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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*-thiocarboxyanhydrides

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Electronic Supplementary Information

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 [RE(OTf)$_3$] and terminated by 2-(*t*-butyloxycarbonyl-amino) ethanol (BAE). After the deprotection 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*-polylysine (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$_{40}$-*b*-PSar$_{32}$ 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

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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.[1,2] With high water stability, low toxicity and resistance of microbial, PTHF plays an important role in spanning, engineering and medical treatment.[1,3–5]

Poly(*α*-amino acid)s (PAAs), including polypeptides and polypeptoids, have attracted wide attention for their excellent biocompatibility mimicking natural proteins. Promising applications have been reported in drug delivery, tissue engineering, biosensor, and bio-imaging.[6–10] 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*.[11] connected PTHF and poly(*γ*-benzyl-L-glutamate) diamine (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/m^3, higher than that of aciniform silk. The *α*-helix of PBLG and random coil of PTHF notably improved the tensile strength and extensibility,[12–14] which was considered as a new strategy towards artificial spider silk. Alternatively, polymerization of *α*-amino acid-*N*-carboxyanhydrides (NCAs) with amine-terminated PTHF has been employed to produce PTHF-*b*-PAA. Feng *et al*.[15] used low molecular weight (M_n=1100) bis(3-aminopropyl)-terminated PTHF to initiate the polymerization of *N*-ε-carbobenzyloxy-L-lysine NCA (zLL-NCA) and obtained PzLL-PTHF-PzLL triblock copolymer. After the introduction of gluconolactone or lactobionolactone on the side chains of PzLL segment, the triblock copolymers were 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.[16] Because of the valuable properties and applica-

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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,[17] 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 PAAs *via* coordination anionic or nucleophilic ring-opening polymerization (ROP) mechanisms.[6,18–28]

Inspired by the successful synthesis of *α*,*ω*-dihydroxyl PTHF by cationic ROP mechanisms in the presence of rare-earth triflate [RE(OTf)$_3$] catalyst,[29] 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-NH$_2$) 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 (PBr_3, 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.) were used as received.

Lutetium triflate [Lu(OTf)$_3$] was synthesized from Lu_2O_3 (>99.99%, Beijing Founde Star Science and Technology Company) and triflic acid (99%, Energy Chemical) and dried in a vacuum (<0.5 mmHg) at 200 °C for 48 h. Propylene oxide (PO, AR, Sinopharm Chemical Reagent Company) was stirred over CaH_2 and distilled. 2-(Boc-amino) ethanol (BAE, 98%, J&K Scientific Ltd.) was stirred over BaO and distilled. zLL-NTA[6] (Fig. S1 in the electronic supplementary information, ESI) and Sar-NTA[18] (Fig. S2 in ESI) were prepared according to reported methods.

Measurements

Nuclear magnetic resonance (NMR) spectra were recorded on a 400 MHz Bruker Avance DMX 400 spectrometer with $CDCl_3$ or DMSO-d_6 as solvent. Diffusion-ordered NMR spectroscopy (DOSY) spectra were tested on a 500 MHz Bruker Avance DMX 500 spectrometer in DMSO-d_6. MWs and polydispersity indices (*Đ*s) of PTHF were obtained by size-exclusion chromatography (SEC) equipped with Waters 150C pump, Waters 2414 refractive index detector and Waters Styragel HR3 and HR4 columns. THF was used as eluent with flow rate of 1 mL/min at 40 °C, and polystyrene (PS) was used as calibration standard. The absolute M_n of PTHF was calibrated by the equation $M_{n,PTHF} = 0.460 \times M_{n,PS}$.[30] MWs and *Đ*s of PTHF-*b*-PAAs were obtained by another SEC equipped with Waters 1515 isocratic HPLC pump, Waters 2414 refractive index detector and KF series columns. Hexafluoroisopropanol (HFIP) with 3 mg/mL dry CF_3COOK was used as eluent with a flow rate of 0.8 mL/min at 40 °C. Poly(methylmethacrylate) (PMMA) was used as the calibration standard. Matrix-assisted laser desorption ionization-time of flight mass spectra (MALDI-ToF MS) were obtained on a Bruker Ultra-FLEX MALDI-ToF mass spectrometer in reflector mode. Dithranol (DIT) and lithium chloride (LiCl) were used as matrices and cationic agent, respectively. The hydrodynamic diameter and zeta-potential of micelles were detected by dynamic lighting scattering (DLS) at 25 °C using Zetesizer Nano Series of Malven Instruments with a wavelength of 657nm and fixed angle of 173°. Transmission electron microscopy (TEM) images were taken on an HT7700 (Hitachi, Japan) instrument. A drop of PTHF$_{40}$-*b*-PLys$_{32}$ micelle solution (2 mg/mL) was dried on a carbon film at an ambient environment following by a drop of 2% phosphotungstic acid solution. In the case of emulsions, a drop of PTHF$_{40}$-*b*-PSar$_{32}$ stabilized emulsion (5 mg/mL) was placed on a carbon film and dried under an infrared lamp for 1 h before TEM analysis.

