Degradable linear and bottlebrush thioester-functional copolymers through atom transfer radical ring-opening copolymerization of a thionolactone

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Abstract.

The radical thiocarbonyl addition–ring-opening (TARO) copolymerization of thionolactones with vinyl comonomers affords selectively degradable thioester functional polymers promising for biomedical applications. Herein, the use of atom transfer radical polymerization (ATRP) is investigated for the first time, using dibenzo[c,e]oxepane-5(7H)-thione (DOT), Cu(I)Br, and tris[2-(dimethylamino)ethyl]amine (Me₆TREN) as thionolactone, catalyst, and ligand, respectively, with the acrylate comonomers poly(ethylene glycol) methyl ether acrylate (PEGA), methyl acrylate, benzyl acrylate, and butyl acrylate. Polymerizations were impeded by a side reaction, the Cu(I)-catalyzed dethionation of DOT to its (oxo)lactone analog, which caused the loss of up to 50 mol% of DOT in the early polymerization stages and limited the final copolymer DOT content. Nonetheless, readily degradable copolymers with low dispersities ($1.10 \leq D \leq 1.26$) were formed using DMSO, acetonitrile, or toluene as solvent. Presuming adventitious water to be the oxygen source, the dethionation side reaction could be minimized (≥ 5 mol-% lactone) by using anhydrous polymerization conditions, which enabled the synthesis of copolymers with higher DOT content. Exploiting documented advantages of ATRP over thermally-initiated RAFT polymerization in the synthesis of brushes, water-soluble molecular brushes were prepared by grafting PEGA–DOT copolymers from a pre-made multi-ATRP initiator. Due to faster incorporation of DOT, the cleavable thioesters were located close to the junctions and enabled the fast (< 1 min) oxidative cleavage of the arms from the core to give water-soluble products using 10 mM oxone. Expanding the scope of the ATRP and TARO methods, this work presents facile access to polymer materials with tailored architectures and degradability.
Introduction

The radical ring-opening polymerization (RROP) of suitable cyclic monomers provides access to (co-)polymers featuring heteroatom backbone functionality including cleavable groups. RROP unfolds its full potential in combination with the architectural control offered by reversible deactivation radical polymerization (RDRP) methods. Especially the combination of cyclic ketene acetals with RAFT polymerization has been exploited to prepare materials with high functional group tolerance, stimulus responsiveness, tailored architectures, and predictable backbone degradability. However, cyclic ketene acetals have disadvantages. They show slow copolymerization behavior due to the high energy of the intermediate acetal carbon-based radical and usually need to be fed in excess to force incorporation during copolymerizations of ‘more-activated’ (meth)acrylic monomers. Furthermore, the resulting backbone ester groups require harsh, non-selective degradation conditions.

Recently, thionolactones were shown to undergo radical ring-opening via thiocarbonyl addition–ring-opening (TARO) which provides backbone thioester functionality. These thioesters can be selectively cleaved through aminolysis, thiolysis (including under biologically relevant conditions) and, very rapidly, through persulfate oxidation. RDRP of thionolactones has been achieved exclusively through RAFT polymerization with which TARO radical polymerization appears to be fully compatible. During the writing of this manuscript, Lages et al reported the successful nitroxide-mediated copolymerization of n-butyl acrylate and styrene with up to 2 mol-% DOT.

Atom transfer radical polymerization is, arguably, more complex than RAFT polymerization. But it has a distinct advantage over (thermally initiated) RAFT in that it does not require a radical initiator (such as AIBN). Consequently, brushes can be grafted from initiator-functional surfaces
and bottle-brush architectures can be derived from macro-initiators without contamination by free chains.\textsuperscript{18} The few reports of radically-made degradable brushes in the literature highlight the potential for biomedical applications.\textsuperscript{19, 20} Riachi and coworkers\textsuperscript{20} reported the surface-initiated atom transfer radical copolymerization of poly(ethylene glycol) methyl ether methacrylate (PEGMA) with the cyclic ketene acetal 5,6-benzo-2-methylene-1,3-dioxepane (BMDO). High BMDO feed ratios (10, 25, and 50 mol-%) were used to compensate for the very low reactivity of BMDO in methacrylic copolymerizations.\textsuperscript{2} The brushes were cleaved over the course of 30 days in the presence of acid (pH 3) or, more slowly still, base (pH 9). These unselective conditions also led to the cleavage of methacrylate side group esters and/or ester or siloxane groups within the surface-anchored initiators. More recently, Raj and coworkers\textsuperscript{19} presented a pH-degradable molecular bottlebrush with potential for intracellular drug delivery applications. The multistep synthesis involved a core polymer carrying ATRP initiators connected via pH cleavable silyloxy linkers. The advantage was that degradation under intracellular conditions occurred at a predefined position directly between the brushes and the core to give fragments of predetermined size.

