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Aminolysis induced functionalization of (RAFT) polymer-dithioesters with thiols and disulfides

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A series of polystyrene- and poly(methyl methacrylate)-dithioesters was subjected to aminolysis under ambient atmospheric conditions, *i.e.*, in the presence of oxygen. Polymer disulfide coupling by oxidation occurred within tens of minutes and the yield of disulfide-coupled polymer increased with decreasing polymer molar mass. Oxidation of thiolates is usually an unwanted side reaction, here it is employed to obtain exclusively polymeric mixed disulfides through *in situ* aminolysis/functionalization in the presence of a thiol. The *in situ* aminolysis/functionalization in the presence of a disulfide, Ellman's reagent or polymer disulfide, resulted in the exclusive formation of polymer-dithionitrobenzoic acid, which can be further reacted with a thiol to exchange the terminal functionality, or block copolymer with dynamic disulfide linker, respectively.

Introduction

Post-polymerization functionalization of polymer materials has been a major area of research in the past years,^{1, 2} as it allows to tailor the properties of polymers with considerable versatility. For example, the thermoresponsive behavior of polymers can be modulated,³ the polarity can be changed from hydrophobic to hydrophilic or vice versa^{4, 5} or the polymer architecture be transformed.⁶ A versatile way to modulate polymer functionality and properties is via dynamic covalent chemistry,⁷ which features covalent bond formation but allows for triggered bond cleavage. Dynamic covalent chemistry can be performed with several triggers, *e.g.*, redox, pH, or temperature. Some of the utilized functional groups include disulfides,⁸ hydrazones,⁹ hydrazides,⁹ imines,¹⁰ boronic esters,¹¹ dienes/enes in Diels-Alder reactions,^{12, 13} or alkoxyamines.⁹

Due to its versatility, dynamic covalent chemistry has had a profound influence on polymer science, as it can be used to generate recyclable polymers,¹⁴ to modulate polymer network properties¹⁵ or to transform polymer architecture.¹⁶ One of the major types of dynamic covalent chemistry is based on the redox driven reaction of thiols to disulfides and vice versa, which is frequently utilized for the purpose of crosslinking polymers in the solid or colloidal state.¹⁷⁻²⁰ For example, disulfide dynamic covalent chemistry was utilized in the formation of redox responsive polymer micelles,²¹ hydrogel capsules,²² or self-healing materials.²³ Recently, we described the formation of polymers with disulfide linkages along the backbone via disulfide metathesis reaction.²⁴⁻²⁶ As such, functional and degradable linear polymers could be generated based on sustainable resources.

reversible deactivation radical polymerization techniques, the RAFT group has been used to produce block copolymers.³¹ Furthermore, RAFT-derived end groups can be transformed into thiols easily via aminolysis enabling various types of functionalization reactions,^{32, 33} *e.g.*, thiol-ene reactions³⁴ or Michael additions.³⁵ Albeit thiol-ene reactions were very effective for small molecules, quantitative polymer-polymer conjugations were difficult to achieve.³⁶

A convenient avenue to dynamic covalent chemistry via end group modification is the formation of disulfides from RAFT originated thiols. Therefore, several approaches to convert RAFT-derived polymer end groups into disulfides have been introduced in the past. The straightforward way is to perform aminolysis of the RAFT end group forming a thiol and subsequent oxidation to the disulfide, which has been exploited for the formation of disulfide linked cyclic polymers.³⁷ In another example, linear polymers were formed in a step growth fashion from α,ω -homotelechelic polymers with thiol end groups.^{38, 39} Theato and coworkers utilized thiosulfonates in order to couple specific groups to RAFT polymers after aminolysis via direct disulfide linkage.⁴⁰ The reaction can also be employed without making use of RAFT end groups, *e.g.*, in hydrogel functionalization⁴¹ and for the conversion of atom transfer radical polymerization-derived chain ends.⁴² Aminolysis of RAFT polymers is based on a multistep mechanism and is frequently used,⁴³ but it suffers from side reactions such as transformation of terminal thiols into thiolactones for poly(methyl methacrylate) (PMMA)⁴⁴ or formation of disulfides in the presence of oxygen.

