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Article

Insertion of Degradable Thioester Linkages into Styrene and Methacrylate Polymers: Insights into the Reactivity of Thionolactones

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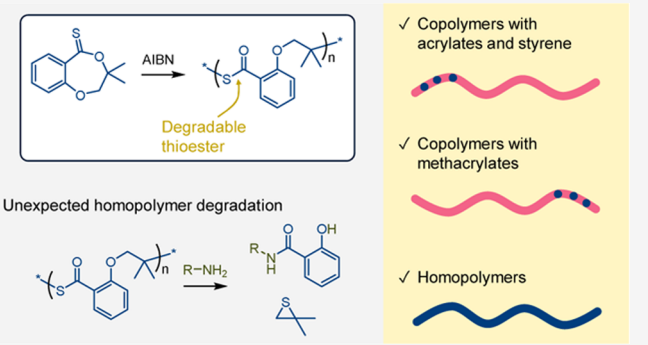
ABSTRACT: The thionolactone 3,3-dimethyl-2,3-dihydro-5*H*-benzo[*e*][1,4]dioxepine-5-thione (DBT) is shown to radically homopolymerize, copolymerize rapidly with acrylates and styrene, and, for the first time, copolymerize with methacrylates, introducing a degradable thioester backbone functionality. Surprisingly, the aminolysis of DBT homopolymers was accompanied by the intramolecular ether cleavage, leading to the formation of 2,2-dimethylthiirane and salicylamides. The rapid copolymerization with styrene was exploited to produce degradable copolymers through free-radical polymerization in a starve-fed semibatch setup. The higher reactivity of DBT compared to the current benchmark thionolactone dibenzo[*c*,*e*]oxepine-5(7*H*)-thione (DOT) was inconsistent with the expected electron-donating effect of the alkoxy substituent in DBT. Using single-crystal XRD structure analysis and DFT modeling, this study rationalized the higher reactivity of DBT by (i) better stabilization of the intermediate radical in DBT by means of a better overlap with the adjacent aromatic, which shifts the addition equilibrium to the right; (ii) an increased ring strain in DBT compared to DOT, which drives the ring-opening; and (iii) better reinitiating efficiency of the tertiary alkyl open-ring radical of DBT compared to the benzylic radical of DOT. These insights are expected to facilitate the development of further thionolactone monomers with tailored copolymerization behavior.



INTRODUCTION

The incorporation of backbone degradability into vinyl copolymers is a remaining frontier in the polymer chemistry arena and offers new prospects in biomedicine and plastic recycling.[1−3] The radical ring-opening polymerization (RROP) of cyclic ketene acetals,[4] allyl sulfide lactones,[5] and allyl sulfone lactones[6,7] is an established method to install ester linkages into the backbone of vinyl copolymers. But these ester groups typically require harsh, nonselective conditions for cleavage. Recently, thionolactones were introduced as a new class of monomers undergoing RROP. The proposed mechanism, termed thiocarbonyl addition−ring-opening (TARO),[8] involves the reversible[9] addition of a radical onto the thiocarbonyl group to give an intermediate (−Ċ(SR)O−) radical, which undergoes irreversible ring-opening through *β*-scission to yield thioester (−C(=O)SR−) backbone functionality (Scheme 1). Significantly, these weak linkages can selectively be cleaved through aminolysis, thiolysis, or oxidative cleavage.[10] The first thionolactone, dibenzo[*c*,*e*]oxepine-5(7*H*)-thione (DOT), was reported separately by our group[8] and the Gutekunst group.[11] DOT copolymerizes with acrylates,[8,11] arcylamides,[10] maleimides,[12] styrene,[13,14] acrylonitrile,[8] and isoprene[15] and is compatible with RAFT,[8,11] ATRP,[16] and NMP.[17] The glutathione-triggered degradation of DOT-derived backbone thioesters is promising for the intracellular delivery of drugs.[18] DOT has also been used to produce degradable gels,[19] networks,[14,20] and pressure-sensitive adhesives.[21] Additionally, the stability of DOT in the presence of water (contrary to the hydrolytically labile cyclic ketene acetals) has enabled the heterogeneous synthesis of degradable particles under aqueous emulsion conditions.[17,22]

Additional thionolactones have since been reported, including DOT derivatives,[14] *ω*-thionoalkanolactones[23−26] compatible with vinyl esters, and thionolactones derived from lactide,[27,28] and isochromanone.[29] But there remain

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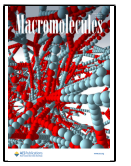
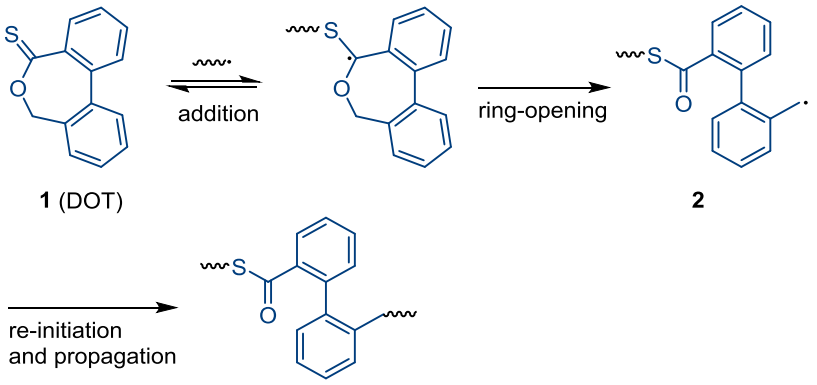


Scheme 1. Thiocarbonyl Addition−Ring-Opening (TARO) Mechanism for the (Co)polymerization of Dibenzo[*c*,*e*]oxepin-5(7*H*)-thione (DOT)



problems with fast and efficient homopolymerization, and there has been no report of copolymerization of a thionolactone with methacrylates.

