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Synthesis and Controlled Organobase-Catalyzed Ring-Opening Polymerization of Morpholine-2,5-Dione Derivatives and Monomer Recovery by Acid-Catalyzed Degradation of the Polymers

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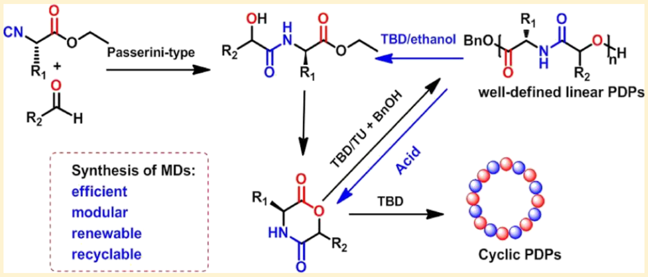
Supporting Information

ABSTRACT: Polydepsipeptides (PDPs) are strictly alternating copolymers of α-hydroxy acids and α-amino acids produced via the ring-opening polymerization (ROP) of morpholino-2,5-dione derivatives (MDs). They have been used as promising biomaterials for their combined high thermal stability and good mechanical properties of polyamides as well as the inherent degradability of polyesters. ROP of MDs is usually carried out at high temperatures with metal catalysts or enzymes, with less control over the polymer molecular weights and dispersities. In this work, we developed a simple and efficient synthetic strategy of a new platform MD via the Passerini-type reaction between an isocyano derivative of the amino acid and an aldehyde, followed by intramolecular esterification. Nine new MDs were synthesized by using this method, and the organobase-catalyzed ROP of these MDs was investigated. When the ROPs of these MDs were catalyzed by either triazabicyclo[4.4.0]dec-5-ene (TBD) or diazabicyclo[5.4.0]undec-7-ene (DBU) in the presence of benzyl alcohol as an initiator, the polymerizations were uncontrolled with the formation of both linear PDPs and cyclic PDPs. By using binary catalytic systems of 1-(3,5-bis(trifluoromethyl)-phenyl-3-cyclohexyl-2-thiourea) (TU) with DBU or TBD ([TU]/[TBD] or [DBU] > 3), the polymerizations became well-controlled, allowing the synthesis of PDPs with controlled molecular weights, low dispersities, as well as block copolymers. Furthermore, cyclic PDPs were obtained when the ROP of these MDs was catalyzed with TBD in the absence of both TU and an initiator. Finally, we used two methods to recover the monomer precursors or pure MD monomers: the TBD-catalyzed alcoholysis of PDPs was very fast and generated the monomer precursors quantitatively, while the acid-catalyzed depolymerization of PDPs led to pure and quantitative monomer recovery.



1. INTRODUCTION

Poly(ester amide)s (PEAs) contain both ester and amide linkages in their backbones, and they exhibit excellent thermal and mechanical properties of polyamides with the degradable characteristics of polyesters. Therefore, they have been widely investigated as promising biodegradable polymers for tissue engineering, drug delivery, etc.[1−4] Polydepsipeptides (PDPs) are a special class of PEAs composed of α-hydroxy acids and α-amino acids in a strictly alternating manner.[5−7] Besides all the advantages of PEAs, PDPs can be synthesized starting from α-amino acids, and their chemical and stereostructures as well as functional side groups can be regulated easily. Additionally, they have low toxicities because of the fully degradation products of α-amino acids and α-hydroxy acids in vitro and in vivo.[8]

PDPs are generally synthesized via the ring-opening polymerization (ROP) of morpholino-2,5-dione derivatives (MDs), six-membered cyclic dimers of α-hydroxy acids and α-amino acids. General synthetic methods of MDs starting from α-amino acids are via the intramolecular cyclization reactions of three intermediates: *N*-(α-haloacyl)-α-amino acids, *N*-(α-hydroxyacyl)-α-amino acids, and *O*-(α-aminoacyl)-α-hydroxycarboxylic acids. Thus, via using different amino acids, various side-chain groups can be easily incorporated at the 3-position.[5−7] Passerini reaction can generate an α-acyloxy amide from an isocyanide, a carboxylic acid, and an aldehyde. This reaction has recently been introduced into polymer science for the synthesis of polyesters, polyamides, and PEAs.[9−14] When a Lewis acid is used instead of a carboxylic acid, the Passerini-type reaction of an isocyanide and an aldehyde can generate an α-hydroxy amide.[15] Furthermore, if the isocyanide is from an amino acid, the reaction product will be *N*-(α-hydroxyacyl)-α-amino acid. Thus, the Passerini-type reaction may be a simple promising method for preparing a

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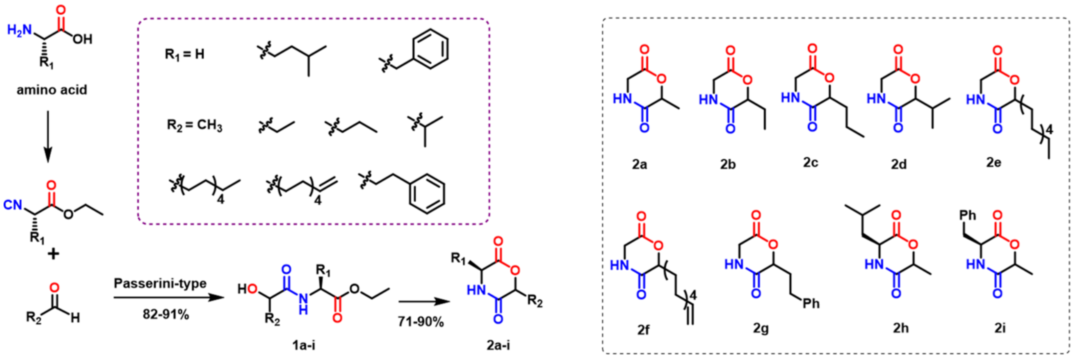
Scheme 1. Synthetic Strategy and Monomer Structures of MDs



platform MD starting from amino acids and different aldehydes.

