Electronic Supporting Information

Sequence-defined oligoampholytes using hydrolytically stable vinyl sulfonamides: design and UCST behaviour

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Table of contents

Figure S1

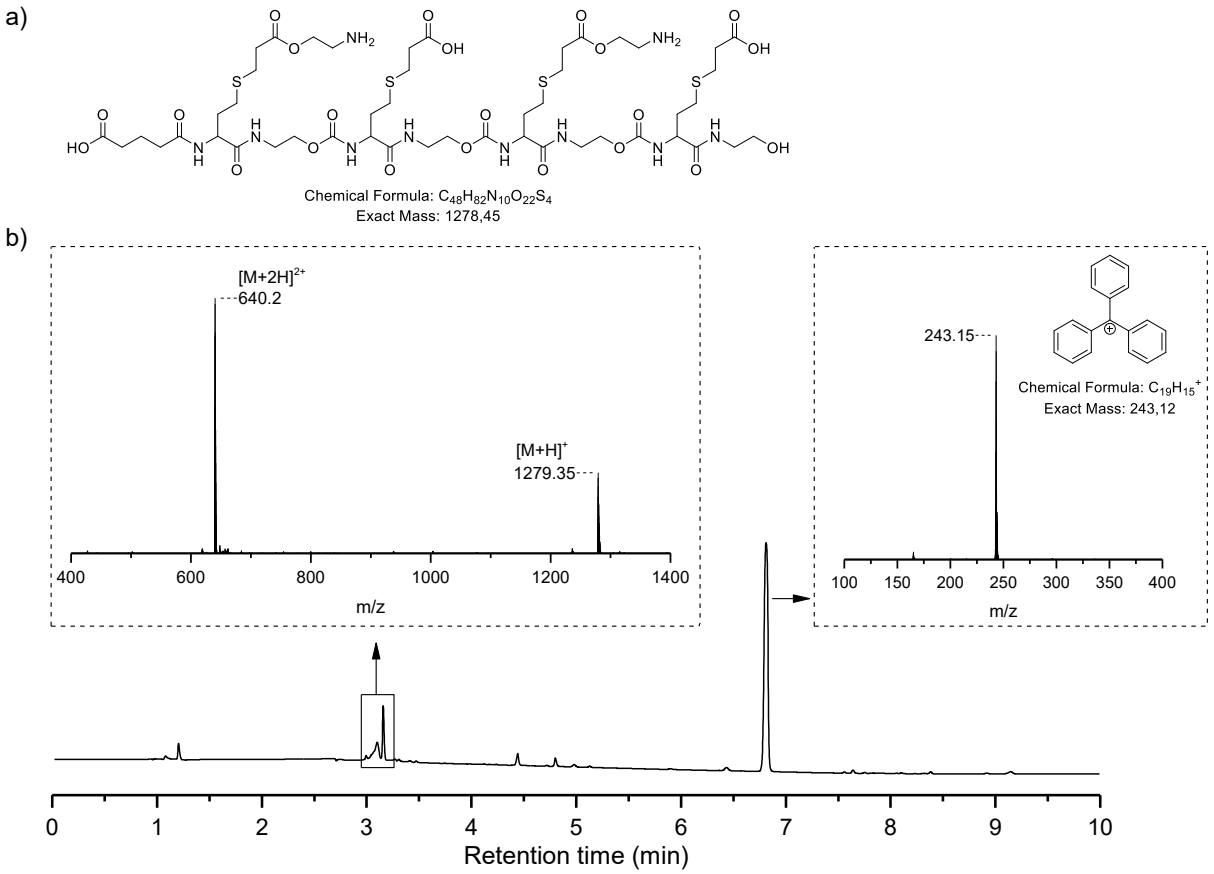


Figure S1: Tetramer with alternating carboxylic acid and primary amine side-chain functionalities: a) molecular structure, b) LCMS analysis (λ = 214 nm).

Figure S2

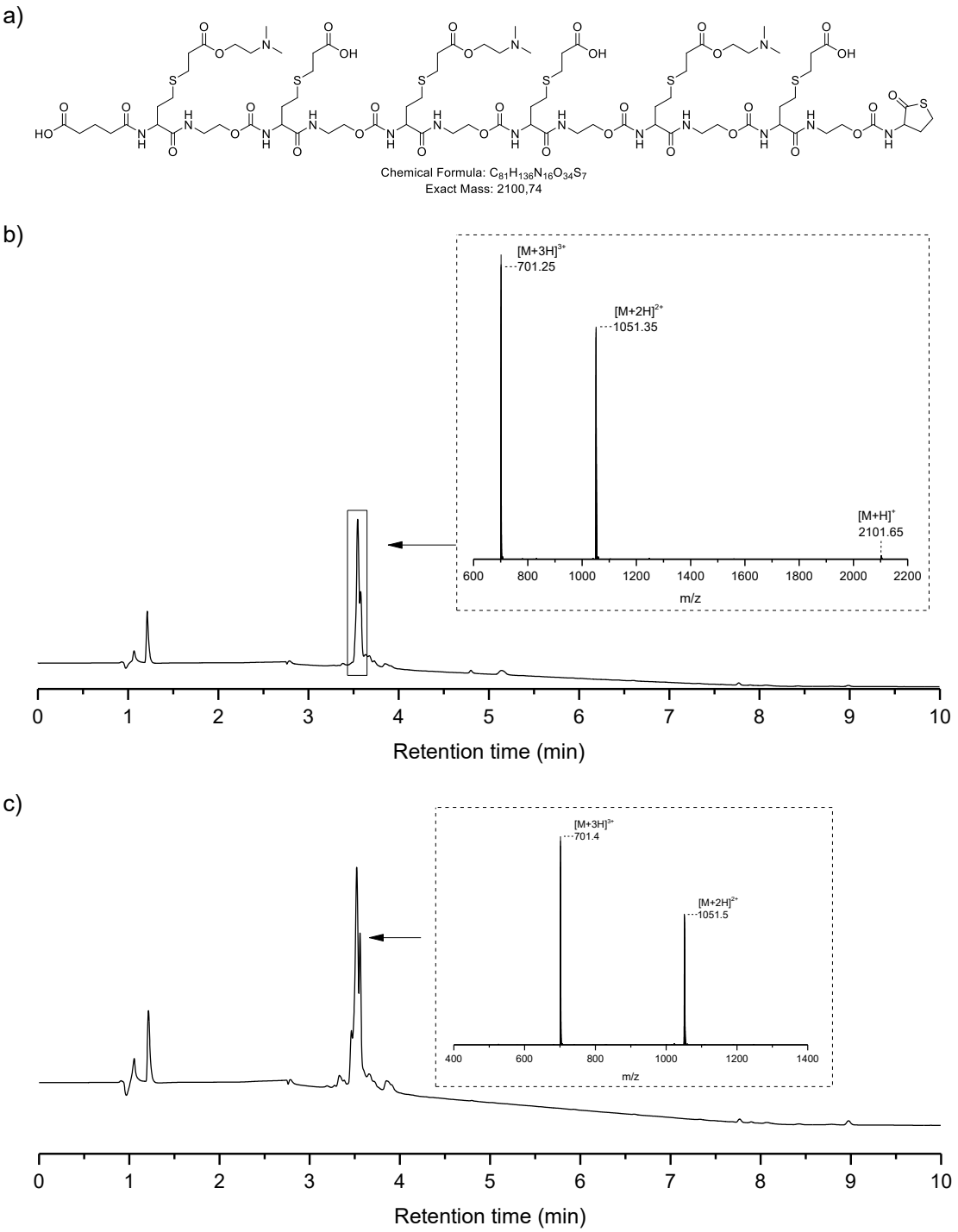


Figure S2: Hexamer with alternating carboxylic acid and tertiary amine side-chain functionalities: a) molecular structure, b) LCMS analysis (λ = 214 nm) of the oligomer that was synthesised manually and c) using the automated procedure.

Figure S3

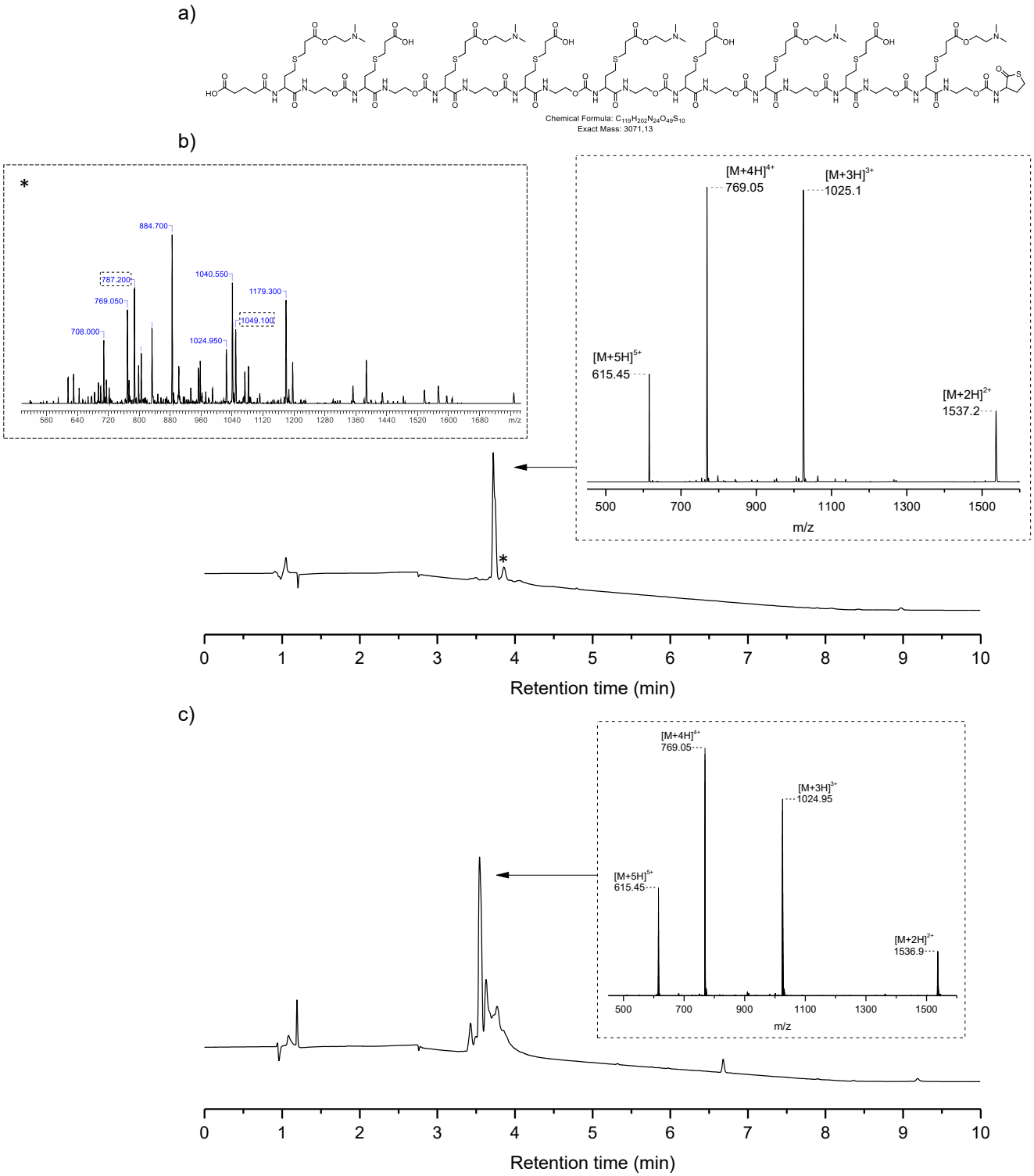
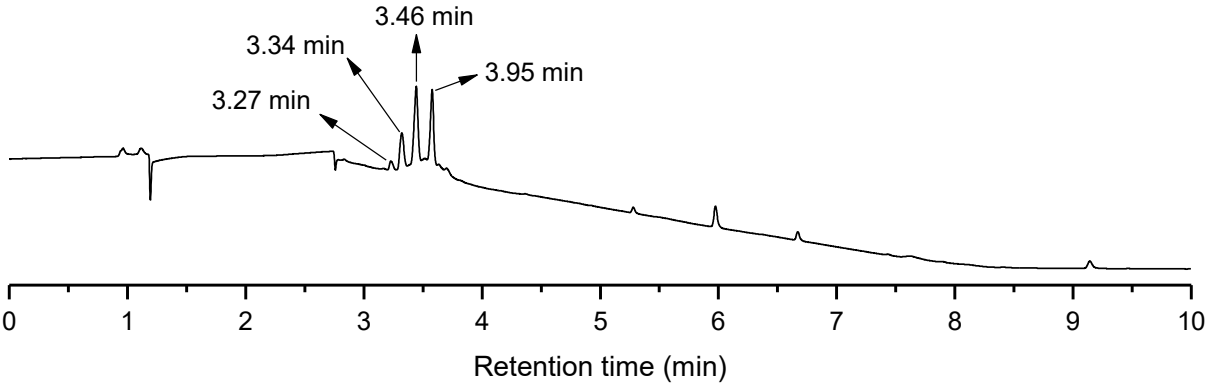
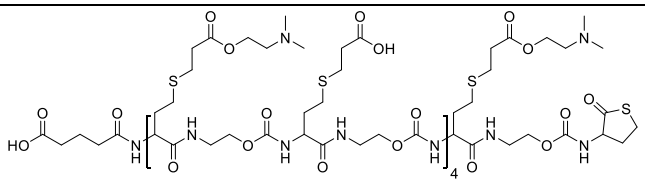
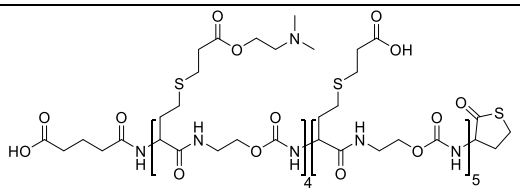
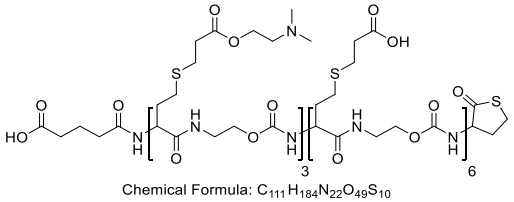
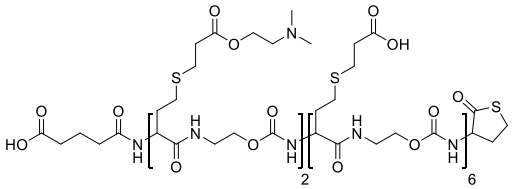


Figure S3: Nonamer with alternating carboxylic acid and tertiary amine side-chain functionalities: a) molecular structure, b) LCMS analysis (λ = 214 nm) of the oligomer that was synthesised manually and c) using the automated procedure. *Unassigned impurity, the mass spectrum indicates the presence of multiple products. The indicated masses could be assigned to an oligomer with a single protected carboxylic acid group.

Figure S4



Retention time (min)	**Structure**
3.95	 Chemical Formula: $C_{119}H_{202}N_{24}O_{49}S_{10}$ Exact Mass: 3071,13
3.46	 Chemical Formula: $C_{115}H_{193}N_{23}O_{49}S_{10}$ Exact Mass: 3000,05
3.34	 Chemical Formula: $C_{111}H_{184}N_{22}O_{49}S_{10}$ Exact Mass: 2928,98
3.27	 Chemical Formula: $C_{107}H_{175}N_{21}O_{49}S_{10}$ Exact Mass: 2857,91

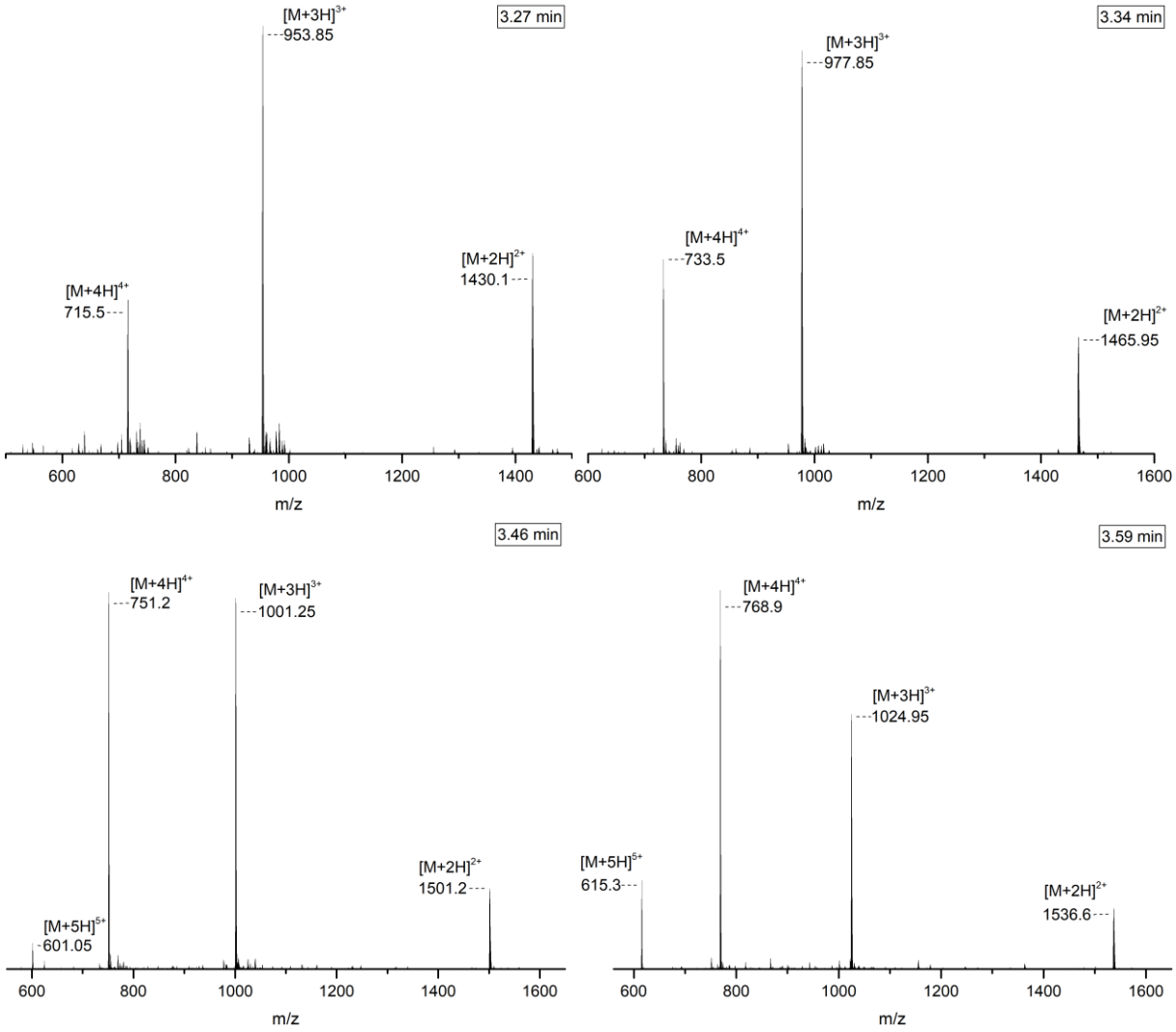


Figure S4: LCMS analysis (λ = 214 nm) of an alternating nonamer (see Figure S3a) after storage for 6 months on resin at room temperature. Besides the intact oligomer, several degradation products were observed, resulting from the hydrolysis of the β-thioester amine side-chains.

Figure S5

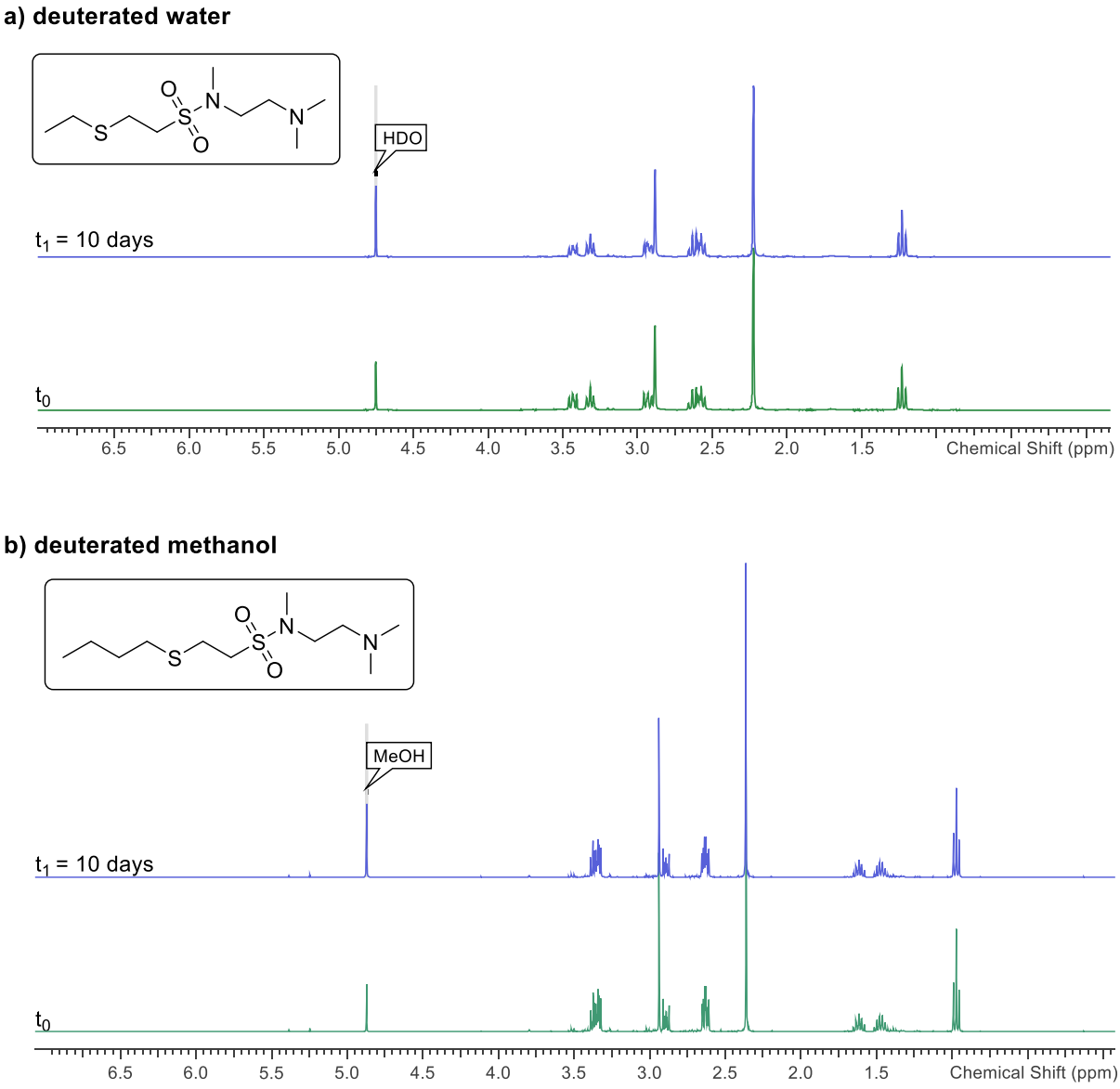


Figure S5: Stability of thiol-Michael adduct of an alkyl thiol and *N*-(2-(dimethylamino)ethyl)-*N*-methylethenesulfonamide assessed by ^{1}H NMR spectroscopy in a) deuterated water and b) deuterated methanol.

Figure S6

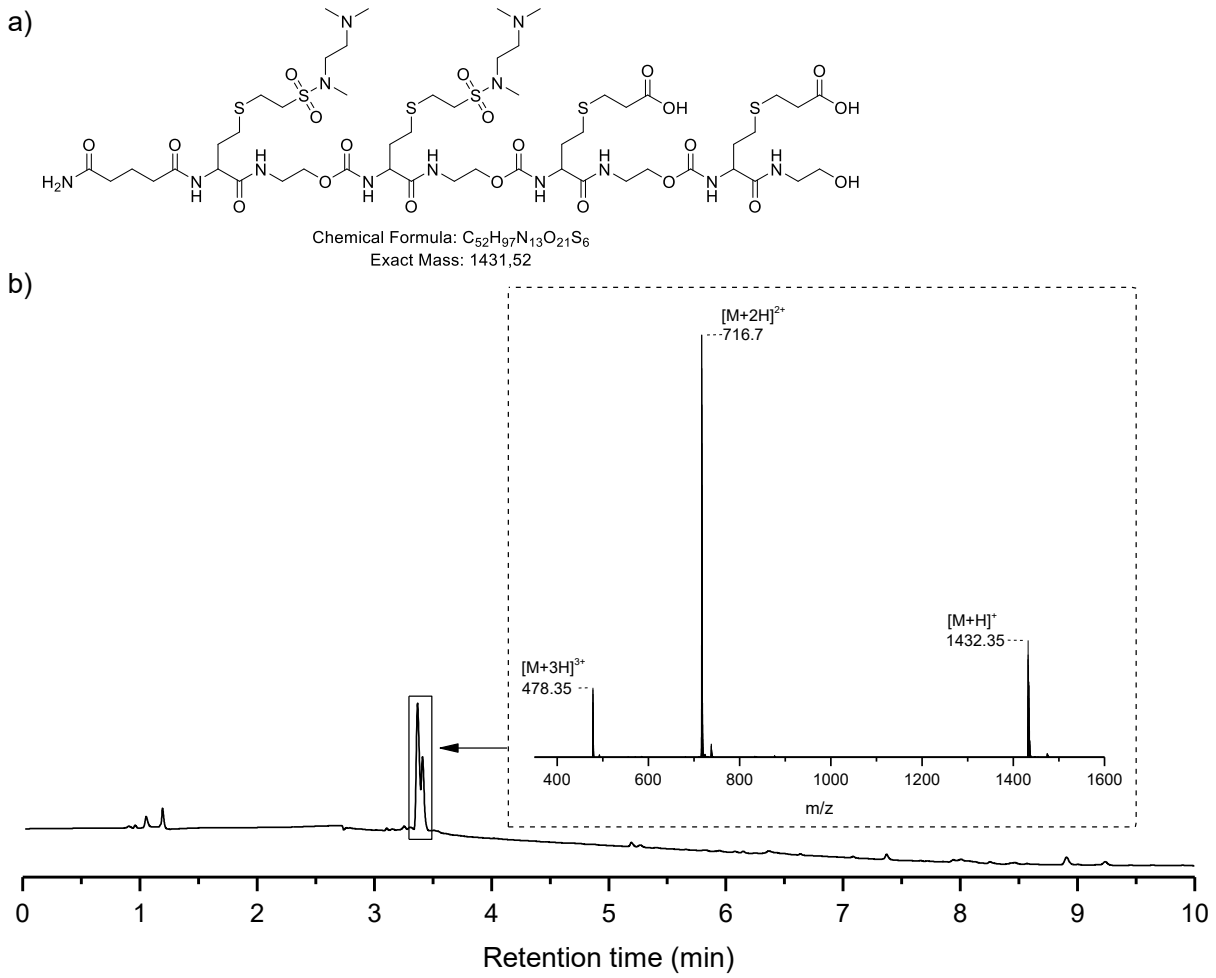


Figure S6: Tetramer (*block*)-CCAA synthesised manually: a) molecular structure, b) LCMS analysis (λ = 214 nm).

Figure S7

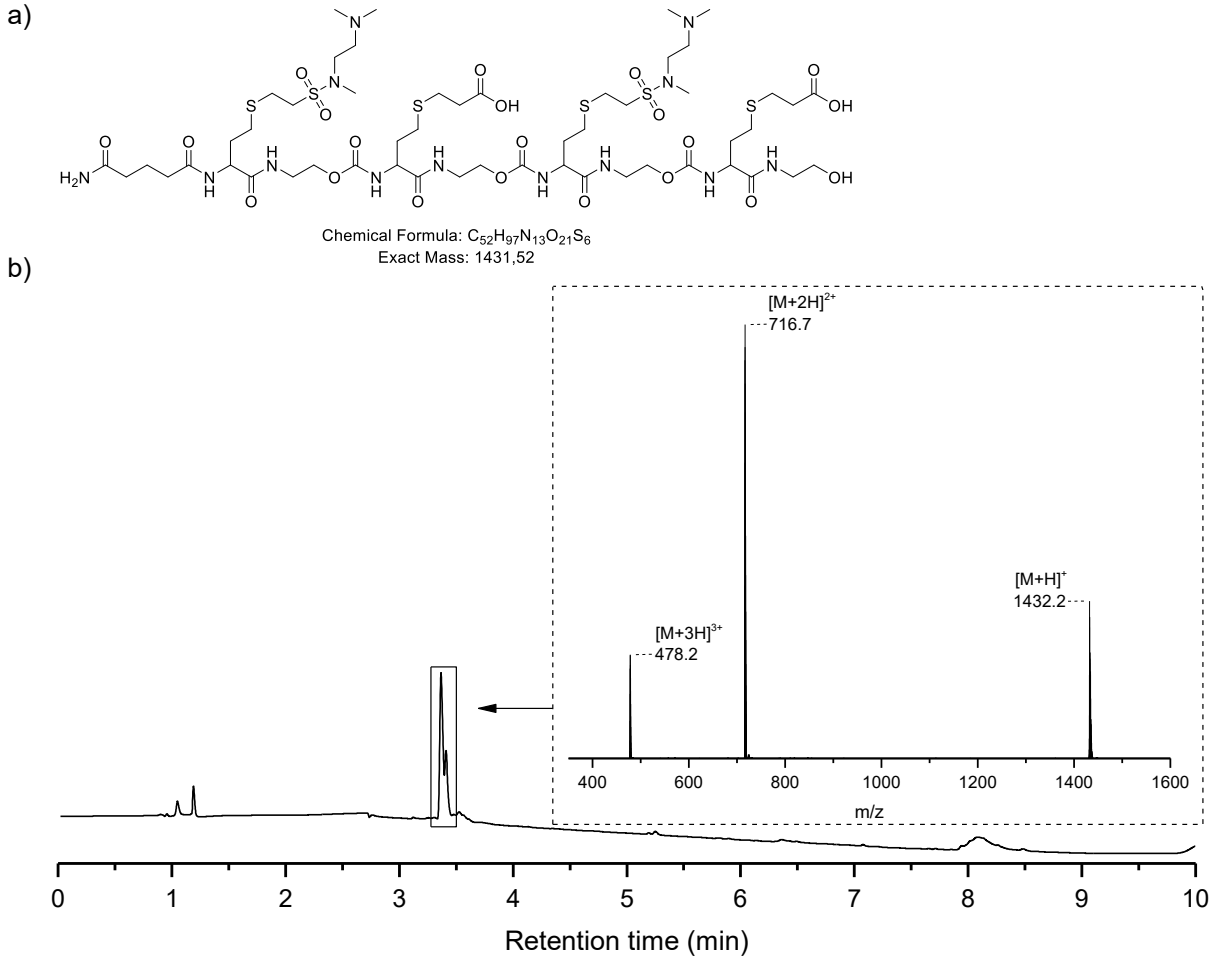


Figure S7: Tetramer (*alt*)-CACA synthesised manually: a) molecular structure, b) LCMS analysis (λ = 214 nm).

Figure S8

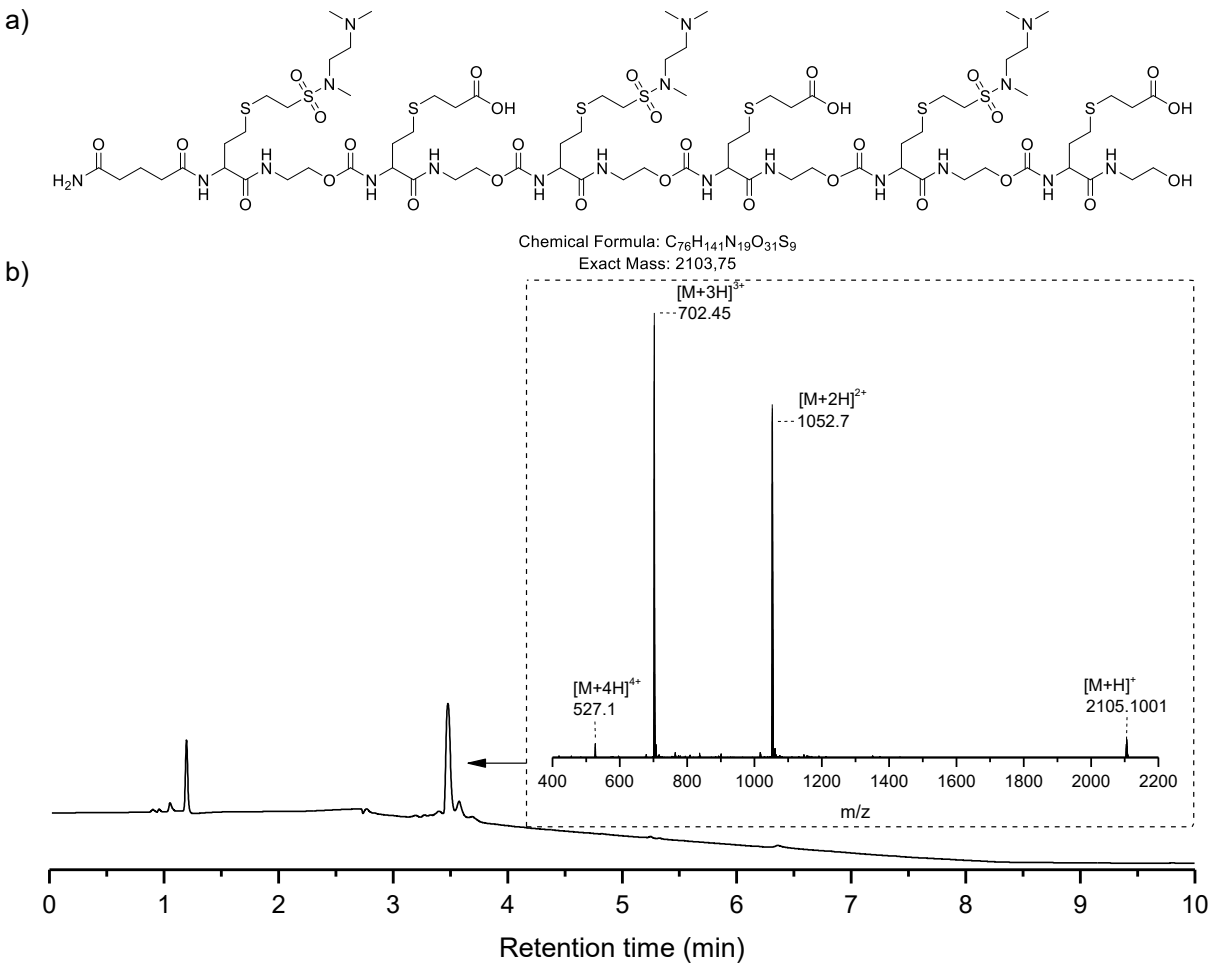


Figure S8: Hexamer (*alt*)-CACACA synthesised manually: a) molecular structure, b) LCMS analysis (λ = 214 nm).

Figure S9

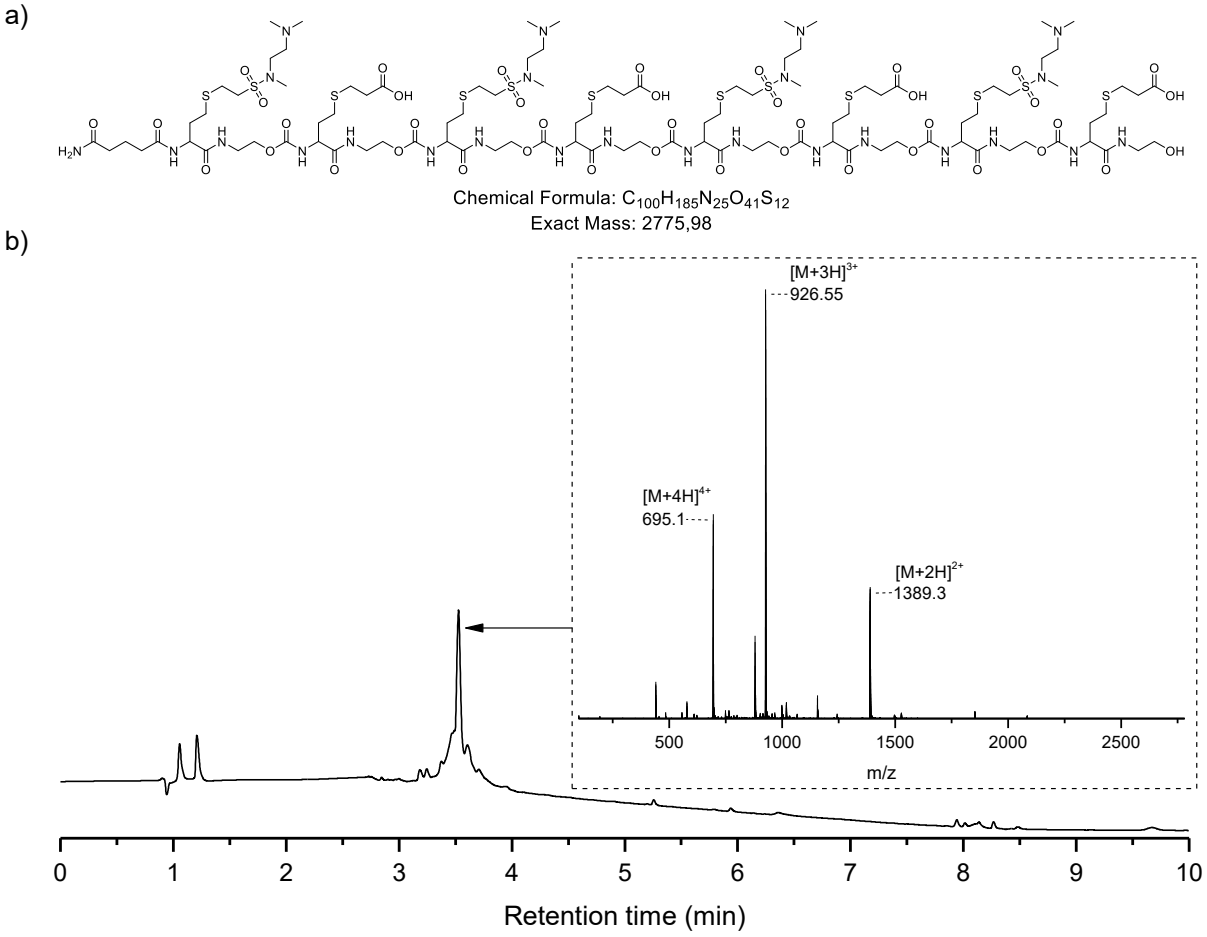


Figure S9: Octamer (*alt*)-CACACACA synthesised manually: a) molecular structure, b) LCMS analysis (λ = 214 nm).

