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Fast Track Access to Multi-Block Copolymers *via* Thiol-Bromo Click Reaction of Telechelic Dibromo Polymers

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Abstract

Multi-block copolymers offer a plethora of exciting properties, easily tuned by modulating parameters such as monomer composition, block length, block number and dispersity. Here, we demonstrate, a highly efficient one-pot synthesis of such materials by combining copper-mediated reversible-deactivation radical polymerisation (Cu-RDRP) with thiol-bromo post-polymerisation modification. Specifically, the use of bifunctional bromo initiators and bithiol compounds furnishes hydrophilic, hydrophobic and amphiphilic architectures in less than 10 minutes *via* a step growth-type mechanism. Furthermore, the degradation characteristics of the obtained polymers are demonstrated in oxidative, methylating and high temperature environments. The rate of degradation and nature of end-group is shown to vary with choice of bithiol linker and other reaction conditions.

Introduction

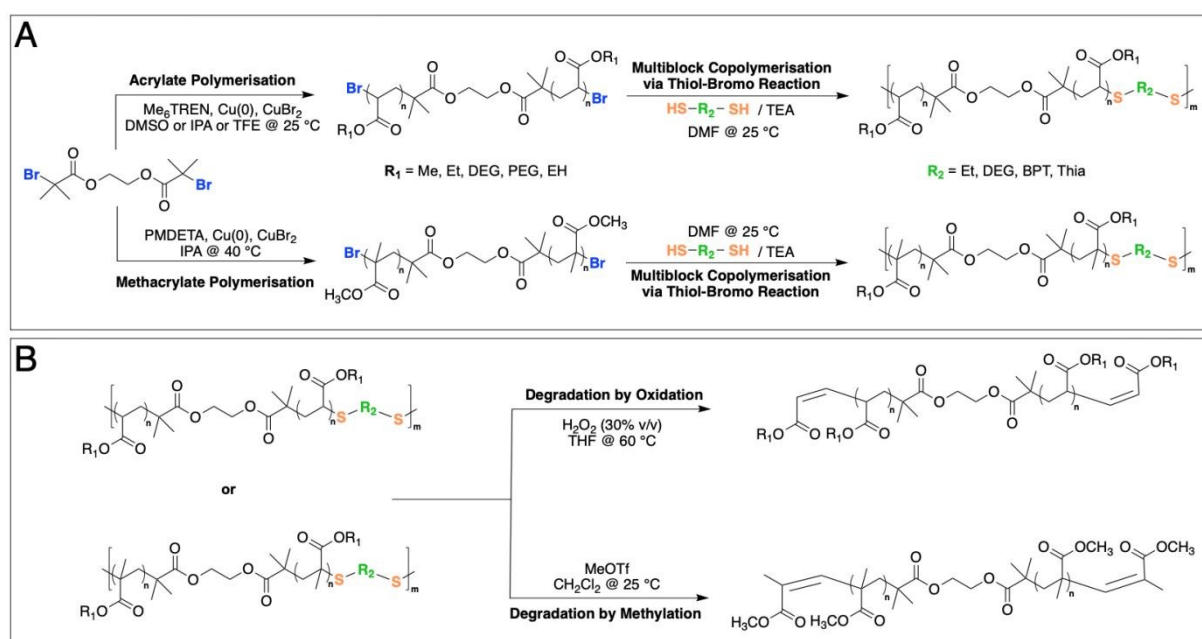
Simple, high throughput synthetic strategies towards multi-block copolymers are of increasing interest given their application in a range of industrial fields such as nano-scale domain geometry, microphase separation, and to enable blending of otherwise immiscible polymers.¹ Multi-block copolymers offer a plethora of exciting properties, easily tuned by modulating parameters such as monomer composition, block length, block number and dispersity. They can be exploited to form self-assembled nanostructures and influence polymer-interfacial activity/phase separation.^{2,3} To prepare such structures, a synthetic technique which offers tight control over the polymerisation process is critical.

Progress in the field of reversible deactivation radical polymerisations such as nitroxide mediated polymerisation (NMP)⁴ and reversible addition-fragmentation chain-transfer (RAFT)^{5–10} polymerisation, has greatly expanded the scope of accessible polymeric materials in the last 20 years. With such methodologies, macromolecules of bespoke architectures comprising narrow molecular weight distributions (MWD), controlled molecular weights and high end-group fidelities can be accessed. The copper-mediated polymerisation systems of supplemental activator and reducing agent atom-transfer radical polymerisation (SARA ATRP)^{11–13} and single-electron transfer living radical polymerisation (SET-LRP)^{14–17} continue to gain increasing attention due to their growing compatibility with a variety of monomers. Although debate still surrounds the “true” mechanism of Cu(0)-RDRP, in practice the two models use the same components and comprise the same reactions, but with different contributions to the overall polymerisation.^{18–21}

Initially, Cu(0)-mediated LRP was carried out in highly polar solvents to achieve sufficient solubility of the catalytic copper-ligand system, decreasing the scope of monomers.²² In recent years, this scope has been expanded. For example, the polymerisation of 8-arm butyl acrylate or lauryl acrylate star polymers was shown to be feasible utilising methanol/toluene mixtures and isopropylalcohol (IPA) as solvents. The observed phase separation during the polymerisation of hydrophobic acrylates reduced star-star coupling and yielded lipophilic, well-defined high molecular weight star polymers.²³ Furthermore, the benefit of this synergistic effect was observed when the solvent mixtures were adjusted. The Cu(0)-RDRP of butyl acrylate was carried out successfully in alcohol/water mixtures²⁴, alcohol/non-polar solvent/water mixtures²⁵ and mixtures of cyclic and linear carbonates, cyclic ethers and dipolar aprotic solvents with water to yield well defined macromolecules at increased reaction rates.²⁶ As a result of the spatial separation of the catalytic system in the polar layer and the growing polymer chain in the organic layer, side reactions were minimised and reaction control was maximised. Since then, acetone/water²⁷ and fluorinated alcohol/water²⁸ mixtures have been shown to be excellent reaction media for the Cu(0)-RDRP of butyl acrylate. Additionally, the dramatic impact of the stirring

rate in biphasic systems was thoroughly investigated.²⁹ Furthermore, one-pot photo-induced Cu-mediated RDRP of hydrophilic, hydrophobic and fluorinated monomers was successfully demonstrated to access ABCDE multiblock copolymers in trifluoroethanol.³⁰ Importantly, the resulting near quantitative bromine chain-end fidelity can be harnessed to further modify the polymer chain ends. For instance, the reaction with acrylic acid sodium salt in a biphasic fashion to achieve further polymerisation has been shown previously.³¹ Most recently, the versatility of Cu-RDRP techniques was underpinned by ultra-low volume experiments, polymerisation without deoxygenation and the development of universal conditions for acrylates, methacrylates and styrene.^{32–34}

