Are *N*-Substituted Glycine *N*-Thiocarboxyanhydride Monomers Really Hard to Polymerize?

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ABSTRACT: *N*-Substituted glycine *N*-thiocarboxyanhydrides (NNTAs) are promising cyclic monomers to synthesize polypeptoids with the advantages of easier preparation and higher stability during purification and storage than *N*-substituted glycine *N*-carboxyanhydrides (NNCAs). NNTAs were commonly considered too stable to polymerize for their low reactivity. In this contribution, we report controlled polymerizations of *N*-ethylglycine NTA (NEG-NTA) and sarcosine NTA (Sar-NTA) using primary amines as initiator under proper polymerization conditions. The controllability has been fully supported by ^{1}H NMR end group analyses, MALDI-ToF mass spectra, kinetic data, block copolymerizations by sequential monomer addition, and low polydispersities (1.14–1.17) of polypeptoids. Variation of the [NNTA]/[initiator] ratio allows well control of the molar mass, and degrees of polymerization (DPs) up to 287 can be reached for poly(*N*-ethylglycine) or DPs up to 262 for polysarcosine. NNTAs exhibit excellent activity and they are potential to synthesize polypeptoids with controllable polymerization. © 2016 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2016**, *00*, 000–000

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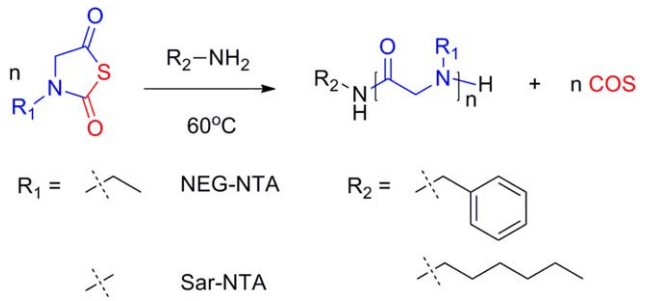
INTRODUCTION Taking the advantages of high reactivity and productivity, ring-opening polymerization (ROP) of *N*-substituted glycine *N*-carboxyanhydrides (NNCAs) is the most efficient method to synthesize polypeptoids.[1–5] Recently, many efforts have been paid on NNCAs to achieve their living polymerizations using different initiators.[6–10] Zhang and coworkers reported *N*-heterocyclic carbenes (NHCs)-mediated living polymerization of NNCAs to prepare cyclic homo- and block-polypeptoids, and investigated the mechanism detailedly.[6,9] Luxenhofer and coworkers carried out living ROP of NNCAs initiated by primary amines,[7,8] as well as surface-initiated[11] and solid support-initiated[12] polymerizations, to synthesize homopolypeptoids, diblock and multiblock copolypeptoids. However, NNCAs have an inherent disadvantage of high sensitivity to moisture and heat.[13] They have to be synthesized and stored in extremely anhydrous and anaerobic environment. Moreover, NNCAs require very careful purification before use, sublimation for instance, as impurities significantly affect the living characteristics of NNCA polymerization.[14–16] Therefore, more stable monomers and easier synthetic approach for preparing polypeptoids have been strongly desired, and successful development of such methods are sure to have great impact on the polypeptoid science and technology.

N-Substituted glycine *N*-thiocarboxyanhydrides (NNTAs), the thio-analogues of NNCAs, are much more stable monomers for polypeptoids synthesis with the potential of large-scale production.[3–5] All the monomer synthesis and purification can be operated in the open air. It is much easier to prepare and store NNTAs with high purity than NNCAs, which also benefits the controllability in polymerization due to fewer side reactions. Although NTA monomers have been discovered since 1950s,[17–19] researches of their polymerizations are very limited,[20–23] not to mention living/controlled polymerizations. Our early study of sarcosine NTA (Sar-NTA) polymerization concludes that Sar-NTA had a much slower polymerization rate than the corresponding sarcosine NCA and they were too inactive to prepare moderate molar mass polypeptoids, that is, low yields $<50\%$ and limited molecular weights (MWs) <5 kg/mol.[22,23] This can be a reason why NNTAs were widely ignored in the past decades.

Additional Supporting Information may be found in the online version of this article.



SCHEME 1 Polymerization of *N*-substituted glycine NTA initiated by primary amines. [Color figure can be viewed at wileyonlinelibrary.com]

Very recently, we found that NNTA monomers were not that inert.[24–27] We improved Sar-NTA polymerization by using highly reactive rare earth borohydrides[25] and specially-designed amine-terminated polymers[24,26] as initiators to produce PSars and its copolymers with quantitative yields, predictable high MWs, and low polydispersity indices (*Đ*). However, the mechanism of rare earth borohydrides-mediated ROP of NNTAs is still unclear,[25] which limits the further modification of the polypeptoid end-groups. Moreover, amine-terminated macroinitiators are not easily available and the products are confined to block copolymers.

