Communication

Radical Cascade-Triggered Controlled Ring-Opening Polymerization of Macrocyclic Monomers

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Radical Cascade-Triggered Controlled Ring-Opening Polymerization of Macrocyclic Monomers

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Supporting Information Placeholder

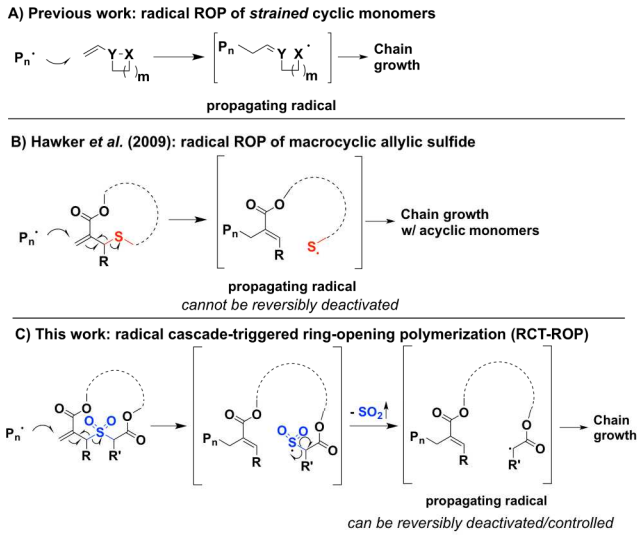
ABSTRACT: A strategy for the controlled radical ring-opening polymerization of macrocyclic monomers is reported. Key to this approach is an allyl alkylsulfone-based ring-opening trigger that can undergo a radical cascade reaction to extrude sulfur dioxide and generate an alkyl radical for controlled chain propagation. A systematic study correlating reaction conditions and polymer molecular weight and molecular weight distribution allowed excellent control over polymerization. The versatility of this radical cascade-triggered ring-opening polymerization (RCT-ROP) approach was further demonstrated through the first radical block copolymerization of macrocyclic monomers, and the incorporation of degradable functionality into the polymer backbone.

Over the recent decades, controlled radical polymerization has emerged as a powerful technique for the preparation of functional polymers with well-defined architectures.[1] Despite the successful incorporation of diverse functional pendant groups, traditional controlled radical polymerization techniques have been limited to simple vinyl (acrylic, methacrylic, and styrenic) monomers. Ring-opening polymerization (ROP) is a powerful approach capable of incorporating functional groups into the polymer backbone,[2] but the majority of ROP reactions that occur through a radical mechanism to date still require highly strained cyclic monomers (**Scheme 1A**),[3] limiting their utility in generating synthetic polymers with extended main-chain structural motifs.[4]

We sought to develop a general strategy for the controlled radical ROP of macrocyclic monomers with low ring strain (size ≥ 12-membered ring[5]). The major challenge for this vision is that the ring-opening products are energetically disfavored for the ROP of macrocyclic monomers.[1d, 6] To overcome this challenge, we envision that a novel "ring-opening trigger" based on the radical cascade reaction, in which substrates undergo sequential radical processes to form or cleave chemical bonds,[7] could be devised to provide the driving force for the ROP of macrocyclic monomers.[8]

Due to their synthetic accessibility and propensity for the homolytic cleavage of the C—S bond under mild conditions, allylic sulfides and allyl sulfones have become ubiquitous radical progenitors in radical coupling and polymerization reactions.[9] Cho *et al.* first reported the radical ROP of α-vinyl cyclic sulfones, but this early example still relies on the relief of ring strain as the primary driving force.[10] Rizzardo[11] and Hawker[12] developed a series of (macro)cyclic allylic sulfide monomers that can undergo radical ROP independent of the ring strain. However, in all of these previous examples, the propagating thiyl or sulfonyl radical resulted from ring opening cannot be reversibly deactivated/controlled, resulting in low reactivity and poor control over polymerization (**Scheme 1B**).[4] Inspired by the seminal work of Quiclet-Sire and Zard, which suggested that the extrusion of SO_2 from alkylsulfonyl radicals can readily occur if the resulting alkyl radical is stabilized,[13] a radical cascade-triggered ring-opening polymerization (RCT-ROP) approach was designed to provide the driving force for ring opening and extrude gaseous SO_2 to generate an alkyl radical (**Scheme 1C**). Central to this design is an allyl alkylsulfone-based ring opening trigger, which can undergo a radical cascade process consisting of the β-elimination of alkylsulfone and a following rapid α-scission to extrude SO_2, resulting in a secondary alkyl radical stabilized by an adjacent carbonyl group.[14] This "stable" secondary alkyl radical is structurally similar to the propagating radical of polyacrylates, thus enabling controlled chain growth via its reversible deactivation.

