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Poly(bromoethyl acrylate): A Reactive Precursor for the Synthesis of Functional RAFT Materials

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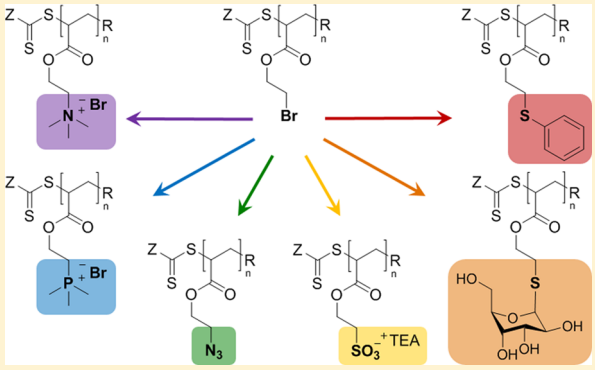
Supporting Information

ABSTRACT: Postpolymerization modification has become a powerful tool to create a diversity of functional materials. However, simple nucleophilic substitution reactions on halogenated monomers remains relatively unexplored. Here we report the synthesis of poly(bromoethyl acrylate) (pBEA) by reversible addition−fragmentation chain transfer (RAFT) polymerization to generate a highly reactive polymer precursor for postpolymerization nucleophilic substitution. RAFT polymerization of BEA generated well-defined homopolymers and block copolymers over a range of molecular weights. The alkylbromine-containing homopolymer and block copolymer precursors were readily substituted by a range of nucleophiles in good to excellent conversion under mild and efficient reaction conditions without the need of additional catalysts. The broad range of nucleophilic species that are compatible with this postmodification strategy enables facile synthesis of complex functionalities, from permanently charged polyanions to hydrophobic polythioethers to glycopolymers.



INTRODUCTION

Synthesis of complex polymers with desirable functionalities as well as well-defined and controlled architectures is a core target of modern polymer science. The development of several "living" or controlled polymerization methods, and in particular reversible deactivation radical polymerization (RDRP), has paved the way for precise control of molecular weights, polymer architecture, and end-group functionality.[1−5] However, inclusion of desirable material properties, in addition to well-controlled polymerization, is limited by the range of chemical functionalities accessible to these polymerization techniques.[6−8] In light of this, postmodification of a reactive polymer precursor provides an attractive approach to overcoming this limitation, enabling synthesis of diversely functional materials, without subjecting them to detrimental polymerization conditions.[9−13]

A variety of postpolymerization methods have previously been explored,[6−9] including copper-catalyzed azide/alkyne click (CuAAC),[14−16] Diels−Alder cycloadditions,[17−20] and active ester couplings.[10,21−23] These methods enable the introduction of complex functional groups targeting applications ranging from drug delivery to organic electronics.[19,24,25] In addition to these more established postmodification methods is a simple yet relatively unexplored reaction—nucleophilic substitution of alkyl halides. Thus far, it is primarily metal-catalyzed polymerizations that have exploited this versatile handle to introduce functionality.[13,26−28] One reason for the limited use of this method in RDRPs may be the susceptibility of alkyl halides to abstraction by radicals, an attribute that is exploited in iodine transfer polymerizations.[29,30] Controlled radical polymerizations have thus far primarily made use of the monomer vinylbenzyl chloride; however, control of this styrene type monomer requires extensive optimization for successful polymerization, often at the cost of very low conversions and yields.[31,32] As an alternative to overcome this limitation, Monnereau et al. used a two-step method by substituting a poly(hydroxyethyl acrylate) generated by ATRP with trimethylsilyl bromide to give the desired polybrominated product.[12] However, the issues described above leave the direct polymerization of simple alkyl halide monomers relatively unexplored, despite convenient monomer synthesis, and a wide range of nucleophiles available for substitution of the precursor. The few examples reported using alkyl bromide monomers by RDRP methods have primarily targeted the synthesis of ammonium-based polycations[33−35] or azide modifications in degradable copolymers.[36,37] While these bromo-containing RDRP polymers were employed effectively to introduce complex functionality, it is fascinating to note that these substitutions focused solely on nitrogen-based nucleophiles, which represent but a fraction of the diverse range of potential substitutions achievable with alkyl halide monomers.

In this contribution, we demonstrate the efficiency of polymerizing bromoethyl acrylate (BEA) using the reversible

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addition−fragmentation chain transfer (RAFT) process. We show the versatility of the resulting BEA polymer in subsequent nucleophilic substitution reactions to generate a library of polymers of diverse and complex functionalities. RAFT polymerization provides a robust system that is both facile and convenient, yet remains tolerant to a broad range of functional groups and monomer varieties.[1] BEA combines the ease of acrylate polymerizations with the high electrophilicity of a carbon adjacent to the bromine group, while the reactivity toward radicals remains low. Kinetic studies of the polymerization shed light on the control and the retention of the active chain end.

The obtained reactive precursor polymer was subsequently used in a range of postpolymerization substitutions to generate a library of functional polyacrylates. To demonstrate the versatility of the method, we used a wide variety of nucleophiles that differ in size, polarity, and charge. An important characteristic of these reactions is the full conversion of the bromine group under very mild reaction conditions. In addition to these modifications, we further illustrated the potential for functionalization of pBEA by formation of block copolymers followed by substitution to create self-assembled copolymer structures from a single reactive polymer precursor.

EXPERIMENTAL SECTION

Materials. Triethylamine, dioxane, and DMSO were purchased from Fisher Scientific. 4,4-Azobis(4-cyanovaleric acid) (ACVA) was purchased from MP Biomedicals. All other compounds were purchased from Sigma-Aldrich. All chemicals were used as received. All solvents were bought from commercial sources and used as received. The synthesis of (4-cyanopentanoic acid)ylethyl trithiocarbonate (CPAETC) is described in the Supporting Information.

