

Sustainable Polyamides Enabled by Controlled Ring-opening Polymerization of 4-Hydroxyproline-derived Lactams

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 Electronic Supplementary Information

Abstract Aliphatic polyamides have been considered as eco-friendly materials, useful for a wide range of applications. However, it still presents obstacle to produce sustainable aliphatic polyamides from abundant renewable sources. Herein, we describe that 4-hydroxyproline (4-HYP), a renewable resource, was readily converted to its corresponding bicyclic bridged lactam monomers bearing pendant Boc-protected secondary amino group, and oligo-ethylene glycol group. Lithium hexamethyldisilazide (LiHMDS)-mediated polymerization of the resulting monomers exhibited a controlled feature, affording sustainable aliphatic polyamides with number-average molecular weight up to 73 kg/mol and a low molecular weight distribution $\bar{D} < 1.28$. Overall, this work can lead to a novel kind of functional and sustainable polyamides with potential applications, including degradable plastics, and drug delivery.

Keywords Polyamides; Renewable; Ring-opening polymerization; 4-Hydroxyproline

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INTRODUCTION

Polyamides, as an important class of polymers containing amide groups in the repeating units of main chain, possess satisfying comprehensive performances like high strength, toughness, thermal/chemical resistance and wearing durability, which endow them with many applications, such as engineering thermoplastics, clothing, and functional materials in drug delivery.^[1–11] However, many commonly used polyamides are based on petrochemical building blocks.^[12] On the other hand, the development of sustainable polymers from renewable resources is a crucial goal but remains a formidable challenge for polymer chemistry.^[13–20] Therefore, the development of sustainable, functional polyamides has received significant attention, which will not only establish a future-oriented and sustainable polymer industry, but also give access to special physical properties and mechanical strengths.^[21–24]

Ring-opening polymerization (ROP) of heterocyclic monomers is an important and useful approach for producing well-defined sustainable polymers.^[25,26] So far, apart from four-member β -lactams, controlled ROPs are difficult to achieve using other lactams.^[27–29] Hashimoto *et al.* first reported that the ROP of bicyclic lactam 8-oxa-6-azabicyclo[3.2.1]

octan-7-one exhibited a controlled character, affording polyamides with predictable molecular weights.^[30] Clearly, in order to accomplish controlled lactam polymerization, judicious design of high-ring strained lactam monomers with high polymerizability is highly required.

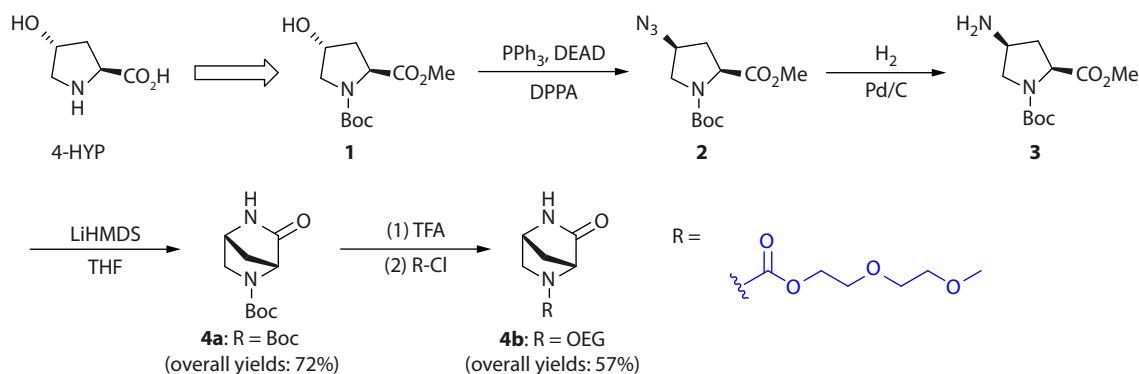
Amino acids, the fundamental building blocks of proteins with diverse functional groups, are ideal renewable building blocks for the production of sustainable polymers.^[31–39] Our group recently demonstrated the producing of poly(ϵ -lysine) and its derivatives with diverse molecular weights, structures and functionality from lysine, one of the most abundant amino acids.^[40–45] 4-Hydroxyproline (4-HYP) is a naturally occurring amino acid and abundant in collagen.^[46] Lu *et al.* recently reported the elegant synthesis of functional, sustainable polythioesters and polyesters using 4-HYP as building block.^[47,48] In this context, 4-HYP could be readily converted to its corresponding bicyclic bridged lactam monomers bearing pendant functional groups (Scheme 1), and further implementation of its ROP, would expand the scope of sustainable and functional polyamides, but surprisingly has not been explored.