In 2009, Percec and co-workers used the rapid base-mediated thiol-bromo reaction to synthesise monodisperse dendrimers in an iterative fashion.³⁵ This approach was extended by harnessing the high bromine end-group fidelity of the polymer and applying a thiol-bromo click reaction to introduce an additional branching unit. This three-step “branch and grow” approach yielded well-defined dendritic macromolecules with up to four polymerisation cycles.³⁶ In a similar fashion, the chain end of RAFT polymers was easily reduced to a thiol functionality and reacted with bromine compounds or Michael systems to obtain step-growth multi-block copolymers or hyperbranched architectures depending on the chosen difunctional compound.^{37–39} However, all of these approaches required polymer end-group modification prior to the thiol-ene/thiol-bromo reaction. This resulted in a decrease of the crucial chain end-fidelity and provided difficulties in maintaining equimolarity of reacting groups that are the two key parameters when targeting efficient coupling.^{40,41}



Scheme 1. (A) Homopolymerisation of acrylates or methacrylates *via* Cu(0)-RDRP and subsequent multi-block copolymerisation *via* thiol-bromo reaction; (B) Degradation of multi-block copolymers *via* oxidation or methylation mechanisms.

Herein, we present a synthetic approach to combine the versatility of Cu(0)-mediated LRP with thiol-bromo click chemistry in a one-pot reaction sequence without any intermediate purification steps (**Scheme 1**). The wide range of applicable monomers and the accessibility of sequential addition allows the synthesis of periodic multi-block polymers linked by different dithiol compounds. Furthermore, the obtained step-growth polymers show tuneable decomposition behaviour upon oxidation, methylation and increased temperature.

Results and discussion

Synthesis of telechelic dibromo polymers *via* Cu(0)-mediated RDRP

Cu(0)-mediated RDRP was employed to produce telechelic polymers from a variety of polar and apolar monomers such as methyl acrylate (MA), ethyl acrylate (EA), 2-ethylhexyl acrylate (EHA), diethyleneglycol ethyl ether acrylate (DEGA) and oligoethylene glycol methyl ether acrylate (PEGA₄₈₀). In order to incorporate these monomers in a multi-block copolymer architecture, various solvents (dimethyl sulfoxide (DMSO), isopropanol (IPA) and trifluoroethanol (TFE)) were assessed in common Cu(0)-mediated RDRP conditions using Me₆TREN as a ligand and CuBr₂ as a deactivator. The bisfunctional initiator ethylene bis(2-bromoisobutyrate) (2f-BiB) was used in all polymerisations in this study. Relatively low dispersity (*D*) values and quantitative monomer conversions were obtained when employing the ratios of [monomer]/[2f-BiB]/[Me₆-TREN]/[CuBr₂] = DP/1/0.36/0.10 and ~7 cm of pre-activated copper wire. These ratios were used for all polymerisation experiments. In the initial polymerisation series, MA, EA and DEGA were successfully homopolymerised with different DPs in less than 5 h with dispersities less than 1.10 (**Table 1**). The molecular weight of homopolymers determined by SEC were found to be very close to the theoretical molecular weights indicating the livingness of the polymerisation system and high chain-end fidelity. However, in the case of DEGA₂₀ (**P3**) homopolymerisation, deconvolution of the SEC data showed 5% of coupled chains (**Figure 1c**). It should be noted that the use of a bisinitiator allows the coupled polymer chains to retain the di-bromo chain end functionality and hence could still participate in the thiol-bromo reaction.

Similarly, pseudo tetrablock copolymers were synthesised by sequential monomer addition. After full conversion, determined by ¹H NMR spectroscopic analysis of the first monomer, a degassed solution of the second monomer dissolved in the reaction solvent was added *via* a nitrogen-purged syringe. Block copolymers of PEGA and EHA (**P6**, **P9**) were obtained with good agreement between theoretical and experimental molecular weights and *D* ≤ 1.20 for PEGA mole ratios of between 9 % and

20 %. When DEGA was copolymerized with EHA (**P11**) at a ratio of DEGA/EHA=10:20, the second block (EHA) failed to reach full conversion (84%) due to a lack of solubility of the growing EHA block during the polymerization. Therefore, it is very critical to note that, due to solubility reasons, block copolymers were synthesised in DMSO by polymerising the polar segment (DEGA/PEGA) first, which is then followed by addition of the apolar segment (EHA).

Table 1: ¹H NMR spectroscopic- and SEC- analysis of telechelic polymers prepared via Cu(0)-RDRP.

Code	Monomers M1:M2	Type	DP M1:M2	Solv.	Time (h)	Conv. (%) M1:M2	$M_{n,theo}$ (Da)	$M_{n,SEC}$ (Da)	\bar{D}
P1	MA : -	Homo	10:-	DMSO	3	>98 : -	1200	1100	1.09
P2	EA : -	Homo	20:-	DMSO	5	>98 : -	2400	2200	1.10
P3	DEGA : -	Homo	20:-	DMSO	2	>98 : -	4000	3600	1.10
P4	EHA : -	Homo	10:-	IPA	3	>98 : -	2200	1800	1.05
P5	EHA : -	Homo	30:-	TFE	7	>98 : -	5900	3700	1.07
P6	PEGA:EHA	Block	10:40	DMSO	18	>98 : >98	12500	13100	1.11
P7	PEGA:EHA	Random	8:40	DMSO	15	>98 : >98	11300	8200	1.20
P8	PEGA:EHA	Random	4:40	DMSO	14	>98 : >98	9600	7300	1.14
P9	PEGA:EHA	Block	4:40	DMSO	30	>98 : >98	9600	10700	1.12
P10	DEGA:EHA	Block	20:40	DMSO	21	>98 : >98	11400	12600	1.30
P11	DEGA:EHA	Block	10:20	DMSO	23	>98 : 84	6000	6400	1.20

