Polypeptide-Based Hybrid Block Copolymer Synthesis by Ring-Opening Polymerization

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Ring-opening polymerization (ROP) of heterocyclic monomers such as lactones, lactides, epoxides and α-amino acid *N*-carboxyanhydrides (NCAs) is an invaluable tool for the preparation of biocompatible and (bio)degradable polymers in a controlled manner. Since polyesters/polyethers prepared by ROP propagate through hydroxyl group, which is a slow initiating group for ROP of NCAs, the synthesis of polypeptide-based hybrid block copolymers usually requires multi-step reactions. To overcome the issue of slow NCA initiation by the hydroxyl group, we separated the slow initiation from the fast propagation and performed them sequentially instead. The developed method has been successfully applied for the synthesis of block copolymers using hydroxyl-terminated macroinitiators [1] and for the one-pot sequential ROP of cyclic esters or carbonates and NCA, which differ not only in their reactivity but also in the type of the propagating species [2]. While the developed synthetic approach enables the preparation of linear hybrid block copolymers, the synthesis of more complex polymer architectures such as miktoarm stars still requires the use of protecting groups, as the coexistence of different functional groups is unavoidable. We have developed synthetic approaches for the preparation of amphiphilic miktoarm star block copolymers to investigate how the architecture of the block copolymers influences their self-assembly. We have prepared AB_2-type amphiphilic miktoarm stars consisting of one hydrophilic arm (A) and two hydrophobic arms (B) to mimic the structure of lipids. We used a heterofunctional core as a multifunctional initiator to prepare the miktoarm stars. The hydroxyl group of the initiator was used to initiate the ring-opening polymerization (ROP) of trimethylene carbonate (TMC) or propylene oxide (PO) to form the hydrophobic arms B, while the hydrophilic block A was prepared by ROP of sarcosine NCA using the amine group for ROP initiation. To selectively initiate ROP, the amine group of the heterofunctional core was protected with a suitable protecting group. While carbamate-based protecting groups such as Boc and Cbz are compatible with the catalytic systems used for TMC polymerization, the incorporation of primary amine functionality into polyethers is more challenging due to the harsher conditions usually employed for ROP of epoxides. To overcome this challenge, we used a two-component Lewis acid-excess organocatalytic system that triggers efficient anionic ROP of epoxides while preserving the integrity of carbamate protection [3]. Despite the higher intrinsic acidity of the carbamate group compared to the hydroxyl group, it is not competitive in both deprotonation and ring-opening steps. This is due to the acidity-reversing effect of the catalyst, which allows site-specific ethoxylation to proceed exclusively from the hydroxyl group.

References

[1] Gradišar Š., Žagar E., Pahovnik D. Ring-Opening Polymerization of *N*-Carboxyanhydrides Initiated by a Hydroxyl Group. *ACS Macro. Lett.* **2017**, *6*, 637.

[2] Gradišar Š., Žagar E., Pahovnik D. Hybrid block copolymers of polyesters/polycarbonates and polypeptides synthesized via one-pot sequential ring-opening polymerization. *Polym. Chem.* **2018**, *9*, 4764.

[3] Češarek, U.; Liu, L.; Chen, Q.; Wen, T.; Žagar, E.; Zhao, J.; Pahovnik, D. Acidity Reversal Enables Site-Specific Ring-Opening Polymerization of Epoxides from Biprotonic Compounds. *J. Am. Chem. Soc.* **2025**, *6*, 5189-5196.