A common approach to introduce disulfide chain ends is the direct reaction of RAFT chain ends with 2,2'-dithiodipyridine after aminolysis, which was pioneered by Davis and coworkers.⁴⁵ The pyridyl disulfide (PDS) chain end constitutes a versatile functional group that is reactive towards thiols and facilitates further functionalization on demand, *e.g.*, with siRNA,⁴⁶ peptides^{47, 48} or dyes.⁴⁸ Another route was investigated by Du Prez and coworkers, who utilized thiolactone chemistry to form cyclic polymers with disulfide linkage.⁴⁹ An intriguing direction is the formation of disulfide linked block copolymers that endow the polymers with the option of stimuli-induced cleavage.^{50, 51} A disulfide-linked block copolymer based on RAFT/aminolysis chemistry was described by Bulmus and Davis, who used PDS chemistry to produce poly(*N*-isopropylacrylamide)-*block*-poly(ethylene glycol) (PNIPAM-*b*-PEG).⁵² Certainly, the formation of block copolymers with dynamic covalent disulfide linkage is a versatile route to form tunable materials and nano- or micro structures.⁵³ As such, in drug-delivery, nanoreactors or emulsion stabilization applications, the critical parameters like permeability can be tailored via external redox stimuli.⁵⁴

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† Electronic Supplementary Information (ESI) available: List of chemicals, experimental procedures for the synthesis of CPADB, polymer disulfides (PEG-S-S-PEG, PLLA-S-S-PLLA, and PBDG-S-S-PBDG), and block copolymers (PS-S-S-PEG, PS-S-S-PLLA, and PS-S-S-PBDG) and additional ¹H NMR and SEC data. See DOI: 10.1039/x0xx00000x

Especially, reversible addition-fragmentation chain transfer (RAFT) chemistry introduces a handle to modification of polymer materials on demand as recently shown by the synthesis of hydrogels capable of growth in consecutive polymerization steps.^{27, 28} The reactivity of the RAFT end group can be utilized for end group modifications of polymers, for example, for single unit monomer insertions²⁹ or removal of the reactive end group.³⁰ As with other

Herein, we synthesized a series of polystyrene (PS)- and PMMA-dithioesters with different molar masses by RAFT polymerization and investigated the aminolysis reaction under ambient air conditions with the presence of oxygen. Oxidation of thiolates is usually an undesired process during the aminolysis of polymer-dithioesters leading to contamination with disulfide-coupled polymer. However, as will be demonstrated, the combination of aminolysis and oxidation of low molar mass thiols can afford polymers with mixed disulfide end groups without chain coupling. This reaction presents an avenue for the *in situ* aminolysis/functionalization of polymers in the presence of a disulfide, *e.g.*, Ellman's reagent or polymer disulfide, which is more convenient than previous procedures and well suited to generate a platform of functional polymers.

Experimental

Chemicals and materials. A list with all used chemicals and protocols for the synthesis of dithiobis[poly(ethylene glycol)] (PEG-S-S-PEG) (M_n^{app} 1.3 kg mol⁻¹, $\bar{D}$ 1.12), dithiobis[poly(L-lactide)] (PLLA-S-S-PLLA) (M_n^{app} 4.0 kg mol⁻¹, $\bar{D}$ 1.12), and dithiobis[poly(γ -benzyl-D-glutamate)] (PBDG-S-S-PBDG) (M_n^{app} 5.4 kg mol⁻¹, $\bar{D}$ 1.20) are provided in the ESI[†].

RAFT polymerization. All RAFT polymerizations were performed in anisole solution at 90 °C for 3 h in 8 mL vials equipped with a septum under nitrogen atmosphere. Polymerizations were initiated by 2,2'-azobisisobutyronitrile (AIBN) in the presence of 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (CPADB) (synthesis described in the ESI[†]) as the chain transfer agent (CTA), [AIBN]₀/[CPADB]₀ = 1:5. After quenching, by cooling the reaction mixtures in an ice bath, the polymers were precipitated into methanol, re-dissolved in dichloromethane (DCM) and precipitated again in methanol (three times).