Herein, a new thionolactone monomer, 3,3-dimethyl-2,3-dihydro-5*H*-benzo[*e*]1,4-dioxepine-5-thione (DBT, **3**), is presented. The work was based on the hypothesis that the primary radical of ring-opened DOT (see Scheme 1) is inefficient at reinitiating acrylic monomers (based on the published initiation rates of the benzylic radical)[30,31] and contributes to the significant retardation observed at higher (>40 mol %) DOT feeds and inefficient homopolymerization (in addition to the retardation associated with the slow β scission and/or intermediate radical termination known for RAFT agents).[32] In the new thionolactone, DBT, the benzene ring stabilizing the reinitiating radical, was substituted with an alkoxy chain while maintaining the 7-membered ring. The reinitiating radical of DBT was chosen to resemble the *tert*-butyl group for which initiation rate constants 2 orders of magnitude larger than the benzylic radical have been reported.[30,31] This change in structure indeed led to a better (but not good) homopolymerization efficiency. Surprisingly, and contrary to the expected influence of the ether substituent, DBT copolymerized much more rapidly than DOT and was even incorporated (albeit sluggishly) into methacrylic polymers. The high reactivity was attributed to the higher ring strain of DBT compared to DOT and to the radical intermediate having a lower torsion angle and better radical stabilization through conjugation with the aromatic compared to DOT. The insights obtained in this study are expected to be helpful in the further development of thionolactone monomers.

RESULTS AND DISCUSSION

DBT, **3**, was synthesized in three steps from salicylic acid through phenol alkylation, lactonization, and thionation (see Scheme 2 and Figures S1−S10). DBT presented as orange crystals and was stable at room temperature for at least 25 days but when heated in refluxing xylene isomerized (51% after 1.8 h) to a 6-membered thionolactone, **4**, which was also identified as a minor impurity in crude DBT (see Figures S11−S14). An attempted copolymerization of isolated **4** and methyl acrylate (MA) resulted in retardation without the incorporation of thioesters. Attempts to synthesize a DBT analogue featuring a thioether instead of the oxoether from thiosalicylic acid failed during the thionation step, which did not give the expected product (Figures S15−S32).

DBT was found to homopolymerize (Table S1, Figures S33−S38) and copolymerize with *N*,*N*-di(m)ethylacrylamide, acrylonitrile, poly(ethylene glycol) methyl ether acrylate (PEGA), *N*-vinyl carbazole, styrene, poly(ethylene glycol) methyl ether methacrylate (PEGMA), and *tert*-butyl methacrylate (tBuMA) (Figures S39−S59). An attempted copolymerization of DBT with *tert*-butyl acrylate under RAFT conditions led to the homopolymerization of DBT (Table S1). This result suggests the faster and preferential polymerization of DBT with strong retardation of acrylate polymerization. This result is similar to the reported homopolymerization of ε-thionocaprolactone in the presence of 50 mol % 2-methylene-1,3-dioxepane.[34] Details of the homo- and copolymers are summarized in Table 1. In all cases, the consumption of DBT was accompanied by the disappearance of its orange color. (Co)polymers exhibited IR absorbance ($\nu_{C-S\ stretch}$ = 899 cm^{-1}, $\nu_{C=O\ stretch}$ = 1671 cm^{-1})[35] and ^{13}C NMR resonance ($\delta_{SC=O}$ = 192 ppm) characteristic of thioesters, and ^{1}H NMR analysis confirmed the presence of the expected ring-opened repeat units, supporting the expected TARO mechanism (Scheme 2C) and the formation of thioester backbone functionality (see Figure 1 for the ^{1}H NMR spectrum of a representative DBT-rich copolymer). No evidence of ring-retaining polymerization was observed.

DBT Homopolymerization. The AIBN-initiated free-radical homopolymerization of DBT in anisole reached 35% conversion after being heated to 70 °C overnight. Two subsequent additions of further AIBN followed by degassing increased the accumulated conversion to 66% and 88%, respectively (Table1, entry 1). Although the need for repeated AIBN addition was not ideal, the homopolymerization of DBT was more efficient than that of DOT (22% accumulated conversion after seven AIBN additions).[12] This improvement was attributed to the tertiary alkyl radical, **5**, being more reactive[30] than the benzylic radical in DOT. The ^{1}H and ^{13}C NMR spectra of the DBT homopolymer (Figures S33−S38) showed relatively narrow signals, presumably due to the absence of backbone stereochemistry. Surprisingly, upon degradation through aminolysis, the DBT homopolymer did not degrade into the expected salicylamide *O*-ether, **6**, but instead *N*-functional salicylamide, **7**, and 2,2-dimethylthiirane (Scheme 3), which were identified through ^{1}H and ^{13}C NMR measurements (Figures S60−S64). These results confirmed the presence of easily cleavable thioester backbone functionality and, additionally, indicated that the ortho-alkoxy substituent provided an additional cleavable linkage.

