

A High-Efficiency Strategy for Synthesizing Cyclic Polymers of Methacryates in One Pot

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An unprecedented strategy for the high-efficiency preparation of the cyclic polymers is developed. In this strategy, the atom transfer radical polymerization, the substitution of chain-end halide by azide group and Cu-catalyzed alkyne—azide cyclization, i.e., the frequently used three separated steps for the preparation of cyclic polymers, are integrated into a one-pot reaction

by the introduction of a "regulator". The kernel of this novel strategy is the utilization of the different rates between the competitive ATRP propagation and $S_N 2$ substitution of a tertiary-carbon halogen and secondary-carbon halogen. 0.55 g (yield = 59%) cyclic poly(methyl methacrylate) is obtained from 3.0 mL reaction solution. This work proposed a high-efficiency and bright promising strategy for the preparation of cyclic polymer, which would evoke more research interests on cyclic polymer.

1. Introduction

Cyclic polymers display some unique physical properties in contrast to linear polymers from their "endless" topology, such as a smaller hydrodynamic volume, reduced viscosity, larger refractive index, and higher glass transition temperature. As a consequence, the stark differences in the cyclic polymer properties have supported certain novel and improved functions in drug delivery, liquid crystals, self-assembly behavior, optoelectronics, among others.^[1-8] Among the diverse approaches for synthesizing cyclic polymers,^[9–19] the intramolecular Cu(I)catalyzed azide–alkyne cycloaddition (CuAAC) cyclization

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"click" reaction for a linear polymer with α -alkyne/ ω azide chain ends has frequently been used because its "click" or effective character produces, for example, highly efficient and quantitative yields. In preparing α -alkyne/ ω azide linear polymers, atom transfer radical polymerization (ATRP) initiated by an alkyne-bearing initiator is the preferred choice given its facile conversion of the terminal halogen to an azide group (using "substitution" in this context).^[20-23] Laurent and Grayson^[24] first reported near-quantitative yields of cyclic polystyrene from the α -alkyne- ω -azide linear precursor through ATRP/substitution/CuAAC "click" cyclization in 2006. Subsequent work demonstrated that ATRP/substitution/CuAAC "click" cyclization could be considered an effective methodology for preparing cyclic polymers given its wide range of available monomers as well as well-controlled architectures and molecular weights.^[25-32]

In general, three tandem steps for the ATRP/substitution/CuAAC cyclization reaction are conducted separately. Moreover, the intramolecular CuAAC cyclization reaction must proceed in a highly dilute solution to avoid intermolecular reactions. These tedious operation procedures and the highly dilute conditions dramatically reduce



Scheme 1. Illustration of different rates between the competitive ATRP propagation and substitution of a terminal-carbon (tertiary or secondary) halogen.

efficiency and output for cyclic polymers,[33] which has become the primary obstacle in the extensive research on and applications for cyclic polymers. Scientists have devoted great efforts and made much progresse on this issue. Monteiro et al.^[33] elegantly conducted CuAAC cyclization from a α -alkyne- ω -azide linear polystyrene at a high concentration (1.85×10^{-3} M) under the Jacobson-Stockmayer theory. Liu and co-workers^[34] successfully generated cyclic block copolymers from α -alkyne- ω -azide linear precursors at a relatively high concentration (7.5 \times 10⁻⁴ м, 0.86 g cyclic polymers in one batch) via a combination of supramolecular self-assembly and "selective click" cyclization. The output from cyclic block copolymers was improved from dozens to hundreds of milligrams; however, limited monomers are accessible using Liu's strategy. Hence, despite these progresses, the low-efficiency in cyclic polymer preparation has not been greatly improved, and the pursuit of a high-efficiency preparation has not ended.

Herein, we report a novel methodology for high-efficiency preparation of cyclic polymers, which integrates three steps for ATRP/substitution/CuAAC cyclization into a one-pot reaction. It is well known that ATRP is initiated by alkyl halides through catalysis of the Cu(I)/ligand, which is also the catalyst for the CuAAC "click" reaction. Certain publications have reported simultaneous ATRP and CuAAC "click" post-modification in one pot.^[35–37] However, to realize one-pot ATRP/substitution/CuAAC "click" cyclization, the challenge is simultaneous conversion of a terminal halogen group to an azide group with a reasonable polymer chain length and maintaining an extremely low concentration of α -alkyne/ ω -azide linear polymer. In this work, a "regulator," that takes advantage of the different rates between competitive ATRP propagation and the bimolecular nucleophilic substitution reaction $(S_N 2)$ of a terminal carbon (tertiary or secondary) halogen, is proposed in a one-pot strategy for high-efficiency cyclic polymers preparations.

