PEG-Amine-Initiated Polymerization of Sarcosine *N*-Thiocarboxyanhydrides toward Novel Double-Hydrophilic PEG-*b*-Polysarcosine Diblock Copolymers

Xinfeng Tao (陶鑫峰, 11029008), Jun Ling, Zhiquan Shen

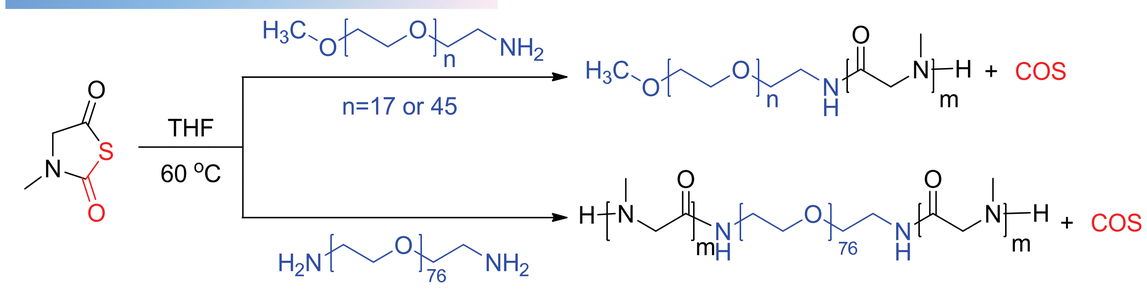
MOE Key Laboratory of Macromolecular Synthesis and Functionalization, Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027

Introduction

Polypeptoids are a class of pseudopeptidic polymers possessing degradable and biocompatible backbone which makes them appropriate for biomedical applications. As an excellent water-soluble polypeptoid, polysarcosine (PSar) is regarded as a competitive alternative of PEG. Among the synthetic methods of polypeptides and polypeptoids, ring opening polymerization (ROP) of amino acid *N*-carboxyanhydride (NCA) is the most widely used one for its high reactivity and productivity. However, all NCAs are very sensitive to moisture and heat and special purification is required before use. Amino acid *N*-thiocarboxyanhydride (NTA), the thioanalog of NCA, is a much more stable monomer first prepared in 1950s. Because of its low reactivity, NTA is usually applied in stepwise synthesis of oligopeptides but rarely in polymerizations. In this work, we design and investigate the controlled ROP of sarcosine NTA (Sar-NTA) with high yield (>90%) using primary amine initiators including methoxy poly(ethylene glycol) amine (mPEG-NH_2). Novel PEG-*b*-PSar copolymers are synthesized for the first time possessing low polydispersity indices (PDIs) (<1.2) and predictable molecular weights (MWs). We investigate properties of PEG-*b*-PSar, especially for the interesting self-assembly behaviors in aqueous and organic solutions.

Results and Discussion

Part I. Polymerization Feature



Scheme 1. Polymerization of sarcosine N-thiocarboxyanhydride (Sar-NTA) initiated by poly(ethylene glycol) amines.

Table 1. Polymerization of Sar-NTA initiated by primary amines[a]

Sample	$[NTA]_0/[NH_2]_0$	Temp. (°C)	Yield (%)	DP_{theo}[b]	Copolymer Composition[c]	M_n[c] (kDa)	M_n[d] (kDa)	PDI[d]
1[e]	20	60	94.1	19	PEG_{17}-*b*-$PSar_{22}$	2.3	4.7	1.12
2[e]	40	60	>99	40	PEG_{17}-*b*-$PSar_{40}$	3.6	6.8	1.15
3[e]	60	60	>99	60	PEG_{17}-*b*-$PSar_{61}$	5.1	7.6	1.18
4[e]	80	60	>99	80	PEG_{17}-*b*-$PSar_{81}$	6.5	8.1	1.20
5[e]	100	60	97.8	98	PEG_{17}-*b*-$PSar_{93}$	7.4	7.8	1.22
6[e]	200	60	88.6	177	PEG_{17}-*b*-$PSar_{162}$	12.3	8.5	1.29
7[f]	40	60	94.1	38	PEG_{45}-*b*-$PSar_{38}$	4.7	7.6	1.19
8[g]	25	60	85.8	21+21	$PSar_{25}$-*b*-PEG_{76}-*b*-$PSar_{25}$	6.9	13.8	1.13
9[h]	100	25	39.2	39	$PSar_{34}$	2.5	3.5	1.13
10[h]	100	60	72.3	72	$PSar_{74}$	5.4	6.1	1.21

