Synthesis of Well-defined Poly(tetrahydrofuran)-b-Poly(α-amino acid)s via Cationic Ring-opening Polymerization (ROP) of Tetrahydrofuran and Nucleophilic ROP of N-thiocardoxanhydrides

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Abstract

The synthesis of block copolymers of poly(tetrahydrofuran)-b-poly(α-amino acid) (PTHF-b-PAA) is challenging since it is difficult to combine the two blocks produced via different/conflicting ring-opening polymerization (ROP) mechanisms. In this contribution, the cationic ROP of THF is catalyzed by rare-earth triflate \( \text{[RE}(\text{OTf})_3] \) and terminated by 2-(t-butyloxycarbonyl-amino) ethanol (BAE). After the depolymerization of t-butyloxycarbonyl (Boc) group, the chain end of PTHF is quantitatively changed to amino group which thereafter initiates the nucleophilic ROP of α-amino acid N-thiocarboxyanhydrides (NTAs). Both polymerizations are well controlled, generating PTHF and PAA segments with designable molecular weights (MWs). PTHF-b-polysilane (PTHF-b-Plys) and PTHF-b-polysarcosine (PTHF-b-Psar) are obtained with MWs between 8.6 and 28.7 kg/mol. The above amphiphilic diblock copolymers form micelles in water. PTHF-b-Psar acts as a surfactant to stabilize oil-in-water emulsions. Both segments of PTHF-b-PAA are biocompatible and promising in the biomedical application.

Keywords: Poly(tetrahydrofuran); Poly(α-amino acid); End group transformation; Quantitation; Copolymer

INTRODUCTION

Poly(tetrahydrofuran) (PTHF) has wide applications in polyurethanes industry to adjust elastic performance of polyurethanes due to its low glass-transition temperature and flexibility. With high water stability, low toxicity and resistance of microbial, PTHF plays an important role in spanning, engineering and medical treatment.

Poly(α-amino acid)s (PAAs), including polypeptides and polypeptoids, have attracted wide interest for their excellent biocompatibility mimicking natural proteins. Promising applications have been reported in drug delivery, tissue engineering, biosensor, and bio-imaging. Polypeptides with secondary structures including α-helix and β-sheet are endowed with high mechanical strength and unique assembly behaviors. Chemical conjugation of PTHF and PAAs allows for the combination of softness and rigidity as well as hydrophobicity and hydrophilicity, making the copolymer a candidate for biomedical applications.

Chain end coupling is an efficient way to prepare PTHF-b-PAA copolymers. Hu et al. connected PTHF and poly(γ-benzyl-L-glutamate) (PBLG) using isophorone diisocyanate and produced multi-block copolymer. Owing to the β-sheet crystalline area of PBLG, toughness of the multi-block copolymer reached 387±35 MJ/m³, higher than that of aciiform silk. The α-helix of PBLG and random coil of PTHF notably improved the tensile strength and extensibility, which was considered as a new strategy towards artificial spider silk. Alternatively, polymerization of α-amino acid-N-carboxyanhydrideries (NCAs) with amine-terminated PTHF has been employed to produce PTHF-b-PAA. Feng et al. low molecular weight \( (M_n=1100) \) bis(3-aminopropyl)-terminated PTHF to initiate the polymerization of N-ε-carboxyloxyl-L-lysine NCA (εLL-NCA) and obtained PzLL-PTHF-PzLL triblock copolymer. After the introduction of gluconolactone or lactobionolactone on the side chains of PzLL segment, the triblock copolymer was able to assemble into micelles with a mean hydrodynamic diameter \( (D_h) \) of 40 nm. Copolymers modified with linoleic acid in PzLL segments were able to load doxorubicin as micelles with a stable drug release rate for 12 h. Because of the valuable properties and applica-
tions of PTHF and PAA copolymers, it is desirable to come up with a method for fabricating well-controlled amine-terminated PTHF for further usage.

NCA monomers are compounds sensitive to nucleophilic attack, resulting in difficulties in preparation and storage. Recently, α-amino acid-N-thiocarboxyanhydrides (NTAs) which are more stable than NCAs are qualified as new monomers to synthesize well-controlled PAs via coordination anionic or nucleophilic ring-opening polymerization (ROP) mechanisms.

