Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supporting Information

Block copolymers comprising degradable poly(2-ethyl-2-oxazoline) analogues *via* copper-free click chemistry

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Experimental details for the preliminary oxidation studies

Synthesis of azido-terminated poly(2-ethyl-2-oxazoline), PEtOx-N_3

The **PEtOx-N_3** used for the treatment under oxidative conditions was synthesized as described in the following: MeOTs (36 mg, 0.19 mmol) and EtOx (385 mg, 3.88 mmol, 20 equiv.) were dissolved in dry CH_3CN (440 mg) in a pre-dried microwave vial to achieve a [monomer] to [initiator] ratio [M]:[I] of 20:1 and a monomer concentration of 4 M. The polymerization proceeded in a microwave synthesizer at 140 °C for 2.5 min. Afterwards, NaN_3 (32 mg, 0.49 mmol, 2.6 equiv.) was added under argon atmosphere. The termination was completed by stirring for 24 h at 70 °C. An aliquot was removed and analyzed by means of ^{1}H NMR spectroscopy (quantitative conversion of EtOx). Subsequently, the reaction solution was diluted with chloroform (100 mL) and washed with sat. aq. sodium bicarbonate solution (3 × 100 mL) as well as brine (3 × 100 mL). The organic layer was dried over $MgSO_4$ and filtered. The volatiles were removed under reduced pressure and the residue was precipitated in cold diethyl ether (−80 °C). Subsequent drying *in vacuo* yielded **PEtOx-N_3** as a colorless solid (yield: 317 mg, 80%).

Synthesis of thioacetate-terminated poly(2-ethyl-2-oxazoline), PEtOx-SAc

The **PEtOx-SH** utilized for the treatment under oxidative conditions to study the end group behavior was synthesized from **PEtOx-SAc**. For the synthesis of **PEtOx-SAc**, MeOTs (82 mg, 0.44 mmol) and EtOx (874 mg, 8.82 mmol, 20 equiv.) were dissolved in dry CH_3CN (975 mg) to achieve a [monomer] to [initiator] ratio [M]:[I] of 20:1 and a monomer concentration of 4 M. The polymerization was performed in a microwave synthesizer at 140 °C for 2 min and was subsequently terminated by addition of potassium thioacetate (151 mg, 1.32 mmol, 3.0 equiv.) under argon atmosphere. The reaction mixture was stirred overnight at room temperature. An

aliquot was removed and analyzed by means of ^{1}H NMR spectroscopy (91% conversion of EtOx). The excess of potassium thioacetate was removed by filtration, the filtrate was diluted with chloroform (100 mL) and washed with sat. aq. sodium bicarbonate solution (2 × 100 mL) as well as brine (1 × 100 mL). The organic phase was dried over $MgSO_4$ and filtered. The volatiles were removed under reduced pressure, followed by precipitation in diethyl ether (−80 °C) twice. After drying *in vacuo*, the **PEtOx-SAc** was obtained as a colorless solid (yield: 608 mg, 67%).

Synthesis of thiol-terminated poly(2-ethyl-2-oxazoline), PEtOx-SH

PEtOx-SAc (450 mg, 0.217 mmol) was dissolved in dry methanol under argon atmosphere. A sodium methoxide solution (43.4 µL, 0.5 M in methanol) was added and the reaction mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and washed with a sat. aq. sodium bicarbonate solution (2 × 30 mL) as well as brine (1 × 30 mL). The aqueous phase was re-extracted with additional dichloromethane (30 mL) after each washing step. The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was precipitated in diethyl ether (−80 °C). Subsequent to drying *in vacuo*, **PEtOx-SH** was obtained as a colorless solid (yield: 364 mg, 74%).

Treatment of PEtOx-N_3 under oxidative conditions

PEtOx-N_3 (100 mg, 0.049 mmol) was dissolved in methanol (2 mL) and hydrogen peroxide solution (70.5 µL, 30% w/w, 0.690 mmol, 0.7 equiv. per amino unit) was added dropwise. The reaction solution was stirred at ambient temperature for 2 d. Subsequently, the solution was diluted with chloroform (20 mL) and extracted with brine (2 × 20 mL) until the peroxide test

was negative. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure, followed by an additional precipitation in cold diethyl ether (−80 °C). After drying *in vacuo*, the polymer was obtained as a colorless solid (yield: 64 mg).

Treatment of PEtOx-SH under oxidative conditions

PEtOx-SH (51 mg, 0.025 mmol) was dissolved in methanol (2.5 mL) and hydrogen peroxide solution (35.1 µL, 30% w/w, 0.344 mmol, 0.7 equiv. per amino unit) was added dropwise. The reaction solution was stirred at ambient temperature for 2 d. Afterwards, the solution was diluted with chloroform (20 mL) and washed with brine (3 × 20 mL) until the peroxide test was negative. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Drying *in vacuo* yielded the oxidized polymer as a colorless solid (yield: 50 mg).

Experimental details for the block copolymer synthesis

Synthesis of PEtOx-*b*-PNonOx

PEtOx-*b*-PNonOx was synthesized following the general procedure using **PEtOx-N$_3$** (40 mg, 20 µmol, 2 equiv.), **PNonOx-DBCO** (23 mg, 10 µmol) and dichloromethane (2 mL). Subsequent to the reaction, the volatiles were removed under reduced pressure and the remaining mixture was dissolved in THF and precipitated in water. The entire suspension was transferred to a dialysis tube (MWCO 3.5 kDa) and dialyzed against water. Freeze-drying yielded the polymer as a white solid (yield: 40 mg, 94%).

$M_{n,theor.}$ = 4,400 g mol^{-1}

^{1}H NMR spectroscopy (300 MHz, CD_2Cl_2): δ = 7.72–6.93 (br, 8H, Ar-H DBCO ring), 4.17–4.08 (br, 2H, CH_2–CH_2-OCO), 3.71–3.12 (br, 118H, CH_2–CH_2 EtOx and NonOx unit), 3.02–2.87 (br, 6H, α-CH_3), 2.46–2.09 (br, 60H, CO–CH_2–CH_3 EtOx unit and CO–CH_2–CH_2–$(CH_2)_6$–CH_3 NonOx unit), 1.63–1.44 (br, 20H, CO–CH_2–CH_2–$(CH_2)_6$–CH_3 NonOx unit), 1.39–1.18 (br, 120H, CO–CH_2–CH_2–(CH_2)$_6$–CH_3 NonOx unit), 1.14–0.99 (br, 60H, CO–CH_2–CH_3 EtOx unit), 0.92–0.81 ppm (br, 30H, CO–CH_2–CH_2–$(CH_2)_6$–CH_3 NonOx unit).

