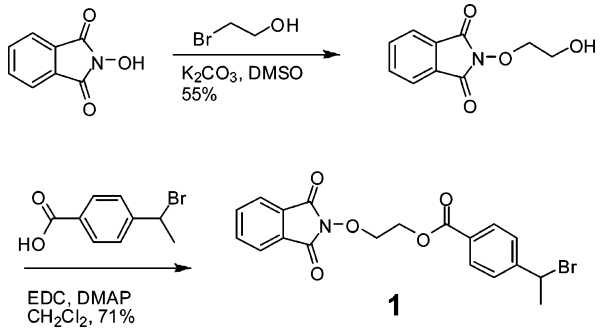


Figure 1. ATRP followed by ATR coupling is a convenient route to telechelic polystyrene.

Scheme 1. Synthesis of a Hydroxyphthalimide Protected ATRP Initiator



Herein, we report the synthesis of polystyrene possessing aminooxy functionality at one or both ends of the polymer. *O*-Hydroxylamines readily undergo reactions with aldehydes and

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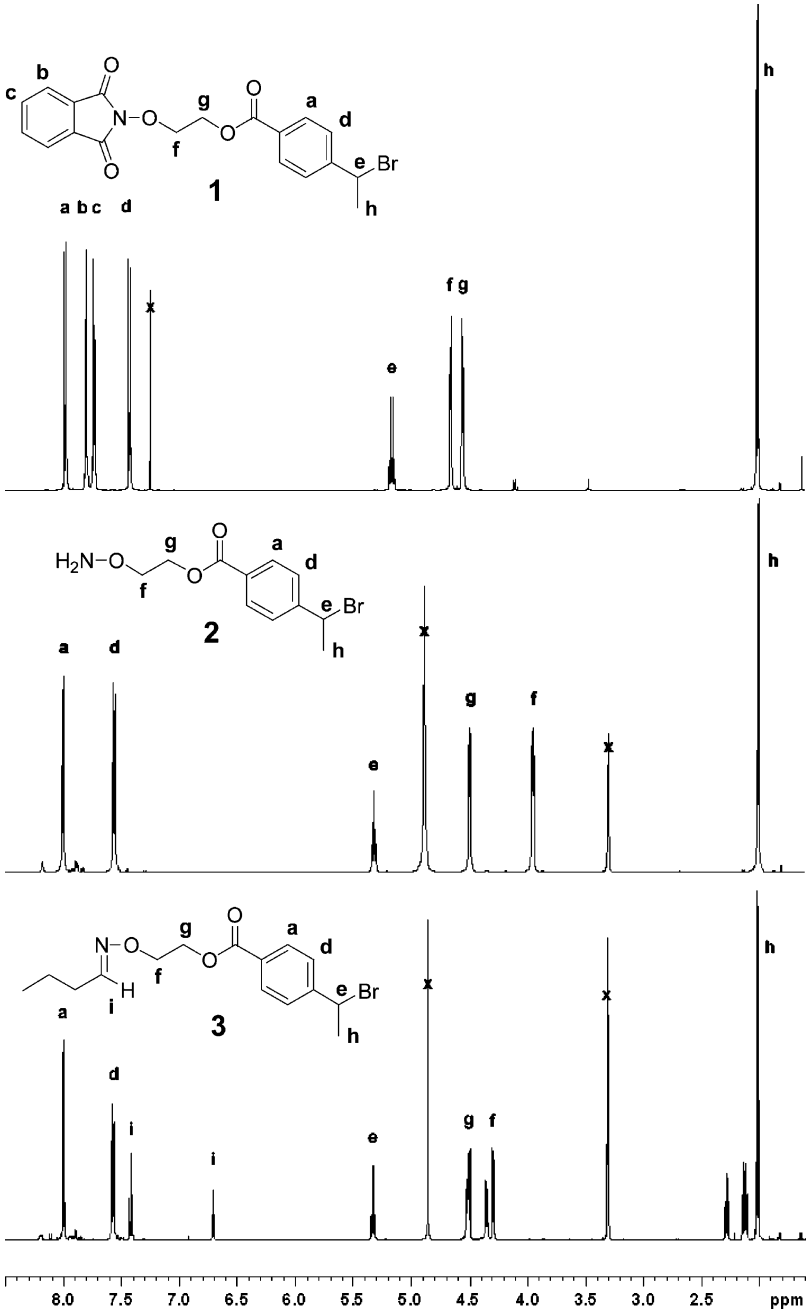


Figure 2. ^{1}H NMR spectra of **1** in $CDCl_3$ (top), deprotected **1** in CD_3OD (middle), and the result of conjugation of **2** and butyraldehyde in CD_3OD (bottom).

ketones to form oxime bonds. This "click" reaction occurs readily and without the addition of other reagents.[38] We hypothesized that the ATRP/ATR coupling strategy could be used to effectively install the reactive groups at one or both ends of a polystyrene chain by polymerizing from a protected aminooxy-functionalized initiator and then coupling. We have previously utilized a Boc-protected aminooxy ATRP initiator to produce α-functionalized aminooxy poly(methacrylates) and poly(acrylamides).[39] However to our knowledge aminooxy-functionalized polystyrenes have not yet been reported. The synthesis and reactivity of the initiator, formation of mono- and bis-functionalized polystyrene, and verification of the end-group reactivity are discussed.