The combination of ATRP with TARO has not been reported but promises to widen the synthetic scope of both methods and to provide access to materials with tailored and selective degradability including such with brush-type architectures. Herein, we fill this gap by investigating the Cu(I)-catalyzed ATRP of the thionolactone dibenzo[c,e]oxepine-5(7\textit{H})-thione (DOT)\textsuperscript{8, 11} with acrylic comonomers. After observing and minimizing a side reaction—the Cu(I)-catalyzed dethionation of the thionolactone monomer which led to loss of DOT and some of the ATRP catalyst—we present the preparation of water-soluble bottlebrush copolymers able to shed their arms rapidly through selective persulfate oxidation.
Experimental Section

Materials and Methods. Dibenzo[c,e]oxepane-5(7H)-thione (DOT, 1) was prepared as previously described.\textsuperscript{14} 2-(2-Bromopropanoyloxy)ethyl methacrylate was prepared in 80% isolated yield from 2-hydroxyethyl methacrylate and 2-bromopropionyl bromide.\textsuperscript{21} CuBr was purified by refluxing in glacial acetic acid followed by filtering, washing, and drying. Vinyl monomers were passed through a plug of basic alumina to remove inhibitors immediately before polymerization. 2,2’-Azobis(isobutyronitrile) (AIBN) was recrystallized from methanol and stored in a freezer.

Nuclear magnetic resonance spectroscopy (NMR) was done on a 400 MHz Bruker instrument in 5 mm NMR tubes. The residual non-deuterated solvent signals of CDCl\textsubscript{3} (δ\textsubscript{H} = 7.26 ppm) was used as reference.

Size exclusion chromatography (SEC) analysis was performed on a Viscotek GPC Max VE 2001 GPC. The system operated at 35 °C with three linear 7.5 mm × 300 mm Phenogel mixed-D columns connected to a refractive index detector. Tetrahydrofuran (THF) was used as mobile phase at a flow rate of 1 mL min\textsuperscript{-1}. The calibration of the system was based on the relative molar mass determination of a series narrow molecular weight distribution poly(methyl methacrylate) (pMMA) standards ranging from 0.88 to 1677 kg mol\textsuperscript{-1} and reported values are PMMA equivalent.

Dynamic Light Scattering (DLS) was performed on a Malvern Zetasizer Nanoseries instrument in glass cuvettes on polymer solutions with a concentration of 1 mg/mL.

General procedure for normal ATRP. Copper (I) bromide (1 equiv) was suspended in solvent (DMSO, acetonitrile, toluene, 1 mL) followed by an addition of ligand Me\textsubscript{6}TREN (1 equiv). The mixture was degassed by purging with nitrogen for 25 minutes in a reaction tube with a sealed septum. The flask was opened with continued bubbling of nitrogen while vinyl comonomer and
DOT (in varying feed ratios as described in the main text) were added. The flask was quickly
closed with the septum and degassed for a further 20 minutes. The mixture was then opened again
with continued bubbling of nitrogen while methyl 2-bromopropionate (1 equiv) was added. The
vial was resealed, degassed for a further 15 minutes, and placed into a preheated oil bath at 70 °C
for 16 h. The polymerization was stopped by cooling and exposure to air. A sample (100 μL) was
withdrawn, diluted with CDCl₃ (500 μL) and analyzed by ¹H NMR spectroscopy to determine
comonomer conversions. The crude polymerization mixture was filtered through basic alumina
and dialyzed against MeOH (and, for water-soluble polymers) water, followed by drying.

