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Phenyl Trimethylsilyl Sulfide-Mediated Controlled Ring-Opening Polymerization of α-Amino Acid *N*-Carboxyanhydrides

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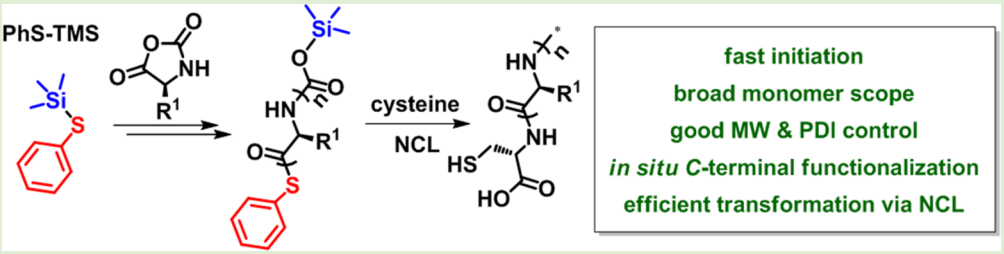
Supporting Information



ABSTRACT: We describe here the first example of trimethylsilyl sulfide (*S*-TMS) mediated controlled ring-opening polymerization (ROP) of α-amino acid *N*-carboxyanhydrides (NCAs). We show that phenyl trimethylsilyl sulfide (PhS-TMS), an inexpensive and commercially available compound, mediates rapid ROP of a broad scope of NCA monomers, produces functional poly(amino acids) (PAAs) with controllable molecular weights (MWs), narrow polydispersity index (PDI), and an in situ generated phenyl thioester group at the *C*-terminus (PAA-SPhs). PhS-TMS offers more rapid chain initiation than previously reported hexamethyldisilazane (HMDS) initiator, ensuring a living polymerization with better control. Mechanistic studies suggest that a reactive trimethylsilyl carbamate (TMSC) was generated during the chain initiation and continued to regulate the chain propagation through a TMS transfer process. Considering the versatility of NCAs, and the potential of leveraging the *C*-terminal phenyl thioester for native chemical ligation (NCL), we believe this method may offer a powerful platform enabling the rapid generation of functional PAAs and their *C*-terminal conjugates for numerous biological applications.

INTRODUCTION

Poly(amino acid)s (PAAs, also known as polypeptides) produced from the ring-opening polymerization (ROP) of α-amino acid *N*-carboxyanhydrides (NCAs)[1−5] are attractive biomaterials for their intriguing properties such as stimuli-responsiveness,[6,7] secondary structures,[8] and hierarchical self-assembly.[9−13] Controlled ROP of NCAs was initially achieved by organometallic catalysts,[14] mainly pioneered by Deming and co-workers in late 1990s. Since then, other organometallic[15,16] and metal-free initiators or catalytic systems were developed based on primary amine-derived initiators (e.g., primary amine hydrochloride,[17,18] primary amine trifluoroboranes,[19] secondary amine-assisted primary amines,[20,21] and thiourea/amine initiation system[22]) under normal or specialized polymerization conditions (e.g., low temperature, high vacuum, or nitrogen flow)[23−27] or *N*-trimethylsilyl (*N*-TMS) amines such as hexamethyldisilazane (HMDS).[28,29] Among which, HMDS works by nucleophilic attacking the NCA ring to generate an amide bond at the *C*-terminus of the PAAs and regulating the chain propagation by a transferring trimethylsilyl carbamate (TMSC) group at the *N*-terminus. Nonetheless, almost all existing metal-free controlled ROP of NCAs rely on nitrogen/amine-based initiators. Giani et al. reported thiol-initiated ROP of NCAs, but with poor control (PDI > 1.8) and very slow kinetics at 0 °C.[30] We speculate that a *S*-trimethylsilyl (*S*-TMS) sulfide would mediate the ROP of NCAs in a controlled manner similar but superior to previously reported *N*-TMS amines because: (1) sulfur is, in general, more nucleophilic but less basic than nitrogen and (2) the S−Si bond is more reactive than the N−Si bond. Thus, a *S*-TMS sulfide may offer faster chain initiation than a *N*-TMS amine with minimized activated-monomer pathway, which together ensure a living polymerization with better control. Moreover, we realize that without additional protection/deprotection step, the *S*-TMS sulfide initiator will in situ generate at the *C*-terminus of the PAA a reactive thioester, which is readily transformable to other functionalities and versatile modules including peptides and proteins via the chemoselective native chemical ligation (NCL).[31,32] Previously, functionalization of the PAAs at the *C*-terminus was realized by initiators bearing another preexisting functional group.[29,33,34] Albeit straightforward and effective in many cases, the synthesis of multifunctional initiators might be challenging for complex substrates (e.g., the synthesis of *N*-TMS amines requires strict moisture-free