Experimental Section

Materials. All materials were purchased from either Sigma-Aldrich or Acros and were used as received unless otherwise noted. Styrene was dried over CaH_2 for 12 h and distilled under reduced pressure. Column chromatography was performed using 200−400 mesh silica gel purchased from Sorbent Technologies. CuBr was purified by sequential washing with glacial acetic acid (3×), absolute ethanol (3×), and ether (3×), followed by drying under vacuum. *N*-(2-Hydroxyethoxy)phthalimide was synthesized following a literature procedure.[40] Solvents and monomers for polymerization reactions were purged with N_2 for at least 30 min prior to transfer to the Schlenk reaction flask via gastight syringes.

Analytical Techniques. NMR spectra were recorded on either a Bruker ARX or Avance DRX 500 MHz spectrometer. Monomer conversions were determined using a Shimadzu GC-2014 gas chromatograph (GC) equipped with a flame ionization detector and a Restek DB-WAX 30 m capillary column. Gel permeation chromatography (GPC) was conducted on a Shimadzu HPLC system equipped with a refractive index detector RID-10A and two 300 mm Polymer Laboratories PLgel 5 μm mixed-D columns (with column guard). THF was used as the eluent (flow rate 0.8 mL/

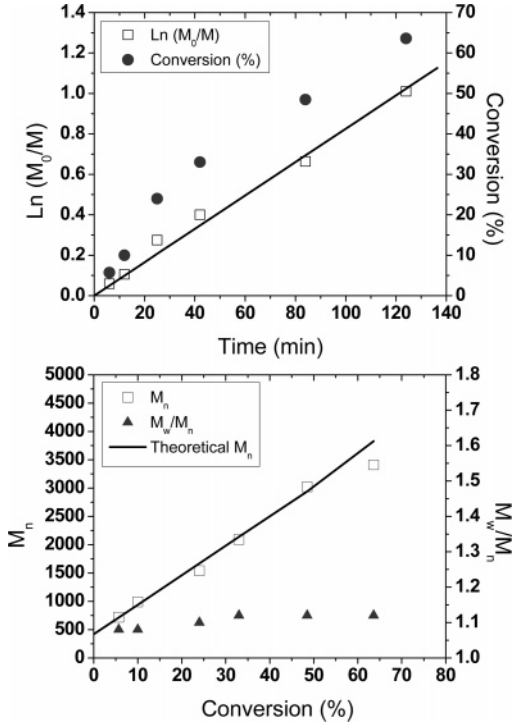


Figure 3. ATRP of styrene from **1**. Kinetic plot derived from GC, molecular weight, and PDI determined from GPC (THF). Reaction conditions: styrene:**1**:CuBr:PMDETA = 50:1:1:1, 90 °C.

min, 23 °C). Near-monodisperse polystyrene (Polymer Laboratories) was employed for calibration, and chromatograms were processed using the EZStart 7.3 chromatography software. GPC characterizations were performed after final purification of the polymer. Mass spectrometry was performed in the UCLA Molecular Instrumentation Center.

Methods. Synthesis of 2-(Hydroxyphthalimidoethyl)-4-(1-bromoethyl)benzoate (1). *N*-(2-Hydroxyethoxy)phthalimide (0.20 g, 0.97 mmol), 4-(1-bromoethyl)benzoic acid (0.27 g, 1.2 mmol), and 4-(dimethylamino)pyridine (DMAP) (12 mg, 0.097 mmol) were dissolved in DCM (10 mL), and the solution was cooled to 0 °C. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.22 g, 1.2 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction solvent was removed in vacuo, and the crude product was purified via column chromatography (1/1 ethyl acetate/hexanes) to yield 290 mg (71%) of **1** as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.00 (d, 2H, J = 8.5), 7.82 (m, 2H), 7.75 (m, 2H), 7.44 (d, 2H, J = 8.5), 5.18 (q, 1H, J = 6.0), 4.67 (t, 2H, J = 2.8), 4.56 (t, 2H, J = 2.8), 2.04 (d, 3H, J = 6.9). ^{13}C NMR ($CDCl_3$): δ 165.9, 163.5, 134.8, 130.3, 129.6, 129.0, 127.0, 123.8, 75.9, 62.8, 48.1, 26.7.