Scheme 1. Development of Radical Ring-Opening Polymerization

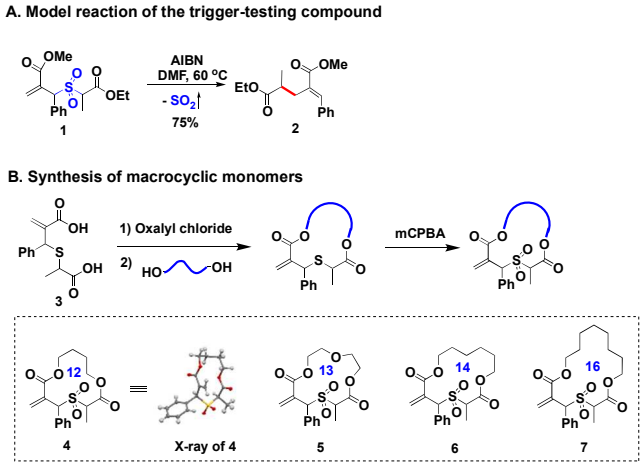


To test this design, a concise route was first devised to synthesize a "trigger-testing" compound **1** (**Scheme 2A**). Benzaldehyde was first coupled with methyl acrylate via the Morita-Baylis-Hillman reaction.[15] Upon protecting the hydroxyl group with acetic anhydride, this intermediate was reacted with ethyl 2-mercaptopropanoate to afford a thioether. Final oxidation of the thioether with *meta*-chloroperoxybenzoic acid (mCPBA) gave the compound **1** (**Scheme S1**). The α-phenyl substitution of the allyl sulfone was introduced to not only accelerate the β-elimination of

sulfonyl radical by forming a conjugated structure, but also sterically inhibit the crosslinking and backbiting at the resulted double bond. Next, the ability of **1** to undergo the radical cascade process was investigated. The reaction in the presence of azobisisobutyronitrile (AIBN) in *N*,*N*-dimethylformamide (DMF) at 60 °C afforded the coupling product **2** in 75% isolated yield over 10 hours (**Scheme 2A**). Notably, the alkylsulfonyl radical byproduct that failed to extrude SO_2 was not detected throughout the reaction, suggesting that the alkylsulfonyl radical was short-lived and could rapidly undergo α-scission to form the alkyl radical.

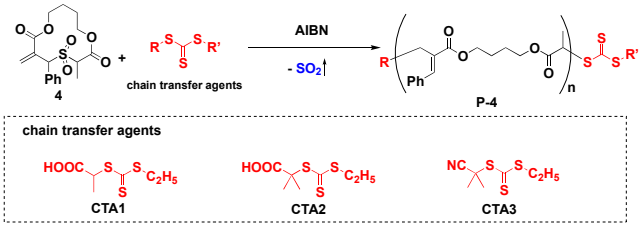
Encouraged by this result, we then developed an efficient and scalable synthesis of the macrocyclic monomers containing the ring-opening trigger. Similar to the synthesis of **1**, the coupling product of benzaldehyde, *tert*-butyl acrylate, and 2-mercaptopropionic acid was deprotected by hydrochloric acid to yield diacid **3**, which was then cyclized in one step by reacting with diols in a highly diluted solution (**Scheme S2**). In order to investigate the RCT-ROP of macrocyclic monomers of different ring sizes, 1,4-butanediol, diethylene glycol, 1,6-hexanediol, and 1,8-octanediol were chosen to couple with **3** to generate the corresponding macrocyclic thioethers, which were further oxidized by mCPBA to give macrocyclic monomers **4**, **5**, **6**, and **7**, respectively, in 4-11% overall yield (**Scheme 2B**). The macrocyclic structure of the monomer **4** was confirmed by X-ray crystallography. Notably, this short route employed inexpensive, commercially available reagents, and up to multi-gram quantities of monomers were readily obtained.

