Supporting Information for:

An insight into the synthesis of *N*-methylated polypeptides

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1 Experimental procedures

1.1 Materials

SCHLENK techniques were used at those reactions with air and moisture sensitive reagents or intermediates, performed under argon atmosphere, using laboratory glassware, dried under high vacuum at 120 °C with a hot air gun. In these instances, solvents and reagents were added through septa by disposable syringes and cannulas.

All used solvents and reagents were purchased from commercial sources. The respective suppliers are ACROS ORGANICS (Thermo Scientific GmbH, Nidderau), ALFA AESAR (Alfer Aesar GmbH & Co. KG, Karlsruhe), CARBOLUTION CHEMICALS (Carbolution Chemicals GmbH, Saarbrücken), IRIS BIOTECH (Iris Biotech GmbH, Markredwitz), MERCK (Merck KGaA, Darmstadt), SIGMA-ALDRICH (Sigma-Aldrich Chemie GmbH, Taufkirchen) and TCI (TCI Deutschland GmbH, Eschborn. Those chemicals were utilized without further purification unless stated otherwise.

Prior to use, water was demineralized, using PURELAB® flex by Elga. Solvents used for air or moisture sensitive reactions were bought anhydrous. DCM was dried using a solvent purification system. Solvents used as the mobile phase at flash- or thin layer chromatography were purchased in technical quality and applied without further purification.

1.2 Chromatography

All performed qualitative thin layer chromatography (TLC) were carried out using silica coated aluminum sheets (60 Å, F_{254}), purchased from MACHEREY-NAGEL (MN GmbH & Co. KG, Düren). Detection of the analytes was performed by the use of UV light (λ = 254 nm) and detection reagents of ninhydrin (0.1 g, 50 mL ethanol, 1.5 mL acetic acid) or $KMnO_4$ (0.75 g, 200 mL H_2O, 2.5 g $NaHCO_3$).

Flash chromatography (FC) was performed for purification by using silica gel with an average grain size of 15-40 µm, provided from ACROS Organics™.

1.3 Medium Pressure Liquid Chromatography

Purification was performed on a Sepacore® Easy Purification System (BÜCHI Labortechnik AG) equipped with a UV-Photometer C-640 (BÜCHI) and a Fraction Collector C-660 (BÜCHI). All runs were performed on a CHROMABOND Flash RS 120 C_{18} column (MACHEREY-NAGEL GmbH & Co. KG).

1.4 Gel permeation chromatography

Gel permeation chromatography (GPC) was performed with hexaflouroisopropanol (HFIP) containing 3 g L-1 potassium trifluoroacetate (KTFA) as eluent at 40 °C. The columns were packed with modified silica (PFG column particle size: 7 µm, porosity: 100 and 4000 Å, purchased from PSS Polymer Standards Service GmbH). For calibration polymethyl methacrylate (PMMA, Polymer Standards

Services GmbH) was used and toluene as the internal standard. A refractive index detector (G1362A RID) and an UV/VIS detector (at 230 nm, Jasco UV-2075 Plus) were used for polymer detection.

1.5 Mass spectroscopy

All mass spectra were recorded on an electrospray ionization spectrometer (ESI) QT of Ultima. The used samples were prepared at a concentration of 0.1 mg/mL in methanol or water as the solvent. The theoretical masses of the respective compounds were calculated by using the molecule editor ChemDraw® Professional 15.0.

1.6 Matrix-assisted laser desorption/ionization (MALDI)

MALDI-ToF mass spectra were recorded using a Bruker rapifleX MALDI-ToF mass spectrometer equipped with a 337 nm N_2 laser. Acceleration of the ions was performed with pulsed ion extraction (PIE, Bruker) at a voltage of 20 kV. The analyzer was operated in reflection mode and the ions were detected using a microchannel plate detector. Mass spectra were processed by the X-TOF 5.1.0 software (Bruker (Billerica, MA, USA)). Sample preparation was performed using trans-2-[3-(4-tert-Butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as the matrix and sodium trifluoroacetate as the cationizing salt and dichloromethane as solvent.

1.7 NMR spectroscopy

All NMR-spectra were recorded on BRUKER Avance II 400 spectrometer and the measurements carried out in deuterated solvents ($CDCl_3$, DMSO-d_6, D_2O). The chemical shifts (δ) are reported in parts per million (ppm), relative to the chemical shifts of the residual protons of the deuterated solvents. The spin multiplicity of the signals is stated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The measured coupling constants (*J*) were calculated in hertz (Hz). All received NMR-spectra were analyzed using the NMR processing software MestReNova v12.0.0.

1.8 Circular dichroism (CD) spectroscopy

CD spectroscopy was performed on a Jasco J-815 spectrometer at 20 °C. The spectra was analyzed with Spectra Manager 2.0. Each measurement were repeated three times and average corrected. The concentrations were adjusted to keep the photomultiplier's high voltage (HV) below 600 V in the range of interest. All spectra were recorded using a quartz cell with a path length of 1 mm at a concentration of c = 0.25 g L^{-1} polymer in HFIP. θ_{MR} was calculated from the following equation:

$$\theta_{MR} = \frac{\theta \cdot M_{repeating\ unit}}{10 \cdot c_M \cdot l} [\mathrm{deg} \cdot cm^2 \cdot dmol^{-1}]$$

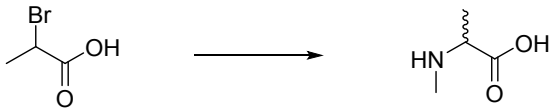
with $M_{repeating\ unit}$ = 147.1 g mol^{-1}, c_M = 0.25 g L^{-1} and l = 0.1 cm.

1.9 Polarimetry

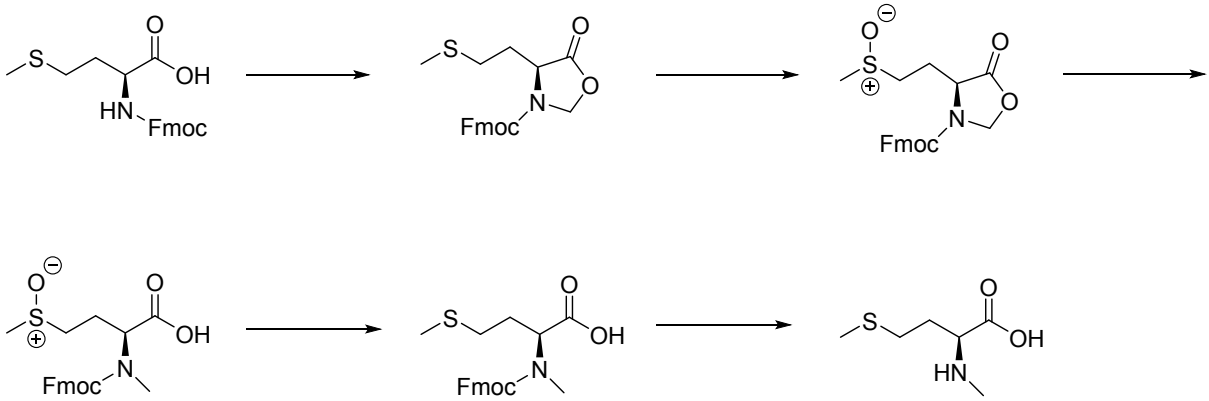
All measurements of optical rotation were carried out with a Perkin Elmer 241 polarimeter at 589 nm. A quartz glass cuvette with a path length of 10 cm was used.

2 Synthetic Route

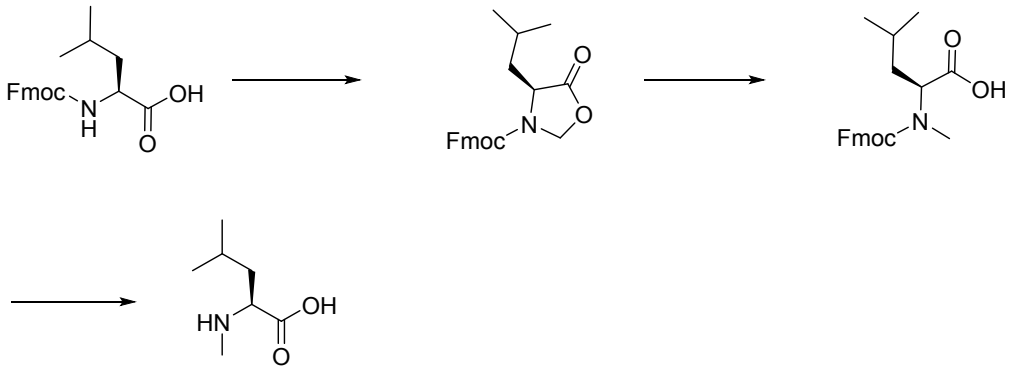
Synthesis of *N*-methyl-alanine



Synthesis of *N*-methyl-L-methionine

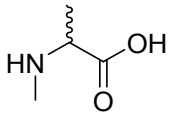


Synthesis of *N*-methyl-L-leucine



Scheme S1: Synthesis of *N*-methylated amino acids.

2.1 *N*-Methyl-alanine

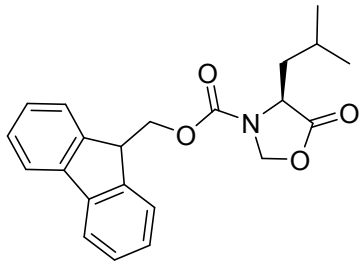


2-Bromopropanoic acid (4.6 g, 30 mmol, 1.0 eq.) was dissolved in ethanol (24 ml) at 0 °C and methylamine (33% wt in EtOH, 15 ml, 120 mmol, 4 eq.) was added to the stirred solution. The reaction mixture was then stirred at rt for 48 h and then evaporated under reduced pressure. Acetone was added and the product precipitated, which was filtered and the product obtained as a white solid (2.5 g, 24 mmol, 80%).[1]

Chemical formula: $C_4H_9NO_2$.