Aminolysis of polymer-dithioester. To a solution of polymer-dithioester (100 mg) in tetrahydrofuran (THF) (1 mL) was added a 1:1 molar mixture of hexylamine/triethylamine (TEA) (4 equiv with respect to dithioester groups) via a syringe (note: the reaction mixture was not subjected to degassing). The mixture was stirred at room temperature and aliquots were taken out of the vial at predetermined periods of time. Samples were precipitated into methanol, dried under vacuum, and analyzed by SEC.

Reaction of partially disulfide-coupled polymer with disulfide/thiol.

(a) To a solution of partially (18 wt%, by SEC) disulfide-coupled PS (100 mg) in THF (1 mL) were added Ellman's reagent (10 equiv) and TEA (5 equiv) via a syringe (note: the reaction mixture was not subjected to degassing). The mixture was stirred at room temperature for 30 min and then precipitated into methanol. The solid was isolated, dried in vacuum and analyzed by SEC. (b) To a solution of partially (18 wt%, by SEC) disulfide-coupled PS (100 mg) in THF (1 mL) were added methyl thioglycolate (10 equiv) and TEA (5 equiv) via a syringe. The mixture was stirred at room temperature for 30 min and then Ellman's reagent (10 equiv) was added. After another 30 min, the mixture was precipitated into methanol. The solid was isolated, dried in vacuum and analyzed by SEC and FT-IR spectroscopy.

***In situ* aminolysis/functionalization of polymer-dithioester with thiol.** A mixture of polymer-dithioester (PS-3') (100 mg), 2-mercaptoethanol (20 equiv), and TEA (216 equiv) in THF (1 mL) was stirred for 10 min at room temperature and then hexylamine (7 equiv) was added via a syringe (note: the reaction mixture was not subjected to degassing). The mixture was stirred for 2 h and then precipitated into methanol. The solid was isolated, re-dissolved in THF (1 mL), and then Ellman's reagent (10 equiv) and TEA (5 equiv)

were added. After another 30 min, the mixture was precipitated into methanol. The solid was isolated, dried in vacuum and analyzed by SEC and ¹H NMR spectroscopy.

***In situ* aminolysis/functionalization of polymer-dithioester with disulfide.** To a solution of polymer-dithioester (PS-3' or PMMA-1') (100 mg) and Ellman's reagent (3 equiv) in THF (2 mL) was added a 1:1 molar mixture of hexylamine/TEA (4 equiv) via a syringe. The mixture was stirred for 2 h at room temperature and then precipitated into methanol. The solid was isolated, dried under vacuum, and analyzed by SEC.

Exchange of polymer-dithionitrobenzoic acid end groups with thiol.

A mixture of polymer-dithionitrobenzoic acid (100 mg), methyl thioglycolate (5 equiv), and TEA (7 equiv) in THF (1 mL) was stirred for 2 h at room temperature and then precipitated into methanol. The solid was isolated, dried in vacuum, and analyzed by SEC.

Synthesis of block copolymers by *in situ* aminolysis/functionalization of polymer-dithioester with polymer disulfide. Exemplary procedure: To a solution of PS-dithioester (PS-2) (100 mg, 0.024 mmol) and PEG-S-S-PEG (100 mg, 0.08 mmol, 3.3 equiv) in THF (2 mL) was added a 1:1 mixture of hexylamine/TEA (0.045 mL). The mixture was stirred for 30 min at room temperature and then precipitated into methanol. The solid was isolated, dried in vacuum and analyzed by SEC and ¹H NMR spectroscopy.

