

ABSTRACT: Targeted drug delivery is one of the most rapidly developing fields in contemporary pharmaceutical science. Cyclic brush (CB) polymers, which are polymer macrocycles densely grafted with polymer side chains, have attracted considerable attention because of their unique topology and potential use in drug delivery, nanomedicine, and new materials.

In this work, we present a successful synthetic pathway to novel CB polymers based on a copolymer macrocycle of poly(2-hydroxyethyl methacrylate) (PHEMA) and poly(methyl methacrylate) (PMMA). To construct this architecture, we employ both "grafting-from" and "grafting-onto" approaches, which allow for well-controlled composition, molecular weight, and graft density. Following this two-pronged approach, CB polymers with adjustable properties can be designed, broadening their prospective applications in targeted delivery and other biomedical fields.

0. General scheme for the synthesis of cyclic brush polymers with a copolymer macrocycle

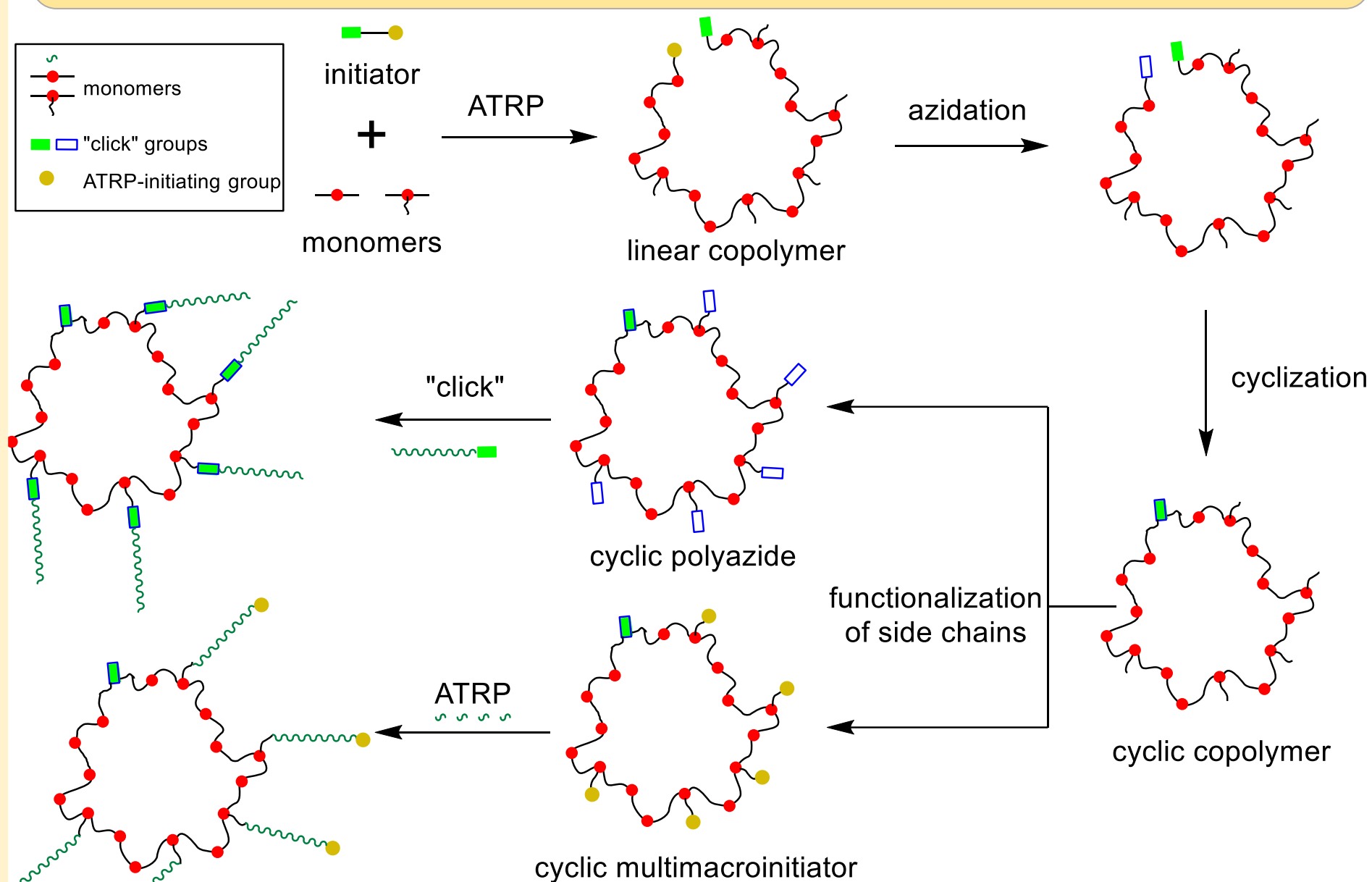


Figure 1 Schematic representation of the synthetic strategy for the preparation of cyclic brush polymers.