SEC (DMAc, 0.21 wt% LiCl, RI detection, PS calibration): M_n = 6,400 g mol^{-1}; Đ = 1.10.

Synthesis of dPEtOx-*b*-PNonOx

The polymer was synthesized according to the general procedure using **dPEtOx-N$_3$** (80 mg, 50 µmol, 2 equiv.), **PNonOx-DBCO** (58 mg, 25 µmol) and dichloromethane (5 mL). Subsequent to the reaction, the solvent was removed under reduced pressure. The crude polymer was dissolved in THF and dialyzed against water (MWCO 1 kDa). After freeze-drying, the polymer was obtained as a light brownish solid (yield: 77 mg, 80%).

$M_{n,theor.}$ = 3,900 g mol^{-1}

^{1}H NMR spectroscopy (300 MHz, CD_2Cl_2): δ = 8.13–7.82 (br, 10H, N*H*–CO–CH_2), 7.71–6.99 ((br, 8H, Ar-H DBCO ring), 4.19–4.01 (br, 2H, CH_2–C*H*$_2$-OCO), 3.57–3.25 (br, 98H, NH–CO–C*H*$_2$ glycine unit, C*H*$_2$–C*H*$_2$ EtOx and NonOx unit), 3.01–2.86 (br, 6H, α-CH_3), 2.48–2.10 (br, 40H, CO–C*H*$_2$–CH_3 EtOx unit CO–C*H*$_2$–CH_2–$(CH_2)_6$–CH_3 NonOx unit), 1.65–1.44 (br, 20H, CO–CH_2–C*H*$_2$–$(CH_2)_6$–CH_3 NonOx unit), 1.40–1.18 (br, 120H, CO–C*H*$_2$–CH_2–(C*H*$_2$)$_6$–CH_3 NonOx unit), 1.16–0.99 (br, 30H, CO–CH_2–C*H*$_3$ EtOx unit), 0.93–0.81 ppm (br, 30H, CO–CH_2–CH_2–$(CH_2)_6$–C*H*$_3$ NonOx unit).

SEC (DMAc, 0.21 wt% LiCl, RI detection, PS calibration): M_n = 5,000 g mol^{-1}; Đ = 1.36.

Synthesis of PEtOx-*b*-PCL

PEtOx-*b*-PCL was synthesized according to the general procedure using **PEtOx-N$_3$** (27 mg, 13 µmol, 2 equiv.), **BCN-PCL** (96 mg, 6.6 µmol) and dichloromethane (2.6 mL). Subsequent to the reaction, the volatiles were removed under reduced pressure. The mixture was dissolved in THF and dialyzed repeatedly against THF and water (MWCO 3.5 kDa). The polymer was freeze-dried, dissolved in THF and precipitated in cold methanol (−80 °C). Drying of the polymer overnight *in vacuo* yielded **PEtOx-*b*-PCL** as a colorless solid (yield: 105 mg, 96%).

$M_{n,theor.}$ = 16,500 g mol^{-1}.

^{1}H NMR spectroscopy (300 MHz, $CDCl_3$): δ = 4.23–3.98 (CO–CH_2–CH_2CH_2–CH_2C*H*$_2$-O εCL unit), 3.61–3.36 (N–C*H*$_2$–C*H*$_2$ EtOx unit), 2.47–2.21 (CO–C*H*$_2$–CH_2CH_2–CH_2CH_2-O εCL unit and CO–C*H*$_2$–CH_3 EtOx unit), 1.86–1.54 (CO–CH_2–C*H*$_2$$CH_2$–$CH_2CH_2$-O εCL unit), 1.54–1.30 (CO–CH_2–CH_2C*H*$_2$–C*H*$_2$$CH_2$-O εCL unit), 1.23–1.02 ppm (CO–CH_2–C*H*$_3$ EtOx unit).

SEC (DMAc, 0.21 wt% LiCl, RI detection, PS calibration): M_n = 39,400 g mol^{-1}; Đ = 1.51.

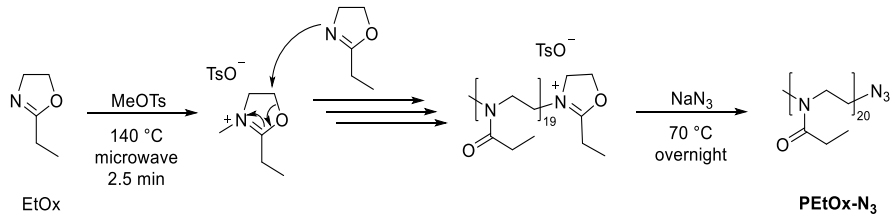
Synthesis of dPEtOx-*b*-PCL

dPEtOx-*b*-PCL was synthesized following the general procedure using **dPEtOx-N$_3$** (20 mg, 12 µmol, 2 equiv.) and **BCN-PCL** (90 mg, 6.2 µmol). The reaction mixture was diluted with dichloromethane (30 mL) and washed with brine (3 × 10 mL). The aqueous phase was re-extracted with dichloromethane (10 mL) after each washing step. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Precipitation into cold diethyl ether (−80 °C) and subsequent dialysis against water (MWCO 3.5 kDa) followed by freeze-drying yielded **dPEtOx-*b*-PCL** as a slightly brownish solid (yield: 52 mg, 52 %).

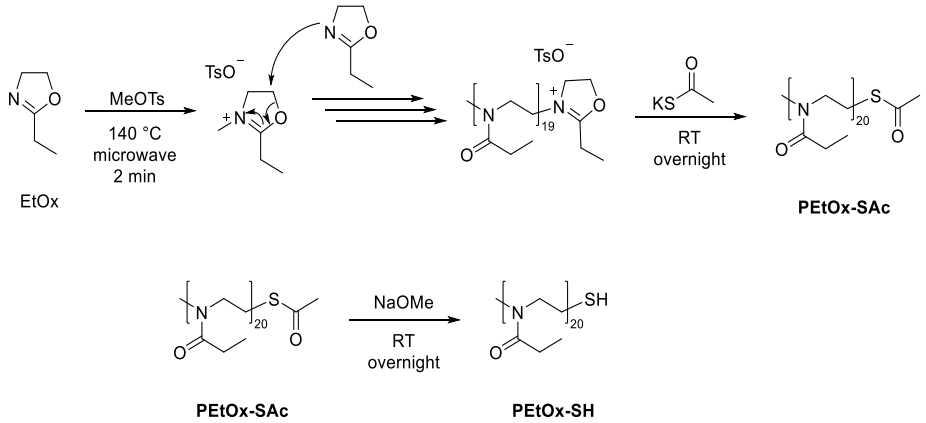
$M_{n,theor.}$ = 16,100 g mol^{-1}.

