Supporting Information

An epoxy thiolactone on stage: Four component reactions, synthesis of poly(thioether urethane)s and respective hydrogels

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1 Experimental part

1.1 Materials

Triethylamine (TEA, ≥99%, Sigma-Aldrich), *para*-nitrophenyl chloroformate (>98%, TCI Chemicals), glycidol (techn, Acros Organics), homocysteine thiolactone hydrochloride (HCTL-HCl, 99%, ABCR), 4-dimethylaminopyridine (DMAP, ≥99%, Fluka), n-hexylamine (HA, >99%, TCI Chemicals), methyl acrylate (MA, >99%, Sigma-Aldrich), dihexylamine (DHA, 97%, Sigma-Aldrich), $LiOH \cdot H_2O$ (99%, Sigma-Aldrich), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, >99%, Fluka), α,ω-bis-amino octa(ethylene glycol) (PEG(7) diamine, Iris Biotech), 2,2'-(ethylenedioxy)bis(ethylamine) (PEG(2) diamine, >97%, Alfa Aesar), trimethylolpropane triacrylate (TMPT, Alfa Aesar) were used without further purification. Unless otherwise indicated, all solvents were purchased from commercial sources and were used without further purification.

1.2 Measurements

^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 FT NMR spectrometer (400 MHz and 100 MHz, respectively) and are reported as follows: chemical shift δ (ppm) (multiplicity, coupling constant *J* (Hz), number of protons, assignment). $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.0 ppm), THF-d_8 (δ_H = 1.73 ppm, δ_C = 25.4 ppm) and dimethylsulfoxide (DMSO, δ_H = 2.50 ppm, δ_C = 39.5 ppm) were used as an internal standard. Chemical shifts are reported in ppm to the nearest 0.01 ppm for ^1H and the nearest 0.1 ppm for ^{13}C.

Molecular weights (M_n and M_w) and dispersity values (M_w/M_n) were determined by size exclusion chromatography (SEC). SEC analyses were carried out with dimethylformamide (DMF) as eluent. SEC with DMF (HPLC grade, VWR) as eluent was performed using an

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Agilent 1100 system equipped with a dual RI-/Visco detector (ETA-2020, WGE). The eluent contained 1 $g \cdot L^{-1}$ LiBr (≥99%, Sigma Aldrich). The sample solvent contained traces of distilled water as internal standard. One pre-column (8x50 mm) and four PSS GRAM gel columns (8x300 mm) were applied at a flow rate of 1.0 $mL \cdot min^{-1}$ at 40 °C. The diameter of the gel particles measured 10 µm, the nominal pore widths were 30, 10^2, 10^3 and 3000 Å. Calibration was achieved using narrowly distributed poly(methyl methacrylate) standards (PSS Std. Mainz). Results were evaluated using the PSS WinGPC UniChrom software (Version 8.1).

Raman spectroscopy was carried out on a Bruker FT-Raman-Spectrometer RFS 100/S with a Nd:YAG laser. The power of the laser was 200 mV at 1064 nm with a spectral resolution of 4 cm^{-1}. For each spectrum 500 scans were recorded. Raman intensity maxima are reported in wavenumbers (cm^{-1}).

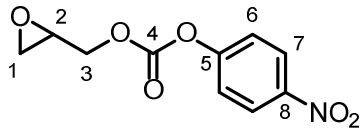
Infrared spectra were carried out on a ThermoNicolet FT-IR Nexus spectrometer and are recorded between KBr disks or using an ATR unit (ThermoNicolet, Smart SplitPEA). Transmission maxima are reported in wavenumbers (cm^{-1}) and only selected intensities are reported.

Differential scanning calorimetry (DSC) analysis was performed on a PerkinElmer DSC 8000 (PerkinElmer LAS, Rodgau, Germany) under nitrogen atmosphere using a scan rate of 10 $K \cdot min^{-1}$. For Mp the local maximum was selected.

ESI mass spectra were recorded on a Finnigan SSQ 7000 spectrometer and HRMS spectra on a Thermo Scientific LTQ Orbitrap XL spectrometer. MALDI-TOF and NALDI-TOF mass spectrometry were performed on a Bruker ultrafleXtreme equipped with a 337 nm smartbeam laser in the reflective mode. For NALDI-TOF, THF solutions of sodium trifluoroacetate (2 µL of 10 $g \cdot mL^{-1}$), and analyte 20 µL of 10 $mg \cdot mL^{-1}$) were mixed and 2 µL thereof were applied on the sample plate. For MALDI-TOF, THF solutions of sodium trifluoroacetate (0.5 µL of 10 $g \cdot mL^{-1}$), analyte (5 µL of 10 $g \cdot mL^{-1}$) and DCTB matrix (20 µL of 20 $g \cdot mL^{-1}$) were mixed and 2 µL thereof were applied on the sample plate. CsI_3 was used as standard for internal calibration. Laser shots (6000) with 24% up to 60% laser power were collected. The laser repetition rate was 1000 Hz.

1.3 Synthesis

1.3.1 *Glycidyl p*-nitrophenyl carbonate



Triethylamine (18.9 mL, 136.7 mmol) was added slowly (18.9 mL/h) to a stirred solution of *p*-nitrophenyl chloroformate (25.0 g, 124.2 mmol) and glycidol (8.67 mL, 130.4 mmol) in CH_2Cl_2

(1M, 124 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2 h. Then, the reaction mixture was filtered. Next, the mixture was washed with $HCl_{(aq)}$ (100 mL, 1M), $NaOH_{(aq)}$ (2 x 100 mL, 1M) and $HCl_{(aq)}$ (100 mL, 1M). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude glycidyl *p*-nitrophenyl carbonate (25.8 g, 87%) as a white solid. Spectroscopic data was consistent with those reported in literature.[1]

Mp. 57.5 °C (determined by DSC). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 9.1 Hz, 1H, H7), 7.39 (d, *J* = 9.1 Hz, 1H, H6), 4.60 (dd, *J* = 12.1, 2.9 Hz, 1H, H3), 4.16 (dd, *J* = 12.1, 6.3 Hz, 1H, H3), 3.33 (tt, *J* = 6.5, 2.8 Hz, 1H, H2), 2.92 (t, *J* = 4.4 Hz, 1H, H1), 2.74 (dd, *J* = 4.7, 2.6 Hz, 1H, H1). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (C5), 152.5 (C4), 145.6 (C8), 125.5 (C7), 121.9 (C6), 69.6 (C3), 48.9 (C2), 44.7 (C1). IR (KBr) 3490, 3079, 1754 (O_2C=O), 1618, 1595, 1524 (NO_2) 1494, 1461, 1347, 1275, 1262 (C-O Epoxide), 1227 (Ph-O), 1052, 911, 867 (Epoxide), 723 cm^{-1}. HRMS (ESI) *m/z* for $C_{10}H_9NO_6$ $(M + H)^+$ 240.04976.

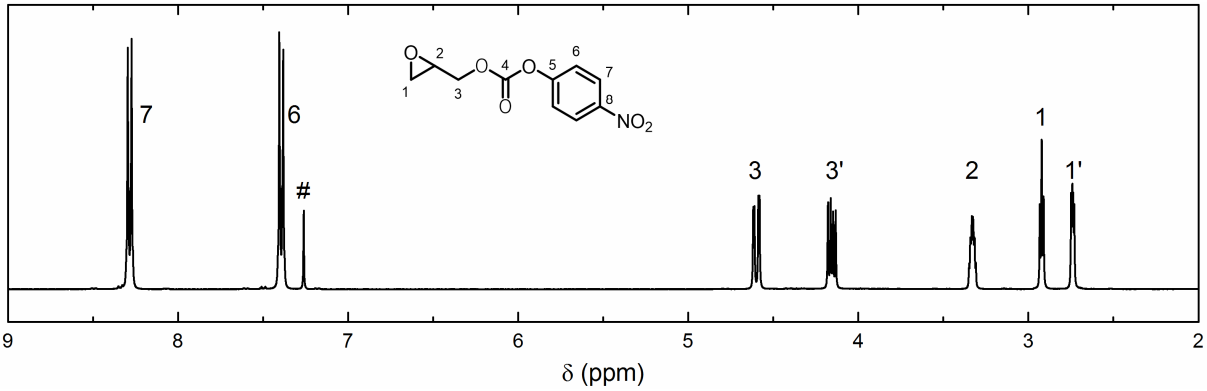


Figure S 1. ^{1}H NMR spectrum of *p*-nitrophenyl glycidyl carbonate. Recorded in chloroform-d (#).

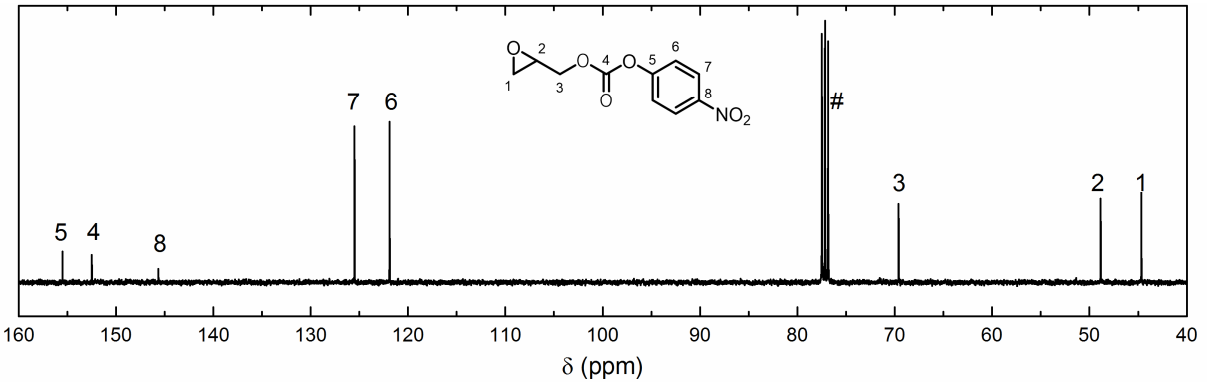
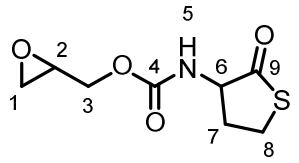


Figure S 2. ^{13}C NMR spectrum of *p*-nitrophenyl glycidyl carbonate. Recorded in chloroform-d (#).

1.3.2 Epoxy thiolactone **1**



1

Triethylamine (2.79 mL, 20.1 mmol) was added slowly (2.79 mL/h) to a stirred solution of glycidyl *p*-nitrophenyl carbonate (1.93 g, 8.06 mmol), HCTL-HCl (1.24 g, 8.06 mmol) and dimethylaminopyridin (98.4 mg, 8.06E-1 mmol) in DMF (0.2M, 40 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 4 h. Then, the reaction mixture was filtered and evaporated under reduced pressure. Next, CH_2Cl_2 (20 mL) was added and the mixture was washed with $HCl_{(aq)}$ (2 x 20 mL, 1M). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude epoxy thiolactone. Purification by flash column chromatography on alumina gel using CH_2Cl_2 / 1% MeOH as eluent gave epoxy thiolactone (1.15 g 65%) as a white crystalline solid.

Mp. 75.8 °C (determined by DSC). R_F (9.9:0.1 CH_2Cl_2-MeOH) 0.29. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, *J* = 8.5, 2.8 Hz, 1H, H5), 4.44 – 4.27 (m, 2H, H3 and H6), 3.76 (ddd, *J* = 12.0, 6.6, 4.3 Hz, 1H, H3), 3.40 (dd, *J* = 11.6, 5.3 Hz, H8), 3.30 – 3.23 (m, 1H, H8), 3.17 (tt, *J* = 6.5, 2.8 Hz, 1H, H2), 2.78 (t, *J* = 4.6 Hz, 1H, H1), 2.65 – 2.59 (m, 1H, H1), 2.43 (dt, *J* = 12.0, 5.9 Hz, 1H, H7), 2.09 (qdd, *J* = 12.1, 7.0, 4.7 Hz, 1H, H7). ^{13}C NMR (101 MHz, DMSO-d_6) δ 205.6, 205.7 (C9), 155.7, 155.8 (C4), 65.3, 65.2 (C3), 59.9 (C6), 49.3 (C2), 43.8 (C1), 29.8 (C7), 26.4 (C8). IR (KBr) 3349 (NH), 2922, 1717 (OCONH), 1698 (COS), 1543 (NH bend), 1244 (CO epoxide), 1053, 907 cm^{-1}. HRMS (ESI) *m/z* for $C_8H_{11}NO_4S$ $(M + H)^+$ 218.04758, $(M + Na)^+$ 240.02962.