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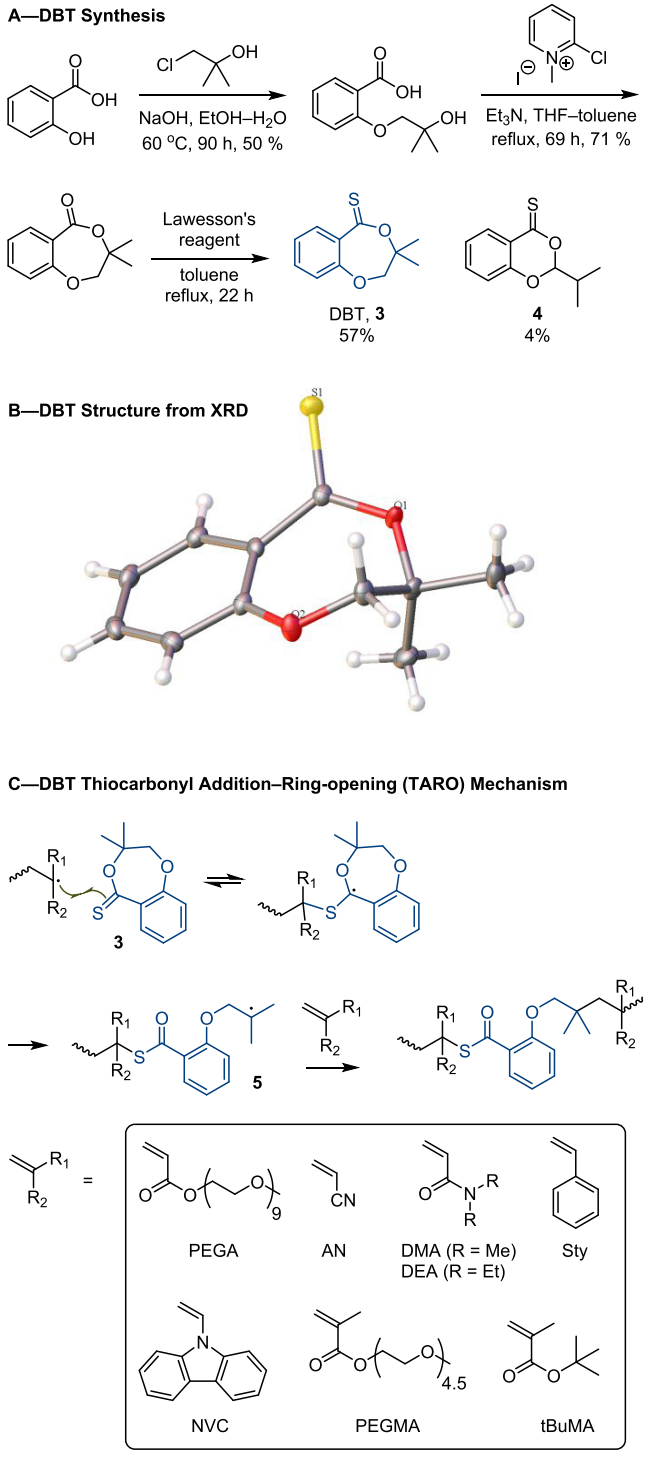
Scheme 2. (A) Synthesis of DBT; (B) X-ray Crystal Structure[33] of DBT; and (C) DBT Copolymerization Mechanism with Structures of Compatible Vinyl Comonomers



DBT Copolymerization. Next, the copolymerization behavior of DBT was investigated. DBT showed higher conversions than the respective vinyl comonomer in copolymerizations with PEGA, acrylonitrile, *N*-vinyl carbazole, *N*,*N*-di(m)ethylacrylamide and styrene (Table1, entries 2–7). For example, in a RAFT copolymerization of DBT (8 equiv) with *N*,*N*-dimethylacrylamide (DMA, 67 equiv) and *N*,*N*-diethylacrylamide (DEA, 9 equiv) (the combination was chosen with the aim of achieving water solubility (deferred by DMA) and visibility in RI detection during SEC (deferred by DEA),Table1, entry 5), DBT was quantitatively consumed after 4 h, at which point the acrylamides had reached less than 15% conversion. After the DBT feed had been depleted, the polymerization rate of the acrylamides increased with the reaction, showing full conversion of all comonomers after 5 h (see Figures S65–S67). These kinetics differ from the behavior of DOT, which was reported to show a more uniform incorporation into acrylamide copolymers.[10]

DOT was originally reported not to copolymerize with styrene but was later shown to undergo nearly ideal copolymerization with styrene.[13,14] Herein, we found DBT to be incorporated into copolymers much faster than styrene (Table1, entries 6,7). The free-radical copolymerization of a 91:9 mol % styrene–DBT mixture was investigated in more detail. Compared to a similar free-radical styrene homopolymerization (measured polymerization rate constant, $k_{sty,homo}$ = 2.7×10^{-5} s^{-1}, not shown), the presence of 9 mol % DBT in a free-radical copolymerization retarded the styrene uptake somewhat ($k_{sty,copo}$ = 1.3×10^{-5} s^{-1}), while the DBT consumption was faster ($k_{DBT,copo}$ = 1.4×10^{-4} s^{-1}; see Figure S68). After 5 h, the DBT conversion exceeded 90%, while only 15% of styrene had been included in the oligomeric product (see Figure 2A). The estimated molar DBT content of the copolymer (Figure 2B) remained near 50% for the first 2.5 h of the copolymerization (suggesting the formation of alternating sequences), and the copolymer became more styrene-rich as the DBT feed was being depleted.

Similarly, another free-radical copolymerization of styrene–DBT 90:10 mol % (Table1, entry 7) reached 100% DBT and 38% styrene conversion after running overnight and gave a product with an average 23 mol % DBT content and an SEC-measured bimodal size distribution, M_n^{SEC} = 7.1 kg/mol and $Đ$ = 2.87. Upon aminolysis of the product, only part of the sample proved to be degradable, with large chains remaining in the sample (see Figure 3A). This undegradable population was presumed to be polystyrene homopolymer formed after the DBT feed had been depleted. Leveraging the very rapid incorporation of DBT, a starve-fed (semibatch) process[36] was investigated, where an overall 5 mol % DBT feed was added continuously via a syringe pump into an active free-radical polymerization of styrene. This approach resulted in a comparable styrene conversion of 42% but a lower DBT conversion of 40%. The product had an average DBT content of 5 mol % and measured M_n^{SEC} = 8.3 kg/mol and $Đ$ = 1.84, showing a narrower size distribution than the batch sample. Gratifyingly, following aminolysis, SEC analysis showed a shift of the entire distribution and a lower M_n^{SEC} = 5.7 kg/mol and $Đ$ = 1.93, indicating that all chains had contained (an albeit small amount of) degradable DBT repeat units (see Figure 3B). While the process still requires optimization to achieve a higher DBT content and more uniform distribution within chains (an elaborate process[36] beyond the current scope), these results demonstrate the usefulness of a rapidly copolymerizing thionolactone to produce degradable styrene copolymers through free-radical polymerization and without the need of RAFT agents.