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Scheme 1. PhS-TMS Mediated Controlled ROP of NCAs for the Production of Poly(amino acid)s (PAAs) Tethering an In Situ Generated Thioester, Which is Amenable to NCL

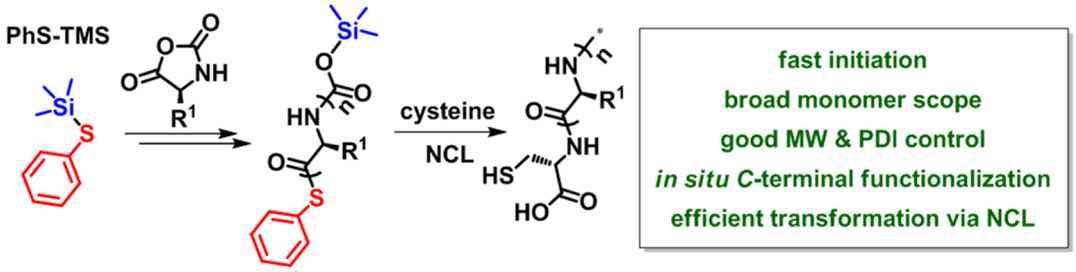
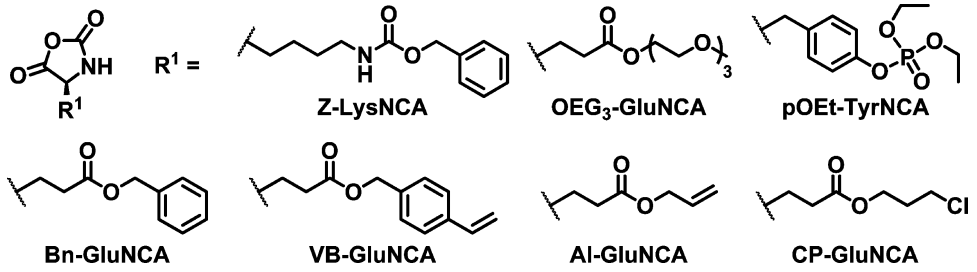


Table 1. PhS-TMS Mediated Controlled ROP of Various NCAs[a]



entry	R^1	PAA-SPh	DP_{exp}[b]	DP_{obt}[c]	PDI[d] (M_w/M_n)
1	Z-LysNCA	PZLL-SPh	100	98	1.06
2	Bn-GluNCA	PBLG-SPh	50	50	1.07
3	VB-GluNCA	PVBLG-SPh	100	87	1.09
4	pOEt-TyrNCA	P(pOEt-Tyr)-SPh	50	52	1.03
5	Al-GluNCA	PALG-SPh	100	100	1.03
6	$(OEG)_3$-GluNCA	P(OEG_3-Glu)-SPh	50	52	1.09
7	CP-GluNCA	PCPLG-SPh	100	66	1.04

[a]All polymerizations were analyzed at 24−30 h of reaction when more than 95% monomer conversions were reached, as determined by monitoring the NCA anhydride absorption peak at 1853 cm^{-1} in FT-IR spectroscopy. [b]DP_{exp} = expected degree of polymerization (feeding M/I ratio). [c]DP_{obt} = obtained degree of polymerization. [d]PDI = polydispersity index, determined by GPC.

condition). Moreover, the preinstalled functionality might potentially attenuate the controlled polymerization in certain cases due to increased initiator complexity or unexpected incompatibility problems between the initiator and monomer. In this context, we believe the in situ generation of a reactive *C*-terminal thioester for different monomers by a universal initiator could significantly simplify the polymerization procedure and offer an attractive approach for the rapid generation of end functionalized PAA conjugates for numerous biological applications.

