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Synthesis of Hetero-Grafted Amphiphilic Diblock Molecular Brushes and Their Self-Assembly in Aqueous Medium

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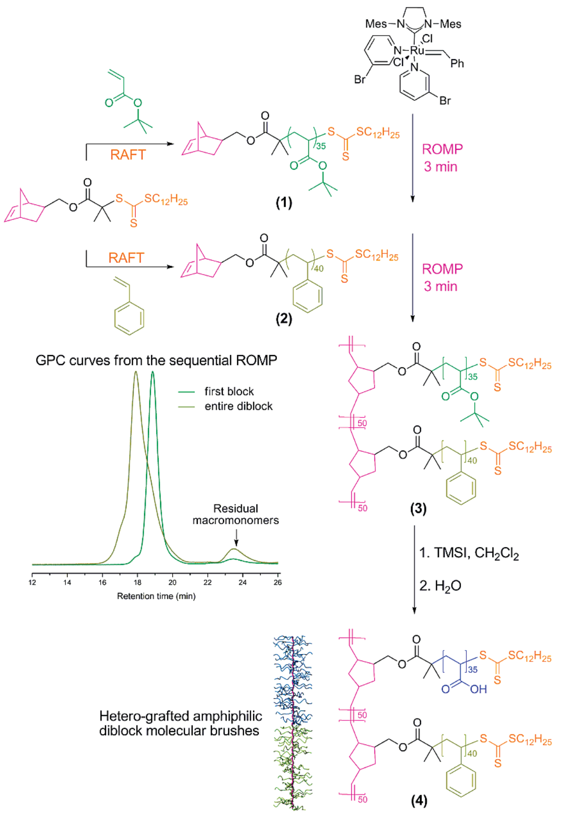
Self-assembly of synthetic macromolecules, inspired by the organization of biomolecules in nature, is a powerful approach for fabricating novel nanostructures, whose potential applications in nanomedicine are of significant interest.[1,2] Using amphiphilic linear copolymers as building blocks, various supramolecular architectures have been constructed, whose compositions, sizes, and morphologies are all tunable.[3−5] In spite of that, those nanostructures, made from synthetic macromolecules, are still primitive compared with those from biomolecules, which exhibit high complexity developed by evolution for millions of years. Our interest to attain nanostructures with higher complexities, approaching those of biological systems, drives our design of more types and sizes of macromolecular and nanoscopic building blocks, extending beyond simple linear block copolymers.

Our initial targets are hetero-grafted diblock molecular brushes,[6,7] in which two different types of polymeric side chains are grafted sequentially along a backbone. These structures are designed as nanoscopic molecular frameworks having defined three-dimensional shape and control over the entire compositional profile, to mimic some features of the globular shape and compositional heterogeneities of protein building blocks. Three strategies are often used to synthesize molecular brushes: "grafting from",[8−11] "grafting onto",[12,13] and "grafting through".[14−18] The first two strategies can afford molecular brushes with relatively long and well-defined backbones. In the synthesis of hetero-grafted diblock molecular brushes,[19−22] for which the block segments of differing compositions are distributed along the primary molecular brush backbone, the "grafting through" strategy has several conveniences and advantages in avoiding many side reactions and providing significant structural control[6] due to the use of presynthesized polymers that are then polymerized to afford the final brush structure. To polymerize the highly diluted chain end groups of the polymers that ultimately become the grafted side chains, ring-opening metathesis polymerization (ROMP) is often applied.[14,15] Herein, by exploiting the orthogonality and livingness of reversible addition−fragmentation chain transfer (RAFT) polymerization[23] and ROMP,[24−26] we have developed a facile and efficient "grafting through" strategy to synthesize hetero-grafted diblock molecular brushes with precisely controlled architecture. These structures were transformed into amphiphilic diblock molecular brushes, which were then investigated as nanoscopic building blocks for the assembly of supramolecular nanostructures in aqueous medium.

