Living Polymerization of *N*-Substituted Glycine *N*-Thiocarboxyanhydrides

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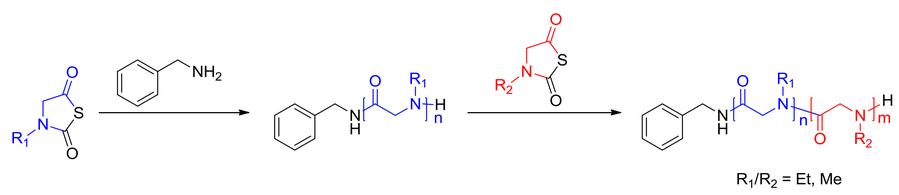
Introduction

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. However, NNCAs have an inherent disadvantage of high sensitivity to moisture and heat, they have to be synthesized and stored in extremely anhydrous and anaerobic environment. Therefore, more stable monomers and easier synthetic approach for preparing polypeptoids have been strongly desired. *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. All the monomer synthesis and purification can be operated in the open air. Although NTA monomers have been discovered since 1950s, researches of their polymerizations are very limited, not to mention living polymerizations. NTAs were arbitrarily considered too stable to polymerize for their low reactivities. In this contribution, we successfully produce polypeptoids with DP up to 287 and *Đ* of 1.14 from living NNTA polymerization using small molecular primary amines, for instance, benzylamine, as initiator in proper polymerization conditions, and suggest a new opinion that NNTA monomers can be active enough with carefully design of polymerization conditions.

Results and Discussion

Part I. Homopolymerization of NNTAs initiated by benzylamine



Scheme 1. Homo- and block co-polymerization of *N*-substituted glycine NTA initiated by benzylamine.

Table 1. Polymerization of *N*-substituted glycine NTA initiated by benzylamine [a]

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

[a] Polymerization conditions: $[M]_0$ = 0.5 mol/L, 24 h at 60 ℃, THF and acetonitrile were used as the solvents for NEG-NTA and Sar-NTA, respectively. [b] As determined by ^{1}H NMR. [c] As determined by SEC. [d] As polymerized for 48 h.

