Electronic Supplementary Information for

Effect of Disulfide Loop Length on Mechanochemical Structural Stability of Macromolecules

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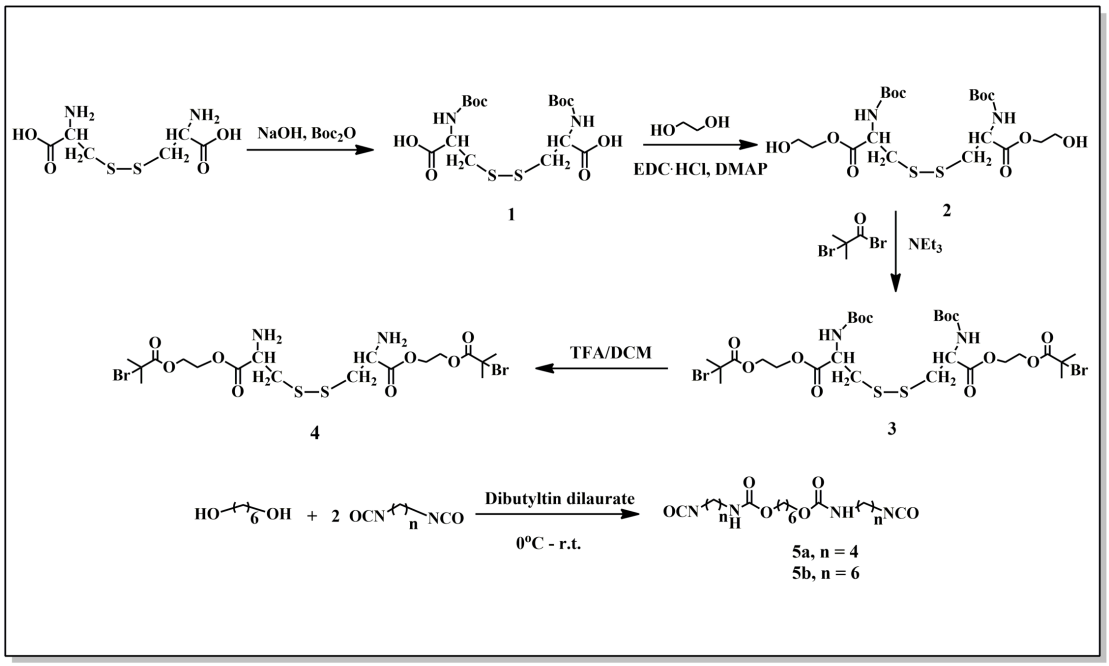
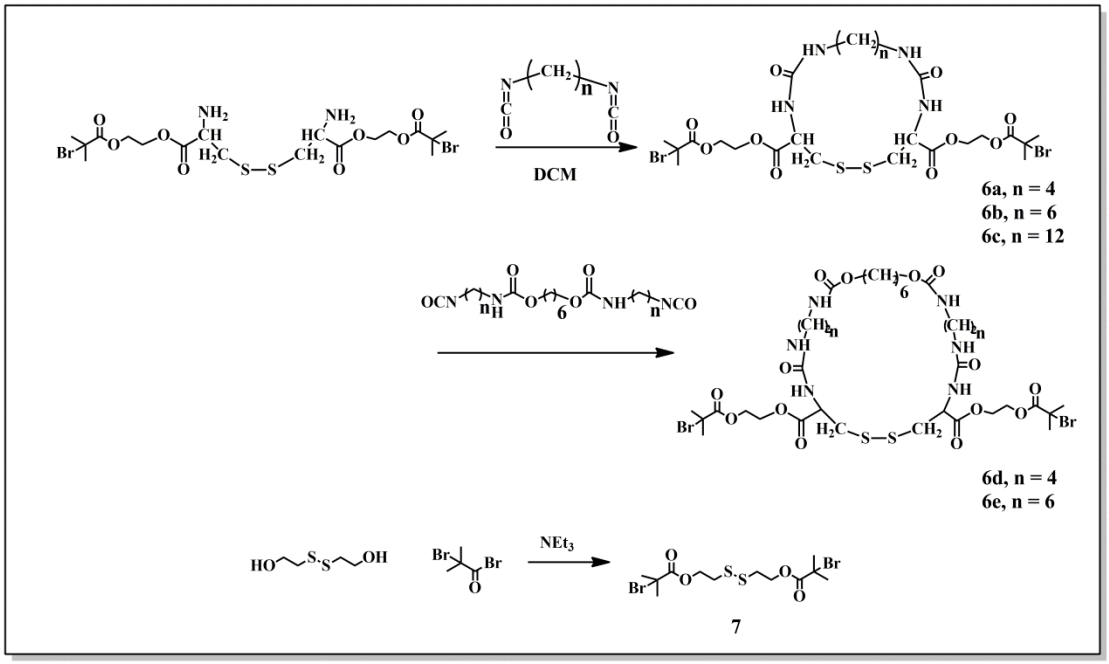
I. General experimental details

α-bromoisobutyryl bromide was provided by Chemada Fine Chemicals and used as received. All other chemicals were purchased from commercial sources and used, unless specified, as received. MA was purified by passing through basic alumina to remove the inhibitor and kept at 0 ºC under argon. Tetrahydrofuran, dichloromethane, dimethylsulfoxide were purified as described by Williams et al.[1] All reactions were carried out in heat-gun-dried glassware under argon atomsphere using standard *Schlenk* techniques.

All ^{1}H and ^{13}C NMR spectra were recorded using an AVANCE II 400 MHz or an AVANCE 300 MHz Bruker spectrometer at the Technion NMR facilities. Proton chemical shifts are express in parts per milllion (ppm, δ scale) and are referenced to teramethylsilane ($(CH_3)_4Si$, 0.00 ppm) or residual protium in the solvent ($CHCl_3$, 7.26 ppm and DMSO-d_5, 2.50 ppm). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = muliplet and /or multiple resonances, br = broad peak), integration, and coupling constant (*J*) in hertz. Carbon chemical shifs are expressed in parts per million (ppm, δ scale) and referenced to the carbon resonance of the NMR solvents ($CDCl_3$, 77.16 ppm or DMSO-d_6, 39.52 ppm). HRMS ESI (*m*/*z*) spectra were recorded on Waters LCT Premier Mass Spectrometer, Waters ACQITY UPLC System: ESI+, MeCN : H_2O (70 : 30) 0.25 mL/min. Gel-Permeation Chromatography (GPC) measurements were performed at a flow rate of 1 ml/min THF at 30 ºC on a Thermo HPLC system consisting of a Dionex ultimate 3000 isocratic pump, four in line TSKgel G4000HHR columns and a series of five detectors, Dionex DAD-3000 UV-VIS detector, a Wyatt Dawn Heleos II 8 multi-angle light scattering, including DLS (Wyatt QELS)， refractometer (Wyatt Optilab-rEX) and viscometer (Wyatt Viscostar II). Data analysis was performed using the ASTRA software from Wyatt. Sonication experiments were performed using Vibra Cell VCX 500 liquid processor under N_2. Thin layer chromatography was carried out on Dynamic Adsorbents silica gel TLC (F-254, 250 μm). Flash column chromatography was conducted with silica gel 60 (230-400 mesh) from Merck.

II. Synthetic details

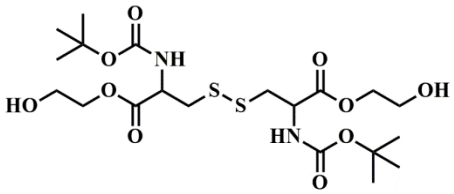




1. L-Boc-cystine (1)

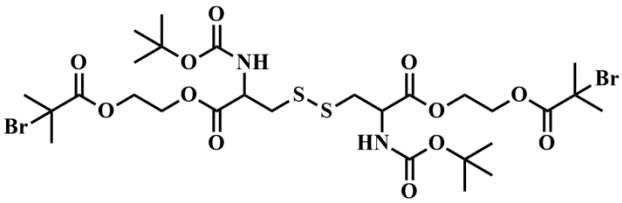
L-Boc-cystine was synthesized as described by Yang et al[2]. ^{1}H and ^{13}C NMR spectra are in accordance with those reported in the literature.

2. Compound 2



A round bottom flask was charged with **1** (4.0 g, 9.08 mmol, 1 equiv), 4-dimethylaminopyridine (DMAP) (0.67 g, 5.45 mmol, 0.6 equiv) and ethylene glycol (25 mL). After a clear solution was obtained, a solution of N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC) (4.35 g, 22.70 mmol, 2.5 equiv) in ethylene glycol (5.0 mL) was added. The mixture was stirred overnight. Water (100 mL) was then added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried over $MgSO_4$ and filtered. The product was purified through silica chromatography (hexane 1 : 2 ethyl acetate). The solvent was removed under vacuum to give **2** (2.1 g, 41.6% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (dd, J = 16.9, 8.3 Hz, 2H, Boc-N**H**-), 4.80 (t, J = 4.7 Hz, 2H, -O**H**), 4.39-4.21 (m, 2H, -CH_2C**H**-), 4.12-4.03 (m, 4H, -COOC$\mathbf{H_2}$-), 3.61-3.52 (m, 4H, -C$\mathbf{H_2}$OH), 3.20-2.84 (m, 4H, -SC$\mathbf{H_2}$-), 1.38 (s, 18H, -C$\mathbf{H_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.17, 155.68, 80.87, 67.53, 60.54, 53.19, 41.33, 28.47. HRMS (ESI) *m/z*: 551.1722 (calcd $C_{20}H_{36}N_2O_{10}S_2Na^+$, 551.1709).

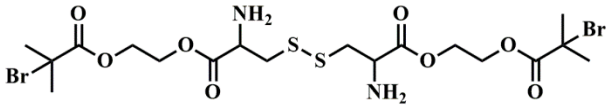
3. Compound 3



Compound **2** (0.50 g, 0.95 mmol, 1 equiv**)** and triethylamine (0.40 ml, 2.84 mmol, 3 equiv) were dissolved in THF (20 mL) under argon and cooled in an ice bath. Then, a solution of 2-bromo-2-methylpropionyl bromide (0.54g, 2.36mmol, 2.5 equiv) in THF (5 mL) was added dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. The insoluble salts were removed via filtration and washed with THF (50 mL). The filtrate was concentrated by vacuum

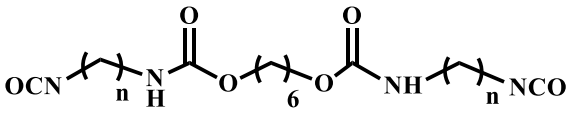
evaporation and the product was purified by silica chromatography (hexane 4:1 ethyl acetate) to afford **3** (0.68 g, yield 86.7%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (d, *J* = 7.3 Hz, 2H, Boc-N**H**-), 4.73-4.56 (m, 2H, -CH_2C**H**-), 4.41 (br s, 8H, -OC**H$_2$CH$_2$**OH), 3.43-3.07 (m, 4H, -SC**H$_2$**-), 1.94 (s, 12H, -C(C**H$_3$**)$_2$Br), 1.45 (s, 18H, -C(C**H$_3$**)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.53, 170.50, 155.10, 80.44, 63.31, 63.05, 55.58, 53.07, 41.22, 30.74, 28.47. HRMS (ESI) *m*/*z*: 847.0750 (calcd $C_{28}H_{46}N_2O_{12}S_2Br_2Na^+$, 847.0757).

4. Compound 4



Compound **3** (0.50 g, 0.60 mmol, 1 equiv) was dissolved in neat trifluoroacetic acid (TFA) (1.80 mL, 24.0 mmol, 40 equiv). The mixture was stirred for 3 h and the TFA was evaporated, affording thick, red oil. A solution of saturated $NaHCO_3$ (10 mL) was added to quench any remaining TFA, until the pH reached 8-9. The solution was then extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford **4** (0.35g, yield 92.1%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (br s, 8H, -OC**H$_2$CH$_2$**OH), 3.96-3.82 (m, 2H, -CH_2C**H**-), 3.40-2.88 (m, 4H, -SC**H$_2$**-), 1.93 (s, 12H, -C(C**H$_3$**)$_2$Br).^{13}C NMR (100 MHz, $CDCl_3$) δ 173.31, 171.54, 63.37, 62.79, 55.59, 53.71, 43.20, 30.76. HRMS (ESI) *m*/*z*: 624.9880 (calcd $C_{18}H_{31}N_2O_8S_2Br_2^+$, 624.9889).

5. Compounds 5a,b



5a, n = 4
5b, n =6

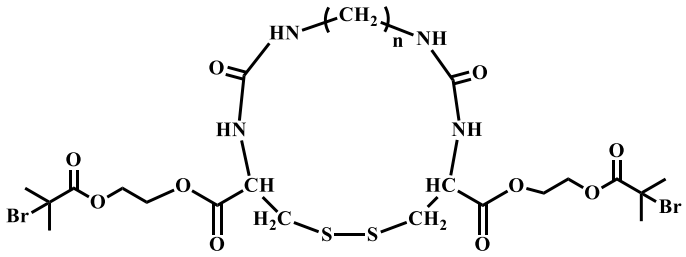
1,6-hexanediol (0.05 g, 0.42 mmol) in anhydrous diethyl either (6 mL) was added dropwise to a solution of the corresponding diisocyanate (10 equiv) in anhydrous diethyl ether (10 mL) at 0 ºC. Then, 4 drops of dibutyltin dilaurate were added. The

reaction mixture was kept at 0 °C for 1 h and further stirred at room temperature for 3 h. The product precipitated as a white solid, which was collected by filtration and dried under vacuum.

5a (0.14 g, yield 85.0%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19-6.94 (m, 2H, -N**H**-), 3.92 (t, J = 6.3 Hz, 4H, -COOC**H**$_2$-), 3.35 (t, J = 6.4 Hz, 4H, OCNC**H$_2$**-), 2.98 (m, 4H, -C**H$_2$**NH-), 1.59-1.47 (m, 8H, -COOCH$_2$(C**H$_2$**)$_4$CH$_2$OOC-), 1.48-1.39 (m, 4H, -OCNCH$_2$C**H$_2$**-), 1.37-1.22 (m, 4H, -C**H$_2$**CH$_2$NH-). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.39, 121.53, 63.51, 42.31 (2C), 28.67, 27.92, 26.53, 25.12. HRMS (ESI) m/z: 421.2057 (calcd $C_{18}H_{30}N_4O_6Na^+$, 421.2063).

5b (0.18 g, yield 90.3%). ^{1}H NMR (400 MHz, DMSO) δ 7.03, 5.71 (m, 2H, -N**H**-), 3.90 (t, J = 6.2 Hz, 4H, -COOC**H**$_2$-), 3.44-3.23 (t, 4H, J = 6.4 Hz, 4H, OCNC**H$_2$**-), 3.04-2.83 (m, 4H, -C**H$_2$**NH-), 1.63-1.10 (m, 24H, -COOCH$_2$(C**H**$_2$)$_4$CH$_2$OOC-, -OCNCH$_2$(C**H**$_2$)$_4$CH$_2$NH-). ^{13}C NMR (151 MHz, DMSO-d_6, 90 °C) δ 155.85, 121.33, 63.08, 42.09, 30.19, 29.54, 28.95, 28.23, 25.49, 25.20, 24.63. HRMS (ESI) m/z: 477.2682, (calcd $C_{22}H_{38}N_4O_6Na^+$, 477.2689).

6. Compounds 6a-c



6a, n = 4
6b, n = 6
6c, n = 12

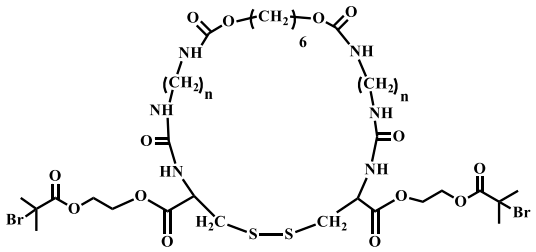
A solution of the corresponding diisocyanate (0.59 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise over a period of 30 - 40 min to a well-stirred and ice-cooled solution of the freshly generated compound **4** (0.37 g, 0.59 mmol) in anhydrous CH_2Cl_2 (170 mL). The reaction mixture was then stirred at room temperature for 72 h. The solvent was evaporated and the residue was separated by silica chromatography (dichloromethane 40: 1 methanol), affording the corresponding product as a white solid.

6a (0.16 g, yield 35.6%). ^{1}H NMR (400 MHz, DMSO) δ 6.35 (dd, *J* = 20.1, 8.1 Hz, 2H, -CHN**H**-), 6.28-6.08 (m, 2H, -CON**H**CH_2-), 4.70-4.44 (m, 2H, -C**H**NH-), 4.32 (br s, 8H, -OC**H_2CH_2**O-), 3.27-2.62 (m, 8H, -C**H_2**NH-, -SC**H_2**-), 1.88 (s, 12H, -C(C**H_3**)$_2$Br), 1.65-0.96 (m, 4H, -NHCH$_2$(C**H_2**)$_2$CH$_2$NH-). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 171.65, 171.10, 158.35, 63.57, 62.90, 55.45, 52.59, 42.24, 39.79, 30.65, 27.25. HRMS (ESI) *m*/*z*: 767.0480 (calcd $C_{24}H_{39}N_4O_{10}S_2Br_2^+$, 767.0454).