As mentioned in the Introduction section, the TARO copolymerization of a thionolactone with a methacrylic comonomer has not been reported. Inspired by the much faster incorporation of DBT compared to DOT, we investigated the copolymerization of DBT with two

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Table 1. Overview of DBT Homopolymers and Copolymers[e]

entry	code	comonomer feed ratio (eq)	conditions[a]	conversion (mol %)[b]	M_n^{SEC} intact (kg/mol), (Đ)	M_n^{SEC} degraded (kg/mol), (Đ)
1	pDBT		FRP	88[c]	insoluble in THF	n.d.
2	p(PEGA$_{52}$-*co*-DBT$_{12}$)	82:12	RAFT-A	63:99	7.7 (1.16)	n.d.
3	p(AN$_{40}$-*co*-DBT$_{10}$)	75:11	RAFT-A	53:97	1.9 (1.86)	n.d.
4	p(NVC$_{0.75}$-*co*-DBT$_{0.25}$)$_n$	91:25	FRP	83:99	1.2 (3.72)	n.d.
5	p(DMA$_{67}$-*co*-DEA$_9$-*co*-DBT$_8$)	67:9:8	RAFT-A[d]	99:99:99	1.5 (1.64)	n.d.
6	p(Sty$_{39}$-*co*-DBT$_5$)	94:5	RAFT-A	42:99	4.0 (1.21)	n.d.
7	p(Sty$_{0.77}$-*co*-DBT$_{0.23}$)$_n$	90:10	FRP	38:100	7.1 (2.87)	2.5 (7.77)
8	p(PEGMA$_{86}$-*co*-DBT$_2$)	90:10	RAFT-B	95:17	17.2 (1.33)	13.8 (1.35)[f]
9	(a) p(PEGMA$_{57}$-*co*-DBT$_3$), (b) p(PEGMA$_{13}$-*co*-DBT$_{51}$)[g]	61:39	RAFT-B	96:17	(a) 9.8 (1.34), (b) insoluble in THF[g]	(a) 5.3 (2.60)[f]
10	p(tBuMA$_{58}$-*co*-DBT$_3$)	88:9	RAFT-B	66:33	7.4 (1.15)	n.d.
11	(a) p(tBuMA$_{54}$-*co*-DBT$_1$), (b) p(tBuMA$_{50}$-*co*-DBT$_{13}$)[g]	60:42	RAFT-B	94:16	(a) 4.9 (1.34), (b) insoluble in THF[g]	(a) 4.6 (1.32)[h]
12	p(tBuMA$_{0.97}$-*co*-DBT$_{0.03}$)$_n$	91:9	FRP	98:27	n.d.	n.d.

[a]Anisole, 70 °C, overnight with (FRP): AIBN (1 equiv) or (RAFT-A): cyanomethyl dodecyl trithiocarbonate (1 equiv) and AIBN (0.2 equiv), or (RAFT-B): 4-cyano-4-[(dodecylsulfanylthiocarbonyl) sulfanyl]pentanoic acid (1 equiv) and AIBN (0.2 equiv). [b]Estimated from ^{1}H NMR analysis of the reaction mixture before purification. [c]Cumulative conversion after three successive additions of AIBN (1 eq with heating overnight each time). [d]Polymerization time 3 h. [e]Isopropylamine in THF (50:50 by volume), RT, overnight. [f]Oxone in water (10 mM), overnight, RT. [g]Two samples were isolated based on methanol solubility: a DBT-poor sample (soluble, a) and a DBT-rich sample (insoluble, b). [h]Ethylamine in THF (2 M), RT, overnight.

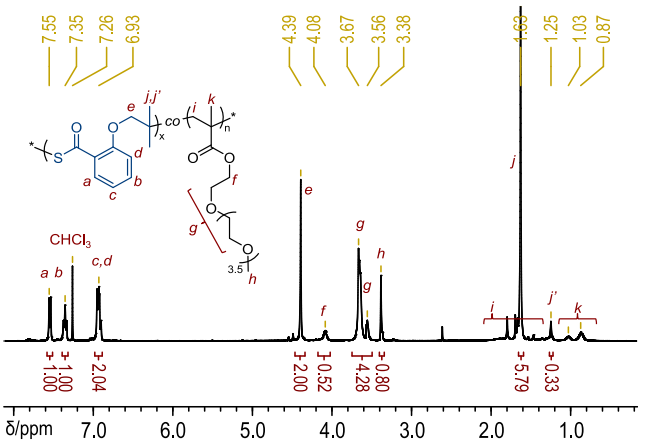
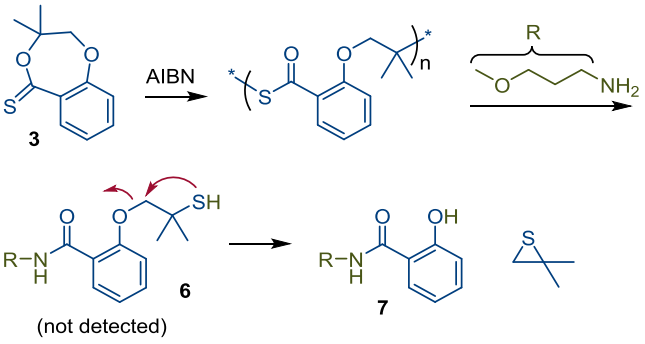


Figure 1. ^{1}H NMR spectrum of p(PEGMA$_{13}$-*co*-DBT$_{51}$) (Table 1, entry 9b) in $CDCl_3$ showing the expected ring-opened DBT repeat units. The chemical shift of the DBT dimethyl groups depended on the subsequent monomer; δ_H = 1.63 ppm in a DBT−DBT diad (labeled *j*) and δ_H = 1.25 ppm in a DBT−PEGMA diad (labeled *j*′).

