Supplementary Information for the Manuscript Entitled

Novel poly(ethylene oxide monomethyl ether)-*b*-poly(ε-caprolactone) diblock copolymers containing a pH-acid labile ketal group as blocks linkage

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Synthesis of the compounds 1-5.

Synthesis of Ethylene glycol monoacetate ***(compound 1)***

Ethylene glycol monoacetate (**1**) was synthesized according to previous procedures.[44,45] Briefly, ethylene glycol (6.7 mL, 0.121 mol), trimethyl orthoacetate (23.1 mL, 0.182 mol), and p-toluene sulfonic acid monohydrate (0.5 g, 0.121 mol) were dissolved in 150 mL of CH_2Cl_2 and stirred at room temperature for 4 h. Water (3.3 mL, 0.182 mol) was added to the reaction mixture and stirred for an additional 1 h. CH_2Cl_2 was removed under reduced pressure and the obtained crude product was purified by silica gel flash chromatography using $CHCl_3$/acetone (9:1) as a mobile phase. The product, 2-hydroxyethyl acetate (**1**), was recovered as a colorless liquid. Yield: 2.45 g, 40%. ^{1}H-NMR ($CDCl_3$, ppm): 2.09 (s, 3H, C*H*$_3$-C(O)-O-), 3.1 (s, 1H, -CH_2-O*H*), 3.8 (t, 2H, -O-CH_2-C*H*$_2$-OH), 4.18 (t, 2H, -O-C*H*$_2$-CH_2-OH). ^{13}C-NMR ($CDCl_3$, ppm): 20.9, 60.9, 66.11, 171.6.

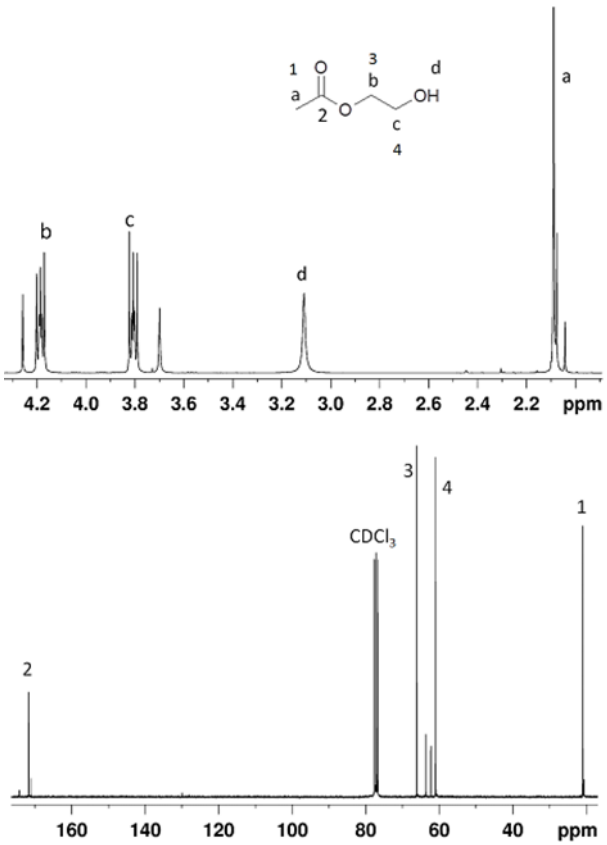

Fig. **S1**. ^{1}H (top) ^{13}C (bottom) NMR spectra of the ethylene glycol monoacetate (**1**) in $CDCl_3$.

Synthesis of 2-Azidoethanol ***(compound 2)***

Compound **2** was synthesized according to the literature.[46] In a typical reaction, 2-chloroethanol (5.22 g, 0.078 mol), sodium azide (15.19 g, 0.234 mol), and TBABr (2.51 g, 0.0078 mol) were mixed in a round-bottom flask equipped with a reflux condenser and stirred at 110 ºC for 18 h (using a safety shield). The mixture was diluted with Et_2O and the solid by-products were filtered off. The solvent was evaporated under reduced pressure (without heating), giving a yellow oil. The crude product was purified by distillation at 12 mbar, yielding 2-azidoethanol (**2**) as a colorless oil. Yield: 2.23 g, 40%. ^{1}H-NMR ($CDCl_3$, ppm): 2.82 (s, 1H, -CH_2-O*H*), 3.45 (t, 2H, -C*H*$_2$-OH), 3.75 (t, 2H, N_3-C*H*$_2$-). ^{13}C-NMR ($CDCl_3$, ppm): 53.58, 61.47.