^{1}H NMR spectroscopy (300 MHz, $CDCl_3$): δ = 8.15–7.85 (N*H*–CO–CH_2 glycine unit), 4.26–3.87 (CO–CH_2–CH_2CH_2–CH_2CH_2-O εCL unit), 3.61–3.28 (N–C*H*$_2$–C*H*$_2$ EtOx unit and NH–CO–C*H*$_2$ glycine unit), 2.59–2.14 (CO–C*H*$_2$–CH_2CH_2–CH_2CH_2-O εCL unit and CO–C*H*$_2$–CH_3 EtOx unit), 1.86–1.54 (CO–CH_2–C*H*$_2$$CH_2$–$CH_2CH_2$-O εCL unit), 1.54–1.30 (CO–CH_2–CH_2-C*H*$_2$–C*H*$_2$$CH_2$-O εCL unit), 1.19–0.98 ppm (CO–CH_2–C*H*$_3$ EtOx unit)

SEC (DMAc, 0.21 wt% LiCl, RI detection, PS calibration): M_n = 30,900 g mol^{-1}; Đ = 1.51.



Scheme SI1: Schematic representation of the synthesis of **PEtOx-N3** *via* CROP of 2-ethyl-2-oxazoline. The polymerization was initiated with methyl tosylate (MeOTs) and terminated with sodium azide.



Scheme SI2: Schematic representation of the synthesis of **PEtOx-SAc** *via* CROP of 2-ethyl-2-oxazoline. The polymerization was initiated with methyl tosylate (MeOTs) and terminated with potassium thioacetate. Deprotection with sodium methoxide solution yielded **PEtOx-SH**.

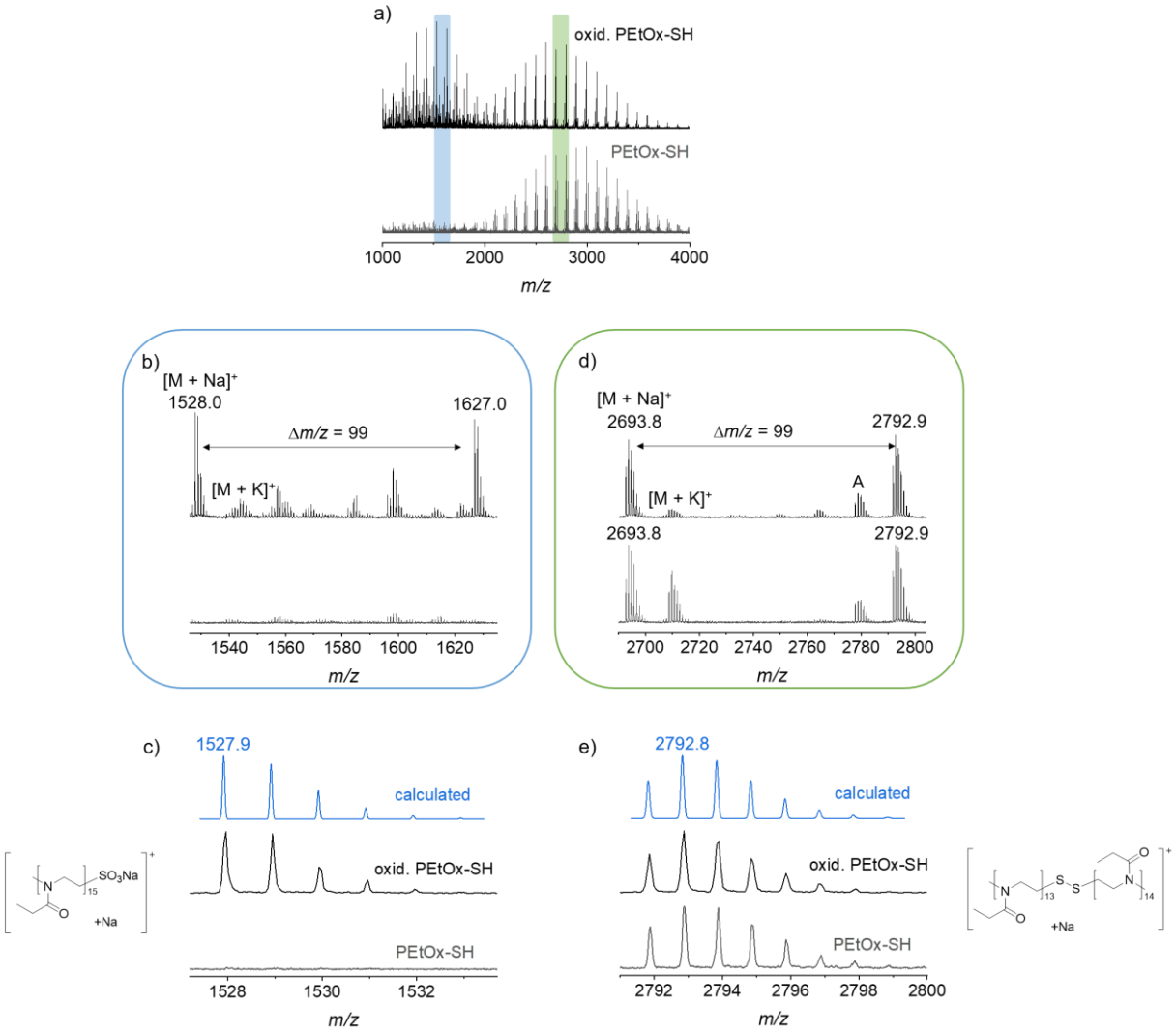


Figure SI1: MALDI TOF MS analysis (matrix CHCA) of **PEtOx-SH** before and after the treatment under oxidative conditions. (a) Overlay of the full spectra. (b) Zoom into a *m/z* region displaying the distance corresponding to one EtOx repeating unit ($\Delta m/z$ = 99) within the distribution at lower *m/z* values including the assignment of the most prominent species. (c) Overlay of the measured and the calculated isotopic patterns of the most prominent species at higher *m/z* ($[M + Na]^+$). (d) Zoom into the *m/z* region of one repeating unit ($\Delta m/z$ = 99) for the distribution at higher *m/z* with the assignment of the most prominent species (A: $[H_3C(C_5H_9NO)_nSS(C_5H_9NO)_nH]^+$). (e) Overlay of the measured and the calculated isotopic pattern of the most prominent species in the lower *m/z* region ($[M + Na]^+$).