The ROPs of MDs have been investigated with either metal catalysts[16−20] or enzymes.[21−25] These polymerizations are usually carried out at temperatures above 100 °C, and in most cases, longer time is needed to get high monomer conversions. Even so, the molecular weights of the PDPs are not very high, and the dispersities of these PDPs are large. In recent years, organocatalytic ROPs of lactides (LAs), lactones, and cyclic carbonates have been developed as alternative polymerization methods to get well-defined polyesters and polycarbonates. These polymerizations are usually carried out under mild conditions with fast polymerization rate and well-controlled polymer structures.[26−33] Especially, the Waymouth's group recently reported the fast and precisely controlled ROP of cyclic monomers via the anions of thiourea and urea.[34,35] MD is similar to LA, with one of the two lactic acids in LA being replaced by an α-amino acid. The organocatalytic ROP of LA has been investigated using several types of organic catalysts, and the polymerization was demonstrated to be living.[26,33,36−49] The organocatalytic ROP of MDs has not been investigated in detail, with only three reports being recorded.[50−52] However, the controllability of ROP of MDs is limited and side reactions occurred, which may result from the deprotonation of MDs under basic conditions.[26,53]

Polymers from renewable resources and chemical recycling of used polymers have become two main research topics in current polymer science. This can not only reduce the use of fossil stocks but also minimize the negative impact on environment. Several excellent reviews have been published on these topics.[54−60] General methods include depolymerization of low T_c polymers or those having reworkable weak bonds, such as polyesters and polyamides.[61−66] PDPs contain both ester and amide linkages in their backbones and should be chemically decomposed into monomers or monomer precursors under appropriate conditions; however, this has not been well addressed before.

Herein, we report a new synthetic strategy of MDs via combination of the Passerini-type reaction and intramolecular cyclization. We also investigated in detail the organocatalytic ROP of MDs in solution with two organic bases: triazabicyclo[4.4.0]dec-5-ene (TBD) and diazabicyclo[5.4.0]-undec-7-ene (DBU). These two bases were used either individually or in combination with 1-(3,5-bis (trifluoromethyl)-phenyl-3-cyclohexyl-2-thiourea) (TU) to form binary catalytic systems. Finally, we tested the possibility of monomer recovery in solution by base- and acid-catalyzed depolymerization of the PDPs.

2. RESULTS AND DISCUSSION

2.1. Synthesis of MDs. We designed and synthesized nine kinds of MDs by using the Passerini-type reaction as the key step to form the *N*-(α-hydroxyacyl)-α-amino acid intermediates. This is a three-step synthetic route starting from different amino acids and aldehydes (Scheme 1). The first step is the synthesis of isocyanides from amino acids. The second step is the Passerini-type reaction between isocyanides and aldehydes, affording the corresponding *N*-(α-hydroxyacyl)-α-amino acid esters (**1a**−**1i**) in yields ranging from 82 to 91%. Finally, acid-catalyzed intramolecular transesterification of **1a**−**1i** generated monomers **2a**−**2i** in yields ranging from 71 to 90%. Monomers **2a**−**2g** are from glycine and different aldehydes, and they contain different substitutes at the 6-position; monomers **2h** and **2i** are from acetaldehyde and leucine or phenylalanine, respectively, and they contain two different substituents at both the 3- and 6-positions. The detailed synthetic procedure and characterization of these compounds are summarized in the Supporting Information.

Specifically, intermediate **1a** was obtained by reacting the commercially available ethyl isocyanate with acetaldehyde in aqueous solution. The reaction was completed within 12 h, and the crude product can be used directly for the next step (Figure S1). Nevertheless, we could get pure **1a** in an 88% isolated yield after simple column separation (Figures S2 and S3).[67] The acid-catalyzed intramolecular transesterification of **1a** with an Amberlyst 15 ion-exchange resin in toluene under reflux for 48 h generated **2a**.[68] After simple column purification, pure monomer **2a** could be obtained in an 87% yield, whose structure was confirmed by spectroscopic characterizations and elemental analysis (Figures S4−S7). Similarly, compounds **1b**−**1g** were also obtained in high yields (82−91%) via the Passerini-type reactions of ethyl isocyanoacetate and propionaldehyde, butyraldehyde, isobutyraldehyde, 10-undecenal, undecanal, and phenylpropyl aldehyde, respectively. The reactions were carried out in dimethylformamide in the presence of boric acid for 24 h at room temperature.[67] Following the same synthetic procedure of **2a**, monomers **2b**−**2g** were synthesized in good yields (71−84%) from **1b**−**1g**, and their structures were also confirmed by spectroscopic characterizations and elemental analysis (Figures S8−S37). To synthesize **2h** and **2i**, ethyl 2-isocyano-4-methylpentanoate and methyl 2-isocyano-3-phenylpropanoate should be prepared first. This was fulfilled starting from L-leucine ethyl ester and L-phenylalanine by following the literature methods[69] (Figures S38−S41). It is worthy to note that the chiral centers of the resulting isocyanides were not affected as confirmed by chiral high-performance liquid chromatography (HPLC) analysis of methyl 2-isocyano-3-phenylpropanoate (Figures S42 and S43). Thereafter, reacting these two isocyanides with acetaldehyde, followed by intramolecular cyclization, generated **2h** and **2i** (Figures S44−S53). Monomers **2h** and **2i** contain two chiral centers at the 3- and 6-positions; the chiral center at the 3-position is determined by the starting amino acid, which does not change during the reaction. The chiral center at the 6-position is in situ formed during the Passerini-type reaction, which could not be controlled at the moment. Therefore, monomers **2h** and **2i** exist as a pair of diastereomers. Fortunately, we could separate the diastereomers by simple silica gel column chromatography. For example, the as-prepared monomer **2i** showed two peaks in the chiral HPLC chromatogram, and the specific rotation was $[\alpha]_{365}^{25} = +51.4$ deg dm^{-1} g^{-1} cm^{3} (Figure S54). After being separated by gel column chromatography, optically pure (3*S*,6*R*)-**2i** ($[\alpha]_{365}^{25} = +244.9$ deg dm^{-1} g^{-1} cm^{3}) and (3*S*,6*S*)-**2i** ($[\alpha]_{365}^{25} = -338.3$ deg dm^{-1} g^{-1} cm^{3}) can be obtained (Figures S55 and S56), and their enantiomeric excess (ee) was all up to 98%. The absolute chiral configuration of (3*S*,6*R*)-**2i** was further identified by its single-crystal structure (Figure S57, Table S1). The chemical shifts of monomers (3*S*,6*R*)-**2i** and (3*S*,6*S*)-**2i** are different in both ^{1}H and ^{13}C NMR spectra (Figures S58 and S59), and the melting points of the two optically pure monomers are similar, but they are about 36 °C higher than that of (3*S*,6*R*/*S*)-**2i** (Figure S60).