Herein, we demonstrated that 4-HYP-derived bridged bicyclic lactam monomers could undergo controlled ROP and afford sustainable and functional polyamides with number-average molecular weight (M_n) up to 73 kg/mol and a narrow dispersity ($\bar{D}$) below 1.28. This work can lead to a novel kind of functional and sustainable polyamides with potential applications, including degradable plastics, and drug delivery.

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Scheme 1 Synthesis of sustainable bicyclic bridged lactam monomers.

EXPERIMENTAL

General Considerations

All moisture/oxygen sensitive reactions were performed using standard glove box or Schlenk techniques under N_2 . Tetrahydrofuran (THF) was refluxed with sodium and distilled under nitrogen before use. All the other reagents and solvents were purchased from Energy Chemical and used as received without further purification unless otherwise stated. All room temperature ^1H -NMR and ^{13}C -NMR spectra were recorded on a Bruker AV-500 spectrometer and a Bruker AV-600 spectrometer, respectively. High resolution mass spectrum (HRMS) conditions were measured by MALDI-TOF mass spectrometry, which was performed on Bruker autoflex III smartbeam mass spectrometer (Locality: Germany) in linear, positive ion mode. DCTB (2-[(2E)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene] malononitrile) was used as the matrix. Size exclusion chromatography (SEC) was conducted on a system composed of a Waters 2414 Refractive Index Detector equipped with a series of connected size exclusion columns (1000 Å and 10000 Å, Phenogel columns, 5 μm , 300 $\times$ 7.8 mm Phenomenex Torrance, CA, USA). The system was operated with 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, containing 0.02 mol/L NaTFAc) as the eluent at a flow rate of 1 mL/min at 35 $^\circ\text{C}$ and calibrated with poly(methyl methacrylate) standards. Due to the poor solubility of the poly(N^{OEG} -DBH) in HFIP, the system was operated with H_2O (containing 0.5 mol/L AcOH and 0.3 mol/L Na_2SO_4) as the eluent at a flow rate of 0.8 mL/min at 35 $^\circ\text{C}$ and calibrated with poly(ethylene glycol) (PEG) standards in the molecular weight range from 1000 Da to 2.18×10^5 Da.

Synthesis of Functional N^{R} -DBH Monomers

Synthesis of 1-(*tert*-butyl)2-methyl(2*S*,4*S*)-4-azidopyrrolidine-1,2-dicarboxylate (**2**)

To a solution of *N*-*tert*-butoxycarbonyl-*trans*-4-hydroxy-L-proline methyl ester (**1**, 5.8 g, 1.0 equiv.) in dry THF (150 mL) was added triphenylphosphine (7.8 g, 1.25 equiv.) in small portions at a rate under an N_2 atmosphere and this mixture was stirred in ice/water bath. After the mixture turned clear, Diethyl azodicarboxylate (DEAD, 4.3 mL, 1.25 equiv.) was added into this mixture. After 15 min, diphenylphosphoryl azide (6.6 mL, 1.29 equiv.) was added slowly into the reaction mixture. The reaction was stirred overnight at room temperature. After completion, the residue was purified by column chromatography (PE/EA=5/1) to give a colourless liquid 1-(*tert*-butyl)2-methyl(2*S*,4*S*)-4-azidopyrrolidine-1,2-dicarboxylate (**2**) (90%

yield). **2**: ^1H -NMR (500 MHz, CDCl_3 , δ , ppm): 4.43–4.30 (m, 1H), 4.20–4.18 (m, 1H), 3.74 (s, 3H), 3.69–3.45 (m, 2H), 2.30–2.12 (m, 2H), 1.46–1.41 (d, 9H).