[a] Polymerization conditions: $[M]_0$ = 0.4 mol/L, 48 h in THF. [b] Theoretical DP, $DP_{theo}=[NTA]_0/[NH_2]_0\times$Yield. [c] As calculated by ^{1}H NMR analyses. [d] As determined by SEC. [e] As initiated by $mPEG_{17}$-NH_2. [f] As initiated by $mPEG_{45}$-NH_2. [g] As initiated by NH_2-PEG_{76}-NH_2. [h] Polymerization initiated by *n*-hexylamine in dioxane.

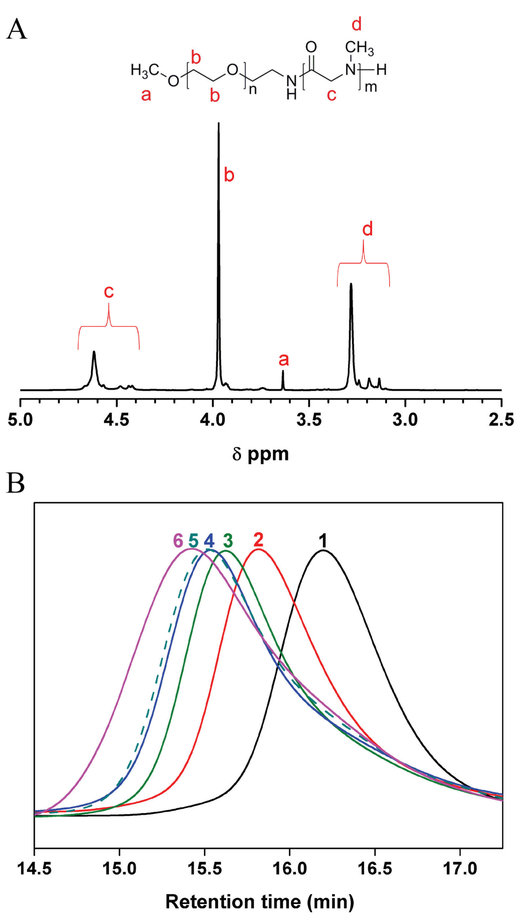


Figure 1. ^{1}H NMR spectrum of **1** in CF_3COOD (A) and SEC traces of **1**-**6** (B).

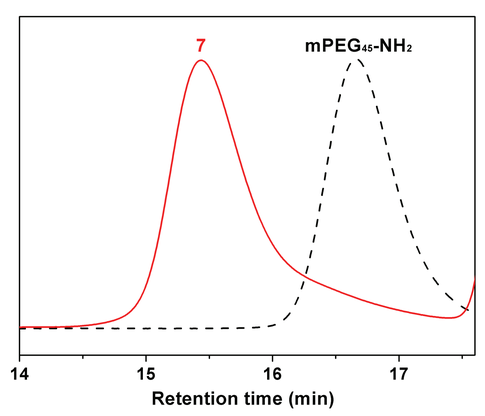


Figure 2. SEC traces of 7, 8, $mPEG_{45}$-NH_2 and NH_2-PEG_{76}-NH_2.