6b (0.49g, yield 42.1%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.47-6.32 (m, 2H, -CHN**H**-), 6.35 (dd, *J* = 20.1, 8.1 Hz, 2H), 6.22-5.96 (m, 2H, -CON**H**CH_2-), 4.68-4.48 (m, 2H, -C**H**NH-), 4.34 (br s, 8H, -OC**H_2CH_2**O-), 3.15-2.83 (m, 4H, -SC**H_2**-), 3.28-2.60 (m, 8H, -C**H_2**NH-, -SC**H_2**-), 1.89 (s, 12H, -C(C**H_3**)$_2$Br), 1.38-1.18 (m, 8H, -NHCH$_2$(C**H_2**)$_4$CH$_2$NH-). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 171.54, 171.08, 158.17, 63.28, 62.86, 55.36, 52.39, 42.01, 37.85, 30.42, 29.26, 24.98 , 23.70. HRMS (ESI) *m*/*z*: 795.0754 (calcd $C_{26}H_{43}N_4O_{10}S_2Br_2^+$, 795.0767)

6c (0.69g, yield 36.6%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.33 (m, 2H, dd, *J* = 20.1, 8.1 Hz, -CHN**H**-), 6.17-6.05 (m, 2H, -CON**H**CH_2-), 4.61-4.42 (m, 2H, -C**H**NH-), 4.40-4.22 (br s, 8H, -OC**H_2CH_2**O-), 3.27-2.74 (m, 8H, -C**H_2**NH-, -SC**H_2**-), 1.95-1.84 (m, 12H, -C(C**H_3**)$_2$Br), 1.43-1.12 (m, 20H, -NHCH$_2$(C**H_2**)$_{10}$CH$_2$NH-). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 171.53, 171.16, 158.18, 63.26, 62.67, 55.37, 52.24, 41.36, 39.74, 30.41, 29.37, 27.43, 27.14, 26.86, 25.65. HRMS (ESI) *m*/*z*: 877.1750 (calcd $C_{32}H_{55}N_4O_{10}S_2Br_2^+$, 877.1726).

7. Compound 6d,e



6d, n = 4
6e, n = 6

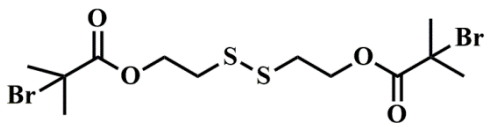
A solution of compound **5a** or **5b** (0.72 mmol) in a mixture of anhydrous DMSO (5 mL) and anhydrous CH_2Cl_2 (40 mL) was added dropwise over a period of 30 - 40

min to a well-stirred and ice-cooled solution of the freshly generated compound **4** (0.45 g, 0.72 mmol) in anhydrous CH_2Cl_2 (200 mL). The mixture was then left stirred at room temperature for 72 h. The solvents was evaporated and the product was purified by silica chromatography (dichloromethane 40 : 1 methanol), affording the corresponding product as white solid.

6d (0.15g, yield 20.1%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.04 (t, J = 5.4 Hz, 2H, -N**H**COO-), 6.34 (d, J = 8.1 Hz, 2H, -CHN**H**-), 6.15 (t, J = 5.5 Hz, 2H, -CH_2N**H**CONH-), 4.61-4.43 (m, 2H, -C**H**NH-), 4.41-4.25 (br s, 8H, -OC**H_2CH_2**O-), 3.91 (t, J = 6.1 Hz, 4H, -OC**H_2CH_2**O-), 3.13-2.81 (m, 12H, -SC**H_2**-, -NHC**H_2**$(CH_2)_4$C**H_2**NH-), 1.88 (s, 12H, -C(C**H_3**)$_2$Br), 1.61-1.21 (m, 16H, -NHCOOCH_2(**CH_2**)$_4$CH_2OOCNH-, -NHCH_2(**CH_2**)$_2$CH_2NH-). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 171.44, 171.03, 158.12, 157.45, 64.23, 63.15, 62.60, 55.24, 52.14, 41.20, 40.04, 39.29, 30.21, 27.96, 27.02, 26.81, 24.73. HRMS (ESI) m/z: 1023.2050 (calcd $C_{36}H_{61}N_6O_{14}S_2Br_2^+$, 1023.2054).

6e (0.16 g, yield 23.2%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.01 (t, J = 5.1Hz, 2H, -N**H**COO-), 6.35 (d, J = 8.3 Hz, 2H, -CHN**H**-), 6.15 (t, J = 5.7 Hz, 2H, -CH_2N**H**CONH-), 4.64-4.41 (m, 2H, -C**H**NH-), 4.32 (br s, 8H, -OC**H_2CH_2**O-), 3.99-2.80 (m, 4H, -OC**H_2CH_2**O-), 3.15-2.80 (m, 12H, -SC**H_2**-, -NHC**H_2**$(CH_2)_4$C**H_2**NH-), 1.87 (s, 12H, -C(C**H_3**)$_2$Br), 1.57-1.45 (m, 8H, -NHCOOCH_2(**CH_2**)$_4$CH_2OOCNH-), 1.42-1.26 (m, 16H, -NHCH_2(**CH_2**)$_4$CH_2NH-). ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 171.45, 171.06, 158.06, 157.32, 64.42, 63.17, 62.66, 55.28, 52.12, 41.38, 40.30, 39.55, 30.29, 29.71, 29.47, 28.58, 26.08 (2C), 25.20. HRMS (ESI) m/z: 1081.2660 (calcd $C_{40}H_{69}N_6O_{14}S_2Br_2^+$, 1081.2659).

8. Bis[2-(2-bromoisobutyryloxy)ethyl] disulfide (BiBS) (7)



7 was synthesized according to a literature procedure.[3, 4] ^{1}H and ^{13}C NMR spectra are in accordance with those reported in the literature.[5]

III. General procedure for the synthesis of *loop*-PMAs and *linear*-PMA.

The polymers with different macrocyclic centers were synthesized through SET-LRP.[5] The procedure described for **1a** was used also for the different initiators.

MA (1.0 mL, 11.10 mmol), solvent (DMSO, 0.5 mL), initiator (**1a**, 5.87 mg, 7.65 μmol), copper wire (diam. 0.5mm, 1 cm length), and ligand (Me_6TREN, 1.0 μL, 3.83 μmol) were added to a 10 mL Schlenk flask under argon in the following order: copper wire, monomer, ligand, solvent and initiator. The flask was immediatly sealed and three freeze-pump-thaw cycles were applied to remove dissolved oxygen. The flask was backfilled with argon and allowed to stir in a water bath for 2 h at room temperature. The polymerization was quenched by opening to air, after which THF (10 mL) was added. The polymer solution was filtered though a pad of silica gel and concentrated by evaporation. The polymer was then precipitated in cold methanol, collected and dried under vacuum overnight.

IV. General procedure for sonication experiments.

Polymer (20 mg) was dissolved in THF (20 mL, containing 50 eq. of BHT) and transferred to a Suslick cell, which was placed into collar and screwed on to the probe. A N_2 line was introduced into the cell and N_2 was started to sparged through the system 30 min ahead of the sonication experiment, during which the Suslick cell was placed in a cooling bath (-9 ^{o}C). Pulsed ultrasound (1.0 s on, 2.0 s off, 500 watt, 20 kHz, 20% amplitude, 9.55 W cm^{-2}) was applied to the system and aliquots of 500 μL were removed at 0, 15, 30, 45, 60, 75, 90, 105 and 120 min. Every sample was filtered through a syringe filter (PTFE, 0.45μm pore size) and analyzed by GPC.

V. NMR spectra

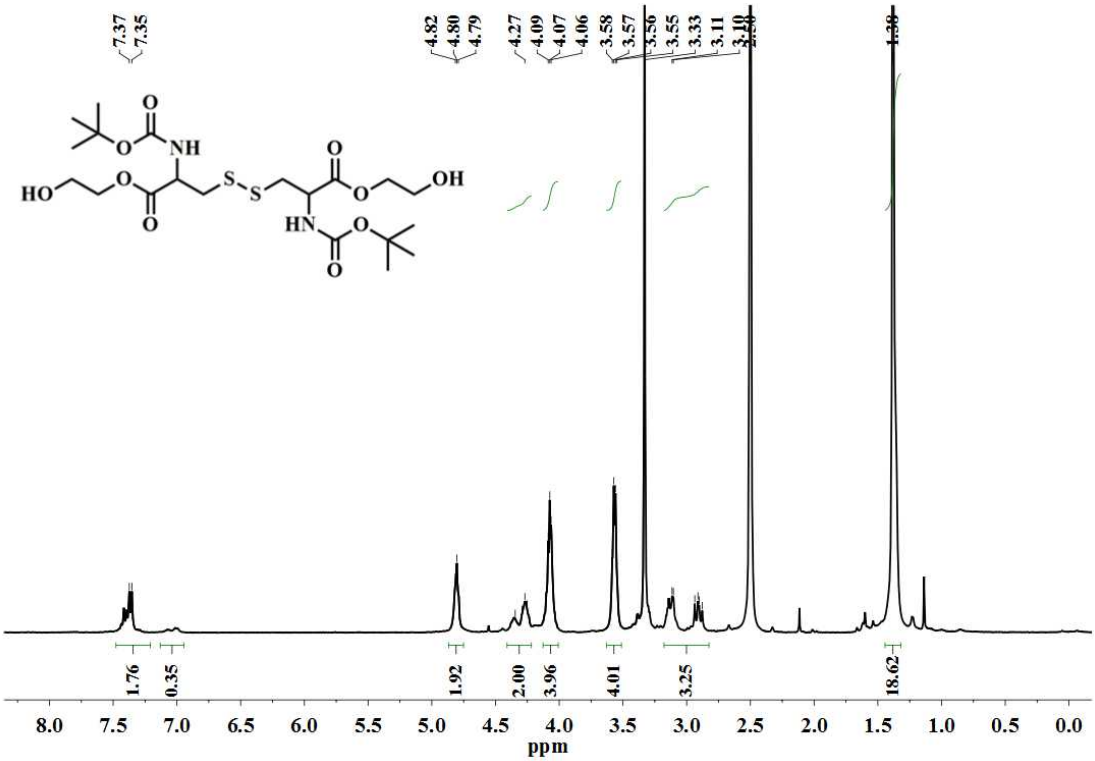


Figure S1. ^{1}H NMR of compound **2** in DMSO-d_6.

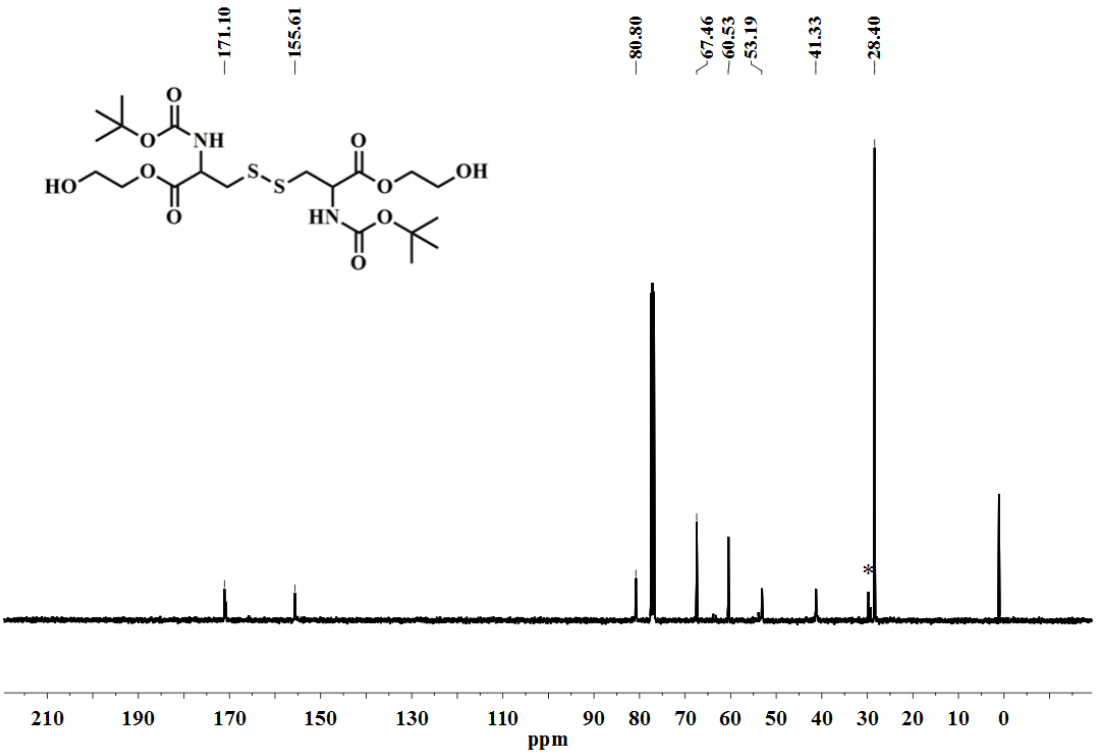


Figure S2. ^{13}C NMR of compound **2** in DMSO-d_6, *grease.

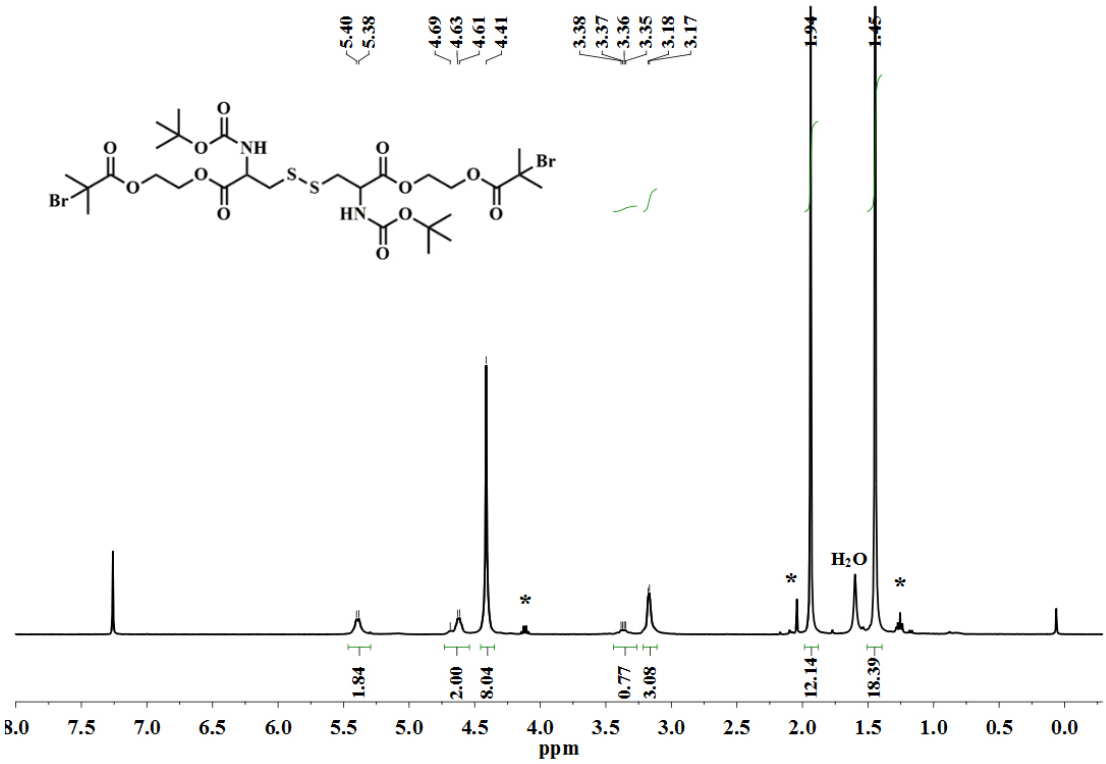


Figure S3. [1] H NMR of compound **3** in $CDCl_3$, *ethyl acetate.

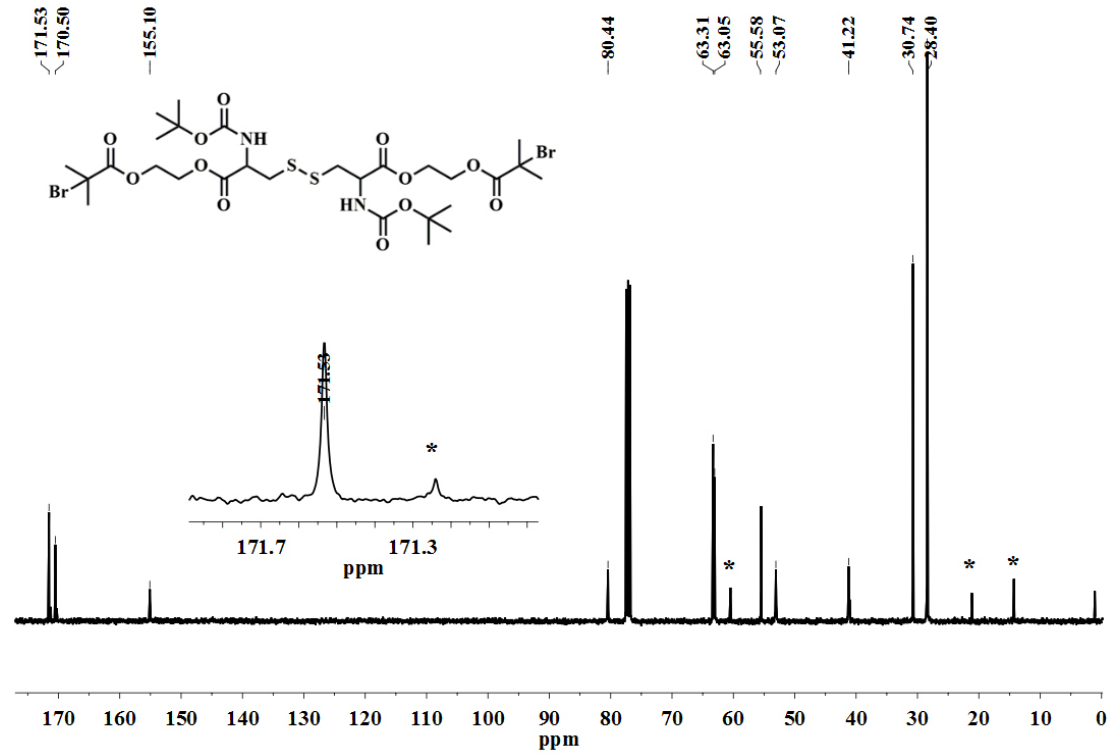


Figure S4. [13] C NMR of compound **3** in $CDCl_3$, *ethyl acetate.

