Supplementary information

One-pot multistep reactions based on thiolactones: extending the realm of thiol-ene chemistry in polymer synthesis

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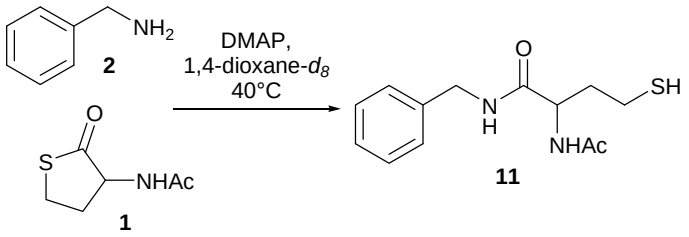
Methods

^{1}H- and ^{13}C-NMR (Attached Proton Test, APT) spectra were recorded in $CDCl_3$ (Eurisotop), DMSO-d_6 (Eurisotop) and 1,4-dioxane-d_8 (Aldrich) on a Bruker AM500 spectrometer at 500 MHz or on a Bruker Avance 300 at 300 MHz. An Agilent technologies 1100 series LC/MSD system equipped with a diode array detector and single quad MS detector (VL) with an electrospray source (ESI-MS) was used for classic reversed phase LC-MS (liquid chromatography mass spectroscopy) and MS analysis. Analytic reversed phase HPLC was performed with a Phenomenex C_{18} (2) column (5 µ, 250 x 4.6 mm) using a solvent gradient (0 → 100% acetonitrile in H_2O in 15 min) and the eluting compounds were detected *via* UV-detection (λ = 214 nm). FT-ATR-IR spectra were recorded on a Perkin-Elmer Spectrum1000 FTIR infrared spectrometer with pike-HATR module. Size Exclusion Chromatography (SEC) was performed on a Waters instrument, with a refractive-index (RI) detector (2414 Waters), equipped with 3 Polymer Standards Services GPC serial columns (1 X GRAM Analytical 30 Å, 10 µm and 2 x GRAM Analytical 1000 Å, 10 µm) at 35 °C. Poly(methyl methacrylate) (PMMA) standards were used for calibration and N,N-dimethylacetamide (DMA), containing LiBr (0.42 g/mL) was used as an solvent at a flow rate of 1 mL/min. Molecular weight and polydispersity index were determined using the Empower software. UV curing was performed by irradiation with 300 nm UV lamps (8 x 25 W) positioned in a metal cylindrical container.

Materials

1,6-Hexanediamine (Acros, 99.5+%), 2,2,4-trimethylpentane (iso-octane, Sigma Aldrich, HPLC), 2,2-dimethoxy-2-phenyl acetophenone (DMPA, Acros, 99%), 4,9-dioxadodecanediamine (Acros, 97%), 4-dimethylaminopyridine (DMAP, Aldrich, 99%), allyl chloroformate (Aldrich, 97%), benzylamine (Acros, 99.5+%), bicyclo[2.2.1]-2-heptene (norbornene, Fluka, ~97%), chloroform (Fisher Scientific, HPLC grade), dichloromethane (Sigma-Aldrich, HPLC), DL-homocysteine thiolactone hydrochloride (Fluka, ≥ 99%), DL-*N*-acetylhomocysteine thiolactone (Aldrich, 99%), ethanolamine (Fluka, ≥ 99%), ethyl acetate (Fluka, HPLC), Jeffamine® D-series (Huntsman) and methanol (Sigma Aldrich, HPLC grade) were used as received. 1,4-Dioxane (Acros, HPLC grade) was degassed (purged with Argon during 30 min) prior to use as a reaction solvent. Silicagel (ROCC, SI 1721, 60 Å, 40 – 63 μm) was used to perform preparative column chromatography, eluting with HPLC-grade solvents. The collected fractions were analyzed by thin layer chromatography (TLC-plates, Macherey-Nagel, SIL G-25 UV_{254}).

Kinetic study of the aminolysis reaction *via* online ^{1}H-NMR monitoring



Scheme S1 - Kinetic study of the aminolysis reaction via online ^{1}H-NMR monitoring: reaction between benzylamine and *N*-acetylhomocysteïne thiolactone.

