Phosgene-free Synthesis of Non-ionic Hydrophilic Polypeptide from Activated Urethane Derivatives of DL-Serine

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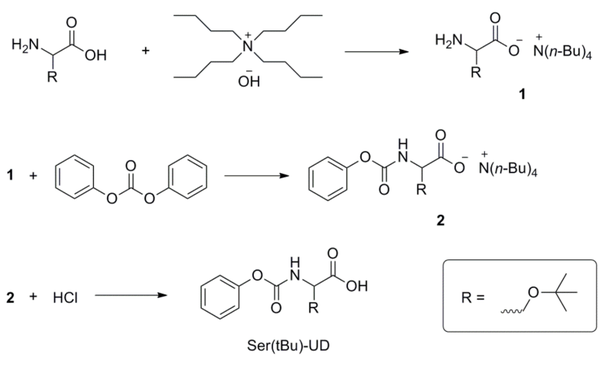
Introduction

A phosgene-free strategy to synthesize non-ionic water-soluble poly-DL-serine (PSer) and its derivatives was described for the first time in this work. An activated urethane-type derivative of α-amino acid (AA-UD), *N*-phenoxycarbonyl-*O*-*tert*-butyl-DL-serine, was synthesized through *N*-carbamylation of onium salt of DL-Ser(*t*Bu) with diphenyl carbonate and served as a precursor of the corresponding *N*-carboxyanhydride (NCA) upon heat in polymerization. The SEC, NMR and MALDI-ToF mass analyses of the resulting polypeptides revealed that the polymerization initiated by primary amine was controllable. The molecular weights of polypeptides were controlled by varying the feed ratio of monomer to initiator. The employment of amine-terminated poly(ethylene glycol) or polysarcosine as initiator resulted in successful syntheses of non-ionic double-hydrophilic diblock copolymers.

Results and Discussion

Part I. Synthesis of Ser(*t*Bu)-UD (monomer)



Scheme 1. Synthesis of Ser(*t*Bu)-UD

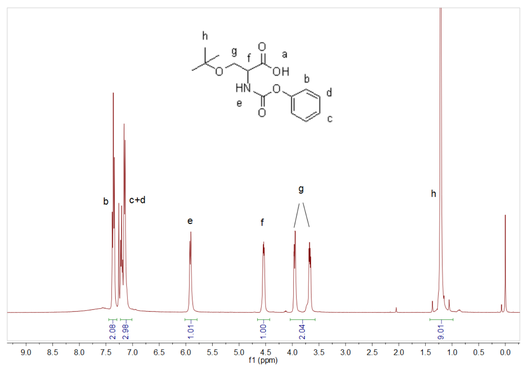
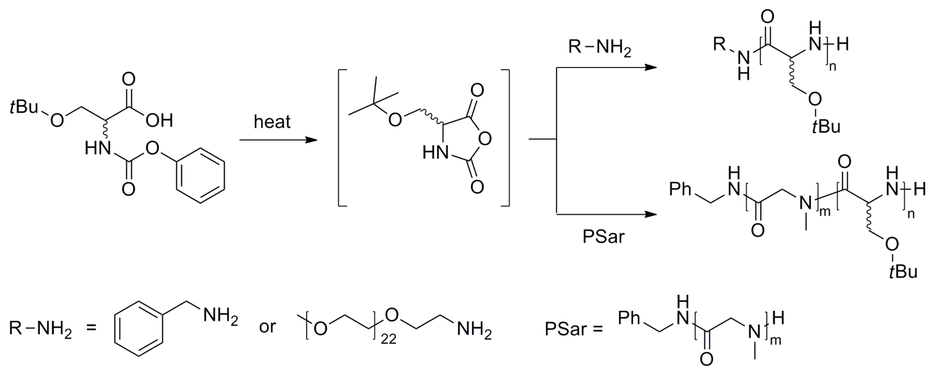


Figure 1. ^{1}H NMR spectrum of Ser(*t*Bu)-UD in $CDCl_3$

Part II. Polymerization of Ser(*t*Bu)-UD



Scheme 2. Polymerization of Ser(*t*Bu)-UD initiated by different initiators.

