Communication

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A Radical Approach to Thioester-Containing Polymers

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Supporting Information Placeholder

ABSTRACT: A new approach to radical ring-opening polymerization is presented that employs a new thionolactone monomer to generate polymers with thioester-containing backbones. The use of a thiocarbonyl acceptor overcomes longstanding reactivity problems in the field to give complete ring-opening and quantitative incorporation into a variety of acrylate polymers. The resulting copolymers readily degrade under hydrolytic conditions, in addition to cysteine-mediated degradation through transthioesterification. The strategy is compatible with reversible addition-fragmentation chain transfer (RAFT) polymerization and permits the synthesis of block polymers for the preparation of well-defined macromolecular structures.

One of the central features of polymers prepared using radical polymerization is an all-carbon backbone. While this feature has led to robust materials, it has also prevented potential pathways for degradation.[1] For next-generation materials, there is a need to upgrade these traditional polymers and establish systems with chemical diversity in the backbone that can breakdown in response to a stimulus.[2] The potential to diversify the backbone chemistry of radical polymers has long been available through radical ring-opening polymerization (rROP). In this process, a radical addition-fragmentation mechanism permits specialized cyclic monomers, such as cyclic ketene acetals (CKAs) **1**, to install esters into the polymer chain (Figure 1A).[3] Although rROP techniques were initially identified by Errede in 1961 and significantly developed by Bailey and Endo through the 1980's, the concept has been recently revived to prepare degradable polymers for biomedical applications.[4] For this end goal, only a minimum number of these monomers needs to be introduced for polymer breakdown, if homogeneously incorporated. Despite significant efforts in the field, classical radical ring-opening monomers have poor reactivity with many common vinyl monomers, thereby limiting this direction.[1, 5]

Two significant challenges exist in current radical ring-opening systems featuring cyclic ketene acetal monomers. The first is minimal control over the rate of addition to the CKA due to the high energy radical intermediate. This leads to reduced rates of copolymerization with less activated monomers, such as acrylates and styrenes, resulting in copolymers of heterogeneous composition.[5-6] Secondly, the rate of propagation of the intermediate radical competes with the rate of ring-opening, leading to nondegradable linkages. Recently, researchers have resolved some of these issues through judicious monomer selection. The O'Reilly, Dove, and Nicolas groups have employed vinyl acetate and vinyl ether derivatives that exhibit good reactivity ratios with CKAs. This method yielded high incorporations of the esters into polyfunctional polymer platforms ideal for biomedical applications.[7] The Sumerlin and Nicolas groups overcame both issues by using maleimides.[8] These charge-transfer mediated copolymerizations offered perfect alternating behavior and were compatible with controlled methods.

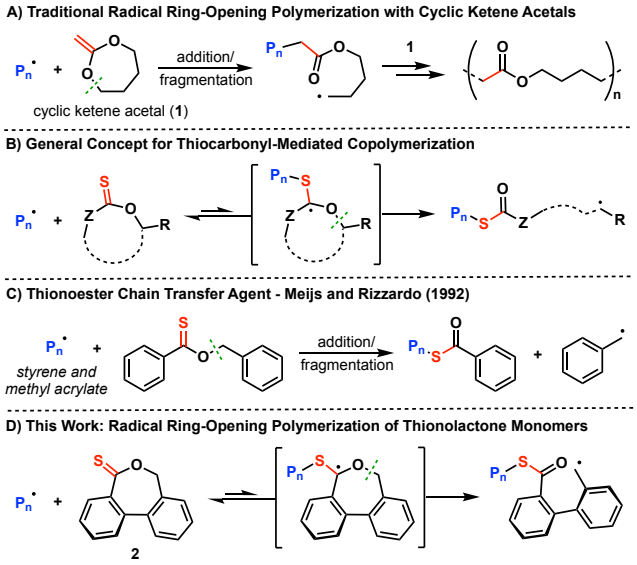
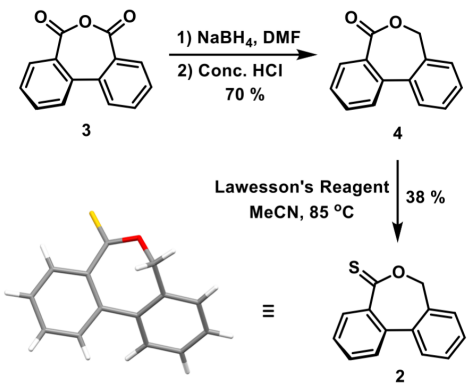


Figure 1. (A) Radical ring-opening polymerization (rROP) with a cyclic ketene acetal; (B) Concept of tunable thiocarbonyl monomers for rROP; (C) Thionoester derivative as chain-transfer agent (CTA) for styrene and methyl acrylate; (D) Developed thionolactone monomer design.