**General procedure for supplemental activation reducing agent (SARA) ATRP.** Cu⁰ wire
(5 cm long, 1 mm diameter) was wrapped around a magnetic stir bar and treated with a solution of
conc. aq HCl–MeOH (1:2 by volume) for 10 minutes, followed by washing with methanol and
drying. PEGA (100 equiv), methyl-2-bromopropionate (1 equiv), CuBr₂ (0.05 equiv), and the
copper-clad stir bar were added to toluene (1 mL) in a septum-sealed vial. The mixture was purged
with nitrogen for 20 min. The flask was opened with continued bubbling of nitrogen and Me₆TREN
(0.1 equiv) was added. Following additional degassing for 15 min, the mixture was heated,
analyzed, and worked up as described above.

**ATRP under anhydrous conditions.** The vinyl comonomers and Me₆TREN were dried over
molecular sieves (4 Å). Toluene was either dried over molecular sieves (4 Å) or by distillation
from sodium and storage over a potassium mirror. All glassware was dried in an oven overnight.
A mixture of dry toluene (0.5 mL), Cu(I)Br (1 equiv), dry vinyl comonomer (varying amounts),
and dry Me₆TREN (1 equiv) was degassed by purging with nitrogen or dry argon for 25 min.
Separately, a mixture of toluene (0.5 mL), DOT (varying amounts), and methyl 2-bromopropionate
(1 equiv) was similarly degassed in a septum-sealed vial. The DOT/initiator solution was then
transferred into the first flask through a canula followed by additional purging with nitrogen or argon for 20 minutes. The mixture was heated, analyzed, and worked up as described above.

**General procedure for degradation of linear copolymers.** Following previous studies, copolymers were degraded by dissolving in a 1:1 (vol:vol) mixture of THF and 7 M ammonia in methanol (final polymer concentration 1 mg/mL) and stirring overnight at RT, followed by evaporation to dryness and analysis by SEC.

**Synthesis of Multi-ATRP initiator (3).** 2-(2-Bromopropanoyloxy)ethyl methacrylate (100 equiv, 0.4 g, 15 mmol), AIBN (0.25 equiv, 0.06 g, 0.377 mmol), and RAFT agent 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid (1 equiv, 6 mg, 0.015 mmol) were added to acetonitrile (1 mL) in a septum-sealed polymerization tube equipped with a stir bar. The solution was sparged with nitrogen for 30 min, immersed in an oil bath pre-set to 70 °C, and left overnight. The polymerization was quenched by exposure to air and cooling it to RT. Following analysis of a withdrawn sample by 1H NMR spectroscopy, the reaction mixture was diluted with DCM and precipitated into diethyl ether–hexane (1:1 by volume).

**Synthesis of bottlebrush copolymer (4).** The bottlebrush copolymer was prepared by classic ATRP following the above description by using the multi-initiator (1 equiv of bromides) and the polymer was isolated by dialysis as for linear PEGA copolymers.

**Degradation of bottlebrush copolymer in aqueous solution.** To achieve fast degradation in aqueous solution, oxone (final concentration 10 mM) was added into a DLS sample (1 mL) containing bottlebrush copolymer (1 mg).
Results and Discussion

The synthesis of DOT-containing copolymers via ATRP is summarized in Scheme 1. Cu(I)Br (1 equiv) was used as catalyst for normal ATRP and methyl 2-bromopropionate (1 equiv) as initiator. To minimize catalyst inactivation (and loss of DOT) through undesired sulfur–copper interactions, tris[2-(dimethylamino)ethyl]amine (Me₆TREN, 1 equiv) was chosen as a strongly complexing ligand known for its high ATRP activity.²² The mixture of solvent, Cu(I)Br and Me₆TREN was degassed by purging with nitrogen before DOT was added, followed by additional degassing, addition of the initiator, and a third degassing step, before the mixture was heated to 70 °C overnight.

Scheme 1. ATRP (normal or supplemental activation reducing agent (SARA)) of various acrylate comonomers with the thionolactone dibenzo[c,e]oxepane-5(7H)-thione (DOT, 1) with the structure of the observed lactone side product (2).