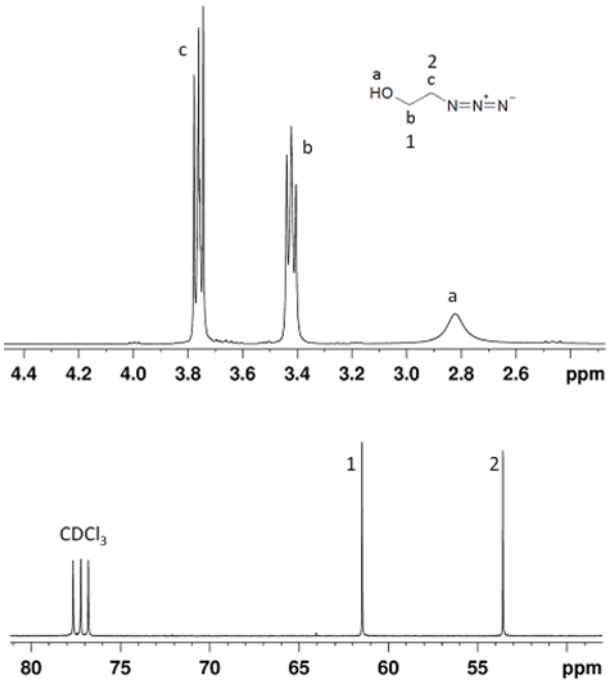

Fig. **S2**. ^{1}H (top) ^{13}C (bottom) NMR spectra of the 2-azidoethanol (**2**) in $CDCl_3$.

Synthesis of 2-{[2-(2-azidoethoxypropan-2-yl]oxy}ethyl acetate ***(compound 3)***

2-{[2-(2-Azidoethoxypropan-2-yl]oxy}ethyl acetate (**3**) was synthesized according to literature procedure.[45] Compound 1 (1.5 g) and 2 (1.3 g) 1/1 mol/mol were dissolved in 50 mL of dry THF. PPTS (0.4 g, 0.00144 mol) was added and stirred for 15 min, followed by addition of molecular sieves (5 Å) (30 g) and additional stirring for 15 min. To this mixture, 2-methoxypropene (1.04 g, 0.0144 mol) was added, and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was neutralized with solid $NaHCO_3$ and kept over Celite bed. The filtrate was evaporated to obtain the crude product, which was purified by column chromatography on silica gel using EtOAc/Hex (1:9) as eluent. The formation of the new 2-{[2-(2-azidoethoxypropan-2-yl]oxy}ethyl acetate (**3**) was determined by collection of different fractions monitored by TLC. The product was recovered as a colorless liquid. Yield: 1 g, 70%. ^{1}H-NMR ($CDCl_3$, ppm): 1.38 (s, 6H, -O-C(C*H*$_3$)$_2$-O-), 2.08 (s, 3H, C*H*$_3$-C(O)-O-), 3.35 (t, 2H, -C(CH$_3$)$_2$-O-C*H*$_2$-CH$_2$-N$_3$), 3.58-3.68 (m, 4H, -C*H*$_2$-O-C(CH$_3$)$_2$-O-CH$_2$-C*H*$_2$-N$_3$), 4.19 (t, 2H, CH$_3$-C(O)-O-C*H*$_2$-). ^{13}C-NMR ($CDCl_3$, ppm): 21.10, 24.80, 51.04, 59.11, 60.01, 63.93, 100.46, 171.07.

