

Insertion of Degradable Thioester Linkages into Styrene and Methacrylate Polymers

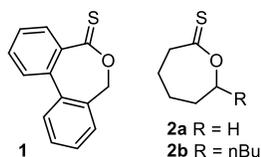
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Supporting Information Placeholder

ABSTRACT: The thionolactone 3,3-dimethyl-2,3-dihydro-5*H*-benzo[e][1,4]dioxepine-5-thione (DBT) is shown to homopolymerize and, for the first time, copolymerize with styrene and methacrylates, introducing degradable thioester backbone functionality. The rapid copolymerization with styrene was exploited to produce copolymers through free-radical polymerization in a starve-fed semi-batch setup. The copolymerization of DBT with *tert*-butyl methacrylate under RAFT conditions was hypothesized to involve selective retardation of DBT-terminal chains that led to a more uniform distribution of degradable thioester linkages between chains. Surprisingly, the aminolysis of DBT homopolymers was accompanied by the intramolecular ether cleavage within the primary degradation product leading to the formation of 2,2-dimethylthiirane and salicylamides.

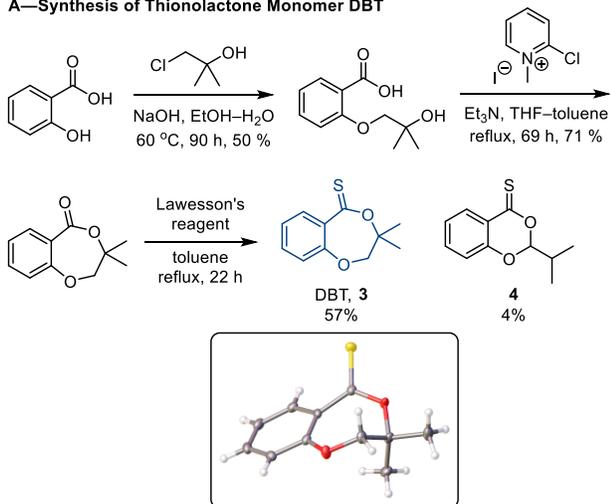
The incorporation of backbone degradability into vinyl copolymers is a remaining frontier in the polymer chemistry arena and offers new prospects in biomedicine.^{1,2} The radical ring-opening polymerization (RROP) of cyclic ketene acetals³ and allyl sulfide lactones⁴ has been used for several decades to install ester linkages into the backbone of vinyl copolymers. But these ester groups typically require harsh, non-selective conditions for cleavage. Recently, thionolactones were introduced as a new class of monomers undergoing radical ring-opening polymerization. The proposed mechanism, termed thiocarbonyl addition–ring-opening (TARO),⁵ involves the reversible⁶ addition of a radical onto the thiocarbonyl group to give an intermediate ($-C(SR)O-$) radical, which undergoes irreversible ring-opening through β -scission to yield thioester ($-C(=O)SR-$) backbone functionality. Significantly, these weak linkages can selectively be cleaved through aminolysis, thiolytic, or oxidative cleavage⁷ and are promising for the intracellular delivery of drugs through glutathione-triggered degradation. To date, three monomers, **1** and **2a–b**, have been shown to undergo TARO polymerization.



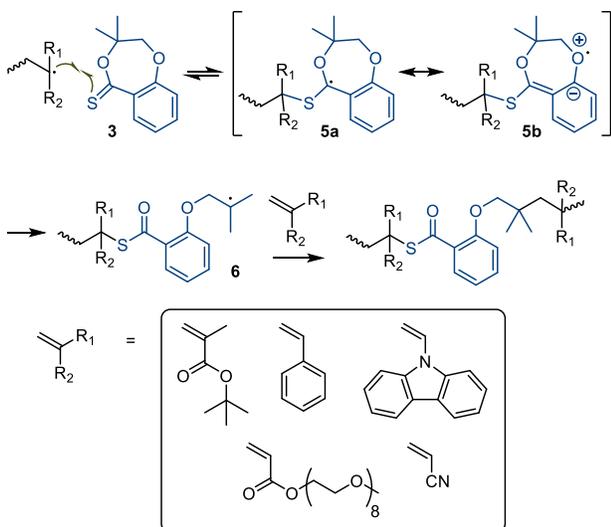
Dibenzo[c,e]oxepine(7*H*)-5-thione (DOT, **1**), is incorporated rapidly into copolymerizations with secondary more activated monomers (acrylates, acrylamides, acrylonitrile, *N*-functional maleimides), while its homopolymerization is slow and low-yielding.^{5, 8, 9} Conversely, the ϵ -thionocaprolactones **2a–b** undergo polymerization with the less activated monomers vinyl acetate and vinyl pivalate.^{10, 11} Notably, TARO copolymerization with styrenic and methacrylic monomers has not been achieved.