In this contribution, we successfully produce polypeptoids with degrees of polymerization (DP) up to 287 and *Đ* of 1.14 from controlled NNTA polymerization using small molecular primary amines, for instance, benzylamine and hexylamine, as initiator in proper polymerization conditions (Scheme 1), and suggest a new opinion that NNTA monomers can be active enough with carefully design of polymerization conditions. Compared with our previous work,[25] small molecular primary amines are more available initiators with the advantages of metal-free and definite end-group of the products, which is promising for block copolypeptoids synthesis and end-group modification for further biomedical applications.

EXPERIMENTAL

Materials

Sarcosine (98%, Energy Chemical, China), ethylamine (70 wt % aqueous solution, Energy Chemical, China), glyoxylic acid (50 wt % aqueous solution, Energy Chemical, China), phosphorous tribromide (99%, Energy Chemical, China), hexylamine (99%, Aldrich), and trioxymethylene (99+%, Acros) were used as received. Tetrahydrofuran (THF) was refluxed before use over potassium/benzophenone ketyl. Acetonitrile was stirred over CaH_2 and distilled. Benzylamine was stirred over CaH_2 and followed by distillation under reduced pressure. Sar-NTA was prepared according to the procedure (Supporting Information Scheme S1 and Figure S1) described in literature[23] and our previous report.[25]

Synthesis of *N*-ethylglycine hydrochloride

An amount of 50 wt % aqueous solution of glyoxylic acid (121.42 g, 0.820 mol) and 70 wt % aqueous solution of ethylamine (26.41 g, 0.410 mol) were added to 450 mL H_2O. After stirred at 25 °C for 24 h, 10 M hydrochloric acid (200 mL) was added. The reaction mixture was refluxed for 12 h. Then the solvent was concentrated. The yellow crude product was recrystallized in methanol/ethyl ether to obtain white crystals (34.05 g, yield 59.5%). ^{1}H NMR (DMSO-d_6/TMS) δ: 1.18 ppm (t, 3H, —CH_3), 2.93 ppm (q, 2H, —CH_2CH$_3$), 3.79 ppm (s, 2H, —CH_2COOH), 9.32 ppm (s, 2H, —NH·HCl—), 13.25 ppm (br, 1H, —COOH).

Synthesis of *N*-ethylglycine NTA (NEG-NTA)

N-Ethylglycine hydrochloride (35.49 g, 0.254 mol), *S*-ethoxythiocarbonyl mercaptoacetic acid[23] (45.77 g, 0.254 mol) and NaOH (30.51 g, 0.763 mol) were dissolved in 400 mL water and reacted for 72 h at 30 °C with stirring. Then the reaction mixture was acidified by concentrated hydrochloric acid. The product *N*-ethoxythiocarbonyl-*N*-ethylglycine was extracted with chloroform. The organic phase was washed with aqueous citric acid (5 wt %), and concentrated under reduced pressure after drying over Na_2SO_4. The remaining product was dissolved in 150 mL dry chloroform in an argon atmosphere. PBr_3 (30 mL, 0.316 mol) was added dropwise in 15 min at 0 °C. The reaction mixture was stirred for additional 10 min at 0 °C and 1 h at room temperature. After washed by saturated solution of $NaHCO_3$ and deionized water, the chloroform solution was dried with $MgSO_4$ and concentrated in vacuum. The crude product was purified by column chromatography (ethyl acetate: petroleum ether = 1:6). Light yellow oil was obtained (13.3 g, yield 36.1%) and stored under argon atmosphere. ^{1}H NMR ($CDCl_3$/TMS) δ: 1.25 ppm (t, 3H, —CH_3), 3.60 ppm (q, 2H, —CH_2CH$_3$), 4.20 ppm (s, 2H, —CH_2CO—). ^{13}C NMR ($CDCl_3$/TMS) δ: 12.57 ppm (CH$_3$CH$_2$—), 38.96 ppm (CH$_3$$CH_2$—), 59.32 ppm (—$CH_2$CO—), 164.40 ppm (—N$C$OSCO—), 194.18 ppm (—NCOSCO—). ESI-MS: 146.11 *m/z* ([NEG-NTA]·H$^+$). Elem Anal: C, 41.06%; H, 4.91%; N, 9.54% (Theoretical value: C, 41.36%; H, 4.86%; N, 9.65%).