Analytical instrumentation. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance 300 MHz or Avance Neo 400 MHz spectrometers; samples were prepared in CDCl₃, and signals were referenced to the solvent peak at δ 7.26 ppm. UV-visible spectra were recorded with a Perkin Elmer Lambda 2 UV/VIS Spectrometer; samples (~1.4 mmol L⁻¹) were prepared in THF. Fourier-transform infrared (FT-IR) spectra were recorded on a Bruker Vertex 70 fitted with a PLATINUM ATR; samples were placed directly on the ATR diamond. Size exclusion chromatography (SEC) with simultaneous UV and RI detection was performed with THF as the eluent (flow rate: 0.5 mL·min⁻¹) at room temperature. The stationary phase used was a 300 x 8 mm² PSS SDV linear M column (3 μ m particle size, molar mass range 10²–10⁶ Da). Solutions containing ~0.15 wt% polymer were filtered through 0.45 μ m filters; the injected volume was 100 μ L. Polystyrene or poly(methyl methacrylate) standards (PSS, Mainz, Germany) were used for calibration. Alternatively, *N*-methyl-2-pyrrolidone (NMP) + 0.5 wt% LiBr was used as the eluent (flow rate: 0.5 mL·min⁻¹) and a 300 x 8 mm² PSS-GRAM analytical linear column (particle size 7 μ m, separation range 10²–10⁶ Da) as the stationary phase.

Results and discussion

In order to study the aminolysis and end group transformation to disulfides, a series of polystyrene (PS, five samples, M_n = 1.9–8.8 kg mol⁻¹) and poly(methyl methacrylate) (PMMA, four samples, M_n = 8.8–21.8 kg mol⁻¹) samples were prepared by reversible addition-fragmentation chain-transfer (RAFT) polymerization of the respective vinyl monomers using 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (CPADB) as the chain transfer agent and 2,2'-azobisisobutyronitrile (AIBN) as the radical source (see Figure 1). All isolated polymer samples exhibited a pink color, due to the presence of the dithiobenzoate group at the ω -terminus of chains, which was also recognized by UV-visible spectroscopy (λ_{max} $\approx$ 500 nm) and ¹H NMR spectroscopy (δ 7.85 2H, -SC(S)-C₆H₅) (data not shown). According to SEC analysis, all samples had a narrow molar mass distribution and contained just marginal amounts (< 5 wt%) of C-C coupled chains (Figure 1).

Figure 1. (Top) Synthesis of polystyrene (PS) and poly(methyl methacrylate) (PMMA) by RAFT polymerization. Number-average molar masses (M_n) and dispersity indexes ($\bar{D}$) of the PS and PMMA samples were determined by SEC using PS or PMMA calibration, respectively. (Bottom) SEC traces of PS and PMMA samples prepared by RAFT polymerization.

The polymers were subjected to aminolysis, by treatment with *n*-hexylamine/triethylamine (1:1) in DMF solution at room temperature, to transform the dithioester end group into a thiolate (Scheme 1). However, under ambient atmospheric conditions, the thiolate groups can afterwards oxidize to disulfides, which results in the formation of disulfide-linked polymer chains with double molar mass. The aminolysis was usually completed within less than a minute, as evidenced by the discoloration of the polymer and by UV-vis spectroscopy (data not shown). The subsequent oxidation of thiolate groups to disulfides was monitored by SEC analysis of the polymers at different reaction times (Figure 2, top). For PS samples, the amount of disulfide-coupled polymer chains seemed to reach a steady state depending on the molar mass of the thiol-terminated polymer. The amount of disulfide-coupled chains decreased with increasing molar mass of the polymer (Figure 2, bottom), which also holds for the rate of thiol oxidation. Aminolysis/oxidation of PS-1 ($M_n = 1.9$ kg mol⁻¹) gave exclusively disulfide-coupled chains already within 10 min (note: the absence of even trace amounts of thiols was also confirmed by the reaction of PS-1 with Ellman's reagent), whereas PS-4 ($M_n = 8.8$ kg mol⁻¹) produced no more than 36 wt% disulfide-coupled chains even after 24 h. For PMMA, the amount of disulfide-coupled chains reached a maximum of ~20 wt% and decreased slightly with increasing reaction time, due to the concurrent conversion of terminal thiols into thiolactones,⁴⁴ thus shifting the thiol-disulfide equilibrium to the left.

Scheme 1. Aminolysis of dithioester-terminated polymer chains and subsequent oxidation of thiols to disulfides (under basic conditions).