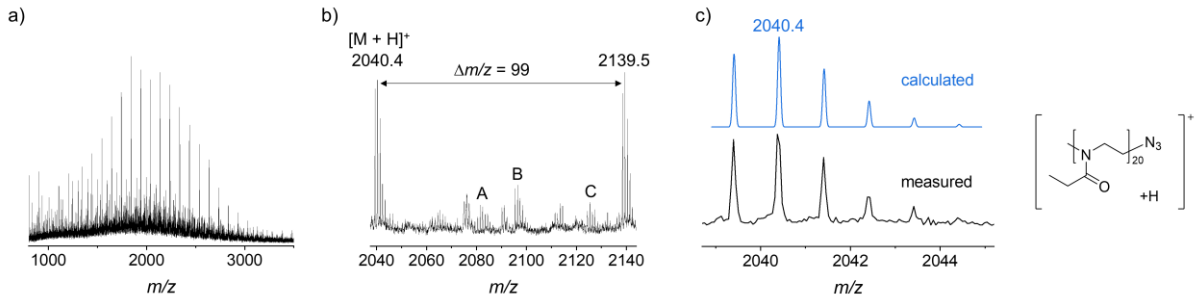


Figure SI2: MALDI TOF MS analysis (matrix dithranol) of **PEtOx-N3**. (a) Overlay of the full spectra. (b) Zoom into the *m/z* region of one repeating unit ($\Delta m/z$ = 99) with the assignment of the most prominent species (A: $[H(C_5H_9NO)_n]^+$; B: $[H_3C(C_5H_9NO)_n]^+$; C: $[H(C_5H_9NO)_nN_3 + H]^+$). (c) Overlay of the measured and the calculated isotopic patterns of the most prominent species ($[M + H]^+$).

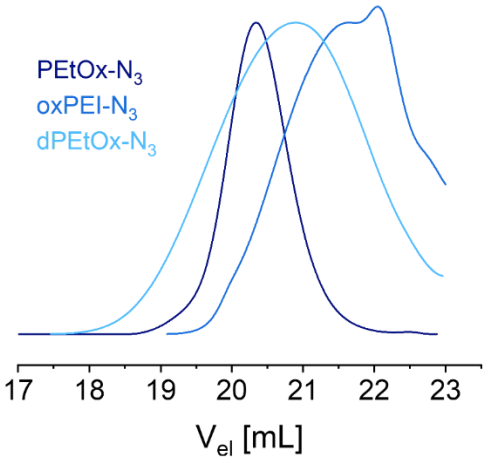
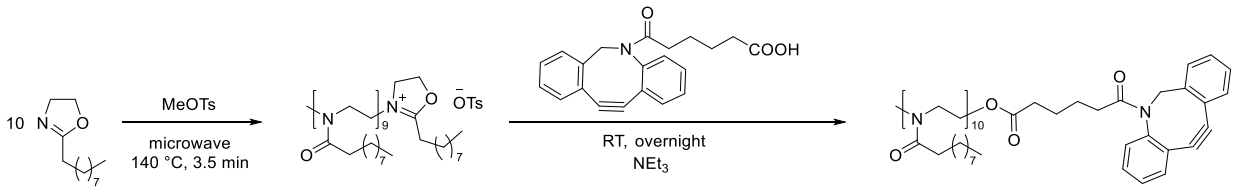


Figure SI3: Overlay of the SEC elugrams (DMAc, 0.21 wt% LiCl, RI detection) of **PEtOx-N3**, **oxPEI-N3** and **dPEtOx-N3**.



Scheme SI3: Schematic representation of the CROP of 2-*n*-nonyl-2-oxazoline yielding **PNonOx-DBCO**. The CROP was initiated with methyl tosylate and terminated with *in situ* deprotonated DBCO. ε

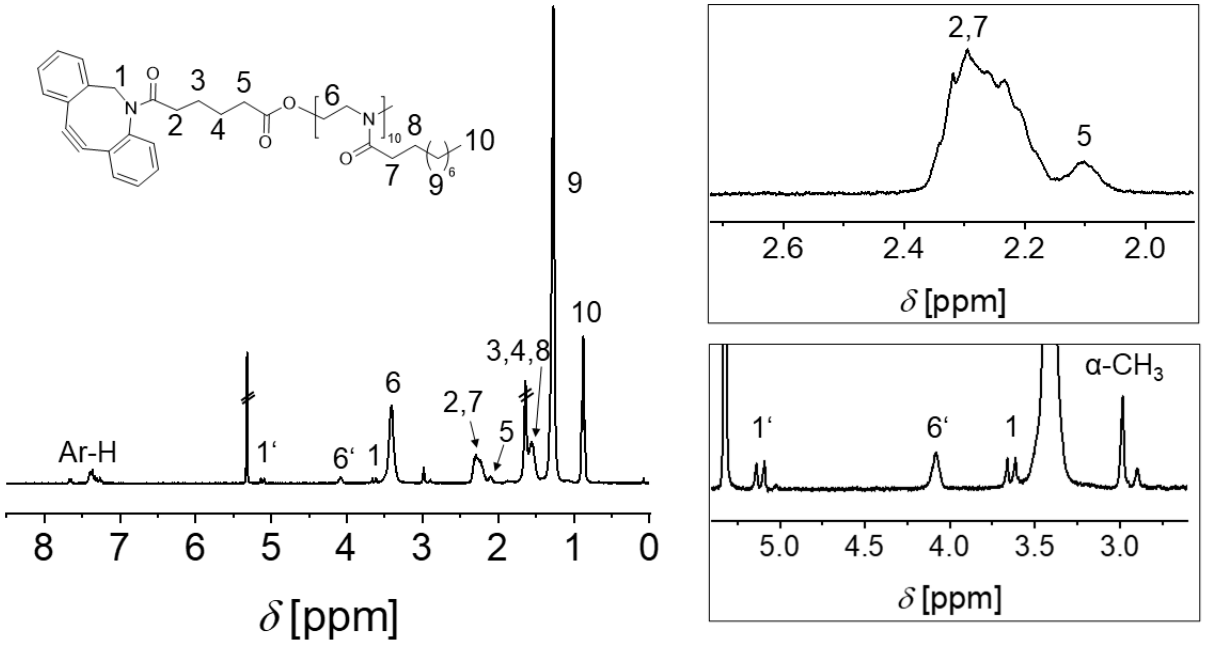
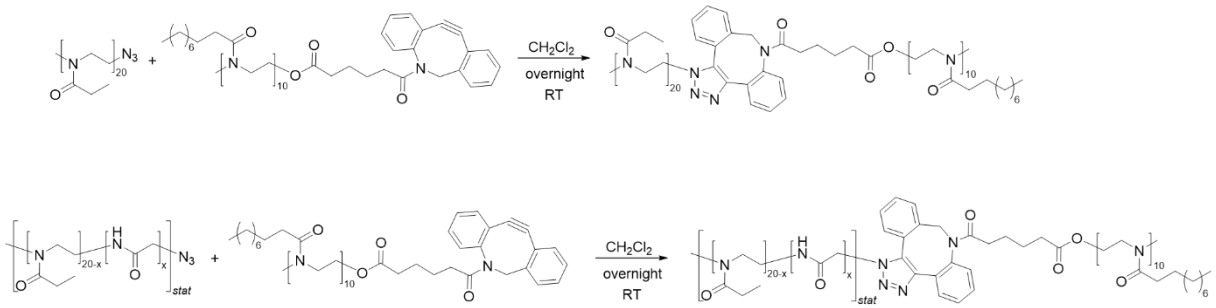