Inspired by the successful synthesis of α,ω-di-dihydroxyl PTHF by cationic ROP mechanisms in the presence of rare-earth triflate [RE(OTf)₃] catalyst, we herein report a versatile approach of quantitative introduction of amino group at PTHF chain end to generate α-hydroxyl-ω-amino-telechelic PTHF (PTHF-NH₂) which initiates nucleophilic ROP of α-amino acid-NTAs, e.g. N-ε-carbobenzyloxy-L-lysine NTA (zLL-NTA) and sarcosine NTA (Sar-NTA). It is a strategy of sequential cationic and nucleophilic ROPs and easy to be extended to the synthesis of other block polymers.

**EXPERIMENTAL**

**Materials**

Tetrahydrofuran (THF, superdry, 99.9%, J&K Scientific Ltd.), sarcosine (98%, Energy Chemical), N-ε-carbobenzyloxy-L-lysine (zLL, 98%, CS-Pharm Chemical Ltd.), phosphorous tribromide (PBr₃, 99%, Energy Chemical), acetic acid (HAc, AR, Sinopharm Chemical Reagent Company), trifluoroacetic acid (TFA, 99.0%, Shanghai Macklin Biochemical Ltd.) and hydrogen bromide (HBr, 30 wt% in acetic acid, Shanghai TCI Development Ltd.) was stirred over BaO and distilled. 2-(Boc-amino) ethanol (BAE, 98%, J&K Scientific Ltd.) and triflic acid (99%, Energy Chemical) and dried in a vacuum (<0.5 mmHg) at 200 °C for 48 h. Propylene oxide (PO, >99.99%, Beijing Founde Star Science and Technology Company) was stirred over BaO and distilled. zLL-NTA (Fig. S2 in ESI) were prepared according to reported methods.

All the polymerizations were performed using Schlenk technique under argon atmosphere in pre-dried reaction tubes.

**Synthesis of PTHF-NH₂**

Trifluoroacetic acid (1.0 mL) was added slowly to a dichloromethane solution (2.0 mL) of PTHF-NH-Boc (0.3582 g). After being stirred for 1 h at room temperature, the solution was washed by 5% NaHCO₃ aqueous solution and saturated NaCl for three times successively before being dried over anhydrous Na₂SO₄. Chloroform was evaporated under vacuum to yield lime-like PTHF-NH₂ (yield 0.3012 g, 84.1%).

**Synthesis of PTHF-b-PAs**

The polymerizations of zLL-NTA and Sar-NTA were performed according to literatures with modifications. zLL-NTA (0.1037 g, 0.3217 mmol) was dissolved in CH₂Cl₂ (1.4 mL), followed by HAc (0.05 mL) in CH₂Cl₂ solution (0.490 mol/L). After CH₂Cl₂ solution (0.20 mL) of PTHF-NH₂ (0.0326 mol/L) was added, the reaction tube was sealed and placed in a 25 °C thermostat for 48 h. PTHF-b-PzLL was isolated by precipitation in ether and dried in vacuum (yield 0.1001 g, 79.9%).

Sar-NTA (0.0742 g, 0.283 mmol) was dissolved in CH₂CN (0.50 mL), followed by THF solution (0.15 mL) of PTHF-NH₂ (0.0368 mol/L). After being polymerized at 60 °C for 18 h, PTHF-b-PSar was isolated by precipitation in hexane and dried in vacuum (yield 0.0168 g, 46.9%).

**Synthesis of PTHF-b-PLys**

The diblock copolymer PTHFω-b-PzLL (0.0164 g, 1.47 mmol) was dissolved in CHCl₃ (2.0 mL), followed by 30% solution of HBr in acetic acid (1.0 mL). After being stirred for 1 h, the mixture was precipitated in ether and PTHF-b-PLys was dried in a vacuum (yield 0.0116 g, 70.7%).

**Micelle Formation**

PThFω-b-PLys (0.0116 g, 1.04 mmol) was dissolved in DMF

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(1.0 mL). Deionized water (1.0 mL) was added at a rate of 3 μg/min. DMF was removed by dialysis for 48 h.

