Synthesis of pH-cleavable poly(trimethylene carbonate)-based block copolymers via ROP and RAFT polymerization

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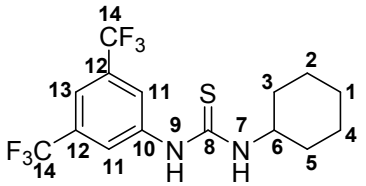
● Synthesis procedures of small molecules

Synthesis of *N'*-[3,5-bis(trifluoromethyl)]phenyl-*N*-cyclohexylthiourea (TU)

TU was synthesized according to the previously published procedure.[1]

In a round bottom flask 0.68 mL (3.7 mmol) 3,5-bis(trifluoromethyl)phenyl isocyanate and 0.42 mL (3.7 mmol) cyclohexylamine were dissolved in 4 mL THF and stirred at 30 °C for 2 h. After removing the solvent *in vacuo* the precipitate was washed with *n*-pentane (4x10 mL) to afford 1.22 g of a white solid. Yield: 89 %



^{1}H NMR (500 MHz, DMSO): δ (ppm) = 1.22-1.98 (m, 10 H, $^{1\text{-}5}CH_2$), 4.12 (b, 1 H, ^{6}CH), 7.66 (s, 1 H, ^{13}CH), 8.11 (b, 1 H, ^{7}NH), 8.25 (b, 2 H, ^{11}CH), 9.81 (b, 1 H, ^{9}NH)

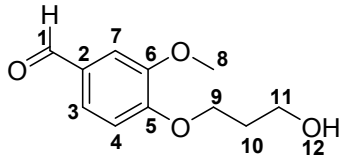
^{13}C NMR (125 MHz, DMSO): δ (ppm) = 24.9 (2 C, $^{2,4}CH_2$), 25.6 (1 C, $^{1}CH_2$), 32.1 (2 C, $^{3,5}CH_2$), 52.8 (1 C, ^{6}CH), 116.3 (1 C, ^{13}CH), 122.2 (2 C, ^{11}CH), 123.7 (q, 2 C, J_{CF} = 272.8 Hz, $^{14}CF_3$), 130.6 (q, 2 C, J_{CF} = 32.4 Hz, $^{12}C_q$), 142.5 (1 C, $^{10}C_q$), 179.7 (1 C, $^{8}C_q$)

Synthesis of 4-(3-hydroxypropoxy)-3-methoxybenzaldehyde (VanProp)

VanProp was synthesized according to the previously published procedure.[2]

2.0 g (13.2 mmol) vanillin, 2.5 g (18.1 mmol) potassium carbonate and 40 mL dimethylformamide were added to a round flask. After adding 1.5 mL (16.6 mmol) 3-bromo-1-propanol, the reaction mixture was stirred at 90 °C for 30 min and then cooled to room temperature. 40 mL water was added, and the resulting mixture was extracted with 4x40 mL ethyl acetate. The organic phase was dried over anhydrous

magnesium sulfate. After removing the solvent, the residue was purified by column chromatography with ethyl acetate/n-hexane (6: 4, R_f = 0.21) to give 0.75 g of a white solid. Yield: 29 %



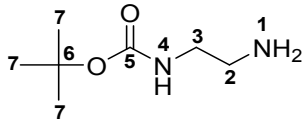
^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm)= 2.10 (m, 2 H, $^{10}CH_2$), 2.55 (s, 1 H, ^{12}OH), 3.86 (t, $^{3}J_{HH}$ = 5.6 Hz, 2 H, $^{11}CH_2$), 3.88 (s, 3 H, $^{8}CH_3$), 4.25 (t, $^{3}J_{HH}$ = 6.1 Hz, 2 H, $^{9}CH_2$), 6.97 (d, $^{3}J_{HH}$ = 8.2 Hz, 1 H, ^{4}CH), 7.37 (d, $^{4}J_{HH}$ = 1.9 Hz, 1 H, ^{7}CH), 7.41 (dd, $^{3}J_{HH}$ = 8.2, $^{4}J_{HH}$ = 1.9 Hz, 1 H, ^{3}CH), 9.81 (s, 1 H, ^{1}CHO)

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 31.7 ($^{10}CH_2$), 56.1 ($^{8}CH_3$), 60.6 ($^{11}CH_2$), 67.7 ($^{9}CH_2$), 109.3, 111.6, 126.8, 130.3, 149.9, 153.9 ($^{2\text{-}7}C_{Ar}$), 191.0 (^{1}CHO)

Synthesis of *tert*-butyl-*N*-(2-aminoethyl)-carbonate (TBAC)

TBAC was synthesized according to the previously published procedure.[3]

In a three-necked round flask 25 mL (37.4 mmol) ethylenediamine was dissolved in 100 mL 1,4-dioxane. A solution of 11.0 g (50 mmol) di-*tert*-butyldicarbonate (Boc_2O) in 100 mL 1,4-dioxane was added dropwise into the flask. The reaction mixture was stirred at room temperature for 2 d. After filtration, the solvent was removed under reduced pressure and the residue was taken up in 200 mL water. The precipitate was filtered off. The aqueous solution was saturated with sodium chloride and extracted with 8x50 mL dichloromethane. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure to give 4.83 g of a yellowish liquid. Yield: 60%



^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.13 (s, 2 H, $^{1}NH_2$), 1.32 (s, 9 H, $^{7}CH_3$), 2.67 (t, $^{3}J_{HH}$ = 5.9 Hz, 2 H, $^{2}CH_2$), 3.05 (b, $^{3}J_{HH}$ = 5.4 Hz, 2 H, $^{3}CH_2$), 5.22 (s, 1 H, ^{4}NH)

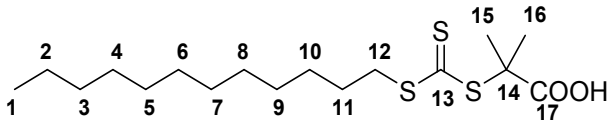
^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) =28.3 (3 C, $^{7}CH_3$), 41.8 (1 C, $^{2}CH_3$), 43.4 (1 C, $^{3}CH_2$),

78.9 (1 C, ^{6}C), 156.2 (1 C, ^{5}C=O)

Synthesis of *S*-1-Dodecyl-*S'*-(*R, R'*-dimethyl-*R''*-acetic acid) trithiocarbonate (CTA-1)

CTA-1 was synthesized according to the previously published procedure.[4]

4.8 mL (0.02 mol) of 1-dodecanethiol, 12.1 mL (0.16 mmol) acetone and 0.37 mL (0.8 mmol) aliquot 336 were placed in a 100-mL Schlenk flask under argon atmosphere, and cooled to 0 °C using an ice-water bath. Then 1.1 mL of a 50 % sodium hydroxide solution was added slowly within 20 min until a white solid precipitated. The solution was stirred for another 15 min and a solution of 1.2 mL (0.02 mol) of carbon disulfide in 2.5 mL acetone was added over 20 min. After 10 min stirring 2.4 mL chloroform was added in one shot and 5.25 mL 50 % sodium hydroxide solution were added over 30 min. The mixture was stirred overnight at room temperature. To isolate the product, 30 mL water and 5 mL concentrated hydrochloric acid were added into the reaction mixture. The acetone was removed under a flow of nitrogen and the yellow precipitate was then suspended in 50 mL 2-propanol. After filtration and removing the solvent, the residue was recrystallization from *n*-hexane to give 3.16 g of a yellow solid. Yield: 63 %.

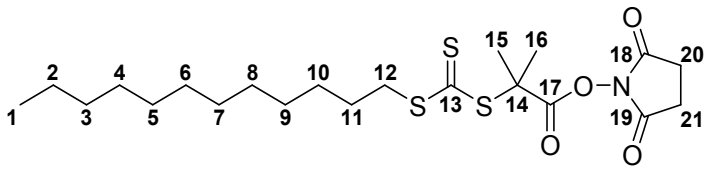


^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.88 (t, $^{3}J_{HH}$ = 7.0 Hz, 3 H, $^{1}CH_3$), 1.25-1.38 (m, 18 H, $^{2\text{-}10}CH_2$), 1.61 (m, 2H, $^{11}CH_2$), 1.73 (s, 6 H, $^{15,16}CH_3$), 3.28 (t, $^{3}J_{HH}$ = 7.5 Hz, 2 H, $^{12}CH_2$)

Synthesis of 2,5-dioxopyrrolidin-1-yl 2-(((dodecylthio)carbonothioyl)thio)-2-methylpropanoate (CTA-2)

CTA-2 was synthesized according to the previously published procedure.[5]

In a round flask, 1 g (2.7 mmol) CTA-1 and 0.38 g (3.3 mmol) *N*-hydroxysuccinimide were dissolved in 100 mL dichloromethane. 0.71 g (3.4 mmol) DCC was then added into the flask at -15 °C. The reaction mixture was stirred at room temperature for 12 h. After filtration, the residue was purified by column chromatography with ethyl acetate/*n*-hexane (1: 5; R_f = 0.18) to give 0.81 g of a yellowish solid. Yield: 65 %.