Synthesis of (2-Aminooxyethyl)-4-(1-bromoethyl)benzoate (2). Initiator **1** (30 mg, 0.068 mmol) was dissolved in THF (2 mL). Hydrazine hydrate (10 μL, 0.34 mmol) was added via syringe, and the solution was refluxed for 2.5 h. The flask was cooled to room temperature and then filtered through a 20 μm syringe filter. The filtrate was condensed in vacuo, and the crude product was purified by column chromatography using dichloromethane/ethyl acetate (5/1) as the mobile phase to yield 42 mg (80%) of **2** as a white solid. ^{1}H NMR (CD_3OD): δ 8.00 (d, 2H, J = 8.5), 7.57 (d, 2H, J = 8.5), 5.32 (q, 1H, J = 6.0), 4.50 (t, 2H, J = 2.8), 3.96 (t, 2H, J = 2.8), 2.01 (d, 3H, J = 6.9). ^{13}C NMR (CD_3OD): δ 167.5, 134.0, 131.1, 131.0, 128.1, 74.5, 63.9, 27.0. Mass spec (ESI MS): expected (MH^+) 288.02; observed 288.0 and bromine isotope (290.0).

^{1}H NMR Study of Conjugation of Butyraldehyde to 2 (3). Deprotected initiator **2** (20 mg, 0.069 mmol) and butyraldehyde (7.5 μL, 0.083 mmol) were dissolved in THF (2 mL), and the reaction was stirred for 15 h. The solvent was removed in vacuo and replaced with 0.7 mL of CD_3OD for ^{1}H NMR analysis of **3**. ^{1}H NMR (CD_3OD): δ 8.00 (d, 2H, J = 8.5), 7.58 (d, 2H, J = 8.5), 7.42, 6.71 (3:2 *syn:anti*, t, 1H, J = 6.2), 5.33 (q, 1H, J = 6.8), 4.54−4.48 (m, 2H), 4.37−4.33, 4.31−4.27 (2:3 *anti:syn*, m, 2H), 2.31−2.25, 2.16−2.10 (2:3 *anti:syn*, m, 2H), 2.02 (d, 3H, J = 6.9), 1.53−1.43 (m, 2H), 0.95−0.87 (m, 3H).

