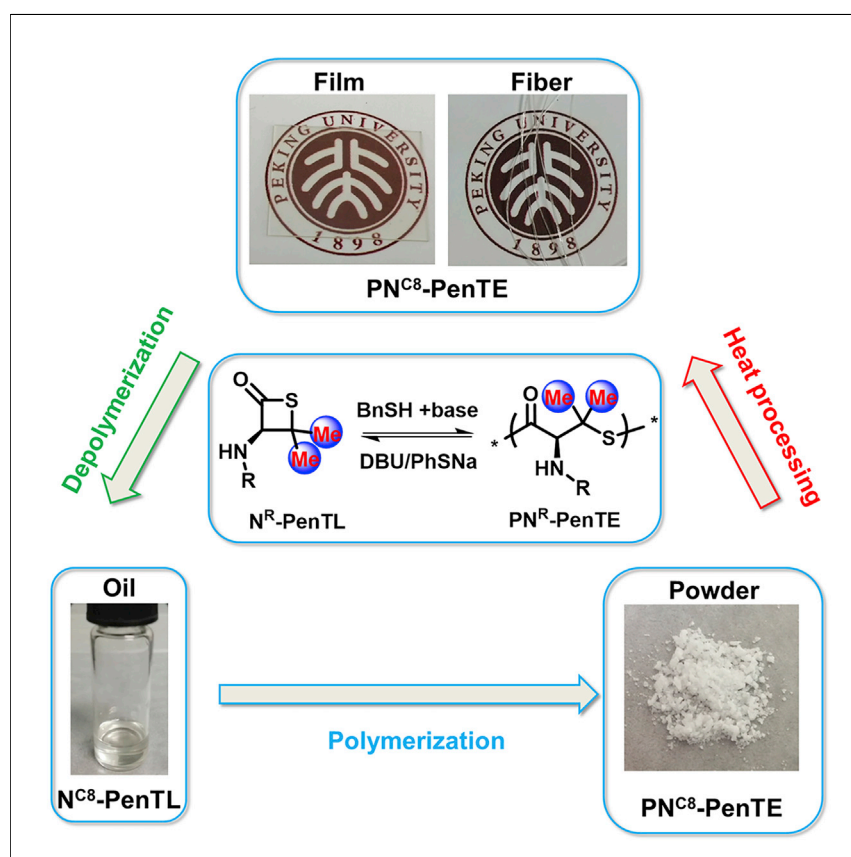


Article

Geminal Dimethyl Substitution Enables Controlled Polymerization of Penicillamine-Derived β -Thiolactones and Reversed Depolymerization



Polythioesters are promising candidates as sustainable polymers, but their controlled and selective (de)polymerization remains a significant challenge. In the current study, we addressed this problem by designing a thermodynamically neutral and kinetically trapped system based on penicillamine-derived β -thiolactones, opening the possibility of establishing a circular economy for plastic materials.

Wei Xiong, Wenying Chang,
Dong Shi, ..., Xuhao Zhou,
Er-Qiang Chen, Hua Lu

eqchen@pku.edu.cn (E.-Q.C.)
chemhualu@pku.edu.cn (H.L.)

HIGHLIGHTS

Highly controlled polymerization using *gem*-dimethyl substituted β -thiolactones

Efficient depolymerization due to a conformationally constrained terminal thiol

Semicrystalline polythioesters with high molar mass and tunable mechanical properties

Thorpe-Ingold effect for tuning the reversibility of ring-opening polymerization

Article

Geminal Dimethyl Substitution Enables Controlled Polymerization of Penicillamine-Derived β -Thiolactones and Reversed Depolymerization

Wei Xiong,¹ Wenying Chang,¹ Dong Shi,¹ Lijiang Yang,² Ziyou Tian,¹ Hao Wang,¹ Zhengchu Zhang,¹ Xuhao Zhou,¹ Er-Qiang Chen,^{1,*} and Hua Lu^{1,3,*}

SUMMARY

To access infinitely recyclable plastics, one appealing approach is to design thermodynamically neutral systems based on dynamic covalent bond, the (de)polymerization of which can be easily manipulated with low energy cost. Here, we demonstrate the feasibility of this concept via the efficient synthesis of polythioesters PN^R-PenTE from penicillamine-derived β -thiolactones and their convenient depolymerization under mild conditions. The *gem*-dimethyl group adjusts the thermodynamics of (de)polymerization to near equilibrium, confers better (de)polymerization control by reducing the activity and conformational possibilities of the chain-end thiolate groups, and stabilizes the thioester linkages in the polymer backbone. PN^R-PenTE with tailored properties is conveniently accessible by altering the side chains. PN^R-PenTE can be recycled to pristine enantiopure β -thiolactones at >95% conversion from minutes to a few hours at room temperature. This work highlights the power of judicious molecular design and could greatly facilitate the development of a wide range of recyclable polymers with immense application potentials.

INTRODUCTION

The annual global production of plastics has increased more than 20-fold since 1964, reaching 348 million metric tons in 2017.¹ The rapid accumulation of petroleum-based plastic wastes has created one of the greatest environmental crises in the world.² Single-use plastics have been banned in Europe, while other countries (e.g., China) are expected to enact similar regulations in the near future. In conjunction to developing methodologies for the degradation of existing plastics,^{3–5} the need for infinitely recyclable new plastics from renewable feedstock has received vast global attention.^{6–12} As previously suggested by Endo, Albertsson, and others, one of the many appealing strategies is to design thermodynamically near-equilibrium systems for easy manipulation of the polymerization and reverse depolymerization.^{13–17} Along this direction, many biomass and CO₂ derived synthetic polymers, mainly polyesters and polycarbonates, have shown their capability of establishing a circular economy of monomer-polymer-monomer.^{18–34} Despite the advancement, the development of recyclable polymers under mild condition and at low energy cost have been limited. Some of the thermodynamically neutral systems may suffer from low selectivity in monomer recovery as a result of the generation of oligomeric mixtures, thus necessitating extra work to push the equilibrium towards monomer formation. Kinetically trapped polymers such as poly(γ -butyrolactone) can be completely recycled, elegantly demonstrated by Chen et al., but the polymerization

The Bigger Picture

Chemically recyclable polymers from renewable feedstock hold great promise for solving the imminent global plastic-waste crisis. Despite recent advances, challenges including high energy consumption, the limited choices of sustainable polymers, and side reactions that could hamper complete monomer recovery are still yet to be addressed. By introducing a *gem*-dimethyl substitution, we succeeded in regulating both the forward polymerization of β -thiolactones and the backward depolymerization of polythioesters in a highly controlled fashion and with low energy input. Moreover, our strategy allows facile access to semicrystalline plastics with tailorable mechanical and thermal properties from biorenewable penicillamine feedstock. We envision that our design principle can facilitate the development of a new generation of chemically recyclable polythioester-based polymers, providing a sustainable solution to the ongoing environmental and economic challenge caused by nondegradable plastics.



of the non-strained γ -butyrolactone requires very low temperatures (-30°C to -60°C) because of unfavorable thermodynamics ($\Delta G_{\text{P}}^{\circ} = +6.4 \text{ kJ/mol}$). Moreover, both the polymerization and depolymerization need strong catalysts and demanding conditions because of the relatively high energy barrier for ester activation.^{19,31} Thus, introducing more dynamic bonds to thermodynamically near-equilibrium system could be a viable but underdeveloped approach to design sustainable polymers.

