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Polymer Chemistry Hot Paper

Recyclable Polythioesters and Poly(thioester-co-peptoid)s via Ring-Opening Cascade Polymerization of Amino Acid *N*-Carboxyanhydrides

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Abstract: Polythioesters (PTEs) are emerging sustainable polymers for their degradability and recyclability. However, low polymerizability of monomers and extensive side reactions often hampered the polymerization process. Moreover, copolymers containing both thioester and other types of functional groups in the backbone are highly desirable but rarely accomplished owing to several synthetic challenges. Here, we report the ring-opening cascade polymerization (ROCAP) of *N*-(2-(acetylthio)ethyl)-glycine *N*-carboxyanhydrides (TE-NCA) to afford recyclable PTEs and unprecedented poly(thioester-co-peptoid)s (P(TE-co-PP)s) in a controlled manner. By developing appropriated carboxylic acid-tertiary amine dual catalysts, intramolecular *S*-to-*N* acyl shift is coupled into the ROCAP process of TE-NCA to yield products with dispersity below 1.10, molecular weight (M_n) up to 84.5 kDa, and precisely controlled ratio of thioester to peptoids. Random copolymerization of sarcosine NCA (Sar-NCA) and TE-NCA gives thioester-embedded polysarcosine with facile backbone degradation while maintaining the water solubility. This work represents a paradigm shift for the ROP of NCAs, enriches the realm of cascade polymerizations, and provides a powerful synthetic approach to functional PTEs and P(TE-co-PP)s that are otherwise difficult or impossible to make.

Introduction

Polythioesters (PTE) have emerged as a promising class of new recyclable polymers owing to their fascinating properties, unique degradability, and potential biomedical applications.[1] The ring-opening polymerizations (ROP) of thiolactones are the conventional ways to generate various recyclable PTEs (Figure 1A).[1a,e,2] To gain recyclability of PTEs, the thiolactone monomers are often designed to possess intrinsically near-equilibrium thermodynamics, which inevitably results in low polymerizability. To address the issue, other types of monomers such as thionolactone,[3] *S*-carboxyanhydrides (SCA),[4] and cyclic thioanhydrides and episulfides,[5] are developed (Figure 1A). Another major challenge for the controlled preparation of the recyclable PTEs are the undesired transthioesterifications. To overcome this, effective strategies have been developed including n-π* stabilization,[2a,e] substitution group engineering, catalyst screening,[6] and so on. To enrich the properties of PTE, the copolymerization of thiolactones with other cyclic monomers has been an appealing approach toward hybrid polymers harnessing the properties of both PTEs and other types of polymers.[7] Yet, this has been rarely explored due to different reactivity of thiolactone with other cyclic monomers. To this end, there is a pressing need to develop new synthetic approaches towards novel PTEs and thioester-containing polymers.

The ring-opening polymerization (ROP) of α-amino acid-derived *N*-carboxyanhydrides (NCAs) holds great potential for the controlled and precision synthesis of high-molecular-weight (HMW) polypept(o)ides (Figure 1B).[8] Conventionally, side reactions other than the chain initiation and propagation should be minimized, often necessitating protection on the side chain of NCA.[8b] Nevertheless, recent works on the synthesis and polymerization of NCAs with reactive/unprotected functional groups (RFG-NCAs) highlight the interplay between functional groups and chain propagation of NCA ROP, providing opportunities for the preparation of polypept(o)ides with new structures, high atom-economy, and improved efficiency.[9] Inspired by these advancements, we envision that, by introducing active electrophilic groups such as thioester into the side chain of NCA, a cascade reaction between the amine intermediate and the thioester could be integrated with the chain propagation.[10] Once realized, a new paradigm of NCA polymerization could be established, creating PTE and unprecedented backbones beyond polypept(o)ides.

Herein, we demonstrate a novel approach to synthesize PTE and thioester-inserted polypeptoids via the ring-opening cascade polymerization (ROCAP) of a novel monomer *N*-[2-(acetylthio)ethyl]glycine NCA (TE-NCA, Figure 1C). Upon ring-opening of the monomer using appropriate catalysts, the terminal amine can undergo intramolecular *S*-to-*N* acyl shift[11] to afford PTE with dispersity below 1.10, molecular weight (M_n) up to 84.5 kDa, and precisely controlled ratio of thioester to amides. Comparing to the

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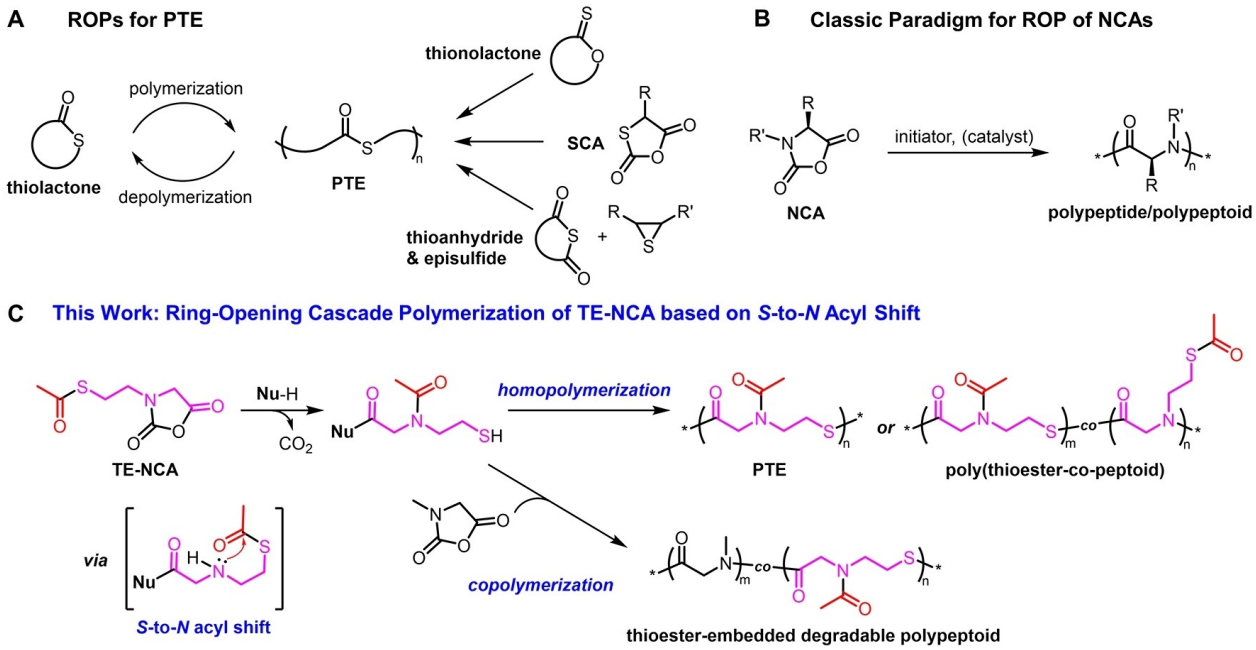