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 3.78 (q, *J* = 7.4 Hz, 1H, -α-CH-), 2.67 (s, 3H, -NCH_3), 1.45 (d, *J* = 7.4 Hz, -(α-CHC$\underline{H}_3$)).

2.2 9H-fluoren-9-ylmethyl (*S*)-4-isobutyl-5-oxo-1,3-oxazolidine-3-carboxylate



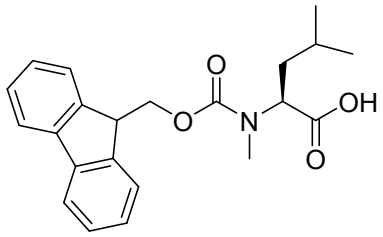
Fmoc-L-Leu-OH (12.0 g, 33.96 mmol, 1.0 eq.), paraformaldehyde (6.83 g, 227.50 mmol, 6.7 eq.) and *p*TsOH (0.585 g, 3.40 mmol, 0.1 eq.) were added to toluene (400 mL) and the suspension was stirred under reflux for 3 h in a DEAN-STARK apparatus. The resulting clear solution was cooled to room temperature, washed with a saturated $NaHCO_3$ solution (4 x 100 mL) and dried over Na_2SO_4. A yellow oil was obtained (product + traces of toluene :15.97 g, 33.96 mmol, quant.) and used without further purification.[2]

Molecular formula: $C_{22}H_{23}NO_4$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.89 (d, *J* = 7.4 Hz, 2H, -CH^{Fmoc}-), 7.66 (dd, *J* = 7.0, 3.9 Hz, 2H, -CH^{Fmoc}-), 7.42 (t, *J* = 8.0 Hz, 2H, -CH^{Fmoc}-), 7.34 (t, *J* = 7.4, 2.5, 1.2, 2H, -CH^{Fmoc}-), 5.32 (d, *J* = 4.3 Hz, 1H, NCH_2O), 5.19 (bs, 1H, NCH_2O), 4.90 – 4.40 (m, 2H, -C$\underline{H}_2$CH^{Fmoc}-), 4.30 (t, *J* = 5.4 Hz, 1H, -$CH_2C\underline{H}^{Fmoc}$-), 4.16 – 3.64 (m, 1H, -α-CH-), 1.77 – 1.16 (m, 3H, -CHC$\underline{H}_2$CH-), 0.71 (bs, 6H, -CH(C$\underline{H}_3$)$_2$).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 172.7 (COOH), 143.6 (CH^{Fmoc}), 140.8 (CH^{Fmoc}), 128.9 (-CH^{Fmoc}-), 128.2 (-CH^{Fmoc}-), 127.7 (-CH^{Fmoc}-), 127.1 (-CH^{Fmoc}-), 125.3 (-CH^{Fmoc}-), 120.1 (-CH^{Fmoc}-), 77.4 (-NCH_2O-), 53.1 (-α-CH-), 46.7 (-$CH_2\underline{C}H^{Fmoc}$-), 22.5 (-CH($\underline{C}H_3$)$_2$), 21.04 (-$\underline{C}H(CH_3)_2$).

2.3 Fmoc-*N*-Me-L-Leu-OH



The crude mixture of 9H-fluoren-9-ylmethyl (*S*)-4-isobutyl-5-oxo-1,3-oxazolidine-3-carboxylate (12.4 g, 33.9 mmol, 1.0 eq.) was dissolved in $CHCl_3$ (80 mL). Triethylsilane (16.27 ml, 101.9 mmol, 3.0 eq.) and TFA (78 mL, 1018.6 mmol, 30.0 eq.) were added and the resulting solution was stirred at room temperature for 2 days. The $CHCl_3$ and TFA were removed under reduced pressure. The residue was co-distilled three times with toluene and further purified by FC on silica gel (DCM:MeOH = 99:2 + 0.05 v/v % HCOOH and then DCM:MeOH (100:0 to 99:1 + 0.05 v/v % HCOOH). A slightly yellow solid (9.560 g, 26.0 mmol, 77% over two steps) was obtained.[2]

Molecular formula: $C_{22}H_{23}NO_4$.

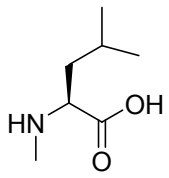
R_f: 0.28 (CH_2Cl_2:MeOH, 98:2 + 0.1 v/v % HCOOC).

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.76 (s, 1H, -COOH), 7.91 – 7.86 (m, 2H, -CH^{Fmoc}-), 7.66 (m, 2H, -CH^{Fmoc}-), 7.44 – 7.35 (m, 2H, -CH^{Fmoc}-), 7.35 – 7.27 (m, 2H, -CH^{Fmoc}-), 4.61 (dd, 1H, -α-CH-), 4.44 – 4.23 (m, 3H, -C$\underline{H}_2$CH^{Fmoc}-), 2.70 (s, 3H, -NCH_3), 1.74 – 1.44 (m, 2H, -CHC$\underline{H}_2$CH$(CH_3)_2$), 1.38 – 1.30 (m, 1H, -C$\underline{H}(CH_3)_2$), 0.90 – 0.67 (m, 6H, -CH(C$\underline{H}_3)_2$).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 173.0 (-COOH), 163.4 (-OCON-), 156.1 (-CH^{Fmoc}-), 155.7 (-CH^{Fmoc}-), 143.9 (-CH^{Fmoc}-), 140.8 (-CH^{Fmoc}-), 127.6 (-CH^{Fmoc}-), 127.1 (-CH^{Fmoc}-), 125.0 (-CH^{Fmoc}-), 120.1 (-CH^{Fmoc}-), 66.7 (-COO$\underline{C}H_2$), 56.1 (-α-CH-), 56.0 (-α-CH-), 46.8 (-COOCH$_2\underline{C}$H-), 46.7 (-COOCH$_2\underline{C}$H-), 37.0 (-α-CH$\underline{C}H_2$-), 36.7 (-α-CH$\underline{C}H_2$-), 30.1 (-NCH_3), 29.9 (-NCH_3), 24.4 (-CH$\underline{C}H_2$CH$(CH_3)_2$), 23.1 (-CH$\underline{C}H_2$CH$(CH_3)_2$), 22.9 (-$\underline{C}H(CH_3)_2$), 21.0 (-CH($\underline{C}H_3)_2$), 20.9 (-CH($\underline{C}H_3)_2$).

ESI-MS (MeOH) (m/z): Calculated for: $[C_{22}H_{23}NO_4+H]^+$: 368.1856, found: 368.1859; $[C_{22}H_{23}NO_4+Na]^+$: 390.1676, found: 390.1675.

2.4 *N*-Me-L-Leu-OH



Fmoc-*N*-Me-L-Leu-OH (1.179 g, 3.21 mmol, 1.0 eq.) was dissolved in DCM (27 ml) and a methanolic solution of 3 N NaOH (3 ml, 9 mmol, 2.8 eq.) was added and the mixture was stirred at room temperature. The reaction was monitored by thin layer chromatography (TLC). After 30 min the starting material was completely converted and the solution became cloudy. Then the solvents were removed under vacuum. The residue was solved in water (20 ml) and extracted with diethyl ether (3 x 30 ml) to remove the fulvene. The aqueous phase was cooled and acidified with conc. HCl to pH 2. Excess of HCl was removed at the SCHLENK line. The salts were removed by MPLC on a CHROMABOND® Flash RS 120 C_{18} column. The aqueous solution was freeze dried and a withe powder (0.317 g, 2.18 mmol, 68%) was obtained.[3]

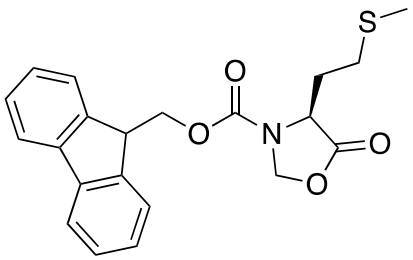
Molecular formula: $C_7H_{15}NO_2$.

^{1}H-NMR (400 MHz, D_2O): δ [ppm] = 3.57 – 3.53 (m, 1H, -α-CH-), 2.68 (s, 3H, -NCH_3), 1.76 – 1.61 (m, 2H, -CHC$\underline{H}_2$-), 0.94 – 0.92 (m, 6H, -CH(C$\underline{H}_3$)$_2$).

^{13}C-NMR (101 MHz, D_2O): δ [ppm] = 173.6 (-COOH), 62.0 (-$\underline{C}HCH_2$-), 38.9 (-CH$\underline{C}H_2$-), 31.7 (-NCH_3), 24.3 (-CH($\underline{C}H_3$)$_2$), 21.8 (-CH($\underline{C}H_3$)$_2$), 21.3 (CH($\underline{C}H_3$)$_2$).

ESI-MS (H_2O) (m/z): Calculated for: $[C_7H_{15}NO_2+H]^+$: 146.1176, found: 146.1178; $[C_7H_{15}NO_2+Na]^+$: 168.0995, found: 168.0998.

2.5 Fmoc-L-4-(2-methylthioethyl)-1,3-oxazolidin-5-one



Fmoc-L-Met-OH (15.0 g, 40.38 mmol, 1.0 eq.), paraformaldehyde (8.12 g, 270.52 mmol, 6.7 eq.) and *p*TsOH (696 mg, 4.04 mmol, 0.1 eq.) were added to toluene (400 mL) and the suspension was stirred under reflux for 3 h in a DEAN-STARK apparatus. The resulting clear solution was cooled to room temperature, washed with a saturated $NaHCO_3$ solution (4 x 100 mL) and dried over $MgSO_4$. Thereby 14.00 g (35.0 mmol, 87%) of a colorless gum could be obtained.[2]

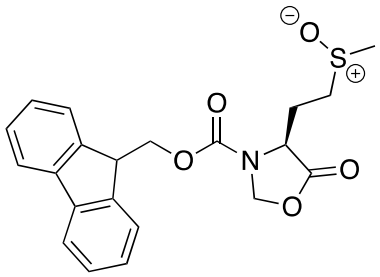
Chemical formula: $C_{21}H_{21}NO_4S$.