N-Acetylhomocysteine thiolactone **1** (58 mg, 0.3643 mmol) and DMAP (2.2 mg, 0.0180 mmol) were dissolved in 1,4-dioxane-d_8 (600 μL) in an NMR tube. Iso-octane (20 μL) was used as an internal standard (reference peak at 0.90 ppm [$C(CH_3)_3$]). The reaction was started (t = 0) with the subsequent addition of benzylamine **2** (20 μL, 0.1829 mmol) (Scheme S1). The reaction medium was sealed and from that moment on, the sample was analyzed every 10 minutes *via* ^{1}H-NMR spectroscopy (500 MHz at 40 °C) with a delay of 15 minutes for the first measurement. The consumption of benzylamine **2** was monitored by the decrease of the signal of the corresponding benzylic protons in the ^{1}H-NMR spectrum (δ = 3.76 ppm). The results are depicted in the figure below (Figure S1). All spectra were calibrated according to the chemical shift of the solvent signal (1,4-dioxane-d_8, δ = 3.53 ppm).

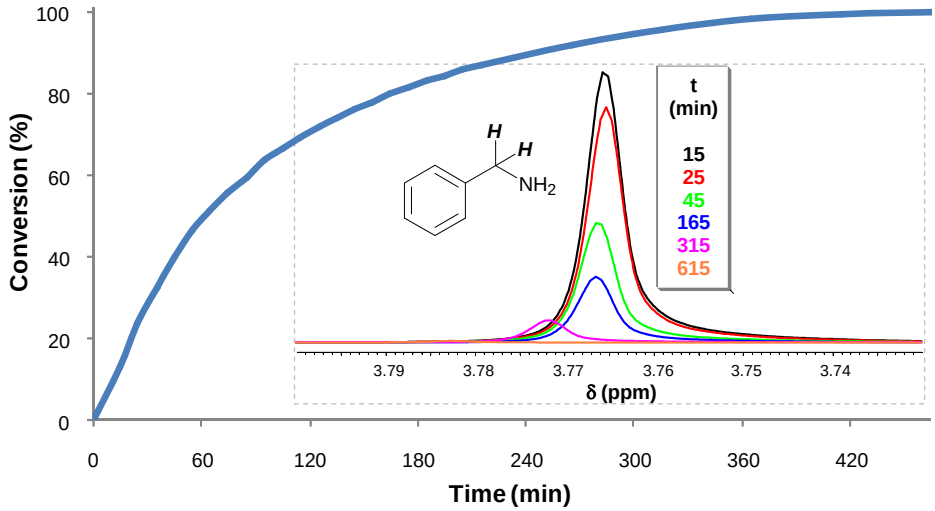
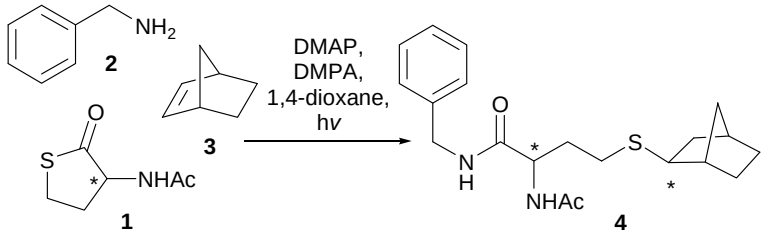


Figure S1 – Aminolysis of *N*-acetylhomocysteine thiolactone **1**: conversion of benzylamine **2** as a function of time. Insert: detail of the ^{1}H-NMR spectrum (500 MHz, 1,4-dioxane-d_8, 40 °C) representing the benzylic protons of benzylamine **2** and their decrease in time.

Model conjugation reaction between benzylamine, *N*-acetylhomocysteine thiolactone and norbornene



Scheme S2 – Model amine-thiol-ene conjugation reaction.

Table S1 – Relative initial quantities of reactants/reagents in the model reaction.