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

Synthesis of PTHF-NH-Boc

As a typical polymerization of THF, Lu(OTf)$_3$ (0.2148 g, 0.345 mmol) was dissolved in 5.1 mL of dry THF, followed by 0.50 mL of PO in THF solution (1.095 mol/L) at 0 °C to start polymerization. After 8 min, 1.7 mL of BAE in THF (2.88 mol/L) was quickly added to terminate the polymerization. PTHF-NH-Boc was isolated by precipitation in cold methanol and dried in a vacuum at room temperature (yield 0.7922 g, 15.9%).

Synthesis of PTHF-NH$_2$

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% $NaHCO_3$ aqueous solution and saturated NaCl for three times successively before being dried over anhydrous Na_2SO_4. Chloroform was evaporated under vacuum to yield lime-like PTHF-NH$_2$ (yield 0.3012 g, 84.1%).

Synthesis of PTHF-*b*-PAAs

The polymerizations of zLL-NTA[31] and Sar-NTA[18] were performed according to literatures with modifications. zLL-NTA (0.1037 g, 0.3217 mmol) was dissolved in CH_2Cl_2 (1.4 mL), followed by HAc (0.05 mL) in CH_2Cl_2 solution (0.490 mol/L). After CH_2Cl_2 solution (0.20 mL) of PTHF-NH$_2$ (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 CH_3CN (0.50 mL), followed by THF solution (0.15 mL) of PTHF-NH$_2$ (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 PTHF$_{40}$-*b*-PzLL$_{32}$ (0.0164 g, 1.47 mmol) was dissolved in $CHCl_3$ (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

PTHF$_{40}$-*b*-PLys$_{32}$ (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

$PTHF_{40}$-*b*-$PSar_{32}$ (0.0050 g, 9.7×10^{-4} mmol) was dissolved in a mixture of deionized water (1.0 mL) and $CHCl_3$ (100 μL) and stirred by an emulsifier at 1.0×10^4 r/min for 5 min.