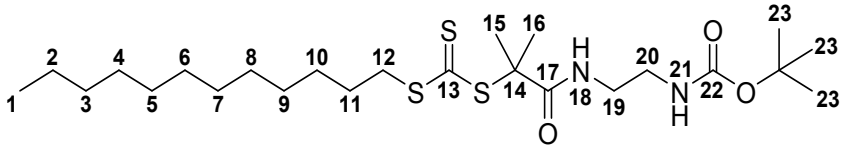


^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.88 (t, $^{3}J_{HH}$ = 7.0 Hz, 3 H, $^{1}CH_3$), 1.25-1.41 (m, 18 H, $^{2\text{-}10}CH_2$), 1.69 (quin, $^{3}J_{HH}$ = 7.4 Hz, 2 H, $^{11}CH_2$), 1.87 (s, 6 H, $^{15,16}CH_3$), 2.80 (s, 4 H, $^{20,21}CH_2$), 3.31 (t, $^{3}J_{HH}$ = 7.5 Hz, 2 H, $^{12}CH_2$)

Synthesis of *tert*-butyl (2-(2-(((dodecylthio)carbonothioyl)thio)-2-methylpropanamido)ethyl)carbamate (CTA-3)

CTA-3 was synthesized according to the previously published procedure.[5]

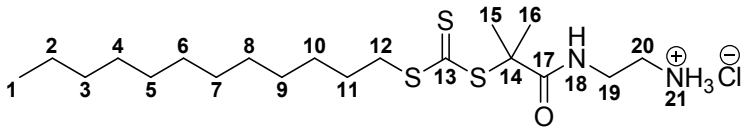
In a round flask, 50 mg (0.29 mmol) TBAC and 33 mg (0.32 mmol) TEA were dissolved in 1.8 mL dichloromethane. After dropwise adding a solution of 200 mg (0.43 mmol) CTA-2 in 2.5 mL dichloromethane at -10 °C, the reaction mixture was stirred at room temperature for 12 h. The organic solution was then washed with 10 mL saturated sodium bicarbonate solution and 10 mL brine. The organic phase was dried over anhydrous magnesium sulfate. After removing the solvent, the residue was purified by column chromatography with ethyl acetate/*n*-hexane (3: 10, R_f = 0.16) to give a yellowish solid. Yield: 91 %



^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.88 (t, $^{3}J_{HH}$ = 7.0 Hz, 3 H, $^{1}CH_3$), 1.20-1.40 (m, 18 H, $^{2\text{-}10}CH_2$), 1.43 (s, 9 H, $^{23}CH_3$), 1.60-1.70 (m, 2 H, $^{11}CH_2$; 6 H, $^{15,16}CH_3$), 3.23-3.33 (m, 6 H, $^{12,19,20}CH_2$), 4.79 (s, 1 H, ^{21}NH), 6.87 (s, 1 H, ^{18}NH)

Synthesis of 2-(2-(((dodecylthio)carbonothioyl)thio)-2-methylpropanamido)ethanamonium chloride (CTA-4)

In a round flask, 100 mg (0.2 mmol) CTA-3 was dissolved in 0.7 mL 1,4-dioxane. After adding 0.3 mL 4M HCl/1,4-dioxane solution, the reaction mixture was stirred at room temperature overnight. The precipitate was filtrated and then dissolved in 100 mL methanol. The solvent was removed by rotary evaporator and this process was repeated three times to remove excess HCl. The product was dried *in vacuo* to give 92 mg yellowish solid. Yield: 100%



^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.87 (t, $^{3}J_{HH}$ = 6.9 Hz, $^{1}CH_3$), 1.20-1.50 (m, 18 H, $^{2\text{-}10}CH_2$), 1.50-1.80 (m, 2 H, $^{11}CH_2$; 6 H, $^{15,16}CH_3$), 3.20-3.70 (m, 6 H, $^{12,19,20}CH_2$), 7.58 (br, 1 H, ^{18}NH), 8.20 (br, 3 H, $^{21}NH_3^+$)

● Synthesis of PTMC using vanillin as initiator

Table S1. ROP of TMC using vanillin as initiator and DBU/TU as catalysts in toluene

	[TMC]: [I]	T (°C)	$M_{n,th}$[a] (g/mol)	Conversion[b] (%)	$M_{n,NMR}$[b] (g/mol)	$M_{n,SEC}$[c] (g/mol)	$Đ_M$[c]
PTMC-Van 1	50: 1	rt	1200	21	-	-	-
PTMC-Van 2	50: 1	50	1800	33	39,700	15,000	1.15

[a]$M_{n,th}$ = ([TMC]/[I]) x $M_{(TMC)}$ x Conversion + $M_{(VanProp)}$; [b]Determined using ^{1}H NMR spectroscopy; [c]Determined using SEC in chloroform with PS standards.

- **Determination of TMC conversions and molar masses of PTMC-CHO by NMR spectroscopy**

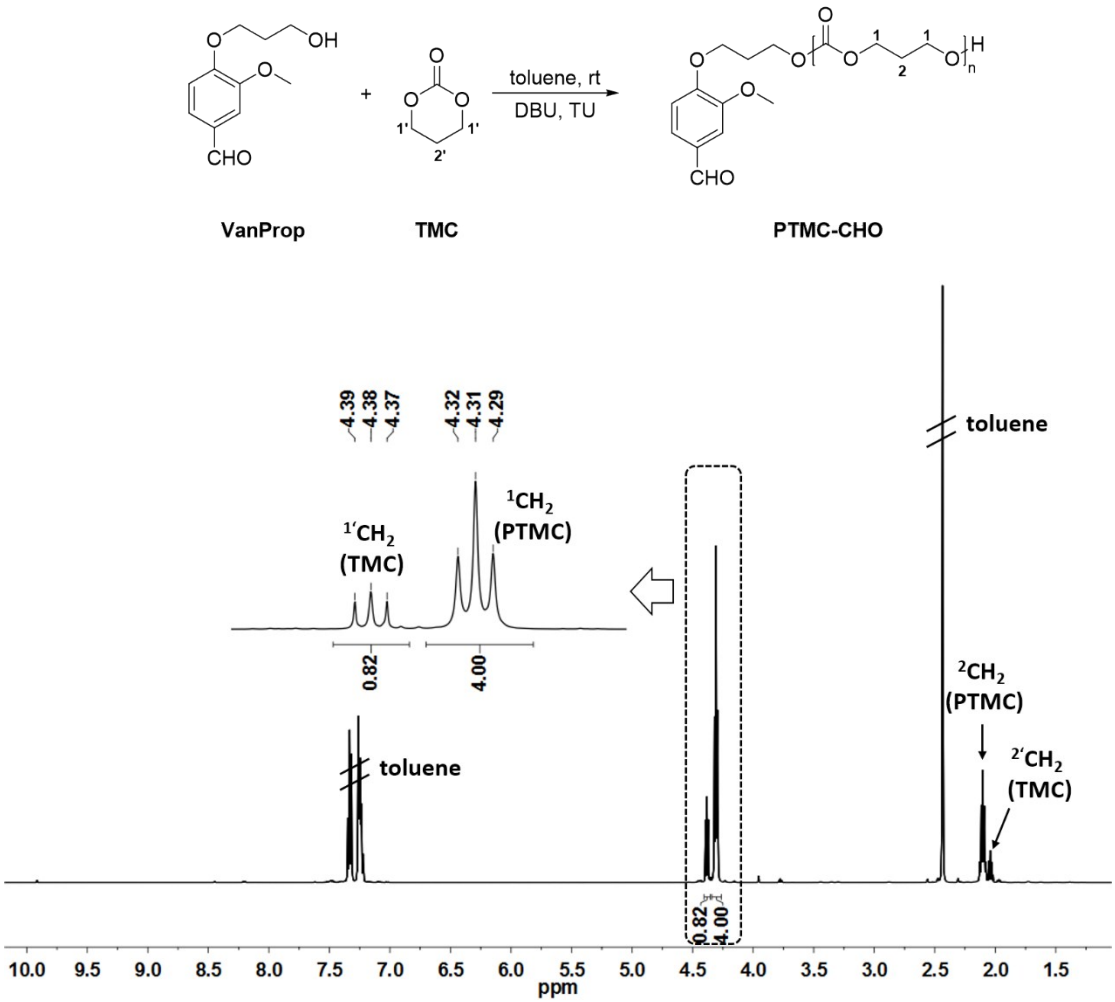


Figure S1. ^{1}H NMR spectrum of crude PTMC-CHO reaction solution in $CDCl_3$-*d* for conversion determination

Determination of TMC conversions by NMR spectroscopy Conversions of TMC were confirmed by calculation from the relative integrals of the monomer (4.38 ppm for TMC (**$^{1'}CH_2$**) and 4.31 ppm for PTMC (**$^{1}CH_2$**)) in ^{1}H NMR spectra. Take the PTMC-CHO 5 reaction solution (**Figure S1**) as an example.