Figure S10

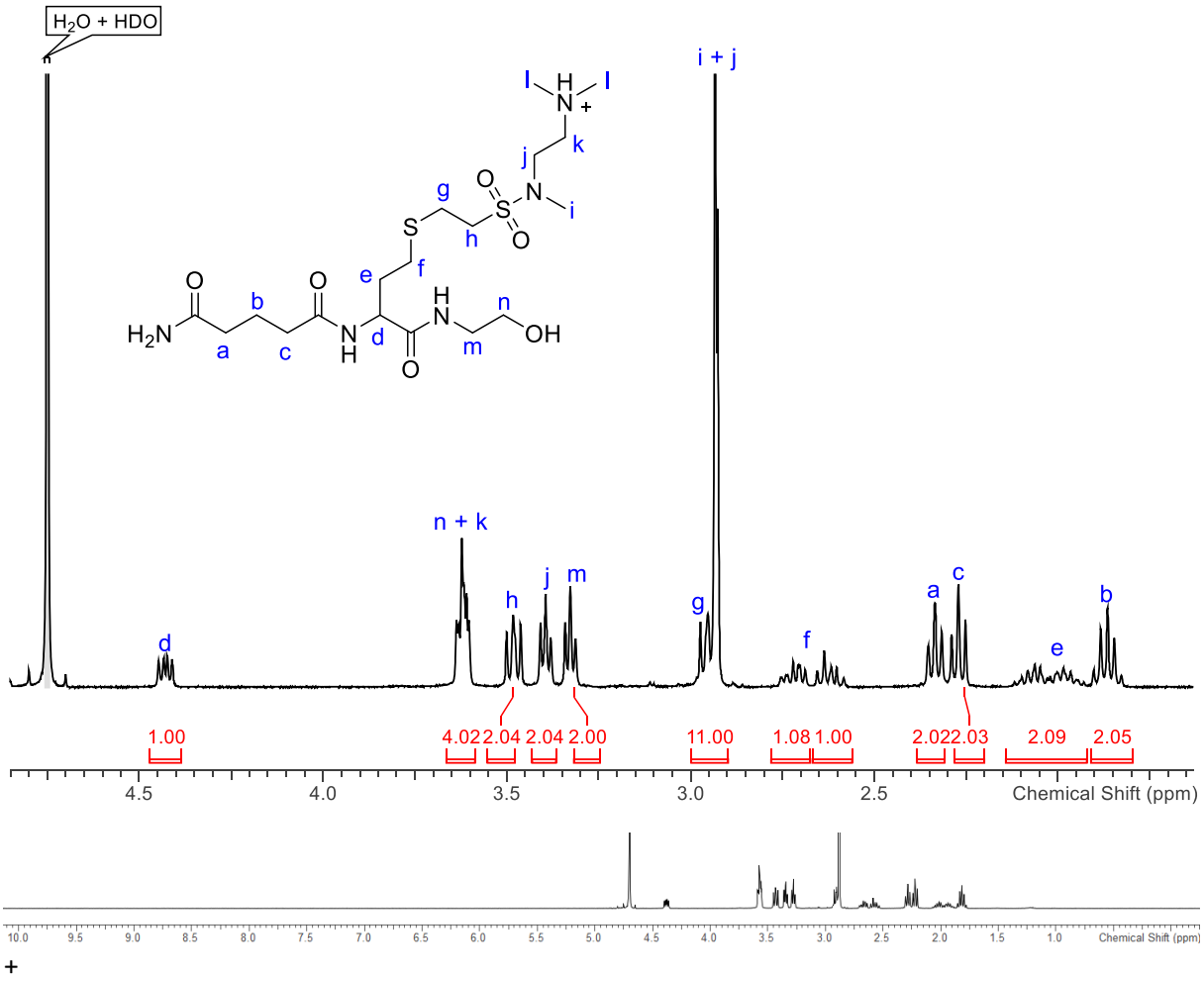


Figure S10a: ^{1}H NMR analysis (D_2O) of a 1-mer with a tertiary amine side-chain. The assignment was aided by 2D NMR techniques.

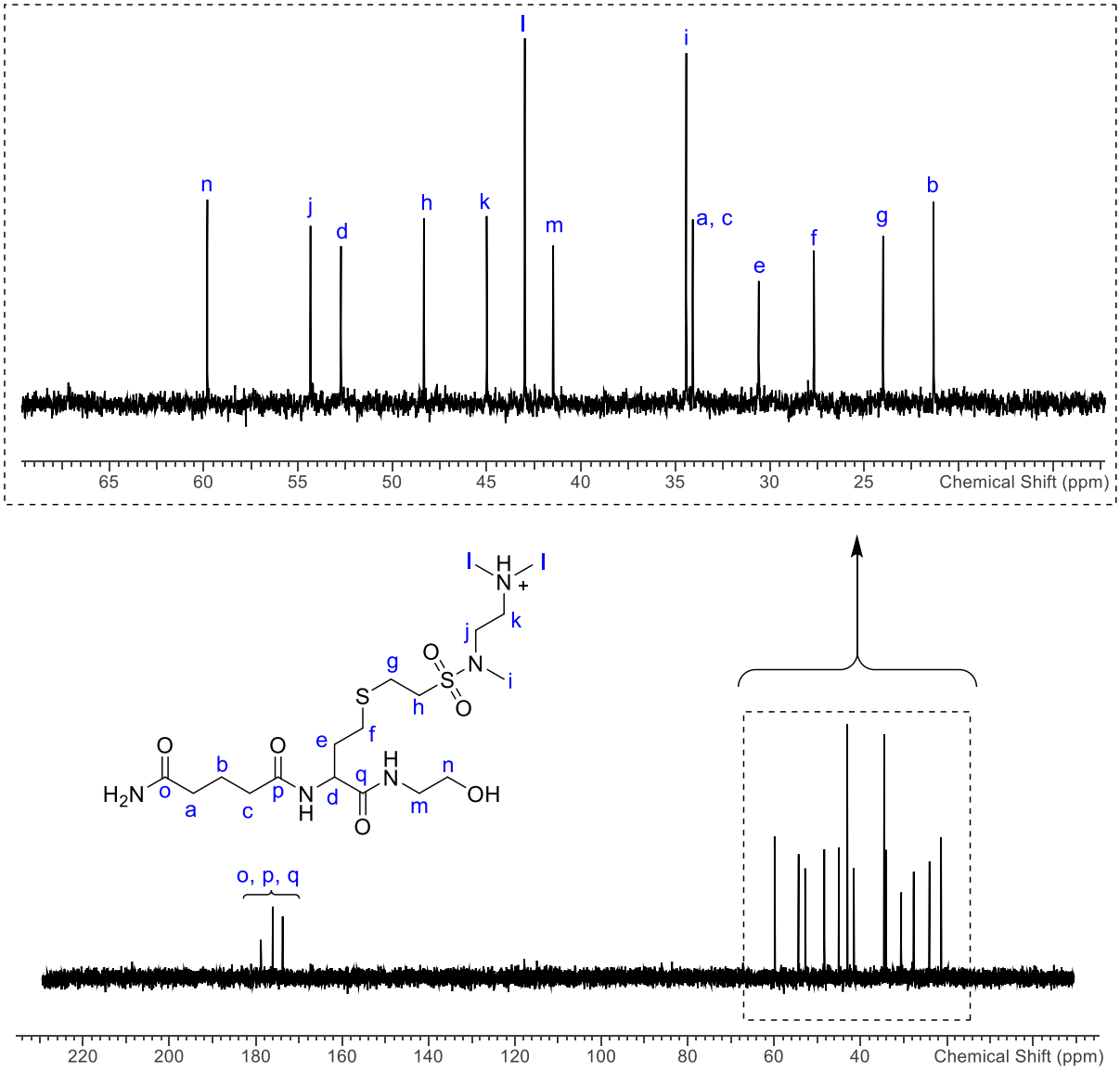


Figure S10b: ^{13}C NMR analysis (D_2O) of a 1-mer with a tertiary amine side-chain. The assignment was aided by 2D NMR techniques.

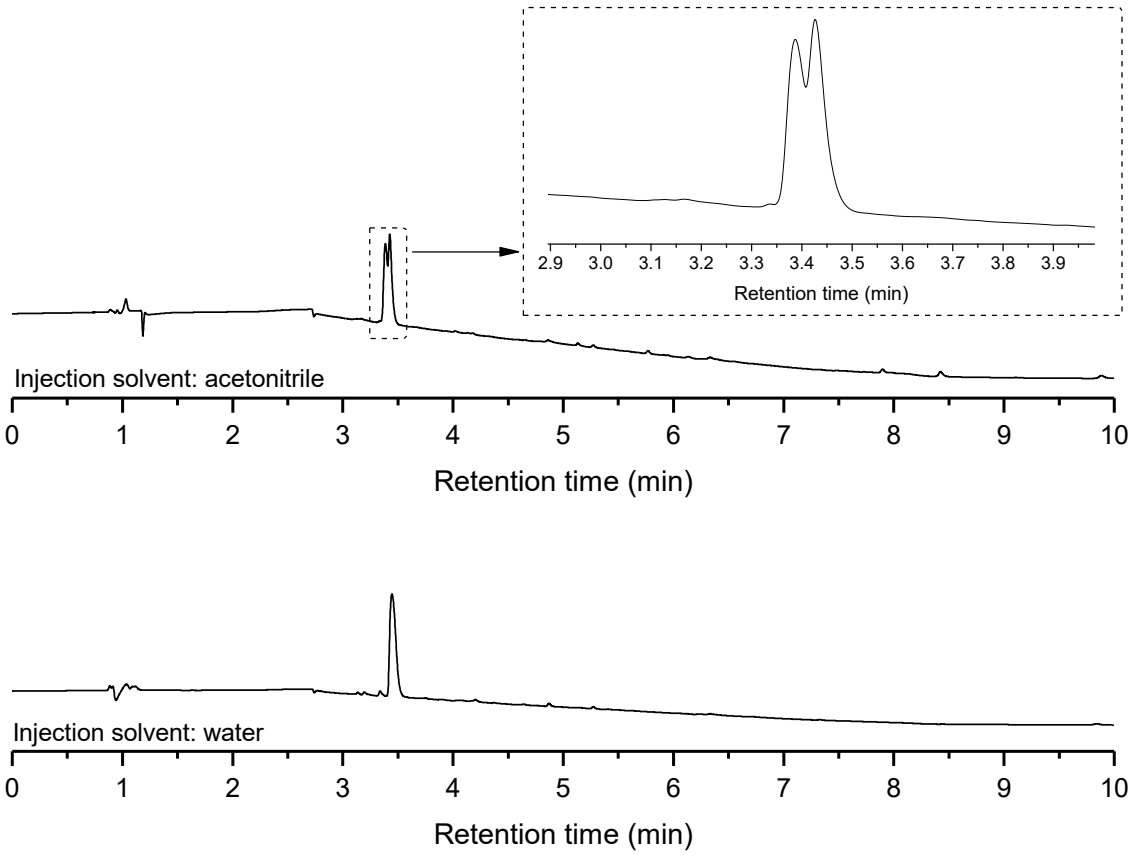


Figure S10c: Influence of the injection solvent (*i.e.* the solvent used to solubilise the sample) on the peak shape during the LCMS analysis. Besides the injection solvent all other parameters were the same during both measurements.

Figure S11

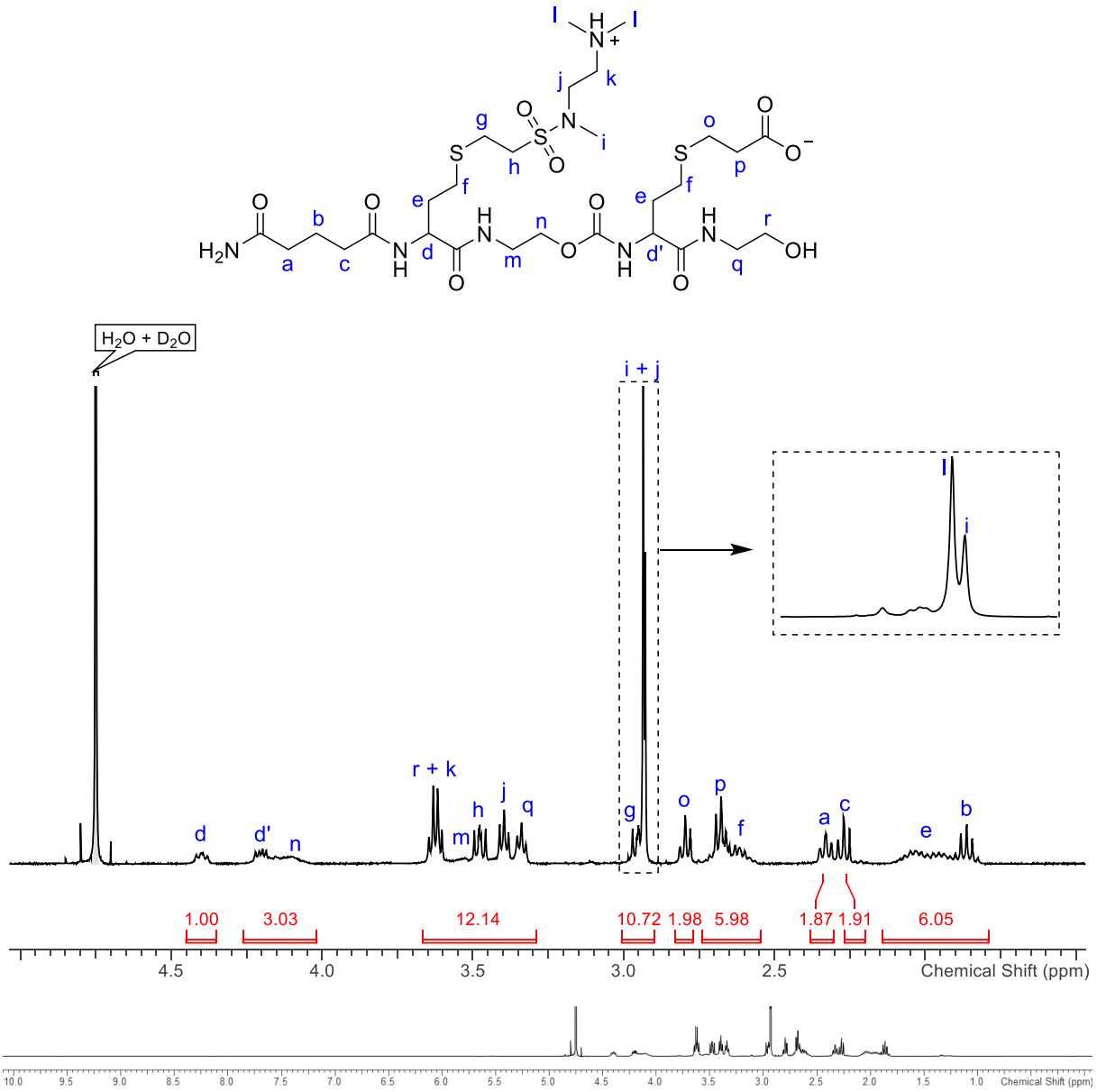


Figure S11a: ^{1}H NMR analysis (D_2O) of an alternating dimer with a tertiary amine and carboxylic acid side-chain. The assignment was aided by 2D NMR techniques.

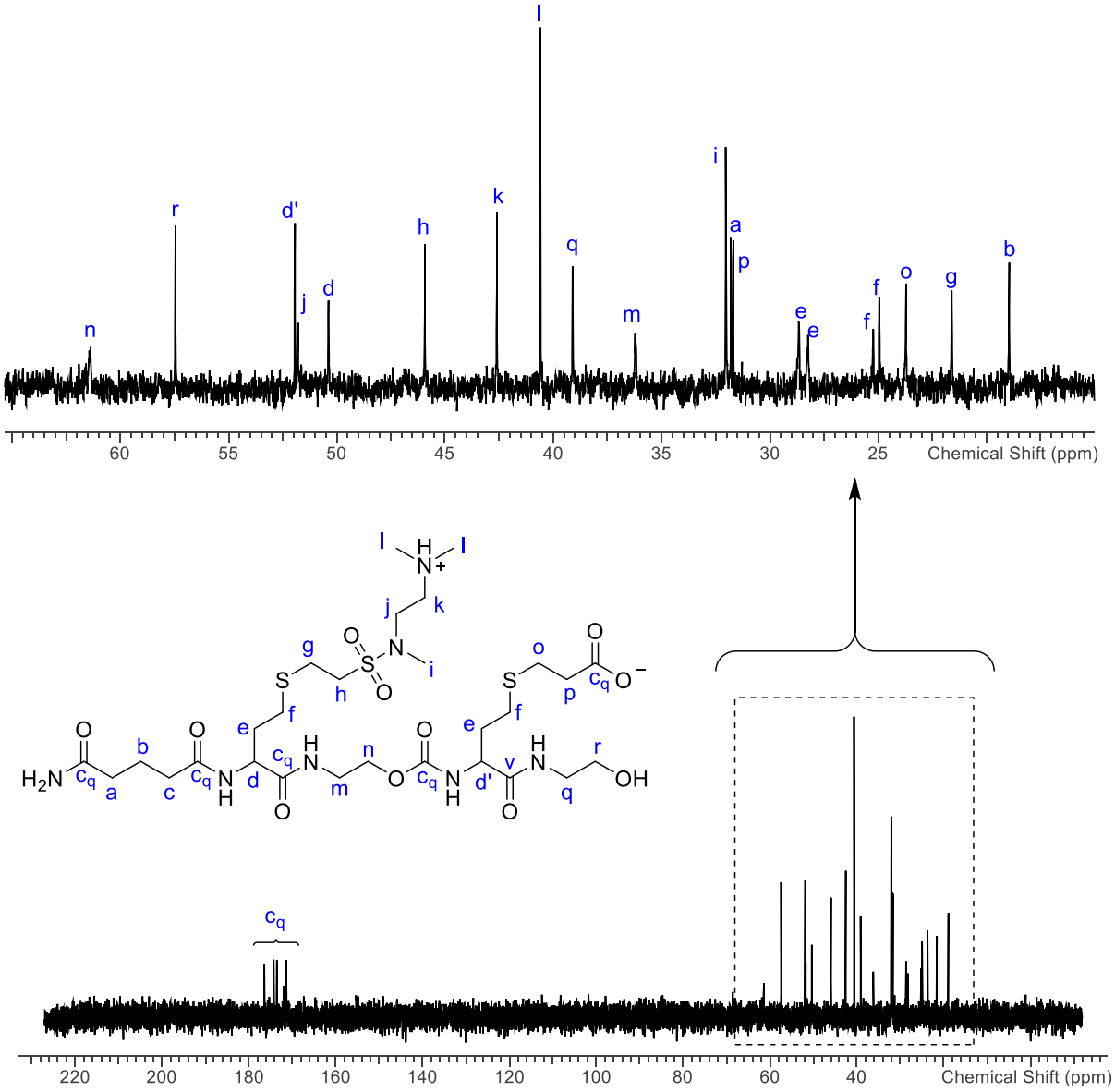
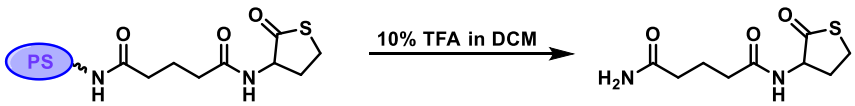


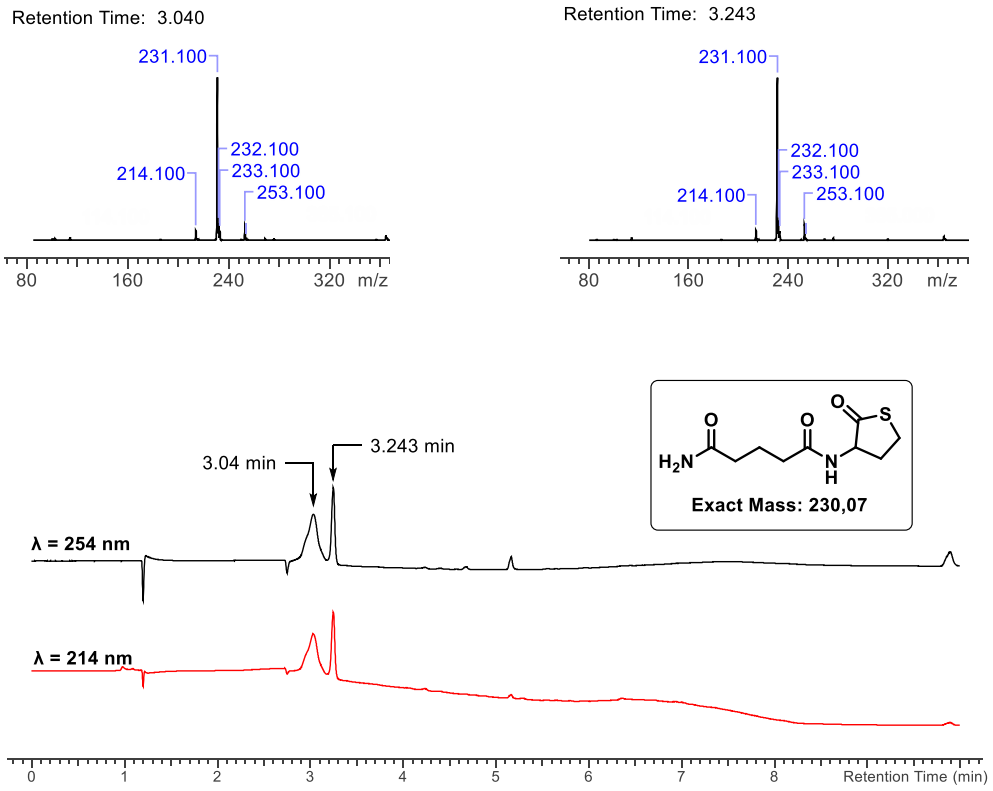
Figure S11b: ^{13}C NMR analysis (D_2O) of an alternating dimer with a tertiary amine and carboxylic acid side-chain. The assignment was aided by 2D NMR techniques.

Figure S12

a)



b)



c)

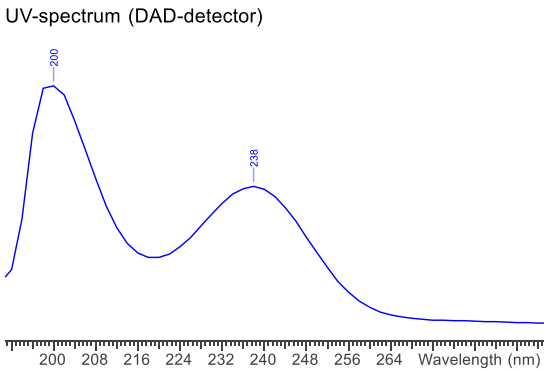


Figure S12: **a)** Cleavage of a thiolactone-loaded Rink-amide resin with 10% TFA in dichloromethane. **b)** LCMS analysis (λ = 214 nm, 254 nm) of the product. **c)** UV-spectrum of product.

Supplementary instrumentation

Manual solid-phase synthesis

The reactions are performed in a disposable solid-phase reactor equipped with a frit, which contains the solid support and reagents. After reaction, the excess reagents are removed by filtration. The reactor is put on a laboratory shaker to ensure efficient mixing.

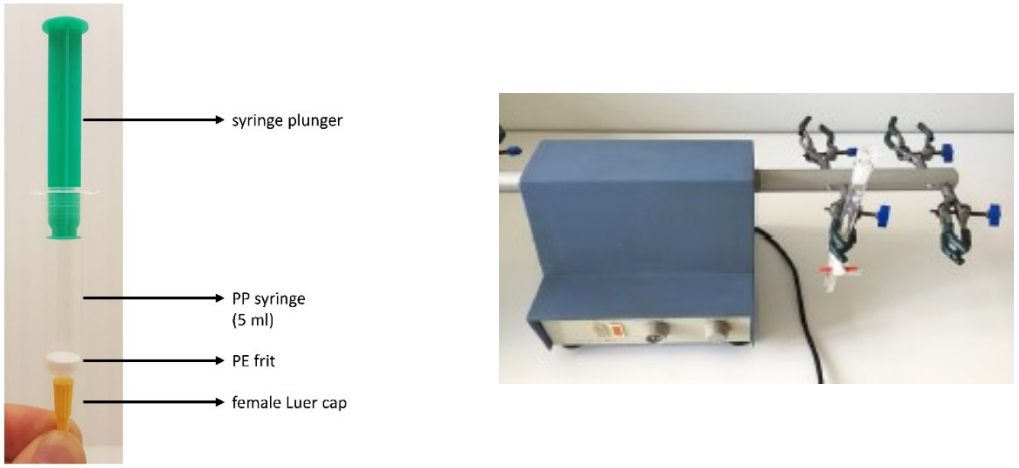


Figure S13: Disposable solid-phase reactor (left) and laboratory shaker (right).

Liquid handling robot

Automated synthesis was performed on a solid-phase peptide synthesiser (Intavis MultiPep RSI), equipped with a vortexing unit (700 rpm) and reactor block with 72 positions for 5 mL reactor columns. During the synthesis, the reactor columns are always open to the air. Reagent solutions are stored in a storage block, which is sealed with a septum sheet to minimise evaporation of volatiles.

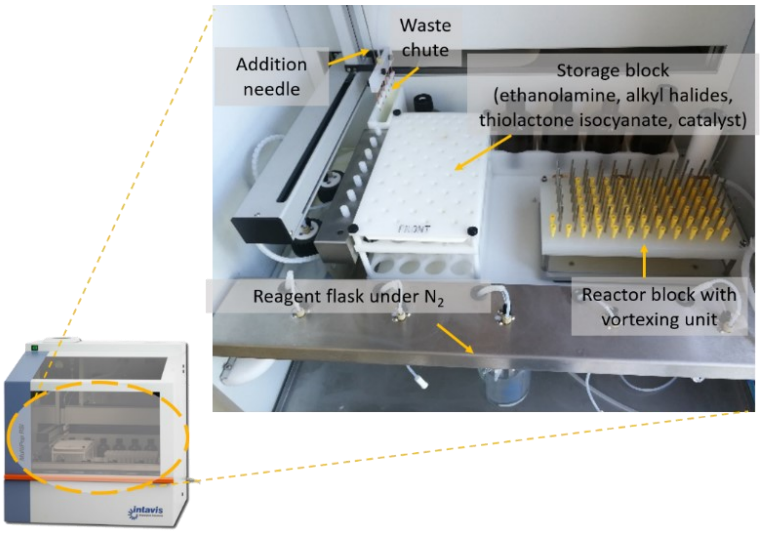
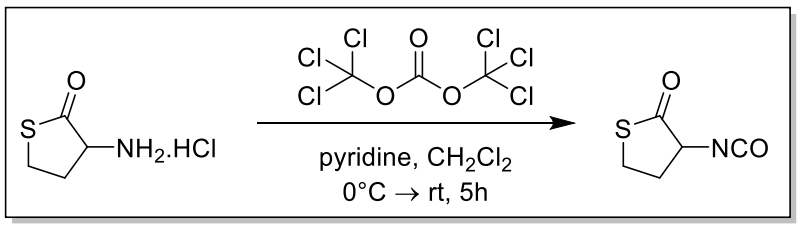


Figure S14: Layout of the liquid handling robot.

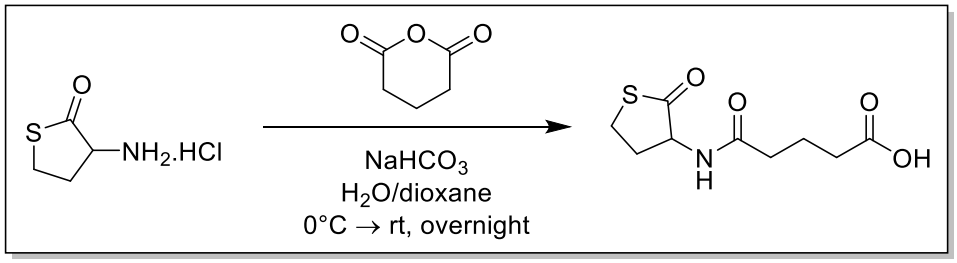
Synthetic Procedures

Synthesis of *α*-isocyanato-*γ*-thiolactone



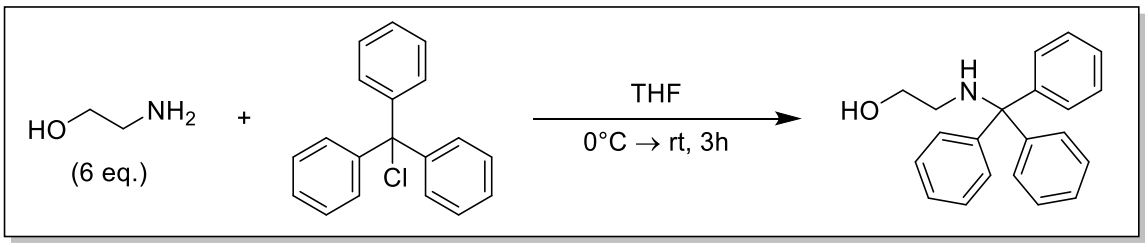
A thiolactone bearing an isocyanate moiety (TLa-NCO) was synthesised according to a previously reported procedure and the characterisation was in good accordance with the reported data.[1,2]

Synthesis of 5-oxo-5-((2-oxotetrahydrothiophen-3-yl)amino)pentanoic acid (TLa-COOH)



A thiolactone bearing a carboxylic acid moiety (TLa-COOH) was synthesised according to a previously reported procedure and the characterisation was in good accordance with the reported data.[3]

Synthesis of 2-(tritylamino)ethan-1-ol



Ethanolamine (19.7 g, 322.8 mmol, 6 eq.) was put in 250 mL flask equipped with a magnetic stirring bar and put under inert atmosphere. Next, the flask was put into an ice bath. In an addition funnel a solution of trityl chloride (15 g, 53.8 mmol, 1 eq.) and 50 mL tetrahydrofuran was prepared. This solution was added dropwise under continues stirring over the timespan of 1h. Afterwards, the ice bath was removed and the reaction was stirred overnight. The crude was transferred to a separation funnel and the organic phase was washed with water (2x 150 mL) and brine (1x 150 mL) and dried with magnesium sulphate. After filtration, the solvent was removed *in vacuo* yielding a viscous oil which crystallised over time (16.26 g, 99.6%).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 7.50 (m, 6H, Ph-*H*), 7.31 (m, 6H, Ph-*H*), 7.23 (m, 3H, Ph-*H*), 3.71 (m, 2H, O-C*H*$_2$), 2.41 (m, 2H, N-C*H*$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) = 145.24 (C_q), 128.62 (CH), 127.92 (CH), 126.53 (CH), 70.93 (Cq), 62.24 (CH_2), 45.99 (CH_2).

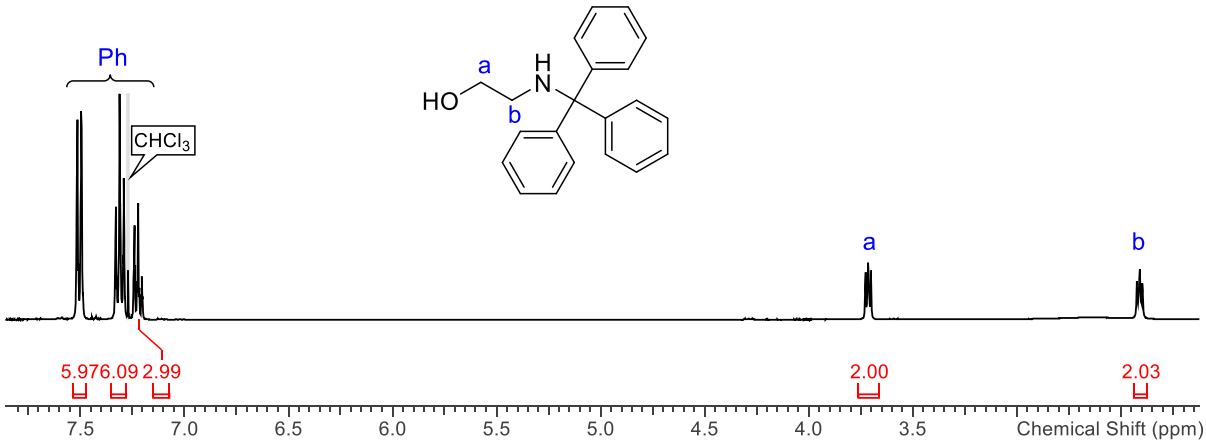


Figure S15: ^{1}H NMR spectra ($CDCl_3$) of 2-(tritylamino)ethan-1-ol.

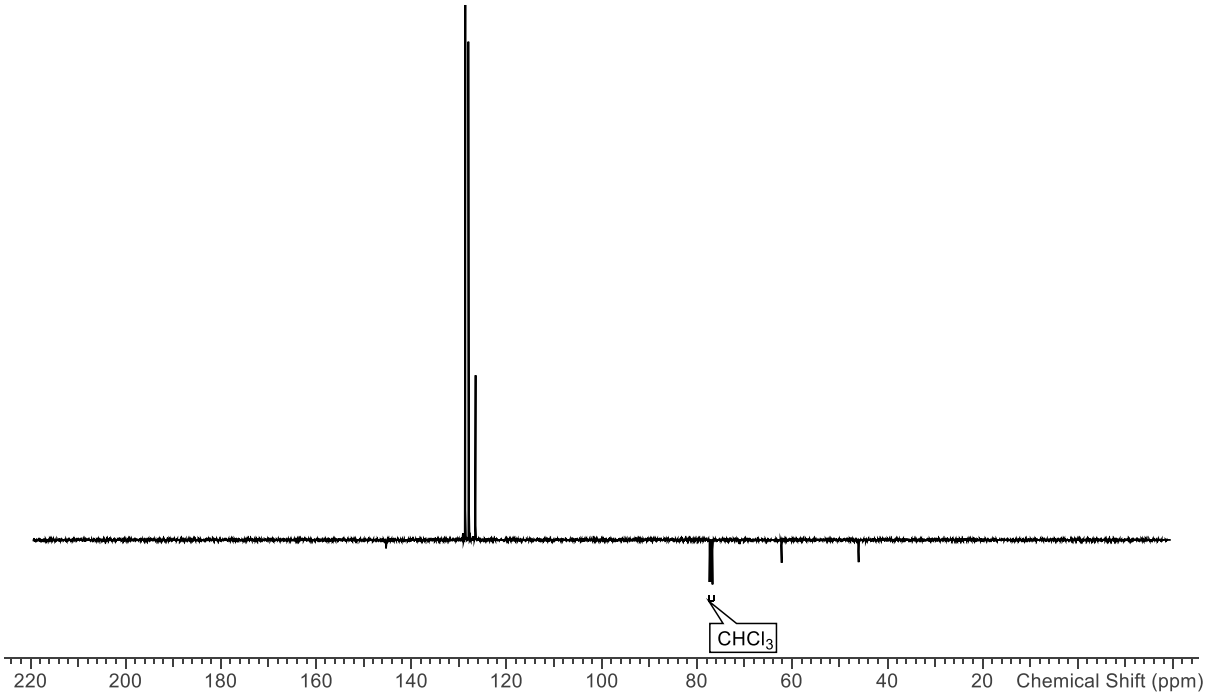
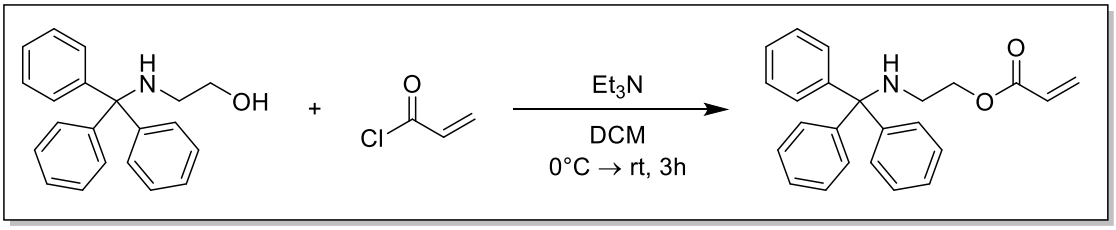


Figure S16: ^{13}C NMR spectra ($CDCl_3$) of 2-(tritylamino)ethan-1-ol.