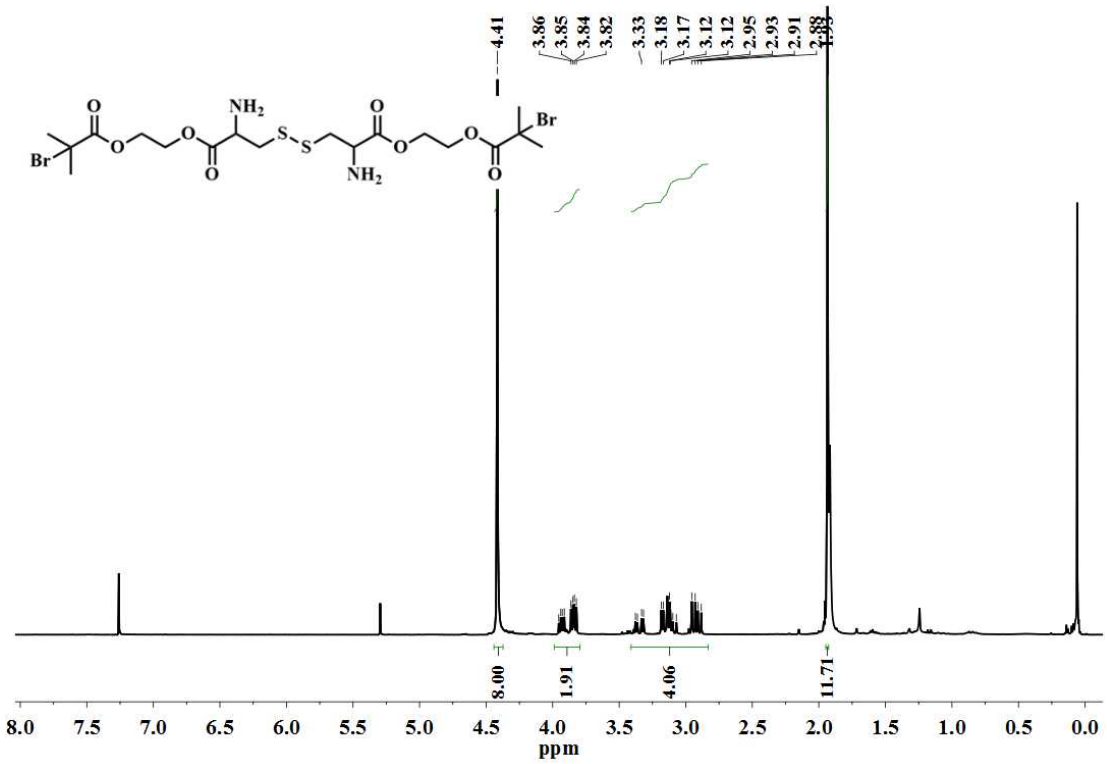


Figure S5. ^{1}H NMR of compound **4** in $CDCl_3$.

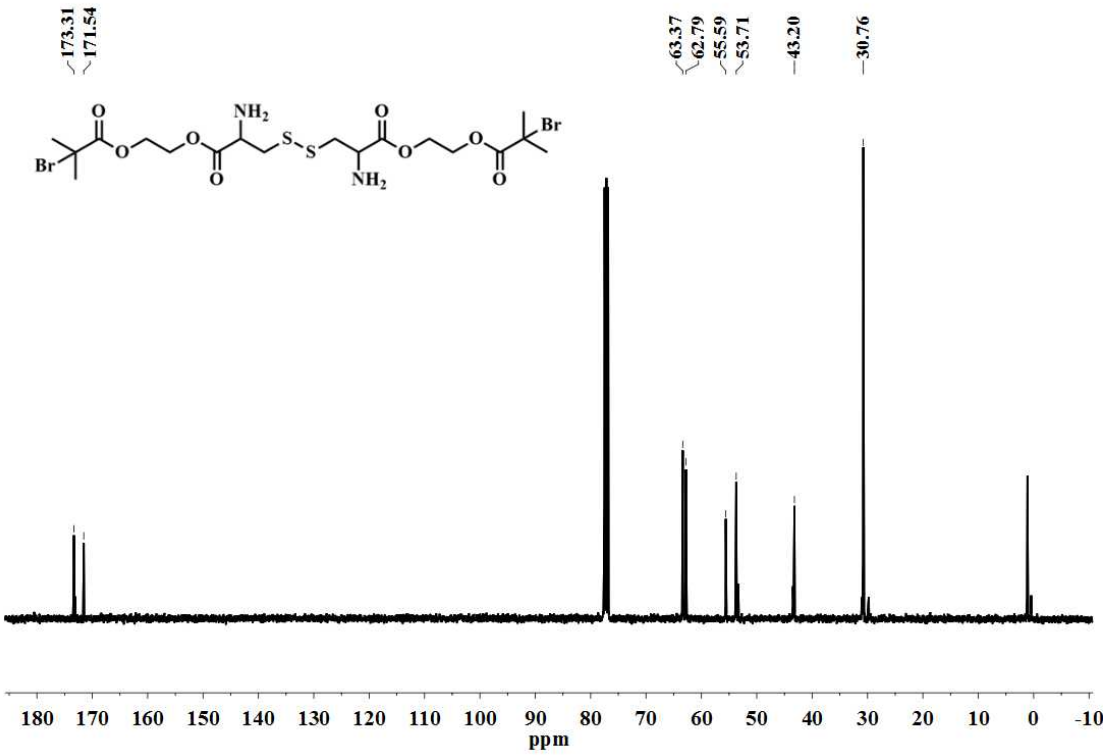


Figure S6. ^{13}C NMR of compound **4** in $CDCl_3$.

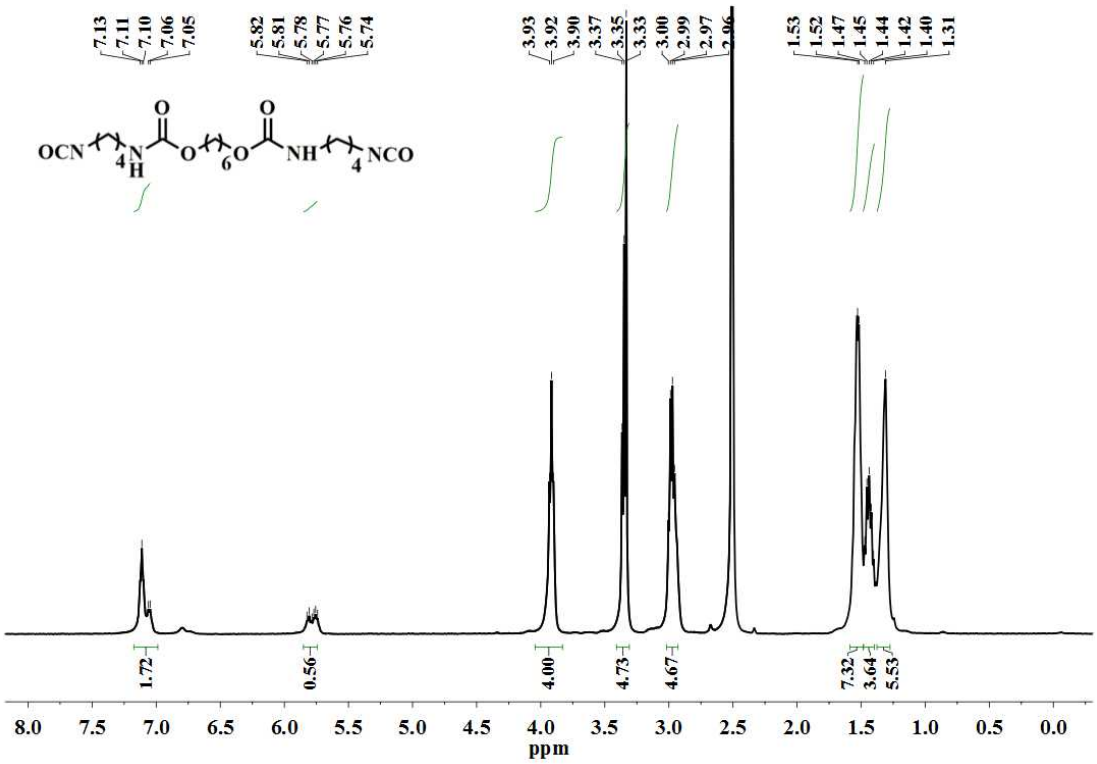


Figure S7. ^{1}H NMR of compound **5a** in DMSO-d_6.

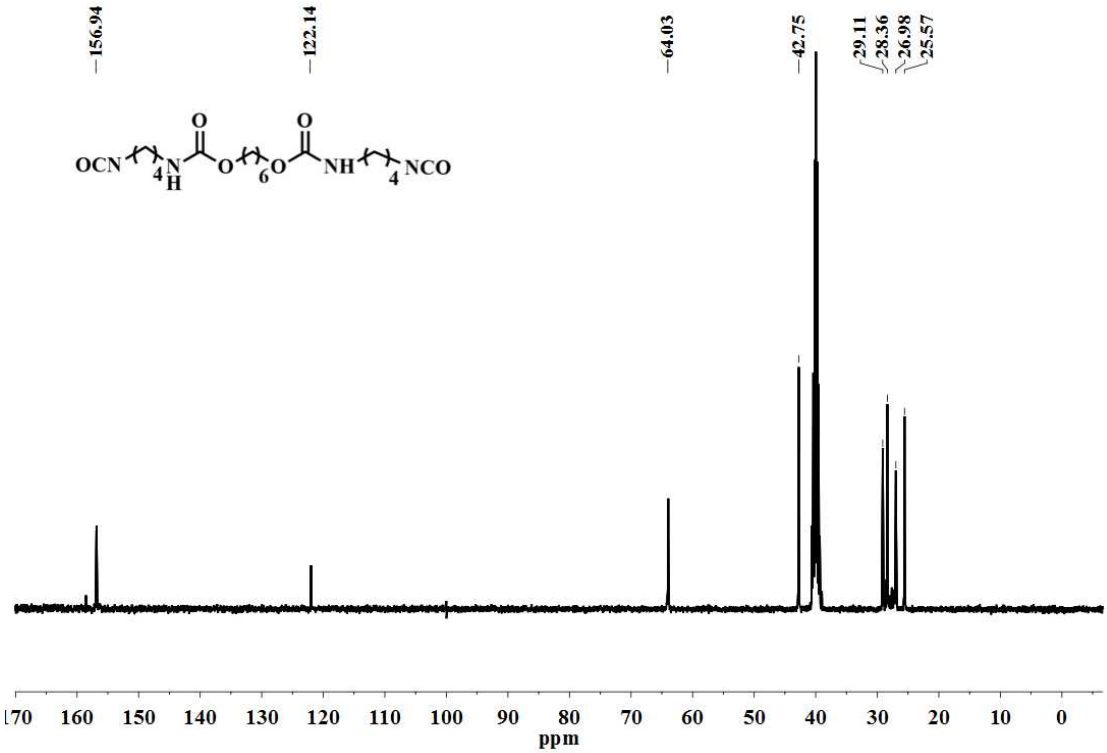


Figure S8. ^{13}C NMR of compound **5a** in DMSO-d_6.

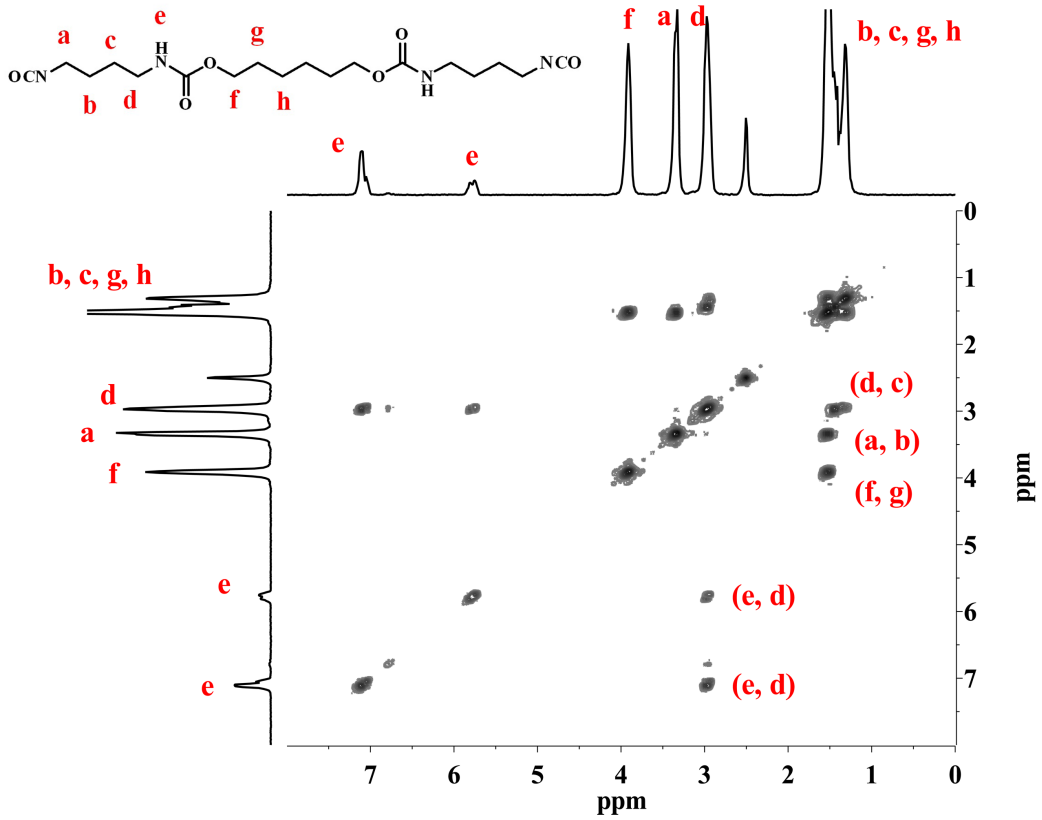


Figure S9. ^{1}H COSY spectrum of **5a** in DMSO-d_6.

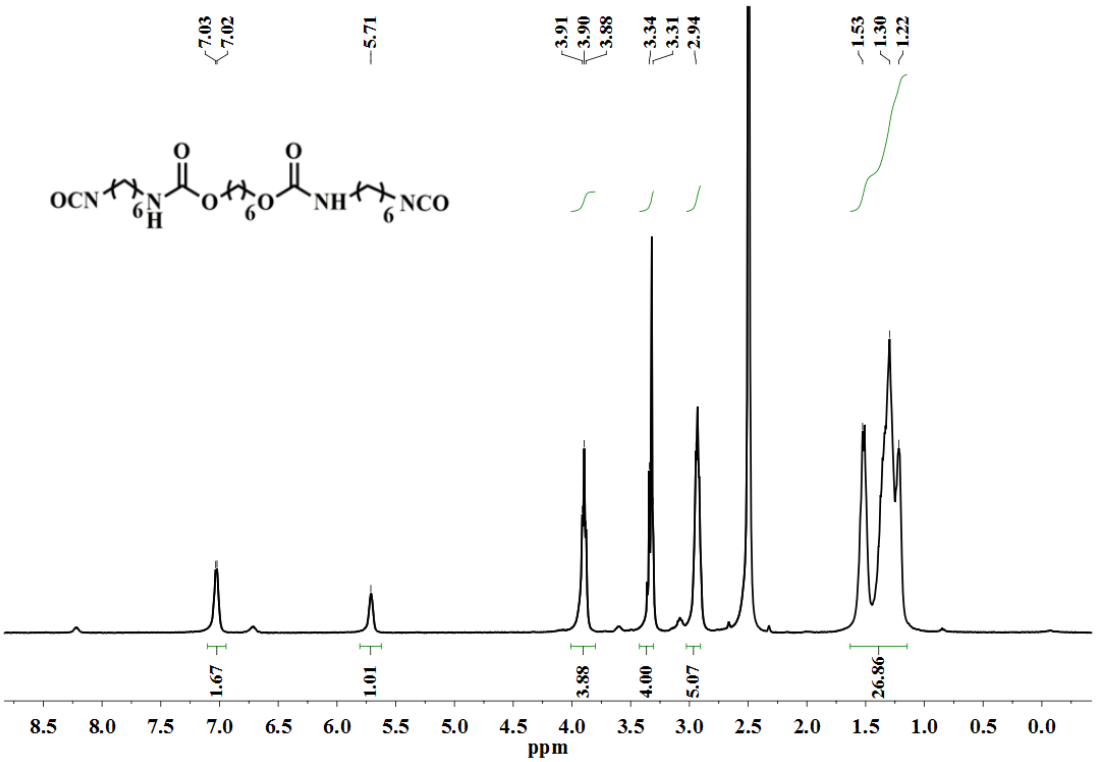


Figure S10. [1] H NMR of compound **5b** in DMSO-d_6.

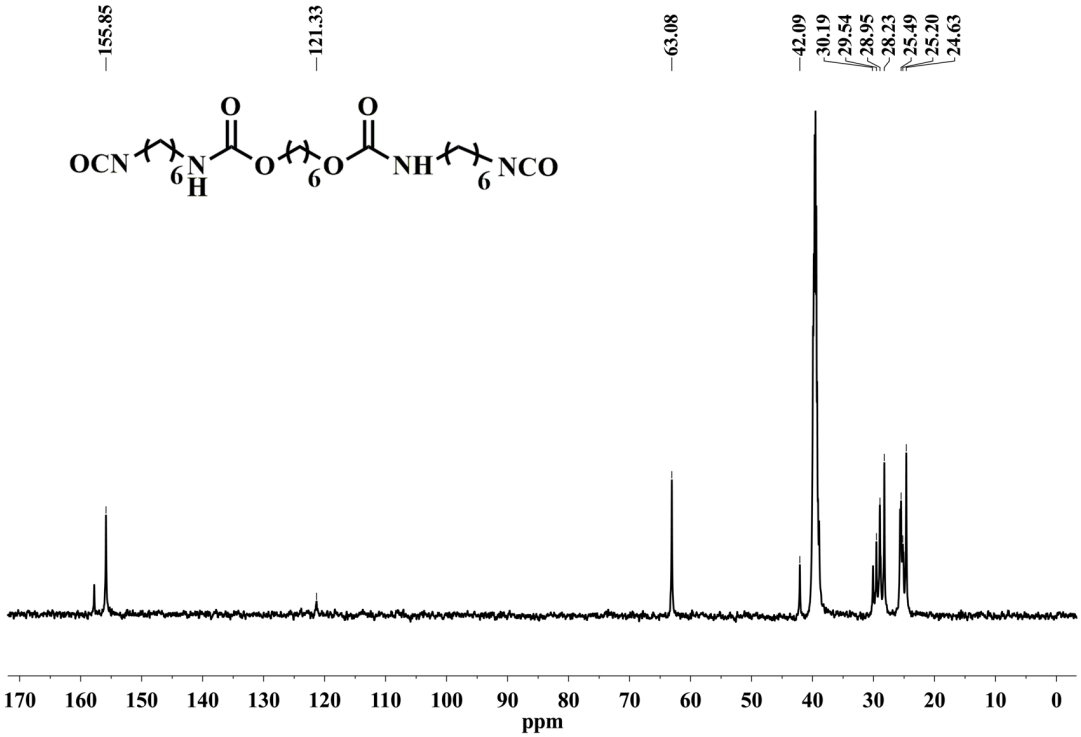


Figure S11. ^{13}C NMR of compound **5b** in DMSO-d_6 at 90 °C.