Polymerization of NEG-NTA and Sar-NTA Initiated by Primary Amines

All polymerizations were performed using Schlenk technique and all polymerization tubes were predried and purged with argon.

As a typical homopolymerization, NEG-NTA (0.382 g, 2.63 mmol) was dissolved in 4.6 mL dry THF, followed by 0.64 mL benzylamine in THF solution (0.2040 mol/L). The tube was sealed and placed in a 60 °C oil bath for 24 h. The polymer was isolated by precipitation from diethyl ether and dried in vacuum (0.228 g, 95.9%).

Sar-NTA (0.431 g, 3.29 mmol) was dissolved in 6.4 mL dry acetonitrile, followed by 0.16 mL benzylamine in acetonitrile solution (0.2023 mol/L). The tube was sealed and placed in a 60 °C oil bath for 24 h. The polymer was isolated by precipitation from diethyl ether and dried in vacuum (0.226 g, 95.3%).

As a typical block copolymerization, NEG-NTA (0.533 g, 3.67 mmol) was dissolved in 6.9 mL dry acetonitrile, followed by 0.44 mL benzylamine in acetonitrile solution (0.2055 mol/L).

TABLE 1 Polymerization of *N*-Substituted Glycine NTA Initiated by Benzylamine[a]

Sample	Monomer	$[M]_0/[BnNH_2]_0$	Yield (%)	$M_{n\ theo}$[b] (kg/mol)	DP[c]	$M_{n\ NMR}$[c] (kg/mol)	$M_{n\ SEC}$[d] (kg/mol)	$Đ$[d]
1	NEG-NTA	20	95.9	1.7	21	1.9	5.4	1.12
2	NEG-NTA	40	>99	3.5	41	3.6	8.4	1.16
3	NEG-NTA	60	>99	5.2	64	5.6	11.2	1.16
4	NEG-NTA	80	>99	6.9	78	6.7	14.6	1.15
5	NEG-NTA	100	>99	8.6	97	8.4	18.5	1.13
6	NEG-NTA	200	97.7	16.7	198	17.0	28.2	1.17
7	NEG-NTA	370	87.1	27.5	287	24.5	40.9	1.14
8	Sar-NTA	20	88.6	1.4	19	1.5	4.2	1.13
9	Sar-NTA	40	90.0	2.7	40	3.0	6.3	1.15
10	Sar-NTA	60	94.4	4.1	59	4.3	7.8	1.16
11	Sar-NTA	100	95.3	6.9	97	7.0	9.0	1.22
12	Sar-NTA	180	97.8	12.6	156	11.2	10.2	1.31
13[e]	Sar-NTA	420	90.1	27.0	262	18.7	12.3	1.28

[a] Polymerization conditions: $[M]_0 = 0.5$ mol/L, 24 h at 60 °C, THF and acetonitrile were used as the solvents for NEG-NTA and Sar-NTA, respectively.
[b] Theoretical M_n, $M_{n,theo} = [M]_0/[BnNH_2]_0 \times$ yield $\times$ MW of repeat units + MW of initiator.
[c] As determined by ^{1}H NMR.
[d] As determined by SEC.
[e] As polymerized for 48 h.

The tube was sealed and placed in a 60 °C oil bath. After 24 h, NEG-NTA was consumed (confirmed by ^{1}H NMR analysis), and 3.5 mL solution was removed from the reaction mixture for the analytical investigations of the first block. Then Sar-NTA (0.501, 3.82 mmol) was added to the reaction mixture of the first block. Additional 24 h the reaction mixture was stirred. The polymer was isolated by precipitation from diethyl ether and dried in vacuum (0.377 g, 87%).

Polymerization Kinetics

Polymerization kinetics of NEG-NTA were measured at 60 °C with a feed molar ratio ($[NEG\text{-}NTA]_0/[benzylamine]_0$) of 20 in sealed tubes using THF as solvent, benzylamine as initiator and trioxymethylene as internal standard. ^{1}H NMR spectra (500 MHz) were collected every 1 h by taking a small amount of reaction mixture and dissolving in DMSO-d_6. Monomer conversions were calculated from the relative integration of the ethylene proton resonance of NEG-NTA and trioxymethylene. Polymerization kinetics of Sar-NTA were measured at the same conditions with a feed molar ratio ($[Sar\text{-}NTA]_0/[benzylamine]_0$) of 75 and acetonitrile as solvent. ^{1}H NMR spectra were collected with an interval of 10–30 min.