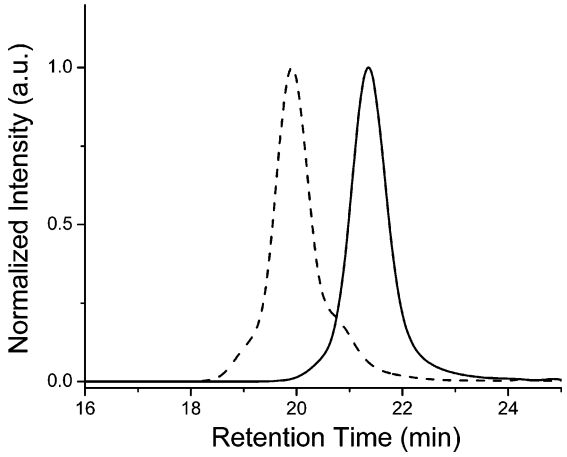


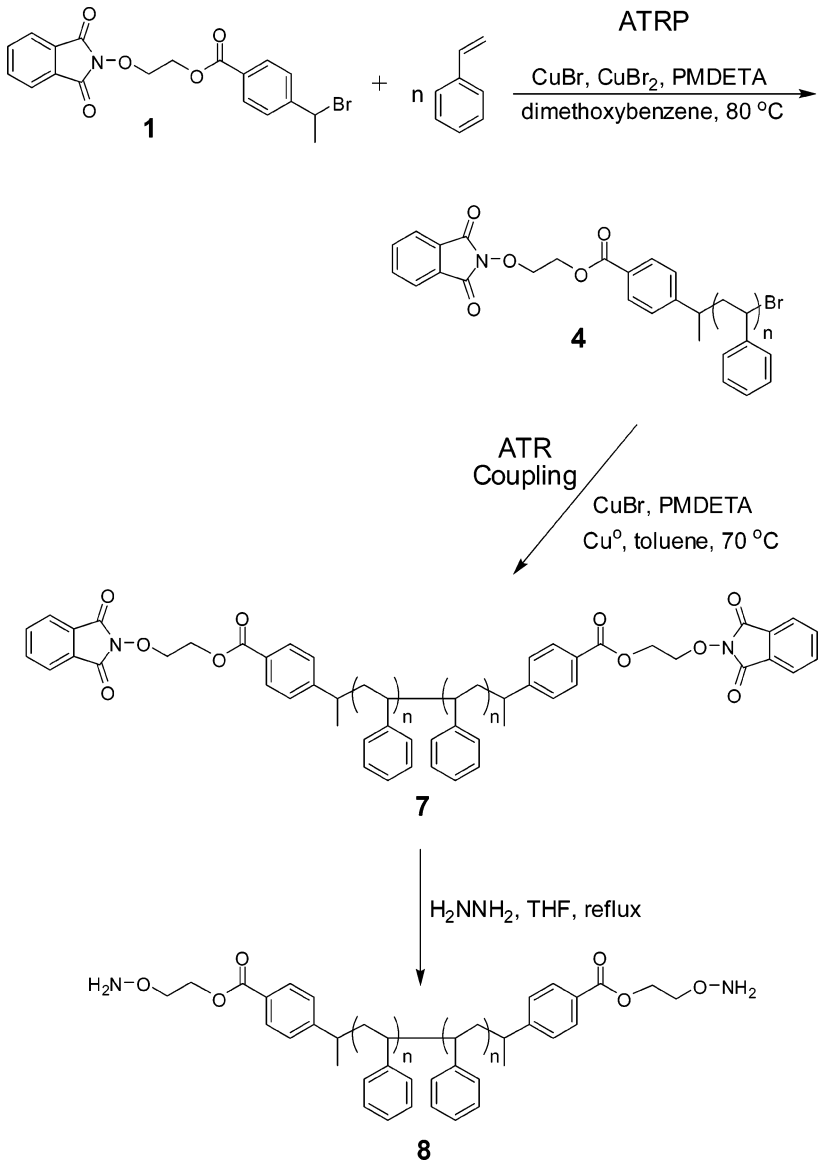
Figure 4. GPC traces for the protected hydroxyphthalimide-polystyrene (**4**) (solid line, M_n = 3170 g mol^{-1}, PDI = 1.10) and its coupling product (**7**) (dotted line, M_n = 7680 g mol^{-1}, PDI = 1.13). [PS−Br]:[CuBr]:[PMDETA]:[Cu^0] = 1:1:1:4. Solvent: toluene; temperature: 70 °C; 4.5 h.

Polymerization Procedure for Kinetic Analysis. CuBr (12 mg, 0.088 mmol), anisole (60 μL, 0.055 mmol), **1** (37 mg, 0.088 mmol), and a stir bar were added into a Schlenk reaction vessel which was subsequently sealed with a rubber septum. The flask was consecutively evacuated and refilled with N_2 a total of three times. Degassed styrene (0.5 mL, 4.4 mmol) was added, and the flask was subjected to three freeze/pump/thaw cycles. Degassed *N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) (18 μL, 0.088 mmol) was then added, and the flask was immediately submerged in a 90 °C oil bath. Kinetic analysis was conducted via removal of small aliquots and monitoring by GC and confirming by ^{1}H NMR spectroscopy. The samples were diluted into THF for GPC analysis.

General Polymerization Procedure (4). CuBr (43 mg, 0.298 mmol), $CuBr_2$ (3.0 mg, 0.015 mmol), dimethoxybenzene (620 mg, 4.4 mmol), **1** (0.125 mg, 0.298 mmol), and a stir bar were added into a Schlenk reaction vessel which was subsequently sealed with a rubber septum. The flask was consecutively evacuated and refilled with N_2 a total of three times. Degassed styrene (3.4 mL, 29.8 mmol) was added, and the flask was subjected to three freeze/pump/thaw cycles. Degassed PMDETA (66 μL, 0.314 mmol) was then added, and the flask was immediately submerged in an 80 °C oil bath. The reaction was terminated by removal from the oil bath and exposure to air after 1 h 40 min. The reaction mixture was diluted with THF (20 mL), and the catalyst was removed by filtration through a silica gel packed fritted filter. The polymer was further purified and isolated by two cycles of precipitation into rapidly stirring methanol (125 mL) followed by centrifugation. The polymer was dried under high vacuum to give **4**.

General ATR Coupling Reaction Procedure (7). A Schlenk flask was loaded with polystyrene **4** (M_n = 3170 g mol^{-1}, 80 mg, 0.029 mmol), CuBr (5.4 mg, 0.037 mmol), and a stir bar. The flask was sealed with a rubber septum and consecutively evacuated and refilled with N_2 a total of three times. Degassed toluene (0.5 mL) was added, followed by degassed PMDETA (8 μL, 0.037 mmol). A separate Schlenk flask was charged with nanosize Cu^0 (9.5 mg, 0.15 mmol), sealed with a rubber septum, and consecutively evacuated and refilled with N_2 a total of three times. The polymer/catalyst solution was then transferred via cannula to the flask containing nanosize Cu, and the flask was submerged in a 70 °C oil bath. After 4.5 h, the reaction flask was removed from the oil bath; the solution was diluted with THF (10 mL) and subsequently filtered through a short plug of silica gel. The polymer was isolated by precipitation into rapidly stirring methanol (25 mL) followed by centrifugation. The solids were dried under vacuum to give **7**.