Polythioesters (PTE) are one such intriguing example because of the dynamic thioester bonds in their backbones, which are more reactive than their oxoester analogues.^{35–47} However, PTEs are significantly less explored than polyesters due to a lack of controlled ring-opening polymerization (ROP) methods that convert thiolactones to high-molar-mass (M_n) polymers with narrow dispersity ($\mathcal{D}$). A few recent advances by the Bowman,³⁷ Lu,⁴⁰ and Gutekunst³⁹ groups achieved modest-to-good control of PTEs, but the recycling of the polymers were not investigated. The use of amino acid as the feedstock is a smart approach to access chiral and semicrystalline polymers. We have recently reported the controlled synthesis of PTEs from 4-hydroxyproline-derived thiolactone (ProTL) monomers and demonstrated that the polymers can be conveniently depolymerized.⁴⁸ Nevertheless, these polymers are found to be brittle due to their prolyl backbone with relatively restricted conformations, necessitating further optimization of appropriate side chain and new backbone design.⁴⁹

An interesting study by Suzuki and coworkers reported the synthesis of PTEs from a cysteine-derived β -thiolactone (CysPTE).⁵⁰ Unfortunately, the resulting polymers are characterized by relatively low molar mass (typical $M_n < 10 \text{ kg/mol}$), broad dispersity ($\mathcal{D} \sim 1.6\text{--}2.4$), and mixed linear and cyclic topologies. The underlying challenges include undesirable chain transfer, reshuffling, and backbiting, all or at least partially attributable to the extensive transthioesterification side reactions. CysPTEs are also difficult to depolymerize for monomer recycling owing to the highly strained 4-membered β -thiolactone ring. One classical strategy of accelerating ring closure and stabilizing strained rings in physical organic chemistry is the *gem*-disubstituent effect, so called Thorpe-Ingold effect.^{51,52} We thus hypothesize that the introduction of a geminal dimethyl (*gem*-DM) group on the four-membered ring could tune the thermodynamics to near equilibrium for improved propensity of depolymerization, and in the meantime mitigate the reactivity of both the chain ends and PTE backbone for reduced transthioesterification (Scheme 1). Notably, such monomers can be easily produced and tailored with various side chains starting from a naturally occurring amino acid, D-penicillamine.^{53,54}

RESULTS

Controlled Polymerization

We first synthesized five penicillamine-derived β -thiolactone monomers (N^{R} -PenTL) with different side-chains (Scheme 1B), including N^{Ac} -PenTL and N^{Boc} -PenTL as white crystals, as well as N^{C^8} -PenTL, N^{ene} -PenTL, and N^{EG^4} -PenTL as colorless oils (^1H and ^{13}C NMR, high-resolution mass spectrometry, and X-ray diffraction in Figures S1–S16). Notably, the monomer synthesis is a simple and robust one-pot process and can be easily scaled up to ten-gram scale per batch in the laboratory. The ROP of each substrate was then initiated by benzyl mercaptan and catalyzed by an organobase of suitable basicity (Scheme 1B). No ROP of N^{Ac} -PenTL or N^{Boc} -PenTL was observed (Table 1, entries 1 and 2), most likely because of their limited solubility (less than $\sim 90 \text{ mg/mL}$ in tetrahydrofuran [THF]), which is lower

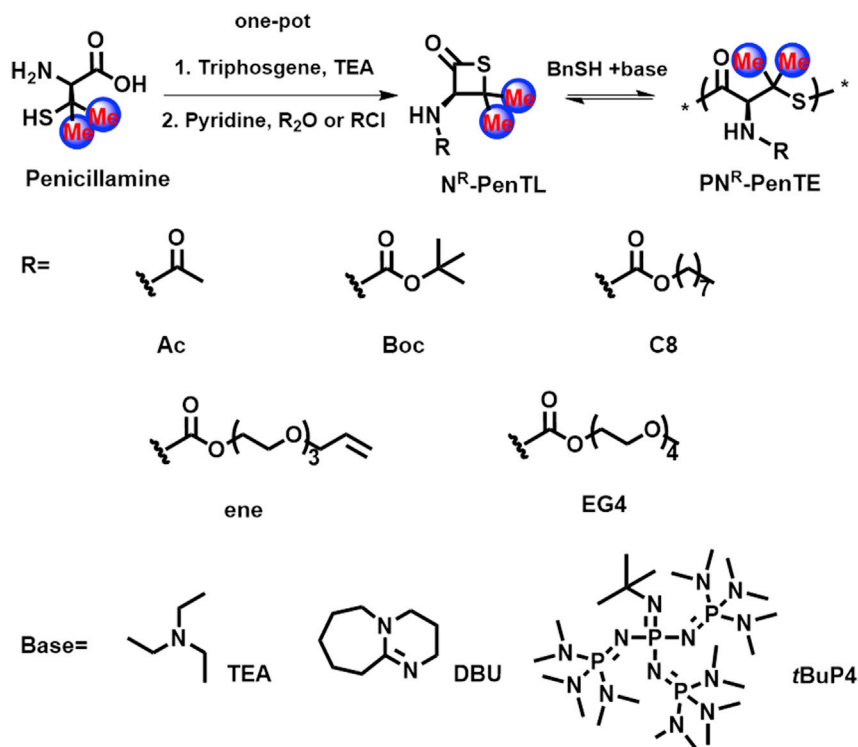
¹Beijing National Laboratory for Molecular Sciences, Center for Soft Matter Science and Engineering, Key Laboratory of Polymer Chemistry and Physics of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, People's Republic of China

²Institute of Theoretical and Computational Chemistry, Biodynamic Optical Imaging Center, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, People's Republic of China

³Lead Contact

*Correspondence:
eqchen@pku.edu.cn (E.-Q.C.),
chemhualu@pku.edu.cn (H.L.)

<https://doi.org/10.1016/j.chempr.2020.06.003>



Scheme 1. Synthesis and Ring-Opening Polymerization of Various N^{ene}-PenTL

than the equilibrium monomer concentration. We therefore focused our effort on the ROP of the three liquid monomers because they were substantially more soluble in common organic solvents or could be even executed for bulk polymerization. We measured the $[M]_{eq}$ of N^{ene}-PenTL at various temperatures to draw the Van't Hoff plot (Figure S17). According to the linear regression, the enthalpy (ΔH_p°) and entropy (ΔS_p°) changes of the ROP were calculated to be -9.4 kJ mol^{-1} and $-28.1 \text{ J mol}^{-1} \text{ K}^{-1}$, respectively. This, in turn, gave a ΔG_p° of -1.0 kJ mol^{-1} ($-0.24 \text{ kcal mol}^{-1}$) at 25°C and a ceiling temperature (T_c) of 61°C at an initial monomer concentration ($[M]_0$) of 1.0 M .