Measurements

Molecular weights (MWs) and polydispersity indices ($Đ$) were determined by size-exclusion chromatography (SEC), which consisted of a Wyatt series 1500 HPLC pump, a Wyatt Opitlab T-rEX interferometric refractometer (RI) and two MZ-Gel SDPlus columns of 10^2 Å 10 μm and 10^4 Å 10 μm. *N*,*N*-dimethylformamide (DMF) containing 0.05 mol/L LiBr and 2‰ (v/v) triethylamine was used as eluent with a flow rate of 0.8 mL/min at 50 °C, and commercial polystyrenes were used as calibration standards. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance DMX 400 spectrometer (^{1}H: 400 MHz and ^{13}C: 100 MHz) with DMSO-d_6 or $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. Matrix-assisted laser desorption ionization-time of fight (MALDI-ToF) mass spectra were collected on a Bruker Ultra-FLEX MALDI-ToF mass spectrometer in the reflector mode. 2,5-Dihydroxybenzoic acid (DHB) was used as matrices and potassium trifluoroacetate was used as the cationic agent. Electrospray ionization mass spectrometry (ESI-MS) spectrum was measured by LCQ DECA XP MAX (Thermo) Liquid Chromatograph Mass Spectrometer. Elemental analysis was measured by varioMICRO CUBE (Elementar Analysensysteme GmbH) elementar analyzer.

RESULTS AND DISCUSSION

We synthesized *N*-ethylglycine NTA (NEG-NTA) through a phosgene-free method as shown in Supporting Information Scheme S2, a novel NNTA monomer prepared for the first time, whose polymer, that is, poly(*N*-ethylglycine) (PNEG), had an excellent solubility in water and common organic solvents such as THF, dioxane, chloroform, ethyl acetate, etc.[7,28,29] Meanwhile, PNEG was a rising biocompatible material promising for biomedical applications.[28,29] The structure of NEG-NTA is well characterized by ESI-MS spectrometry, elemental analysis and NMR spectra (Supporting Information Figure S2–S5). NEG-NTA polymerizations were carried out in THF at 60 °C initiated by benzylamine with various feed molar ratios changing from 20 to 370 (sample **1**–**7** in Table 1). Quantitative yields (> 95%) were achieved in all polymerizations and DPs agreed well with the design when the feed molar ratios of $[NEG]_0/[BnNH_2]_0$ were below 200, which demonstrated that NEG-NTA had a well-controlled polymerization under optimal conditions. PNEG

