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Hydroxyl Group Tolerated Polymerization of N-Substituted Glycine N-Thiocarboxyanhydride Mediated by Aminoalcohols

Botuo Zheng(11629016), Xinfeng Tao, Tianwen Bai, Baoku Zhu, Jun Ling*

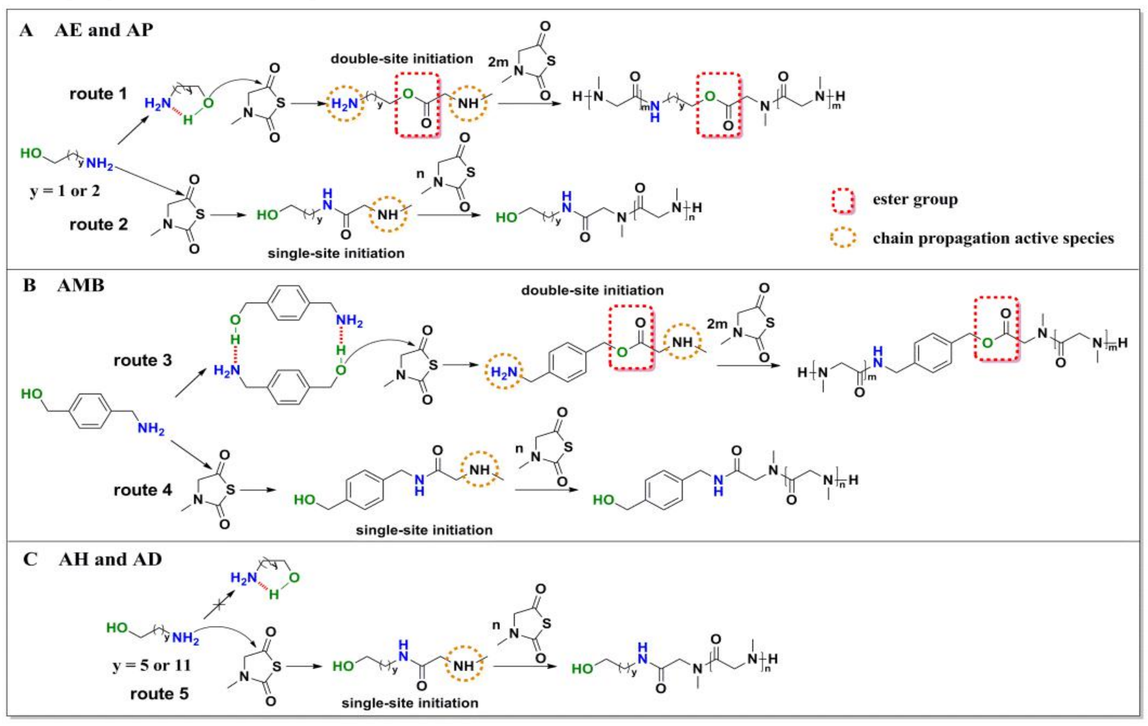
MOE Key Laboratory of Macromolecular Synthesis and Functionalization, Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027, China

Introduction: Polypeptides and polypeptoids are mainly synthesized by ring-opening polymerization (ROP) of α-amino acid N-carboxyanhydride (NCA) and N-substituted glycine N-carboxyanhydride (NNCA). NCA polymerization cannot tolerate nucleophilic groups that have the ability of initiation, e.g., hydroxyl group. In contrast, N-thiocarboxyanhydride (NTA) is a much more stable monomer to tolerate them. NTAs had been considered too stable to polymerize for their low reactivity. In our previous work, we improved NNTA polymerization under proper conditions by using primary amines, highly reactive rare earth borohydrides, and specially-designed amine-terminated polymers as initiators to produce polypeptoids with quantitative yields, predictable high MWs, and low polydispersity indices (PDIs). We hypothesize that NNTA does not react with alcohol alone and thus aminoalcohols can synthesize α-hydroxyl-ω-aminotelechelic polypeptoids directly. In this work, we investigate aminoalcohols including 2-amino-1-ethanol (**AE**), 3-amino-1-propanol (**AP**), 4-aminomethylbenzyl alcohol (**AMB**), 6-amino-1-hexanol (**AH**), and 12-amino-1-dodecanol (**AD**) as initiators. Hydroxyl groups of **AE**, **AP** and **AMB** are activated by hydrogen bonding with amino groups, which results in a mixture of α,ω-diaminotelechelic and α-hydroxyl-ω-aminotelechelic polypeptoids. Pure α-hydroxyl-ω-aminotelechelic polypeptoids are synthesized for the first time initiated by **AH** and **AD** with controlled molecular weights and low polydispersity indices. Hydroxyl groups in **AH** and **AD** remain inactive to generate hydrogen bonding due to the long distance from amino groups.

