

Supporting Information

Synthesis of Cyclic Poly(2-ethyl-2-oxazoline) with Degradable Disulfide Bond

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Synthesis of alkyne-PEtOx-N₃. Alkyne-PEtOx-N₃ was synthesized using a previously described method.^[1] The synthesis of alkyne-PEtOx-N₃ (2K) is typically described as follows. In a pre-dried long neck round bottom flask, propargyl tosylate (0.10 g, 0.48 mmol), EtOx (0.99 g, 9.98 mmol), and 3 mL of acetonitrile were added. The system was degassed by using three freeze-pump-thaw cycles. The reaction was carried out at 80 °C for 24 h. A small amount of the polymer was precipitated in diethyl ether for SEC and ¹H NMR determinations. The living polymer was further reacted with NaN₃ at 80 °C for 18 hrs to be ω-end capped with azido group. $M_n(\text{NMR}) = 2450 \text{ g mol}^{-1}$, $M_n(\text{SEC}) = 1440 \text{ g mol}^{-1}$, $M_w/M_n = 1.19$.

Synthesis of cyclic PEtOx by CuAAC reaction. The cyclic PEtOx was prepared as previously described with a little modification.^[1] Briefly in a 1 L round bottom flask with an N₂ inlet and outlet, 900 mL of CH₂Cl₂ and 4 mL PMDETA was added. PMDETA/CH₂Cl₂ solution was degassed by bubbling nitrogen for 10 hrs. Alkyne-PEtOx-N₃ (2K, 0.159 g) was dissolved in 100 mL dichloromethane and degassed by bubbling nitrogen gas for 1 hr. CuBr (0.3 g) was added to PMDETA/CH₂Cl₂ solution. After removing air from both solutions, a 25 mL gas tight syringe was filled with the polymer/CH₂Cl₂ solution and added to PMDETA/CuBr/CH₂Cl₂ solution at a rate of 2 mL/hr. The solution was then exposed to air to oxidize Cu(I) salt, so that it can be easily removed by stirring with a saturated NH₄Cl solution for a few hours. The solvent was removed using rotary evaporator and the residue was dissolved in 1 mL THF. The polymer was precipitated from ten-fold excess diethyl ether. The cyclic PEtOx (2K) was dried in a vacuum oven at room temperature. Similarly, DMF was also used for the synthesis of cyclic PEtOx instead of CH₂Cl₂ under the same reaction conditions. $M_n(\text{NMR}) = 2450 \text{ g mol}^{-1}$, $M_n(\text{SEC}) = 1280 \text{ g mol}^{-1}$, $M_w/M_n = 1.20$.

Route B in Scheme 1 represents the alternative synthesis of the cyclic PEtOx using the intramolecular CUAAC reaction through an extremely dilute conditions. To compare with the degradable disulfide-bonded cyclic PEtOx using the thiol/disulfide exchange chemistry, we also synthesized the same cyclic polymer using the famous alkyne-azide click chemistry as described previously. First, polymerization of EtOx using propargyl tosylate as an initiator under $[M]_0/[I]_0 = 20:1$ was conducted in acetonitrile at 80°C for 24 hrs, and the living polymer was further reacted with sodium azide to be ω -end capped by azido group to afford alkyne-PEtOx-N₃ (2K) with $M_n(\text{SEC}) = 1440 \text{ g mol}^{-1}$, $M_n(\text{NMR}) = 2450 \text{ g mol}^{-1}$, and $M_w/M_n = 1.19$. The ¹H NMR spectra of the polymers alkyne-PEtOx-OTs (2K), alkyne-PEtOx-N₃ (2K), and cyclic PEtOx (2K) are shown in Figure S1. After polymerization three new peaks appeared at 1.20, 2.32-2.44 and 3.47-3.49 ppm respectively, which are characteristic peaks of PEtOx. The protons signals at 1.20 ppm are assigned to the pendant methyl protons (C-CH₂-CH₃-), the signals at 3.47-3.49 ppm correspond to the backbone proton signals (N-CH₂-CH₂-), and the peaks at 2.32-2.44 ppm represent the side chain methylene protons (C-CH₂-CH₃-). The proton signal of initiator residue appears around 7.37 ppm and 7.73 ppm respectively, which correspond to the aromatic protons (*phenyl*-CH₃), respectively. The living polymer was terminated using sodium azide. After end capping the proton signals at 7.37 and 7.73 disappear completely, which confirms the successful introduction of the azide group as shown in Figure 5(b). Cyclic PEtOx (2K) was obtained by the intramolecular click reaction of the telechelic alkyne-PEtOx-N₃ (2K). After cyclization, two new peaks appeared at 4.42 ppm (CH₂-CH₂-N) and 4.60 ppm (N-CH₂-CH₂-) which represents the terminal methylene protons of the oxazoline repeat unit, respectively. The peak of the triazole ring appears around 7.65 ppm but can be seen only when proton NMR was taken after 512 scans as shown in Figure S3 respectively. Similarly, alkyne-PEtOx-