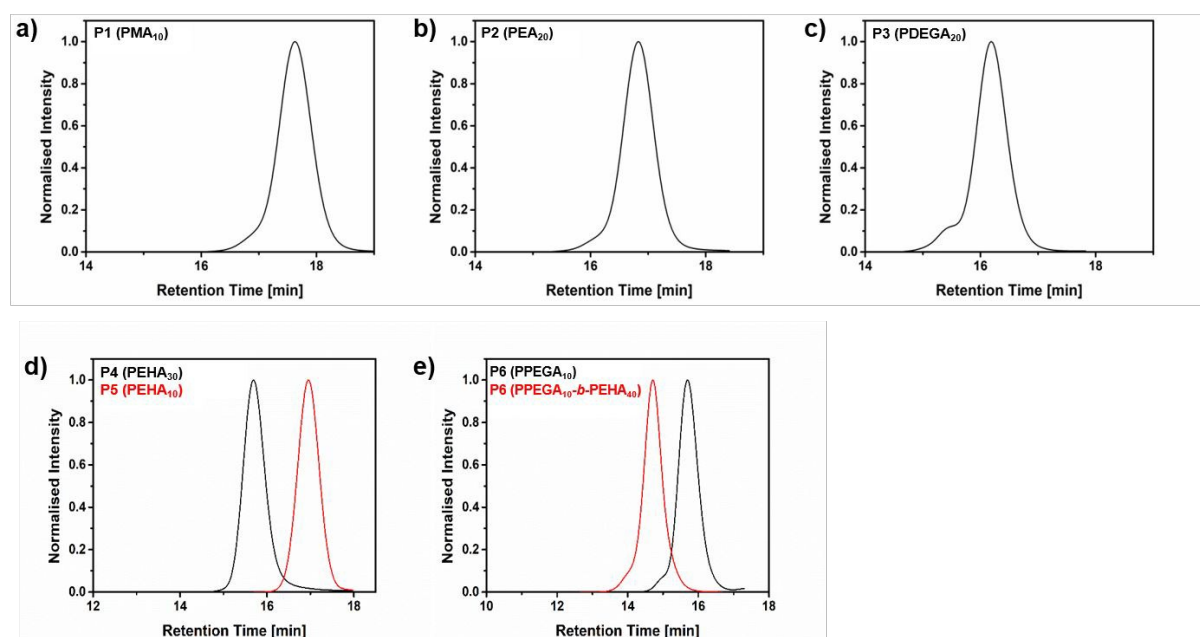


Figure 1. SEC traces of bis-initiated: a) MA10 (**P1**); b) EA20 (**P2**); c) DEGA20 (**P3**); d) EHA (**P4**-**P5**) homopolymers and e) block polymer of PEGA and EHA (**P6**).

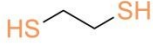
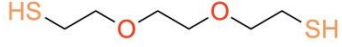
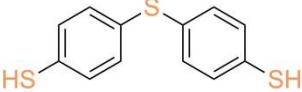
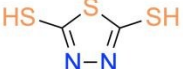
DMSO was used as the solvent of choice for Cu(0)-RDRP as it facilitates disproportionation of the catalytic copper system. However, due to the insolubility of a wide range of monomers in DMSO, we have also investigated the use of IPA and TFE for the polymerisation of more hydrophobic monomers.^{23,30,42} Thus, the highly apolar EHA was homopolymerised to full monomer conversion in IPA (**P4**) and TFE (**P5**) with excellent D values (~ 1.05 - 1.07). The experimental M_n differs from the theoretical M_n , which is likely to be due to the hydrophobicity of the polymer and differences from the calibration standards (PMMA). Finally, the obtained well defined telechelic polymers which are listed in **Table 1**, were further used as macromonomers in the subsequent thiol-bromo step-growth polymerisation.

Thiol-bromo click reaction of telechelic polymers

It is widely reported in the literature that the end-group fidelity of polymers obtained from copper-mediated living radical polymerisation is commonly determined by reacting the ω -end group (typically bromine) of the polymer chain with thiophenol in the presence of a base.⁴³⁻⁴⁷ By using a similar approach, a series of polymers (as listed in **Table 1**) were reacted with a range of bithiols (1:1 stoichiometric ratio between the bisinitiator and thiol compound) using dimethylformamide (DMF) and triethylamine (TEA) as a solvent and a base, respectively.

As shown in **Table 2**, inclusion of a bithiol results in a dramatic increase in the molecular weight due to thioether bond formation along the backbone of the multiblock copolymer (MBC). Furthermore, the rate of thiol-bromo step growth reaction is extremely high, reacting to completion in 10 minutes at room temperature. All synthesised MBCs in **Table 2** (except **MB7**) were prepared in a one-pot setup, thus removing the need for additional purification steps. In order to study the effect of catalyst used in the Cu(0)-RDRP, **MB7** was prepared from an isolated PDEGA20 homopolymer, which was purified by filtration over basic alumina to remove copper species and removal of the solvents under reduced pressure. The polymer was dissolved in DMSO and used for the subsequent thiol-bromo step growth reaction. The SEC result demonstrates that the polymers can be purified prior to thiol-bromo step-growth without impacting the step-growth process significantly. In short, the chain end fidelity of the polymer has proved to be stable during the purification step. It should be noted that, purification of the telechelic polymer (**MB7**) prior to bithiol addition is more likely to cause problems in terms of achieving the crucial equimolarity of thiol to bromine end groups. This could be a potential reason for the increased polydispersity obtained for **MB7**. Therefore, it is beneficial to conduct the reaction sequence in a one-pot fashion.

Table 2: Thiol-bromo step-growth polymerisation using homopolymers of MA, EA, DEGA, and EHA.

		Et-BT		DEG-BT		BPT-BT		Thia-BT	
									
Code	Homo-polymer	Solv	Thiol	$M_{n,SEC}$ (Da) Homo / (\bar{D})	Conv ^a (%)	$M_{n,theo}$ ^b MBC, (Da)	$M_{n,SEC}$ ^c (Da) MBC / (\bar{D})		
MB1	PMA ₁₀	DMSO	BPT-BT	1100 / (1.10)	86	7900	7200 / (1.86)		
MB2	PEA ₂₀	DMSO	BPT-BT	2200 / (1.10)	89	20000	15400 / (1.89)		
MB3	PEA ₂₀	DMSO	Thia-BT	1700 / (1.13)	91	18800	6800 / (3.13)		
MB4	PEA ₂₀	DMSO	DEG-BT	1900 / (1.11)	87	14600	4800 / (3.63)		
MB5	PEA ₂₀	DMSO	Et-BT	2300 / (1.09)	90	23000	17000 / (2.16)		
MB6	PDEGA ₂₀	DMSO	BPT-BT	3600 / (1.10)	88	30000	18300 / (1.87)		
MB7^d	PDEGA ₂₀	DMSO	BPT-BT	3400 / (1.10)	93	48600	37400 / (4.02)		
MB8	PEHA ₁₀	IPA	BPT-BT	1800 / (1.05)	93	25700	14400 / (1.72)		
MB9	PEHA ₁₀	IPA	Thia-BT	1900 / (1.05)	89	17300	15100 / (1.82)		
MB10	PEHA ₃₀	IPA	BPT-BT	5000 / (1.11)	87	38500	14400 / (1.80)		
MB11	PEHA ₃₀	TFE	BPT-BT	4000 / (1.07)	30	5700	6100 / (1.82)		
MB12^e	PMMA ₄₀	IPA	BPT-BT	3600 / (1.40)	n.d	n.d	13600 / (1.39)		

^a Conversion values are calculated by deconvolution of the homopolymer and MBC in SEC.