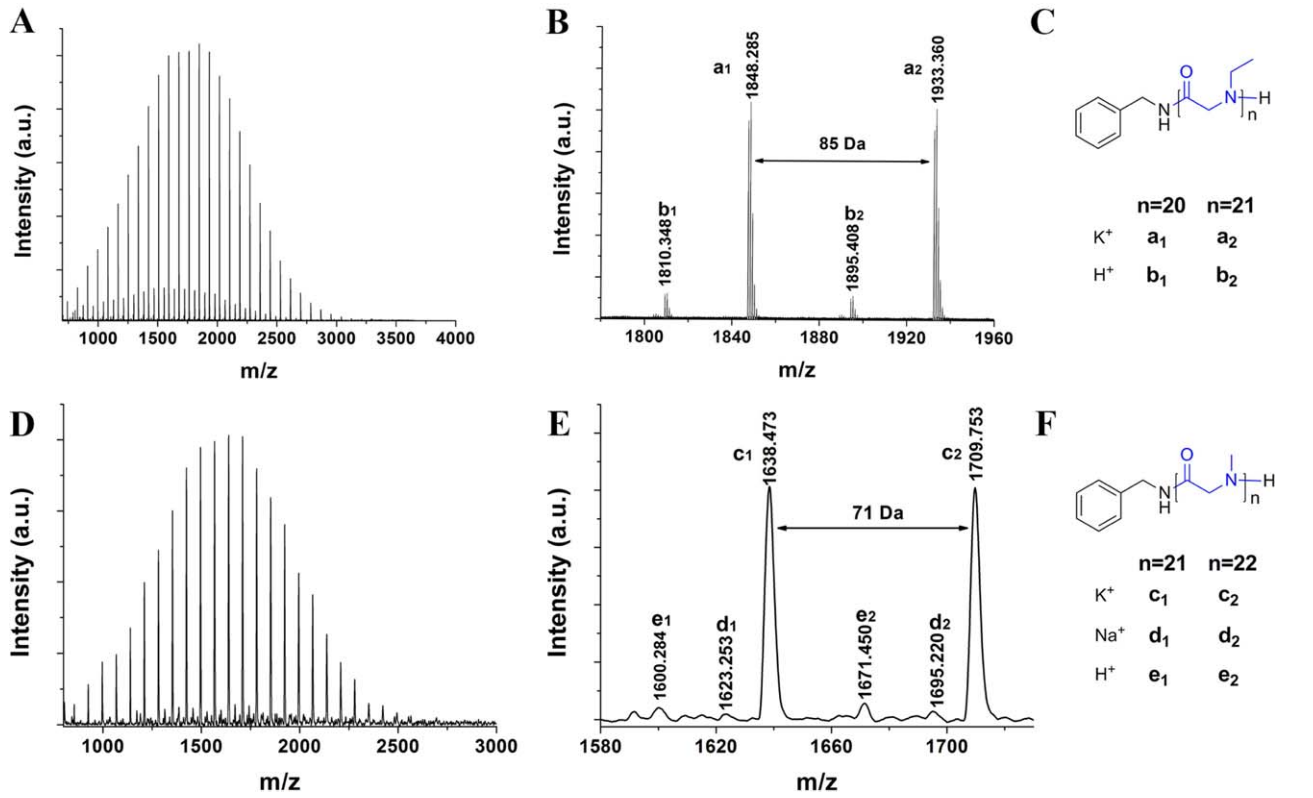


FIGURE 1 MALDI-ToF mass spectra of sample **1** (A) and **8** (D) with zoom-in views (B and E) and the corresponding polypeptoid structures (C and F). [Color figure can be viewed at wileyonlinelibrary.com]

with an absolute M_n of 24.5 kg/mol ($Đ$ =1.14), that is, DP of 287 was obtained shown as sample **7** in Table 1. It is worthy of mentioning that DP of 287 is also regarded as a long chain in NCA polymerization. A monomodal profile of PNEG in MALDI-ToF mass spectrum [Fig. 1(A–C)] reveals benzyl and amino end groups, which is in accordance with normal amine mechanism (NAM; Supporting Information Scheme S3).[23,30,31] All protons in PNEG are assigned in ^{1}H NMR spectrum as reported [Fig. 2(A)].[7] The DPs of the obtained PNEGs are calculated from signals H^a with H^e in ^{1}H NMR, consistent well with the feed molar ratios based on single-site initiation by benzylamine. All SEC traces (Fig. 3) of PNEGs **1**-**7** are monomodal and symmetrical with narrow MW distribution, that is, $Đ$ between 1.12 and 1.17, even $[NEG]_0/[BnNH_2]_0$ rising to 370. Samples **3**-**5** show high MW shoulders in SEC, which is attributed to nonoptimized SEC conditions and polymer aggregations in solvents (see below), as also observed in some cases of NNCA polymerizations.[6,7,32–34] M_ns measured by SEC ranging from 5.4 to 40.9 kg/mol demonstrate

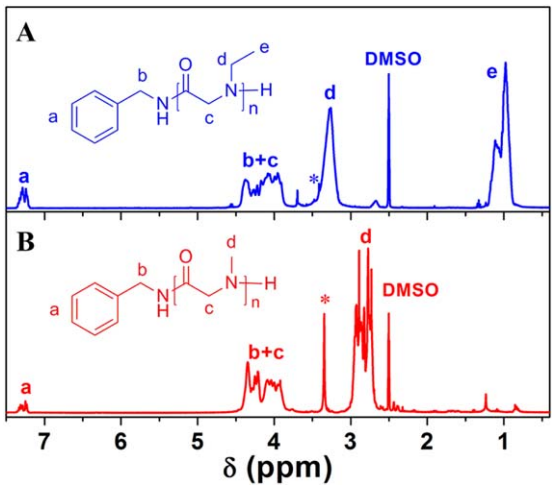


FIGURE 2 ^{1}H NMR spectra of samples **1** (A) and **10** (B) in DMSO-d_6 (*: water). [Color figure can be viewed at wileyonlinelibrary.com]

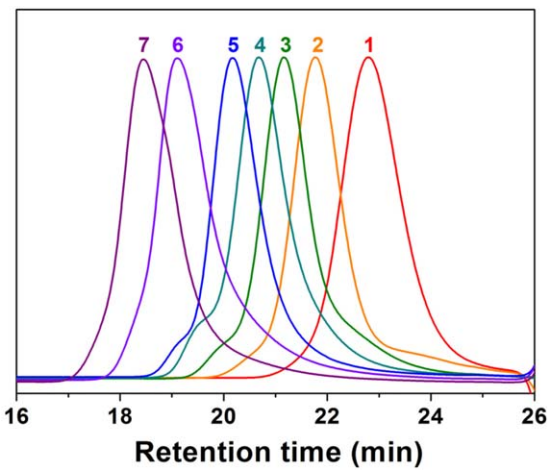


FIGURE 3 SEC traces of PNEG samples **1**-**7**. [Color figure can be viewed at wileyonlinelibrary.com]