Scheme 3. Synthesis of DBT Homopolymer and Aminolysis with the Expected (Though Not Detected) Primary Degradation Fragment (6) and Proposed Mechanism Leading to the Formation of the Observed Products



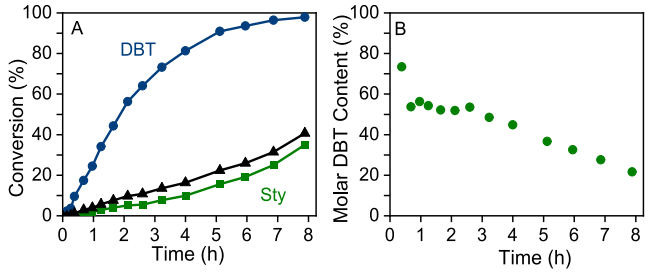


Figure 2. Free-radical copolymerization kinetics of styrene/DBT (91:9 feed ratio) with (A) conversions of DBT (blue circles), styrene (green squares), and global conversion (black triangles) and (B) cumulative molar compositions estimated from the conversions.

representative methacrylates, poly(ethylene glycol) methyl ether methacrylate (PEGMA, monomer MW = 300 g/mol) and *tert*-butyl methacrylate (tBuMA).

In a RAFT-mediated copolymerization of PEGMA/DBT 90:10 (Table1, entry 8), the methacrylic comonomer converted faster than DBT (Figure 4A). However, DBT was not an unreactive bystander but was consumed, too. After 6 h of copolymerization, consumptions of 85% PEGMA and 10% DBT were found, which increased to 95 and 17% for PEGMA and DBT, respectively, after heating overnight. This lower reactivity of DBT was attributed to the TARO addition equilibrium (Scheme 1) lying more on the side of the methacrylic radical as opposed to the addition of an acrylic chain. SEC analysis showed molecular weights increasing with the consumption as expected for a RAFT copolymerization (see Figure 4B).

The copolymers withdrawn from the copolymerization after different times were subjected to degradation with 10 mM aqueous oxone, conditions that cleave backbone thioesters rapidly.[18] SEC elugrams of the intact and degraded copolymers are shown in Figure 5. For the sample withdrawn after 20 min, attempted degradation led to only a slight shift of the lower molecular weight flank of the curve, suggesting that only some copolymers contained minor amounts of DBT, in agreement with the negligible conversion of DBT observed at this time.

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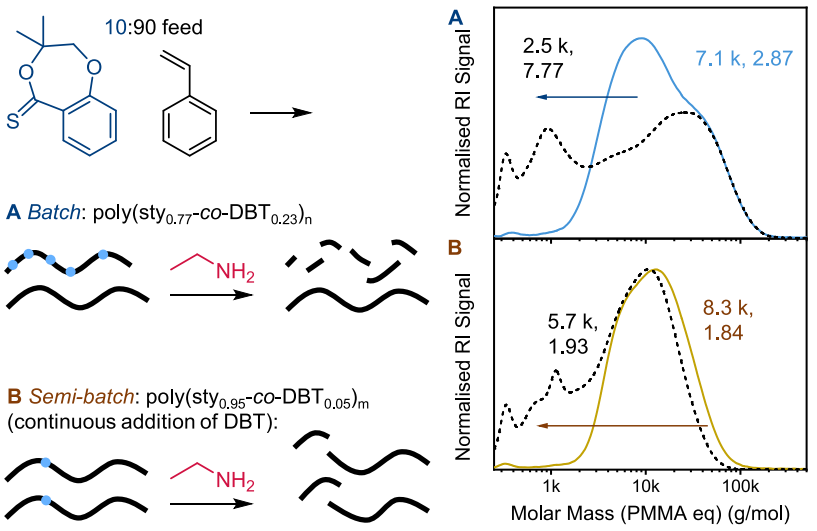

Figure 3. Size exclusion chromatograms (right, where dashed curves show measurements done on aminolyzed samples) and cartoon (left) for the free-radical copolymerization of DBT and styrene in batch (all monomers together, (A)) and in semibatch (B), where all DBT was added continuously during the polymerization.

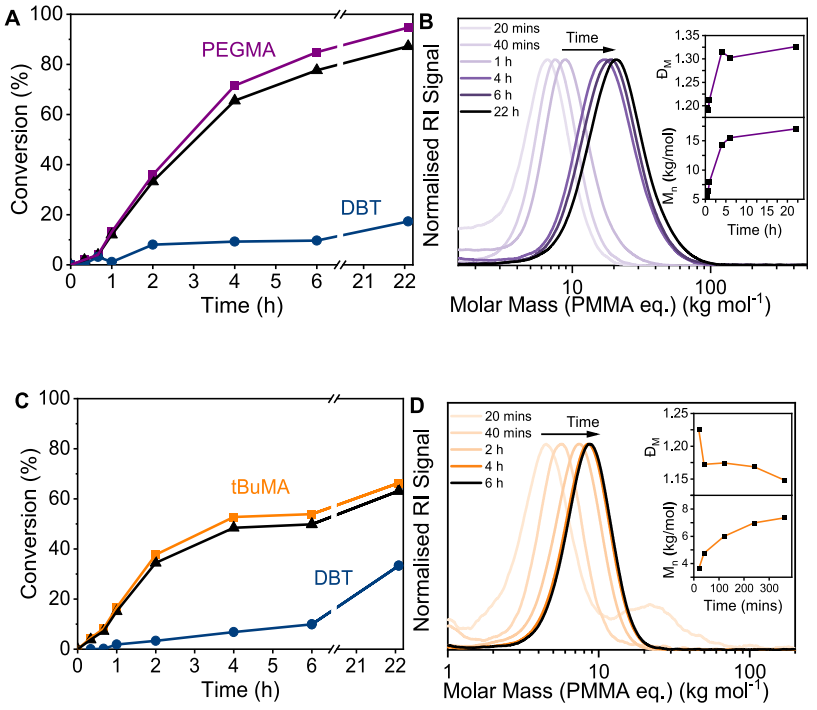

Figure 4. RAFT copolymerization kinetics of PEGMA–DBT 90:10 (Table1 entry 8): (A) conversion of PEGMA (purple squares), DBT (blue circles), and global conversion (black triangles) and (B) SEC traces with inset molar mass and molar mass dispersity. RAFT copolymerization kinetics of tBuMA–DBT 88:9 (Table1 entry 10): (C) conversion of tBuMA (orange squares), DBT (blue circles), and global conversion (black triangles) and (D) SEC traces with inset molar mass and molar mass dispersity.