Synthesis of 2-(tritylamino)ethyl acrylate



2-(tritylamino)ethan-1-ol (10 g, 33 mmol, 1 eq.) and triethylamine (5.97 mL, 42.9 mmol, 1.3 eq.) was solubilised in 100 mL tetrahydrofuran. This solution was cooled in an ice-bath and under continuous stirring acryloyl chloride (3.2 mL, 39.6 mmol, 1.2 eq.) was added dropwise. After 1h the ice bath was removed and the reaction was left overnight. Next, the crude was transferred to an extraction funnel and washed with a saturated solution of $NaHCO_3$, water and brine. The organic fraction was collected and dried with magnesium sulphate. After filtration, the solvent was removed *in vacuo*. This crude product was than further purified using column chromatography (7.16 g, 60.7 %). rf = 0.57 (EtOAc:hexane, 1:2)

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 7.52 (m, 6H, Ph-*H*), 7.30 (m, 6H, Ph-*H*), 7.22 (m, 3H, Ph-*H*), 6.44 (dd, J=17.33, 1.46 Hz, 1H, CH=C*H*$_2$), 6.17 (m, 1H, C*H*=CH$_2$), 5.86 (dd, J=10.50, 1.46 Hz, 1H, CH=C*H*$_2$), 4.29 (t, 2H, O-C*H*$_2$), 2.47 (m, 2H, N-CH$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) = 166.19 (C_q), 145.78 (CH_2), 130.77 (CH_2), 128.53 (CH), 128.37 (CH), 127.88 (CH), 127.22 (CH), 126.35 (CH), 64.71 (CH_2), 42.65 (CH_2)

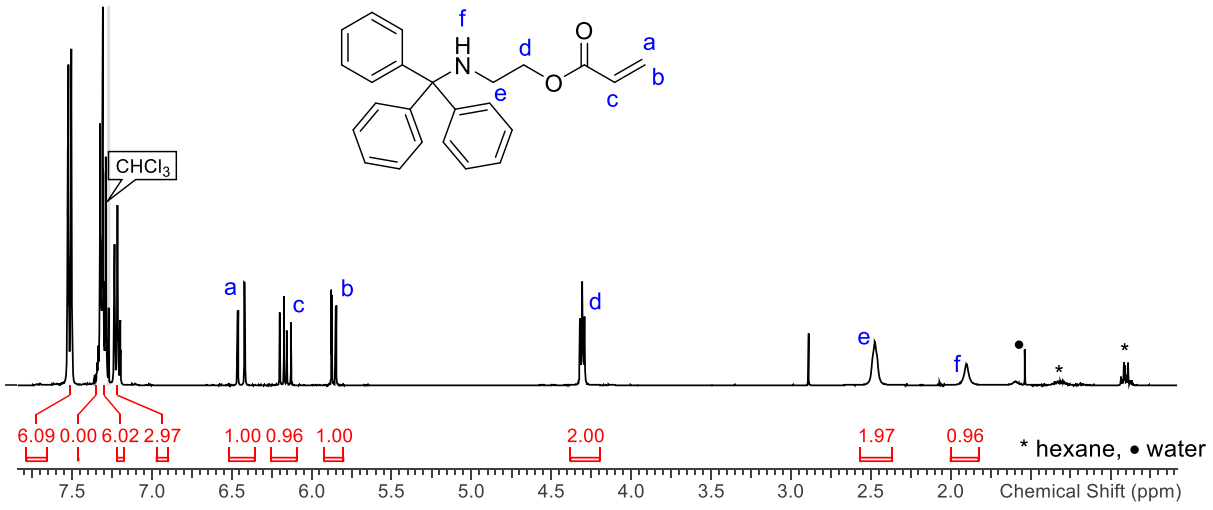


Figure S17: ^{1}H NMR spectra ($CDCl_3$) of 2-(tritylamino)ethyl acrylate.

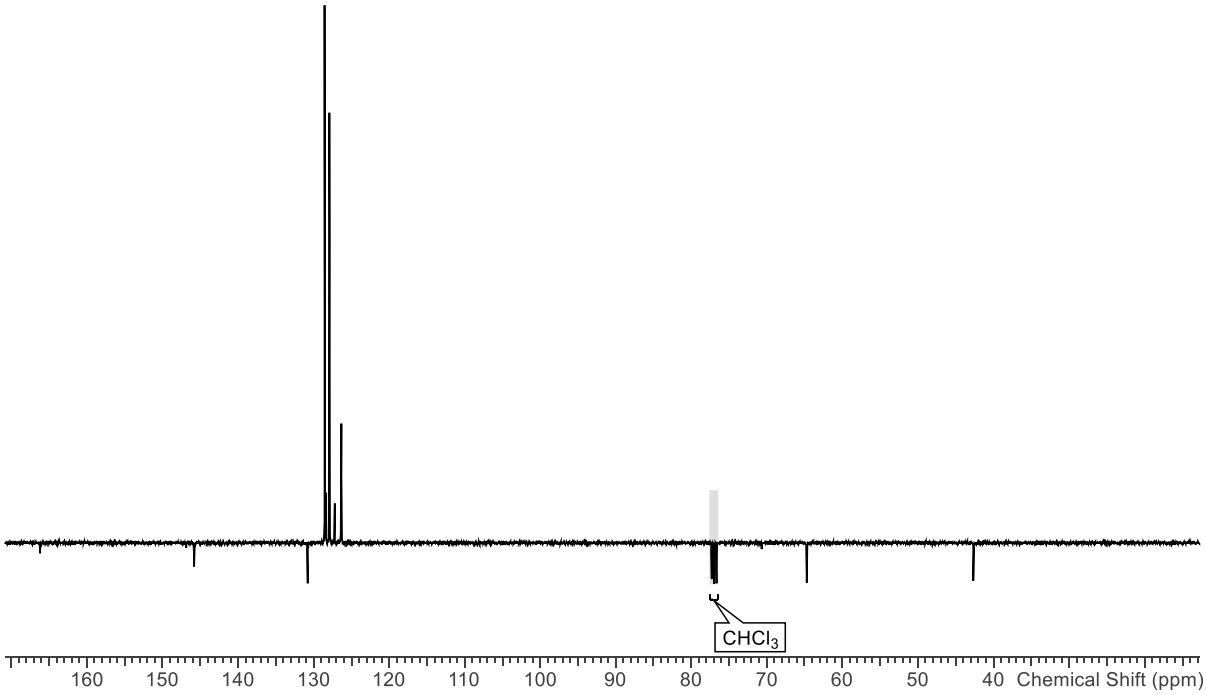
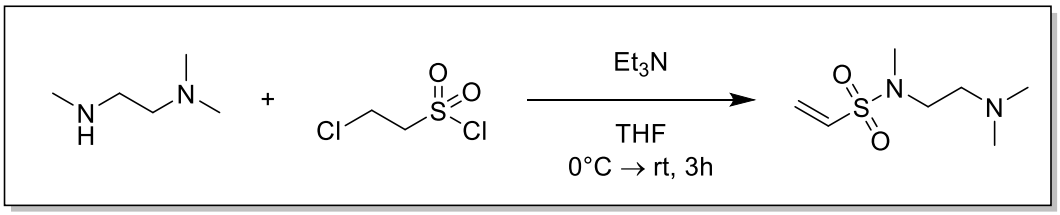


Figure S18: ^{13}C NMR spectra ($CDCl_3$) of 2-(tritylamino)ethyl acrylate.

Synthesis of *N*-(2-(dimethylamino)ethyl)-*N*-methylethenesulfonamide



N^1,N^1,N^2-trimethylethane-1,2-diamine (63.3 mL, 50.0 g, 0.489 mol, 1 eq.), triethylamine (157 mL, 1.13 mol, 2.3 eq.) was solubilised in 1 L tetrahydrofuran in a two-neck flask equipped with a large magnetic stirring bar and placed under inert atmosphere. The mixture was cooled in an ice bath while 2-chloroethanesulfonyl chloride (56.3 mL, 87.7 g, 0.538 mol, 1.1 eq.) was added dropwise over a time span of one hour. After complete addition, the ice bath was removed and the reaction was stirred for an additional three hours at room temperature. A large amount of triethylamine hydrochloride salt was formed during the reaction, which was removed by filtration. The filtrate was concentrated *in vacuo*. This crude was further purified by vacuum distillation (~ 80°C, 0.08 mbar). *N*-(2-(dimethylamino)ethyl)-*N*-methylethenesulfonamide was obtained as a faint yellow liquid (50.4 g – 53.6%).

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 6.45 (dd, J=16.58, 9.98 Hz, 1H, C*H*=CH_2), 6.11 (d, J=16.77 Hz, 1H, CH=C*H*$_2$), 5.89 (d, J=9.98 Hz, 1H, CH=C*H*$_2$), 3.14 (t, 2H, $N(CH_3)_2$-CH_2-C*H*$_2$), 2.73 (s, 3H, N-C*H*$_3$), 2.39 (t, 2H, $N(CH_3)_2$-C*H*$_2$), 2.16 (s, 6H, N-(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 133.26 (CH), 126.85 (CH_2), 57.02 (CH_2), 47.59 (CH_2), 45.21 (CH_3), 34.46 (CH_3)

LCMS (m/z): 193.1 $[M+H]^+$

***ρ*:** 1.056 g/mL

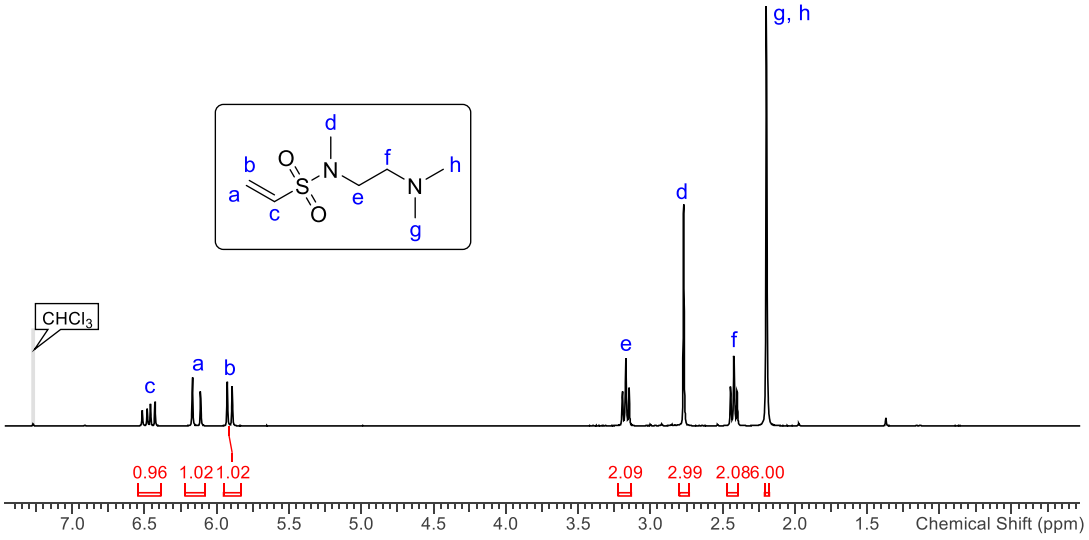


Figure S19: ^{1}H NMR spectra ($CDCl_3$) of *N*-(2-(dimethylamino)ethyl)-*N*-methylethenesulfonamide.

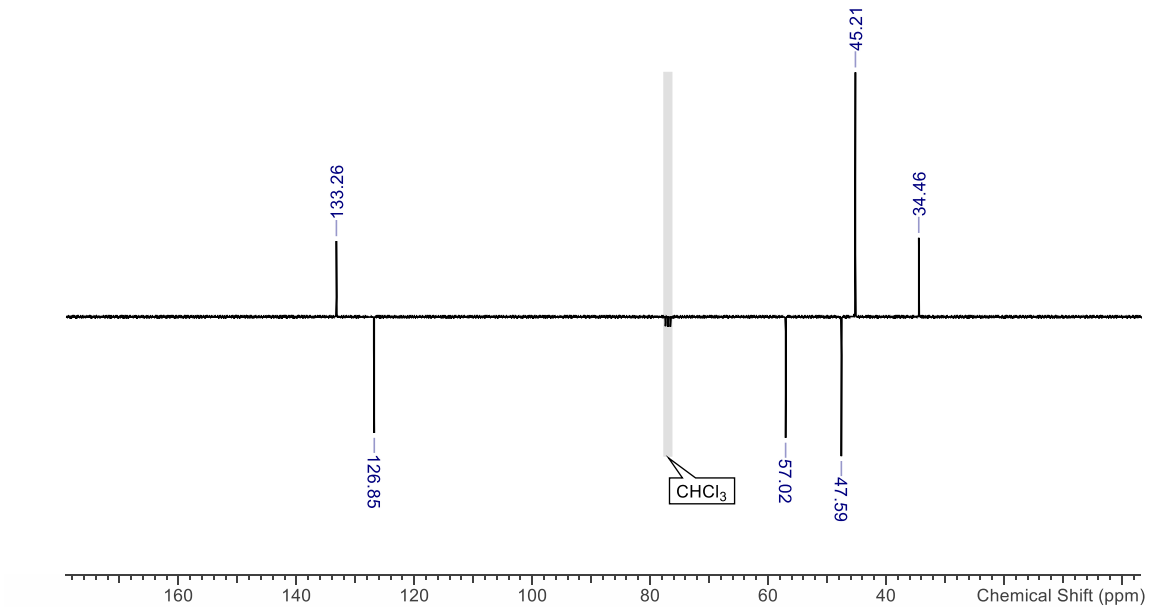
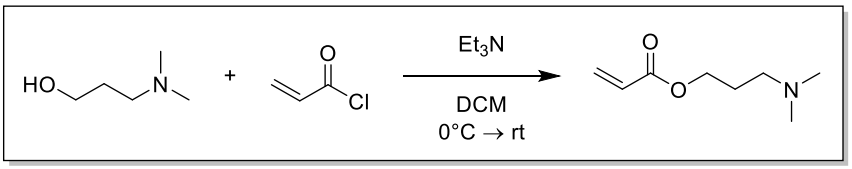


Figure S20: ^{13}C NMR spectra ($CDCl_3$) of *N*-(2-(dimethylamino)ethyl)-*N*-methylethenesulfonamide.

Synthesis of 3-(dimethylamino)propyl acrylate



3-(dimethylamino)propan-1-ol (17.05 mL, 145 mmol, 1 eq.) and dry triethylamine (30.4 mL, 218 mmol, 1.5 eq.) were put in a two-neck flask under inert atmosphere. 200 mL dry dichloromethane was added and the mixture was cooled in an ice bath. Next, acryloyl chloride (12.92 mL, 160 mmol, 1.1 eq.) was added dropwise to the stirred solution. After the addition the ice bath was removed and the reaction was stirred overnight at room temperature. The salt that was formed during the reaction was removed by filtration and the residue was rinsed with additional dichloromethane. The solution was transferred to a separation funnel and washed with a cold sodium bicarbonate solution and brine. The organic fraction was isolated and concentrated *in vacuo*. The obtained crude was further purified by vacuum distillation (6.2 g, 24.9 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 6.27 (dd, J=17.33, 1.51 Hz, 1H, CH=C*H*$_2$), 5.99 (dd, J=17.33, 10.36 Hz, 1H, C*H*=CH$_2$), 5.69 (dd, J=10.36, 1.51 Hz, 1H, CH=C*H*$_2$), 4.09 (t, 2H, O-C*H*$_2$), 2.23 (t, 2H, N-C*H*$_2$), 2.10 (s, 6H, N-(C*H*$_3$)$_2$), 1.72 (q, 2H, CH$_2$-C*H*$_2$-CH$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 165.83 (C$_q$), 130.18 (CH$_2$), 128.31 (CH), 62.74 (CH$_2$), 55.93 (CH$_2$), 45.19 (CH$_3$), 26.87 (CH$_2$)

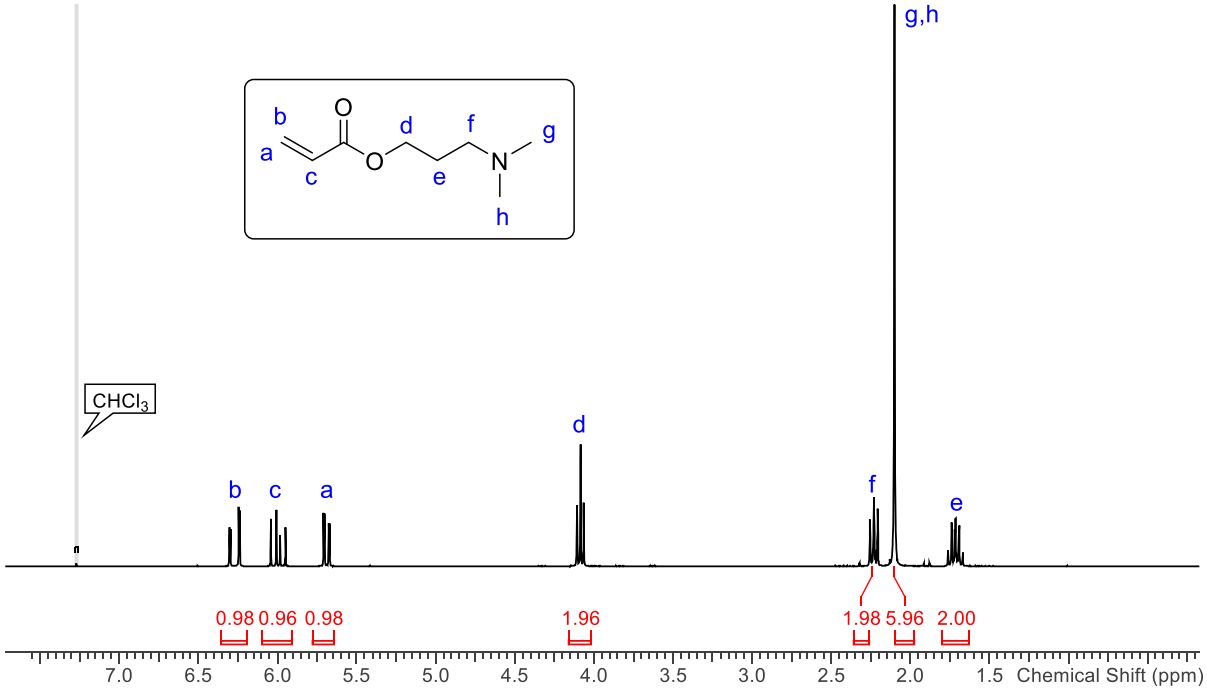


Figure S21: ^{1}H NMR spectra ($CDCl_3$) of 3-(dimethylamino)propyl acrylate.

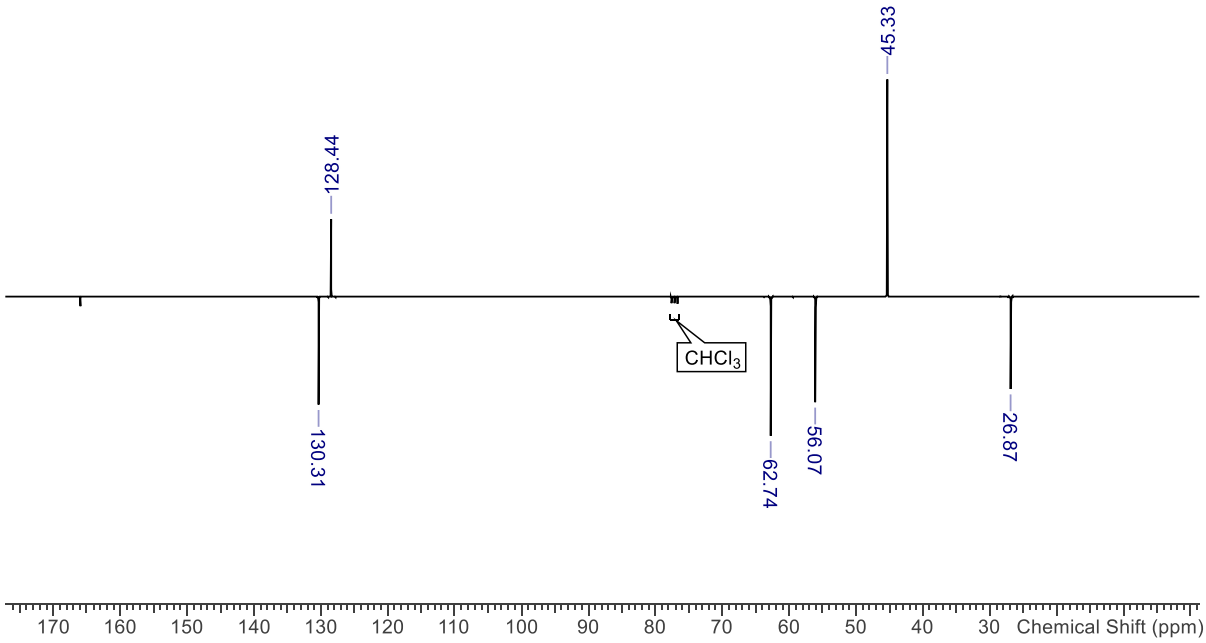
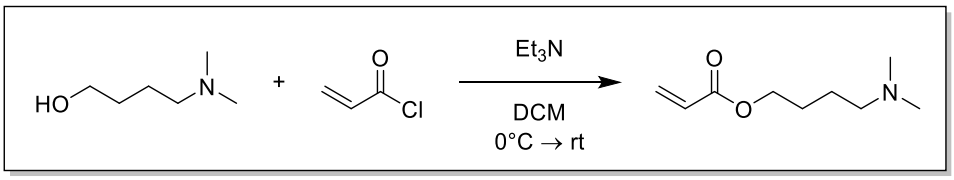


Figure S22: ^{13}C NMR spectra ($CDCl_3$) of 3-(dimethylamino)propyl acrylate.

Synthesis of 4-(dimethylamino)butyl acrylate



4-(dimethylamino)butan-1-ol (8 mL, 60 mmol, 1 eq.) and dry triethylamine (12.56 mL, 90 mmol, 1.5 eq.) were put in a two-neck flask under inert atmosphere. 100 mL dry dichloromethane was added and the solution was cooled in an ice bath. Under continuous stirring acryloyl chloride (5.34 mL, 66 mmol, 1.1 eq.) was added drop-wise. After complete addition, the ice bath was removed and the reaction was stirred overnight at room temperature. The crude reaction mixture was transferred to a separation funnel and additional dichloromethane was added. The organic layer was washed with a saturated sodium bicarbonate solution, however, an emulsion was formed which did not separate after ~ 6h. Therefore this emulsion was filtered over celite, which resulted in a separated organic and aqueous layer. The organic layer was dried with magnesium sulfate and concentrated *in vacuo*, followed by vacuum distillation to obtain the desired product (4.3 g, 46.5%).

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 6.24 (dd, *J*=17.33, 1.70 Hz, 1H, CH=CH_2), 5.97 (dd, J=17.33, 10.36 Hz, 1H, , C*H*=CH_2), 5.66 (dd, *J*=10.36, 1.70 Hz, 1H, , CH=CH_2), 4.02 (t, *J*=6.59 Hz, 2H, O-CH_2), 2.13 (m, 2H, N-CH_2), 2.06 (s, 6H, N-(CH_3)$_2$), 1.48 (m, 4H, O-CH_2-(CH_2)$_2$-CH_2-N)

^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 165.88 (C_q), 130.06 (CH_2), 128.30 (CH), 64.04 (CH_2), 58.91 (CH_2), 45.13 (CH), 26.21 (CH_2), 23.85 (CH_2)

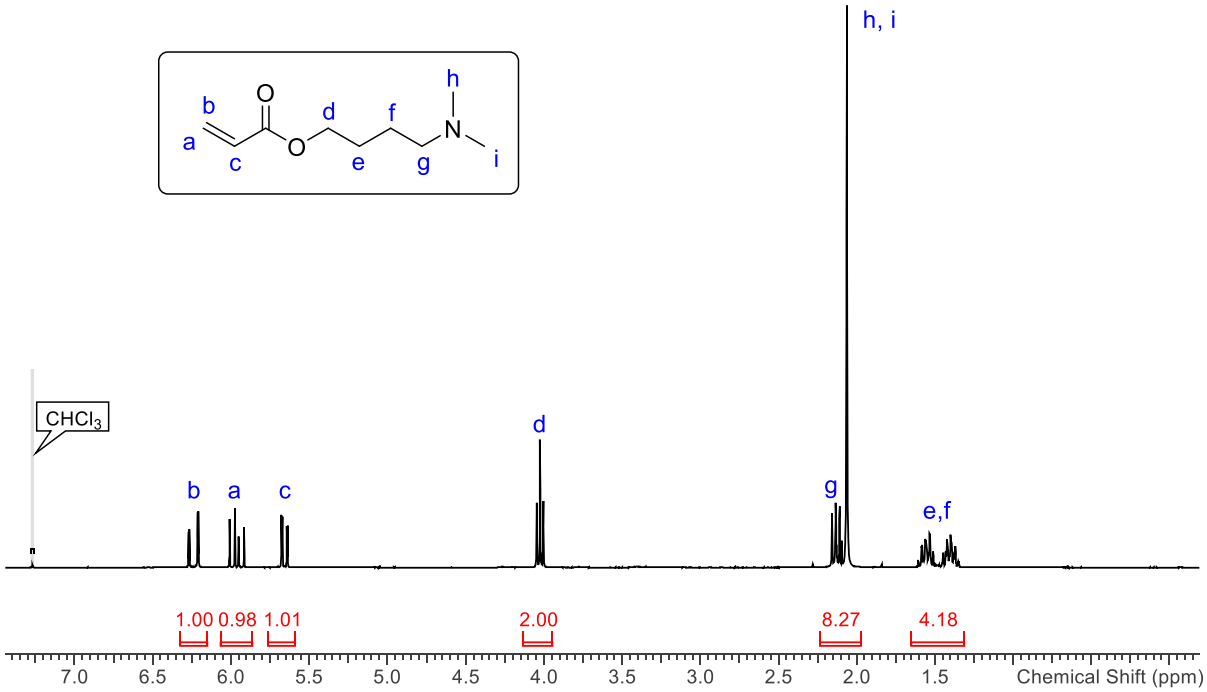


Figure S23: ^{1}H NMR spectra ($CDCl_3$) of 4-(dimethylamino)butyl acrylate.

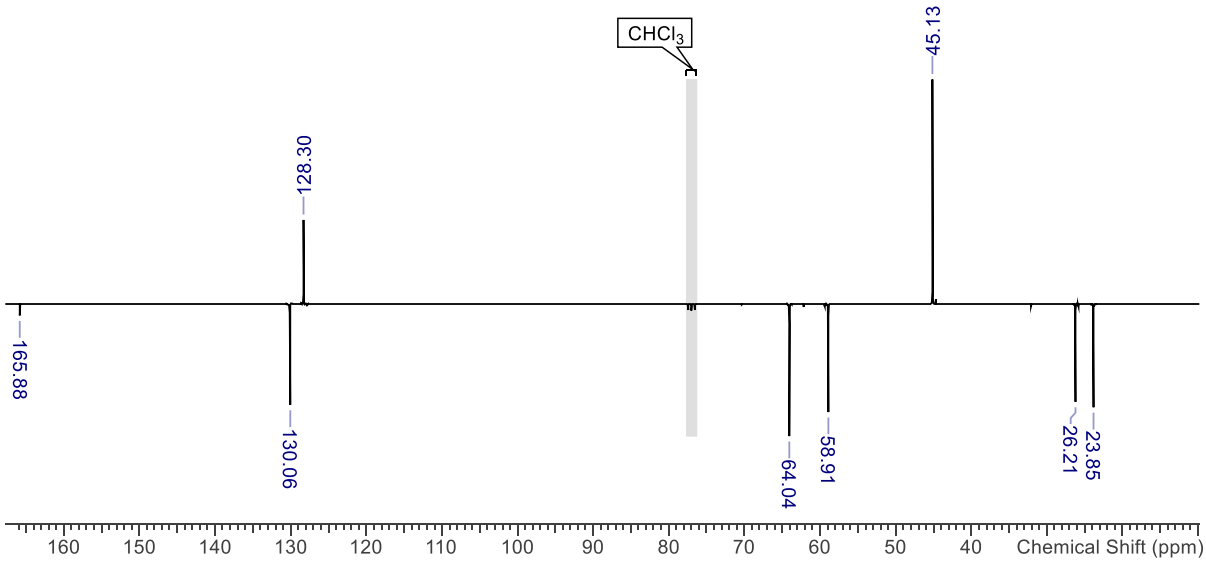
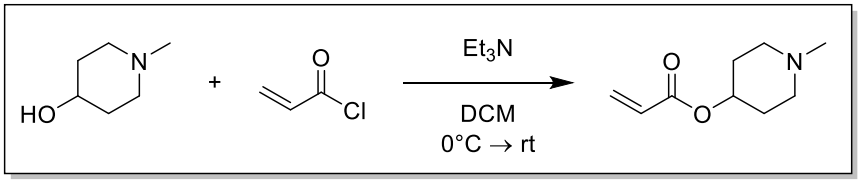


Figure S24: ^{13}C NMR spectra ($CDCl_3$) of 4-(dimethylamino)butyl acrylate.

Synthesis of 1-methylpiperidin-4-yl acrylate



1-methylpiperidin-4-ol (5.2 g, 45 mmol, 1 eq.) and dry triethylamine (6.75 mL, 58.69 mmol, 1.3 eq.) was put in a two-neck flask under inert atmosphere. Next 75 mL dry dichloromethane was added and the solution was cooled in an ice bath. Under continuous stirring, acryloyl chloride (4 mL, 50 mmol, 1.1 eq.) was added drop-wise. After complete addition the ice bath was removed and the solution was stirred for an additional 4 hours. Next the crude was transferred to a separation funnel and washed with a saturated sodium bicarbonate solution and brine. The organic layer was dried with magnesium sulfate and dried *in vacuo*. The crude product was further purified by vacuum distillation (2.442 g, 31.96 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 6.26 (dd, *J*=17.33, 1.70 Hz, 1H, CH=C*H*$_2$), 5.99 (dd, 1H, C*H*=CH$_2$), 5.68 (dd, *J*=10.36, 1.51 Hz, 1H, CH=C*H*$_2$), 4.72 (m, 1H, O-C*H*), 2.52-2.07 (m, 4H, N-(C*H*$_2$)$_2$), 2.15 (s, 3H, N-CH$_3$), 1.73 (m, 4H, CH-(C*H*$_2$)$_2$)

^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 165.24 (C$_q$), 130.13 (CH$_2$), 128.64 (CH), 69.58 (CH), 52.64 (CH$_2$), 45.89 (CH$_3$), 30.58 (CH$_2$)

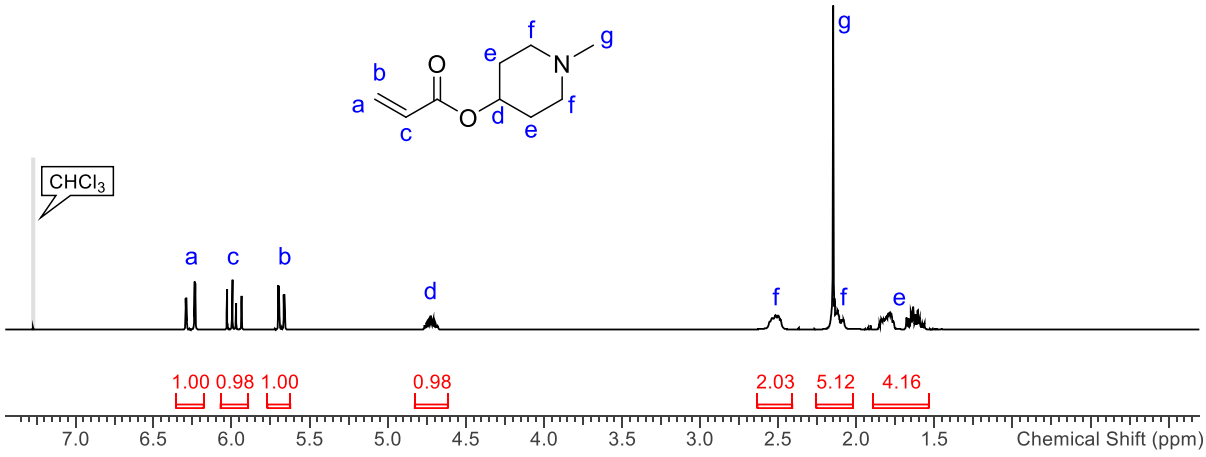


Figure S25: ^{1}H NMR spectra ($CDCl_3$) of 1-methylpiperidin-4-yl acrylate.

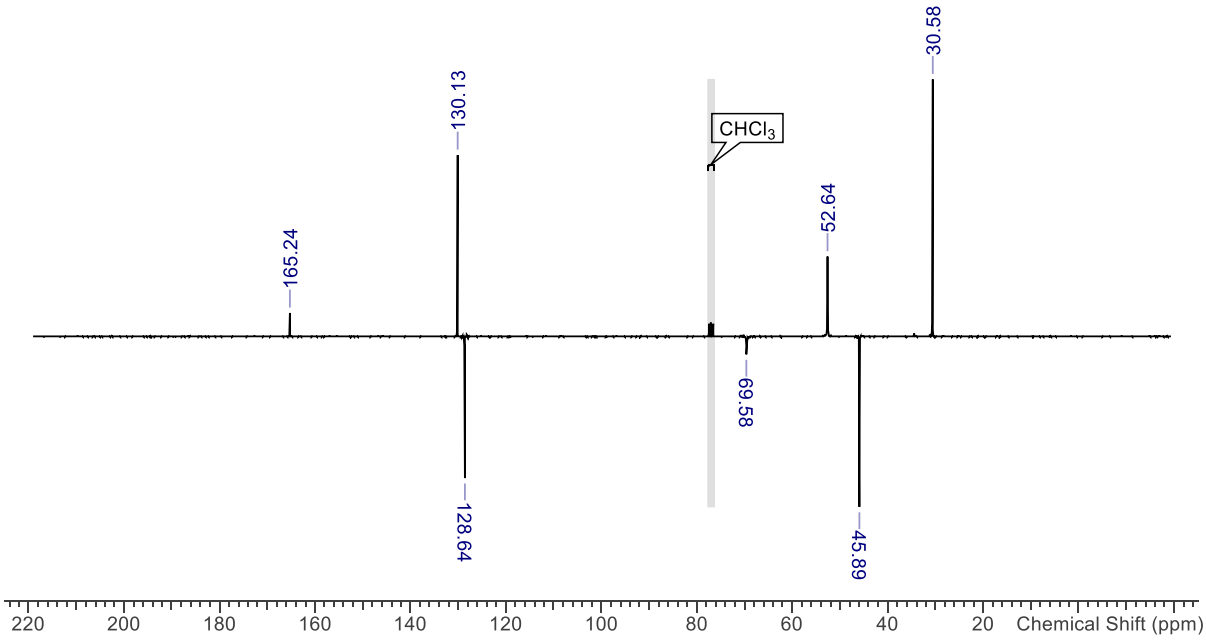
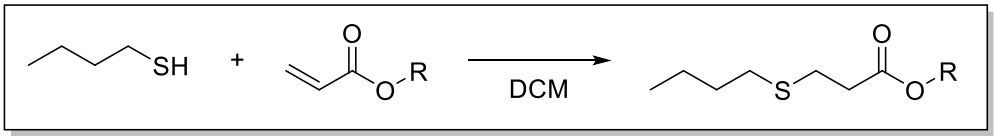


Figure S26: ^{13}C NMR spectra ($CDCl_3$) of 1-methylpiperidin-4-yl acrylate.

General procedure for the thiol-Michael addition



500 mg of the acrylate derivative was weighted out in a glass headspace vial and equipped with a stirring bar before being closed with a crimp seal with septa. In a second vial a solution of butanethiol (1.05 eq.) and 3 µl of dimethylphenylphosphine was solubilised in 800 µL dichloromethane. This solution was then transferred to the first vial containing the acrylate and the reaction mixture was stirred overnight. Next, the solvent was removed *in vacuo*. Afterwards, a high vacuum was applied, while the sample was heated to 50°C, to remove traces of the residual solvent and excess of reagents to obtain the pure product.

Synthesis of 2-(dimethylamino)ethyl 3-(butylthio)propanoate

See general procedure. 2-(dimethylamino)ethyl acrylate (500 mg, 3.49 mmol, 1 eq.) and 1-butanethiol (318 µL, 3.1 mmol, 1 eq.) were utilised.

^{1}H NMR (300 MHz, CD_2Cl_2): δ(ppm) = 4.12 (m, 2H, O-CH_2), 2.74 (m, 2 H, N-CH_2), 2.54 (m, 6H, CH_2-S-CH_2-CH_2), 2.22 (m, 6H, N-(CH_3)$_2$), 1.54 (m, 2H, CH_3-CH_2-CH_2), 1.37 (m, 2H, CH_3-CH_2-CH_2), 0.89 (t, 3H, CH_2-CH_3).

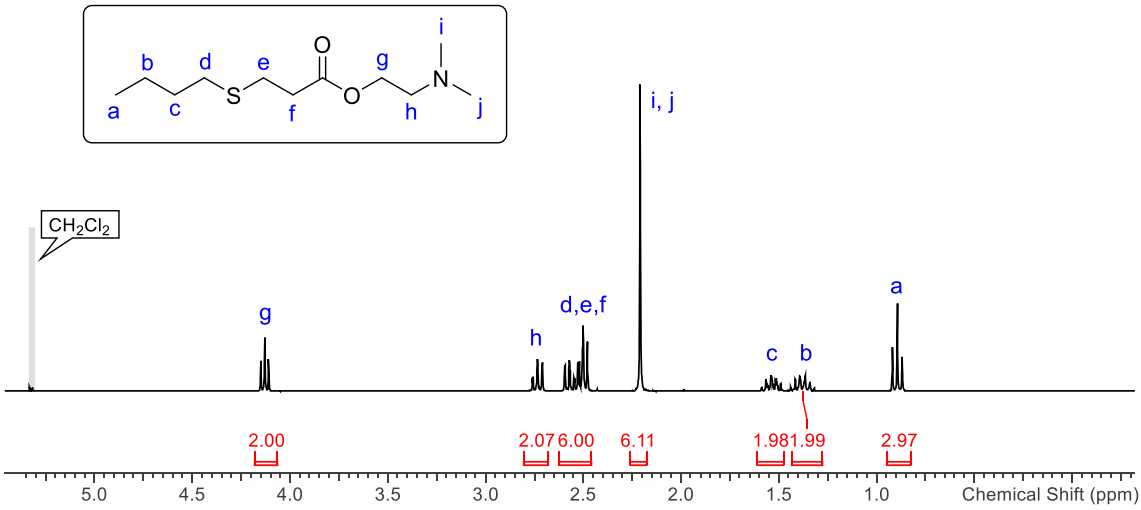


Figure S27: ^{1}H NMR spectra ($CDCl_3$) of 2-(dimethylamino)ethyl 3-(butylthio)propanoate.