However, the required use of maleimides greatly limits the scope of this strategy. A creative strategy to polymerize macrocycles was recently reported by Niu and coworkers.[9] This work does not rely on a ketene acetal functionality, and instead fragments through an allyl sulfone addition/fragmentation cascade with sulfur dioxide extrusion. In this communication, a new concept for radical ring-opening polymerization is described using a thionolactone monomer to achieve excellent copolymerization with a range of acrylates to broaden the scope of rROP methodologies.

The thiocarbonyl motif has a privileged status in the history of small molecule and macromolecular radical chemistry.[10] Its use as a radicophile was initially exploited by Barton in the development of powerful deoxygenation and decarboxylation technologies that have significantly impacted small molecule synthesis.[11] Later, this reactivity was employed by Rizzardo, Moad, and Thang in the design of reversible-activation fragmentation-transfer radical (RAFT) polymerization.[12] When considering a new design for rROP, a thiocarbonyl radical acceptor appeared to solve two of the limitations of existing rROP monomers. Depending on the substituents, the thiocarbonyl acceptor would permit variable rates of radical addition, while preventing undesired 1,2 polymerization pathways due to its reversible reaction with radical species. The general concept for this design is shown in Figure 1B in which the Z and R groups could be modified to tune the radical stability for different

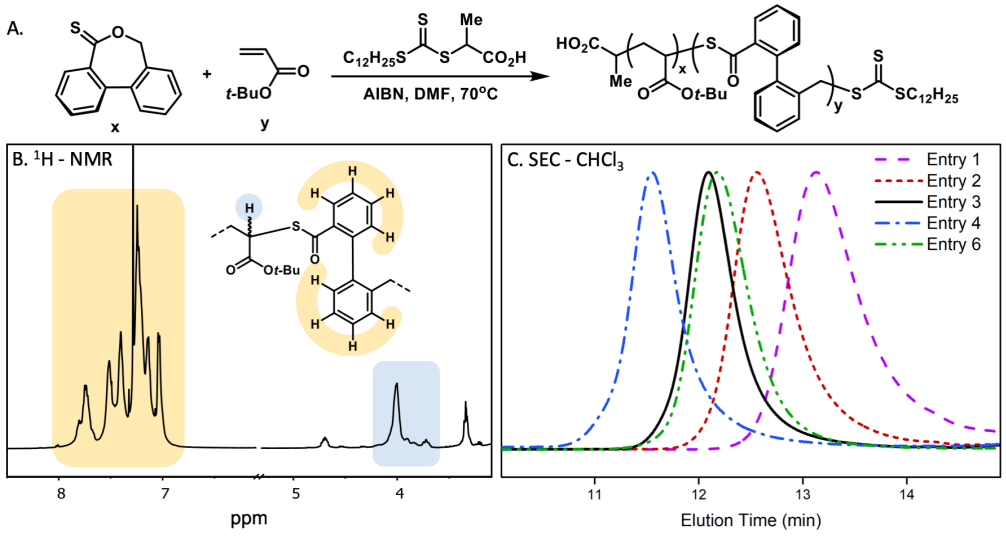
Scheme 1. Synthesis of Thionolactone Monomer 2.



monomer families, in analogy to the RAFT process. Despite some suggestions of this potential reaction pathway via computation[13] and in a patent[14], this approach has not been successfully demonstratedin the literature to date.[15] A key precedent for this concept was reported by Meijs and Rizzardo in 1992 where acyclic thionoesters were used as chain-transfer agents (Figure 1C). Importantly, this report demonstrated successful control of styrene and methyl acrylate, both of which exhibit poor copolymerization behavior with CKAs.[16] From this work, a first-generation rRO monomer system was envisioned by cyclizing the known transfer agent, leading to thionolactone **2**. If competent in radical ring-opening polymerization, thioester functional groups would be incorporated into the polymer backbone which are resistant to further radical chemistry (Figure 1D).[17] In addition to its synthetic utility in native chemical ligation[18], the Fukuyama reduction[19], and the Liebeskind-Srogl reaction[20], the thioester is an emerging functional group in polymer science for the design of responsive materials.[21] Further, it was anticipated that the benzylic radical resulting from fragmentation could be reversibly deactivated for compatibility with controlled polymerization methods.[22]