Table 1. Polymerization of Sar-NTA initiated by **AE**, **AP**, **AMB**, **AH**, **AD**[a]

Initiator	Entry	[M]/[I]	Yield (%)	DP[b]	$M_{n\,NMR}$[b] (kg/mol)	$M_{n\,GPC}$[c] (kg/mol)	$Đ$[c]
HO–NH$_2$ **AE**	1	20	91.6	18	1.3	4.4	1.17
	2	50	93.3	53	3.8	7.6	1.24
	3	100	94.1	-[d]	-[d]	9.9	1.32
	4	200	97.5	-[d]	-[d]	11.3	1.37
	5	420	95.6	-[d]	-[d]	13	1.39
HO–(CH$_2$)$_y$–NH$_2$, y = 2 **AP**	6	20	91.6	16	1.2	4.1	1.11
	7	50	87.8	45	3.3	6.8	1.14
	8	100	90.8	96	6.9	8.7	1.2
	9	200	93.7	196	14	10	1.28
HO–CH$_2$–C$_6$H$_4$–CH$_2$–NH$_2$ **AMB**	10	20	92.3	21	1.6	5.3	1.17
	11	50	94.1	51	3.8	8.2	1.24
	12	100	95.8	107	7.7	9.7	1.3
	13	200	94	197	14.1	10.9	1.32
HO–(CH$_2$)$_y$–NH$_2$, y = 5 **AH**	14	20	82.1	17	1.3	4.2	1.15
	15	50	94	38	2.8	6.7	1.2
	16	100	87.9	70	5.1	8.3	1.27
	17	200	75.2	117	8.4	9.6	1.3
HO–(CH$_2$)$_y$–NH$_2$, y = 11 **AD**	18	20	87.5	18	1.5	5	1.1
	19	50	89.6	49	3.7	7.4	1.14
	20	100	87.2	98	7.2	9.3	1.18
	21	200	84.8	172	12.4	10.6	1.23

[a] Polymerization conditions: $[M]_0$ = 0.5 mol/L, 24 h at 60 °C in acetonitrile. [b] Determined by ^{1}H NMR, DP = the average number of repeat unit on one aminoalcohol molecule. [c] Determined by SEC. [d] The ^{1}H NMR integral of the end group is not accurate enough for the calculation.



Scheme 1. Mechanisms of Sar-NTA polymerizations initiated by **AE** and **AP** (A), **AMB** (B), and **AH** and **AD** (C).

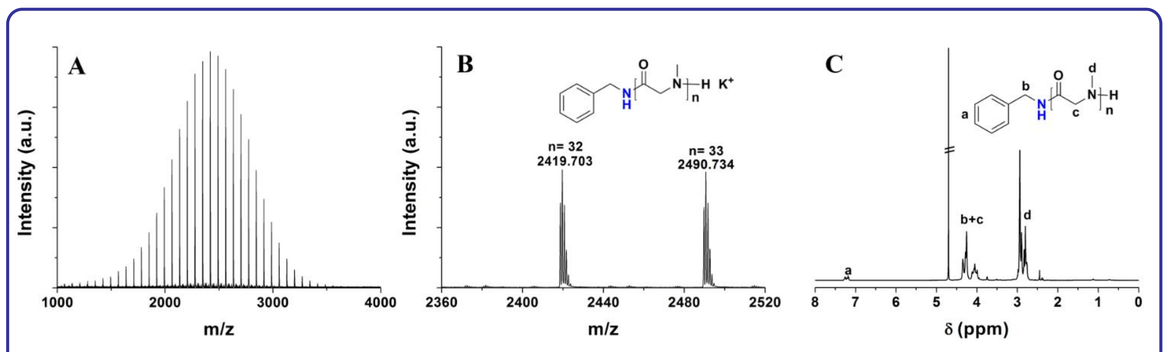


Figure 1. MALDI-ToF mass spectra (A) with zoom-in view (B) and ^{1}H NMR spectrum (C) of PSar initiated by benzylamine with equivalent ethanol.