Synthesis of 3-(dimethylamino)propyl 3-(butylthio)propanoate

See general procedure. 3-(dimethylamino)propyl acrylate (500 mg, 3.18 mmol, 1 eq.) and 1-butanethiol (360 µL, 3.34 mmol, 1.05 eq.) were utilised.

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 4.07 (t, 2H, O-CH_2), 2.71 (t, 2H, S-CH_2), 2.55-2.42 (m, 4H, CH_2-S-CH_2-CH_2), 2.28 (t, 2H, N-CH_2), 2.14 (s, 6H, N-(CH_3)$_2$), 1.73 (q, 2H, O-CH_2-CH_2), 1.51 (q, 2H, CH_3-CH_2-CH_2), 1.33 (q, 2H, CH_3-CH_2-CH_2), 0.83 (t, 3H).

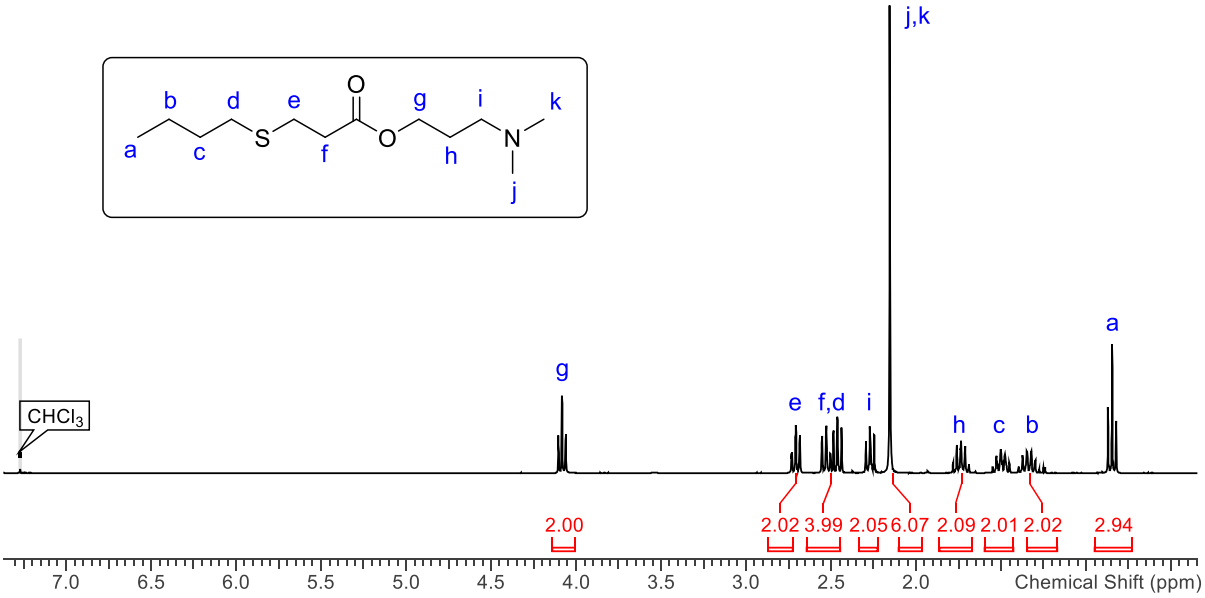


Figure S28: ^{1}H NMR spectra ($CDCl_3$) of 3-(dimethylamino)propyl 3-(butylthio)propanoate.

Synthesis of 4-(dimethylamino)butyl 3-(butylthio)propanoate

See general procedure. 4-(dimethylamino)butyl acrylate (500 mg, 2.92 mmol, 1 eq.) and 1-butanethiol (315 µL, 2.92 mmol, 1.05 eq.) were utilised.

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 4.06 (t, 2H, O-CH_2), 2.72 (t, 2H, S-CH_2), 2.50 (m, 4H, CH_2-S-CH$_2$-CH_2), 2.23 (t, 1H, N-CH_2), 2.16 (s, 6H, N-(CH_3)$_2$), 1.68-1.29 (m, 8H, CH$_3$-CH_2-CH_2 , O-CH$_2$-CH_2-CH_2), 0.86 (t, 3H, CH$_2$-CH_3).

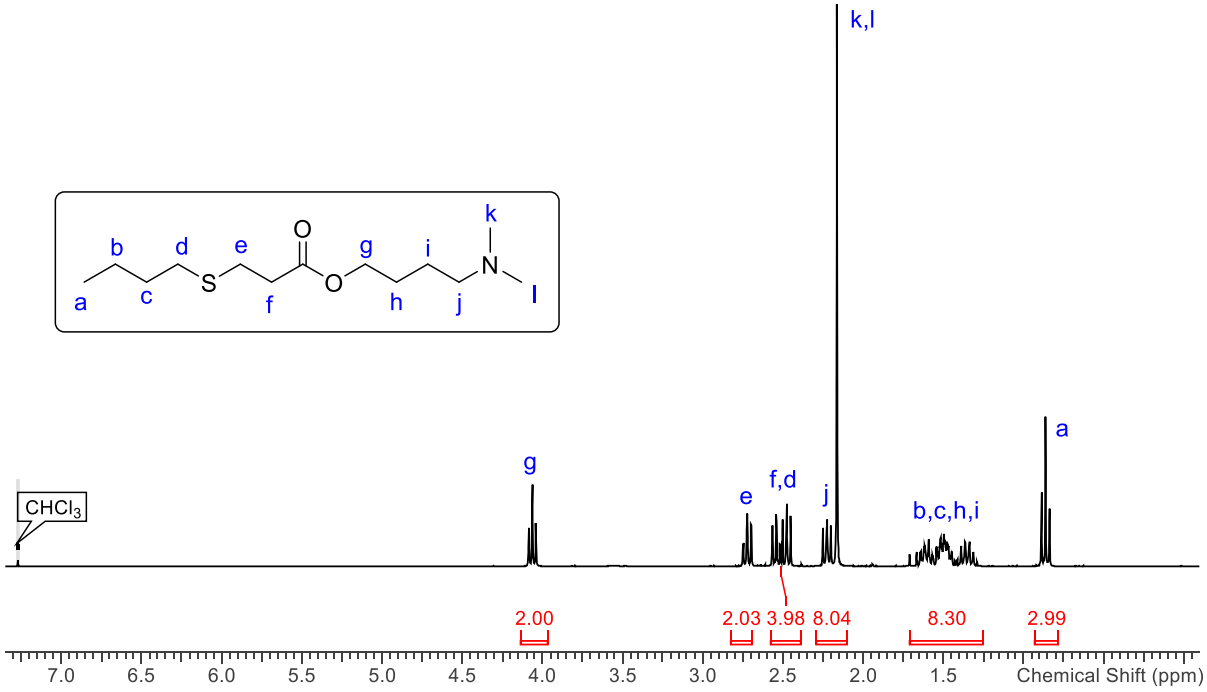
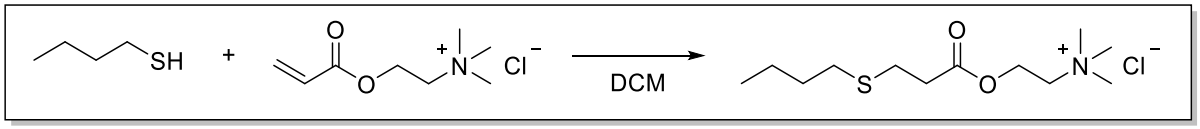


Figure S29: ^{1}H NMR spectra ($CDCl_3$) of 4-(dimethylamino)butyl 3-(butylthio)propanoate.

Synthesis of 2-((3-(butylthio)propanoyl)oxy)-*N*,*N*,*N*-trimethylethan-1-ammonium



See general procedure. 2-(Acryloyloxy)ethyl]trimethylammonium chloride solution (80 wt% in water, 625 mg, 3.16 mmol, 1 eq.) and 1-butanethiol (357 µL, 3.32 mmol, 1.05 eq.) were utilised.

^{1}H NMR (300 MHz, CD_3OD): δ(ppm) = 4.62 (m, 2H, O-C*H*$_2$), 3.80 (m, 2H, N-C*H*$_2$), 3.28 (s, 9H, N-(C*H*$_3$)$_3$), 2.86-2.55 (m, 6H, C*H*$_2$-S-C*H*$_2$-C*H*$_2$), 1.54 (m, 4H, CH$_3$-C*H*$_2$-C*H*$_2$), 0.97 (m, 3H, CH$_2$-C*H*$_3$).

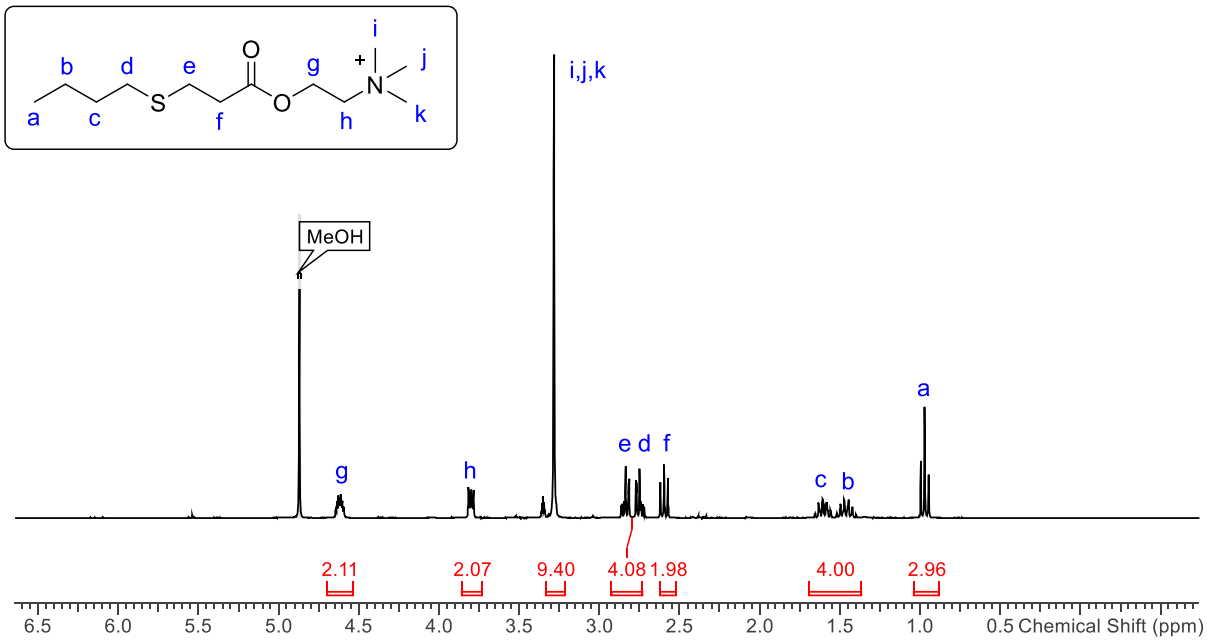
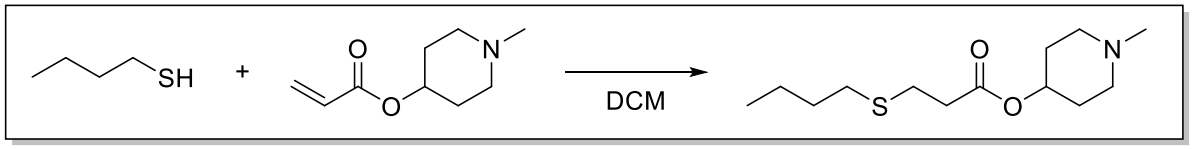


Figure S30: ^{1}H NMR spectra (CD_3OD) of 2-((3-(butylthio)propanoyl)oxy)-*N*,*N*,*N*-trimethylethan-1-aminium.

Synthesis of 1-methylpiperidin-4-yl 3-(butylthio)propanoate



See general procedure. 1-methylpiperidin-4-yl acrylate (500 mg, 2.95 mmol, 1 eq.) and 1-butanethiol (334 µL, 3.1 mmol, 1.05 eq.) were utilised.

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 4.74 (m, 1H, O-C*H*), 2.71 (t, 2H, S-CH_2), 2.50 (m, 6H, N-(CH_2)$_2$, S-CH_2-CH_2), 2.20 (s, 3H, N-CH_3), 2.16 (m, 2H, S-CH_2), 1.83-1.59 (m, 4H, CH-(CH_2)$_2$), 1.50 (m, 2H, CH_3-CH_2-CH_2), 1.33 (m, 2H, CH_3-CH_2-CH_2), 0.85 (t, 3H, CH_2-CH_3).

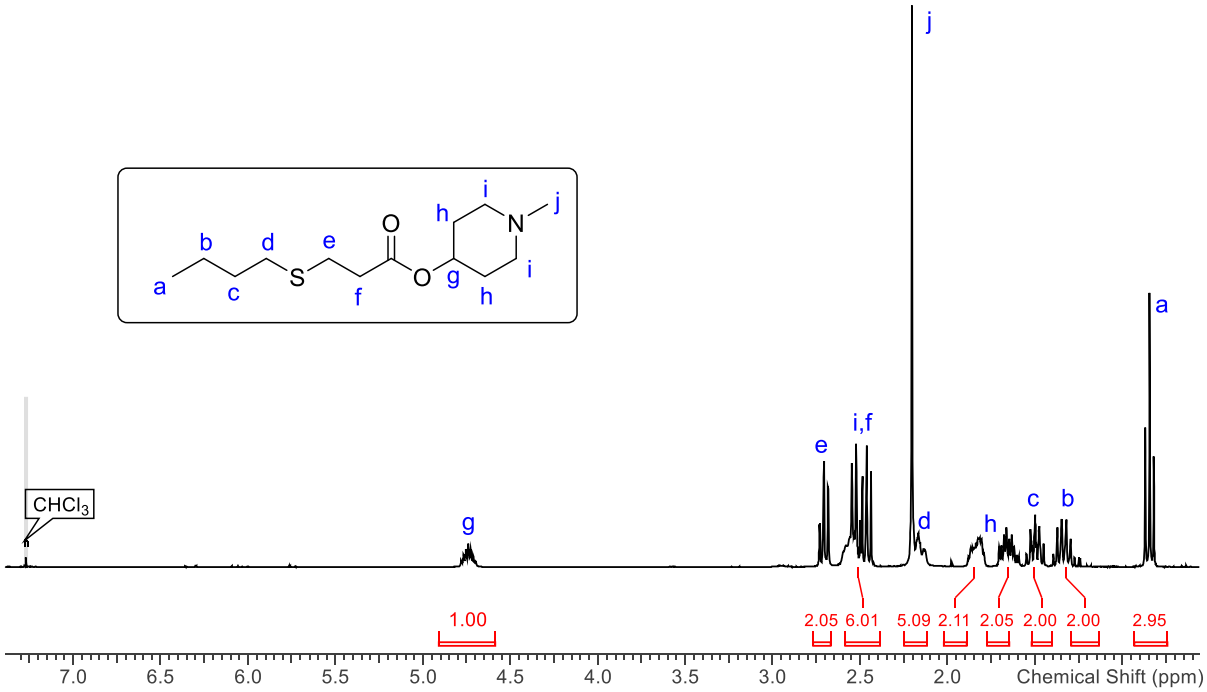


Figure S31: ^{1}H NMR spectra ($CDCl_3$) of 1-methylpiperidin-4-yl 3-(butylthio)propanoate.

Synthesis of 2-(butylthio)-*N*-(2-(dimethylamino)ethyl)-*N*-methylethane-1-sulfonamide

See general procedure. *N*-(2-(dimethylamino)ethyl)-N-methylethenesulfonamide (250 mg, 1.30 mmol, 1 eq.) and 1-butanethiol (147 µL, 1.37 mmol, 1.05 eq.) were utilised.

^{1}H NMR (400 MHz, CD_3OD): δ(ppm) = 3.35 (m, 4H, N-C*H*$_2$, S-C*H*$_2$), 2.94 (s, 3H, SO_2-N-C*H*$_3$), 2.90 (m, 2H, SO_2-CH_2-C*H*$_2$), 2.63 (m, 4H, C*H*$_2$-S-CH_2-C*H*$_2$), 2.36 (s, 6H, N(C*H*$_3$)$_2$), 1.61 (m, 2H, CH_3-CH_2-C*H*$_2$), 1.46 (m, 2H, CH_3-C*H*$_2$-CH_2), 0.97 (t, 2H)

^{13}C NMR (100 MHz, CD_3OD): δ(ppm) = 57.94 (CH_2), 50.94 (CH_2), 48.53 (CH_2), 45.45 (CH_3), 35.28 (CH_3), 32.67 (CH_2), 32.56 (CH_2), 25.80 (CH_2), 22.90 (CH_2), 14.02 (CH_3)

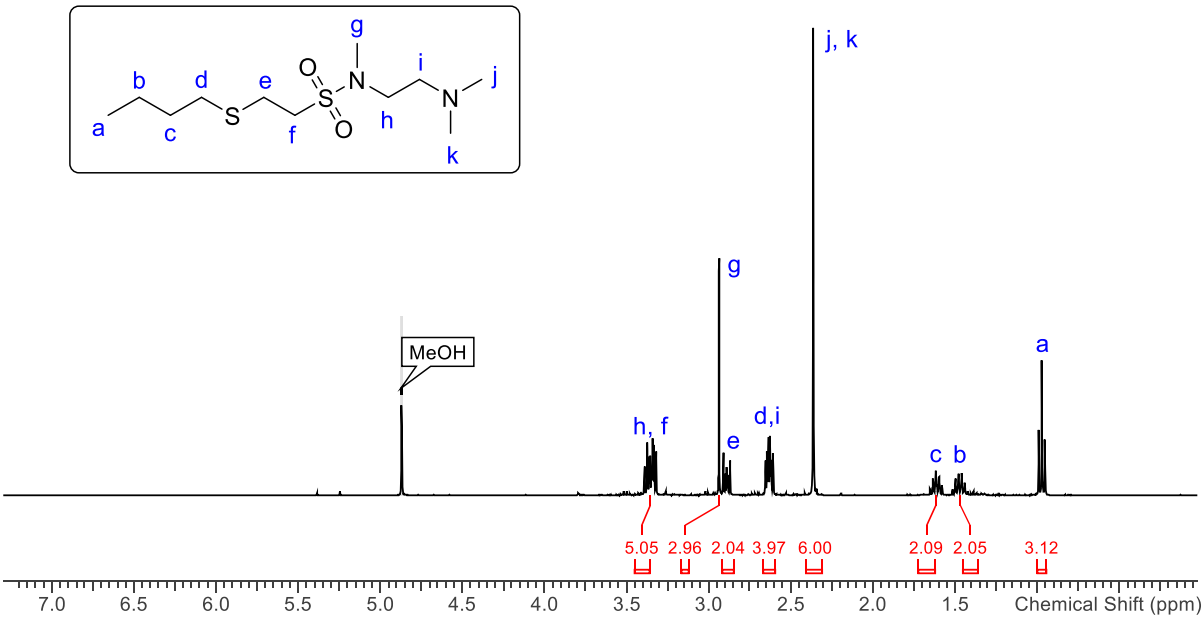


Figure S32: ^{1}H NMR spectra (CD_3OD) of 2-(butylthio)-*N*-(2-(dimethylamino)ethyl)-*N*-methylethane-1-sulfonamide.

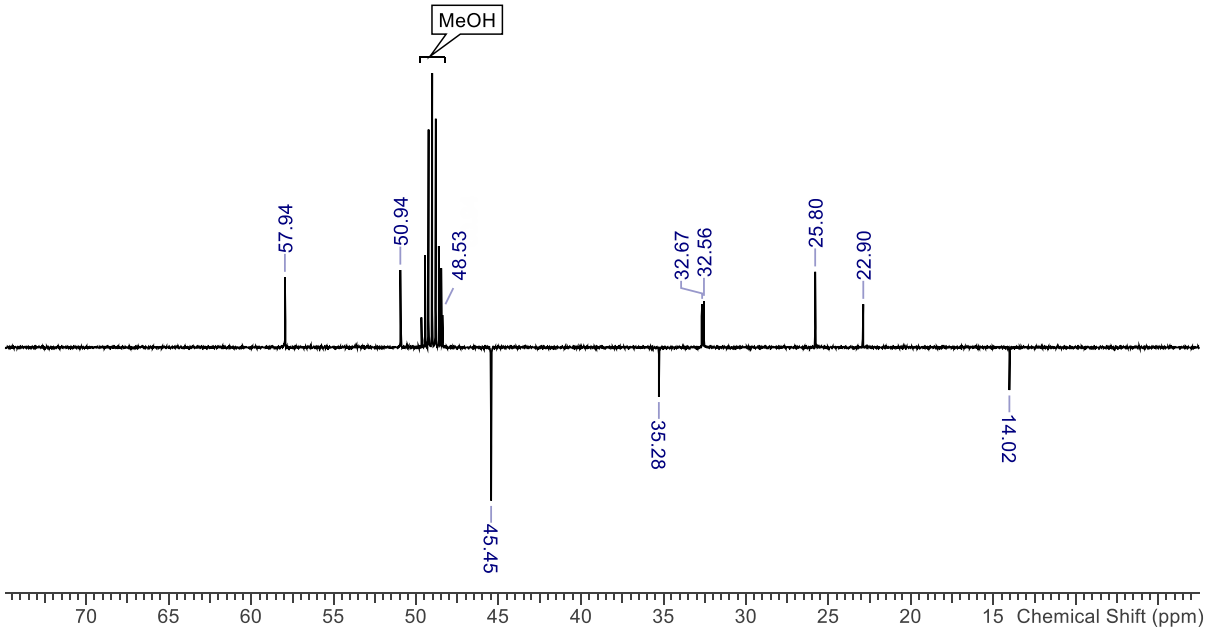
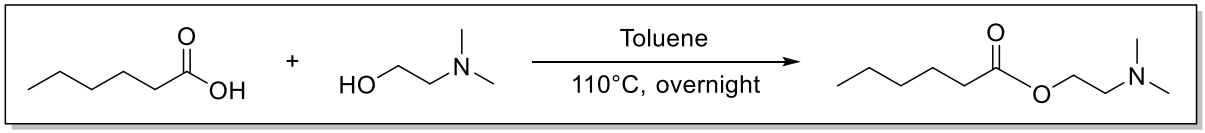


Figure S33: ^{13}C NMR spectra (CD_3OD) of 2-(butylthio)-*N*-(2-(dimethylamino)ethyl)-*N*-methylethane-1-sulfonamide.

Synthesis of 2-(dimethylamino)ethyl hexanoate



2-(dimethylamino)ethyl hexanoate was synthesised according to a literature procedure.[4]

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 4.16 (t, *J*=5.75 Hz, 2H, O-C*H*$_2$), 2.55 (t, *J*=5.75 Hz, 2H, C*H*$_2$-N-(CH$_3$)$_2$), 2.31 (br t, *J*=7.54 Hz, 2H, C*H*$_2$-CO), 2.27 (s, 6H, N-(C*H*$_3$)$_2$), 1.61 (m, 2H, C*H*$_2$-CH$_2$-CO), 1.29 (m, 4H, C*H*$_2$-C*H*$_2$-CH$_3$), 0.88 (m, 3H, CH$_2$-C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 173.92 (C_q), 61.99 (CH_2), 57.83 (CH_2), 45.68 (CH_3), 34.20 (CH_2), 31.27 (CH_2), 24.60 (CH_2), 22.29 (CH_2), 13.88 (CH_3)

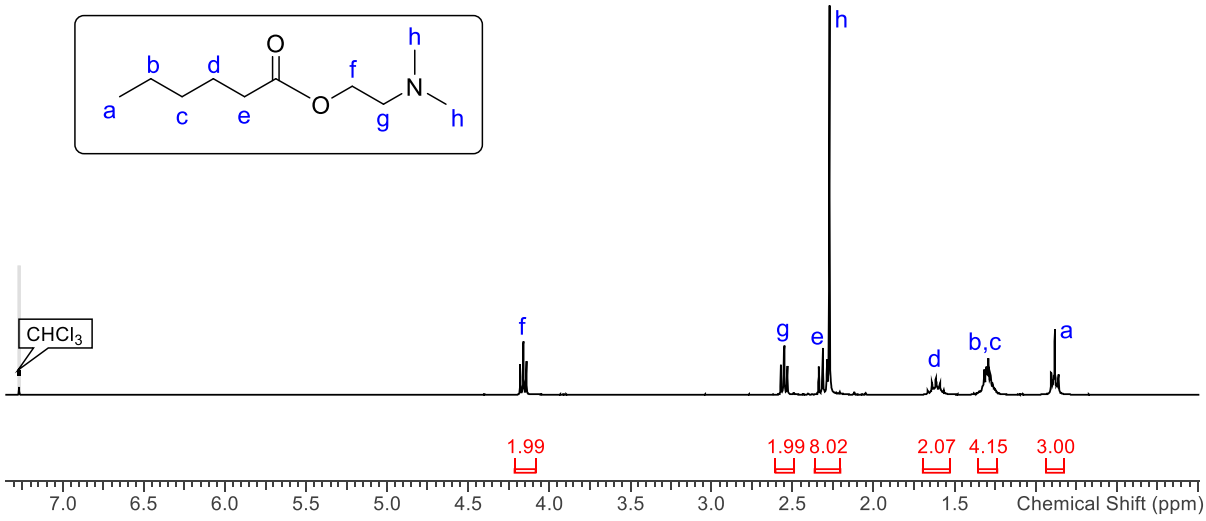


Figure S34: ^{1}H NMR spectra ($CDCl_3$) of 2-(dimethylamino)ethyl hexanoate.

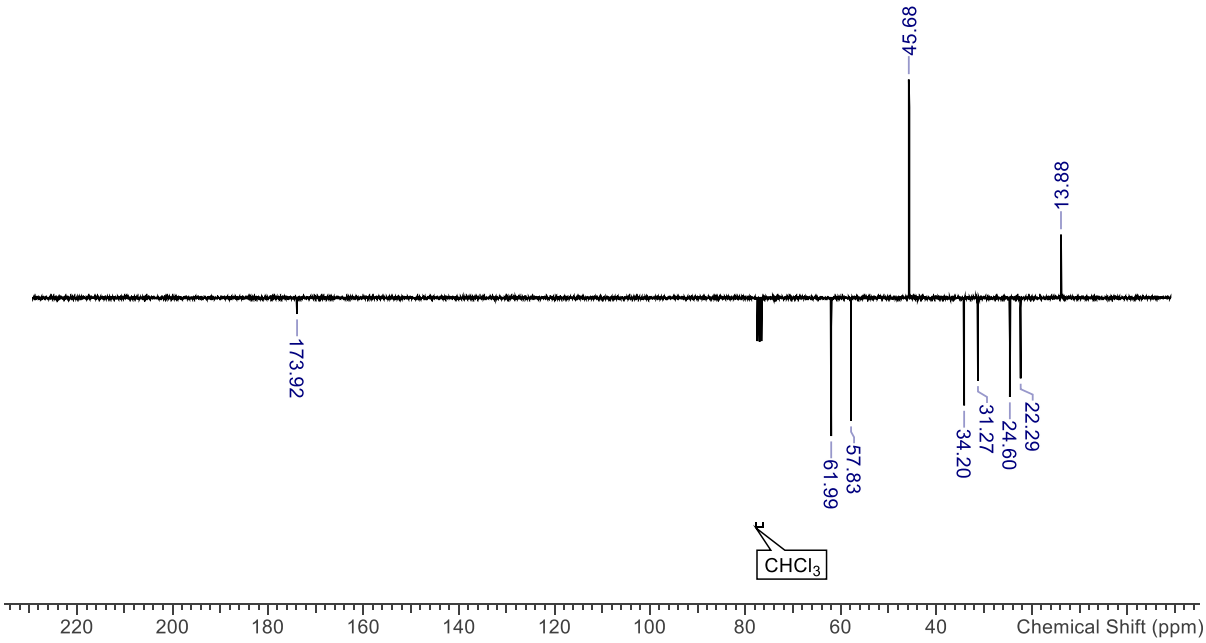
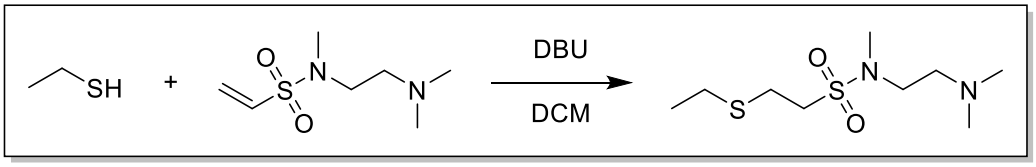


Figure S35: ^{13}C NMR spectra ($CDCl_3$) of 2-(dimethylamino)ethyl hexanoate.

Synthesis of *N*-(2-(dimethylamino)ethyl)-2-(ethylthio)-*N*-methylethane-1-sulfonamide



N-(2-(dimethylamino)ethyl)-*N*-methylethenesulfonamide (500 mg, 2.6 mmol, 1 eq.) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 8 mg, 0.02 eq.) was solubilised in 10 mL dichloromethane. Next, ethanethiol (206 µL, 177.7 mg, 2.86 mmol, 1.1 eq.) was added. The resulting reaction mixture was stirred overnight before removal of the solvent *in vacuo.* The resulting product was obtained quantitatively and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 3.25 (m, 2H, N-CH_2), 3.19 (m, 2H, S-CH_2), 2.85 (m, 5H, N-CH_3, S-CH_2-CH_3), 2.52 (q, 2H, CH_3-CH_2), 2.41 (t, 2H, $N(CH_3)_2$-CH_2), 2.19 (m, 6H, $N(CH_3)_2$), 1.21 (t, 2H, CH_2-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) = 57.43 (CH_2), 50.89 (CH_2), 47.94 (CH_2), 45.57 (CH_3), 34.84 (CH_3), 26.11 (CH_2), 24.64 (CH_2), 14.64 (CH_3)

ESI-MS: *calc.*: 255.11, *found:* 255.1 $[M+H]^+$

pKa = 8.46

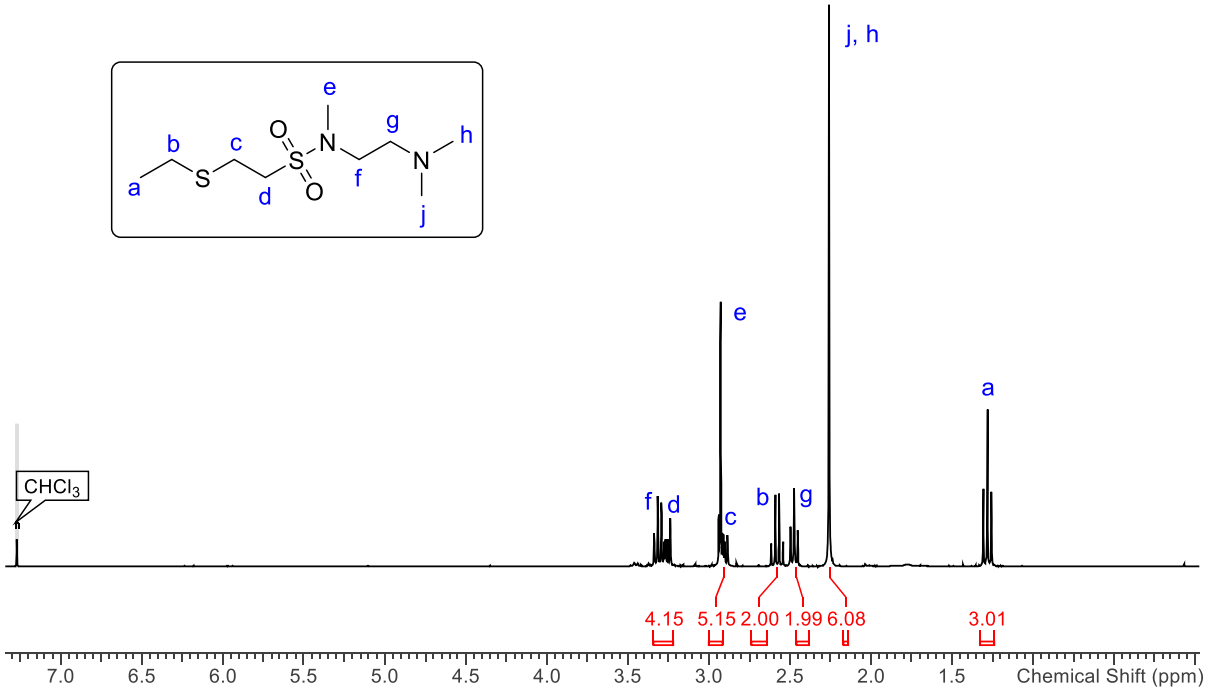


Figure S36: ^{1}H NMR spectra ($CDCl_3$) of *N*-(2-(dimethylamino)ethyl)-2-(ethylthio)-*N*-methylethane-1-sulfonamide.

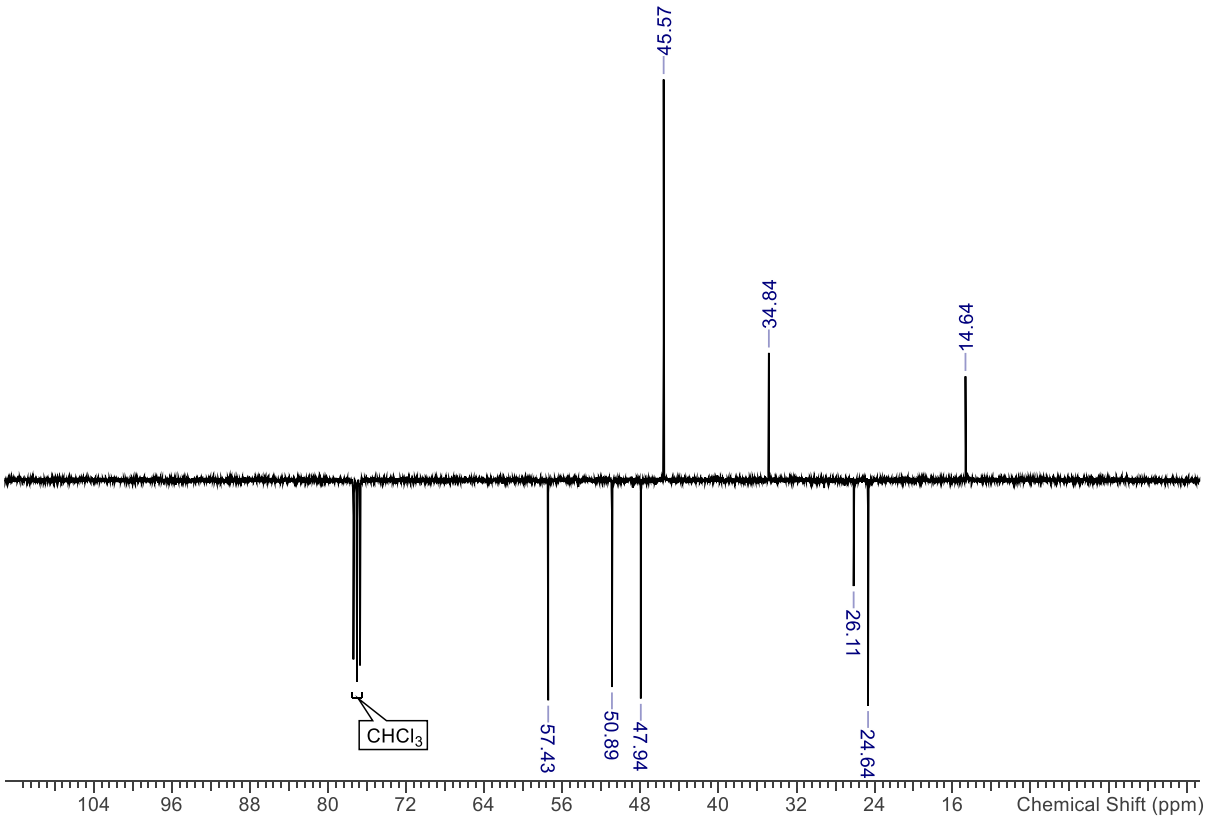


Figure S37: ^{13}C NMR spectra ($CDCl_3$) of *N*-(2-(dimethylamino)ethyl)-2-(ethylthio)-*N*-methylethane-1-sulfonamide.