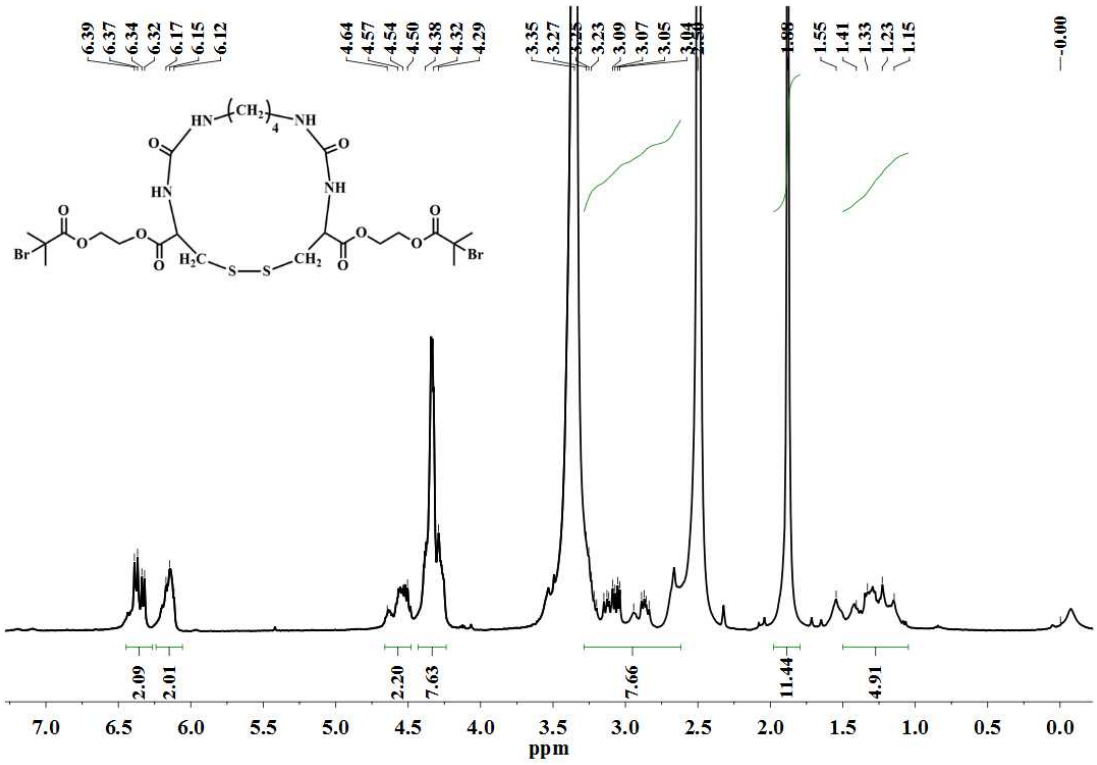


Figure S12. ^{1}H NMR of compound **6a** in DMSO-d_6.

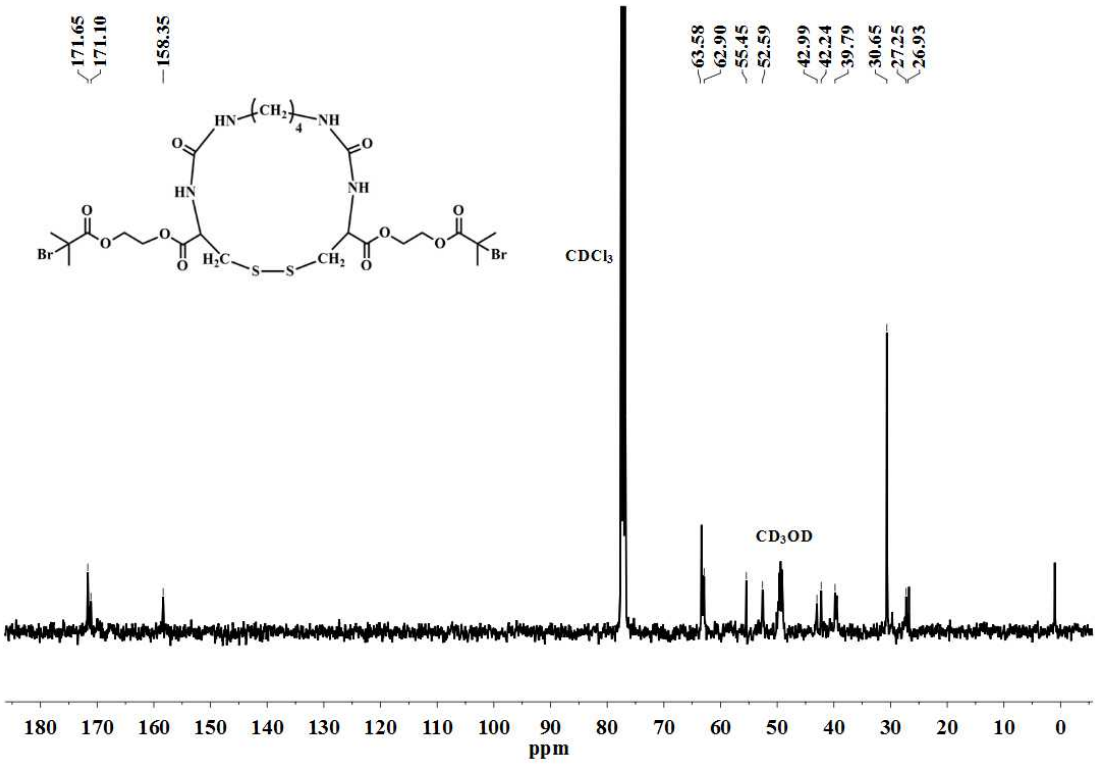


Figure S13. ^{13}C NMR of compound **6a** in $CDCl_3$ + CD_3OD.

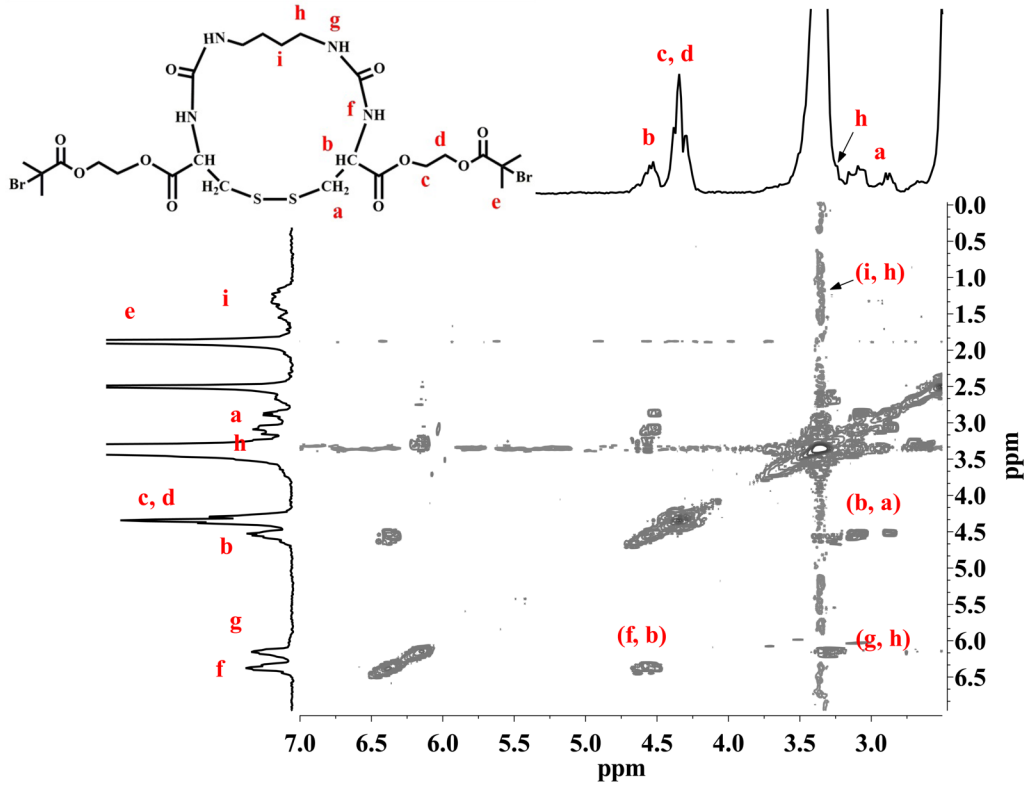


Figure S14. ^{1}H COSY spectrum of **6a** in DMSO-d_6.

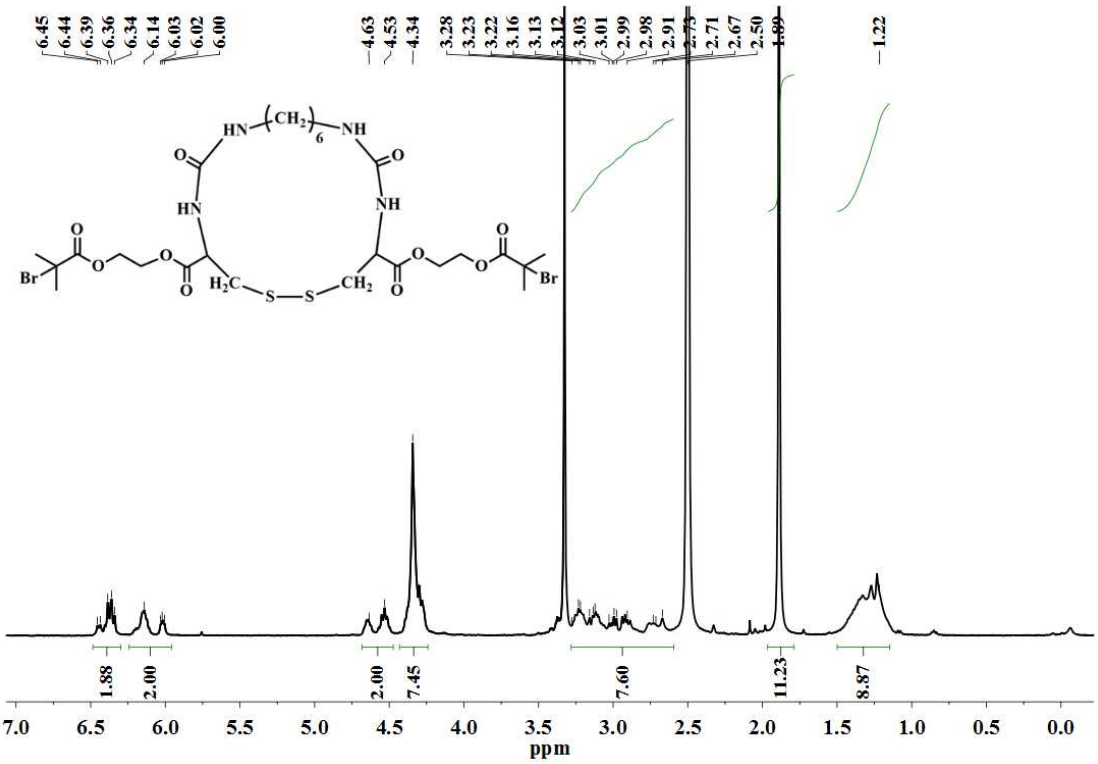


Figure S15. ^{1}H NMR of compound **6b** in DMSO-d_6.

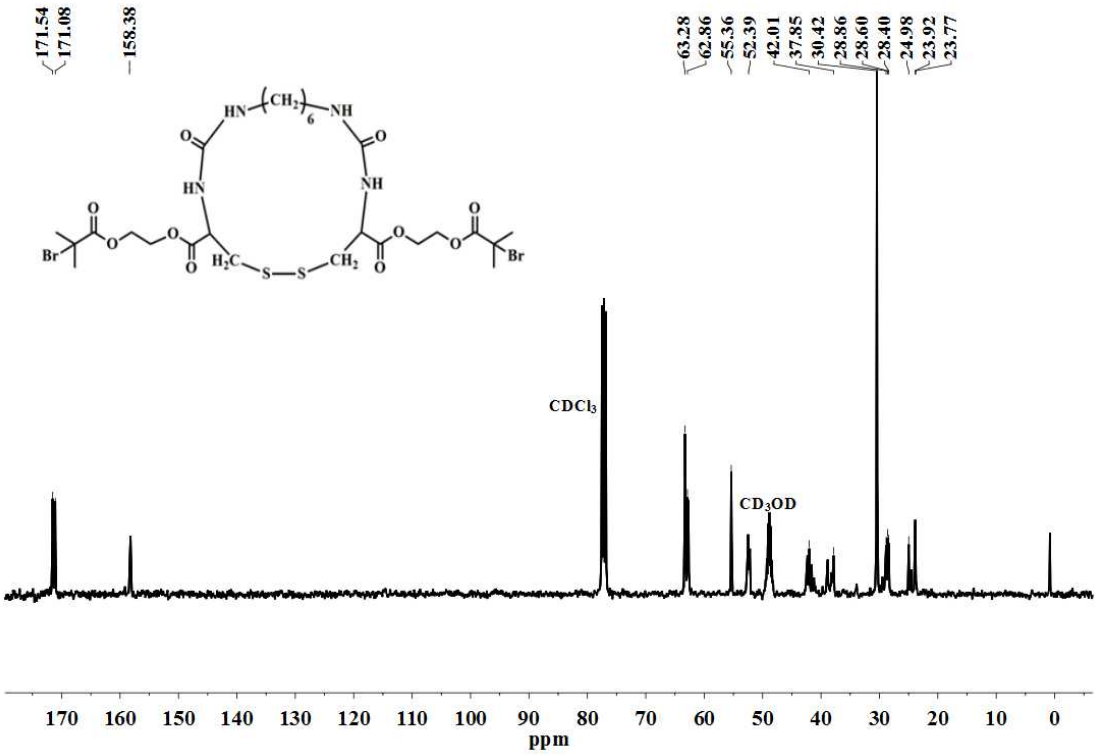


Figure S16. ^{13}C NMR of compound **6b** in $CDCl_3$ + CD_3OD.

