Polymer Chemistry

COMMUNICATION

Facile Thiolation of Hydroxyl Functional Polymers

O. C. J. Andrén[a] and a M. Malkoch[a]*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

[a] KTH Royal Institute of Technology. Department of Fiber and Polymer Technology. Teknikringen 56-68, SE-100 44 Stockholm, Sweden.

Material

2,2-bis(hydroxymethyl) propionic acid (bis-MPA) was kindly provided by Perstorp. Di-methyl amino pyridine (99%) (DMAP), trifluoroacetic acid sodium salt (98%), trans-2-[3-(4-tert-Butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB), Dithranol, 2-(4-Hydroxyphenylazo)benzoic acid (HABA), 9-Nitroanthracene (9-Na), 3,3'-Dithiodipropionic acid (99%), Dowex w50, trimethylamine (TEA) 1,4-Dithiothreitol (DTT) and Glutathione were obtained from Sigma Aldrich. Chloroform-D ($CDCl_3$) (99.8%) were acquired from Cil. Chloroform (HPCL grade) ($CHCl_3$), diethylether (analytical reagent grade) (Ether), were acquired from Fisher Chemicals. Dichloromethane (analytical grade) (DCM), toluene-4-sulfonic acid (98%) (pTSA), n-Heptane and ethyl acetate (EtOAc) were purchased from Merck. TMP-Gx-OH was acquired from Polymer factory.

Methods

Nuclear magnetic resonance (NMR) was performed on a Bruker AM NMR. ^{1}H-NMR and ^{13}C-NMR were recorded at 400 MHz and 101 MHz respectively. Spectra were acquired using a Bruker Avance instrument. ^{1}H-NMR spectra were acquired using a spectral window of 20 ppm, a relaxation delay of 1 second and 16 scans. ^{13}C-NMR spectra were acquired using a spectral window of 240 ppm, a relaxation delay of 2 seconds and 512 scans. Analyses of obtain spectra were performed using MestReNova version 7.1.1-9649 (Mestrelab Research S.L 2012).

SEC was performed in dimethylformamide (DMF) (0.2 mL min^{-1}) with 0.01 M LiBr as the mobile phase at 50 °C using a TOSOH EcoSEC HLC-8320GPC system equipped with an EcoSEC RI detector and three columns (PSS PFG 5µm; Microguard, 100Å, and 300Å) (MW resolving range: 300-100 000 Da) from PSS GmbH. Sample solutions with a concentration of 2.5 mg mL^{-1} were used. A conventional calibration method was created using narrow linear poly(methyl methacrylate) standards. Corrections for flow rate fluctuations were made using toluene as an internal standard. PSS WinGPC Unity software version 7.2 was used to process data.

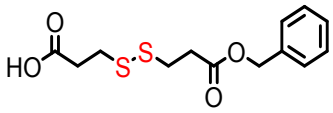
Matrix-assisted laser desorption/ionization time of flight mass spectroscopy (MALDI-TOF-MS) were performed on a Bruker UltraFlex MALDI-TOF MS with SCOUT-MTP Ion Source (Bruker Daltonics, Bremen) with a gridless ion source and the N_2-laser operating at 337 nm. The intensity of the laser was set to the lowest possible for acquisition of high resolution spectra of the product and all spectra were acquired using a reflector-positive mode. The instrument was calibrated using SpheriCal™ calibrants purchased from Polymer Factory Sweden AB. The received spectra were analyzed with FlexAnalysis Bruker Daltonics, Bremen, version 2.2. Matrixes were prepared by dissolution at a concentration of 10 mg/ml and used matrix is specified for each sample, salts at a concentration of 1 mg mL^{-1} and analyte at a concentration of 1mg/ml all in THF. Samples were prepared at a ratio of 20:5:2.5 for the matrix, counter ion and analyte respectively. A 2 µl droplet was deposited on an MPT 284 Target ground steel TF Target plate purchased from Bruker Daltonics.

Rheological measurements were conducted on a TA Instruments (New Castle, DE, USA) Discovery Hybrid 2 (DHR2) rheometer. Samples where measured in the linear viscoelastic region (LVR) region and all samples were evaluated in triplicates. More details can be found in hydrogel formation procedure below.

Column chromatography were performed using a Isolera 4 automated flash purification system from Biotage, LLC (Charlotte, NC, USA). Biotage® SNAP Ultra prepacked columns where used with either 10 or

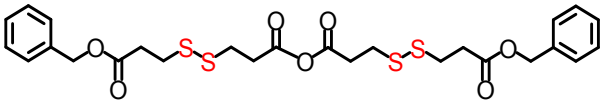
25 grams of silica as appropriate. A method was developed for each sample; more details can be found where appropriate below.

3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic acid (1)



3,3'-Dithiodipropionic acid (20g, 95.1 mmol) was dissolved in 500 mL THF in a round bottom flask equipped with a magnetic stir bar. Benzyl alcohol (8.6 g, 79.2 mmol) and DMAP (1.93 g, 13.85 mmol) was added and the reaction was cooled to 0 ˚C. DCC (24.5 g, 119 mmol) dissolved in 100 mL THF was slowly added to the reaction over 3 hours, subsequently the reaction was sealed with a septum and allowed to proceed for 16 hours. The crude reaction mixture was filtered through a pour 4 solid filter after which 100 mL of water was added and the reaction allowed to stir for one hour. The solvent was evaporated and 300 mL of DCM was added, the organic phase was washed with 50 mL of aqueous $NaHSO_4$ (10 wt%) five times, the organic phase was dried using $MgSO_4$ and the solvent evaporated. The white solid was dissolved in DCM and adsorbed onto 50 g of silica and purified using column chromatography (length:30 cm, radius: 2.5 cm, 400g silica Column fractions 250 mL) using Heptane: EtOAc starting from 100% Heptane Δ: 1% to 10 % EtOAc and Δ: 2 % to 50 % EtOAC. The product was recrystallized from DCM:Heptane 1:5 and attained as a white fluffy powder (Rf: 0.45 in Heptane:EtOAc 1:1) (19.6 g, 82.4%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.28 (m, 5H), 5.15 (s, 2H), 2.93 (dtd, *J* = 20.2, 7.1, 0.8 Hz, 4H), 2.78 (dtd, *J* = 10.0, 7.1, 0.9 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.53, 171.68, 135.74, 128.72, 128.48, 128.45, 66.81, 34.25, 33.99, 33.18, 32.84.

3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (2)



3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic acid (19.6 g, 65.0 mmol) was dissolved in 100 mL of DCM in a round bottom flask equipped with magnetic stirrer. The mixture was cooled to 0 ˚C and DCC (6.71 g, 32.5 mmol) was slowly added dissolved in 100 mL DCM was slowly added. The reaction was allowed to proceed for 16 hours under rigorous stirring. The crude reaction was filtered through a pour 4 solid filter, the filtrate was collected and the solvent evaporated. The obtained viscous yellow liquid was recrystallized from 300 mL of boiling ether; product was collected as a white powder. (14.0 g, 73 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.31 (m, 10H), 5.17 (d, *J* = 1.0 Hz, 4H), 3.01 – 2.90 (m, ^{13}H), 2.82 (td, *J* = 7.1, 0.8 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.59, 167.37, 135.74, 128.75, 128.52, 128.48, 66.83, 35.22, 35.19, 34.21, 33.09, 31.97.

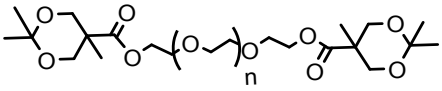
Acetonide protected bis-MPA (3)

Was synthesized according to previously published procedure.[1]

Acetonide protected bis-MPA anhydride (4)

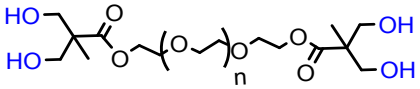
Was synthesized according to previously published procedure.[1]

PEG10k-G1-Acet (5)



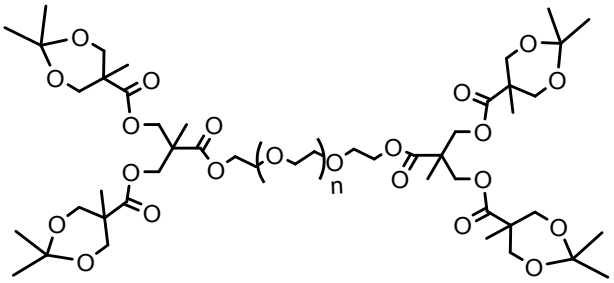
PEG10k-OH (50 g, 5.00 mmol) was dissolved in pyridine (2.50 mL, 30.0 mmol) and 50 mL DCM in a round bottom flask equipped with magnetic stir bar. DMAP (250 mg, 2.00 mmol) and acetonide protected bis-MPA anhydride (6.60 g, 20.0 mmol) was added. The reaction was allowed to proceed for 16 hours, the completion was confirmed using ^{13}C-NMR monitoring the presence of excess anhydride by the retention of the characteristic anhydride peak ((101 MHz, $CDCl_3$) δ 169.56). The crude reaction mixture was concentrated to half the original volume and subsequently precipitated trice in 500 mL ether. Product was collected as a white fluffy powder (47.8 g, 92.8 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.33 – 4.25 (m, 4H), 4.18 (d, *J* = 11.7 Hz, 4H), 3.63 (s, 955H), 1.40 (d, *J* = 16.3 Hz, 12H), 1.21 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.15, 97.11, 69.81, 68.20, 65.10, 63.07, 40.96, 23.51, 22.43, 17.96. M_w (Theoretical) = 10462.54 g/mol,M_w (SEC $_{DMF}$) = 11273 g/mol, Đ = 1.09.

PEG10K -G1-OH (6)



PEG10k-G1-Acet (46.0 g, 4.45 mmol) was dissolved in 500 mL of MeOH in a round bottom flask equipped with magnetic stirrer. Dowex W50 (75 g, 150 wt%) was added to the reaction and it was stirred vigorously for one hour. The progress vas monitored by NMR looking for the disappearance of peaks associated with the acetonide ^{13}C NMR (101 MHz, $CDCl_3$) δ: 23.51, 22.43 and ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 1.40 (d, *J* = 16.3 Hz, 12H). The Dowex was removed by filtration and the solvent subsequently evaporated, this sequence was repeated until full deprotection could be confirmed. The resulting white cake was dissolved in 50 mL of DCM and precipitated in 500 mL of ether, trice. Product was collected as a white fluffy powder (43.6 g, 95.7 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.42 – 4.28 (m, 4H), 3.66 (s, 963H), 1.14 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.79, 70.01, 69.87, 68.26, 65.90, 62.71, 49.22, 16.64. M_w (Theoretical) = 10382.41 g/mol, M_w (SEC $_{DMF}$) = 11188 g/mol, Đ = 1.07.

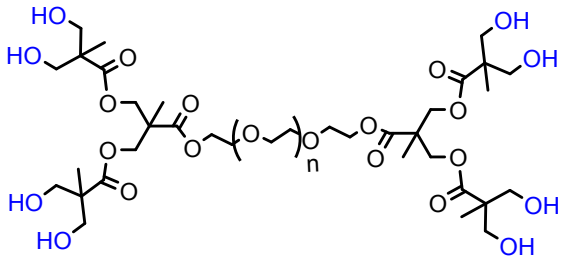
PEG10K -G2-Acet (7)



PEG10k-G1-OH (35.0 g, 3.42 mmol) was dissolved in pyridine (6.60 mL, 82.1 mmol) and 50 mL DCM in a round bottom flask equipped with magnetic stir bar. DMAP (669 mg, 5.47 mmol) and acetonide protected bis-MPA anhydride (9.04 g, 27.3 mmol) was added. The reaction was allowed to proceed for 16 hours, the completion was confirmed using ^{13}C-NMR monitoring the presence of excess anhydride by the retention

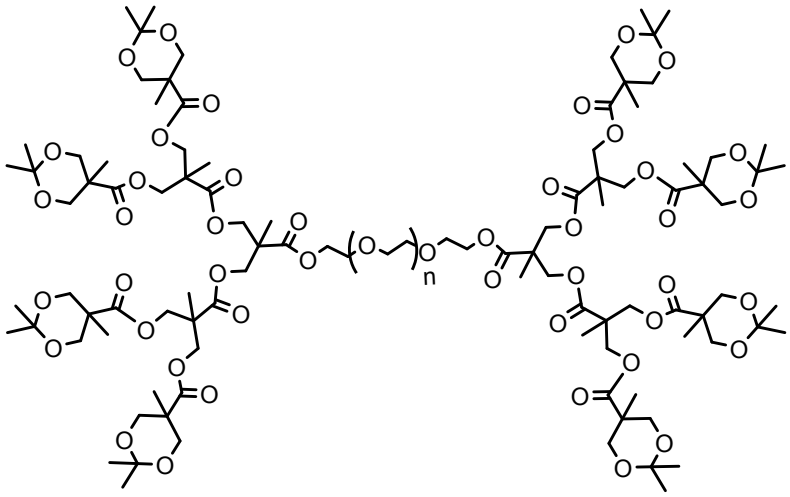
of the characteristic anhydride peak ((101 MHz, $CDCl_3$) δ 169.56). The crude reaction mixture was concentrated to half the original volume and subsequently precipitated trice in 500 mL ether. Product was collected as a white fluffy powder (32.9 g, 88.7 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.29 (s, 8H), 4.29 – 4.19 (m, 4H), 4.11 (d, *J* = 11.9 Hz, 9H), 3.61 (s, 1015H), 1.35 (d, *J* = 22.9 Hz, 25H), 1.26 (s, 6H), 1.12 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.15, 172.18, 97.73, 70.28, 68.52, 65.65, 65.62, 64.90, 63.97, 46.43, 41.72, 24.81, 21.92, 18.25, 17.45. M_w (Theoretical) = 11007.13 g/mol, M_w (SEC $_{DMF}$) = 12411 g/mol, Đ = 1.03.