R_f: 0.36 (Cyclohexane:EtOAc, 3:1 + 0.1 v/v % HCOOH).

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.78 (d, *J* = 7.5 Hz, 2H, -CH^{Fmoc}-), 7.59 – 7.52 (m, 2H, -CH^{Fmoc}-), 7.42 (t, *J* = 7.4 Hz, 2H, -CH^{Fmoc}-), 7.33 (td, *J* = 7.5, 1.1 Hz, 2H, -CH^{Fmoc}-), 5.50 – 5.16 (m, 1H, -CH_2^{Oxaz}-), 5.12 (d, *J* = 4.0 Hz, 1H, -CH_2^{Oxaz}-), 4.93 – 4.45 (m, 2H, -C$\underline{H}_2$CH^{Fmoc}-), 4.24 (t, *J* = 5.0 Hz, 1H, -CH_2C$\underline{H}^{Fmoc}$-), 4.07 – 3.65 (m, 1H, -α-CH-), 2.64 – 1.50 (m, 7H, -C$\underline{H}_2$-/ -SC$\underline{H}_2$-/ -C$\underline{H}_3$).

ESI-MS (MeOH) (m/z): Calculated for: $[C_{21}H_{21}NO_4S+H]^+$: 384.1264, found: 384.1253.

2.6 Fmoc-L-4-(2-methylsulfinylethyl)-1,3-oxazolidin-5-one



Fmoc-L-4-(2-methylthioethyl)-1,3-oxazolidin-5-one (14.0 g, 35.0 mmol, 1.0 eq.) was dissolved in DCM (300 mL) and cooled to 0 °C. A solution of *m*CPBA (6.9 g, 40.2 mmol, 1.1 eq.) in DCM (150 mL) was cooled to 0 °C as well and added dropwise to the stirred solution. After the addition the mixture was stirred for 20 min at room temperature and then washed with a Na_2CO_3-solution (10 w/v %, 4 x 100 mL). The aqueous layers were combined, and remaining product extracted with DCM (2 x 100 mL). The organic layers were combined and dried over $MgSO_4$. The volatiles were removed *in vacuo* to obtain 14.45 g (36.1 mmol, 99%) of a colorless hygroscopic solid.[2]

Chemical formula: $C_{21}H_{21}NO_5S$.

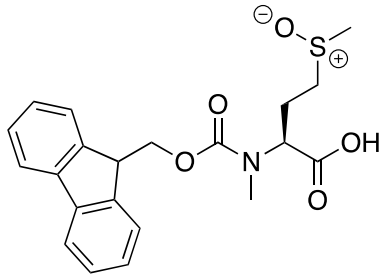
R_f: 0.30 ($CHCl_3$:MeOH, 98:2 + 0.1 v/v % HCOOH).

^{1}H-NMR (400 MHz, DMDO-d_6): δ [ppm] = 7.90 (d, *J* = 7.4 Hz, 2H, -CH^{Fmoc}-), 7.69 – 7.66 (m, 2H, -CH^{Fmoc}-), 7.43 (t, *J* = 7.4 Hz, 2H, -CH^{Fmoc}-), 7.35 (m, 2H, -CH^{Fmoc}-), 5.36 – 5.35 (m, 1H, -CH_2^{Oxaz}-), 5.32 – 5.20 (m, 1H, -CH_2^{Oxaz}-), 4.53 – 4.38 (m, 2H, -$C\underline{H}_2CH^{Fmoc}$-), 4.35 – 4.28 (m, 1H, -$CH_2C\underline{H}^{Fmoc}$-), 4.25 – 4.03 (m, 1H, -α-CH-), 2.86 – 1.73 (m, 7H, -CH_2-/ -SCH_2-/ -CH_3).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 171.2 (-$CH\underline{C}OOCH_2$-), 153.0 (-COONH-), 143.3 (-CH^{Fmoc}-), 141.5 (-CH^{Fmoc}-), 128.2 (-CH^{Fmoc}-), 127.5 (-CH^{Fmoc}-), 124.6 (-CH^{Fmoc}-), 120.3 (-CH^{Fmoc}-), 53.9 (-α-CH-), 53.8 (-α-CH-), 47.2 (-$CH_2\underline{C}H^{Fmoc}$-), 38.7 (-$CH_3$).

ESI-MS (MeOH) (m/z): Calculated for: $[C_{21}H_{21}NO_5S+H]^+$: 400.1213, found: 400.1219, $[C_{21}H_{21}NO_5S+K]^+$: 438.0772, found: 438.0780, $[2C_{21}H_{21}NO_5S+3H]^{3+}$: 267.0833, found: 267.1722, $[2C_{21}H_{21}NO_5S+Na]^+$: 821.2173, found: 821.2178 .

2.7 Fmoc-*N*-methyl-L-methionine sulfoxide



Fmoc-L-4-(2-methylsulfinylethyl)-1,3-oxazolidin-5-one (15.0 g, 37.6 mmol, 1.0 eq.) was dissolved in $CHCl_3$ (80 mL). Triethylsilane (13.11 g, 112.8 mmol, 3.0 eq.) and TFA (86 mL, 1127.5 mmol, 30.0 eq.) were added and the resulting solution was stirred at room temperature for 3 days. The product (11.6 g, 28.9 mmol, 77% was used without further purification.[2]

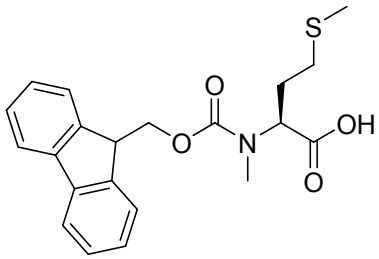
Chemical formula: $C_{21}H_{23}NO_5S$.

R_f: 0.31 ($CHCl_3$:MeOH, 96.25:3.75 + 0.1 v/v % HCOOC).

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 7.90 (t, J = 6.5 Hz, 2H, -CH^{Fmoc}-), 7.67 – 7.62 (m, 2H, -CH^{Fmoc}-), 7.44 – 7.40 (m, 2H, -CH^{Fmoc}-), 7.36 – 7.29 (m, 2H, -CH^{Fmoc}-), 4.59 – 4.41 (m, 1H, -α-CH-), 4.39 – 4.21 (m, 3H, -C$\underline{H}_2$C$\underline{H}^{Fmoc}$-), 2.79 – 2.75 (m, 3H, -NCH_3), 2.54 – 2.51 (m, 3H, -SCH_3-), 2.30 – 1.92 (m, 4H, -SC$\underline{H}_2$-, -C$\underline{H}_2$-).

ESI-MS (MeOH) (m/z): Calculated for: $[C_{21}H_{23}NO_5S+H]^+$: 402.1370, found: 402.1371; $[2C_{21}H_{23}NO_5S+Na]^+$: 825.2486, found: 825.2503.

2.8 Fmoc-*N*-methyl-L-methionine



The crude mixture of Fmoc-*N*-methyl-L-methionine sulfoxide (15.894 g, 39.6 mmol, 1.0 eq.) in chloroform and TFA was cooled to 0 °C and dimethyl sulfide (8.68 ml, 118.8 mmol, 3.0 eq.) was added. Then portion wise ammonium iodide (17.213 g, 118.8 mmol, 3.0 eq.) was added and the solution turned brown. The solution was stirred for 3 h at 0 °C and then the volatiles were removed at the SCHLENK line, which was connected with a big cooling trap. The residue was solved in DCM (50 ml), transferred in a separatory funnel and washed with a 5% thiosulfate solution (150 ml). The organic layer was extracted with a sat. $NaHCO_3$ solution (100 ml). The combined aqueous layers were extracted ones with DCM (150 ml). Then the combined organic layers were dried over $NaSO_4$, filtered, the solvent removed under reduced pressure and three times co-distilled with toluene. The product was purified by FC on silica gel (DCM:EtOAC = 9:1 + 0.05 v/v % HCOOH) and afterwards by FC on silica gel (DCM:MeOH = 99:1 + 0.05 v/v % HCOOH). 9.88 g (25.6 mmol, 65% over two steps) of a colorless product were obtained.[2]

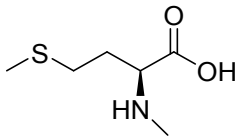
Molecular formula: $C_{21}H_{23}NO_4S$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 12.89 (s, 1H, COOH), 7.89 (t, *J* = 7.2 Hz, 2H, -CH^{Fmoc}-), 7.65 (d, *J* = 7.2 Hz, 2H, -CH^{Fmoc}-), 7.42 (td, *J* = 7.4, 2.9 Hz, 2H, -CH^{Fmoc}-), 7.35-7.28 (m, 2H, -CH^{Fmoc}-), 4.56 (ddd, *J* = 27.6, 10.4, 4.7 Hz, 1H, -α-CH-), 4.42-4.22 (m, 3H, -C<u>H</u>C<u>H$_2$</u>^{Fmoc}-), 2.75 (s, 3H, -NCH_3), 2.42-2.19 (m, 2H, -SCH_2-), 2.11-1.85 (m, 5H, -SC<u>H$_3$</u>-, -C<u>H$_2$</u>-).