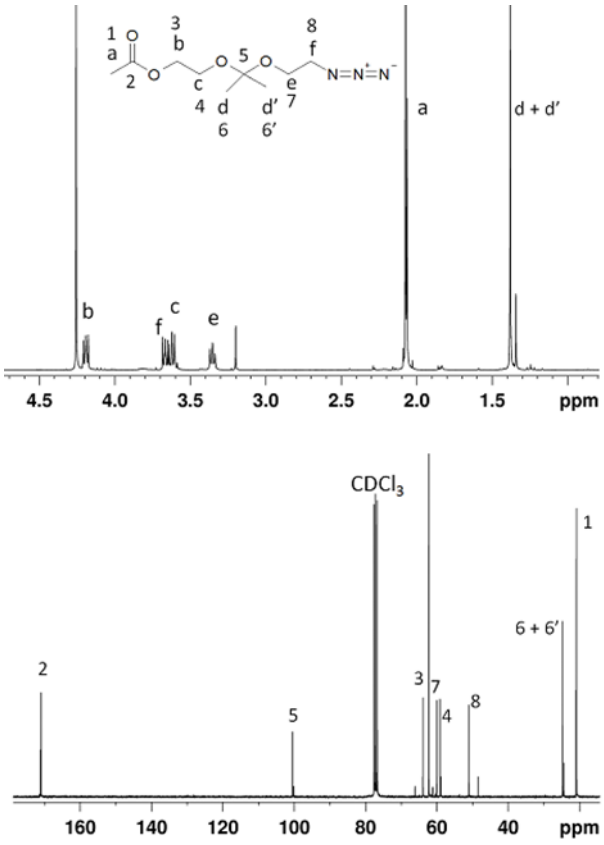

Fig. **S3**. ^{1}H (top) and ^{13}C (bottom) NMR spectra of the 2-{[2-(2-azidoethoxypropan-2-yl]oxy}ethyl acetate (**3**) in $CDCl_3$.

Synthesis of 2-{[2-(2-azidoethoxy)propan-2-yl]ethan-1-ol ***(compound 4)***

Compound **4** was synthesized according to previous procedure.[45] Deprotection of the acetyl group of the compound **3** was carried out by treating with sodium hydroxide in CH_3OH/H_2O at room temperature for 2 h. After the reaction, brine was added and the product was extracted with CH_2Cl_2. The combined organic phases were evaporated under reduced pressure. The product (**4**) was recovered as a colorless liquid. Yield: 0.8 g, 80%. ^{1}H-NMR ($CDCl_3$, ppm): 1.35 (s, 6H, -O-C(CH_3)$_2$-O-), 3.34-3.38 (t, 2H, -C(CH_3)$_2$-O-CH_2-CH_2-N_3), 3.56-3.59 (m, 4H, --C(CH_3)$_2$-O-CH_2-CH_2-OH), 3.62-3.68 (t, 2H, -CH_2-N_3). ^{13}C-NMR ($CDCl_3$, ppm): 21.10, 24.40, 48.62, 51.08, 59.93, 100.35.