PEG10K -G2-OH (8)



PEG10k-G2-Acet (32.0 g, 2.94 mmol) was dissolved in 500 mL of MeOH in a round bottom flask equipped with magnetic stirrer. Dowex W50 (60 g, 150 wt%) was added to the reaction and it was stirred vigorously for one hour. The progress vas monitored by NMR looking for the disappearance of peaks associated with the acetonide ^{13}C NMR (101 MHz, $CDCl_3$) δ: 23.51, 22.43 and ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 1.40 (d, *J* = 16.3 Hz, 12H). The Dowex was removed by filtration and the solvent subsequently evaporated, this sequence was repeated until full deprotection could be confirmed. The resulting white cake was dissolved in 50 mL of DCM and precipitated in 500 mL of ether, trice. Product was collected as a white fluffy powder (29.8 g, 96.6 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.45 – 4.28 (m, 8H), 4.33 – 4.26 (m, 3H), 3.64 (s, 956H), 1.31 (s, 6H), 1.07 (s, 12H).). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.78, 172.05, 69.74, 69.61, 68.00, 65.02, 63.98, 63.45, 49.21, 45.64, 17.17, 16.33. M_w (Theoretical) = 10382.41 g/mol, M_w (SEC $_{DMF}$) = 11796 g/mol, Đ = 1.04.

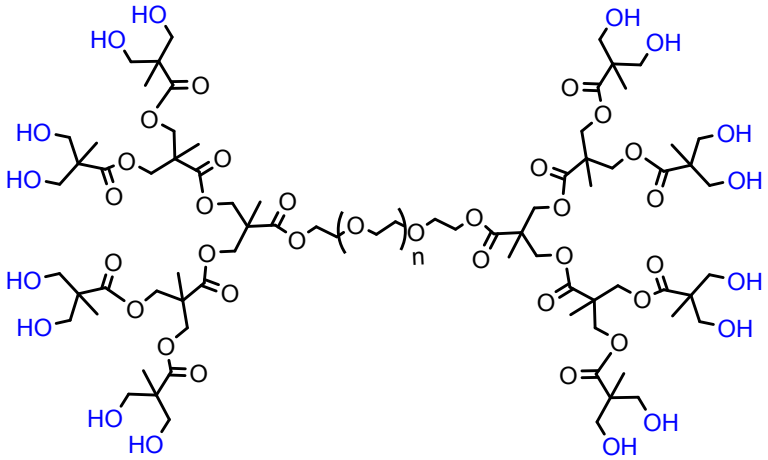
PEG10K -G3-Acet (9)



PEG10k-G2-OH (15.0 g, 1.43 mmol) was dissolved in pyridine (2.77 mL, 34.3 mmol) and 50 mL DCM in a round bottom flask equipped with magnetic stir bar. DMAP (279 mg, 2.29 mmol) and acetonide protected

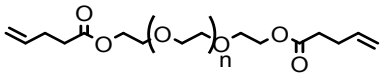
bis-MPA anhydride (7.55 g, 22.9 mmol) was added. The reaction was allowed to proceed for 16 hours, the completion was confirmed using ^{13}C-NMR monitoring the presence of excess anhydride by the retention of the characteristic anhydride peak ((101 MHz, $CDCl_3$) δ 169.56). The crude reaction mixture was concentrated to half the original volume and subsequently precipitated trice in 500 mL ether. Product was collected as a white fluffy powder (15.1 g, 89.9 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.27 (dt, *J* = 14.8, 2.9 Hz, 27H), 4.12 (d, *J* = 11.7 Hz, 17H), 3.62 (s, 996H), 1.36 (d, *J* = 24.1 Hz, 48H), 1.25 (s, 17H), 1.12 (s, 24H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.95, 171.57, 171.34, 97.55, 70.13, 68.30, 65.49, 65.44, 64.41, 63.93, 46.40, 46.12, 41.57, 24.86, 21.58, 18.05, 17.25. M_w (Theoretical) = 12096.32 g/mol, M_w (SEC $_{DMF}$) = 13374 g/mol, Đ = 1.03.

PEG10K -G3-OH (10)



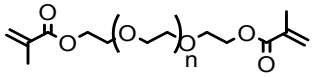
PEG10k-G3-Acet (14.5 g, 1.23 mmol) was dissolved in 500 mL of MeOH in a round bottom flask equipped with magnetic stirrer. Dowex W50 (30 g, 150 wt%) was added to the reaction and it was stirred vigorously for one hour. The progress vas monitored by NMR looking for the disappearance of peaks associated with the acetonide ^{13}C NMR (101 MHz, $CDCl_3$) δ: 23.51, 22.43 and ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 1.40 (d, *J* = 16.3 Hz, 12H). The Dowex was removed by filtration and the solvent subsequently evaporated, this sequence was repeated until full deprotection could be confirmed. The resulting white cake was dissolved in 50 mL of DCM and precipitated in 500 mL of ether, trice. Product was collected as a white fluffy powder (13.2 g, 93.6 ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.37 (d, *J* = 3.9 Hz, 2H), 4.34 (d, *J* = 3.8 Hz, 5H), 4.33 – 4.25 (m, 20H), 3.63 (s, 965H), 1.29 (s, 12H), 1.28 (s, 6H), 1.07 (s, 24H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.55, 172.07, 171.94, 70.27, 68.46, 66.18, 66.09, 65.64, 64.41, 64.21, 49.66, 46.29, 17.70, 17.33, 16.87. M_w (Theoretical) = 13185.78.41 g/mol, M_w (SEC $_{DMF}$) = 12815 g/mol, Đ = 1.02.

PEG10k-Allyl (11)



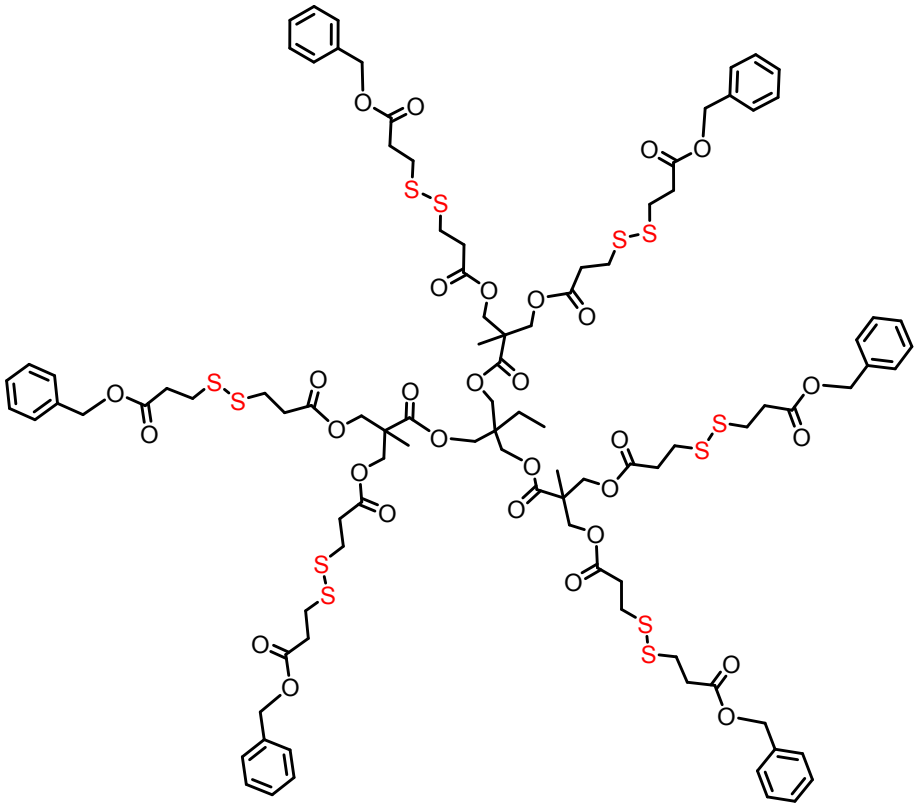
PEG10k-OH (10g, 1.00 mmol) was dissolved in pyridine (300 µL, 6.00 mmol) and 10 mL of DCM in a round bottom flask equipped with magnetic stirrer. DMAP (48.6 mg, 0.40 mmol) and 4-Pentenoic anhydride (731 µL, 4 mmol) was added and the reaction vas stirred rigorously for 16 hours. The completion was confirmed using ^{13}C-NMR monitoring the presence of excess anhydride by the retention of the characteristic anhydride peak ((101 MHz, $CDCl_3$) δ 168.45). The crude reaction mixture was precipitated in 700 mL of ether, the white solid collected and redissolved in 10 mL of DCM and precipitated in 300 mL of ether. Product was collected as a white powder (9.8 g, 96.4 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.82 (ddt, *J* = 16.5, 10.2, 6.2 Hz, 2H), 5.15 – 4.90 (m, 4H), 4.34 – 4.04 (m, 4H), 3.64 (s, 1096H), 2.49 – 2.33 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.74, 135.83, 114.69, 69.70, 68.22, 62.56, 32.45, 27.95. M_w (Theoretical) = 10258.27 g/mol, M_w (SEC $_{DMF}$) = 11016 g/mol, Đ = 1.05

PEG10k-Acrylate (12)



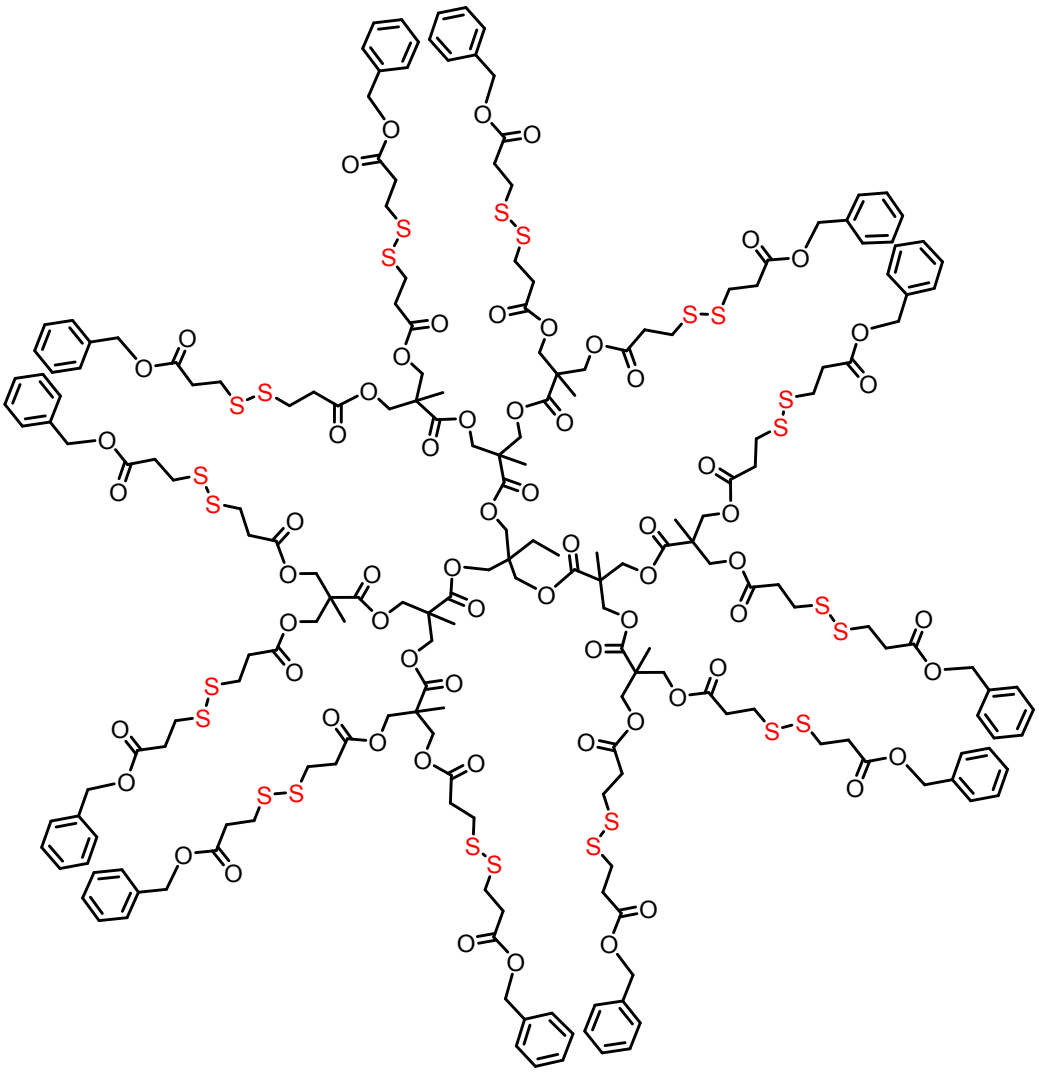
PEG10k-OH (15.0 g, 1.50 mmol) was dissolved in 100 mL of toluene in a round bottom flask equipped with a magnetic stir bar and distillation equipment, the mixture was distilled at 50 ˚C, 10^{-3} Pa for one hour. The distillation equipment was removed and the temperature lowered to 45 ˚C, 35 mL of toluene and TEA (843 µL, 6.00 mmol) was added and the white cake allowed to dissolved. The reaction vessel was sparged with nitrogen and acryloyl chloride (485 µL, 6.00 mmol) was added in 48.5 µl portions over 30 minutes. The reaction was allowed to proceed 16 hours and subsequently filtered through a pour 4 solid filter while warm. The filtrate was collected and evaporated to dryness, redissolved in 30 mL of DCM and precipitated twice in 700 mL of ether. Product was collected as a white powder (14.2 g, 93.6 %) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.40 (dd, *J* = 17.4, 1.5 Hz, 2H), 6.13 (dd, *J* = 17.3, 10.4 Hz, 2H), 5.82 (dd, *J* = 10.4, 1.5 Hz, 2H), 4.29 (dd, *J* = 5.8, 3.9 Hz, 4H), 3.62 (s, 949H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.22, 131.10, 128.36, 70.71, 70.65, 69.19, 63.78. M_w (Theoretical) = 10314.38 g/mol, M_w (SEC $_{DMF}$) = 11541 g/mol, Đ = 1.02.