2.2. Organocatalytic ROP of MDs and Synthesis of Polymers.

LA has been successfully polymerized in a controlled way by a variety of organic catalysts.[36−49] However, the organocatalytic ROP of MDs has not been investigated in detail, and only limited success on the controllability has been achieved as demonstrated very recently by Schubert et al.[52] In this report, the TBD-catalyzed ROP of MDs initiated by benzyl alcohol in tetrahydrofuran was investigated. The polymerization can only be well-controlled below 50% monomer conversion, beyond which the polymerization became slow, and the dispersities of the polymers became larger. Therefore, we investigated the organocatalytic ROP of our MDs in detail with the aim to get a good control over the ROP.

Initially, we explored the ROP of our MD monomers catalyzed by either TBD or DBU using monomer **2f** as an example. The polymerization was carried out in dichloromethane (DCM) at room temperature with BnOH as the initiator ($[\mathbf{2f}]_0 = 0.64$ M, $[\mathbf{2f}]_0/[\mathrm{BnOH}]_0/[\mathrm{Cat}] = 100/1/1$). In both cases, monomer **2f** could reach high conversions as monitored by ^{1}H NMR (Table 1, entries 1 and 2), but the size-exclusion chromatography (SEC) traces of the resultant polymer $\mathbf{P_{2f}}$ were bimodal, implying that the polymerizations were uncontrollable (Figure 1). Our control experiments of the TBD- and DBU-catalyzed ROP of *rac*-LA under identical conditions gave PLA with unimodal SEC traces (Figures S62 and S63), which are consistent with literature reports,[36,37] indicating that the catalysts and our experimental protocols are reliable. Therefore, the uncontrolled ROP of **2f** can only be attributed to the monomer structure. We speculate that TBD or DBU as a strong base may deprotonate the amides of MDs, leading to the unavoidable side reactions with the formation of oligomers.[53]

We used recycling preparative HPLC to separate the two polymer fractions as shown in Figure 1a, and these two fractions were characterized by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS). The high-molecular-weight fraction was confirmed to be the expected linear $\mathbf{P_{2f}}$ initiated by BnOH (Figure S64a). The MALDI-TOF mass spectrum of the oligomer showed identical spacing between the two adjacent peaks as in the linear polymer (Figure S64b), and the molar mass was the integrated multiple of the monomer unit. This oligomer could be a cyclic $\mathbf{P_{2f}}$ formed by other side reactions. Possible mechanism of the formation of cyclic $\mathbf{P_{2f}}$ will be discussed later.

Table 1. Organocatalytic ROP of 2f[a]

entry	cat. (C)	ratio (**2f**/C/I/TU)	time (min)	conv. (%)[b]	$M_{\mathrm{n,calcd}}$ (kDa)[c]	M_{n} (kDa)[d]	$Đ$[d]
1	TBD	100:1:1:0	120	95	24.2	bimodal	
2	DBU	100:1:1:0	230	92	23.5	bimodal	
3	DBU	100:1:1:5	300	92	23.5	21.5	1.05
4	DBU	100:1:2:5	120	90	11.5	11.0	1.03
5	DBU	100:1:5:5	60	93	4.83	5.10	1.04
6	TBD	100:1:1:5	300	94	24.0	21.6	1.09

[a] All polymerizations were conducted in DCM (1 mL, $[\mathbf{2f}]_0 = 0.64$ M) with BnOH as the initiator at 25 °C; the polymers were not purified for ^{1}H NMR and SEC characterization. [b] The monomer conversion was determined by ^{1}H NMR spectroscopy. [c] $M_{\mathrm{n,calcd}} = ([\mathbf{2f}]_0/[\mathrm{I}]_0) \times$ conv. % × (molar mass of monomer) + (molar mass of BnOH). [d] Molar mass and dispersity were measured with SEC and calibrated with polystyrene standard.

To achieve a living ROP of MDs, we investigated the ROP of **2f** using the DBU/TU binary system in DCM at room temperature ($[\mathbf{2f}]_0/[\mathrm{DBU}]/[\mathrm{BnOH}]_0/[\mathrm{TU}] = 100/1/1/5$, Table 1, entry 3). The conversion of **2f** reached 92% after 5 h, and the molecular weight of the obtained $\mathbf{P_{2f}}$ was close to the theoretical value with a low dispersity ($M_{\mathrm{n}} = 21.5$ kDa, $Đ = 1.05$). We also investigated the polymerization kinetics of **2f** by ^{1}H NMR and SEC. The results confirmed that the polymerization is living: the polymerization follows first-order kinetics; the molecular weight increases linearly with monomer conversion; the dispersities of the obtained $\mathbf{P_{2f}}$ remain low ($Đ < 1.1$) throughout the whole process even until almost complete monomer conversion (Figures 2 and S65). We then prepared a $\mathbf{P_{2f}}$ sample with relatively low M_{n} and characterized the polymer sample by NMR spectra (Figures S66 and S67). The spectra confirmed the expected structure; however, the end groups were difficult to be detected because of the overlap with other protons. The MALDI-TOF-MS spectrum of this sample was then measured as shown in Figure 3. A series of peaks with the adjacent spacing of 253 mass units, which are the molar mass of **2f**, were detected. By taking the polymer with the degree of polymerization of 27 as an example, $m/z = 6971.2$ is the molar mass of the sodium adduct of linear $\mathbf{P_{2f}}$ initiated by BnOH (red circle), and $m/z = 6987.2$ is the potassium adduct of the same polymer (blue square). These results confirmed that $\mathbf{P_{2f}}$ was formed by the BnOH-initiated ROP of **2f**.