^{13}C-NMR (101 MHz, DMSO-d_6): δ [ppm] = 172.3 (-COOH), 156.0 (-COONH-), 143.8 (-CH^{Fmoc}-), 140.8 (-CH^{Fmoc}-), 127.7 (-CH^{Fmoc}-), 127.1 (-CH^{Fmoc}-), 125.05 (-CH^{Fmoc}-), 120.1(-CH^{Fmoc}-), 66.7 (-<u>C</u>H$_2$CH^{Fmoc}-), 57.6 (-α-CH-), 46.7 (-CH$_2$<u>C</u>H^{Fmoc}-) , 31.0 (-NCH_3) , 30.0 (-SCH_2-), 27.8 (-CH_2-), 14.6 (-SCH_3).

ESI-HRMS (MeOH) (m/z): Calculated for $[C_{21}H_{23}NO_4S+H]^+$: 386.1421, found: 386.1420, $[C_{21}H_{23}NO_4S+Na]^+$: 408.1240, found 408.1235.

2.9 *N*-Methyl-L-methionine



Fmoc-*N*-methyl-L-methionine (5.592 g, 1.25 mmol, 1.0 eq.) was dissolved in a solution of 20% piperidine in DMF (10 mL) and stirred for 2 h at room temperature. The precipitated colorless solid was filtered and washed with a slight amount of DCM to yield 1.007 g (0.63 mmol, 42%) of the colorless water-soluble product.

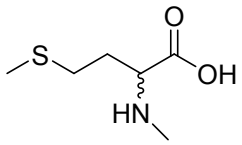
Molecular formula: $C_6H_{13}NO_2S$.

^{1}H-NMR (400 MHz, D_2O): δ [ppm] = 3.69 (t, *J* = 6.0 Hz, 1H, -α-CH-), 2.71 (s, 3H, -NCH_3), 2.62 – 2.57 (m, 2H, -SCH_2-), 2.18 – 2.12 (m, 5H, -$SC\underline{H}_3$, -$C\underline{H}_2$-).

^{13}C-NMR (101 MHz, D_2O): δ [ppm] = 173.0 (-COOH), 62.7 (-α-CH-), 31.8 (-NCH_3), 28.7 (-CH_2-), 28.5 (-SCH_2-), 14.0 (-SCH_3).

ESI-HRMS (MeOH) (m/z): Calculated for $[C_6H_{13}NO_2S + Na]^+$:186.0559, found 186.1141.

2.10 *N*-Methyl-DL-methionine



N-Methyl-L-methionine (500 mg, 3.063 mmol, 1.00 eq.) was dissolved in glacial acid (15 ml) and salicylaldehyde (18.7 mg, 0.153 mmol, 0.05 eq.) was added. The solution was stirred and heated at 100 °C for 2 days. Then the solvents were removed *in vacuo* and recrystallized in MeOH to yield a slightly yellow solid (200 mg, 1.225 mmol, 40%).[4]

$[\alpha]_D^{24.5}$: 0 ± 0.02 (c = 1.0, 3 M HCl).

3 FT-IR Spectra

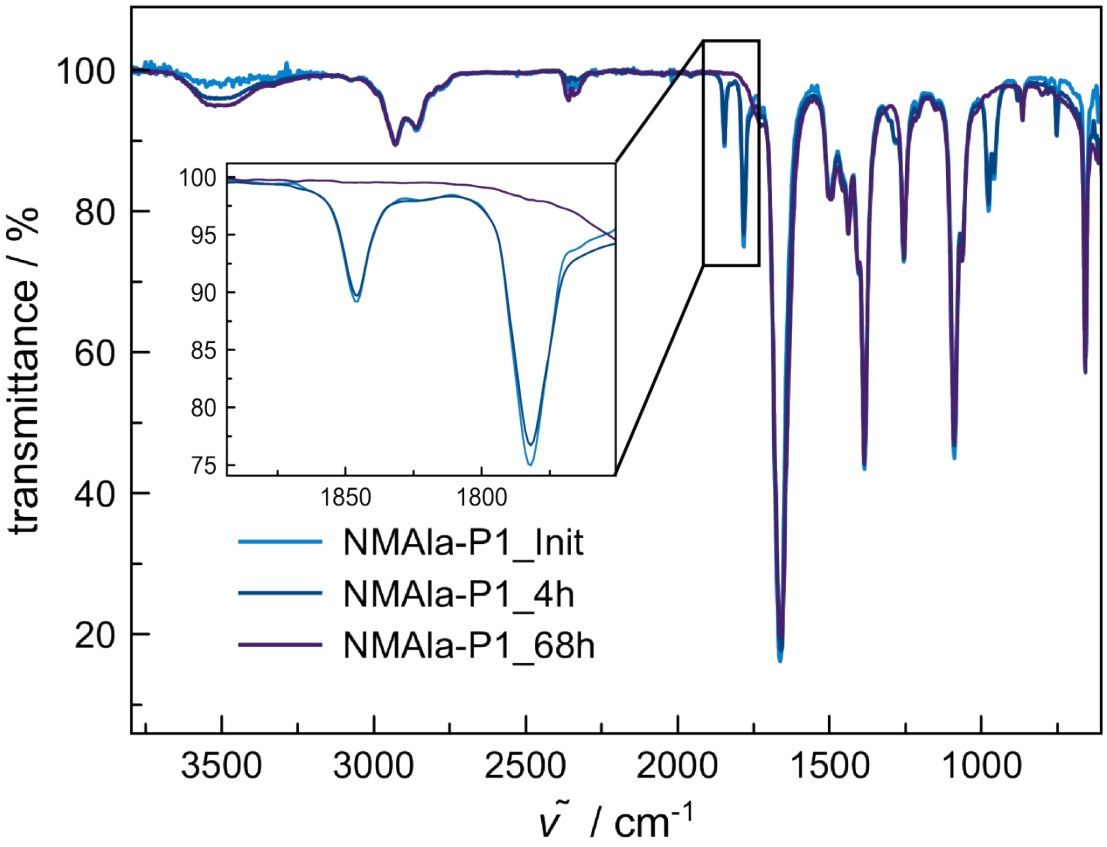


Figure S1: Generic FT-IR spectrum of a polymerization of NMAla-NCA in DMF (liquid film). Full conversion was ensured in all cases by FT-IR monitoring of the carbonyl attributed peaks at 1782 and 1845 cm^{-1}.

4 NMR Spectra

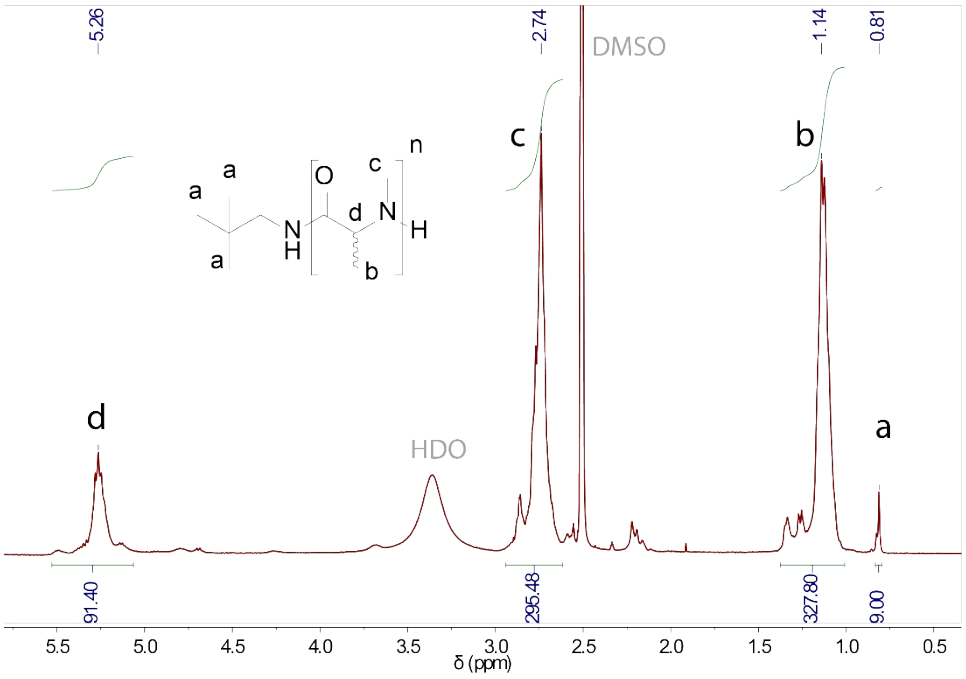


Figure S2: ^{1}H NMR spectrum of NMAla-P1 in d_6-DMSO.