Instrumentation. ^{1}H NMR spectra were recorded on a Bruker AV-300, HD-300, or AV-400 in $CDCl_3$, D_2O, or DMSO-d_6. Shift values (δ) are reported in ppm. The residual proton signal of the solvent was used as an internal standard ($CDCl_3$ δ_H 7.26, D_2O δ_H 4.79, DMSO-d_6 δ_H 2.50). Size exclusion chromatography (SEC) was carried out on a Polymer Laboratories PL-GPC 50 Plus. All anionic polymers were analyzed on a Polymer Laboratories PL-GPC 50 Plus system using a PL aquagel-OH guard column (5 μm, 7.5 × 50 mm) followed by two PL aquagel-OH 30 columns (7.5 × 300 mm). Water (0.1 M $NaNO_3$) was used as eluent at 1.0 mL min^{-1} at 30 °C. All other polymers were analyzed on a Polymer Laboratories PL-GPC 50 Plus system using a PolarGel-M guard column (7.5 × 50 mm) followed by two PolarGel-M columns (7.5 × 300 mm). DMF (0.1% LiBr) was used as eluent at 1.0 mL min^{-1} at 50 °C. Commercial narrow linear poly(methyl methacrylate) standards in range of 2.0 × 10^2−1.0 × 10^6 g mol^{-1} were used to calibrate the DMF SEC system. Analyte samples were filtered through polytetrafluoroethylene (PTFE) membrane with either 0.2 or 0.45 μm pore size before injection (100 μL). Centrifugal filtration was carried out using Vivaspin 20, 3000 MWCO centrifuge tubes. Experimental $M_{n,SEC}$ and $Đ$ values of synthesized polymers were determined using Agilent GPC software. Elemental analyses for CHN were carried out on a CE440 CHN elemental analyzer, and bromine was analyzed using classical oxygen flask methods by Warwick Analytical Service.

Synthesis of 2-Bromoethyl Acrylate (BEA). BEA monomer was synthesized according to a previously reported procedure.[46] In a typical reaction, 2-bromoethanol (67 g, 38 mL, 0.54 mol) was dissolved in CH_2Cl_2 (300 mL), to which triethylamine (82.2 mL, 59.7 g, 0.59 mol) was added under a nitrogen atmosphere, and the reaction was cooled to 0 °C. Acryloyl chloride (47.9 g, 53.4 mL, mol) in CH_2Cl_2 (30 mL) was subsequently added dropwise over an hour with stirring. The reaction was allowed to warm to room temperature overnight with continued stirring. Upon completion, the reaction mixture was filtered, the solid residue washed with CH_2Cl_2, and the organic layer washed with water (2 × 100 mL) and then brine (2 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed via rotary evaporation. The product was purified by distillation under reduced pressure (∼1 mbar, 39−40 °C) to give 2-bromoethyl acrylate as a clear colorless liquid in 80% yield; bp 41−43 °C (0.68 mmHg). ^{1}H NMR (300 MHz, 293 K, $CDCl_3$, δ): 6.46 (dd, J = 17.3, 1.5 Hz, 1 H, C═CH_2), 5.62 (dd, J = 17.3, 10.4 Hz, 1 H, CH_2═CH−), 5.89 (dd, J = 10.5, 1.4 Hz, 1 H, C═CH_2), 4.47 (t, J = 6.1 Hz, 2 H, −OCH_2CH$_2$−), 3.55 (t, J = 6.2 Hz, 2 H, −CH$_2$CH_2Br) ppm.

RAFT Polymerization of BEA. Polymers were synthesized by the following general method. A small vial was charged with a magnetic stirrer and (4-cyanopentanoic acid)ylethyl trithiocarbonate (0.0535 g, 0.203 mmol), BEA (2.0 g, 11.17 mmol), ACVA (5.69 mg, 0.0203 μmol), and 1,3,5-trioxane (∼5 mg) as an internal standard. The mixture was dissolved in dioxane (2 mL), and the vial was sealed with a rubber septum and deoxygenated by a stream of bubbled nitrogen for 10 min. The vial was then suspended in a preheated oil bath at 70 °C and allowed to stir for 3 h. Upon completion the solution was cooled to rt, opened to air, and precipitated in diethyl ether to give compound **1**. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ = 4.34 (m, 2nH), 3.65 (m, 2nH), 2.39−1.54 (4m, 3nH), 1.29 (t, 3H). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 4.41 (m, 2nH), 3.55 (m, 2nH), 2.45 (m, nH), 2.03 (m, 0.5nH), 1.76 (m, nH), 1.59 (m, 0.5nH), 1.36 (t, 3H). IR (thin film) ν_{max}: 2962, 2929, 1733, 1444, 1386, 1280, 1244, 1219, 1161, 1084 cm^{-1}. See Figure S1 for ^{1}H NMR in $CDCl_3$.

RAFT Block Copolymerization of p(BEA)-*b*-p(BA). Block copolymers were synthesized by the following general method. A small vial was charged with magnetic stirrer and pBEA$_{50}$ (compound **S1** in Supporting Information) homopolymer macro-chain transfer agent (macro-CTA) (0.243 g, 0.026 mmol), BA (0.4 g, 3.121 mmol), ACVA (0.73 mg, 0.0026 μmol), and 1,3,5-trioxane (∼5 mg) as an internal standard. The mixture was dissolved in dioxane (0.4 mL), and the vial was sealed with a rubber septum and deoxygenated by a stream of bubbled nitrogen for 10 min. The vial was then suspended in a preheated oil bath at 70 °C and allowed to stir for 2 h. Upon completion the solution was cooled to rt, opened to air, and precipitated in methanol. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 4.41 (m, 2nH), 3.96 (m, 2mH), 3.55 (m, 2nH), 2.45 (m, nH), 2.27 (m, mH), 2.03 (m, 0.5nH), 1.89 (m, 0.5mH), 1.76 (m, nH), 1.60 (br d, [2mH + 0.5nH]), 1.36 (br d, [2mH + 3H]), 0.93 (br t, 3mH). For more details see Tables 1 and 3 in the Supporting Information, Figure S2 for ^{1}H NMR in $CDCl_3$, and Figure S3 for ^{1}H NMR in DMSO-d_6.

