

Rapid Communication

CLICK CYCLIZATION OF LINEAR TRIBLOCK COPOLYMERS AT BLOCK JUNCTIONS UNDER HIGH CONCENTRATION DUE TO END-BLOCK SHIELDING*

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Abstract Linear triblock copolymers of poly(*N*-isopropylacrylamide) (PNIPAM) and poly(ethylene glycol) (PEG) with two azide groups at both block junctions (PNIPAM- N_3 -PEG- N_3 -PNIPAM) are click reacted with dipropargyl oxalylate under high polymer concentration (250 g/L). Benefiting from rapid feature of alkyne-azide click reaction and spatial shielding of PNIPAM end blocks, PEG center block of PNIPAM- N_3 -PEG- N_3 -PNIPAM remains separated although PNIPAM end blocks keep in contact under this high concentration. Therefore, PNIPAM- N_3 -PEG- N_3 -PNIPAM undergoes self-cyclization at block junctions to form tadpole-shaped architecture while N_3 -PEG- N_3 without PNIPAM end blocks inter-connects linearly. The influence of block lengths of PEG and PNIPAM on the unusual cyclization under high polymer concentration is studied.

Keywords: Self-cyclization; Click chemistry; Triblock copolymer; High concentrated solution; Spatial shielding.

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INTRODUCTION

Although polymers with cyclic architectures have attracted increasing research interest, there exists the challenge of controlled and scale-up synthesis^[1–9]. Generally, the synthetic strategies can be catalogued into ring closure from linear polymer precursors^[10–14] and ring expansion polymerization from limited monomers, such as cyclic esters^[15, 16], *N*-substituted *N*-carboxylanhydrides^[17] and cyclic alkenes^[18, 19].

The first reported cyclic polymers should come from random intramolecular cyclization of linear chains in step polymerization and their molecular weight distribution are inherently polydispersed^[2, 9]. Thus, living/controlled polymerizations have been deliberately adopted to synthesize narrowly distributed linear precursors^[20–22]. To ensure the prerequisite of strict stoichiometry for ring closure, hetero-telechelic linear precursors are preferred^[13, 14, 20]. Recently, the combination of controlled radical polymerization and click chemistry further improves the efficiency of ring closure and extends monomer choice^[11, 23–26]. However, ring closure strategy suffers from one spontaneous limitation: highly dilute concentration, 10^{-5} mol·L⁻¹ for initial monomer or 10^{-3} g·L⁻¹ for final polymer^[20–27].

Although the popular synthesis routines suffer from low productivity of cyclic polymers, several scale-up attempts have been reported^[24, 28, 29]. Taking advantage of dynamic equilibrium between micelles and unimers of

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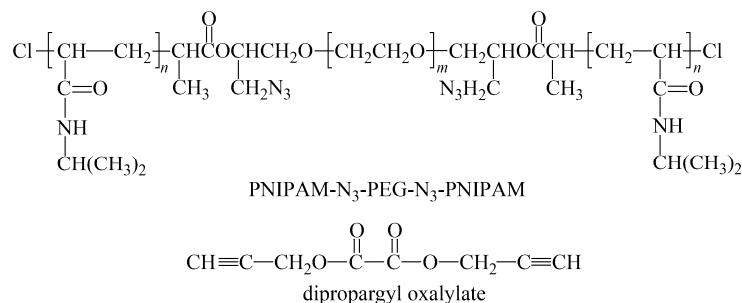
responsive block copolymer, Liu *et al.* succeeded in preparing a cyclic block copolymer *via* alkynyl-azido click chemistry under polymer concentration (c_{polymer}) of $10 \text{ g} \cdot \text{L}^{-1}$ [28]. Li *et al.* prepared cyclic PSt-*b*-linear PEG *via* ATRP and click chemistry under the same concentration through the continuous addition of linear precursors [24].