Figure SI4: ^{1}H NMR spectrum (300 MHz, CD_2Cl_2) of **PNonOx-DBCO** including the assignment of the signals to the schematic representation of the structure. The degree of functionalization was determined by integration of the methylene proton signal of the cyclooctyne moiety (1') *vs.* the signals of the α-CH_3 end group (see zoom on the bottom right).



Scheme SI4: Schematic representation of the SPAAC of **PNonOx-DBCO** and **PEtOx-N$_3$** or **dPEtOx-N$_3$**, yielding the **PEtOx-*b*-PNonOx** and **dPEtOx-*b*-PNonOx** block copolymers, respectively.

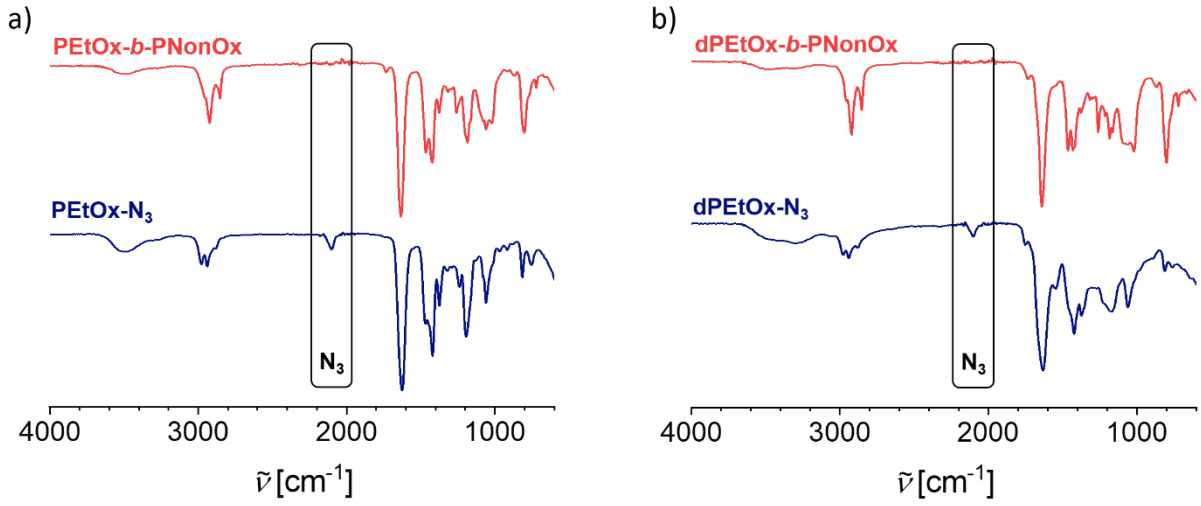


Figure SI5: Overlay of the ATR-IR spectra of the PNonOx-based block copolymers. (a) Overlay of **PEtOx-N$_3$** and **PEtOx-*b*-PNonOx** with assignment of the characteristic N_3 band. (b) Overlay of **dPEtOx-N$_3$** and **dPEtOx-*b*-PNonOx** with assignment of the characteristic N_3 band.

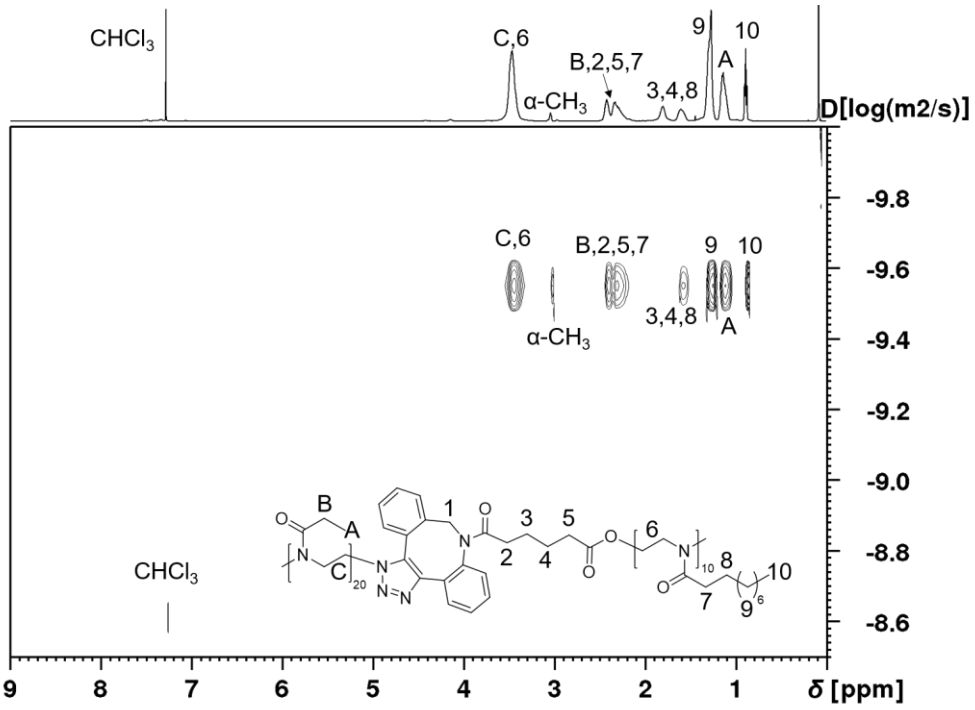


Figure SI6: DOSY NMR spectrum (500 MHz, $CDCl_3$) of **PEtOx-*b*-PNonOx** including the assignment of the signals to the schematic representation of the structure.