Herein, we describe our investigation on the controlled ROP of a broad spectrum of NCA monomers mediated by a novel initiator, phenyl trimethylsilyl sulfide (PhS-TMS; Scheme 1). We show that this polymerization produces well-defined PAAs with controlled molecular weights (MWs), low polydispersity index (PDI, generally below 1.10), and an in situ formed phenyl thioester (PAA-SPh). Notably, PhS-TMS adopts similar mechanism to previously reported *N*-TMS amines but with more rapid chain initiation. Mechanistic studies suggest that a reactive TMSC was generated during the chain initiation and continues to regulate the chain propagation through a TMS transferring process. To our best knowledge, this is the first example of *S*-TMS based initiator of, and may imply a paradigm shift for, the controlled ROP of NCAs.

MATERIALS AND METHODS

Materials. All chemicals were purchased from commercial sources and used as received unless otherwise specified. Ultrapure water (15.0 MΩ, Milli-Q) was used in all experiments. PhS-TMS and HMDS were purchased from Sigma-Aldrich (St. Louis, MO, U.S.A.). Anhydrous dichloromethane (DCM), hexane, and tetrahydrofuran (THF) were obtained by passing HPLC grade solvents through columns packed with neutral alumina or activated 4 Å molecular sieves. Anhydrous *N*,*N*-dimethylformamide (DMF) was purchased from Sigma-Aldrich and treated with methyl isocyanate bounded polystyrene beads (Sigma-Aldrich, St. Louis, U.S.A.) prior to polymerization. Amino acid derivatives were purchased from GL Biochem Ltd. (Shanghai, China). As shown in Table 1, ε-carboxybenzyl L-lysine NCA (Z-LysNCA, entry 1), γ-benzyl L-glutamate NCA (Bn-GluNCA, entry 2), γ-(4-vinylbenzyl) L-glutamate NCA (VB-GluNCA, entry 3),[35] *O*-diethylphospho L-tyrosine NCA (pOET-TyrNCA, entry 4),[36] γ-allyl L-glutamate NCA (Al-GluNCA, entry 5),[37] and γ-(2-(2-(2-methoxyethoxy)ethoxy)ethyl L-glutamate NCA (OEG_3-GluNCA, entry 6),[38] γ-chloropropyl L-glutamate NCA (CP-GluNCA, entry 7),[39] and *N*-butyl glycine NCA (N^{Bu}-GlyNCA)[40] were synthesized following previously reported procedures.

Characterizations. NMR spectra were recorded on a 400 MHz Bruker ARX400 FT-NMR spectrometer. Fourier transform infrared (FT-IR) spectra were recorded on a Bruker Vector 22 FT-IR spectrometer and quantification was realized by using a KBr cell with a fixed path length of 0.2 mm. High resolution electrospray ionization mass spectrometry (HR-ESIMS) analyses were recorded on a Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (APEX IV, Bruker). Tandem gel permeation chromatography (GPC) experiments

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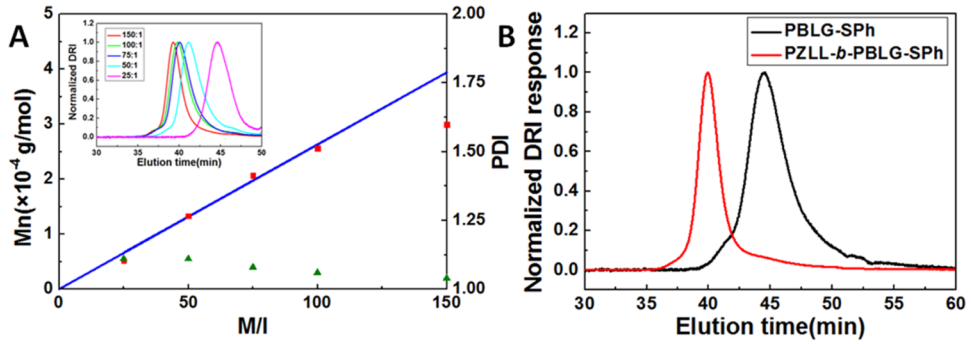