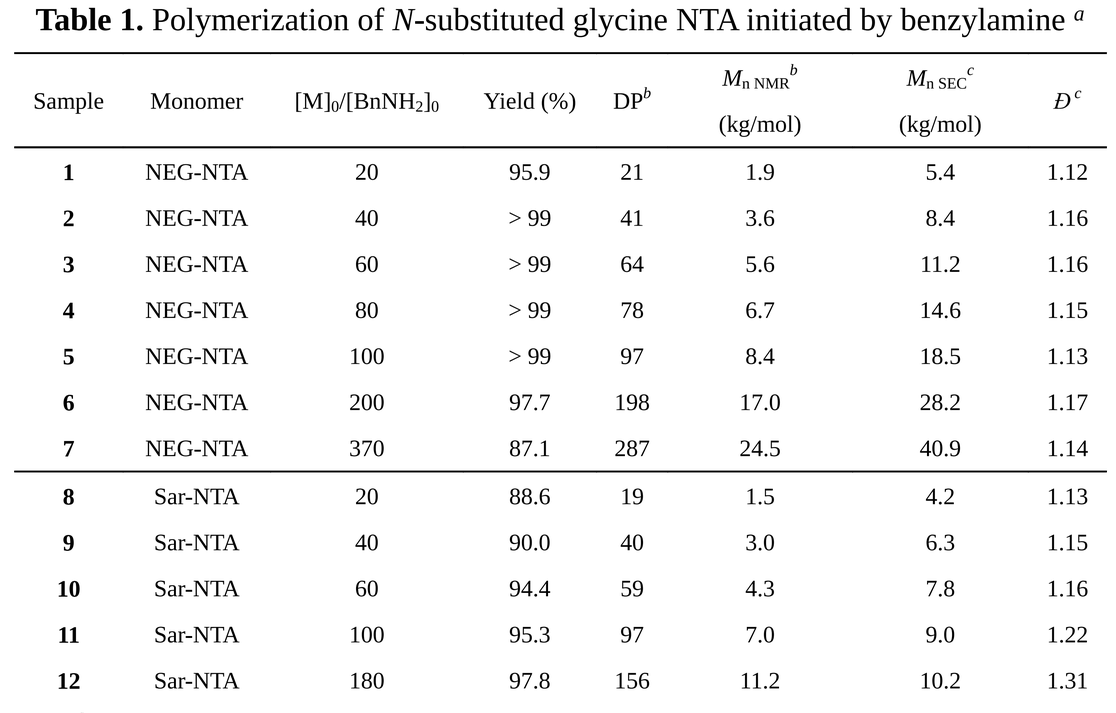


Figure 1. MALDI-ToF mass spectra of sample **1** (A) and **8** (D) with zoom-in views (B and E) and the corresponding polypeptoid structures (C and F).

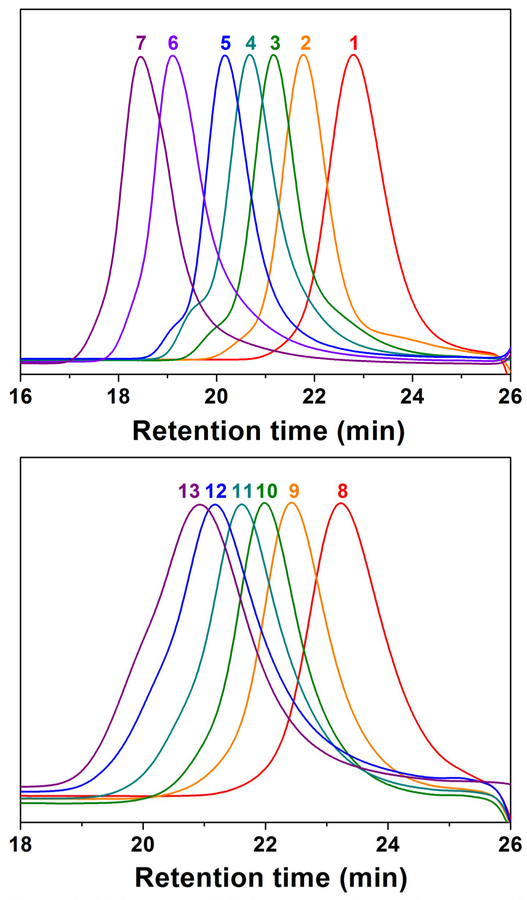
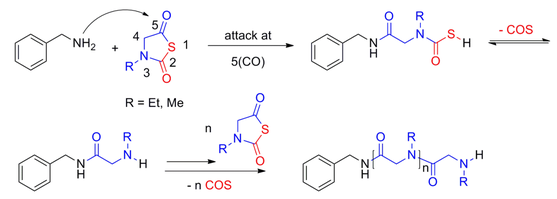


Figure 2. SEC traces of PNEG samples **1**-**7** and PSar samples **8**-**13**.



Scheme 2. Mechanism of polymerization of *N*-substituted glycine NTA initiated by benzylamine.

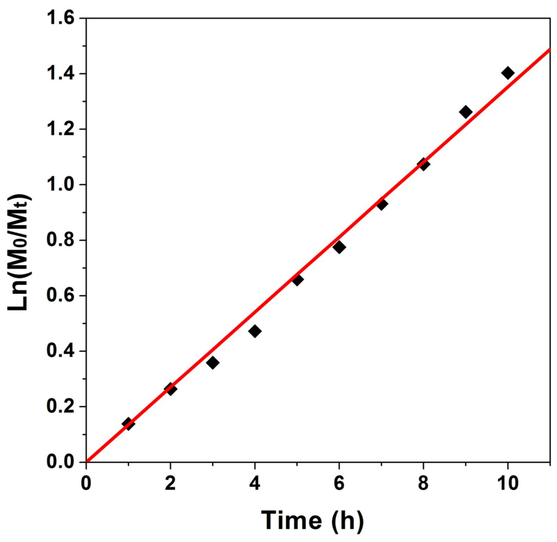


Figure 3. Kinetic plots of the polymerization of NEG-NTA in THF initiated by benzylamine in sealed tube ($[NEG]_0$ = 0.5 mol/L, $[NEG]_0/[BnNH_2]_0$ = 20, 60 °C).