2. Synthesis and cyclization of linear PHEMA-PMMA copolymer

2.1. Synthesis of I -(PHEMA_x-co-PMMA_y)-Br via atom-transfer radical polymerization:

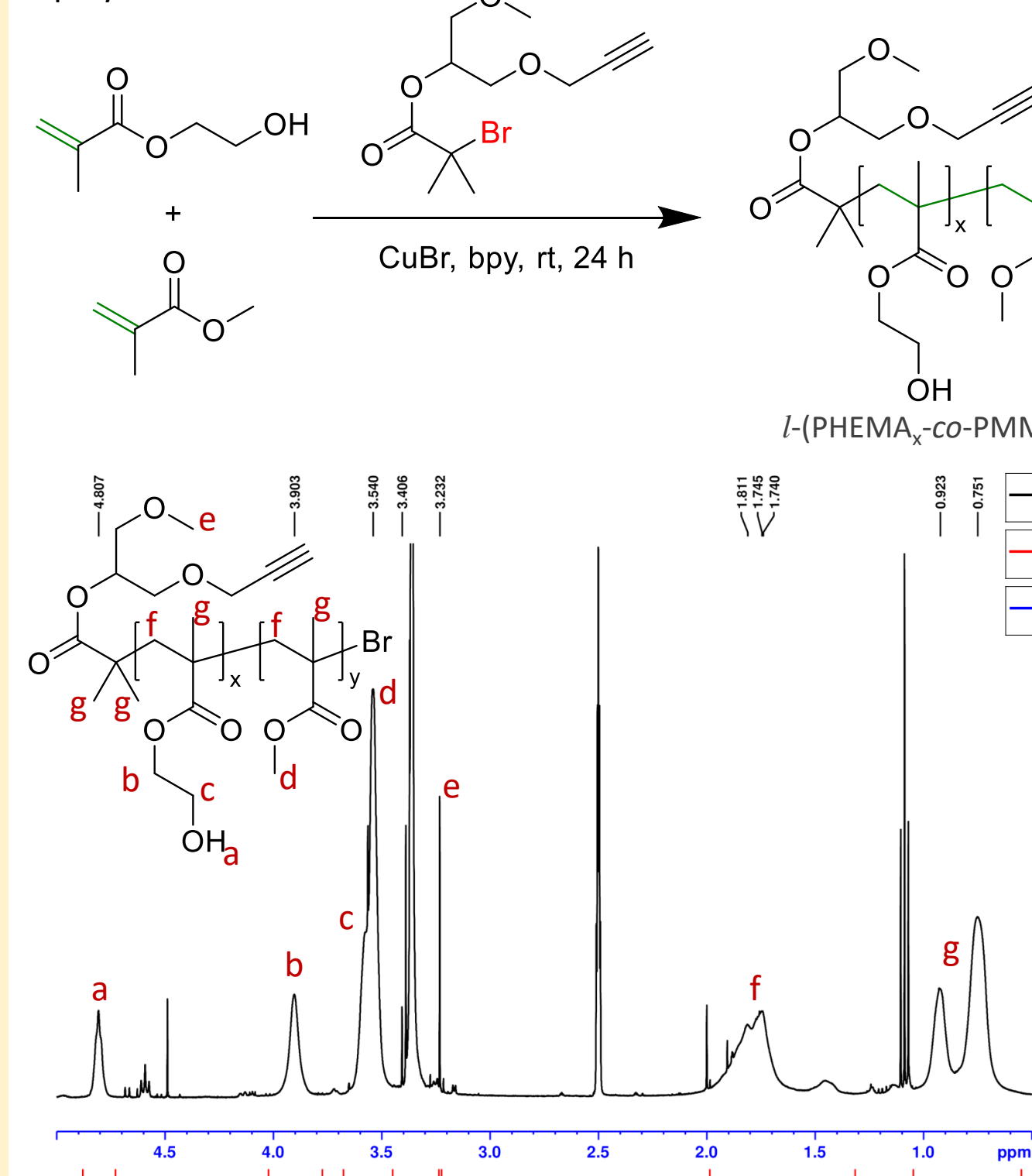


Figure 3 ¹H NMR spectrum of I -(PHEMA₁₅-co-PMMA₃₀)-Br ($M_{n,NMR} = 5250$) in DMSO-*d*₆ at 400 MHz. The presence of water (3.37 ppm) and Et₂O (3.38 ppm, 1.09 ppm) is visible.

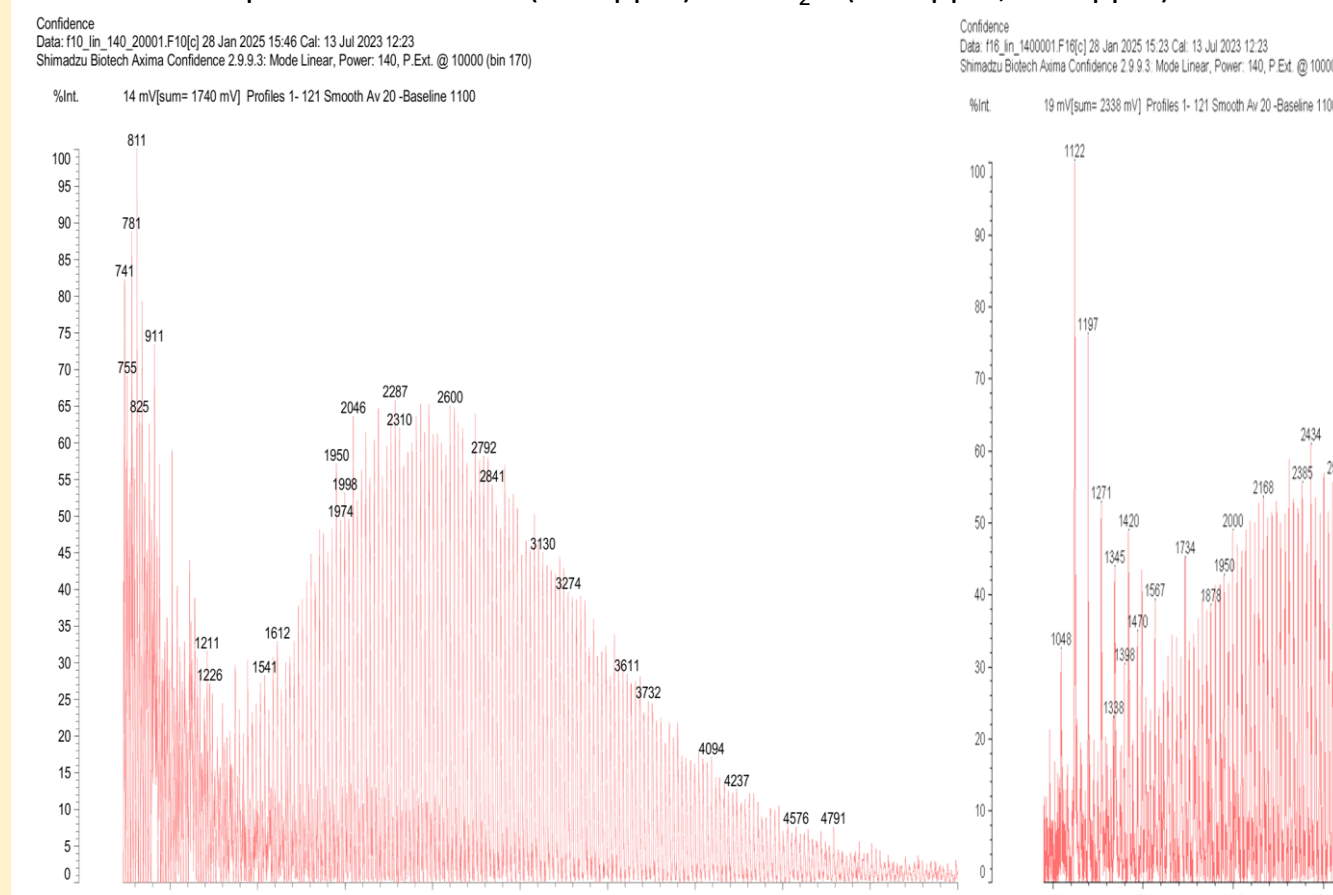


Figure 6 MALDI-TOF mass spectrum of I -(PHEMA₁₅-co-PMMA₃₀)-N₃.