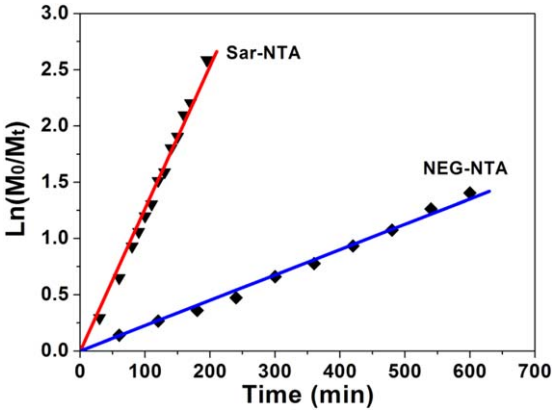


FIGURE 4 Kinetic plots of the polymerization of NEG-NTA in THF ($R^2 = 0.998$) and Sar-NTA in acetonitrile ($R^2 = 0.998$) initiated by benzylamine in sealed tube ($[M]_0 = 0.5$ mol/L, $[NEG]_0/[BnNH_2]_0 = 20$, $[Sar]_0/[BnNH_2]_0 = 75$, 60 °C). [Color figure can be viewed at wileyonlinelibrary.com]

that calibration with polystyrene overestimates the real M_n of the polypeptoids products due to the higher hydrodynamic volume of these polar polymers.

Furthermore, polymerization kinetics of NEG-NTA were measured at 60 °C with a feed molar ratio of 20 ($[NEG]_0/[BnNH_2]_0$) in sealed tube using THF as solvent, benzylamine as initiator and trioxymethylene as internal standard. The plots of $\ln(M_0/M_t)$ vs. time appear linear up to relatively high monomer conversions (~80%), supporting pseudo-first order kinetics with regard to monomer (Fig. 4), differing from the acceleration at high conversion of rare earth borohydrides system.[25] The result indicates constant concentration of chain propagation active species and living character of NEG-NTA polymerization, in spite of the much smaller apparent propagating rate (1.50×10^{-3} L mol^{-1} s^{-1}) than that of NEG-NCA polymerization under the same monomer concentration and higher feed molar ratio of 50 (8.54×10^{-3} L mol^{-1} s^{-1}, 20 °C in benzonitrile) as reported.[7]

Hexylamine-initiated polymerizations of NEG-NTA were also conducted in THF at 60 °C to produce PNEG with high yields (>86%), controlled MWs and narrow MW distribution (1.14–1.23; Supporting Information Table S1). The structure of the products is well confirmed by the ^{1}H NMR spectrum (Supporting Information Figure S6). The MALDI-ToF mass spectrum of PNEG sample **S1** reveals a monomodal distribution without shoulders (Supporting Information Figure S7) though its SEC profile (Supporting Information Figure S8) shows a high MW shoulder. Therefore, we attributed the high MW shoulder to nonoptimized SEC conditions and polymer aggregations in solvents rather than side reactions, which was also observed in our previous work of copolypeptoids.[27] The MALDI-ToF mass spectrum supports that the polymerizations undergo NAM. In summary, polymerizations of NNTA initiated by primary amines exhibit a much better controllability than our previous work of rare earth borohydrides initiators, since the latter produce polypeptoids with moderate $Đ$ (1.3–1.5) and indefinite end-group.[25]

With the help of the exciting results above, we realize that polymerizing NNTA in good solvents, that is, good solubility for polymer and no side reaction, are essential. Therefore, searching a suitable solvent is the key to achieve controlled polymerization of Sar-NTA. THF and dioxane are usual reaction media for NCA polymerization[22,35–37] but not suitable in the case of Sar-NTA. The poor solubility of PSar in them leads to uncontrolled polymerization and limitation of DP below 100 due to heterogeneous reactions.[23–25] However, most good solvents for PSar, such as DMF, *N*,*N*-dimethylacetamide, dimethylsulfoxide (DMSO), and *N*-methyl pyrrolidone (NMP), result in uncontrollable Sar-NTA polymerization at 60 °C producing PSar with low MWs and low yields (< 30%) because they alone initiate NNTA polymerization and cause chain transfer.