Figure 1. PhS-TMS mediated controlled ROP of NCAs. (A) Plots of MW and PDI of poly(ε-carboxybenzyl L-lysine) (PZLL-SPh) as a function of monomer/initiator (M/I) ratio in the PhS-TMS mediated ROP of Z-LysNCA; Inset: overlay of GPC curves of the PZLL-SPhs at different M/I ratios. (B) Overlay of the GPC curves of PBLG-SPh (black, obtained DP = 44, PDI = 1.07) and block copolymer PZLL-*b*-PBLG-SPh (red, the obtained DP of PZLL block = 56, PDI = 1.02); the expected DPs of both blocks are 50.

were performed on a system equipped with an isocratic pump (Model 1100, Agilent Technology, Santa Clara, CA), a DAWN HELEOS 18-angle laser light scattering detector (also known as multiangle laser light scattering (MALLS) detector, Wyatt Technology, Santa Barbara, CA) and an Optilab rEX refractive index detector (Wyatt Technology, Santa Barbara, CA). The detection wavelength of MALLS was set at 658 nm. The temperature of both the refractive index and the MALLS detectors was 25 °C. Separations were performed using serially connected size exclusion columns (100, 500, 10^3, 10^4, and 10^5 Å Phenogel columns, 5 μm, 7.8 × 300 mm, Phenomenex, Torrance, CA) at 60 °C using DMF containing 0.1 M LiBr as the mobile phase. The molecular weights (MWs) of all polymers were determined based on the dn/dc values of all samples calculated offline by using the internal calibration system processed by the ASTRA V software version 5.1.7.3 provided by Wyatt Technology. MALDI-TOF MS spectra were acquired by a Bruker Daltonics ultraflex TOF mass spectrometer.

PhS-TMS Mediated NCA Polymerization. In a glovebox, Z-LysNCA (20.0 mg, 0.0653 mmol, 100 equiv) dissolved in anhydrous DMF (400 μL) was added to a PhS-TMS stock solution in DMF (1.31 μL × 0.5 M, 1.0 equiv) and stirred for 25 h at room temperature. The conversion of NCA was obtained by monitoring the peak area centered at 1858 cm^{-1} in FT-IR spectroscopy and fitting into a standard working curve drawn from the same NCA monomer in known concentrations. Upon complete consumption of the monomer, an aliquot of the reaction mixture was diluted to 10 mg/mL in DMF containing 0.1 M LiBr and injected to GPC for molecular weight (MW) and polydispersity index (PDI) analysis. To obtain purified PAA-SPh, the reaction solution was poured into diethyl ether (40 mL), and the precipitate was separated by centrifugation, washed extensively by diethyl ether (40 mL × 2), and dried under vacuum. Typical yields were weighted ~70−95%. All PAA-SPhs were stored in a −20 °C freezer for up to 2 months. PhS-TMS mediated polymerization of other NCAs were similarly carried out.

Kinetic Studies. In a glovebox, a solution of N^{Bu}-GlyNCA (10.0 mg, 0.0645 mmol, 1.0 equiv) in DMF (75 μL) was mixed with PhS-TMS (0.129 mmol, 2.0 equiv. in 100 μL DMF) at room temperature under stirring. The reaction was monitored by FT-IR spectroscopy by injecting an aliquot of reaction solution (40 μL) into a KBr cell with a fixed path length of 0.2 mm at various time intervals to obtain the NCA conversion. Quantification was achieved by calculating the peak area at 1858 cm^{-1} and fitting to a standard working curve. Other kinetic studies were done in a similar fashion.

Mechanism Studies. In a glovebox, a N^{Bu}-GlyNCA (20.0 mg, 0.127 mmol, 1.0 equiv) solution in $CDCl_3$ (100 μL) was mixed with a PhS-TMS solution (0.129 mmol, 2.0 equiv in 100 μL of $CDCl_3$) at room temperature and stirred for 2 h. An aliquot of the reaction mixture was diluted with dry acetonitrile and analyzed by HR-ESIMS under careful moisture-free operation and mild ionization condition. The remaining solution was transferred to an oven-dried NMR tube, sealed by parafilm in the glovebox, and analyzed by ^{13}C NMR spectroscopy. Other mechanism studies, such as the reaction of Bn-GluNCA and PhS-TMS, were done in a similar fashion. To gain information about the end-group transformation from moisture-free to ambient condition, the same reaction mixture was later exposed to moisture and analyzed by ESIMS.