To further confirm that the polymerization is living, we carried out the ROP of **2f** with varying $[\mathbf{2f}]_0/[\mathrm{BnOH}]_0$ ratios from 20 to 100. All the polymerizations could reach high conversions (>90%), the molecular weights of the resultant $\mathbf{P_{2f}}$ increased linearly with increasing $[\mathbf{2f}]_0/[\mathrm{BnOH}]_0$ ratio, and the dispersities of the polymers were very low (Table 1, entries 3−5, Figure S68).

We further investigated the ROP of **2f** with the binary TBD/TU system ($[\mathbf{2f}]_0/[\mathrm{TBD}]/[\mathrm{BnOH}]_0/[\mathrm{TU}] = 100/1/1/5$, Table 1, entry 1). Controlled ROP was also achieved as demonstrated by the kinetic results (Figure S69). With these exciting results of the living ROP of MDs via either the DBU/

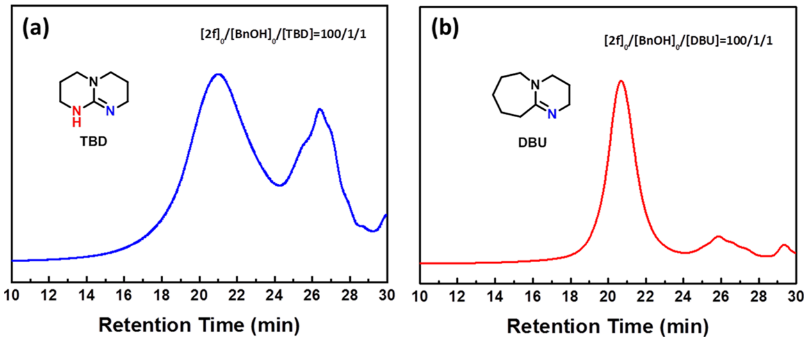


Figure 1. SEC traces of crude $\mathbf{P_{2f}}$: (a) TBD-catalyzed ROP of **2f**. $[\mathbf{2f}]_0/[\mathrm{BnOH}]_0/[\mathrm{TBD}] = 100/1/1$ (120 min, 95%); (b) DBU-catalyzed ROP of **2f**. $[\mathbf{2f}]_0/[\mathrm{BnOH}]_0/[\mathrm{DBU}] = 100/1/1$ (230 min, 92%).

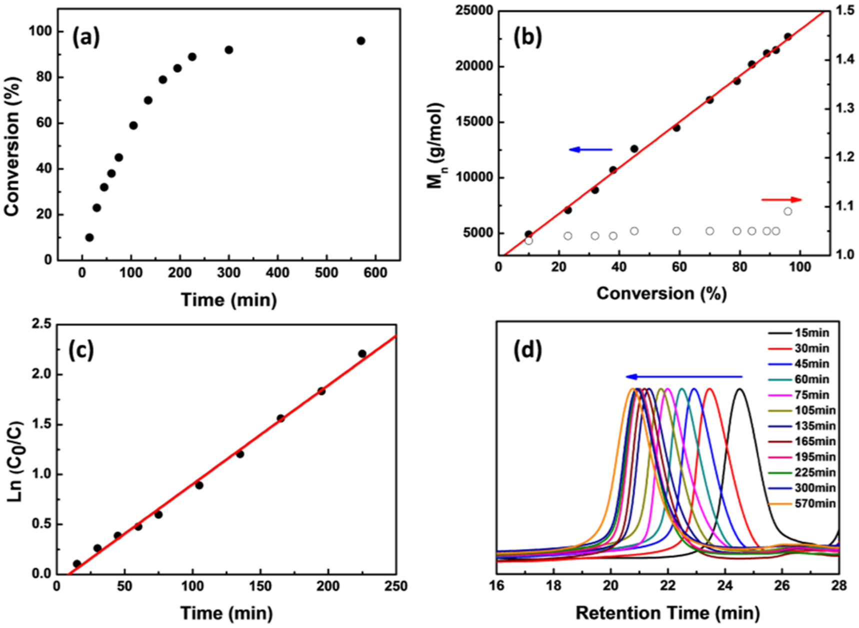


Figure 2. DBU-/TU-catalyzed ROP of **2f**. (a) Plot of monomer conversion vs time; (b) plots of molecular weight (M_n) and dispersity (M_w/M_n) vs monomer conversion; (c) semilogarithmic kinetic plot; (d) SEC traces of $\mathbf{P_{2f}}$ obtained at different polymerization times. $[\mathbf{2f}]_0/[\mathrm{DBU}]/[\mathrm{BnOH}]_0/[\mathrm{TU}] = 100/1/1/5$, $[\mathbf{2f}]_0 = 0.64$ M in DCM, $T = 25$ °C.