**Emulsion Formation**

PTHF<sub>α2</sub>-b-PS<sub>α4</sub> (0.0050 g, 9.7×10<sup>-4</sup> mmol) was dissolved in a mixture of deionized water (1.0 mL) and CHCl<sub>3</sub> (100 μL) and stirred by an emulsifier at 1.0×10<sup>4</sup> r/min for 5 min.

**RESULTS AND DISCUSSION**

### Synthesis of PTHF-NH<sub>2</sub>

Living PTHF was produced via living/controlled cationic ROP initiated by PO and catalyzed by Lu(OTf)<sub>3</sub>.<sup>[29]</sup> We successfully used BAE as terminator to endcap oxonium of PTHF chain and obtain PTHF-NH-Boc quantitatively (Step 1 in Scheme 1, samples 1–7 in Table 1). According to the <sup>1</sup>H-NMR spectra (Fig. 1A), proton signals at 3.41 ppm (H<sub>b2</sub>) and 1.61 ppm (H<sub>c2</sub>) are attributed to THF unit. Protons of PO methyl residue and tertiary butyl as well as methylene next to urethane of BAE residue locate at 1.12–1.14 ppm (H<sub>a2</sub>), 3.41 ppm (H<sub>d2</sub>) and 1.44 ppm (H<sub>e2</sub>) respectively. Different from the <sup>1</sup>H-NMR spectrum of hydroxyl-capped PTHF terminated by water (PTHF-OH), no proton signal is detectable at 3.60–3.65 ppm belonging to the methylene (H<sub>f</sub>) neighboring the hydroxyl end group, which confirms that all the oxonium ions at the growing chain end transfer to Bae groups. MALDI-ToF MS spectra (Figs. 1B–1D and Fig. S3 in ESI) revealed that every PTHF chain carries Boc group at one chain end and PO residue at the other, which also proves quantitative termination by BAE. Moreover, the MWs and Ds of PTHF-NH-Boc are controllable. As shown in Table 1 and Fig. S4 (in ESI), MWs of PTHF-NH-Boc are adjustable between 1.6 and 2.8 kg/mol with Ds below 1.20. It is worth mentioning that both initiator and terminator are easy to carry functional groups like ethynyl group for post-modification. In order to further initiate NTAs through nucleophilic ROP, PTHF-NH-Boc is deprotected in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and TFA (V/V=2:1) at room temperature to release the amino chain ends (Step 2 in Scheme 1). The disappearance of H<sub>x</sub> of BAE residue in <sup>1</sup>H-NMR (Fig. 1A) evidences the complete removal of Boc group. The above results demonstrate that we have developed an efficient method for preparing well-defined PTHF-NH<sub>2</sub>.

### Polymerization of NTAs Initiated by PTHF-NH<sub>2</sub>

Initiated by PTHF-NH<sub>2</sub>, zLL-NTA was successfully polymerized (Step 3 in Scheme 1) with quantitative conversion (Table 2, samples 8–10). PTHF-b-PzLL was characterized by <sup>1</sup>H-NMR in DMSO-d<sub>6</sub> (Fig. 2A). Proton signals of methyl group coming from PO and methylene next to acylamino locate at 1.01 ppm (H<sub>y</sub>) and 3.33 ppm (H<sub>x</sub>), respectively. The signals at 3.33 ppm (H<sub>x</sub>) and 1.50 ppm (H<sub>y</sub>) belong to the methylene of PTHF block. The signal at 4.22 ppm (H<sub>z</sub>) corresponds to the methenyl of α-carbon in zLL residue. Methylenes of side group are observed at 1.10–1.70 ppm (H<sub>m</sub>, H<sub>h</sub>, H<sub>i</sub>, and H<sub>j</sub>, respectively). In the DOSY spectrum (Fig. 2E), the same diffusion coefficient (−10.5 m<sup>2</sup>/s) of PzLL and PTHF segments is detected, which is different from that of DMSO (−9.25 m<sup>2</sup>/s), confirming the block topology and the chemical linkage of the two segments. According to the <sup>1</sup>H-NMR results, the degree of polymerization (DP) of zLL agrees well with the feed ratio of [zLL-NTA]/[PTHF-NH<sub>2</sub>] and the chemical linkage of the two segments. According to the <sup>1</sup>H-NMR results, the degree of polymerization (DP) of zLL agrees well with the feed ratio of [zLL-NTA]/[PTHF-NH<sub>2</sub>]. SEC curves (Fig. 2B) exhibit unimodal peaks and narrow Ds (S1.25) of the copolymers, which confirms the quantitative and controllable ROP of NTAs initiated by PTHF-NH<sub>2</sub>.