Fortunately, we found that acetonitrile was an appropriate polymerization medium for Sar-NTA[25] and also applied in Sar-NCA polymerization.[38,39] Therefore, polymerizations of Sar-NTA initiated by benzylamine were carried out in acetonitrile at 60 °C (Table 1). All polymerizations exhibited high yields (>88%) with various feed molar ratios of $[Sar]_0/[BnNH_2]_0$ ranging from 20 to 420 (sample **8**–**13** in Table 1) within 24 h (sample **13** for 48 h). The PSar polymers with quantitative benzyl chain-end are confirmed by MALDI-ToF and NMR analyses [Figs. 1(D–F) and 2(B)], indicating the NAM mechanism of NTA polymerization in absent of side reactions (Supporting Information Scheme S3). The DPs of the obtained PSars are consistent well with the feed molar ratios based on single-site initiation by the benzylamine at low molecular weight range ($[Sar]_0/[BnNH_2]_0 < 100$), indicating the good controllability of the polymerization. When $[Sar]_0/[BnNH_2]_0$ is higher than 180 (sample **12** in Table 1), the NMR-based DPs become smaller than the theoretical values, and the deviation is pronounced when $[Sar]_0/[BnNH_2]_0$ ratio is 420. The largest absolute M_n of PSar (sample **13** in Table 1) reaches 18.7 kg/mol, that is, DP of 262, which is comparable to many products obtained in Sar-NCA polymerization. It is a great improvement compared with Sar-NTA

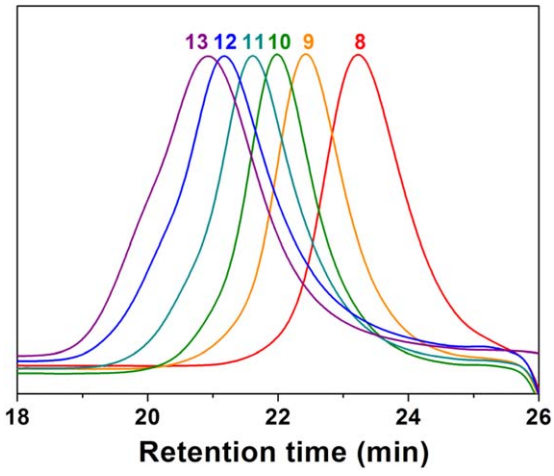


FIGURE 5 SEC traces of PSar samples **8**–**13**. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Synthesis of Block Copolypeptoids in Acetonitrile Initiated by Benzylamine[a]

Sample	Feed molar ratio	First block			Final product		
	[Sar]/[NEG]/[I]	DP[b]	M_n (kg/mol)[c]	$Đ$[c]	Composition[b]	M_n (kg/mol)[c]	$Đ$ [c]
14	20/55/1	21	4.3	1.09	Bn-PSar$_{21}$-*b*-PNEG$_{50}$	8.9	1.18
	[NEG]/[Sar]/[I]						
15	40/80/1	38	6.5	1.12	Bn-PNEG$_{38}$-*b*-PSar$_{78}$	13.3	1.24

[a] The first block was polymerized at 60 °C for 24 h with $[M]_0 = 0.5$ mol/L, and the second block was polymerized at 60 °C for additional 24 h.
[b] As determined by ^{1}H NMR.
[c] As determined by SEC.

polymerizations in dioxane, not a solvent as good as acetonitrile for PSar, where the DPs were less than 80.[23,24] Slight gels were observed during the Sar-NTA polymerization in acetonitrile when $[Sar]_0/[BnNH_2]_0$ was higher than 100, which was responsible for the deviation of DP and the broadening of MW distribution (from 1.13 to 1.31). Acetonitrile is not an ideal solvent for PSar with higher MW. All SEC traces of the products are monomodal and symmetrical with narrow MW distribution (Fig. 5). We also carried out polymerization kinetics of Sar-NTA at 60 °C with a feed molar ratio of 75 ($[Sar]_0/[BnNH_2]_0$) in sealed tube using acetonitrile as solvent. The plots of $\ln(M_0/M_t)$ vs. time appear linear up to high monomer conversions (>90%; Fig. 4), indicating pseudo-first order kinetics with regard to monomer and constant concentration of chain propagation active species and living character of Sar-NTA polymerization. Sar-NTA shows a much faster polymerization rate (31.67×10^{-3} L mol^{-1} s^{-1}) than NEG-NTA due to the smaller substituent on the chain-end of secondary amine and higher solvent polarity of acetonitrile than THF.[7,9] The polymerization rate is even comparable with Sar-NCA polymerization under the same monomer concentration and a feed molar ratio of 50 (28.78×10^{-3} L mol^{-1} s^{-1}, 20 °C in NMP) as reported,[7] which indicates NNTA also can be reactive enough under proper conditions. Thus, we have distinctly improved Sar-NTA polymerization by simply replacing the solvent of dioxane with acetonitrile and increasing the temperature of 20 °C to 60 °C.