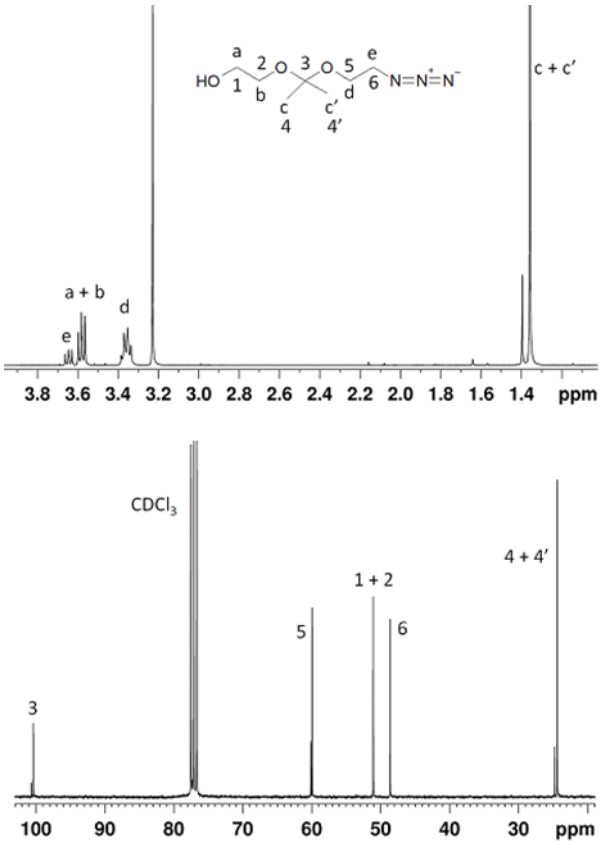

Fig. **S4**. ^{1}H (top) and ^{13}C (bottom) NMR spectra of the 2-{[2-(2-azidoethoxy)propan-2-yl]ethan-1-ol (**4**) in $CDCl_3$.

Synthesis of α-methoxy-ω-alkyne-poly(ethylene oxide) ***(compound 5)***

α-Methoxy-*ω*-alkyne-poly(ethylene oxide) (**5**) was synthesized according to the literature.[47] In a flame-dried and argon-purged two-neck round-bottom flask equipped with three-port valves *α*-methoxy-*ω*-hydroxyl-poly(ethylene oxide) (9g, 0.0045 mol, 1800 g/mol) was dried by repeated azeotropic distillations (three times) of dry toluene. After, 0.5 mL of 5-hexynoic acid (0.0045 mol), 0.055 g of DMAP (0.00045 mol) and 0.93 mg of DCC (0.0045 mol) were transferred to the flask under inert gas blanket followed by the addition of 107 mL of dry CH_2Cl_2 by using a flame-dried and argon-flushed glass syringe equipped with a metallic cannula. The solution was stirred at room temperature for 36 h under argon. The solvent was evaporated under vacuum and the solid residue was dissolved in THF. The resulted solution was filtered to remove the dicyclohexylurea (by-product) and the polymer was precipitated in cold Et_2O. After filtration the solid was dried under vacuum at room temperature. Yield: 8.09 g, 90%. ^{1}H-NMR ($CDCl_3$, ppm): 1.83 (p, 2H, -C*H*$_2$-CH$_2$-C≡H), 1.96 (t, 1H, -C≡*H*), 2.25 (td, 2H, -C*H*$_2$-C≡H), 2.47 (t, 2H, -C*H*$_2$-CH$_2$-CH$_2$-C≡H), 3.39 (s, 3H, -O-C*H*$_3$), 3.63 (m, 4H, -C*H*$_2$-C*H*$_2$-O-), 3.86 (t, 2H, -O-C*H*$_2$-CH$_2$-O-C(O)), 4.22 (t, 2H, -O-CH$_2$-C*H*$_2$-O-C(O)).

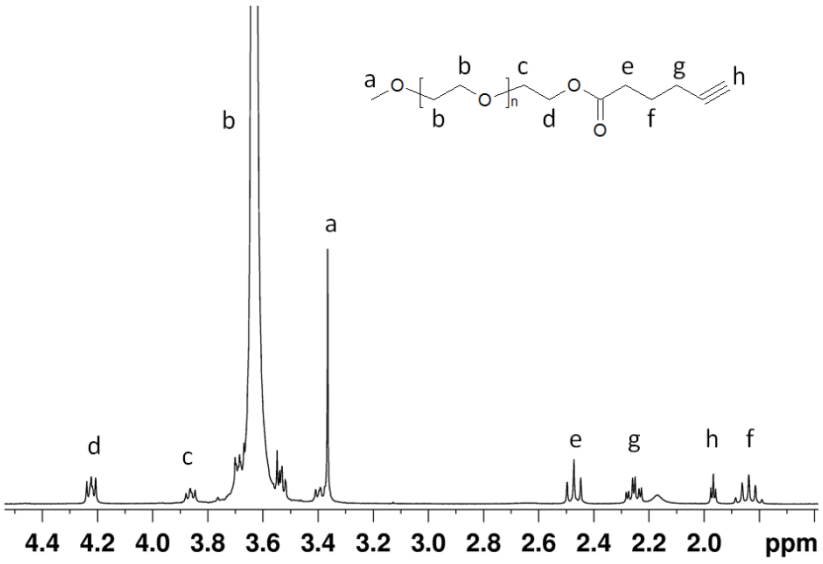

Fig. **S5**. ^{1}H NMR spectrum of the α-methoxy-ω-alkyne-PEO (**5**) in $CDCl_3$.