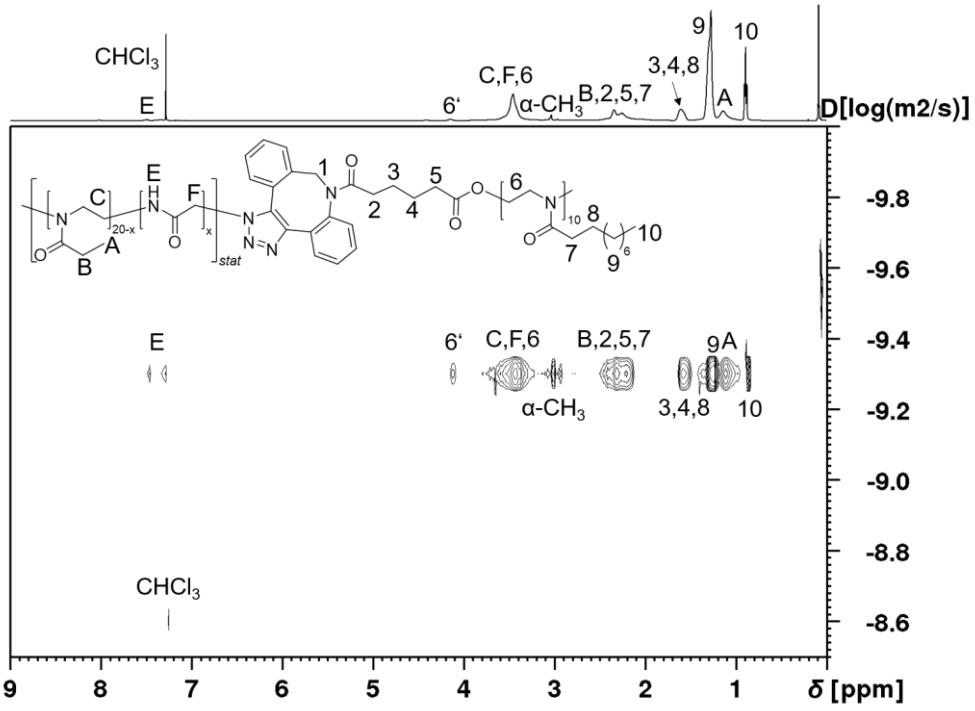
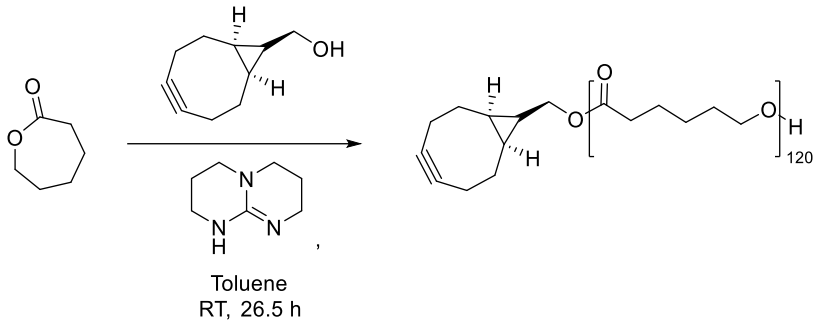


Figure SI7: DOSY NMR spectrum (500 MHz, $CDCl_3$) of **dPEtOx-*b*-PNonOx** including the assignment of the signals to the schematic representation of the structure.



Scheme SI5: Schematic representation of the synthesis of the clickable poly(*ε*-caprolactone) (**BCN-PCL**) *via* BCN-initiated ROP of *ε*-caprolactone.

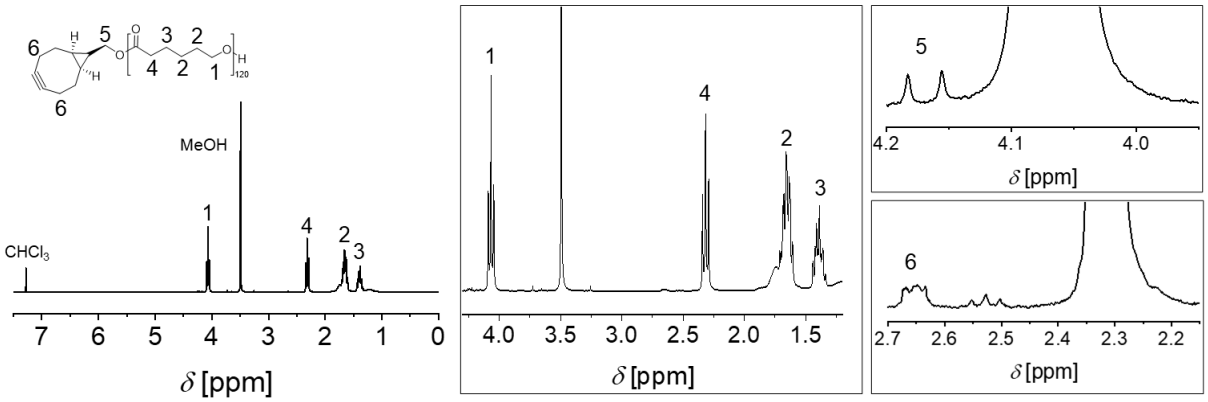


Figure SI8: ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **BCN-PCL** including the assignment of the signals to the schematic representation of the structure. The zooms show the methylene proton signals of the BCN moiety (5) and (6) confirming its attachment to the PCL.