Synthesis of 1-(*tert*-butyl)2-methyl(2*S*,4*S*)-4-aminopyrrolidine-1,2-dicarboxylate (**3**)

A solution of compound **2** (3.0 g, 10.94 mmol) in 1/1 mixture of ethyl acetate and ethanol (25 mL/25 mL) was stirred overnight at room temperature under H_2 in the presence of 10% Pd/C (0.3 g). The reaction mixture was filtered through celite, and the filtrate was concentrated as colorless oil (2.6 g, 100%). **3**: ^1H -NMR (500 MHz, CDCl_3 , δ , ppm): 4.34–4.21 (m, 1H), 3.74 (s, 3H), 3.69–3.61 (m, 1H), 3.56–3.48 (m, 1H), 3.29–3.21 (m, 1H), 2.49–2.38 (m, 1H), 1.83–1.77 (m, 1H), 1.46–1.41 (d, 9H).

Synthesis of *tert*-butyl (1*R*,4*R*)-6-oxo-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**4a**)

To a solution of **3** (1.0 mmol) in anhydrous THF (4.0 mL) was added LiHMDS solution (1.0 mol/L, 1.2 mL, 1.2 mmol) under nitrogen at room temperature. The resulted solution was stirred at room temperature for 15 min, and then quenched by adding AcOH (1 equiv. to LiHMDS). The solvent was removed under reduced pressure. Dichloromethane and water were added, and the separated aqueous layer was extracted again with dichloromethane. The combined organic layers were washed with water and brine, dried over anhydrous MgSO_4 , and evaporated. The residue was purified by column chromatography (EA/MeOH=10/1) to give a white solid (80% yield). **4a**: ^1H -NMR (500 MHz, CDCl_3 , δ , ppm): 5.99 (s, 1H), 4.38 (m, 1H), 4.10 (m, 1H), 3.47–3.44 (m, 1H), 3.26–3.23 (m, 1H), 2.03–2.00 (m, 1H), 1.82–1.71 (m, 1H), 1.47 (s, 9H).

Synthesis of 2-(2-methoxyethoxy)ethyl(1*S*,4*S*)-6-oxo-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**4b**)

To a solution of **4a** (500 mg, 1.0 equiv.) in DCM (2 mL) was slowly added trifluoroacetic acid (1.75 mL, 10 equiv.) under ice bath, and the reaction mixture was stirred 4 h at room temperature. Then the solvent was removed under reduced pressure and the residue was vacuumed to obtain white solid. The solid was used directly for next step without further purification. Dissolved the product from the previous step in dichloromethane (2 mL) and added triethylamine (2 mL, 3 equiv.), 2-(2-methoxyethoxy)ethyl carbonochloridate (851 mg, 1 equiv.), the reaction mixture was stirred at room temperature overnight. After the reaction is completed, the reaction solution was washed successively with water, dilute hydrochloric acid and saturated brine. Then the organic layer was dried with

anhydrous sodium sulfate (Na_2SO_4) and concentrated with a rotary evaporator. The residue was purified by column chromatography (PE/EA=1/1) to afford **4b** as a colourless liquid (80% yield). **4b**: $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ , ppm): 4.36 (s, 1H), 4.14–4.10 (m, 3H), 3.63–3.47 (m, 7H), 3.29 (s, 3H), 3.23–3.10 (m, 2H), 1.96–1.81 (m, 2H). ESI-MS: calcd. for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$: 281.3; found: 281.3.

Synthesis of *tert*-Butyl(1*R*,4*R*)-5-benzoyl-6-oxo-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (N-Bz-N^{Boc}-DBH)

To a solution of **4a** (1.06 g, 1 equiv.) in anhydrous DMF (10 mL) was added 60% NaH (240 mg, 1.2 equiv.) under an ice bath and the mixture was stirred at room temperature for 0.5 h. Then the benzoyl chloride (0.70 mL, 1.2 equiv.) was added dropwise and the reaction mixture was stirred overnight. H_2O was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated with rotary evaporator. The residue was purified by column chromatography using PE/EA (1/1) as eluent and recrystallized with PE/EtOAc (1/1) to afford the product as white crystal (65% yield). N-Bz-N^{Boc}-DBH: $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ , ppm) 7.65–7.39 (m, 5H), 5.04 (m, 1H), 4.54 (m, 1H), 3.59 (m, 2H), 2.16–2.02 (m, 2H), 1.44 (s, 9H).

