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High-Efficiency Preparation of Macrocyclic Diblock Copolymers via Selective Click Reaction in Micellar Media

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Their unique "endless" topology endows cyclic polymers with distinctly different physical properties in solution and bulk as compared to their linear counterparts. In the past few decades, a variety of synthetic strategies have been explored for the preparation of cyclic polymers, such as intramolecular ring closure of linear precursors,[1] lactone ring expansion,[2a−c] and ring-opening metathesis polymerization from cyclic ruthenium catalysts.[2d] In terms of controllable ring sizes and a rich choice of monomer species, the cyclization of α,ω-difunctional linear precursors has emerged to be the most popular approach. Grayson et al.[3a,b] reported the quantitative synthesis of cyclic polystyrene via intramolecular ring closure by "click" chemistry, taking advantage of its high coupling efficiency.[3c,d] Just recently, Deffieux et al.[4] reported the synthesis of high molar mass cyclic polymers employing linear ABC triblock precursors possessing multiple reactive sites along the short A and C blocks. However, these intramolecular cyclization reactions typically need to be conducted at high dilution (<0.1 g/L) to avoid interchain coupling, though this situation has been much improved by the slow-addition technique.[1]

Herein, we report an alternate strategy for the high-efficiency preparation of cyclic diblock copolymers via the combination of supramolecular self-assembly and "selective" click reaction (Figure 1a), taking advantage of the unimer−micelle exchange equilibrium.[5] Within self-assembled aggregates, reactive alkynyl and azide groups are spatially separated, and intramolecular click reactions occur exclusively for unimers, the concentration of which is well-known to be the critical micellization concentration (CMC). This leads to the facile preparation of cyclic diblock copolymers from linear precursors at relatively high concentration.

α-Alkynyl-ω-azidoheterodifunctionalpoly(2-(2-methoxy-ethoxy)-ethyl methacrylate)-*b*-poly(oligo(ethylene glycol) methyl ether methacrylate), *linear*-$PMEO_2MA$-*b*-POEGMA-N_3, was synthesized via the azidation of alkynyl-terminated $PMEO_2MA$-*b*-POEGMA-*Br* prepared via successive atom transfer radical polymerization (Scheme S1). Three α-alkynyl-ω-azido linear precursors were prepared, and their end group functionalities were determined to be in the range 0.90−0.94 (Scheme S2, Figures S1−S6, and Table S1).

linear-$PMEO_2MA$-*b*-POEGMA-N_3 behaves as a typical stimuli-responsive double hydrophilic block copolymer (DHBC).[6] It molecularly dissolves in aqueous solution at room temperature and spontaneously self-assembles into micelles consisting of $PMEO_2MA$ cores and well-solvated POEGMA coronas at elevated temperatures (Table S1). Dynamic laser light scattering (LLS) reveals an average hydrodynamic radius, $\langle R_h \rangle$, of ∼34 nm at 40 °C for *linear*-$PMEO_2MA_{35}$-*b*-$POEGMA_{12}$-N_3 (Figure 2). The CMC value was determined to be 1.02×10^{-2} g/L by the probe fluorescence technique (Figure S7). It is noteworthy that, in $PMEO_2MA$-core micelles, terminal alkynyl and azide groups are located at the core and corona surface, respectively.[6] We can safely speculate that reactive terminal alkynyl and azide moieties are apart from each other and click reactions within micelles will not occur (Figure 1a). On the other hand, it is quite expected that intramolecular click reactions can proceed unhindered for unimer chains.