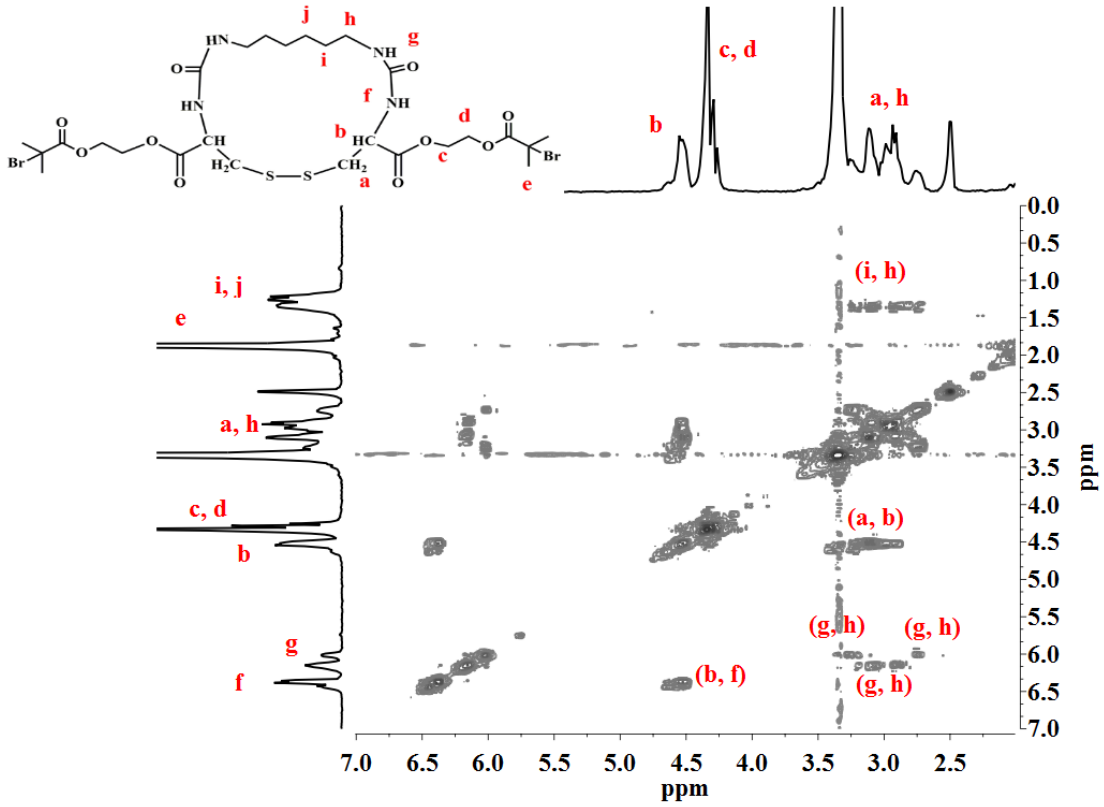


Figure S17. ^{1}H COSY spectrum of **6b** in DMSO-d_6

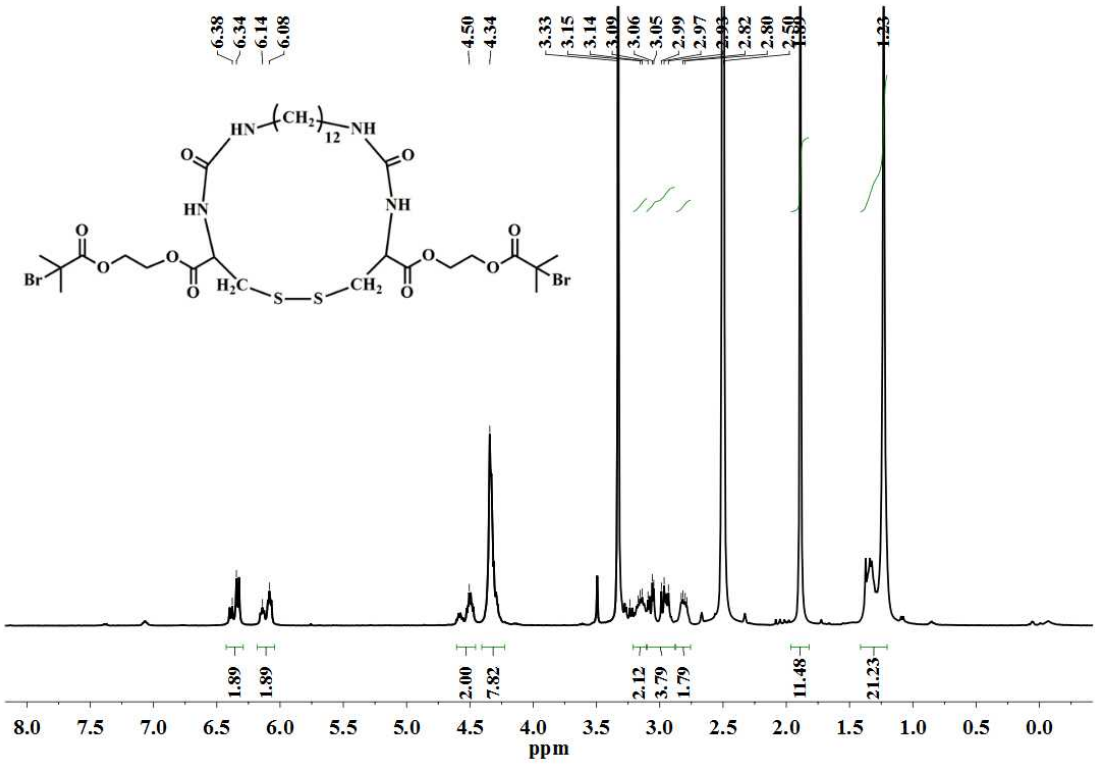


Figure S18. [1] H NMR of compound **6c** in DMSO-d_6.

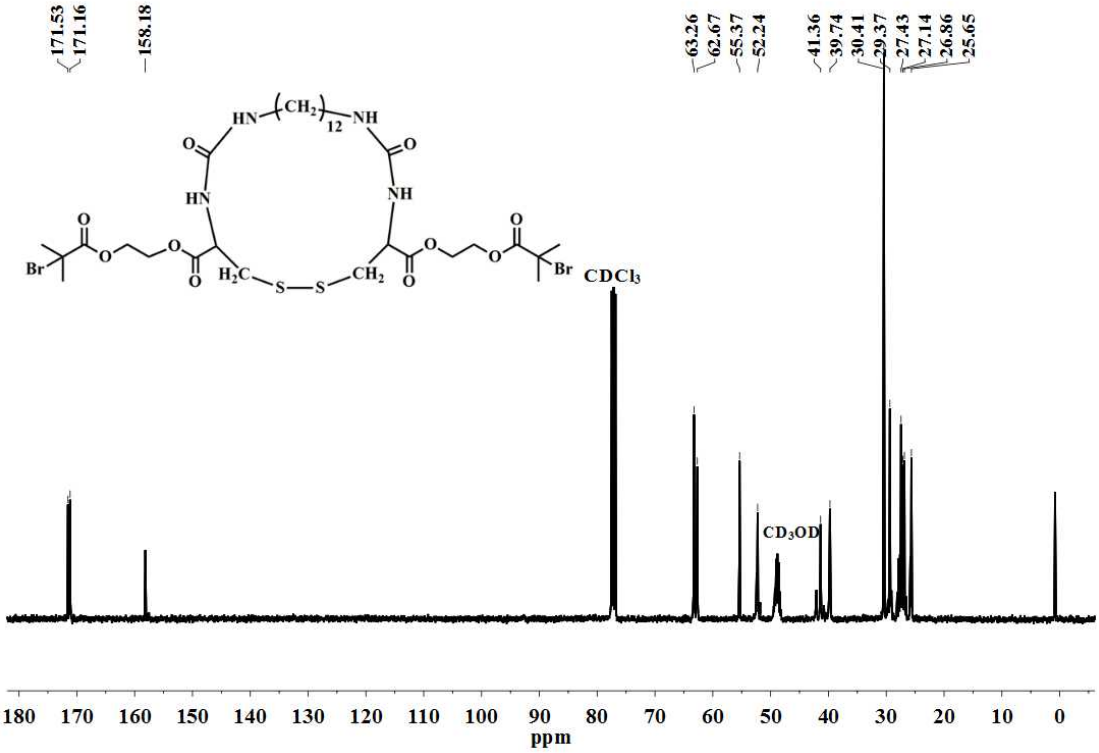


Figure S19. ^{13}C NMR of compound **6c** in $CDCl_3$ + CD_3OD.

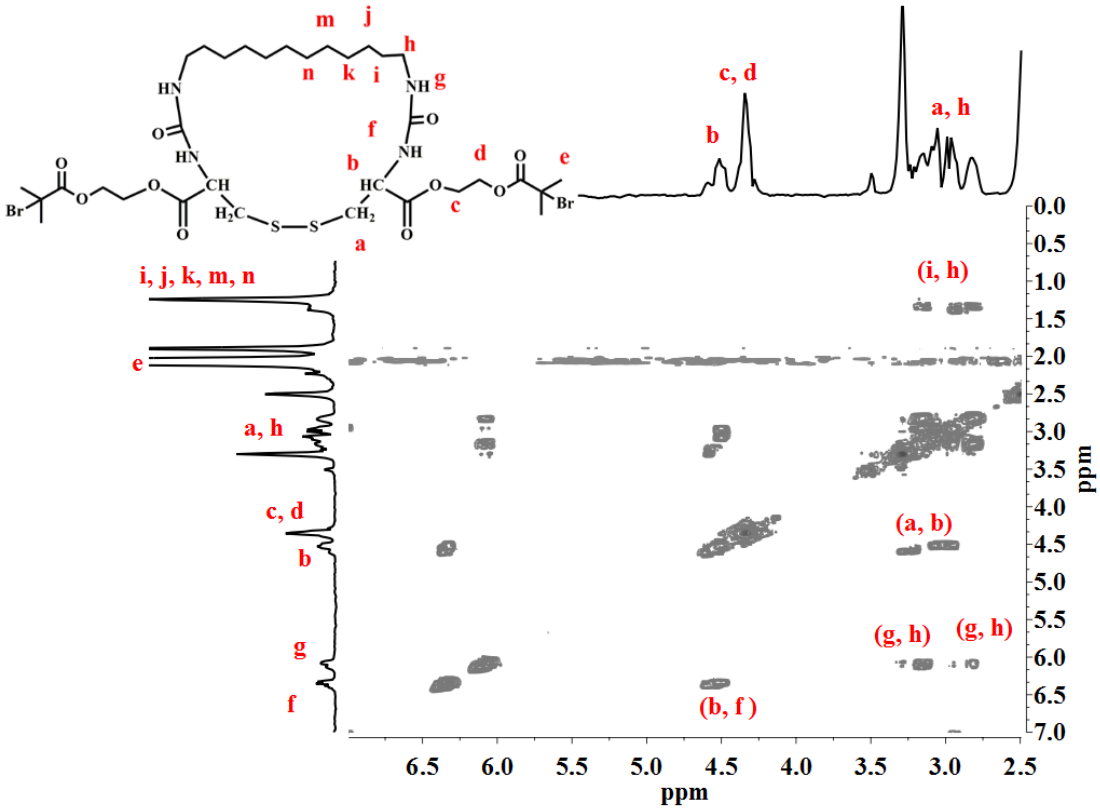


Figure S20. ^{1}H COSY spectrum of **6c** in DMSO-d_6

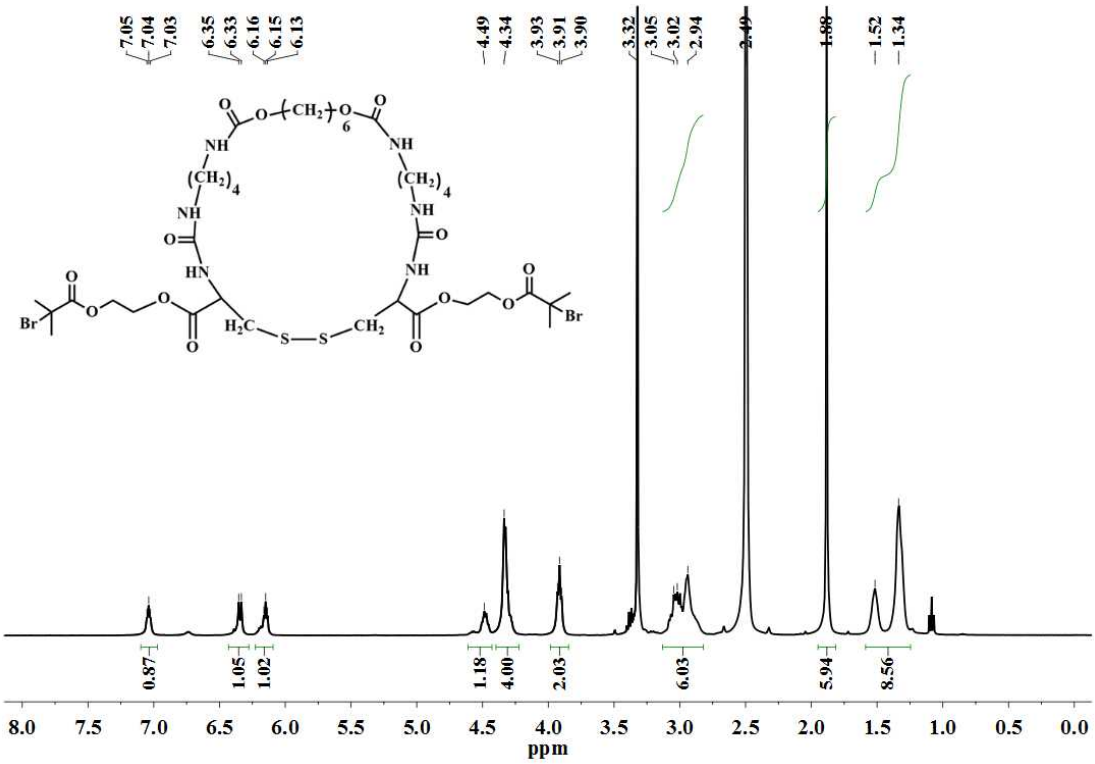


Figure S21. ^{1}H NMR of compound **6d** in DMSO-d_6.

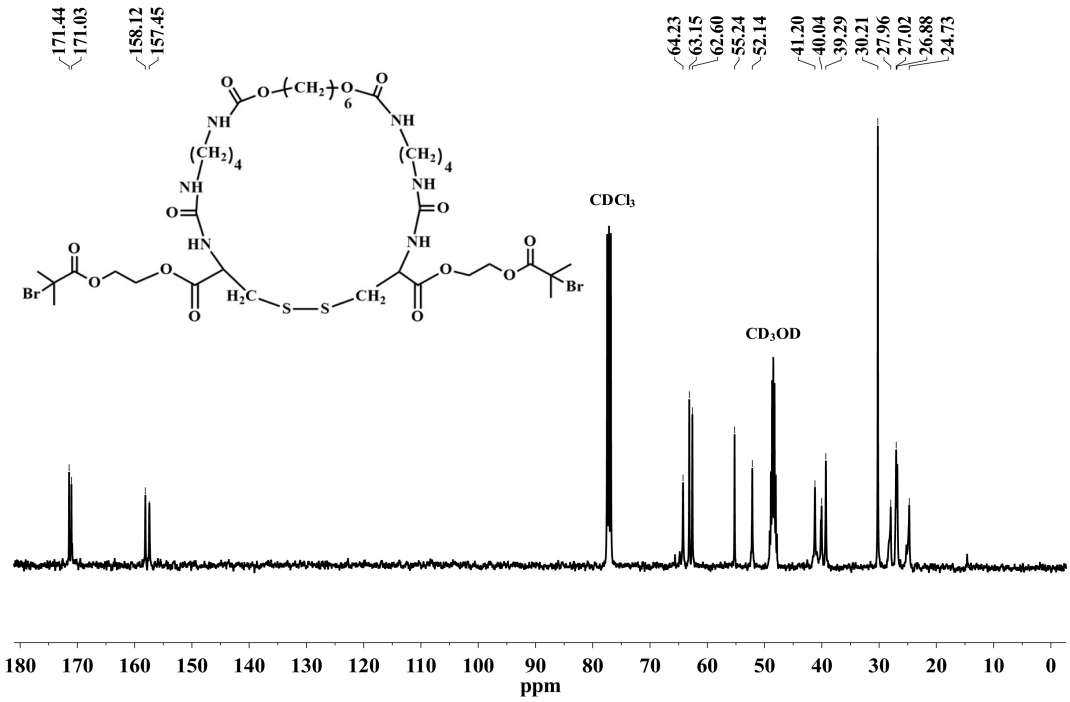


Figure S22. ^{13}C NMR of compound **6d** in $CDCl_3$ + CD_3OD.

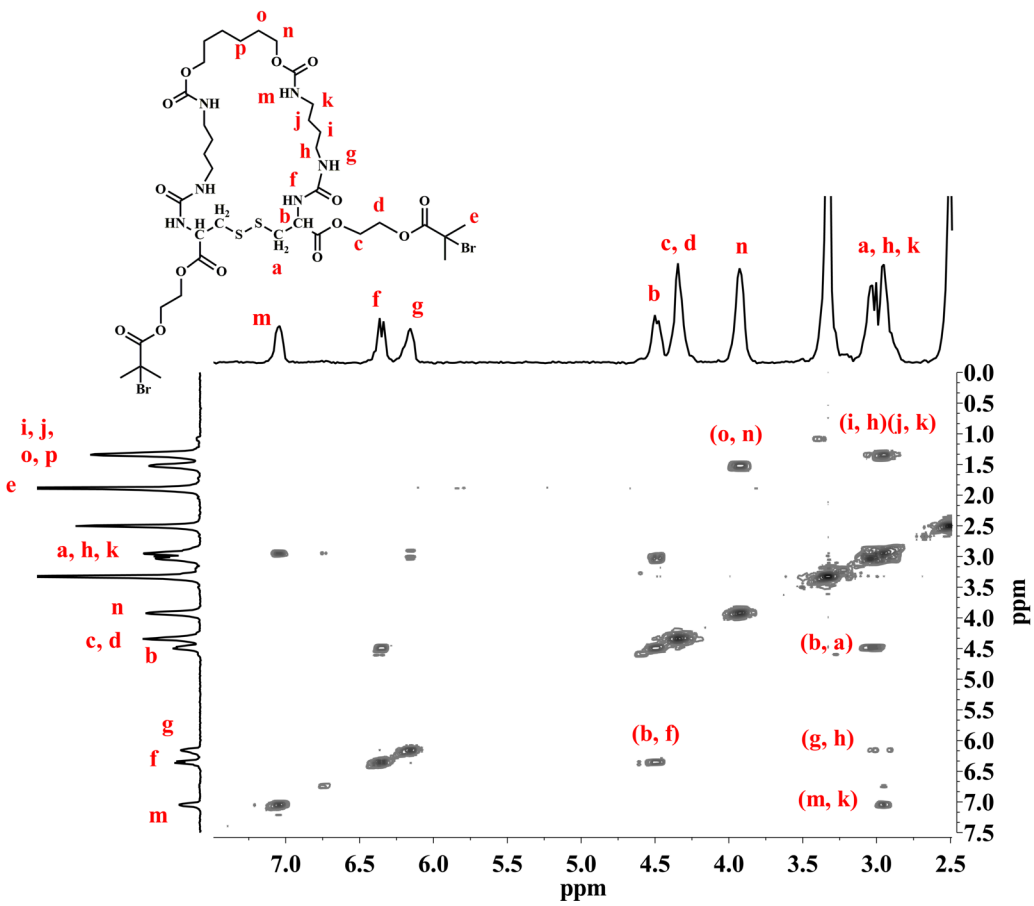


Figure S23. ^{1}H COSY spectrum of **6d** in DMSO-d_6

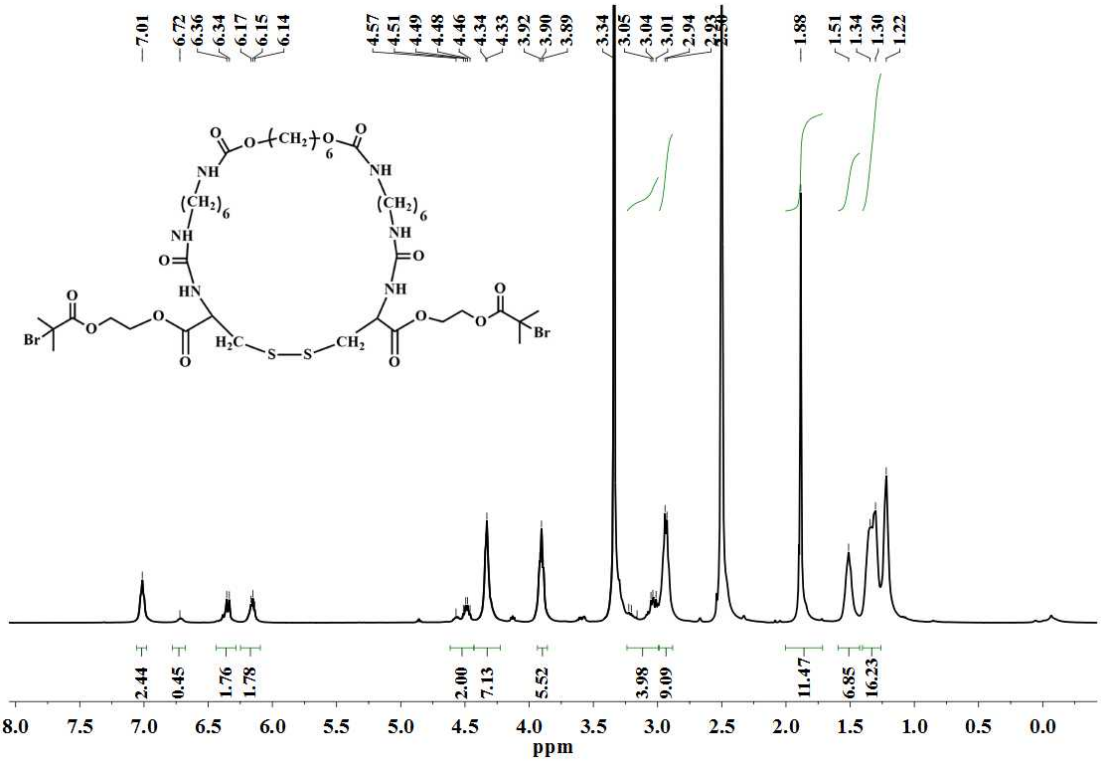


Figure S24. [1] H NMR of compound **6e** in DMSO-d_6.