2.2. Synthesis of I -(PHEMA_x-co-PMMA_y)-N₃ via azidation of I -(PHEMA_x-co-PMMA_y)-Br:

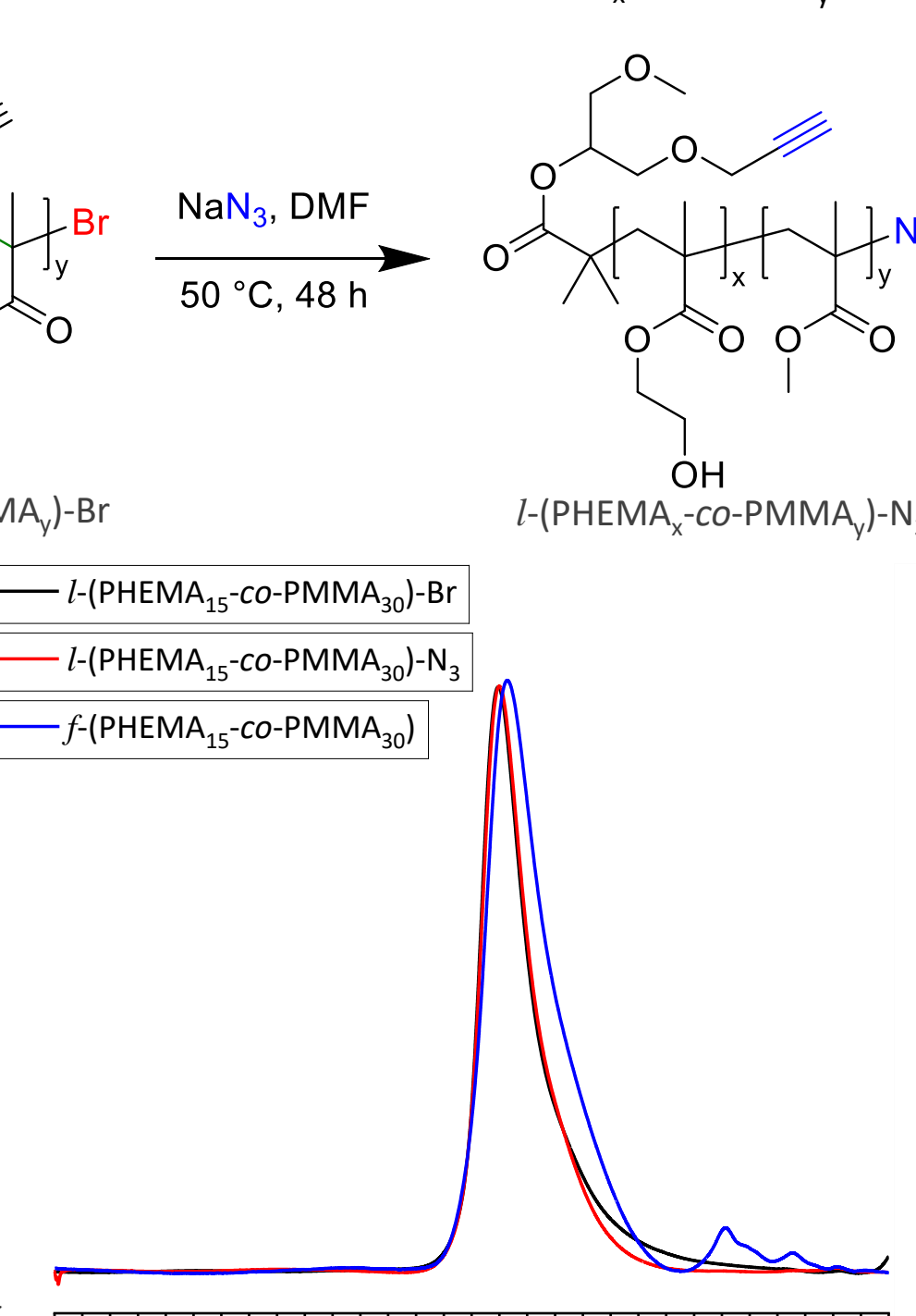


Figure 4 GPC chromatogram (RI trace, THF) of: I -(PHEMA₁₅-co-PMMA₃₀)-Br ($M_{n,GPC} = 8200$, $M_w/M_n = 1.50$); I -(PHEMA₁₅-co-PMMA₃₀)-N₃ ($M_{n,GPC} = 8690$, $M_w/M_n = 1.41$); I -(PHEMA₁₅-co-PMMA₃₀)-Br ($M_{n,GPC} = 8460$, $M_w/M_n = 1.30$).

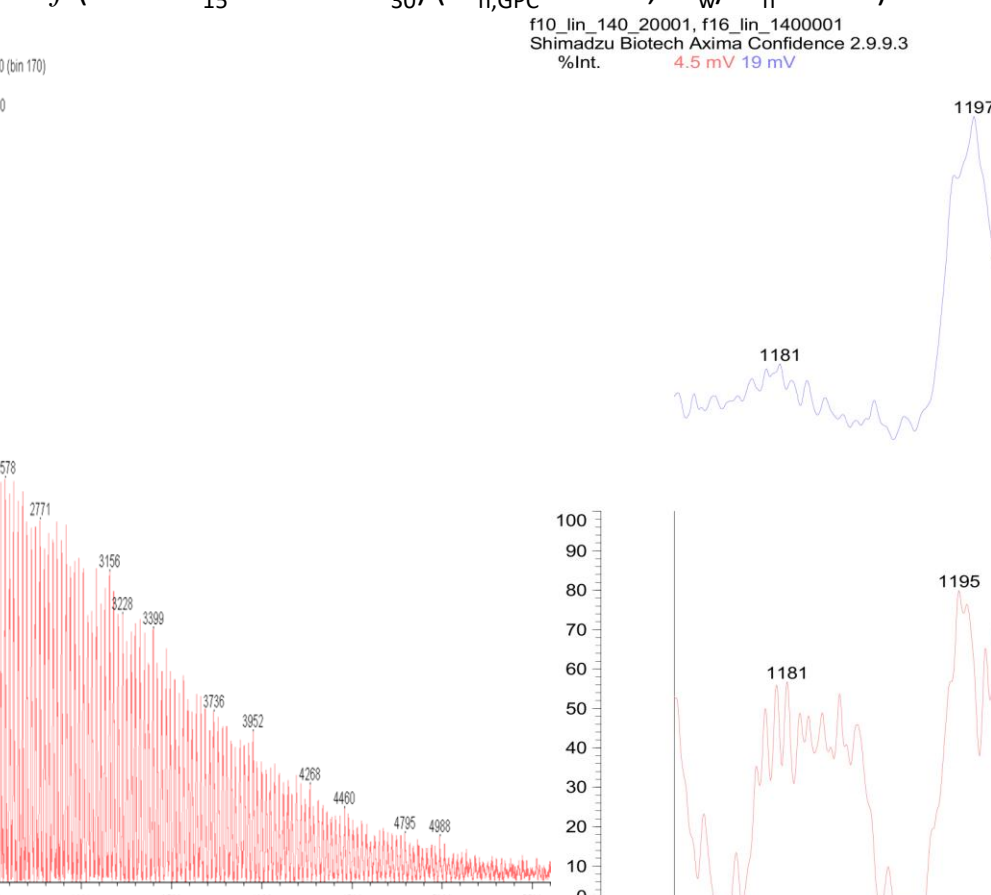


Figure 7 MALDI-TOF mass spectrum of I -(PHEMA₁₅-co-PMMA₃₀)-N₃.