OTs (4K), alkyne-PEtOx-N₃ (4K), and cyclic PEtOx (4K) with number-average molecular mass around 4000 g mol⁻¹ were also obtained by the same synthetic procedures.

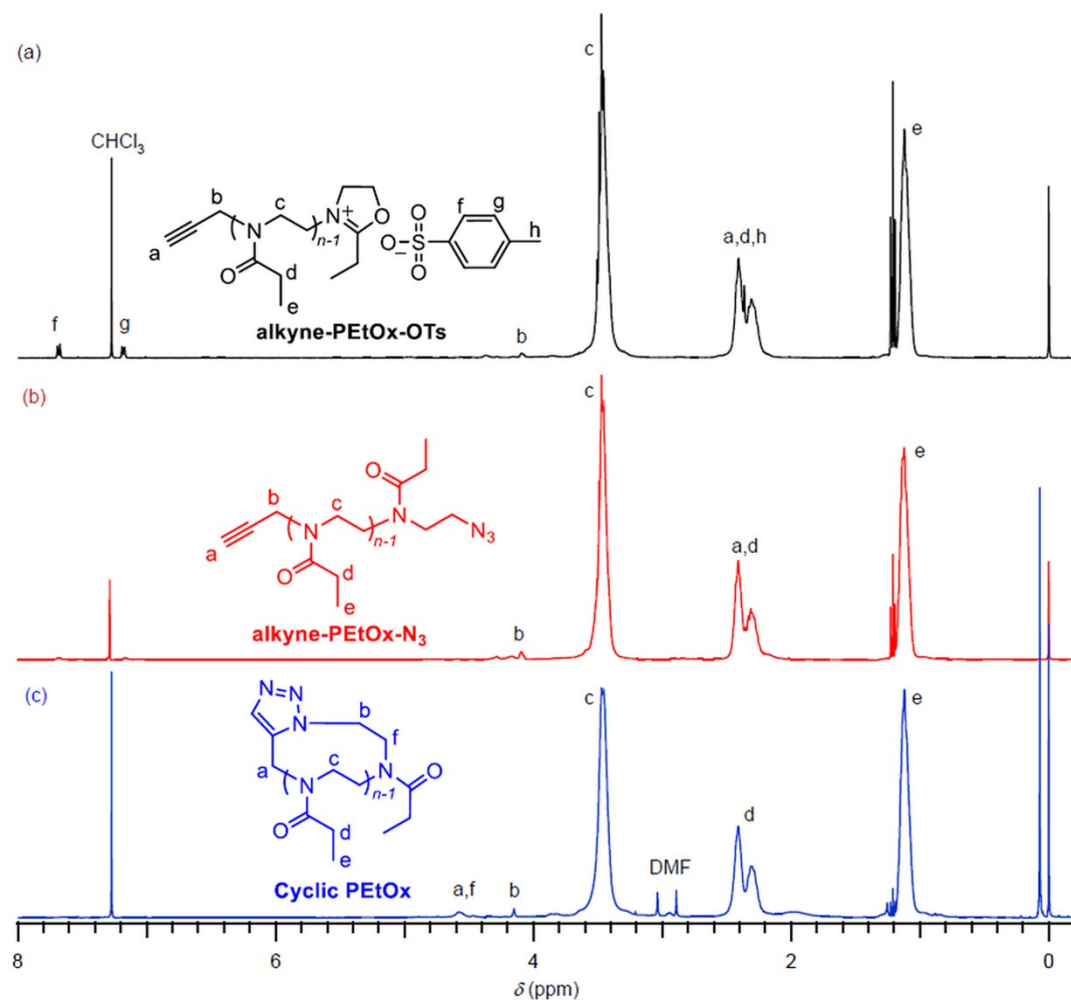


Figure S1. ¹H NMR spectra of (a) alkyne-PEtOx-OTs (2K), (b) alkyne-PEtOx-N₃ (2K), and (c) cyclic PEtOx (2K) synthesized by CuAAC reaction.