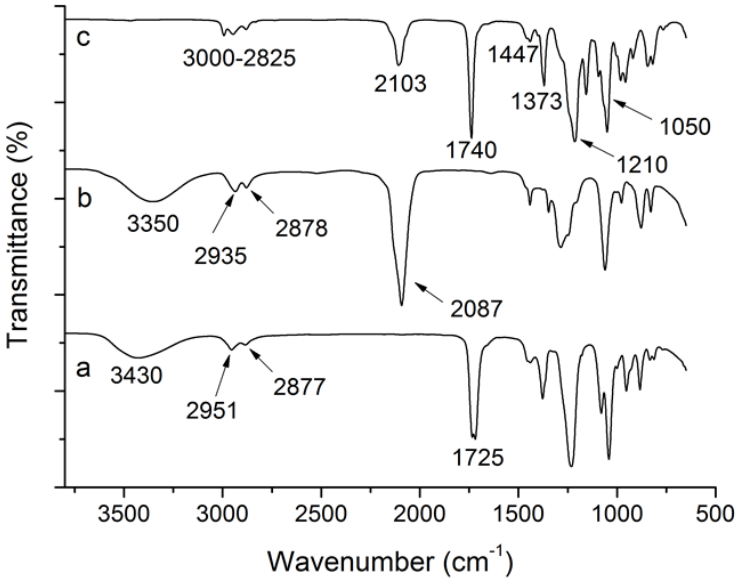

Fig. **S6**. FT-IR spectra of the (a) ethylene glycol monoacetate **(1)**, (b) 2-azidoethanol **(2)**, and (c) 2-{[2-(2-azidoethoxy)propan-2-yl]oxy}ethyl acetate **(3)**.

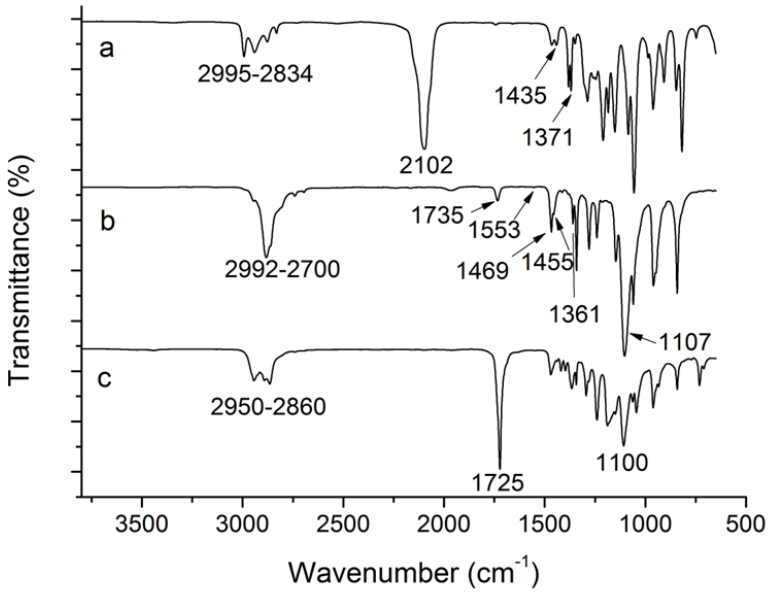

Fig. **S7**. FT-IR spectra of the (a) 2-{[2-(2-azidoethoxy)propan-2-yl]ethan-1-ol (**4**), (b) α-methoxy-ω-hydroxy-poly(ethylene oxide) containing ketal group (**6**), and (c) MPEO-*b*-PCL diblock copolymer (**7**).

The characteristic peaks observed are the following; 1725 cm^{-1} for the ester bond (C=O stretching) from the ε-CL repeated units in the PCL block, 1100 cm^{-1} for the ether bond (C–O–C stretching) of the EO repeated units of the PEO backbone and at 2950 and 2860 cm^{-1} the C–H vibrations bands typical for both monomer units.