Herein, a new monomer, 3,3-dimethyl-2,3-dihydro-5*H*-benzo[e][1,4]dioxepine-5-thione (DBT, **3**) is presented that homopolymerized and copolymerized with styrene and methacrylates. DBT was synthesised in three steps from salicylic acid through phenol alkylation, lactonization, and thionation (see Scheme 1A and Figure S1–S9). DBT was hypothesised to be superior to DOT for two reasons. Firstly, the re-initiating radical (**6**) was chosen to resemble the *tert*-butyl radical which has initiation rate constants two orders of magnitude larger than the benzylic radical in DOT.^{12, 13} Secondly, the observed lack of copolymerization of DOT with styrene and methacrylates was attributed to the addition equilibrium lying on the side of the growing styrenic/methacrylic radical. In DBT, the ortho-alkoxy substituent was hypothesised to stabilise the intermediate radical through lone pair donation (resonance structure **5b** in Scheme 1B).¹⁴ Indeed, preliminary *ab initio* molecular orbital theory and DFT calculations performed at the G3(MP2)-RAD(+) level 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 S10). Notably, both changes (lowering the energy of the intermediate and increasing the energy of the open-ring radical) disfavor ring-opening. It was, however, hypothesized that the energy change associated with the thionolactone–thioester isomerization would be sufficient to drive the ring-opening. DBT 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 Figure S11–14. An attempted copolymerization of isolated **4** and methyl acrylate (MA) resulted in retardation without incorporation of thioesters.

A—Synthesis of Thionolactone Monomer DBT



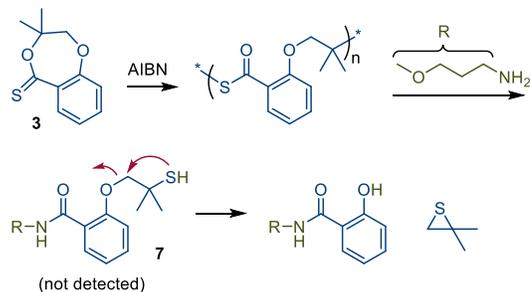
B—DBT Thiocarbonyl Addition–Ring-opening (TARO) Mechanism



Scheme 1. (A) Synthesis of DBT, **3**, with X-ray crystallographic structure¹⁵ and (B) TARO copolymerization mechanism of DBT with resonance forms of the intermediate radical (**5a–b**) and structures of the compatible vinyl comonomers.

DBT was found to homopolymerize (Table S1, Figure S13–S20) and copolymerize with acrylonitrile, poly(ethylene glycol) methyl ether acrylate, *N*-vinyl carbazole, styrene, and *tert*-butyl methacrylate (Figure S21–S35). The consumption of DBT was accompanied by the disappearance of its orange colour. Copolymers exhibited IR absorbances (ν_{C-S} stretch = 899 cm^{-1} , $\nu_{C=O}$ stretch = 1671 cm^{-1})¹⁶ and ¹³C NMR resonances ($\delta_{SC=O}$ = 192 ppm) characteristic of thioesters, supporting the expected TARO mechanism and the formation of thioester backbone functionality. No evidence of ring-retaining polymerization was observed. Surprisingly, an attempted copolymerization of DBT with *tert*-butyl acrylate under RAFT conditions led to the homopolymerization of DBT (Figure S36–S37). This result is similar to the recently reported homopolymerization of ϵ -thionocapro lactone **2a** in the presence of 50 mol-% 2-methylene-1,3-dioxepane.¹¹ Unlike this literature precedent, however, DBT also homopolymerized in the absence of *tert*-butyl acrylate. An AIBN-initiated free-radical polymerization reached 35% conversion after heating to 70 °C overnight. Two subsequent additions of further AIBN followed by degassing