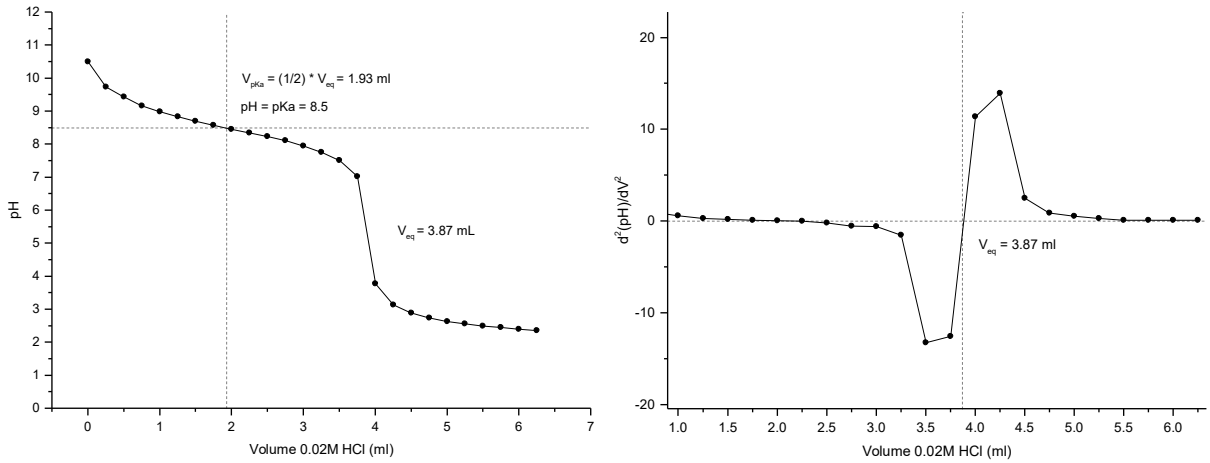
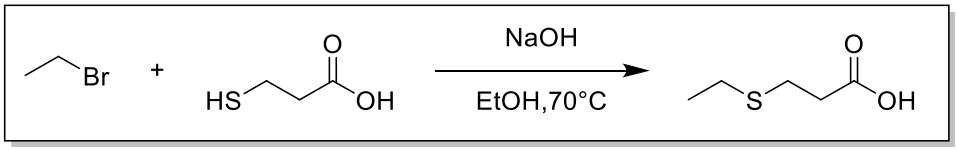


Figure S38: Determination of the pKa of *N*-(2-(dimethylamino)ethyl)-2-(ethylthio)-*N*-methylethane-1-sulfonamide *via* titration with 0.02M HCl: (left) titration curve and (right) the first derivative.

Synthesis of 3-(ethylthio)propanoic acid



3-Mercaptopropanoic acid (562 mg, 5.3 mmol, 1 eq.) and sodium hydroxide (445 mg, 11.13 mmol, 2.1 eq.) were weighed out in a flask and solubilised in 10 mL ethanol. Than 1-bromoethane (500 µL, 5.83 mmol, 1.1 eq.) was added and the temperature was increased to 70°C. After stirring overnight, the reaction mixture was cooled down to room temperature. Next, 1M HCl was added till a pH of 1 was reached. The mixture was transferred to an extraction funnel and the product was extracted with ethyl acetate. The organic fractions were collected and dried with magnesium sulphate. After filtration, the solvent was removed *in vacuo*, yielding the pure product (612 mg, 93.9%).

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) = 2.81 (t, 2H, CO-C*H*$_2$), 2.68 (t, 2H, CO-CH$_2$-C*H*$_2$), 2.58 (q, 2H, CH$_3$-C*H*$_2$), 1.27 (m, 3H, C*H*$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) = 178.17 (Cq), 34.63 (CH_2), 26.12 (CH_2), 25.99 (CH_2), 14.63 (CH_3)

pKa = 4.26

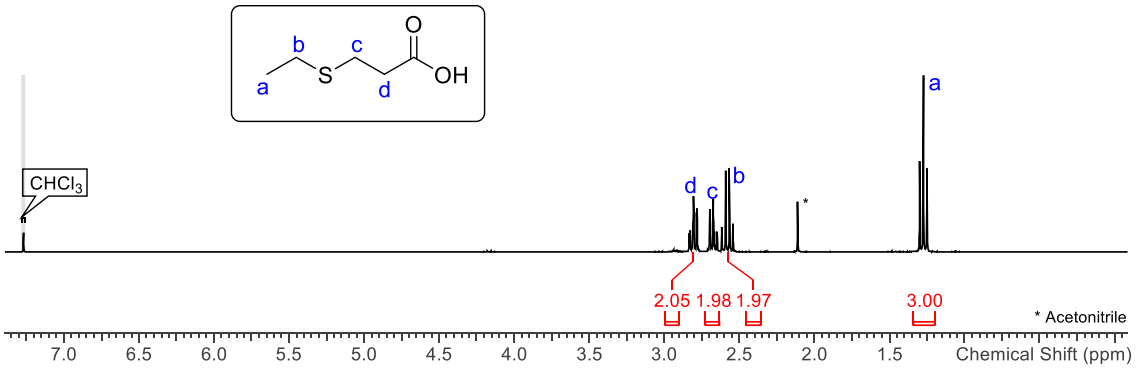


Figure S39: ^{1}H NMR spectra ($CDCl_3$) of 3-(ethylthio)propanoic acid.

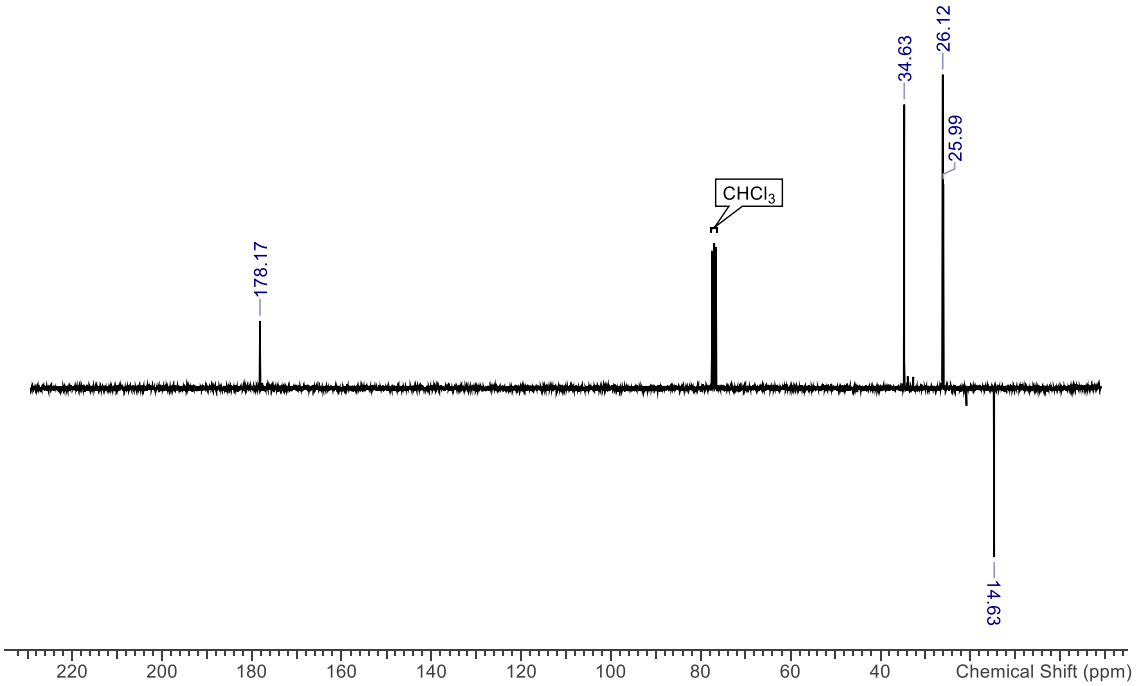


Figure S40: ^{13}C NMR spectra ($CDCl_3$) of 3-(ethylthio)propanoic acid.

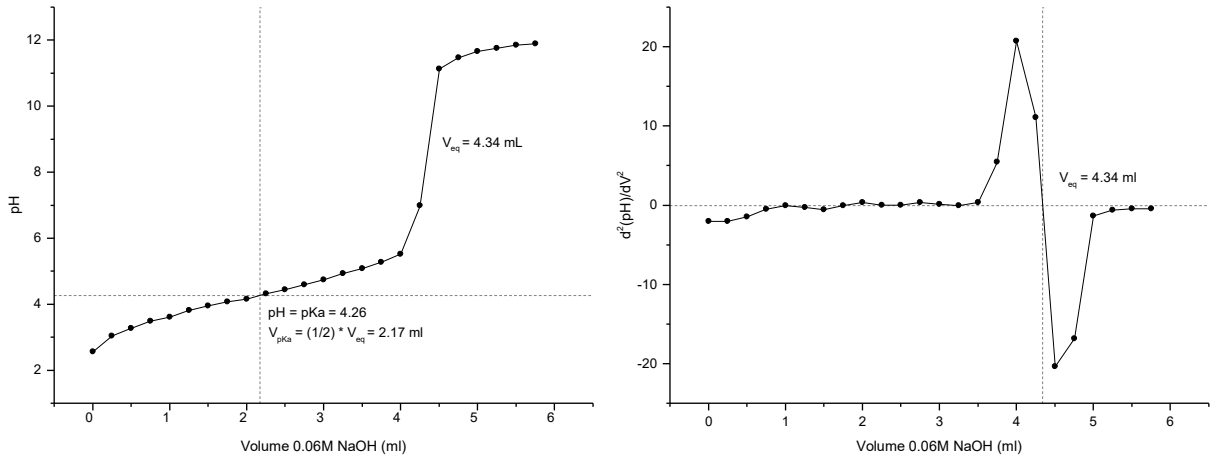
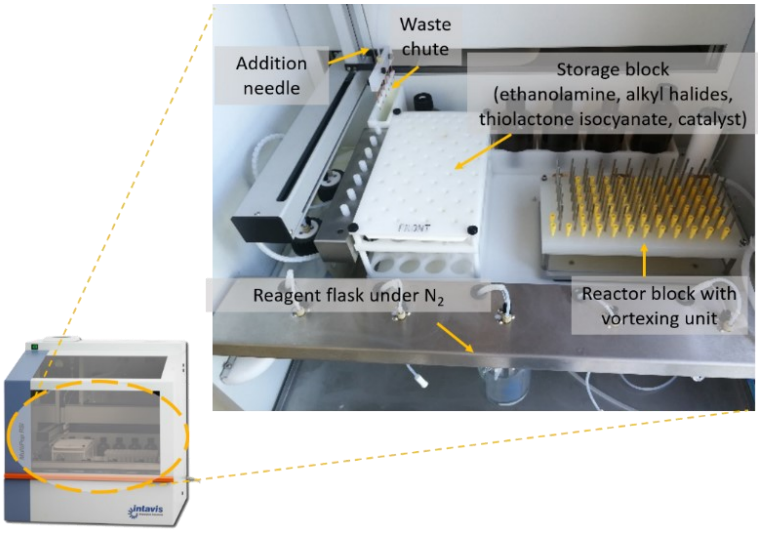


Figure S41: Determination of the pKa of *N*-(2-(dimethylamino)ethyl)-2-(ethylthio)-*N*-methylethane-1-sulfonamide *via* titration with 0.06M NaOH: (left) titration curve and (right) the first derivative.

Automated oligoampholytes synthesis

Layout of the liquid handling robot



Reagent stock solutions

Dimethylformamide used for washing of the resin was taken directly from a 2.5 L solvent bottle, while chloroform and methanol were stored in reagents flask under a N_2 atmosphere.

Stock solutions placed in storage bock:

- Solution 1 [EA]: ethanolamine (1.2 mol/l) in $CHCl_3$
- Solution 2 [TLa-NCO]: α-isocyanato-γ-thiolactone (1.1 mol/l) in dry $CHCl_3$
- Solution 3 [Catalyst]: zirconium(IV) acetylacetonate (0.2 mol/l) in dry $CHCl_3$
- Other solutions: [Michael acceptor]: 1.2 mol/l in $CHCl_3$

Procedure

The equivalents used in the automated synthesis are analogous to the manual synthesis. 100 mg of thiolactone functionalised resin (0.5 mmol/g) was put in a reactor. For the amine-thiol-Michael conjugation 834 µL of the Michael acceptor solution was put in the reactor and 417 µL of the ethanolamine solution. The reactor was vortexed for 30 min and subsequently the reagent mixture was removed by filtration. This step was then repeated twice, after which the resin was washed with dimethylformamide (4 x 1.5 mL), methanol (3 x 1.5 mL) and chloroform (4 x 1.5 mL). During the chain extension step 910 µL of the TLa-NCO solution was first deposited in the reactor, followed by 250 µL of the catalyst solution. The reactor was vortexed for one hour. Next, 0.5 mL of dimethylformamide was added to the reactor to solubilise the urea by-product that is formed, due to the reaction of the isocyanate with air humidity (see manuscript). The reactor is then vortexed for one minute. The resin was then washed with dimethylformamide (4 x 2 mL), methanol (3 x 1.5 mL) and chloroform (4 x 1.5 mL). This step was performed three times in total.

Alcoholysis/hydrolysis of butanethiol-acrylate adducts

The β-thioester model compound (10 mg) was solubilised in deuterated methanol (0.6 mL) and measured periodically to follow the methanolysis via 1H NMR. In between the different measurements the NMR tube was kept in a thermostatic water bath at 25°C.

Methanolysis of 2-(dimethylamino)ethyl 3-(butylthio)propanoate

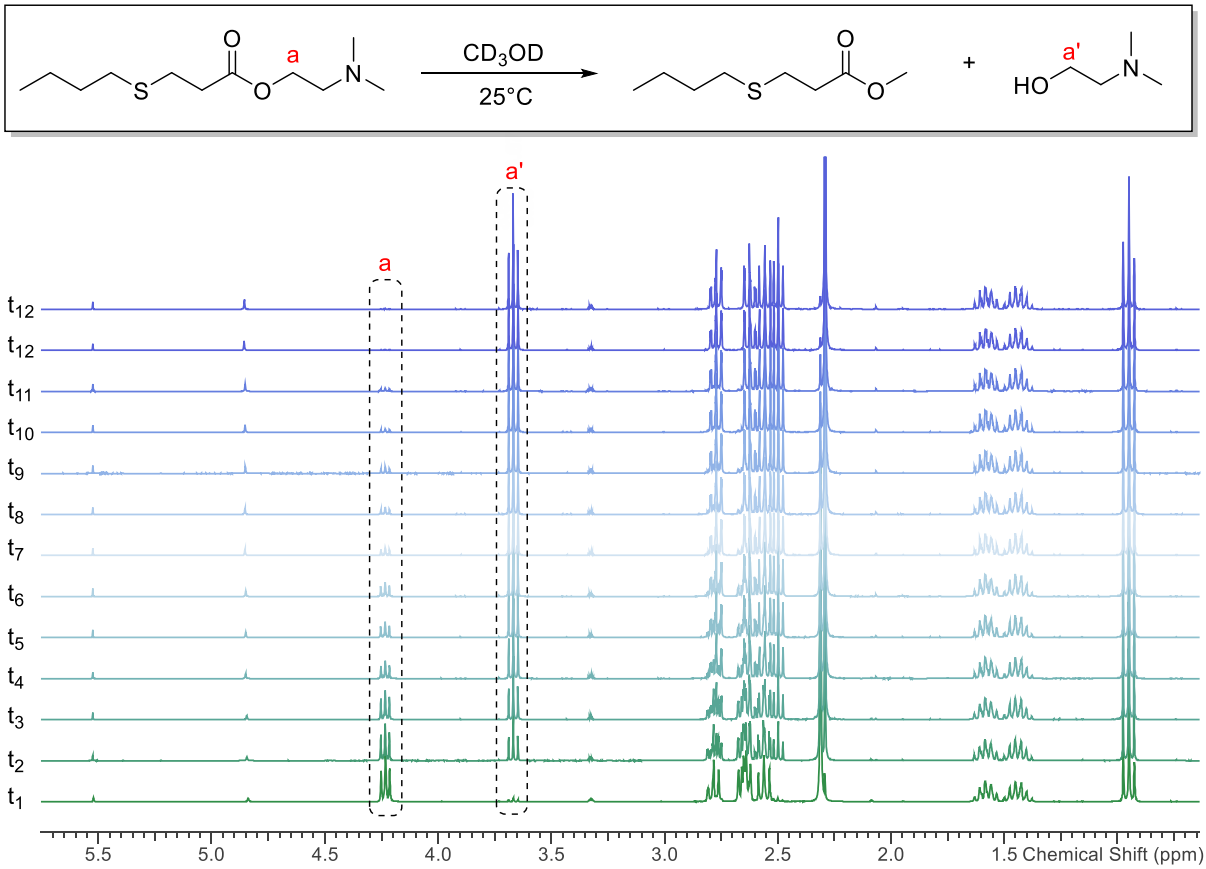


Figure S42: ^{1}H NMR spectra recorded over time to follow the methanolysis of 2-(dimethylamino)ethyl 3-(butylthio)propanoate.

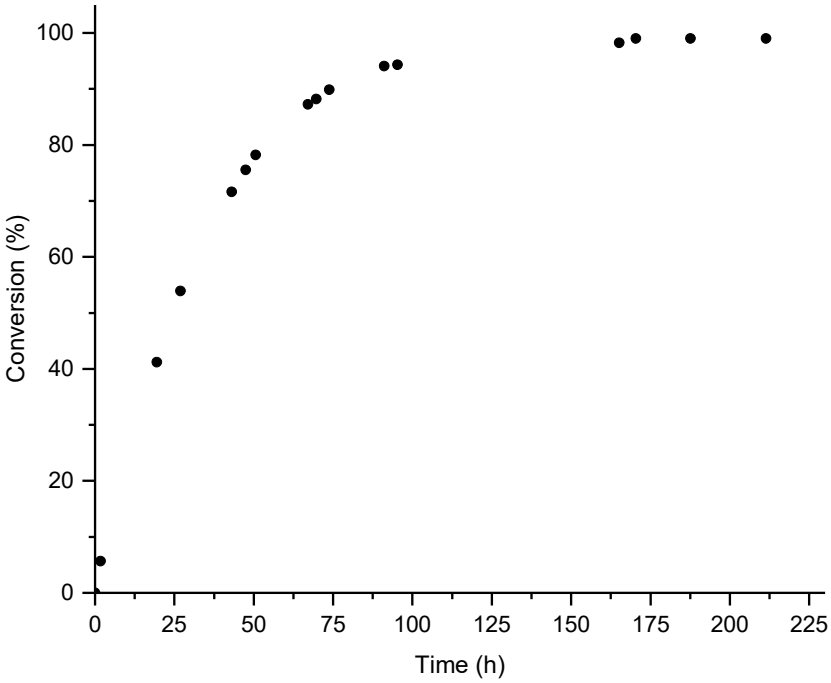


Figure S43: Methanolysis of 2-(dimethylamino)ethyl 3-(butylthio)propanoate as a function of time assessed by ^{1}H NMR spectroscopy.

Hydrolysis of 2-(dimethylamino)ethyl 3-(butylthio)propanoate

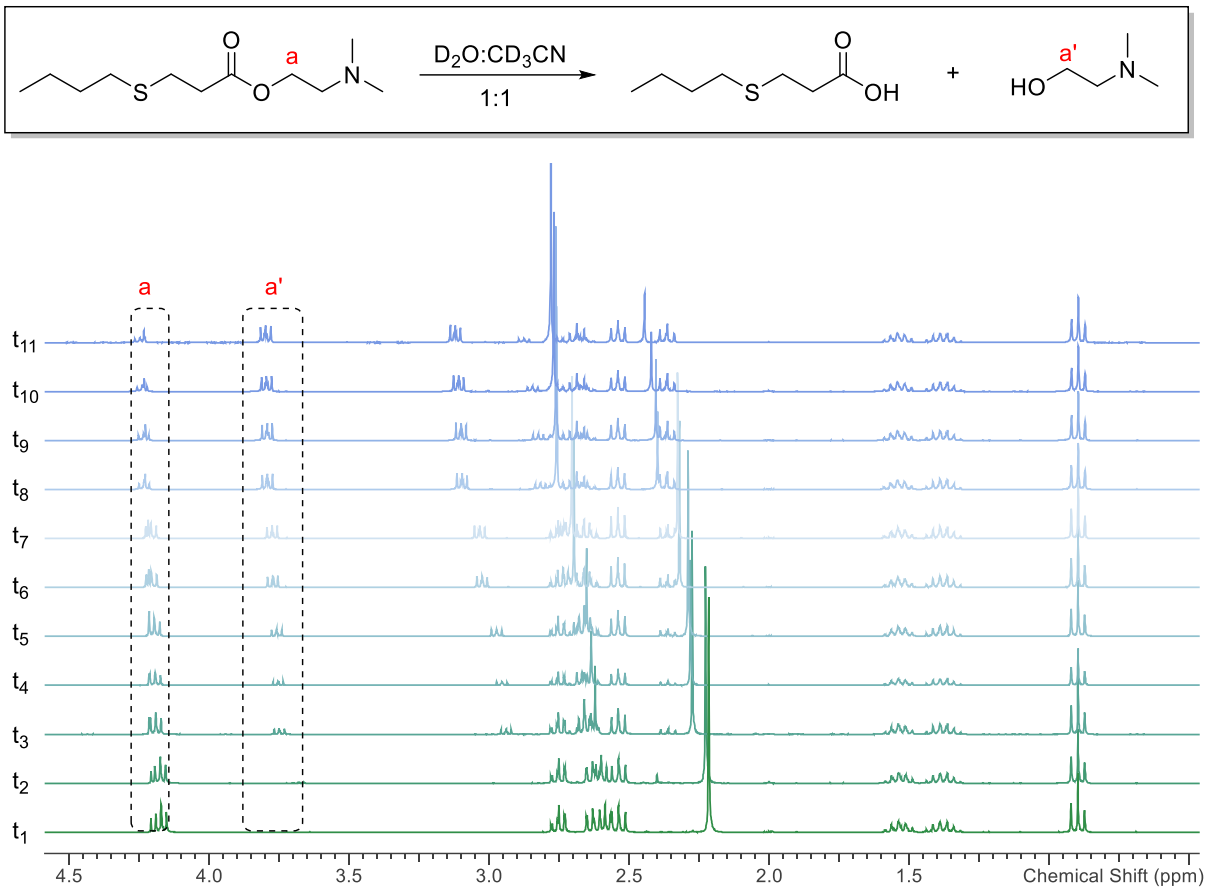


Figure S44: ^{1}H NMR spectra recorded over time to follow the hydrolysis of 2-(dimethylamino)ethyl 3-(butylthio)propanoate in a 1:1 mixture of deuterated water and acetonitrile.

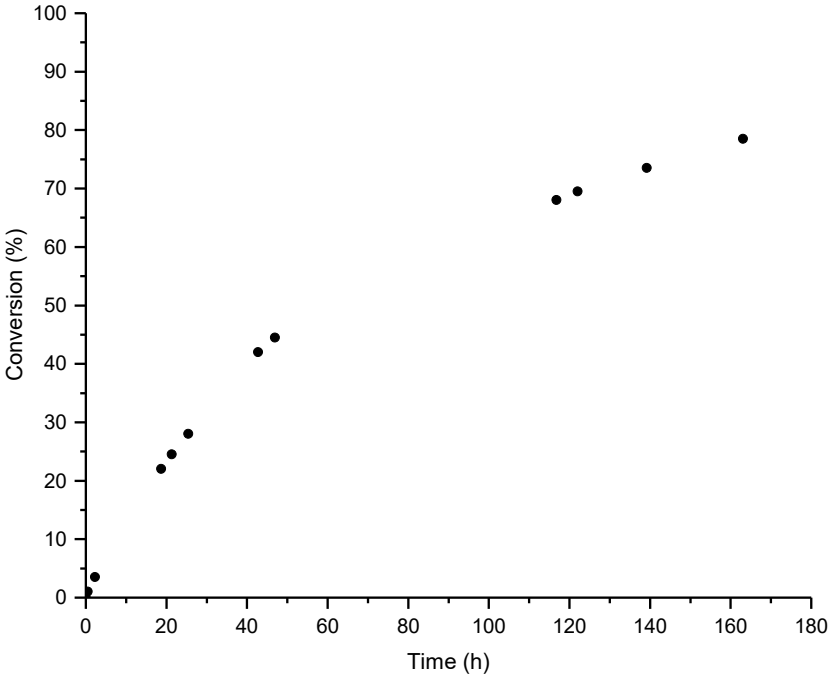


Figure S45: Hydrolysis of 2-(dimethylamino)ethyl 3-(butylthio)propanoate as a function of time assessed by ^{1}H NMR spectroscopy in a 1:1 mixture of deuterated water and acetonitrile.

Methanolysis of 3-(dimethylamino)propyl 3-(butylthio)propanoate

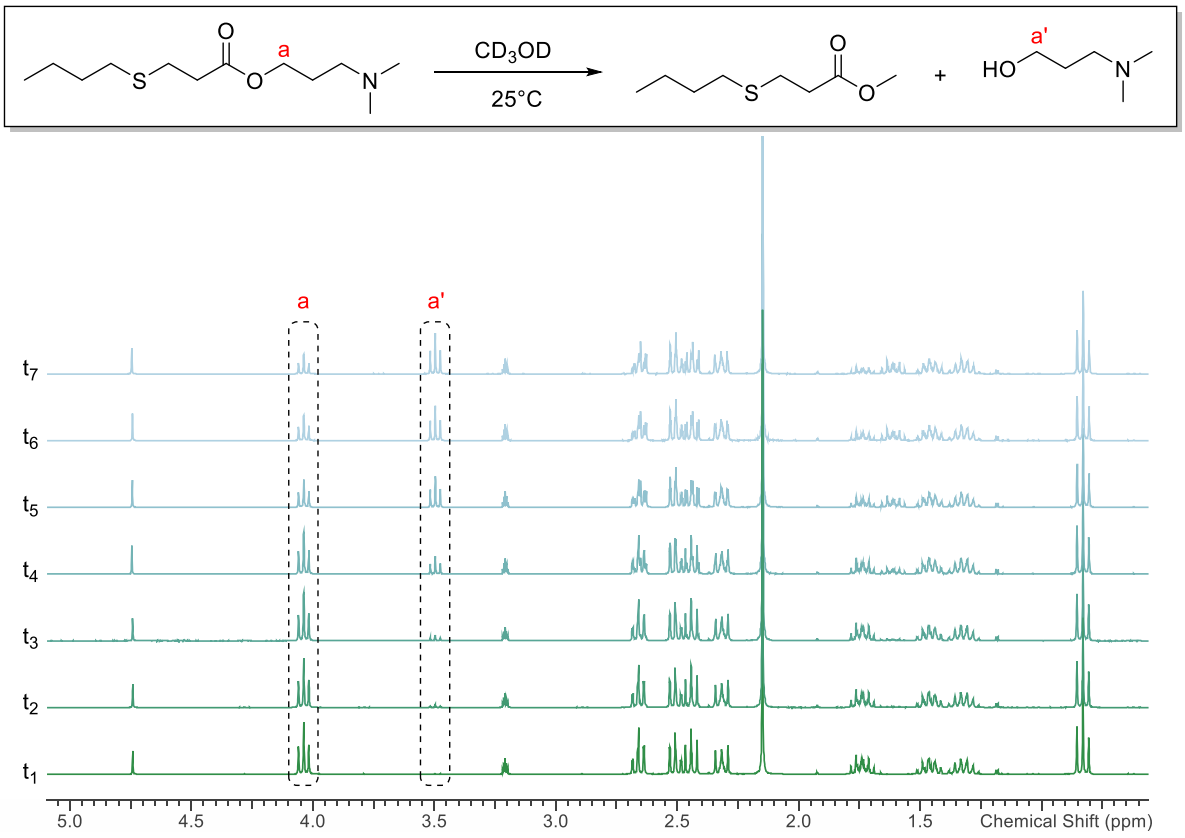


Figure S46: ^{1}H NMR spectra recorded over time to follow the methanolysis of 3-(dimethylamino)propyl 3-(butylthio)propanoate.

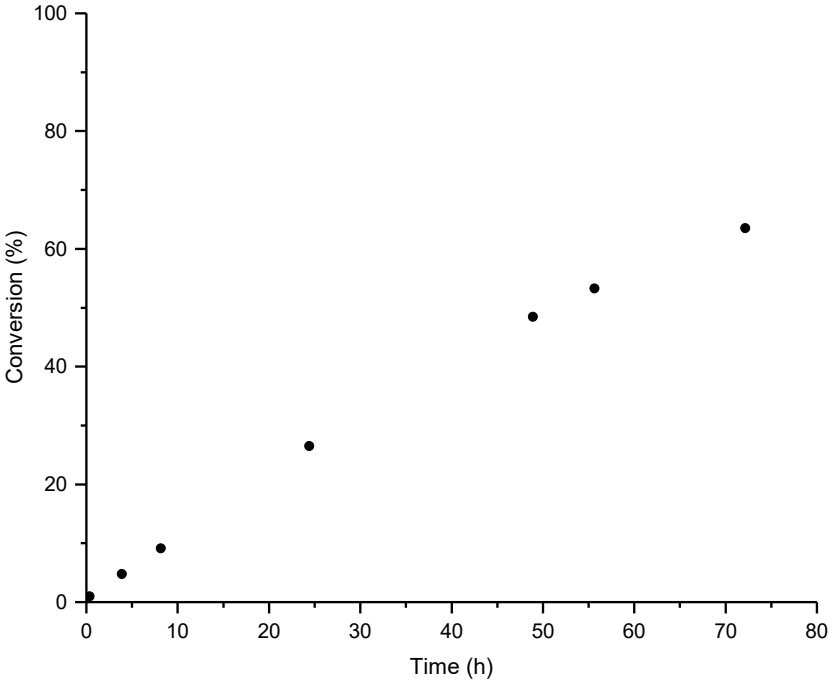


Figure S47: Methanolysis of 3-(dimethylamino)propyl 3-(butylthio)propanoate as a function of time assessed by ^{1}H NMR spectroscopy.

Methanolysis of 4-(dimethylamino)butyl 3-(butylthio)propanoate

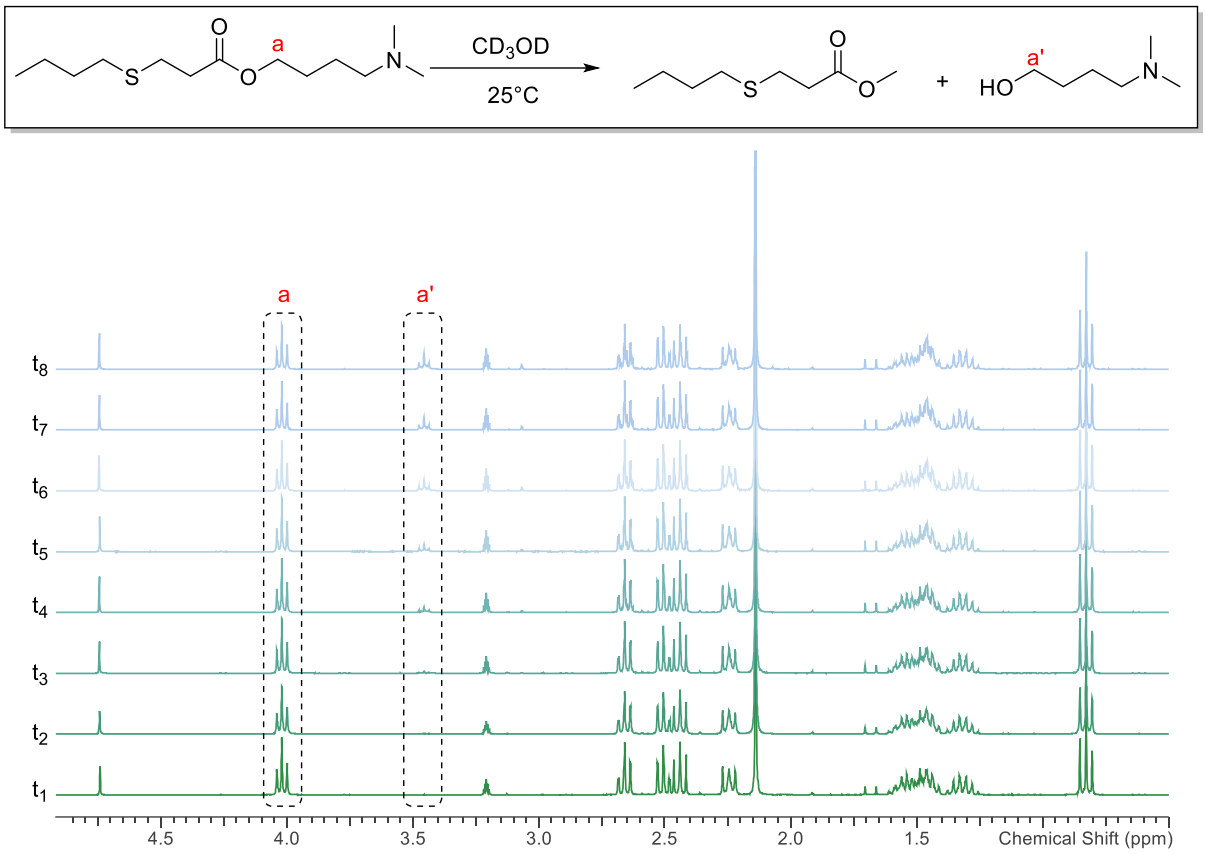


Figure S48: ^{1}H NMR spectra recorded over time to follow the methanolysis of 4-(dimethylamino)butyl 3-(butylthio)propanoate.

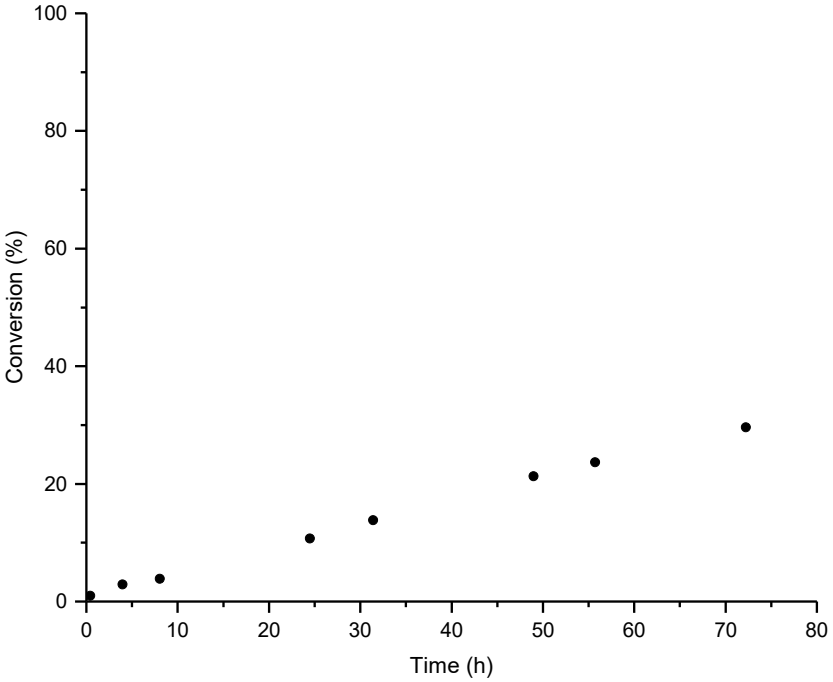


Figure S49: Methanolysis of 4-(dimethylamino)butyl 3-(butylthio)propanoate as a function of time assessed by ^{1}H NMR spectroscopy.

Methanolysis of 1-methylpiperidin-4-yl 3-(butylthio)propanoate

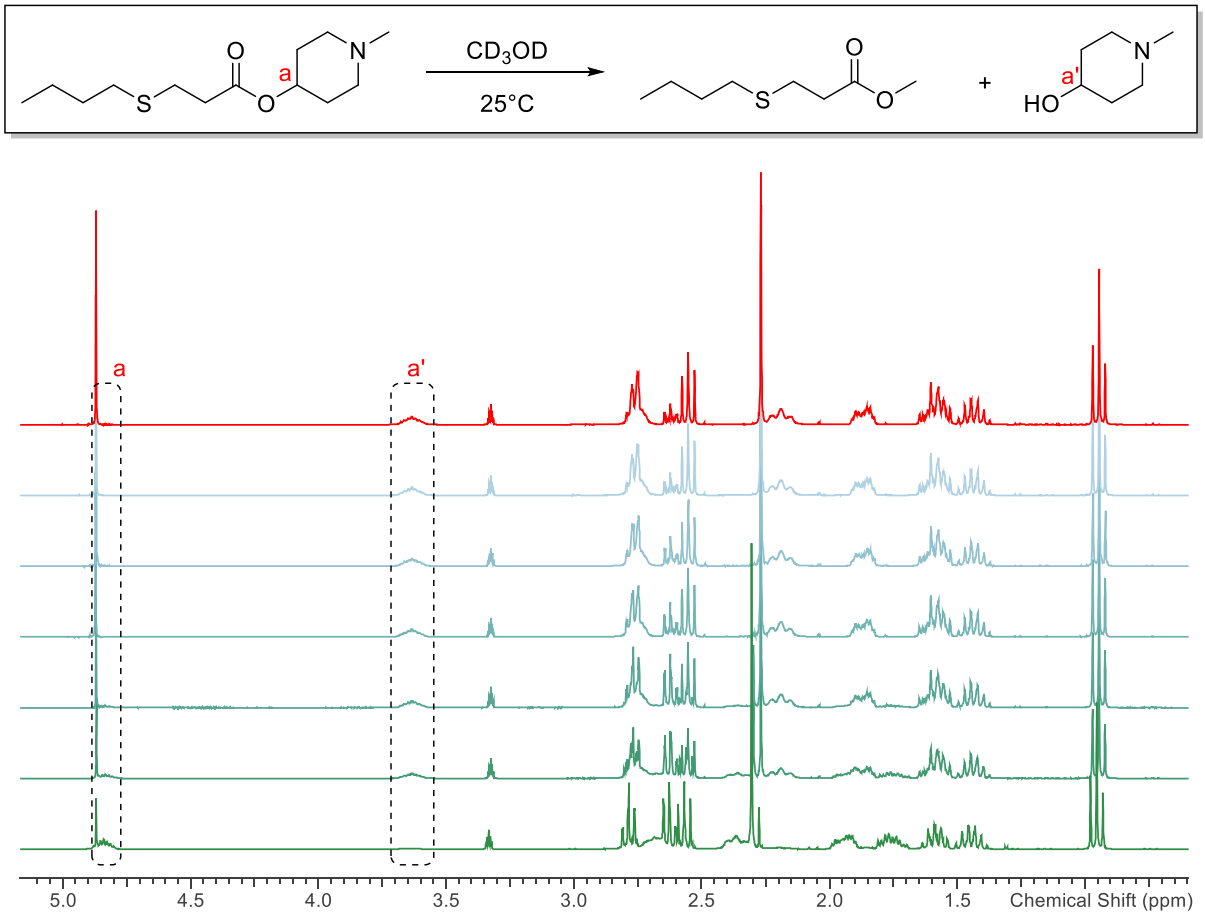


Figure S50: ^{1}H NMR spectra recorded over time to follow the methanolysis of 1-methylpiperidin-4-yl 3-(butylthio)propanoate.