Scheme 2. Synthesis of α,ω-Aminooxy Polystyrene



Typical Deprotection of 4 and 7 (5 and 8). Either 50 mg of **4** or 50 mg of **7** was dissolved in THF (5.0 mL), and hydrazine hydrate (5 equiv) was added. The solution was refluxed for 2.5 h. Purification of the deprotected polymer was performed by filtration through a short column of silica gel, followed by precipitation into rapidly stirring methanol and isolation by centrifugation. The pellet was redissolved in benzene and lyophilized to afford **5** or **8**, respectively, as white solids.

^{1}H NMR Study of Conjugation of 4-Bromobenzaldehyde to Aminooxy Polymers (6 and 9). Polystyrene **5** (8 mg) or **7** (8 mg) and 4-bromobenzaldehyde (2 mg) were dissolved in 1 mL of $CDCl_3$ with or without a catalytic amount (2 μL) of deuterated trifluoroacetic acid to form **6** or **9**, respectively. ^{1}H NMR spectra were recorded after either 1 h (with addition of acid) or 18 h (without acid addition).

Results and Discussion

Initiator Synthesis. In designing the initiator, several factors were considered. First, the aminooxy protecting group needed to be stable to the ATRP and ATR coupling processes. Second, it had to be easily removed when required. Therefore, we chose to use an *N*-hydroxyphthalimide as a latent *O*-hydroxylamine, since this group is stable to ATRP and ATR coupling temperatures and is readily removed by standard hydrazinolysis. Additionally, we chose a 1-bromoethylphenyl fragment as the initiating halogen due to its structural resemblance to styrene and its known ATRP reactivity.[41,42] The designed initiator **1** was prepared in two steps (Scheme 1). *N*-(2-Hydroxyethoxy)-phthalimide was synthesized according to a standard literature procedure using 2-bromoethanol and *N*-hydroxyphthalimide.[40] The alcohol was subsequently esterified with 4-(1-bromoethyl)-benzoic acid using EDC and DMAP to afford the initiator **1** in 71% yield.

Deprotection Study. The stability of the 2-(hydroxyphthalimidyl)ethyl ester to deprotection was of particular concern, since it has been reported that similar (2-phthalimidyl)ethyl initiators have the propensity to isomerize to form 2-hydroxylethyl amides during hydrazinolysis.[30,31] To ensure that the deprotection of the phthalimide moiety would not result in any unwanted side reactions rendering the aminooxy group unavailable, we conducted a study on the initiator. Using a standard protocol, deprotection of initiator **1** was performed by refluxing with 5 equiv of hydrazine for 2.5 h in THF. After purification, ^{1}H NMR analysis of the resulting product **2** indicated removal of the phthalimide group as evidenced by the disappearance of the aromatic multiplets at 7.75 and 7.82 ppm (Figure 2).

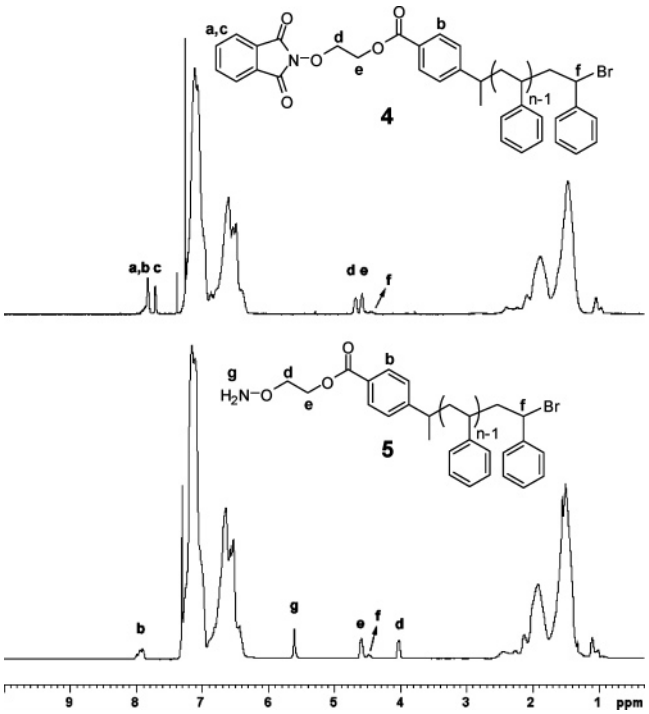


Figure 5. ^{1}H NMR spectra in $CDCl_3$ of *N*-hydroxyphthalimide end-functionalized polystyrene **4** (top) and deprotected aminooxy end-functionalized polystyrene **5** (bottom).