PTHF-b-PzLL was treated with HBr in HAc solution to re-

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**Scheme 1** Synthetic routes to PTHF-NH-Boc and PTHF-b-PAAs.

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move carbobenzyloxy group (cbz) and fabricate amphiphilic PTHF-b-PLys. In the 1H-NMR spectra (Fig. 2A), the proton signals of cbz group at 4.96 ppm (H_l) and 7.29 ppm (H_o) disappear while DP of lysine units remains unchanged (Table 2), indicating high efficiency of deprotection and stability of PTHF-b-PLys backbone in acidic environment. The chemical shift of water moves from 3.33 ppm to 3.66 ppm due to residual acid.

Polymerizations of Sar-NTA were initiated by PTHF-NH₂ quantitatively with full conversion (Table 2, samples 11−13). 1H-NMR spectrum (Fig. 2C) confirms the structure of PTHF-b-PSar. The proton signals of PTHF segment are the same as those mentioned above. The signals at 2.67−3.00 ppm (H_f) move and those at 3.66 ppm (H_o) broaden out due to residual acid.

Table 1  Synthesis of PTHF-NH-Boc with quantitative end-capping. a

| Sample | Time (min) | Termination efficient | M_n (kg/mol) | M_w (kg/mol) | Đ
|--------|------------|-----------------------|--------------|--------------|---
| 1      | 8          | >99%                  | 1.6          | 1.3          | 1.18
| 2      | 9          | >99%                  | 1.8          | 1.4          | 1.17
| 3      | 10         | >99%                  | 1.9          | 1.5          | 1.17
| 4      | 11         | >99%                  | 2.3          | 1.7          | 1.09
| 5      | 13         | >99%                  | 2.5          | 2.0          | 1.12
| 6      | 16         | >99%                  | 2.8          | 2.2          | 1.13
| 7      | 10         | >99%                  | 2.8          | 2.5          | 1.15

a Catalyzed by Lu(OTf)_3, initiated by PO and terminated by BAE at 0 °C. [Lu(OTf)_3]:[PO]:[THF]:[BAE]=1:1.5:200:10. b Every living PTHF chain was terminated by BAE successfully according to 1H-NMR results. c Determined by 1H-NMR in CDCl_3. d Determined by SEC with THF and universally calibrated by M_n=0.460×M_n,PS. [30]

Table 2  Polymerization of zLL-NTA and Sar-NTA initiated by PTHF-NH₂.

| Sample | NTA [NTA]:[HAc]:[PTHF-NH₂] (mol/L) | c_omonomer (mol/L) | Yield (%) | DP b | DP * (LLys) | M_n d (kg/mol) | Đ d |
|--------|------------------------------------|-------------------|-----------|------|-------------|----------------|----|
| 8      | zLL-NTA 10:4:1                     | 0.20              | 82.8      | 22   | 21          | 8.6            | 1.20 |
| 9      | zLL-NTA 20:4:1                     | 0.20              | 96.5      | 32   | 32          | 11.6           | 1.21 |
| 10     | zLL-NTA 50:4:1                     | 0.20              | >99       | 52   | 52          | 20.6           | 1.25 |
| 11     | Sar-NTA 5:0:1                      | 0.33              | 79.9      | 15   | –           | 8.8            | 1.24 |
| 12     | Sar-NTA 30:0:1                     | 0.43              | 54.3      | 32   | –           | 18.7           | 1.16 |
| 13     | Sar-NTA 50:0:1                     | 0.37              | 46.9      | 45   | –           | 28.7           | 1.18 |

a The M_n of PTHF-NH₂ is 2.8 kg/mol. zLL-NTA was polymerized at 25 °C for 48 h. Sar-NTA was polymerized at 60 °C for 24 h. NTA conversions were all over 99%. b DP of zLL or Sar units, determined by 1H-NMR in DMSO-d_6. c DP of LLys units after deprotection, determined by 1H-NMR in DMSO-d_6. d Determined by SEC with HFIP as eluent.