Entry	**1**	**2**	**3**	DMAP	DMPA	Time (h)
(1)	2	1	-	0.2	-	2
(2)	2	1	1.2	0.2	0.1	2
(3)	-	1	-	-	0.1	3
(4)	2	1	5	0.1	-	6

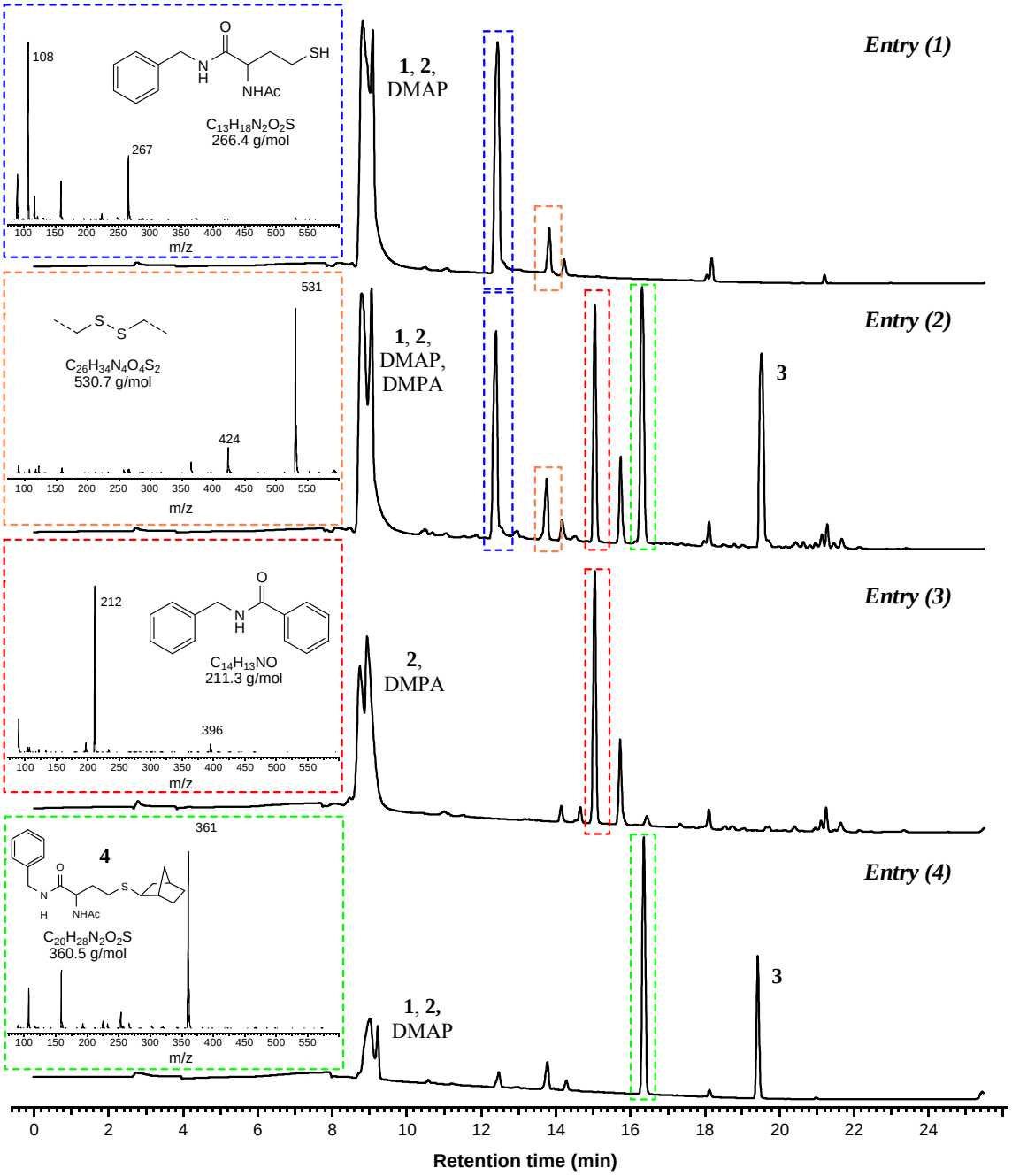


Figure S2 - LC-MS analysis of the crude reaction mixtures, corresponding to *entries (1)* → *(4)* in Table S1. Inserts: ESI-MS spectra of relevant compounds of the model reaction.