For large-scale synthesis, the following procedure was used:

Triethylamine (15.1 mL, 109.2 mmol) was added slowly (15.1 mL/h) to a stirred solution of epoxy nitrophenyl carbonate (10.5 g, 43.7 mmol), HCTL·HCl (6.71 g, 43.7 mmol) and dimethylaminopyridin (534 mg, 4.37 mmol) in DMF (0.4M, 109 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 4 h. Then, the reaction mixture was filtered and evaporated under reduced pressure. Next, CH_2Cl_2 (100 mL) was added and the mixture was washed with $HCl_{(aq)}$ (100 mL, 0.1M), $K_2CO_{3(aq)}$ (6 x 100 mL, 0.1M) and again $HCl_{(aq)}$ (100 mL, 0.1M). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude epoxy thiolactone (5.7 g, 60%) as a white solid.

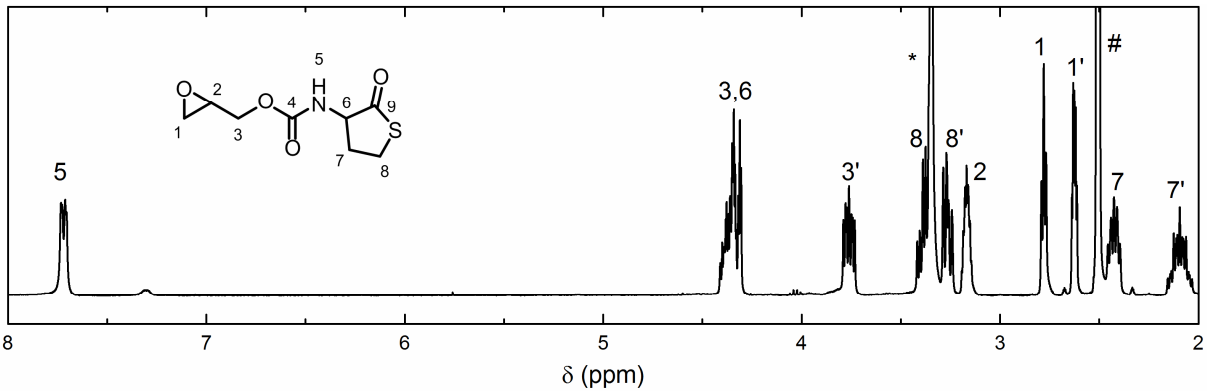


Figure S 3. ^{1}H NMR spectrum of epoxy thiolactone **1**. Recorded in DMSO-d_6 (#), residual solvent peaks: # H_2O and HDO.

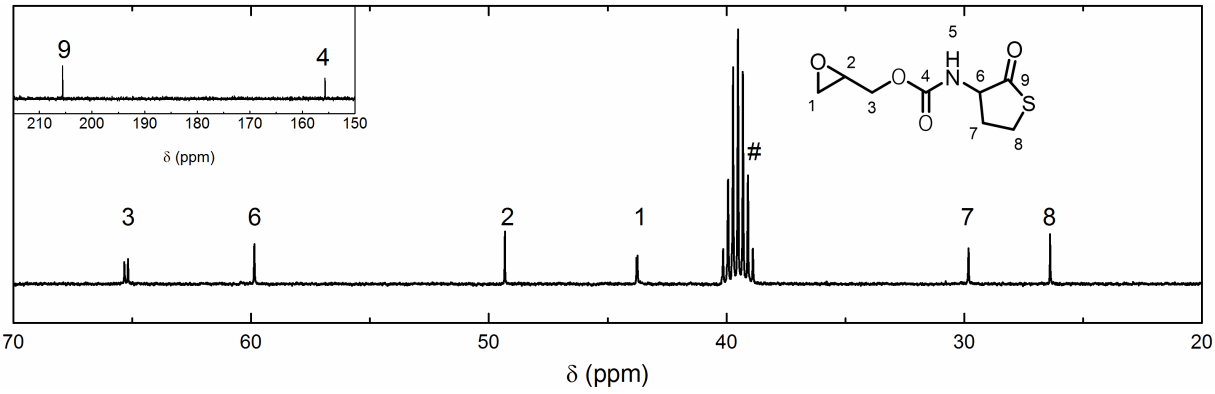


Figure S 4. ^{13}C NMR spectrum of epoxy thiolactone **1**. Recorded in DMSO-d_6 (#).

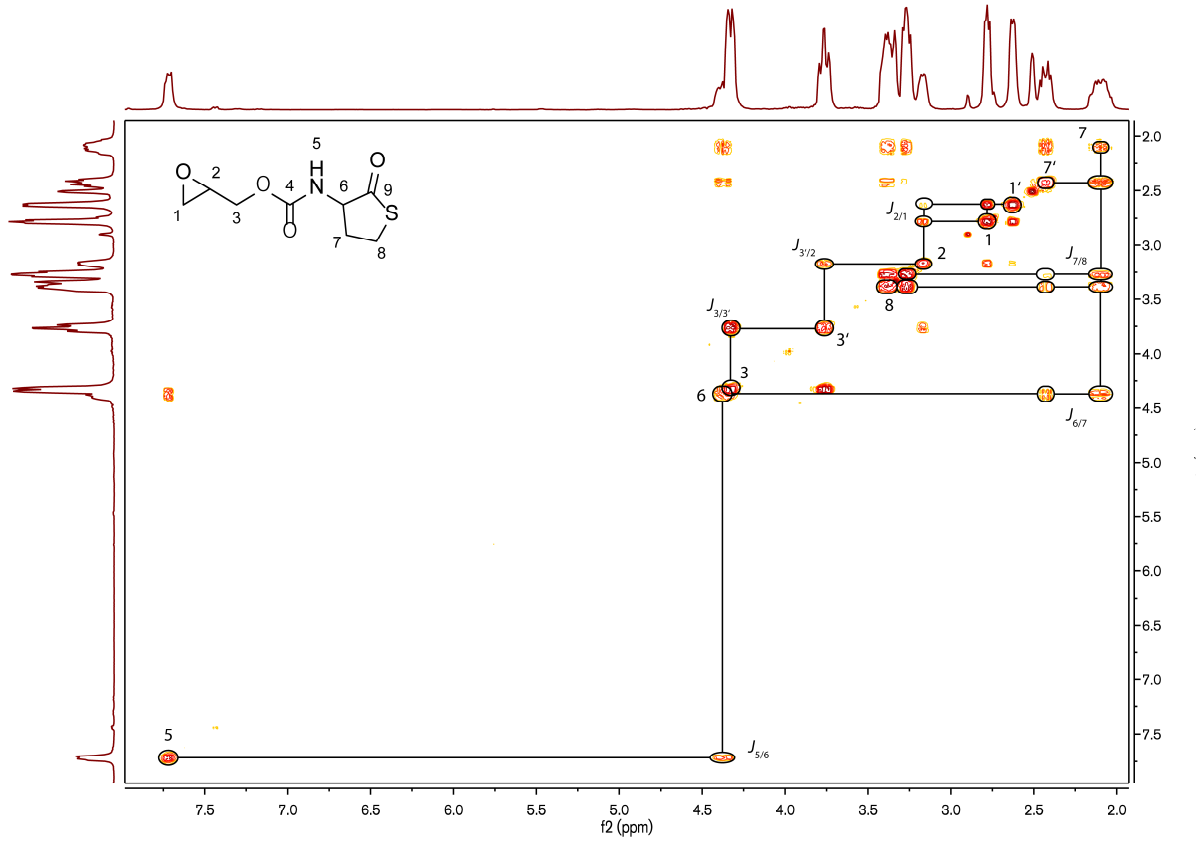


Figure S 5. COSY spectrum of epoxy thiolactone **1**. Recorded in DMSO-d_6.

1.3.3 Crystallographic data of **1**

Suitable crystals for single crystal X-ray diffraction were obtained by recrystallization from CH_2Cl_2 as colourless blocks. Intensity data were collected on a Bruker D8 goniometer with a Bruker SMART APEX CCD area detector in ω-scan mode using Mo-K_α radiation (λ = 0.71073 Å) from an Incoatec microsource with multilayer optics at 100 K. Temperature was controlled with an Oxford Cryostream 700 instrument. Data were processed with *SAINT+*[2] and multi-scan absorption corrections were applied with *SADABS*[3].

The structure was solved by direct methods using *SHELXS97*[4] and refined by full-matrix least-square procedures based on F^2 as implemented in *SHELXL-2013*[5]. Non-hydrogen atoms were refined with anisotropic displacement parameters. The amino-H was found in difference fourier map; its coordinates were refined, and its U_{iso} was constrained to U_{iso}(H) = 1.2 U_{eq}(N); all other hydrogen atoms were placed in idealized positions with U_{iso}(H) = 1.2 U_{eq}(C).

The asymmetric unit contains only one molecule which reveals to be disordered (Figure S 6). The disorder has been found around the stereocenter of the epoxide group, thus, representing a solid solution of diastereomers of the organic molecule.

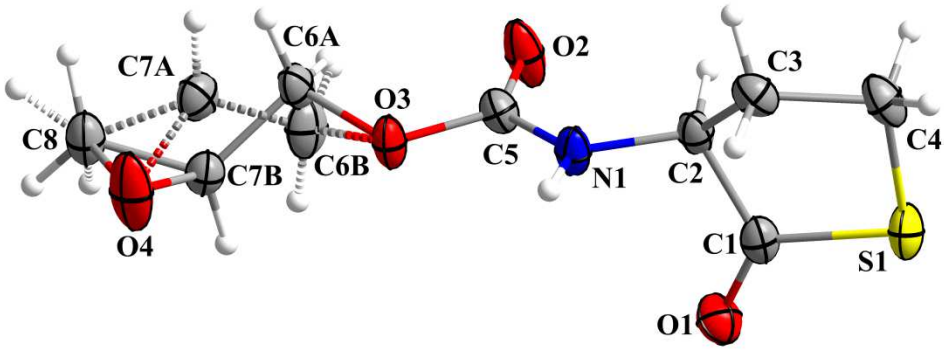


Figure S 6. Displacement ellipsoid plot of the asymmetric unit of **1** showing the majority (*S,S*)-isomer (solid line) and the disordered, minority (*R,S*)-epimer (dotted line) (drawn at 70 % probability, labeled).

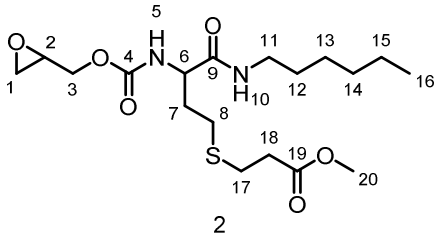
Within the epoxide end, carbon C8 and oxygen O4 are common to both isomers, and their coordinates and displacement parameters were constrained to be equal in either isomer (SHELX commands *EXYZ*, *EADP*). In addition, restraints for the distances between C6A and C7A, and C6B and C7B were introduced. This similarity restraint (*SADI*) also restrains the distances between O3/C6A, O3/C6B, and O4/C7A, O4/C7B, and C8/C7A, C8/C7B (Figure S 6).

Supplementary crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif (CCDC 1447028).

Table S 1. Crystal data and refinement results of compound **1**.