Fig. 1  1H-NMR spectra of PTHF-OH, PTHF-NH-Boc and PTHF-NH₂ with * representing signal of CHCl_3 (A). MALDI-ToF MS spectrum of PTHF-NH-Boc (B) with a zoom-in view (C), and corresponding chemical structures (D).
and 3.86–4.42 ppm (Hα) correspond to the methyl and methylene groups of PSar, respectively. The block topology is evidenced by identical diffusion coefficient (−10.6 m²/s) of PSar and PTHF segments in the DOSY NMR (Fig. 2F). DP of Sar units calculated by NMR results agrees with the feed ratio, and SEC curves (Fig. 2D) show unimodal peaks and narrow Đs (<1.24). The moderate yield is caused by slight solubility of PTHF-b-PSar in ether used as precipitant.

Although both hydroxyl group and amino group are possible to initiate NTA polymerization, hydroxyl group requires activation by forming intramolecular hydrogen bond as H-donor to increase nucleophilicity. Herein, α-hydroxyl and ω-amino of PTHF-NH₂ are separated by long backbone and difficult to form intramolecular hydrogen bond. All amino end

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groups initiate NTA polymerization and generate block copolymer of PTHF-b-PAA.

**Self-assembly Behavior of PTHF-b-PAAs in Water/Emulsion**

After the removal of cbz group, the amphiphilic diblock copolymer PTHF-b-PLys form micelles in water. PTHF$_{40}$-b-PLys$_{32}$ micelles were obtained according to the solvent exchange method. DLS measures the $D_h$ of micelles as 68 nm (Fig. S5 in ESI), and zeta potential as 45±1 mV. TEM characterizes the spherical morphology of the micelles with diameter between 10 and 20 nm (Figs. 3a and 3b). $D_h$ from DLS results corresponds to both core and swollen corona of micelles, while only dried PTHF core is observed in TEM. Thus, DLS always gives a higher micellar size than TEM.

As PSar segment is miscible with water at any PSar/water ratio,[33] PTHF-b-PSar is able to assemble into micelles in water. For instance, PTHF$_{40}$-b-PSar$_{15}$ micelles were prepared after being dissolved in DMF/water solution and dialyzed. The DLS results exhibit unimodal distribution, and $D_h$ of micelles is 17 nm (Fig. S5 in ESI). Zeta potential of the micelles is 10±1 mV, which is lower than that of PTHF$_{40}$-b-PLys$_{32}$, indicating less stability of PTHF$_{40}$-b-PSar$_{15}$ micelles than PTHF$_{40}$-b-PLys$_{32}$.[34] The amphiphilicity of PTHF-b-PSar can stabilize oil-in-water emulsion. By dissolving PTHF$_{40}$-b-PSar$_{15}$ in CHCl$_3$/water (V:V=1:10) solution and then stirring it under 1.0x10$^4$ r/min for 5 min, stable emulsion (which can be stabilized over 3 days) was obtained. In TEM images, emulsion droplets can be observed with diameters among 100–300 nm (Figs. 3c and 3d).

The above-mentioned results indicate that these well-controlled PTHF-b-PAAs are easy to form micelles in water and stabilize oil-in-water emulsion, providing the copolymers with further potential in drug loading and delivery fields.

**CONCLUSIONS**

We report an efficient methodology to synthesize well-controlled PTHF-NH$_2$ with narrow $Đ$ (<1.20) by quantitatively transferring the hydroxyl group of PTHF chain end into amino group after controlled cationic ROP of THF. Sequentially initiated by PTHF-NH$_2$, well-defined PTHF-b-PAAs are synthesized through nucleophilic ROP mechanism. In view of the amphiphilicity and biocompatibility of PTHF-b-PAAs, our strategy is promising to prepare biomedical materials.

**Electronic Supplementary Information**

Electronic supplementary information (ESI) is available free of charge in the online version of this article at https://doi.org/10.1007/s10118-021-2539-6.

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