^b $M_{n,theo}$ MBC values were calculated using Carother's equation ($DP=1/(1-Conversion)$).

^c $M_{n,SEC}$ values were obtained using PMMA calibration standards in THF/TEA(2%) eluent.

^d **MB7** copolymer was prepared from a purified homopolymer, whereas all other MBCs are done in one-pot reaction.

^e **MB12** copolymer was prepared using polymerisation conditions of [MMA]:[2f-BiB]:[PMDETA]:[CuBr₂]=40:1:0.72:0.1 at 40 °C, all other experiments (**MB1-MB11**) were prepared using standard Cu(0)-RDRP conditions of [M]:[2f-BiB]:[Me₆TREN]:[CuBr₂]= [DP]:1:0.36:0.1 at 25 °C.

Successful incorporation of thioether linkages was confirmed by two methods (**Figure 2**, exemplifying **MB1**). Firstly, SEC analysis (**Figure 2a**) showed a significant increase in molecular weight (RI detection) post thiol-treatment and the presence of aromatic species on the polymer chain (UV detection at 308 nm). Secondly, ¹H NMR spectroscopy (**Figure 2b**) showed good agreement between the integrated resonances and the proposed thioether-linked MBC. Furthermore, MALDI-ToF analysis indicates the high chain-end fidelity showing only one major mass distribution, which corresponds to the dibromo terminated polymer **P1** (**Figure 2c**). The step growth nature of **MB1** is also demonstrated by MALDI-ToF MS (**Figure 2d**). The intensity of the signals does not fit to the actual molecular weight

distribution obtained by SEC, which was expected due to larger polymers being less likely to undergo sufficient ionisation. It should also be noted that the residual **P1** was removed by dialysis. One possible reason for the residual **P1** might be due to the formation of cyclic polymers, which cannot contribute the formation of MBCs as well as terminated chains. It is evident in the MALDI-ToF-MS spectrum of **MB1** (Figure S7) that there is a distribution at low molar mass region, which fits to the calculated molar mass of the cyclic **P1**. However, these structures would have a very similar molar mass to their linear counterparts without the bromine end group as well.

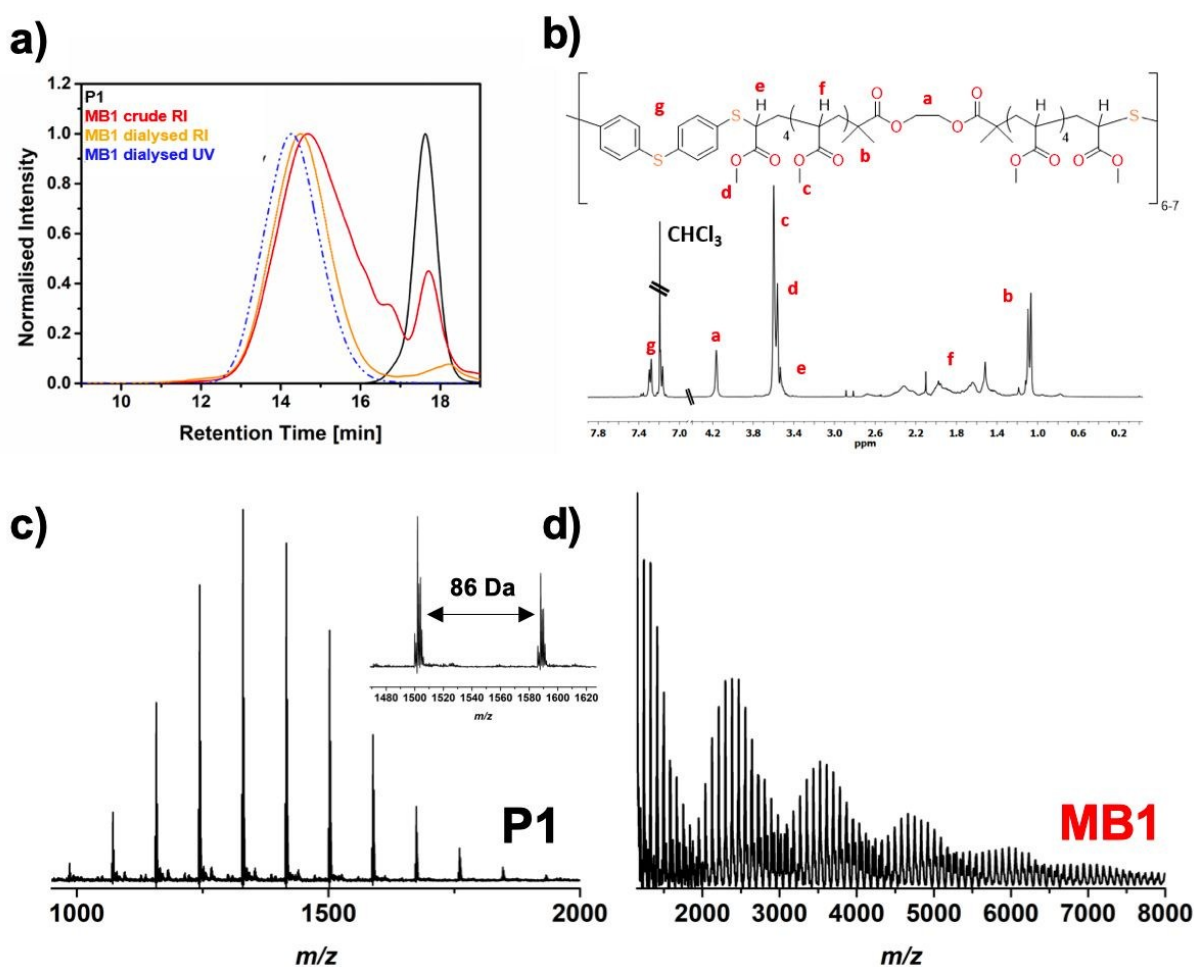


Figure 2: (a) SEC traces of PMA (DP=10) pre- (**P1**) and post- (**MB1** crude RI) BPT-BT thiol addition; **MB1** purified by dialysis (RI & UV detection (308 nm)); (b) assigned ^1H NMR spectrum after dialysis of the step-growth polymer; (c) MALDI-ToF MS spectrum of **P1**; (d) MALDI-ToF MS spectrum of thiol-bromo step-growth polymer **MB1**