Chemical formula	C8 H11 N O4 S
M_r	217.24
Crystal system, space group	Triclinic, $P\bar{1}$
T (K)	100(2)
a, b, c (Å)	6.4922(13), 8.3800(17), 9.896(2)
α, β, γ (°)	74.212(3), 73.241(3), 80.346(3)
V (Å^3)	493.75(17)
Z	2
μ (mm^{-1})	0.316
Crystal shape, crystal size (mm)	Colourless block, 0.29 x 0.21 x 0.15
Index ranges	-7 ≤ h ≤ 7, -10 ≤ k ≤ 10, -11 ≤ l ≤ 11
Reflections collected	5316
Independent reflections	1787 [R_{int} = 0.0331]
T_{min}, T_{max}	0.6612, 0.7452
Data/ restraints/ parameters	1787/ 4/ 150
Goodness-of-fit on F^2	1.044
Final R indices [I>2σ(I)]	R_1 = 0.0339, wR_2 = 0.0800
R indices (all data)	R_1 = 0.0397, wR_2 = 0.0832
Largest diff. peak and hole (e Å^{-3})	0.207, -0.191

1.3.4 Epoxy thioether **2** - Three component reaction



2

Hexylamine (24.6 µL, 0.178 mmol) and methyl acrylate (16.1 µL, 0.178 mmol) were added to a stirred solution of epoxy thiolactone **1** (38.6 mg, 0.178 mmol) in THF (0.888 mL, 0.2 M) at room temperature. The reaction mixture was stirred at room temperature for 24 h. Then, the solvent was evaporated under reduced pressure to give the crude epoxy thioether **2** (quant) as a slightly yellow waxy solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (t, J = 5.0 Hz, 1H, H10), 7.53 (d, J = 8.1 Hz, 1H, H5), 4.36 (ddd, J = 12.2, 4.9, 2.7 Hz, 1H, H3), 4.03 (dq, J = 15.4, 7.8, 7.4 Hz, 1H, H6), 3.79 (dd, J = 12.2, 6.6 Hz, 1H, H3), 3.66 (s, 3H, H20), 3.26 – 3.18 (m, 1H, H2), 3.18 – 3.00 (m, 2H, H11), 2.82 (q, J = 4.2 Hz, 1H, H1), 2.80 – 2.71 (m, 2H, H18), 2.71 – 2.62 (m, 3H, H1 and

H17), 2.60 – 2.35 (m, 2H, H8), 1.96 – 1.74 (m, 2H, H7), 1.50 – 1.37 (m, 2H, H12), 1.31 (d, *J* = 14.8 Hz, 6H, H13-15), 0.92 (t, *J* = 6.7 Hz, 3H, H16). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.9 (C19), 171.0 (C9), 155.7 (C4), 54.0 (C6), 51.4 (C20), 49.4 (C2), 43.7 (C1), 38.5 (C11), 34.1 (C17), 32.2 (C7), 31.0 (C13), 29.0 (C12), 27.5 (C8), 26.0 (C14 and C18), 22.1 (C15), 13.9 (C16). IR (KBr) 3293 (NH), 2953, 2929, 2858, 1731 (COOMe), 1689 (OCONH), 1643 (CONH), 1538 (NH), 1437, 1351, 1280, 1241 (COC Epoxide, OCONH 2), 1195, 1172, 1051, 687 cm^{-1}. HRMS (NALDI) *m/z* for $C_{18}H_{32}N_2O_6S$ $(M + Na)^+$ 427.242.

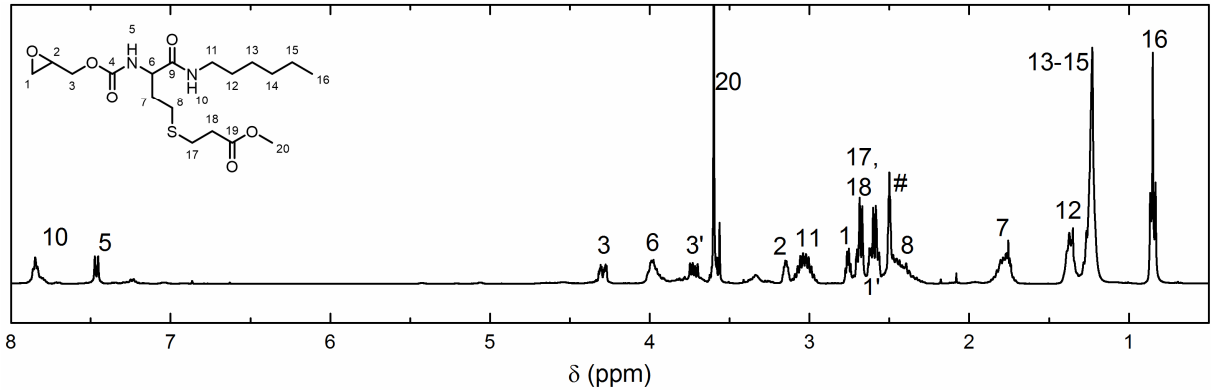


Figure S 7. ^{1}H NMR spectrum of epoxy thioether **2**. Recorded in DMSO-d_6 (#).

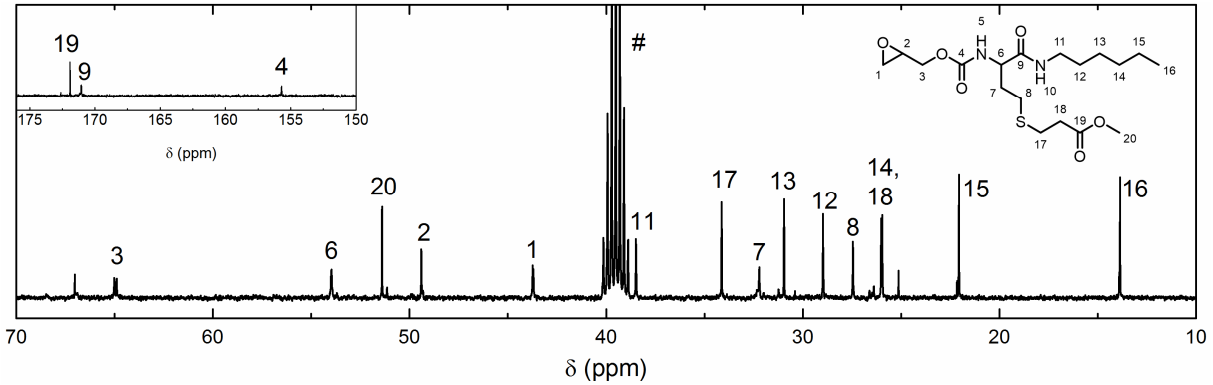


Figure S 8. ^{13}C NMR spectrum of epoxy thioether **2**. Recorded in DMSO-d_6 (#).

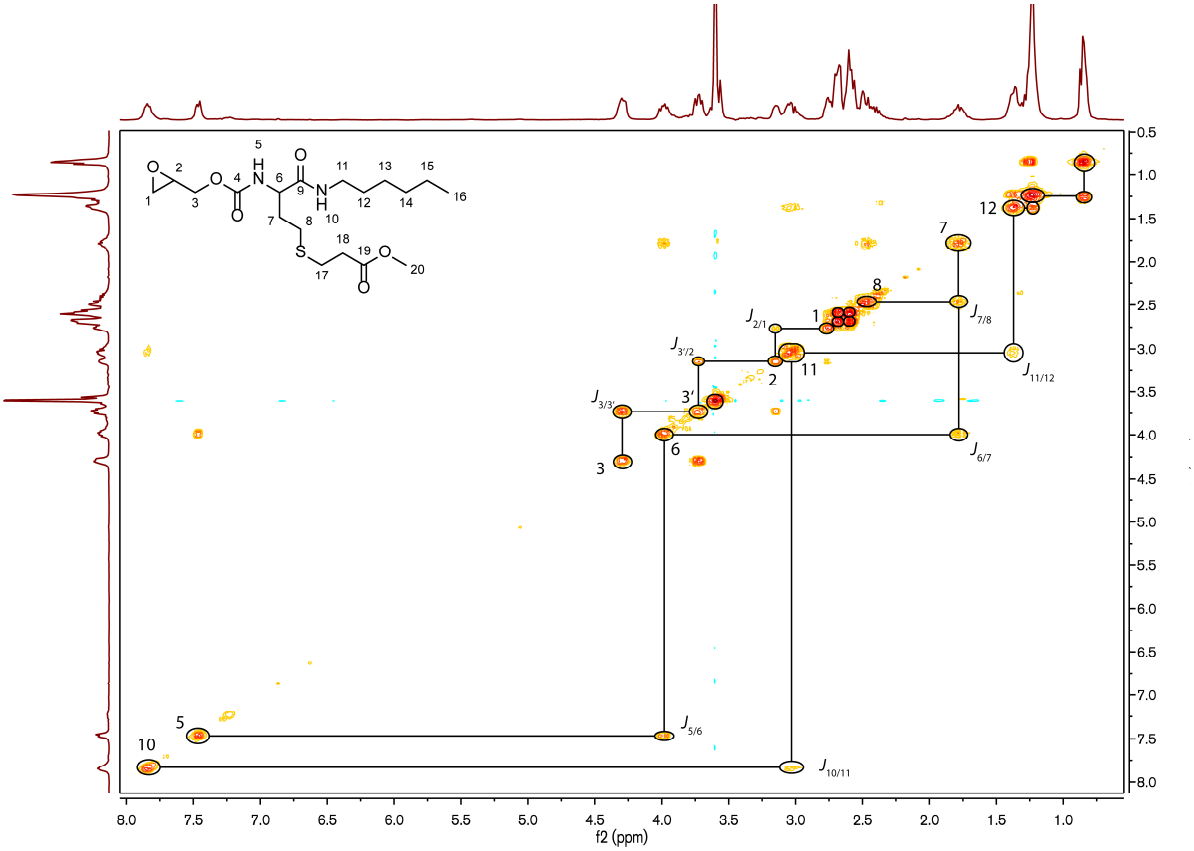


Figure S 9. COSY spectrum of epoxy thioether **2**. Recorded in DMSO-d_6.

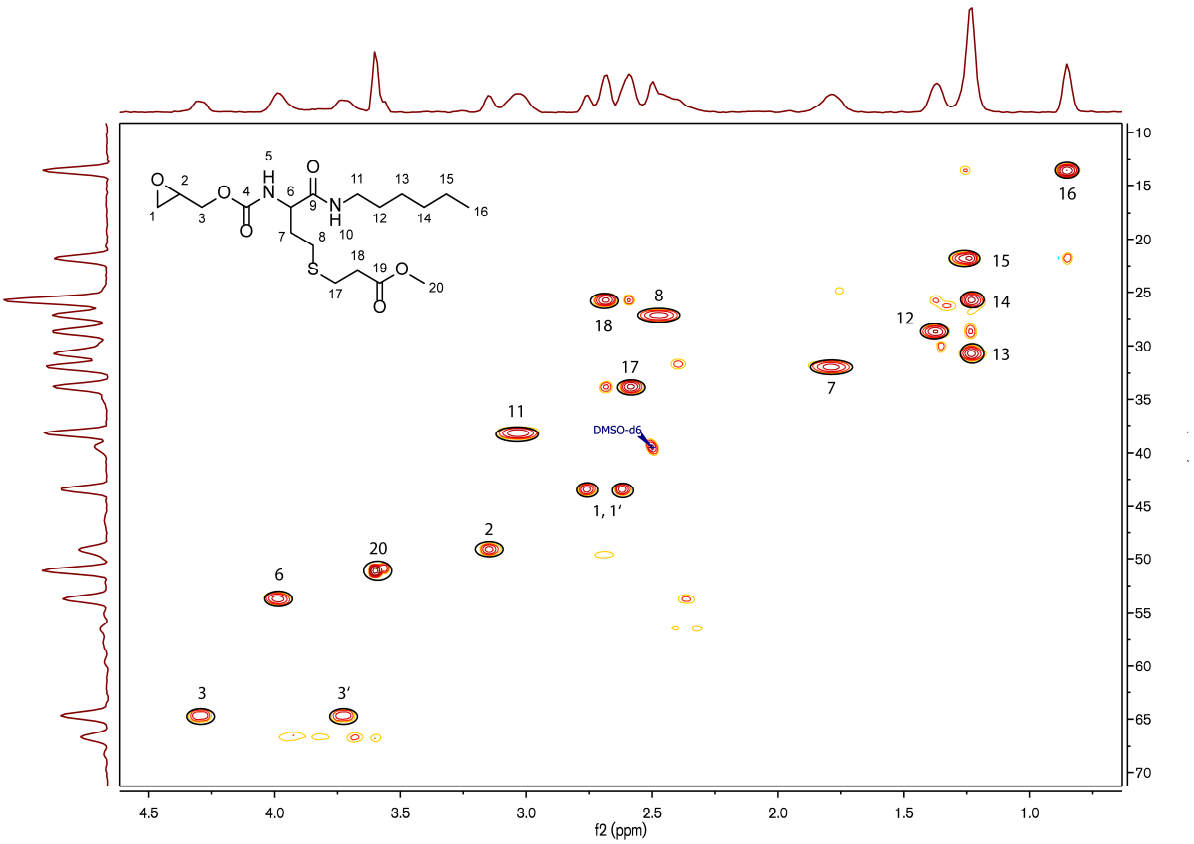
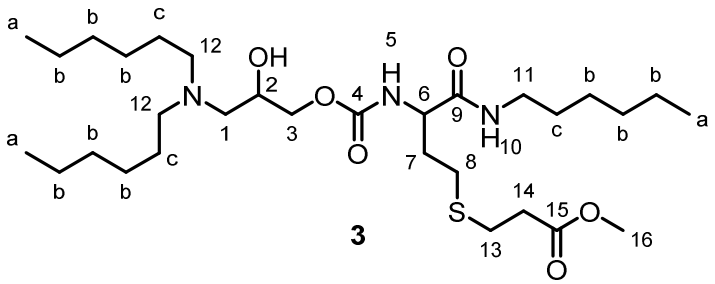