Detailed procedure (*entry 4*) and characterization of conjugation compound **4**

To a solution of norbornene **3** (861 mg, 9.146 mmol) in degassed 1,4-dioxane (6 mL) were sequentially added benzylamine **2** (200 µL, 1.830 mmol), DMAP (22.4 mg, 0.183 mmol) and *N*-acetylhomocysteine thiolactone **1** (582 mg, 3.658 mmol). The reaction medium was sealed and stirred during 6 hours at 40 °C while being cured by UV light. The reaction mixture was filtered over a short path of silica gel to quench the reaction, the silica was rinsed with EtOAc and the eluent was concentrated. Purification of the crude mixture (Figure S2, bottom) by column chromatography (silicagel, EtOAc) yielded the compound **4** (528 mg, 1.465 mmol, 80%) as a white solid. $C_{20}H_{28}N_2O_2S$ (360.51 g/mol); *m/z* (ESI-MS) 361; ν_{max} / cm^{-1} 3313, 3258, 2950, 2868, 1649, 1546, 1452, 1369, 1287, 1070, 1029, 1016, 748, 705, 677, 596, 582, 544.

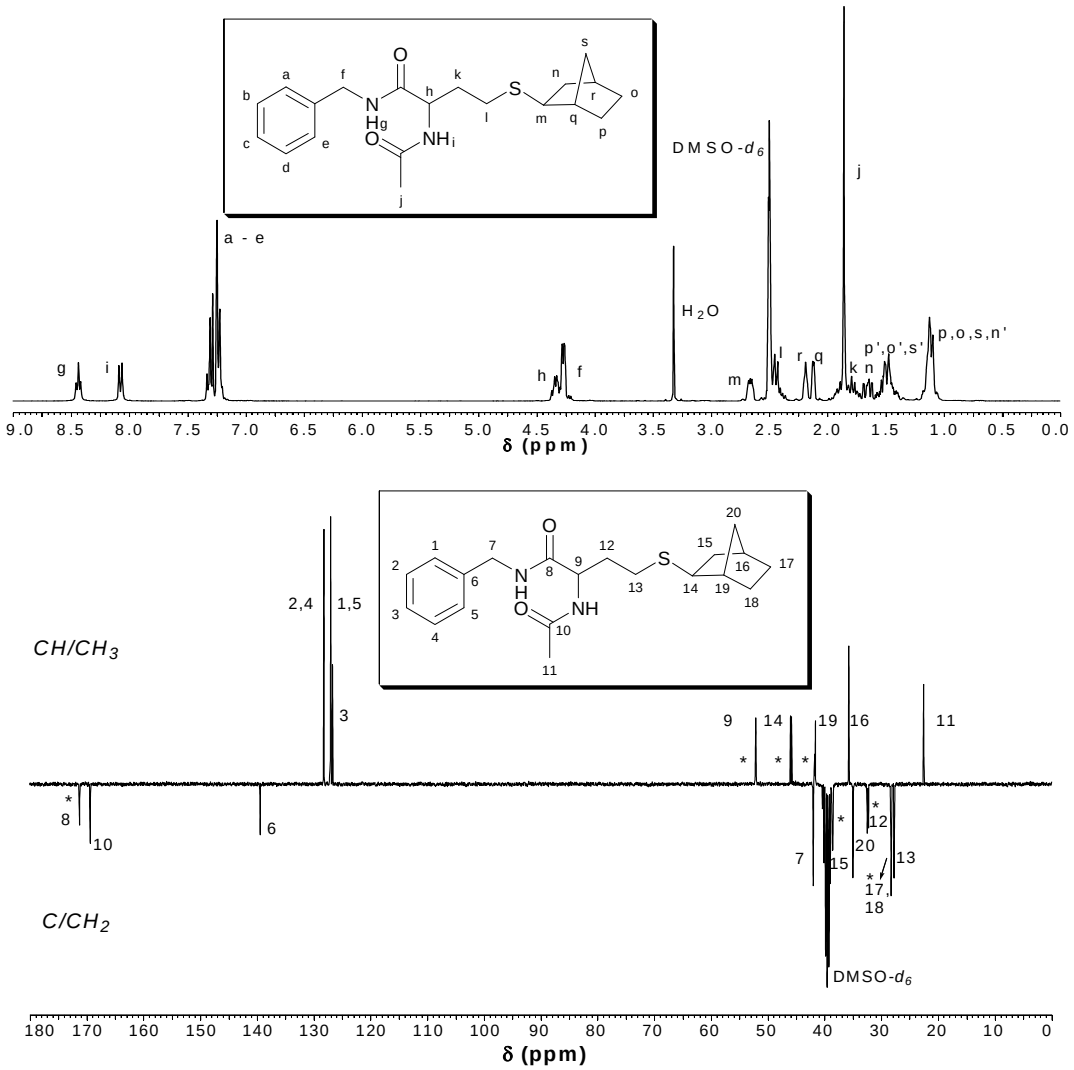
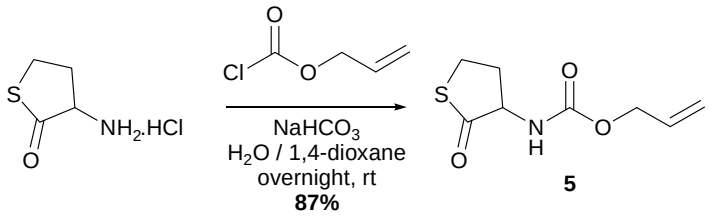