2. Experimental Section

Details of the materials used, syntheses, and analysis and characterization methods are provided in the Supporting Information.

3. Results and Discussion

In a nonpolar solvent, the S_N^2 rate for a tertiary-carbon halogen can be much lower than that a secondary-carbon halogen (~1/500).^[38,39] The halogen attached at the terminal carbon of a polymer chain should also be amenable to this criterion. For ATRP of a 1-monosubstituted vinyl compound, as shown in Scheme 1, because the terminal halogen is attached to a secondary carbon, the radical addition rate (r_2) of the secondary carbon is expected to be much lower than the S_N^2 substitution rate (r_1) in the presence of a nucleophilic agent, NaN₃. S_N2 substitution is preferred in generating an azide-terminal chain end, which ceases polymerization. For ATRP of a 1,1-disubstituted vinyl monomer, the terminal halogen is attached to a tertiary carbon; the propagation rate (r_4) is expected to be much higher than the S_N^2 substitution rate (r_3); and the polymerization should proceed in a well-controlled manner with negligible S_N^2 reactions. Thus, when small amounts of 1-monosubstituted vinyl monomer with a proper reactivity ratio are added to ATRP in a 1,1-disubstituted vinyl monomer, polymerization likely proceeds at a reasonable rate for an early stage due to a high molar ratio of 1,1-disubstituted vinyl monomer to 1-monosubstituted vinyl monomer and beacuse $r_4 >> r_3$. During polymerization, the 1,1-disubstituted vinyl monomer is progressively consumed, and the polymer chains are expected to gradually attach to the 1-monosubstituted vinyl monomer. When the polymer chain is attached by one 1-monosubstituted vinyl monomer unit (i.e., the terminal tertiary carbon is converted to the secondary carbon), the S_N^2 substitution





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Figure 1. Evolution of conversion with reaction time of the MMA polymerization under different experimental conditions. (\bullet) [MMA]_o/[PBMP]_o/[CuBr]_o/[PMDETA]_o = 100/1/1/3; (\Box) [MMA]_o/[PBMP]_o/[NaN₃]_o/[CuBr]_o/[PMDETA]_o = 100/1/1.2/1/3; (\bullet) [MMA]_o/[AN]_o/[PBMP]_o/[NaN₃]_o/[CuBr]_o/[PMDETA]_o = 100/2/1/1.2/1/3. MMA = 1.0 mL, anisole = 2.0 mL, 60 °C.

of halogen by an azide group proceeds spontaneously because $r_1 >> r_2$. Thus, simultaneous ATRP and conversion of the halogen end-group to an azide group are realized. The supposed different rates between competitive ATRP propagation and substitution of a tertiary or secondary carbonhalogen are illustrated in Scheme 1.

To validate the assumptions that $r_4 >> r_3$ and $r_1 >> r_2$ in Scheme 1 for a real ATRP and substitution system, control experiments with ATRP in anisole (a nonpolar solvent for nucleophilic substitution reaction^[38,39]) were conducted either with or without NaN₃. Methyl methacrylate (MMA) was selected as the 1,1-disubstituted vinyl monomer. CuBr and pentamethyldiethylenetriamine (PMDETA) were used in the catalyst system. Propargyl 2-bromo-2-methylpropanoate (PBMP) was used as the alkyne group-bearing ATRP initiator. As shown in Figure 1, ATRP polymerization of MMA with NaN_3 (\Box) produces a similar polymerization profile as in the absence of NaN_3 (\bullet), which indicates that $S_N 2$ substitution of the tertiary carbon-attached halogen is negligible, and r_4 is much larger than r_3 as supposed in Scheme 1. The control experiments for ATRP of acrylonitrile (AN), which is a 1-monosubstituted vinyl monomer, were also investigated under identical conditions. The polymerization reaction did not produce a polymer because the chain-end halogen was rapidly and quantitatively converted to an inactive azide group, which verified that r_1 (S_N2 substitution rate) is much higher than r_2 (ATRP propagation rate) for a secondary-carbon halogen.