Figure 2. (Top) Exemplary SEC-RI traces of polymers produced during the aminolysis of the dithioester end groups at different reaction times. The appearance of the peak at lower elution volume is due to disulfide-coupled polymer chains from oxidation of thiolate end groups. (Bottom) Time-dependent evolution of the weight fraction of disulfide-coupled polymer chains in the polystyrene (PS) and poly(methyl methacrylate) (PMMA) samples during aminolysis.

The (partially) disulfide-coupled polymer samples can be further reacted with either thiols or disulfides under basic conditions (Scheme 2). The reaction with a thiol, or rather a thiolate, affords the desired cleavage of disulfide-coupled polymer chains, however the produced polymer fragments may carry different – either mixed disulfide or thiolate – end groups. If, however, thiolates were oxidized to disulfides under ambient atmospheric conditions, the reaction might result in the exclusive formation of cleaved polymer chains with mixed disulfide end groups.

Scheme 2. Possible reactions of disulfide-coupled polymer chains with thiols (R-SH) or disulfides (R-S-S-R) (R = alkyl or aryl) under basic conditions and ambient atmosphere.

Exemplarily, we used a PS sample containing 82 wt% of thiol-terminated chains and 18 wt% of disulfide-coupled chains (see the SEC trace in Figure 3, top), which was obtained by the aminolysis of PS-3' after a reaction time of 20 min. The sample was first reacted with Ellman's reagent (5,5'-dithiobis(2-nitrobenzoic acid)) (10 equiv) in the presence of triethylamine (5 equiv). Subsequent SEC analysis with UV tracing at $\lambda = 365$ nm (which is a characteristic absorption wavelength of the dithionitrobenzoic acid group) indicated that the low molar mass polymer-thiol fraction was labelled by the reaction with Ellman's reagent, as expected, but not the disulfide-coupled chains (Figure 3, left). Remarkably, the sample still contained virtually the same amount of disulfide-coupled chains, suggesting that under the given reaction conditions the intermediately formed (red-colored) 3-carboxylato-4-nitro-thiophenolate was not able to cleave the polymer disulfides. (Note: Ellman's reagent is otherwise known to react quantitatively with either thiol or disulfide groups in proteins in aqueous basic media).⁵⁵ Cleavage of the polymer-disulfides did not occur even in the presence of a very large excess of TEA (>200 equiv).

Figure 3. Post-treatment of partially disulfide-coupled PS, as obtained by the aminolysis of PS-3', with either Ellman's reagent or methyl thioglycolate (MTG, R = methyl glycolate) (10-fold excess with respect to polymer disulfide and thiol groups) in the presence of TEA (5 equiv). SEC analysis of the product revealed that the amount of disulfide-coupled PS chains decreased from 18 wt% to 8 wt% (Figure 3, right A), hence cleavage of the polymer disulfides by MTG took place but however was not complete. The low molar mass polymer fraction contained polymer-thiol chains, ~50% as estimated from the RI/UV absorption at $\lambda = 365$ nm in the SEC trace after the reaction with Ellman's reagent, as well as PS-S-S-R mixed disulfides, as recognized by an ester carbonyl band at 1740 cm^{-1} in the FT-IR spectrum (a thiol band at $\sim 2600\text{ cm}^{-1}$ was not observed). Apparently, the mixed disulfide was formed but the amount of the disulfide produced by oxidation of MTG was not sufficient to endcap all

Following the reaction pathway described in Scheme 2, the PS sample containing thiol/disulfide chains was treated with methyl thioglycolate (MTG, R = methyl glycolate) (10-fold excess with respect to polymer disulfide and thiol groups) in the presence of TEA (5 equiv). SEC analysis of the product revealed that the amount of disulfide-coupled PS chains decreased from 18 wt% to 8 wt% (Figure 3, right A), hence cleavage of the polymer disulfides by MTG took place but however was not complete. The low molar mass polymer fraction contained polymer-thiol chains, ~50% as estimated from the RI/UV absorption at $\lambda = 365$ nm in the SEC trace after the reaction with Ellman's reagent, as well as PS-S-S-R mixed disulfides, as recognized by an ester carbonyl band at 1740 cm^{-1} in the FT-IR spectrum (a thiol band at $\sim 2600\text{ cm}^{-1}$ was not observed). Apparently, the mixed disulfide was formed but the amount of the disulfide produced by oxidation of MTG was not sufficient to endcap all