Additionally, there was a significant shift from 4.67 ppm of the methylene proton signals adjacent to the *N*-hydroxyphthalimide group to 3.96 ppm after deprotection. ESI MS indicated that the bromine was not displaced during the deprotection. The exact mass of **2** was observed as well as the typical bromine isotope peak.

In order to verify end-group reactivity, the deprotected initiator **2** was subjected to butyraldehyde. The appearance of oxime protons at 7.42 and 6.71 ppm in a 3:2 ratio of *syn* to *anti* was good evidence that the aminooxy group on the initiator was available for reaction (Figure 2). Furthermore, the resonances of the methylene protons next to the aminooxy group shifted to 4.32 ppm as a result of the conjugation. Taken together, these results indicated that the phthalimide moiety was removed and that no side reactions that disrupted the reactivity of the aminooxy group occurred.

Kinetic Studies. With the success of the initiator deprotection studies, we moved forward with the polymerizations. Initially kinetic studies were undertaken. Copper-catalyzed ATRP of styrene was conducted using initial monomer-to-initiator ratios of 50:1 and molar ratios of 1:1:1 for **1**, CuBr, and PMDETA, respectively, at 90 °C. Progress of the polymerization was monitored by GC and confirmed by ^{1}H NMR spectroscopy. A semilogarithmic plot (Figure 3) of monomer conversion vs time was constructed and showed first-order kinetic correlation. Polymerization control was further illustrated by the linear increase of molecular weight with respect to conversion and the low polydispersity indices (PDIs) observed throughout the polymerization. The initiator exhibited excellent efficiency, as exhibited by a close correlation with a theoretical line plot in the molecular weight vs conversion curve (Figure 3). The final number-average molecular weight (M_n) was 3400 g mol^{-1}, and PDI was 1.12.

α-Aminooxy Polystyrene Synthesis. The kinetic studies demonstrated that **1** was efficient for the polymerization of styrene. We therefore carried out the synthesis of the monofunctionalized polystyrene. It was determined that inclusion of

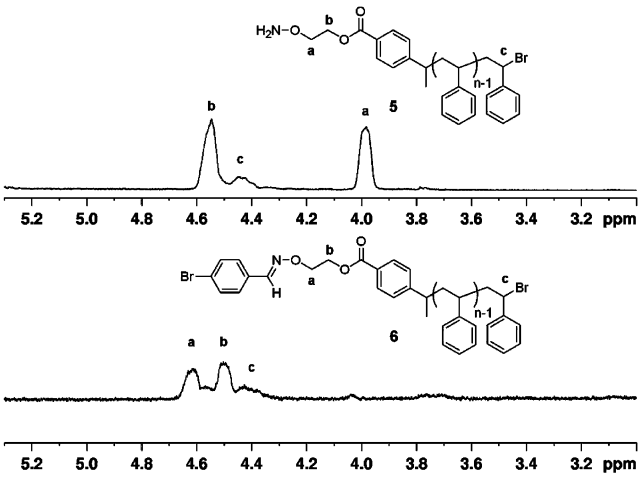


Figure 6. ^{1}H NMR spectra in $CDCl_3$ of deprotected monoaminooxy end-functionalized polystyrene (top) and conjugation product of deprotected monoaminooxy end-functionalized polystyrene and 4-bromobenzaldehyde (bottom).

5% $CuBr_2$ in the reaction mixture was optimal for the later coupling reactions (vide infra). Therefore, the polymerization was undertaken with ratios 50:1:1:1.05:0.05 of styrene, initiator **1**, CuBr, PMDETA, and $CuBr_2$, respectively (Scheme 2). The temperature was also kept at 80 °C in order to maximize retention of the halogen chain end and minimize the occurrence of thermal initiation which would reduce net initiator functionality in the polymer sample.[34,43] The resulting polymer (**4**) had a monomodal GPC trace (Figure 4) with a M_n of 3170 g mol^{-1} and PDI of 1.10. In addition, the ^{1}H NMR spectrum (Figure 5) showed the characteristic peaks for the initiator, with a broad signal centered at 4.68 ppm for the α-aminooxy methylene protons and another centered at 4.58 ppm for the methylene protons adjacent to the ester. The aromatic signals for the hydroxyphthalimide were observed as two peaks centered at 7.83 and 7.72 ppm, overlapping with aromatic signals of protons **b** of the initiator centered at 7.87 ppm. All the signals had the correct integrations with respect to one another. Additionally, the distinct resonance at 4.45 ppm characteristic of the halogen chain end[36,37] was observed.