2.3. Synthesis of f -(PHEMA_x-co-PMMA_y) via azide-alkyne cycloaddition of I -(PHEMA_x-co-PMMA_y)-N₃:

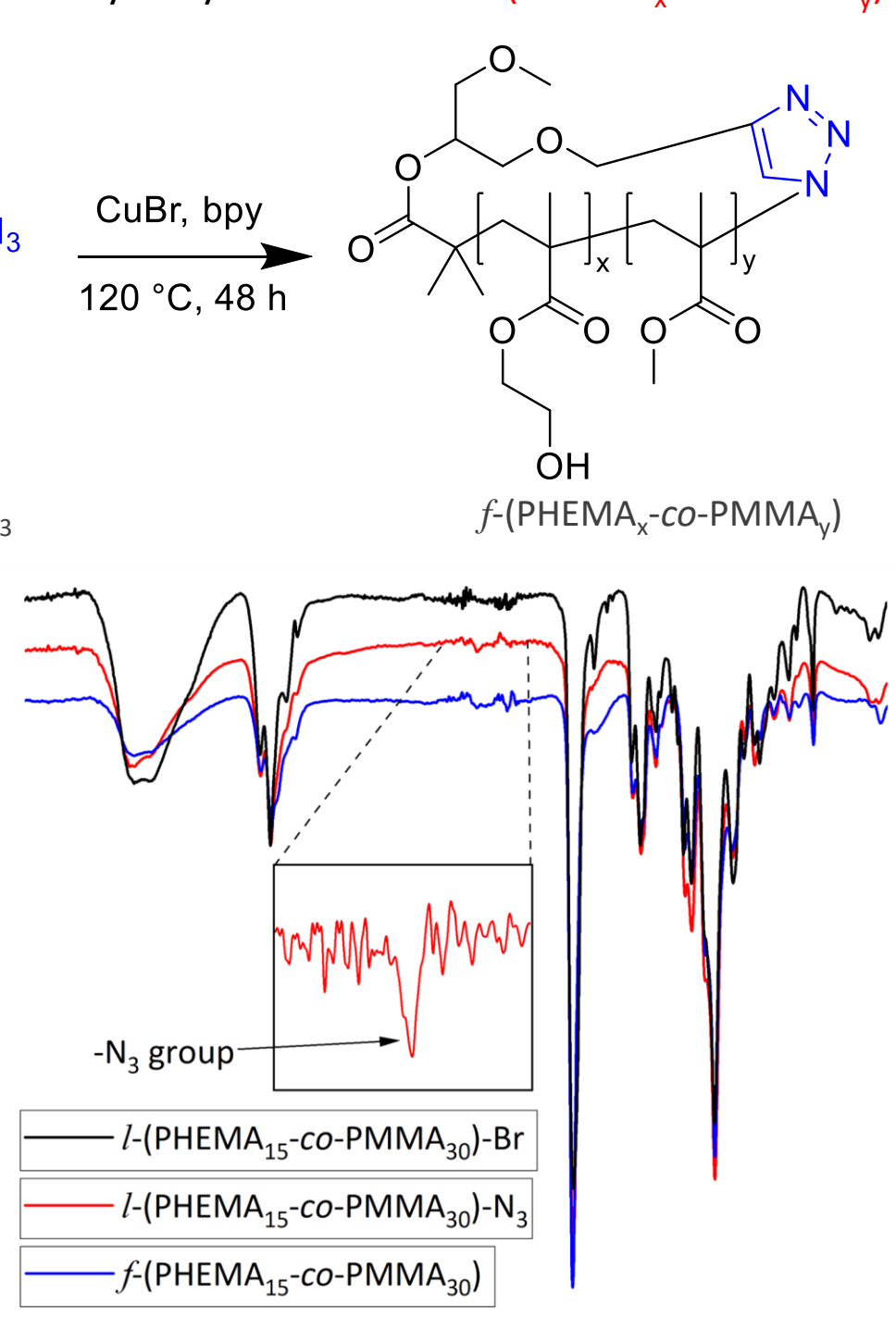


Figure 5 IR spectra of I -(PHEMA₁₅-co-PMMA₃₀)-Br, I -(PHEMA₁₅-co-PMMA₃₀)-N₃ and f -(PHEMA₁₅-co-PMMA₃₀).

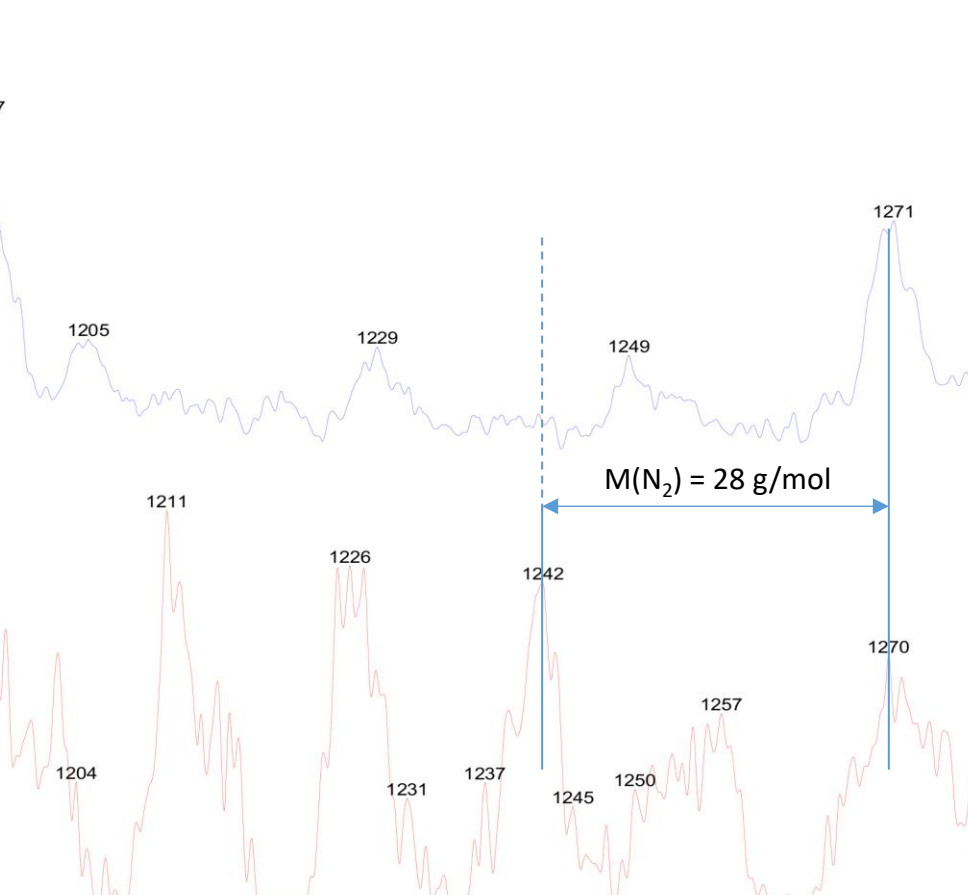
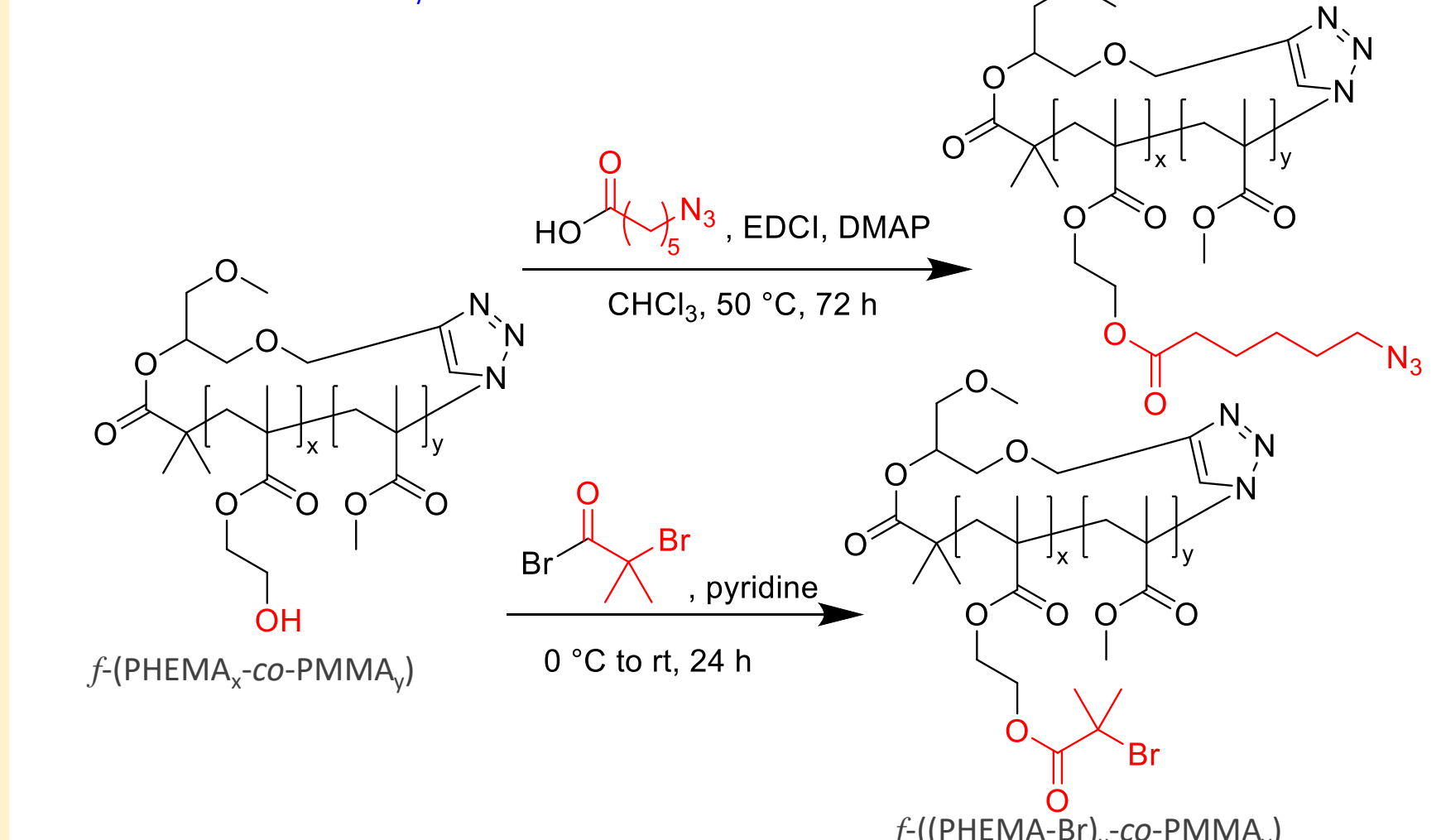