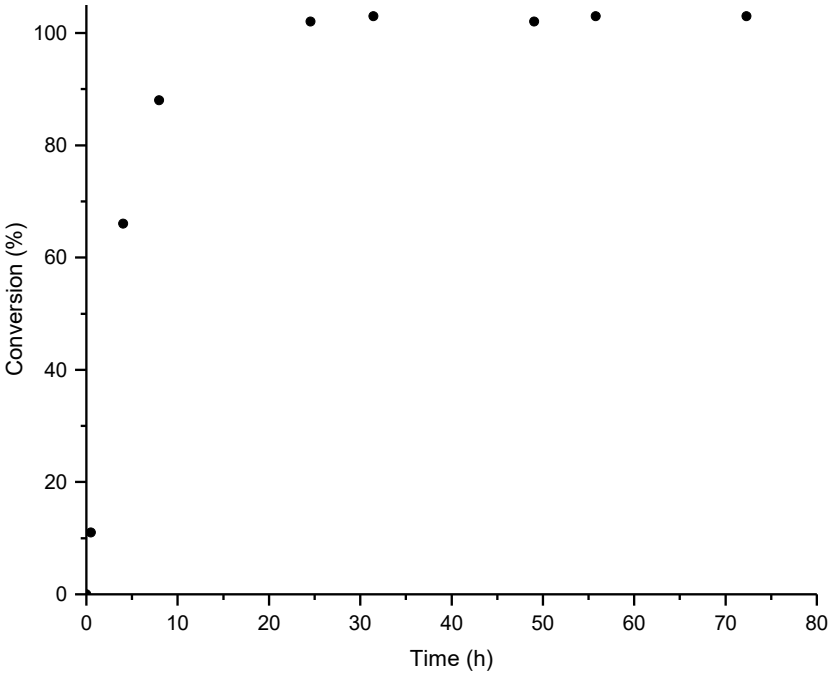


Figure S51: Methanolysis of 1-methylpiperidin-4-yl 3-(butylthio)propanoate as a function of time assessed by ^{1}H NMR spectroscopy.

Methanolysis of 2-((3-(butylthio)propanoyl)oxy)-*N*,*N*,*N*-trimethylethan-1-aminium

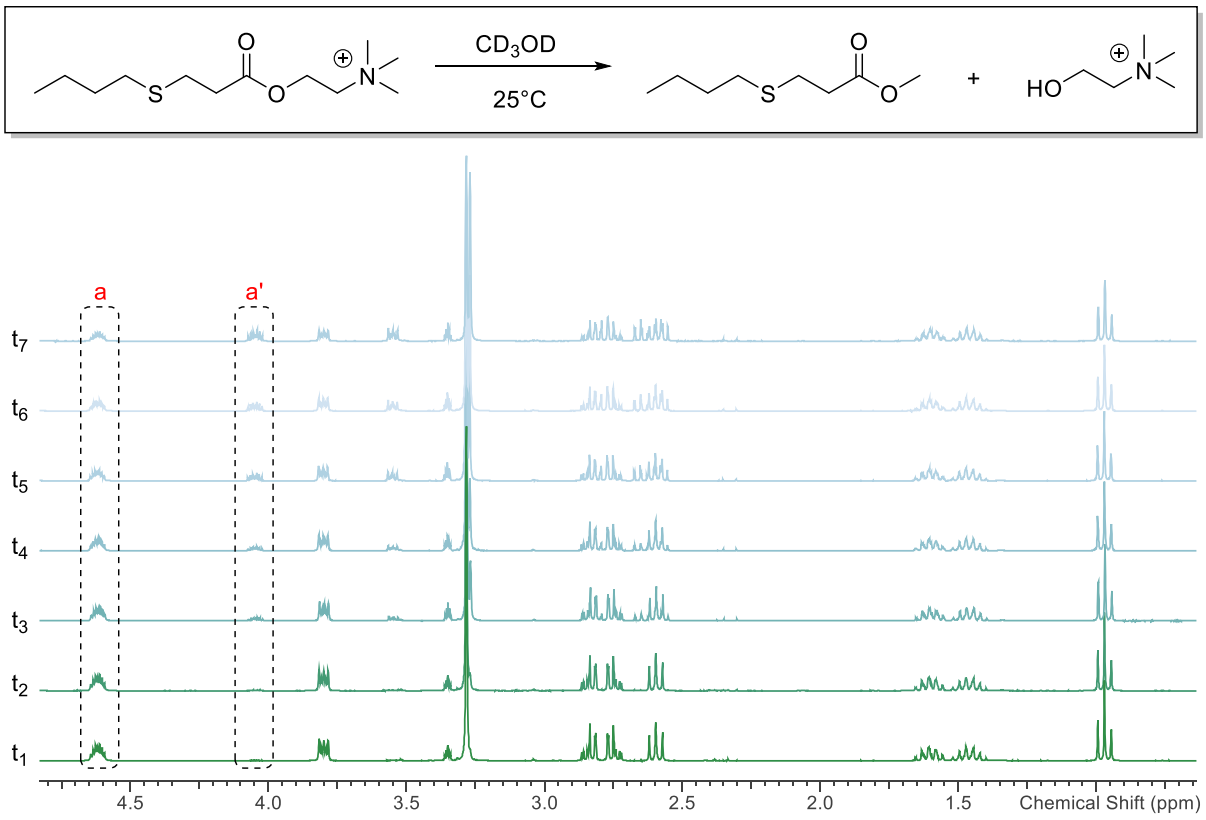


Figure S52: ^{1}H NMR spectra recorded over time to follow the methanolysis of 2-((3-(butylthio)propanoyl)oxy)-*N*,*N*,*N*-trimethylethan-1-aminium.

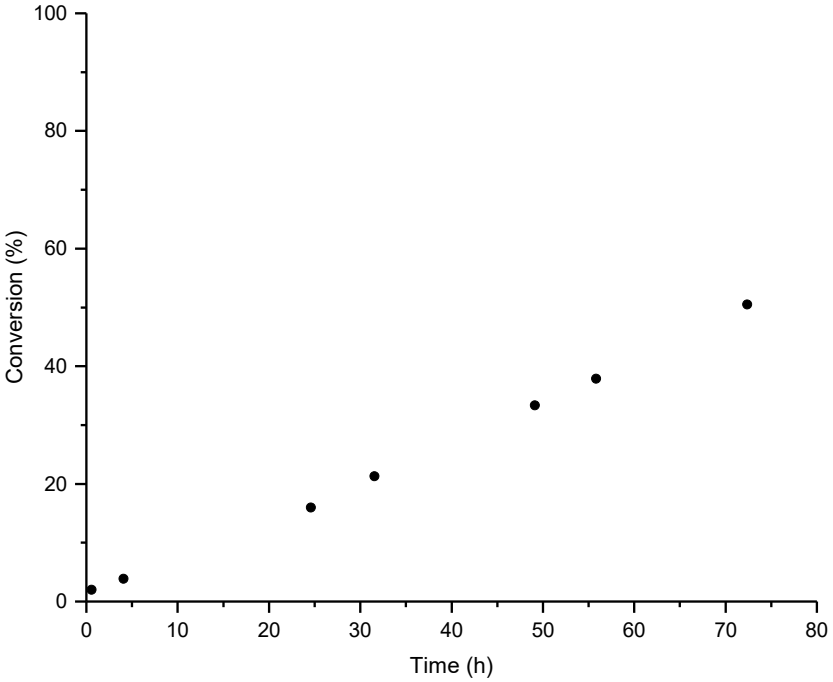


Figure S53: Methanolysis of 2-((3-(butylthio)propanoyl)oxy)-*N*,*N*,*N*-trimethylethan-1-aminium as a function of time assessed by ^{1}H NMR spectroscopy.

Turbidimetry

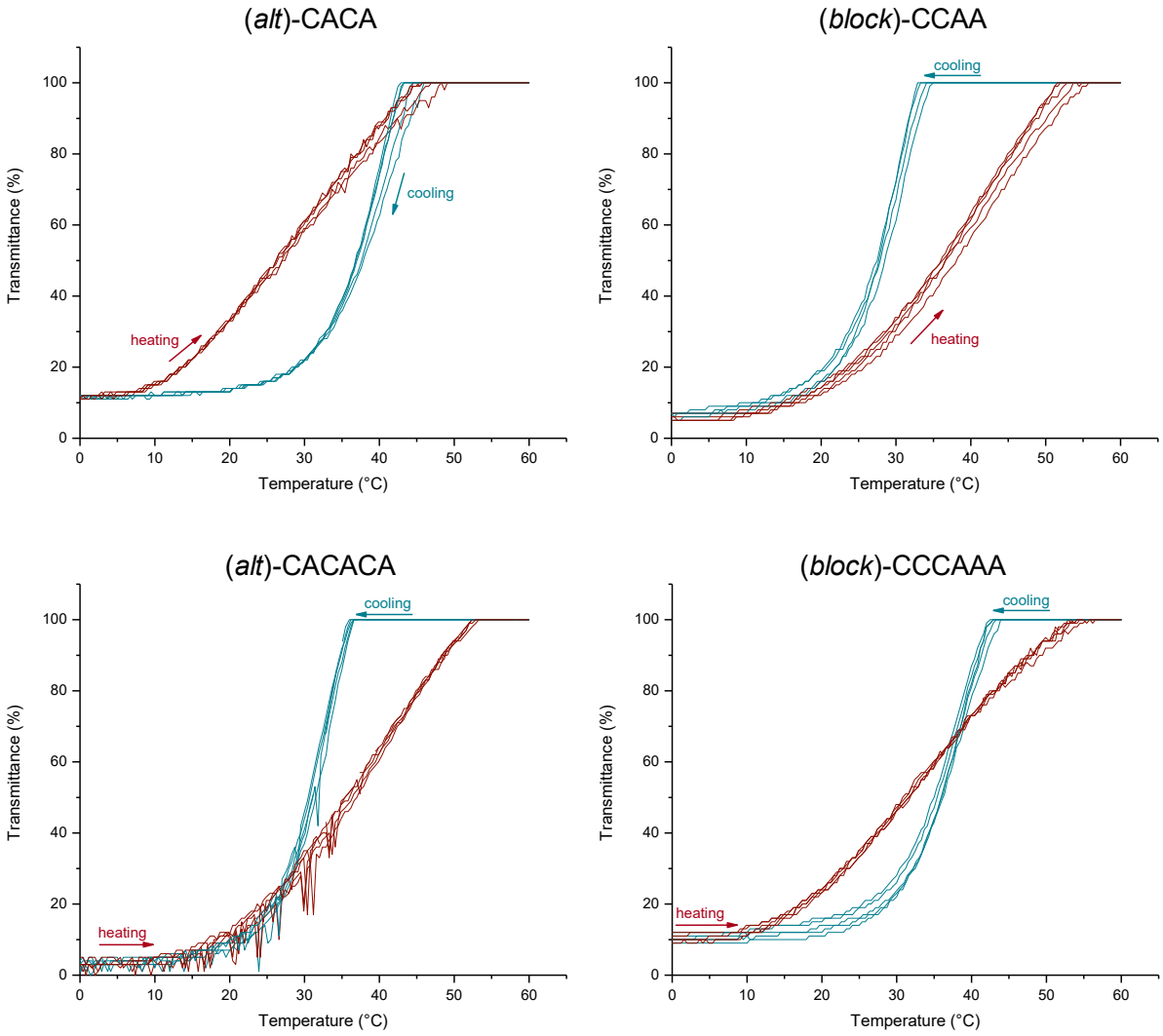
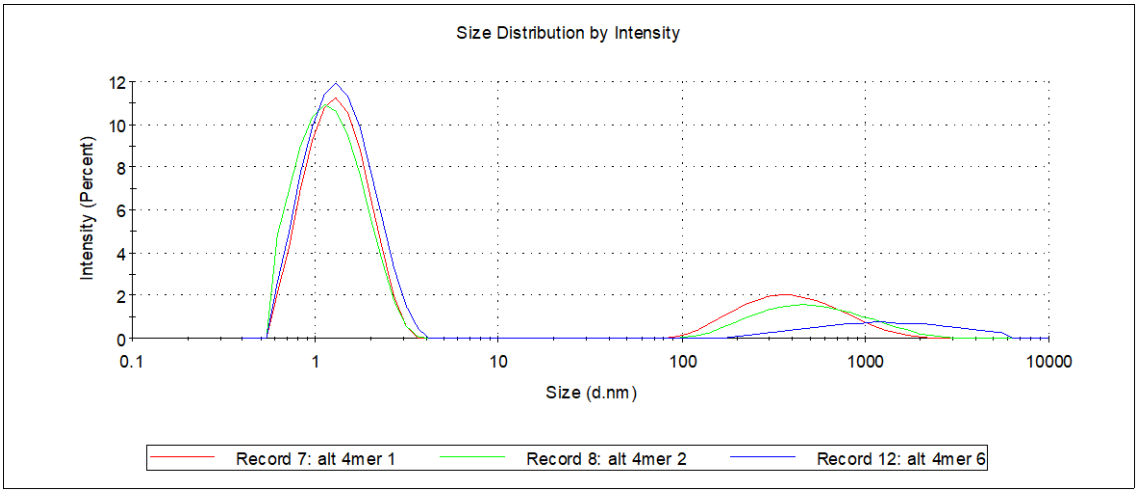


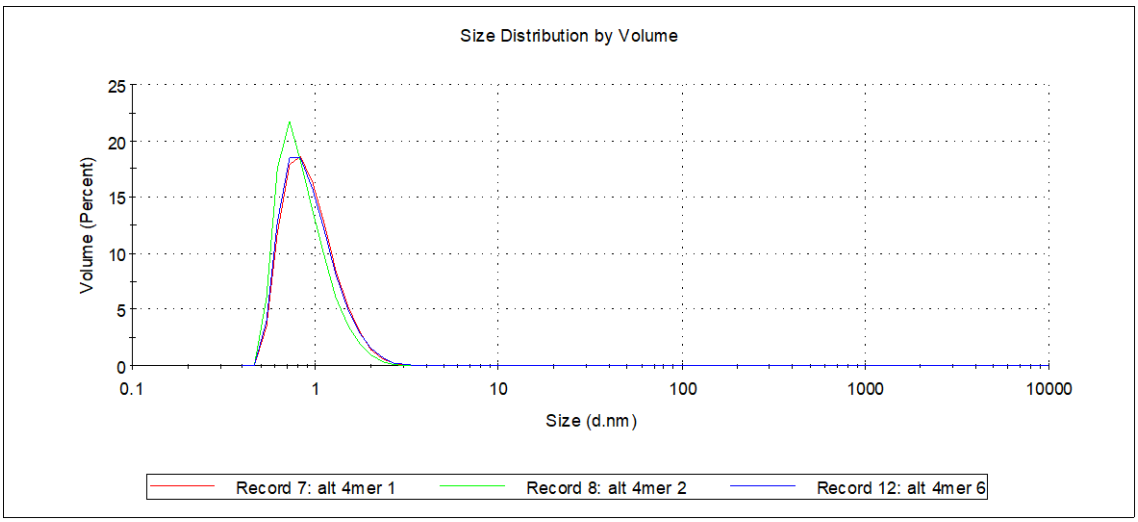
Figure S54: Turbidimetry analysis of a 5 mg/mL oligoampholytes solution in a water/isopropanol mixture (25/85 vol%), each sample underwent five heating and cooling cycles.

Dynamic light scattering measurements

(*alt*)-CACA

85 vol% isopropanol (60°C), 5 mg/mL





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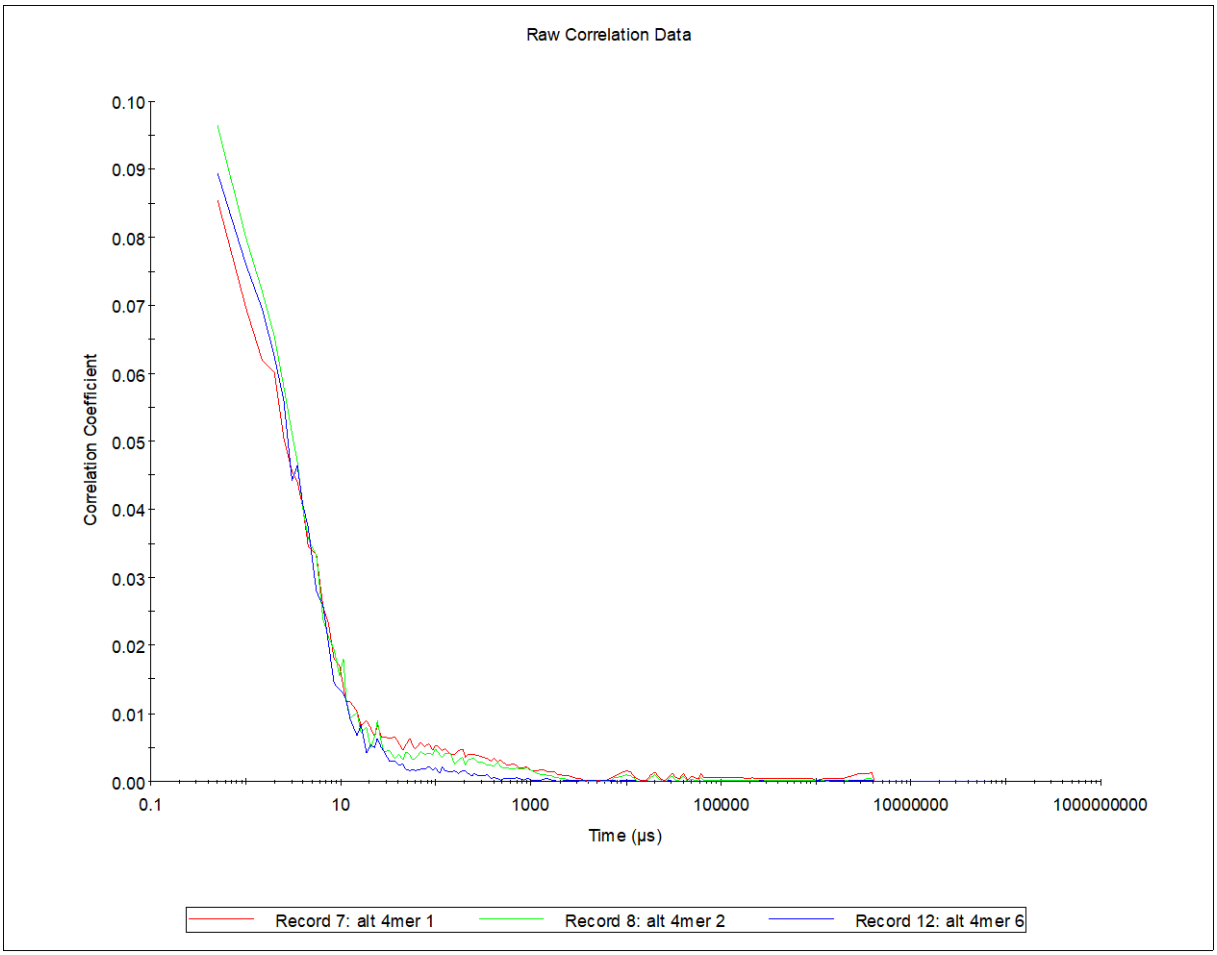
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Record 8: alt 4mer 2
Record 12: alt 4mer 6

Water (5 mg/mL)

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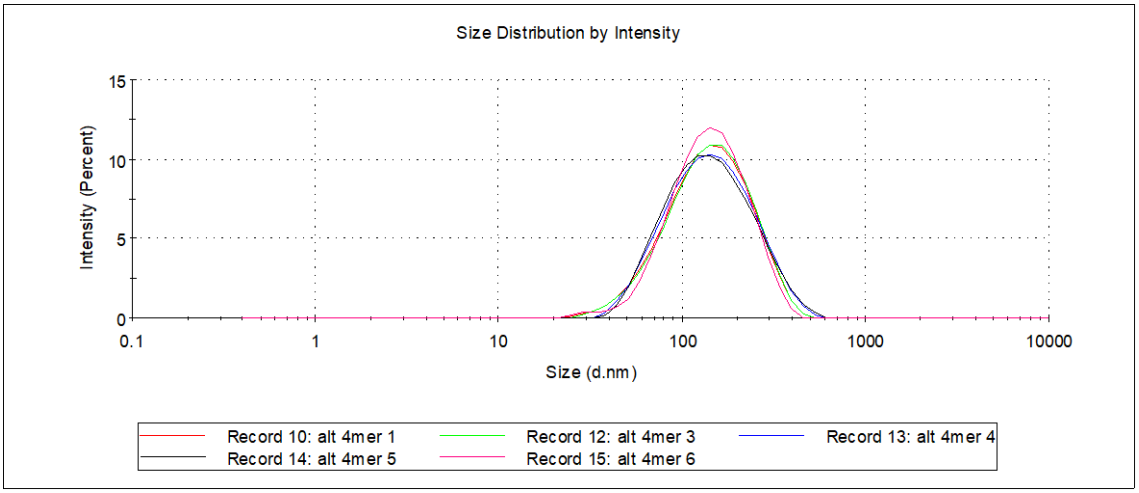
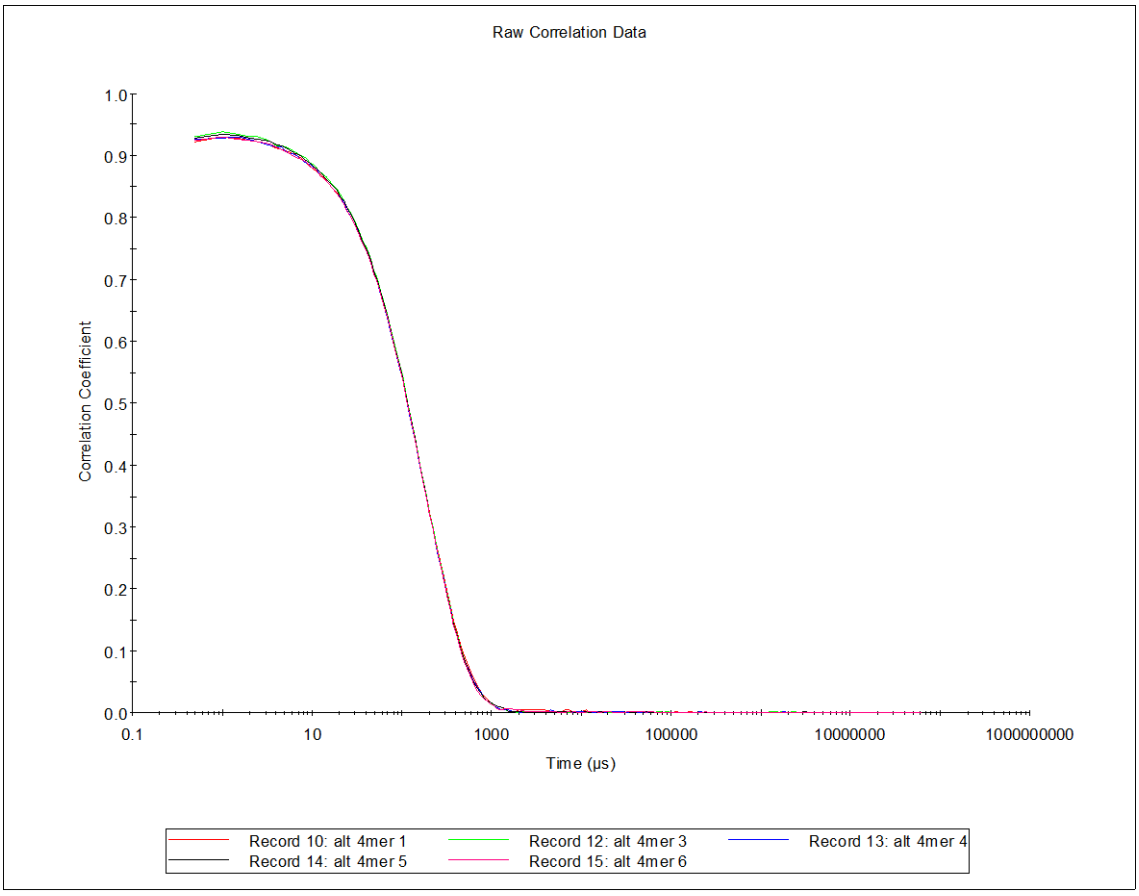
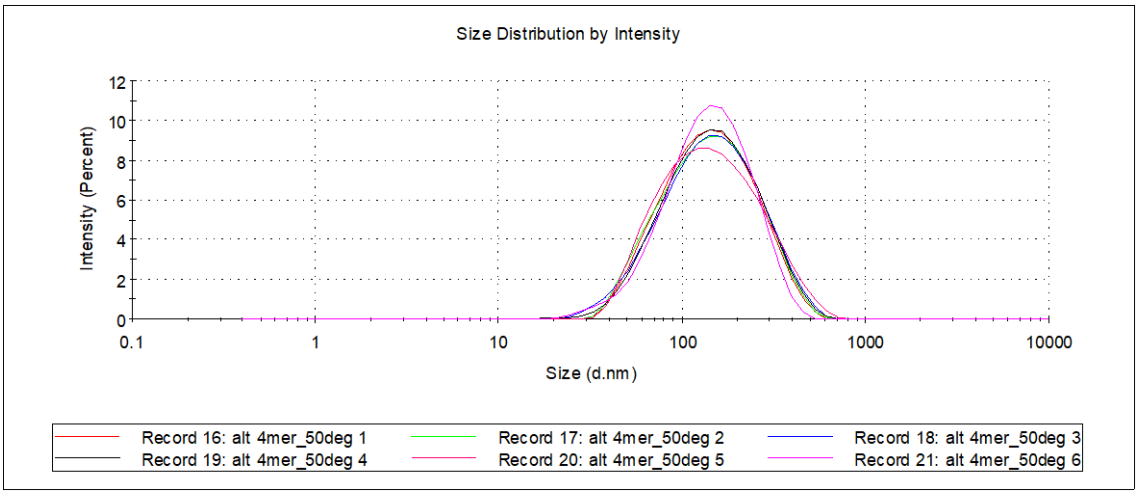
Z-average (nm)	116.8	122.7	121.1
PDI	0.229	0.229	0.225

25°C





50°C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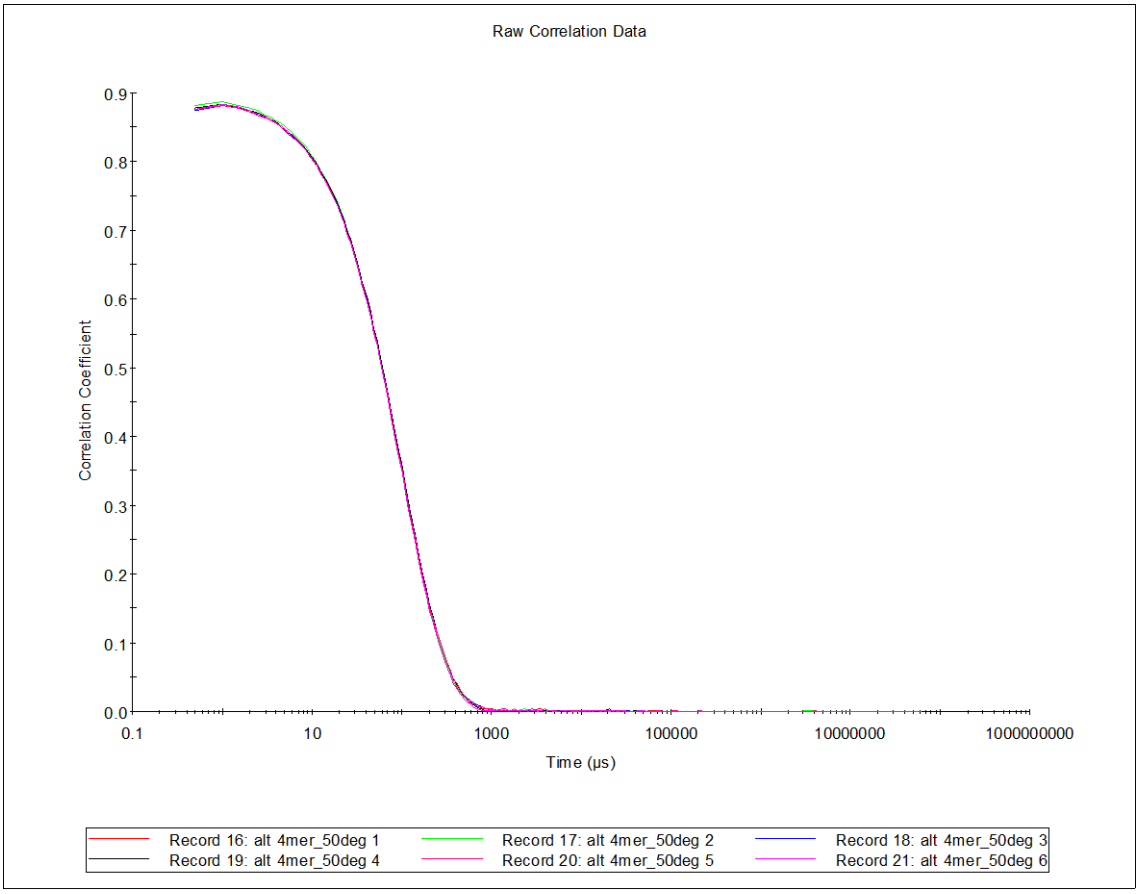
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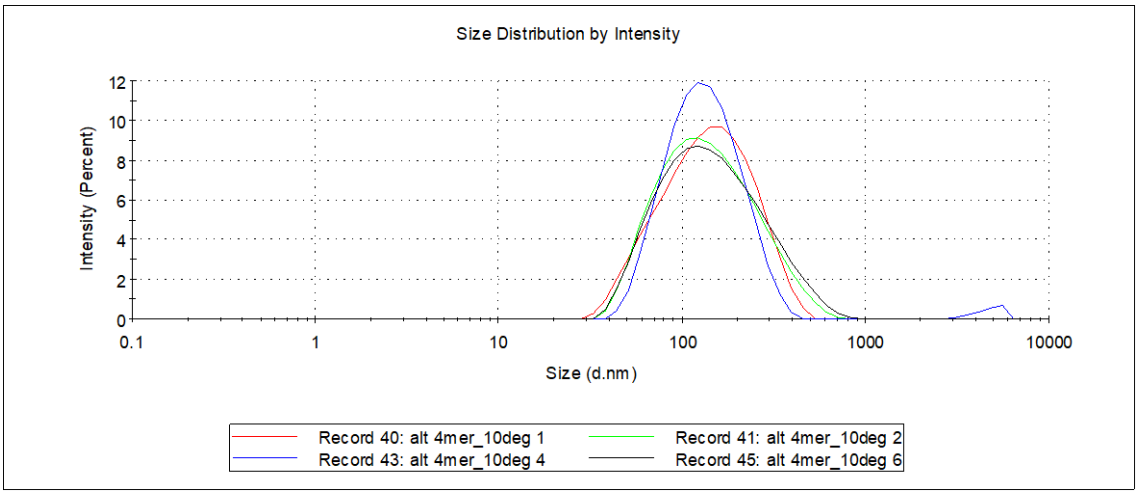
10 °C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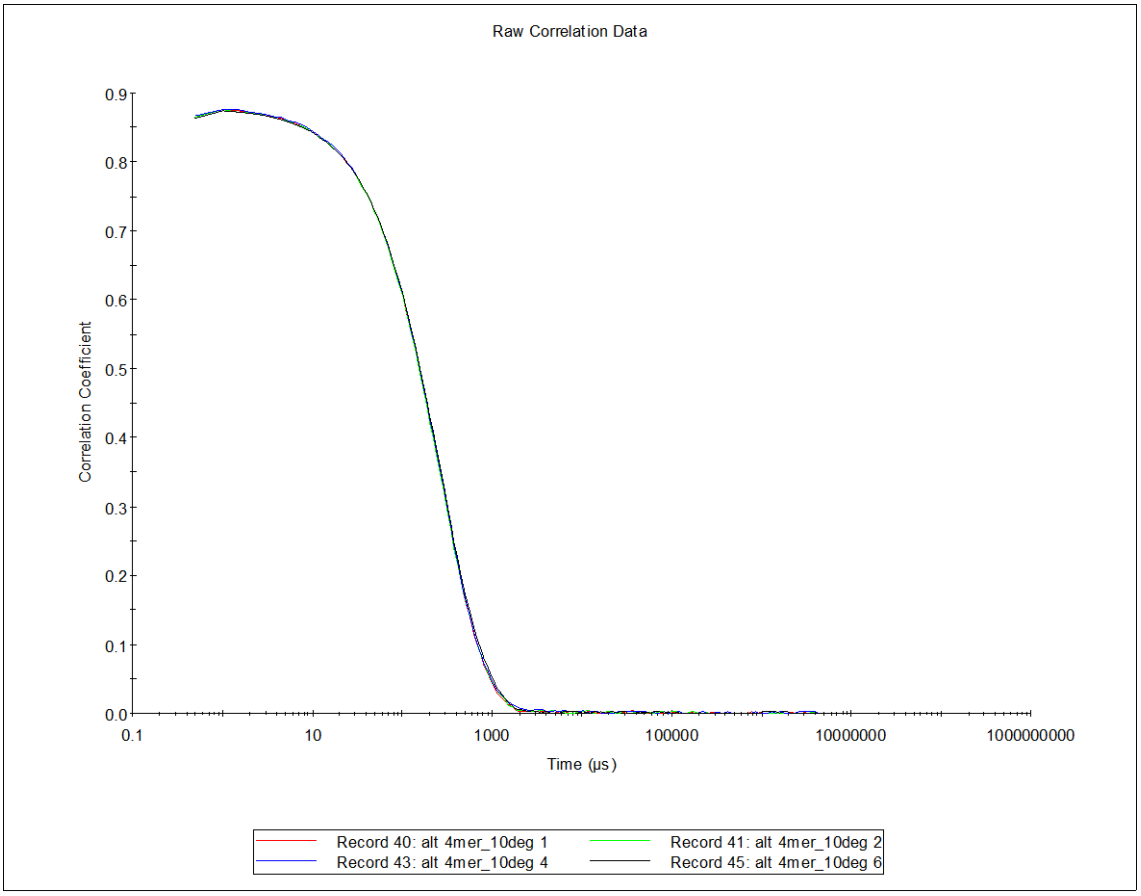
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Time (µs)
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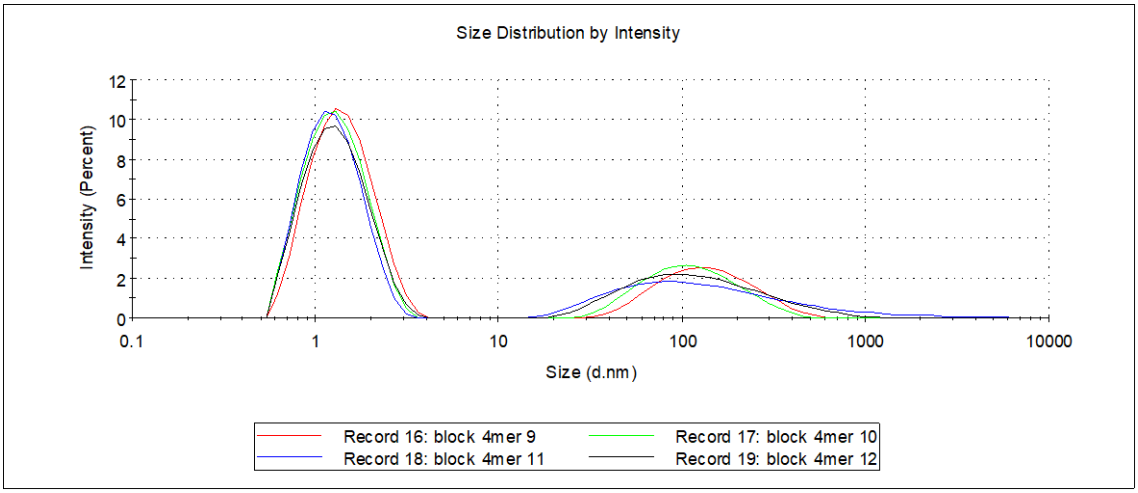
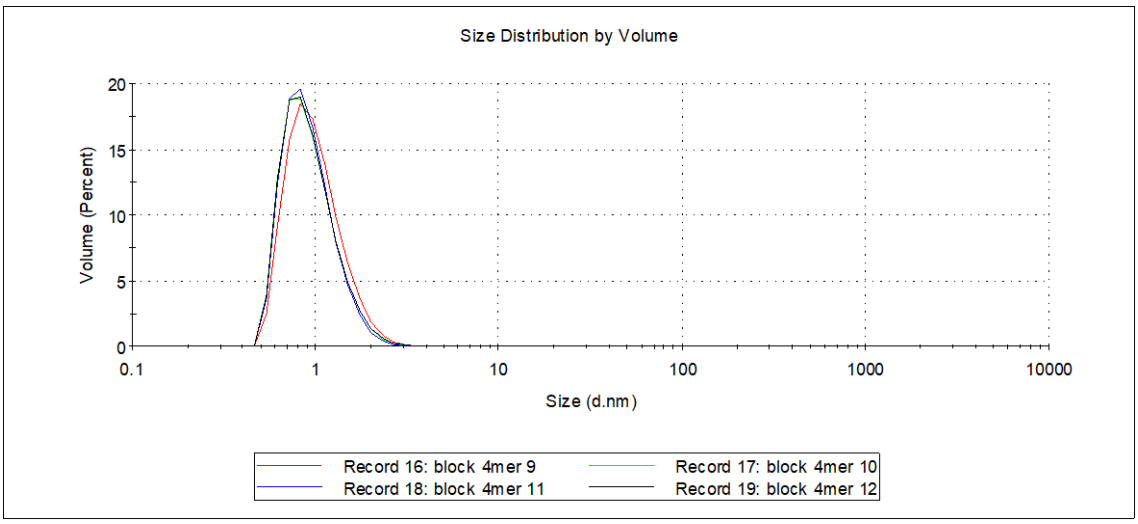
(*block*)-CCAA