To increase reaction efficiency, we conducted bulk polymerization of N^{ene}-PenTL and N^{C8}-PenTL at room temperature and a feeding monomer/initiator ratio (M/I) of $100/1$. To our gratification, the ROP of N^{ene}-PenTL, catalyzed by a weak organobase, triethylamine (TEA, $pK_a^{\text{DMSO}} = 9.0$),⁵⁵ afforded the desired polymer product PN^{ene}-PenTE ($^1\text{H NMR}$ in Figure S18) with a considerably larger M_n and narrower dispersity (entry 3, Table 1; $M_n = 19.4 \text{ kg/mol}$, $\mathcal{D} \sim 1.10$) than those of similar PTEs synthesized previously from CysTLs ($M_n \sim 8.8 \text{ kg/mol}$, $\mathcal{D} \sim 2.4$) at the same M/I ratio.⁵⁰ Replacing TEA (1.0 equiv relative to initiator) with 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, 0.1 equiv), a stronger base with a pK_a^{DMSO} of 12,⁵⁵ greatly accelerated the ROP reaction (Table 1, entries 4–7; Figure 1A) while preserving the controllability, as evidenced by the unimodal peaks in size-exclusion chromatography (SEC) analysis. Increasing the M/I ratio resulted in a corresponding linear elevation in the M_n of PN^{ene}-PenTE (Figure 1A). The DBU-catalyzed ROP of N^{ene}-PenTL also demonstrated other typical features of controlled polymerization, such as the observation that the monomer conversion displayed a linear relationship with M_n (Figure 1B). The ROP of N^{C8}-PenTL showed very similar controllability to that of N^{ene}-

Table 1. Ring-Opening Polymerization of N^R-PenTL

Entry	Monomer	Base	[M] ₀ /[I] ₀ /[Base] ₀	Time (h)	M _n ^{cal} (g mol ⁻¹) ^a	M _n ^{obt} (g mol ⁻¹) ^b	Đ ^c	Conv. ^d
1	N ^{Ac} -PenTL	TEA	50/1/1	24	8,700	–	–	0
2	N ^{Boc} -PenTL	TEA	50/1/1	24	11,600	–	–	0
3	N ^{ene} -PenTL	TEA	100/1/1	72	34,700	19,400	1.10	61%
4	N ^{ene} -PenTL	DBU	30/1/0.1	1	10,400	6,400	1.11	58%
5	N ^{ene} -PenTL	DBU	50/1/0.1	3	17,400	9,900	1.09	60%
6	N ^{ene} -PenTL	DBU	75/1/0.1	4.5	26,000	13,700	1.15	61%
7	N ^{ene} -PenTL	DBU	100/1/0.1	6	34,700	18,500	1.14	59%
8	N ^{C8} -PenTL	DBU	100/1/1	0.3	28,700	20,100	1.21	70%
9	N ^{C8} -PenTL	tBuP4	250/1/1	20	71,800	52,400	1.26	69%
10	N ^{C8} -PenTL	tBuP4	350/1/1	24	100,500	70,600	1.23	70%
11	N ^{Boc} -PenTL, N ^{C8} -PenTL	DBU	30/70/0.5/1	1	27,000	14,100	1.24	42%, 56%
12	N ^{EG4} -PenTL	DBU	50/1/1	6	18,300	13,900	1.30	57%

Polymerizations were initiated with benzyl mercaptan in a glovebox at room temperature. All entries were performed as bulk polymerizations except for entries 1 and 2, which were conducted in THF.

^aM_n^{cal} = calculated number-average molar mass based on the feeding M/I ratio.

^bM_n^{obt} = obtained number-average molar mass determined by SEC in DMF with 0.1 M LiBr.

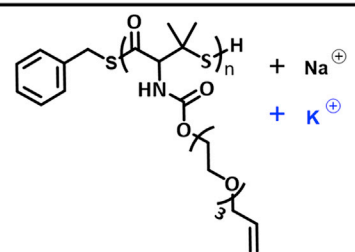
^cĐ = dispersity.

^dMonomer conversion, determined by ¹H NMR spectroscopy.

PenTL (Table 1, entries 8–10). For example, DBU-catalyzed formation of PN^{C8}-PenTE (¹H NMR in Figure S19) at a M/I ratio of 100/1 exhibited a M_n of 20.1 kg/mol and Đ of 1.21 (Table 1, entry 8). Employing tBuP4, a phosphazene superbases with a pK_a^{DMSO} of 30.3,⁵⁵ further boosted the M_n to 52.4 and 70.6 kg/mol at a M/I ratio of 250/1 and 350/1, respectively, while maintaining a Đ less than 1.30 (Table 1, entries 9 and 10). Copolymerization of N^{C8}-PenTL and N^{Boc}-PenTL mixture gave a random copolymer with a M_n of 14.1 kg/mol and a Đ ~1.24 (Table 1, entry 11). The ROP of N^{EG4}-PenTL, a monomer containing an oligoethyleneglycol side chain, afforded a PEG-like polymer PN^{EG4}-PenTE (¹H NMR in Figure S20) also with satisfactory control (Table 1, entry 12). Notably, all polymerizations became viscous immediately after the addition of base and gelized eventually as a result of the high concentration. It is also noteworthy that the polymerizations needed to be carefully quenched before subsequent processing because of the reversibility.

Facile Functionalization

Next, we examined the chain-end group of the resulting PN^{ene}-PenTE and its ability to undergo post-polymerization modification. Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrum of benzyl mercaptan-initiated PN^{ene}-PenTE₁₅ contained only one set of molecular ion peaks with a spacing of 347 Da between two adjacent peaks, which corresponded to the molar mass of the monomer (Figure 1C). Moreover, the end groups were unambiguously assigned to the initiating PhCH₂S– group on the α end and free tertiary thiol on the ω terminus (Figure 1C, plus Na⁺ or K⁺). When the ROP was quenched with a small molecular capping agent, such as iodoacetamide, MALDI-TOF analysis gave exclusively PN^{ene}-PenTE bearing PhCH₂S– and –CH₂CONH₂ as the α and ω end groups, respectively (Figure S21). Similarly, PN^{C8}-PenTE also gave well-defined chain end groups in the MALDI-TOF analysis (Figures S22 and S23). Moreover, PN^{ene}-PenTE (ω end capped) was found to withstand typical UV-triggered thiol-ene reactions, and the side chain alkenes were converted to long alkyls (Figure S24) or anionic sulfate



(A) Plots of M_n and $\bar{D}$ as a function of the $[M]_0/[I]$ ratio. Inset: overlay of SEC curves at different $[M]_0/[I]$ ratios.
 (B) Plots of M_n and $\bar{D}$ as a function of monomer conversion at the $[M]_0/[I]$ ratio of 100/1. Inset: overlay of SEC curves at different monomer conversions.
 (C) MALDI-TOF mass spectrum of benzyl-mercaptan-initiated PN^{ene} -PenTE₁₅.

Thermal and Mechanical Properties

Next, we studied the thermal properties of PN^{C8}-PenTE ($M_n \sim 70.6$ kg/mol) via thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). PN^{C8}-PenTE showed a 5%-weight-loss decomposition temperature (T_d) of $\sim 192^\circ\text{C}$ regardless of the capping status at the ω end (Figure S27). DSC depicted a weak glass transition at $\sim 50^\circ\text{C}$ (T_g), and a large endotherm peaked at $\sim 100^\circ\text{C}$, which corresponds to crystal melting in the heating scan (Figure 2A). Upon cooling, an exothermic peak was observed at a temperature slightly lower than the melting temperature (T_m). Dilatometry testing suggested that the T_g and T_m of the same polymer were $\sim 45^\circ\text{C}$ and $\sim 100^\circ\text{C}$ (Figure S28), respectively, which agreed well with the DSC results. In the tensile test using dynamic mechanical analysis (DMA), PN^{C8}-PenTE showed a Young's modulus of 300 MPa at 30°C and a catastrophic failure before yielding with a strain of 2.8% (Figure 2B). Above T_g , the Young's modulus reduced to 110 MPa, and on the other hand, the breaking strain increased to 170% at 60°C .