Figure 8 In the mass spectrum of I -(PHEMA₁₅-co-PMMA₃₀)-N₃ (bottom), pairs of peaks corresponding to loss of N₂ are observed. This pairing is absent in the mass spectrum of f -(PHEMA₁₅-co-PMMA₃₀) (top).

3. Side-chain functionalization of f -(PHEMA_x-co-PMMA_y)

3a. Synthesis of f -(PHEMA-N₃)_x-co-PMMA_y via esterification of f -(PHEMA_x-co-PMMA_y) with 6-azidoheptanoic acid:



3b. Synthesis of f -(PHEMA-Br)_x-co-PMMA_y via esterification of f -(PHEMA_x-co-PMMA_y) with 2-bromoisobutyrylbromide:

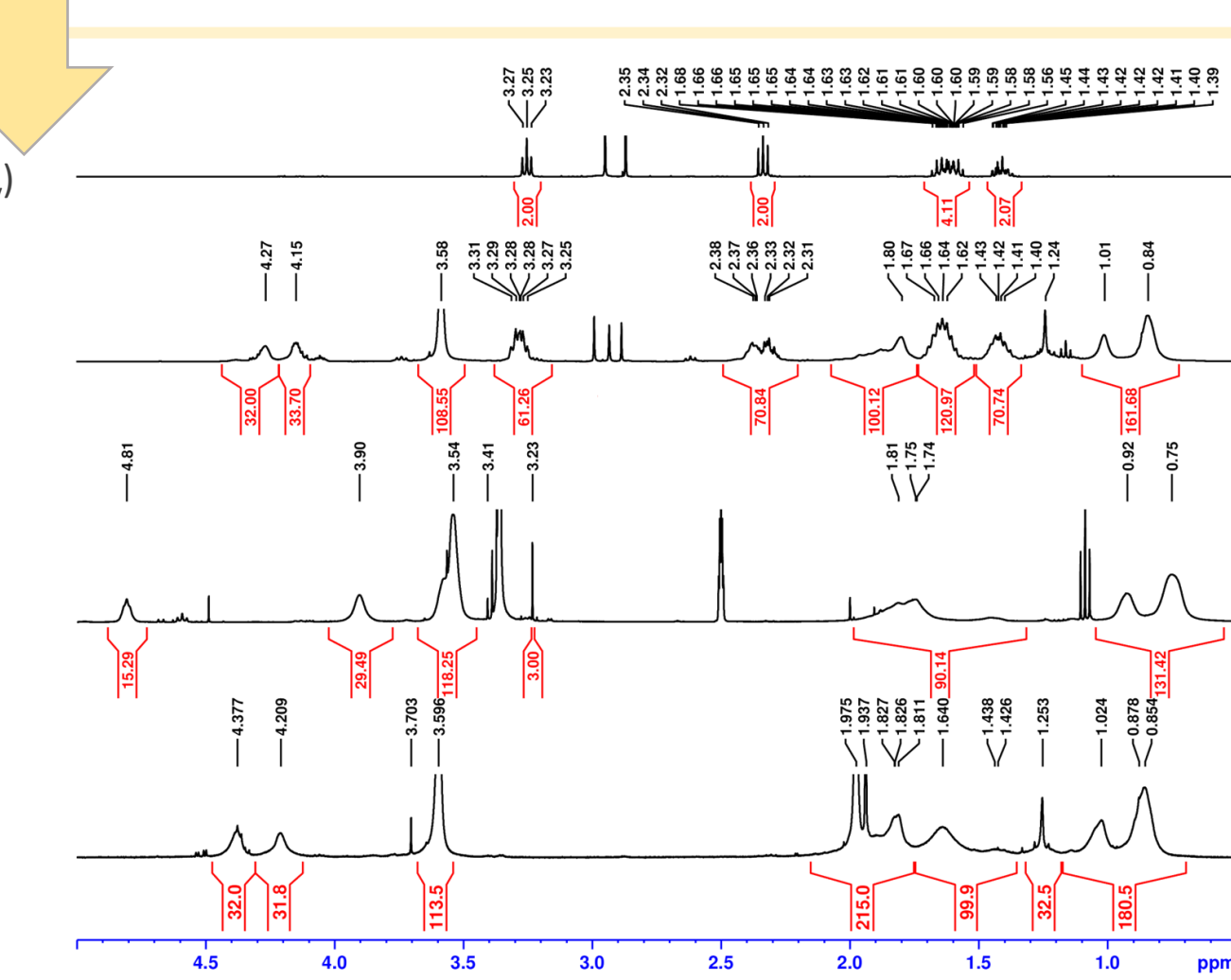
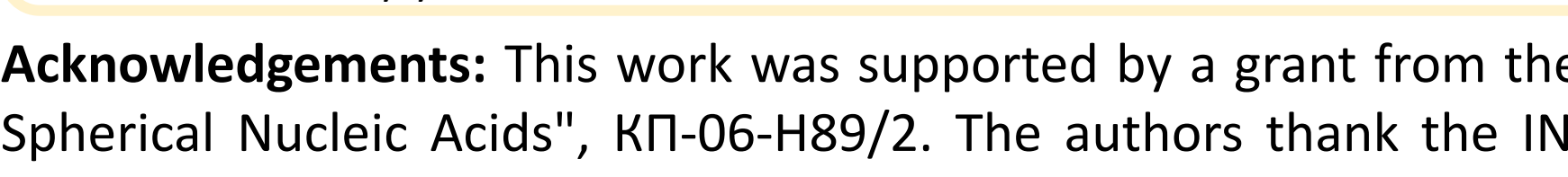


Figure 9 ¹H NMR spectra (400 MHz) of (top-to-bottom): f -(PHEMA₁₅-co-PMMA₃₀); f -(PHEMA-N₃)₁₅-co-PMMA₃₀ (CDCl₃) (note: unreacted 6-azidoheptanoic acid is visible); f -(PHEMA₁₅-co-PMMA₃₀)-Br (DMSO-*d*₆) (see caption of Figure 4); f -(PHEMA-Br)₁₅-co-PMMA₃₀ (CDCl₃).