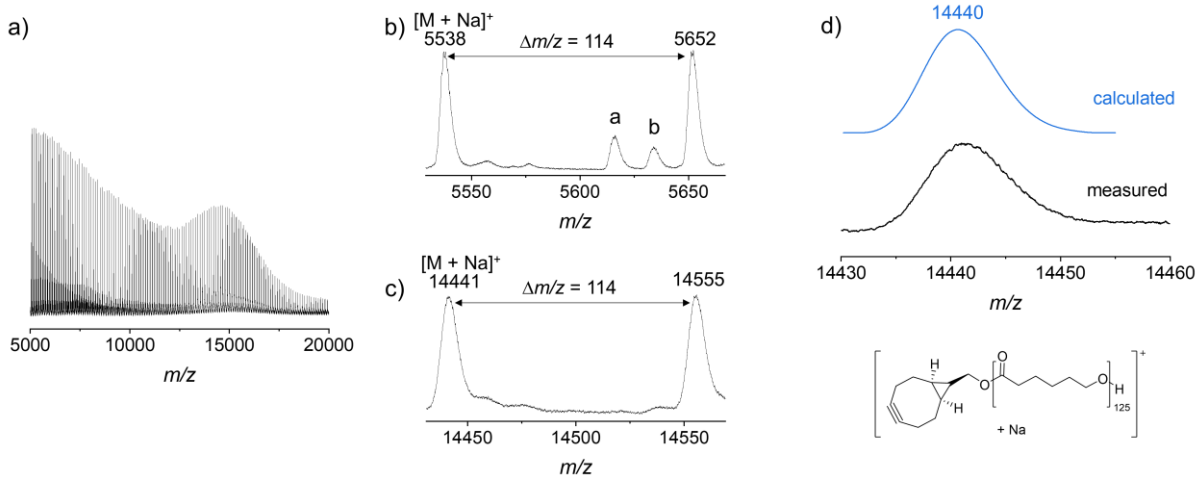
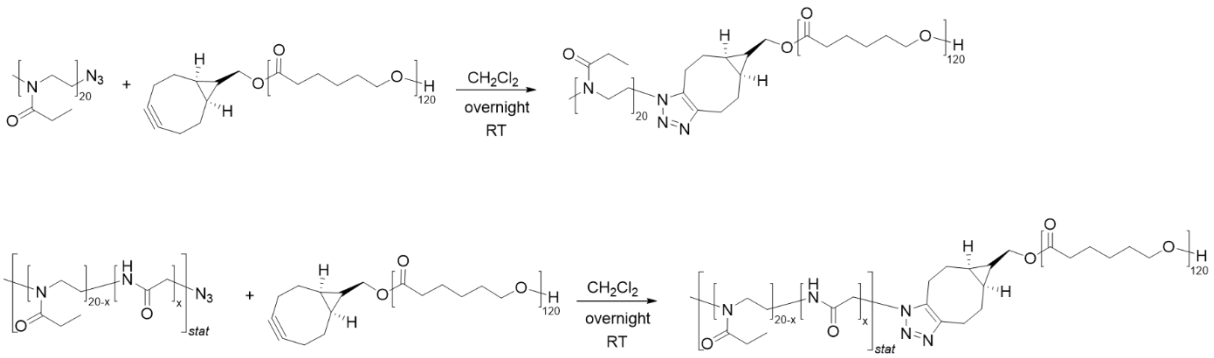


Figure SI9: MALDI TOF MS analysis (matrix DCTB + NaI) of **BCN-PCL**. (a) Full spectrum. (b) Zoom into *m/z* region of one repeating unit (Δ*m/z* =114) of the distribution at lower *m/z* values (A: Cyclic PCL: $[(C_6H_{10}O_2)_n + Na]^+$; B: $[HO(C_6H_{10}O_2)_nH + Na]^+$). (c) Zoom into *m/z* region of one repeating unit (Δ*m/z* = 114) of the distribution at higher *m/z* values. (d) Overlay of the measured and the calculated isotopic pattern of the most abundant species ($[M + Na]^+$).



Scheme SI6: Schematic representation of the SPAAC of **BCN-PCL** and **PEtOx-N$_3$** or **dPEtOx-N$_3$**, respectively, yielding the **PEtOx-*b*-PCL** and **dPEtOx-*b*-PCL** block copolymers.

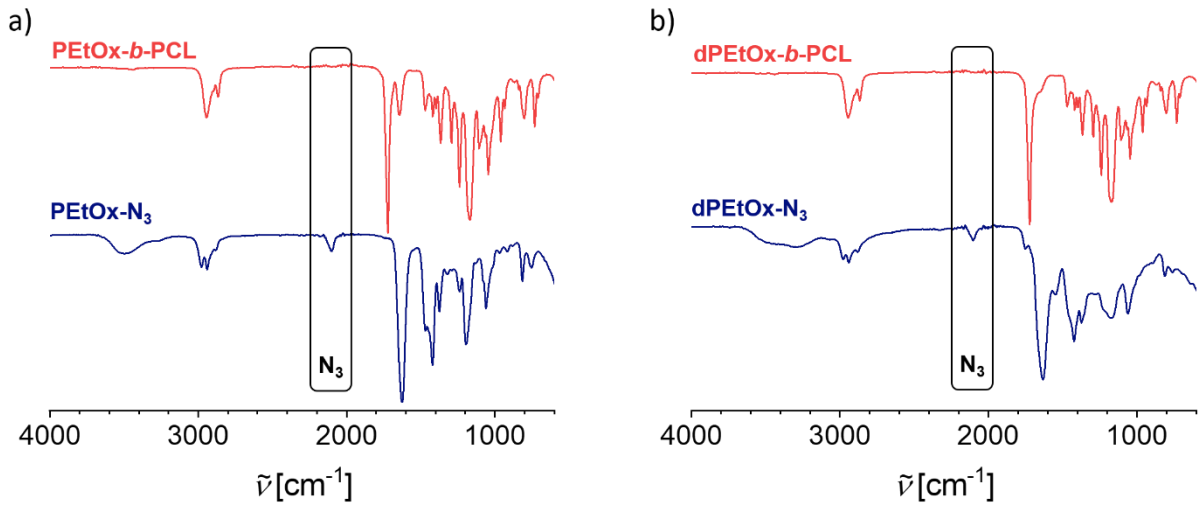


Figure SI10: Overlay of the ATR-IR spectra of the PCL-based block copolymers. (a) Overlay of **PEtOx-N$_3$** and **PEtOx-*b*-PCL** with assignment of the characteristic N_3 band. (b) Overlay of **dPEtOx-N$_3$** and **dPEtOx-*b*-PCL** with assignment of the characteristic N_3 band.