Figure 1. Research background and the design of ROCAP of TE-NCA.

traditional ROP of thiolactones, the ROCAP of TE-NCA features irreversible polymerization thermodynamics that bypasses the limitations of equilibrium monomer concentration. Copolymerizations of TE-NCA with regular NCA such as sarcosine NCA (Sar-NCA) generate unprecedented poly(thioester-co-peptoid)s (P(TE-co-PP)s), namely thioester-embedded polysarcosine (pSar) with facile backbone degradation while maintaining the water solubility.

Results and Discussion

Monomer Synthesis and Model Reactions

TE-NCA was synthesized with high purity via a four-step process starting from ethanolamine (Figure 2A,B and Figure S1–S5).[9a] The 1:1 model reaction of benzylamine and TE-NCA in deuterated dichloromethane (DCM-d_2) at room temperature (RT), revealed an initial rapid 93 % consumption of TE-NCA in 3 minutes, yielding the intermediate M1 and the acyl shift product M2 at 78 % and 15 %, respectively (Figure 2C,D and Figure S6–S8). Over the next 135 minutes, M1 was gradually converted to M2 at a slow rate, as confirmed by NMR and high-resolution mass spectrometry (HRMS) (Figure S8–S11). To facilitate the acyl shift, acetic acid (AcOH, 2 eq. to amine) was introduced, resulting in the complete conversion of TE-NCA to M2 in 3 minutes without observing M1, demonstrating the high efficiency of AcOH in catalyzing the *S*-to-*N* acyl shift (Figures 2E, S12). Density functional theory (DFT) computations suggested the AcOH-catalyzed nucleophilic addition-elimination pathway as the most favored mechanism, in which AcOH acted as a bifunctional catalyst (Figure 2G and Figure S13–S17).[8o–q,12] Next, the reaction of TE-NCA and benzylamine at 4/1 was monitored to study the feasibility of chain growth from the thiol group of M2. Without catalyst, only 25 % of NCA was converted to M2 with no further conversion of monomer, implying the failure of chain propagation from a free thiol chain end (Figure 2F and Figure S18). To boost the nucleophilicity of the thiols, triethylamine (TEA, 1 eq. to benzylamine) was added (Figure 2C). In 5 minutes, the conversion of NCA increased from 25 % to 49 % and the formation of intermediate M3 was observed by ^{1}H NMR (Figure 2F and Figure S19–S20). Further conversion of NCA by M3, however, was relatively slow.

ROCAP of TE-NCA Achieved by Acid-Base Dual Catalysis

Based on the model reactions, it came clear that AcOH was needed to promote *S*-to-*N* acyl shift and TEA was needed to facilitate thiol-mediated ROCAP of TE-NCA. Therefore, both AcOH and TEA were added to the benzylamine-initiated ROCAP of TE-NCA to simultaneously accelerate the above two processes (Table 1). The polymerization with a feeding ratio of $[M]_0/[I]_0/[B]_0/[A]_0$ (the initial concentrations of monomer, initiator, TEA, and acetic acid, respectively; $[M]_0 = 1.0$ M) of 25/1/1/2 achieved complete monomer conversion within 15 minutes under ambient conditions (Table 1, entry 1). Size exclusion chromatography (SEC) characterization revealed a sharp and symmetrical peak of the polymer product (Figure 3A), with a number-average molecular weight (M_n) of 6.8 kDa and dispersity ($Đ$) of 1.07. Minor by-products BP–A and BP–B, which accounted for 12 % and 9 % conversion of monomer, respectively, were also identified from ^{1}H NMR spectrum of the reaction mixture and confirmed by NMR and HRMS (Figure S21–S28). Subsequently, ROCAPs with higher $[M]_0/[I]_0$ ratios