polymer-thiol chains. We therefore repeated the experiment by using a larger excess of MTG (20 equiv) and TEA (216 equiv) aiming at increasing the amount of oxidizable thiolate species. SEC analysis (Figure 3, right B) indicated that the so obtained product contained merely no polymer-thiol chains (<5%) and slightly less amounts of disulfide-coupled chains (6 wt%). Disulfide-coupled polymer was however still present, possibly because the amount of MTG thiolate was too low (due to a too fast oxidation to disulfide) and/or polymer-thiolate chains underwent oxidative coupling (see above).

Encouraged by these results, we attempted the *in situ* aminolysis of sample PS-3' in the presence of 2-mercaptoethanol (ME) (R = ethanol). A mixture of the polymer, ME (20 equiv) and TEA (216 equiv) was stirred for 10 min at room temperature and then hexylamine (7 equiv) was added. After 2 h, the reaction was terminated by precipitation into methanol. The product was treated with Ellman's reagent/TEA for the selective labelling of any polymer-thiolate chains. SEC analysis (Figure 4) of the colorless product showed virtually no disulfide-coupled chains (<1 wt%) and no UV absorbance at $\lambda = 365$ nm, suggesting a quantitative transformation of the PS-dithioester into the mixed disulfide PS-S-S-CH₂CH₂OH. ¹H NMR analysis also confirmed the absence of the original dithioester ($\delta 7.85$ ppm, see above) and presence of mixed disulfide end groups ($\delta 3.95$ (t) and 2.92 (t), -SCH₂CH₂OH; compare to ME: $\delta 3.73$ (t) and 2.71 (m)) (Figure 4).

Figure 4. *In situ* aminolysis of PS-3' in the presence of 2-mercaptoethanol (ME) and subsequent reaction with Ellman's reagent; SEC trace (black: RI, red: UV absorption at $\lambda = 365$ nm) and ¹H NMR spectrum (400 MHz, CDCl₃) of the final product.

Although the *in situ* aminolysis of dithioester-terminated polymer chains and functionalization with a thiol is well possible, the direct use of a disulfide appears more convenient and efficient – as earlier described in the literature.^{52, 56, 57} By this procedure, the intermediately formed polymer-thiolates are immediately scavenged and transformed into mixed disulfides, thus avoiding the formation of disulfide-coupled chains and/or other side-products (like thiolactone-terminated chains as for PMMA).

We performed the *in situ* aminolysis/functionalization of samples PS-3' and PMMA-1' in the presence of Ellman's reagent. The dithioester-terminated polymer was mixed with Ellman's reagent (3 equiv) in THF solution and then hexylamine/TEA (1:1, 4 equiv with respect to dithioester end groups) was added; the mixture was stirred for 2 h at room temperature. SEC analyses of the colorless products revealed that the polymer chains were labelled with dithionitrobenzoic acid (as seen by the UV trace at $\lambda = 365$ nm) and that no disulfide chain-chain coupling occurred (Figure 5). The dithionitrobenzoic acid-terminated samples were further reacted with MTG (5 equiv) and TEA (7 equiv) to exchange the nitrobenzoic acid end group by a methyl ester. SEC-UV analysis confirmed the

quantitative exchange of end groups (no UV absorption at $\lambda = 365$ nm) while preserving the molar mass distribution of the sample (Figure 5). This exchange reaction should not be limited to just MTG but applicable to other thiols, hence this strategy could serve to generate a platform of well-defined functionalized polymers.

Figure 5. *In situ* aminolysis of PS-3' and PMMA-1' in the presence of Ellman's reagent and subsequent end group exchange with methyl thioglycolate (MTG); SEC traces (black: RI, red: UV absorption at $\lambda = 365$ nm) of the products.