This measurement also confirmed that PEGMA homopolymers were not affected by treatment with oxone. With an increasing reaction time (and increasing molar content of DBT in the copolymers), there was an increasing shift between the SEC traces of the intact and degraded samples (see Figure 5F). The maximum shift of 17.2 kg/mol → 13.8 kg/mol found after copolymerizing overnight was far from the ideal (where a 90:10 copolymer would be expected to degrade into average nine-mer fragments) but did confirm a first successful copolymerization of a thionolactone with a methacrylate.

Lower reactivities of cyclic comonomers than vinyl comonomers are common in the RROP arena and well-documented for the copolymerization of CKAs with (meth)-acrylates.[3] A typical strategy involves adding a sacrificial cyclic monomer to push incorporation through a higher concentration. Indeed, starting with a comonomer ratio of 61:39 PEGMA–DBT led to a main product, p($PEGMA_{57}$-*co*-DBT_3), containing 5 mol % DBT (Table1, entry 9a) that showed a 46% mass loss (based on the ratio of SEC-measured molecular weights) upon degradation with oxone (see Figure 6). The copolymerization yielded another minor product, which was

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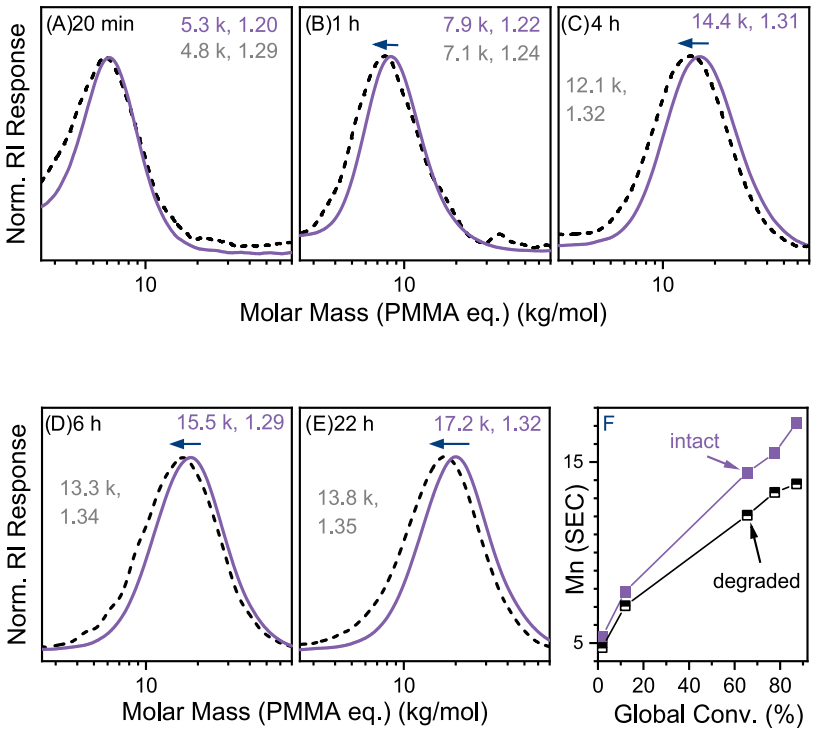


Figure 5. (A–E) SEC traces of intact copolymers from the PEGMA–DBT 90:10 RAFT copolymerization (solid purple lines, the same as shown in Figure 4B) and after oxone degradation (dashed black lines) for polymerization times of (A) 20 min, (B) 1 h, (C) 4 h, (D) 6 h, and (E) 22 h, and (F) average molar mass of intact (purple data points) and degraded (half black data points) copolymers versus global conversion.

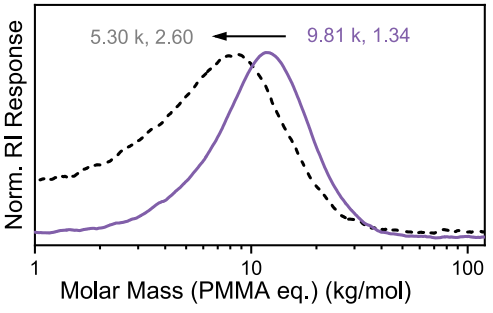
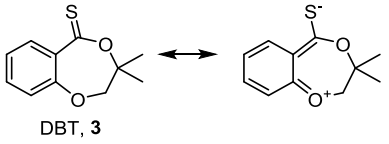


Figure 6. SEC traces of intact p(PEGMA$_{57}$-*co*-DBT$_3$) (Table1, entry 9a) (solid purple line) and after oxone degradation (dashed black line).

Scheme 4. Supported by Ample Literature Examples, Conjugation of the Alkoxy Oxygen Lone Pair into the Thiocarbonyl Group of DBT Is Expected to Decrease the C=S Double Bond Character and Lower the Reactivity toward Radicals—Contrary to the Observations Made Here



DBT, **3**

isolated based on its insolubility in methanol (Table1, entry 9b). Analysis by ^{1}H NMR spectroscopy (spectrum shown in Figure 1) revealed this side product to be DBT-rich with an estimated average composition of p(PEGMA$_{13}$-*co*-DBT$_{51}$) and to contain DBT-DBT and DBT–PEGMA diads. Presumably, this species was formed after most PEGMA had been depleted. Unfortunately, the copolymer was insoluble in THF and was not analyzed by SEC.