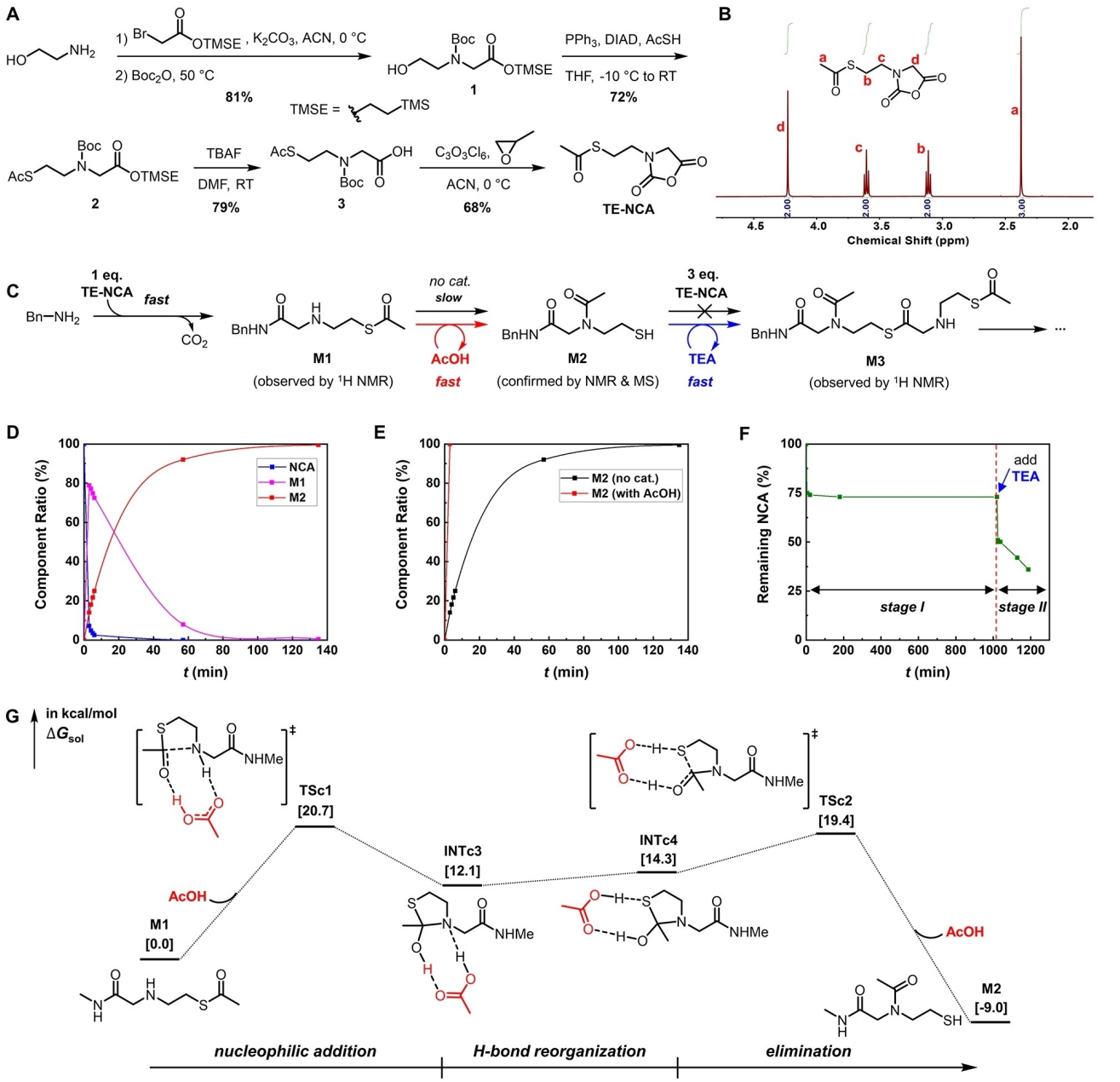
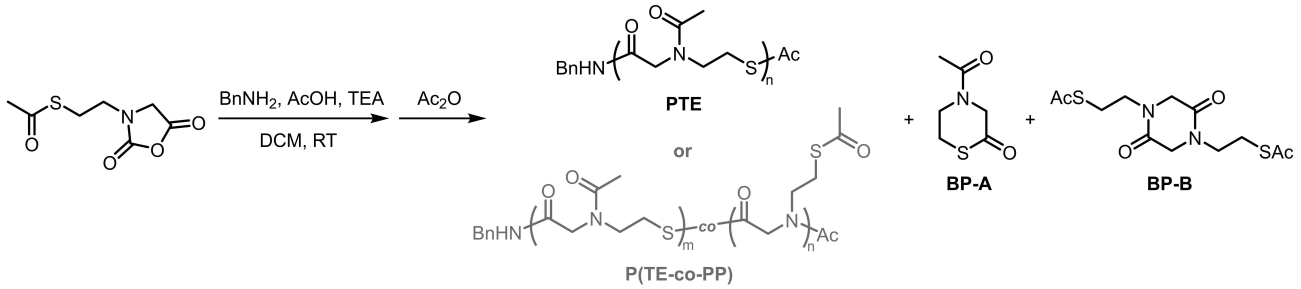


Figure 2. Synthesis of monomer and small molecule model reactions. (A) Synthesis of TE-NCA. (B) ^{1}H NMR spectrum of TE-NCA. (C) Reaction scheme for small molecule model reactions of TE-NCA and benzylamine. (D) Kinetic plots of component ratios versus time for 1 : 1 reaction of TE-NCA and benzylamine without catalyst. (E) Kinetic plots of component ratios versus time for 1 : 1 reaction of TE-NCA and benzylamine catalyzed by AcOH. (F) Kinetic plot of remaining NCA versus time for 4 : 1 reaction of TE-NCA and benzylamine. (G) Computed potential energy surface of AcOH-catalyzed *S*-to-*N* acyl shift (benzyl group was simplified as methyl).

were attempted while fixing the $[I]_0/[B]_0/[A]_0$ ratio at 1/1/2 (Table 1, entries 2–6). All the ROCAPs achieved full monomer conversion from 45 minutes to 2 days, producing narrowly dispersed polymers in 72–76 % yield (Figure 3A and Figure S29–S35). Among these polymerizations, the conversions of monomer into BP–A and BP–B were generally below 23 %. Within the $[M]_0/[I]_0$ range of 25–200, the M_n of the polymer linearly increased with $[M]_0/[I]_0$, showing the characteristics of controlled chain polymerization (Figure 3B).

Matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) spectrum of PTE_{25} ($[M]_0/[I]_0 = 25/1$, Table 1, entry 1) gave a set of peaks in which the m/z of the neighboring two peaks differed in 159, matching the expected mass of TE-NCA after losing CO_2. The α- and ω-end groups were identified as BnNH- and -Ac, both in line with expectations (Figure 3C). Further structural verification was conducted on PTE_{100} ($[M]_0/[I]_0 = 100/1$, Table 1, entry 3) through ^{1}H NMR, ^{13}C NMR, HSQC, and HMBC (Figure 3D–E and Figure S36–S37). The most direct

Table 1: ROCAP of TE-NCA[a]



entry	base	$[M]_0/[I]_0/[B]_0/[A]_0$	time	M_n^{cal} (kDa)[b]	conv. (%)[c]	BP–A (%)[c]	BP–B (%)[c]	polymer (%)[c]	S_{PTE} (%)[d]	M_n^{obt} (kDa)[e]	$Đ$[e]
1	TEA	25/1/1/2	15 min	3.2	97	12	9	76	96	6.8	1.07
2	TEA	50/1/1/2	45 min	6.0	92	8	10	74	97	12.9	1.04
3	TEA	100/1/1/2	2.0 h	11.9	97	12	11	74	95	23.1	1.06
4	TEA	200/1/1/2	5.5 h	24.3	95	7	12	76	94	43.5	1.10
5[f]	TEA	500/1/1/2	18 h	58.3	94	8	13	73	98	67.7	1.12
6[f]	TEA	1000/1/1/2	48 h	114.8	95	6	17	72	98	84.5	1.25
7[g]	TEA	100/1/1/2	1.5 h	12.4	97	6	14	77	87	23.2	1.06
8	TEA	100/1/1/1	2.5 h	11.8	96	11	12	73	86	20.7	1.11
9	TEA	100/1/1/5	2.0 h	11.3	91	9	12	70	77	22.3	1.09
10	TEA	100/1/1/10	7.0 h	11.3	91	8	13	70	60	18.5	1.14
11	TEA	100/1/0.5/2	2.5 h	12.2	94	8	10	76	85	21.8	1.07
12	TEA	100/1/2/2	2.0 h	10.2	>99	25	12	63	91	15.5	1.11
13	TEA	100/1/5/2	3.0 h	10.3	99	23	12	64	88	10.3	1.11
14	DMAP	100/1/1/2	2.0 h	10.8	94	16	11	67	93	20.4	1.06
15	DBU	100/1/1/2	1.0 h	12.1	96	10	11	75	93	18.4	1.08
16[h]	TEA	100/1/1/1	9.0 h	10.2	99	16	20	63	97	13.1	1.10
17[i]	TEA	25/1/1/2	1.0 h	3.3	96	10	7	79	85	6.8	1.07
18[i]	TEA	50/1/1/2	3.0 h	6.3	95	10	8	77	88	12.5	1.04

[a]The polymerizations were performed in DCM at RT (20–25 °C) under air atmosphere with the $[M]_0$ of 1.0 M unless otherwise specified. All polymerizations were quenched by excess acetic anhydride when high conversions (>90%) of monomer were reached (monitored by infrared spectroscopy). [b]Theoretical number-average molecular weight based on feed ratios and the conversion of monomer to polymer (conv.(polymer)), M_n^{cal} = [MW(TE-NCA) − 44]×$[M]_0/[I]_0$×conv.(polymer) + MW(terminal group). [c]Determined by ^{1}H NMR spectra of reaction mixtures. [d]Determined by ^{1}H NMR spectra of purified polymer products. [e]Determined by SEC using dimethyl formamide (DMF) containing 0.1 M LiBr as the mobile phase relative to polystyrene standards. [f]The polymerizations were performed at N_2 atmosphere. [g]$[M]_0$ = 2.0 M. [h]2-Hydroxypyridine was used as a bifunctional catalyst to replace AcOH. [i]The polymerizations were performed at 0 °C.

evidence came from HMBC, in which strong correlation signals of α-H (H_a) with the carbonyl carbons of both amide (AM) and thioester (TE) were observed, which was only possible for the proposed PTE structure after cascade polymerizations (Figure 3E). Detailed inspection of the ^{1}H NMR spectrum further unveiled small peaks at the region of acetyl thioesters (δ = 2.32–2.42), which was assigned to both the end-capping and side chains AcS- moieties through the help of HSQC and HMQC (Figure S38–S40). The side chain AcS- was likely a result of insufficient *S*-to-*N* shift that gave regular peptoid linkage in the backbone. This information, in turn, allowed us to calculate the selectivity of PTE (S_{PTE}) in all polymer products, defined as the ratio of thioester over peptoid in the backbone (Table 1, Figure S38 and S41–S45). In the case of PTE_{100} (entry 3, Table 1), since the peaks at δ = 2.32–2.42 accounted for 6% of the total Ac signals (the percentage denoted as I_{TE}), the S_{PTE} of this sample was calculated as 95% (see calculation formula and detailed discussion in Figure S38). The S_{PTE} of other PTEs were calculated by the same method and were found to be above 94% for entry 1–6 in Table 1.

Monitoring the kinetics of TE-NCA polymerization with the $[M]_0/[I]_0/[B]_0/[A]_0$ ratio of 100/1/1/2 via ^{1}H NMR revealed that the polymer yield peaked at 74% when NCA conversion reached 97%. Further reaction led to a decrease in polymer yield and the generation of more BP–A due to the depolymerization of PTE into thiolactone (Figure 3F and Figure S46).[2a,e,13] This result emphasized the importance of quenching the reaction in time to obtain high yield and high MW PTEs. The controlled/living polymerization character was confirmed by the linear increase in M_n with conversion of NCA to polymer (conv.(polymer)), during which all SEC traces exhibited a unimodal, symmetrical, narrow peak shape (Figure 3G–H).