Figure S3 – NMR-analysis and structure elucidation of the conjugation compound **4**. 2D-NMR techniques allowed for the full assignment of the corresponding ^{1}H-NMR (300 MHz, DMSO-d_6, top) and the ^{13}C-NMR (APT, 75 MHz, DMSO-d_6, bottom) spectra. Because the reaction was performed with racemic *N*-acetylhomocysteine thiolactone **1** and the thiyl radical adds to the *exo* side[1] of a norbornene double bond in a non-enantioselective way, compound **4** is a mixture of diastereoisomers and consequently some signals (*) in the APT spectrum are split.

Synthesis of AB' type monomer, *N*-(allyloxy)carbonylhomocysteine thiolactone 5



DL-Homocysteine thiolactone hydrochloride (28 g, 0.1823 mol) was slowly added to a solution of $NaHCO_3$ (76.44 g, 0.91 mol) in H_2O/1,4-dioxane (1/1, 400 mL) and this mixture was stirred for 30 minutes. Allyl chloroformate (38.76 mL, 0.3644 mol) was added dropwise and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with brine (800 mL) and extracted with EtOAc (4 x 800 mL). The organic phase was dried ($MgSO_4$). The drying agent was filtered and the resulting clear solution was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH: 98/2) to furnish the title compound **5** (32.23 g, 0.1602 mmol, 87% yield) as a white solid. $C_8H_{11}NO_3S$ (201.24 g/mol); *m/z* (ESI-MS) 202, 174, 130, 113; ν_{max} / cm^{-1} 3307, 1691, 1546, 1445, 1302, 1267, 1249, 1174, 1098, 1056, 925, 851, 778, 762, 686, 655, 615, 582, 557; ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 5.90 (*ddt*, 17.2, 10.4, 4.7 Hz, 1H), 5.30 (*m*, 1H), 5.29 (*ddd*, 17.2, 3.0, 1.5 Hz, 1H), 5.25 (*ddd*, 10.4, 2.6, 1.3 Hz, 1H), 4.57 (*dt*, 17.2, 5.6, 1.4 Hz, 2H), 4.32 (*m*, 1H), 3.28 (*m*, 2H), 2.83 (*m*, 1H), 2.01 (*m*, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, ppm) δ 205.1 (C), 156.2 (C), 132.6 (CH), 118.2 (CH_2), 66.2 (CH_2), 60.9 (CH), 32.0 (CH_2), 27.3 (CH_2).