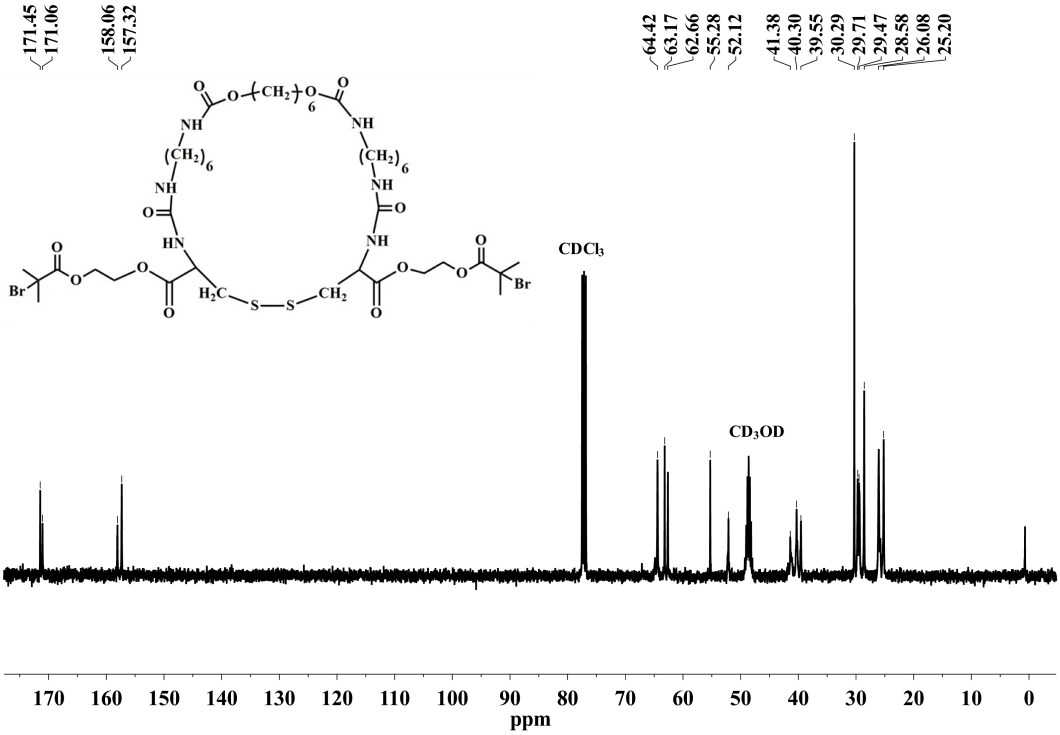


Figure S25. ^{13}C NMR of compound **6e** in $CDCl_3$ + CD_3OD.

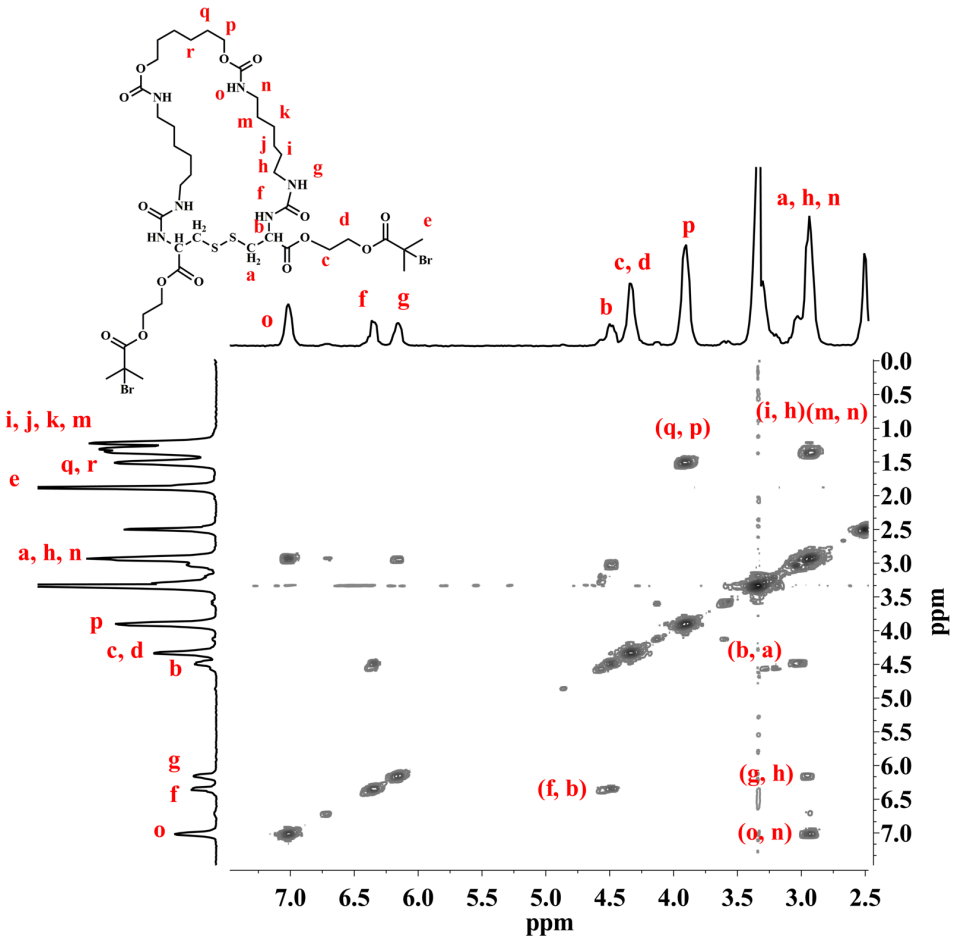


Figure S26. ^{1}H COSY spectrum of **6e** in DMSO-d_6

VI. Kinetic GPC curves

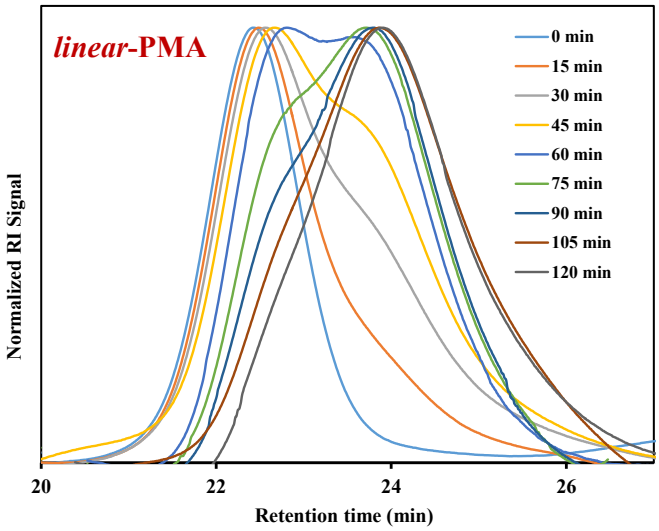


Figure S27. Evolution of GPC traces for sample *linear*-PMA upon sonication in THF.

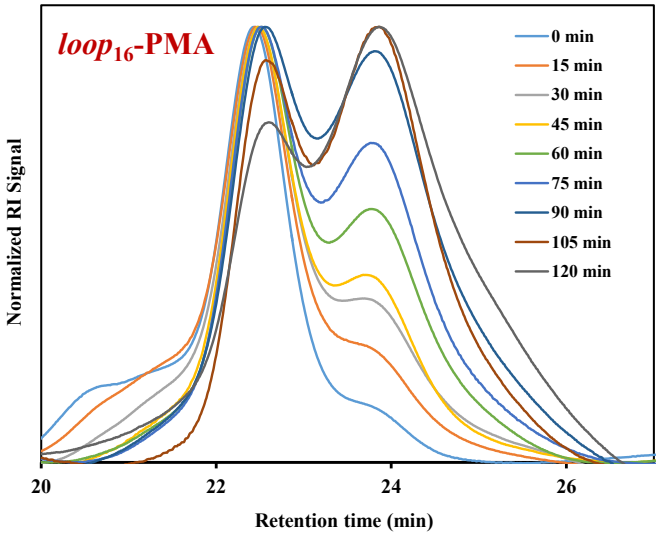


Figure S28. Evolution of GPC traces for sample $loop_{16}$-PMA upon sonication in THF.

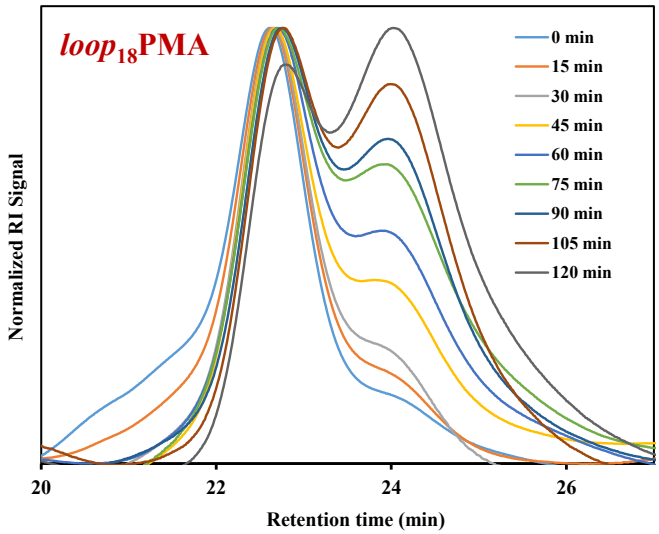


Figure S29. Evolution of GPC traces for sample *loop*$_{18}$-PMA upon sonication in THF.

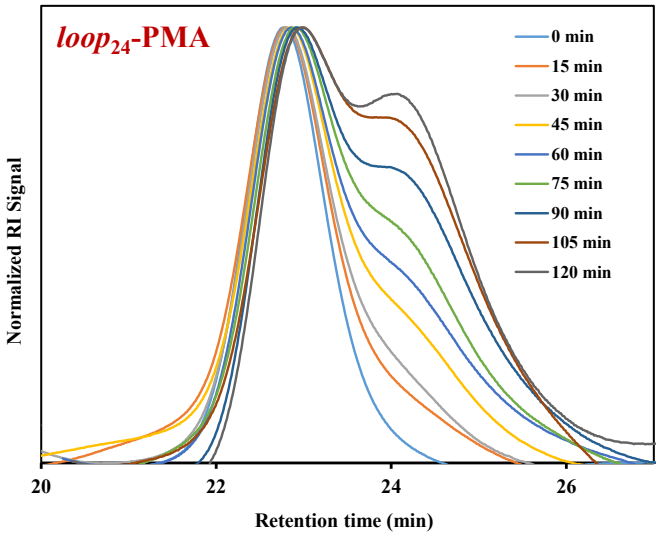


Figure S30. Evolution of GPC traces for sample *loop*$_{24}$-PMA upon sonication in THF.

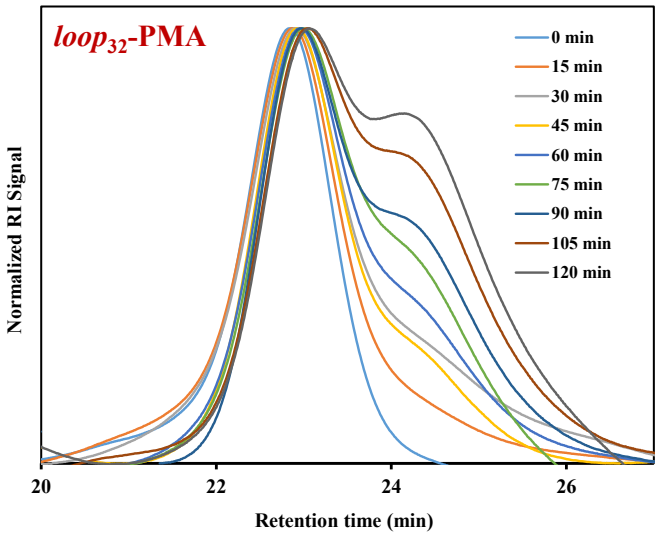


Figure S31. Evolution of GPC traces for sample *loop*$_{32}$-PMA upon sonication in THF.

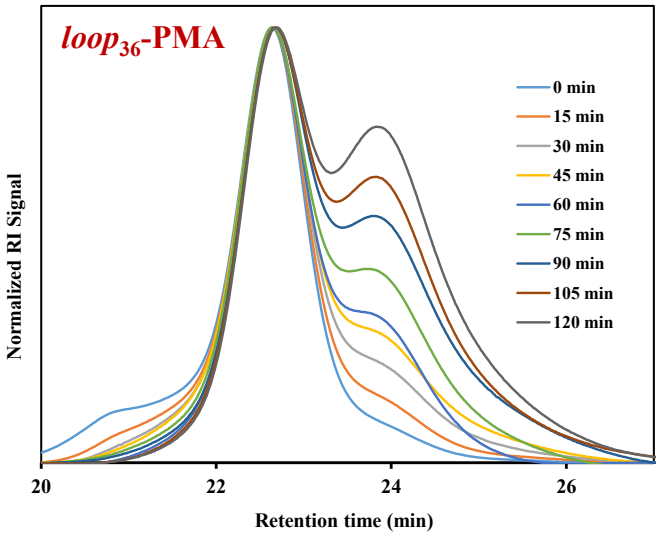


Figure S32. Evolution of GPC traces for sample *loop*$_{36}$-PMA upon sonication in THF.

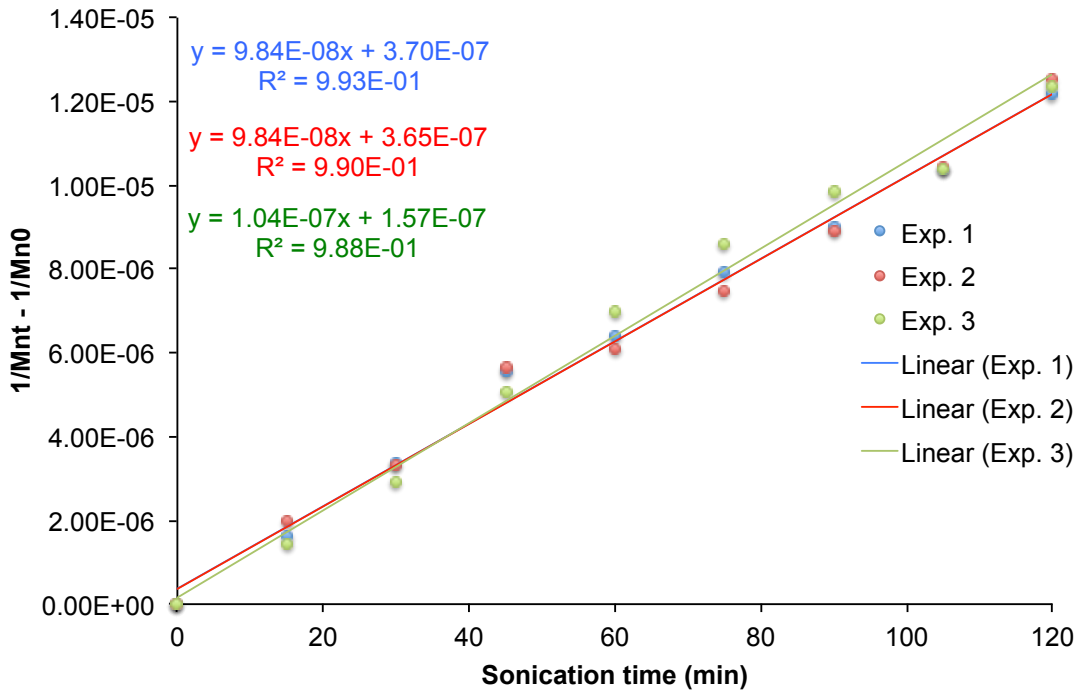


Figure S33. Plots of $1/M_{n,t}$ - $1/M_{n,0}$ as a function of sonication time and linear fits according to $1/M_{n,t}$ - $1/M_{n,0} = k't$ for ***linear*-PMA**s.