Scheme 2. Synthesis of Trigger-Testing Compound 1 and the Macrocyclic Monomers 4-7 (numbers in the structure indicate ring size)



Next, the RCT-ROP of **4** under different reaction conditions was examined (see supplementary information for details), with the representative results summarized in **Table 1**. Consistent with the trigger-testing reaction, free radical polymerization of monomer **4** in the presence of the initiator AIBN in DMF at 65 °C under nitrogen atmosphere successfully yielded a polymer with a number average molecular weight (M_n) by size-exclusion chromatography (SEC) of 9.8 kg/mol and dispersity ($Đ$, defined as the ratio of weight average molecular weight to M_n) of 1.70 (**Table 1**, Entry 1). With this promising result, we then focused on achieving control over the polymerization. Noting that secondary alkyl radical formed after the radical cascade reaction resembled the structure of the propagating radical of polyacrylates, we hypothesized that existing controlled radical polymerization techniques, such as the reversible addition-fragmentation chain transfer (RAFT) polymerization mediated by chain transfer agents (CTAs),[16] can be applied to reversibly deactivate/control the chain propagation of this alkyl radical. **CTA1-3** (**Table 1**, Entries 2-4) and other trithiocarbonates (**Table S2**) were evaluated by their ability to achieve control over polymerization. Among all CTAs screened, **CTA2** achieved better control over polymerization than others, indicated by the high M_n and the low $Đ$ of the resulting polymer (**Table 1**, Entry 3). Next, polymerization in various solvents, including DMF, dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), dioxane, chlorobenzene, and toluene was investigated (**Table S3**), and toluene was found to yield polymers with the highest M_n among all solvents screened (**Table 1**, Entry 5). Investigation on the effect of monomer concentration on the polymerization found that increasing monomer concentration did not lead to changes over the M_n and $Đ$, but reaction became sluggish at monomer concentrations lower than 0.1 M (**Table S4**). Consistent with controlled polymerization, M_n was found to be proportional to the ratio of monomer/CTA (**Table 1**, Entry 6). Further improvement of polymerization control was achieved by decreasing the amount of AIBN (**Table S5**). Lastly, increasing the reaction temperature to 100 °C was found to improve the polymerization rate while still maintaining good control (**Table S6**). As such, the optimal condition of the polymerization at a monomer/CTA/initiator ratio of 100:1:0.3 in toluene at 100 °C resulted in 62% monomer conversion in two hours (M_n = 12.1 kg/mol, $Đ$ = 1.15, **Table 1**, Entry 7). Higher monomer/CTA ratio of 300:1 under the same condition was found to increase polymer molecular weight and $Đ$ (M_n = 21.6 kg/mol, $Đ$ = 1.32, **Table 1**, Entry 8). The chain growth nature of the polymerization and the excellent control are further confirmed by the linear increase of the molecular weights with respect to the monomer conversion and low $Đ$ (**Figure 1A**). Notably, the linear relationship between $\ln([M]_0/[M]_t)$ versus reaction time indicates a first-order kinetics consistent with controlled polymerization, where $[M]_0$ is the initial monomer concentration and $[M]_t$ is the monomer concentration at a given time (t) (**Figure S7**).[17]

Table 1. RCT-ROP of Macrocyclic Monomer 4



Entry	[M]/[CTA]/[initiator][a]	CTA	Solvent	Conversion[b]	$M_{n\,(SEC)}$[c]	$Đ$[c]
1	50/0/1	-	DMF	86%	9800	1.70
2	50/1/1	**CTA1**	DMF	42%	4300	1.17
3	50/1/1	**CTA2**	DMF	50%	4900	1.20
4	50/1/1	**CTA3**	DMF	31%	3100	1.32
5	50/1/1	**CTA2**	Toluene	76%	7500	1.21
6	100/1/1	**CTA2**	Toluene	76%	13100	1.29
7[d]	100/1/0.3	**CTA2**	Toluene	62%	12100	1.15
8[e]	300/1/0.3	**CTA2**	Toluene	42%	21600	1.32

[a] Experimental conditions: monomer concentration [M] = 0.2 M, 65 °C under nitrogen for 15 h, unless otherwise noted. [b] Monomer conversion was determined by ^{1}H NMR spectroscopy. [c] Molecular weight and dispersity ($Đ$) were determined by SEC analysis calibrated to polystyrene standards. [d] 100 °C, 2 h. [e] 100 °C, 3 h.

The controlled synthesis of polymers with desired main-chain structural motifs was further confirmed by NMR and mass spectrometry analyses of **P-4**, the polymerization product of **4**. In order to increase the molar fraction of the chain ends with respect to the polymer backbone to facilitate the quantitative chain-end analysis using ^{1}H-NMR spectroscopy, polymerization with