To test this hypothesis, a short synthesis of thionolactone **2** was developed starting from commercial diphenic anhydride (**3**) (Scheme 1). Following literature procedures,[23] the anhydride was reduced with sodium borohydride to give a desymmetrized carboxy alcohol that cyclizes to lactone **4** on workup with hydrochloric acid. Thionation with Lawesson's reagent[24] provided the desired thionolactone **2** in 38% yield as bright yellow-orange crystals. Unambiguous characterization was provided by single molecule X-ray diffraction, highlighting the nonplanar nature of the thionolactone biaryl axis. Initial tests to examine the efficacy of **2** in rROP were performed with *tert*-butyl acrylate (95:5) under free radical conditions. Compared to *tert*-butyl acrylate homopolymerization, the rate of copolymerization was slower, but a visual change of the reaction solution from orange to colorless strongly suggested consumption of the thionolactone (Figure S1). Further isolation and examination of the polymer by ^{1}H NMR spectroscopy (Figure S2) highlighted the presence of broad aromatic peaks, suggesting incorporation of the biaryl in the backbone.

To better understand the radical copolymerization, controlled polymerization techniques were explored. It was anticipated that the copolymerization would readily operate under RAFT conditions, as both methods rely fundamentally on thiocarbonyl additions. This was found to be true, and results of the optimized system are shown in Figure 2. From ^{1}H NMR, the RAFT chain-ends are clearly intact after polymerization at 3.4 and 4.7 ppm, and new peaks emerge in the 3.7 - 4.0 ppm range consistent with α-thioester protons. Analysis by size-exclusion chromatography (SEC) offered further evidence of the controlled polymerization. Using a 5% feed of the thionolactone, a variety of polymer molecular weights could



Entry [a]	Target DP	Thionolactone Feed	Thionolactone Conversion [b]	*t*BA Conversion [b]	Theoretical M_n (g/mol)	M_n (g/mol) [c]	$Đ$ [c]
1	25	5 %	≥ 98 %	≥ 98 %	3.3 k	4.4 k	1.05
2	50	5 %	≥ 98 %	≥ 98 %	6.5 k	7.6 k	1.05
3	100	5 %	≥ 98 %	97 %	12.9 k	13.4 k	1.10
4	250	5 %	≥ 98 %	95 %	31.7 k	32.6 k	1.27
5	100	10 %	≥ 98 %	96 %	13.3 k	16.8 k	1.12
6	100	35 %	94 %	76 %	13.8 k	14.5 k	1.08
7	100	50 %[c]	67 %	57 %	11.2 k	12.2 k	1.06

[a]Copolymerization of *t*BA and **2** was carried out using DoPAT and AIBN in DMF at 70 ºC. [b] Conversions were determined by ^{1}H NMR. [c] Molecular weights and molecular weight distributions were obtained using MALS.

Figure 2. (A) RAFT polymerization of *t*BA and thionolactone; (B) ^{1}H-NMR of copolymer highlighting diagnostic protons; (C) Size exclusion chromatograms selected entries.

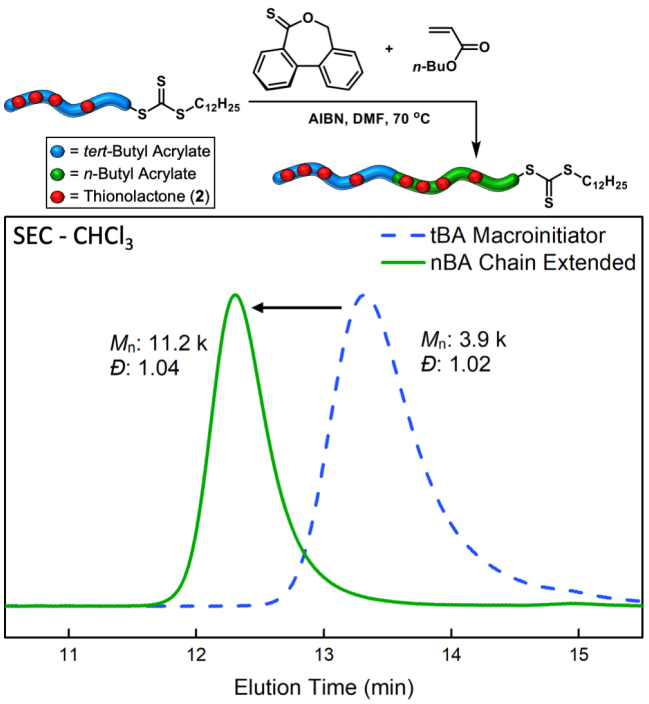


Figure 3. Synthetic scheme and SEC trace of 5% *t*BA copolymer chain extension with 5% *n*BA copolymer.