TMP-G1-S-S-Bz (13)



TMP-G1-OH (250 mg, 518 µmol) was dissolved in pyridine (750 µL, 9.32 mmol) and 2 mL of chloroform in a round bottom flask equipped with magnetic stir bar. DMAP (76.0 mg, 622 µmol) and the reaction was cooled to 0 ˚C using an ice bath. 3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (2.70 g, 4.66 mmol) was slowly added. The reaction was allowed to proceed for 16 hours at room temperature. The reaction was monitored using ^{13}C-NMR looking for the retention of characteristic anhydride peak at ^{13}C NMR (101 MHz, $CDCl_3$) 167.37 and MALDI-TOF-Ms looking for mass of complete dendrimer. The reaction mixture was diluted in 20 mL of chloroform and the organic phase washed trice with 10 mL of aqueous $NaHSO_4$ (10 wt%), trice with 10mL of aqueous Na_2CO_3 (10wt%) and once with 10mL of brine. The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. Resulting yellow viscous solid was dissolved in 1 mL of DCM and adsorbed onto 1 g of silica and subsequently purified by column chromatography using Biotage Isolera 4 automatic column system in EtOAc: Heptane. A SNAP Ultra 25g column was used at a flow rate of 75 mL/min, a linear gradient from 1:0 to 0:1 Heptane EtOAC was run over 15 column volumes (CV) with an initial length of 3 CV at 1:0 and a final length of 2 CV at 0:1. The progression was monitored at 254 and 280 nm with a collection threshold of 20 mAU. Product was collected as a yellow viscous solid (376.1 mg, 32.0 %) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 2.7 Hz, 29H), 5.13 (d, *J* = 2.1 Hz, 12H), 4.36 – 4.16 (m, 13H), 4.05 (s, 6H), 2.90 (dt, *J* = 21.2, 7.0 Hz, 27H), 2.75 (dt, *J* = 21.4, 7.1 Hz, 24H), 1.47 (q, *J* = 7.0 Hz, 2H), 1.25 (s, 9H), 0.91 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.13, 171.55, 171.15, 135.80, 128.70, 128.45, 128.42, 66.73, 65.43, 46.59, 34.08, 33.20, 33.09, 33.00, 32.94, 24.83, 18.05, 7.59. MALDI (Ditranol, NaTFA) calc [M+Na$^+$] = 2197.46 Da, Obtained [M+Na$^+$] = 2196.7 Da. M_w (theoretical) = 2176,67 g mol^{-1}, SEC (DMF) M_n =1821.6 g mol^{-1}, Đ = 1.03.

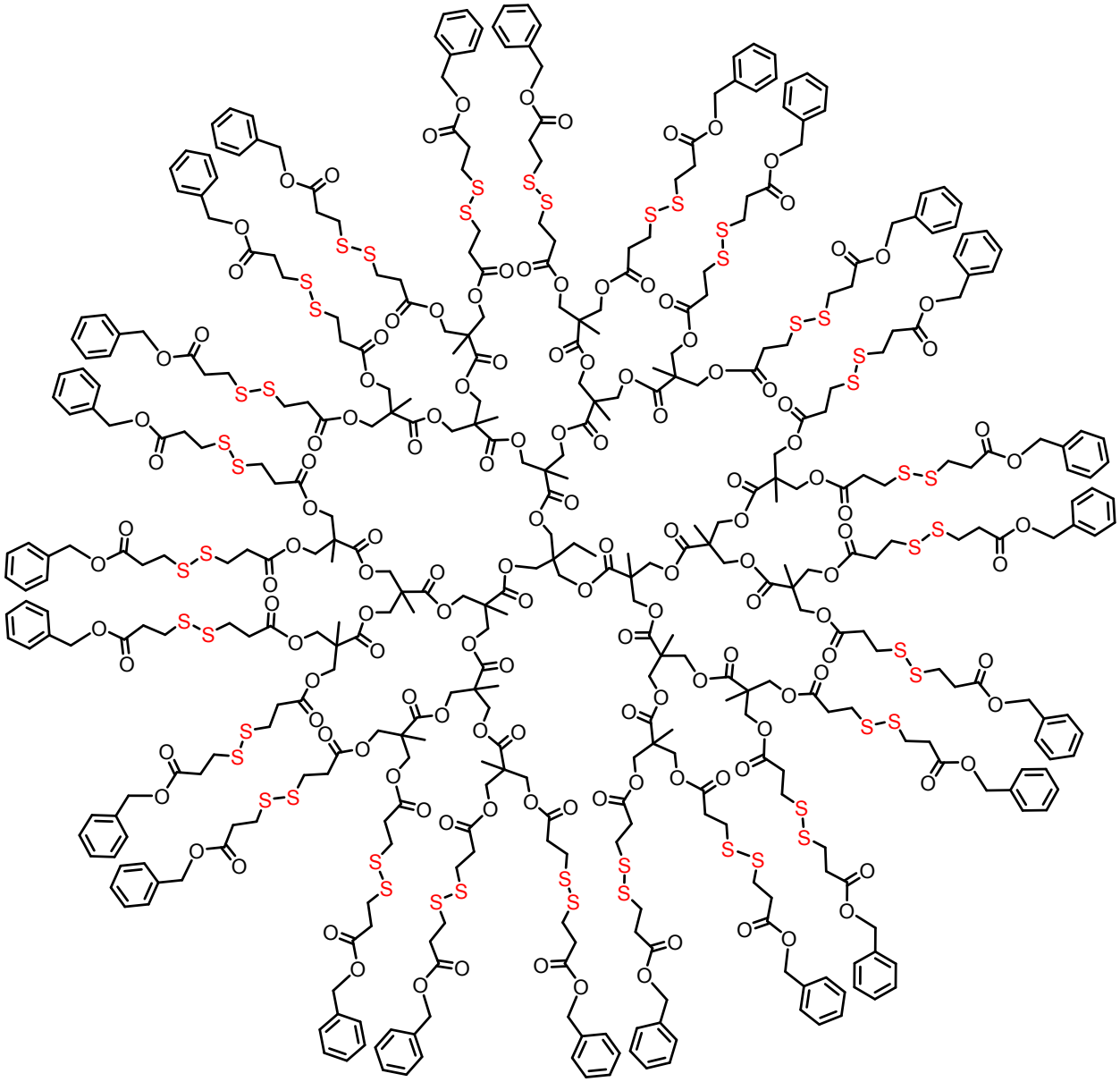
TMP-G2-S-S-Bz (14)



TMP-G2-OH (250 mg, 212 µmol) was dissolved in pyridine (604 µL, 7.63 mmol) and 2 mL of chloroform in a round bottom flask equipped with magnetic stir bar. DMAP (62.2 mg, 509 µmol) and the reaction was cooled to 0 ˚C using an ice bath. 3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (2.22 g, 4.66 mmol) was slowly added. The reaction was allowed to proceed for 16 hours at room temperature. The reaction was monitored using ^{13}C-NMR looking for the retention of characteristic anhydride peak at ^{13}C NMR (101 MHz, $CDCl_3$) 167.37 and MALDI-TOF-Ms looking for mass of complete dendrimer. The reaction mixture was diluted in 20 mL of chloroform and the organic phase washed trice with 10 mL of aqueous $NaHSO_4$ (10 wt%), trice with 10mL of aqueous Na_2CO_3 (10wt%) and once with 10mL of brine. The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. Resulting yellow viscous solid was dissolved in 1 mL of DCM and adsorbed onto 1 g of silica and subsequently purified by column chromatography using Biotage Isolera 4 automatic column system in EtOAc: Heptane. A SNAP Ultra 25g column was used at a flow rate of 75 mL/min, a linear gradient from 1:0 to 0:1 Heptane EtOAC was run over 15 column volumes (CV) with an initial length of 3 CV at 1:0 and a final length of 2 CV at 0:1. The progression was monitored at 254 and 280 nm with a collection threshold of 20 mAU. Product was collected as a yellow viscous solid (300.25 mg, 30.4 %) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 32.6

Hz, 60H), 5.12 (s, 24H), 4.23 (p, *J* = 10.4, 8.6 Hz, 36H), 4.08 (s, 6H), 2.89 (dt, *J* = 20.6, 6.9 Hz, 49H), 2.74 (dt, *J* = 18.8, 7.1 Hz, 47H), 1.70 (dt, *J* = 13.5, 3.9 Hz, 2H), 1.27 (s, 9H), 1.23 (s, 19H), 1.03 – 0.80 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.95, 171.54, 171.15, 135.83, 128.70, 128.45, 128.42, 66.75, 66.71, 65.33, 46.46, 34.24, 34.09, 33.89, 33.33, 33.21, 33.09, 32.95, 18.05. MALDI (Ditranol, NaTFA) calc [M+Na$^+$] = 4585.97 Da, Obtained [M+Na$^+$] = 4883.18 Da. M_w (theoretical) = 4567.68 g mol^{-1}, SEC (DMF) M_n =3320.4 g mol^{-1}, Đ = 1.02.

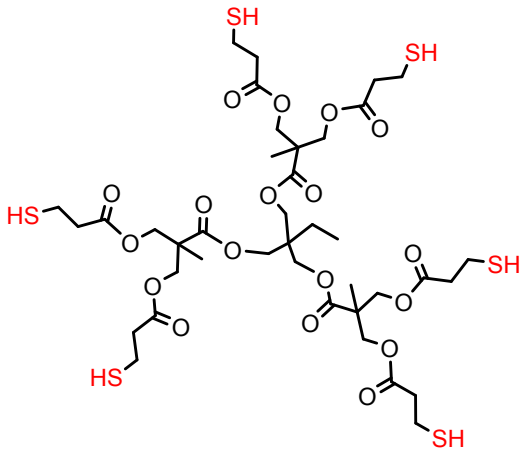
TMP-G3-S-S-Bz (15)



TMP-G3-OH (250 mg, 97.1 µmol) was dissolved in pyridine (565 µL, 7.00 mmol) and 2 mL of chloroform in a round bottom flask equipped with magnetic stir bar. DMAP (57.0 mg, 466 µmol) and the reaction was cooled to 0 ˚C using an ice bath. 3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (2.04 g, 3.50 mmol) was slowly added. The reaction was allowed to proceed for 16 hours at room temperature.

The reaction was monitored using ^{13}C-NMR looking for the retention of characteristic anhydride peak at ^{13}C NMR (101 MHz, $CDCl_3$) 167.37 and MALDI-TOF-Ms looking for mass of complete dendrimer. The reaction mixture was diluted in 20 mL of chloroform and the organic phase washed trice with 10 mL of aqueous $NaHSO_4$ (10 wt%), trice with 10mL of aqueous Na_2CO_3 (10wt%) and once with 10mL of brine. The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. Resulting yellow viscous solid was dissolved in 1 mL of DCM and adsorbed onto 1 g of silica and subsequently purified by column chromatography using Biotage Isolera 4 automatic column system in EtOAc: Heptane. A SNAP Ultra 25g column was used at a flow rate of 75 mL/min, a linear gradient from 1:0 to 0:1 Heptane EtOAC was run over 15 column volumes (CV) with an initial length of 3 CV at 1:0 and a final length of 2 CV at 0:1. The progression was monitored at 254 and 280 nm with a collection threshold of 20 mAU. Product was collected as a yellow viscous solid (293 mg, 31.6 %) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 3.4 Hz, 121H), 5.11 (s, 48H), 4.40 – 4.14 (m, 85H), 4.10 (s, 6H), 2.88 (dt, *J* = 19.6, 7.1 Hz, 113H), 2.73 (dt, *J* = 17.8, 7.1 Hz, 108H), 1.29 (s, 9H), 1.24 (s, 18H), 1.22 (s, 37H), 0.93 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 171.97, 171.53, 171.14, 135.86, 128.71, 128.48, 128.44, 128.42, 66.80, 66.69, 65.27, 55.89, 46.43, 35.06, 34.24, 34.10, 33.99, 33.90, 33.22, 33.08, 32.95, 18.06. MALDI (Ditranol, NaTFA) calc [M+H$^+$] = 9326.01 Da, Obtained [M+H$^+$] = 9326.34 Da. M_w (theoretical) = 9340.01 g mol^{-1}, SEC (DMF) M_n =6101.4 g mol^{-1}, Đ = 1.01.