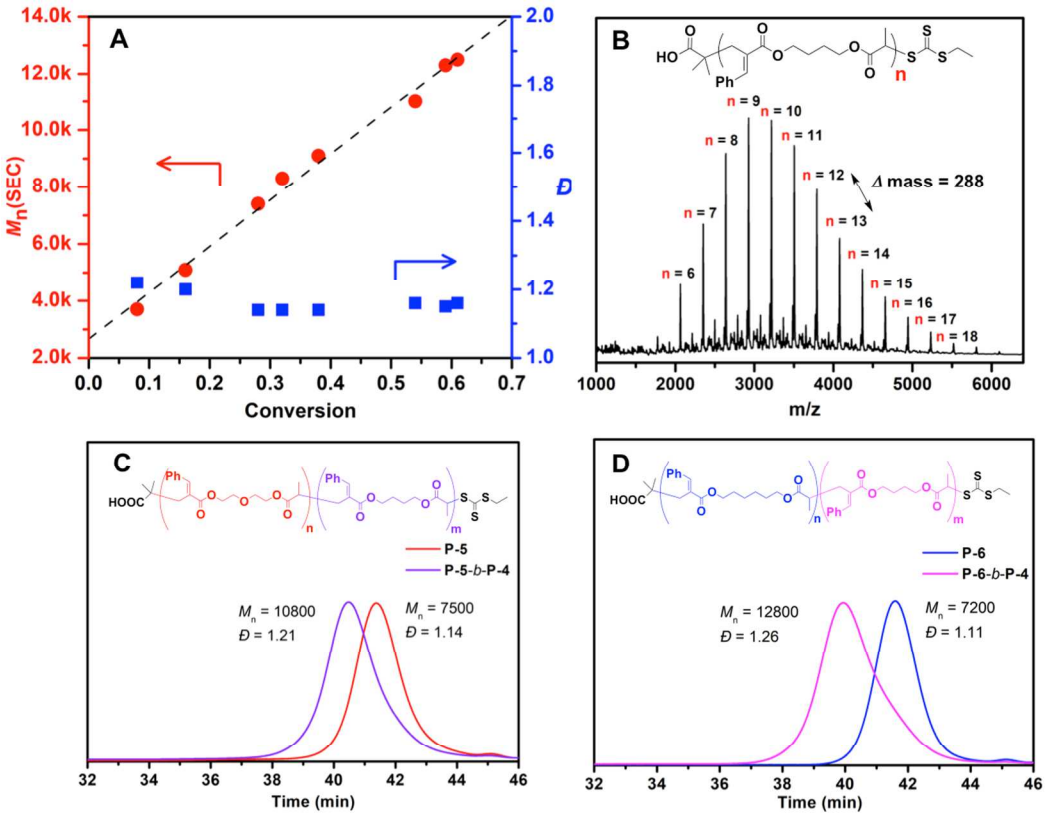


Figure 1. Controlled synthesis of homopolymers and block copolymers by RCT-ROP. (A) Plot of M_n (red) and $Đ$ (blue) versus monomer conversion. (B) MALDI analysis of **P-4-3k**. SEC analysis of block copolymers: (C) **P-5**-*b*-**P-4** and (D) **P-6**-*b*-**P-4**.

reduced monomer/CTA ratio (20/1) and limited monomer conversion (49 %) was conducted, affording **P-4-3k** with low molecular weight measured by SEC ($M_{n(SEC)}$ = 3.3 kg/mol). The molecular weight of **P-4-3k** determined by the ^{1}H-NMR peak integration ratio of polymer backbone to the chain-end group is 3.4 kg/mol, consistent with the theoretical value based on monomer conversion $M_{n(theo)}$ = 3.1 kg/mol and $M_{n(SEC)}$, indicating a quantitative preservation of the polymer chain-end groups (**Figure S8**). Subsequent analysis of **P-4-3k** by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry further confirmed intact chain-end groups of the individual oligomers of **P-4-3k** (**Figure 1B** and **Figure S9**).[18] The spacing between these discrete oligomers was consistent with the expected mass of the repeating unit (288 g/mol), unambiguously validating the RCT-ROP process. The high chain-end fidelity highlights the capability of RCT-ROP to generate well-defined polymer architectures, such as block copolymers.

To demonstrate the utility of the RCT-ROP technique in preparing block copolymers, chain extension experiments were studied in detail. First, RCT-ROP of a 13-membered macrocyclic monomer **5** yielded a macroinitiator **P-5** (M_n = 7.5 kg/mol, $Đ$ = 1.14), to which monomer **4** was polymerized. A clear shift to higher molecular weight was observed, yielding a diblock copolymer **P-5**-*b*-**P-4** (M_n = 10.8 kg/mol, $Đ$ = 1.21, **Figure 1C**). Next, the ability of our approach to incorporate macrocyclic monomers with increased ring sizes was investigated. Encouragingly, RCT-ROP of macrocyclic monomer **6** (14-membered ring) and **7** (16-membered ring) successfully yielded the controlled polymers **P-6** (M_n = 7.2 kg/mol, $Đ$ = 1.11) and **P-7** (M_n = 8.3 kg/mol, $Đ$ = 1.09), respectively. **P-6** was chosen to be further extended by monomer **4** to yield **P-6**-*b*-**P-4** (M_n = 12.8 kg/mol, $Đ$ = 1.26, **Figure 1D**). To the best of our knowledge, these are the first examples of controlled radical block copolymerization of macrocyclic monomers. These results illustrate the potential to incorporate diverse main-chain structural motifs by RCT-ROP into synthetic polymers, allowing for material properties ranging from biodegradability to self-assembly to biomimicry.