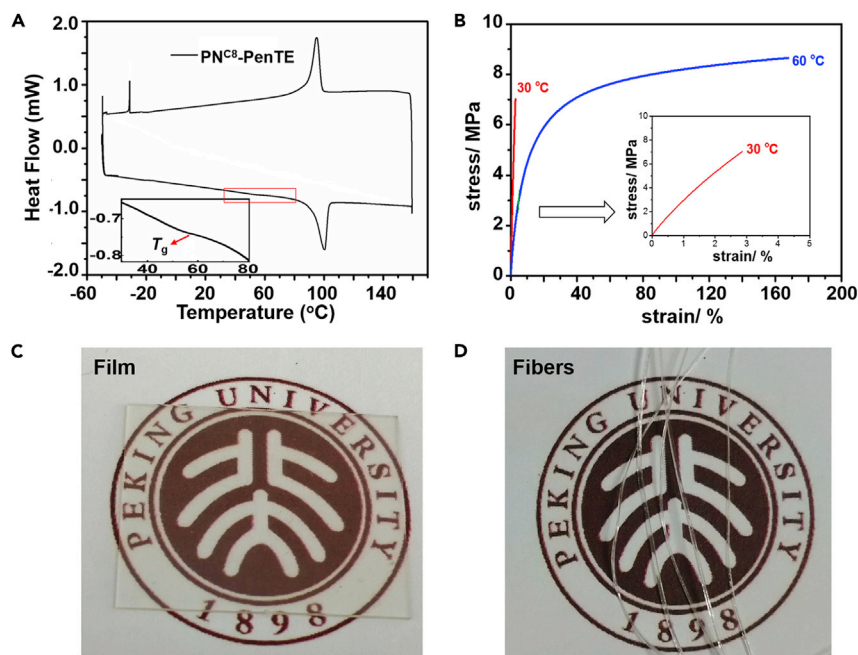


Figure 2. Thermal and Mechanical Properties of PNC⁸-PenTE Materials

(A) DSC curve of PNC⁸-PenTE.

(B) Stress-strain curves of PNC⁸-PenTE test by DMA using a constant force rate of 0.5 N/min at 30°C (red) or 60°C (blue).

(C and D) Photographs of PNC⁸-PenTE as a transparent film (C) and fibers (D) obtained by hot compression and melting drawing at 140°C, respectively.

(Figure 2B). PNC⁸-PenTE can be manufactured into a transparent film by hot compression or flexible fibers by melt drawing at 140°C with no detectable decomposition (Figures 2C and 2D).

Controlled and Complete Depolymerization

To investigate the depolymerization of the ω -end-uncapped PNC⁸-PenTE, we tested all reactions in diluted CDCl₃ (initial polymer concentration = 5.0 mg/mL) by employing various bases and temperatures. When PNC⁸-PenTE was mixed with 0.05 equiv DBU (relative to the number of polymer chains) at 65°C, the gradual regeneration of N^{C8}-PenTL was confirmed by ¹H NMR spectroscopy and SEC. The conversion of depolymerization exhibited an inverse linear relationship with the remaining M_n of the polymer (Figure 3B). Moreover, only unimodal peaks were observed in the SEC analysis of the depolymerization of PNC⁸-PenTE, implying that no oligomerization occurred (Figure 3C). Meanwhile, as shown in Figure S29, the DBU (0.5 equiv)-mediated depolymerization of PNC⁸-PenTE (degree of polymerization $\sim$ 40) at room temperature gave a linear correlation of the conversion as a function of time (zero order kinetics). All these data offer convincing evidence for a domino-like unzipping depolymerization process. However, $[\alpha]_D$ testing of the 65°C recycled monomer indicated racemization (Table 2, entries 1 and 2). Interestingly, at reduced temperatures such as 25°C, PNC⁸-PenTE₄₀ was completely depolymerized (>95%) into enantiopure monomers (Figure 3D; Table 2, entry 3) within 4 h, catalyzed by 0.1 equiv DBU. Thus, it appears that lower temperature could prevent racemization effectively. This notion was further confirmed by the fact that complete depolymerization without racemization of PNC⁸-PenTE₄₀ was achievable within 10 min with 1 equiv DBU at −25°C (Table 2, entry 4). PN^{ene}-PenTE showed a very similar result

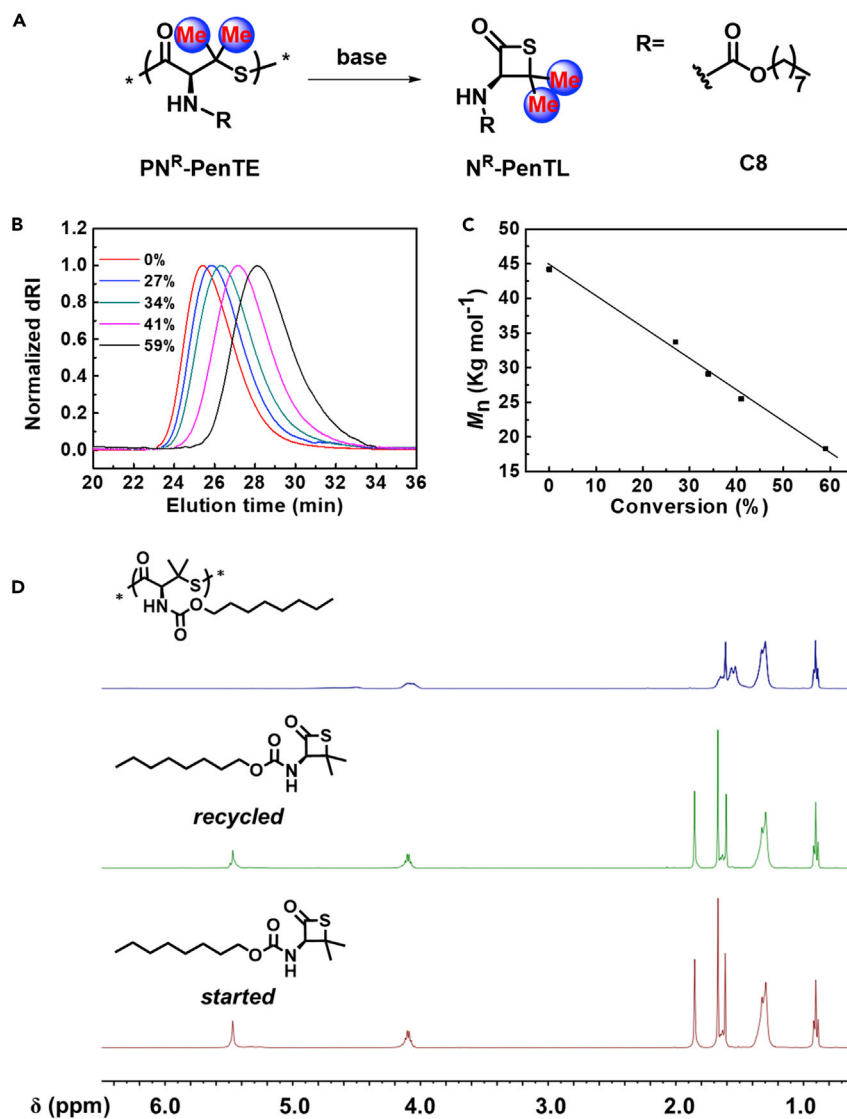


Figure 3. DBU-Catalyzed Depolymerization of $\text{PN}^{\text{C}_8}\text{-PenTE}$

(A) Scheme of $\text{PN}^{\text{C}_8}\text{-PenTE}$ depolymerization.

(B) Overlay of SEC curves at different depolymerization conversions.

(C) Plot of the remaining M_n of $\text{PN}^{\text{C}_8}\text{-PenTE}$ as a function of the conversion of the depolymerization.