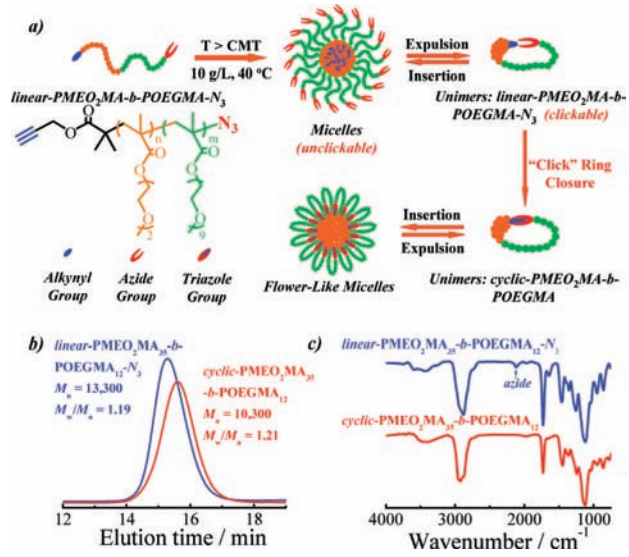

Figure 1. (a) Schematic illustration for the high-efficiency preparation of macrocyclic diblock copolymers via the combination of supramolecular self-assembly and "selective" intramolecular "click" ring closure. (b) THF GPC traces and (c) FT-IR spectra recorded for *linear*-$PMEO_2MA_{35}$-*b*-$POEGMA_{12}$-N_3 and *cyclic*-$PMEO_2MA_{35}$-*b*-$POEGMA_{12}$.

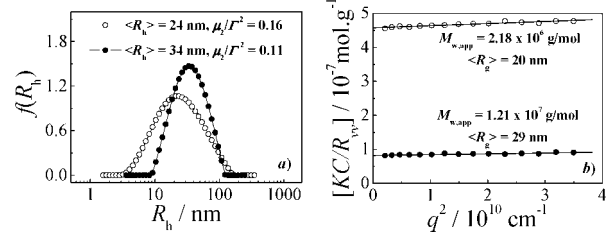

Figure 2. (a) Typical hydrodynamic radius distributions, $f(R_h)$, and (b) angular dependence of the Rayleigh ratio, $R_{vv}(q)$, obtained for micelles of *linear*-$PMEO_2MA_{35}$-*b*-$POEGMA_{12}$-N_3 (●) and *cyclic*-$PMEO_2MA_{35}$-*b*-$POEGMA_{12}$ (○) in aqueous solutions at 40 °C.

The click reaction in aqueous micellar media was conducted at 40 °C for 24 h in the presence of $CuSO_4$ and sodium ascorbate.

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The polymer concentration (10 g/L) was much higher than that typically employed in intramolecular cyclization reactions of heterodifunctional linear precursors.[1] A combination of FT-IR, ^{1}H NMR, and GPC verified the successful intramolecular cyclization reaction. Figure 1c shows FT-IR spectra of *linear*-$PMEO_2MA_{35}$-*b*-$POEGMA_{12}$-N_3 and *cyclic*-$PMEO_2MA_{35}$-*b*-$POEGMA_{12}$. After the click reaction, the characteristic azide absorbance peak at ~2100 cm^{-1} completely disappeared. ^{1}H NMR spectra revealed a new signal at $\delta = 7.8$ ppm after the click reaction, indicating the presence of 1,2,3-triazole linkage. The methylene proton signal shifted from 4.6 ppm in the linear precursor to 5.2 ppm in the cyclic one (Figure S8). Thus, both FT-IR and ^{1}H NMR results confirmed the efficient click reaction of terminal functionalities.[3]

Compared to linear chains, cyclic chains possess a much smaller hydrodynamic volume in solution, i.e., intramolecular cyclization leads to a more compact conformation.[1] Figure 1b shows the GPC trace of *cyclic*-$PMEO_2MA_{35}$-*b*-$POEGMA_{12}$, which is clearly shifted to the lower molecular weight side compared to that of the linear precursor. It should be noted that both elution peaks were relatively symmetric, giving an M_n of 10.3 kDa and an M_w/M_n of 1.21 for the cyclic product. In addition, we did not observe any higher MW peaks resulting from interchain coupling reactions, suggesting that click reaction occurred intramolecularly. The "selective" click reactions of two other linear precursors under micellar conditions were also conducted, and the results are summarized in Table S1.