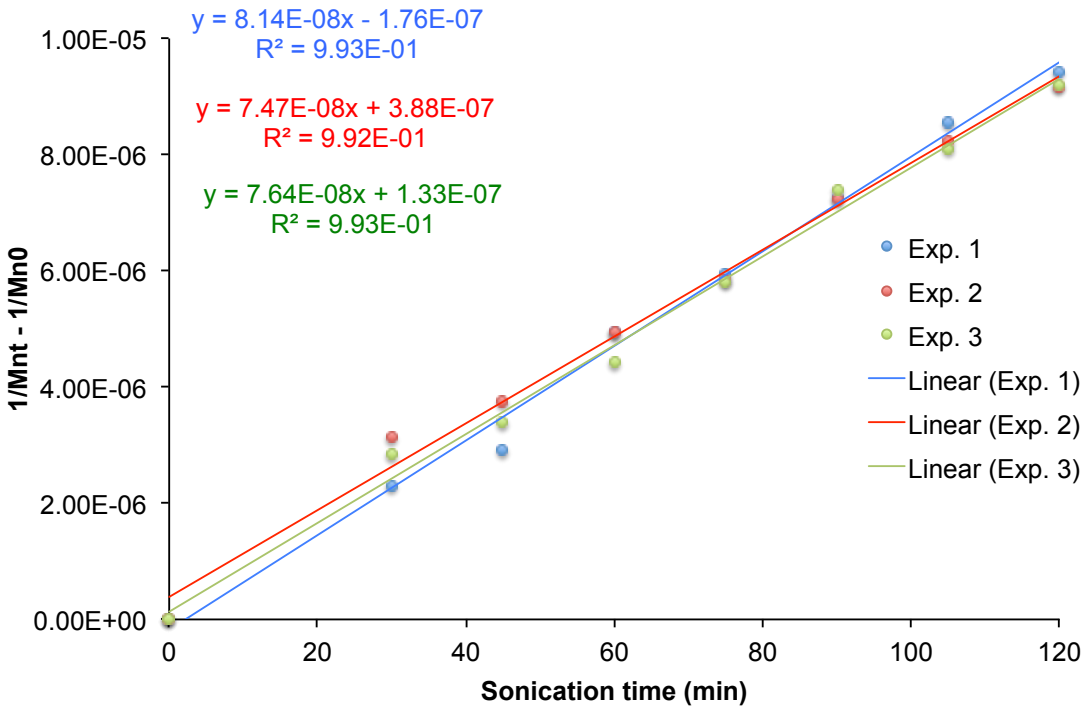


Figure S34. Plots of $1/M_{n,t}$ - $1/M_{n,0}$ as a function of sonication time and linear fits according to $1/M_{n,t}$ - $1/M_{n,0} = k't$ for ***loop16*-PMA**s.

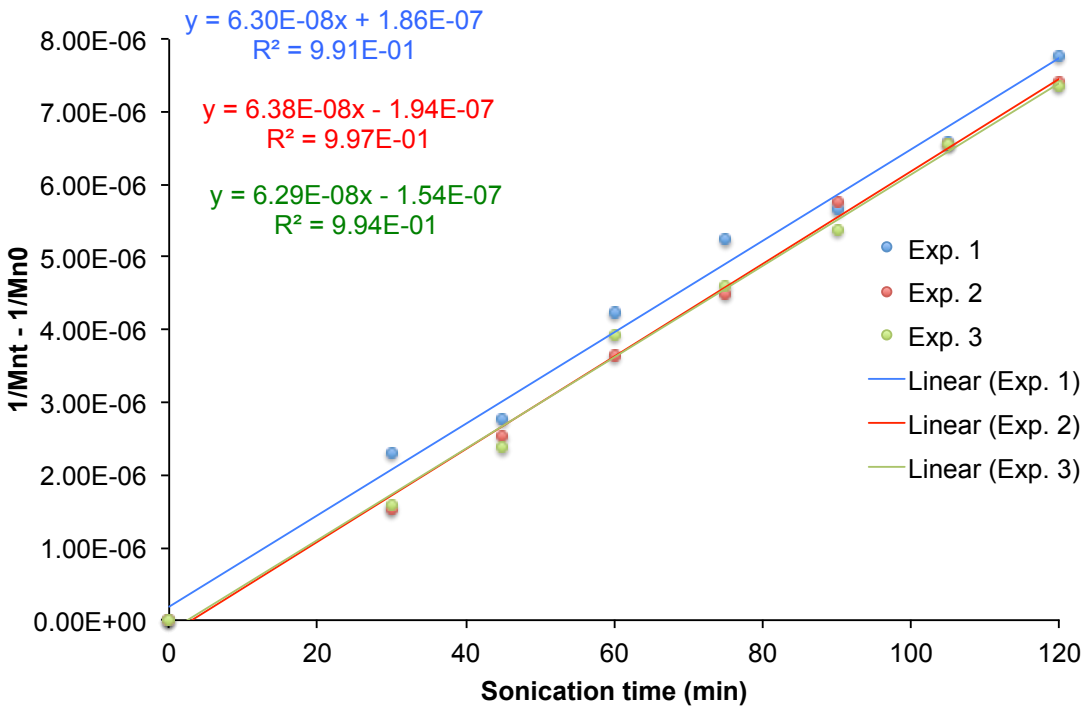


Figure S35. Plots of $1/M_{n,t}$ - $1/M_{n,0}$ as a function of sonication time and linear fits according to $1/M_{n,t}$ - $1/M_{n,0}$ = k't for ***loop18*-PMA**s

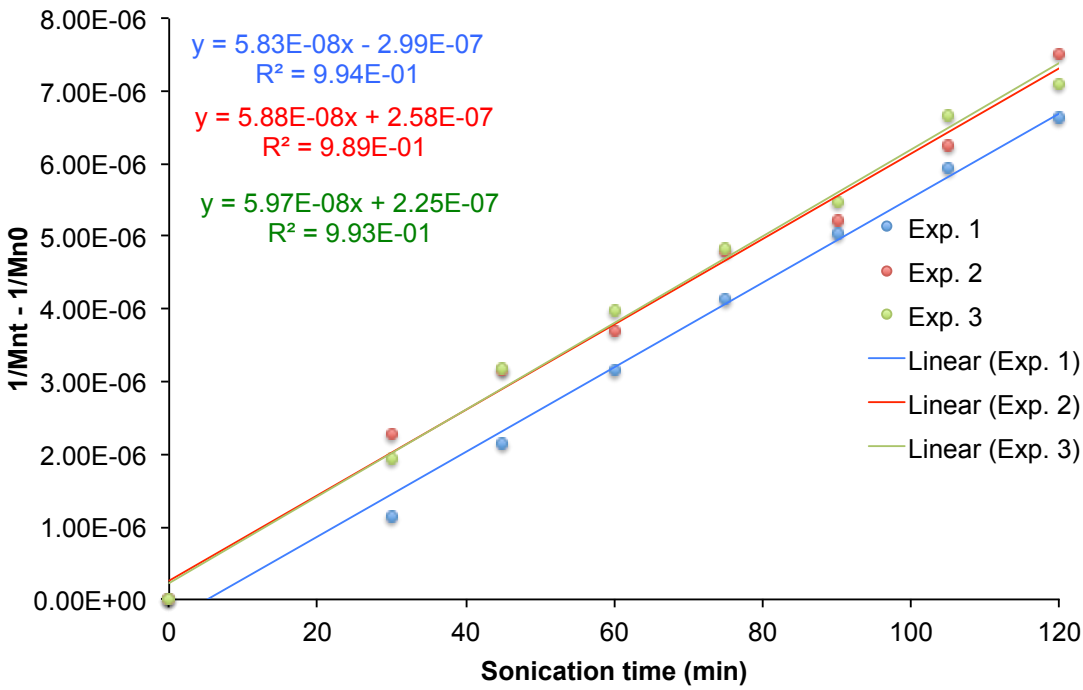


Figure S36. Plots of $1/M_{n,t}$ - $1/M_{n,0}$ as a function of sonication time and linear fits according to $1/M_{n,t}$ - $1/M_{n,0}$ = k't for ***loop24*-PMA**s

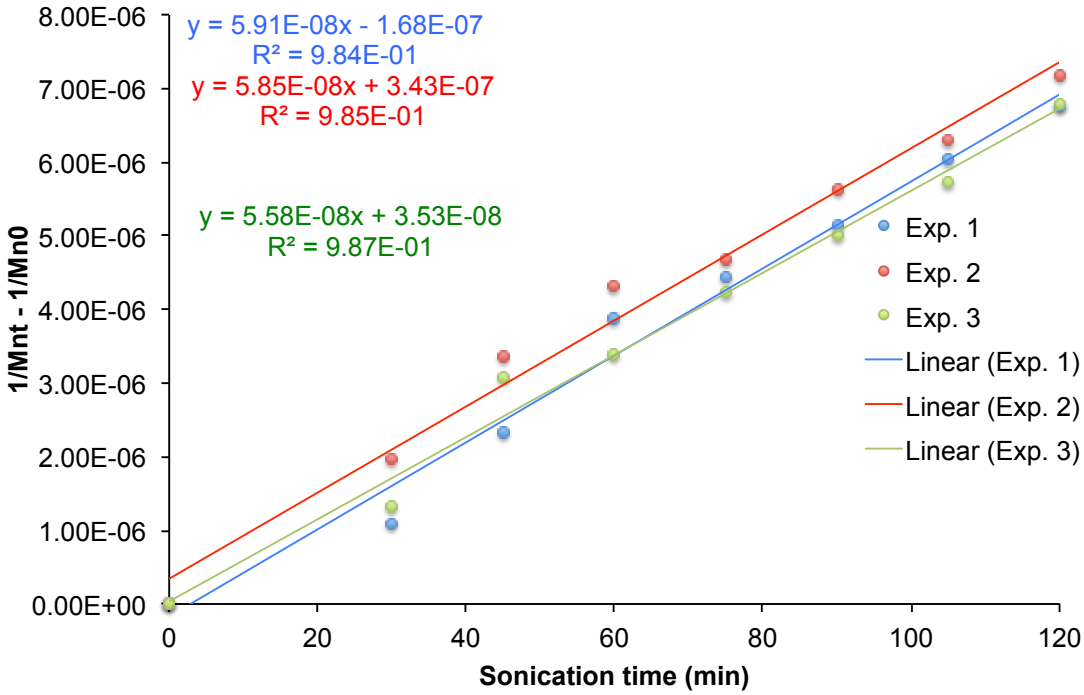


Figure S37. Plots of $1/M_{n,t}$ - $1/M_{n,0}$ as a function of sonication time and linear fits according to $1/M_{n,t}$ - $1/M_{n,0} = k't$ for ***loop32*-PMA**s

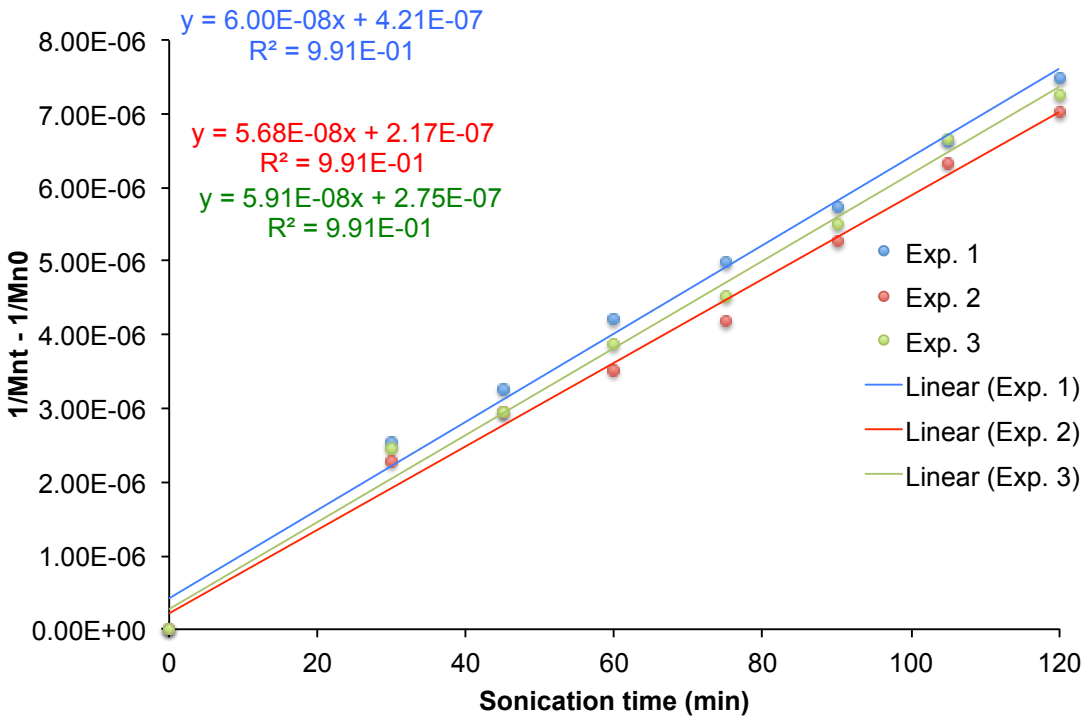


Figure S38. Plots of $1/M_{n,t}$ - $1/M_{n,0}$ as a function of sonication time and linear fits according to $1/M_{n,t}$ - $1/M_{n,0} = k't$ for ***loop36*-PMA**s

Table S1. Rate constants k' calculated for all sonication experiments.

Sample	k'_1 ($x10^{-8}$ mol/g*min)	k'_2 ($x10^{-8}$ mol/g*min)	k'_3 ($x10^{-8}$ mol/g*min)	Average ($x10^{-8}$ mol/g*min)	Std. Dev. ($x10^{-8}$ mol/g*min)	k ($x10^{-6}$ min^{-1})	Std. Dev. ($x10^{-6}$ min^{-1})
linear-PMA	9.84 ± 0.32	9.84 ± 0.37	10.40 ± 0.43	10.03	0.32	8.63	0.28
loop$_{16}$-PMA	8.14 ± 0.28	7.47 ± 0.27	7.64 ± 0.27	7.75	0.35	6.67	0.30
loop$_{18}$-PMA	6.30 ± 0.25	6.38 ± 0.15	6.29 ± 0.15	6.32	0.05	5.44	0.04
loop$_{24}$-PMA	5.83 ± 0.19	5.88 ± 0.25	5.97 ± 0.21	5.89	0.07	5.07	0.06
loop$_{32}$-PMA	5.91 ± 0.31	5.85 ± 0.29	5.58 ± 0.26	5.78	0.17	4.97	0.15
loop$_{36}$-PMA	6.00 ± 0.24	5.68 ± 0.22	5.91 ± 0.22	5.88	0.16	5.06	0.14

VII. Statistical analysis

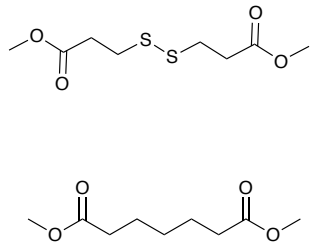
Statistical analysis was performed using a Student's t-test with a minimum confidence level of 0.1 for statistical significance and assuming equal sample sizes and unequal variance. All values are reported as the mean and standard deviation of the mean. The calculated values (using GraphPad Prism software) are listed in **Tables S2**, for all pairs of polymers. The standard deviation used in the t-test was the highest of the observed in the each of the three linear regressions or from the averaging of the k'.

Table S2. Student t test results comparing individual rate constants of every polymer pair in *gem*-DCC activation experiments. Red color indicates no significant difference between the pair.

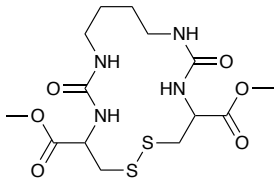
	loop$_{16}$-PMA	*loop*$_{18}$-PMA	*loop*$_{24}$-PMA	*loop*$_{32}$-PMA	*loop*$_{36}$-PMA
linear-PMA	0.0015	0.0001	0.0001	0.0001	0.0001
loop$_{16}$-PMA		0.0045	0.0017	0.0018	0.0013
loop$_{18}$-PMA			0.0943	0.0755	0.0735
loop$_{24}$-PMA				0.6388	0.8771
loop$_{32}$-PMA					0.7172

VIII. CoGEF Analysis

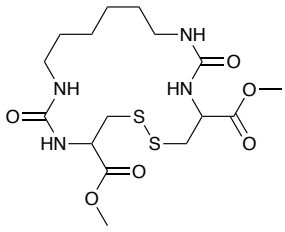
CoGEF calculations were performed on Spartan '14.[6] Each macrocycle, taken as methyl esters, was minimized by DFT using the B3LYP/6-31G* level of theory. Then, the distance between the methyl carbons was increased in increments of 0.2 Å, followed by minimization and energy calculation (B3LYP/6-31G*) at each step. The energies were plotted against the energies. After disulfide bond scission, the calculations failed in a few steps, and therefore, were followed after addition of hydrogens to the thioradicals. F_{max} values were determined from the slopes before each bond scission (H-bond, S-S and C-C). The model molecules that were used in this studies are the following:



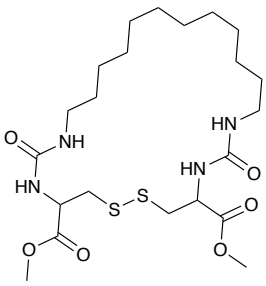
linear (S-S and C-C)



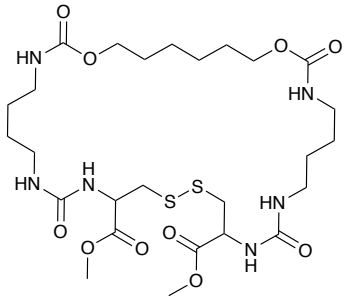
loop 16



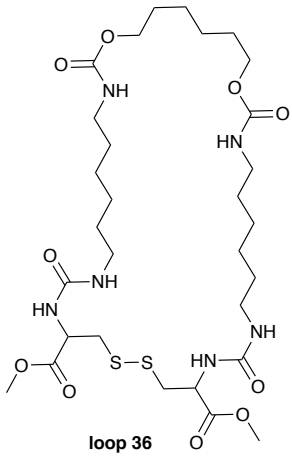
loop 18



loop 24



loop 32



loop 36

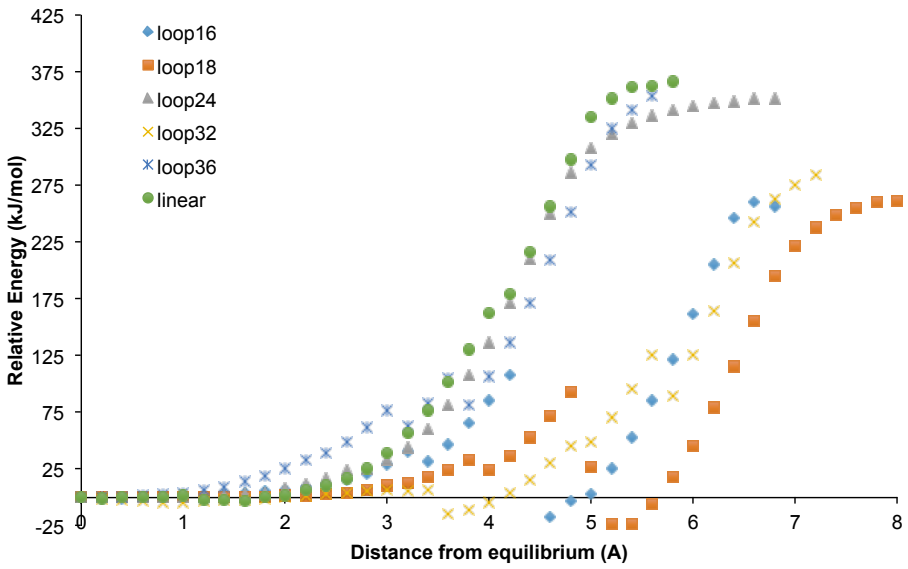


Figure S39. CoGEF for different macrocyclic models up to S-S bond scission.