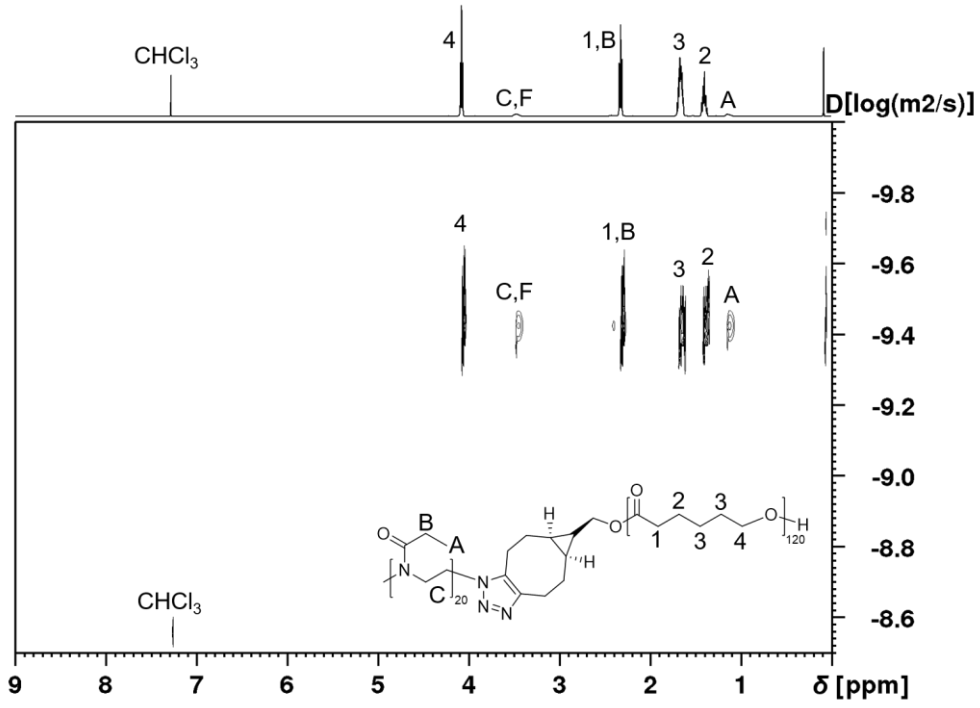


Figure SI11: DOSY NMR spectrum (500 MHz, $CDCl_3$) of **PEtOx-*b*-PCL** including the assignment of the signals to the schematic representation of the structure.

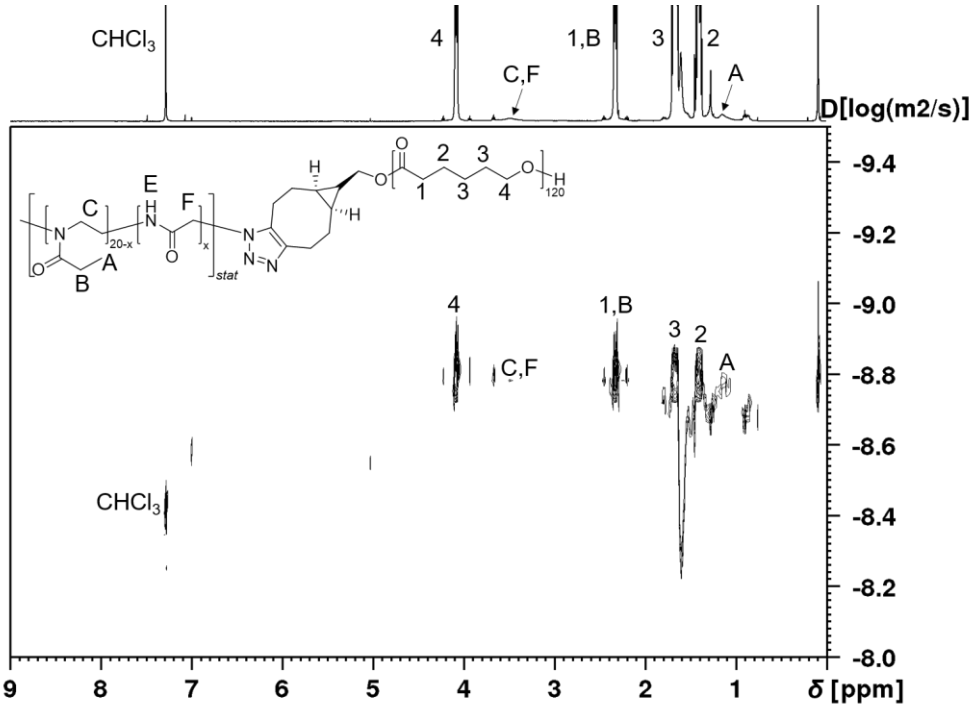


Figure SI12: DOSY NMR spectrum (500 MHz, $CDCl_3$) of **dPEtOx-*b*-PCL** including the assignment of the signals to the schematic representation of the structure.

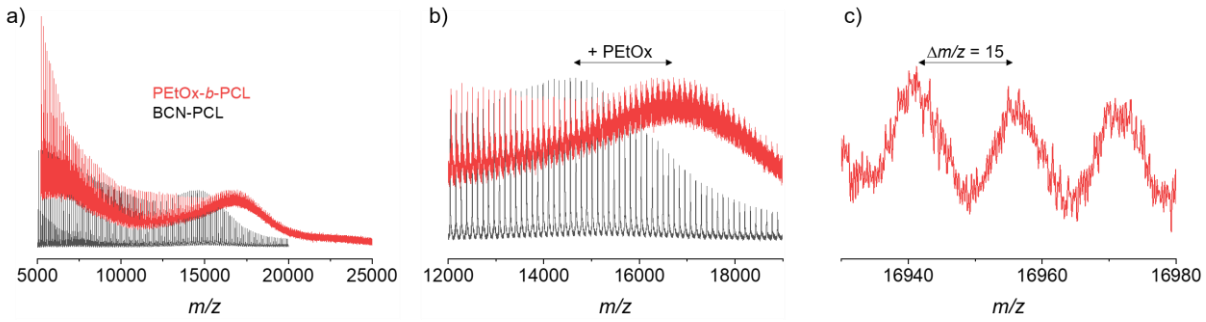


Figure SI13: Overlay of the MALDI TOF mass spectra of **BCN-PCL** and **PEtOx-b-PCL**. (a) full spectra. (b) Zoom into the higher m/z region, clearly displaying a shift towards higher m/z values which correlates with the molar mass of **PEtOx-N3**. (c) Zoom into displaying individual m/z distributions, revealing Δm/z = 15 as the difference between the molar mass of one EtOx (99 g/mol) and one CL (114 g/mol) repeating unit.