RESULTS AND DISCUSSION

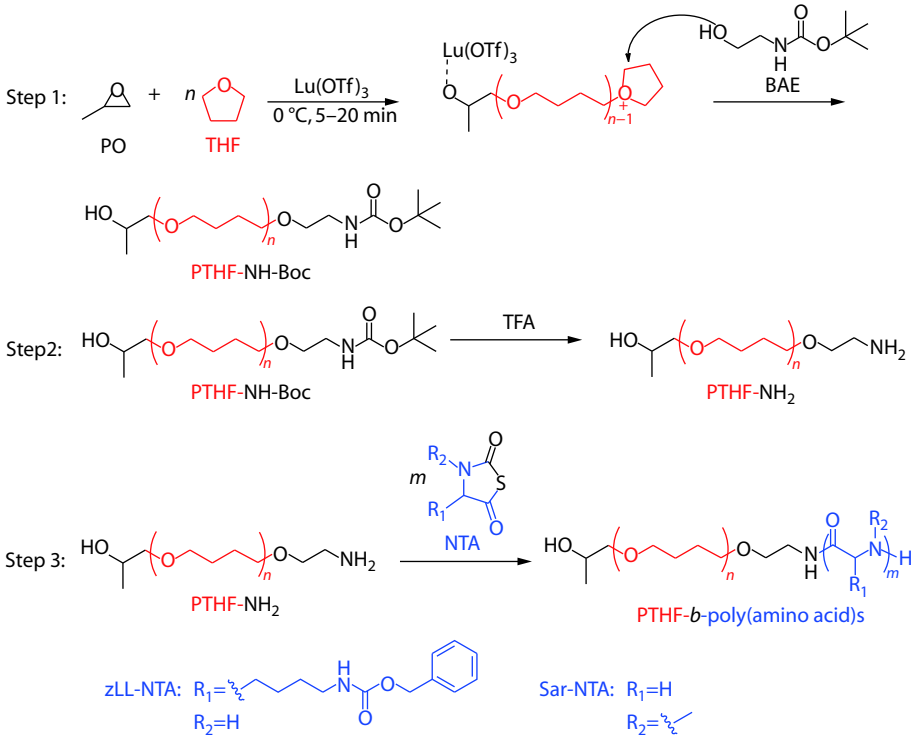
Synthesis of PTHF-NH_2

Living PTHF was produced *via* living/controlled cationic ROP initiated by PO and catalyzed by $Lu(OTf)_3$.[29] 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 ^{1}H-NMR spectra (Fig. 1A), proton signals at 3.41 ppm (H_{b2}) and 1.61 ppm (H_{c2}) 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_{a2}), 3.41 ppm (H_{d2}) and 1.44 ppm (H_e), respectively. Different from the ^{1}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_f) neighboring the hydroxyl end group, which confirms that all the oxonium ions at the growing chain end transfer to be Boc groups. MALDI-ToF MS spectra (Figs. 1B–1D and Fig. S3 in ESI) reveal 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 *Đ*s 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 *Đ*s 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_2Cl_2 and TFA (*V*:*V*=2:1) at room temperature to release the amino chain ends (Step 2 in Scheme 1). The disappearance of H_e of BAE residue in ^{1}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_2.

Polymerization of NTAs Initiated by PTHF-NH_2

Initiated by PTHF-NH_2, zLL-NTA was successfully polymerized (Step 3 in Scheme 1) with quantitative conversion (Table 2, samples 8–10). PTHF-*b*-PzLL was characterized by ^{1}H-NMR in DMSO-d_6 (Fig. 2A). Proton signals of methyl group coming from PO and methylene next to acylamino locate at 1.01 ppm (H_a) and 3.33 ppm (H_d), respectively. The signals at 3.33 ppm (H_b) and 1.50 ppm (H_c) belong to the methylene of PTHF block. The signal at 4.22 ppm (H_e) corresponds to the methenyl of *α*-carbon in zLL residue. Methylenes of side group are observed at 1.10–1.70 ppm (H_g, H_h, H_i), 2.93 ppm (H_j) and 4.96 ppm (H_l). Aromatic proton signals present at 7.29 ppm (H_m). In the DOSY spectrum (Fig. 2E), the same diffusion coefficient (–10.5 m^2/s) of PzLL and PTHF segments is detected, which is different from that of DMSO (–9.25 m^2/s), confirming the block topology and the chemical linkage of the two segments. According to the ^{1}H-NMR results, the degree of polymerization (DP) of zLL agrees well with the feed ratio of [zLL-NTA]/[PTHF-NH_2]. SEC curves (Fig. 2B) exhibit unimodal peaks and narrow *Đ*s (≤1.25) of the copolymers, which confirms the quantitative and controllable ROP of NTAs initiated by PTHF-NH_2.