Figure S 10. HSQC spectrum of epoxy thioether **2**. Recorded in DMSO-d_6.

1.3.5 Trialkylamino thioether **3**



3

Hexylamine (16.6 µL, 0.127 mmol) and methyl acrylate (11.5 µL, 0.127 mmol) were added to a stirred solution of epoxy thiolactone **1** (27.5 mg, 0.127 mmol) in THF-d_8 (0.633 mL, 0.2 M) at room temperature. The reaction mixture was stirred at room temperature for 24 h. Full conversion to the crude epoxy thioether intermediate (**2**) was verified by ^{1}H NMR spectroscopy. Next, dihexylamine (29.5 µL, 0.127 mmol) was added and the reaction mixture was stirred at 60 °C for 6 days. Then, the solvent was evaporated under reduced pressure and the crude product was separated between CH_2Cl_2 (1.50 mL) and $NH_4HCO_{3(aq)}$ (1.50 mL. 0.05 M). The organic layer was evaporated under reduced pressure to give the trialkylamino thioether **3** (quant.) as a slightly yellow viscous oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 – 7.76 (m, 1H, H10), 7.24 (t, *J* = 8.3 Hz, 1H, H5), 4.06 – 3.89 (m, 2H, H6 and H3'), 3.87 – 3.73 (m, 1H, H3), 3.72 – 3.63 (m, 1H, H2), 3.60 (s, 3H, H16), 3.13 – 2.91 (m, 2H, H11), 2.75 – 2.63 (m, 2H, H14), 2.63 – 2.55 (m, 2H, H13), 2.55 – 2.22 (m, 8H, H1/H8 and H12), 1.90 – 1.66 (m, 2H, H7), 1.50 – 1.14 (m, 24H, Hb/c), 0.96 – 0.73 (m, 9H, Ha). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.9 (C15), 171.2 (C9), 156.2 (C4), 67.0 (C2 and C3), 57.4, 57.2 (C1), 54.3 (C12), 53.9 (C6), 51.4 (C16), 38.5 (C11), 34.1 (C13), 32.3 (C7), 31.3, 31.2, 31.0 (Cb), 29.0, 28.7 (Cc), 27.5 (C8), 26.7 (Cb), 26.5, 26.4 (Cc), 26.0 (C14), 22.2, 22.1 (Cb), 13.9 (Ca). IR (KBr) 3313 (NH), 2955, 2929, 2857, 1739 (OCONH/COOMe), 1658 (CONH), 1537 (NH), 1459, 1438, 1357, 1246, 1170, 1052 cm^{-1}. HRMS (MALDI) *m/z* for $C_{30}H_{59}N_3O_6S$ $(M + Na)^+$ 612.344.

One-pot four component reaction

Hexylamine (15.5 µL, 0.118 mmol), methyl acrylate (10.7 µL, 0.118 mmol) and dihexylamine (27.6 µL, 0.118 mmol) were added to a stirred solution of epoxy thiolactone **1** (25.7 mg, 0.118 mmol) in THF (0.592 mL, 0.2 M) at room temperature. The reaction mixture was stirred at 60 °C for 260 h. Then, the solvent was evaporated under reduced pressure and the crude product was separated between CH_2Cl_2 (1.50 mL) and $NH_4HCO_{3(aq)}$ (1.50 mL. 0.05 M). The organic layer was evaporated under reduced pressure to give the trialkylamino thioether **3** (quant.) as a slightly yellow viscous oil.

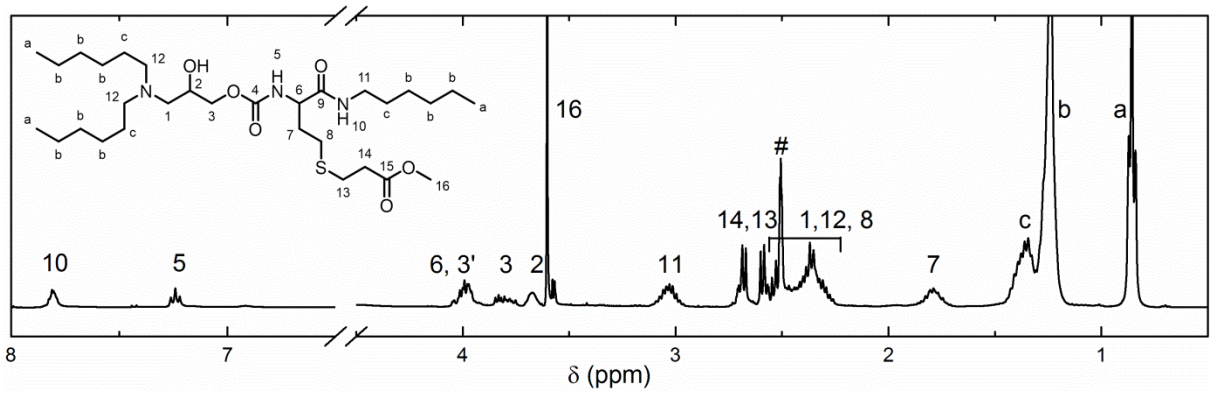


Figure S 11. ^{1}H NMR spectrum of trialkylamino thioether **3**. Recorded in DMSO-d_6 (#).

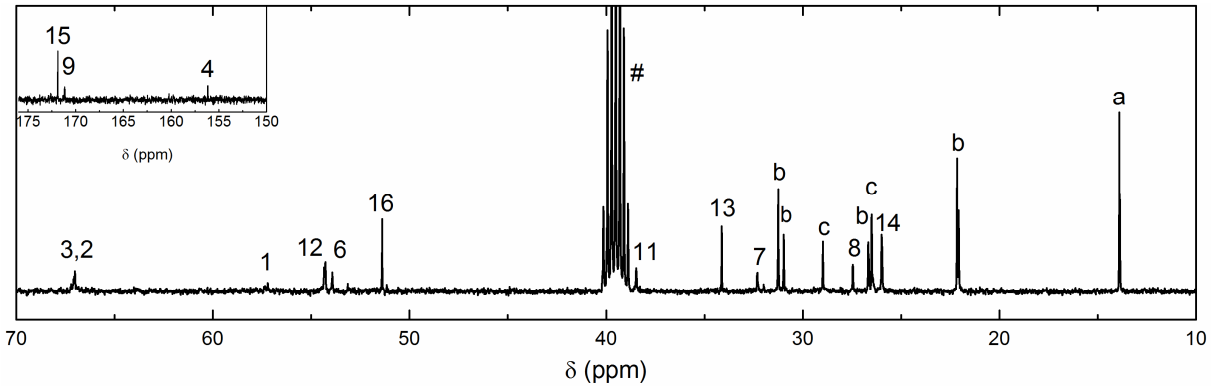


Figure S 12. ^{13}C NMR spectrum of trialkylamino thioether **3**. Recorded in DMSO-d_6 (#).

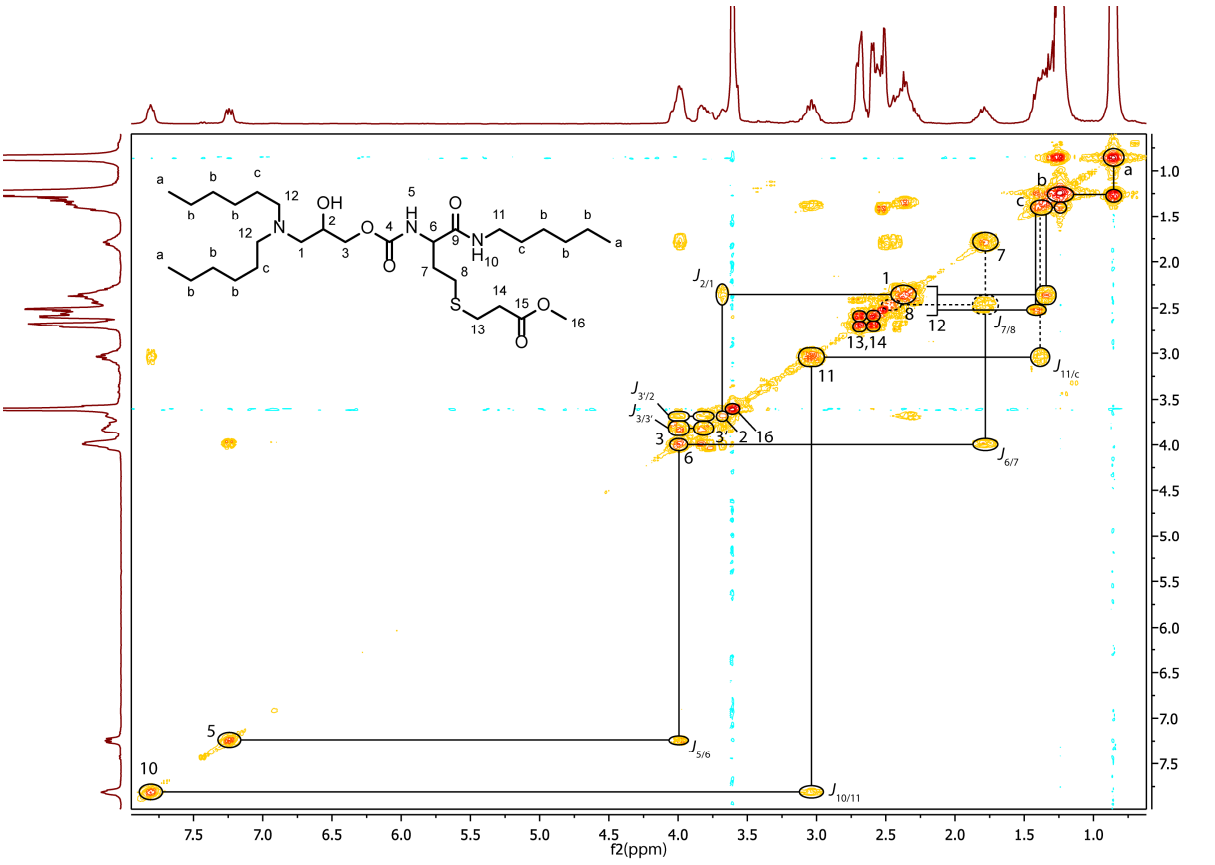


Figure S 13. COSY spectrum of trialkylamino thioether **3**. Recorded in DMSO-d_6.