RAFT Polymerization of BA. Polymers were synthesized by the following general method. A small vial was charged with a magnetic stirrer and (4-cyanopentanoic acid)ylethyl trithiocarbonate (0.0137 g, 0.052 mmol), BA (1.0 g, 7.802 mmol), ACVA (1.46 mg, 0.0052 μmol), and 1,3,5-trioxane (∼5 mg) as an internal standard. The mixture was dissolved in dioxane (1 mL), and the vial was sealed with a rubber septum and deoxygenated by a stream of bubbled nitrogen for 10 min. The vial was then suspended in a preheated oil bath at 70 °C and allowed to stir for 2 h. Upon completion the solution was cooled to rt, opened to air, and precipitated in diethyl ether. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 4.01 (m, 2mH), 2.29 (m, mH), 1.89 (m, 0.5mH), 1.60 (br m, 2mH), 1.39 (br m, 2mH), 0.94 (br t, 3mH). For more details see Table 2 in the Supporting Information. Anal. Calcd for $C_{259}H_{363}Br_{50}NO_{102}S_3$: C 33.76%, H 3.97%, N 0.15%, Br 43.36%. Found: C 34.19%, H 4.04%, N 0.14%, Br 45.14%.

RAFT Block Copolymerization of p(BA)-*b*-p(BEA). Block copolymer was synthesized by the following general method. A small vial was charged with magnetic stirrer and pBA$_{115}$ (compound **S3** in Supporting Information) homopolymer macro-chain transfer agent (macro-CTA) (0.502 g, 0.037 mmol), BEA (0.4 g, 2.23 mmol), ACVA (1.04 mg, 0.0037 μmol), and 1,3,5-trioxane (∼5 mg) as an internal standard. The mixture was dissolved in dioxane (0.4 mL), and the vial was sealed with a rubber septum and deoxygenated by a stream of bubbled nitrogen for 10 min. The vial was then suspended in a preheated oil bath at 70 °C and allowed to stir for 2 h. Upon completion the solution was cooled to rt, opened to air, and precipitated in methanol. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 4.38 (m, 2nH), 4.01 (m, 2mH), 3.52 (m, 2nH), 2.43 (m, nH), 2.25 (m,

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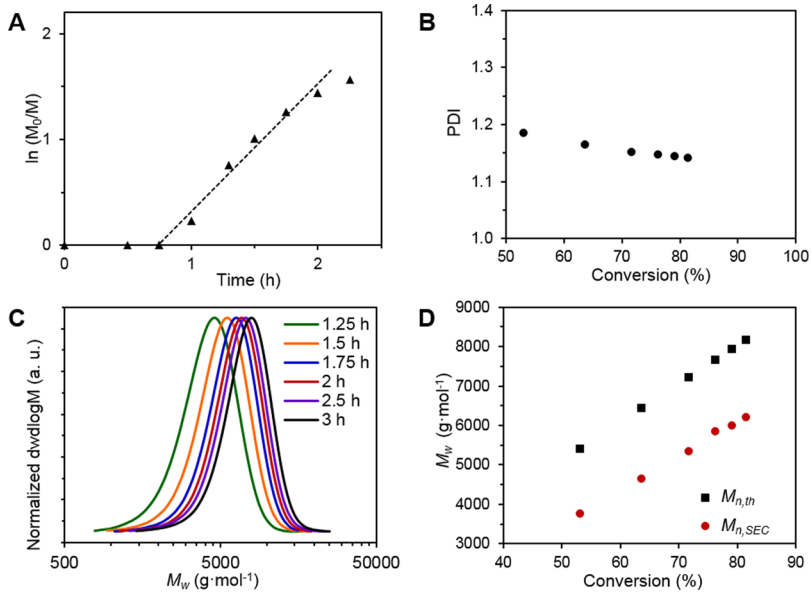

Figure 1. Kinetic data for pBEA targeting DP 50. (A) First-order kinetic plot for the RAFT polymerization of pBEA as determined by ^{1}H NMR spectroscopy. Dashed line indicates line of best fit for the linear region. (B) Plot of polymer dispersity vs conversion. (C) SEC traces of kinetic samples. (D) Theoretical M_n vs M_n from SEC values.

*m*H), 1.99 (*m*, 0.5*n*H), 1.87 (*m*, 0.5*m*H), 1.73 (*m*, *n*H), 1.57 (br *m*, [2*m*H + 0.5*n*H]), 1.35 (br *m*, [2*m*H + 3H]), 0.91 (br *t*, 3*m*H). For more details see Table 4 in the Supporting Information and Figure S4 for ^{1}H NMR in $CDCl_3$.

Postpolymerization Substitutions of Homopolymers. *Substitution with Trimethylamine.* Typical reaction of trimethylamine with pBEA: $pBEA_{50}$ (0.10 g, 12.6 μmol) was suspended in 3 mL of DMSO in a small vial with a stir bar, to which was added 2 equiv of trimethylamine (4.2 M in ethanol, 300 μL, 1.26 mmol) and stirred for 24 h under a N_2 atmosphere. Upon completion, the solution was diluted with H_2O, purified by dialysis, and lyophilized to give the desired poly(trimethylammonium bromide ethyl acrylate). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 4.53 (*m*, 2*n*H), 3.91 (*m*, 2*n*H), 3.34 (br *m*, 9*n*H), 2.41−1.61 (4*m*, 3*n*H). See Figure S6 for ^{1}H NMR in DMSO-d_6.

Substitution with Trimethylphosphine. Typical reaction of trimethylphosphine with pBEA: $pBEA_{50}$ (0.10 g, 12.6 μmol) was suspended in 2.5 mL of DMSO in a small vial with stir bar, to which was added 2 equiv of trimethylphosphine (1 M in THF, 1.30 mL, 1.30 mmol) and stirred for 24 h under a N_2 atmosphere. Upon completion, the solution was diluted with H_2O, purified by dialysis, and lyophilized to give the desired poly(trimethylphosphonium bromide ethyl acrylate). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 4.33 (*m*, (2 × *n*)H), 2.80 (*m*, (2 × *n*)H), 2.30 (*m*, *n*H), 2.04 (br *m*, (9 × *n*)H), 1.75−1.50 (2*m*, (2 × *n*)H). See Figure S8 for ^{1}H NMR in DMSO-d_6.

Substitution with Tetraethylammonium Sulfite. Typical synthesis of tetraethylammonium sulfite salt: In a small vial 1 equiv of dimethyl sulfite (0.197 mL, 2.32 mmol) and 1.9 equiv of tetraethylammonium hydroxide (1.5 M solution in methanol, 2.936 mL, 4.04 mmol) are combined and stirred vigorously for 5 h. The turbid solution of tetraethylammonium sulfite in methanol is used directly in the substitution of pBEA.