Ring-opening Polymerization of N^R-DBH

Take the entry 5 (Table 1) for example. Monomer (53 mg) and co-initiator (1.5 mg) were weighted and added to a flame-dried

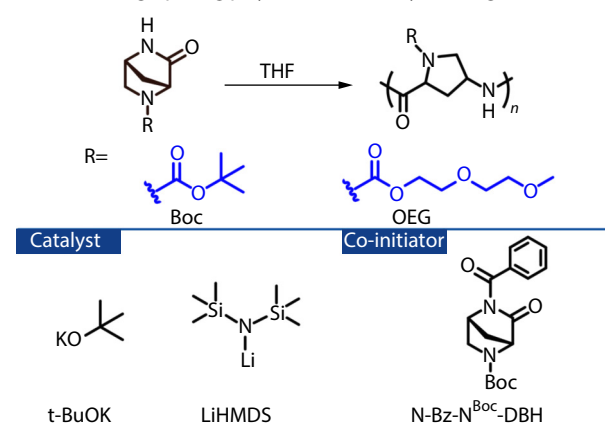
polymerization tube. The mixtures were dried in vacuum and purged with nitrogen for 30 min. Then anhydrous THF (500 μL) and LiHMDS (5 μL , 1 mol/L in THF) were added under N_2 atmosphere and the polymerization proceed at 25 $^\circ\text{C}$ under N_2 atmosphere. After 3 min, the polymerization was quenched by addition of 1 mL of formic acid/ CHCl_3 (1 mol/L). An aliquot was taken from the resulting solution to determine N^R-DBH conversion by $^1\text{H-NMR}$. The quenched mixture was then precipitated in methanol to get the neat polymer. The product was isolated by centrifugation and dried under vacuum for 24 h.

RESULTS AND DISCUSSION

Synthesis and Characterization of Monomers

One aspect of this work was to prepare a series of bicyclic bridged lactam monomers with pendant functional groups using sustainable 4-hydroxyproline as a feedstock. As depicted in Scheme 1, bicyclic bridged lactam monomer bearing pendant Boc-protected secondary amino group (N^{Boc}-DBH) was synthesized in three steps from *N*-*tert*-butoxycarbonyl-*trans*-4-hydroxy-L-proline methyl ester via Mitsunobu reaction, hydrogenation reaction, and lactamization reaction (Scheme 1).^[49] The obtained compounds were confirmed by nuclear magnetic resonance (NMR) (Figs. S1–S3 in the electronic supplementary information, ESI). The Boc protecting group of N^{Boc}-DBH was then removed with excess trifluoroacetic acid (TFA) and the oligo-ethylene glycol (OEG) functionalized lactam

Table 1 Results of ring-opening polymerization of bicyclic bridged lactam monomers. ^a

								
Entry	Monomer	Catalysts	$[\text{M}]_0/[\text{Cat}]_0/[\text{I}]_0$	Time (min)	Conv. ^b (%)	$M_{n,\text{calcd.}}$ ^c (kg/mol)	$M_{n,\text{SEC}}$ ^d (kg/mol)	$\bar{D}$ ^d (M_w/M_n)
1	N ^{Boc} -DBH	<i>t</i> -BuOK	25/1/1	3	>99	5.3	13.8	1.72
2	N ^{Boc} -DBH	LiHMDS	25/1/0	120	>99	5.3	50.5	1.68
3	N ^{Boc} -DBH	LiHMDS	25/1/1	3	>99	5.3	5.7	1.25
4	N ^{Boc} -DBH	LiHMDS	10/1/1	1	>99	2.1	2.2	1.21
5	N ^{Boc} -DBH	LiHMDS	50/1/1	15	>99	10.6	10.1	1.28
6	N ^{Boc} -DBH	LiHMDS	100/1/1	60	>99	21.2	21.0	1.27
7	N ^{Boc} -DBH	LiHMDS	200/1/1	120	>99	42.4	42.3	1.28
8	N ^{Boc} -DBH	LiHMDS	400/1/1	300	>99	84.8	73.3	1.24
9 ^e	N ^{OEG} -DBH	LiHMDS	25/1/1	5	>99	6.4	5.1	1.08
10 ^e	N ^{OEG} -DBH	LiHMDS	50/1/1	10	>99	12.8	10.9	1.10