The copolymerization behavior of an 88:9 tBuMA–DBT RAFT copolymerization (Table1, entry 10 and Figures S69–S70) was similar to that with PEGMA. The comonomer conversions reached 54% (tBuMA) and 10% (DBT) after 6 h and increased to 66% (tBuMA) and 34% (DBT) overnight (Figure 4C). The observed molecular weights increased expectedly with conversion (Figure 4D). Despite the unequal radical leaving group abilities of methacrylate- and DBT-terminated chains from intermediate RAFT radicals (unlike the methacrylic chain, the tertiary DBT open-ring radical is not stabilized through conjugation), the observed dispersities were low, $Đ \leq 1.17$, for all samples collected after 40 min of copolymerization. As with PEGMA, two copolymers, p(tBuMA$_{54}$-*co*-DBT$_1$) and p(tBuMA$_{50}$-*co*-DBT$_{13}$), were isolated from a RAFT copolymerization with an increased feed of DBT, 60:42 tBuMA–DBT (Table1, entries 11a and 11b and Figure S71). These observations confirmed a large compositional gradient formed when the less reactive comonomer is added in excess (and can, as in the case of DBT, homopolymerize) and suggest that the estimated compositions of the samples isolated by solubility differences give only average compositions.

The AIBN-initiated free-radical copolymerization kinetics of DBT and *tert*-butyl methacrylate were determined for a 91:9 tBuMA–DBT feed ratio (Figures S72–S73). The consumption of both comonomers followed was fitted through first-order kinetics with estimated rate constants $k_{\mathrm{tBuMA,copo}} = 1.29 \times 10^{-4}$ s^{-1} and $k_{\mathrm{DBT,copo}} = 3.93 \times 10^{-6}$ s^{-1}. For comparison, a homopolymerization with a 100% tBuMA feed under the same conditions (and with the same overall monomer concentration) had an observed $k_{\mathrm{tBuMA,homo}} = 1.35 \times 10^{-4}$ s^{-1}. This data indicated that the consumption of tBuMA was not inhibited by the presence of 9 mol % DBT. The DBT

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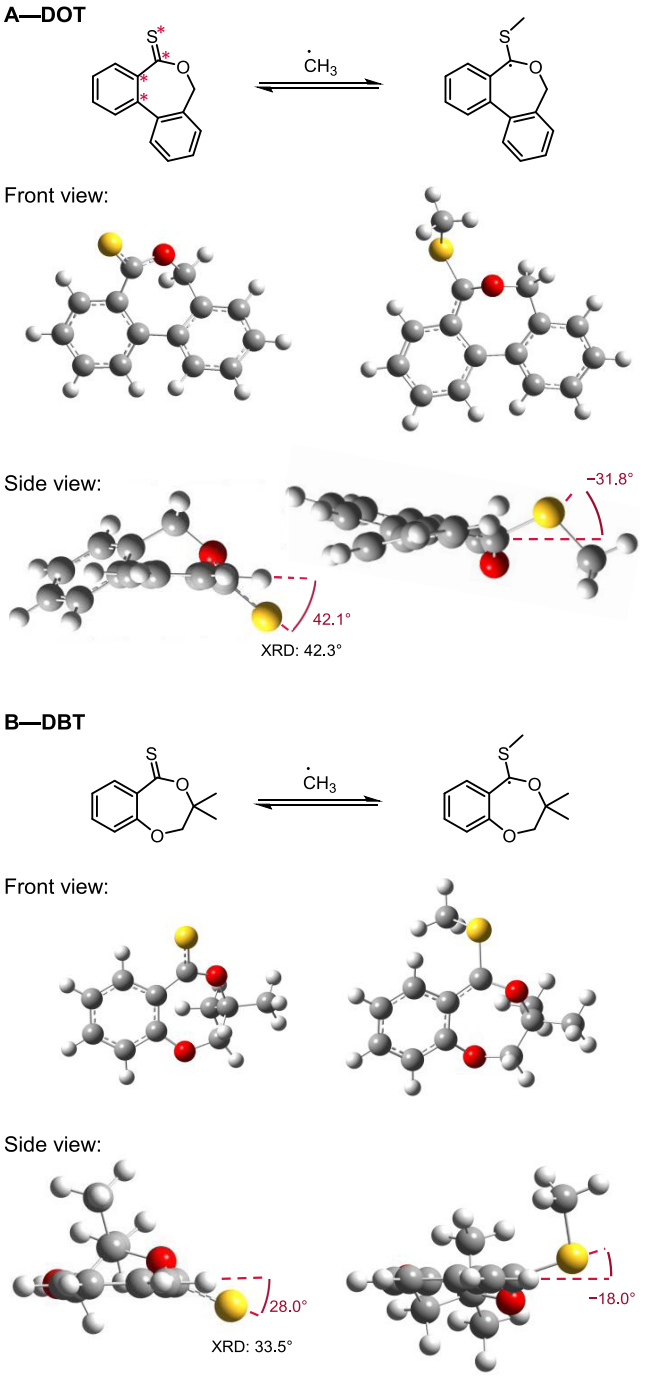
Scheme 5. Ball-and-Stick Structures of Thionolactone Monomers (measured by XRD) and of Methyl Radical Adducts for (A) DOT and (B) DBT[a]



[a]Estimated by optimization at the B3LYP/6-31G(d) level. The four atoms used to determine torsion angles are indicated by asterisks in the structure of DOT (the same atoms were used for other structures). Negative angles refer to a twist in the opposite direction. The side views are of the molecules tilted forward and viewed from the left. The XRD data for DOT was taken from the literature.[11]

consumption increased as the tBuMA feedstock was depleted and reached 27% after polymerizing overnight, corresponding to an overall DBT content of 3 mol %, comparable to the results found for RAFT copolymerization.