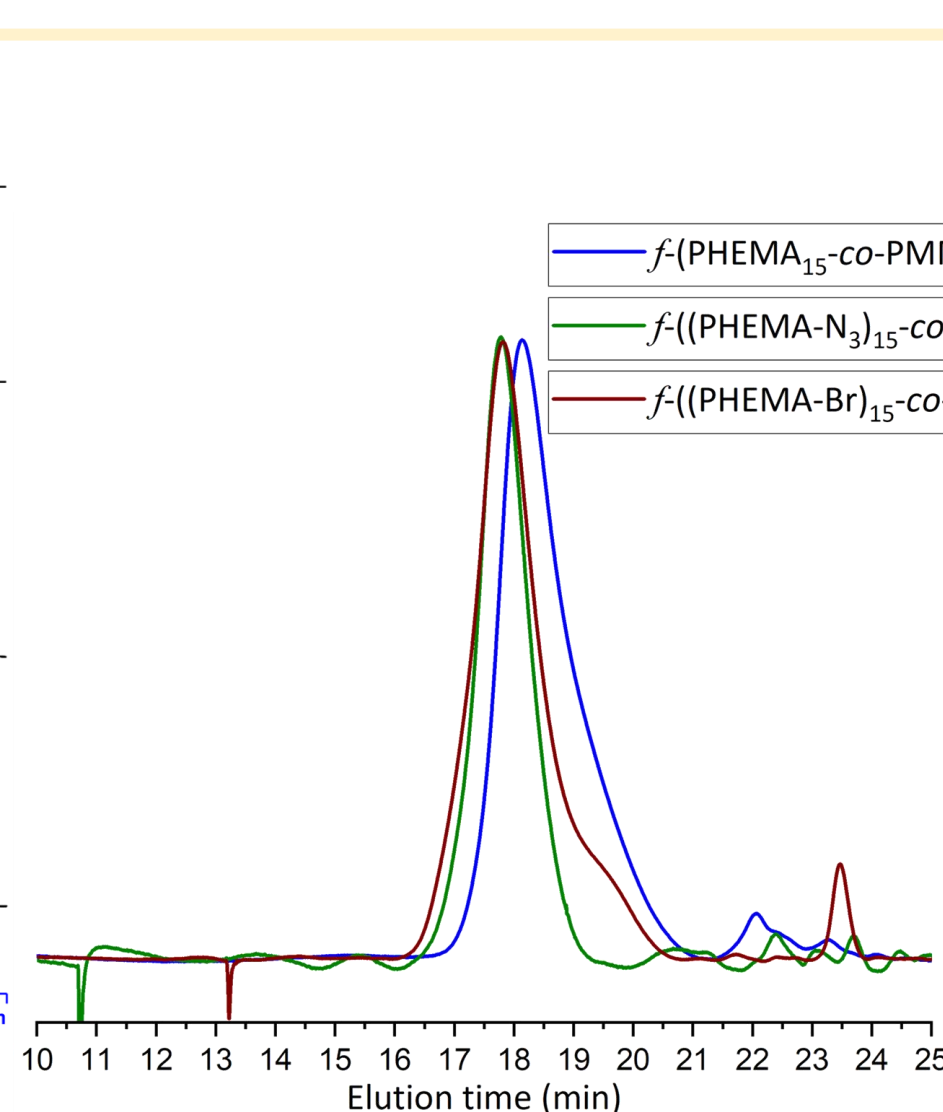


Figure 10 GPC chromatogram (RI trace, THF) of: f -(PHEMA₁₅-co-PMMA₃₀) ($M_{n,GPC} = 8460$, $M_w/M_n = 1.30$); f -(PHEMA-Br)₁₅-co-PMMA₃₀ ($M_{n,GPC} = 12860$, $M_w/M_n = 1.67$); f -(PHEMA-N₃)₁₅-co-PMMA₃₀ ($M_{n,GPC} = 15280$, $M_w/M_n = 1.26$).