^a Polymerizations were conducted in THF at 25 $^\circ\text{C}$ with $[\text{M}]_0=0.5$ mol/L; ^b Determined by $^1\text{H-NMR}$; ^c Calculated molecular weight based on $[\text{M}]_0/[\text{I}]_0$ ratio and conversion; ^d Determined by SEC in HFIP (0.02 mol/L NaTFAc) relative to poly(methyl methacrylate) standards; ^e Determined by SEC in H_2O (containing 0.5 mol/L AcOH, 0.3 mol/L Na_2SO_4) relative to PEG standards.

monomer (N^{OEG} -DBH) was generated upon substitution with the corresponding chloride nucleophile (Scheme 1). The structure of N^{OEG} -DBH was identified by $^1\text{H-NMR}$ and ESI-MS (Fig. S4 in ESI).

ROP of Functional N^{R} -DBH Monomers

The ROP of N^{Boc} -DBH was first examined using an inorganic base, $t\text{-BuOK}$, as catalyst. The polymerization was implemented in tetrahydrofuran (THF) at 25 °C with $N\text{-Bz-}N^{\text{Boc}}$ -DBH as co-initiator ($[M]_0/[Cat]_0/[I]_0=25/1/1$). Indeed, the ROP of N^{Boc} -DBH delivered ultrafast polymerization and achieved complete conversion in just 3 min (Table 1, entry 1). However, uncontrolled polymerization occurred, producing poly(N^{Boc} -DBH) with a number average molecular weight (M_n) of 13.8 kg/mol and a molecular weight distribution $\mathcal{D}$ of 1.72, much higher than the calculated one ($M_{n,\text{calcd.}}=5.3$ kg/mol). In an effort to enhance the molecular weights (MWs) control, we turned our attention to LiHMDS, which has previously been used to mediate the controlled ROP of β -lactams.^[27,28] Then, we studied the polymerization of N^{Boc} -DBH using LiHMDS alone (4.0 mol%) in THF at 25 °C. The polymerization proceeded to afford poly(N^{Boc} -DBH) with broader $\mathcal{D}$ of 1.68 (Table 1, entry 2). When applying 1 equiv. of co-initiator, relative to LiHMDS, we were delighted to note that the LiHMDS-mediated ROP of N^{Boc} -DBH ($[M]_0/[Cat]_0/[I]_0=25/1/1$, entry 3 in ESI) achieved complete conversion in 3 minutes, affording poly(N^{Boc} -DBH) with a low molecular weight distribution $\mathcal{D}$ of 1.25 and M_n close to the theoretical value.

Encouraged by the promising initial data, we studied the LiHMDS-mediated polymerization of N^{Boc} -DBH for more detail. Poly(N^{Boc} -DBH) with predictable M_n ranging from 2.2 kg/mol to 73.3 kg/mol could be successfully produced via regulating $[M]_0/[I]_0$ ratio (entries 3–8). The structure of poly(N^{Boc} -DBH) was determined by $^1\text{H-NMR}$ and MALDI-TOF-MS (Fig. 1 and Fig. 2). The polymerization was confirmed by observing a decrease in the $C_\alpha\text{-H}$ peak at 6.0 ppm of the monomer and a corresponding broadened multiplets at 4.6 ppm of the polymer using $^1\text{H-NMR}$. The experimental M_n values of poly(N^{Boc} -DBH) generally concur with the theoretical values calculated from the conversion and $[M]_0/[I]_0$ ratio and the SEC profiles displayed unimodal distributions with low $\mathcal{D}$ (<1.28) at different $[M]_0/[I]_0$ ratios (Fig. 2). The MALDI-TOF