Typical reaction of tetraethylammonium sulfite with pBEA: $pBEA_{50}$ (0.10 g, 12.6 μmol) was suspended in 2 mL of DMSO in a small vial with stir bar, to which was added 5 equiv of tetraethylammonium sulfite (0.75 M in methanol, 3.72 mL, 5.87 mmol) and stirred for 24 h under a N_2 atmosphere. Upon completion, the solution was diluted with H_2O, purified by dialysis, and lyophilized to give the desired poly(ethyl acrylate tetraethylammonium sulfonate). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ = 3.55−3.47 (*m*, (2 × *n*)H), 3.23 (*q*, (8 × *n*)H), 2.35−1.32 (4*m*, (3 × *n*)H), 1.16 (*t*, (12 × *n*)H). See Figure S11 for SEC traces.

Substitution with Sodium Azide. $pBEA_{50}$ (0.05 g, 6.17 μmol) was suspended in 1 mL of DMF in a small vial with stir bar, to which was added sodium azide (0.0426 g, 0.49 mmol) in DMF 1.5 and stirred for 24 h under a N_2 atmosphere. Upon completion, the solution was precipitated in a 1:1 brine:water mixture; the precipitate was washed with water and dried under a stream of nitrogen to give the desired poly(azido ethyl acrylate). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 4.17 (*m*, (2 × *n*)H), 3.54 (*m*, (2 × *n*)H), 2.36−1.54 (4*m*, (3 × *n*)H). IR (thin film) ν_{max} 2958, 2929, 2098, 1733, 1444, 1392, 1302, 1278, 1263, 1162 cm^{-1}. See Figure S12 for SEC trace.

Substitution with Thiophenol. $pBEA_{50}$ (0.04 g, 5.44 μmol) was suspended in 1.5 mL of DMF in a small vial with stir bar, to which was added 2 equiv of thiophenol (50 μL, 0.49 mmol) and DIPEA (77.9 μL, 0.45 mmol) and stirred for 24 h under a N_2 atmosphere. Upon completion, the solution was precipitated in methanol and dried under vacuum to give the desired poly(thiophenol ethyl acrylate). ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 7.26−7.11 (*m*, (5 × *n*)H), 4.06 (*m*, (2 × *n*)H), 3.07 (*m*, (2 × *n*)H), 2.27−1.39 (4*m*, (3 × *n*)H). See Figures S13 and S14 for ^{1}H NMR spectra in $CDCl_3$. Anal. Calcd for $C_{559}H_{613}NO_{102}S_{53}$: C 62.88%, H 5.79%, N 0.13%. Found: C 60.13%, H 5.62%, N 0.15%.

Substitution with 1-β-D-Thioglucose. $pBEA_{50}$ (0.014 g, 1.7 μmol) was suspended in 1 mL of DMSO in a small vial with stir bar, to which was added 1.5 equiv of β-D-thioglucose sodium salt (21.8 mg, 0.1 mmol) and stirred for 24 h under a N_2 atmosphere. Upon completion, the solution was diluted with H_2O, purified by centrifugal filtration (3000 MWCO), and lyophilized to give the desired poly(β-D-thioglucose ethyl acrylate). ^{1}H NMR (400 MHz, D_2O, ppm): δ = 4.57 (*d*, *n*H), 4.34(*br m*, 2*n*H), 3.89 (*d*, *n*H), 3.72 (*br d*, *n*H), 3.45 (*br m*, 3*n*H), 3.34 (*br t*, *n*H), 3.05 (*br m*, *n*H), 2.99 (*br m*, *n*H), 2.42 (*br m*, *n*H), 2.00 (*br m*, 0.5*n*H), 1.79 (*br m*, *n*H), 1.64 (*br m*, 0.5*n*H). See Figure S15 for ^{1}H NMR in D_2O, Figure S16 for ^{1}H NMR in DMSO-d_6, and Figure S17 for SEC trace.

Postpolymerization Substitutions of Block Copolymers. Block copolymers of pBEA were substituted in the same manner as the homopolymers (*vide supra*).

Substitution with Trimethylamine. Block copolymers of pBEA were substituted in the same manner as the homopolymers (*vide supra*). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ = 4.36 (*m*, 2*n*H), 3.96 (*m*, [2*m*H + 2*n*H]), 2.19 (*m*, *m*H), 2.05 (*m*, [*m*H + 0.5*n*H]), 1.95 (*m*, *n*H), 1.77 (*m*, [0.5*m*H + *n*H]), 1.53 (br *d*, [2*m*H + 2*n*H]), 1.32 (br *d*, [2*m*H + *n*H]), 0.87 (br *t*, 3*m*H). See Figure S7 for ^{1}H NMR in DMSO-d_6.

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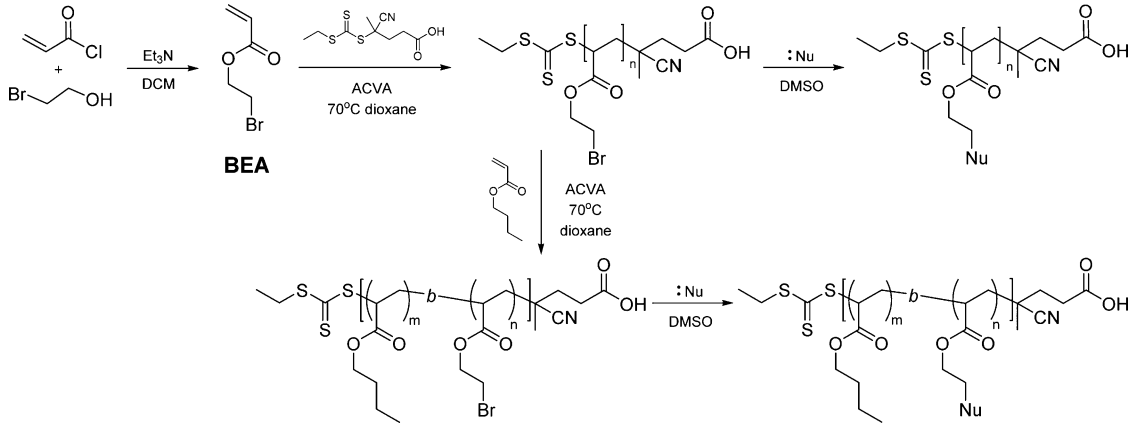
Table 1. Summary of BEA RAFT Homopolymerization