Radical (photo)polymerization of Alloc-TL 5: linear polymer

A solution of *N*-(allyloxy)carbonylhomocysteine thiolactone **5** (402 mg, 2 mmol) in 1,4-dioxane (1 mL) was treated with DMAP (49 mg, 0.4 mmol), DMPA (25 mg, 0.1 mmol) and ethanolamine (241 µL, 4 mmol) and irradiated with UV light during 1 h. The liquid fraction was decanted. The obtained white precipitate was rinsed with $CHCl_3$ (4 x 1.5 mL), dried, redissolved in MeOH (1.5 mL) and precipitated in cold $CHCl_3$ (15 mL). Decantation and drying yielded a white solid, which was subjected to analysis. ν_{max} / cm^{-1} 3425, 2924, 1710, 1248, 1058; M_n^{SEC} 22 kDa; PDI 1.6; M_n^{NMR} 7.8 kDa.

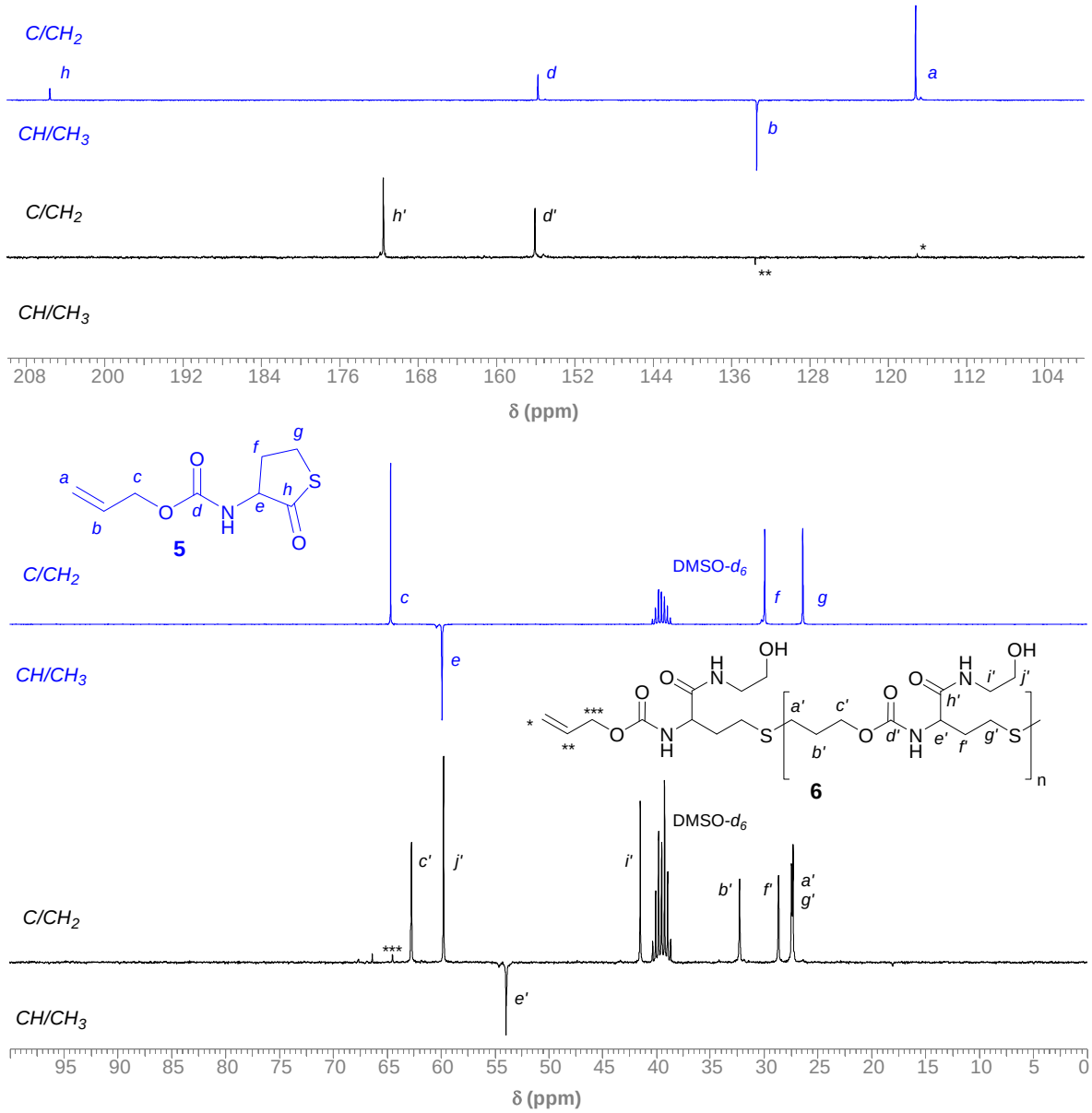


Figure S4 - ^{13}C-NMR-analysis (APT, 75 MHz, DMSO-d_6) and structure elucidation of the AB' type monomer **5** and the linear polythioether/polyurethane **6**. The allyl endgroup of the linear polymer **6** was detected in the corresponding APT spectrum (*, ** & ***).