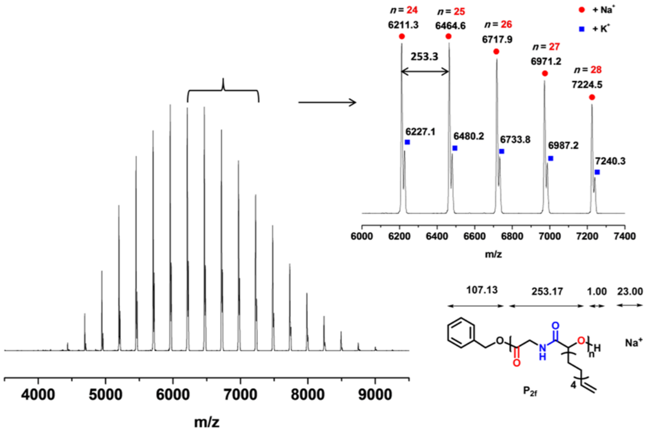


Figure 3. MALDI-TOF mass spectra of $\mathbf{P_{2f}}$. The polymer sample was produced by the DBU-/TU-catalyzed ROP of **2f** ($[\mathbf{2f}]_0/[\mathrm{DBU}]/[\mathrm{BnOH}]_0/[\mathrm{TU}] = 100/1/1/5$, $[\mathbf{2f}]_0 = 0.64$ M in DCM, $T = 25$ °C, quenched by benzoic acid at 44% monomer conversion).

TU or TBD/TU binary system, the ROPs of other eight monomers under identical conditions were then performed. Because of the low solubility of monomers **2a**, **2b**, and **2d** in DCM, the ROPs of these three monomers were not well-controlled, whereas the polymerizations of the other five monomers (**2c**, **2e**, **2g**, **2h**, and **2i**) were all living and well-defined homopolymers were obtained (Figures S70−S84). In addition, block copolymer $\mathbf{P_{2f}}$-***b***-$\mathbf{P_{2i}}$ was also successfully prepared by sequential addition of monomers. A $\mathbf{P_{2f}}$ sample (M_n = 6.5 kDa, $Đ$ = 1.09, Figure 4a) was first obtained from the ROP of **2f** ($[\mathbf{2f}]_0/[\mathrm{TBD}]/[\mathrm{BnOH}]_0/[\mathrm{TU}] = 100/1/4/5$, 2 h, 95% conversion), and then 100 equiv of **2i** was added to the polymerization system and polymerized for another 2 h. The final $\mathbf{P_{2f}}$-***b***-$\mathbf{P_{2i}}$ (M_n = 12.0 kDa, $Đ$ = 1.11, Figures 4a and S85) was obtained. The structure of the block copolymer was confirmed by the ^{1}H NMR spectra as shown in Figure 4b.

Considering that both TBD and DBU produced BnOH-initiated linear $\mathbf{P_{2f}}$ and a small portion of cyclic $\mathbf{P_{2f}}$, while the DBU or TBD/TU binary system gave well-controlled ROP of MDs, we decided to clarify the effects of TU in the base-catalyzed ROP of MDs. First, we fixed the amount of TBD (1 mol % equiv of **2f**) with varied ratios of [TU]/[TBD] (0, 1, 3, 5, 10). The results confirmed that as the ratio of [TU]/[TBD] increased, the polymerization rates decreased significantly, but

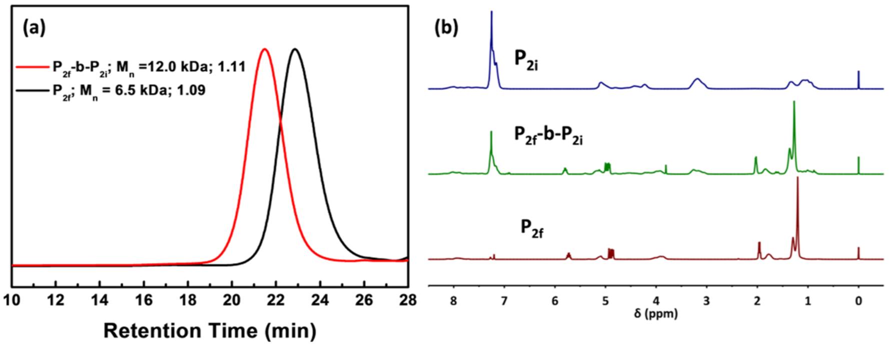


Figure 4. (a) SEC traces of $\mathbf{P_{2f}}$ (black line) and $\mathbf{P_{2f}}$-*b*-$\mathbf{P_{2i}}$ (red line); (b) ^{1}H NMR of $\mathbf{P_{2f}}$, $\mathbf{P_{2i}}$, and $\mathbf{P_{2f}}$-*b*-$\mathbf{P_{2i}}$.

the controllability of the polymerization became better (Table 2, entries 1−5, Figure S86). When the ratio of [TU]/[TBD] > 3, the side reaction was negligible, and the ROP of **2f** exhibited the feature of living polymerization. We then fixed the amount of TU (5% equiv of **2f**) with varied ratios of [TBD]/[TU] (1/5, 3/5, 5/5). The results showed that as the ratio of [TBD]/[TU] increased, the polymerization rate increased obviously, but the controllability of the polymerization decreased significantly (Table 2, entries 4, 6, and 7, Figure S87). Bimodal SEC traces existed at the high ratio of [TBD]/[TU], and the cyclic oligomer peak remained unchanged with the change of [TBD]/[TU] ratios.

Table 2. TBD-/TU-Catalyzed ROP of 2f[a]

entry	ratio (**2f**/TBD/I/TU)	time (min)	conv. (%)[b]	$M_{n,calcd}$ (kDa)[c]	M_n (kDa)[d]	$Đ$[d]
1	100:1:1:0	60	93	23.7	bimodal	
2	100:1:1:1	164	95	24.2	19.5	1.39
3	100:1:1:3	164	95	24.2	18.1	1.15
4	100:1:1:5	300	94	24.0	21.6	1.09
5	100:1:1:10	960	94	24.0	21.7	1.05
6	100:3:1:5	45	79	20.1	bimodal	
7	100:5:1:5	45	87	22.2	bimodal	

[a] All reactions were conducted in DCM (1 mL, $[\mathbf{2f}]_0$ = 0.64 M) with BnOH as the initiator at 25 °C; the polymers were not purified for ^{1}H NMR and SEC characterization. [b] The monomer conversion was determined by ^{1}H NMR spectroscopy. [c] $M_{n,calcd} = ([\mathbf{2f}]_0/[I]_0) \times$ conv. % × (molar mass of monomer) + (molar mass of BnOH). [d] Molar mass and dispersity were measured with SEC and calibrated with polystyrene standard.