Synthesis of Ac-P(OEG$_3$-Glu)$_n$-SPh. PhS-TMS mediated ROP of OEG$_3$-GluNCA was carried out following the procedure described above. Upon completion of the polymerization, acetic anhydride (2 equiv) was added to the polymer solution (1 equiv of P(OEG$_3$-Glu)$_n$-SPh) in DMF at room temperature and stirred for 1 h. The desired product denoted as Ac-P(OEG$_3$-Glu)$_n$-SPh, where n is the feeding M/I ratio, was recovered by precipitation in diethyl ether (40 mL), washed by the diethyl ether (40 mL × 2), and dried under vacuum. The final products were characterized by MALDI-TOF mass spectrometry.

Synthesis of Ac-P(OEG$_3$-Glu)$_7$-Cys. Ac-P(OEG$_3$-Glu)$_7$-SPh (6.3 mg, 3.2 μmol, 1.0 equiv) solution in water (1.10 mL) was added to a solution containing cysteine hydrochloride (0.50 mg, 3.2 μmol, 1.0 equiv) and tris(2-carboxyethyl) phosphine hydrochloride (TCEP, 0.90 mg, 3.2 μmol, 1.0 equiv) with pH adjusted to ~7.0. The mixture was stirred at room temperature for 3 h, and UPLC analysis depicted completion of the reaction, as seen from the disappearance of Ac-P(OEG$_3$-Glu)$_7$-SPh peaks and the emergence of new peaks corresponding to Ac-P(OEG$_3$-Glu)$_7$-Cys. The product was purified by passing the mixture through a PD-10 size exclusion column (GE Healthcare Corp.) and recovered by lyophilization to afford a white powder (6.1 mg, yield 97%). The product was confirmed by MALDI-TOF mass spectrometry.

Synthesis of Ac-P(OEG$_3$-Glu)$_7$-Cys(Fl). Ac-P(OEG$_3$-Glu)$_7$-Cys (6.1 mg, 3.05 μmol, 1.0 equiv) and fluorescein-5-maleimide (1.3 mg, 3.05 μmol, 1.0 equiv) were dissolved and stirred in a H_2O/acetonitrile mixture (v/v = 3/1) at room temperature for 3 h. The reaction mixture was purified by a PD-10 desalting column and recovered by lyophilization to yield the final product as an orange powder (5.8 mg, yield 79%). The MW of the product was confirmed by MALDI-TOF mass spectrometry.

RESULTS AND DISCUSSION

PhS-TMS Mediated Controlled ROP of NCAs. To test the hypothesis of *S*-TMS sulfide initiators, we selected PhS-TMS, an inexpensive and commercially available compound, to polymerize a group of NCA monomers with diverse side-chain structures, as shown in Table 1. Remarkably, PhS-TMS led to rapid reaction and good control for six out of the seven NCAs tested at monomer/initiator (M/I) molar ratios of 50/1 or 100/1 (Table 1, entries 1−6). GPC analyses of these PAA-SPhs showed low PDI below 1.10 and the MWs obtained were all measured less than 15% deviation from the MWs expected (Table 1 and Figure S1). Because of the high nucleophilicity of sulfide, we also examined whether PhS-TMS could obtain good control for monomers bearing thiol-reactive side-chains such as

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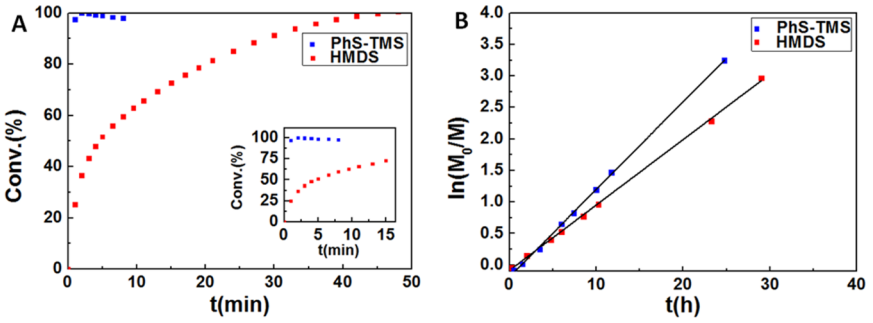

Figure 2. Kinetics of PhS-TMS mediated ROP of NCAs, as determined by FT-IR spectroscopy. (A) Plot of conversion (conv) vs time for the reactions of (PhS-TMS + N^{Bu}-GlyNCA) (blue) and (HMDS + N^{Bu}-GlyNCA) (red) at 2/1 molar ratio. (B) Plot of $\ln(M_0/M)$ vs time for PhS-TMS (blue) and HMDS (red) mediated Z-LysNCA polymerizations at M/I ratio of 100/1. The k_{obs}s were calculated as 0.13 and 0.10 h^{-1} for PhS-TMS and HMDS, respectively.