The synthetic achievement of cyclic PEtOx is also confirmed from SEC, from which the molar masses and distributions of cyclic PEtOx(2K) and cyclic PEtOx(4K) were calculated to be $M_n(\text{SEC}) = 1280 \text{ g mol}^{-1}$, $M_n(\text{NMR}) = 2450 \text{ g mol}^{-1}$, $M_w/M_n = 1.20$, and $M_n(\text{SEC}) = 2450 \text{ g mol}^{-1}$, $M_n(\text{NMR}) = 4790 \text{ g mol}^{-1}$, $M_w/M_n = 1.23$, respectively (Table 1). We can also see from Figure S2 that the peak from the cyclic PEtOx shifts to higher retention volume due to the absence of the end groups and

more compact size. The molar masses of the polymers before and after cyclization are almost the same and confirmed from ^1H NMR which supports the SEC analysis.

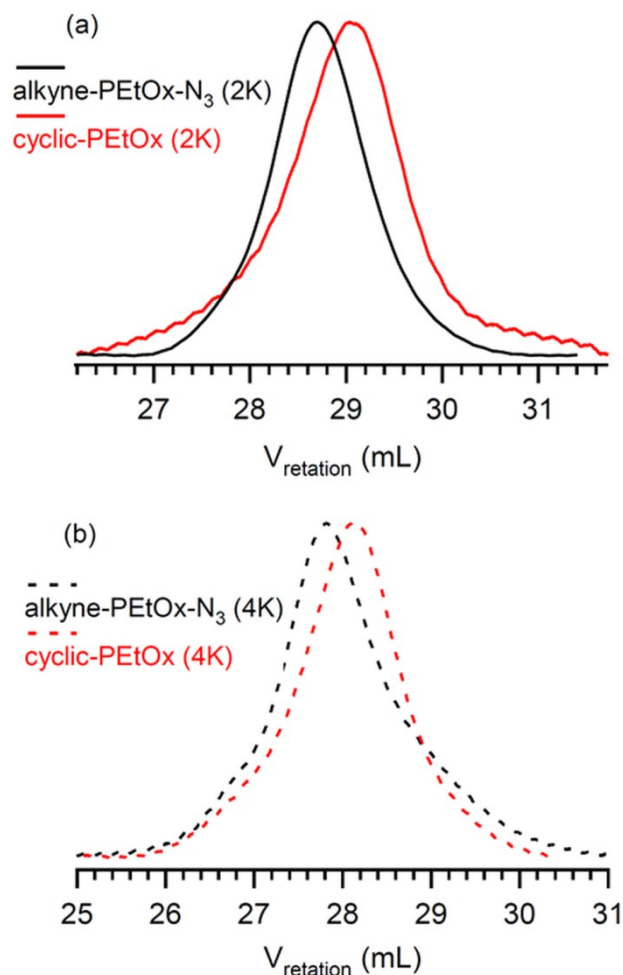


Figure S2. SEC traces of (a) alkyne-PEtOx- N_3 (2K) and cyclic-PEtOx (2K) and (b) alkyne-PEtOx- N_3 (4K) and cyclic-PEtOx (4K) synthesized by CuAAC reaction.

FT-IR was also used for the confirmation of the cyclic polymer using the alkyne-azide click chemistry method. As before cyclization the polymer contains an azido group which has a characteristic peak at 2102 cm^{-1} as shown in Supporting Figure S3, while after cyclization the peak completely disappeared, which confirms and supports the SEC and ^1H NMR results.

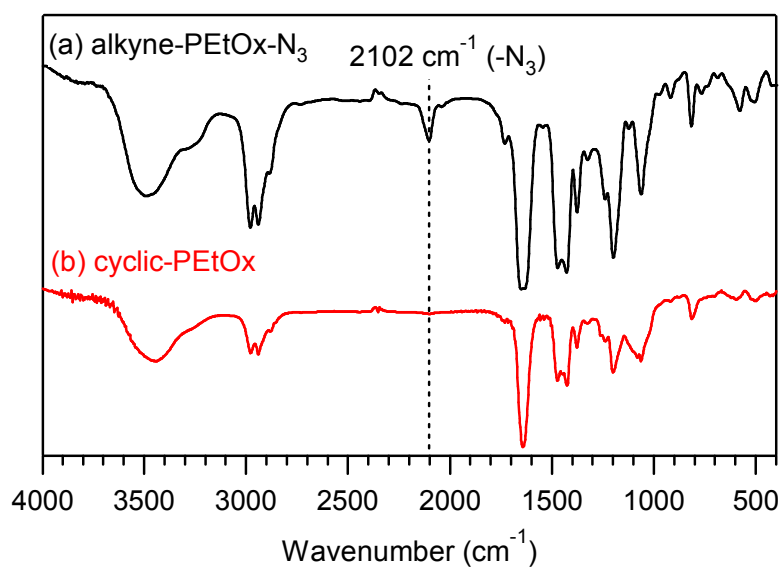


Figure S3. FT-IR spectra of (a) alkyne-PEtOx-N₃ (2K) and (b) cyclic-PEtOx (2K) synthesized by the CuAAC reaction.