In an initial set of experiments, poly(ethylene glycol) methyl ether acrylate (PEGA, monomer $M_n = 480$ g/mol) was used as vinyl comonomer and DMSO as solvent. The combination of this polar solvent with Me₆TREN as ligand causes some Cu(I) disproportionation.²³ While the
possibility of fast polymerization rates and low dispersities associated with this formulation have widely been appreciated, the mechanism has been the subject of debate.\textsuperscript{24-27} Herein, a homopolymerization of PEGA under these conditions gave 82\% monomer conversion and an SEC-measured $M_n$ of 6.3 kg/mol and a low dispersity of $D = 1.19$ (Table 1, entry 1). When 5–15 mol-% of DOT was added into the formulations (Table 1, entries 2–5), \textsuperscript{1}H NMR analysis of the reaction mixtures before purification showed high PEGA conversions (64–85\%) and that DOT had been partially converted (25–47\%) into the expected thiobenzoate backbone units. SEC analysis of two isolated copolymers, p(PEGA\textsubscript{82-DOT}$\textsubscript{2}$) and p(PEGA\textsubscript{58-DOT}$\textsubscript{4}$) (Table 1, entries 2 and 4), gave low dispersities of $D = 1.14$ and 1.26, respectively. For an attempted copolymerization containing a 20 mol-% DOT feed (Table 1, entry 6), no polymer was formed. This was in contrast to free radical and RAFT polymerizations, in which retardation is observed at higher DOT feed but copolymerizations with 30–40 mol-% DOT feed still proceed to reasonably high conversions.\textsuperscript{6} Notably, when DOT was added into the polymerization mixtures, we observed the formation of brown and black precipitates, presumed to be copper sulfides leading to the irreversible loss of some of the ATRP catalyst and the cause for the absence of polymerization at higher DOT:Cu(I)Br feed ratios. For this reason, lower catalyst concentrations (equivalent to higher DOT:catalyst ratios) were not attempted despite literature reports on successful ATRP of similar systems with 100-times lower catalyst loads.\textsuperscript{28} Herein, surprisingly, an unexpected side reaction was observed: the crude polymerization mixtures contained dibenzo[c,e]oxepane-5(7\textsubscript{H})-one (2, scheme 1), \textit{i.e.}, the (oxo)lactone, the synthetic precursor for DOT, see Figure 1. A control experiment containing DOT (5 equiv), CuBr (1 equiv), and Me\textsubscript{6}TREN (1 equiv) in DMSO (Table 1, entry 7, degassed as described above) gave 55\% conversion to the lactone, while a similar
experiment without Me₆tren (i.e., DOT (5 equiv), CuBr (1 equiv) in DMSO, entry 8) led to quantitative dethionation.
Table 1. Overview of atom transfer radical copolymerizations.