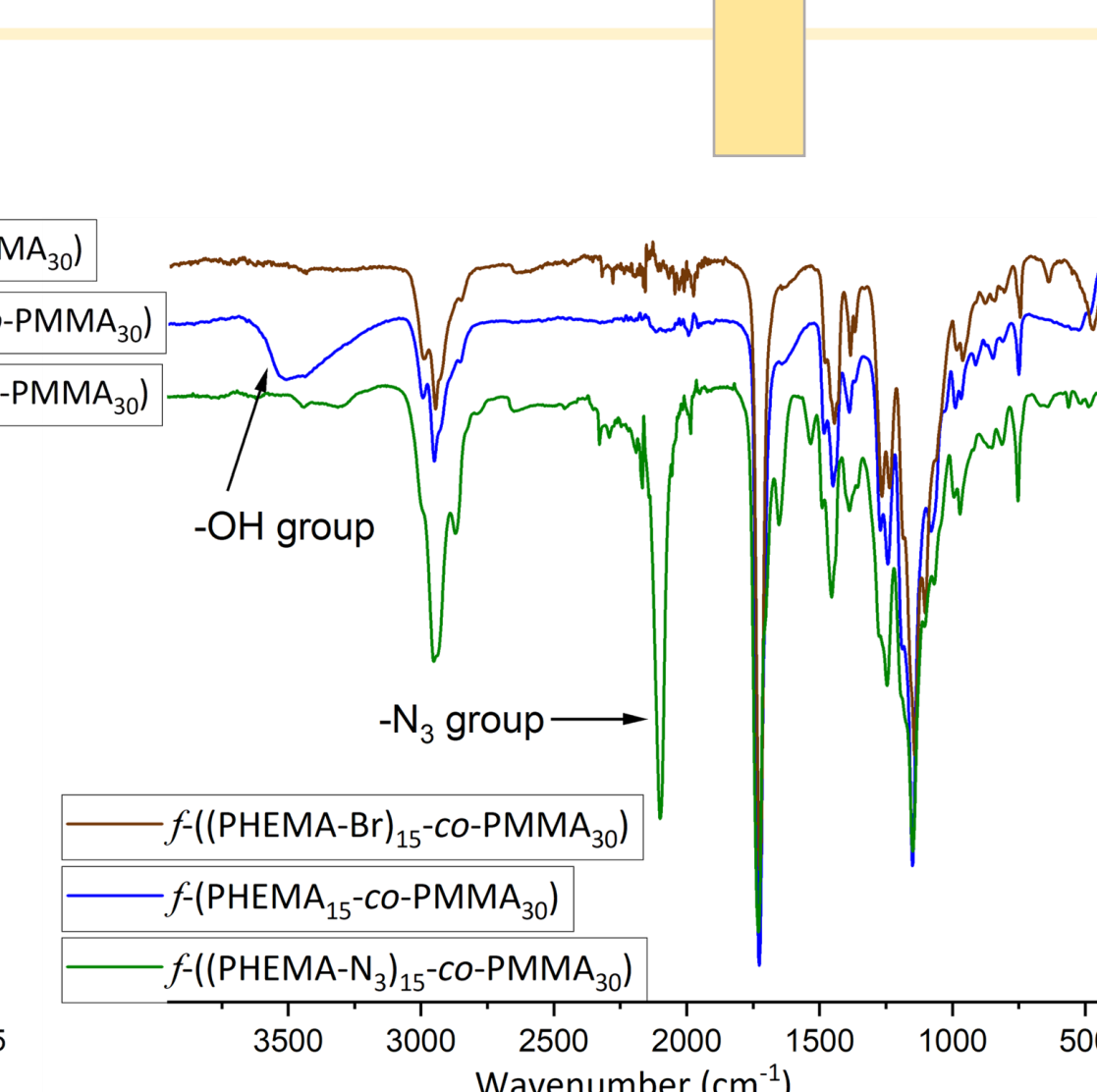


Figure 11 IR spectra of f -(PHEMA₁₅-co-PMMA₃₀), f -(PHEMA-Br)₁₅-co-PMMA₃₀ and f -(PHEMA-N₃)₁₅-co-PMMA₃₀ (top-to-bottom).

4. Synthesis of cyclic brush polymers

4a. via "grafting-onto" approach

Synthesis of f -(PHEMA-*g*-PEO)_x-co-PMMA_y and f -(PHEMA-*g*-PiPOx)_x-co-PMMA_y:

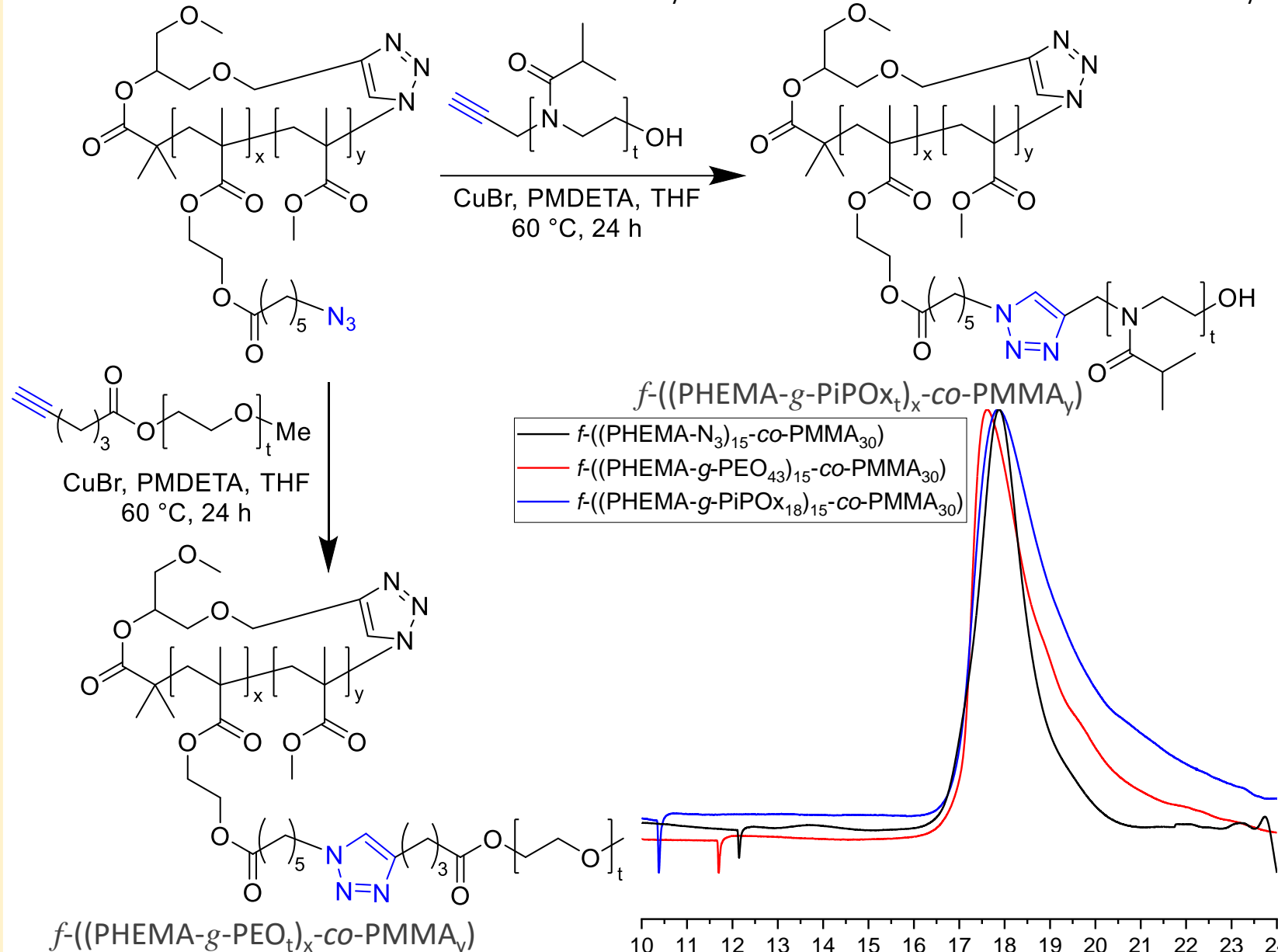


Figure 12 GPC chromatogram (RI trace, THF) of: f -(PHEMA-N₃)₁₅-co-PMMA₃₀ ($M_{n,GPC} = 15280$, $M_w/M_n = 1.26$); f -(PHEMA-*g*-PEO)₁₅-co-PMMA₃₀ ($M_{n,GPC} = 8000$, $M_w/M_n = 1.89$); f -(PHEMA-*g*-PiPOx)₁₅-co-PMMA₃₀ ($M_{n,GPC} = 7400$, $M_w/M_n = 1.88$).