$$conv.(TMC) = \frac{I(PTMC,\ 4.31\ ppm)}{I(PTMC,\ 4.31ppm) + I(TMC,\ 4.38\ ppm)} \times 100\%$$
$$= \frac{4.00}{4.00 + 0.82} \times 100\% = 83\%$$

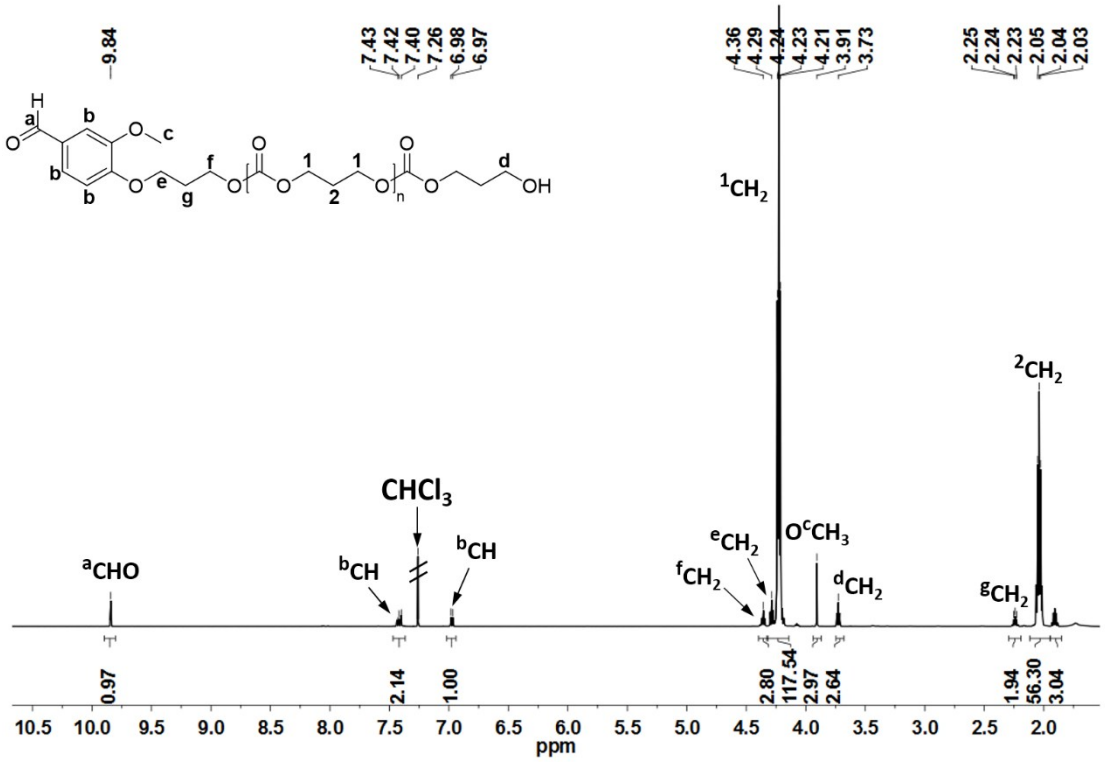


Figure S2. ^{1}H NMR spectrum of PTMC-CHO 2 in $CDCl_3$-*d* for molar mass determination

Determination of $M_{n,NMR}$ by NMR spectroscopy Molar masses of PTMC-CHO were confirmed by calculation from the relative integrals of the repeating units (2.04 ppm for PTMC (**^{2}CH2, 2 H**)) and VanProp end group (3.91 ppm for VanProp (O^{C}**CH_3, 3 H**) in ^{1}H NMR spectra of purified PTMC-CHO. Take the PTMC-CHO 2 (**Figure S2**) as an example.

$$M_{n,NMR}\,(PTMC-CHO\ 2) = \frac{I(PTMC, 2.04\ ppm)}{I(VanProp, 3.91\ ppm)} \times M(PTMC) + M(VanProp)$$
$$= \frac{56.30/2}{2.97/3} \times 102\frac{g}{mol} + 210\frac{g}{mol} = 3100\frac{g}{mol}$$

- **Structure analysis of PTMC-Imine-Boc**

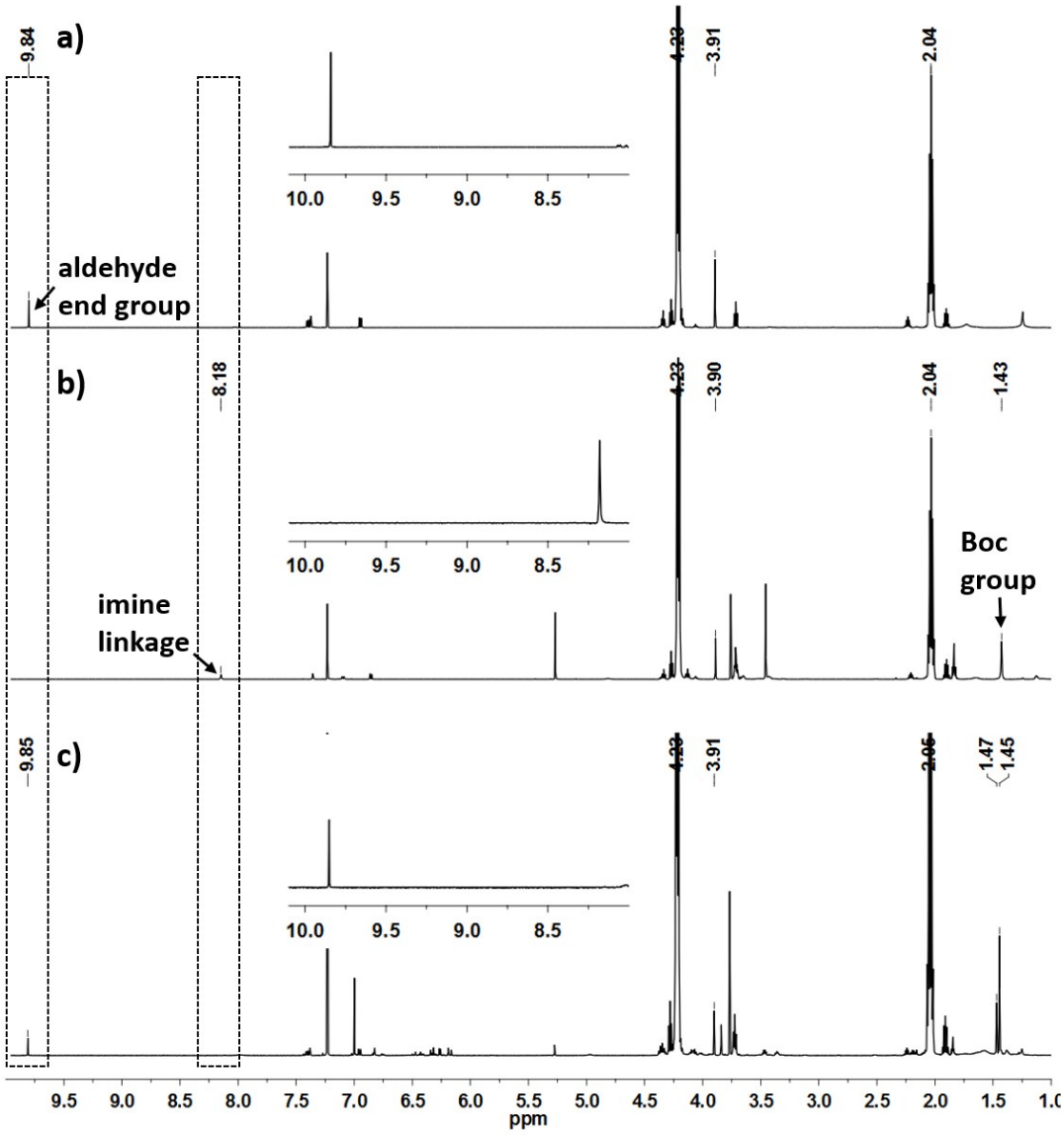


Figure S3. ^{1}H NMR spectra of a) PTMC-CHO 2; b) PTMC-Imine-Boc and c) PTMC-Imine-Boc after 48 h in freezer without inert gas.