| Entry | Polymer Code | Solvent, Conditions | Comonomer | Feed comonomer DOT (equiv) | Vinyl Comonomer Conversion (%) | DOT Conversion; residual : lactone incorporated (%) | $M_n$ (kg/mol) | SEC analysis (intact) | SEC analysis (degraded) |
|-------|--------------|---------------------|------------|----------------------------|---------------------------------|-----------------------------------------------------|-----------------|------------------------|------------------------|
| 1     | pPEGAm2      | DMSO, A             | PEGA       | 100:0                      | 82                              | —                                                  | 39.5            | 6.3                     | 1.19                   | n.d.                   | n.d.                   |
| 2     | pPEGAm-DOTm2 | DMSO, A             | PEGA       | 95:5                       | 85                              | 0.53:47                                            | 40.0            | 8.3                     | 1.14                   | 6.6                    | 1.14                   |
| 3     | pPEGAm-DOTm2 | DMSO, A             | PEGA       | 45:5                       | 68                              | 0.68:32                                            | 15.5            | n.d.                   | n.d.                   | n.d.                   | n.d.                   |
| 4     | pPEGAm-DOTm2 | DMSO, A             | PEGA       | 90:10                      | 64                              | 28:31:40                                           | 28.9            | 9.5                     | 1.26                   | 5.7                    | 1.21                   |
| 5     | pPEGAm-DOTm2 | DMSO, A             | PEGA       | 85:15                      | 64                              | 52:23:25                                           | 27.0            | n.d.                   | n.d.                   | n.d.                   | n.d.                   |
| 6     | no polymer   | DMSO, A             | PEGA       | 82:20                      | 0                               | 80:20:0                                            | —               | —                       | —                      | —                      | —                      |
| 7     | control      | DMSO, B             | —          | 0.5                        | —                               | 45:55:0                                            | —               | —                       | —                      | —                      | —                      |
| 8     | control      | DMSO, C             | —          | 0.5                        | —                               | 0:100:0                                            | —               | —                       | —                      | —                      | —                      |
| 9     | pPEGAm-DOTm2 | MeCN, A             | PEGA       | 95:5                       | 88                              | 0:44:56                                            | 41.2            | 7.8                     | 1.14                   | 5.7                    | 1.19                   |
| 10    | pPEGAm-DOTm2 | Tol., A             | PEGA       | 95:5                       | 96                              | 0:43:57                                            | 44.5            | 6.7                     | 1.20                   | 5.4                    | 1.20                   |
| 11    | pPEGAm-DOTm2 | Tol., A             | PEGA       | 90:10                      | 96                              | 0:47:53                                            | 42.6            | 7.0                     | 1.18                   | 5.5                    | 1.28                   |
| 12    | pPEGAm-DOTm2 | Tol., A             | PEGA       | 45:5                       | 70                              | 0:55:45                                            | 16.0            | 5.3                     | 1.10                   | 4.3                    | 1.10                   |
| 13    | pPEGAm-DOTm2 | Tol., A             | PEGA       | 145:5                      | 45                              | 0:44:56                                            | 32.0            | n.d.                   | n.d.                   | n.d.                   | n.d.                   |
| 14    | pPEGAm-DOTm2 | Tol., A             | PEGA       | 50:2                       | 99                              | 0:30:70                                            | 24.4            | n.d.                   | n.d.                   | n.d.                   | n.d.                   |
| 15    | pPEGAm-DOTm2 | Tol., A, D          | PEGA       | 95:5                       | 80                              | 0:30:70                                            | 37.6            | 9.2                     | 1.18                   | n.d.                   | n.d.                   |
| 16    | no polymer   | Tol., A             | PEGA       | 80:20                      | 0                               | 80:20:0                                            | —               | —                       | —                      | —                      | —                      |
| 17    | pPEGAm-DOTm2 | Tol., E             | PEGA       | 95:5                       | 92                              | 0:54:46                                            | 42.4            | 8.5                     | 1.16                   | 5.8                    | 1.24                   |
| 18    | pPEGAm-DOTm2 | Tol., A, F          | PEGA       | 95:5                       | 75                              | 10:10:80                                           | 33.7            | 5.1                     | 1.25                   | 4.8                    | 1.24                   |
| 19    | control      | Tol., A, B, F       | —          | 0.5                        | —                               | 87:13:0                                            | —               | —                       | —                      | —                      | —                      |
| 20    | pPEGAm-DOTm2 | Tol., A             | PEGA       | 80:20                      | 40                              | 13:11:76                                           | 18.9            | 6.6                     | 1.38                   | 3.2                    | 1.24                   |
| 21    | pBnAm-DOTm2  | Tol., A, F          | BnA        | 95:5                       | 91                              | 0:5:95                                             | 15.2            | 17.1                    | 1.95                   | 8.1                    | 2.24                   |
| 22    | pMAm-DOTm2   | Tol., A, F          | MA         | 95:5                       | 90                              | 0:22:78                                            | 8.5             | 4.9                     | 1.42                   | 3.6                    | 1.46                   |
| 23    | p(nBuAm-DOTm2| Tol., A, F          | nBuA       | 95:5                       | 94                              | 0:8:92                                             | 12.7            | 8.6                     | 1.48                   | 2.9                    | 2.24                   |

$^a$ conditions: A: classic ATRP; B: control experiment of DOT (5 equiv), CuBr (1 equiv), and MesTREN (1 equiv) in DMSO; C: control experiment DOT (5 equiv) and CuBr (1 equiv) in DMSO; D: 6 h polymerization time; E: SARA ATRP; F: anhydrous conditions; Tol. = toluene; $^b$ estimated by $^1$H NMR analysis of the polymerization mixture before workup; $^c$ degradation by aminolysis in THF
Figure 1. Sections of $^1$H NMR spectra of lactone (2) synthesised during the preparation of DOT$^{14}$ (curve a), its thionated cousin DOT (1, curve b) and, as an exemplary ATRP, PEGA (45 equiv) and DOT (5 equiv) after heating in DMSO to 70 °C overnight (Table 1, entry 3) (curve c). The polymerization mixture shows residual PEGA vinyl groups (labelled $v$), DOT units incorporated into the polymer (labelled $p$), no residual DOT, but surprisingly, lactone 2 (highlighted are the signals of the aryl-H ortho to the ester ($\delta = 8.0$ ppm) and the methylene group ($\delta = 5.0$ ppm)).