Radical (photo)polymerization of Alloc-TL 5: network film

A solution of *N*-(allyloxy)carbonylhomocysteine thiolactone **5** (402 mg, 2 mmol) in 1,4-dioxane (1 mL) was treated with DMAP (49 mg, 0.4 mmol), DMPA (25 mg, 0.1 mmol) and 4,9-dioxadodecanediamine (204 mg, 1 mmol). The homogeneous reaction mixture was injected between 2 glass plates, separated by a silicon spacer (1 mm) and irradiated with UV light during 3 h. The obtained clear, yellow and non-tacky film was washed several times with dioxane and dried.

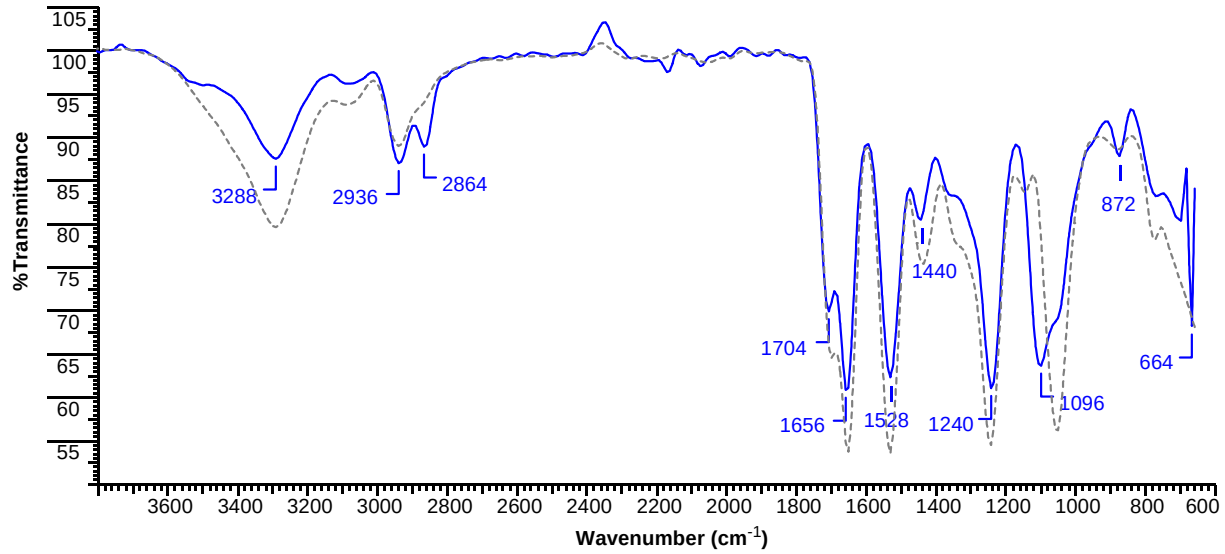


Figure S5 – Overlay of the FT-ATR-IR spectra of the network film **8** (4,9-dioxadodecanediamine as cross-linker) and the linear polythioether/polyurethane **6**.

References

(1) Cristol, S. J.; Brindell, G. D. *J. Am. Chem. Soc.* **1954**, *76*, 5699-5703.