The *in situ* aminolysis/functionalization of PS-dithioester (PS-2 or PS-3') was also performed with a series of three polymer disulfides, *i.e.*, dithiobis[poly(ethylene glycol)] (PEG-S-S-PEG) (M_n^{app} 1.3 kg mol⁻¹, $\bar{D}$ 1.12), dithiobis[poly(L-lactide)] (PLLA-S-S-PLLA) (M_n^{app} 4.0 kg mol⁻¹, $\bar{D}$ 1.12), and dithiobis[poly(γ -benzyl-D-glutamate)] (PBDG-S-S-PBDG) (M_n^{app} 5.4 kg mol⁻¹, $\bar{D}$ 1.20) (see the chemical structures and SEC traces in Figure 6). The polymer disulfides were used in excess (3.3–7.3 equiv) with respect to dithioester end groups to ensure a quantitative functionalization of the PS chains. All by-products (*N*-hexyl benzamide and polymer-thiol) and unreacted polymer disulfides could be removed from the crude polymer samples by precipitation to yield pure block copolymers PS-S-S-PEG (M_n^{app} 6.4 kg mol⁻¹, $\bar{D}$ 1.07), PS-S-S-PLLA (M_n^{app} 7.4 kg mol⁻¹, $\bar{D}$ 1.09), and PS-S-S-PBDG (M_n^{app} 7.7 kg mol⁻¹, $\bar{D}$ 1.19), respectively, as revealed by SEC (Figure 6) (¹H NMR spectra of the block copolymers are shown in the ESI†). Notably, all three block copolymer samples exhibit monomodal and narrow molar mass distributions with $\bar{D} < 1.2$. Hence, this strategy can be applied to produce block copolymers, which are – due to the dynamic disulfide linker between the block segments – potentially responsive or degradable in a reductive environment.

Figure 6. *In situ* aminolysis of PS-2 or PS-3' in the presence of polymer disulfides PEG-S-S-PEG, PLLA-S-S-PLLA, and PBDG-S-S-PBDG; SEC-RI traces of PS-dithioester (black), polymer disulfides (red) and block copolymers PS-S-S-PEG, PS-S-S-PLLA, and PS-S-S-PBDG (blue) (top to bottom).

Conclusions

The aminolysis of a series of PS- and PMMA-dithioesters under ambient atmospheric conditions was investigated. Polymer disulfide coupling occurred within tens of minutes and the amount of disulfide-coupled chains decreased with increasing molar mass of the polymer. Disulfide coupling was quantitative within 10 min for a PS with molar mass of 1.9 kg mol⁻¹. The aminolysis of the PMMA-dithioesters was further complicated by the occurrence of side reactions (thiolactone formation).

A partially disulfide-coupled PS sample was treated with a thiol (methyl thioglycolate, MTG) or a disulfide (Ellman's reagent) under ambient basic conditions. Ellman's reagent reacted selectively with the PS-thiol chains, as expected, but disulfide-coupled chains remained untouched. Reaction with MTG produced less amounts of disulfide-coupled chains and a mixture of PS-thiol and mixed disulfide chains. Mixed disulfide chains are produced when MTG cleaves disulfide-coupled chains or PS-thiolate reacts with disulfide, which is *in situ* formed by the oxidation of MTG (see Scheme 2). An increasing amount of base (TEA), and with it the amount of oxidizable MTG thiolate, further promoted the formation of mixed disulfide chains. The *in situ* aminolysis/oxidation of PS-dithioester in the presence of 2-mercaptoethanol resulted in the exclusive formation of mixed disulfide chains and no disulfide-coupled chains.

The *in situ* aminolysis/functionalization of polymer-dithioester with Ellman's reagent resulted in the exclusive formation of polymer-dithionitrobenzoic acid. The dithionitrobenzoic acid end group can be quantitatively exchanged by the treatment with a thiol – this reaction can therefore serve as a platform for the synthesis of well-defined end-functionalized polymers. Finally, *in situ* aminolysis/functionalization with polymer disulfides was used to prepare block copolymers with a dynamic disulfide linker.

Future work will be devoted to the use of *in situ* aminolysis/functionalization for the synthesis of reductively cleavable amphiphilic block copolymers and production of

responsive polymer aggregates or particles for drug delivery purposes.

Conflicts of interest

There are no conflicts to declare.

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