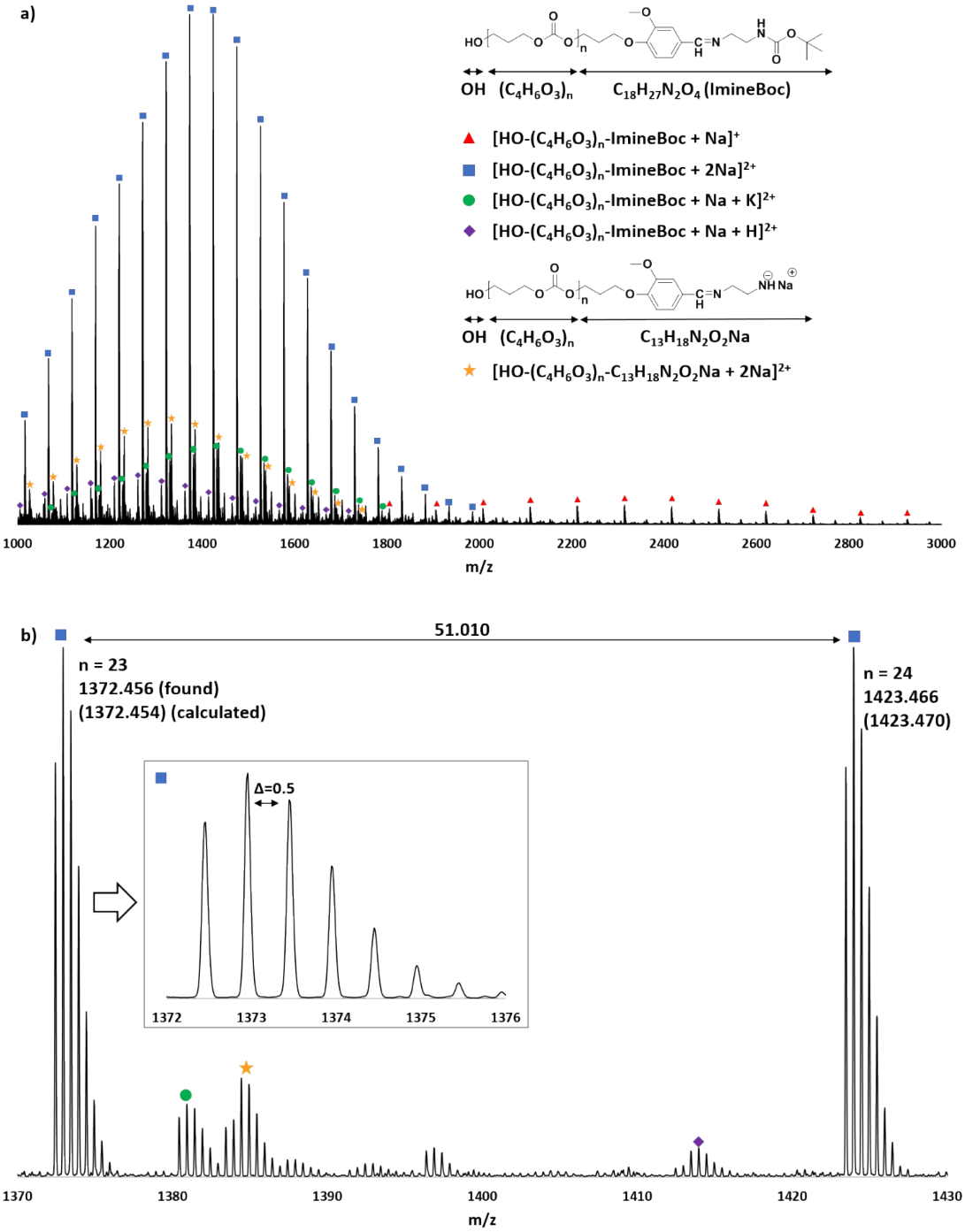


Figure S4. a) ESI-ToF-MS spectrum of PTMC-Imine-Boc in the m/z region of 1000 to 3000; b) detailed spectrum of PTMC-Imine-Boc in the m/z region of 1370 to 1430

- **Structure analysis of PTMC-CTA**

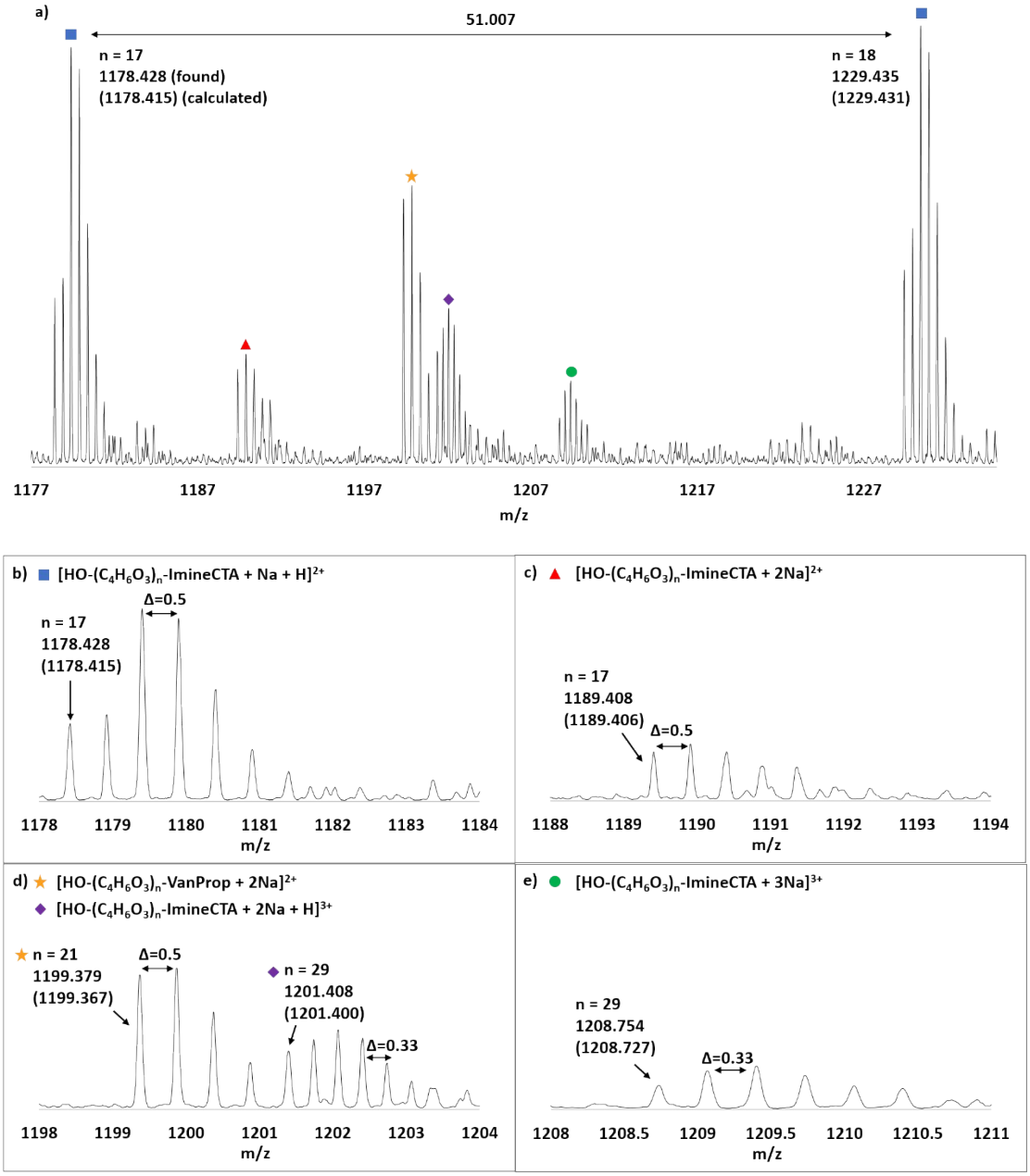


Figure S5. a) Detailed ESI-Tof-MS spectrum of PTMC-CTA in the m/z region of 1177 to 1235; detailed spectrum of the series b) $[OH\text{-}(C_4H_6O_3)_n\text{-ImineCTA + Na + H}]^{2+}$; c) $[OH\text{-}(C_4H_6O_3)_n\text{-ImineCTA + 2Na}]^{2+}$; d) $[OH\text{-}(C_4H_6O_3)_n\text{-VanProp + 2Na}]^{2+}$ and $[OH\text{-}(C_4H_6O_3)_n\text{-ImineCTA + 2Na + H}]^{3+}$; and e) $[OH\text{-}(C_4H_6O_3)_n\text{-ImineCTA + 3Na}]^{3+}$