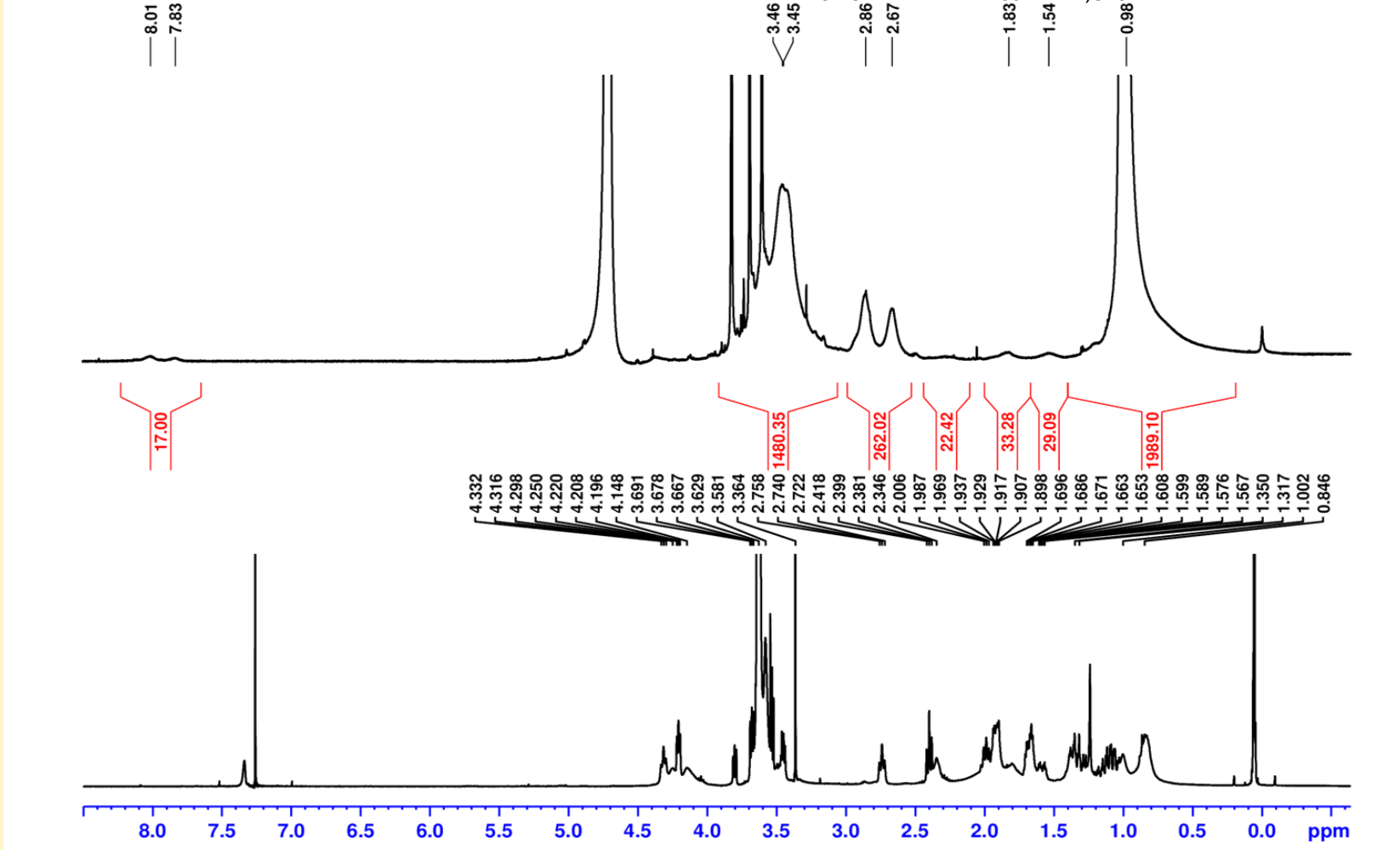


Figure 13 ¹H NMR spectra of f -(PHEMA-*g*-PiPOx)_x-co-PMMA_y (D₂O, 600 MHz, top) and f -(PHEMA-Br)₁₅-co-PMMA₃₀ (CDCl₃, 400 MHz, bottom).

4b. via "grafting-from" approach

Example: synthesis of f -(PHEMA-*g*-PTBA)_x-co-PMMA_y via ATRP using f -(PHEMA-Br)_x-co-PMMA_y as a macroinitiator

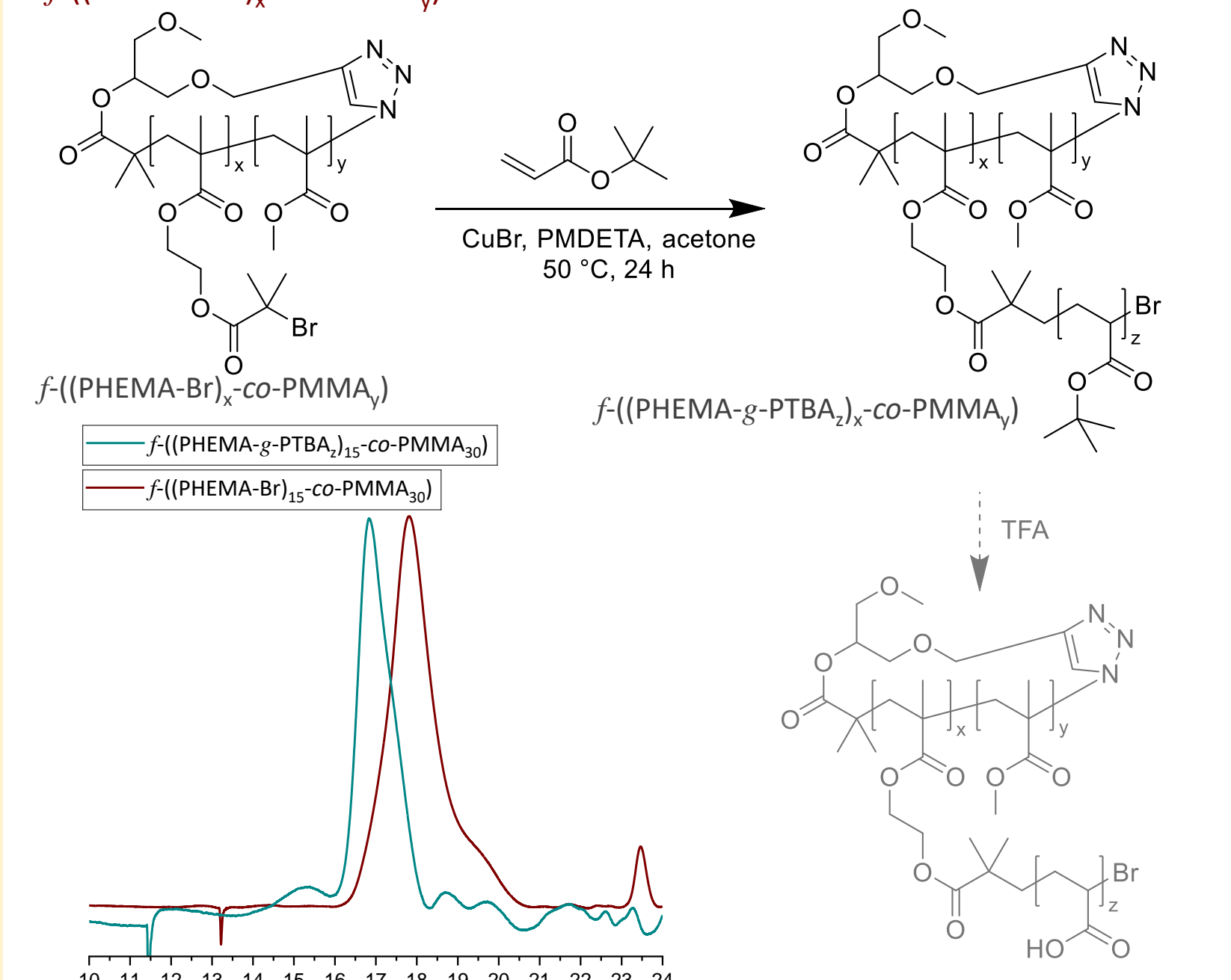


Figure 14 GPC chromatogram (RI trace, THF) of: f -(PHEMA-Br)₁₅-co-PMMA₃₀ ($M_{n,GPC} = 12860$, $M_w/M_n = 1.67$); f -(PHEMA-*g*-PTBA)₁₅-co-PMMA₃₀ ($M_{n,GPC} = 34640$, $M_w/M_n = 1.48$).

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