Previously, linear triblock copolymers with two poly(*N*-isopropylacrylamide) (PNIPAM) end blocks and one poly(ethylene glycol) (PEG) center block having two azido groups at the block junctions (PNIPAM- N_3 -PEG- N_3 -PNIPAM) were observed occasionally to self-cyclize with dipropargyl oxalylate (DPO) to form tadpole-shaped cyclic-PEG with two PNIPAM tails [*tail*-(PNIPAM) $_2$ -*c*-PEG] under c_{polymer} as high as $250 \text{ g} \cdot \text{L}^{-1}$ [11]. That observation is solely different from the primary principle of step polymerization and popular knowledge of ring closure strategy: high dilution and strict stoichiometry for the end-to-end closure of linear polymer. Herein, systematic investigations are present to disclose the influence of block lengths on self-cyclization of linear PNIPAM- N_3 -PEG- N_3 -PNIPAM under highly concentrated condition: shielding from end blocks inhibits the encounter of central block to prompt the sole self-cyclization.

EXPERIMENTAL

Preparation of N_3 -PEG- N_3 and PNIPAM- N_3 -PEG- N_3 -PNIPAM

PEG with hydroxyl and azide groups at both chain ends (N_3 -PEG- N_3) was prepared through the epoxidation of HO-PEG-OH with epichlorohydrin followed with ring-opening of epoxy group with sodium azide. After the esterification of N_3 -PEG- N_3 with 2-chloropropionyl chloride, single electron transfer living radical polymerizations of NIPAM were carried out in DMF/water at 25°C with CuCl and *N,N,N',N'',N''',N'''*-hexamethyltriethylenetetramine (Me_6TREN) as the catalyst and ligand. Thus, PNIPAM- N_3 -PEG- N_3 -PNIPAM copolymers with different PNIPAM lengths (n_{PNIPAM}) and PEG lengths (n_{PEG}) were prepared and characterized by GPC, NMR and FTIR. The chemical structure of PNIPAM- N_3 -PEG- N_3 -PNIPAM is demonstrated in Scheme 1, and the details of synthesis and structural determination can be referred in Supporting Information [11].



Scheme 1 Chemical structure of PNIPAM- N_3 -PEG- N_3 -PNIPAM and DPO

Click Reaction of Azido-containing Linear Polymers with Dipropargyl Oxalylate

Click reaction of N_3 -PEG- N_3 or PNIPAM- N_3 -PEG- N_3 -PNIPAM (0.5 g) with equivalent dipropargyl oxalylate was performed in DMF (2.0 mL) at 35°C for 2 h. CuBr and *N,N,N',N'',N'''*-pentamethyldiethylenetriamine (PMDETA) were used as catalyst and ligand. The product was purified by dialyzing against distilled water for 2 d using dialysis membrane of regenerated cellulose with cutoff molecular weight of 3500 and lyophilization. A parallel reaction for PNIPAM- N_3 -PEG- N_3 -PNIPAM was carried out at alkynyl/azido = 2 in mole.

Structural Characterization

The molecular weight and its polydispersity index were determined on a Waters 150C gel permeation chromatography (GPC) equipped with three Ultrastaygel columns (500, 10^3 , 10^4 Å) in series and RI detector at 30°C , using monodispersed polystyrene as calibration standard. THF was used as solvent at a flow rate of 1.0 mL/min. Fourier transform infrared spectra (FTIR) were recorded on a Bruker VECTOR-22 IR spectrometer in KBr pellets. All proton nuclear magnetic resonance (^1H -NMR, 300 MHz) measurements were performed on a Bruker DMX300 spectrometer at 22°C .

RESULTS AND DISCUSSION

Linear Growth of N_3 -PEG- N_3 without PNIPAM End Blocks

N_3 -PEG $_n$ - N_3 ($n_{\text{PEG}} = 32, 90$ and 227) without PNIPAM end blocks was clicked with equivalent DPO under $c_{\text{polymer}} = 250 \text{ g}\cdot\text{L}^{-1}$ at 35°C . Figure 1 shows GPC diagrams of the obtained products. Before click reaction, N_3 -PEG- N_3 with $n_{\text{PEG}} = 32, 90$ and 227 has apparent number-average molecular weight (M_n^{app}) of 1600, 5400 and 11200 with PDI of 1.03–1.07. After click reaction, all the products have larger M_n^{app} (9600, 12600 and 34500) and their molecular weight distribution becomes broader. These results suggest that N_3 -PEG- N_3 without PNIPAM end blocks would undergo linear growth other than self-cyclization through click reaction. The result is consistent with the common sense: high concentration is facilitated to linear growth of polycondensation.