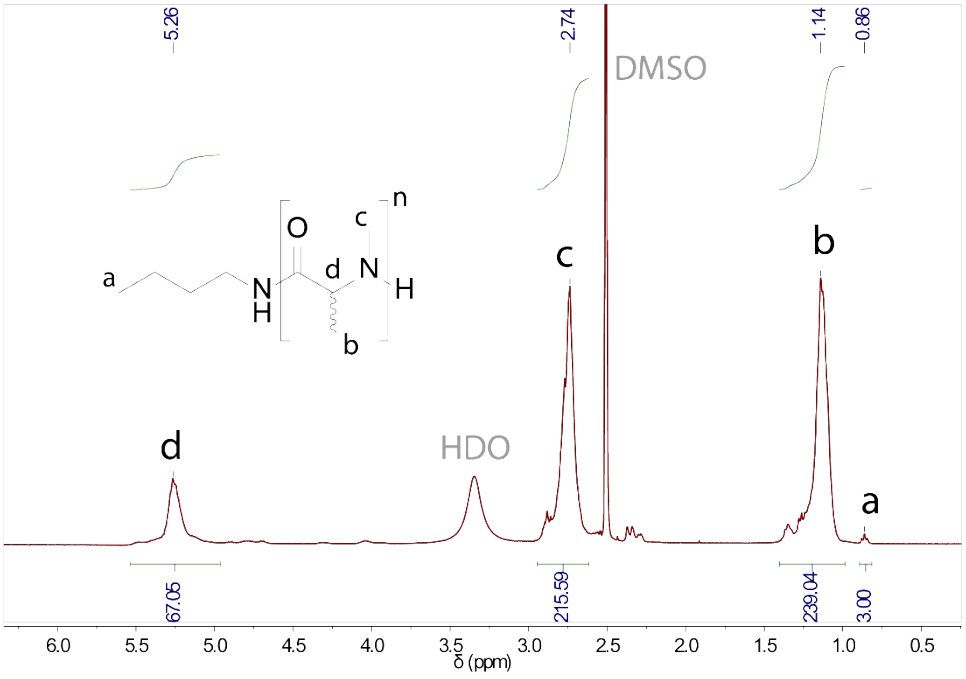
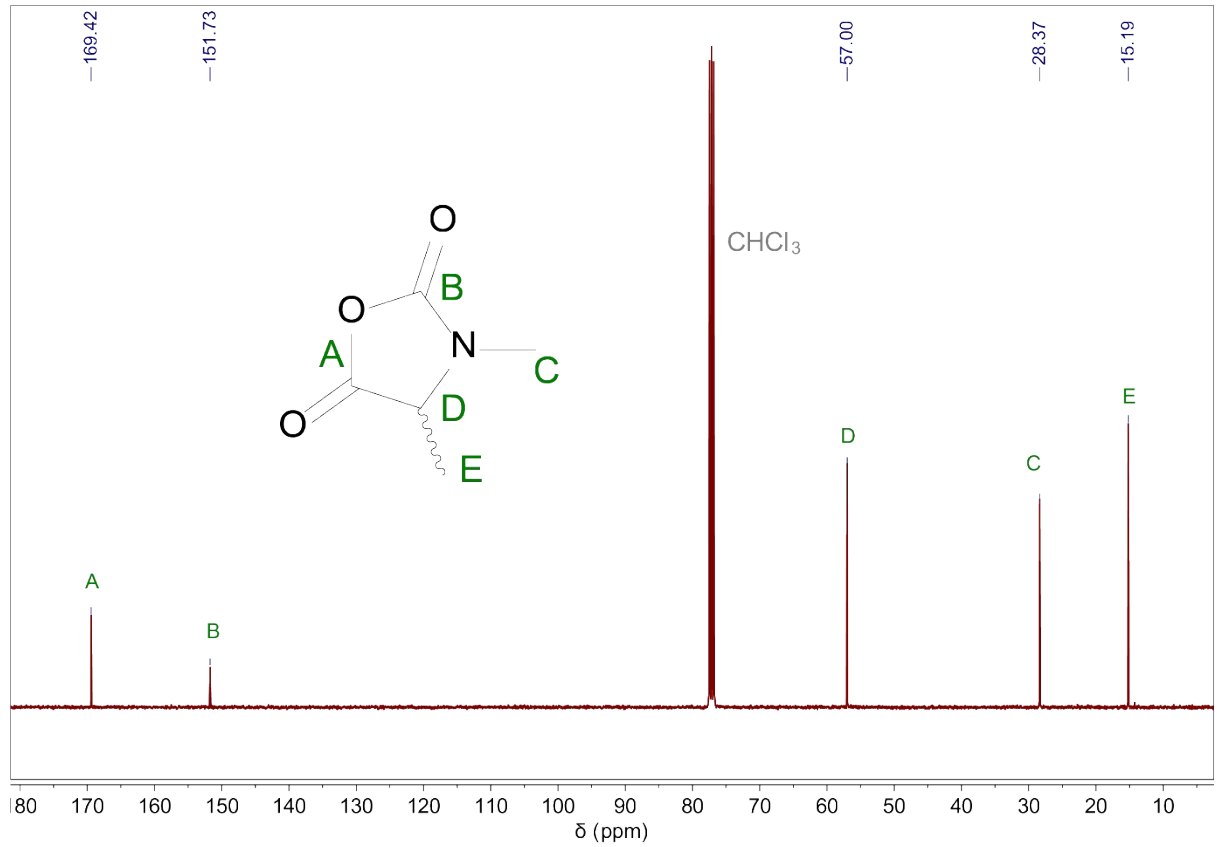
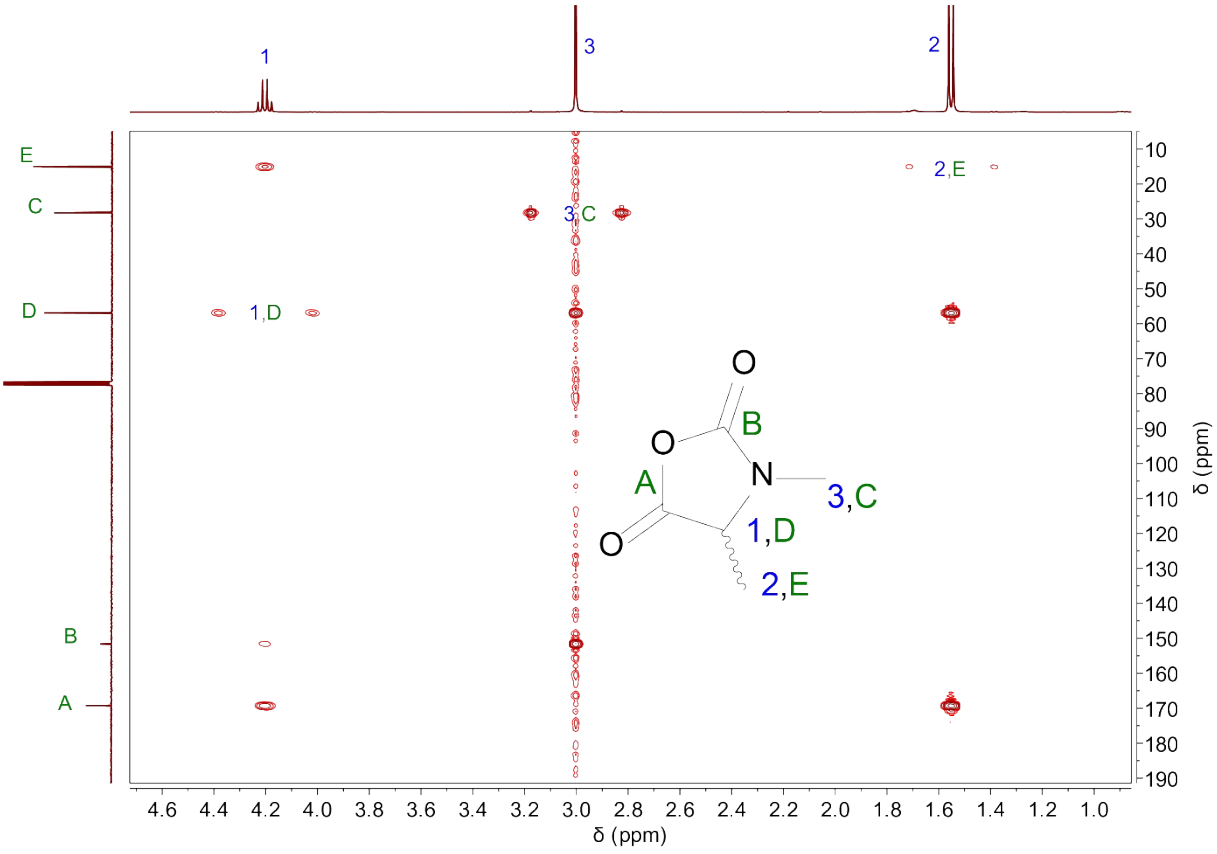
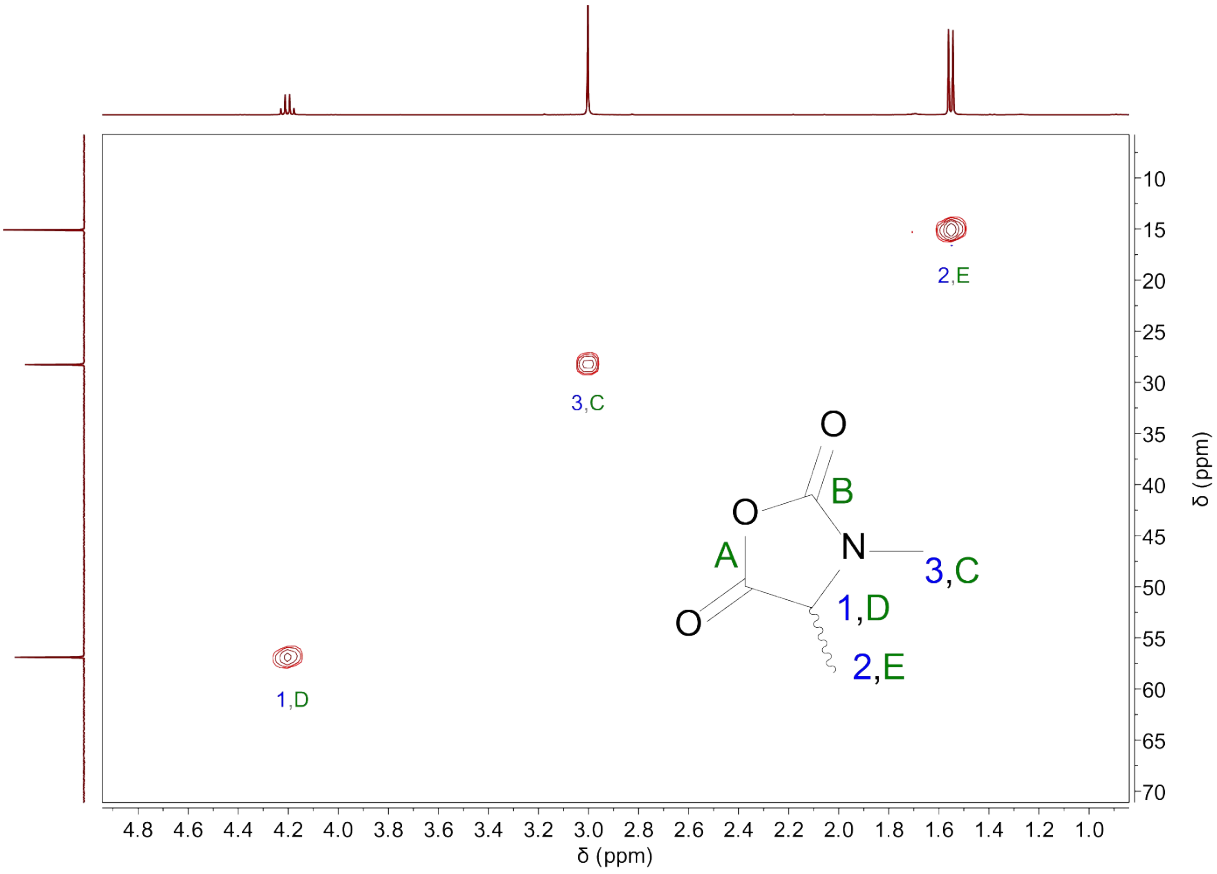
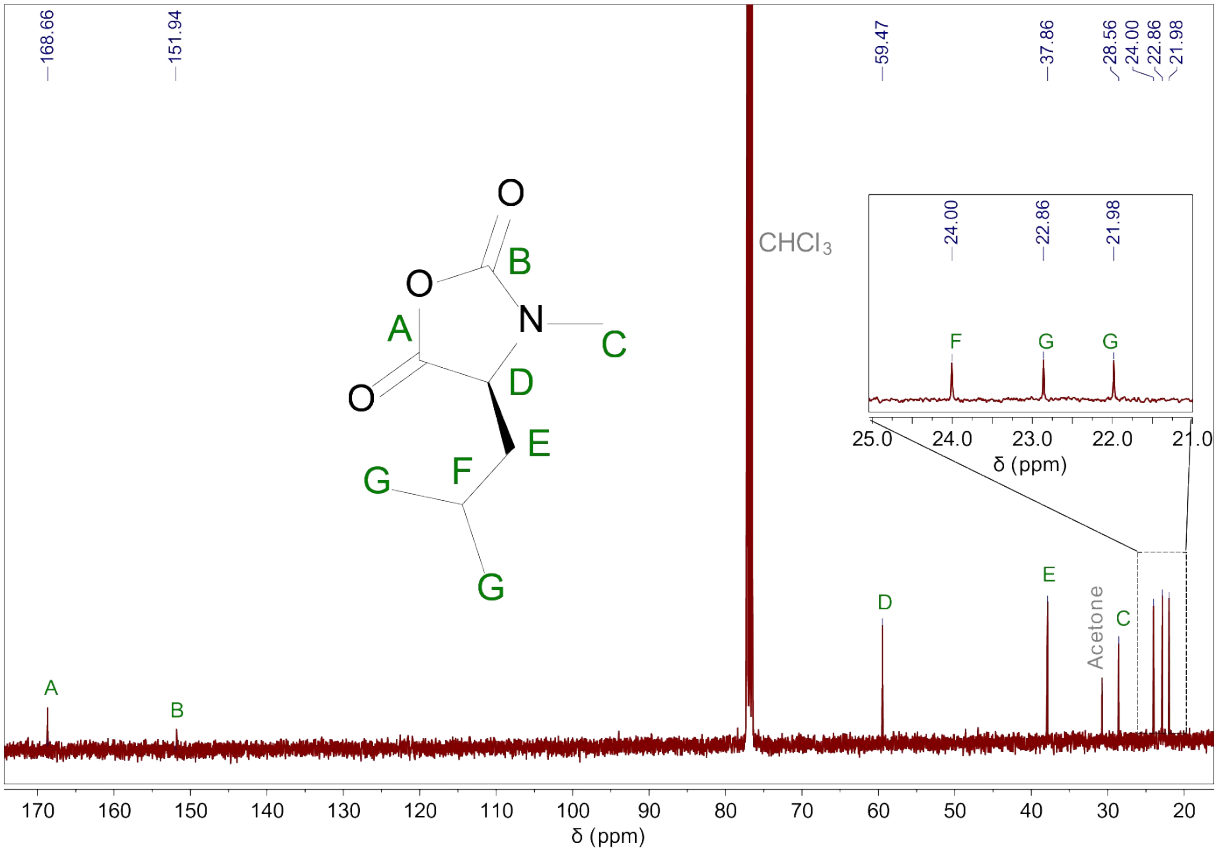