	$[M]_0/[CTA]_0$	$[CTA]_0/[I]_0$	conv[a] (%)	$M_{n,th}$[b]	$M_{n,NMR}$[c]	$M_{n,SEC}$[d]	$Đ$
	13	10	94	2200	2500	1800	1.12
	25	10	96	5000	4700	4200	1.10
1	50	10	94	8000	8300	6500	1.12
2	100	10	90	16500	16800	15100	1.10
3	200	10	78	26200	28000	24600	1.17

[a]Determined from ^{1}H NMR. [b]Calculated from conversion and characteristics of the parent polymer. [c]Calculated from ^{1}H NMR end-group analysis. [d]From SEC analysis (DMF LiBr, pMMA-Std.).

Scheme 1. Scheme of Entire Synthesis, Beginning with Monomer Synthesis, RAFT Homopolymerization and Block Copolymerization of BEA, and Nucleophilic Subsitution of pBEA Precursors



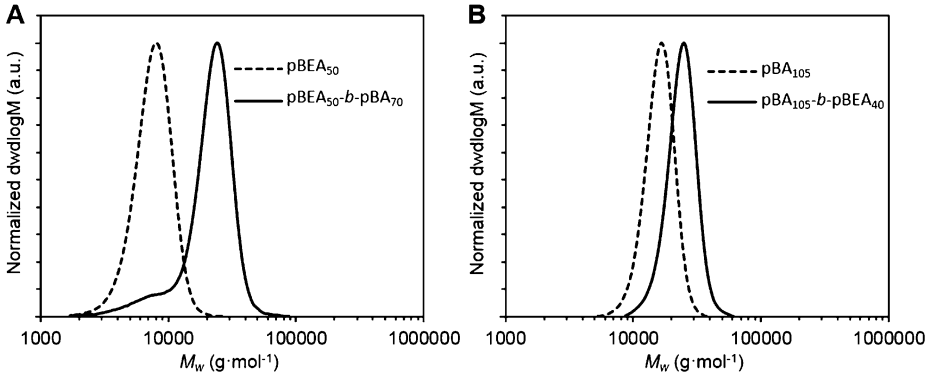


Figure 2. (A) Chain extension of $pBEA_{50}$ macro-CTA with pBA_{70}. (B) Chain extension of pBA_{105} macro-CTA with $pBEA_{40}$.

Substitution with Trimethylphosphine. Block copolymers of pBEA were substituted in the same manner as the homopolymers (*vide supra*). ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ = 4.36 (*m*, 2*n*H), 3.97 (*m*, 2*m*H), 3.70 (*m*, 2*n*H), 2.80 (*m*, *n*H), 2.19 (*m*, *m*H), 2.05 (br *m*, [(9 × *n*)H]), 1.78 (*m*, [0.5*m*H + 2*n*H]), 1.53 (br *d*, [2*m*H + 2*n*H]), 1.32 (br *d*, [2*m*H + *n*H]), 0.87 (br *t*, 3*m*H). See Figure S9 for ^{1}H NMR in DMSO-d_6.

RESULTS AND DISCUSSION

RAFT Homopolymerization. For RAFT polymerization of BEA, (4-cyanopentanoic acid)ylethyl trithiocarbonate (CPAETC) was used as the chain transfer agent (CTA) and dioxane as the solvent. To confirm the control of radical polymerization of BEA, we followed the kinetics of the polymerization by ^{1}H NMR and SEC (DMF LiBr). After an induction period of approximately 30 min, the pseudo-first-order rate plot (Figure 1A) is initially linear, indicative of a RDRP mechanism.[38−40] The increase in M_n with monomer conversion is linear, and dispersity of the polymer remains narrow ($Đ$ < 1.2), thus indicating a controlled radical polymerization. At longer polymerization times (>2 h) the plot deviates from linearity, but the SEC traces (Figure 1C) still show a narrow dispersity (Figure 1B). The downturn in the kinetic rate plot (Figure 1A) is due to a decrease in the total radical concentration during polymerization.[41] Despite 85% of the initiator ACVA remaining at 2 h, radical generation by the initiator was less than the amount of radicals undergoing termination reactions.[5,42] By limiting the polymerization time to the period in which the rate is linear, we can avoid unnecessary termination products that occur at longer reaction times, ensuring we reduce the number of dead chains present. It should also be noted that molecular weights obtained by SEC (Figure 1D) consistently underestimate M_n due to calibration of the SEC using poly(methyl methacrylate) standards; however, dispersity and molecular weight distribution remain representative. Furthermore, the M_n by NMR cannot be calculated for kinetic samples due to the ethyl end on the CTA *Z* group overlapping with the backbone polymer peaks (at ∼1.2

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ppm), and the dioxane solvent peak interfering with the peak at ~3.35 ppm, giving incorrect integrations and erroneous M_n NMRs.

Based on these kinetics, a range of polymer DPs were targeted by varying the monomer/CTA ratio, the results of which are summarized in Table 1. The prepared polymers were purified by precipitation using either methanol or diethyl ether and were obtained in high yield. In all cases high conversions (>75%) were obtained with short polymerization times (2 h) and a low consumption of initiator (<2%).[43,44] These results clearly demonstrate the ease of polymerizing the halogenated monomer BEA using RAFT.