Where simultaneous ATRP and substitution of the terminal halogen by an azide group are realized, the subsequent CuAAC reaction is expected to proceed readily in

a "click" or an "efficient linking" manner.^[40] However, to guarantee an intramolecular end-to-end CuAAC reaction, a low loading molar ratio for a 1-monosubstituted vinyl monomer to 1,1-disubstituted vinyl monomer should be utilized for an extremely low concentration of the linear precursor polymer. Based on these assumptions and the primary results, the suggested one-pot ATRP/substitution/ CuAAC cyclization of a 1,1-disubstituted vinyl monomer should proceed by utilizing a 1-monosubstituted vinyl monomer as a "regulator." In this work, MMA was selected as the model monomer for methacrylates and AN as the "regulator." Initially, MMA, AN, PBMP, NaN₃, and CuBr/PMDETA at [MMA]₀/[AN]₀/[PBMP]₀/[NaN₃]₀/ $[CuBr]_0/[PMDETA]_0 = 100/2/1/1.2/1/3$ were added to an ampoule, and a typical ATRP procedure was followed. The evolution of conversion with reaction time was monitored as shown in Figure 1 (\blacksquare). In general, the polymerization reaction produced fewer conversions compared with the control experiments without AN (\Box). Within 123 h, the conversion was approximately 65%. Additional reactions did not increase the monomer conversion. Before 65% conversion, the probability of MMA propagation was much higher than AN propagation given the much higher feed ratio and higher reactivity ratio for MMA to AN. During this period, the MMA monomer was consumed gradually, which resulted in a progressively higher probability of polymeric radical addition to AN. The tertiary-carbon Br was gradually converted to secondary-carbon Br during polymerization. When the conversion reachen approximately 65%, a large proportion of the MMA monomer was consumed, and the probability of polymeric radical addition to AN remarkably increased, (i.e., most of the tertiarycarbon Br was converted to a secondary-carbon Br). As discussed above, subsequent $S_N 2$ substitution of the secondary-carbon Br was rapid and produced an azide endcapped polymer chain. As a result, polymerization and propagation ceased after 123 h. Given the gradual conversion of a tertiary carbon-Br to a secondary carbon-Br, the instant concentration of the α -alkyne/ ω -azide linear PMMA was maintained at a low level, which ensured intramolecular end-to-end ring closure in generating cyclic polymers. Therefore, most polymers produced at 123 h (65% conversion) or thereafter are likely non-Br endcapped polymers, (i.e., azide- terminal linear polymer or cyclic polymer or both). To verify this assumption, the polymers generated at 96 h (sample b) and 123 h (sample a) in Figure 1 was used as the macroinitiators for a chain extension reaction. Most of the polymers produced at 96 hrs should be linear polymer end-capped by Br, which are extended after adding fresh monomer; whereas, polymers at 123 hrs should be azide-terminal linear polymers or cyclic polymers or a mixture of both, which were inactive and cannot undergo chain extension. The results in Figure S1 (Supporting Information) and Figure S2







Figure 2. The SEC trace and ¹H NMR spectrum of the *Cycli*-PMMA obtained *via* the one-pot strategy. $\overline{M}_{n,SEC} = 16$ 600 g mol⁻¹, $\overline{M}_w/\overline{M}_n = 1.13$. [MMA]_o/[AN]_o/[PBMP]_o/[NaN₃]_o/[CuBr]_o/ [PMDETA]_o = 100/2/1/1.2/1/3, 168 h.

(Supporting Information) validated, respectively, the above assumptions, thus the one-pot ATRP/Substitution/ CuAAC cyclization reaction should be feasible.