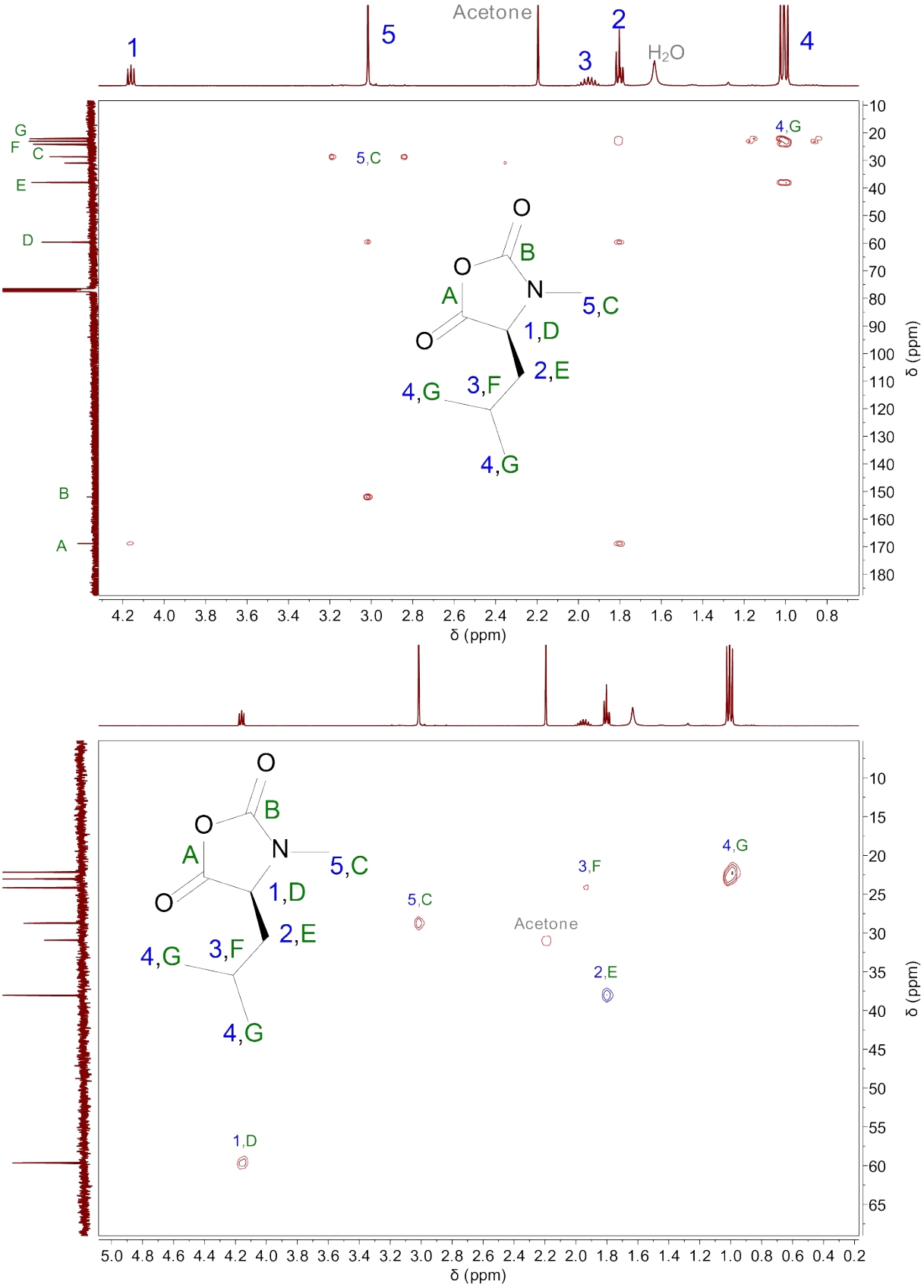
Figure S3: ^{1}H NMR spectrum of NMAla-P3 in d_6-DMSO.