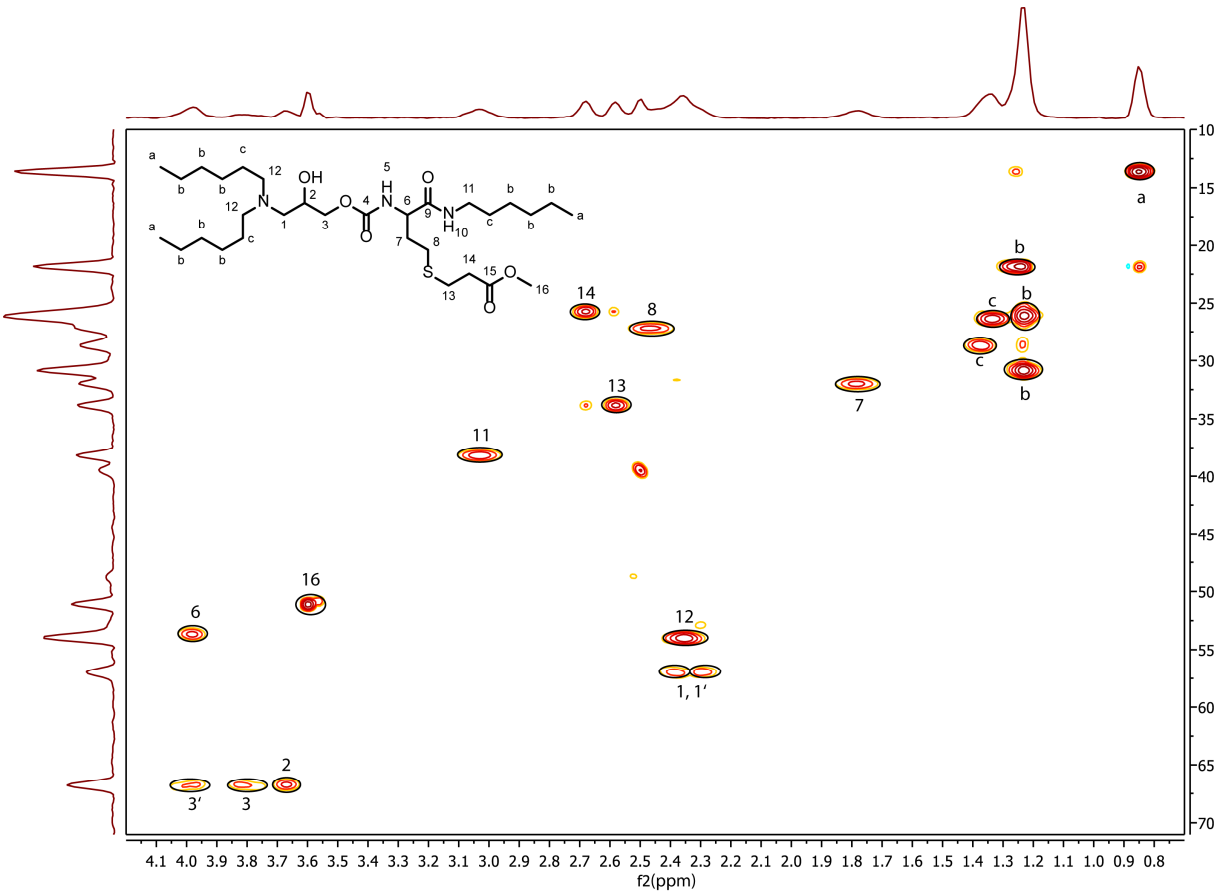
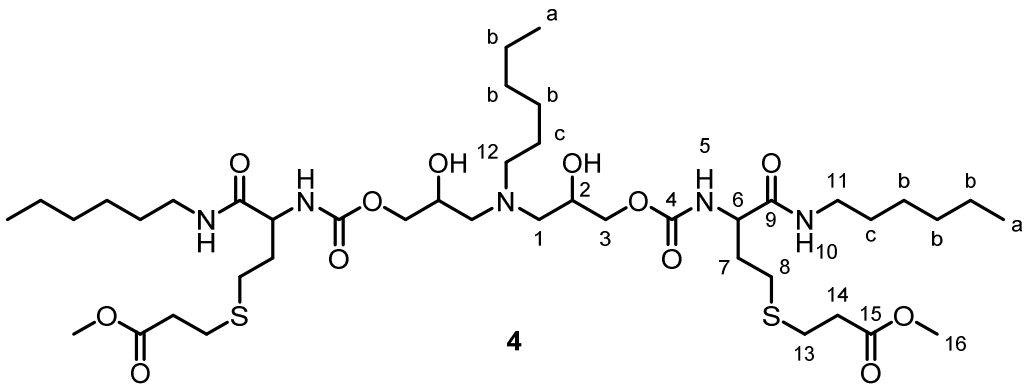


Figure S 14. HSQC spectrum of trialkylamino thioether **3**. Recorded in DMSO-d_6.

1.3.6 Trialkylamino *bis*(thioether) **4**



4

Hexylamine (25.0 µL, 0.190 mmol) and methyl acrylate (11.5 µL, 0.127 mmol) were added to a stirred solution of epoxy thiolactone **1** (27.5 mg, 0.127 mmol) in THF-d_8 (0.633 mL, 0.2 M) at room temperature. The reaction mixture was stirred at 60 °C for 260 h. Then, the solvent was evaporated under reduced pressure and the crude product was separated between CH_2Cl_2 (1.50 mL) and $NH_4HCO_{3(aq)}$ (1.50 mL. 0.05 M). The organic layer was evaporated under reduced pressure to give the crude trialkylamino *bis*(thioether) **4** (quant.) as a slightly yellow viscous oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (t, 2H, H10), 7.31 – 7.19 (m, 2H, H5), 4.69 (s, 2H, O*H*), 4.04 – 3.90 (m, 4H, H6 and H3‘), 3.90 – 3.77 (m, 2H, H3), 3.74 – 3.64 (m, 2H, H2), 3.60 (s, 6H, H16), 3.13 – 2.95 (m, 4H, H11), 2.73 – 2.65 (m, 4H, H14), 2.63 –

2.55 (m, 4H, H13), 2.54 – 2.28 (m, 10H, H1 and H8 and H12), 1.88 – 1.69 (m, 4H, H7), 1.44 – 1.32 (m, 6H, Hc), 1.32 – 1.17 (m, 18H, Hb), 0.86 (s, 9H, Ha). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.9 (C15), 171.2 (C9), 156.1 (C4), 66.9 (C3 and C2), 57.9 (C1), 53.9 (C12 and C6), 51.4 (C16), 38.5 (C11), 34.1 (C13), 32.3 (C7), 31.3 (Cb), 31.0 (Cb), 29.0 (Cc), 27.5 (C8), 26.5, 26.4 (Cc), 26.0 (C14 and Cb), 22.2, 22.1 (Cb), 14.0, 13.9 (Ca). IR (KBr) 3310 (NH), 2954, 2929, 2857, 1737 (OCONH/COOMe), 1657 (CONH), 1537 (NH), 1438, 1357, 1246, 1149, 1051 cm^{-1}. HRMS (MALDI) *m/z* for $C_{42}H_{79}N_5O_{12}S_2$ $(M + Na)^+$ 932.471.

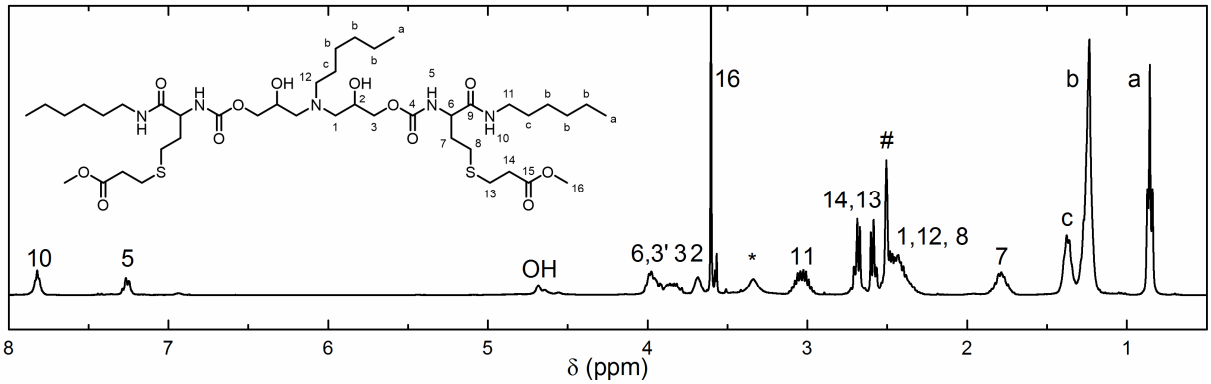


Figure S 15. ^{1}H NMR spectrum of trialkylamino *bis*(thioether) **4**. Recorded in DMSO-d_6 (#). Residual solvent peaks: * H_2O.

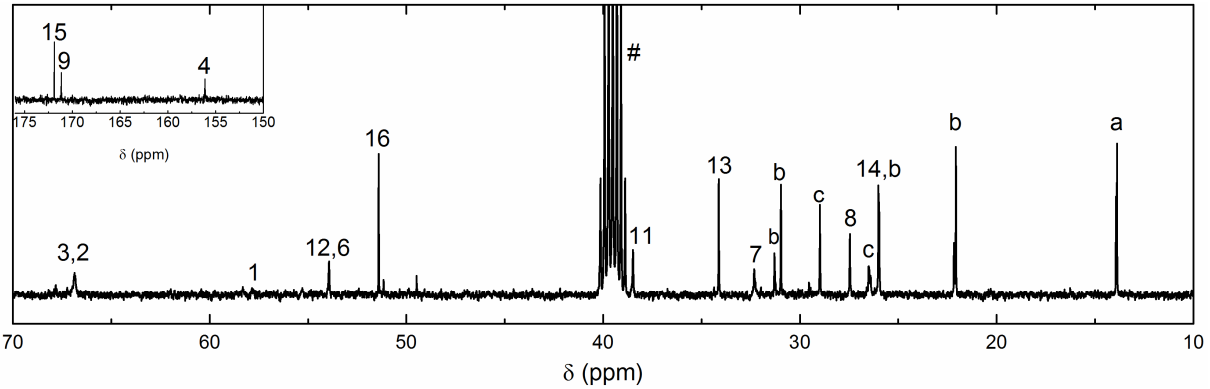
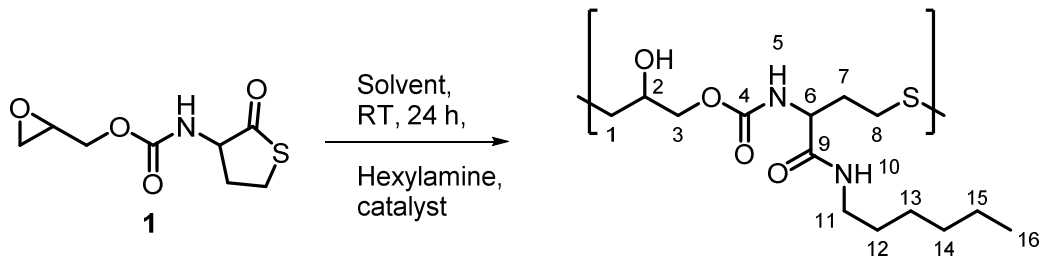


Figure S 16. ^{13}C NMR spectrum of trialkylamino *bis*(thioether) **4**. Recorded in DMSO-d_6 (#).