Indeed, recent work by Shibahara et al.$^{29}$ demonstrated the copper(I)-catalyzed dethionation of thionoamides, thioureas, a dithioimid, and a thioester in the presence of 20 mol-% (based on thiocarbonyl groups) CuCl in DMF or DMSO at 80 °C. The authors determined that an oxygen atmosphere and polar solvents were necessary for the reaction to proceed to completion and identified molecular oxygen and DMSO as oxygen sources. We therefore tried other solvents. Unfortunately, a polymerization with a PEGA–DOT feed of 95:5 equiv in acetonitrile (Table 1, entry 9) similarly gave 44% lactone with 56% DOT incorporated and a low SEC-measured dispersity of $D = 1.14$. Similarly low dispersities ($D = 1.10–1.20$) were observed when toluene
was used as solvent (Table 1, entries 10–15). Despite our best efforts to keep oxygen at bay, however, only 45–70 mol-% of DOT was converted into the desired thioester backbone units, with the remainder converted into lactone and with no unreacted DOT observed. Changing the solvent to toluene also did not alleviate the problem of no conversion when using a 20 mol-% DOT feed. The attempted polymerization (entry 16) gave no vinyl conversion and the formation of 20 mol-% lactone. Next, we trialed ATRP under supplemental activation reducing agent (SARA) conditions. This ATRP variant involves a Cu(II) salt and Cu(0) wire which form low quantities of the required Cu(I) catalyst \textit{in situ}.\textsuperscript{24} It was hoped that the low Cu(I) concentration would suppress the dethionation reaction. Unfortunately, however, in a PEGA–DOT 95:5 equiv feed polymerization 54 mol-% of DOT was converted to lactone (entry 17) and the SARA route was not pursued further. Notably, many polymerizations gave low dispersities ($D < 1.20$), suggesting, despite the observed problems, controlled copolymerization. The isolated copolymers also proved readily degradable. Following aminolysis, the measured molar masses decreased suggesting the successful incorporation and cleavage of thioester backbone functionalities, see Figure 2A–C.
Figure 2. SEC chromatograms of intact polymers (solid lines) and after aminolysis (dashed lines) for A) PEGA–DOT 95:5 in wet DMSO (Table 1 entry 2); B) PEGA–DOT 90:10 in wet DMSO (entry 4); C) PEGA–DOT 90:10 in wet toluene (entry 11); D) BnA–DOT 95:5 in dry toluene (entry 20); E) MA–DOT 95:5 in dry toluene (entry 21); and F) nBuA–DOT 95:5 in dry toluene, where “dry” refers to the removal of water from all reagents prior to polymerization.
To further understand the copolymerization behavior, kinetics were measured for a PEGA–DOT feed of 95:5 using toluene under normal ATRP conditions (Table 1, entry 15). The conversion of the PEGA comonomer increased with time, reaching a value of 70% after 4.5 h, see Figure 3A. Similar to the situation observed with RAFT and free radical polymerization,\textsuperscript{6, 8, 11} the incorporation of DOT into the copolymer was faster, with 60% of the DOT feed included after 1.5 h of polymerization. These unequal polymerization rates suggested the formation of gradient copolymers and explained the relatively small SEC shifts observed for degradation (Figure 2). In other words, polymers containing an average of two thioester backbone units were not cleaved into three fragments of a third molar mass each because a homo-vinyl section produced after the DOT feed had been depleted remained nondegradable. Surprisingly, the kinetics showed that the amount of lactone formed through the undesired dethionation side reaction did not change throughout the reaction but remained around 30 mol-% as first determined after 15 min. This observation suggested that the lactone was formed quickly and depleted the DOT feed early in the polymerization. Despite this drawback, SEC analysis of the withdrawn polymerization samples showed narrow mono-modal size distributions with molar masses increasing over time as expected for controlled ATRP, see Figure 3B.
**Figure 3.** Kinetics for an ATRP of PEGA–DOT (95:5) in toluene: A) Conversions of PEGA (black triangles), of DOT into backbone thioester units (red squares) and of DOT into lactone side product (blue circles); dotted lines were added to guide the eye; B) SEC chromatograms showing low dispersities and an increase of the measured molar masses with time.