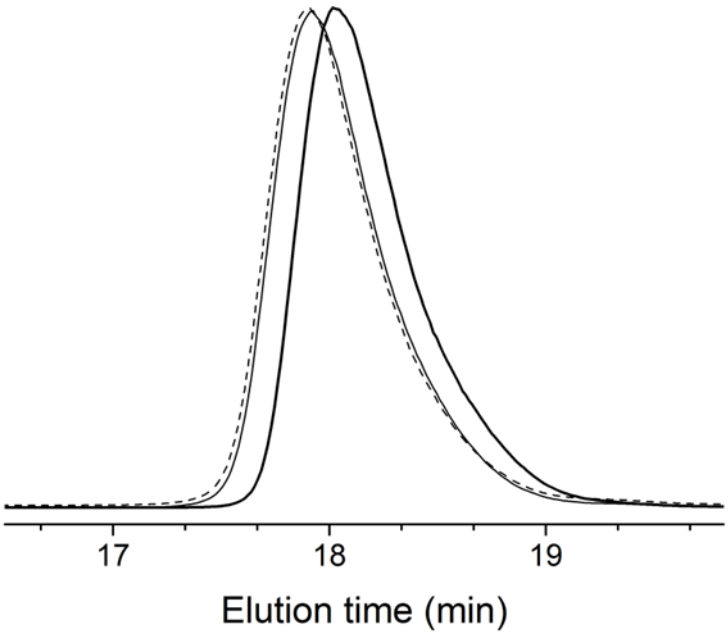

Fig. **S8**. SEC chromatograms in THF of MPEO (bold line), ω-alkyne-MPEO (regular line) and α-methoxy-ω-hydroxy-MPEO containing ketal group (**6**) (dotted line).

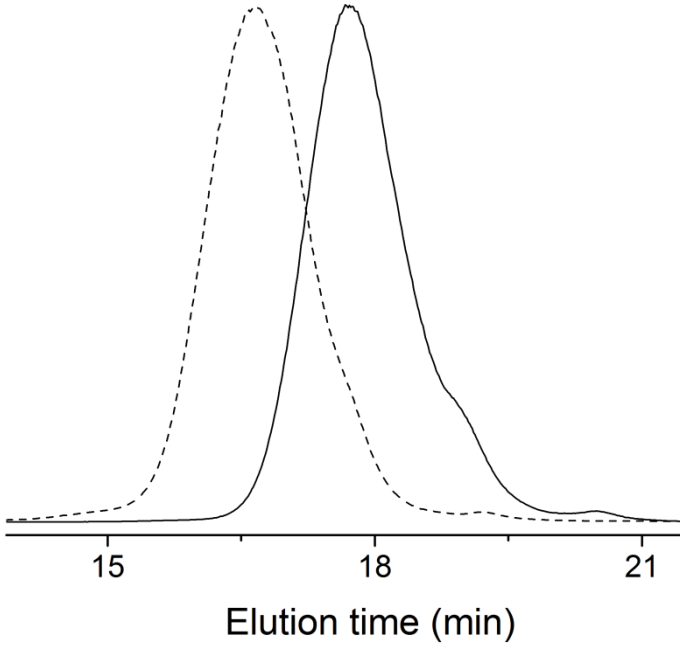

Fig. **S9**. SEC chromatograms in THF of $MPEO_{44}$-*b*-PCL_{17} diblock copolymer (—) (1, in Table 2) and $MPEO_{44}$-*b*-PCL_{44} diblock copolymer (---) (2, in Table 2).