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



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

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

Sample	Time (min)	Termination efficient [b]	M_n [c] (kg/mol)	M_n [d] (kg/mol)	$Đ$ [d]
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 ^{1}H-NMR results. [c] Determined by ^{1}H-NMR in $CDCl_3$. [d] Determined by SEC with THF and universally calibrated by $M_n = 0.460 \times M_{n,PS}$.[30]

move carbobenzyloxy group (cbz) and fabricate amphiphilic PTHF-*b*-PLys. In the ^{1}H-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.[32]

Polymerizations of Sar-NTA were initiated by PTHF-NH_2 quantitatively with full conversion (Table 2, samples 11–13). ^{1}H-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)

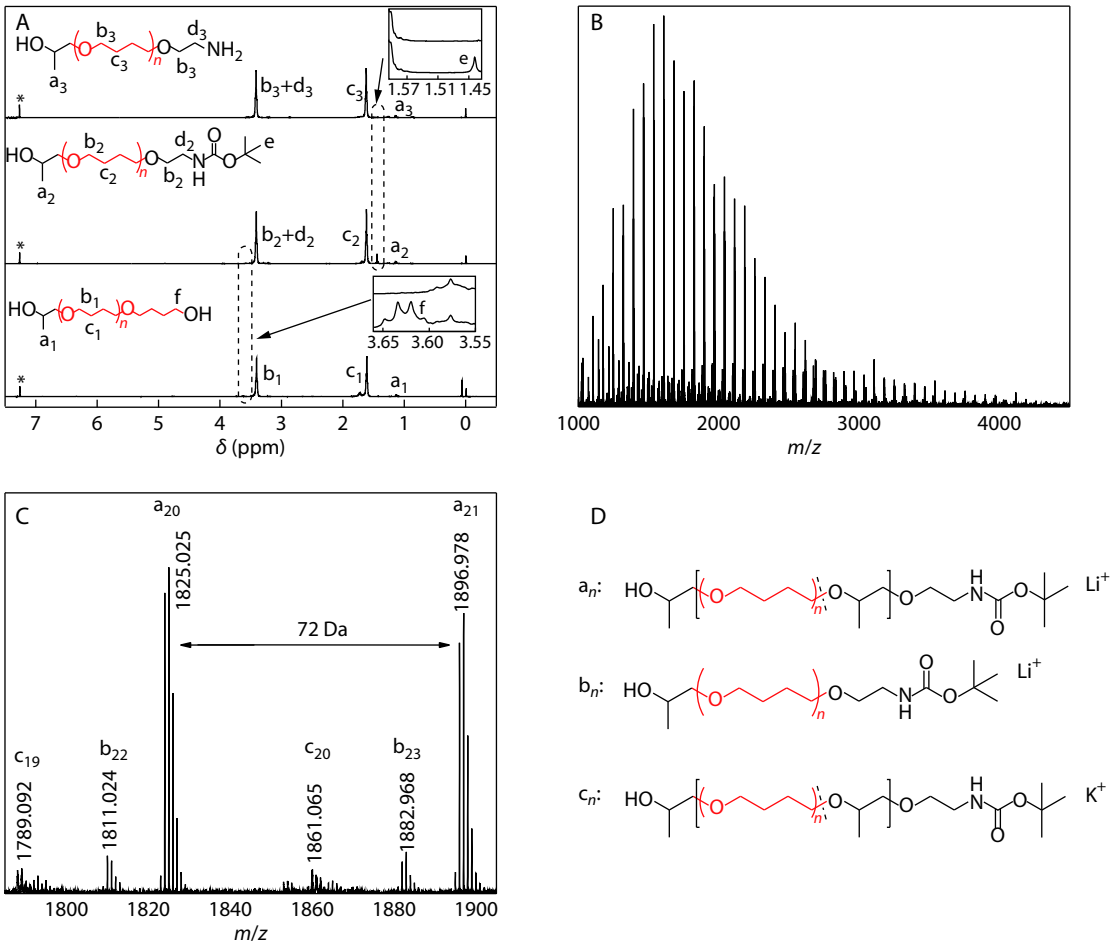

Fig. 1 ^{1}H-NMR spectra of PTHF-OH, PTHF-NH-Boc and PTHF-NH_2 with * representing signal of $CHCl_3$ (A). MALDI-ToF MS spectrum of PTHF-NH-Boc (B) with a zoom-in view (C), and corresponding chemical structures (D).