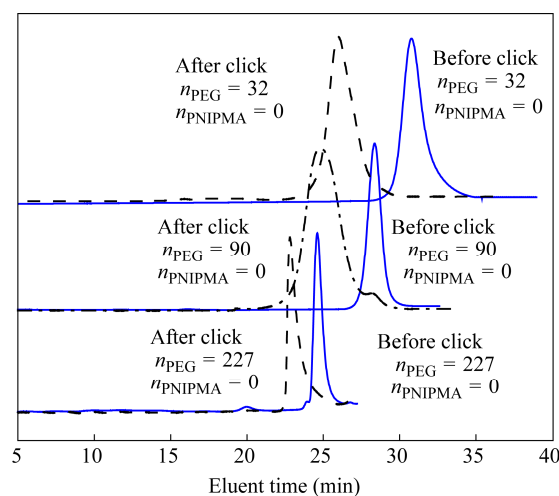


Fig. 1 GPC diagrams of linear N_3 -PEG- N_3 samples and the products after click reaction with equivalent DPO ($c_{\text{polymer}} = 250 \text{ g}\cdot\text{L}^{-1}$)

Dependence of PNIPAM- N_3 -PEG- N_3 -PNIPAM Self-cyclization on PNIPAM Block Length

After the introduction of PNIPAM blocks onto the both ends of N_3 -PEG- N_3 block, the resultant triblock copolymers experienced the opposite routine in click reaction. Figure 2 elucidated the dependence of self-cyclization of PNIPAM- N_3 -PEG $_{90}$ - N_3 -PNIPAM on PNIPAM block length. Each product from three linear precursors only has one peak with eluent time longer than that of its counterpart, while GPC diagram remains similar in shape after click reaction. As well, FTIR (Fig. 3) shows the complete disappearance of the characteristic azido absorbance at *ca.* 2110 cm^{-1} after the click reaction, indicating the complete reaction of azido groups. The results imply that PNIPAM- N_3 -PEG $_{90}$ - N_3 -PNIPAM with $n_{\text{PNIPAM}} = 25, 50$ and 150 undertook self-cyclization and no linear growth occurred during click reaction under polymer concentration as high as $250 \text{ g}\cdot\text{L}^{-1}$.

Dependence of PNIPAM- N_3 -PEG- N_3 -PNIPAM Self-cyclization on PEG Block Length

By modulating the molar ratio of NIPAM to PEG macroinitiator (PEG-3 in Supporting Information) and monomer conversion, PNIPAM- N_3 -PEG- N_3 -PNIPAM samples with fixed n_{PNIPAM} (50) and varied n_{PEG} (32, 90 and 227) were obtained. After that, these linear precursors were reacted with equivalent DPO under $c_{\text{polymer}} = 250 \text{ g}\cdot\text{L}^{-1}$. Figure 4 exemplifies the comparison of polymers before and after click reaction. Similarly, no signal with higher M_n^{app} appears for each product and GPC peak is located at the eluent time longer than that of the precursor, indicating that the introduction of end PNIPAM blocks may be essential to the self-cyclization under high polymer concentration.

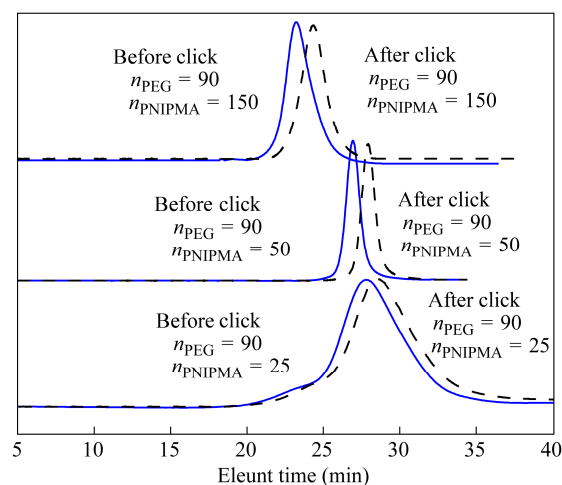


Fig. 2 GPC diagrams of linear PNIPAM-N₃-PEG₉₀-N₃-PNIPAM samples and their self-cyclization products after click reaction with equivalent DPO ($c_{\text{polymer}} = 250 \text{ g} \cdot \text{L}^{-1}$)