- **Determination of DMAAm conversions by NMR spectroscopy**

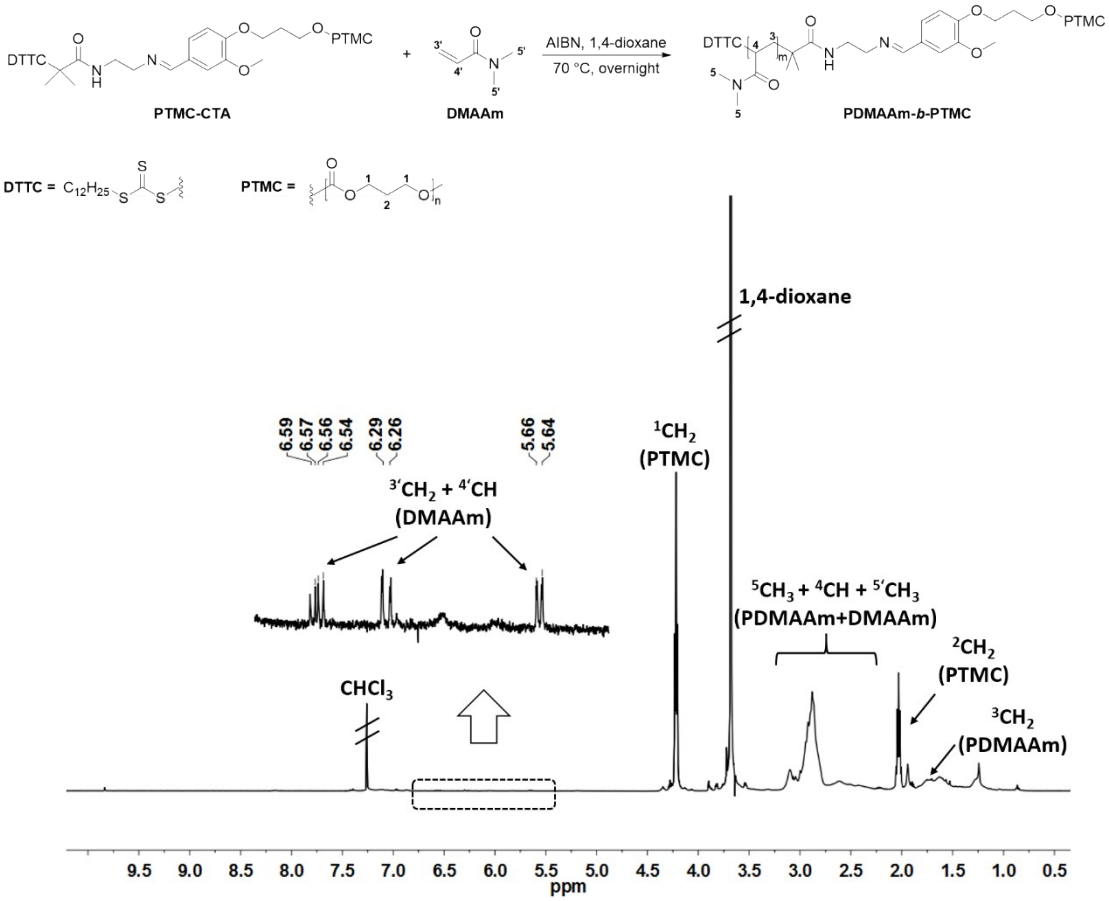


Figure S6. ^{1}H NMR spectrum of PDMAAm-*b*-PTMC 4 reaction solution in $CDCl_3$-*d* for conversion determination

Determination of DMAAm conversions by NMR spectroscopy Conversions of DMAAm were confirmed by calculation from the relative integrals of the monomer (5.60 ppm – 6.65 ppm for DMAAm ($^{3'}$**CH$_2$ + $^{4'}$CH**) and 2.25 ppm – 3.25 ppm for PDMAAm (^{5}**CH$_3$ + ^{4}CH + $^{5'}$CH$_3$**)) in ^{1}H NMR spectra. Take the PDMAAm-*b*-PTMC 4 polymerization solution (**Figure S3**) as an example. After overnight polymerization the signals for DMAAm ($^{3'}$**CH$_2$ + $^{4'}$CH**) have almost completely disappeared. Hence, we confirmed that the conversion of DMAAm reached almost 100 %. Moreover, the same phenomena were observed for other copolymerizations (PDMAAm-*b*-PTMC 1 – 3) as well.

- **^{1}H NMR analysis of PDMAAm-*b*-PTMC 3 after acidic degradation**

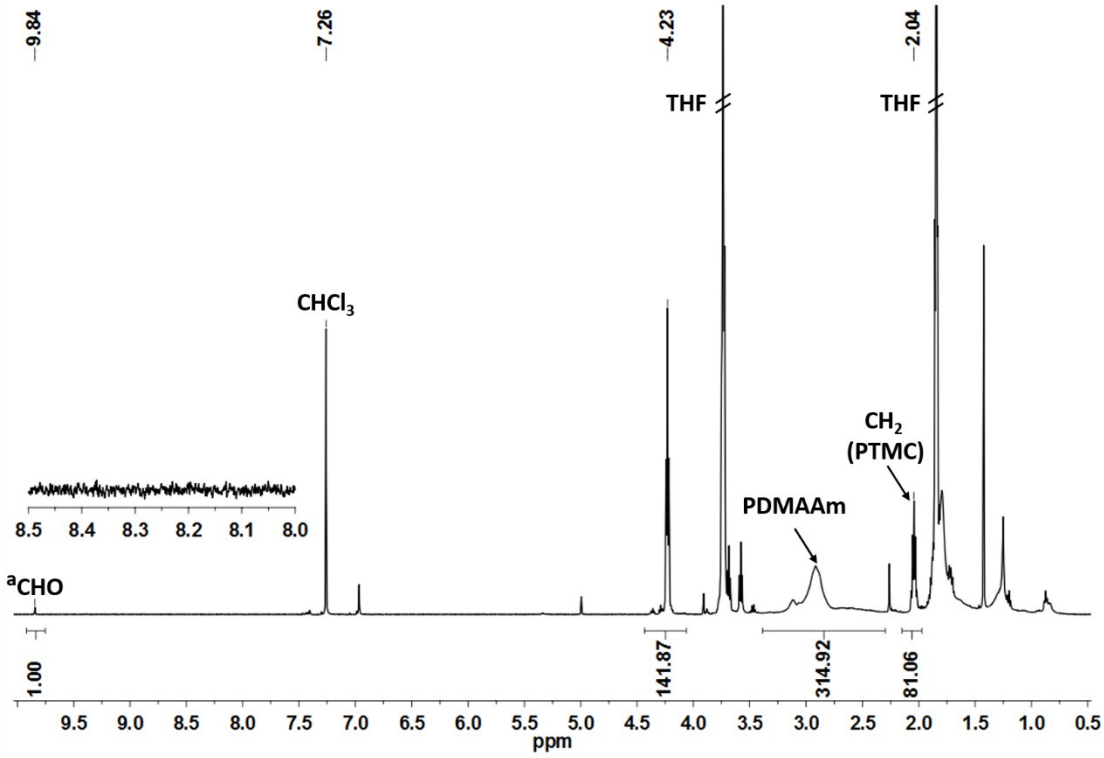


Figure S7. ^{1}H NMR spectrum of PDMAAm-*b*-PTMC 3 after acidic degradation

- **Particles prepared from PDMAAm-*b*-PTMC block copolymers**

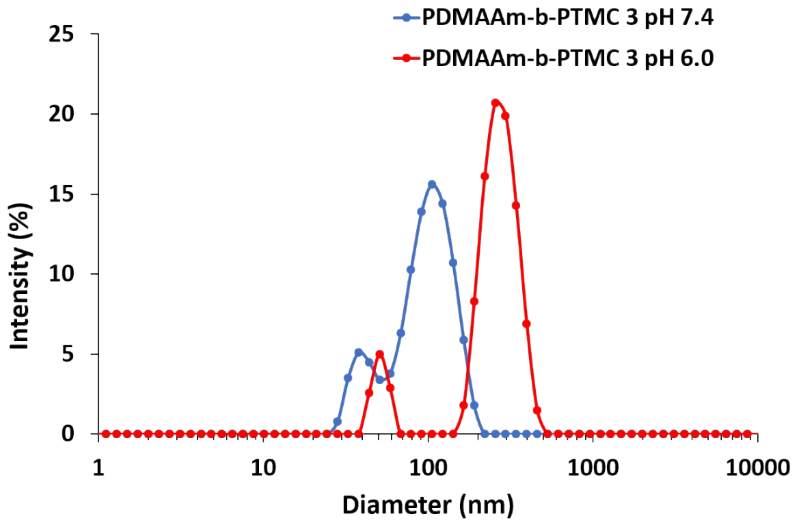


Figure S8. Hydrodynamic diameter (intensity average) distributions of PDMAAm-*b*-PTMC 3 micelles at pH 7.4 and 6.0 determined by DLS.

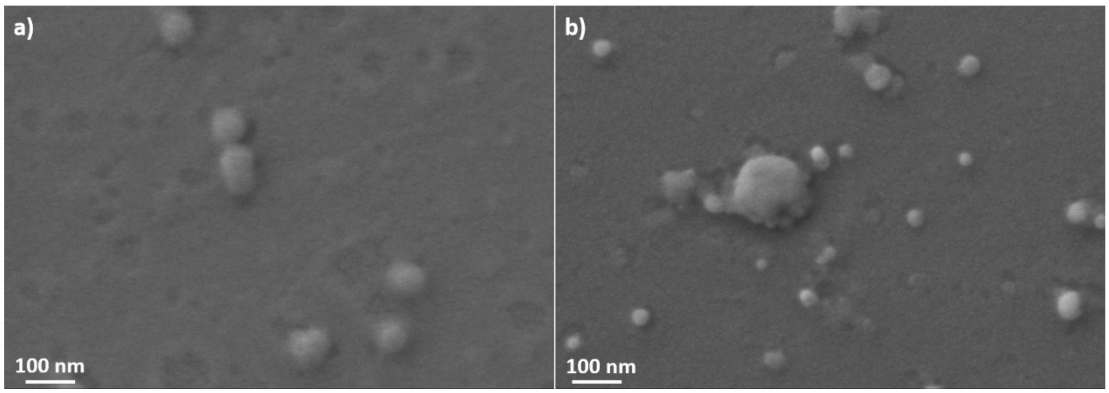


Figure S9. Detailed SEM images of PDMA-*b*-PTMC 4 micelles assembled in aqueous solution at pH 7.4 (a) and after 4 h incubation at pH 6.0 (b).