To investigate the versatility of the thiol-bromo step-growth procedure, PEA (DP 20) was reacted with four different bithiols (Table 2, **MB2**-**MB5**). In all cases, based on the kinetics and the conversion values, similar step-growth efficiencies were observed highlighting the robustness of this process to a range of aliphatic, aromatic and heterocyclic compounds. This approach was also shown to be suitable when using the highly apolar EHA in IPA (solvent required for appropriate solubility during

polymerisation, *vide supra*) (**MB8-MB10**). To exemplify **MB10**, addition of the aromatic bithiol yielded a step growth polymer with close to 90% of coupled polymer chains and an increase in M_n from 5000 Da to 14400 Da (**Figure 3A**), providing a potential approach towards amphiphilic MBCs. Interestingly, when using TFE as solvent (known to be suitable for SET LRP of various monomers)³⁰, an adverse effect on the thiol-bromo coupling efficiency was observed, yielding only 30% of coupled chains (**MB11**, **Figure 3B**). This is hypothesised to be due to the increased acidity of TFE compared with IPA, which potentially interferes with the base-mediated thiol-bromo reaction.⁴⁸

Finally, the scope of this method was extended to methyl methacrylate containing polymers. Although methacrylates have traditionally been shown to offer limited compatibility with Cu(0) mediated polymerisation systems, headway has been made recently towards their applicability in Cu(0)-RDRP.⁴⁹ Methyl methacrylate (MMA) was polymerised according to literature conditions using 2f-BiB as initiator to yield PMMA (DP 40) with, $D = 1.40$ and $M_n = 3600$ Da. The subsequent thiol-bromo click reaction with the aromatic bithiol **BPT-BT** yielded **MB12** with a number average molecular weight of 13600 Da (**Figure 3C**), demonstrating the suitability of bisinitiated methacrylate polymers for thiol-bromo step growth. It should be noted that step growth reaction has proceeded similarly in the case of the methacrylate polymer and the possible reason for this might be due to the preferred mode of termination in methacrylate polymerisation. It is known that methacrylate type of monomers undergo a disproportionation reaction as a mode of termination and this would result in end groups as a vinyl instead of bromine. Owing to the high reactivity of thiols towards vinyl groups, the undesired termination reactions in Cu(0)-RDRP of MMA has actually no drawback for the subsequent step growth reaction.

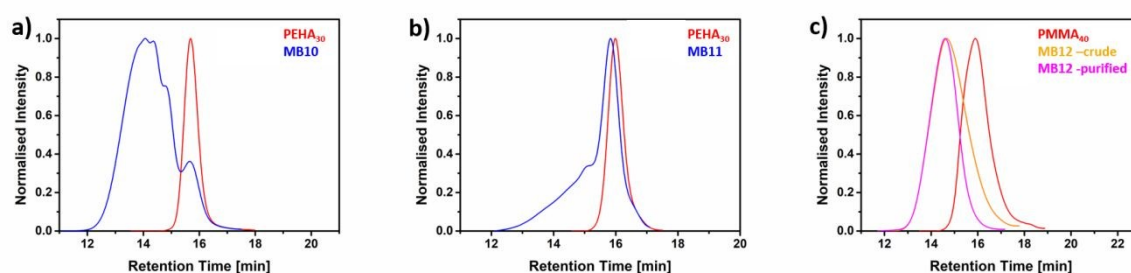


Figure 3: (a) SEC traces of EHA (**MB10**) polymerisation with subsequent step growth by aromatic dithiol addition in IPA; (b) and TFE (**MB11**); (c) analysis of bisinitiated MMA (DP 40) (red trace) and the obtained step growth polymer after thiol-bromo click reaction before (orange trace) and after (magenta trace) dialysis (**MB12**).

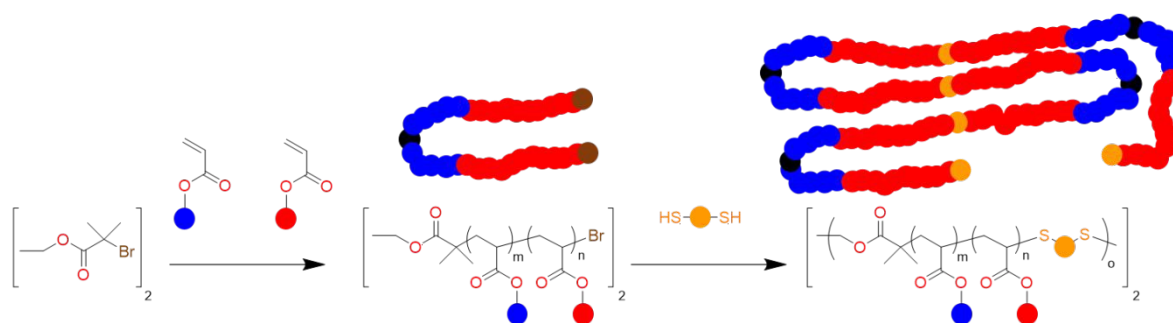
Synthesis of periodic multi-block copolymers

The high compatibility of a plethora of different monomers in Cu(0)-RDRP enables the preparation of well controlled block copolymers.^{15,49} It was envisaged that the thiol-bromo-driven, step-growth procedure described above would provide a new route towards building progressively larger structures

without the need for individual block synthesis. To demonstrate this, amphiphilic bis-initiated block copolymers comprising the ethylene glycol derived monomers DEGA or PEGA and the highly apolar monomer EHA were prepared in DMSO (**Table 3**). There is literature precedence to suggest that DMSO is unsuitable for the controlled synthesis of apolar monomers.⁵⁰ To circumvent this, the polar monomer (DEGA/PEGA) was polymerised first to ensure sufficient solubility before adding the apolar EHA. These polymers were subsequently reacted with BPT-BT to obtain periodic MBCs.