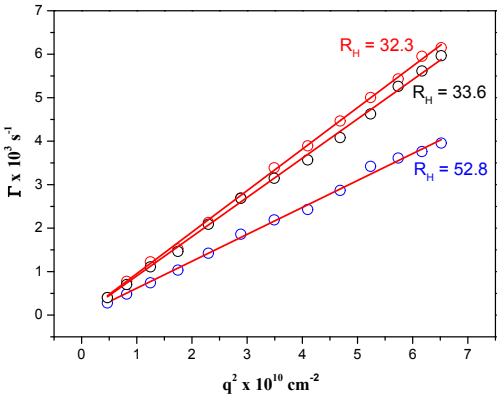

Fig. **S10**. Angular variation of the frequency $\Gamma = 1/\tau$ as a function of q^2 at 37 ºC for: (○) $MPEO_{44}$-*b*-PCL_{17} micelles in PBS (pH ~ 7.4) and 0h, (○) in PBS (pH ~ 7.4) and 24h and (○) in acetate buffer (pH ~ 5) after 24 hours.

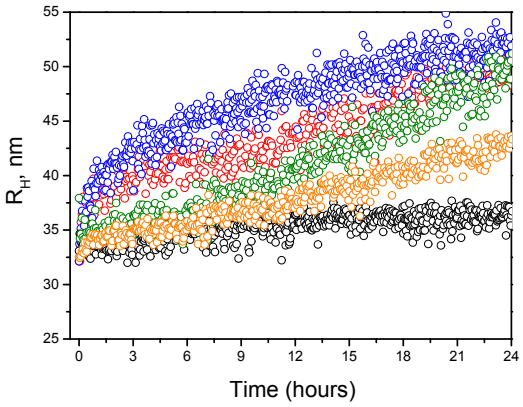

Fig. **S11**. Temporal dependence on R_H distribution of $MPEO_{44}$-*b*-PCL_{17} micelles in (○) PBS (pH ~ 7.4) and in acetate buffer (○) pH ~ 6.5, (○) pH ~ 6.0, (○) pH ~ 5.5 and (○) pH ~ 5.0 at 37 °C.

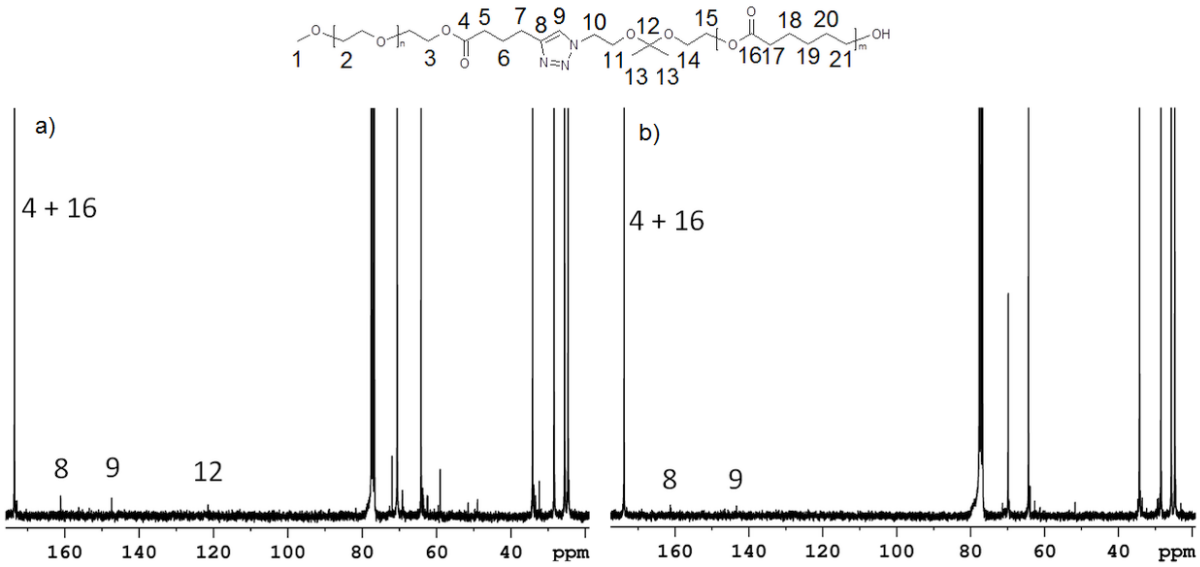

Fig. **S12**. ^{13}C NMR spectra of $MPEO_{44}$-*b*-PCL_{17} diblock copolymer (a) before degradation and (b) after degradation.