- **NMR spectra of small molecules and polymers**

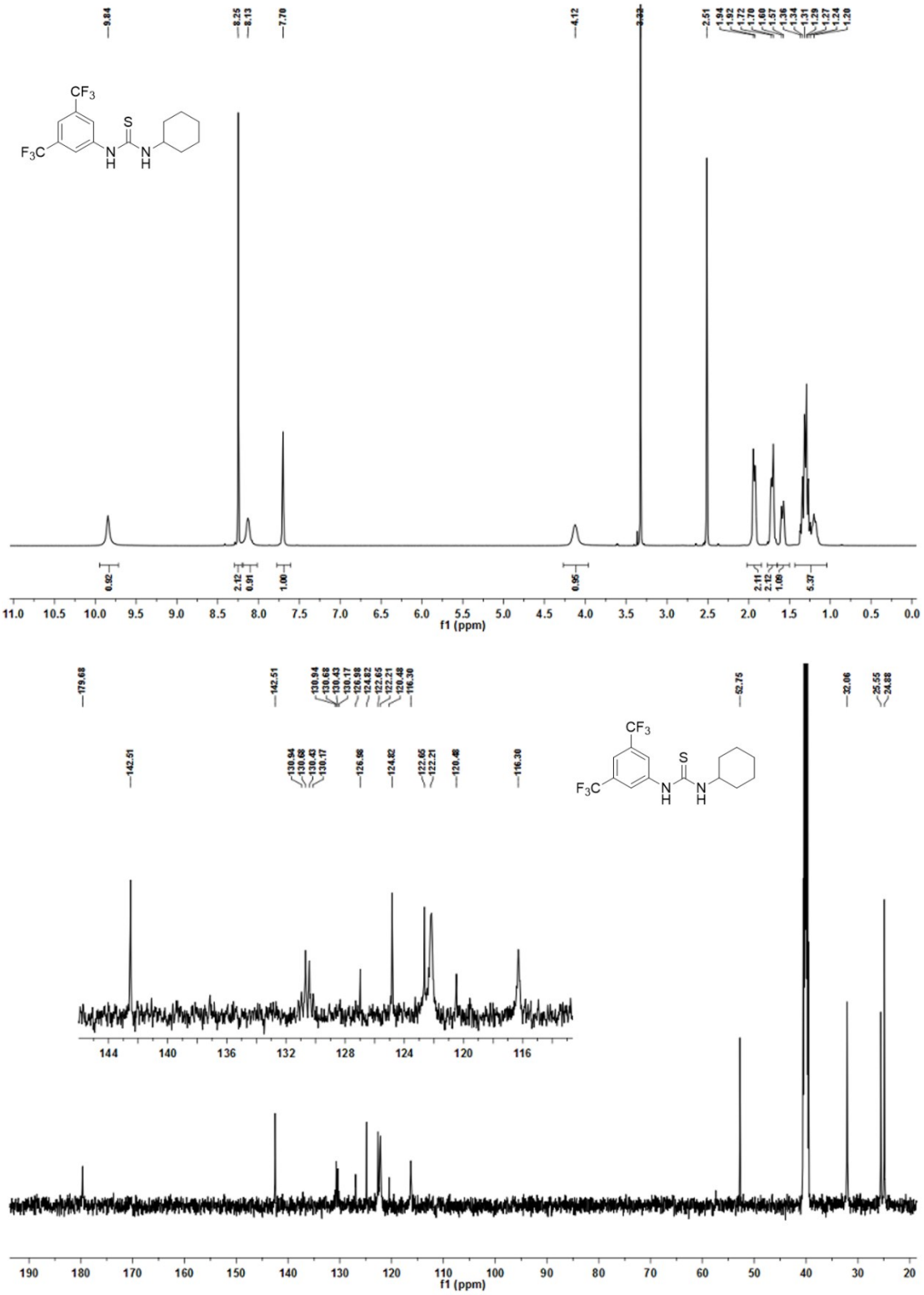


Figure S10. ^{1}H and ^{13}C NMR spectra of TU in DMSO-d_6

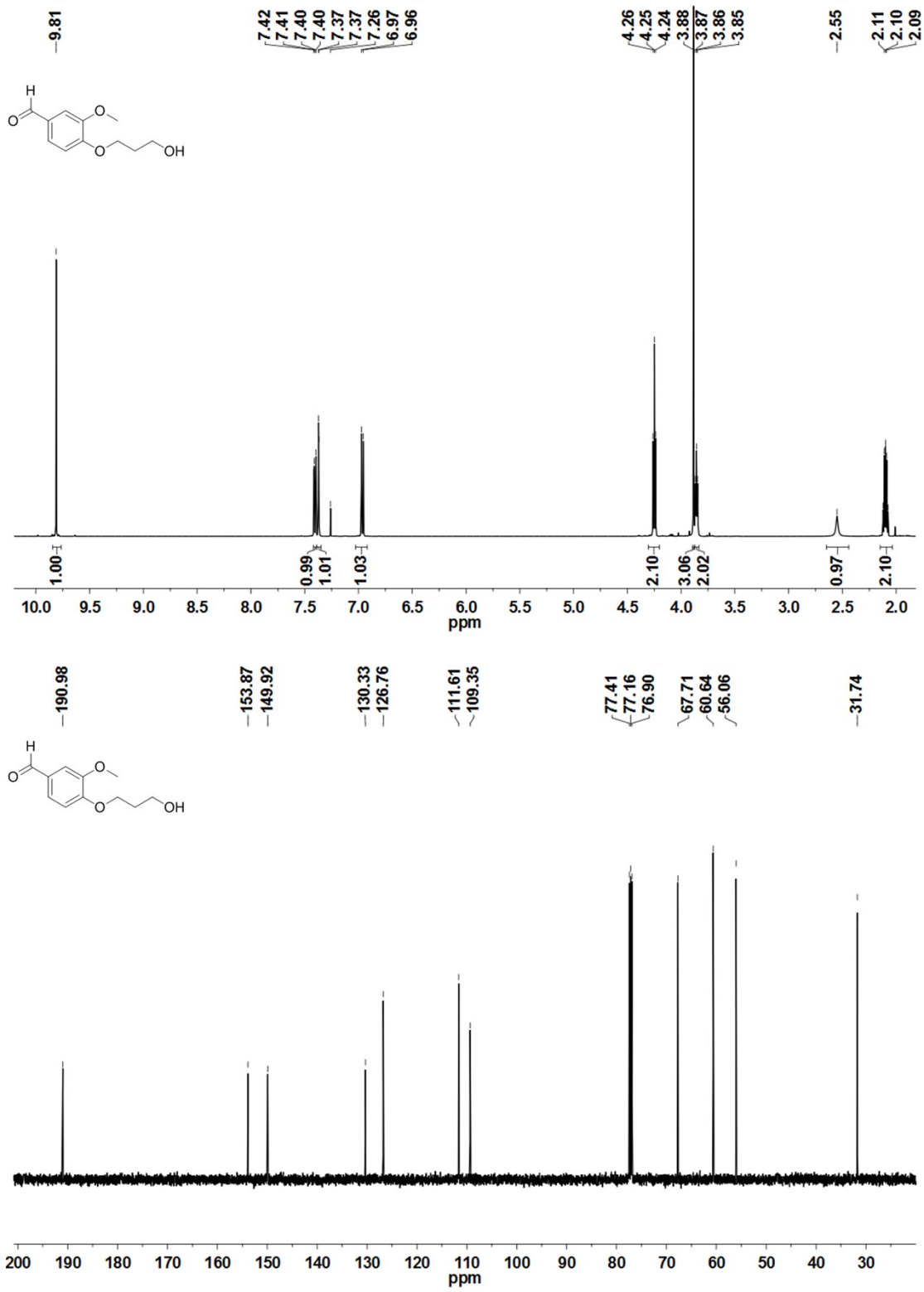


Figure S11. ^{1}H and ^{13}C NMR spectra of VanProp in $CDCl_3$-*d*

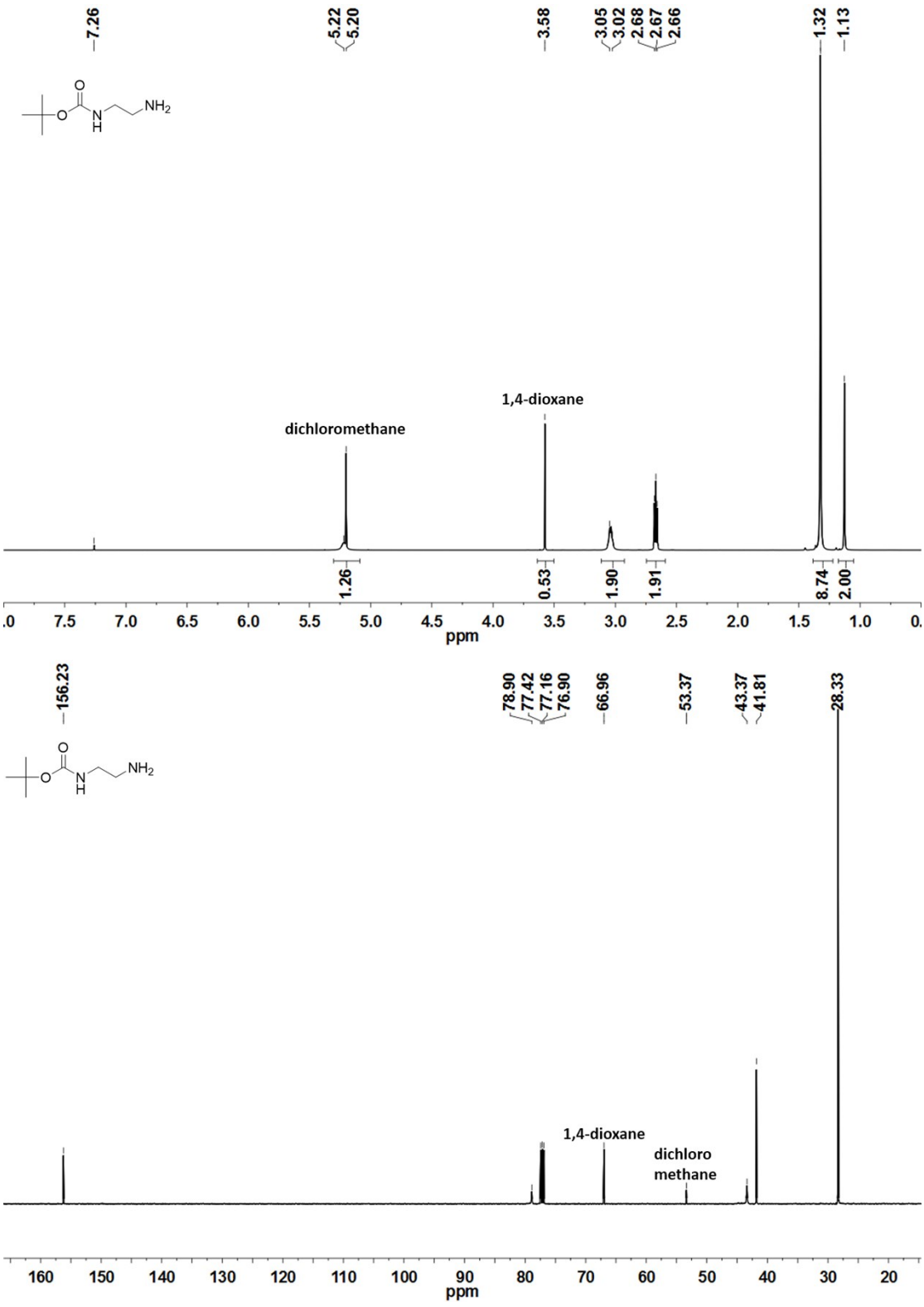