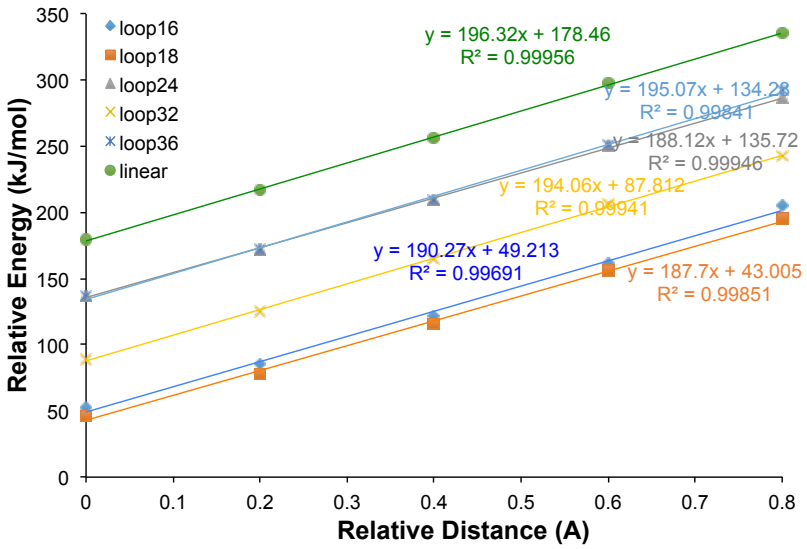


Figure S40. F_{max} calculation in S-S bond scission.

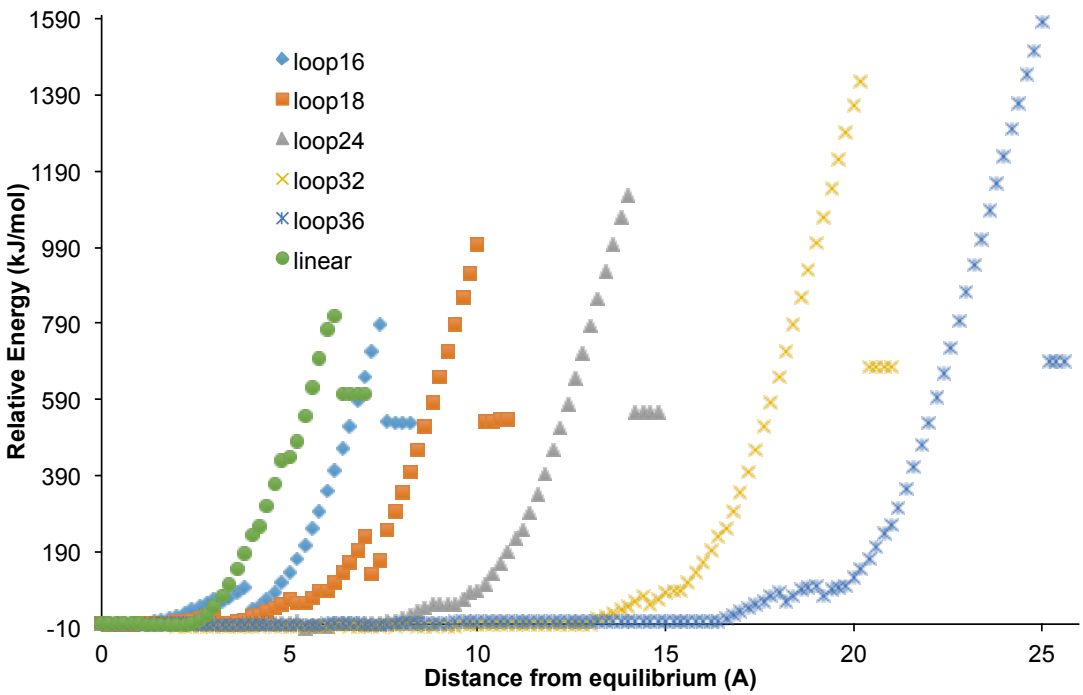


Figure S41. CoGEF for different macrocyclic models showing C-C bond scission.

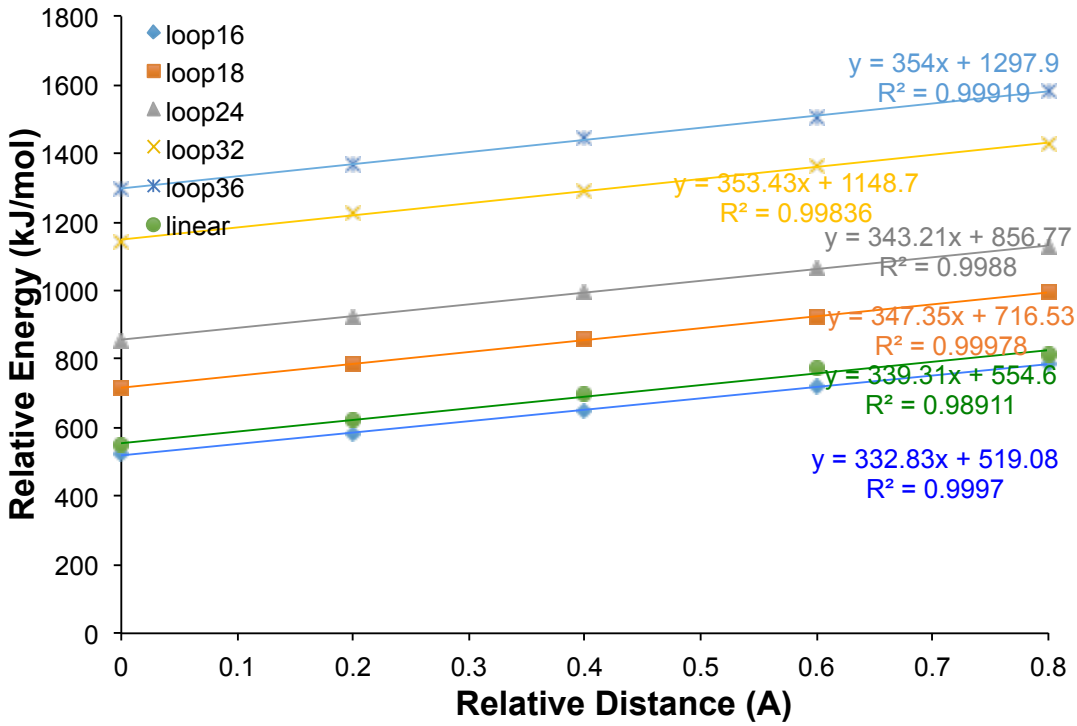


Figure S42. F_{max} calculation in C-C bond scission (before conversion to nN unit).

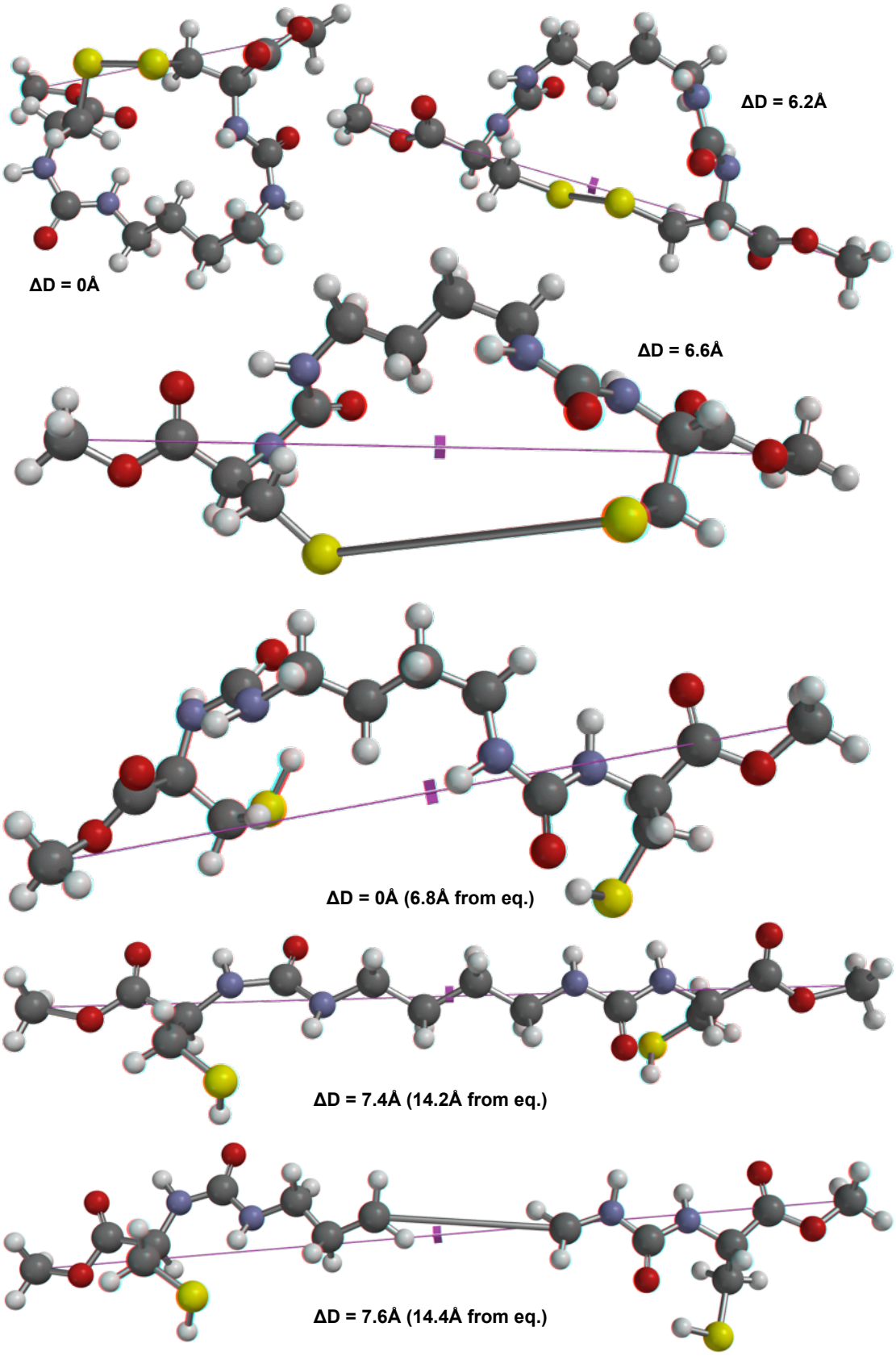


Figure S43. Structures from CoGEF for loop16 at equilibrium, before and after S-S bond scission; reduced after S-S bond scission, before and after C-C bond scission.

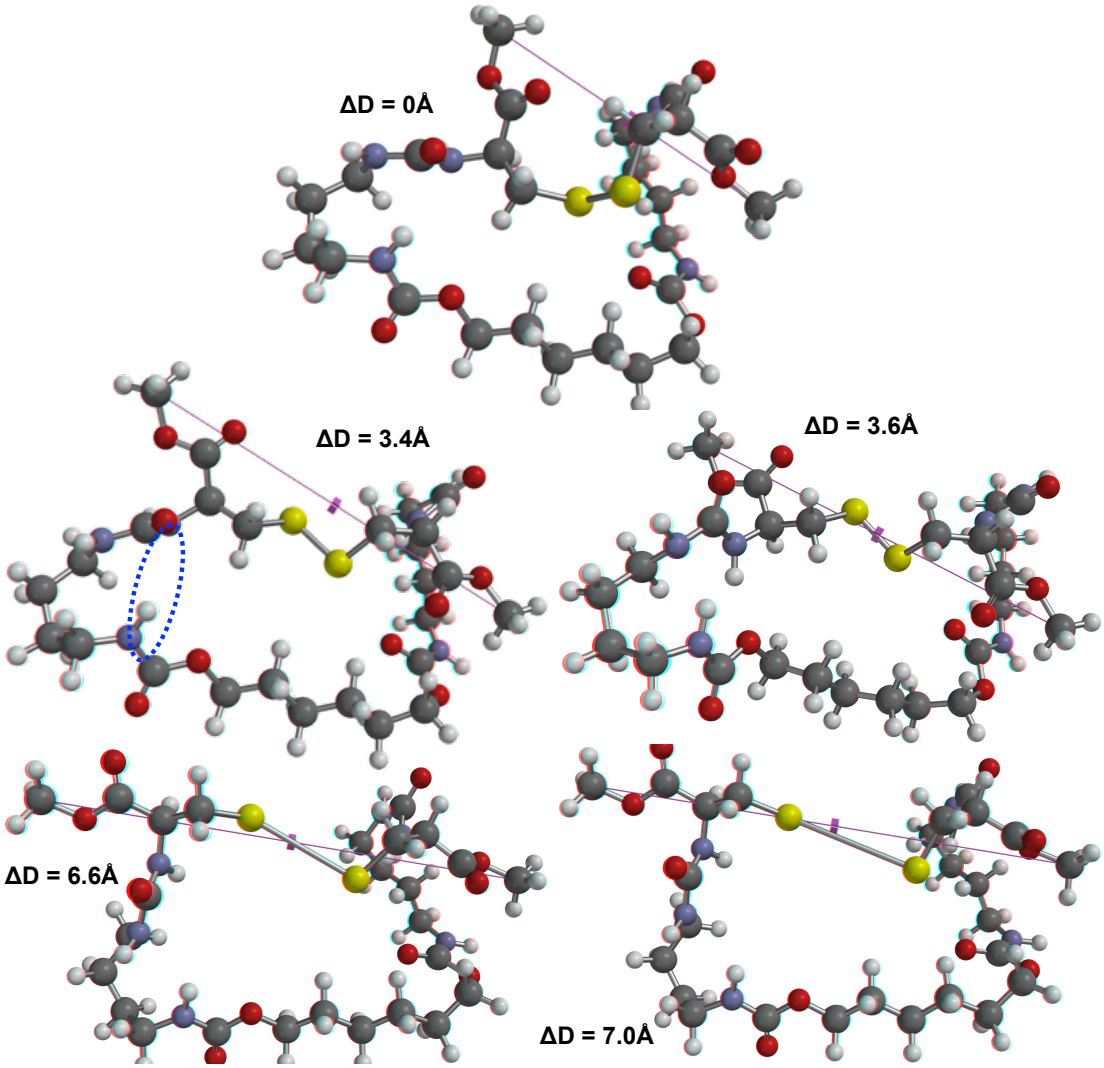


Figure S44. Structures from CoGEF for loop32 at equilibrium; before and after transannular H-bond scission (marked in blue); before and after S-S bond scission.

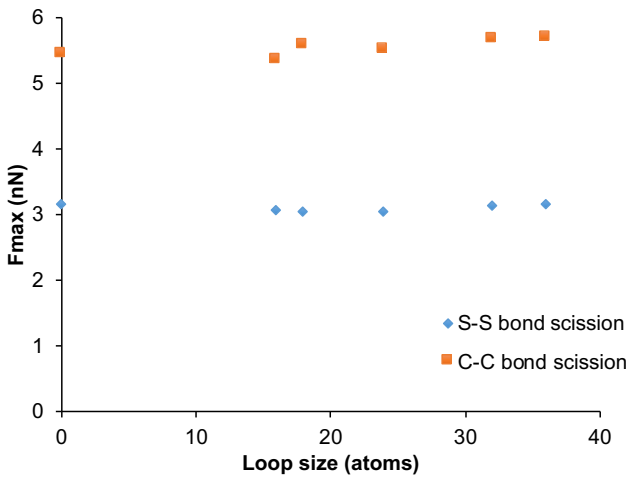


Figure S45. CoGEF (DFT) calculated force required for scission of S-S and C-C bonds in different loops and linear models.

IX. References

1. D. B. G. Williams and M. Lawton, *J. Org. Chem.*, 2010, **75**, 8351-8354.
2. Y. Zheng, Y. Guo, Y. Li, Y. Wu, L. Zhang and Z. Yang, *New J. Chem.*, 2014, **38**, 4952-4962.
3. J. Madsen, S. P. Armes, K. Bertal, H. Lomas, S. MacNeil and A. L. Lewis, *Biomacromolecules*, 2008, **9**, 2265-2275.
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