To exemplify **MB13**, a significant increase in molecular weight and \bar{D} after bithiol addition is observed. The results from SEC analysis show a 5-fold increase from 13 100 Da to 55 900 Da of number average molecular weight, suggesting an average of 5 pseudo tetrablock polymer chains coupling to form a periodic multi-block copolymer. Some material with retention time equivalent to the starting copolymer is observed by UV detection suggesting imperfect chain-end fidelity where at least one of the ω -bromines was lost. Another possibility, which is more likely, is the potential formation of the cyclic structures. The retention time in the SEC is slightly lower than the starting material, which is an indication of cyclisation.

Table 3: Thiol-bromo step-growth polymerisation using random and block copolymers of PEGA or DEGA and EHA utilising BPT-BT as the bithiol linker.



Code	Polymer	Solv.	$M_{n,SEC}$ (Da) Block / (\bar{D})	Conv. ^a (%)	$M_{n,theo}$ ^b (Da) MBC	$M_{n,SEC}$ ^c (Da) MBC / (\bar{D})
MB13	PEGA ₁₀ - <i>b</i> - EHA ₄₀	DMSO	13100 / (1.11)	95	262000	55900 / (2.42)
MB14	PEGA ₅ - <i>b</i> - EHA ₄₀	DMSO	10400 / (1.13)	92	130000	46200 / (3.91)
MB15	PEGA ₈ - <i>r</i> - EHA ₄₀	DMSO	8200 / (1.20)	50	16400	12400 / (1.61)
MB16	PEGA ₄ - <i>r</i> - EHA ₄₀	DMSO	7300 / (1.44)	66	21470	12400 / (1.77)
MB17	DEGA ₂₀ - <i>b</i> - EHA ₄₀	DMSO	12600 / (1.32)	91	140000	22600 / (2.16)

^a Conversion values are calculated by deconvolution of pre-polymer and MBC.

^b $M_{n,theo}$ MBC values were calculated using Carother's equation ($DP=1/(1-Conversion)$).

^c $M_{n,SEC}$ MBC values were obtained using PMMA calibration standards in THF/TEA(2%) eluent.

Following this procedure, multi-block copolymers with PEGA DP of 5 and 10 were polymerised and underwent thiol-bromo step-growth in a smooth fashion yielding >90% of coupled polymer chains (**MB13-MB14**). The slightly less polar DEGA was copolymerised with EHA to yield a tetrablock copolymer with the composition of DEGA₂₀-*b*-EHA₄₀ (**MB17**). The dispersity of the obtained polymer was higher than usual with a *D* value of 1.32, which was caused by an increased viscosity after chain extension with EHA. However, the step growth polymerisation with the aromatic bithiol also yielded **MB17** with >90% of coupled chains. On the contrary, the decrease of the DEGA block to 10 units whilst keeping its ratio at 33% caused extreme gelling of the polymerisation mixture after chain extension, yielding only 84% conversion for the second block (EHA).

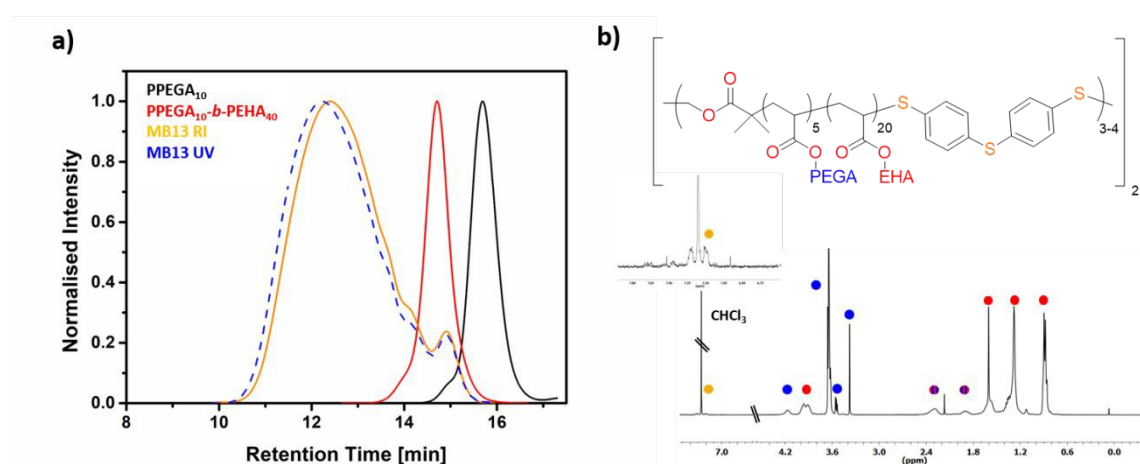
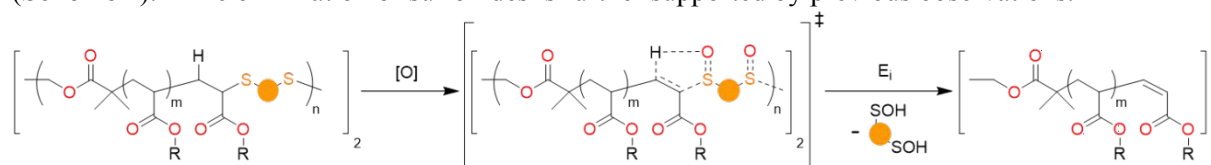


Figure 4: (a) SEC traces poly(PEGA₅-*b*-EHA₂₀-*b*-EHA₂₀-*b*-PEGA₅) (black and red) and post step-growth (**MB13**, orange line = RI, blue dashed line = UV detection at 308 nm), (b) the chemical structure of **MB13** and its corresponding ¹H NMR spectra.

Degradation of thioether containing multi-block copolymers

The effect of oxidative, thermal and methylating conditions on the obtained thiol-bromo step growth copolymers was investigated. Interestingly, instead of oxidation or methylation of the thioether groups, the degradation of the multi-block copolymers in their step growth units was observed, proposing the cleavage of the thioether bonds. In literature, the reactive oxygen species (ROS) responsiveness of ϵ -caprolactone with pendant thio- or seleno ether groups supports these findings. Polymers with aromatic thioether groups underwent an intramolecular elimination reaction of sulfenic acid derivatives due to the increasing electrophilic character of the sulphur atom upon oxidation to sulfone and sulfoxide (**Scheme 2**).⁵¹ The elimination of sulfoxides is further supported by previous observations.⁵²⁻⁵⁴



Scheme 2: Schematic illustration of thioether oxidation followed by elimination of sulfonic acid and subsequent degradation of the MBC.