Figure S12. ^{1}H and ^{13}C NMR spectra of TBAC in $CDCl_3$-*d*

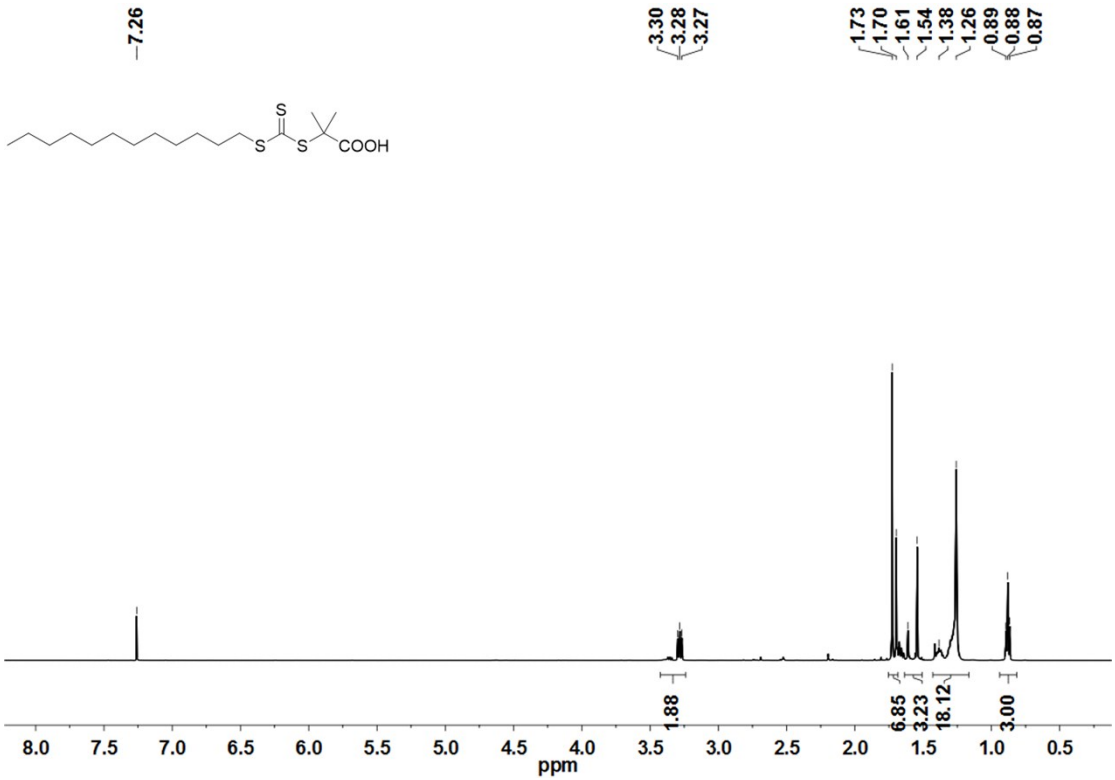


Figure S13. ^{1}H NMR spectrum of CTA-1 in $CDCl_3$-*d*

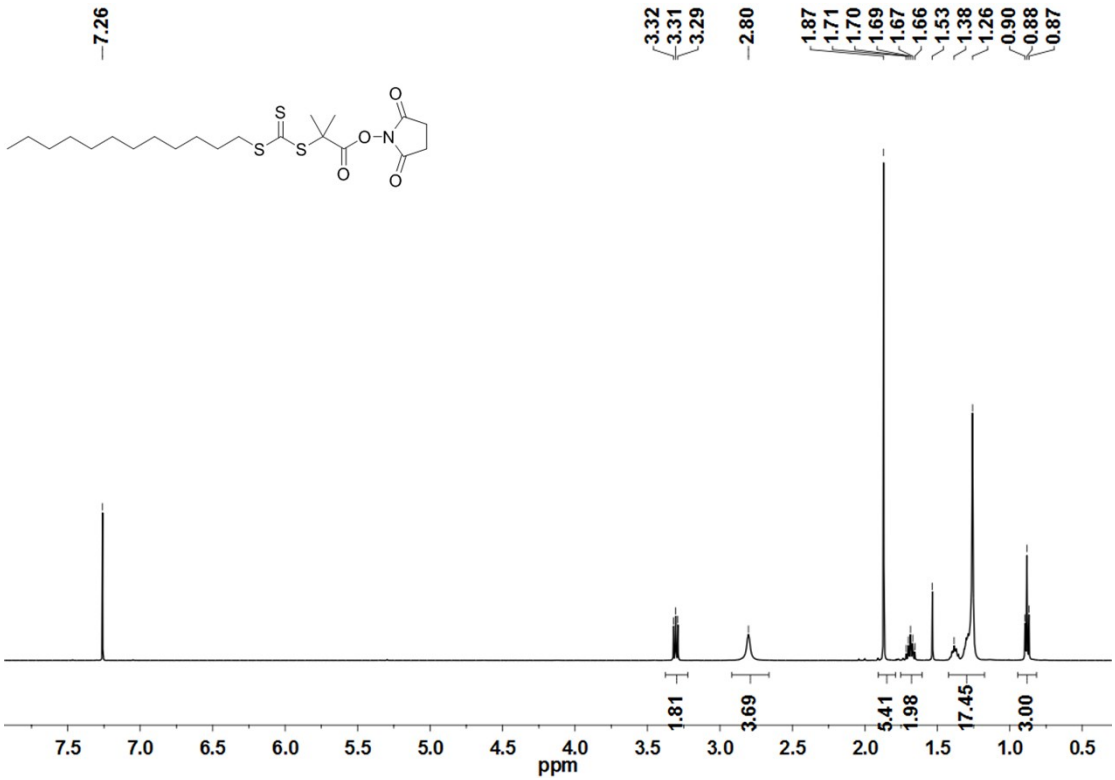


Figure S14. ^{1}H NMR spectrum of CTA-2 in $CDCl_3$-*d*