RAFT Block Copolymerization. On the basis of the promising previous results, we further investigated the formation of block copolymers comprising BEA monomer to demonstrate that the RAFT chain ends are still present and functional. The advantage of RAFT polymerization is that it enables facile synthesis of well-defined block copolymers by chain extending the remaining trithiocarbonate end-group moiety. To examine this "livingness" of the precipitated homopolymer, pBEA was chain extended using the hydrophobic monomer butyl acrylate (BA). The polymerization of the second pBA block was achieved in an analogous fashion to BEA homopolymerization, but instead the BEA polymer was utilized as a macro-CTA (Scheme 1). The shift in the SEC trace to high molecular weights clearly demonstrates the successful chain extension of the pBEA with pBA; however, a low molecular weight shoulder can be observed, which corresponds to the macro-CTA (Figure 2A). Calculating the initiator decomposition under our reaction conditions, we would expect a number of dead chains in the system to be below 2%.[43,44] Considering the highly reactive nature of the monomer due to the bromine group, additional loss of the CTA end group cannot be fully excluded. Nevertheless, more than 90% of the chains reinitiate, and the SEC traces of the second block were in good agreement with theoretically expected values for the block copolymer (Figure 2A).

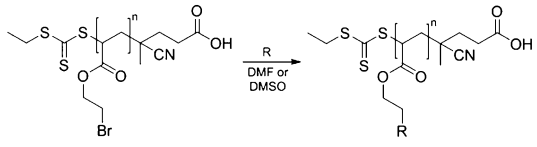
To eliminate the possibility of the shoulder being formed by side reactions at high conversion in the polymerization of the pBEA macro-CTA, we limited the conversion of the macro-CTA polymerization to 75%, before repeating the chain extension with pBA. The low molecular weight shoulder remained (see Figure S5), despite limiting conversion of the first block, suggesting that poor reinitiation of the macro-CTA is the cause of the shoulder. Formation of well-defined block copolymers requires that the first block have an R-group with a similar or greater leaving ability than that of the second polymer radical.[45,46] In this case, despite both blocks being formed of acrylates, the polymer side chain appears to have influenced the stability of the macroradical.[43] The pBEA likely forms a macroradical of lower stability than that formed by pBA, resulting in an adduct radical that partitions in favor of the starting materials, which causes the broadening of the molecular weight distribution indicative of the remaining macro-CTA seen in Figure 2A.

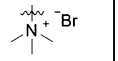
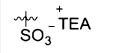
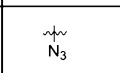
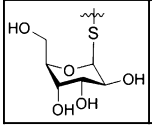
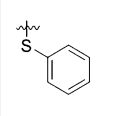
In addition to the previous polymer sequence, we examined the chain extension of a pBA macro-CTA with BEA monomer. Using similar conditions, we observed a well-defined block copolymer, with a symmetrical, monomodal SEC trace (Figure 2B). These results support our hypothesis that pBA forms a more stable macroradical, resulting in a better defined block copolymer due to complete reinitiation of the macro-CTA. Thus, we have demonstrated that BEA is suitable for the formation of pure block copolymers without any apparent side reactions with the bromine group; however, synthesis does require planning of the block order and consideration of the second block macroradical stability.

Postpolymerization Modification. After demonstrating the successful polymerization of BEA, we investigated the reactivity of this precursor in nucleophilic substitutions testing a range of nucleophiles. Since pBEA consists of primary alkyl halides, we envisioned it would readily undergo an S_N2 reaction with various nucleophilic species. We were interested in testing if very high conversions (>95%) could be reached in the absence of side reactions, both of which are crucial for an effective postpolymerization modification.

To investigate the versatility of our method, we selected five different types of nucleophiles: amines, phosphines, azides, sulfites, and thiols (Scheme 2). The substitutions of pBEA were conveniently followed by ^{1}H NMR, by observing the shifts on the ethyl acrylate pendant arms both before and after substitution.

Scheme 2. Summary of the Substitutions



R =	Nucleophile	R =	Nucleophile
	Trimethyl amine		Tetraethyl ammonium sulfite
	Trimethyl phosphine		Sodium azide
	β-D-Thioglucose		Thiophenol

As a first example, we examined the substitution of the bromine by thiophenol (Figure 3). Thio−bromo substitutions have previously been reported to be rapid and efficient reactions to introduce end-group functionality.[47−52] However, thio−bromo substitutions have not been thoroughly explored for main chain functionalization of polymers by controlled radical polymerization.

Thiophenol was selected to representatively probe substitution efficacy, since aromatic protons in the ^{1}H NMR (~7.1 ppm) are well separated from any peaks in the pBEA precursor simplifying the comparison. Initially the substitution was attempted using only 2 equiv of thiophenol. To our surprise less than 5% conversion was observed after 3 h as indicated by the ^{1}H NMR spectra (Figure S13). In a subsequent reaction we added 2 equiv of the sterically hindered base *N*,*N*-diisopropylethylamine (DIPEA) to deprotonate the thiol, thereby increasing its nucleophilicity. This change resulted in a quantitative conversion to the desired polythiophenol product, as determined by the shift of proton signals from 4.34 and 3.65 ppm to 4.08 and 3.09 ppm, respectively, the appearance of aromatic signals at ~7.1 ppm in ^{1}H NMR (Figure 3B and Figure S13), and the SEC trace also shifts to higher M_w (Figure 3A). Purification was conveniently achieved by precipitation in methanol. Comparison of the elemental analysis of the

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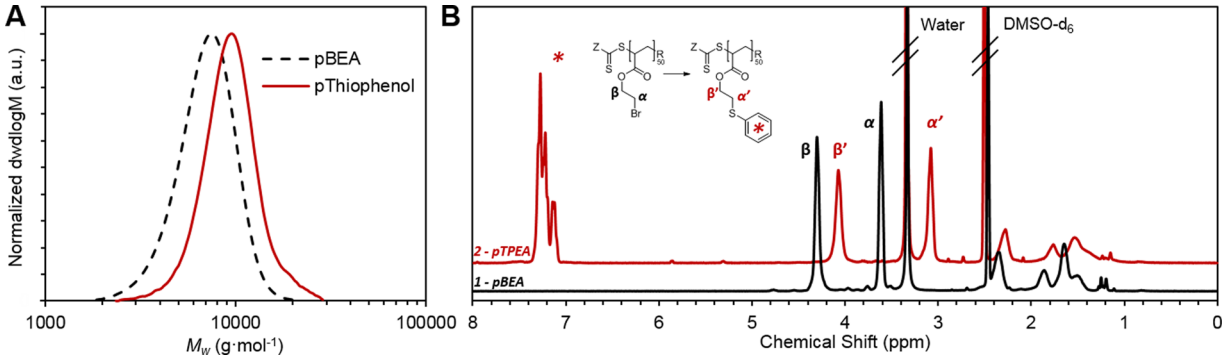

Figure 3. (A) SEC trace of precursor $pBEA_{50}$ (**1**), and postsubstitution $pTPEA_{50}$, showing the similarity in distribution. (B) ^{1}H NMR in DMSO-d_6 indicating the shifts of the pendant ethyl acrylate chain for protons α and β of $pBEA_{50}$ (**1**) and protons α' and β' of $pTPEA_{50}$.