Table 2 Polymerization of zLL-NTA and Sar-NTA initiated by PTHF-NH_2.[a]

Sample	NTA	[NTA]:[HAc]:[PTHF-NH_2]	$c_{monomer}$ (mol/L)	Yield (%)	DP [b]	DP [c] (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-NH_2 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 ^{1}H-NMR in DMSO-d_6. [c] DP of LLys units after deprotection, determined by ^{1}H-NMR in DMSO-d_6. [d] Determined by SEC with HFIP as eluent.

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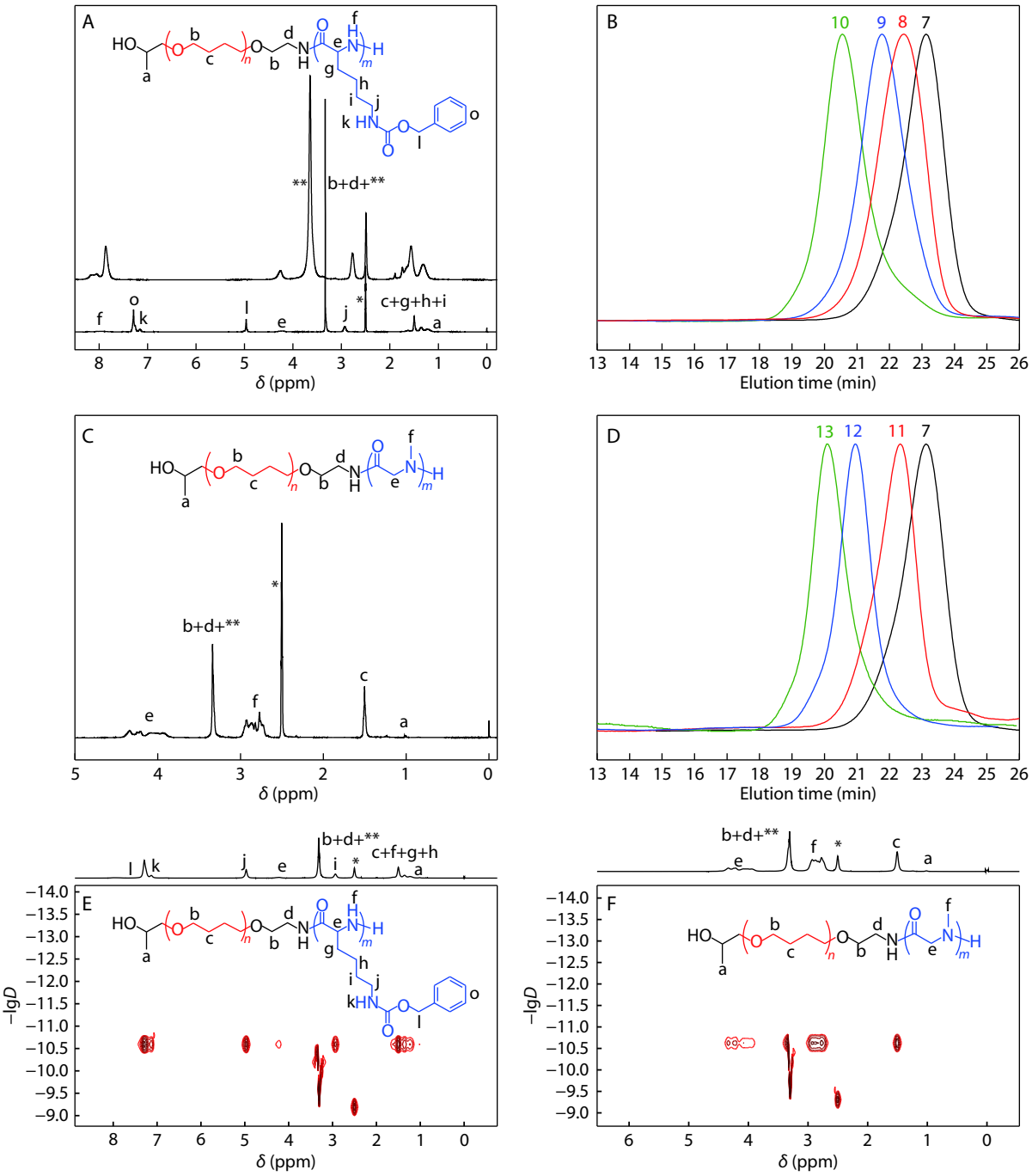