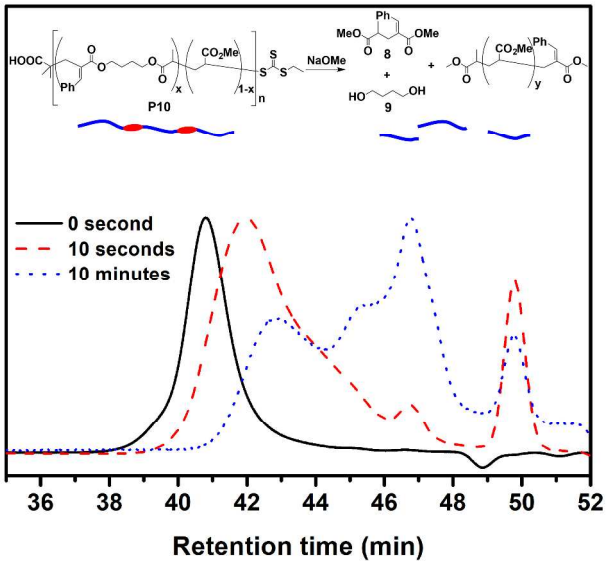


Figure 2. Degradation of Copolymer P10.

Despite their wide-spread utilities, acrylic polymers are extremely resistant to chemical and biological degradation processes, causing serious environmental consequences.[19] We envi-

sion that RCT-ROP of macrocyclic monomers consisting of hydrolytically degradable ester linkages offers a promising solution to this challenge. In order to test this concept, the degradation reactivity of the homopolymer **P-4** was first investigated. **P-4** was treated with sodium methoxide using the conditions developed by Hawker and coworkers,[12] and the degradation products **8** and **9** from the cleavage of the ester linkages were unambiguously confirmed by NMR (**Scheme S9**). Next, the degradation of **P10**, a copolymer of methyl acrylate (88 mol%) and monomer **4** (12 mol%) (M_n = 10.2 kg/mol, $Đ$ = 1.17, **Figure S12**) was investigated (see Supplementary Information for the synthesis and compositional analysis of the copolymer). SEC analysis of the degradation of **P10** exhibited a dramatic molecular weight reduction after only 10 seconds, with the reaction reaching completion after 10 minutes (**Figure 2**). These degradation experiments highlight the utility of RCT-ROP to fabricate synthetic polymers with functional main-chain structures such as novel (bio)degradable materials.

In summary, macrocyclic monomers containing an allyl alkylsulfone motif that can undergo radical cascade-triggered ring-opening polymerization have been developed for the controlled synthesis of polymers with extended main-chain structures. Excellent control over polymerization and high chain-end fidelity allows for the preparation of polymeric systems with well-defined architectures, exemplified by the first radical block copolymerization of macrocyclic monomers, and the incorporation of degradable structural elements in polymer backbone. Future work will investigate the generality of the radical cascade-triggered transformations in polymer chemistry. The application of this approach to the synthesis of polymers with diverse main-chain structural motifs with tailored functions will be another focus of our future exploration.

ASSOCIATED CONTENT

Supporting Information

Complete synthetic experiments, optimization tables, experimental methods, and additional experimental data. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare the following competing financial interest(s): A provisional patent based on this work has been filed (U.S. no. 62/684,810).

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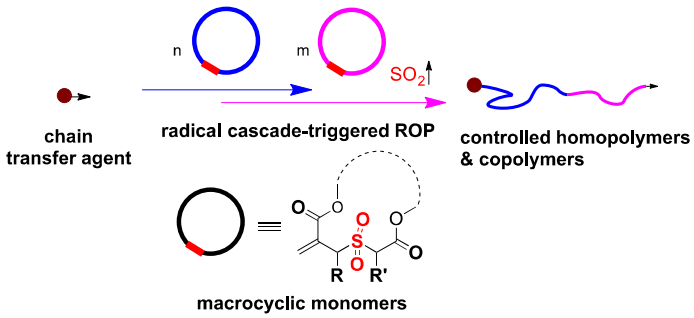
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