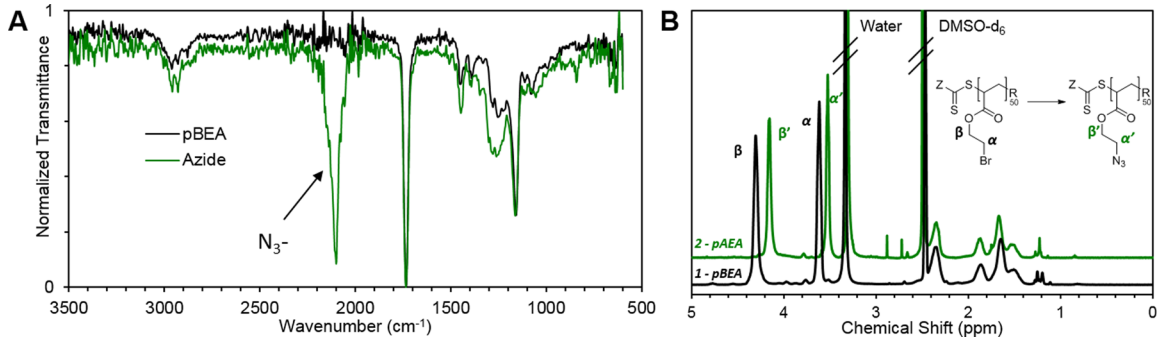

Figure 4. (A) IR overlay showing the absorbance of the $pBEA_{50}$ (**1**) vs $pAEA_{50}$. (B) ^{1}H NMR in DMSO-d_6 indicating the shifts of the pendant ethyl acrylate chain for protons α and β of $pBEA_{50}$ (**1**) and protons α' and β' of $pAEA_{50}$.

precursor pBEA with the polythiophenol product further demonstrates that the final product is pure and free from unreacted bromine sites. Remarkably, the ability to limit or promote reactivity by a change of pH offers the unique potential to combine this reaction with other thiol targeting conjugations such as the radical thiol−ene "click" and Micheal addition to an acceptor.

Another highly desirable functionality to introduce is the azide group, which provides a potent platform for further postmodification reactions.[6,53,54] The direct synthesis of polyazides requires polymerization of azido monomers at low temperatures,[55,56] and numerous steps involve handling the toxic and potentially explosive azido derivatives. In our case, 2 equiv of sodium azide was used, and the reaction proceeded smoothly at room temperature, yielding full conversion after 16 h, with the excess sodium azide conveniently removed by precipitation in a brine/water mixture. Conversion was readily observed by the shift in the ^{1}H NMR (Figure 4B), 4.34 and 3.65 ppm to 4.17 and 3.54 ppm in DMSO-d_6, and the appearance of a strong signal at 2200 cm^{-1} in the IR spectrum (Figure 4A) that corresponds to the $-N_3$ stretch frequency. This postmodification strategy for the synthesis of polyazides circumvents the use of highly reactive azido monomers, yet still readily provides the desired polymer.

Another example where direct synthesis by controlled radical polymerization is very demanding includes preparation of polyelectrolytes.[57] The usual method of synthesis requires either protection of the ionic group or use of water as the polymerization medium, rendering it incompatible with hydrophobic comonomers. The use of BEA as a precursor enables the synthesis of random and block copolymers in a hydrophobic environment before subsequent modification to give the polyelectrolyte.[58,59] Cationic polyelectrolytes were prepared via quarternization with trimethylamine or trimethylphosphine. Tertiary amines are known to be strong nucleophiles; however, sterically demanding groups encumber reaction on the amine as in the case of the sterically hindered DIPEA. Strong nucleophiles are also able to cleave trithiocarbonates, resulting in a free thiol at the terminus of polymer chains, as in the case of aminolysis.[60] However, generally this requires a substantial excess of nucleophile to cleave all chain ends, and the nucleophile is likely to react preferentially with the alkyl halide than with the trithiocarbonate. For the less hindered trimethylamine, the reaction proceeded rapidly to yield quantitative conversion of the bromine group (Figure S6) and a highly charged polyelectrolyte is obtained. We then proceeded to synthesize the structurally and nucleophilically similar reaction of trimethylphosphine with the bromine precursor. This reaction was carried out under identical conditions to that of trimethylamine and provided a particularly hygroscopic, polycationic polymer species (Figure S8).

As previously mentioned, this postmodification route facilitates preparation of well-defined ionic copolymers starting from hydrophobic monomers. To demonstrate the versatility of this method, we tested the substitution reaction on the previously described block copolymers pBA-*b*-pBEA using trimethylamine. Similar to the corresponding homopolymers, the reaction proceeds smoothly. The obtained pTMABEA-*b*-pBA block copolymer enables the formation of micellar structures due to the opposing polarity of polyelectrolyte and pBA blocks. Dispersing the copolymer in water gives a highly turbid solution, which was analyzed using DLS and zeta potential. The results confirm the formation of uniform

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micelles with a positive surface charge (see Table 5 in Supporting Information and Figure S10 for details).