Fig. 2 ^{1}H-NMR spectra of PTHF-*b*-PzLL and PTHF-*b*-PLys with * and ** representing the signals of DMSO and water, respectively (A). SEC traces of PTHF-*b*-PzLL in HFIP with the same sample numbers in Tables 1 and 2 (B). ^{1}H-NMR spectrum of PTHF-*b*-PSar with * and ** representing the signals of DMSO and water, respectively (C). SEC traces of PTHF-*b*-PSar in HFIP with the same sample numbers in Tables 1 and 2 (D). DOSY NMR spectra of PTHF-*b*-PzLL (E) and PTHF-*b*-PSar (F) with * and ** representing the signals of DMSO and water, respectively.

and 3.86–4.42 ppm (H_e) correspond to the methyl and methylene groups of PSar, respectively. The block topology is evidenced by identical diffusion coefficient (–10.6 m^2/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 *Đ*s (<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.[23] Herein, *α*-hydroxyl and *ω*-amino of PTHF-NH_2 are separated by long backbone and difficult to form intramolecular hydrogen bond. All amino end

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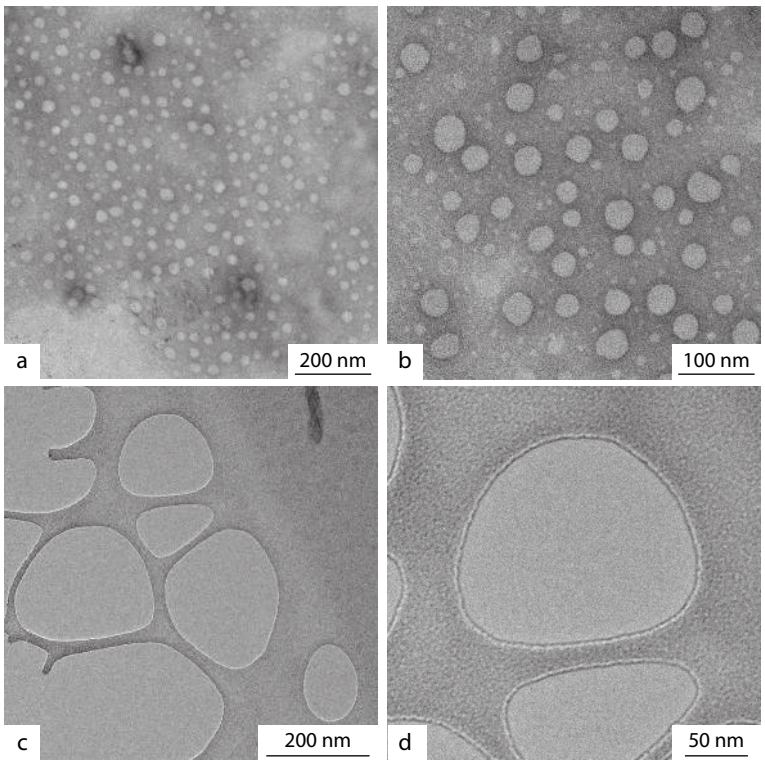

Fig. 3 TEM images of $PTHF_{40}$-*b*-$PLys_{32}$ micelles (a, b) and $PTHF_{40}$-*b*-$PSar_{15}$ emulsions (c, d).

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*-$PSar_{32}$ in $CHCl_3$/water (*V*:*V*=1:10) solution and then stirring it under 1.0×10^4 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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