Based on the above experiments, the proposed reaction mechanism for ROCAP of TE-NCA was depicted and discussed (Figure 4). First, as the dominant product of the polymerization is PTE, the main reaction was undoubtably the chain propagation of ROCAP that consisted of consecutive ring-opening reaction and *S*-to-*N* acyl shift. Although

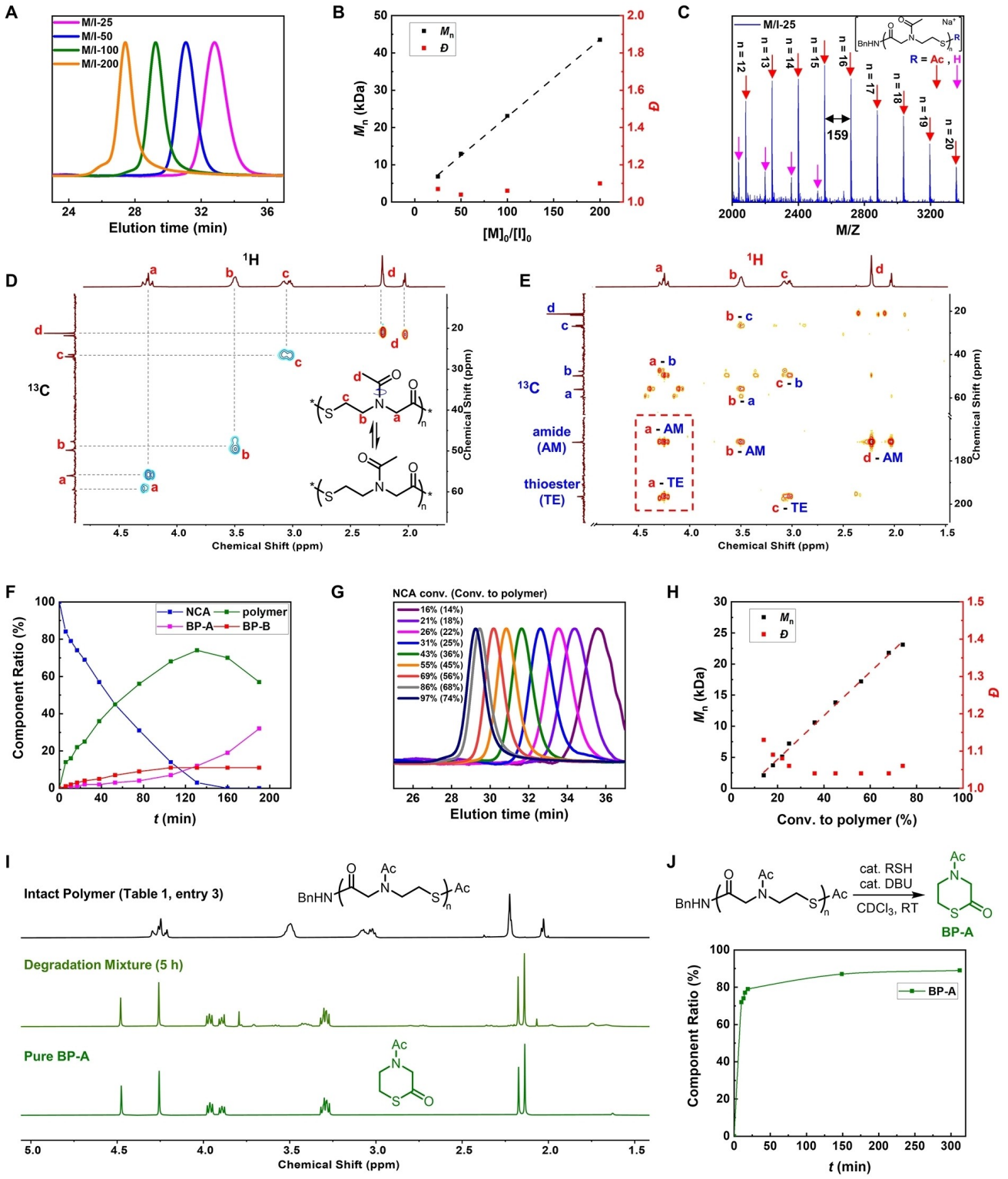


Figure 3. ROCAP of TE-NCA and depolymerization of PTE. (A) SEC traces of PTEs at different $[M]_0/[I]_0$ ratios with $[I]_0/[B]_0/[A]_0$ fixed at 1/1/2. (B) Plots of M_n and $Đ$ as a function of the $[M]_0/[I]_0$ ratio. (C) MALDI-TOF MS spectrum of PTE_{25} prepared by $[M]_0/[I]_0/[B]_0/[A]_0 = 25/1/1/2$. (D) HSQC NMR spectrum of PTE_{100} prepared by $[M]_0/[I]_0/[B]_0/[A]_0 = 100/1/1/2$. (E) HMBC NMR spectrum of PTE_{100}. (F) Kinetic plots of component ratios versus time for TE-NCA ROCAP at the $[M]_0/[I]_0/[B]_0/[A]_0$ ratio of 100/1/1/2. (G) SEC traces at different monomer conversions at the $[M]_0/[I]_0/[B]_0/[A]_0$ ratio of 100/1/1/2. (H) Plots of M_n and $Đ$ as a function of conversion of monomer to polymer at the $[M]_0/[I]_0/[B]_0/[A]_0$ ratio of 100/1/1/2. (I) Overlay ^{1}H NMR spectra of intact PTE_{100}, degradation mixture, and pure BP–A. (J) Kinetic plots of the conversion ratio of BP–A versus time of the degradation of PTE_{100}.