The deprotection of hydroxyphthalimide end-functionalized polystyrene was undertaken applying the same method as described for the initiator. Polymer **4** was refluxed in a solution of hydrazine in THF for 2.5 h. Deprotection was evidenced by the appearance of the phthalylhydrazide byproduct as a white precipitate in the flask. Immediately following the completion of the reaction, the precipitate was removed via filtration and the polymer (**5**) purified by precipitation into methanol. Removal of the hydroxyphthalimide protecting group was evident by the disappearance of the peaks at 7.72 and 7.83 ppm in the ^{1}H NMR spectrum (Figure 5) There was also a significant shift to 3.99 ppm for the α-aminooxy methylene protons after deprotection, as was observed for the initiator. Additionally, a resonance at 5.56 ppm that corresponded to the $-ONH_2$ protons was observed.

End-group reactivity was confirmed by a ^{1}H NMR study of the conjugation of 4-bromobenzaldehyde. Unlike the small molecule system, spectroscopic confirmation of the reaction was complicated by overlap of the polymer peaks with the oxime proton peaks. Therefore, the shift of the resonance corresponding to the methylene protons alpha to the aminooxy was examined. The peak shifted to 4.62 ppm, indicating that oxime bond formation occurred and that the aminooxy group was reactive (Figure 6). Not unexpectedly, addition of a catalytic amount of

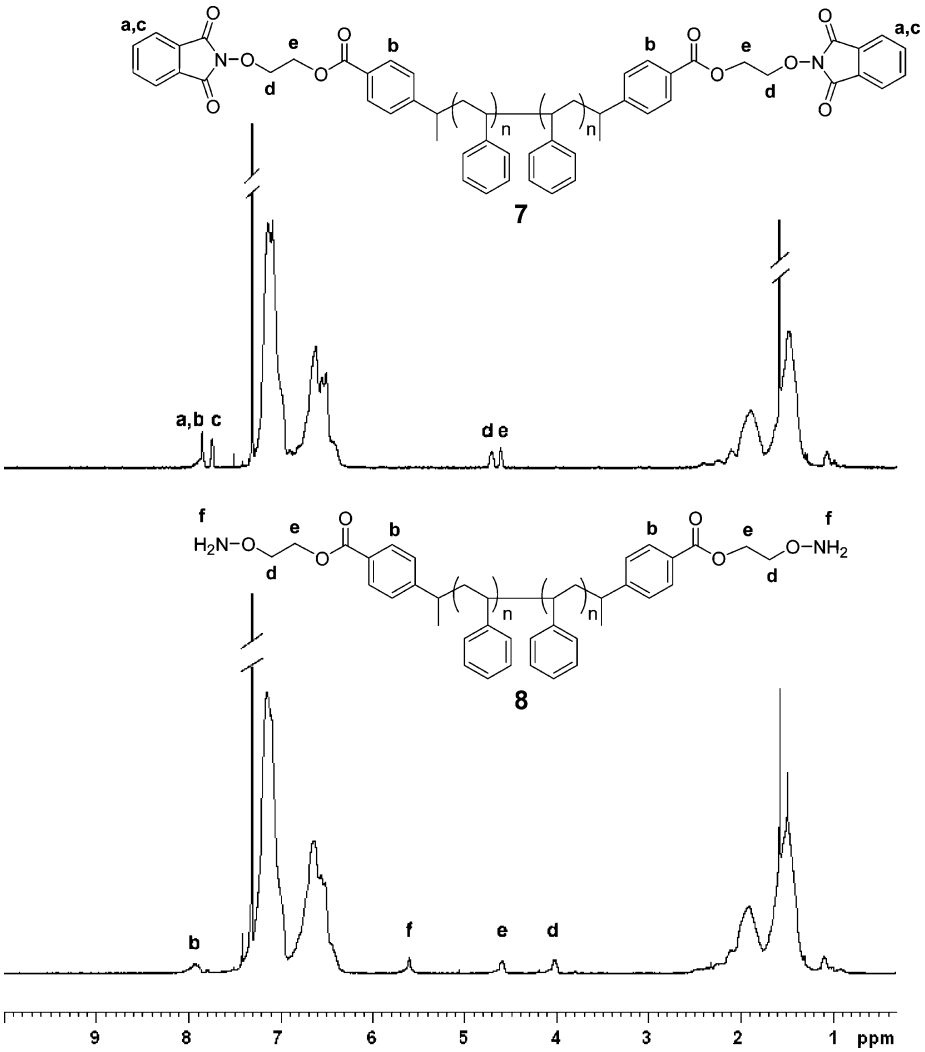


Figure 7. ^{1}H NMR spectra in $CDCl_3$ of hydroxyphthalimide end-functionalized polystyrene dimer (**7**, top) and deprotected aminooxy end-functionalized dimer (**8**, bottom).