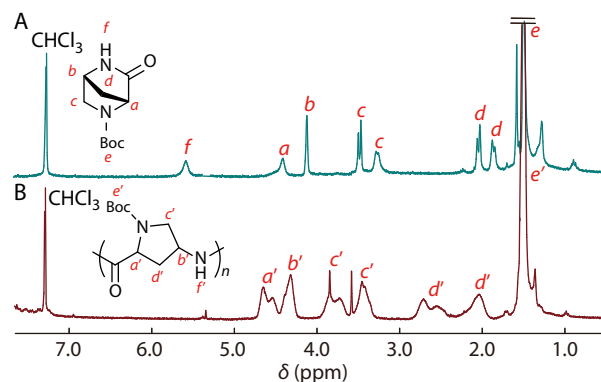


Fig. 1 $^1\text{H-NMR}$ spectra of N^{Boc} -DBH (A) and poly(N^{Boc} -DBH) (B) in CDCl_3 at 25 °C. Polymers were prepared by $[M]_0/[Cat]_0/[I]_0 = 25/1/1$ at 25 °C.

mass spectrum of poly(N^{Boc} -DBH) consisted of two sets of signals, attributing to the structure **a** with benzoyl/acetylated lactam chain ends and the structure **b** with H/acetylated lactam chain ends.^[50] Overall, these results demonstrate that LiHMDS-mediated ROP of N^{Boc} -DBH exhibited a controlled feature.

The ROP of N^{OEG} -DBH displayed very similar controllability to that of N^{Boc} -DBH (Table 1, entries 9 and 10). For example, LiHMDS-mediated formation of poly(N^{OEG} -DBH) with hydrophilic side chains ($^1\text{H-NMR}$ in Fig. 3) at a $[M]_0/[I]_0$ ratio of 50/1 exhibited a M_n of 10.9 kg/mol and $\mathcal{D}$ of 1.10 (Table 1, entry 10). In brief, LiHMDS-mediated ROP of bridged bicyclic lactam is an efficient approach for the generation of functional and sustainable polyamides based on 4-hydroxyproline, which encodes various functional side groups to expand its versatility and has the potential feasibility for tuning physical properties.^[51]

After the successful synthesis of poly(N^{Boc} -DBH), the corresponding poly(N^{H} -DBH) with secondary amino groups were recovered by removal of protecting groups (Fig. 4). $^1\text{H-NMR}$ spectrum of the deprotected cationic polymer poly(N^{H} -DBH) showed the disappearance of all of the *tert*-butyl protons around 1.47 ppm (Fig. 4), demonstrating the complete removal of the protecting groups. Before deprotection, poly(N^{Boc} -DBH) was only soluble in strong polar solvents, such

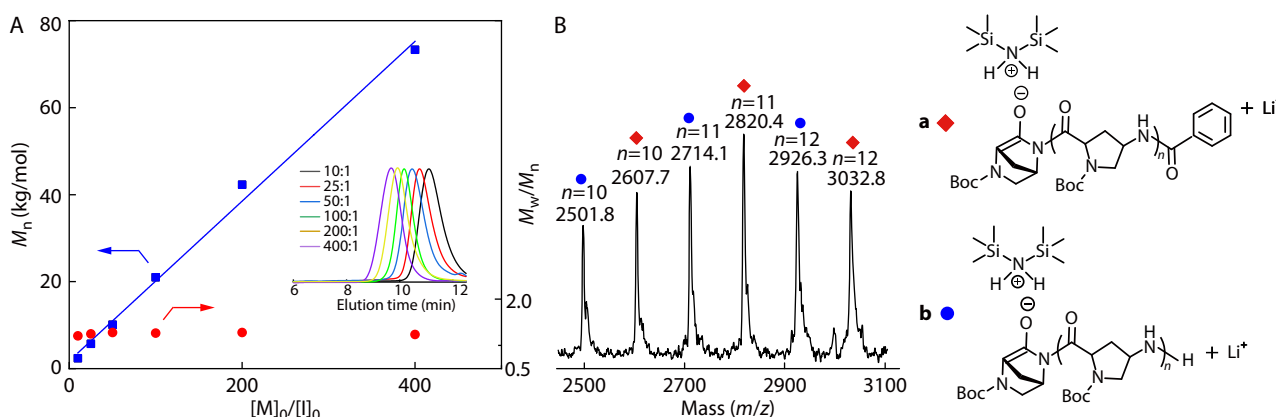


Fig. 2 (A) Plots of M_n and $\mathcal{D}$ as a function of the $[M]_0/[I]_0$ ratio. Inset: overlay of SEC profiles at different $[M]_0/[I]_0$ ratios. (B) MALDI-TOF-MS spectrum of poly(N^{Boc} -DBH).