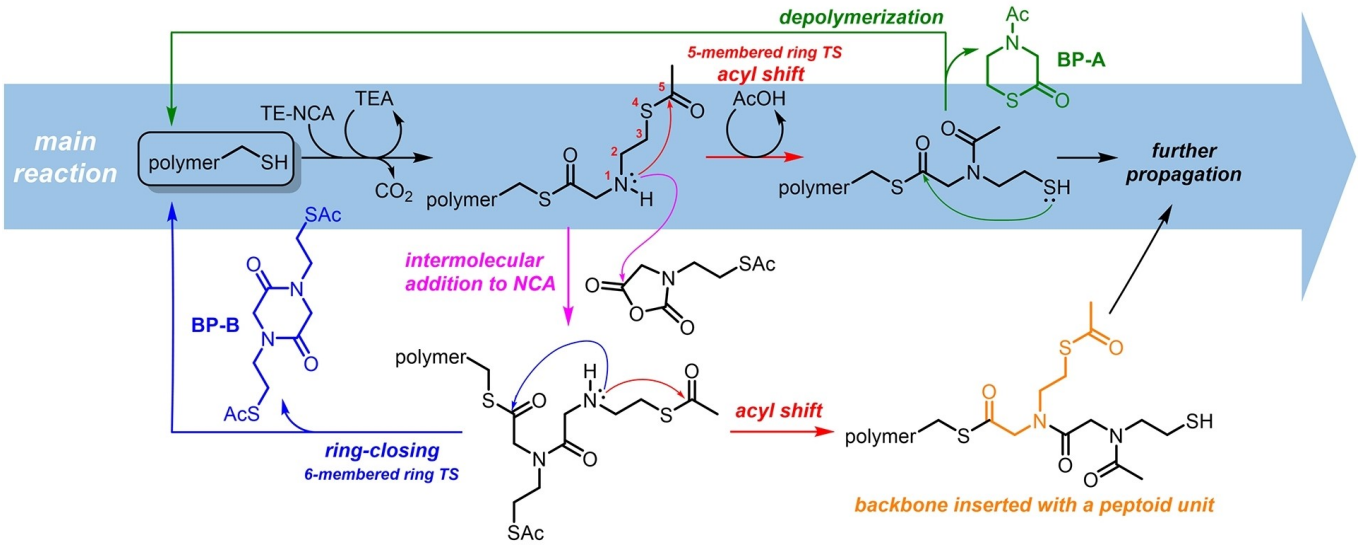


Figure 4. Proposed reaction mechanism for ROCAP of TE-NCA.

the PTE underwent spontaneous depolymerization into BP–A (Figure 3F) at late stage of the ROCAP, this side reaction can be largely ignored in the early and middle stage as the anhydride monomer is considerably more electrophilic (reactive) than the thioester backbone. This kinetic resolution confers sufficient selectivity of chain propagation over undesired chain backbiting or chain transfer, thereby leading to highly controlled ROCAP process as long as the reaction was quenched in time (Figure S47). The mechanism for the formation of BP–B, however, was more complex than BP–A. We speculated that it was formed by the two consecutive ring-opening reactions of NCA without acyl shift and the subsequent backbiting between the secondary amine chain end and the adjacent (n−2) main chain thioester bond (Figure 4).

To enhance yields and polymerization rate, polymerization parameters including monomer concentration ($[M]_0$), acid-to-base ratio, catalyst structure, and reaction temperature were optimized (Table 1, entries 7–18 and Figure S48–S60). Increasing $[M]_0$ from 1.0 M to 2.0 M reduced reaction time but lowered the S_{PTE} from 95 % to 87 % (Table 1, entry 7). Higher AcOH loadings slowed the polymerization and decreased S_{PTE}, providing a feasible method to control the ratios of thioester and amide bond repeat unit in the polymer (Table 1, entries 8–10). For instance, 10 eq. of AcOH extended polymerization time to 7 hours and reduced S_{PTE} to 60 %. The chemical structure of P(TE-co-PP) (S_{PTE} = 60 %) was further confirmed by ^{13}C NMR, HSQC, and HMBC (Figure S61–S63). The dependence of S_{PTE} on AcOH equivalent was attributed to the fact that carboxylic acids not only catalyzed the intramolecular *S*-to-*N* acyl shift but also facilitated the intermolecular reaction of the chain end amine with NCA, known as the carboxylic acid-catalyzed ROP of NCAs.[8o–q,9b,14] Higher AcOH loadings likely favored the latter, resulting in more peptoid repeating units in the backbone and thus lower S_{PTE} values. Changes in $[M]_0$ or acid loading ($[A]_0$) did not significantly affect M_n, while a higher $[B]_0$ led to a notable M_n reduction and the formation of more BP–A, suggesting side reactions related to high base loading (Table 1, entries 11–13).[8k,l] Substitution of TEA by other organic bases, such as 4-*N*,*N*-dimethylaminopyridine (DMAP) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), showed no distinct improvement (Table 1, entries 14–15). The replacement of AcOH by another bifunctional catalyst, 2-hydroxypyridine, resulted in much slower kinetics and a lower yield (Table 1, entry 16).[12a,b] Lowering reaction temperature to 0 °C gave much slower polymerization kinetics as well as compromised S_{PTE} (Table 1, entries 17–18). Briefly, the initial conditions ($[M]_0/[I]_0/[B]_0/[A]_0$ = 100/1/1/2, $[M]_0$ = 1.0 M, RT) were found to be optimal for synthesizing PTEs with high S_{PTE}, while increasing $[M]_0$ or AcOH loading promoted the synthesis of P(TE-co-PP) with more amide bond repeat units along the main chain.