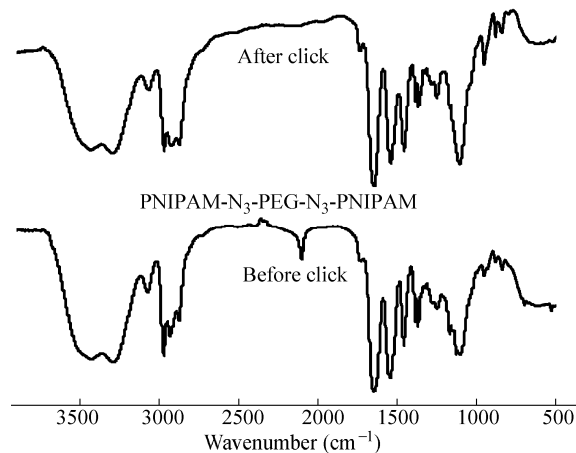


Fig. 3 FTIR spectra of PNIPAM-N₃-PEG₉₀-N₃-PNIPAM before and after click reaction

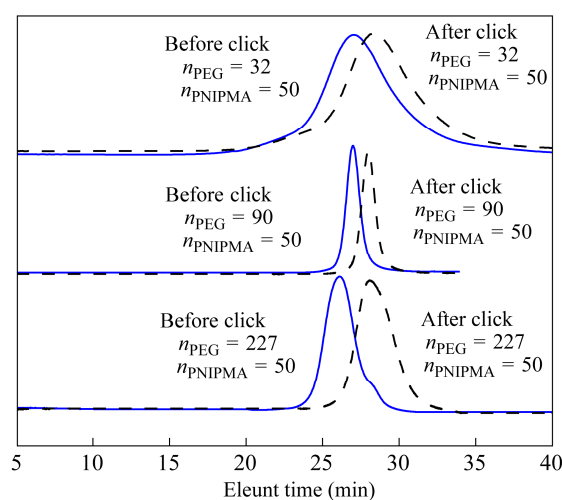


Fig. 4 GPC diagrams of linear PNIPAM₅₀-N₃-PEG-N₃-PNIPAM₅₀ samples and their self-cyclization products after click reaction with equivalent DPO ($c_{\text{polymer}} = 250 \text{ g} \cdot \text{L}^{-1}$)

Besides high dilution, strictly stoichiometric reaction is another claimed keypoint to self-cyclization of linear precursor^[19, 30]. However, it is not necessary in the present case. Click reactions between PNIPAM-N₃-PEG-N₃-PNIPAM and DPO were also performed under non-stoichiometric condition with [alkynyl]/[azido] = 0.5 or 2. Parallely, all linear triblock copolymers mentioned above inevitably self-cyclized to form *tail*-(PNIPAM)₂-*c*-PEG.

Besides GPC evidence, the results of temperature-dependent turbidimetry (Fig. S1) and laser light scattering (Fig. S2) also support the self-cyclization of PNIPAM-N₃-PEG-N₃-PNIPAM under $c_{\text{polymer}} = 250 \text{ g}\cdot\text{L}^{-1}$. The heating-cooling hysteresis of *tail*-(PNIPAM)₂-*c*-PEG is weaker comparing with its linear precursor while the difference between their lower critical solution temperatures depends on PEG block length.