85 vol% isopropanol (60°C), 5 mg/mL





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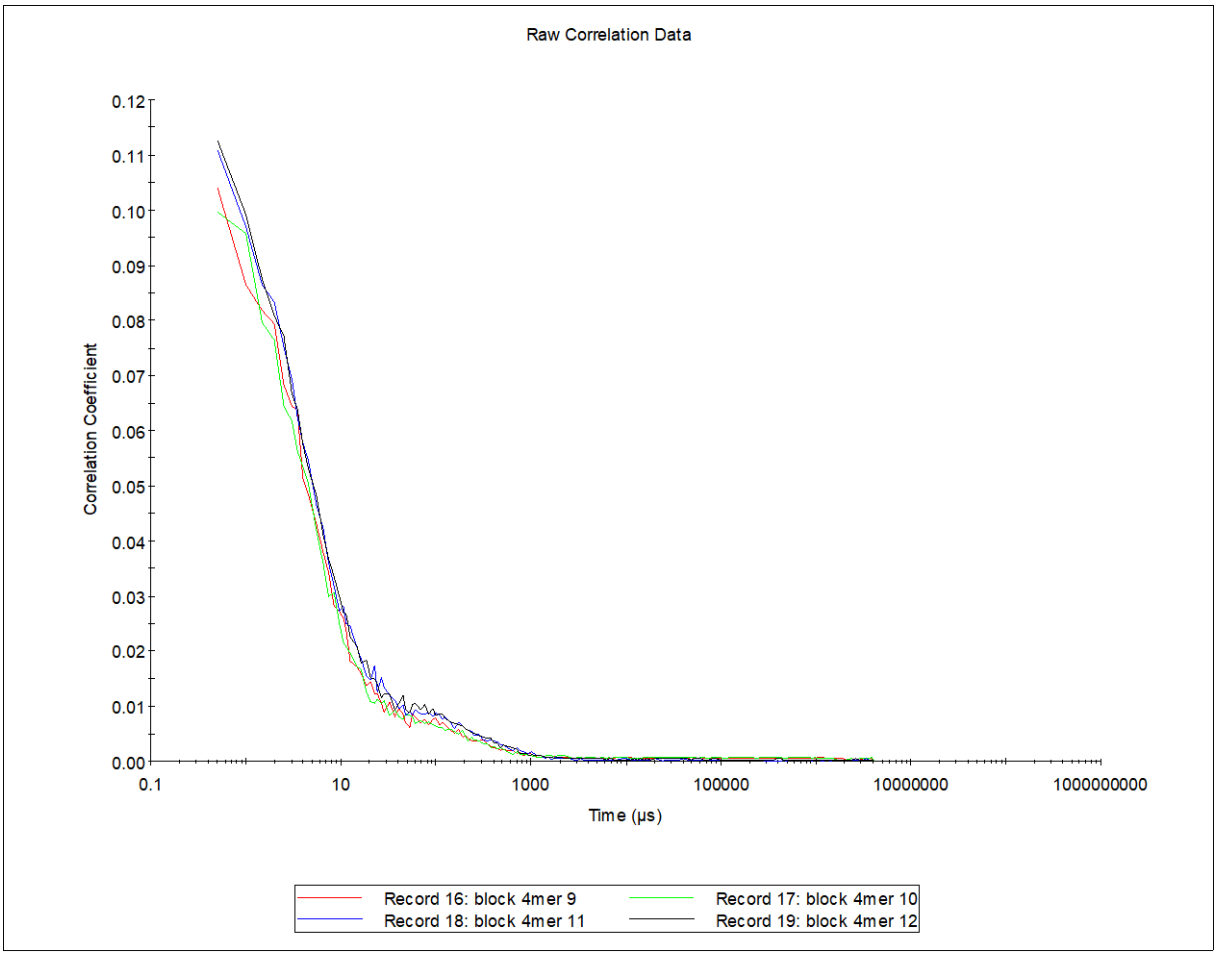
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Time (µs)
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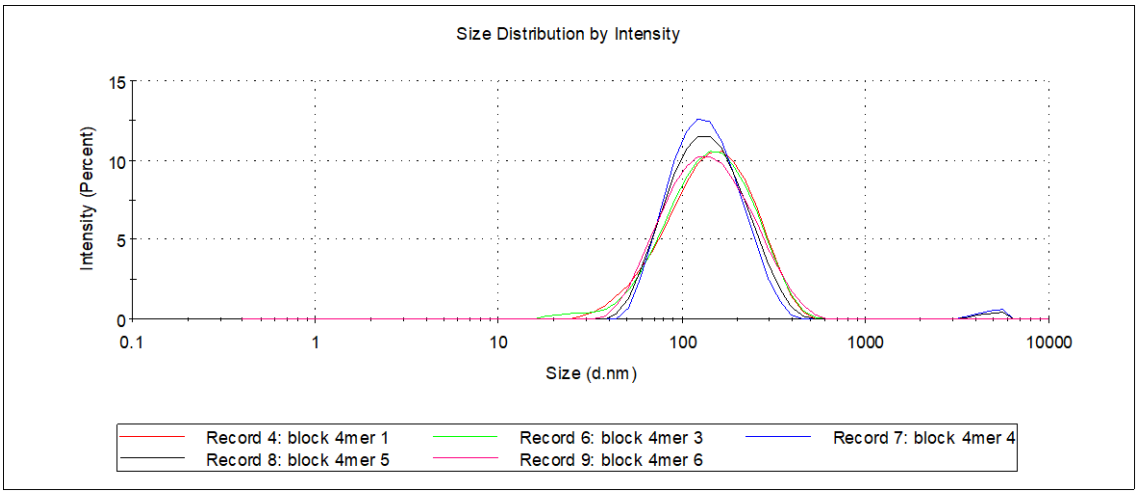
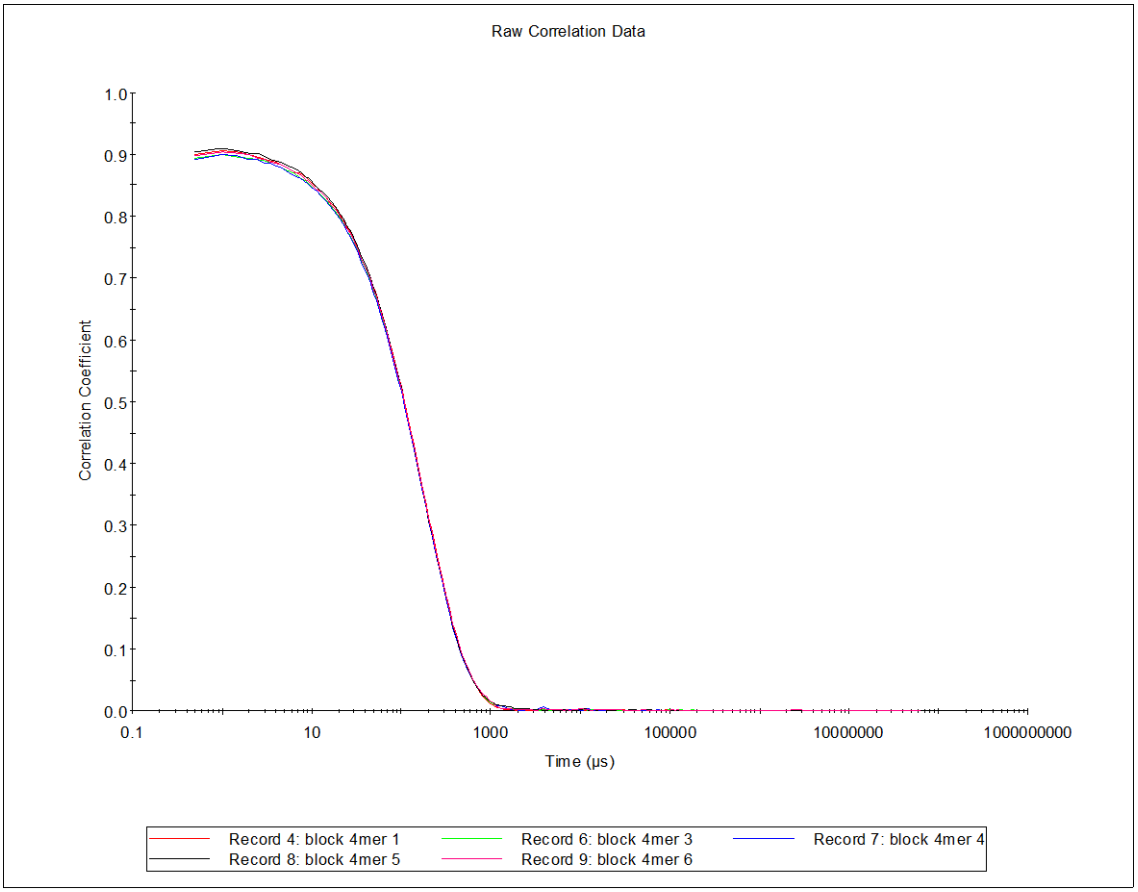
Record 17: block 4mer 10
Record 18: block 4mer 11
Record 19: block 4mer 12

Water (5 mg/mL)

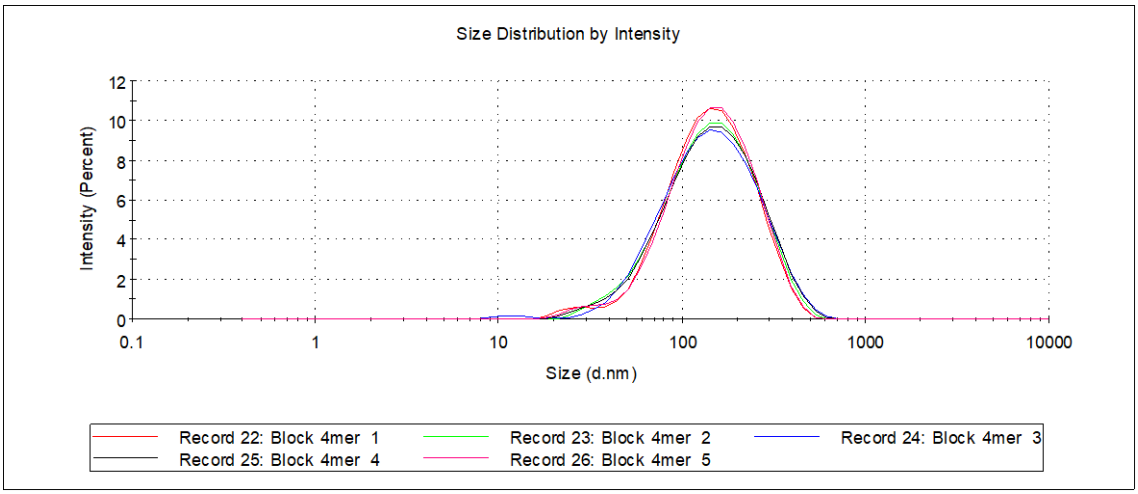
	10 °C	25 °C	50 °C
Z-average (nm)	116.8	119.6	119.3
PDI	0.269	0.250	0.241

25 °C





50 °C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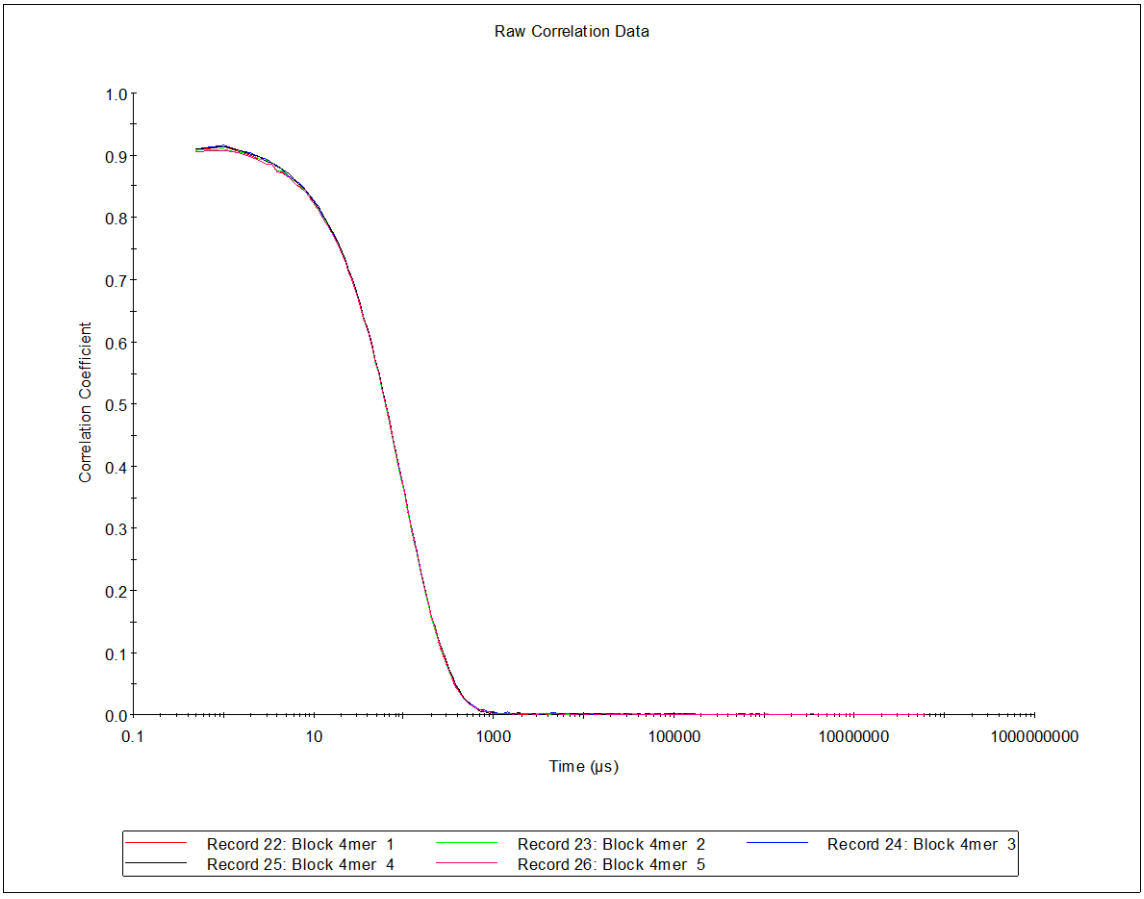
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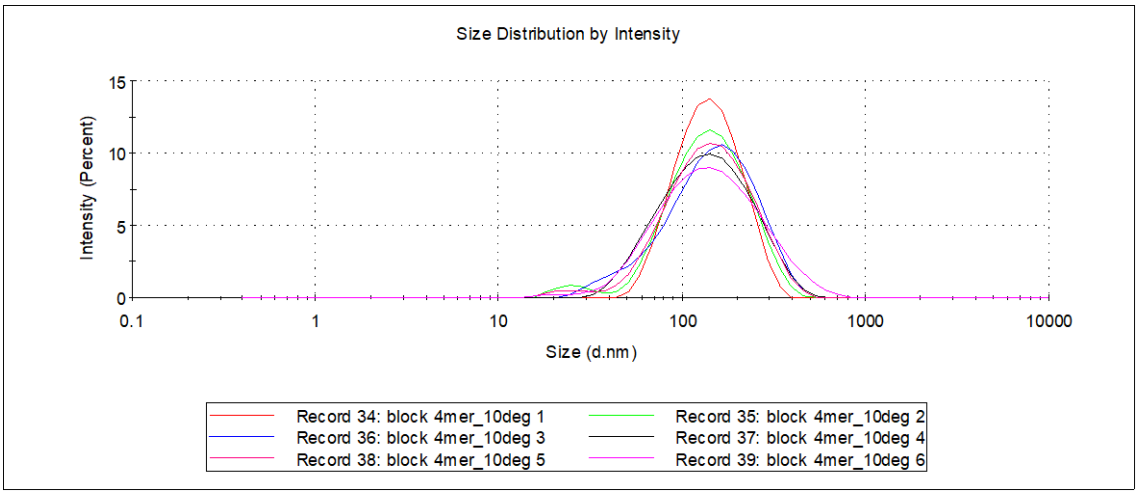
10 °C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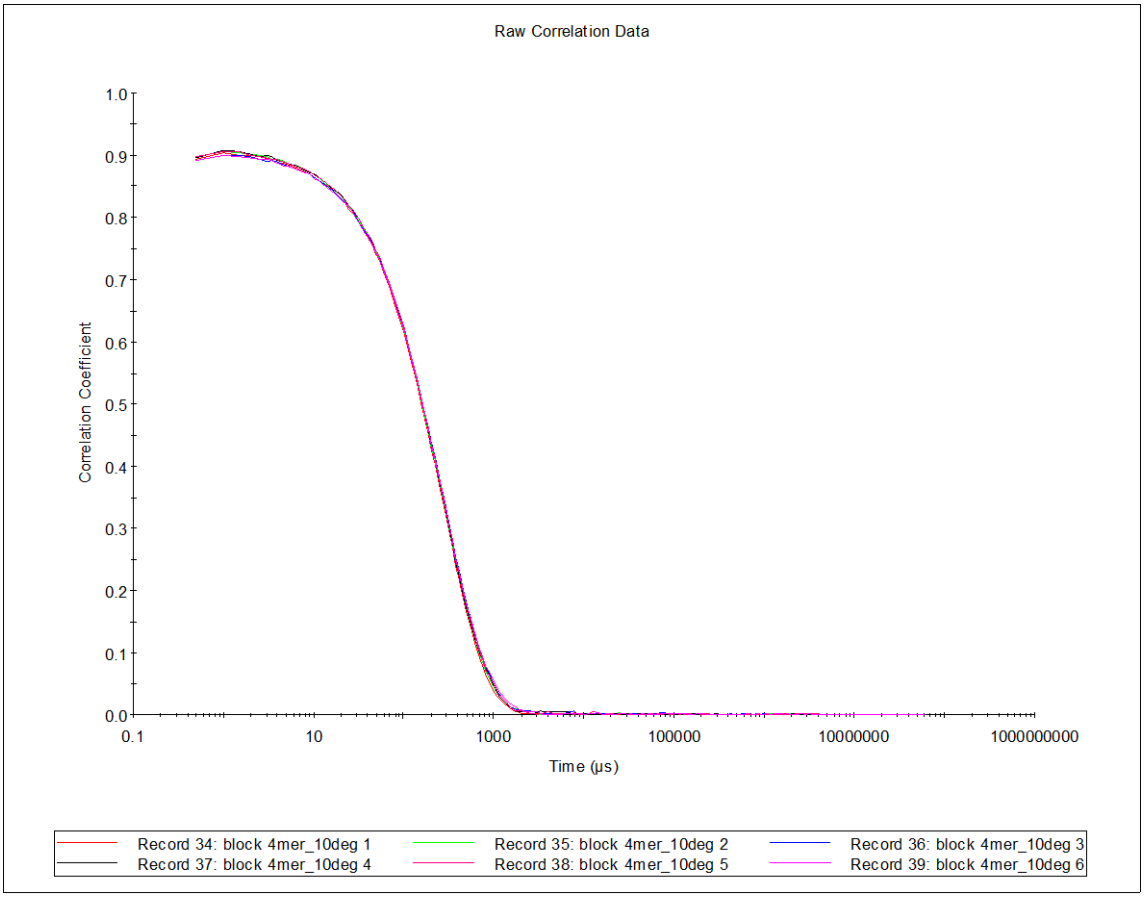
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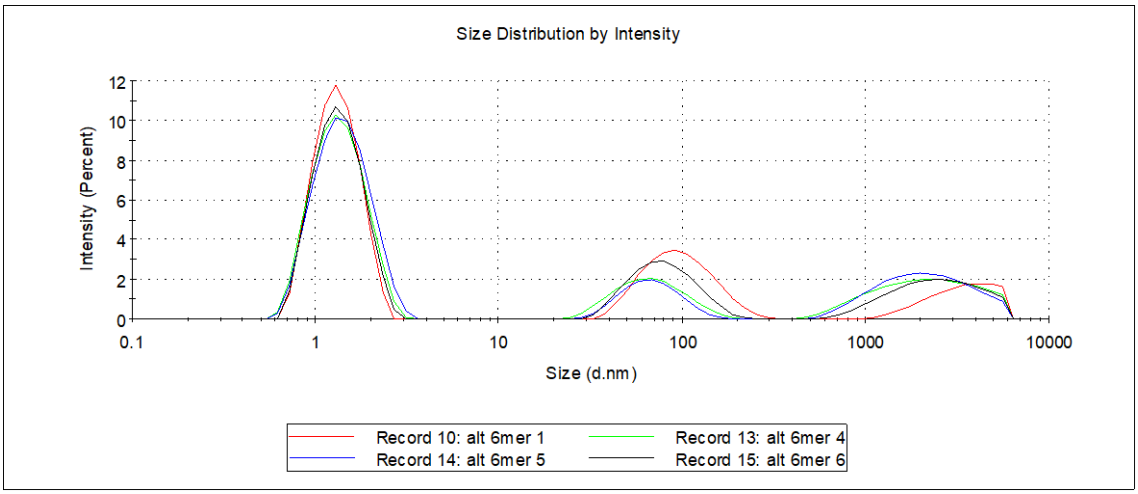
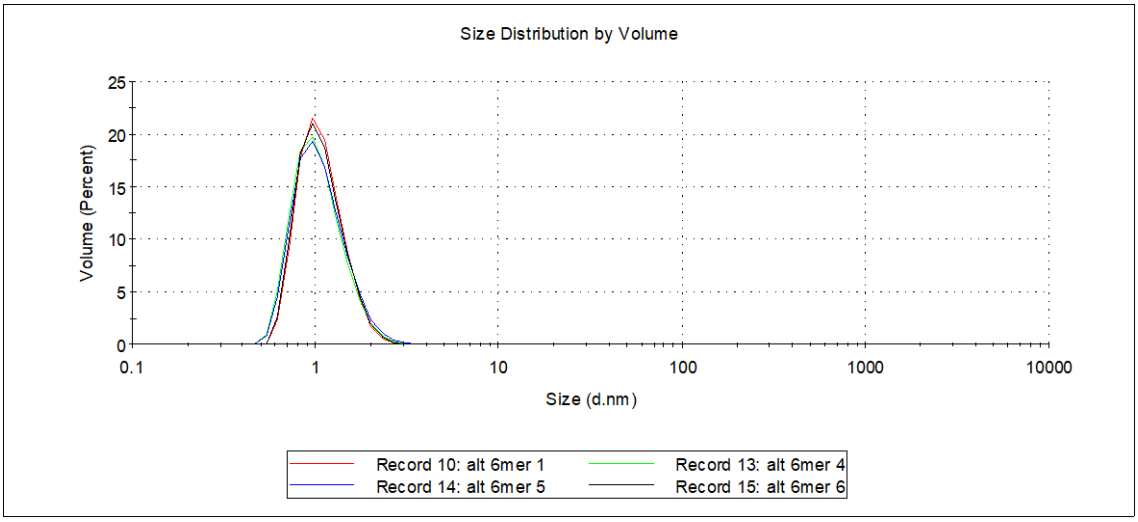
Record 36: block 4mer_10deg 3
Record 37: block 4mer_10deg 4
Record 38: block 4mer_10deg 5
Record 39: block 4mer_10deg 6

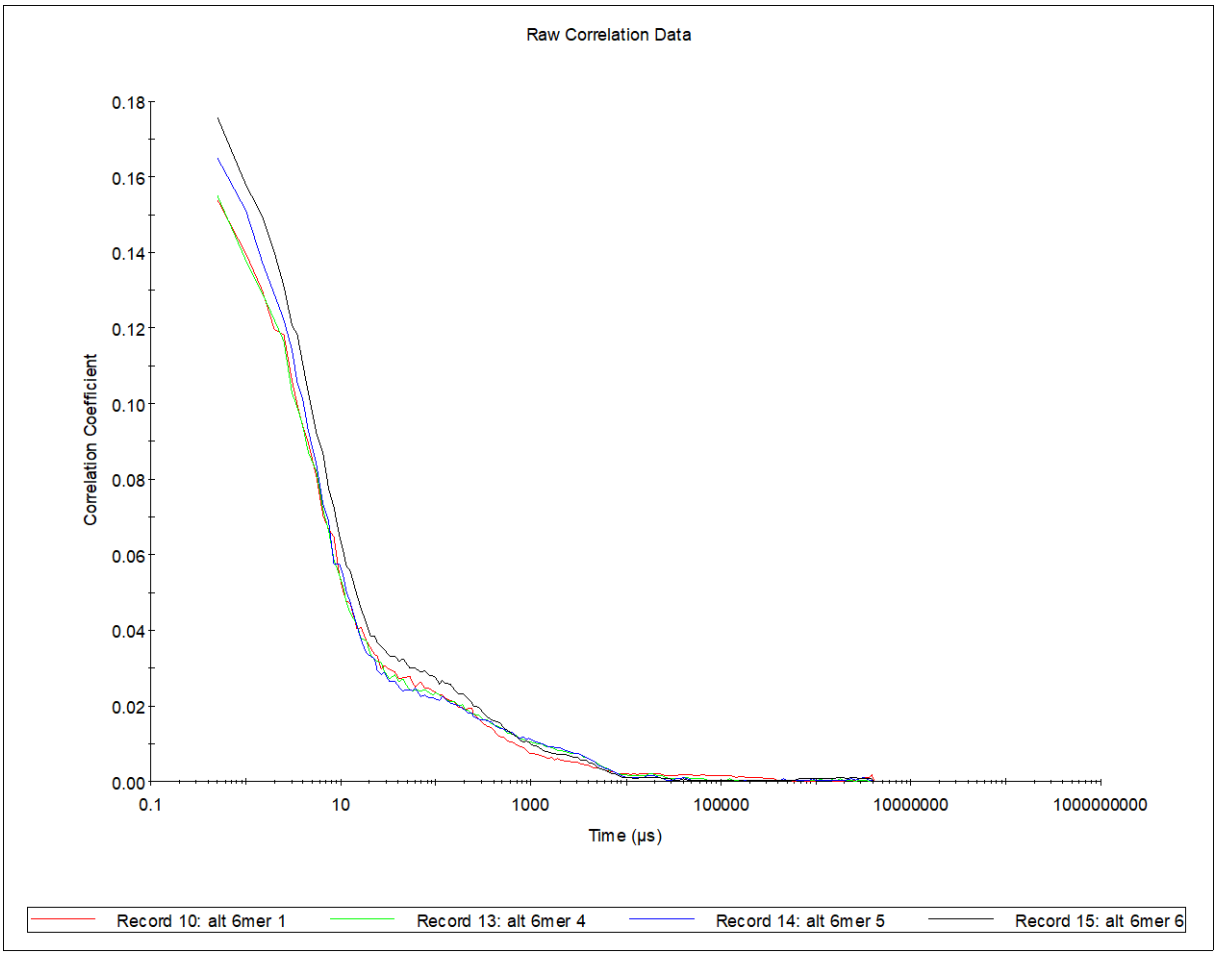
(*alt*)-CACACA

85 vol% isopropanol (60°C), 5 mg/mL





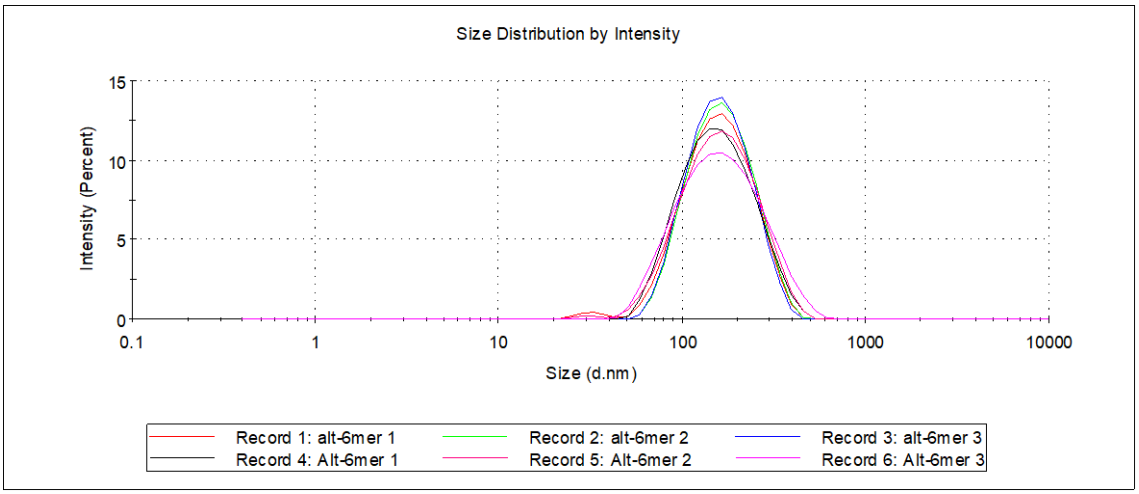
Size: 1.093 nm
Z-average: 22.81 nm
PDI: 0.299

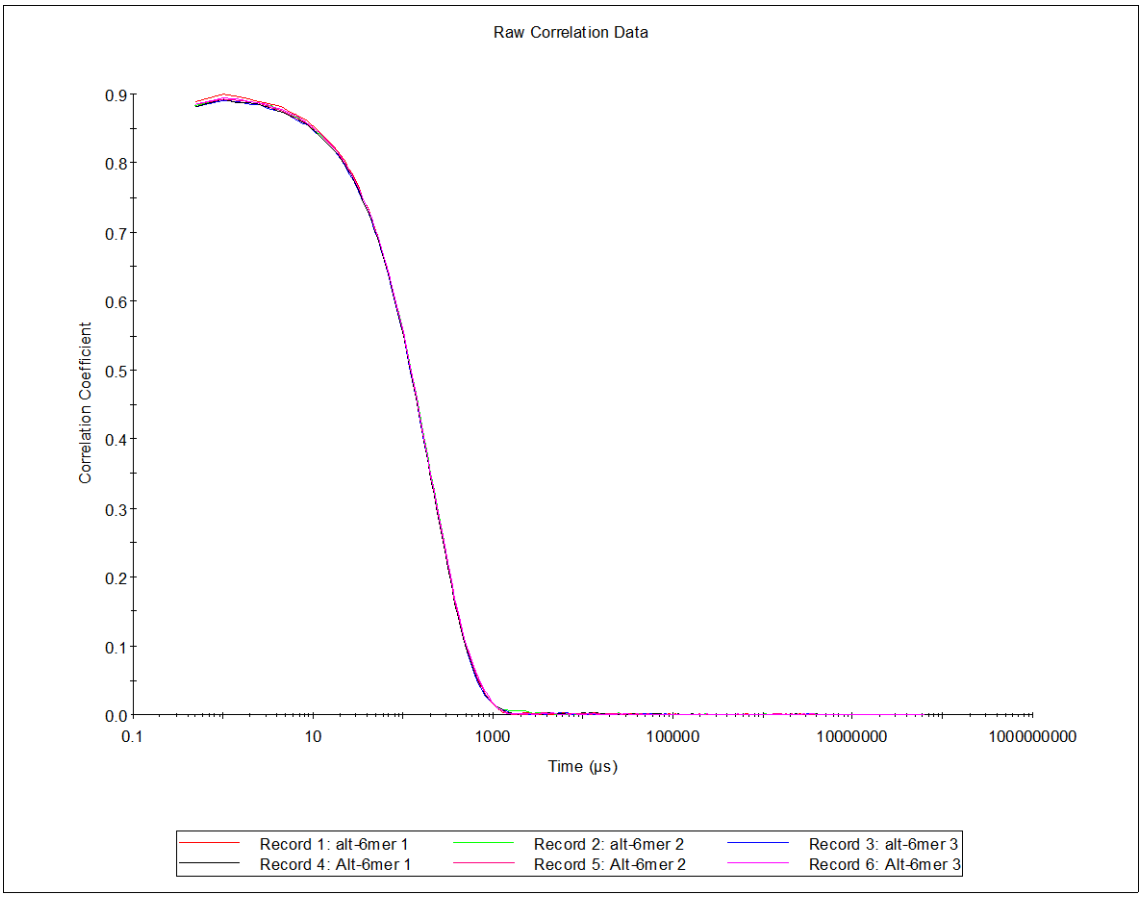

Raw Correlation Data
Correlation Coefficient
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0.1
10
1000
100000
10000000
1000000000
Time (µs)
Record 10: alt 6mer 1
Record 13: alt 6mer 4
Record 14: alt 6mer 5
Record 15: alt 6mer 6

Water (5 mg/mL)

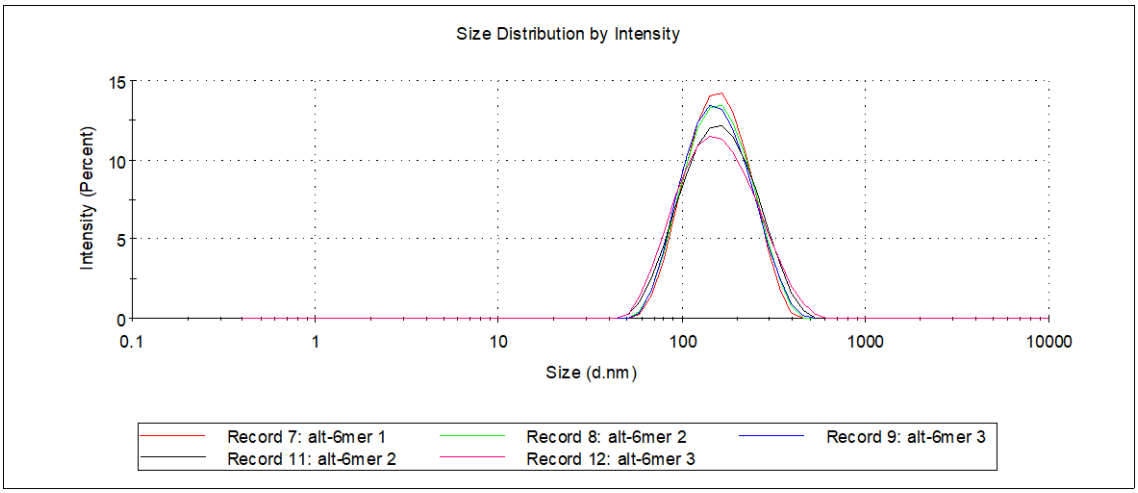
	10 °C	25 °C	50 °C
Z-average (nm)	133.4	138.6	138.9
PDI	0.198	0.180	0.160