increased the accumulated conversion to 66% and 88%, respectively. Surprisingly, upon aminolysis, DBT homopolymer did not degrade into the expected salicylamide *O*-ether **7**, but *N*-functional salicylamide and 2,2-dimethylthiirane, which were identified through ¹H and ¹³C NMR measurements (Figure S38–S42). These results confirmed the presence of easily cleavable thioester backbone functionality and that the ortho-alkoxy substituent provided an additional cleavable linkage (see Scheme 2).



Scheme 2. Synthesis of DBT homopolymer and aminolysis with the expected (though not detected) primary degradation fragment (**7**) and proposed mechanism leading to the formation of the observed products.

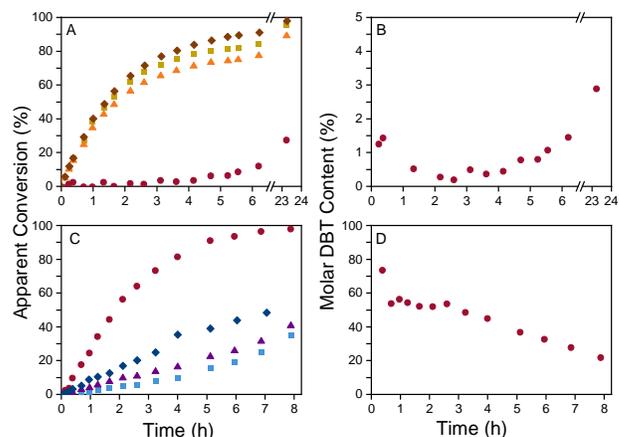


Figure 1. (A) Free-radical copolymerization kinetics of DBT-*t*BuMA (9:1 feed ratio) with the ¹H NMR-measured conversions of DBT (red circles) and *t*BuMA (yellow squares), global conversion (orange triangles) and *t*BuMA conversion in a comparable homopolymerization (brown diamonds); (B) Estimated overall molar DBT content of the DBT-*t*BuMA copolymer; (C) Free-radical copolymerization kinetics of DBT-styrene (9:1 feed ratio) with conversions of DBT (red circles) and styrene (light blue squares), global conversion (purple triangles) and styrene conversion in a comparable homopolymerization (dark blue diamonds); and (D) Estimated overall molar DBT content of the DBT-styrene copolymer.

Apart from homopolymerization, major advantages of DBT over DOT are its successful copolymerization with methacrylates and styrene. The AIBN-initiated free-radical copolymerization kinetics of DBT and *tert*-butyl methacrylate (*t*BuMA), as a representative methacrylic monomer, were determined for a 9:91 mol-% DBT-*t*BuMA feed ratio, see Figure 1A. The consumption of both comonomers was determined by ¹H NMR spectroscopy and followed first-order kinetics with estimated half-lives, $t_{1/2}(t\text{BuMA}) = 1.49$ h and $t_{1/2}(\text{DBT}) = 49$ h. For comparison, a homopolymerization with a 100% *t*BuMA feed un-

der the same conditions (and with the same overall monomer concentration) had an observed $t_{1/2}(t\text{BuMA}_{\text{homo}}) = 1.43$ h (Figure S43). This data indicated the uninhibited polymerization of $t\text{BuMA}$ in the presence of DBT with slow incorporation of the degradable repeat units. The DBT consumption increased as the $t\text{BuMA}$ feedstock was depleted and reached 27% after polymerizing overnight, corresponding to an overall DBT content of 3 mol-%, see Figure 1B. This situation is a well-documented dilemma with cyclic ketene acetals (the most widely used RROP monomer type) showing similarly low reactivity not only with methacrylates but also acrylates and acrylamides.⁴ Higher incorporation can typically be forced through a higher feed of the cyclic monomer although this process still leads to a compositional gradient.