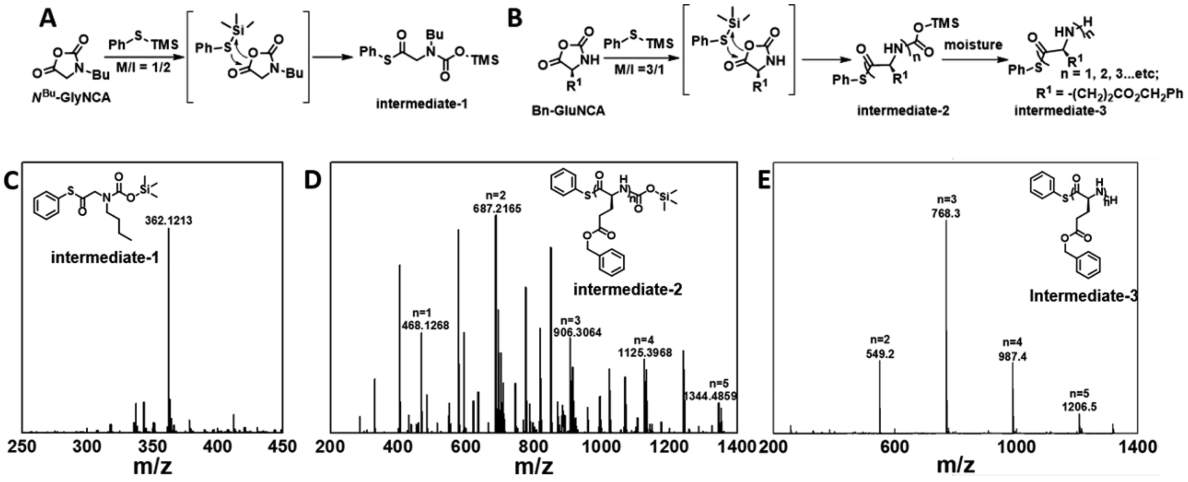

Figure 3. Mechanistic studies of PhS-TMS mediated ROP of NCAs. Scheme of the generation and structure of the proposed intermediate-**1** (A), intermediate-**2** and -**3** (B). (C) High resolution electrospray ionization mass spectrometry (HR-ESIMS) analysis of the reaction of (N^{Bu}-GlyNCA + PhS-TMS) at M/I ratio of 1/2 (D) HR-ESIMS analysis of (Bn-GluNCA + PhS-TMS) at M/I ratio of 3/1. Both HR-ESI mass spectra were recorded under careful air-free operation and mild ionization condition. (E) ESIMS analysis of the reaction of (Bn-GluNCA + PhS-TMS) at M/I ratio of 3/1 exposed to air and moisture for a short time.

CP-GluNCA. Interestingly, the obtained DP and PDI of the PCPLG-SPh at feeding M/I ratio of 100/1 were measured as 66 and 1.04, respectively (Table 1, entry 7). The reason for this relatively less controlled MW of CP-GluNCA, which implied certain limitation of the system, is under our careful investigation. We next investigated the ROP of the above NCAs at various M/I ratios and obtained remarkable control over most polymerizations tested (Table S1). Taking the ROP of Z-LysNCA as an example and as shown in Figure 1A, the resulting poly(ε-carboxybenzyl L-lysine)s (PZLL-SPh) displayed linearly increased MWs perfectly matching the expected MWs as the feeding M/I ratios were elevated from 25/1 to 100/1 (obtained degree of polymerizations (DPs) were 20, 51, 79, and 98, for feeding M/I ratios of 25/1, 50/1, 75/1, and 100/1, respectively). At M/I ratio of 150/1, the obtained DP was ~114, ~25% deviation from the expected DP. All polymers showed sharp and monomodal GPC peaks with PDI less than 1.10 (Figure 1A, inset). Moreover, successive ROP of Bn-GluNCA and Z-LysNCA by PhS-TMS generated poly(ε-carboxybenzyl L-lysine)-*block*-poly(γ-benzyl L-glutamate) (PZLL-*b*-PBLG-SPh) block copolymer with excellent MW and PDI control, as illustrated by the shift of the monomodal GPC curves in Figure 1B. Overall, our data verified that PhS-TMS mediates rapid ROP of NCAs, affording well-defined PAAs with good MW and PDI control at M/I below 150/1. Notably, small shoulder peaks were occasionally observed as shown in Figure 1A, inset, suggesting potential aggregation or minor species with MWs deviated from the major species. The attenuated MW control might be partially attributed to the small amount of impurities derived from the initiator (97% purity), monomer, and DMF.[41]