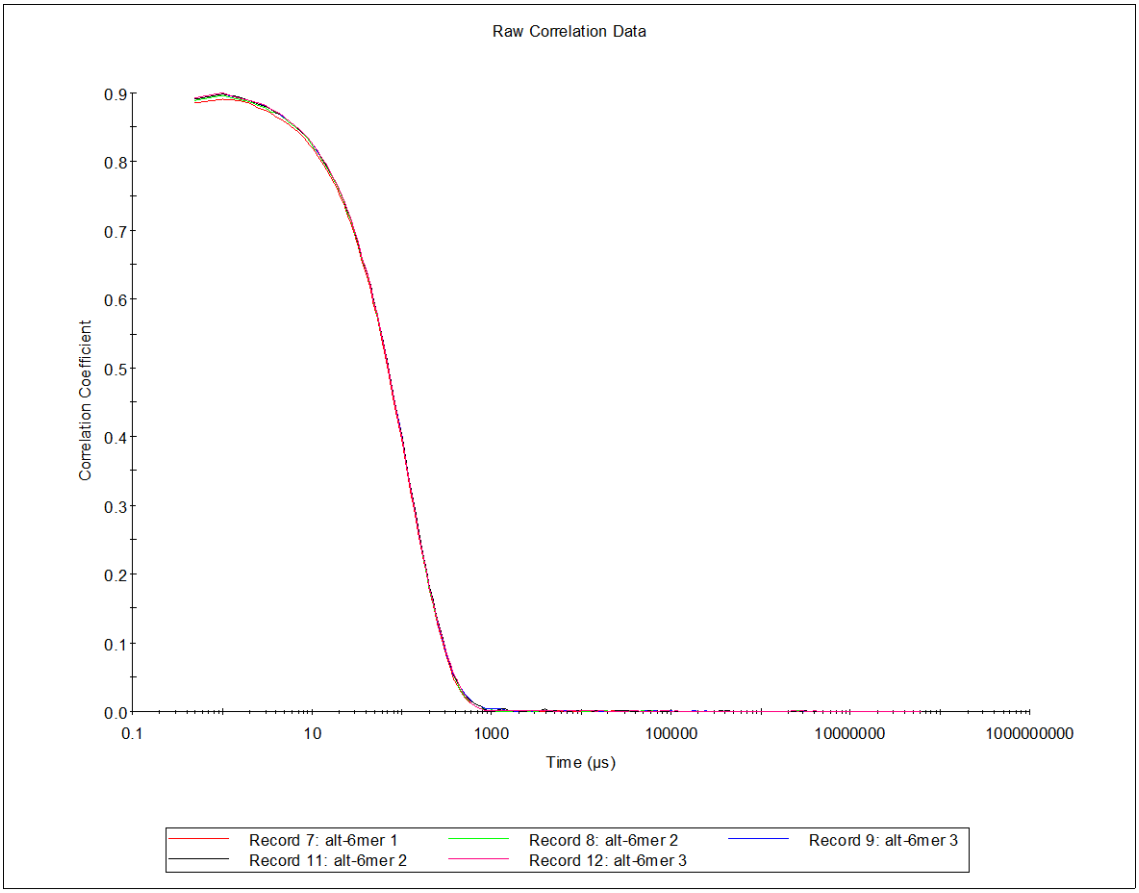
25°C



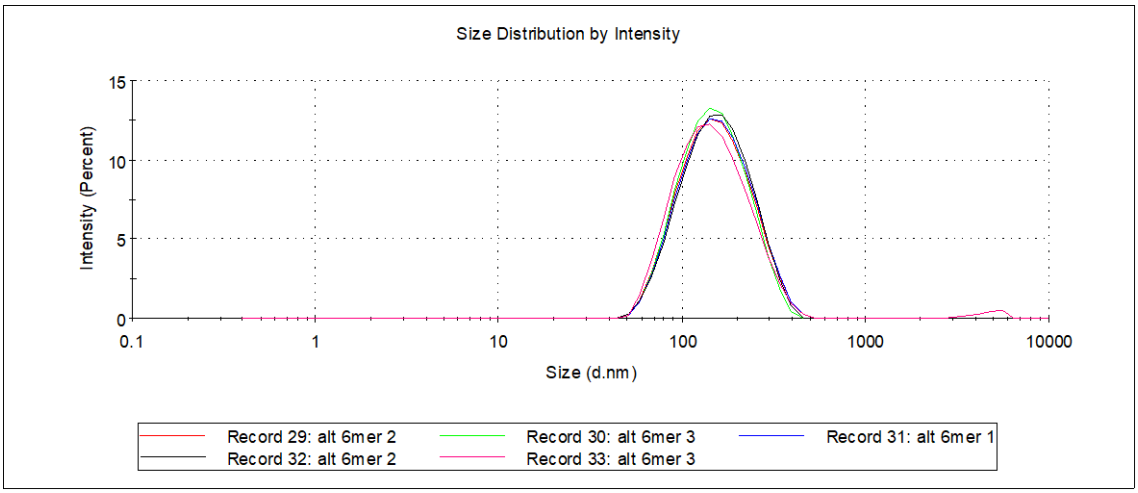


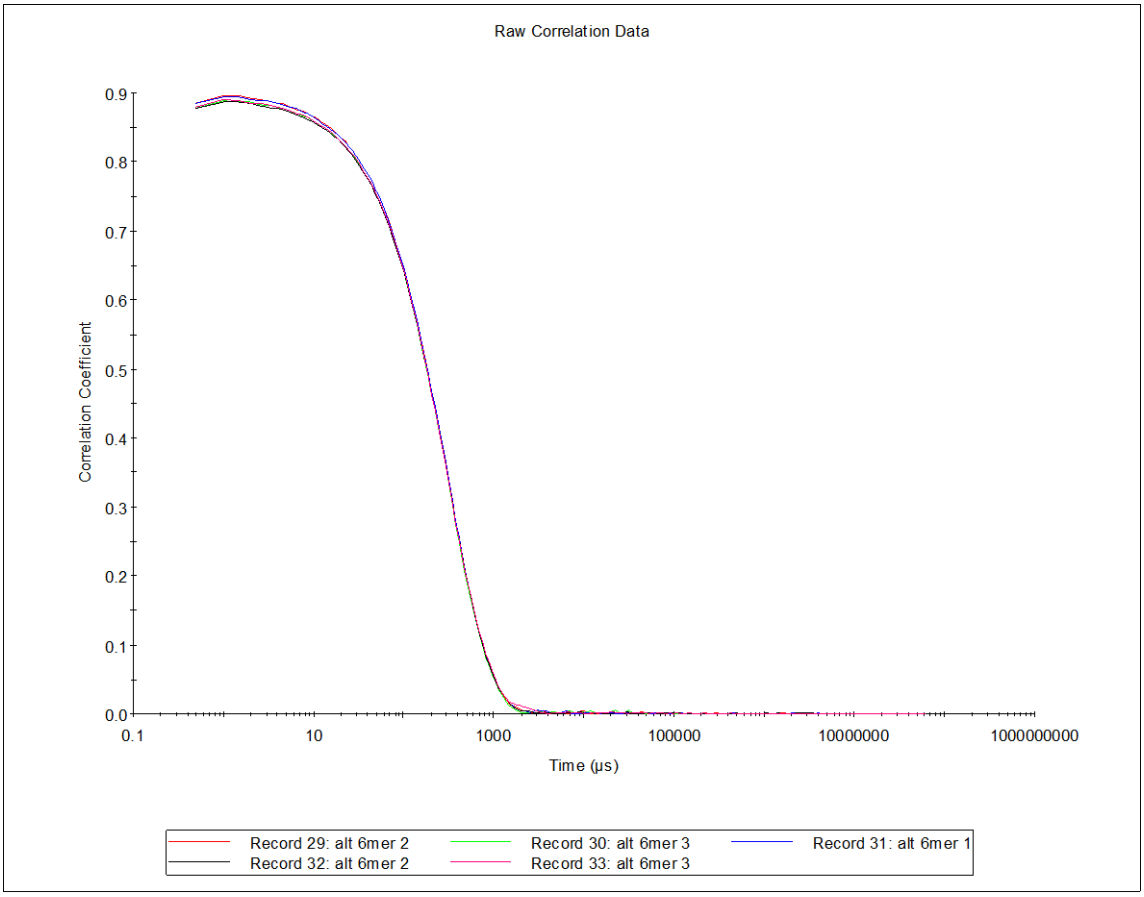
50 °C


Size Distribution by Intensity
Intensity (Percent)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 7: alt-6mer 1
Record 8: alt-6mer 2
Record 9: alt-6mer 3
Record 11: alt-6mer 2
Record 12: alt-6mer 3


Raw Correlation Data
Correlation Coefficient
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.1
10
1000
100000
10000000
1000000000
Time (µs)
Record 7: alt-6mer 1
Record 8: alt-6mer 2
Record 9: alt-6mer 3
Record 11: alt-6mer 2
Record 12: alt-6mer 3

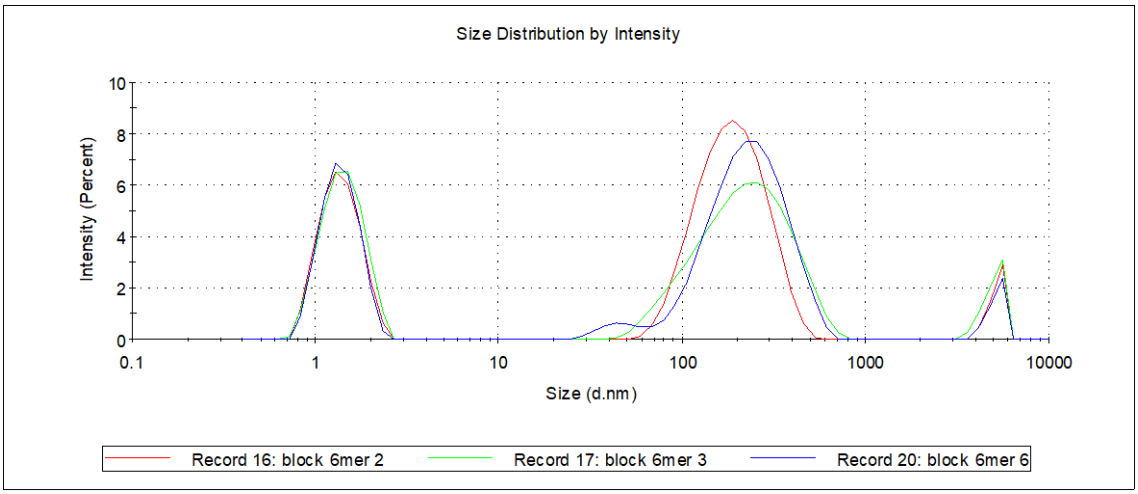
10 °C

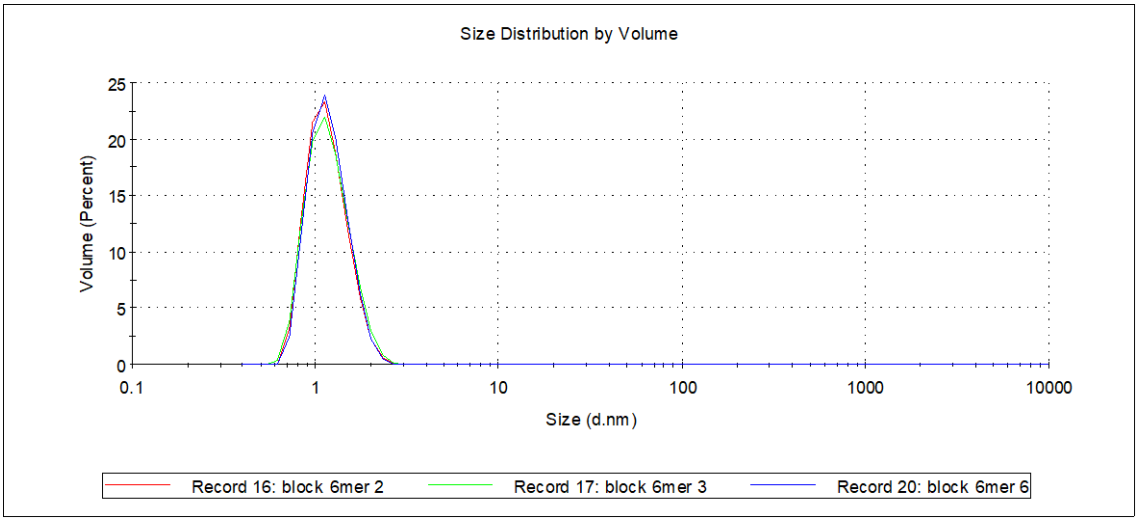

Size Distribution by Intensity
Intensity (Percent)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 29: alt 6mer 2
Record 30: alt 6mer 3
Record 31: alt 6mer 1
Record 32: alt 6mer 2
Record 33: alt 6mer 3


Raw Correlation Data
Correlation Coefficient
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.1
10
1000
100000
10000000
1000000000
Time (µs)
Record 29: alt 6mer 2
Record 30: alt 6mer 3
Record 31: alt 6mer 1
Record 32: alt 6mer 2
Record 33: alt 6mer 3

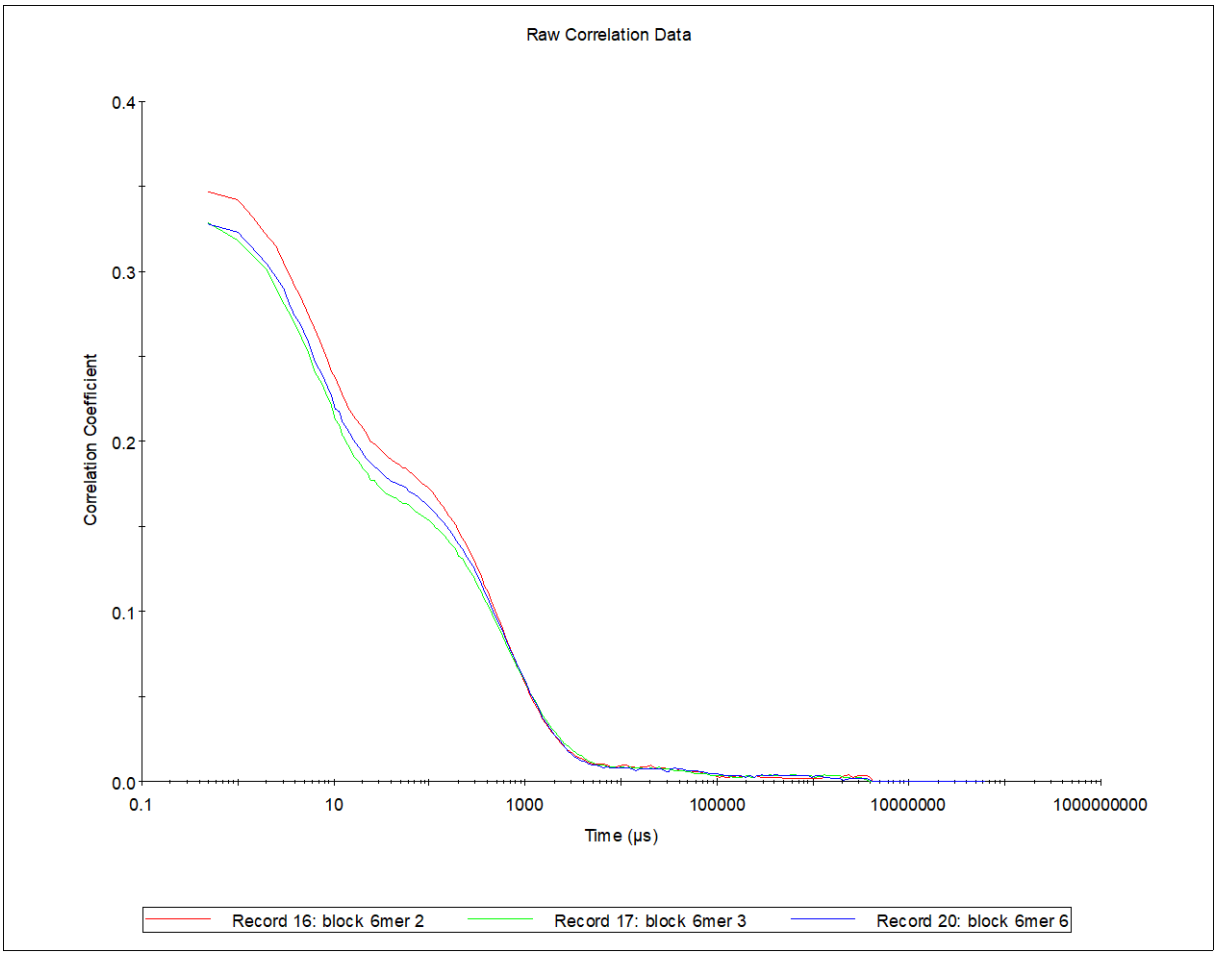
(*bl*ock)-CCCAAA

85 vol% isopropanol (60°C), 5 mg/mL





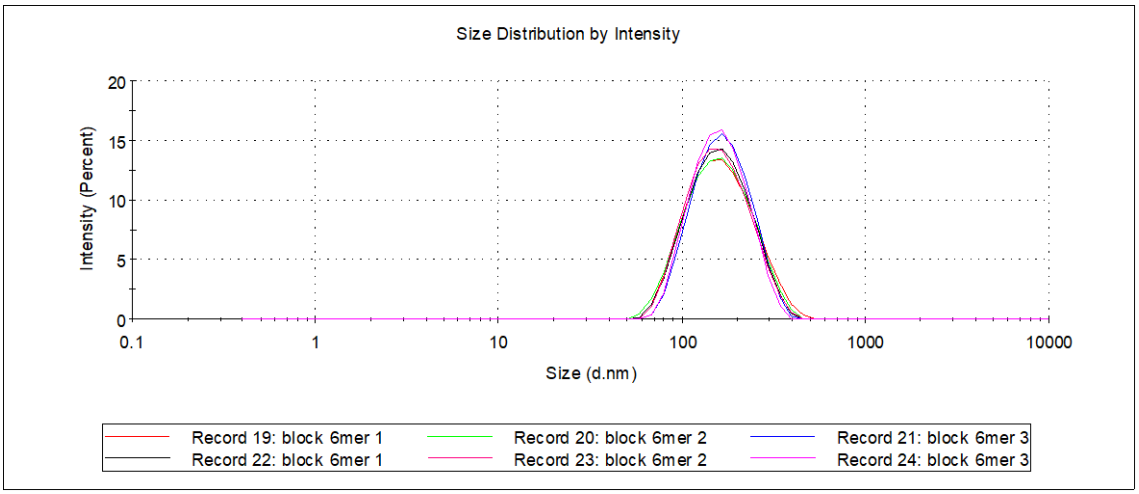
Size: 1.195 nm
Z-average: 118.4 nm
PDI: 0.502

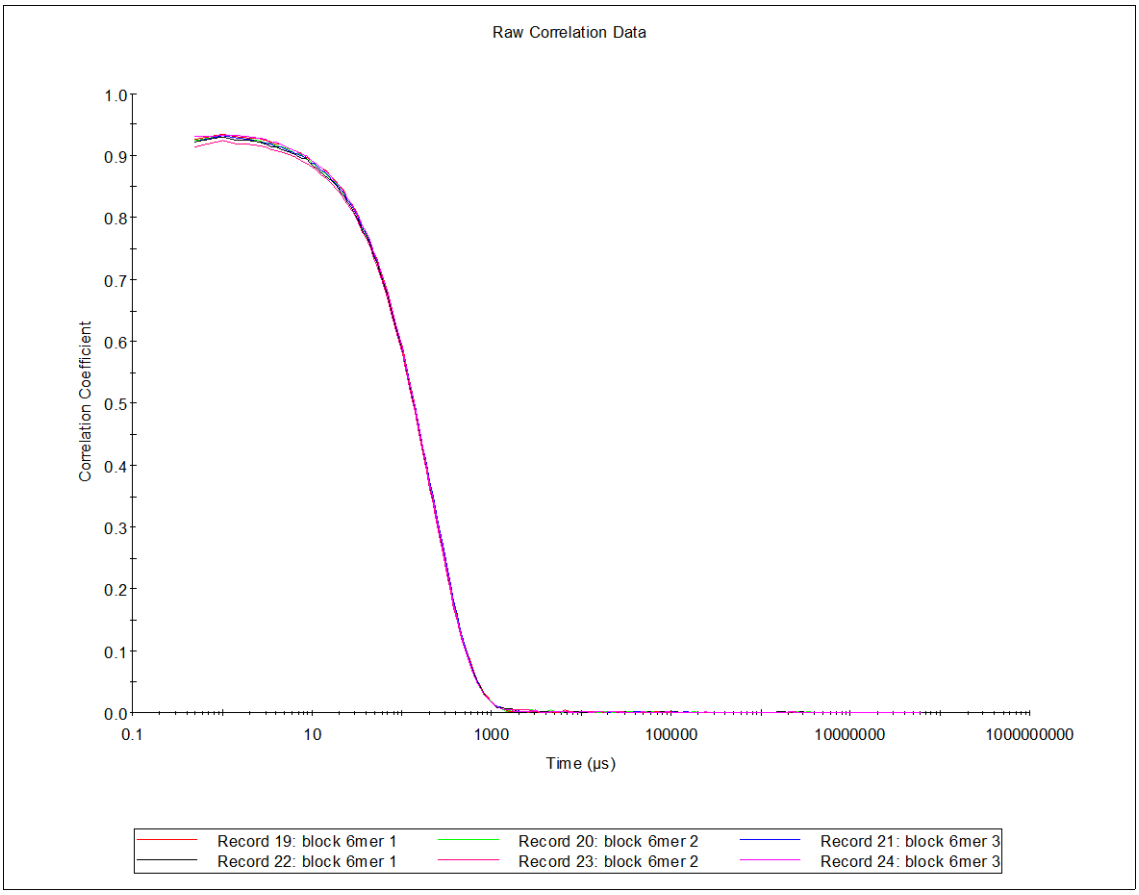

Raw Correlation Data
Correlation Coefficient
0.4
0.3
0.2
0.1
0.0
0.1
10
1000
100000
10000000
1000000000
Time (µs)
Record 16: block 6mer 2
Record 17: block 6mer 3
Record 20: block 6mer 6

Water (5 mg/mL)

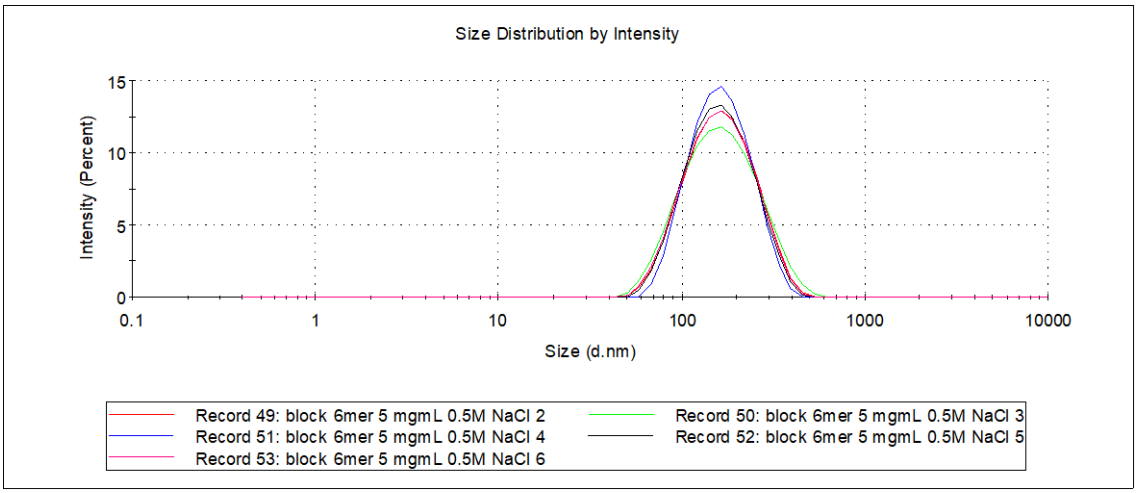
	10 °C	25 °C	25°C + 0.5M NaCl	50 °C
Z-average (nm)	143.3	146.1	138.4	150
PDI	0.143	0.126	0.203	0.116

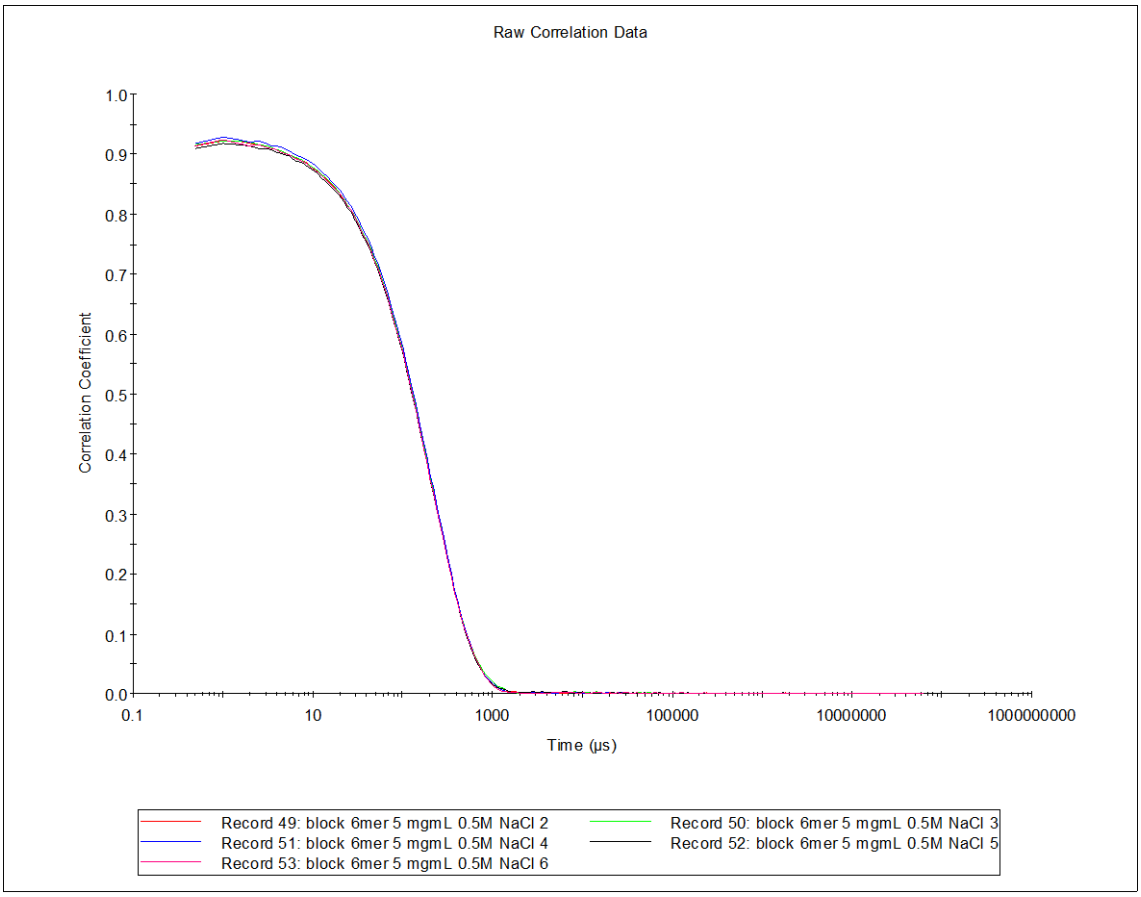
25 °C



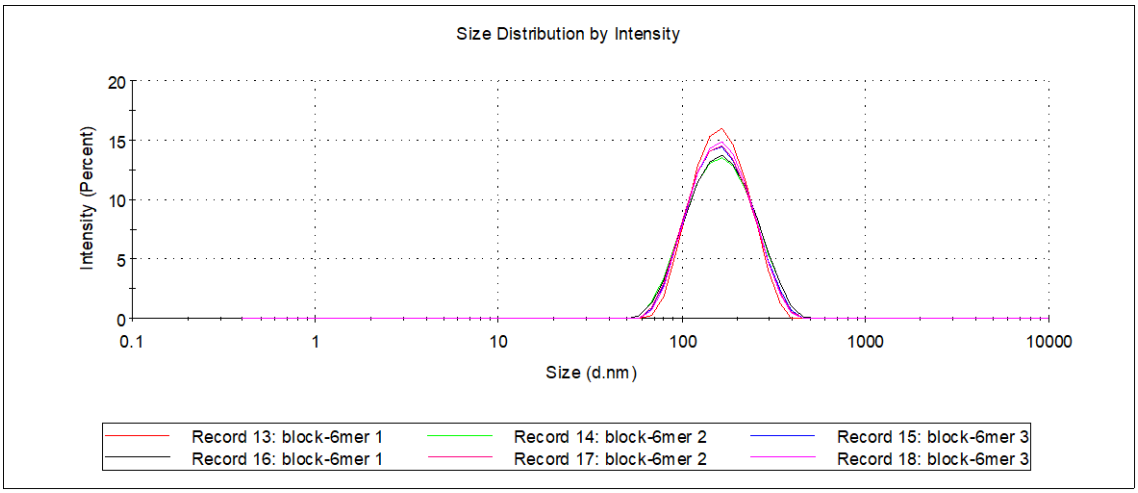


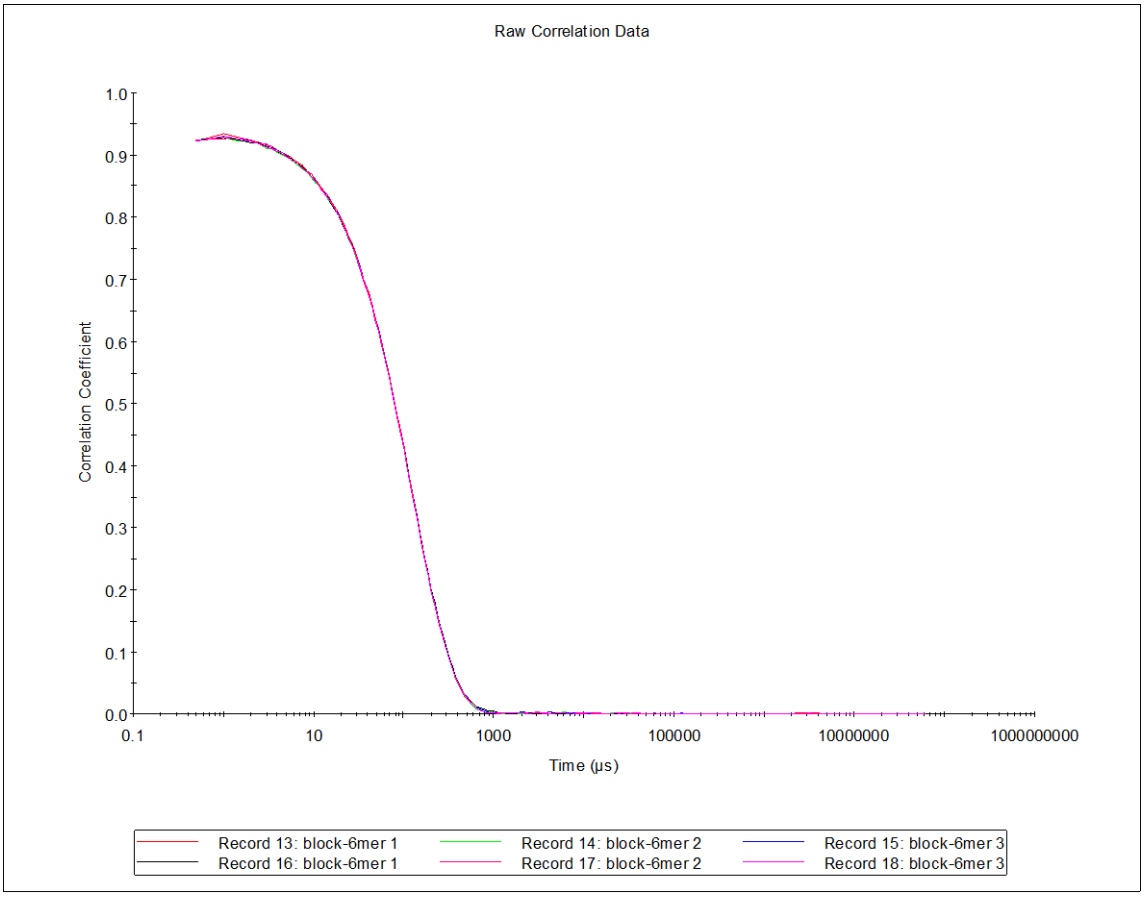
25 °C + 0.5M NaCl


Size Distribution by Intensity
Intensity (Percent)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 49: block 6mer 5 mgmL 0.5M NaCl 2
Record 50: block 6mer 5 mgmL 0.5M NaCl 3
Record 51: block 6mer 5 mgmL 0.5M NaCl 4
Record 52: block 6mer 5 mgmL 0.5M NaCl 5
Record 53: block 6mer 5 mgmL 0.5M NaCl 6

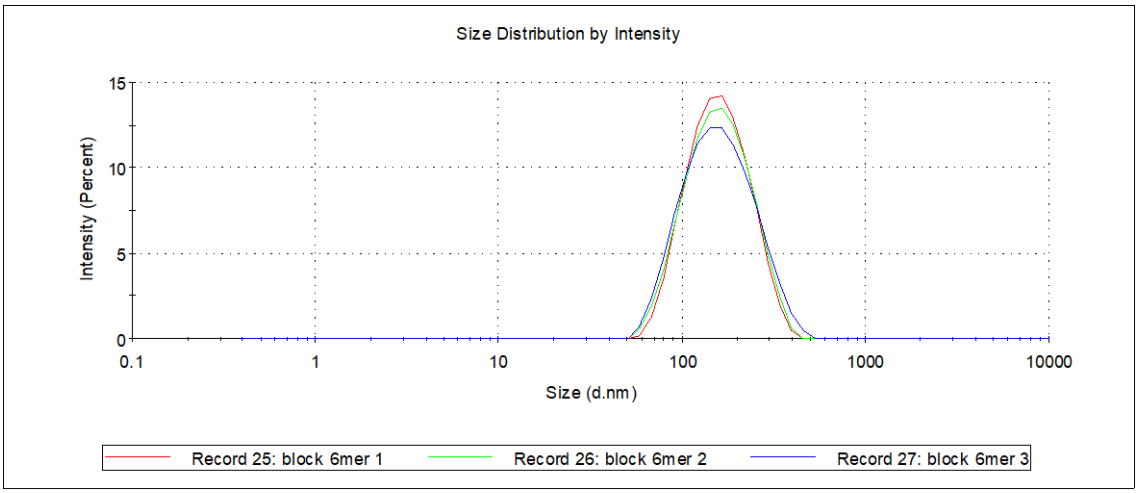

Raw Correlation Data
Correlation Coefficient
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.1
10
1000
100000
10000000
1000000000
Time (µs)
Record 49: block 6mer 5 mgmL 0.5M NaCl 2
Record 50: block 6mer 5 mgmL 0.5M NaCl 3
Record 51: block 6mer 5 mgmL 0.5M NaCl 4
Record 52: block 6mer 5 mgmL 0.5M NaCl 5
Record 53: block 6mer 5 mgmL 0.5M NaCl 6

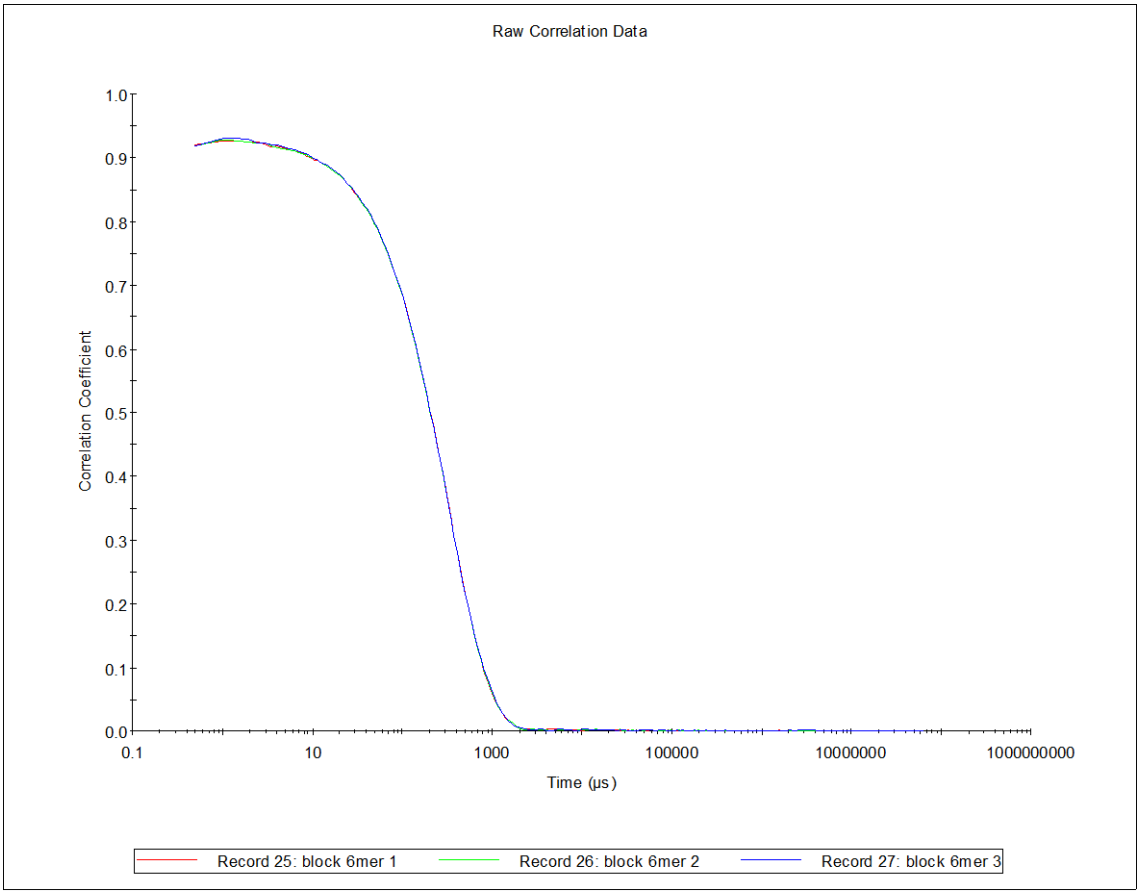
50 °C


Size Distribution by Intensity
Intensity (Percent)
20
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 13: block-6mer 1
Record 16: block-6mer 1
Record 14: block-6mer 2
Record 17: block-6mer 2
Record 15: block-6mer 3
Record 18: block-6mer 3


Raw Correlation Data
Correlation Coefficient
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.1
10
1000
100000
10000000
1000000000
Time (µs)
Record 13: block-6mer 1
Record 16: block-6mer 1
Record 14: block-6mer 2
Record 17: block-6mer 2
Record 15: block-6mer 3
Record 18: block-6mer 3

10 °C


Size Distribution by Intensity
Intensity (Percent)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 25: block 6mer 1
Record 26: block 6mer 2
Record 27: block 6mer 3


Raw Correlation Data
Correlation Coefficient
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.1
10
1000
100000
10000000
1000000000
Time (µs)
Record 25: block 6mer 1
Record 26: block 6mer 2
Record 27: block 6mer 3

References

1 S. Martens, J. Van den Begin, A. Madder, F. E. Du Prez and P. Espeel, *J. Am. Chem. Soc.*, 2016, **138**, 14182–14185.

2 C. Mertens, M. Soete, M. L. Ślęczkowski, A. R. A. Palmans, E. W. Meijer, N. Badi and F. E. Du Prez, *Polym. Chem.*, 2020, **11**, 4271–4280.

3 J. O. Holloway, S. Aksakal, F. E. Du Prez and C. R. Becer, *Macromol. Rapid Commun.*, 2017, **38**, 1700500.

4 S. Breitenlechner and T. Bach, *Z. Für Naturforschung B*, 2006, **61**, 583–588.