Part II. Block copolymerization of NNTAs initiated by benzylamine

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	40/35/1	39	6.5	1.13	Bn-PSar$_{39}$-*b*-PNEG$_{27}$	9.2	1.19
	[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 ℃ for 24 h with $[M]_0$ = 0.5 mol/L, and the second block was polymerized at 60 ℃ for additional 24 h. [b] As determined by ^{1}H NMR. [b] As determined by SEC.

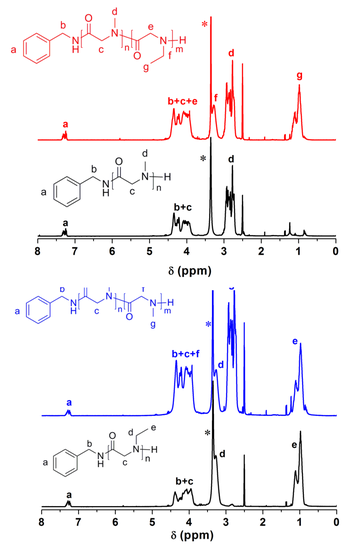


Figure 4. ^{1}H NMR spectra of the first block and final product of Bn-PSar-*b*-PNEG (sample **14**) in DMSO-d_6. (*: water)

Figure 5. ^{1}H NMR spectra of the first block and final product of Bn-PNEG-*b*-PSar (sample **15**) in DMSO-d_6. (*: water)

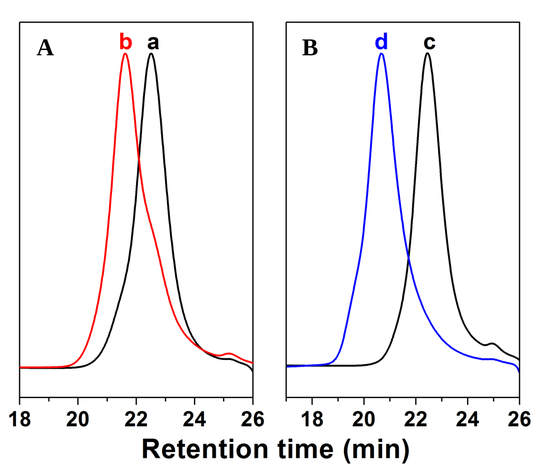


Figure 6. (A) SEC traces of the first block (a) and final product (b) of Bn-PSar-*b*-PNEG (sample **14**). (B) SEC traces of the first block (c) and final product (d) of Bn-PNEG-*b*-PSar (sample **15**).

Conclusion

For the first time we successfully carried out living polymerizations of *N*-substituted glycine NTA monomers using benzylamine as initiator. Under optimized reaction media and appropriate temperature, polymerizations of NNTAs were excellent controllable and comparable to, if not better than those of NNCAs. For instance, the benzylamine-mediated living NNTA polymerization produced poly(*N*-ethylglycine) with quantitative yield (> 95%), high degree of polymerization (DP = 287, M_n= 24.5 kg/mol) and narrow polydispersities ($Đ$ = 1.14). Polysarcosines with predictable molecular weights from 1.5 to 18.7 kg/mol could be obtained in the same way. Our findings correct the thinking of “low activity in polymerization” of NNTAs and smooth away the obstacle in the NTA-approach to synthesize polypeptoids. Due to the advantages of NNTAs in preparation and storage, NTA-approach deserves intensive efforts of further investigation.

Acknowledgement

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