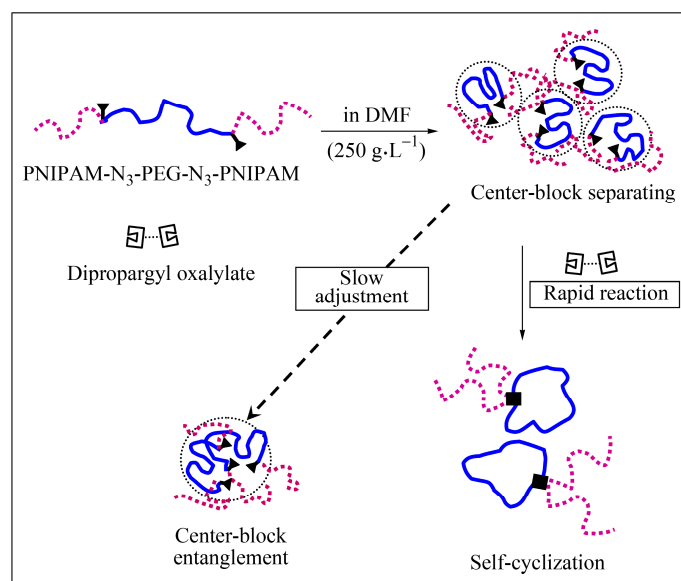
Self-cyclization Mechanism for PNIPAM-N₃-PEG-N₃-PNIPAM

The unusual observation should be attributed to the kinetics of click reaction and the conformation of polymer chains. Based on kinetic consideration, high dilution condition is commonly necessary for self-cyclization of bifunctional linear polymer, since cyclization is a unimolecular (intramolecular) reaction while linear growth is a bimolecular (intermolecular) one^[9]. As well, compacted coil conformation should be advantageous over loose coil conformation since end-to-end distance of polymer chain is shorter in the former case.

In step polycondensations under thermodynamic control^[9, 31, 32], such as those for polyester and polyamide, linear growth and chain interchange coexist in the dynamic equilibrium. Thus, cyclized polymers are present due to intramolecular interchange (backbiting) even under bulk polymerization. For kinetic control polycondensations, these being irreversible reactions and having no chain interchange, there exists a continuous increase of cyclic products even though the rate of cyclization decreases with group conversion, suggesting the so-called self-dilution law^[33]. In this manuscript, the employed reaction is alkynyl-azido click reaction, belonging to kinetic control mechanism. Thus, it might partially contribute the extraordinary self-cyclization of PNIPAM-N₃-PEG-N₃-PNIPAM, but not completely.

For telechelic linear polymer chains, linear growth necessitates the condition where separate chains should be overlapped to make the reactive groups from different chains meet with each other, while self-cyclization requires the persistence of individual chain being separate from each other to offer more opportunities for the two groups of one chain to get in contact. In dilute polymer solution, chains keep as independent coils. As polymer concentration exceeds a critical overlapping value (c^* , *ca.* 0.1 wt%), polymer chains could overlap. The entanglement of polymer chains may not happen until the concentration reaches c_e (critical entanglement concentration), being in the range of 0.5 wt%–10 wt%. In the highly concentrated solutions, PNIPAM-N₃-PEG-N₃-PNIPAM underwent self-cyclization but N₃-PEG-N₃ did linear growth. This discrepancy should be caused by the introduction of PNIPAM end blocks. Thus, a probable mechanism for the self-cyclization of linear triblock PNIPAM-N₃-PEG-N₃-PNIPAM under high concentration is present in Scheme 2.

In the present case of PNIPAM-N₃-PEG-N₃-PNIPAM, click reaction was performed just after linear triblock copolymer was dissolved in DMF. Comparing with rapid and efficient virtue of azido-alkynyl click reaction^[34–36], chain entanglement is a slow process. Even though end blocks of PNIPAM kept contact and entangled, the azido groups attached at the block junctions of PEG and PNIPAM blocks from different chains should not encounter with each other, because the multi-chain cluster (Scheme 2) with center PEG blocks entangling with each other did not have sufficient time to form. Thus, center PEG blocks remained as single-chain bulbs surrounded with end PNIPAM blocks. As well, the compatibility difference between PEG and PNIPAM blocks might make PEG bulb compressed, inducing less spatial distance between two azido groups of the same PNIPAM-N₃-PEG-N₃-PNIPAM chain.



Scheme 2 Proposed mechanism for the formation of *tail*-(PNIPAM)₂-*c*-PEG from its linear triblock precursor under high concentration

CONCLUSIONS

In conclusion, by using rapid click chemistry without side reaction and limiting deep entanglement of inner segments from shielding of end blocks, PNIPAM-N₃-PEG-N₃-PNIPAM underwent unavoidably self-cyclization to produce *tail*-(PNIPAM)₂-*c*-PEG.

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