Table 1. Polymerization of Ser(*t*Bu)-UD

Sample[a)]	[M]/[I]	Initiator	DP[b)]	Yield (%)	$M_{n,\,SEC}$[c)] (kDa)	Đ[c)]
1	25	Benzyl amine	27	78	9.7	1.09
2	50	Benzyl amine	49	72	15.6	1.17
3	100	Benzyl amine	76	79	20.2	1.27
4	25	PEG_{22}-NH_2	34	68	16.9	1.14
5	50	PEG_{22}-NH_2	54	76	21.6	1.18
6	100	PEG_{22}-NH_2	95	70	22.2	1.29
7	75	$PSar_{17}$	70	93	17.6	1.29

a) Polymerization conditions: $[M]_0$ = 1.0 mol L^{-1}, for 48 h;
b) As calculated by ^{1}H NMR analyses;
c) As determined by SEC in HFIP.

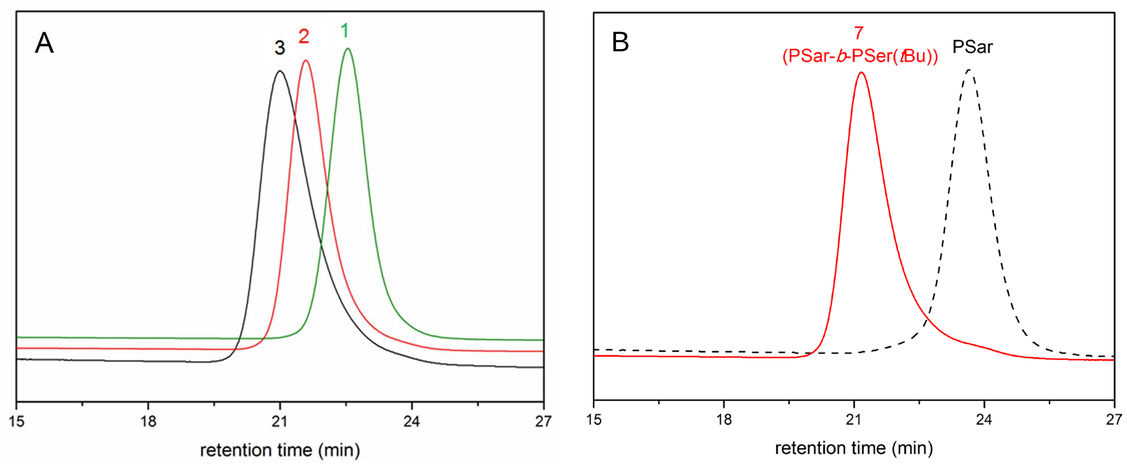
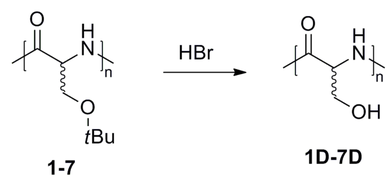


Figure 2. SEC traces of **1**, **2**, **3** (A), **7** and $PSar_{17}$ (B)

Part III. Deprotection and Cytotoxicity Studies



PSer is achieved by deprotection of *tert*-butyl groups on the side chains of PSer(*t*Bu). The resulting PSer is water-soluble without pH limit.