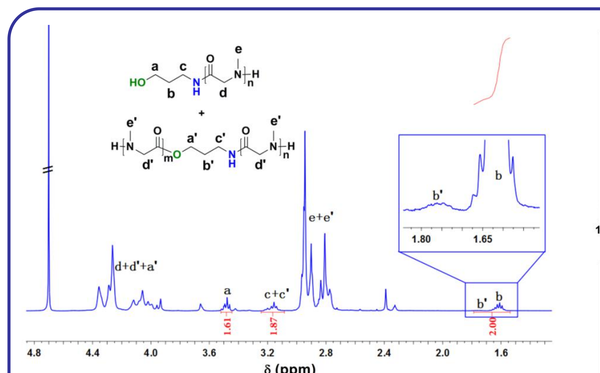
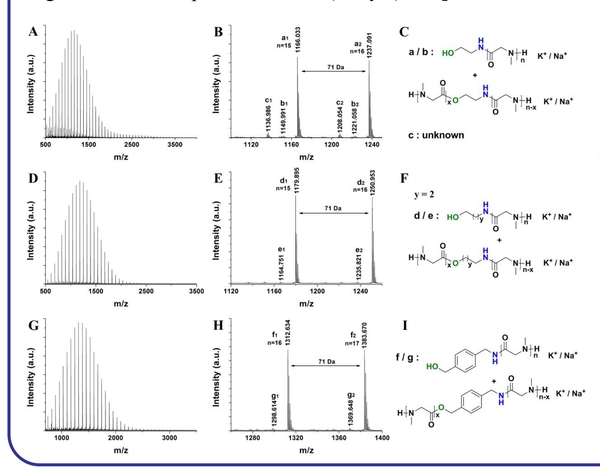


Figure 2. ^{1}H NMR spectrum of PSar (Entry 6) in D_2O.



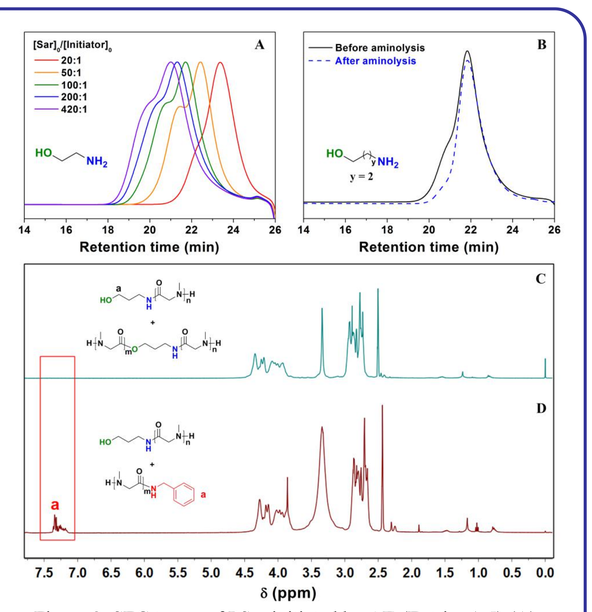


Figure 3. SEC traces of PSar initiated by **AE** (Entries 1-5) (A), and PSar initiated by **AP** (Entry 8) before and after aminolysis (B). ^{1}H NMR spectrum in DMSO-d_6 of PSar initiated by **AP** (Entry 8) before (C) and after (D) aminolysis.

Figure 4. MALDI-ToF mass spectra of PSars in Entries 1 (A), 6(D) and 10(G) with zoom-in views (B, E and H), and the corresponding chemical structures (C, F and I).

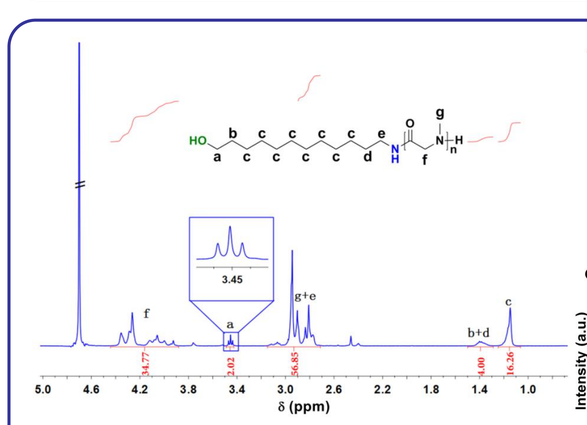


Figure 5. ^{1}H NMR spectrum of PSar (Entry 18) in D_2O.