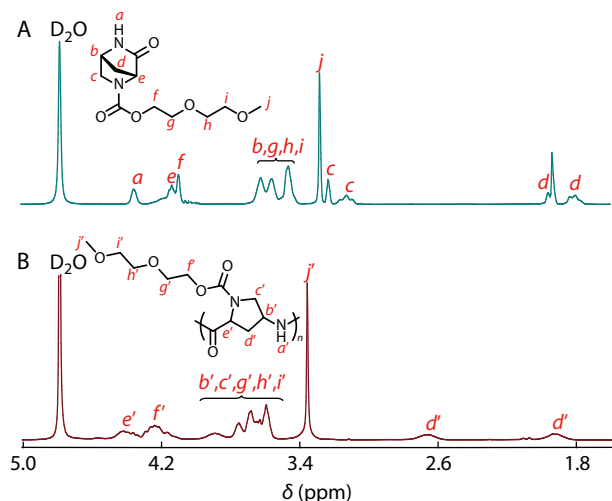


Fig. 3 ^1H -NMR spectra of $\text{N}^{\text{OEG}}\text{-DBH}$ (A) and $\text{poly}(\text{N}^{\text{OEG}}\text{-DBH})$ (B) in D_2O at $25\text{ }^\circ\text{C}$. Polymers were prepared by $[\text{M}]_0/[\text{Cat}]_0/[\text{I}]_0 = 25:1:1$ at $25\text{ }^\circ\text{C}$.

as formic acid, HFIP and TFA, but was insoluble in water and dimethyl sulfoxide (DMSO). However, after deprotection, $\text{poly}(\text{N}^{\text{H}}\text{-DBH})$ was soluble in water and DMSO. Additionally,

the $\text{poly}(\text{N}^{\text{Boc}}\text{-DBH})$ with an M_n value of 42.3 kg/mol resulted in the deprotected polymer $\text{poly}(\text{N}^{\text{H}}\text{-DBH})$ with an M_n value of 24.5 kg/mol (Fig. 4B), which is in excellent agreement with the expected M_n (22.9 kg/mol). We have thus manifested that LiHMDS-mediated polymerization of bridged bicyclic lactam offers a relatively facile method for functional polyamides.^[52,53]

Based on the aforementioned experimental data, we tentatively proposed the LiHMDS-mediated ROP of $\text{N}^{\text{Boc}}\text{-DBH}$ monomers in Scheme 2. Initially, LiHMDS, a non-nucleophilic base, can deprotonate a lactam monomer to produce the lactamate anion. Then, the propagating step proceeds through two pathways. The pathway **a** is the nucleophilic reaction of the lactamate anion on the endocyclic carbonyl group of the co-initiator, and following the transfer of a proton from another lactam monomer to the resultant amidate anion, which regenerates the lactamate anion. The pathway **b** is the nucleophilic reaction of the lactamate anion on the carbonyl group of the monomer, which is much slower than pathway **a**. Compared with non-acylated lactams, co-initiator is easily opened and promoted lactam ROP due to their significantly more electron-deficient character. Overall, the mechanism shown in Scheme 2 is consistent with the polymerization and MALDI-TOF results.