Furthermore, we also carried out the TBD-catalyzed ROP of **2f** without adding BnOH as an exogenous protic initiator. When $[\mathbf{2f}]_0$/[TBD] = 100/1 (Table S2, entry 1, Figure S88), a bimodal SEC trace of polymer was obtained, the high-molecular-weight polymer peak was attributed to the trace water-initiated linear $\mathbf{P_{2f}}$, and the oligomer peak was from the cyclic $\mathbf{P_{2f}}$ (Figures S89 and S90). Increasing the TBD loading ($[\mathbf{2f}]_0$/[TBD] = 100/3) gave similar bimodal SEC trace (Table S2, entry 2), but the amount of the linear $\mathbf{P_{2f}}$ decreased. Further increasing the TBD loading ($[\mathbf{2f}]_0$/[TBD] = 100/10) led to dominant cyclic $\mathbf{P_{2f}}$, and the water-initiated linear $\mathbf{P_{2f}}$ was negligible (Table S2, entry 3, Figure S91). Therefore, control of polymer topology was possible by optimizing the ROP conditions of **2f** (linear $\mathbf{P_{2f}}$, linear + cyclic $\mathbf{P_{2f}}$, cyclic $\mathbf{P_{2f}}$) (Figure S91). Similarly, applying this method to the ROP of **2c** and **2g** could result in the formation of the corresponding cyclic polymers with moderate molecular weights as confirmed by MALDI-TOF mass spectra (Figures S92−S94).

2.3. Effects of TU on the Base-Catalyzed ROP of MDs.

The above results clearly demonstrated that TU played an important role in controlling the ROPs of the MDs. We speculate that TBD or DBU as a strong base may deprotonate the amides of MDs, leading to the formation of cyclic polymers in the absence of TU. To elucidate the mechanism in the TBD-/TU-catalyzed ROP of MD, we investigated the interactions of TBD and **2c**, TBD and TU, and TU and **2c** in CD_2Cl_2 via both ^{1}H and ^{13}C NMR spectra.[70,71] When an

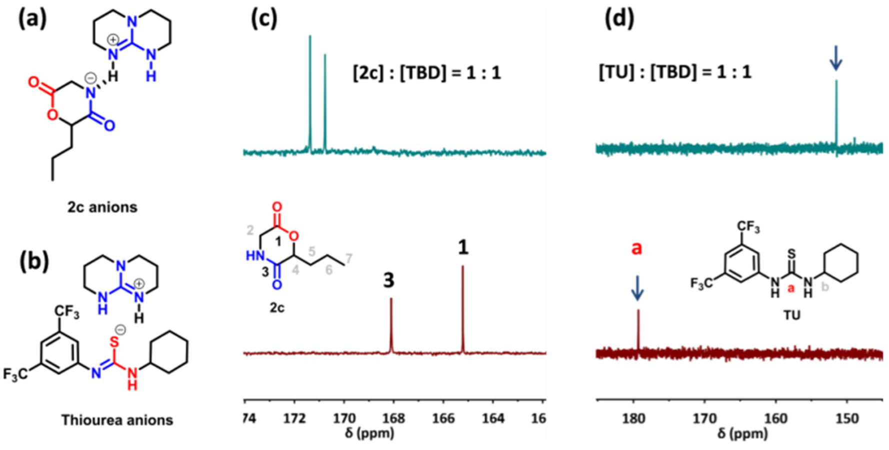


Figure 5. (a) **2c** and TBD complex, (b) TU and TBD complex, (c) stacked ^{13}C NMR spectra of **2c**, **2c** + TBD ($[\mathbf{2c}]_0$ = 0.167 mol/L, CD_2Cl_2), (d) stacked ^{13}C NMR spectra of TU, TU + TBD ($[TU]_0$ = 0.033 mol/L, CD_2Cl_2).

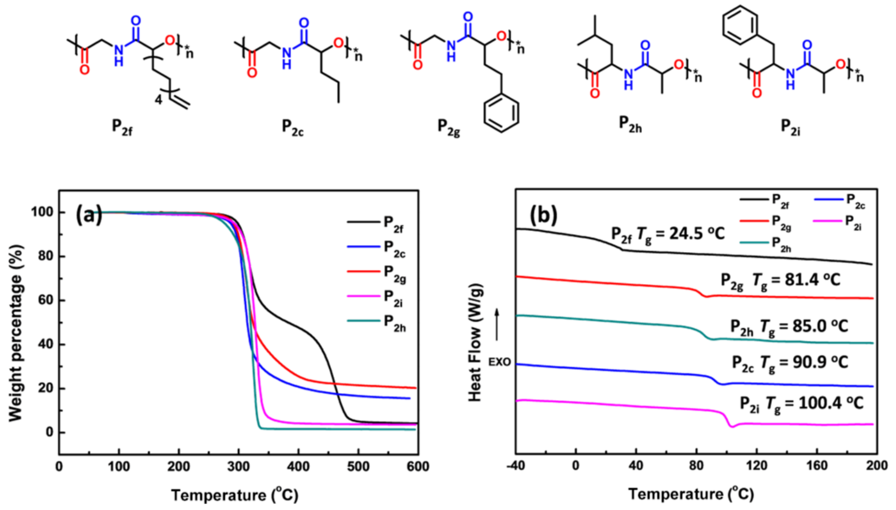


Figure 6. TGA (a) and DSC (b) thermograms of **P$_{2f}$** (M_n = 21.5 kDa; $Đ$ 1.05), **P$_{2c}$** (M_n = 11.5 kDa; $Đ$ = 1.09), **P$_{2g}$** (M_n = 13.0 kDa; $Đ$ = 1.07), **P$_{2h}$** (M_n = 15.2 kDa; $Đ$ = 1.07), and **P$_{2i}$** (M_n = 20.1 kDa; $Đ$ = 1.08).