Given that all above ATRPs proceeded in the presence of lactone, we investigated whether its presence led to chain transfer. A recent study concluded that chain transfer to the lactone was not significant during free radical polymerization.\(^{30}\) In agreement, we found that the addition of up to 20 mol-% of lactone (2) to ATRPs of PEGA in toluene did not cause observable chain transfer, see Figure S1.
Despite the ability to make degradable copolymers with narrow size distributions, the seemingly unpreventable loss of typically 50% of the DOT feed and the inability to form polymers from formulations containing more than 15 mol-% of DOT meant that it was not possible to make copolymers containing more than ~7 mol-% DOT through the above methods. In a typical copolymerization, approximately 25 μmol of DOT were converted to lactone. Assuming a 1:1 thiocarbonyl–oxygen stoichiometry, the absence of dissolved oxygen, and using ideal gas law, this reaction required approx. 2.8 mL of air. It seemed unlikely that this volume of air remained in polymerization tubes of 10–15 mL volume following degassing by purging with nitrogen—a procedure used routinely in our group for radical polymerizations. Instead, we hypothesized that the oxygen source for the dethionations was adventitious water. Indeed, mercury-catalyzed dethionations have been reported to use water as the oxygen source. Consequently, we performed ATRP under anhydrous conditions; the vinyl comonomers and Me₆TREN were dried over molecular sieves and toluene was dried similarly or by distilling from sodium. To avoid exposure to ambient moisture, separately dried and degassed reagents were combined through canula transfer before the mixture was degassed further and then heated to 70 °C. Gratifyingly, a 95:5 PEGA–DOT copolymerization under anhydrous conditions led to 75% PEGA conversion, 10% residual DOT, 10% lactone formation, and 80% DOT conversion into the desired thioester backbone units, see Table 1 entry 18. The SEC-measured dispersity of $D = 1.25$ was marginally higher than most of the above samples. A control experiment done under anhydrous conditions in the absence of PEGA and initiator (entry 19) similarly led to 13 mol-% of lactone, confirming the large impact of removing adventitious water. Recall that without drying, polymerizations with a DOT feed of 20 mol-% failed. With drying, however, a 80:20 PEGA–DOT polymerization proceeded with 40% PEGA conversion and 76% DOT incorporation to give species p(PEGA₃₂-
$\text{DOT}_{15}$ (containing 32 mol-% of thioester repeat units) with an SEC-measured $D = 1.38$ (entry 20). The same anhydrous procedure was also applied to benzyl acrylate, $n$-butyl acrylate, and methyl acrylate (entries 21–23) using 95:5 acrylate–DOT feed ratios. All polymerizations proceeded with high (> 90%) vinyl comonomer conversion and high (72–95%) DOT incorporation, although the measured dispersities were high ($D = 1.42–2.12$). Notably, these anhydrous polymerizations involved considerably less formation of brown and black precipitates. Surprisingly however, even under the strictest anhydrous and oxygen-free conditions, lactone ($\geq 5$ mol-%) was still formed. The isolated copolymers all proved degradable. As detailed above, the faster incorporation of DOT compared to the vinyl species led to the formation of gradient copolymers with nondegradable homo-vinyl tails, see Figure 2D–E.