Scheme 1. "Grafting Through" Synthetic Route to Hetero-Grafted Amphiphilic Diblock Molecular Brushes by Combined RAFT, ROMP, and Chemical Transformation



The amphiphilic hetero-grafted diblock molecular brush was produced by a highly efficient, one-pot "grafting-through" process, involving the sequential ROMP of norbornenyl-terminated macromonomers, followed by a deprotection reaction (Scheme 1). α-Norbornenyl poly(*tert*-butyl acrylate) (NB-P*t*BA) (**1**) and α-norbornenyl polystyrene (NB-PS) (**2**) macromonomers were first synthesized by selective RAFT polymerizations of *tert*-butyl acrylate and styrene, respectively, from a norbornenyl-functionalized chain transfer agent (NB-CTA).[14] In order to suppress reaction of the NB group, reduce biradical coupling, and control the RAFT polymerizations, moderate temperature (50 °C) and low feed amount of the radical initiator, 2,2-azobis(isobutyronitrile) (AIBN) ($[\text{NB-CTA}]_0/[\text{AIBN}]_0 = 20{:}1$), were employed. The well-defined structures of **1** and **2** were verified by ^{1}H NMR spectroscopy and gel permeation chromatography (GPC). Little to no side reaction of the NB group during the RAFT polymerizations was confirmed by ^{1}H NMR spectroscopy, based on the integral ratio of the NB alkenyl protons (6.02−6.10 ppm) to the RAFT agent chain end $C\boldsymbol{H}_2SC(S)S$ methylene protons (3.33−3.53 ppm) being *ca.* 1:1. As analyzed by GPC, both **1** and **2** had monomodal molecular weight distributions with polydispersities (PDIs) less than 1.12. The number-averaged molecular weights (M_n) calculated from ^{1}H NMR spectroscopy (M_n^{NMR}) agreed well with those from GPC (M_n^{GPC}) (**1**, M_n^{NMR} = 4950 Da, M_n^{GPC} = 4670 Da; **2**, M_n^{NMR} = 4630 Da, M_n^{GPC} = 4560 Da), further supporting the controlled nature of the selective RAFT polymerizations.

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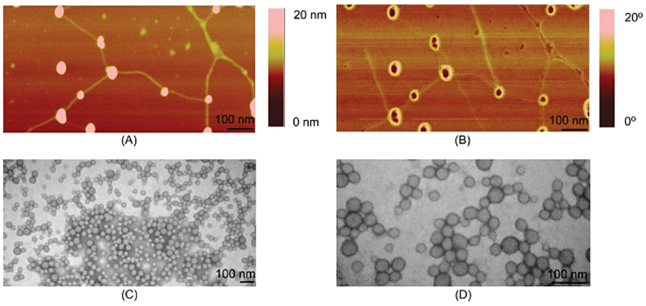

Figure 1. Images of the supramolecular micelles: (A) Tapping-mode AFM height image; (B) Tapping-mode AFM phase image; (C) TEM image (80k×); (D) TEM image (200k×).