equal molar amount of TBD and monomer **2c** (0.167 mol/L) was mixed in CD_2Cl_2, the carbonyl signals of 1 and 3 in **2c** shifted to lower field as compared to those of the free **2c** in ^{13}C NMR (Figures 5c and S95). Similar chemical shifts of typical protons in **2c** were also observed in the ^1H NMR spectra (Figure S96). In addition, the amide proton signals of **2c** and the guanidyl proton signals of TBD were merged into one broad signal and shifted to lower field in the mixture, indicating that these two protons exchanged rapidly. Similarly, in the ^{13}C NMR spectra of an equal molar mixture of TBD and TU (0.033 mol/L) (Figure 5d), the carbonyl signal of TU (peak a) shifted to higher field as compared to that of pure TU, and proton exchange of the guanidyl and thiourea protons was also observed in the ^1H NMR spectra (Figure S97). However, in the mixture of TU and **2c**, the interaction between these two components was much weaker than the above two mixtures (Figure S98). Overall, these results indicated that TBD, as a strong base, could deprotonate both **2c** and TU to form amide or thiourea anions. Because of the stronger acidity of TU than **2c**, in the mixture of **2c**, TBD, and TU, TU was selectively deprotonated via TBD, and no amide anions of **2c** could be formed.

On the basis of the above results, we proposed a mechanistic hypothesis for the formation of linear and cyclic PDPs in the TBD-catalyzed ROP of MD in Figure S99. When only TBD was used, it can deprotonate the amide groups in MD to form MD cyclic amidate/imidate anions. In the presence of a protic initiator such as BnOH, the ROP of MDs initiated by BnOH is dominant to form a linear PDP. However, the formed MD cyclic amidate/imidate anions can also initiate the ROP of MD, though it is slower and minor than the BnOH- or water-initiated ROP. When the polymer grows to a certain chain length, the end alkoxide anions may attack the carbonyl group of the iminomethyl ester at the α-chain end to form the cyclic PDP. In the absence of BnOH, this reaction is dominant, and cyclic PDP can be obtained exclusively when high TBD loading was used. However, when TU was added, it was preferentially deprotonated by TBD because of its higher acidity than the MD, thus inhibiting the deprotonation of MD and suppressing the formation of cyclic PDP. The formed TU anion could act as an efficient bifunctional catalyst to promote the BnOH-initiated ROP of MDs in a controlled manner to form exclusively linear PDPs.[72,73] To be noted, this is just a simple mechanistic hypothesis which can explain our experimental results. The exact mechanism can be more complicated; further detailed investigation is definitely needed to clarify it.

2.4. Thermal Properties of PDPs.

The thermal properties of **P$_{2f}$**, **P$_{2c}$**, **P$_{2g}$**, **P$_{2h}$**, and **P$_{2i}$** were characterized by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) as shown in Figure 6. These polymers are thermally stable as expected, and the $T_{d,5\%}$ of these polymers are around 295 °C, implying that the thermal stabilities of these polymers are dominated by the main-chain structure (Figures 6a and S100−S104). It is noteworthy that the TGA thermogram of **P$_{2f}$** is a two-step degradation process; both steps account for 50% weight loss (Figure S100). We suspected that the double bond of **P$_{2f}$** could be polymerized during the heating process. As the temperature rises to about 300 °C, the side chains could be polymerized to form a PE-like polymer which was finally decomposed at 400 °C.[74] This hypothesis was further confirmed by monitoring the thermal decomposition process of **P$_{2f}$** and **P$_{2c}$** with TG−infrared−gas chromatography/MS (Figures S105 and S106).

All these polymers are amorphous with the glass-transition temperatures (T_g) ranging from 24.5 to 100.4 °C (Figure 6b). The absence of melting temperature of these polymers is attributed to the irregular chiral center at the 6-position of monomers. **P$_{2f}$** exhibited the lowest T_g (24.5 °C) among all these polymers, which was due to the plasticization of the long alkyl side chains. **P$_{2i}$** displayed the highest T_g (100.4 °C) because of the existence of a methyl group at the 6-position and a bulky benzyl substitute at the 3-position, which restrict the chain mobility of **P$_{2i}$**. Therefore, by changing the substituents of the MDs, PDPs with tunable T_g could be obtained.

2.5. Polymer Degradation and Monomer Recovery.

Chemical recycling of polymers into monomers or monomer precursors is an ideal strategy to reduce the need of petroleum-based raw materials and minimize the negative impact on environment. PLA, the most widely studied biodegradable polymer, has been thermally degraded into complex products.[75−78] PDPs contain alternating amide and ester linkages in the backbone, and it is anticipated that they can be chemically degraded into small molecules under either basic or acidic conditions.

2.5.1. TBD-Catalyzed Alcoholysis of PDPs. Under optimized basic conditions, the alcoholysis of PDPs would generate *N*-(α-hydroxyacyl)-α-amino acid esters which are the precursors to synthesize MDs. We used TBD to degrade $\mathbf{P_{2c}}$ in a mixture of ethanol and DCM (ethanol/DCM = 2/1) at room temperature, followed by ^{1}H NMR (Figure 7). To our surprise, when 1 mol % equiv of TBD was used, $\mathbf{P_{2c}}$ degraded completely and cleanly into ethyl 2-(2-hydroxy pentanamido)-acetate (**1c**) in 3 min. Reducing the amount of TBD to 0.5 mol % could still trigger the fast degradation of $\mathbf{P_{2c}}$, and the monomer precursor was fully recovered within 4 min (Figure S107). We also confirmed that the degradation product **1c** could be efficiently transformed into monomer **2c** under acidic conditions (Figure S108). Similar results were obtained for the other polymers ($\mathbf{P_{2g}}$, $\mathbf{P_{2f}}$, $\mathbf{P_{2h}}$, and $\mathbf{P_{2i}}$) (data not shown).