Kinetic Studies of PhS-TMS Mediated ROP of NCAs. Next, we studied the kinetics of PhS-TMS mediated ROP of NCAs. To solely investigate the chain initiation and rule out the contribution from chain propagation, we chose *N*-butyl glycine NCA (N^{Bu}-GlyNCA) as a model monomer for the reason that it can be ring-opened with negligible degree of chain propagation at room temperature due to the steric hindrance of butyl group.[42] The reaction of HMDS and N^{Bu}-GlyNCA was also examined for comparison. As more than 95% N^{Bu}-GlyNCA was consumed by PhS-TMS within 1 min, it required ~45 min for HMDS to react with all N^{Bu}-GlyNCA (Figure 2A). Although this model monomer does not reflect the situation of normal NCAs with full fidelity, the results indeed provide us meaningful information regarding the relative reactivity of PhS-TMS and HMDS in the ring opening process of NCAs and, thus, support the notion of faster chain initiation of PhS-TMS than HMDS. To study the chain propagation, we monitored

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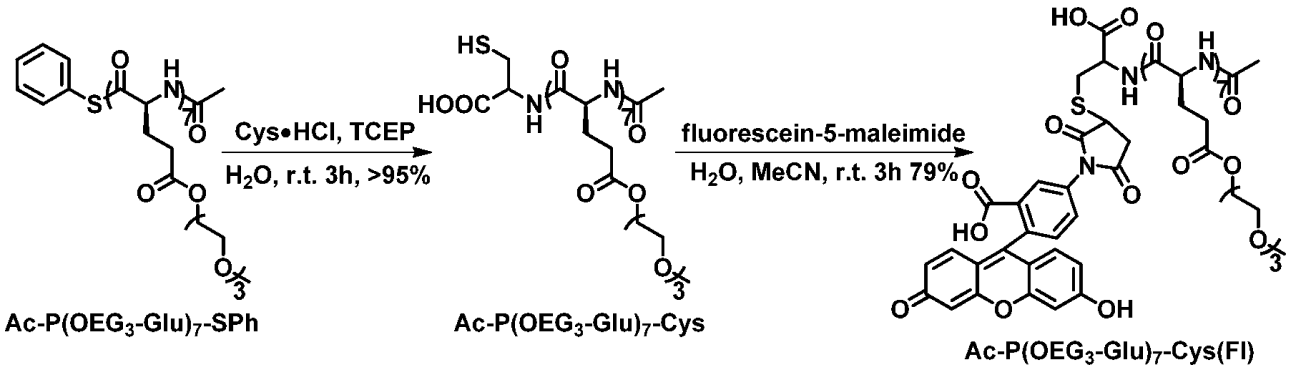
Scheme 2. Conjugation of Ac-P(OEG_3-Glu)$_n$-SPh to Cysteine and Subsequent Reaction with Fluorescein-5-maleimide



the ROPs of Z-LysNCA initiated by PhS-TMS and HMDS at M/I ratio of 100/1. Both reactions exhibited first-order kinetic character on the monomer concentration and gave comparable observed polymerization rate constants (k_{obs} = 0.13 and 0.10 h^{-1}, respectively, Figure 2B), suggesting a similar major chain propagation mechanism was shared by the two polymerizations. The overall slightly faster polymerization of PhS-TMS than HMDS may be a combined results of the rate difference in chain initiation and other possible minor pathways.