These α-norbornenyl-functionalized macromonomers, NB-P*t*BA (**1**) and NB-PS (**2**), were readily used to synthesize hetero-grafted diblock molecular brushes (**3**) by sequential ROMP. We and Grubbs' group[14,15] have reported that the modified second generation Grubbs' catalyst[27] is highly efficient for the synthesis of homo-grafted molecular brushes by ROMP using the "grafting through" strategy. In this study, we further explored the utilization of this Grubbs' catalyst in the sequential ROMP to synthesize heterografted molecular brushes. As shown in Scheme 1, brush copolymer PNB-*g*-P*t*BA was synthesized by ROMP of **1** in CH_2Cl_2. Without purification, a solution of **2** was added into the living PNB-*g*-P*t*BA polymerization mixture to afford the diblock brush copolymer P(NB-*g*-P*t*BA)-*b*-P(NB-*g*-PS), **3**, with regio-selective grafts. During ROMP, small aliquots were withdrawn and measured by GPC. As shown in Scheme 1, nearly quantitative conversions of NB-P*t*BA and NB-PS were observed, with little residual macromonomer at each stage of the ROMP process. The well-defined structures of both PNB-*g*-P*t*BA and P(NB-*g*-P*t*BA)-*b*-P(NB-*g*-PS) were supported by GPC, with monomodal molecular weight distributions and narrow PDIs (<1.20). The successful incorporation of **2** to produce an overall diblock backbone structure is reflected by evolution of the GPC curve after the second ROMP reaction. Synthesis of the diblock molecular brushes was accomplished in 6 min (3 min for growth of each block), indicating the fast and efficient ROMP reactions.[28] The amphiphilic diblock molecular brush P(NB-*g*-PAA)-*b*-P(NB-*g*-PS) (**4**) was obtained after deprotection of **3** with trimethylsilyl iodide (TMSI) and hydrolysis of the intermediate TMS esters.

Supramolecular assembly of the nanoscopic, amphiphilic block graft copolymers was investigated by using phase-segregation micellization methods that are traditional for linear block copolymers.[29] Dissolution of **4** in a common solvent for the entire framework, *N,N*-dimethylformamide (DMF), was followed by dialysis against nanopure water to afford the aqueous micelle solution **5**. The assemblies were characterized by dynamic light scattering (DLS), atomic force microscopy (AFM), and transmission electron microscopy (TEM).

The data from DLS, TEM, and AFM were compared and contrasted to evaluate the nature of the supramolecular structures **5**, from the aqueous assembly of **4**. The number-averaged hydrodynamic diameter ($D_{\mathrm{h,n}}$) of **5** was 48 $\pm$ 5 nm according to DLS. Similarly sized aggregates of globular shape were observed by both TEM and tapping-mode AFM. The TEM diameter of **5** was measured as 43 $\pm$ 7 nm; the unimers **4** were not observed well. By AFM, however, two populations were observed from spin-coating of an aqueous solution of **5** onto mica: an aggregate having an average diameter (D_{AFM}) of 73 $\pm$ 8 nm (not corrected for tip-broadening effects) and average height of 28 $\pm$ 8 nm, together with what appeared to be unimers having an average diameter of 47 $\pm$ 5 nm and average height of 1.9 $\pm$ 0.4 nm. The average diameter and height of unimers, obtained by spin-coating a DMF solution of **4** onto mica, were 53 $\pm$ 5 and 1.6 $\pm$ 0.3 nm (Figure S2), respectively. Taking into account the diameter as measured by TEM and the height as measured by AFM, the supramolecular assemblies underwent only low degrees of shape deformation upon adsorption onto the solid substrates. If it is assumed that the AFM tip diameter is the difference between the TEM- and AFM-measured diameters, *ca.* 30 nm, then the diameter of the unimers was *ca.* 20 nm, giving an aggregation number of *ca.* 60 of **4** within the assembled structures **5**. This aggregation number is smaller than that of micelles typically from linear amphiphilic copolymers (usually a few hundred[29]). It should be noted that both AFM and TEM showed that **5** had a broad size distribution, which may be explained by the large size of the building blocks relative to the assembled structure.

In summary, we have demonstrated the synthesis of hetero-grafted diblock molecular brushes via a "grafting through" strategy, based on the orthogonality of ROMP and RAFT polymerizations. These diblock molecular brushes were converted to amphiphilic nanostructures, whose aqueous solution self-assembly behaviors were studied. Further work ongoing in our group and the laboratory of Robert H. Grubbs (we acknowledge clever designs of block brush copolymers under study by Grubbs' group[30]) is expected to lead to advanced macromolecular-based building blocks that are capable of hierarchical supramolecular assembly into complex, functional nano- and microscopic objects.

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Supporting Information Available: Detailed synthetic procedure, spectral data, and DLS and AFM results. This material is available free of charge via Internet at http://pubs.acs.org.

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