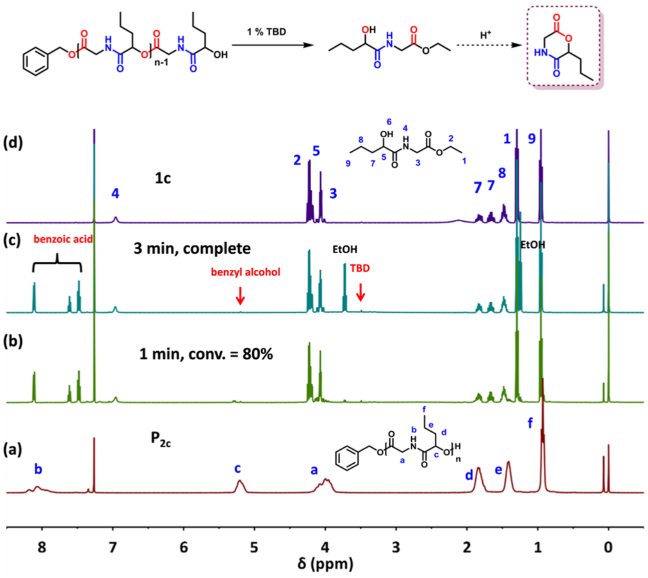


Figure 7. Time-dependent ^{1}H NMR spectra of the TBD-catalyzed degradation of $\mathbf{P_{2c}}$. [$\mathbf{P_{2c}}$] = 0.1 mol/L, 1 mol % TBD, EtOH/DCM = 2/1, 25 °C.

2.5.2. Acid-Catalyzed Depolymerization of PDPs. We then tried the direct recovery of MDs by the acid-catalyzed depolymerization of PDPs. For example, $\mathbf{P_{2i}}$ was dissolved in toluene, Amberlyst 15 ion-exchange resin was added as the acid catalyst, and the mixture was refluxed at 120 °C for different times. After 18 h, about 50% of $\mathbf{P_{2i}}$ was converted into monomer **2i** as determined by the ^{1}H NMR spectrum (Figure 8). The SEC trace of the mixture showed the existence of monomers and oligomers. After 46 h, $\mathbf{P_{2i}}$ was quantitatively depolymerized into monomer **2i** (Figure 8). The solid acid Amberlyst 15 ion-exchange resin can be easily removed from the reaction mixture to get pure **2i** toluene solution. Other polymers ($\mathbf{P_{2c}}$, $\mathbf{P_{2g}}$, $\mathbf{P_{2f}}$, and $\mathbf{P_{2h}}$) could also be depolymerized into their corresponding monomers under similar conditions (data not shown). Thus, this is a simple and clean monomer recovery method for PDPs.

3. SUMMARY

We developed a simple method for the efficient synthesis of a platform MD monomer, whose structure can be easily regulated by changing the starting amino acids and aldehydes. The organocatalytic ROP of these MDs was investigated in detail, and successful living ROP was achieved. The organic-base catalyzed ROP of MDs is much more complicated and difficult to control than LAs and lactones because of the presence of amide groups in the monomers. When a strong base, either TBD or DBU, was used as the single catalyst, even when BnOH was added as the initiator, the ROP of MDs could not be well-controlled, and both linear polymers and cyclic oligomers were formed. By using binary TBD/TU and DBU/TU catalytic systems (([TU]/[TBD] or [DBU] > 3), the living ROP of MDs can be achieved to get high-molecular-weight PDPs with expected molecular weights and low dispersities. We experimentally proved that TU played an important role in controlling the polymerization. When strong bases such as TBD existed, the MDs will be deprotonated to form the cyclic amidate/imidate anions, which may initiate the ROP of MDs to form cyclic PDPs. Adding TU to the base-catalyzed system can inhibit the deprotonation of MDs and selectively result in the formation of high-molecular-weight linear PDPs in a controlled way. On the basis of these findings, a mechanistic hypothesis was proposed, but further detailed work is definitely needed to verify it. Finally, the obtained PDPs can be quantitatively alcoholyzed into *N*-(α-hydroxyacyl)-α-amino acid ethyl esters (MD precursors) in several minutes at room temperature in the presence of the catalytic amount of TBD. Moreover, we also realized the monomer

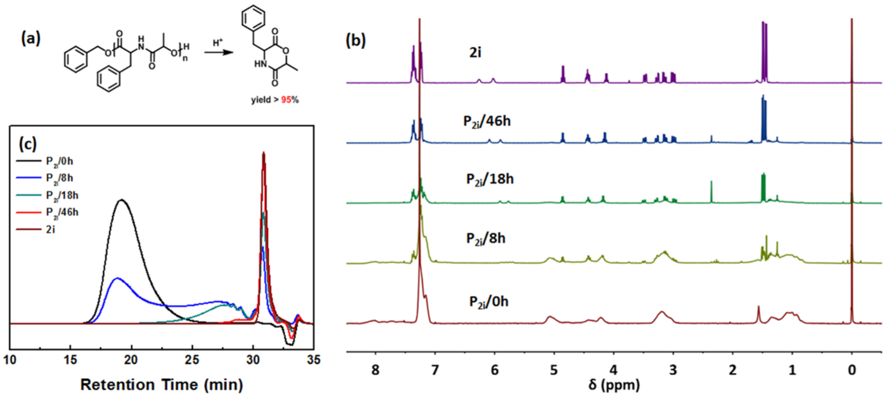


Figure 8. (a) Acid-catalyzed degradation of $\mathbf{P_{2i}}$, (b) time-dependent ^{1}H NMR spectra, and (c) time-dependent SEC traces of the degradation process of $\mathbf{P_{2i}}$.

recovery in a quantitative manner by the acid-catalyzed depolymerization of PDPs.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.8b02498.

> Synthetic procedures, structural characterization of all the monomers and polymers (^{1}H and ^{13}C NMR spectra, ESI-MS spectra, MALDI-TOF-MS spectra, and SEC traces), polymerization kinetics, thermal property of the polymers by TGA and DSC, and degradation of polymers (PDF)

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Notes

The authors declare no competing financial interest.

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