Next, a 23:77 mixture of DBT- $t\text{BuMA}$ was polymerized in the presence of 1 equiv of the trithiocarbonate RAFT agent 4-cyano-4-[[dodecylsulfanylthiocarbonyl]sulfanyl]pentanoic acid yielding poly($t\text{BuMA}_{74}\text{-co-DBT}_2$) with a measured $M_n^{\text{SEC}} = 8.5$ kg/mol and $\mathcal{D} = 1.22$. This copolymer was then used as macro-RAFT agent for the chain extension with a $t\text{BuMA}$ homoblock (the same vinyl comonomer was chosen to facilitate SEC analysis) to give poly[($t\text{BuMA}_{74}\text{-co-DBT}_2$)-*bl*- $t\text{BuMA}_{60}$] ($M_n^{\text{SEC}} = 10.0$ kg/mol and $\mathcal{D} = 1.31$). Upon treatment of the block copolymer with *N*-ethylamine in THF, a species with $M_n^{\text{SEC}} = 5.8$ kg/mol and $\mathcal{D} = 1.34$ was obtained, see Figure 2. These results demonstrated that (i) TARO copolymerization of DBT was compatible with RAFT; the initial macro-RAFT agent had a low dispersity and retained the RAFT end group necessary for chain extension; (ii) all copolymers contained degradable backbone functionality with no residual block copolymer observed after aminolysis; (iii) the degradation product had a smaller apparent molar mass than the macro-RAFT agent, indicating that cleavage occurred within the first block rather than at the junction of the two blocks. RAFT polymerization has previously been demonstrated on thionolactones^{5, 8, 10, 11} but the case of DBT warrants further consideration. Notably, the RAFT copolymerization was strongly retarded. The kinetics of a 9:91 mol-% DBT- $t\text{BuMA}$ feed ratio gave estimated half-lives ($t_{1/2}(t\text{BuMA}) = 14$ h and $t_{1/2}(\text{DBT}) = 159$ h) much higher than a comparable homopolymerization of $t\text{BuMA}$ under RAFT conditions ($t_{1/2}(t\text{BuMA}_{\text{homo}}) = 4.5$ h) (Figure S44-S45). The retardation was presumed to arise from the attack of DBT-terminal chains on a RAFT agent because the DBT-derived radical (**6**) is a worse homolytic leaving group than the tertiary resonance-stabilised radical of a growing methacrylic chain.¹⁴ As the above results indicated, this did not lead to irreversible termination, but chains continued to grow (and could be extended) after adding the first DBT unit. It was hypothesised that the selective retardation of DBT-terminal chains would lead to a more uniform distribution of thioester linkages between chains, because a DBT-terminal chain is likely to “wait” until most other chains have added a DBT unit, too, and symmetrical RAFT intermediates are formed. Even the low DBT content of poly($t\text{BuMA}_{74}\text{-co-DBT}_2$) (for which a Poisson distribution would result in 14% of chains with zero DBT units) could thus result in the observed degradability of all chains.

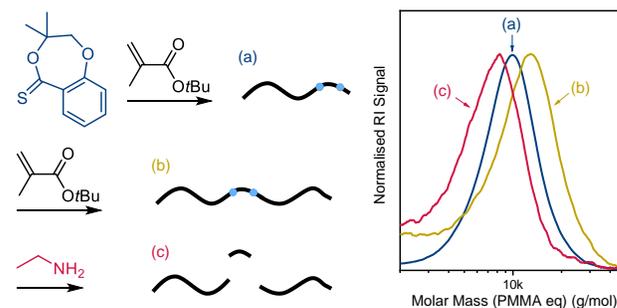


Figure 2. Size exclusion chromatograms of (a) RAFT-made poly($t\text{BuMA}_{74}\text{-co-DBT}_2$), (b) poly[($t\text{BuMA}_{74}\text{-co-DBT}_2$)-*bl*- $t\text{BuMA}_{60}$], and (c) the products of the aminolysis of the diblock (right) with cartoon showing the expected positions of thioester groups (light blue circles) within the chains (left).