be accurately targeted by varying the monomer to initiator ratio from 25 to 250. In each case, high degrees of conversion were obtained with complete consumption of **2** while retaining low dispersities. The feed ratio of thionolactone **2** was varied in a separate series of polymerizations. It was found that the comonomer feed could be increased up to 50%, though lower conversion was obtained. Interestingly, further increase of the comonomer feed failed entirely under the reaction conditions (Table S3). The low conversion at higher feed ratios and lack of homopolymerization is possibly due to the slow initial rates of polymerization, as each comonomer can act as a reversible deactivating group before ring-opening.

To support the livingness of the product polymer, chain-extension experiments were performed (Figure 3). A 3.9 k molecular weight poly(*tert*-butyl acrylate) copolymer was prepared containing 5 mol% of the thioesters. Resubjection of the isolated macroinitiator to RAFT polymerization conditions with *n*-butyl acrylate

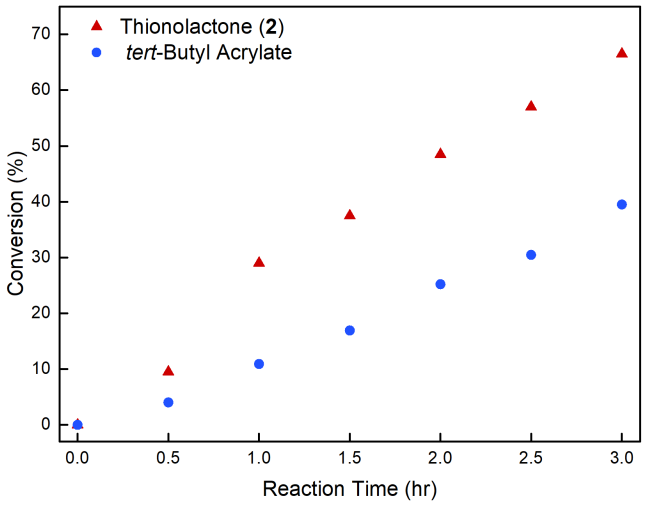


Figure 4. Kinetic plot showing the faster conversion of **2** compared to *t*BA in a 5% copolymerization experiment.

and **2** delivered a higher molecular weight diblock polymer (M_n 11,200). Importantly, a complete shift in the retention time of the diblock without residual macroinitiator highlights the high degree of chain-end fidelity and livingness of the polymers produced in the thionolactone rROP. This also shows the compatibility with other acrylate monomers. Further experiments with methyl, benzyl, and trifluoroethyl acrylates gave low dispersity copolymer products suggesting this process is quite general (Figure S12).

A central challenge in radical ring-opening polymerization is the slow rate of copolymerization with more-activated monomer families. For instance, when methyl acrylate is copolymerized with CKA **1**, only 7% of the ester linkages are integrated into the polymer chain starting from a 50% monomer feed.[6] To explore the kinetics of this system, a series polymerizations were initiated with a target DP of 100 using 5% thionolactone **2** and stopped at different time intervals to determine the relative rates of monomer conversion (Figure 4). The unusual kinetic behavior of this system is ascribed to the high concentration of reversibly deactivating thionoesters early in the polymerization, combined with the decrease in total monomer concentration over time. Importantly, these results demonstrate that **2** not only readily copolymerizies with *tert*-butyl acrylate but is consumed at an even *faster* rate – a trend not previously observed for acrylates in the rROP literature. This implies the product polymer possesses a slight gradient of comonomer distribution, though thioesters should still be present throughout the polymer chain.