Depolymerization of PTE and Thermal Properties

Inspired by the depolymerization of PTEs if not quenched in time, we envisioned that the PTEs prepared from TE-NCA held great potential for chemical recycling to monomer (BP–A).[13,15] To verify this hypothesis, 60 mM solution of PTE_{100} in $CDCl_3$ was treated with 4-methoxybenzyl mercaptan (4-OMe-BnSH) and DBU (both 5 mol % to repeat units) and monitored by ^{1}H NMR in situ (Figure 3I,J). 72 % of the polymer was converted to BP–A after merely 10 minutes, and the conversion finally reached 89 % after 5 hours (Figure S64). This conversion rate was slightly lower than the 95 % S_{PTE} of PTE_{100}, which we attributed to the fact that one amide bond repeat unit would cause one adjacently connected thioester repeat unit also lose the recyclability (Figure S65). In theory, the thiolactone BP–A also had the potential to polymerize back into PTEs. However, the equilibrium monomer concentration $[M]_{eq}$ of

BP–A at RT was estimated to be 0.8 M based on a polymerization-depolymerization equilibrium experiment, which indicated a low polymerizability (Figure S66). Indeed, the polymerization of BP–A was found to be of low conversion and poorly controlled due to this reversibility, highlighting the thermodynamically favorable ROCAP of TE-NCA overcoming the limitation of $[M]_{eq}$ for the preparation of otherwise less accessible PTEs.

Utilizing the optimized ROCAP conditions, PTE (S_{PTE} = 96 %, M_n = 23.1 kDa, $Đ$ = 1.03) and P(TE-co-PP) (S_{PTE} = 75 %, M_n = 19.4 kDa, $Đ$ = 1.08) were scaled up to hundred-milligram scale or gram scale (hereafter referred to as PTE and P(TE-co-PP), Table S1) and characterized by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) (Figure S67 and S68). TGA results showed that PTE and P(TE-co-PP) had similar thermal decomposition temperatures ($T_{d,5\%}$), which were 206 and 210 °C, respectively. Unlike the single-stage decomposition of PTE, P(TE-co-PP) displayed a two-stage decomposition at 200–250 and 300–350 °C, respectively. We attributed this pattern to the early-stage decomposition of the thioester units and the later loss of amide units. In DSC experiments, after eliminating thermal history, both PTE and P(TE-co-PP) showed a single glass transition temperature (T_g), which were 62 °C and 61 °C, respectively, suggesting a statistical random distribution of thioester and amide units in P(TE-co-PP).

Copolymerization of Sar-NCA and TE-NCA and Degradation of Copolymer

The successful homopolymerization of TE-NCA led to the exploration of copolymerizing TE-NCA with other NCA such as Sar-NCA. Polysarcosine (pSar) is a neutral, water-soluble polypeptoid widely considered a promising alternative to polyethylene glycol (PEG).[16] Although the in vivo biodegradability of pSar was still inconclusive, in vitro studies by Ling et al. indicated pSar resistant to common proteases.[17] We reasoned that the copolymerization of Sar-NCA with a small portion of TE-NCA would produce pSar with enhanced degradability owing to thioesters embedded in the backbone.[18] Our copolymerization started with a fixed $[I]_0/[B]_0/[A]_0$ ratio at 1/1/2 and $[Sar\text{-}NCA]_0/[TE\text{-}NCA]_0$ at 9/1. Two polymerizations with $[NCA]_0/[I]_0$ of 100/1 and 500/1 were attempted (Figure 5A and Table S2), and the polymer products of which were named p($Sar_{90}TE_{10}$) and p($Sar_{450}TE_{50}$), respectively. SEC characterization showed that both polymers exhibited narrow MWDs, with M_n values of 14.5 kDa and 50.5 kDa, and $Đ$ of 1.19 and 1.08, respectively (Figure 5B). Kinetic study of the copolymerization showed that the two monomers were essentially consumed synchronously throughout the polymerization with a similar reactivity (Figure 5C and Figure S69), suggesting a statistically random copolymerization. The polymer products had good solubility in water (> 5 mg/mL). The ^{1}H NMR spectrum of p($Sar_{450}TE_{50}$) in D_2O showed new peaks apart from peaks derived from pSar, which were assigned as thioester units from TE-NCA (Figure 5D). To verify the presence of thioester bonds in the backbone of p($Sar_{450}TE_{50}$), we dissolved this polymer in DMF (with 0.1 M LiBr, the mobile phase of SEC), added 5 eq. of 4-OMe-BnSH and 1 eq. of DBU (relative to the thioester bond), and monitored the degradation process using SEC (Figure 5E–F). SEC showed a significant shift of the polymer towards low-molecular-weight region after 20 minutes of reaction, with M_n decreasing from the initial 50.5 kDa to 1.3 kDa ($Đ$ = 2.9). The degradation products were identified by MADLI-TOF MS as cyclic macrothiolactone oligomers composed of one thioester residue from TE-NCA (red) and *n* sarcosine residues (blue) (Figure 5G–H). In contrast, pSar showed no change in SEC under the same condition (Figure S70).

Conclusion

In summary, this work reported the first ROCAP of NCA and the random copolymerization of TE-NCA and Sar-NCA based on a carefully designed *S*-to-*N* acyl shift reaction. With the acid-base binary catalysis of AcOH and TEA, the polymer chain smoothly propagated via repetitive ring-opening and intramolecular acyl shift processes with high selectivity, producing narrowly dispersed PTEs up to 84.5 kDa. The PTEs are easily recyclable under mild conditions. The proportion of thioester repeat units in the polymer main chain was tunable by adjusting the relative ratio of acid and base catalyst, enabling the preparation of otherwise impossible P(TE-co-PP) copolymers from a single TE-NCA monomer. The copolymerization of Sar-NCA and a minor fraction of TE-NCA led to the first synthesis of copolymers with randomly embedded thioester bonds along the main chain of pSar, imparting enhanced degradability while maintaining the good water solubility. This work greatly enriched the basic understanding of NCA chemistry and expanded the portfolio of cascade polymerization. As thiolactone and NCA have distinct polymerizability and different chain end functional groups, copolymerizations of them have been very challenging and unrealized, and this work provided a unique approach to merging polypept(o)ides and PTE and creating unprecedented polymer backbones.

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Conflict of Interest

The authors declare no competing interests.