(D) Overlay of the ¹H NMR spectra in CDCl₃ of $\text{PN}^{\text{C}_8}\text{-PenTE}_{40}$ (top), recycled $\text{N}^{\text{C}_8}\text{-PenTL}$ after depolymerization (middle), and the started $\text{N}^{\text{C}_8}\text{-PenTL}$ as a reference (bottom).

to $\text{PN}^{\text{C}_8}\text{-PenTE}$ in depolymerization (Table 2, entries 5 and 6; Figure S30). Of note, the ω -end-capped $\text{PN}^{\text{ene}}\text{-PenTE}$ remained almost unchanged when mixed with 0.1 equiv DBU at 25°C for 12 h (Figure S31). The depolymerization could also be catalyzed by 1.0 equiv sodium thiophenolate (PhSNa), a weaker base but stronger nucleophile than DBU, which gave >95% conversion in less than 2 h at ambient temperature, again with no detectable racemization (Table 2, entry 5). More interestingly, even the ω -end-capped $\text{PN}^{\text{C}_8}\text{-PenTE}$ could be completely depolymerized when treated with 1.0 equiv PhSNa at room temperature (Figure S32), implying a complementary (mechanistic) approach to the previously described DBU-catalyzed depolymerization (Figure S33).

Table 2. Depolymerization of PN^R-PenTE in Dilute Solution

Entry	Monomer or Polymer	Catalyst	Equivalents ^a	Time (min)	Temperature (°C)	[α] _D ^{17.2b}
1	N ^{C8} -PenTL	–	–	–	–	–35.8
2	PN ^{C8} -PenTE	DBU	0.05	1	65	0
3	PN ^{C8} -PenTE	DBU	0.1	240	25	–34.2
4	PN ^{C8} -PenTE	DBU	1	10	–25	–35.8
5	PN ^{C8} -PenTE	PhSNa	1	120	25	–35.6
6	N ^{ene} -PenTL	–	–	–	–	–37.4
7	PN ^{ene} -PenTE	DBU	0.1	240	25	–36.6

All entries were conducted in THF at a concentration of 5.0 mg/mL.

^aRelative to the number of polymer chains.

^bSpecific optical rotation, determined by polarimeter in THF at 17.2°C.

Mechanism of ROP and Depolymerization

We further studied the ROP and depolymerization of N^R-PenTL by density functional theory (DFT) calculation and molecular dynamics (MD) simulation. To simplify the calculation, we used N^{Ac}-PenTL as a model monomer and considered the reactive chain end to consist of a dissociated anionic thiolate. The free energies of key intermediates (INTs) and transition states (TSs) in both the chain propagation and chain transfer are summarized in Figure 4A. The change in free energy of the ROP was calculated to be 0.8 kcal/mol (INT₁ to INT₂), agreeing well with the previous Van't Hoff plot (–0.24 kcal/mol). The energy barrier for the chain propagation (INT₁ to TS₁) and chain transfer (INT₁ to 2TS₁) was 6.6 and 19.2 kcal/mol, respectively (Figure 4B). The ~12.6 kcal/mol difference in energy barrier, according to the Eyring equation, suggested that the rate constants of the two pathways differed from each other by an order of magnitude of ~6, which ensured that the ROP would proceed in a highly controlled fashion as we observed. Interestingly, the energy barrier of chain propagation and chain transfer in the ROP of N^{Ac}-CysTE were substantially lower, 0.5 and 2.2 kcal/mol, respectively (Figure S34). Such low energy barriers suggest that the rate of both propagation and transfer reactions was fast and that it was difficult to minimize chain transfer.

For depolymerization of PN^{Ac}-PenTE, the energy barrier was 5.8 kcal/mol (INT₂ to TS₁; Figure 4B), which served as a key contributor to the amenability of PN^R-PenTE to depolymerization. On the other hand, for N^{Ac}-CysTE, the change in free energy was favored for the ROP (–14.4 kcal/mol), making the reverse depolymerization pathway highly unfavorable thermodynamically (C-INT₂ to C-TS₁; Figure S34). DFT calculation further suggested that in the low-energy conformation of PN^R-PenTE, the terminal tertiary thiolate and the adjacent thioester took a gauche conformation with a S–C=O distance of ~2.96 Å and a S–C–C–CO dihedral angle (Ψ) of 66.4° (Figure 4C), which required no extra rotary energy for the ring-closing depolymerization. On the contrary, the low-energy conformation of N^{Ac}-CysTE was the staggered conformation in which the same S–C=O distance was ~4.17 Å (Figure 4C). All-atom MD simulation (Figures 4D and 4E) of the 20-mer of PN^{Me}-PenTE also suggested that the most populated conformation (Ψ = 67.7%) is characterized by an average S–C=O distance of 3.4 Å between the terminal thiol and its adjacent thioester carbon, whereas the staggered conformations with a longer distance (4.20 Å in average) were less populated (18.2%). This restrained conformation is a clear indication of the Thorpe-Ingold effect induced by the gem-DM.^{51,52}

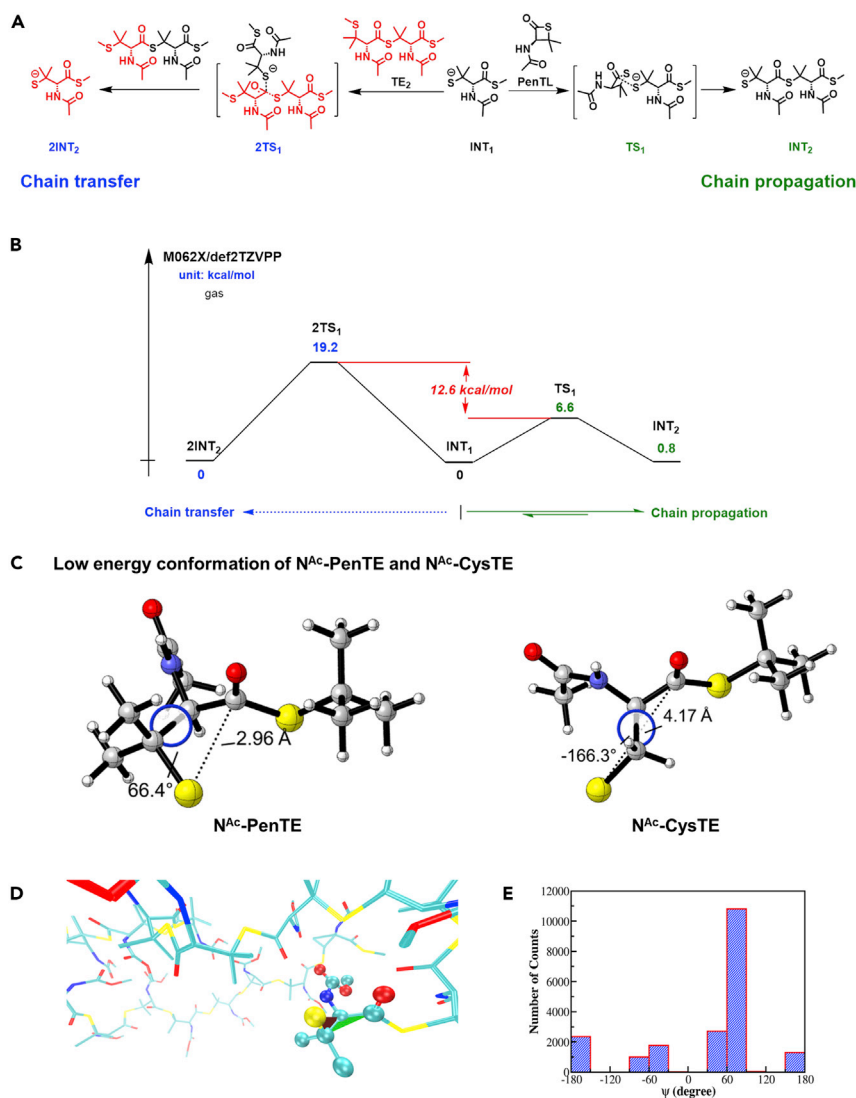


Figure 4. Mechanistic Investigation of the ROP and Chain Transfer by DFT Calculation and MD Simulation

(A) Proposed chain propagation and transfer intermediates (INTs) and transition states (TSs) in the ROP of N^R-PenTL in gas.