1.3.7 Polymer synthesis – typical procedure



LiOH (6.20 µL, 2.60E-3 mmol, 10 mg/mL solution) and water (28.4 µL) were added to a stirred solution of epoxy thiolactone **1** (18.8 mg, 8.65E-2 mmol) in THF (311 µL, $[\mathbf{1}]_{total}$ = 0.25 M and THF/water 9:1) at room temperature. Next, hexylamine (11.4 µL, 8.65E-2 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. Then, the solvent

was evaporated under reduced pressure to give the crude poly(thioether urethane) (quant.) as a slightly yellow solid. M_n = 1850 g/mol, M_w/M_n = 2.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (t, *J* = 5.5 Hz, 1H, H10), 7.27 (d, *J* = 8.1 Hz, 1H, H5), 5.12 – 5.01 (m, 1H, O*H*), 4.05 – 3.80 (m, 3H, H3 and H6), 3.80 – 3.63 (m, 1H, H2), 3.13 – 2.93 (m, 2H, H11), 2.64 – 2.39 (m, 4H, H1 and H8), 1.90 – 1.68 (m, 2H, H7), 1.44 – 1.31 (m, 2H, H12), 1.31 – 1.13 (m, 6H, H13/14/15), 0.85 (t, *J* = 6.6 Hz, 3H, H16). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.2 (C9), 156.0 (C4), 68.5 (C2), 66.9 (C3), 54.0 (C6), 38.5 (C11), 35.0 (C1), 32.4 (C7), 31.0 (C13), 29.0 (C12), 28.6 (C8), 26.0 (C14), 22.1 (C15), 13.9 (C16).

For every catalyst a 10 mg/mL stock solution was prepared, LiOH in water or D_2O, TBD/DMAP in THF or THF-d8. Unless otherwise noted, the temperature was always maintained at 25 °C, one eq of hexylamine was used and t = 24 h.

All polymerizations of **1** with hexylamine were conducted in an analogue manner (Table S 2).

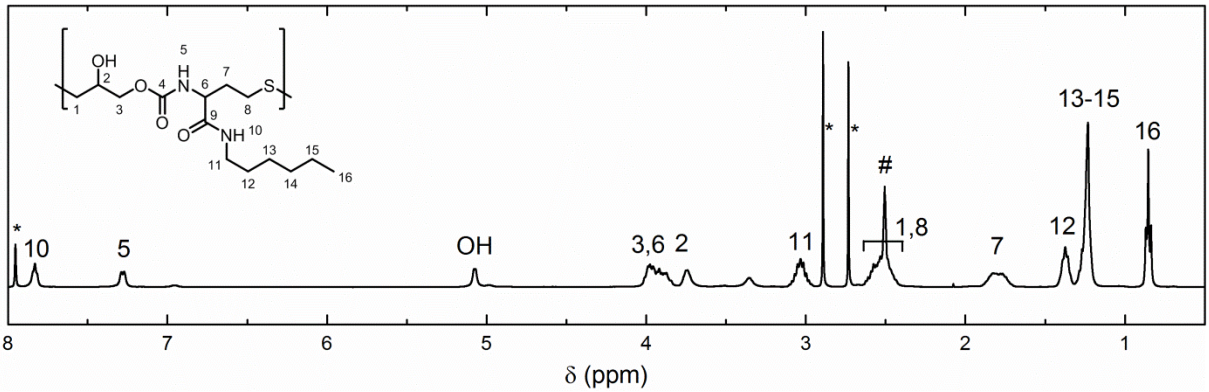


Figure S 17. ^{1}H NMR spectrum of poly(TEU). Recorded in DMSO-d_6 (#). Residual solvent peaks: * DMF.

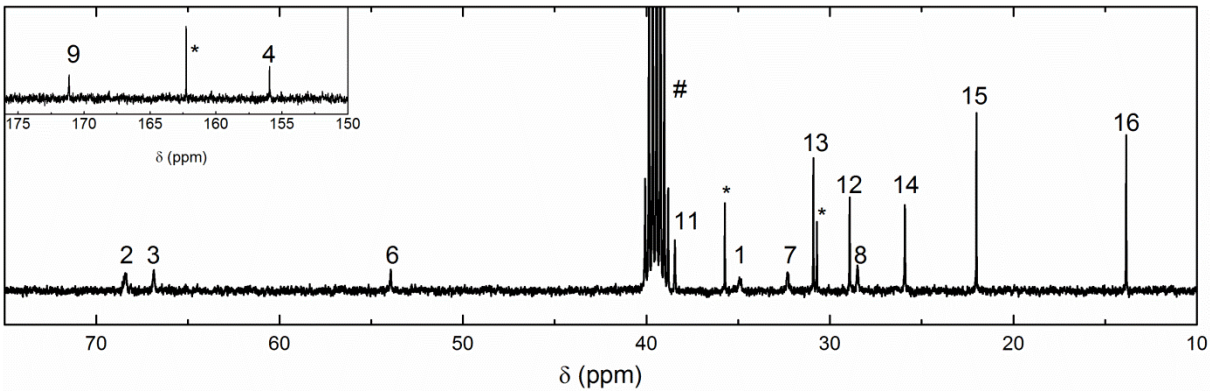
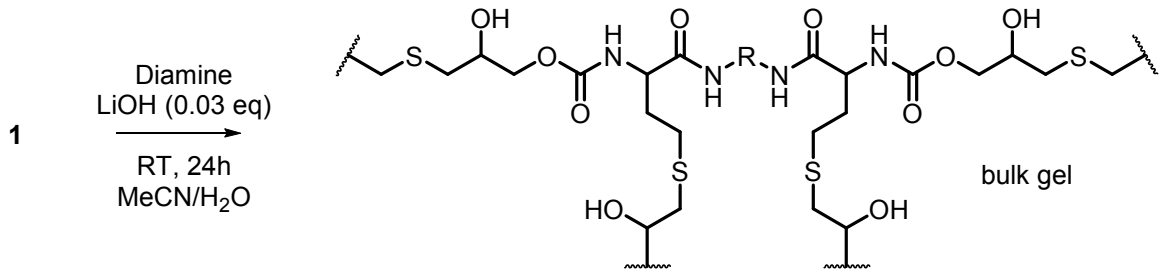


Figure S 18. ^{13}C NMR spectrum of poly(TEU). Recorded in DMSO-d_6 (#). Residual solvent peaks: * DMF.

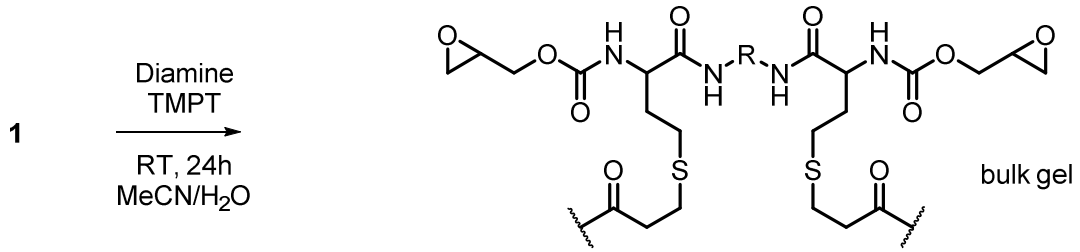
1.3.8 Gel synthesis

Gelation via thiol-epoxy polymerization (G1)



LiOH (6.59 µL, 2.80E-3 mmol, 10 mg/mL solution in H_2O) and water (12.5 µL) were added to a stirred solution of epoxy thiolactone **1** (19.9 mg, 9.17E-2 mmol) and PEG(7) diamine (16.9 mg, 4.59E-2 mmol) in MeCN (26.6 µL, $[\mathbf{1}]_{total}$ = 2 M or 50 wt%) at room temperature. The reaction mixture was stirred at room temperature for 24 h. After 24 h a slightly yellow bulk hydrogel was formed.

Gelation via thiol-ene Michael addition – typical procedure



PEG(2) diamine (7.77 µL, 5.29E-2 mmol) and trimethylolpropane triacrylate (9.51 µL, 3.53E-2 mmol) were added to a stirred solution of epoxy thiolactone **1** (23.0 mg, 0.106 mmol) in an MeCN/water mixture (30.5/22.0 µL, $[\mathbf{1}]_{total}$ = 2 M or 50 wt%) at room temperature. The reaction mixture was stirred at room temperature for 5 min. After 5 min a slightly yellow bulk hydrogel was formed.

Hydrogel preparations via multicomponent reaction of **1** were conducted in an analogue manner (Table S 2).

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Table S 2. One-pot polymerization of epoxy thiolactone **1** with hexylamine.

No	**1**		V_{Total}	catalyst			solvent		hexylamine
	mg, (mmol)	M	µL		eq	µL, (mmol)		µL	µL, (mmol)
1	36.2, (0.167)	0.25	667	-	-	-	THF-d8[a]	667	21.9
2	36.9, (0.170)	0.25	679	DMAP	0.06	125, (1.02E-3)	THF-d8[b]	554	22.3
3	35.3, (0.163)	0.25	650	LiOH[c]	0.03	11.7, (4.88E-3)	THF-d8/D_2O (9:1)[a]	585/53.3	21.4
4	36.7, (0.169)	0.25	676	DBU[d]	0.06	1.51, (1.01E-3)	THF-d8[b]	676	22.2
5	91.5, (0.421)	0.25	1.685	LiOH	0.03	30.3, (1.26E-2)	THF	1.685	55.4
6	92.2, (0.424)	0.25	1.698	TBD	0.03	177, (1.27E-2)	THF	1.698	55.8
7	90.5, (0.417)	0.25	1.666	NaOEt	0.03	85.0, (1.25E-2)	THF	1.666	54.7
8	92.6, (0.426)	0.25	1.705	DBU[d]	0.03	1.91 (1.28E-2)	THF	1.705	56.0
9	96.0, (0.442)	0.25	1.768	KO^{t}Bu	0.03	12.1, (1.33E-2)	THF	1.768	58.1
10	18.8, (8.65E-2)	0.25	346	LiOH	0.03	6.22, (2.60E-3)	THF/H_2O (9:1)	311/28.4	11.4
11	19.5, (8.98E-2)	0.25	359	NaOH	0.03	10.8 ,(2.69E-3)	THF/H_2O (9:1)	323/25.1	11.8
12	21.7, (9.99E-2)	0.25	400	CsOH[e]	0.03	22.4 ,(3.00E-3)	THF/H_2O (9:1)	360/17.6	13.1
13	19.5, (8.98E-2)	0.25	359	$NaHCO_3$	0.03	22.6 ,(2.69E-3)	THF/H_2O (9:1)	323/13.3	11.8
14	18.8, (8.65E-2)	0.25	346	LiOH	1.00	2.1 mg,[f] (8.65E-2)	THF/H_2O (9:1)	311/34.6	11.4
15	20.2, (9.30E-2)	0.25	372	CsOH	1.00	13.9 mg,[f] (8.65E-2)	THF/H_2O (9:1)	335/37.2	12.2
16	14.4, (6.63E-2)	0.25	265	NaOAc	0.03	16.3 (1.99E-3)	THF/H_2O (9:1)	239/10.2	8.71
17	15.1, (6.95E-2)	0.25	278	NaOAc	1.00	5.7 mg,[f] (6.95E-2)	THF/H_2O (9:1)	250/27.8	9.13
18	18.2, (8.38E-2)	0.25	335	NaOTFAc	0.03	34.2, (2.51E-3)	THF/H_2O (9:1)	302/0.7	11.0
19	14.9, (6.86E-2)	0.25	274	NaOTFAc	1.00	9.33 mg,[f] (6.86E-2)	THF/H_2O (9:1)	247/27.4	9.01
20	15.0, (6.90E-2)	0.25	276	Et_3N	0.03	21.0, (2.07E-3)	THF/H_2O (9:1)	248/6.6	9.07
21	15.9, (7.32E-2)	0.25	293	Et_3N	1.00	10.15,[g] (7.32E-2)	THF/H_2O (9:1)	264/29.3	9.62
22	16.2, (7.46E-2)	0.25	298	Pyridine	0.03	17.7, (2.24E-3)	THF/H_2O (9:1)	268/12.1	9.80