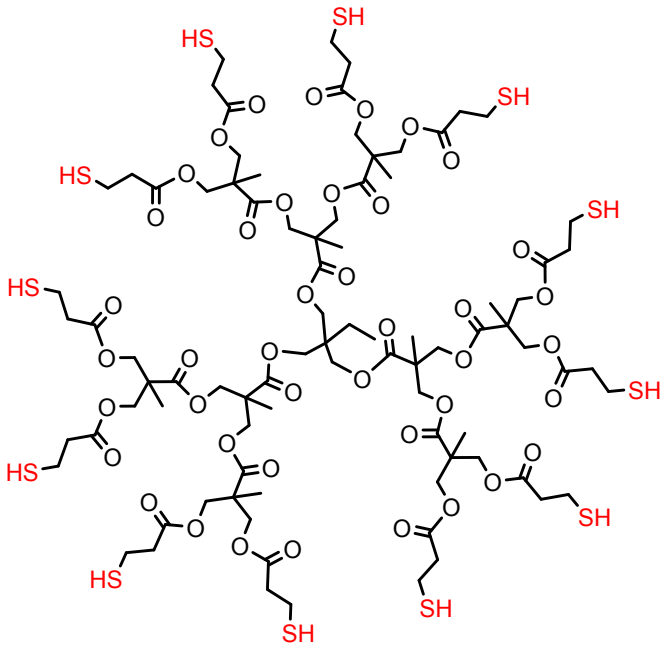
TMP-G1-SH (16)



TMP-G1-S-S-Bz (150 mg, 67.5 µmol) was dissolved in 1 mL $CHCl_3$ in a small vial equipped with magnetic stir bar. The vial was fitted with a septum and an argon inlet and outlet, the reaction was purged with Argon for 15 minutes. TEA (187 µL, 1.52 mmol) and DTT (150 mg, 1.01 mmol) was added to the reaction mixture and it was vacuum argon cycled twice at -78˚C ending with an argon fill. The reaction was allowed to reach room temperature and stirred vigorously for 15 minutes. The reaction progression was monitored by MALDI-TOF-Ms looking for the transformation to completely deprotected dendrimer. Upon completion the reaction mixture was diluted to 20 mL with $CHCl_3$ and washed trice with aqueous $NaHSO_4$ (10 wt%), trice with deionized water and once with brine. Subsequently, it was dried using $MgSO_4$, filtered and evaporated to dryness. The dry film was washed with 10 mL of heptane trice, dissolved in DCM and adsorbed onto 200 mg of silica. The product was purified by silica filtration by adding the compound onto a column (length:5 cm, radius: 0.5 cm) it was flushed with 20 mL 4:1 heptane: EtOAc and then product was eluted with 4:1 heptane: EtOAc product was collected as transparent viscous solid (61.5 mg, 86.6 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.35 – 4.21 (m, 12H), 4.07 (s, 6H), 2.81 – 2.69 (m, 12H), 2.66 (dd, *J* = 7.6, 6.4 Hz, 12H), 1.65 (t, *J* = 8.3 Hz, 6H), 1.50 (q, *J* = 7.5 Hz, 2H), 1.27 (s, 9H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR

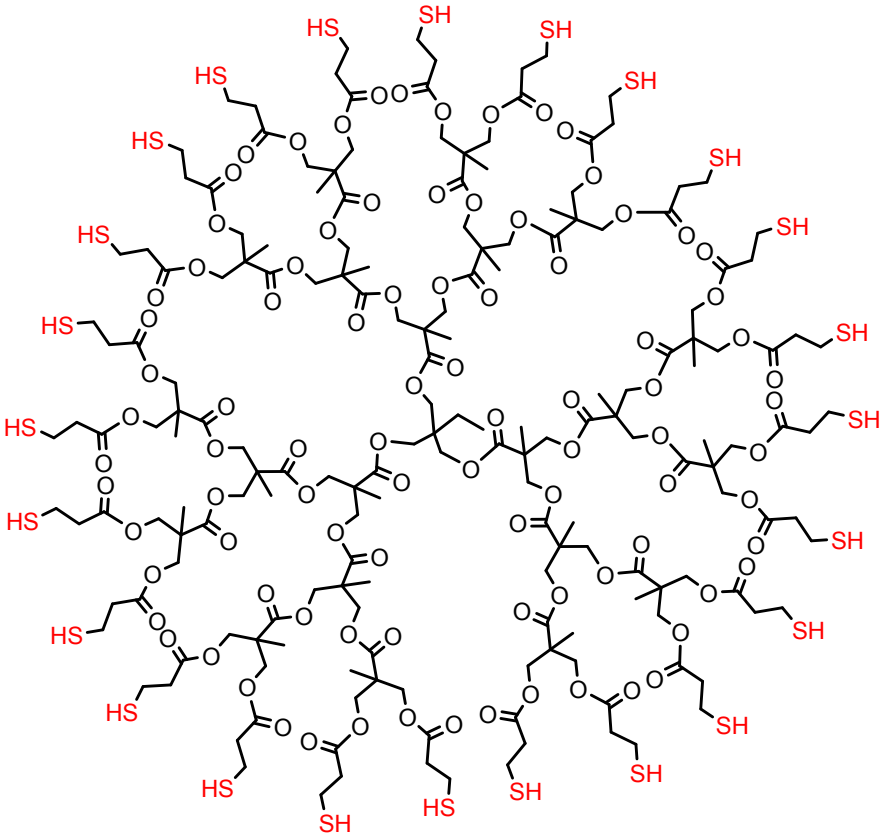
(101 MHz, $CDCl_3$) δ 172.26, 171.18, 65.44, 64.00, 46.67, 41.69, 38.38, 23.17, 19.77, 18.08, 7.62. MALDI (DHB, NaTFA) calc [M+Na^+] = 1033.22 Da, Obtained [M+Na^+] = 1032.16 Da. M_w (theoretical) = 1011.27 g mol^{-1}, SEC (DMF) M_n =785.4 g mol^{-1}, Đ = 1.02.

TMP-G2-SH (17)



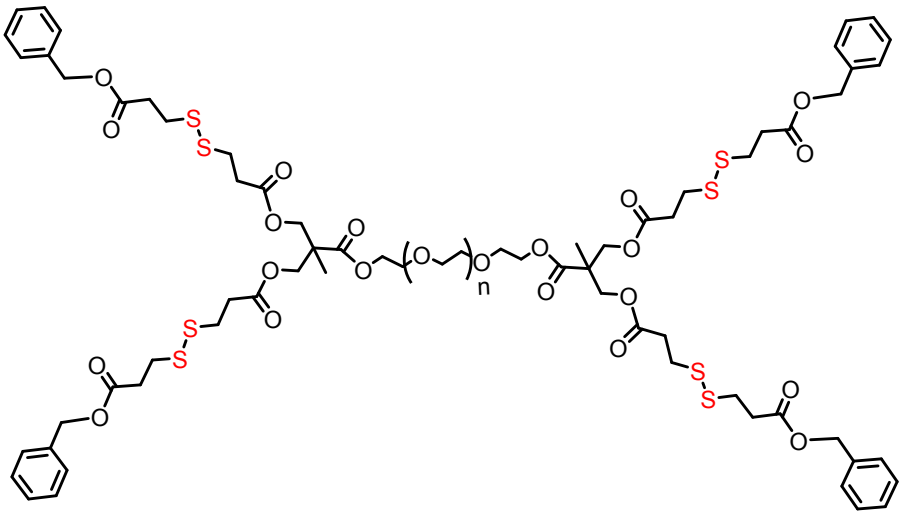
TMP-G2-S-S-Bz (100 mg, 21.5 µmol) was dissolved in 1 mL $CHCl_3$ in a small vial equipped with magnetic stir bar. The vial was fitted with a septum and an argon inlet and outlet, the reaction was sparged with Argon for 15 minutes. TEA (119 µL, 986 µmol) and DTT (150 mg, 644 µmol) was added to the reaction mixture and it was vacuum argon cycled twice at -78˚C ending with an argon fill. The reaction was allowed to reach room temperature and stirred vigorously for 15 minutes. The reaction progression was monitored by MALDI-TOF-Ms looking for the transformation to completely deprotected dendrimer. Upon completion the reaction mixture was diluted to 20 mL with $CHCl_3$ and washed trice with aqueous $NaHSO_4$ (10 wt%), trice with deionized water and once with brine. Subsequently, it was dried using $MgSO_4$, filtered and evaporated to dryness. The dry film was washed with 10 mL of ether trice. The product was collected as transparent viscous solid (61.5 mg, 83.0 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.39 – 4.18 (m, 36H), 4.11 (s, 6H), 2.85 – 2.71 (m, 24H), 2.67 (t, *J* = 6.6 Hz, 25H), 1.65 (t, *J* = 8.2 Hz, 12H), 1.29 (s, 9H), 1.26 (s, 18H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.07, 171.18, 65.38, 46.56, 38.42, 19.80, 18.07. MALDI (DHB, NaTFA) calc [M+Na^+] = 2257.49 Da, Obtained [M+Na^+] = 2257.65 Da. M_w (theoretical) = 2236.71 g mol^{-1}, SEC (DMF) M_n =1485.8 g mol^{-1}, Đ = 1.03.

TMP-G3-SH (18)



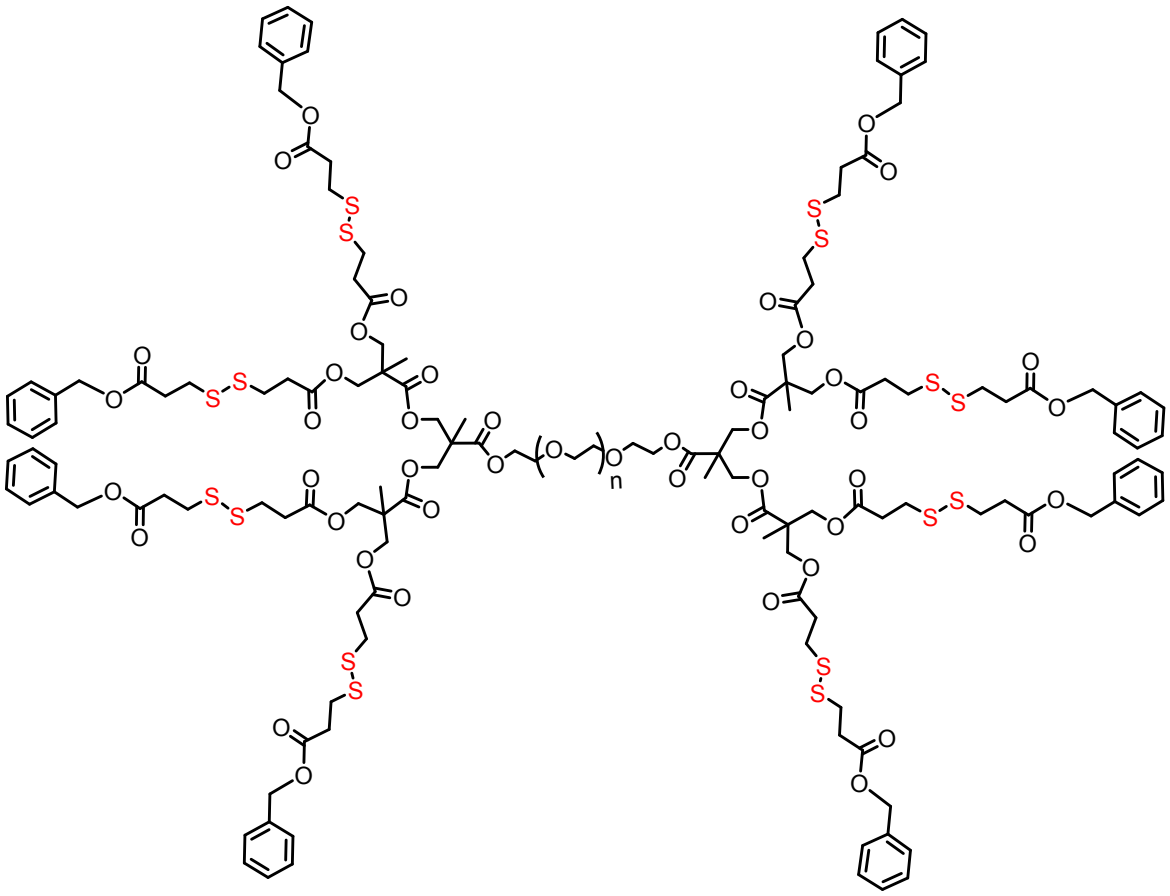
TMP-G3-S-S-Bz (100 mg, 10.7 µmol) was dissolved in 1 mL $CHCl_3$ in a small vial equipped with magnetic stir bar. The vial was fitted with a septum and an argon inlet and outlet, the reaction was sparged with Argon for 15 minutes. TEA (93.0 µL, 749 µmol) and DTT (99.1 mg, 642 µmol) was added to the reaction mixture and it was vacuum argon cycled twice at -78˚C ending with an argon fill. The reaction was allowed to reach room temperature and stirred vigorously for 15 minutes. The reaction progression was monitored by MALDI-TOF-Ms looking for the transformation to completely deprotected dendrimer. Upon compleation the reaction mixture was diluted to 20 mL with $CHCl_3$ and washed trice with aqueous $NaHSO_4$ (10 wt%), trice with deionized water and once with brine. Subsequently, it was dried using $MgSO_4$, filtered and evaporated to dryness. The dry film was washed with 10 Ml mL of heptane trice. The product was collected as transparent viscous solid (57.0 mg, 94.2%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.38 – 4.18 (m, 84H), 4.13 (s, 6H), 2.85 – 2.70 (m, 49H), 2.67 (t, *J* = 6.3 Hz, 48H), 1.66 (t, *J* = 8.2 Hz, 24H), 1.32 (s, 9H), 1.27 (d, *J* = 3.2 Hz, 54H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.08, 171.16, 65.35, 46.84, 46.54, 38.42, 19.81, 18.06, 17.82. MALDI (DHB, NaTFA) calc [M+H$^+$] = 4684.06 Da, Obtained [M+H$^+$] = 4686.20 Da. M_w (theoretical) = 4687.59 g mol^{-1}, SEC (DMF) M_n =2784.8 g mol^{-1}, Đ = 1.03.