(B) Calculated free energy of each INT and TS.

(C) Low-energy conformation of N^{Ac}-PenTE and N^{Ac}-CysTE.

(D) The most popular conformation of PNMe-PenTE₂₀.

(E) Ψ dihedral angle distribution of different conformations of PN^{Me}-PenTE₂₀.

DISCUSSION

The unique thermomechanical, optical, and dynamic properties of PTE polymers, coupled with a global emphasis on environmental sustainability, have propelled a resurgence in their popularity.^{35,56,57} Although chemical production⁴⁷ and biosynthesis⁵⁸ of PTEs were first reported in 1968 and 2001, respectively, controlled chemical synthesis of high *M_n* PTEs remains a technological bottleneck because of the dynamic nature of thioesters. In this work, we achieved the controlled ROP of β-thiolactones by introducing a *gem*-DM group on the four-membered ring (Figure 1; Table 1). The facile access to high *M_n* PTEs under mild conditions could provide a significant boost to their industrial and biomedical application.

Functionalization of both the termini and side groups in PN^{R} -PenTE opens up opportunities to create novel, high-performance materials by introducing different combinations of substituents to the polymer chain. As demonstrated earlier, the *N*-octanoyloxy groups in PN^{C8} -PenTL confer semicrystallinity and increase processability and durability (Figure 2). On the other hand, PN^{EG4} -PenTE (Table 1, entry 12) exhibits excellent water solubility and degradability, making it an attractive alternative to PEG and a promising high-value biomaterial for temperature-induced self-assembly and/or therapeutic protein conjugation.^{59,60} The physicochemical properties of PN^{R} -PenTE could be further expanded or fine-tuned by copolymerizing several types of monomers with different side chains (Table 1, entry 11).

Previously reported strategies for polymer recycling predominantly involved reverting back to cyclic monomers bearing a five- or six-membered ring, which are relatively unstrained.^{17,19,22,31,61} We recently succeeded in extending the scope of such regenerative building blocks to bridged bicyclic thiolactones.⁴⁸ In the current study, we further demonstrated, on the basis of both experimental data and theoretical calculations, that the presence of *gem*-DM played a key role in enabling fast, selective, and highly controlled depolymerization of PN^{R} -PenTEs (Figures 3 and 4). Of note, although depolymerizable polymers were not uncommon, the domino-like unzipping fashion in the depolymerization of PN^{R} -PenTEs without the generation of thermodynamic equilibrium mixture of oligomeric intermediates (Figures 3A, 3B, and S29) was relatively rare. This control was again most likely empowered by the presence of *gem*-DM (Figures 4C–4E). It is also worth pointing out that similar ring-closure reactions that are driven by the Thorpe-Ingold effect have been frequently employed.^{62–64} Thus, we envisage that our current strategy can be broadly applied to the design of various recyclable polymers beyond PN^{R} -PenTEs. The PhSNa-mediated complete depolymerization of both ω -end-capped and -uncapped PN^{R} -PenTEs allows more versatile end-group functionalization without jeopardizing the recycling capability of PTEs and thus opens new opportunities to a broader scope of applications.

It should be noted that the relatively high price of penicillamine could pose a challenge to our method when applied on an industrial scale. Nevertheless, cost mitigation could potentially be achieved by further optimizing the chemical and/or biosynthetic-based routes to produce similar substrate monomers in a more affordable manner.⁶⁵ Overall, the strategy can be utilized to rapidly and efficiently generate a wide range of high-value, recyclable polymers with immense application potential as self-immolative materials,^{66,67} covalent adaptable networks,⁶⁸ sacrificial domain for composites and nanolithography, and responsive biomaterials.⁵⁶

EXPERIMENTAL PROCEDURES

Resource Availability

Lead Contact

Requests for further information should be directed to and will be fulfilled by the Lead Contact, Hua Lu (chemhualu@pku.edu.cn).

Materials Availability

This study did not generate new unique materials.

Data and Code Availability

The accession number for the crystallographic data reported in this paper is CCDC: 2004873. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre at <https://www.ccdc.cam.ac.uk/structures/>.

The Cartesian coordinates of structures can be found in [Data S1](#).

General Procedure for the Ring-Opening Polymerization of N^R-PenTL

In a glovebox, benzyl mercaptan (2.0 M, 29.5 μ L, 1.0 equiv) and DBU (2.0 M, 3.0 μ L, 0.10 equiv) in THF were added to N^{C8}-PenTL (1,740 mg, 0.35 mmol, 100 equiv). The polymerization was kept at ambient temperature for 24 h. Upon reaching equilibrium, iodoacetamide (1.0 M, 300 μ L, 5.0 equiv) in THF or trifluoroacetic acid (1.0 equiv) was added to quench the polymerization. The mixture was diluted with DCM (10 mL), precipitated in isopropanol (450 mL), and collected with centrifugation. The crude product was further purified by repeating the solution-precipitation-centrifugation cycle twice to obtain a white solid before drying under vacuum (920 mg, yield 53%).

Full experimental procedures are provided in the [Supplemental Information](#).

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at <https://doi.org/10.1016/j.chempr.2020.06.003>.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21722401 to H.L. and 21634001 to E.-Q.C.). Z.Y.T. was supported by the National Postdoctoral Program for Innovative Talents of China (BX20190004). The computation was supported by the High-Performance Computing Platform of Peking University. We thank Prof. Suwei Dong and Prof. Zichen Li for inspiring discussions.

AUTHOR CONTRIBUTIONS

H.L. and W.X. conceived the project and designed the experiments. W.X., Z.T., H.W., X.Z., and Z.Z. performed synthesis. W.X., W.C., and D.S. prepared and characterized the bulk materials. W.X. conducted the DFT calculation. L.Y. performed the MD simulation. W.X., D.S., E.-Q.C., and H.L. analyzed data and wrote the manuscript. All authors approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: February 28, 2020

Revised: April 30, 2020

Accepted: May 29, 2020

Published: June 22, 2020

REFERENCES

1. Tang, X., and Chen, E.Y.-X. (2019). Toward infinitely recyclable plastics derived from renewable cyclic esters. *Chem* 5, 284–312.
2. Geyer, R., Jambeck, J.R., and Law, K.L. (2017). Production, use, and fate of all plastics ever made. *Sci. Adv.* 3, e1700782.
3. Jehanno, C., Flores, I., Dove, A.P., Müller, A.J., Ruipérez, F., and Sardon, H. (2018). Organocatalysed depolymerisation of Pet in a fully sustainable cycle using thermally stable protic ionic salt. *Green Chem* 20, 1205–1212.
4. Jia, X.Q., Qin, C., Friedberger, T., Guan, Z.B., and Huang, Z. (2016). Efficient and selective degradation of polyethylenes into liquid fuels and waxes under mild conditions. *Sci. Adv.* 2, e1501591.
5. Jehanno, C., Pérez-Madrugal, M.M., Demarteau, J., Sardon, H., and Dove, A.P. (2019). Organocatalysis for depolymerisation. *Polym. Chem.* 10, 172–186.
6. Zhu, Y.Q., Romain, C., and Williams, C.K. (2016). Sustainable polymers from renewable resources. *Nature* 540, 354–362.
7. Albertsson, A.C., and Hakkarainen, M. (2017). Designed to degrade. *Science* 358, 872–873.
8. Garcia, J.M., and Robertson, M.L. (2017). The future of plastics recycling. *Science* 358, 870–872.
9. Hillmyer, M.A. (2017). The promise of plastics from plants. *Science* 358, 868–870.
10. García, J.M., Jones, G.O., Virwani, K., McCloskey, B.D., Boday, D.J., ter Huurne, G.M., Horn, H.W., Coady, D.J., Bintaleb, A.M., Alabdulrahman, A.M.S., et al. (2014).