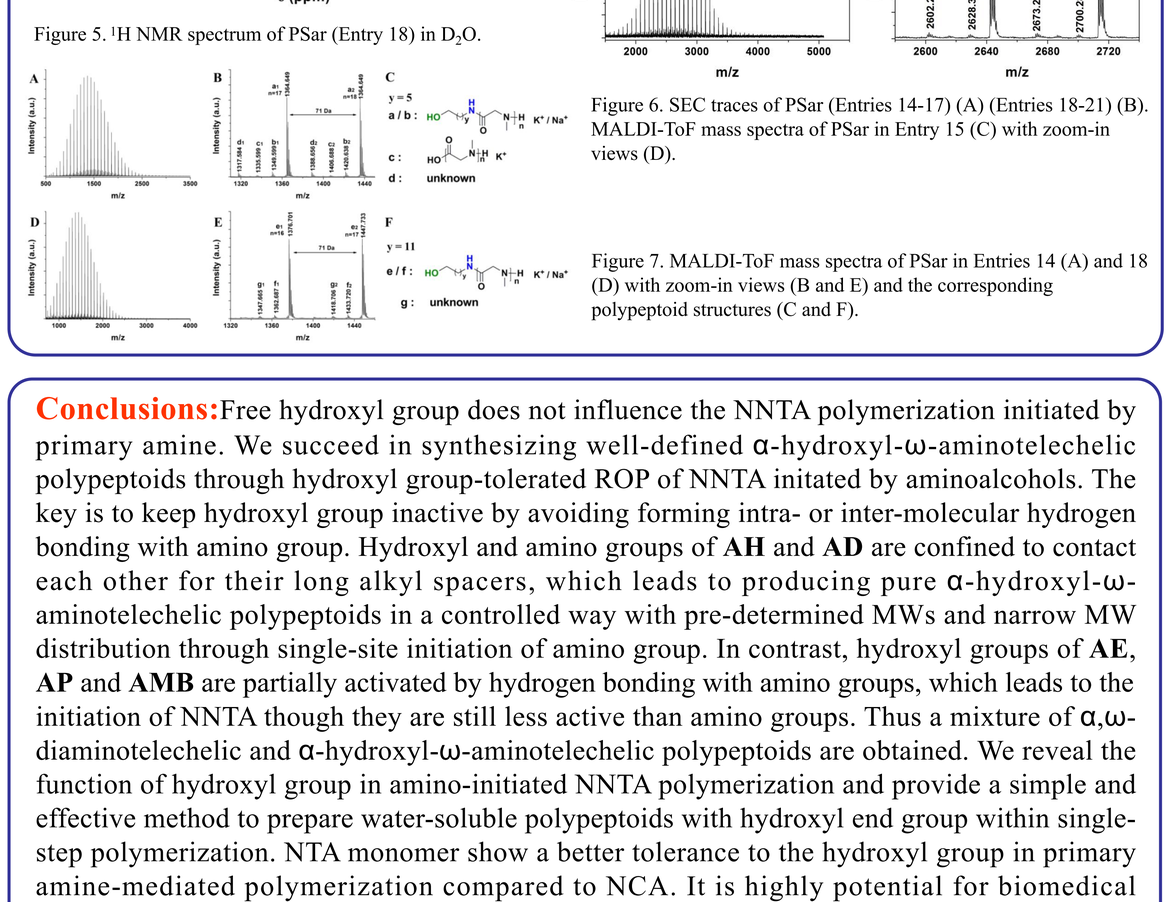


Figure 6. SEC traces of PSar (Entries 14-17) (A) (Entries 18-21) (B). MALDI-ToF mass spectra of PSar in Entry 15 (C) with zoom-in views (D).

Figure 7. MALDI-ToF mass spectra of PSar in Entries 14 (A) and 18 (D) with zoom-in views (B and E) and the corresponding polypeptoid structures (C and F).

Conclusions: Free hydroxyl group does not influence the NNTA polymerization initiated by primary amine. We succeed in synthesizing well-defined α-hydroxyl-ω-aminotelechelic polypeptoids through hydroxyl group-tolerated ROP of NNTA initated by aminoalcohols. The key is to keep hydroxyl group inactive by avoiding forming intra- or inter-molecular hydrogen bonding with amino group. Hydroxyl and amino groups of **AH** and **AD** are confined to contact each other for their long alkyl spacers, which leads to producing pure α-hydroxyl-ω-aminotelechelic polypeptoids in a controlled way with pre-determined MWs and narrow MW distribution through single-site initiation of amino group. In contrast, hydroxyl groups of **AE**, **AP** and **AMB** are partially activated by hydrogen bonding with amino groups, which leads to the initiation of NNTA though they are still less active than amino groups. Thus a mixture of α,ω-diaminotelechelic and α-hydroxyl-ω-aminotelechelic polypeptoids are obtained. We reveal the function of hydroxyl group in amino-initiated NNTA polymerization and provide a simple and effective method to prepare water-soluble polypeptoids with hydroxyl end group within single-step polymerization. NTA monomer show a better tolerance to the hydroxyl group in primary amine-mediated polymerization compared to NCA. It is highly potential for biomedical applications and worthy of deeper investigations.

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