Apart from homopolymerization, a major advantage of DBT over DOT is its copolymerization (albeit slowly) with methacrylates under RAFT and free radical conditions. In order to facilitate the development of further thionolactone monomers, we sought to understand the observed behavior based on its structural differences to DOT. The initial aim of this study was to replace the benzylic reinitiating radical of DOT with a tertiary alkyl radical. The intended effect of reducing retardation was found with homopolymerization being more successful than with DOT. Changing the reinitiating radical could potentially affect the reactivity ratio between the thionolactone and vinyl comonomer adding onto this reinitiating radical and could, in the case of preferential reactivity toward the thiocarbonyl moiety, lead to DBT−DBT diads. The introduction of the new reinitiating radical also provided an ortho-alkoxy substituent on the aromatic ring. Strikingly, the presence of this substituent is not consistent with the observed faster incorporation of DBT in acrylate, acrylamide, styrene, and methacrylate polymerizations compared to DOT. The literature on radical C═S polymerization,[37] a multitude of functional and switchable RAFT agents,[38,39] and a first study into substituted DOT derivatives[14] agree that electron donation into a thiocarbonyl group reduces its reactivity toward radicals by decreasing the C═S double bond character (Scheme 4). Indeed, the measured ^{13}C NMR chemical shift of the thiocarbonyl group of DBT, δ (C═S) = 213.4 ppm, showed that it was more shielded (electron-rich) than the thiocarbonyl group of DOT (δ (C═S) = 216.1 ppm).[8]

To rationalize the observed *higher* reactivity of DBT compared to DOT, we compared the X-ray crystallographic structure of DBT (Figure 2B and Supporting Information) to that of DOT reported by Smith et al.[11] The measured thionoester C−O bond lengths of 1.33 Å (DOT) and 1.34 Å (DBT) were similar and between typical lengths of single bonds (1.43 Å) and double bonds (1.23 Å), suggesting a bond order of 1.5 and conjugation of the lone pairs of the thionoester for both thionolactones. The C−O−C angles at the thionoester were 118.7° (DOT) and 123.7° (DBT), close to 120° expected for sp^2 hybridization of the oxygens in agreement with the C(−S$^-$)═O$^+$ partial double bond character. Although there are differences between DOT and DBT, these C−O−C angles were not assumed to account for the observed reactivity differences. As a crude measure of ring strain, the absolute deviations from ideal angles (using 120° for sp^2 hybridized atoms, including the thionoester oxygens and 109.5° for the alkoxy bridge in DBT) were summed (see Table S2). Interestingly, DOT was found to have very little ring strain (total deviation of 10.6° from ideal angles), while the ring strain in DBT was considerably larger (40.2° total deviation). If the larger ring strain of DBT was associated with a faster ring-opening, it could shift the dynamic addition equilibrium to the right and thereby account for the faster incorporation.

Further, we examined the torsion angles between the C═S group and the attached ring. For a planar molecule (e.g., methyl thionobenzoate), this angle would be zero, with nonzero angles, indicating a twist of the thiocarbonyl group out of the aryl plane. A higher reactivity of thionolactones with lower torsion angles was recently proposed by Gutekunst.[40] Indeed, the relevant torsion angle determined by single-crystal XRD for DBT was 33.5°, somewhat lower than 42.3° reported[11] for DOT. These values agreed reasonably well

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with the torsion angles estimated computationally by optimizing the geometries at the B3LYP/6-31G(d) level (see Scheme 5). In addition, we calculated the Ar−C═S torsion angles of the intermediate radicals following the addition of a methyl radical (chosen for simplicity). Two observations were made. First, addition of the methyl radicals led to an inversion of the relevant torsion angles in DOT and DBT. Second, the estimated torsion angle of the methyl-DBT adduct (18.0°) was considerably lower than that estimated for the methyl-DOT adduct (31.8°). A lower torsion angle means better overlap and conjugation of the -SMe-based radical with the adjacent aryl π system. The resulting better stabilization of the intermediate radical in DBT shifts the addition equilibrium further to the right than for DOT. This torsion angle of the intermediate radical was therefore considered a main reason (together with lower ring strain) for the reactivity differences between DBT and DOT. This hypothesis was supported by *ab initio* molecular orbital theory and DFT calculations performed at the G3(MP2)-RAD(+) level, which estimated that the addition of a methyl radical onto DBT was 6.9 kJ/mol more favorable than the addition of a methyl radical onto DOT, see Figure S74.

During the writing of this manuscript, Luzel et al.[34] published DFT-calculated rate constants for the addition, reverse addition, and β scission for DOT and DBT (as well as other known and novel thionolactones). Their results confirmed the faster addition and more efficient ring-opening of DBT compared to DOT. A comparison of the transfer rate constant (which encompasses the reversible addition and subsequent ring-opening) with vinyl homopolymerization rates indicated the preferential (homo)polymerization of DBT in the presence of acrylates and styrene, as found here.

CONCLUSIONS

Structural modifications of the previously described thionolactone DOT resulted in drastically different (co)-polymerization properties, with several advantages over DOT. DBT formed homopolymers that showed an unexpected degradation of the ether bond. The very fast incorporation of DBT into styrene could be exploited in starve-fed formulations. Uniquely, DBT copolymerized, albeit sluggishly, with methacrylates. The discussion of the structure−property relationships revealed important insights for the design of novel thionolactones. In addition to the electronic effects well-documented for (noncyclic) RAFT agents, consideration needs to be given to the cyclic 3-D structure and the effects torsion angles and ring strain have on stabilizing the intermediate radical and releasing the reinitiating radical. The inclusion of XRD measurements and computational chemistry is thus relevant to the quest and understanding of novel thionolactone comonomers with tailored copolymerization behavior.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.macromol.3c01811.

Experimental section, homo- and copolymer NMR and IR data, copolymerization kinetics, homo- and copolymer degradation data (PDF)

Crystal structure data (CIF)

Accession Codes

CCDC 2124098 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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