Part II. Emulsions in Aqueous Solution

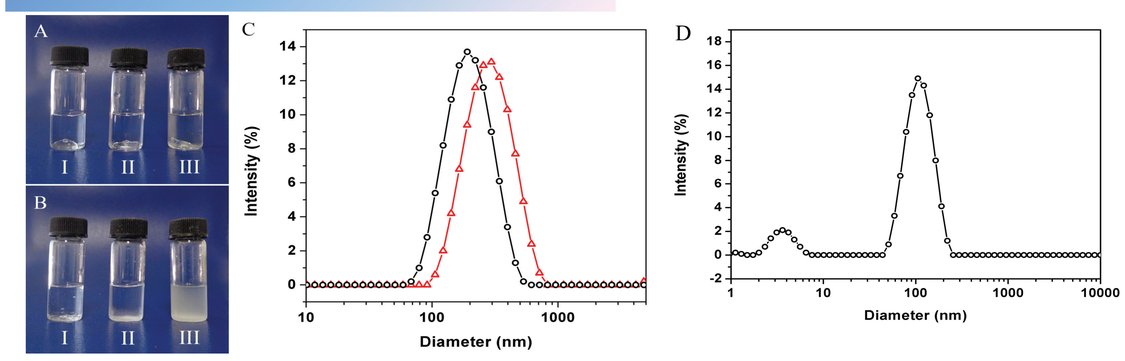


Figure 3. Photographs of mixtures before (A) and after (B) shaking: I) pure water and CH_2Cl_2 (5 vol%); II) aqueous solutions of PEG750 (13.3 mmol/L) and CH_2Cl_2 (5 vol%); III) aqueous solutions of **4** (1.5 mmol/L) and CH_2Cl_2 (5 vol%). DLS profiles of emulsions of **3** (△, 2.0 mmol/L) and **4** (○, 1.5 mmol/L) at 25 °C after shaking and standing for 48 h (C). DLS result of **4** in 1.5 mmol L^{-1} aqueous solution at 25 °C without addition of organic solvent (D).

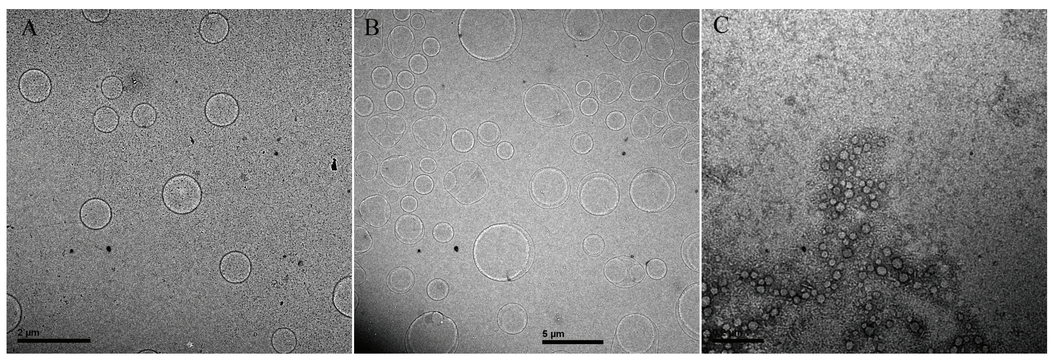


Figure 4. TEM images of emulsions of **4** (A) and **3** (B) at 25 °C after shaking and standing for 48 h at a concentration of 1.5 mmol/L and 2.0 mmol/L, respectively. TEM image of **4** in 1.5 mmol/L aqueous solution at 25 °C without addition of organic solvent (C).