Degradation behaviour of step growth polymers under oxidative stress

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The amphiphilic step-growth polymer **MB13**, obtained from the aromatic dithiol was reacted with H₂O₂ (30% in H₂O) in THF at different temperatures and analysed by ¹H NMR spectroscopic analysis and SEC. According to the results, full degradation of the multi-block copolymer was observed after 3 days at 60 °C, yielding the original prepolymer used to prepare **MB13** now bearing a double bond functionality at the chain end. Additionally, ¹H NMR spectroscopic analysis and SEC confirmed a complete loss of all aromatic functionalities within the polymer (**Figure 5**), in good agreement with a previous literature report.⁵¹ The degradation rate was found to be temperature-dependent, requiring 25 days to degrade fully at 37 °C (**Figure S4**).

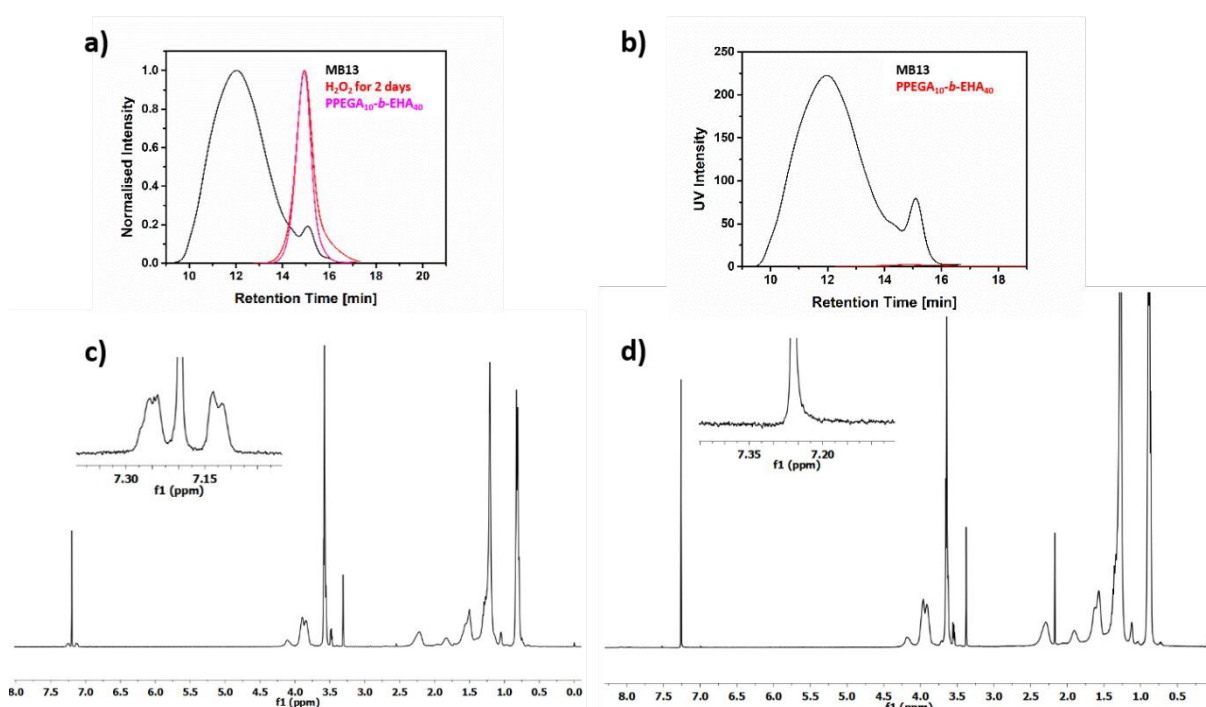


Figure 5: Characterisation of **MB13** pre- and post-H₂O₂ treatment (a) SEC traces (RI detection) pre-treatment; (b) SEC trace (UV detection, 308 nm) post-treatment; (c) ¹H NMR spectrum pre-treatment, aromatic region magnified; (d) ¹H NMR spectrum post-treatment, aromatic region magnified.

In order to investigate the influence of the thiol compound on the degradation behaviour, bisinitiated PEA (DP 20) was polymerised via thiol-bromo step growth with the heterocyclic thiol **Thia-BT**, the ethylene glycol derived dithiol **DEG-BT** and ethanedithiol **Et-BT**. These polymers were also reacted with excess H₂O₂ (30%) at 60 °C and the degradation was monitored by SEC. The heterocyclic dithiol showed full degradation after 9 days, whereas the diethylene glycol derived dithiol and ethanedithiol species had not fully degraded after 17 and 15 days, respectively. The observed trend in degradation rate was as follows: aromatic **BPT-BT** > heterocyclic **Thia-BT** > diethylene glycol derived **DEG-BT** = ethanedithiol **EtBT** (**Figure 6**).

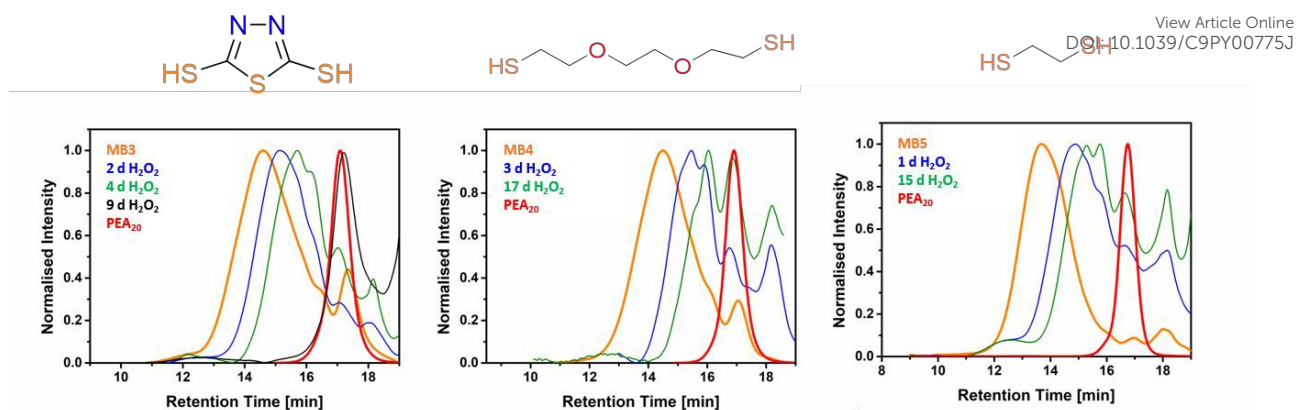


Figure 6: SEC traces (RI detection) of multi-block copolymers upon treatment with H_2O_2 at 60°C over time.