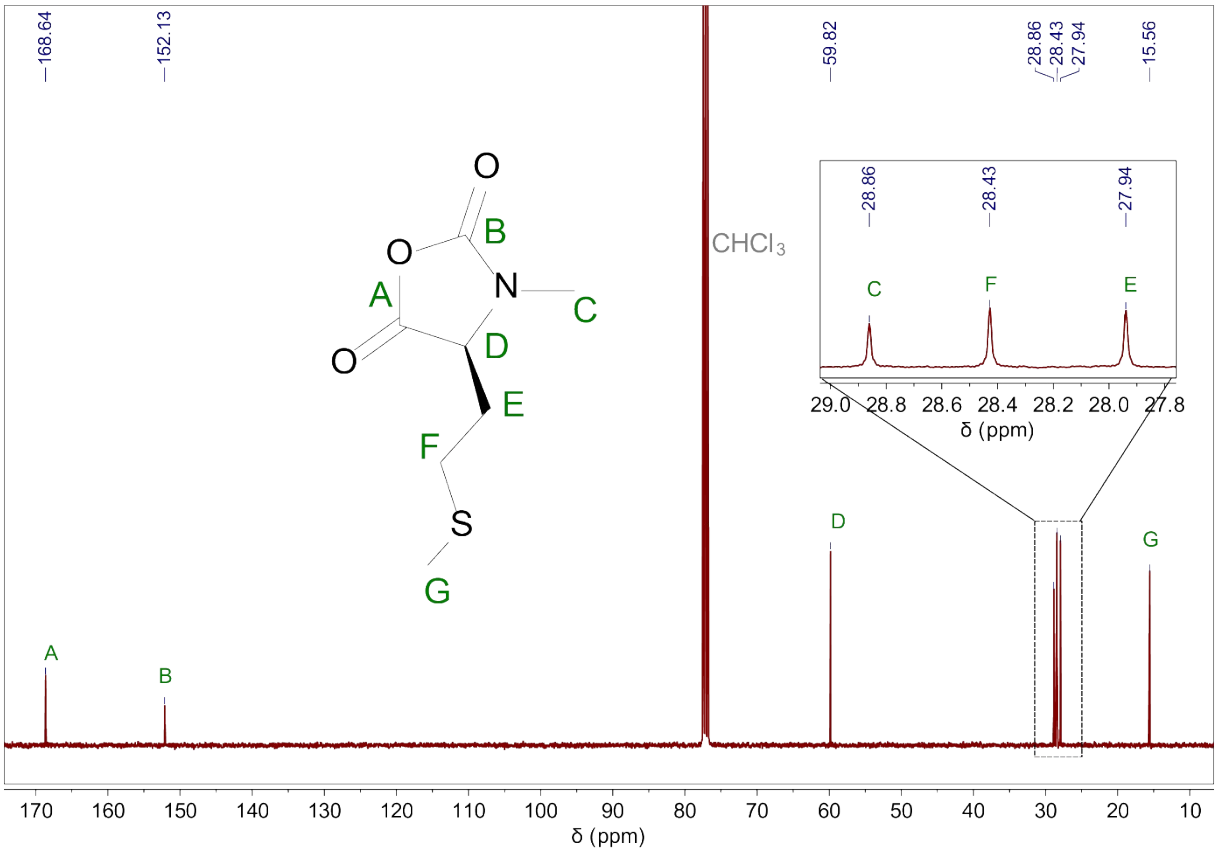

169.42
151.73
57.00
28.37
15.19
CHCl3
A
B
C
D
E
δ (ppm)

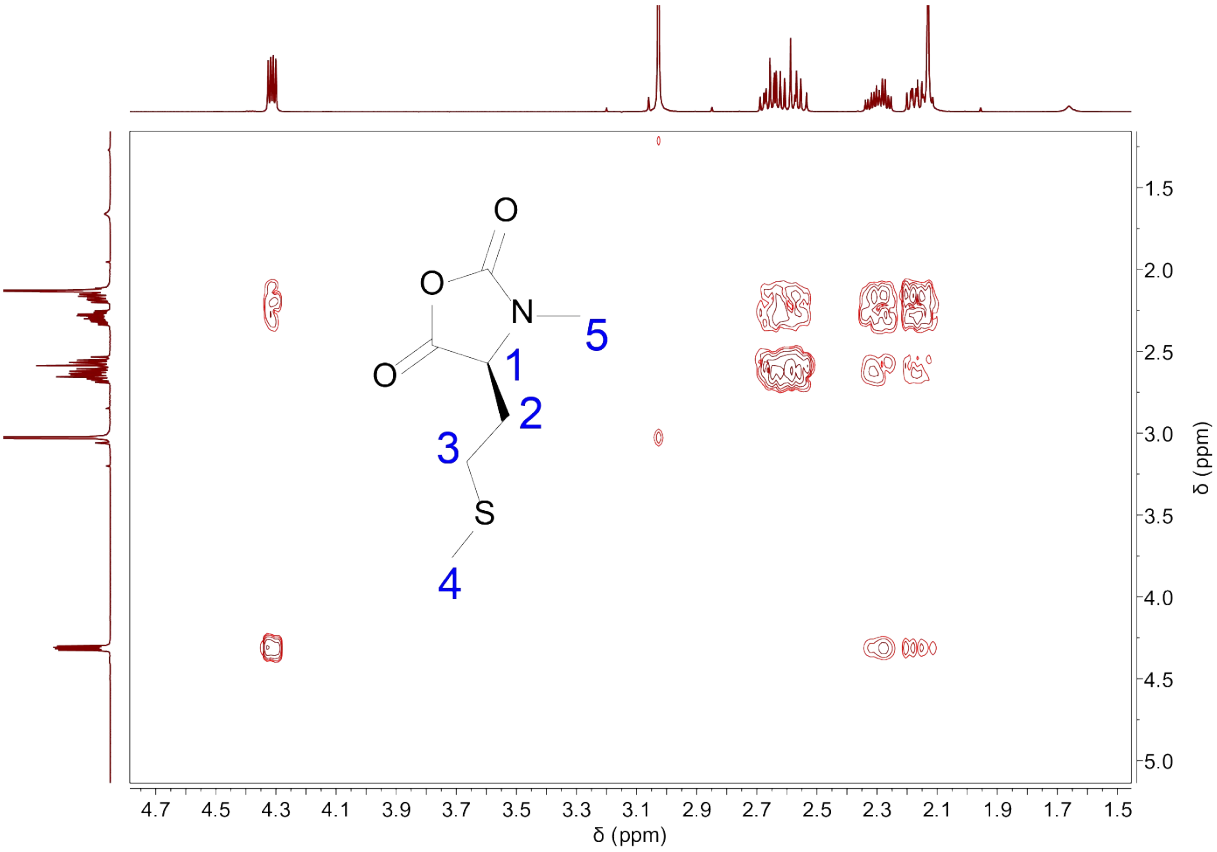

1
3
2
E
C
D
B
A
2,E
3,C
1,D
δ (ppm)

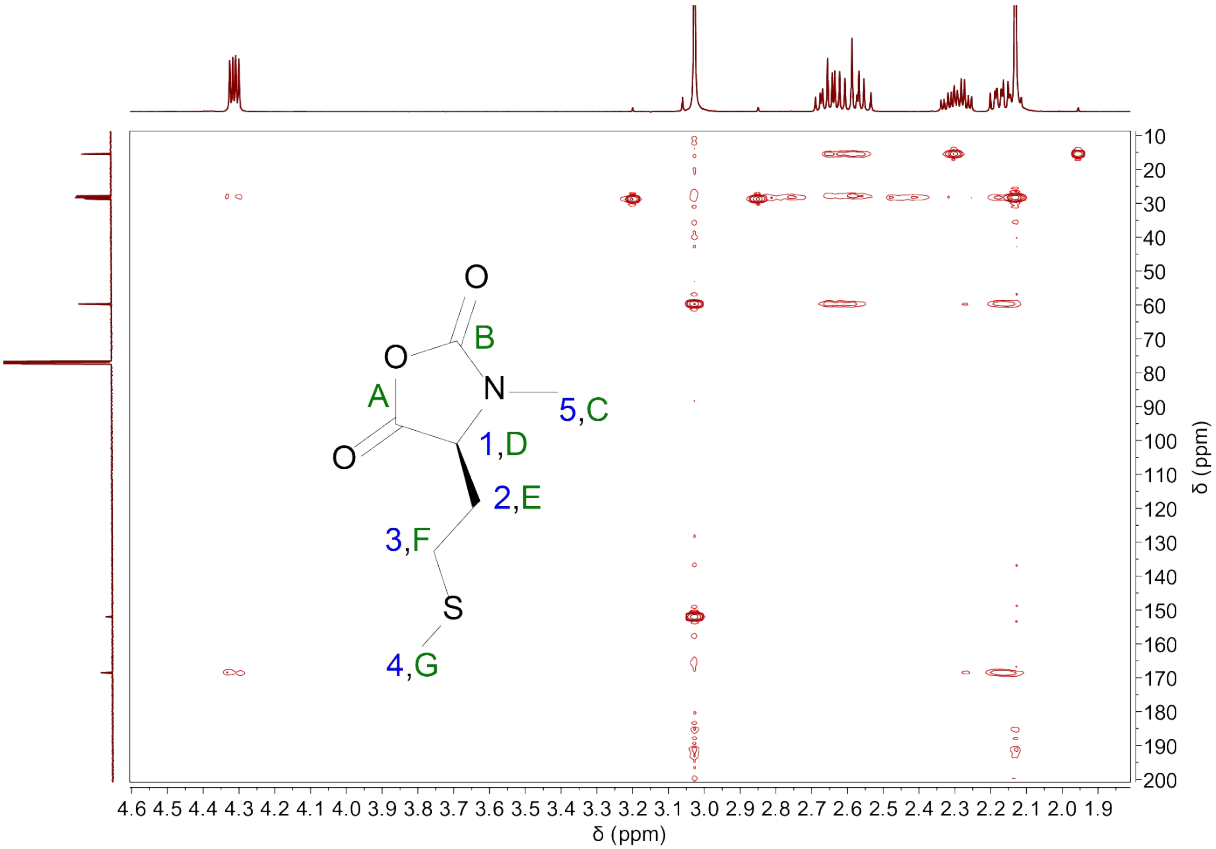

2,E
3,C
1,D
O
B
O
N
A
O
3,C
1,D
2,E
δ (ppm)
δ (ppm)