PEG10k-G1-S-S-Bz (19)



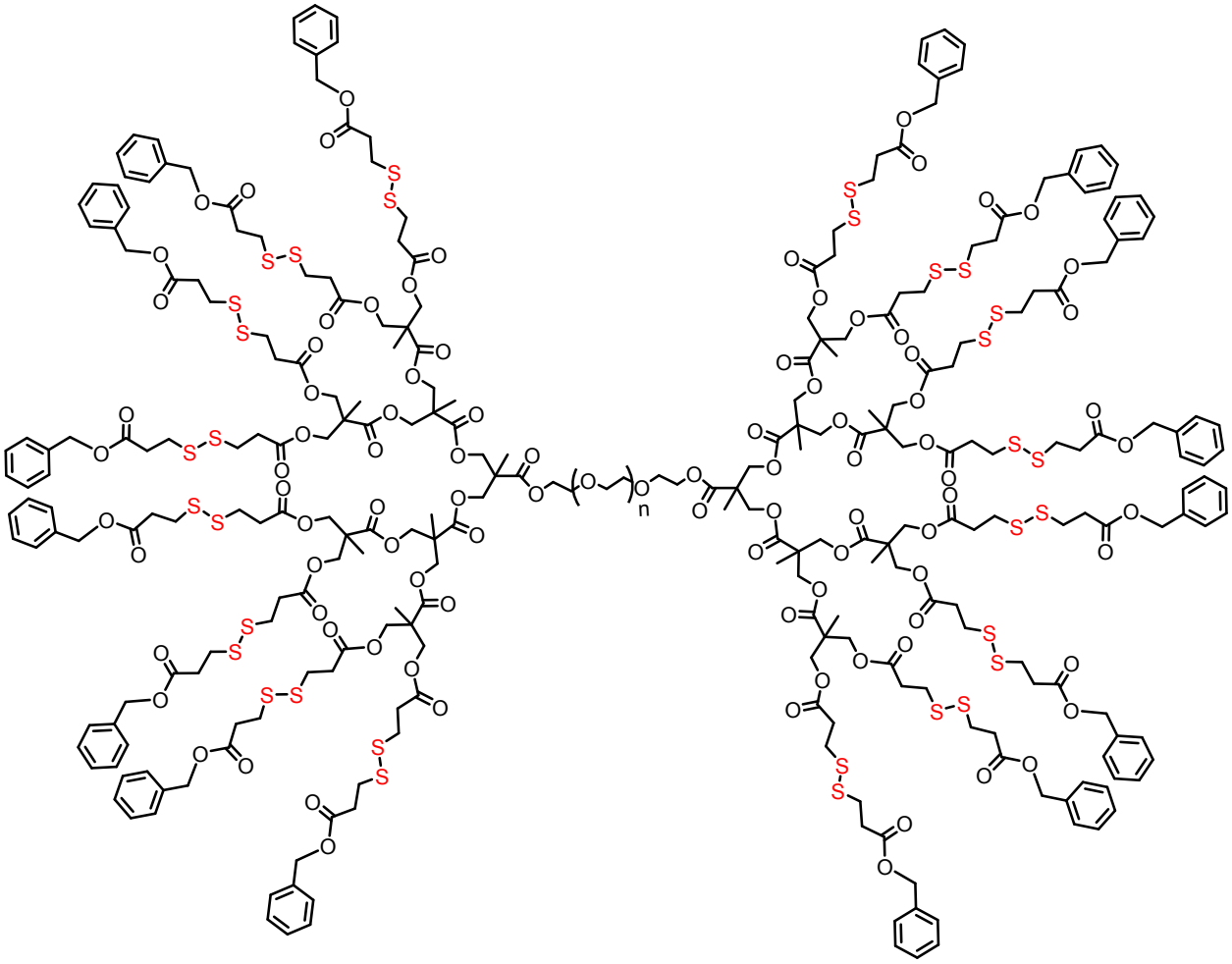
PEG10k-G1-OH (2.00 g, 195 µmol) was dissolved in 1 mL DCM and pyridine (189 µL, 2.34 mmol) in a round bottom flask equipped with magnetic stirrer. DMAP (19.1 mg, 156µmol) was added and subsequently 3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (683 mg, 1.17 mmol) was slowly added. The reaction was monitored using ^{13}C-NMR looking for the retention of characteristic anhydride peak at ^{13}C NMR (101 MHz, $CDCl_3$) 167.37. The reaction mixture was diluted in 50 mL of chloroform and the organic phase washed trice with 10 mL of aqueous $NaHSO_4$ (10 wt%), trice with 10mL of aqueous Na_2CO_3 (10wt%) and once with 10mL of brine. The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. Resulting off white solid was dissolved in 3 mL of DCM and precipitated trice in 300 mL of ether. Product was collected as a white fluffy powder (1.58 g, 71.1 %) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.27 (m, 20H), 5.13 (s, 8H), 4.34 – 4.18 (m, 12H), 3.63 (s, 987H), 2.99 – 2.88 (m, 8H), 2.91 – 2.82 (m, 8H), 2.77 (t, *J* = 6.9 Hz, 8H), 2.71 (t, *J* = 6.8 Hz, 8H), 1.25 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.30, 171.23, 170.85, 135.52, 128.42, 128.15, 70.41, 68.67, 66.42, 65.29, 64.08, 46.07, 33.94, 33.65, 32.86, 32.71, 17.75. M_w (theoretical) = 11511.89 g mol^{-1}, SEC (DMF) M_n =12336 g mol^{-1}, Đ = 1.03.

PEG10k-G2-S-S-Bz (20)



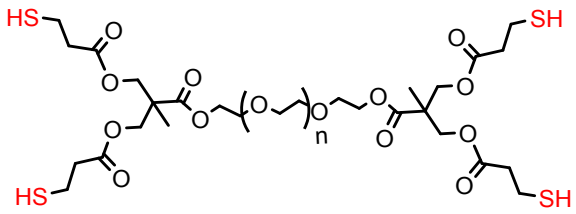
PEG10k-G2-OH (2.00 g, 187 µmol) was dissolved in 1 mL DCM and pyridine (362 µL, 4.48 mmol) in a round bottom flask equipped with magnetic stirrer. DMAP (36.5 mg, 299 µmol) was added and subsequently 3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (1.31 g, 2.24 mmol) was slowly added. The reaction was monitored using ^{13}C-NMR looking for the retention of characteristic anhydride peak at ^{13}C NMR (101 MHz, $CDCl_3$) 167.37. The reaction mixture was diluted in 50 mL of chloroform and the organic phase washed trice with 10 mL of aqueous $NaHSO_4$ (10 wt%), trice with 10mL of aqueous Na_2CO_3 (10wt%) and once with 10mL of brine. The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. Resulting off white solid was dissolved in 3 mL of DCM and precipitated trice in 300 mL of ether. Product was collected as a white fluffy powder (1.57 g, 64.8 %) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.28 (m, 40H), 5.12 (s, 16H), 4.21 (dd, *J* = 17.7, 11.0 Hz, 28H), 3.63 (s, 1052H), 2.91 (t, *J* = 7.1 Hz, 16H), 2.86 (t, *J* = 7.0 Hz, 16H), 2.76 (t, *J* = 7.1 Hz, 16H), 2.71 (t, *J* = 7.0 Hz, 16H), 1.24 (s, 6H), 1.22 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.82, 171.60, 171.16, 170.78, 135.47, 128.35, 128.07, 70.34, 68.54, 66.33, 65.38, 65.10, 64.14, 46.36, 46.11, 33.86, 33.52, 32.76, 32.61, 17.66, 17.43. M_w (theoretical) = 13105.85 g mol^{-1}, SEC (DMF) M_n =12528 g mol^{-1}, Đ = 1.05.

PEG10k-G3-S-S-Bz (21)



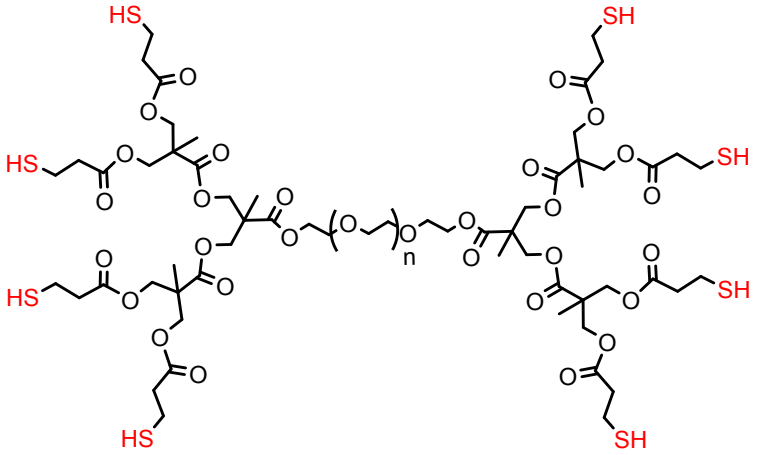
PEG10k-G3-OH (2.00 g, 195 µmol) was dissolved in 1 mL DCM and pyridine (189 µL, 2.34 mmol) in a round bottom flask equipped with magnetic stirrer. DMAP (19.1 mg, 156µmol) was added and subsequently 3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (683 mg, 1.17 mmol) was slowly added. The reaction was monitored using ^{13}C-NMR looking for the retention of characteristic anhydride peak at ^{13}C NMR (101 MHz, $CDCl_3$) 167.37. The reaction mixture was diluted in 50 mL of chloroform and the organic phase washed trice with 10 mL of aqueous $NaHSO_4$ (10 wt%), trice with 10mL of aqueous Na_2CO_3 (10wt%) and once with 10mL of brine. The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. Resulting off white solid was dissolved in 3 mL of DCM and precipitated trice in 300 mL of ether. Product was collected as a white fluffy powder (1.58 g, 71.1 %) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (s, 81H), 5.13 (s, 32H), 4.23 (dd, *J* = 12.2, 7.7 Hz, 56H), 3.64 (s, 960H), 2.92 (t, *J* = 7.1 Hz, 32H), 2.87 (t, *J* = 7.0 Hz, 32H), 2.77 (t, *J* = 7.1 Hz, 33H), 2.72 (t, *J* = 7.0 Hz, 32H), 1.28 (s, 6H), 1.23 (s, 12H), 1.23 (s, 24H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.78, 171.73, 171.68, 171.26, 170.87, 135.56, 128.44, 128.16, 70.43, 66.42, 65.12, 64.26, 46.54, 46.18, 33.95, 33.61, 32.82, 32.68, 17.75, 17.44. M_w (theoretical) = 16293.75 g mol^{-1}, SEC (DMF) M_n =16969 g mol^{-1}, Đ = 1.04.