In order to investigate the oxidative degradation pathway of multi-block copolymers, **MB1** was incubated with meta-chloroperbenzoic acid (MCPBA) at room temperature and the reaction was monitored by ^1H NMR spectroscopy and SEC (**Figure 7**). ^1H NMR spectra show the evolution of resonances between 5.5 and 7 ppm (**a** and **b**), indicative of vinyl group formation, whilst the SEC data show progressive decrease in the retention time of the polymer sample. Although degradation reaction did not proceed to completion, the results support the proposed mechanism of sulfenic acid elimination at the polymer chain end. MALDI-ToF analysis supports the double bond formation, which corresponds to the major mass distribution, but also other degradation products are visible (**Figure S6**).

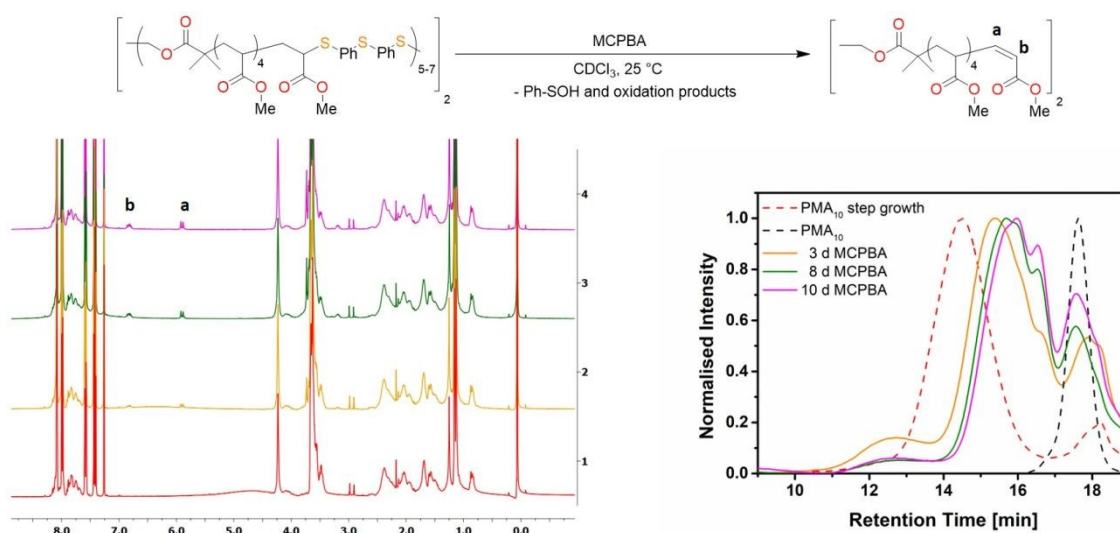


Figure 7: ^1H NMR spectrum and SEC traces of **MB1** when incubated with MCPBA at ambient temperature.

Degradation behaviour of step growth polymers under thermal stress and methylating conditions

Complete decomposition of **MB13** into its macro units was demonstrated by heating up a 1 w% solution in dodecane after only one day (**Figure 8**). In contrast, the obtained MBC from ethanedithiol **MB5**

showed only minor degradation after 15 days at 120 °C in toluene. Dodecane and toluene were selected as solvents due to their high boiling points and inert character.

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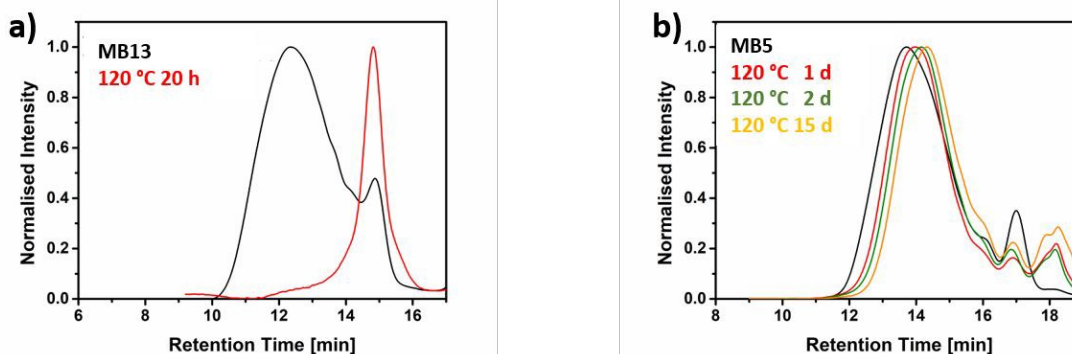


Figure 8: SEC traces (RI response) for thermal degradation of thioether linked polymers at 120 °C: a) amphiphilic copolymer **MB13** with aromatic dithiol linker **BPT-BT**; B) ethyl acrylate copolymer **MB5** with ethanedithiol linker **Et-BT**.

The thermolysis of sulfoxides was previously described in literature and supports the findings in here.⁵⁴ Therefore, by carefully choosing the thiol linker, a fine tuning of the degradability is easily achieved, which enables the synthesis of a wide range of degradable polymers with different architectures. Furthermore, the amphiphilic periodic multi-block polymer **MB13** with the aromatic thiol linker **BPT-BT** was investigated under the influence of methyl triflate at ambient temperature. The periodic multi-block polymer fully decomposed into its polymeric precursors after less than 3 days (**Figure S5**). Evidently, the strong methylating agent increases the electrophilicity of the sulphur atom by methylation and thus facilitated an elimination reaction.

Conclusion

A fast and facile method was developed to synthesise multi-block copolymers by combining the versatility and livingness of Cu-mediated RDRP with rapid thiol-bromo induced step growth reaction. The scope of a conventional DMSO based Cu(0)-RDRP system enabled the synthesis of periodic amphiphilic multi-block copolymers and was further expanded by utilising isopropanol to achieve MBCs with increasing apolar content. One-pot synthesis approach without any chemical modification or purification steps yielded amphiphilic MBCs with up to 20 blocks, which could potentially be extended further by preparing starting polymers with a larger number of blocks. Finally, the obtained materials were shown to be responsive to oxidation, methylation and thermal degradation pathways with different functionalities at the chain ends.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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