Mechanism Studies of PhS-TMS Mediated ROP of NCAs. On the basis of the above kinetic experiments, we expected that PhS-TMS mediated NCA polymerization would yield a PAA with a phenyl thioester and a TMSC at its *C*-terminus and *N*-terminus, respectively[28] (intermediate-**1** and -**2**, Figure 3A,B). To confirm this hypothesis in the chain initiation step, we again studied the model reaction of N^{Bu}-GlyNCA and PhS-TMS at M/I molar ratio of 1/2 by means of high resolution electrospray ionization (HR-ESI) mass spectrometry and ^{13}C NMR spectroscopy. The HR-ESI mass spectrum of the reaction mixture (under careful air-free operation and mild ionization condition) exhibited the expected mass (Figure 3C) and confirmed the molecular formula (Table S2) of the proposed intermediate-**1**. The formation of intermediate-**1** was also verified by the ^{13}C NMR spectrum of the same reaction mixture, as evidenced by the characteristic thioester and TMCS carbonyl peaks (Figure S2). Similar results were also observed in the reaction of Bn-GluNCA and PhS-TMS at molar ratio of 1/2 (Figure S3). To interrogate the chain propagation mechanism, we conducted the reaction of Bn-GluNCA and PhS-TMS at M/I molar ratio of 3/1 and observed a set of peaks corresponding to intermediate-**2** containing both the phenyl thioester and TMSC in the HR-ESI mass spectrum (Figure 3D and Table S3). The same reaction mixture, upon exposure to air and moisture, gave a clean mass spectrum of a set of peaks corresponding to intermediate-**3** containing the *C*-terminal phenyl thioester and *N*-terminal free amine, a result of TMSC decomposition (Figure 3B,E). Importantly, all peaks appeared in the Figure 3E were calculated with the phenyl thioester attached, an unambiguous evidence of highly efficient initiation and quantitative end group functionalization of the PAAs.

Native Chemical Ligation of PAA-SPhs to Cysteine. To demonstrate the potential application of the phenyl thioester tethered on the PAAs for NCL, we examined the conjugation of PAA-SPh to free cysteine (Scheme 2). For this, *N*-terminal acetyl capped poly(γ-(2-(2-(2-methoxyethoxy)ethoxy)ethyl L-glutamate) (Ac-P(OEG_3-Glu)$_n$-SPh, n = feeding M/I ratio) was used for its excellent aqueous solubility, thermal responsiveness, and stealth side chain.[38,43] In our first attempt, Ac-P(OEG_3-Glu)$_7$-SPh (characterization in Figure S4) and free cysteine were mixed at molar ratio of 1/1 and incubated at room temperature for 3 h. Almost quantitative transformation of phenyl thioester group was observed as no starting material was detected in the MALDI-TOF mass spectrum of the reaction mixture (Figure S5). The clean reaction at 1/1 molar ratio confirmed the high reactivity of the phenyl thioester on the PAAs. Thanks to the quantitative transformation, the product Ac-P(OEG_3-Glu)$_7$-Cys can be readily recovered by a simple desalt step with >95% separation yield. Moreover, this reaction represents an example of gain-of-function, as a free thiol and a carboxylic acid were generated after the ligation. We were able to further react Ac-P(OEG_3-Glu)$_7$-Cys to fluorescein-5-maleimide by the classical thiol-maleimide reaction, generating the fluorescein labeled Ac-P(OEG_3-Glu)$_7$-Cys(Fl) with separation yield of ∼79% (Figure S6).

CONCLUSIONS

In conclusion, we report here the first sulfide-based controlled polymerization method for NCAs. By using the commercially available PhS-TMS as the initiator, well-defined PAAs with a variety of functional side-chains, controlled MWs and narrow PDIs were facilely produced. The PhS-TMS mediated ROP features in more rapid chain initiation than previously reported HMDS, which is a prerequisite for living polymerization. Moreover, this method in situ creates a reactive thioester allowing convenient installation of functionality via NCL on the *C*-terminus of PAAs. Considering the simplicity and the high efficiency of NCL, we believe our method offers a powerful platform to generate well-defined PAA-biomolecule conjugates. We are currently investigating the bioconjugation of PAA-SPhs to a variety of biomolecules including drugs, peptides and proteins under mild biological conditions and low stoichiometric ratios; these results will be separately reported in another manuscript shortly.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.biomac.5b01588.

Supporting figures and tables (PDF).

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Notes

The authors declare no competing financial interest.

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