Part III. Self-assembly in Organic Solvents and Encapsulation of Metal Cations

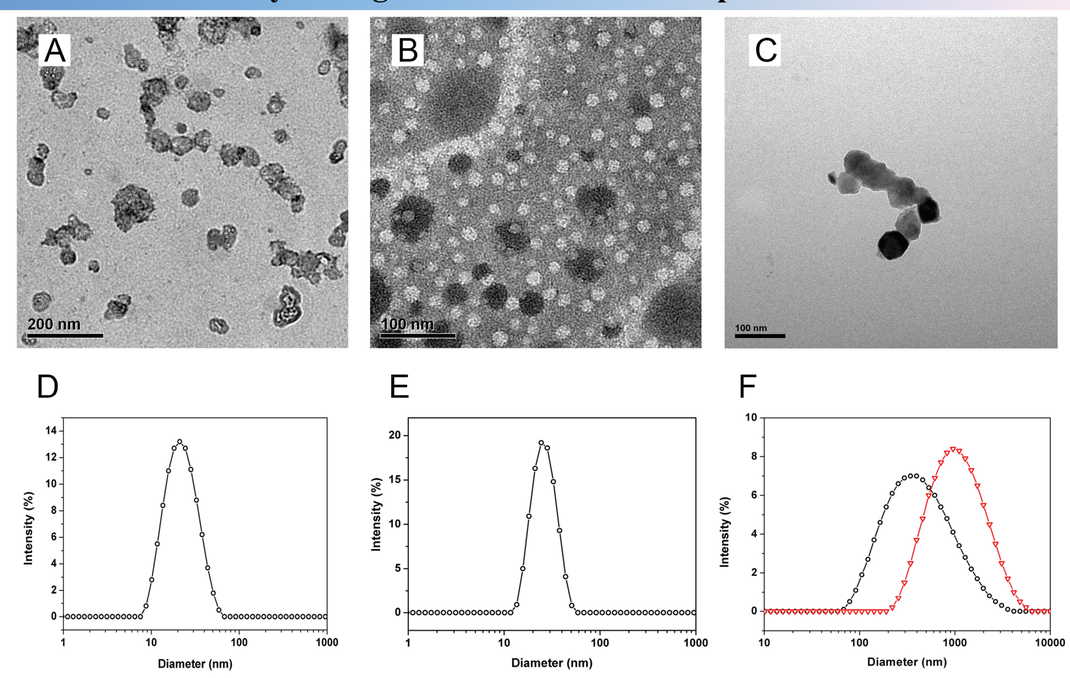
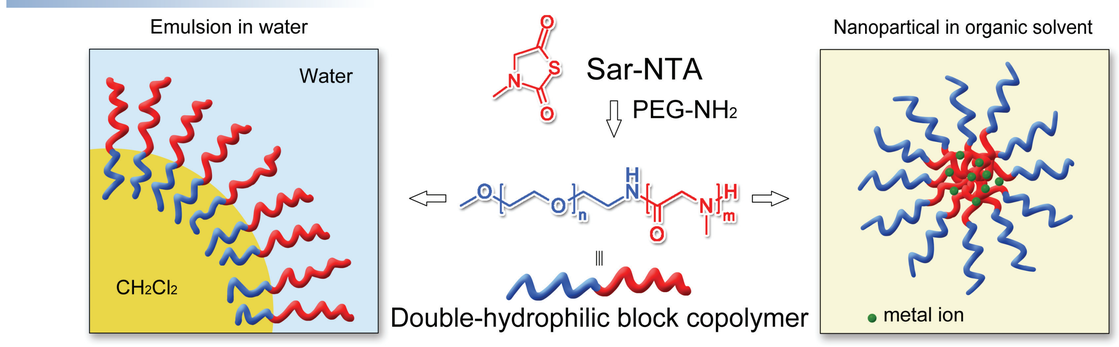


Figure 5. TEM images (A-C) and the corresponding DLS results (D-F) of **7** nanoparticles in dioxane (A and D), ethyl acetate (B and E) and the case encapsulating $Cu(Ac)_2$ in ethyl acetate(C and F (○)) at 0.5 mg/mL at 25 °C, as well as DLS results of **7** nanoparticles encapsulating $Ni(Ac)_2$ in ethyl acetate(F (△)) at 0.5 mg/mL at 25 °C.

Conclusion



We achieve a convenient preparation and a controlled ROP of Sar-NTA to develop a versatile and practical synthetic method to prepare well-defined polyether-polypeptoids. NTA polymerization with quantitative yield is realized by using poly(ethylene glycol) amine initiators. The chain lengths of PSar are designable by setting the feed ratios of monomer to initiator. PEG-*b*-PSar products are novel dual-hydrophilic diblock copolymers and able to emulsify organic droplets in water at nano- and micro-scale. Furthermore, PEG-*b*-PSar also self-assembles into micelles in selected organic solvents with different morphologies, and demonstrates the potential to encapsulate metal cations. PEG-*b*-PSar is totally nontoxic, biocompatible and biodegradable for both segments, which makes it very promising as a new environmental responsive surfactant in food and medical applications. Easily accessible PEG-*b*-PSar polymers as potential biomaterials deserve more detailed investigation.

Acknowledgement

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Reference:

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(2) J. A. Hanson, C. B. Chang, S. M. Graves, Z. B. Li, T. G. Mason, T. J. Deming, *Nature* **2008**, *455*, 85.