The copolymerization kinetics of 9:91 mol-% DBT-styrene formulations, on the other hand, showed a strikingly different situation, see Figure 1C (free-radical polymerization) and Figure S47-S48 (RAFT). Compared to a comparable free-radical styrene (sty) homopolymerization ($t_{1/2}(\text{sty}_{\text{homo}}) = 7.1$ h), the presence of 9 mol-% DBT in a free-radical copolymerization retarded the styrene uptake to $t_{1/2}(\text{sty}) = 15$ h, while the DBT consumption was very rapid with a measured $t_{1/2}(\text{DBT}) = 1.4$ h (Figure S46). After 5 h, the DBT conversion exceeded 90%, while only 15% of styrene had been included into the oligomeric product. The estimated molar DBT content of the copolymer (Figure 1D) remained at 50% for the first 2.5 h of the copolymerization (suggesting the formation of alternating sequences) and became more styrene-rich as the DBT feed was being depleted. Similarly, a free radical copolymerization of a 10:90 mol-% DBT-sty feed had 100% DBT and 38% styrene conversions after running overnight and gave a product with an average 23 mol-% DBT content and an SEC-measured bimodal size distribution, $M_n^{\text{SEC}} = 8.2$ kg/mol and $\mathcal{D} = 2.53$. 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. Conversely, adding the overall 10-mol-% DBT feed continuously into an active free-radical polymerization of styrene in a starve-fed (semi-batch) process¹⁷ resulted in a comparable styrene conversion of 42% but lower DBT conversion of 20%. The product had an average DBT content of 5 mol-%, and measured $M_n^{\text{SEC}} = 8.7$ kg/mol and $\mathcal{D} = 1.83$, showing a narrower size distribution than the batch sample. Gratifyingly, following aminolysis, SEC analysis showed a clear shift of the entire distribution and a lower $M_n^{\text{SEC}} = 7.3$ kg/mol and $\mathcal{D} = 1.82$, indicating that all chains had contained (an albeit small amount of) degradable DBT repeat units, see Figure 3B. While the process still requires optimisation to achieve a higher DBT content and more uniform distribution within chains (an elaborate process¹⁷ 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.

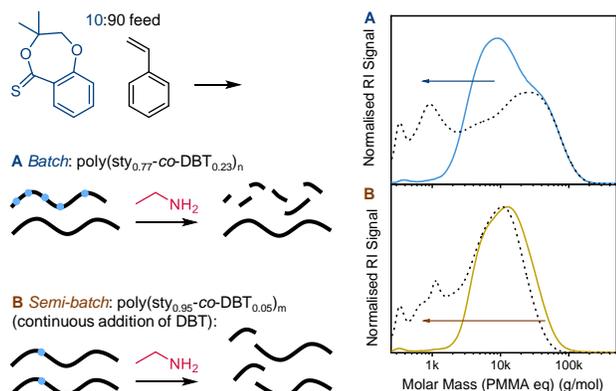


Figure 3. Size exclusion chromatograms (right, where dashed curves show measurements done on aminolysed samples) and cartoon (left) for the free-radical copolymerization of DBT and styrene in batch (all monomers together, A) and in semi-batch (B) where DBT was added continuously during the polymerization.

Concluding, structural modifications of the previously described thionolactone DOT resulted in drastically different (co)polymerization properties. Specifically, DBT outperformed DOT in three key challenges. Firstly, DBT formed homopolymers that showed an unexpected self-degradation of the ether bond. Secondly, DBT copolymerized with methacrylates. Although the incorporation of thioesters was sluggish and RAFT polymerization significantly retarded, the high energy re-initiating radical of DBT was hypothesised to cause to selective retardation that led to a more uniform distribution of degradable thioesters between chains. Thirdly, the very rapid incorporation of DBT into styrene copolymers was exploited through a starve-fed setup to produce degradable copolymers through free-radical polymerization. These novelties demonstrate that cyclic thionocarbonyl monomers can be adapted to be compatible with other monomer types, broadening the scope and applicability of TARO radical polymerization.

ASSOCIATED CONTENT

Supporting Information

Experimental section, homo- and copolymer NMR and IR data, copolymerization kinetics, homo- and copolymer degradation data.

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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interests.

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A novel thionolactone is shown to undergo free and RAFT radical homopolymerization and copolymerization with styrene and methacrylate comonomers, providing copolymers with selectively degradable thioester backbone functionality.