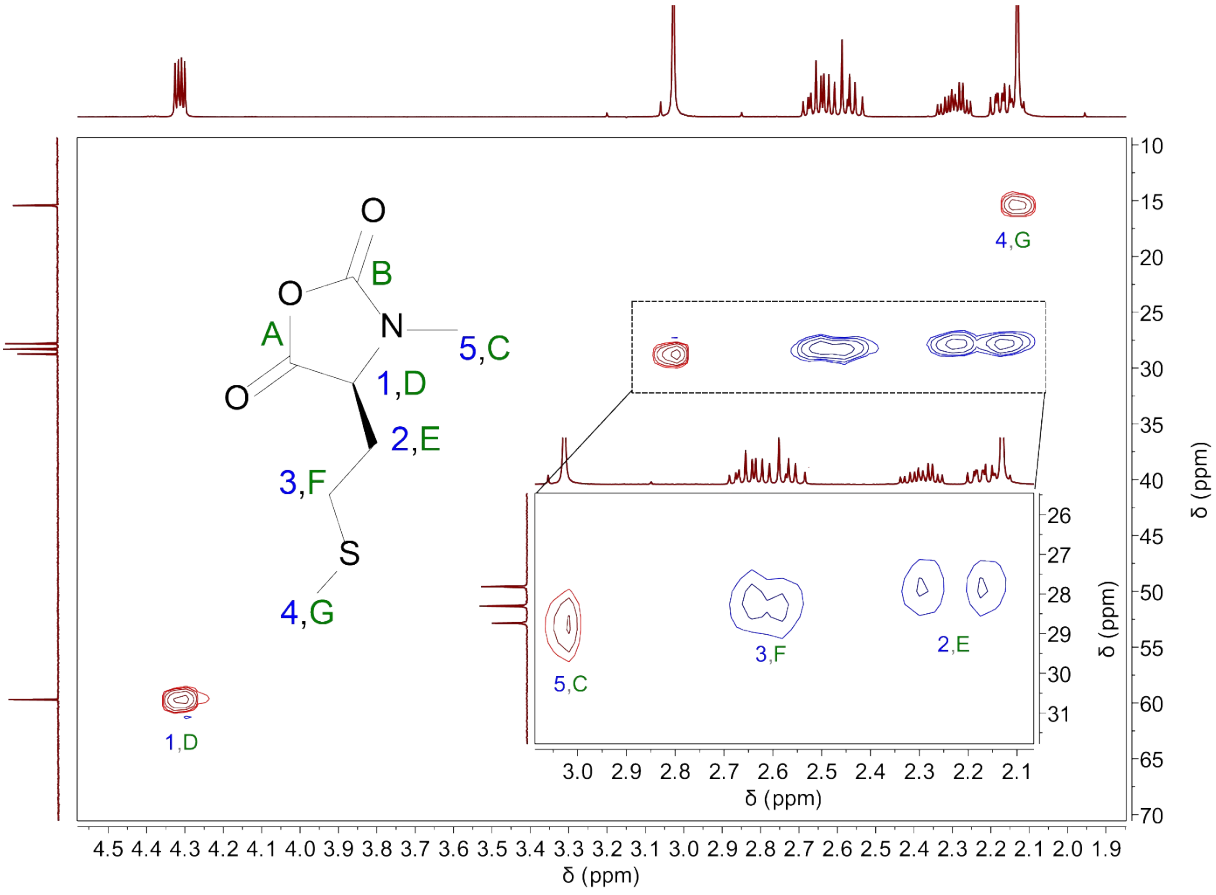

168.66
151.94
59.47
37.86
28.56
24.00
22.86
21.98
CHCl3
O
B
O
N
A
C
O
D
E
G
F
G
A
B
D
E
C
Acetone
F
G
G
δ (ppm)
δ (ppm)


Acetone
H2O
1
5
3
2
4
G
F
C
E
D
B
A
5,C
4,G
1,D
2,E
3,F
O
B
N
A
δ (ppm)
4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2
10 15 20 25 30 35 40 45 50 55 60 65


168.64
152.13
59.82
28.86
28.43
27.94
15.56
CHCl3
A
B
C
D
E
F
G
δ (ppm)


1
2
3
4
5
δ (ppm)
δ (ppm)


O
B
O
N
A
5,C
O
1,D
2,E
3,F
S
4,G
δ (ppm)
δ (ppm)


O
B
O
N
A
5,C
O
1,D
2,E
3,F
S
4,G
1,D
4,G
5,C
3,F
2,E
δ (ppm)
δ (ppm)
δ (ppm)

5 MALDI-ToF data

Table S1: Values of the peaks shown in the magnified area of the MALDI-ToF spectrum of figure 4 (Poly(N-methyl-DL-alanine)).

Initiator	X_n	Additional Ion	m/z (found)	m/z (calc)
*n*Bu	22	Na^+	1968,39	1968,68
*n*Bu	23	Na^+	2053,46	2053,8
NPA	22	Na^+	1981,83	1982,7
NPA	23	Na^+	2066,89	2067,82
H_2O	23	Na^+	1998,32	1998,66
H_2O	23	K^+	2011,39	2014,86
H_2O	24	Na^+	2083,42	2083,78
H_2O	24	K^+	2096,41	2099,98

Table S2: Values of the peaks shown in the magnified area of the MALDI-ToF spectrum of figure 6 (Poly(N-methyl-L-methionine)).

Initiator	X_n	Additional Ion	m/z (found)	m/z (calc)
H_2O	6	-	889,55	889,44
H_2O	6	Na^+	911,42	912,43
H_2O	6	K^+	925,42	928,54
H_2O	7	-	1034,64	1034,68
*n*Bu	6	-	943,42	944,58
*n*Bu	6	Na^+	966,46	967,57
*n*Bu	6	K^+	982,51	983,68
NPA	6	-	958,64	958,58

6 GPC data

Table S3: Molecular weights and dispersities determined *via* HFIP-GPC (based on PMMA standards)

Sample	M_n	M_w	PDI
DL-NMMet-P1	1639	2532	1.55
NMMet-P1	971	1965	2.02
NMMet-P2	2223	2401	1.49
NMMet-P3	2357	3306	1.40
NMMet-P4	713	1425	2.11
$pMet_{50}$	7683	10066	1.31
NMAla-P1	2285	2761	1.21
NMAla-P2	2880	3460	1.20
NMAla-P3	4213	5073	1.20
NMLeu-P1	526	713	1.89
$pSar_{50}$	15768	16115	1.17

7 Coupled cluster (CC) calculations

For the monomers NMMet-NCA and Met-NCA the molecule related parameters were obtained from x-ray data. These structures and the structure of ethylamine were optimized with Gaussian 16, Rev. A.03[5] using DFT methods and the IEFPCM solvation model[6] for DMF. All conformers were confirmed as local minima by frequency analysis ($N_{imag} = 0$). The B3LYP functional[7–10] was used in conjunction with the 6-311G(d,p) Pople basis set.[11,12]

Energy and NBO calculations were performed using orca 4.1.0[13] with the DLPNO-CCSD(T)[14] method and the cc-pVDZ[15,16] and cc-pVDZ/C[17,18] basis sets. The frontier orbitals were visualized using Chemcraft (Version 1.8, build 562b).[19]

Computational input lines

DFT optimization and frequency calculation:

```
#p opt=tight freq=noraman b3lyp/6-311g(d,p) scrf=(iefpcm,solvent=n,n-dimethylformamide)
```

The following keyword lines were used as input for Orca:

```
! DLPNO-CCSD(T) cc-pVDZ cc-pVDZ/C
%nbo
NBOKEYLIST      = "$NBO NBO NPA AONBO=C ARCHIVE PLOT $END"
end
```

XYZ Coordinates

NMMet-NCA

0 1

C	0.57042	0.19486	1.15955
H	1.02180	0.14514	2.15959
C	0.21999	-1.23469	0.77790
O	1.05547	-1.62537	-0.23674
C	1.90238	-0.55984	-0.59642

N	1.58544	0.51141	0.16506
O	-0.58072	-1.96905	1.27700
O	2.73557	-0.68981	-1.45263
C	2.41079	1.71043	0.20947
H	2.97324	1.75604	1.14631
H	1.79281	2.60485	0.11978
H	3.10581	1.67453	-0.62660
C	-0.62690	1.15677	1.23560
H	-0.30656	2.06045	1.76292
H	-1.37497	0.68419	1.87720
C	-1.24288	1.58808	-0.09709
H	-0.50278	2.09051	-0.72226
H	-2.04422	2.30422	0.09560
S	-1.90197	0.25827	-1.17507
C	-3.28552	-0.38570	-0.17045
H	-2.91951	-0.92971	0.69981
H	-3.83595	-1.07330	-0.81272
H	-3.94840	0.42522	0.13360

Met-NCA

0 1

C	0.41926	0.15203	-0.16057
H	-0.10741	0.21788	-1.11914
C	1.47598	1.24418	-0.11595
O	2.71413	0.65234	-0.09020
C	2.57990	-0.75255	-0.11782

N	1.26026	-1.03289	-0.10747
H	0.93578	-1.97446	-0.26459
O	1.32740	2.42878	-0.09083
O	3.53896	-1.47108	-0.13997
C	-0.58922	0.28924	0.98731
H	-0.05676	0.21369	1.94088
H	-1.01151	1.29559	0.93436
C	-1.70364	-0.76092	0.97106
H	-2.33469	-0.63800	1.85324
H	-1.29112	-1.77147	1.01261
S	-2.78545	-0.75451	-0.51273
C	-3.72422	0.79375	-0.25730
H	-4.23898	0.77299	0.70386
H	-4.46288	0.84171	-1.05734
H	-3.07940	1.66981	-0.32029

Ethylamine

0 1

N	-1.21209	-0.32640	-0.12258
C	-0.04788	0.55918	0.05385
H	-2.06468	0.22615	-0.08952
H	-1.26950	-0.95940	0.67196
H	-0.06996	1.30180	-0.75019
C	1.25079	-0.23799	-0.02697
H	-0.07014	1.11998	1.00120
H	1.31376	-0.77450	-0.97757

H	1.30709	-0.97515	0.78077
H	2.12060	0.41878	0.06016

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