Recyclable, strong thermosets and organogels via paraformaldehyde condensation with diamines. *Science* 344, 732–735.

11. Zhang, X.Y., Fevre, M., Jones, G.O., and Waymouth, R.M. (2018). Catalysis as an enabling science for sustainable polymers. *Chem. Rev.* 118, 839–885.
12. Tretbar, C.A., Neal, J.A., and Guan, Z.B. (2019). Direct silyl ether metathesis for vitrimers with exceptional thermal stability. *J. Am. Chem. Soc.* 141, 16595–16599.
13. Höcker, H., and Keul, H. (1994). Ring-opening polymerization and ring-closing depolymerization. *Adv. Mater.* 6, 21–36.
14. Endo, T., Kakimoto, K., Ochiai, B., and Nagai, D. (2005). Synthesis and chemical recycling of a polycarbonate obtained by anionic ring-opening polymerization of a bifunctional cyclic carbonate. *Macromolecules* 38, 8177–8182.
15. Endo, T., and Nagai, D. (2005). A novel construction of ring-opening polymerization and chemical recycling system. *Macromol. Symp.* 226, 79–86.
16. Olsén, P., Odellius, K., and Albertsson, A.C. (2016). Thermodynamic presynthetic considerations for ring-opening polymerization. *Biomacromolecules* 17, 699–709.
17. Olsén, P., Undin, J., Odellius, K., Keul, H., and Albertsson, A.C. (2016). Switching from controlled ring-opening polymerization (crop) to controlled ring-closing depolymerization (Crcdp) by adjusting the reaction parameters that determine the ceiling temperature. *Biomacromolecules* 17, 3995–4002.
18. Sangroniz, A., Zhu, J.B., Tang, X., Etxeberria, A., Chen, E.Y.X., and Sardon, H. (2019). Packaging materials with desired mechanical and barrier properties and full chemical recyclability. *Nat. Commun.* 10, 3559.
19. Hong, M., and Chen, E.Y.X. (2016). Completely recyclable biopolymers with linear and cyclic topologies via ring-opening polymerization of gamma-butyrolactone. *Nat. Chem.* 8, 42–49.
20. Zhu, J.B., Watson, E.M., Tang, J., and Chen, E.Y.X. (2018). A synthetic polymer system with repeatable chemical recyclability. *Science* 360, 398–403.
21. Xu, S., Lamm, M.E., Rahman, M.A., Zhang, X., Zhu, T., Zhao, Z., and Tang, C. (2018). Renewable atom-efficient polyesters and thermosetting resins derived from high oleic soybean oil. *Green Chem* 20, 1106–1113.
22. Liu, Y., Zhou, H., Guo, J.Z., Ren, W.M., and Lu, X.B. (2017). Completely recyclable monomers and polycarbonate: approach to sustainable polymers. *Angew. Chem. Int. Ed.* 56, 4862–4866.
23. Liu, Y., and Mecking, S. (2019). A synthetic polyester from plant oil feedstock by functionalizing polymerization. *Angew. Chem. Int. Ed.* 58, 3346–3350.
24. Myers, D., Witt, T., Cyriac, A., Bown, M., Mecking, S., and Williams, C.K. (2017). Ring opening polymerization of macrolactones: high conversions and activities using an yttrium catalyst. *Polym. Chem.* 8, 5780–5785.
25. Song, Y., Ji, X., Dong, M., Li, R., Lin, Y.N., Wang, H., and Wooley, K.L. (2018). Advancing the development of highly-functionalizable glucose-based polycarbonates by tuning of the glass transition temperature. *J. Am. Chem. Soc.* 140, 16053–16057.
26. Miyaji, H., Satoh, K., and Kamigaito, M. (2016). Bio-based polyketones by selective ring-opening radical polymerization of alpha-pinene-derived pinocarvone. *Angew. Chem. Int. Ed.* 55, 1372–1376.
27. Bhaumik, A., Peterson, G.I., Kang, C., and Choi, T.L. (2019). Controlled living cascade polymerization to make fully degradable sugar-based polymers from D-glucose and D-galactose. *J. Am. Chem. Soc.* 141, 12207–12211.
28. Saxon, D.J., Nasiri, M., Mandal, M., Maduskar, S., Dauenhauer, P.J., Cramer, C.J., LaPointe, A.M., and Reineke, T.M. (2019). Architectural control of isosorbide-based polyethers via ring-opening polymerization. *J. Am. Chem. Soc.* 141, 5107–5111.
29. De Hoe, G.X., Zumstein, M.T., Tiegs, B.J., Brutman, J.P., McNeill, K., Sander, M., Coates, G.W., and Hillmyer, M.A. (2018). Sustainable polyester elastomers from lactones: synthesis, properties, and enzymatic hydrolyzability. *J. Am. Chem. Soc.* 140, 963–973.
30. Chen, X., Chen, G., Tao, Y., Wang, Y., Lu, X.-B., Zhang, L., Zhu, J., Zhang, J., and Wang, X. (2019). Research progress in eco-polymers. *Acta Polym. Sin.* 50, 1068–1082.
31. Zhao, N., Ren, C., Li, H., Li, Y., Liu, S., and Li, Z. (2017). Selective ring-opening polymerization of non-strained gamma-butyrolactone catalyzed by a cyclic trimeric phosphazene base. *Angew. Chem. Int. Ed.* 56, 12987–12990.
32. Feist, J.D., and Xia, Y. (2020). Enol ethers are effective monomers for ring-opening metathesis polymerization: synthesis of degradable and depolymerizable poly(2,3-dihydrofuran). *J. Am. Chem. Soc.* 142, 1186–1189.
33. Zhang, C.-J., Hu, L.-F., Wu, H.-L., Cao, X.-H., and Zhang, X.-H. (2018). Dual organocatalysts for highly active and selective synthesis of linear poly(gamma-butyrolactone)s with high molecular weights. *Macromolecules* 51, 8705–8711.
34. Shen, Y., Xiong, W., Li, Y.-Z., Zhao, Z.-C., Lu, H., and Li, Z.-B. (2020). Chemoselective polymerization of fully biorenewable alpha-methylene-gamma-butyrolactone using organophosphazene/urea binary catalysts system towards a sustainable polyesters. *CCS Chem.* <https://doi.org/10.31635/ccschem.020.202000232>.
35. Aksakal, S., Aksakal, R., and Becer, C.R. (2018). Thioester functional polymers. *Polym. Chem.* 9, 4507–4516.
36. Wang, C., Mavila, S., Worrell, B.T., Xi, W.X., Goldman, T.M., and Bowman, C.N. (2018). Productive exchange of thiols and thioesters to form dynamic polythioester-based polymers. *ACS Macro Lett* 7, 1312–1316.
37. Mavila, S., Worrell, B.T., Culver, H.R., Goldman, T.M., Wang, C., Lim, C.H., Domaille, D.W., Pattanayak, S., McBride, M.K., Musgrave, C.B., and Bowman, C.N. (2018). Dynamic and responsive DNA-like polymers. *J. Am. Chem. Soc.* 140, 13594–13598.
38. Espeel, P., Carrette, L.L.G., Bury, K., Capenberghs, S., Martins, J.C., Du Prez, F.E., and Madder, A. (2013). Multifunctionalized sequence-defined oligomers from a single building block. *Angew. Chem. Int. Ed.* 52, 13261–13264.
39. Smith, R.A., Fu, G., McAteer, O., Xu, M., and Gutekunst, W.R. (2019). Radical approach to thioester-containing polymers. *J. Am. Chem. Soc.* 141, 1446–1451.
40. Yue, T.J., Zhang, M.C., Gu, G.G., Wang, L.Y., Ren, W.M., and Lu, X.B. (2019). Precise synthesis of poly(thioester)s with diverse structures by copolymerization of cyclic thioanhydrides and episulfides mediated by organic ammonium salts. *Angew. Chem. Int. Ed.* 58, 618–623.
41. Bannin, T.J., and Kieseewetter, M.K. (2015). Poly(thioester) by organocatalytic ring-opening polymerization. *Macromolecules* 48, 5481–5486.
42. Ura, Y., Al-Sayah, M., Montenegro, J., Beierle, J.M., Leman, L.J., and Ghadiri, M.R. (2009). Dynamic polythioesters via ring-opening polymerization of 1,4-thiazine-2,5-diones. *Org. Biomol. Chem.* 7, 2878–2884.
43. Kricheldorf, H.R., and Schwarz, G. (2007). Poly(thioester)s. *J. Macromol. Sci. A* 44, 625–649.
44. Ghobril, C., Charoen, K., Rodriguez, E.K., Nazarian, A., and Grinstaff, M.W. (2013). A dendritic thioester hydrogel based on thiol-thioester exchange as a dissolvable sealant system for wound closure. *Angew. Chem. Int. Ed.* 52, 14070–14074.
45. Lütke-Eversloh, T., Fischer, A., Remminghorst, U., Kawada, J., Marchessault, R.H., Bögershausen, A., Kalwei, M., Eckert, H., Reichelt, R., Liu, S.J., and Steinbüchel, A. (2002). Biosynthesis of novel thermoplastic polythioesters by engineered *Escherichia coli*. *Nat. Mater.* 1, 236–240.
46. Kato, M., Toshima, K., and Matsumura, S. (2007). Enzymatic synthesis of polythioester by the ring-opening polymerization of cyclic thioester. *Biomacromolecules* 8, 3590–3596.
47. Overberger, C.G., and Weise, J.K. (1968). Anionic ring-opening polymerization of thiolactones. *J. Am. Chem. Soc.* 90, 3533–3537.
48. Yuan, J., Xiong, W., Zhou, X., Zhang, Y., Shi, D., Li, Z., and Lu, H. (2019). 4-Hydroxyproline-derived sustainable polythioesters: controlled ring-opening polymerization, complete recyclability, and facile functionalization. *J. Am. Chem. Soc.* 141, 4928–4935.
49. Yuan, J., Shi, D., Zhang, Y., Lu, J., Wang, L., Chen, E.-Q., and Lu, H. (2020). 4-Hydroxy-L-proline as a general platform for stereoregular aliphatic polyesters: controlled ring-opening polymerization, facile functionalization, and site-specific bioconjugation. *CCS Chem* 2, 236–244.
50. Suzuki, M., Makimura, K., and Matsuoka, S. (2016). Thiol-mediated controlled ring-opening polymerization of cysteine-derived beta-thiolactone and unique features of