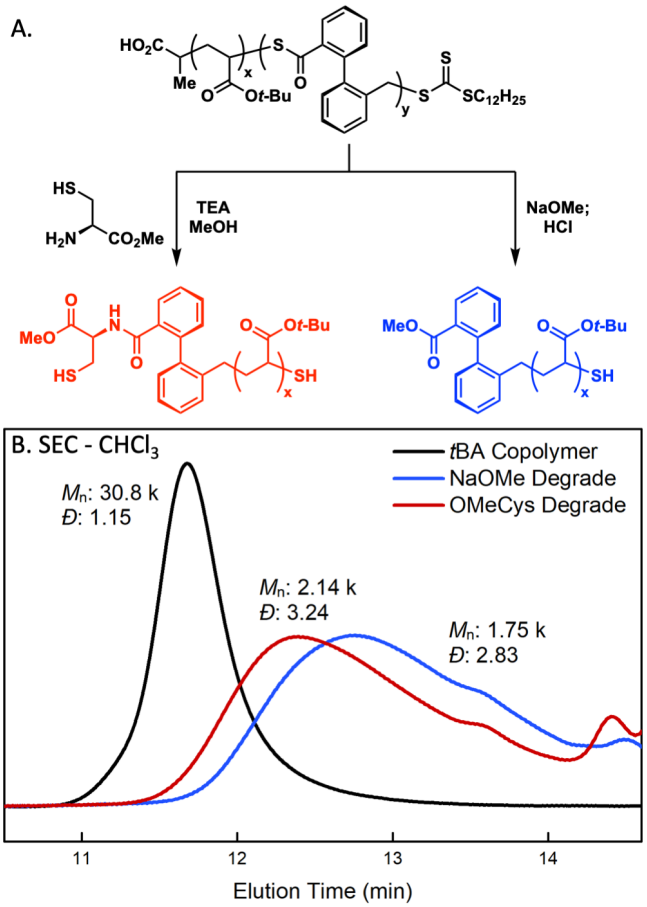


Figure 5. (A) Reaction scheme and (B) SEC traces of the degradation of a 5% *t*BA copolymer using sodium methoxide and cysteine methyl ester.

To support the kinetics study and verify the presence of thioesters in the copolymer, a set of degradation experiments were performed (Figure 5). Initial conditions explored sodium methoxide in

methanol at room temperature, as these conditions should rapidly lead to thioester methanolysis. This was confirmed by SEC where an initial copolymer (M_n 30,800) containing 5% thioester was reduced to a broad low molecular weight oligomer. This significant degree of degradation is consistent with the kinetic profile observed, where the thioesters are evenly distributed along the polymer backbone. To further confirm the presence of thioesters in the polymer backbone, a distinct approach for degradation was conducted using cysteine methyl ester. Thioesters are well known to undergo rapid thiol-thioester exchange.[21c, 21d, 25] When this process is used with cysteine derivatives, an intramolecular *S*-to-*N* acyl transfer occurs to give a stable amide bond. Upon reaction with cysteine methyl ester, once again a substantial reduction in the polymer molecular weight was observed by SEC analysis. This product had slightly higher molecular weight fragments, which could derive from cysteine chain-end effects or slightly less efficient polymer degradation. This presents significant evidence for a thioester linkage, as virtually no other functional groups would give degraded products under these conditions.

The twisted biaryl units that result in the backbone of the copolymers are foreign to radical polymerization. Given the expected rigidity of these monomer units, effects on the thermal properties was investigated. Using dynamic scanning calorimetry (DSC), a direct correlation of the glass transition temperature (T_g) to the monomer incorporation ratio was found, leading to materials with T_g's ranging from 46–81 ºC (Figure S10). Thermogravimetric analysis (TGA) of this copolymer series provided additional insight into the polymer compositions. Degradation of *tert*-butyl acrylate has an early onset of 295 ºC due to facile thermolysis of the *tert*-butyl esters. As the comonomer percentage increases, the relative loss of mass at this stage decreases, correlating well with the relative comonomer ratios seen by NMR analysis (Figure S11).

In conclusion, thionolactones have been introduced as a new monomer class for radical ring-opening polymerization. Through the application of a thiocarbonyl radical acceptor, historical challenges in the field have been addressed to prevent unwanted side reactions and enable polymerization with a variety of acrylate monomers to generate well-defined materials. The introduction of thioester functional groups into radical polymer backbones offers new directions for the engineering of materials that can respond to chemical stimuli and modulate thermal properties. Further, the potential to tune reactivity of this thiocarbonyl monomer platform will lead to control of the copolymer microstructure and compatibility with other monomer families.[26]

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:.

Experimental details and characterization data (PDF)

X-ray crystallographic data for **2** (CIF)

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Notes
The authors declare no competing financial interests.

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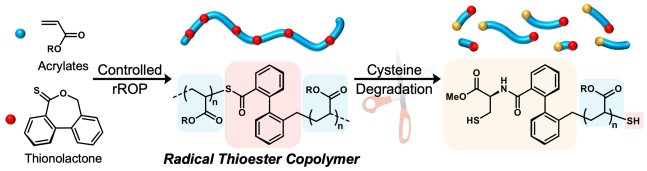
TOC Graphic


Acrylates
Thionolactone
Controlled
rROP
Radical Thioester Copolymer
Cysteine
Degradation