In contrast to cationic polymers, strong anionic polyelectrolytes such as polysulfonates are so far only accessible via the direct polymerization of the respective sulfonate monomers, which require either stringent reaction conditions or protecting group strategies. Surveying the literature on preparation of sulfonates, we discovered that sulfite salts are known to be excellent nucleophiles (the Strecker reaction), which have thus far been neglected for decades likely due to the limited solubility of these salts in organic solvent.[61,62] On the basis of a recent report,[26] we synthesized the tetraethylammonium salt starting from dimethyl sulfite, a salt that displays superior solubility in polar organic solvents such as methanol or DMSO. With this material in hand, we tested the substitution efficiency of the sulfite on our bromine polymer. Astonishingly, this reaction rapidly generates the desired sulfonate polymer in quantitative yield without any need for further optimization (Figure 5). The success of this reaction highlights the strong

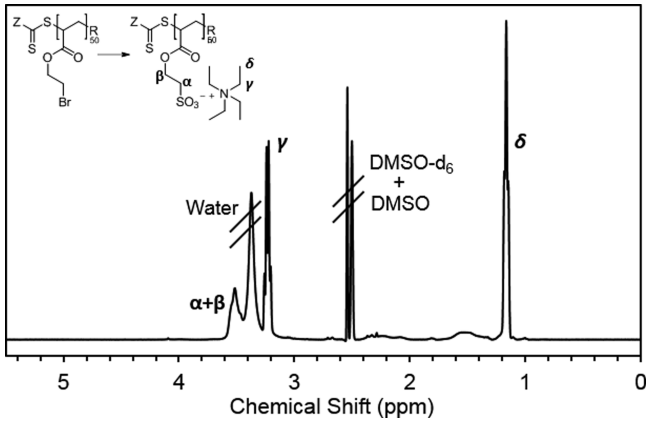

Figure 5. ^{1}H NMR in DMSO-d_6 of tetraethylammonium sulfonate polymer from pBEA$_{50}$ (**1**).

nucleophilic character of sulfites, and the preparation of alkylammonium salts drastically improves their solubility in organic media, which is crucial for such polymer analogous reactions.

Finally, we focused on more biological relevant polymers. Glycopolymers have recently attracted considerable attention due to their exclusive binding properties to surface proteins.[63] The direct polymerization of the respective glycomonomers still remains a challenge, and thus far the most common routes are via polymerization of protected sugar monomers[64] or postmodification such as using CuAAC or activate ester strategies.[14,22,65,66] Nevertheless, these attachments create additional linker groups such as triazoles that may impact on binding affinity.[67,68] The presented substitution of BEA does not create such expansive linkers. Given the success of the thio−bromo substitution using thiophenol, we used the commercially available thiolated sugar, β-thioglucose sodium salt. Anticipating that the thiolate anion would be sufficiently nucleophilic for the substitution, the reaction was conducted in the absence of any additional base. As confirmed by ^{1}H NMR (Figures S15 and S16), substitution was quantitative after 48 h, using only 1.5 molar excess of the sugar, at room temperature. The SEC trace (Figure S17) indicates there was some end-group removal of the RAFT agent that caused minor disulfide formation, resulting in a shoulder at high molecular weight. Any additional sugar starting material was then easily and rapidly separated from the obtained glycopolymer by centrifugal filtration. Considering the convenient synthesis of the precursor polymer by RAFT, the availability of various thiosacharides, and the efficiency of the substitution, this synthesis represents a cost-effective and scalable route toward accessible and well-defined glycopolymers. Furthermore, by proceeding without catalysts nor protecting groups, and under very mild conditions, this is a protocol that could be widely applicable due to the ease of characterization of the precursor, which with limited synthetic effort could rapidly generate a library of glycopolymers.

CONCLUSION

Our work demonstrates that nucleophilic substitutions of a halogen side group polymer, a reaction that has been widely disregarded in polymer science to date, enables access to highly reactive and yet well-defined homopolymers. These polymers can be synthesized without the need of stringent polymerization conditions nor at the cost of polymer yield. We have demonstrated a convenient and versatile synthesis of the alkylbromo polymer, pBEA, that can be readily synthesized under RAFT conditions. A series of pBEA polymers were synthesized with varied molecular weights (2.0−26.2 kg mol^{-1}) and narrow dispersities (PDI = 1.10−1.17). Chain extension of these macro-CTAs proved that the majority of the chain ends remain active, and no significant side reactions were observed despite the high reactivity of the bromine groups. We have shown the versatility of pBEA in nucleophilic substitutions for

Table 2. Summary of pBEA Substitutions and Structural Characteristics of Polymers and Derivatives

nucleophile	conv[a] (%)	DP	pBEA	$M_{n,th}$[b] pBEA	$M_{n,SEC}$[c] pBEA	$M_{n,th}$[b] substituted	$M_{n,SEC}$[c] substituted	M_w/M_n[c]
trimethylamine	>99	50	**1**	8000	6500	10600		
trimethylamine	>99	100	**2**	16500	15100	24200		
trimethylphosphine	88	50	**1**	8000	6500	11300		
TEA sulfite	>99	50	**1**	8000	6500	13600	6500	1.21
TEA sulfite	>99	150	**3**	26200	24600	45100	18200	1.34
sodium azide	>99	50	**1**	8000	6500	7200	6800	1.16
β-D-thioglucose	>99	50	**1**	8000	6500	15100	21400	1.16
thiophenol	>99	50	**1**	8000	6500	10800	9500	1.18
trimethylamine (block)	>99	50-*b*-70		22800	24600	21200		
trimethylphosphine (block)	>99	50-*b*-70		22800	24600	22100		

[a]Determined from ^{1}H NMR. [b]Calculated from the conversion and characteristics of the parent polymer. [c]From SEC analysis (DMF LiBr, pMMA-Std.).

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efficient production of a diverse library of functional polymers. Therefore, a variety of nucleophiles were examined including well-known nitrogen-based substituents such as azides or tertiary amines, but also the unreported sulfites and sugars were tested. Across all these nucleophilic species the substitution of pBEA proceeded with almost quantitative conversion (>88%). A major advantage of this simple substitution are the mild conditions employed, i.e., room temperature and no need for additional catalysts.

In combination with the good control provided by RAFT, this strategy enables us to synthesize well-defined, highly charged polycations, permanently charged polyanions, stable polythiol ethers, a highly reactive polyazide, and even synthetically demanding glycopolymers with minimal synthetic effort. In particular, the substitution using thiols is not limited to the demonstrated materials but can certainly be extended to encompass other available thiolates. Considering the potential to create libraries of various materials with minimal effort and originating from a single precursor polymer, the presented synthesis route represents a unique and versatile tool for material science.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.6b00721.

Experimental information; ^{1}H NMR spectra and GPC traces of polymers not depicted in the article (PDF)

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Notes

The authors declare no competing financial interest.

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