- product polythioester. *Biomacromolecules* 17, 1135–1141.
51. Jung, M.E., and Piizzi, G. (2005). Gem-disubstituent effect: theoretical basis and synthetic applications. *Chem. Rev.* 105, 1735–1766.
52. Bachrach, S.M. (2008). The gem-dimethyl effect revisited. *J. Org. Chem.* 73, 2466–2468.
53. Chen, H., Xiao, Y.X., Yuan, N., Weng, J.P., Gao, P.C., Breindel, L., Shekhtman, A., and Zhang, Q. (2018). Coupling of sterically demanding peptides by beta-thiolactone-mediated native chemical ligation. *Chem. Sci.* 9, 1982–1988.
54. Wang, Y., Han, L., Yuan, N., Wang, H., Li, H., Liu, J., Chen, H., Zhang, Q., and Dong, S. (2018). Traceless beta-mercaptan-assisted activation of valinyl benzimidazolinones in peptide ligations. *Chem. Sci.* 9, 1940–1946.
55. Tshepelevitsh, S., Kütt, A., Lõkov, M., Kaljurand, I., Saame, J., Heering, A., Plieger, P.G., Vianello, R., and Leito, I. (2019). On the basicity of organic bases in different media. *Eur. J. Org. Chem.* 2019, 6735–6748.
56. Brown, T.E., Carberry, B.J., Worrell, B.T., Dudaryeva, O.Y., McBride, M.K., Bowman, C.N., and Anseth, K.S. (2018). Photopolymerized dynamic hydrogels with tunable viscoelastic properties through thioester exchange. *Biomaterials* 178, 496–503.
57. Mutlu, H., Ceper, E.B., Li, X., Yang, J., Dong, W., Ozmen, M.M., and Theato, P. (2019). Sulfur chemistry in polymer and materials science. *Macromol. Rapid Commun.* 40, e1800650.
58. Lütke-Eversloh, T., Bergander, K., Luftmann, H., and Steinbüchel, A. (2001). Identification of a new class of biopolymer: bacterial synthesis of a sulfur-containing polymer with thioester linkages. *Microbiology (Reading Engl.)* 147, 11–19.
59. Lu, J., Wang, H., Tian, Z., Hou, Y., and Lu, H. (2020). Cryopolymerization of 1,2-dithiolanes for the facile and reversible grafting-from synthesis of protein–polydisulfide conjugates. *J. Am. Chem. Soc.* 142, 1217–1221.
60. Hou, Y., and Lu, H. (2019). Protein peptylation: a new paradigm of protein–polymer conjugation. *Bioconjug. Chem.* 30, 1604–1616.
61. MacDonald, J.P., and Shaver, M.P. (2016). An aromatic/aliphatic polyester prepared via ring-opening polymerisation and its remarkably selective and cyclable depolymerisation to monomer. *Polym. Chem.* 7, 553–559.
62. Huang, H.C., Wang, W.Q., Zhou, Z.F., Sun, B.H., An, M.R., Haeffner, F., and Niu, J. (2019). Radical ring-closing/ring-opening cascade polymerization. *J. Am. Chem. Soc.* 141, 12493–12497.
63. Gutekunst, W.R., and Hawker, C.J. (2015). A general approach to sequence-controlled polymers using macrocyclic ring opening metathesis polymerization. *J. Am. Chem. Soc.* 137, 8038–8041.
64. Lee, H.K., Lee, J., Kockelmann, J., Herrmann, T., Sarif, M., and Choi, T.L. (2018). Superior cascade ring-opening/ring-closing metathesis polymerization and multiple olefin metathesis polymerization: enhancing the driving force for successful polymerization of challenging monomers. *J. Am. Chem. Soc.* 140, 10536–10545.
65. Kulkarni, G.M., Kulkarni, S., and Sharma, N. (2018). A novel, feasible and cost effective process for the manufacture of D–penicillamine. Patent WO 2018/134836 A1, filed August 21, 2017, and published July 26, 2018.
66. Sagi, A., Weinstein, R., Karton, N., and Shabat, D. (2008). Self-immolative polymers. *J. Am. Chem. Soc.* 130, 5434–5435.
67. Peterson, G.I., Larsen, M.B., and Boydston, A.J. (2012). Controlled depolymerization: stimuli-responsive self-immolative polymers. *Macromolecules* 45, 7317–7328.
68. Bowman, C.N., and Kloxin, C.J. (2012). Covalent adaptable networks: reversible bond structures incorporated in polymer networks. *Angew. Chem. Int. Ed.* 51, 4272–4274.