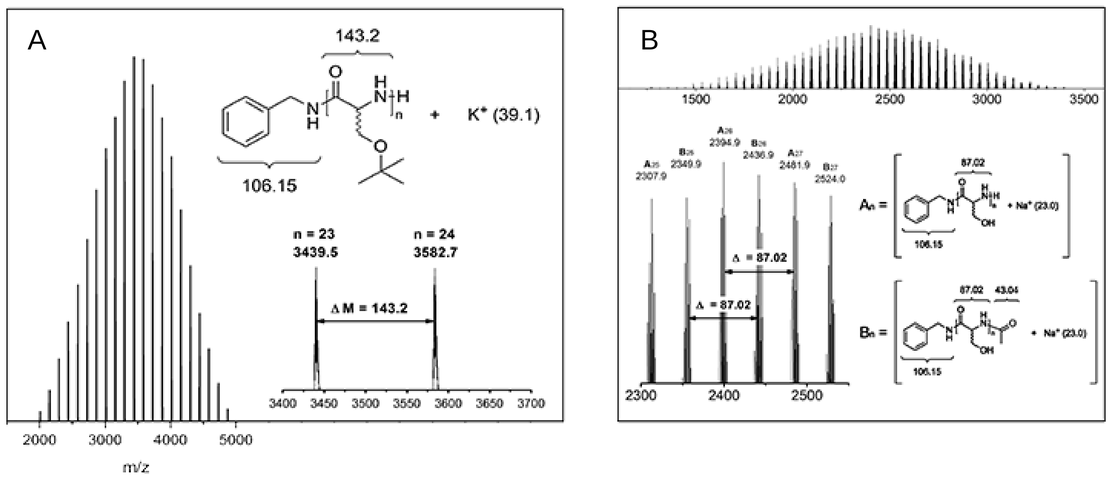


Figure 3. MALDI-ToF mass spectra of sample **1** (A) and **1D** (B)

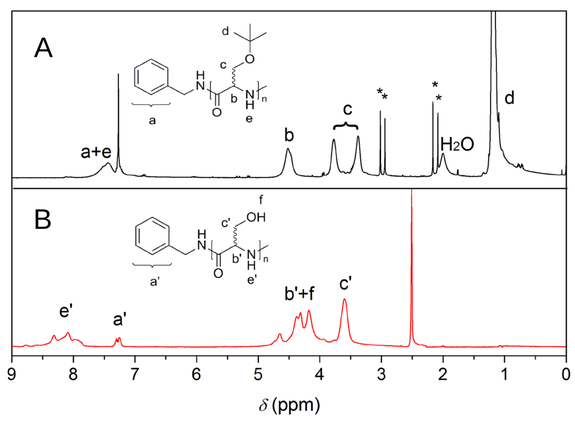


Figure 4. ^{1}H NMR spectra of sample **1** (A) and **1D** (B)

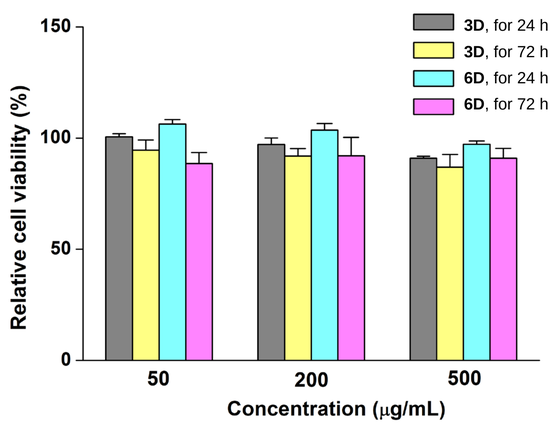


Figure 5. MTT assays of samples **3D** and **6D**.

Conclusion

PSer containing 50-80% L-serine is a novel non-ionic and hydrophilic polypeptide with repeating units of natural α-amino acids. PSer with narrow MW distributions and predetermined DPs can be synthesized via a phosgene-free and easily handling polymerization of Ser(*t*Bu)-UD followed by deprotection. Two double-hydrophilic diblock copolymers, *i.e.* PEG-b-PSer and PSar-*b*-PSer are also prepared. Highly hydrophilic and low toxic properties make PSer a candidate material for biomedical applications.

Acknowledgement

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Reference:

[1] Yamada S, Sudo A,Gotoa M, Endo T. RSC Adv 2014; 4(56): 29890-6.
[2] Tao XF, Deng C, Ling J. Macromol Rapid Commun 2014; 35(9): 875-81.