23	14.3, (6.58E-2)	0.25	263	Pyridine	1.00	5.31,[h] (6.58E-2)	THF/H_2O (9:1)	237/26.3	8.65
24	39.9, (0.184)	0.25	736	LiOH	0.03	13.2, (5.51E-3)	THF/H_2O (9:1)	662/60.4	24.1
25	41.6, (0.192)	0.25	768	LiOH	0.05	22.9, (9.58E-3)	THF/H_2O (9:1)	691/53.9	25.2
26	45.0, (0.207)	0.25	828	LiOH	0.10	49.6, (2.07E-2)	THF/H_2O (9:1)	745/33.2	27.2
27	7.9, (3.64E-2)	0.25	145	DBU	0.03	16.6, (1.09E-3)	THF	129	4.78
28	8.8, (4.05E-2)	0.25	162	DBU	0.06	37.0, (2.43E-3)	THF	125	5.32
29	11.0, (5.06E-2)	0.25	203	DBU	0.08	61.7, (4.05E-3)	THF	141	6.65
30	9.8, (4.51E-2)	0.25	180	DBU	0.10	68.7, (4.51E-3)	THF	112	5.93
31	38.1, (0.175)	0.50	351	LiOH	0.03	12.6, (5.26E-3)	THF/H_2O (9:1)	316/22.5	23.0
32	36.7, (0.169)	0.75	225	LiOH	0.03	12.1, (5.07E-3)	THF/H_2O (9:1)	203/10.4	22.2
33	38.1, (0.175)	1.00	175	LiOH	0.03	12.6, (5.26E-3)	THF/H_2O (9:1)	158/4.9	23.0
34	16.2, (7.46E-2)	1.25	60.0	LiOH	0.03	5.36, (2.24E-3)	THF/H_2O (9:1)	54/0.64	9.80
35	40.2, (0.185)	1.50	123	LiOH	0.03	13.3, (5.55E-3)	THF/H_2O (9:1)	111/0	24.3
36	9.6, (4.42E-2)	0.25	177	LiOH	0.03	3.18, (1.33E-3)	DMF	174	5.81
37	11.2, (5.16E-2)	0.25	206	LiOH	0.03	3.70, (1.55E-3)	CH_2Cl_2	203	6.78
38	8.8, (4.05E-2)	0.25	162	LiOH	0.03	2.91, (1.22E-3)	MeOH	159	5.32
39	9.9, (4.56E-2)	0.25	182	LiOH	0.03	3.27, (1.37E-3)	MeCN	179	5.99
40	8.4, (3.87E-2)	0.25	155	LiOH	0.03	2.78, (1.16E-3)	MeCN/H_2O (9:1)	139/12.7	5.08
41	11.5, (5.29E-2)	0.25	212	LiOH	0.03	3.80, (1.59E-3)	MeCN/H_2O (7:3)	148/59.7	6.96
42	8.3, (3.82E-2)	0.25	153	LiOH	0.03	2.75, (1.15E-3)	MeCN/H_2O (5:5)	76.4/73.7	5.02
43	9.8, (4.51E-2)	0.25	180	LiOH	0.03	3.24, (1.35E-3)	MeCN/H_2O (3:7)	54.1/123	5.93

[a)] Benzene (1.00 eq) was added as constant reference for integration purposes. [b)] idem to a), just DCM was used as reference [c)] LiOH was prepared as a 10 mg/mL stock solution. Thereoff the amounts needed (µL) was taken and subtracted from the residual water which had to be added. [d)] Here, DBU was added in bulk (d = 1.018 g/mL). [e)] For CsOH, a 20 mg/mL solution in water was used. [f)] Base was added as solid to the reaction mixture. [g)] Here, Et_3N was added in bulk (d = 0.73 g/mL). [h)] Here, pyridine was added in bulk (d = 0.98 g/mL).

Table S 3. Gelation experiments for the hydrogel formation of **1** with selected acrylates and diamines via thiol-ene Michael addition.

No	**1**	diamine		acrylate		wt%	$V(H_2O)$	V(MeCN)	gelation time
	mg, (mmol)		mg, (mmol)		mg, (mmol)		µL	µL	min
G2	23.0, (0.106)	PEG(2) diamine	7.85, (0.0529)	TMPT	10.5, (0.0353)	50	22.0	30.5	5 min
G3	21.8, (0.100)	PEG(7) diamine	18.5, (0.0502)	TMPT	9.91, (0.0334)	50	20.9	29.1	5 min

2 Kinetic data

By online ^{1}H NMR spectroscopy the conversion of thiolactone ring (delivering k_1) and the disappearance of the epoxy signals (similar to the formation of polymer and rate constant k_2) was monitored. The samples were shimmed to the appropriate solvent without hexylamine at first. Then, hexylamine was added, the reaction started and the sample was reshimmed as fast as possible prior to the start of the kinetic measurement series. Once the first measurement of the reactive mixture was started, measurements (which lasted exactly 18 s) were conducted in a time interval of 30 minutes for a total time of 24 or 50 hours. Therefore, the final times used for the fitting of the kinetic data plots were corrected. The resulting data plots were fitted to the first order kinetic law, shown below:

$$a = a_0 \cdot \exp(-k \cdot t)$$

The fact, that without the use of the catalyst only the thiolactone ring is opened, makes a step-wise reaction possible. Thus, the efficiency of the catalysts only in the thiol-epoxy reaction was evaluated first. To achieve this, the thiolactone was opened in absence of a base. After 20 to 24 h, a corresponding base was added, and conversion vs. time plots were produced. This time DMAP was excluded as it turned out to be not effective for the polymerization. Instead and additionally to LiOH and DBU, TBD, NaOEt and KOtBu were used (each 3 mol%). The conversion vs. time plot shows that KOtBu (pK_a = 17) works equally fast as LiOH, both reaching a conversion plateau after only four to six hours. DBU (pK_a = 13.5) shows a slower start but reaches the same conversion (~85%) at 26 h as KO^{t}Bu. Yet from the progression of the data points it is assumed, that the reaction is not finished at 26 h, since no plateau is detected. With the use of TBD (pK_a = 15.2) and after 24 h, only 51% of the epoxy thiol is converted to the product polymer. And finally using NaOEt (pK_a = 15.9) as base, a very slow conversion is found. After 24 h only 30% of the epoxy thiol has reacted (Figure S 19).

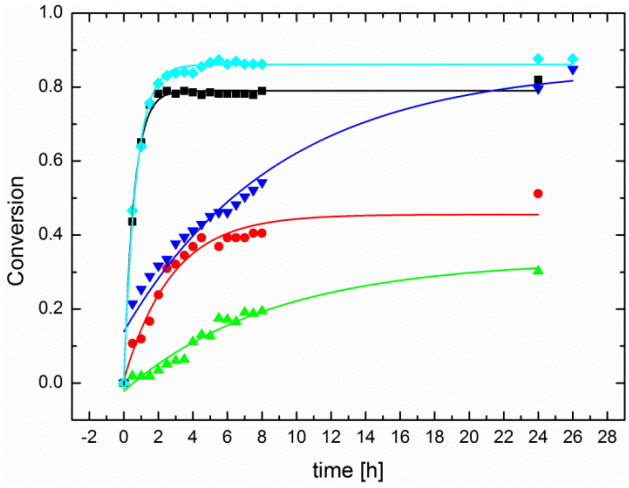

Figure S 19. Conversion Vs. time plot of the thiol-epoxy reaction using 3 mol% of LiOH (■), TBD (●), NaOEt (▲), DBU (▼) and KO^{t}Bu (◆) as base.

3 Polymerization parameters

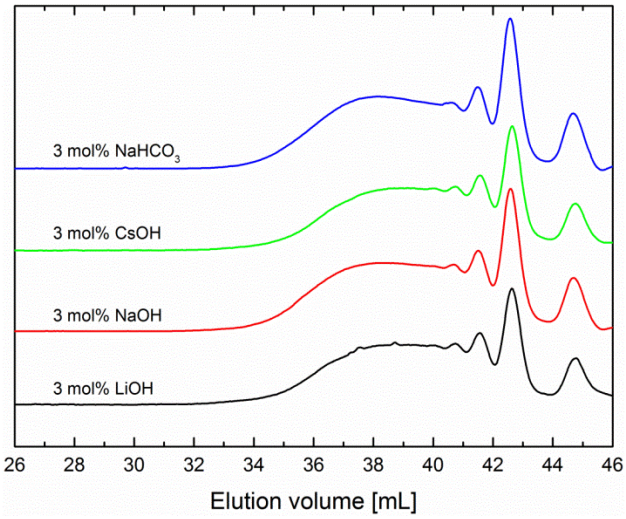

Figure S 20. Influence of the alkaline catalysts on the SEC elution curves of the resulting poly(thioether urethane)s.

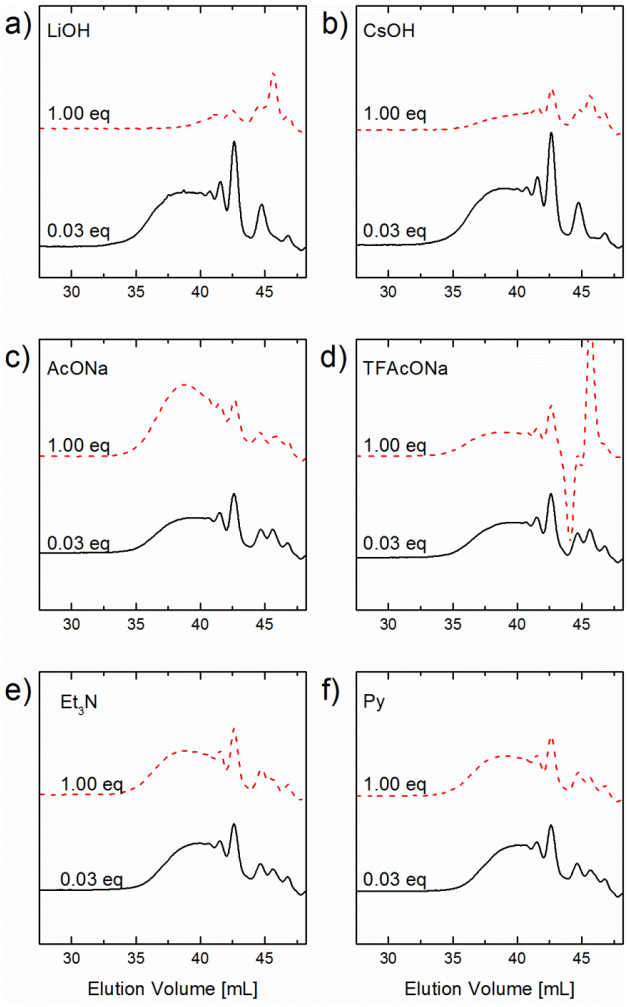

Figure S 21. SEC elution curves for poly(thioether urethane)s with 0.03 eq (solid black lines) or 1.00 eq (dashed red lines) of a) LiOH, b) CsOH, c) sodium acetate, d) sodium trifluoroacetate, e) triethylamine and f) pyridine.

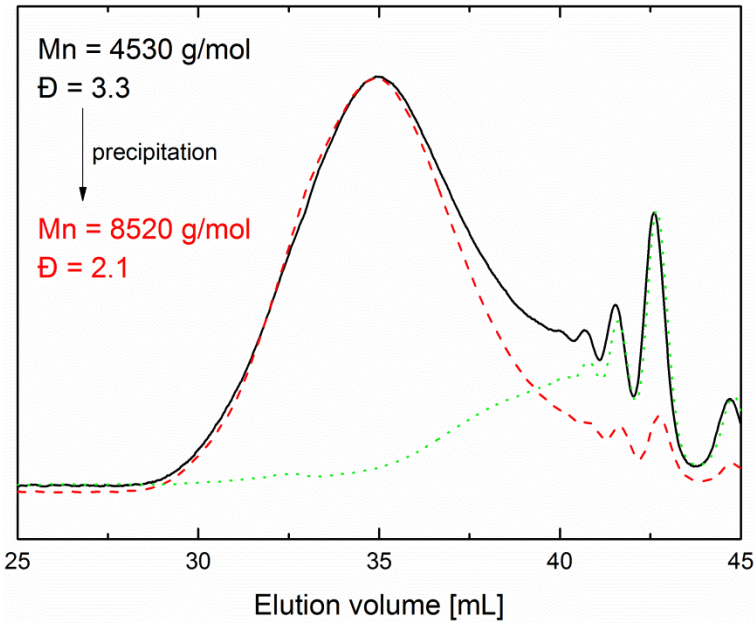

Figure S 22. Precipitation of poly(TEU) from DMF in MeCN showing the elugram of the crude unpurified poly(TEU) (solid black line) the purified polymer (dashed red line) and the mother liquor (dotted green line). Synthesis conditions: c(**1**) = 1.50 M, THF/H_2O (90:10), RT, 24 h, 3 mol% LiOH, 1 eq hexyl amine.