PEG10k-G1-SH (22)



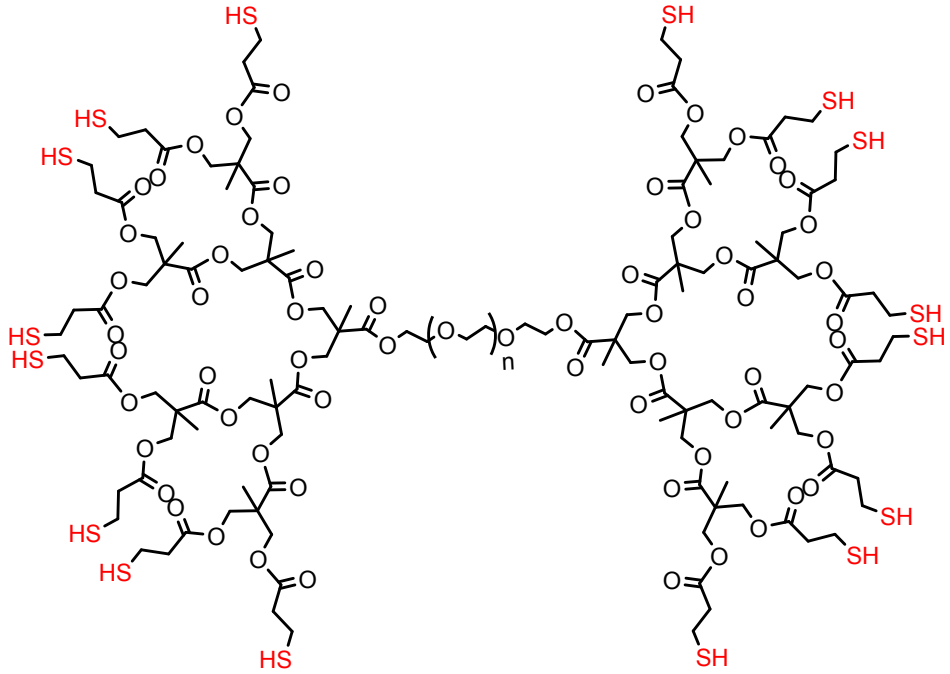
PEG10k-G1-S-S-Bz (1.00 g, 88.0 µmol) was dissolved in 2 mL $CHCl_3$ in a small vial equipped with magnetic stir bar. The vial was fitted with a septum and an argon inlet and outlet, the reaction was sparged with Argon for 15 minutes. TEA (110 µL, 792 µmol) and DTT (109 mg, 704 µmol) was added to the reaction mixture and it was vacuum argon cycled twice at -78˚C ending with an argon fill. The reaction was allowed to reach room temperature and stirred vigorously for 30 minutes. The reaction was monitored by ^{1}H-NMR looking for a shift ^{1}H NMR (400 MHz, Chloroform-*d*) δ from 5.12 to 5.15. Upon completion the reaction mixture was precipitated trice from $CHCl_3$ to 300 mL of ether, product was collected as white fluffy powder (785 mg, 84.2 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.44 – 4.19 (m, 12H), 3.64 (s, 959H), 2.85 – 2.70 (m, 8H), 2.66 (td, *J* = 6.6, 1.1 Hz, 8H), 1.64 (t, *J* = 8.3 Hz, 4H), 1.27 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.21, 170.67, 99.79, 70.27, 68.55, 65.08, 63.97, 63.37, 46.00, 38.03, 19.33, 17.64. M_w (theoretical) = 10734.90 g mol^{-1}, SEC (DMF) M_n =11352.4 g mol^{-1}, Đ = 1.06.

PEG10k-G2-SH(23)



PEG10k-G2-S-S-Bz (1.00 g, 77.2 µmol) was dissolved in 2 mL $CHCl_3$ in a small vial equipped with magnetic stir bar. The vial was fitted with a septum and an argon inlet and outlet, the reaction was sparged with Argon for 15 minutes. TEA (194 µL, 1.39 mmol) and DTT (190 mg, 1.23 mmol) was added to the reaction mixture and it was vacuum argon cycled twice at -78˚C ending with an argon fill. The reaction was allowed to reach room temperature and stirred vigorously for 30 minutes. The reaction was monitored by ^{1}H-NMR looking for a shift ^{1}H NMR (400 MHz, Chloroform-*d*) δ from 5.12 to 5.15. Upon completion the reaction mixture was precipitated trice from $CHCl_3$ to 300 mL of ether, product was collected as white fluffy powder (776 mg, 87.1 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.44 – 4.19 (m, 27H), 3.64 (s, 1011H), 2.85 – 2.70 (m, 16H), 2.66 (ddd, *J* = 7.2, 6.3, 1.1 Hz, 16H), 1.65 (t, *J* = 8.3 Hz, 6H), 1.27 (s, 6H), 1.25 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.77, 170.88, 170.81, 99.90, 70.44, 70.44, 65.48, 65.15, 64.26, 46.46, 46.26, 38.12, 19.49, 17.77, 17.55. M_w (theoretical) = 11550.86 g mol^{-1}, SEC (DMF) M_n =11109 g mol^{-1}, Đ = 1.09.

PEG10k-G3-SH (24)



PEG10k-G3-S-S-Bz (1.00 g, 62.7 µmol) was dissolved in 2 mL $CHCl_3$ in a small vial equipped with magnetic stir bar. The vial was fitted with a septum and an argon inlet and outlet, the reaction was sparged with Argon for 15 minutes. TEA (315 µL, 2.25 mmol) and DTT (310 mg, 2.01 mmol) was added to the reaction mixture and it was vacuum argon cycled twice at -78˚C ending with an argon fill. The reaction was allowed to reach room temperature and stirred vigorously for 30 minutes. The reaction was monitored by ^{1}H-NMR looking for a shift ^{1}H NMR (400 MHz, Chloroform-*d*) δ from 5.12 to 5.15. Upon completion the reaction mixture was precipitated trice from $CHCl_3$ to 300 mL of ether, product was collected as white fluffy powder (754 mg, 91.2 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.29 (dd, *J* = 9.9, 6.1 Hz, 62H), 3.67 (s, 999H), 2.88 – 2.73 (m, 33H), 2.69 (t, *J* = 6.3 Hz, 32H), 1.67 (s, 34H), 1.33 (s, 6H), 1.28 (s, 36H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.87, 171.03, 170.97, 170.94, 99.91, 65.27, 64.59, 64.51, 64.44, 46.62, 46.43, 38.26, 19.64, 19.62, 17.89, 17.70, 17.52. M_w (theoretical) = 13185.78 g mol^{-1}, SEC (DMF) M_n =13421 g mol^{-1}, Đ = 1.12.

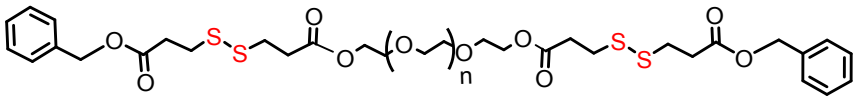
Filter paper–S-S-Bz (25)

Filter paper vas cut into six pieces each 2 by 2 cm, the pieces (31.3-33.6 mg) where washed with water, EtOH, THF, acetone and trice with toluene by submerging for a few minutes. The pieces were placed in small vials equipped with magnetic stir bar. In each vial 3 mL of toluene was added so the piece was submerged under the liquid subsequently DMAP (1-1.2 mg, 0.263 mmol/g) and pyridine (10-12 µL, 3.945 mmol/g) was added to each vial. To three of the vials -((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (73.0 - 77,2 mg, 3.945 mmol/g) was added. The reaction was allowed to proceed for 16 hours under mild stirring for all six samples. All six pieces where then washed with toluene twice and soxhlet extracted with DCM for 24 hours. The samples where then dried at ambient conditions for 16 hours and then dried in a vacuum oven at 50 ˚C for 48 hours.

Filter paper-SH (26)

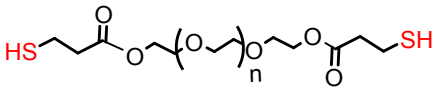
Three pieces of filterpaper-S-S-Bz as well as three reference pieces (the same as previously mentioned) where swelled in $CHCl_3$ in a vial equipped with magnetic stir bar. DTT (38.4 -40.9 mg, 7.890 mmol/g) and TEA (69.1 - 73.5 µL, 15.78 mmol/g) was added to all the samples. All vials where sealed with a septum vacuum/ argon cycled trice ending with an argon fill. The reaction was allowed to proceed for one hour, all six pieces where then washed with DCM trice and soxhlet extracted with DCM for 24 hours. The samples where then dried at ambient conditions for 16 hours and then dried in a vacuum oven at 50 ˚C for 48 hours.

PEG6k-S-S-Bz (27)



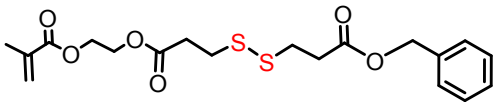
PEG6k-OH (500 mg, 83.3 µmol) was dissolved in 1 mL DCM and pyridine (41.0 µL, 500 µmol) in a round bottom flask equipped with magnetic stirrer. DMAP (4.06 mg, 33.6 µmol) was added and subsequently 3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (1.31 g, 2.24 mmol) was slowly added. The reaction was monitored using ^{13}C-NMR looking for the retention of characteristic anhydride peak at ^{13}C NMR (101 MHz, $CDCl_3$) 167.37. The reaction mixture was diluted in 50 mL of chloroform and the organic phase washed trice with 10 mL of aqueous $NaHSO_4$ (10 wt%), trice with 10mL of aqueous Na_2CO_3 (10wt%) and once with 10mL of brine. The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. Resulting off white solid was dissolved in 3 mL of DCM and precipitated trice in 300 mL of ether. Product was collected as a white fluffy powder (0.47 g, 85.4 %) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.28 (m, 10H), 5.14 (s, 4H), 4.30 – 4.17 (m, 3H), 3.64 (s, 450H), 3.02 – 2.84 (m, 9H), 2.84 – 2.64 (m, 9H). MALDI (DCTB, NaTFA) calc [M+H$^+$] = 6637.10 Da, Obtained [M+H$^+$] = 6636.40 Da.

PEG6k-SH (28)



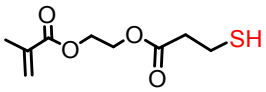
PEG6k-S-S-Bz (10.0 mg, 0.16 µmol) was dissolved in 100 µL $CHCl_3$ in a small vial equipped with magnetic stir bar. The vial was fitted with a septum and an argon inlet and outlet, the reaction was sparged with Argon for 15 minutes. TEA (1.00 µL, 0.61 µmol) and DTT (0,7 mg, 0.47 µmol) was added to the reaction mixture and it was vacuum argon cycled twice at -78˚C ending with an argon fill. The reaction was allowed to reach room temperature and stirred vigorously for 30 minutes. The reaction was monitored by ^{1}H-NMR looking for a shift ^{1}H NMR (400 MHz, Chloroform-*d*) δ from 5.12 to 5.15. Upon completion the reaction mixture was precipitated trice from $CHCl_3$ to 300 mL of ether, product was collected as white fluffy powder (754 mg, 91.2 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.28 (m, 10H), 5.14 (s, 4H), 4.30 – 4.17 (m, 3H), 3.64 (s, 450H), 3.02 – 2.84 (m, 9H), 2.84 – 2.64 (m, 9H). MALDI (DCTB, NaTFA) calc [M+H$^+$] = 6249.02 Da, Obtained [M+H$^+$] = 6249.00 Da.

HEMA-S-S-Bz (29)



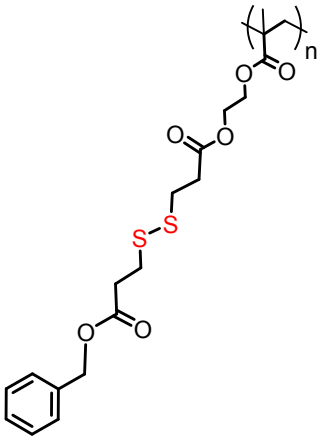
HEMA-OH (9.33 µL, 76.8 µmol) was dissolved in pyridine (18.4 µL, 230 µmol) and 200 µL DCM in a small vial equipped with magnetic stirrer. DMAP (1.8mg, 13.4 µmol) and ((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (67.2 mg, 115 µmol) was added, the reaction was allowed to proceed for 16 hours under rigorous stirring. Water 50 µL was added and allowed to react for 1 hour, the reaction was diluted with 5 mL of DCM and the organic phase washed trice with 1 mL of aqueous $NaHSO_4$ (10 wt%), trice with 1mL of aqueous Na_2CO_3 (10wt%) and once with 1mL of brine. The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. The resulting yellow liquid was pushed through a silica plug (diameter 0.5 cm, length 5 cm in Heptane EtOAc 50:50, product was collected as a yellow liquid (28.0 mg , 85.4%) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (s, 5H), 6.58 (d, *J* = 6.4 Hz, 1H), 6.13 (s, 1H), 5.14 (d, *J* = 2.3 Hz, 2H), 4.35 (s, 2H), 3.64 (s, 2H), 3.00 – 2.85 (m, 4H), 2.75 (dp, *J* = 22.4, 7.2, 6.7 Hz, 4H), 1.94 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.79, 171.57, 167.88, 136.15, 128.73, 128.47, 128.42, 126.20, 70.70, 66.57, 61.52, 34.27, 34.04, 33.17, 33.11, 18.48.

Poly HEMA6k-OH (30)



HEMA-OH (1-867 mL, 15.4 mmol) and Ethyl α-bromoisobutyrate (28.5 µL, 200 µmol) was dissolved in 2 mL of MeOH.H_2O (1:1). 2,2'-Bipyridyl (62.3 mg, 399 µmol) was added and the reaction was freeze pump thawed and argon filled. Copper(I) chloride (19.7 mg, 200 µmol) and Copper(II) chloride (4.02 mg, 29.9 µmol) was added. The reaction was vacuum/ argon cycled twice in a water ice bath and then allowed to proceed for 15 minutes at 0 ˚C. The conversion was determined by ^{1}H-NMR to 66.8 %, DP = 51. The product was dialyzed in a 1 KDa membrane against aqueous Ethylenediaminetetraacetic acid 0.5 wt% chanting the solution at 0.5, 1, 2 ,4 hours and water chanting at 0.1, 1, 2, 4, 20 hours. The retentate was freeze-dried, product was attained as a white solid (996 mg, 73.7 %). ^{1}H NMR (400 MHz, Methanol-d_4) δ 4.04 (s, 98H), 3.82 – 3.70 (m, 102H), 3.60 (d, *J* = 5.5 Hz, 4H), 2.15 – 1.71 (m, 90H), 1.11 (s, 52H), 0.94 (s, 93H). ^{13}C NMR (101 MHz, MeOD) δ 179.70, 179.46, 178.63, 168.91, 137.65, 126.32, 67.72, 67.26, 61.01, 60.71, 60.58, 55.04, 46.39, 46.02, 18.40, 17.60. M_w (theoretical) = 6693.88 g mol^{-1}, SEC (DMF) M_n =4808.6 g mol^{-1}, Đ = 1.78.