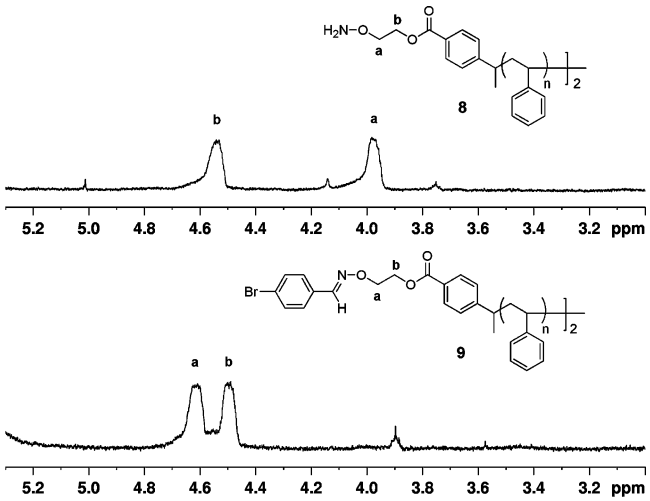


Figure 8. ^{1}H NMR spectra in $CDCl_3$ of **8** (top) and the product after conjugation with 4-bromobenzaldehyde (bottom).

deuterated trifluoroacetic acid significantly decreased the conjugation time, and the reaction was complete in less than 1 h.

α,ω-Aminooxy Polystyrene. ATR coupling was carried out on monofunctional hydroxyphthalimide end-functionalized polystyrene **4** with CuBr and PMDETA in the presence of Cu^0 at 70 °C (Scheme 2). Initially, our ATR coupling experiments had very poor coupling efficiencies, in some cases less than 50% based on rough estimation from the GPC traces. However, as described by Matyjaszewski and co-workers,[34] when the initial ATRPs were conducted at a lower polymerization temperature of 80 °C and with 5% CuBr, the coupling efficiencies in the subsequent coupling reaction were dramatically improved. This was presumably due to better retention of the halogen chain end of the monofunctionalized polymer.[34] The GPC trace (Figure 4) of the resulting polymer (**7**) exhibited the desired shift to lower retention time and higher molecular weight (M_n = 7680 g mol^{-1} and PDI = 1.13). Minor residual uncoupled polymer was observed as a lower molecular weight shoulder.

The ^{1}H NMR spectrum (Figure 7) of **7** exhibited the signals from the protected initiator at 7.70 and 7.80 ppm, in addition to 4.66 and 4.56 ppm. Noticeably absent was the signal at 4.45 ppm from the CH−Br at the polymer chain end, further confirming polymer coupling. Deprotection of **7** resulted in the disappearance of the signals at 7.80 and 7.70 ppm, along with the characteristic shift of the α-aminooxy methylene protons to 3.97 ppm. End-group reactivity of the aminooxy polystyrene dimer (**8**) was confirmed by conjugation with 4-bromobenzaldehyde. As observed from the previous analysis with the monofunctional polymer, a significant shift of the peaks of the α-aminooxy protons from 3.97 to 4.61 ppm occurred upon reaction with 4-bromobenzaldehyde (Figure 8). These results

confirmed that the bis-functionalized aminooxy polystyrene was synthesized and that the end-groups were amenable to further reaction.

Conclusions

We have synthesized semitelechelic and telechelic polystyrene possessing reactive aminooxy end groups. An initiator containing an *N*-hydroxyphthalimide moiety as a latent aminooxy group was synthesized. The initiator was subsequently used in an ATRP of styrene, which displayed normal kinetics and produced polymers with predictable molecular weights and narrow size distributions. Deprotection and oxime bond formation with a model aldehyde were verified via NMR spectroscopy, and the reaction was found to occur without the addition of any other reagents. ATR coupling was then utilized to dimerize the *N*-hydroxyphthalimide modified chains, which were subsequently deprotected to afford aminooxy telechelic polystyrene. Aminooxy groups are excellent for chemoselective conjugation of polymers to proteins, and there is significant interest in coupling hydrophobic polymers such as polystyrene to biomolecules to form bioactive nanostructures.[44,45] Therefore, the methodology reported herein may be useful for preparing protein−polystyrene, where the polymer chain is attached to a specific site on the protein. In addition, bis-conjugated polystyrene may form interesting and novel self-assembled structures in aqueous solutions or in the bulk phase. This and other applications of this methodology in biotechnology and nanotechnology are envisioned.

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