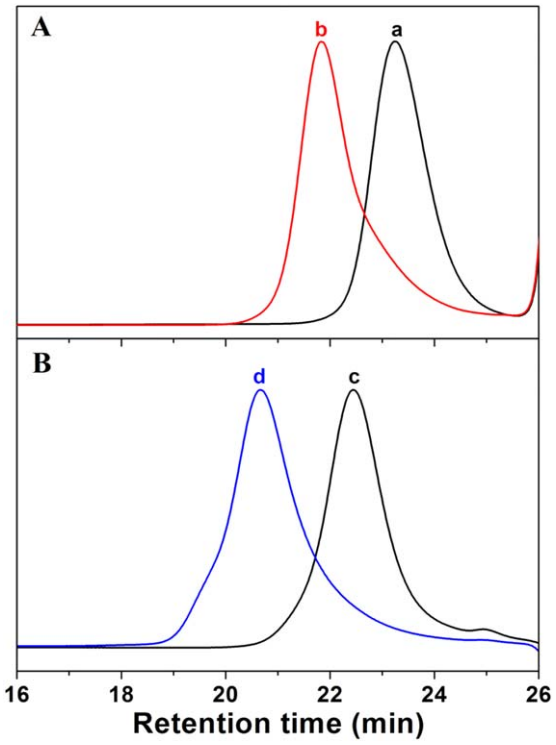


FIGURE 6 A: SEC traces of the first block (a) and final product (b) of Bn-PSar-*b*-PNEG (sample **14**). B: SEC traces of the first block (c) and final product (d) of Bn-PNEG-*b*-PSar (sample **15**). [Color figure can be viewed at wileyonlinelibrary.com]

Block copolypeptoids were prepared to further verify the controllability of the NNTA polymerization. Bn-PSar-*b*-PNEG and Bn-PNEG-*b*-PSar were successfully synthesized by changing monomer feeding sequence (Table 2). In consideration of the solubility of the whole diblock copolymer chains, acetonitrile was selected since it was good solvent for both PSar and PNEG. A polymerization of the first block ($[M_1]_0/[BnNH_2]_0 = 20$ or 40) was conducted at 60 °C for 24 h to reach quantitative monomer conversion as monitored by ^{1}H NMR. A batch of the second monomer ($[M_2]_0/[BnNH_2]_0 = 55$ or 80) was subsequently added and allowed for further chain propagation. SEC traces exhibit MW increases from the first blocks to the corresponding block copolymers as shown in Figure 6. Both signals of Sar and NEG units are observed in ^{1}H NMR spectra of the final products (Supporting Information Figure S9 and S10). DPs of the first block and final products calculated by NMR meet the feed molar ratio quite well. Accordingly, the compositions of the two copolypeptoids are calculated as Bn-PSar$_{21}$-*b*-PNEG$_{50}$ (sample **14**) and Bn-PNEG$_{38}$-*b*-PSar$_{78}$ (sample **15**). It is the first report of block copolypeptoids synthesized from NNTA monomers.

CONCLUSIONS

In summary, we achieved primary amine-initiated controlled polymerizations of NNTA by optimizing the polymerization conditions, especially using ideal reaction media and high temperature. For instance, controlled polymerizations of NEG-NTA were carried out in the good solvent THF at 60 °C with quantitative yield (>95%) and low $Đ$ (1.12–1.17) even at high feed molar ratios. PNEG with an absolute M_n of 24.5 kg/mol (DP = 287, $Đ = 1.14$) was synthesized, which was comparable to those prepared from NEG-NCA by amine initiator. In the case of Sar-NTA, benzylamine-mediated polymerizations were

distinctly improved by employing acetonitrile as reaction medium at 60 °C. In this way, PSars with predictable MWs from 1.5 to 18.7 kg/mol were obtained. Kinetic study and block copolypeptoid synthesis further confirm the controllability of primary amine-initiated polymerization of NNTA. We afford a positive model of NNTA controlled polymerization and develop a versatile and practical synthetic method to prepare high-MW polypeptoids. These findings pave the way for controllable syntheses of polypeptoids from NNTAs. NTA-approach deserves further intensive effort of investigations.

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