The ratio of the apparent peak molar masses ($M_{p,c}/M_{p,l}$), denoted as $\langle G \rangle$, derived from GPC traces of cyclic, and precursor polymers can reflect the cyclization efficiency.[1f−k] For the three macrocyclic $PMEO_2MA$-*b*-POEGMA diblocks, $\langle G \rangle$ values are in the range 0.74−0.77 (see Table S1 and detailed discussion in the Supporting Information), which agrees reasonably well with those reported for other cyclic vinyl polymers (0.70−0.97).[1] Based on the above results, we conclude that linear precursors have been completely transformed into macrocyclic polymers via click reaction in micellar media. We thus established for the first time that "clean" intramolecular cyclization of heterodifunctional precursors can be conducted at a relatively high concentration.

We also investigated the intramolecular cyclization of α-alkynyl-ω-azido heterodifunctional poly(2-(dimethylamino)-ethyl methacrylate)-*b*-poly(2-(diethylamino)ethyl methacrylate), *linear*-PDMA-*b*-PDEA-N_3, which undergoes pH-responsive micellization in aqueous solution (Scheme S3).[6] In this case, the end group functionality of *linear*-PDMA-*b*-PDEA-N_3 precursor was determined to be 0.8 (Scheme S4, Figure S9). ^{1}H NMR, GPC, FT-IR, and MALDI-TOF again confirmed the successful intramolecular "click" cyclization under micellar conditions (pH 9) at a concentration of 10 g/L (Figures S10−S12). However, due to the presence of ~20% unfunctionalized linear precursors, the $\langle G \rangle$ value determined for *cyclic*-PDMA-*b*-PDEA (0.81) was relatively high compared to literature values.[1]

The successful application of the "click cyclization in micellar media" principle to two different systems described above can be rationalized as follows. First, under click conditions, most of the chains exist in micellar assemblies, and we speculate that within micelles click reactions cannot occur due to spatial separation between reactive groups (Figure 1). On the other hand, click cyclization can occur exclusively for unimers, and its low concentration (CMC) ensures that the reaction proceeds intramolecularly. Second, unimer chains adopt a "tadpole" conformation with an inner collapsed core (of insoluble block) stabilized by the well-solvated block to minimize the Gibbs free energy.[7] The partial burial of one type of reactive terminal groups within unimers can effectively preclude their click reaction with complementary reactive groups of neighboring unimers in bulk solution and those at the corona surface or core−shell interface within micelles. Finally, due to presence of the dynamic unimer−micelle exchange equilibrium,[5] all linear precursors will eventually undergo intramolecular cyclization.

The aggregation properties of cyclic polymers can differ significantly from those of their linear counterparts.[8] It was found that macrocyclic diblock copolymers, *cyclic*-$PMEO_2MA$-*b*-POEGMA and *cyclic*-PDMA-*b*-PDEA, possess higher CMC values, smaller $\langle R_h \rangle$, and lower average aggregation numbers (N_{agg}) in self-assembled micelles, as compared to their linear precursors (Figures 2, S7, and S13−S14).

In summary, the high efficiency synthesis of water-soluble cyclic diblock copolymers has been achieved via "selective" click reaction in aqueous micellar solutions of α,ω-heterodifunctional linear precursors at a relatively high concentration, which relies on controlling the spatial accessibility between terminal reactive groups within micellar entities and the "tadpole" conformation of unimers. We expect that this novel strategy can be generalized to the synthesis of macrocyclic polymers with more complex architectures from self-assembled nanostructures of a higher level of hierarchy.

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Supporting Information Available: Experimental details and spectroscopic/analytical data of ^{1}H NMR, FT-IR, MALDI-TOF MS, and fluorescence measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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