PolyHEMA6k-S-S-Bz (31)



Poly HEMA6k-OH (100 mg, 16.7 µmol) was dissolved in pyridine (186 µL, 2.30 mmol) and 1 mL of DCM in a vial equipped with magnetic stir bar. DMAP (18.7 mg, 15.2 µmol) and 3-((3-(benzyloxy)-3-oxopropyl)disulfanyl)propanoic anhydride (680 mg, 1.67 mmol) was added and the reaction was allowed to proceed for 16 hours at room temperature. The reaction was monitored using ^{13}C-NMR looking for the retention of characteristic anhydride peak at ^{13}C NMR (101 MHz, $CDCl_3$) 167.37. The reaction mixture was diluted in 10 mL of chloroform and the organic phase washed trice with 2 mL of aqueous $NaHSO_4$ (10 wt%), trice with 2 mL of aqueous Na_2CO_3 (10wt%) and once with 2 mL of brine. The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. The resulting yellow viscous solid was washed with 5 mL of ether five times and dried under high vacuum. Product was collected as a yellow transparent solid (295 mg, 91.5 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.28 (m, 786H), 5.15 (s, 93H), 4.29 – 4.18 (m, 143H), 4.13 (s, 102H), 2.92 (dd, *J* = 8.5, 5.7 Hz, 200H), 2.77 (t, *J* = 7.3 Hz, 286H), 1.19 – 0.96 (m, 73H), 0.87 (d, *J* = 11.5 Hz, 118H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.62, 171.55, 171.45, 135.87, 135.79, 128.73, 128.45, 66.78, 49.31, 34.26, 34.10, 33.99, 33.22, 33.08, 25.76, 25.09. M_w (theoretical) = 21269,81.88 g mol^{-1}, SEC (DMF) M_n =19895.7 g mol^{-1}, Đ = 1.57.

General hydrogel formation method Thiol-ene

Rheological measurements were conducted on a TA Instruments (New Castle, DE, USA) Discovery Hybrid 2 (DHR2) rheometer. Curing was studied *in situ* using the TA UV-LED accessory with an Ø 20 mm quartz parallel plate setup, with a primary peak at 365 nm, and a measured intensity at the interface of 10 mW/cm^2. PEG10k-Gx-SH where x =1,2 or 3 was dissolved in water: EtOH (4:1 v%) together with PEG10k-Allyl in a one to one SH: allyl ratio at 30 wt% dry weight. Dimethoxy-2-phenylacetophenone (DMPA) (425 µmolar, 0.0036 wt% per dry weight). (for an absorbance of A =0.4, ε= 470). The solution was deposited in the rheometer, 30 seconds of baseline were collected followed by an UV exposure for 30 seconds for a total dose of 300 mJ/cm^2 after which a total of 240 seconds was recorded to ensure steady state. Time sweeps for a 300 seconds using strain (ϒ) = 1% and frequency (ω) = 1 Hz, were used to study gelation and measure crossover, to ensure all measurements were carried out in the linear viscoelastic region (LVR), complimentary frequency and amplitude sweeps were carried out from 0.01 to 100 rad/s and 0.01 to 100% strain. All measurements where performed in triplicates.

General hydrogel formation method Michael addition.

Rheological measurements were conducted on a TA Instruments (New Castle, DE, USA) Discovery Hybrid 2 (DHR2) rheometer, equipped with a Peltier plate-plate accessory, using a stainless-steel upper geometry (ø = 20 mm) at a temperature of 26˚C. The thiol-PEG (PEG10k-Gx-SH, where x =1, 2 or 3) was dissolved in water: EtOH (4:1 v/v) together with 25, 29 and 32µL of a 0.2 M stock solution of aqueous $NaHCO_3$ (1 equivalent per cross-link). The acrylate-PEG (PEG10k-Acryl, 1 eq. per thiol) was dissolved in a separate vial using water:EtOH (4:1 v/v). Both components were deposited separately in the rheometer (final composition 30 wt-% PEG) and mixed with a pre shear program of 30 rad/s for 3 seconds. Time sweeps were conducted at strain (ϒ) = 1% and frequency (ω) = 1 Hz, for a total of 3000 seconds, to study gelation and measure crossover. To ensure all measurements were carried out in the linear viscoelastic region (LVR), complimentary frequency and amplitude sweeps were carried out from 0.01 to 100 rad/s and 0.01 to 100% strain. All measurements where performed in triplicates.

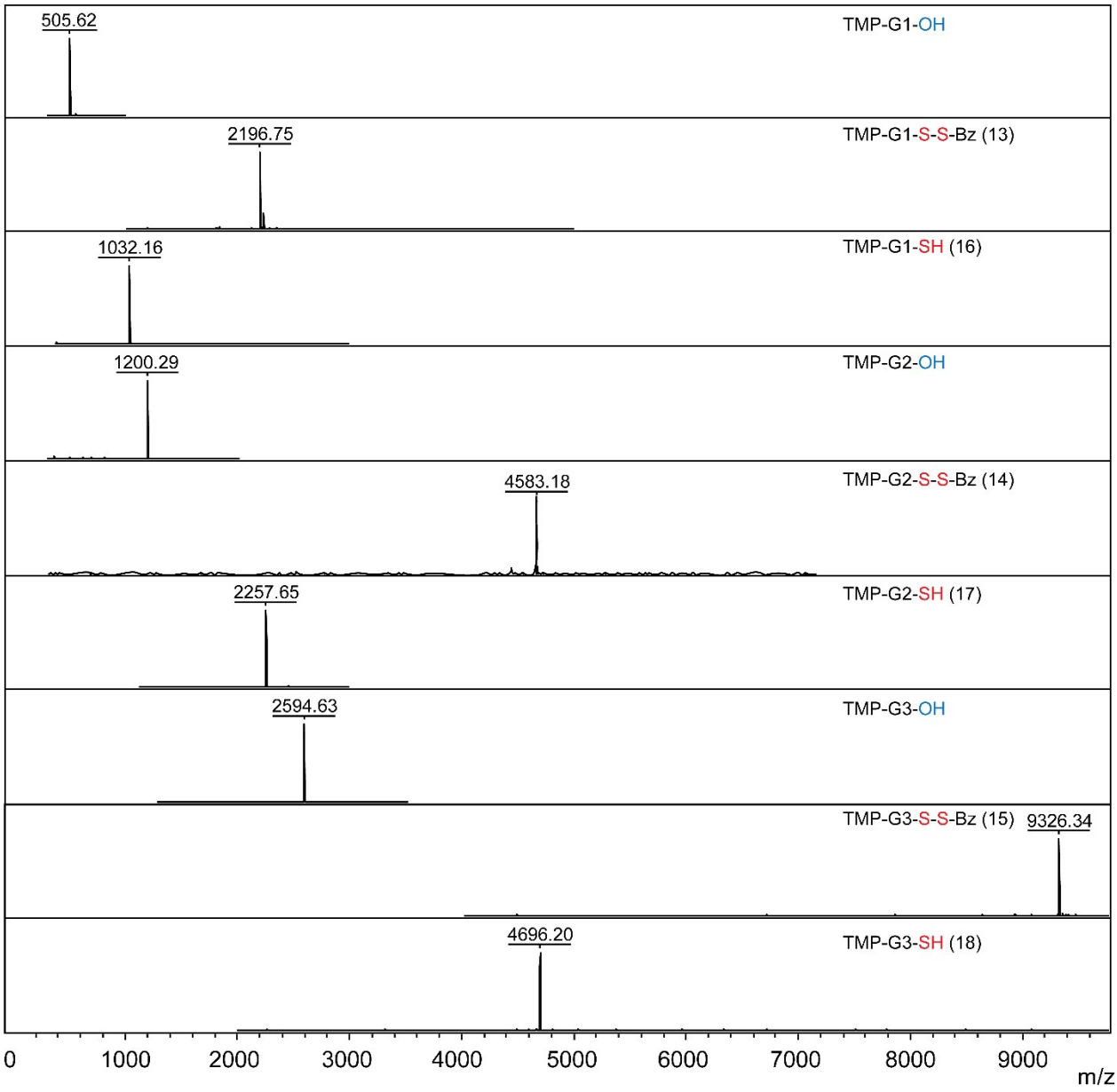


Figure S1 MALDI-TOF-MS of dendritic structures TMP-Gx-OH, TMP-Gx-S-S-Bz (**13**-**15**) and TMP-Gx-SH (**16**-**18**) where x = 1, 2 and 3.

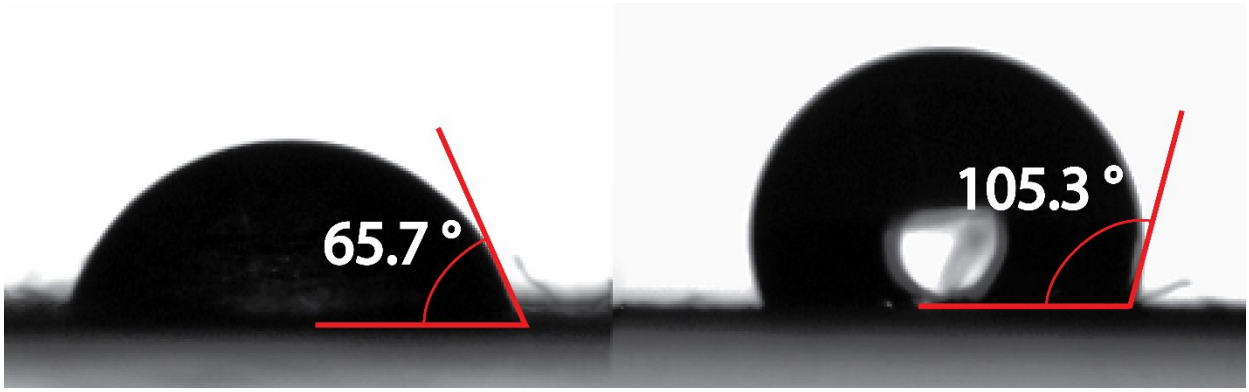


Figure S2 typical contact angle of Filter Paper-SH (left) and Filter paper-S-S-Bz (Right). Filter paper-OH both treated the same as samples mentioned and untreated had a contact angle of 0.

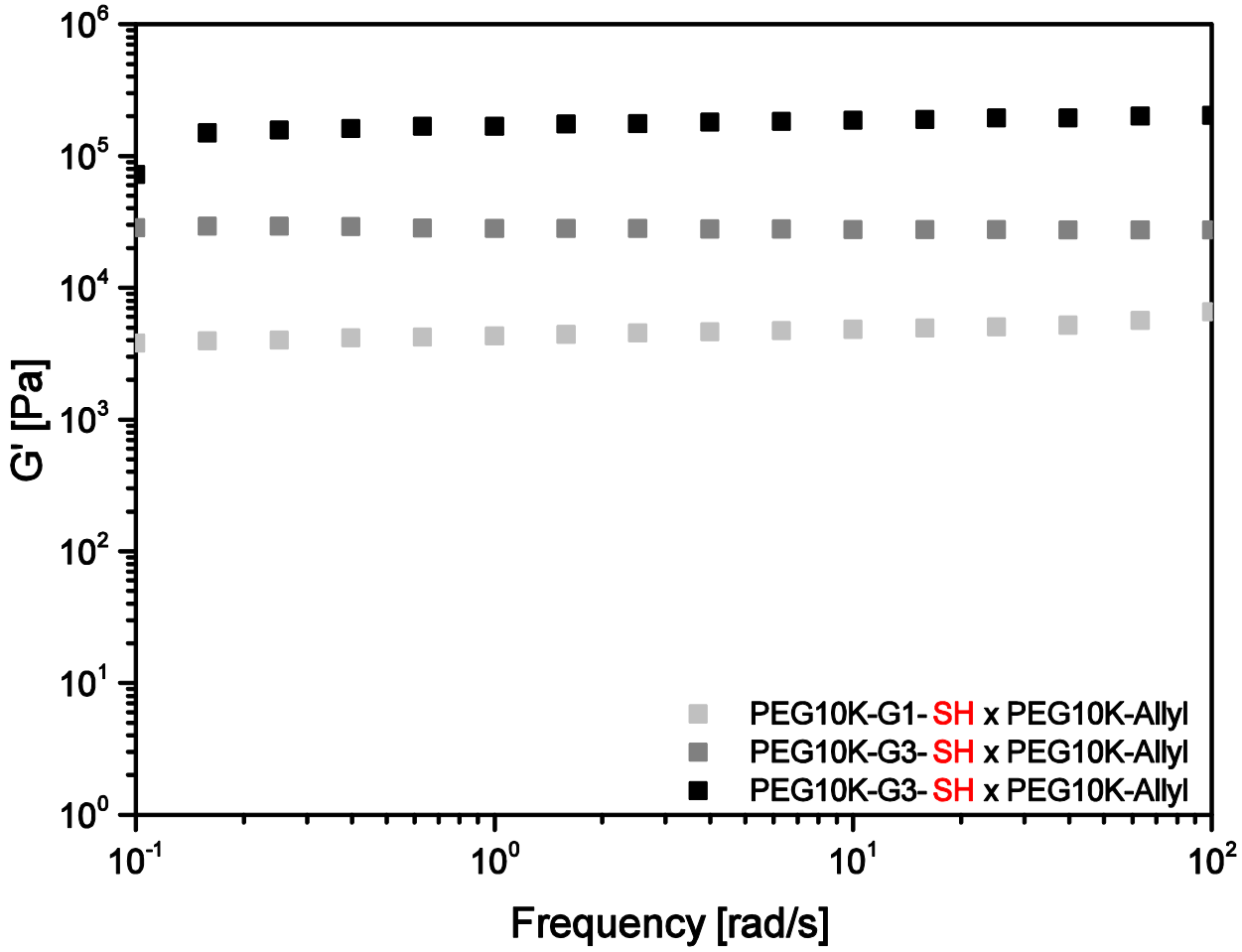


Figure S3 Frequency sweep of gels formed from PEG10k-Gx-SH with PEG10k-Allyl where x = 1, 2 and 3, further rheological measurements where preformed at 1Hz (6.28 rad s^{-1}).