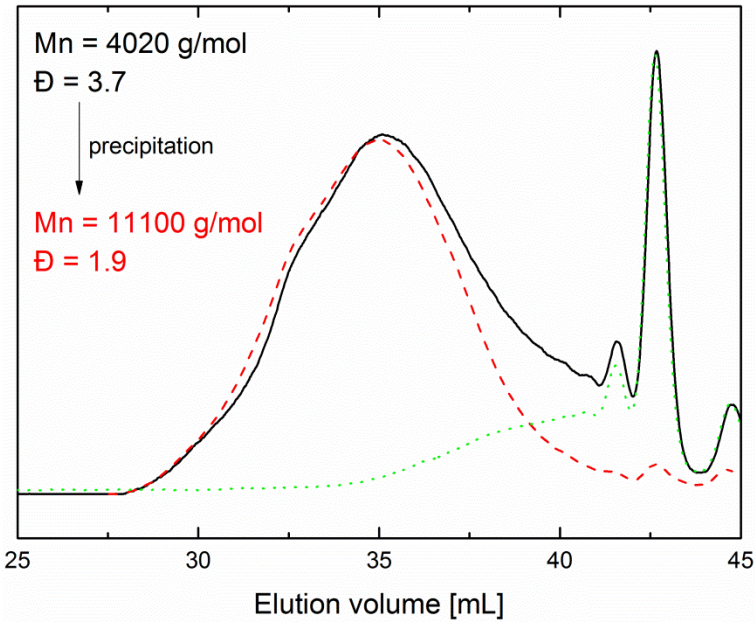

Figure S 23. Precipitation of poly(TEU) from DMF in MeCN showing the elugram of the crude unpurified poly(TEU) (solid black line), the purified polymer (dashed red line) and the mother liquor (dotted green line). Synthesis conditions: c(**1**) = 0.25 M, H_2O/MeCN (70:30), RT, 24 h, 3 mol% LiOH, 1 eq hexyl amine.

4 Cyclic oligomer assessment test

To verify if in the lower molecular weight region cyclisation occurs, a cyclic oligomer assessment test was carried out. Selected samples were dissolved in THF (10 mg mL^{-1}) and stirred with H_2O_2 for a maximum of 2 hours at room temperature. After 2 hours, 5 µL of the reaction mixtures were mixed with solutions of sodium trifluoroacetate (0.5 µL of 10 $g \cdot mL^{-1}$) and DCTB matrix (20 µL of 20 $g \cdot mL^{-1}$) and directly spotted on the MALDI-TOF target.

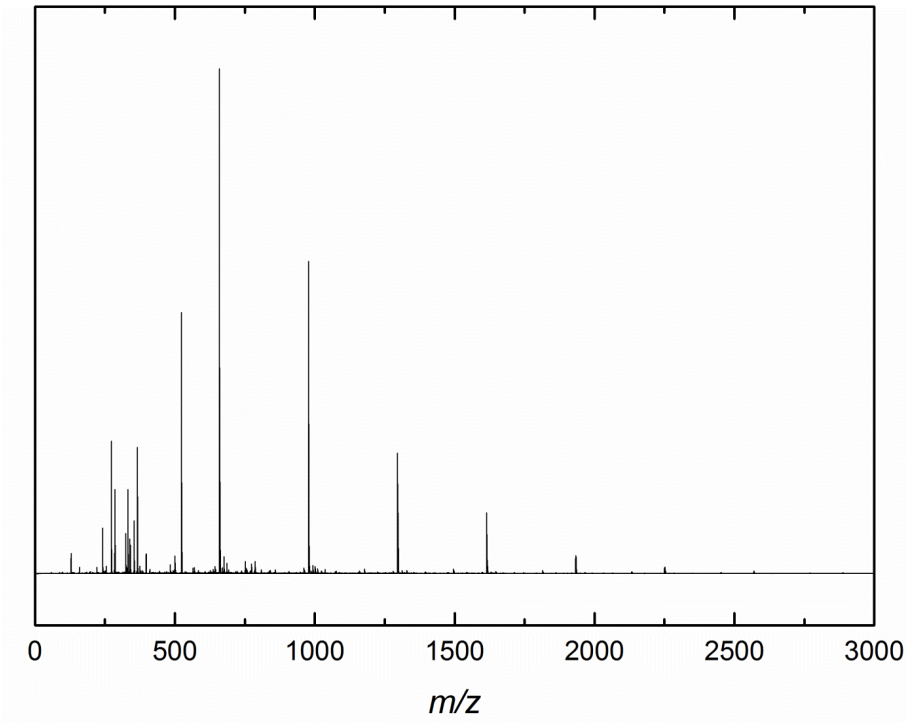

Figure S 24. MALDI-TOF MS spectrum of poly(thioether urethane) prior oxidation by H_2O_2.

Table S 4. MALDI-TOF MS data of poly(thioether urethane) prior oxidation by H_2O_2. Reported peaks describe masses of [M + Na^+] (MW = 22.99 g/mol).

N(Thioether Urethane)	*m/z*(calculated)	*m/z*(found)	Intensity (a.u.)
2	659.31	659.312	236966.94
3	977.47	977.469	143271.72
4	1295.63	1295.630	65216.42
5	1613.79	1613.794	28243.79
6	1931.95	1931.949	10005.37
7	2250.11	2250.118	2675.82
8	2568.27	2568.282	1037.08
9	2886.43	2886.444	383.80

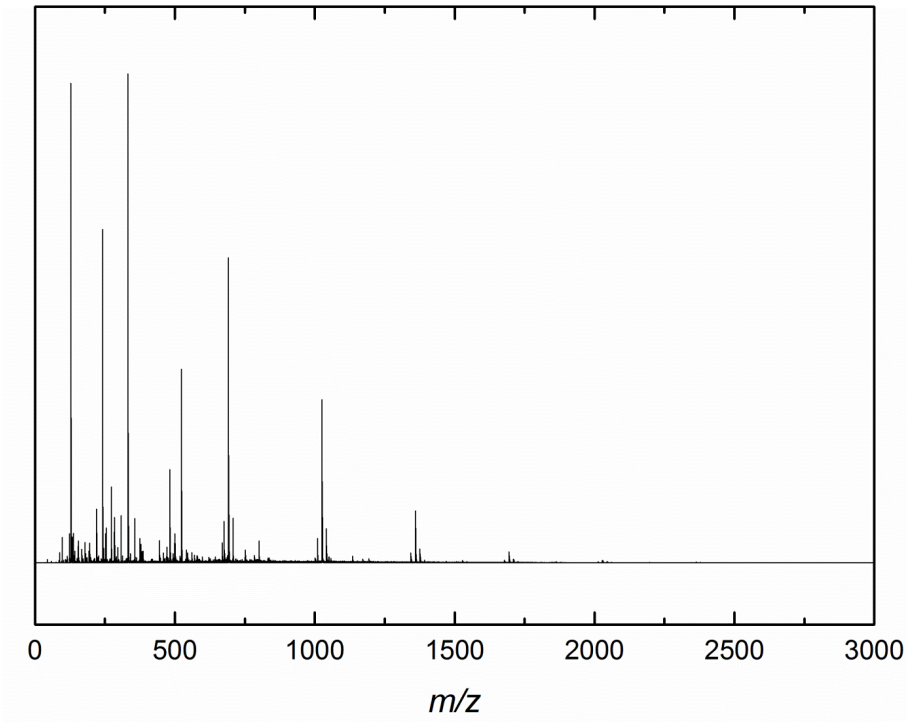

Figure S 25. MALDI-TOF MS spectrum of poly(sulfoxide urethane)s obtained through oxidation with H_2O_2.

Table S 5. MALDI-TOF MS data of poly(sulfoxide urethane)s obtained through oxidation with H_2O_2. Reported peaks describe masses of [M + Na^+] (MW = 22.99 g/mol).

N(Thioether Urethane)	*m/z*(calculated)	*m/z*(found)	Intensity (a.u.)
2	691.31	691.334	207487.33
3	1025.47	1025.498	109529.30
4	1359.63	1359.665	34936.90
5	1693.79	1693.831	7591.84
6	2027.95	2027.996	1601.10

5 Additional Data

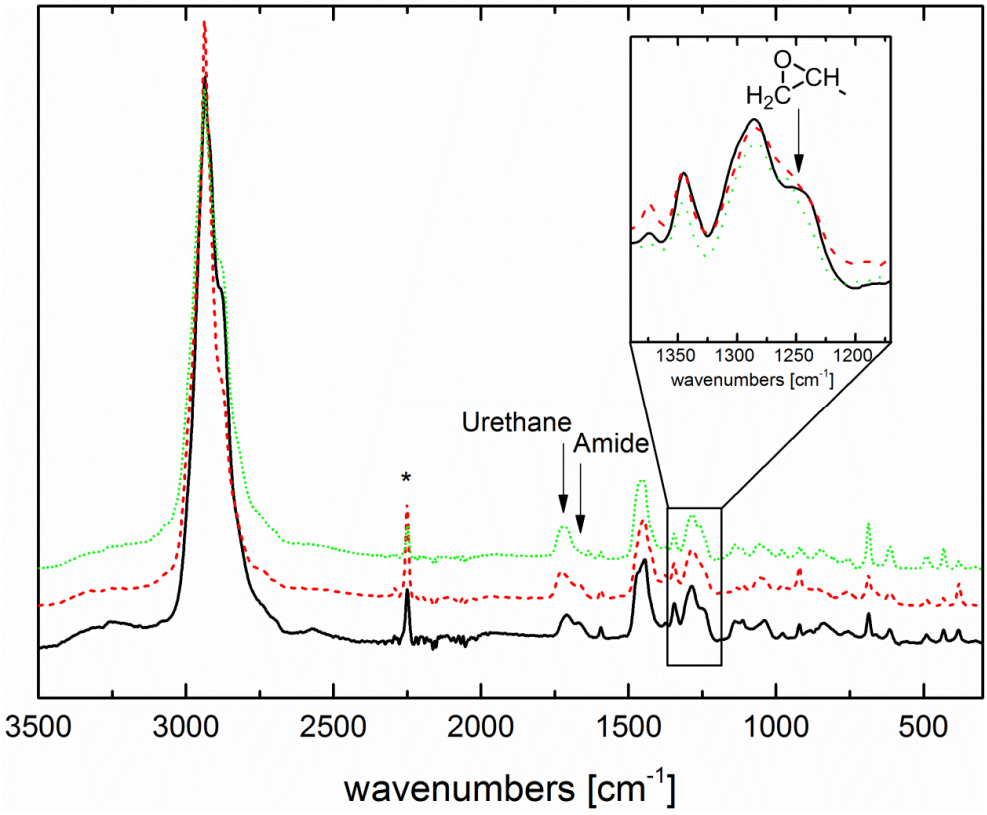

Figure S 26. Raman spectra of hydrogels obtained by thiol-epoxy polymerization (solid black line), and by multicomponent reaction using thiol-ene Michael addition with a PEG(X) diamine and TMPT (X = 2, dashed red line; X = 7, dotted green line). Inset graph shows the ring stretch band of the monosubstituted epoxide.

6 References

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