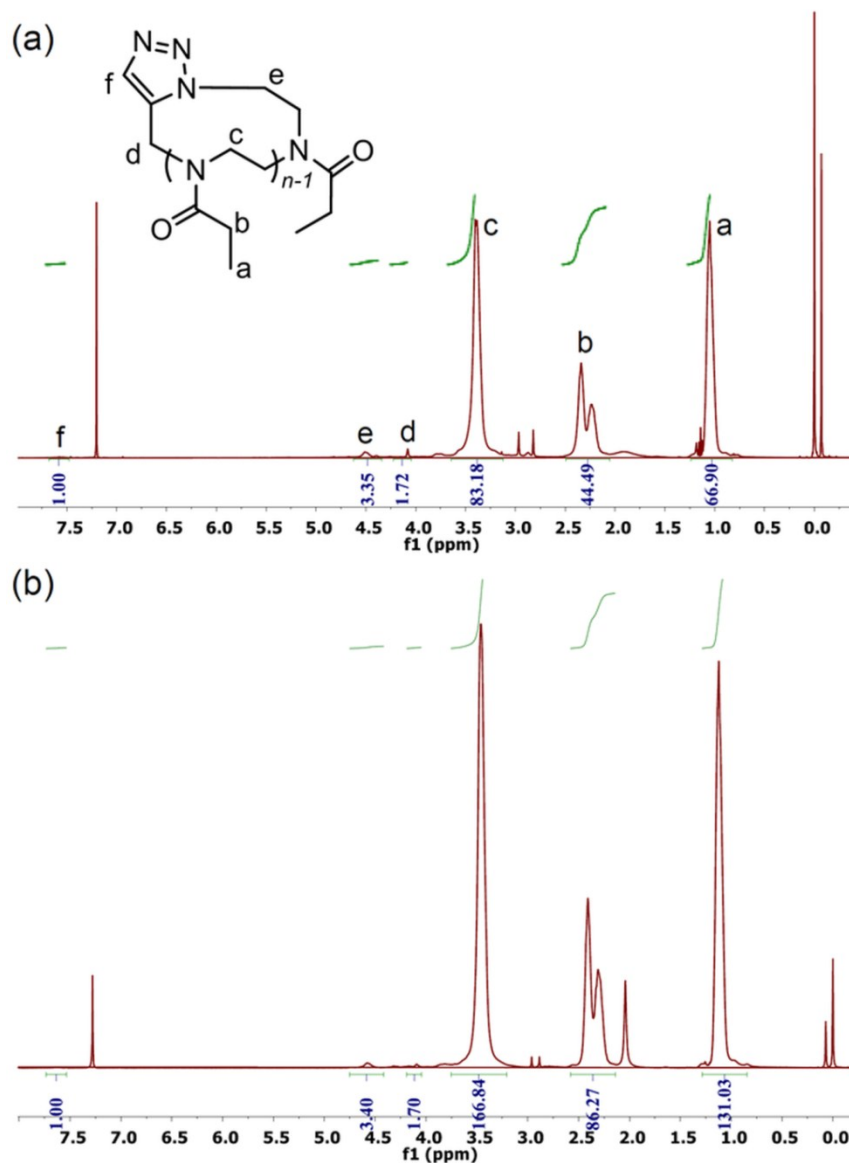


Figure S4. ^1H NMR spectra of (a) cyclic-PEtOx (2K) and (b) cyclic-PEtOx (4K) synthesized by CuAAC reaction, from which the $M_n(\text{NMR})$ s of cyclic-PEtOx (2K) and cyclic-PEtOx (4K) were calculated to be 2450 and 4790 g mol^{-1} , respectively.

Reference

1. M. A. Cortez, W. T. Godbey, Y. Fang, M. E. Payne, B. J. Cafferty, K. A. Kosakowska and S. M. Grayson, *J. Am. Chem. Soc.* **2015**, *137*, 6541-6549.