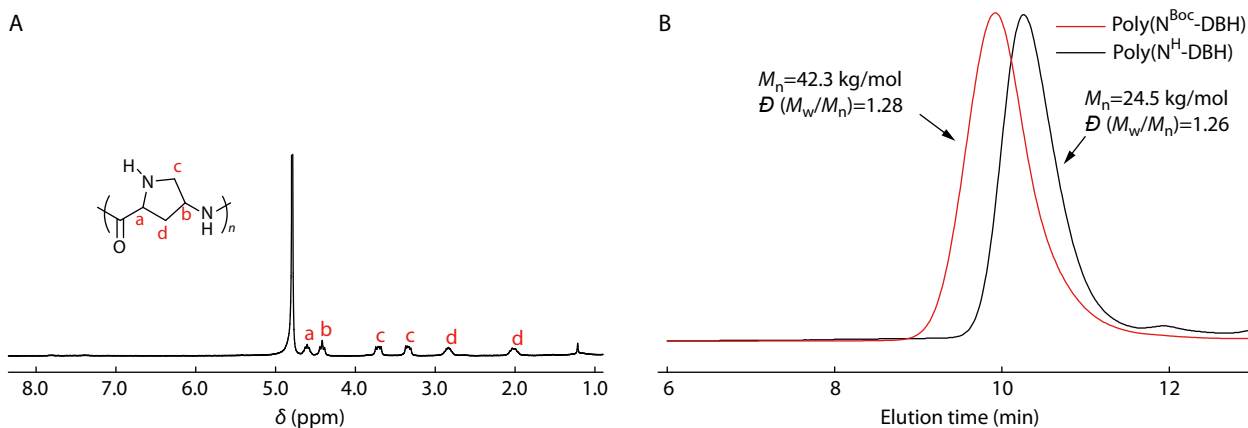
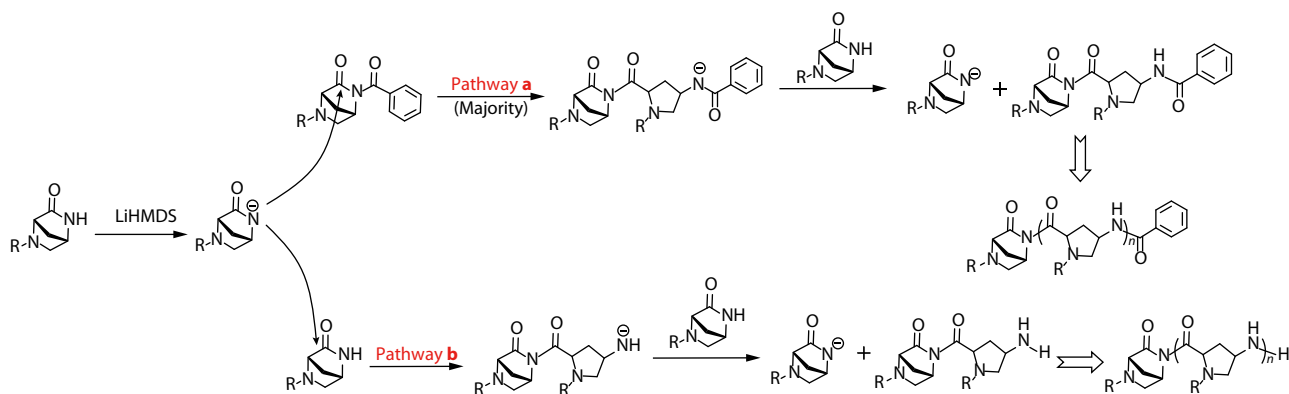


Fig. 4 (A) ^1H -NMR spectrum of $\text{poly}(\text{N}^{\text{H}}\text{-DBH})$ in D_2O at $25\text{ }^\circ\text{C}$; (B) Overlay of SEC profiles of $\text{poly}(\text{N}^{\text{Boc}}\text{-DBH})$ (red) and $\text{poly}(\text{N}^{\text{H}}\text{-DBH})$ (black) derived from the deprotection of the Boc group of $\text{poly}(\text{N}^{\text{Boc}}\text{-DBH})$ in TFA. Both the SEC measurements were conducted in HFIP relative to poly(methyl methacrylate) standards.



Scheme 2 Proposed mechanism for the ROP of bicyclic bridged lactam monomers by LiHMDS in the presence of co-initiator.

CONCLUSIONS

In summary, we have described the facile preparation of a series of 4-hydroxyproline-derived bridged bicyclic lactams bearing pendant Boc-protected secondary amino group, and oligo-ethylene glycol group. Lithium hexamethyldisilazide (LiHMDS)-mediated polymerization of the resulting monomers exhibited a controlled feature. This process afforded sustainable aliphatic polyamides with M_n up to 73 kg/mol and a low $\bar{D}$ <1.28. Overall, our work can lead to a novel kind of functional and sustainable polyamides with potential applications, including degradable plastics, and drug delivery.

NOTES

The authors declare no competing financial interest.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at <http://doi.org/10.1007/s10118-022-2871-5>.

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