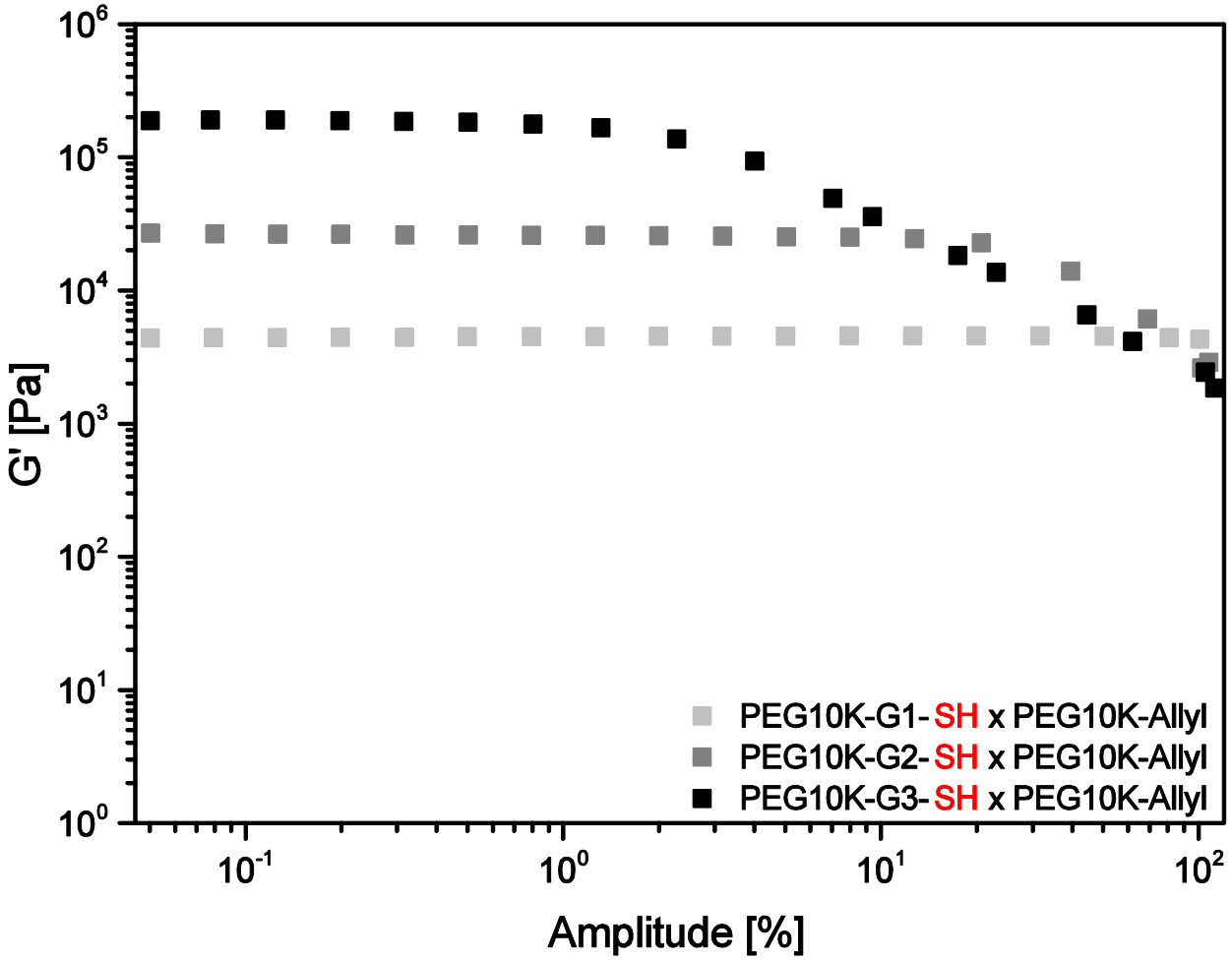


Figure S4 Amplitude sweep of gels formed from PEG10k-Gx-SH with PEG10k-Allyl where x = 1, 2 and 3, further rheological measurements where preformed at 1% strain.

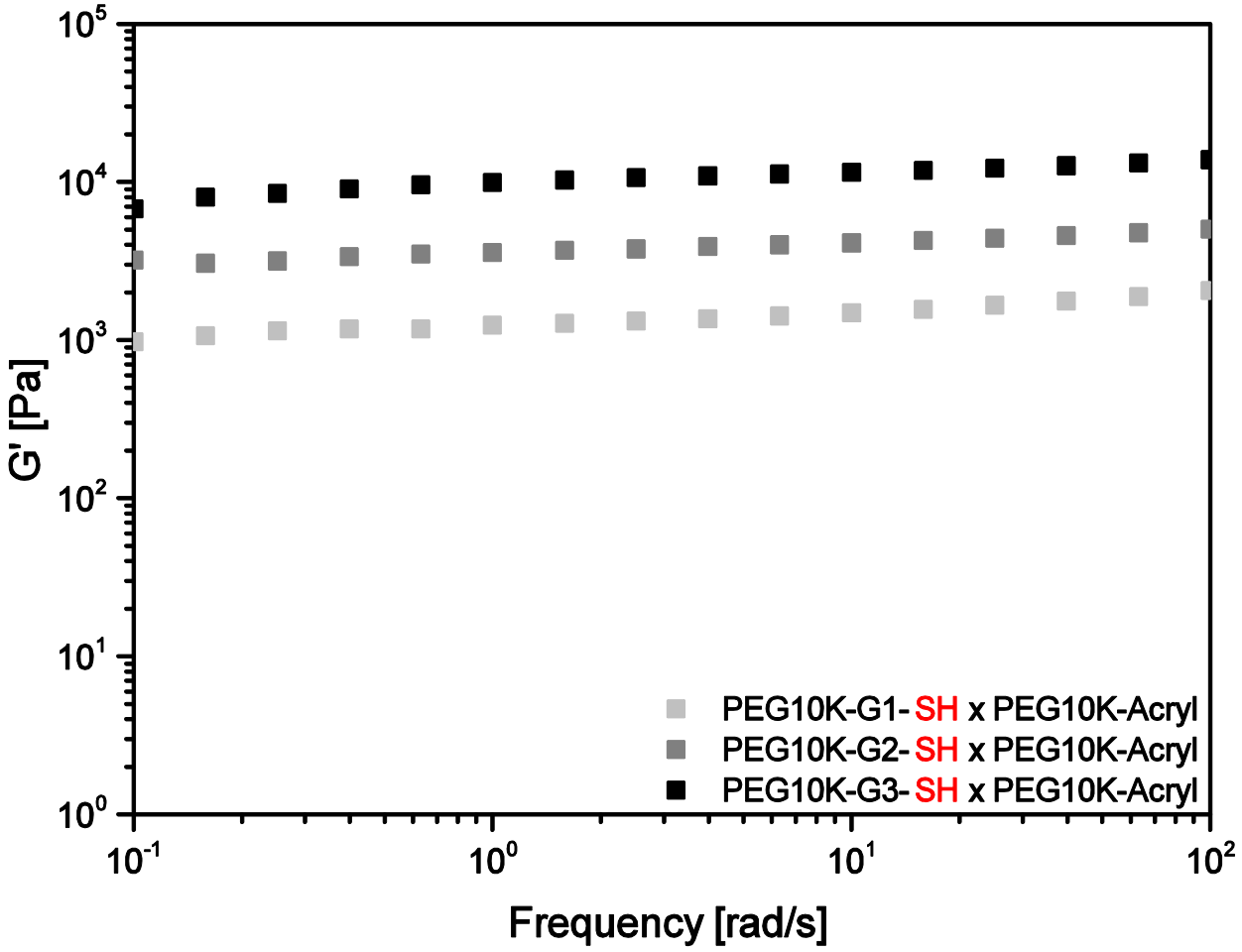


Figure S5 Frequency sweep of gels formed from PEG10k-Gx-SH with PEG10k-acryl where x = 1, 2 and 3, further rheological measurements where preformed at 1Hz (6.28 rad s^{-1}).

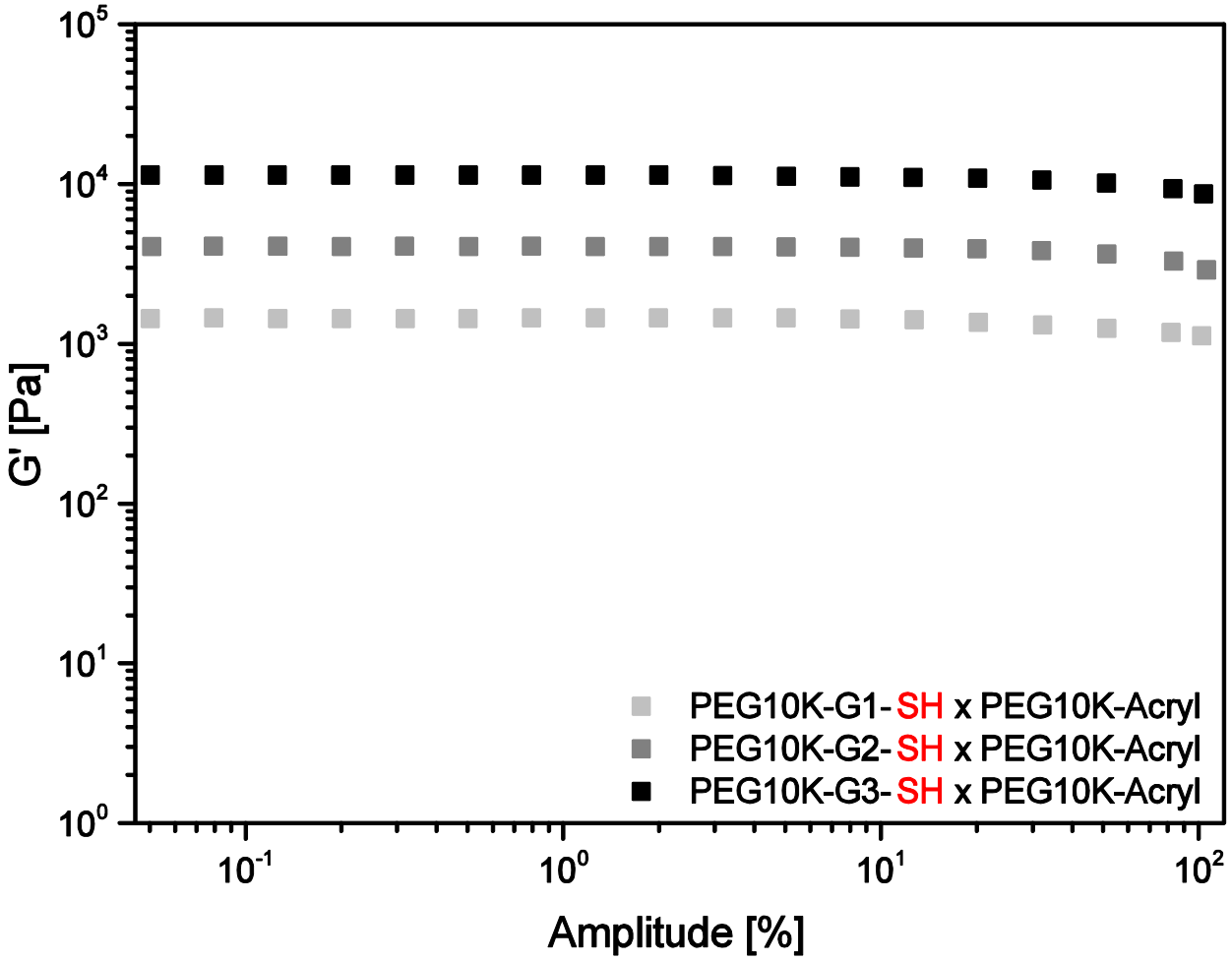


Figure S6 Amplitude sweep of gels formed from PEG10k-Gx-SH with PEG10k-acryl where x = 1, 2 and 3, further rheological measurements where preformed at 1% strain.

1. O. C. J. Andren, Y. N. Zhang, P. Lundberg, C. J. Hawker, A. M. Nystrom and M. Malkoch, *Chem Mater*, 2017, **29**, 3891-3898.