To generate the cyclic polymers at a high purity, the reaction time was extended to 168 h (sample c), the sample was then subjected to SEC, FT-IR, and ¹H NMR measurements to test the validity of this strategy. The SEC trace showed a unimodal and symmetric shape with relatively narrow molecular weight distributions $(\overline{M}_w/\overline{M}_n = 1.13)$ (Figure 2), which implies that polymerization was wellcontrolled. Proton signals for the triazole (7.60–7.66 ppm) were detected in the ¹H NMR spectra for the cyclic PMMA (Figure 2), which is convincing evidence of the CuAAC "click" reaction. FT-IR spectroscopy (Figure S3, Supporting Information) indicated that within 168 h of reaction, the terminal azide signals (2100 cm⁻¹) and alkynyl signals (3290 cm⁻¹) were undetectable, which implies that most of the CuAAC reactions were an intramolecular cyclization, and most of the polymers were cyclic with high purity. The matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) (Figure S4, Supporting Information) were convincing evidence for polymer composition, which indicates that S_N2 substitution of the tertiary carbon–bromine can also proceed to a certain extent with production of certain cyclic PMMA fractions that have no terminal AN unit. Control experiments showed that when the AN feed ratio is increased, a dramatic decreases in both polymerization rate and molecular weight were observed (Figure S5, Supporting Information). These results imply that the molecular weights of cyclic polymers via the one-pot strategy could also be tuned by adjusting the molar ratio of AN/MMA. This result showed that the "regulator" AN is a dominating factor in effective intramolecular cyclization. The above evidence demonstrates that the proposed one-pot strategy was successful in synthesizing cyclic methacrylates polymers. The mechanism is illustrated in Scheme 2. It is notable that in this process, selection of a workable regulator is pivotal, because it should integrate the three steps ATRP, substitution of a terminal Br with an azide, and CuAAC intramolecular cyclization in a simultaneous process. The accessible regulator should tolerate the chemical environments for the processes and have a proper polymerization reactivity to monomer ratio, which ensures that a polymer chain is attached at a reasonable polymer chain length. Except for AN, certain some other 1-substituted vinyl compounds (e.g., propenyl alcohol) can also be used as a "regulator" in the one-pot strategy.

The highest reported concentration of a linear α -alkynyl- ω -azido homopolymer for intramolecular CuAAC cyclization is 1.85×10^{-3} m.^[31] The concentration of the cyclic polymers herein were calculated at 1.1 imes10⁻² м. Further, 0.55 g of cyclic -PMMA was produced from 3.0 mL of the reaction solution without further purification (yield = 59%), and the cyclic-PMMA was highly reproducible (Table S1, Supporting Information). In theory, this one-pot strategy should be applicable to preparing cyclic polymers for all methacrylate-based monomers. To confirm the universality, a methacrylate monomer with an azobenzene-bearing group (e.g., (4-(4'-methoxyl azophenyl) methacrylate (AzoMA))) was used as the monomer under similar conditions. In addition, 0.44 g of cyclic-PAzoMA ($\overline{M}_{n,SEC} = 2300$, $\overline{M}_w/\overline{M}_n = 1.07$, yield = 64%) was generated, which was verified by SEC, IR, and ¹H NMR as shown in Figures S6, S7, and S8, respectively. Moreover, the much higher glass transition temperatures (T_{σ}) for the cyclic-PAzoMA (106.2 °C) comoared with linear-PAzoMA produced by the control experiments ($\overline{M}_{n,SEC}$ = 2000, $\overline{M}_{\rm w}/\overline{M}_{\rm n}$ = 1.15, $T_{\rm g}$ = 87.1 °C) confirmed successful preparation of the cyclic polymers.

4. Conclusion

An unprecedented strategy for the high-efficiency preparation of methacrylate cyclic polymers was developed, wherein three separate steps that are typically used in conventional cyclizations (i.e., ATRP, substitution of halogen by azide, and CuAAC intramolecular cyclization) was integrated into one step in one pot. Methacrylate cyclic polymers (e.g., 0.55 g of cyclic PMMA and 0.44 g of cyclic-PAzoMA bearing-azobenzene groups) were generated from 3.0 mL of a reaction solution. A "regulator" is crucial for success in this strategy, which facilitates effective synthesis of a methacrylate cyclic polymer by utilizing different rates





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Scheme 2. Schematic illustration of the one-pot strategy for preparation of cyclic polymers of methacrylates.

between competitive ATRP propagation and $S_N 2$ substitution of a terminal (tertiary or secondary) carbon halogen. Further explorations of the universality into this one-pot strategy with higher output and more available monomers, such as styrene, is ongoing in our lab. This novel methodology would greatly improve current low-efficiency cyclic polymers perparations and induce more research interest in and applications for cyclic polymers.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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