With the need for strictly anhydrous conditions, low conversions for DOT feeds of 20 mol-%, and relatively high measured dispersities, ATRP (at least under the conditions trialed herein) was less versatile than RAFT polymerization in the synthesis of linear DOT-derived copolymers. We therefore explored the synthesis of bottlebrush copolymers through ATRP. As mentioned in the introduction, ATRP has an advantage because chains grow only from the ATRP initiators (i.e., halides), while in thermally initiated RAFT polymerizations some chains are initiated by the thermal initiator (e.g., AIBN) and thus do not carry the $\alpha$-functionality derived from the chain transfer agent. The synthesis of bottlebrush copolymers is summarized in Scheme 2. 2-(2-Bromopropanoyloxy)ethyl methacrylate was homopolymerized by RAFT to give a multifunctional ATRP initiator, 4, with SEC-measured $M_n = 9.4$ kg/mol and $D = 1.30$ (see Figure 4A). PEGA–DOT copolymers were grafted from the initiator to give bottlebrush species 4. Conversions estimated from $^1$H NMR measurements suggested an average DOT content of 1.7 units per arm and an overall number-average molar mass of 1,361 kg/mol. Taking advantage of the established
faster incorporation of DOT compared to PEGA, the DOT repeat units were expected to be close to the bottlebrush core and to enable the removal of the arms very close to the “shoulders”. Unfortunately, a THF solution of bottlebrush species 4 blocked a 0.2 μm syringe filter and the solution was not analyzed by SEC. Possibly, termination reactions led to arm–arm coupling and the formation of connected brushes. The bottlebrush copolymer was fully soluble in water, suggesting successful grafting of the hydrophilic PEGA–DOT copolymers onto the hydrophobic multi-initiator. Analysis of an aqueous solution by dynamic light scattering (DLS) showed species with a volume-average hydrodynamic diameter of 39.6 nm, significantly larger than expected of linear unimeric polymers, see Figure 4B. To confirm degradation of the dissolved brushes, oxone (a triple salt containing the strong oxidizing agent potassium peroxomonosulfate) was added. Immediate analysis by DLS (approx. 1 min after oxone addition) showed the complete disappearance of the large species and a new monomodal size distribution with a volume average hydrodynamic diameter of 10.9 nm, see Figure 4B. This observation agreed with previous reports of very rapid oxidative thioester hydrolysis into carboxylates and sulfonates and confirmed the expected degradation of the bottlebrush species. Following freeze-drying of the degraded sample, the residue was analyzed by SEC in THF. The chromatogram (Figure 4A, $M_n = 2.91$ kg/mol, $D = 1.63$) showed a distribution of lower size than the multi-initiator. This was interpreted to show the cleaved PEGA-based arms, 6. The ‘arm-less’ cores, expected to have formed polysulfonates (5) following oxidative cleavage, were not visible in the SEC measurement either because of poor solubility in THF and/or its low concentration (there were, on average, 93 arms per one core). Together, this data confirmed the successful synthesis of very large molecules incorporating multiple degradable thioester linkages through ATRP, and the rapid degradation into smaller fragments through oxidation. Compared to literature examples of radically made
degradable bottlebrushes, using DOT thus has the advantages of rapid incorporation (precluding the need for sacrificial feed), cleavage close to the core (without the need for elaborate synthesis of a core containing the cleavable site), and selective cleavage of the backbone thioesters without harming the more stable (oxo)esters.

**Scheme 2.** Synthesis (A) and Degradation (B) of PEGA-based bottlebrush copolymers carrying degradable thioester units in the arms.
Figure 4. A) Size exclusion chromatograms of (a) the multifunctional ATRP initiator (3, green curve) and (b) of the oxone-degraded bottlebrush showing THF-soluble fragments (6, dashed black curve); B) Five separate volume distributions obtained by dynamic light scattering each of (c) intact bottlebrushes in water (4), and (d) following degradation with aqueous oxone showing the water-soluble species 5 and 6.

Conclusion

The Cu(I)-catalyzed atom transfer radical copolymerization of the thionolactone DOT is possible but is hampered by the dethionation of DOT in the presence of traces of oxygen or water. This side reaction is fast and leads to the depletion of potentially large amounts of the thionolactone monomer. While Cu(I) has been used in the literature as a catalyst for similar dethionations, herein, the formation of black precipitates, believed to be copper sulfides, were observed and suggested irreversible loss of some ATRP catalyst. The lactone side product did not appear to interfere with the polymerization and, despite the above setbacks, degradable copolymers with low dispersities were formed, albeit with low (< 7 mol-%) thioester content without using strictly anhydrous conditions. Under anhydrous conditions, the formation of lactone could be minimized (to ≥ 5%) but not fully prevented. For the synthesis of well-defined linear DOT copolymers, we recommend using RAFT polymerization, for which side reactions (apart from retardation) have not been
reported. An advantage of ATRP lies in “grafting-from” polymerizations, demonstrated herein in the production of a water-soluble bottlebrush species that degraded rapidly through oxidative hydrolysis into smaller, water-soluble species.

ASSOCIATED CONTENT

Supporting Information.

Chain transfer experiments.

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