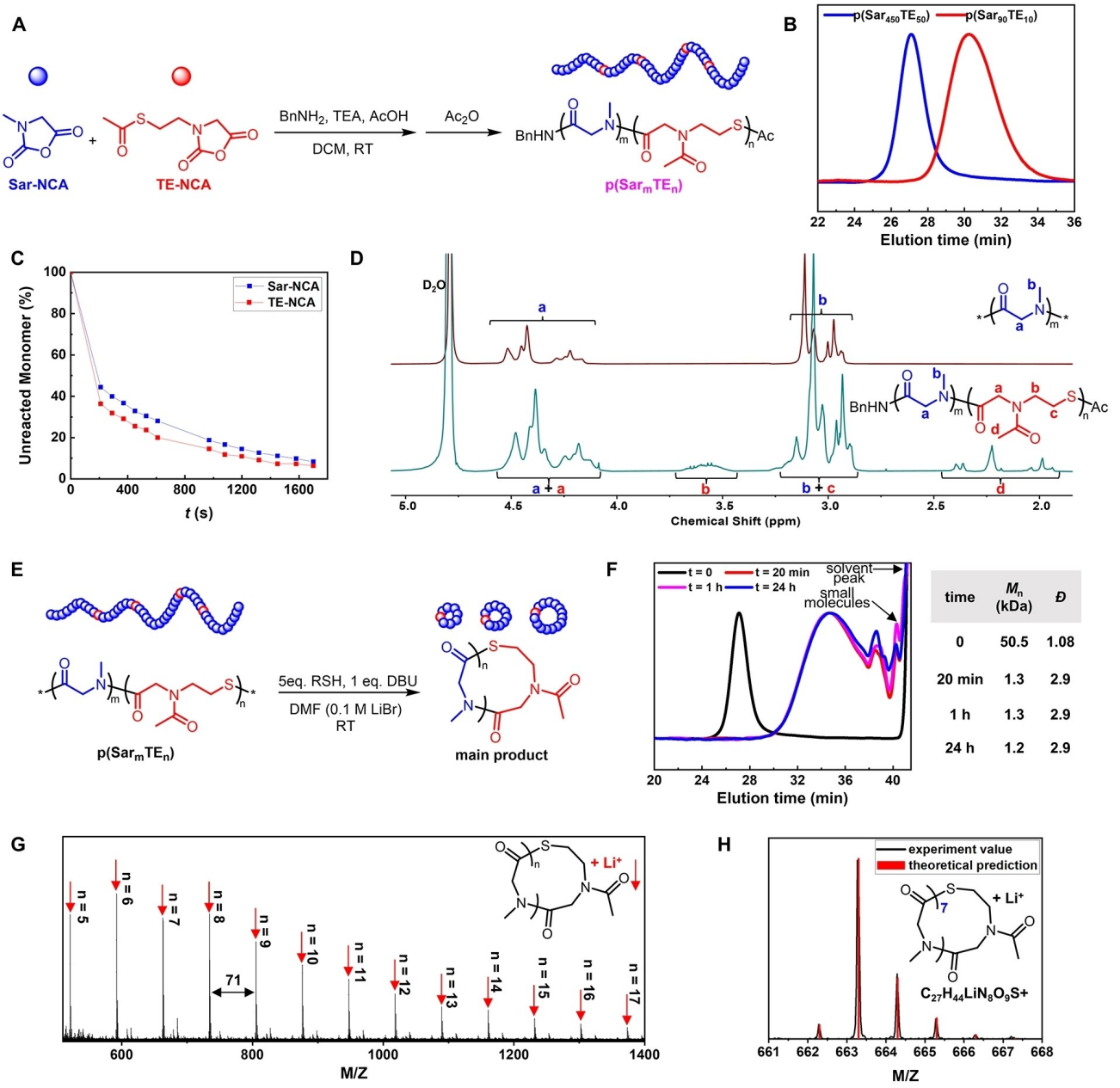

Figure 5. Copolymerization of Sar-NCA and TE-NCA and the degradation of copolymer. (A) Reaction scheme for the copolymerization of Sar-NCA and TE-NCA. (B) SEC traces of $p(Sar_{90}TE_{10})$ and $p(Sar_{450}TE_{50})$. (C) Copolymerization kinetics of $[Sar\text{-}NCA]_0/[TE\text{-}NCA]_0/[I]_0 = 90/10/1$ characterized by ^1H NMR in situ. (D) Stacked ^1H NMR spectra for pSar and $p(Sar_{450}TE_{50})$ in D_2O. (E) Scheme for the degradation of $p(Sar_mTE_n)$ copolymers. (F) SEC traces recording the degradation of $p(Sar_{450}TE_{50})$. (G) MALDI-TOF MS spectrum of the degradation product of $p(Sar_{450}TE_{50})$. (H) Zoom-in spectrum of (G) for $n = 7$.

Data Availability Statement

The data that support the findings of this study are available in the supplementary of this article.

Keywords: cascade polymerization · *N*-carboxyanhydride · organocatalysis · polythioester · ring-opening polymerization

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Research Article

Polymer Chemistry

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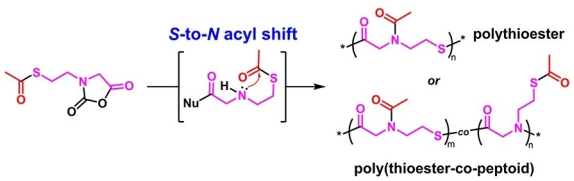
Recyclable Polythioesters and Poly(thioester-co-peptoid)s via Ring-Opening Cascade Polymerization of Amino Acid *N*-Carboxyanhydrides



This work opens a new paradigm for polymerization of *N*-carboxyanhydride based on a *S*-to-*N* shift reaction, producing unexpected recyclable polythioesters and unprecedent poly(thioester-co-peptoid)s.