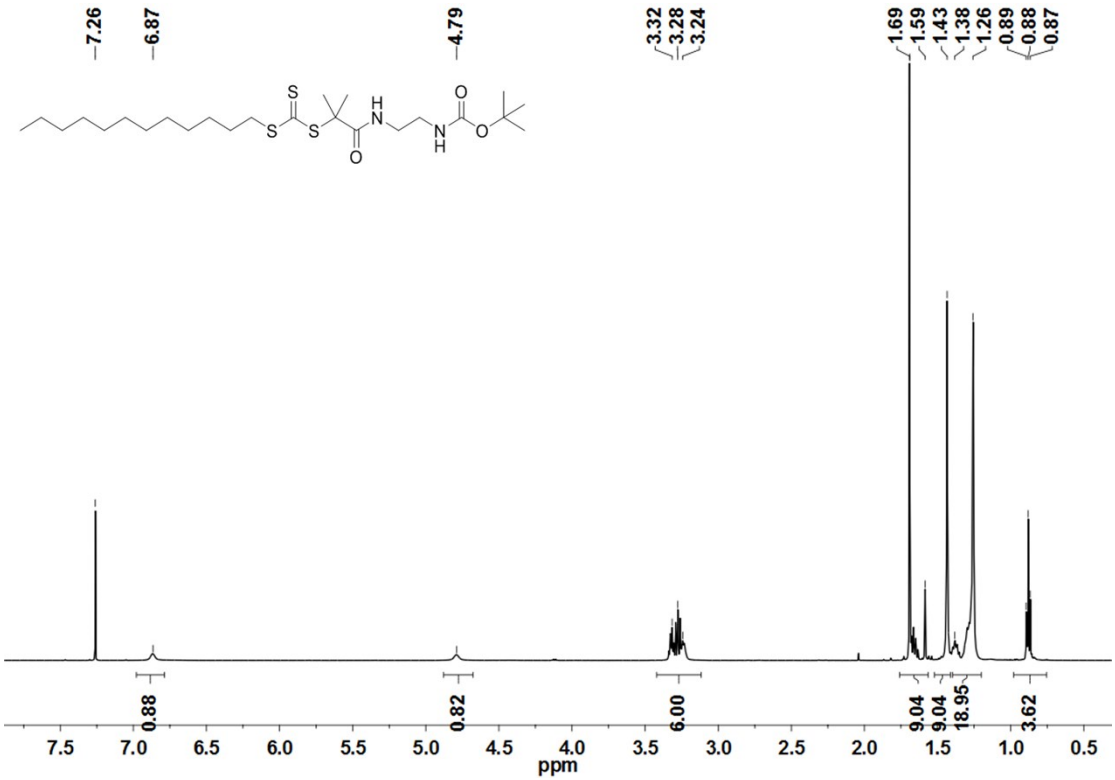


Figure S15. ^{1}H NMR spectrum of CTA-3 in $CDCl_3$-*d*

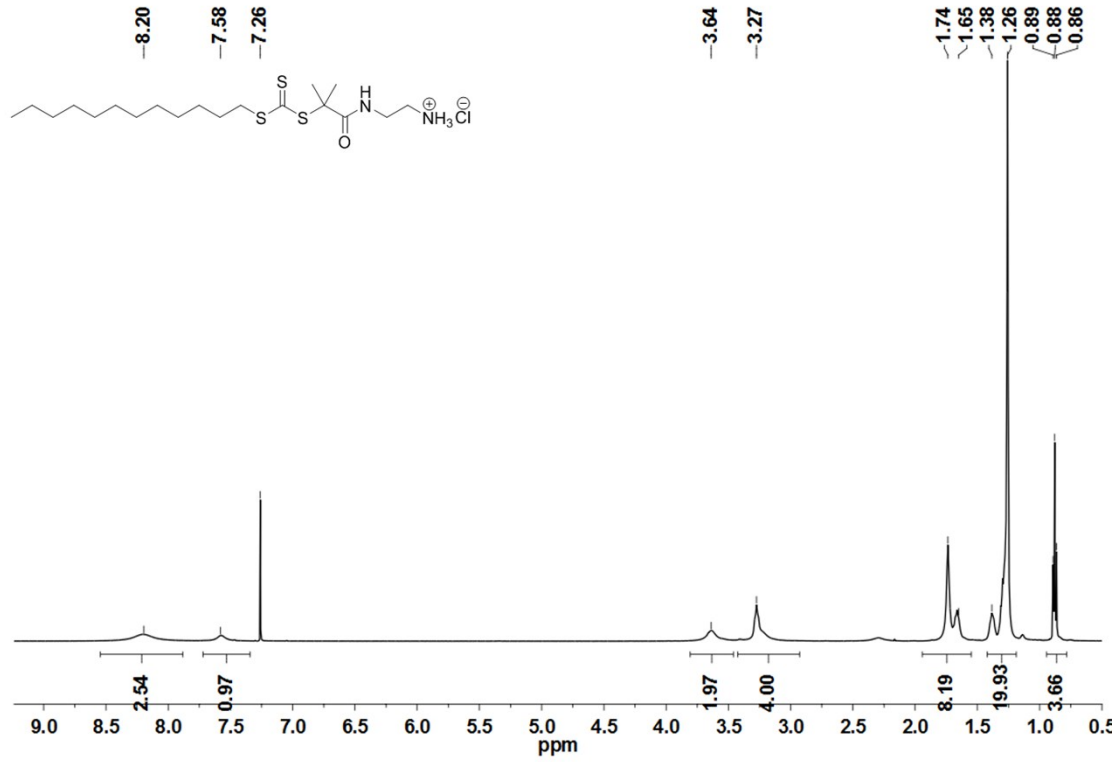


Figure S16. ^{1}H NMR spectrum of CTA-4 in $CDCl_3$-*d*

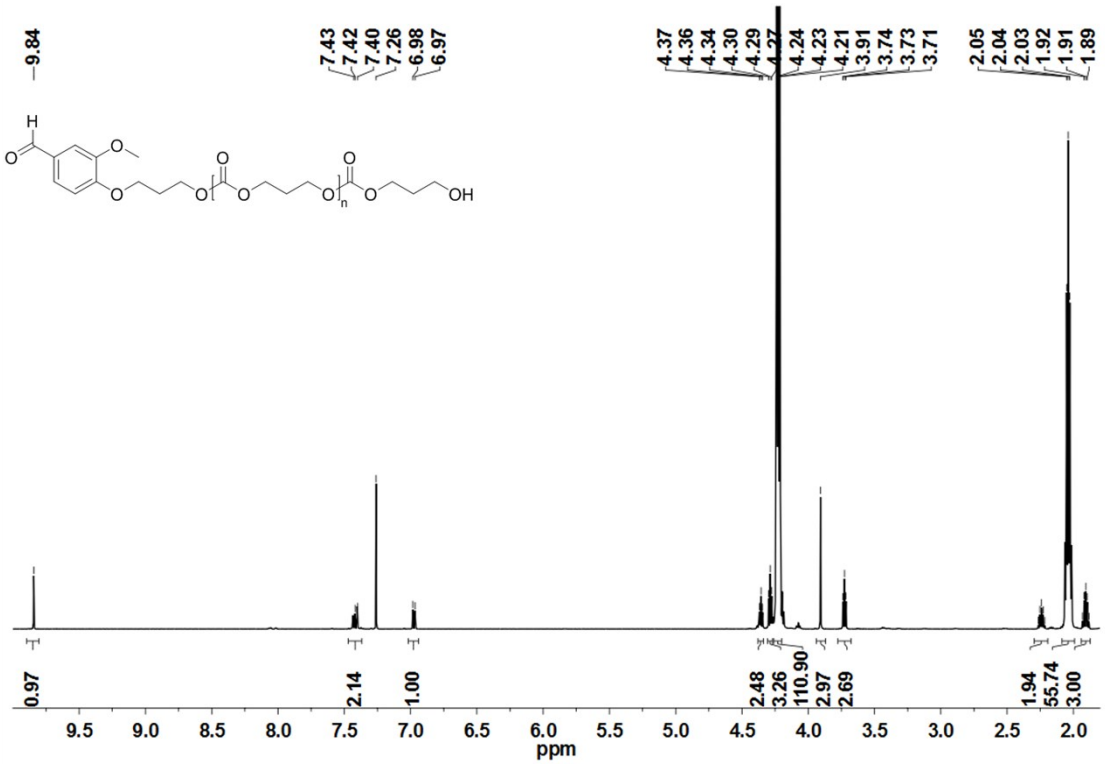


Figure S17. ^{1}H NMR spectrum of PTMC-CHO 2 in $CDCl_3$-*d*

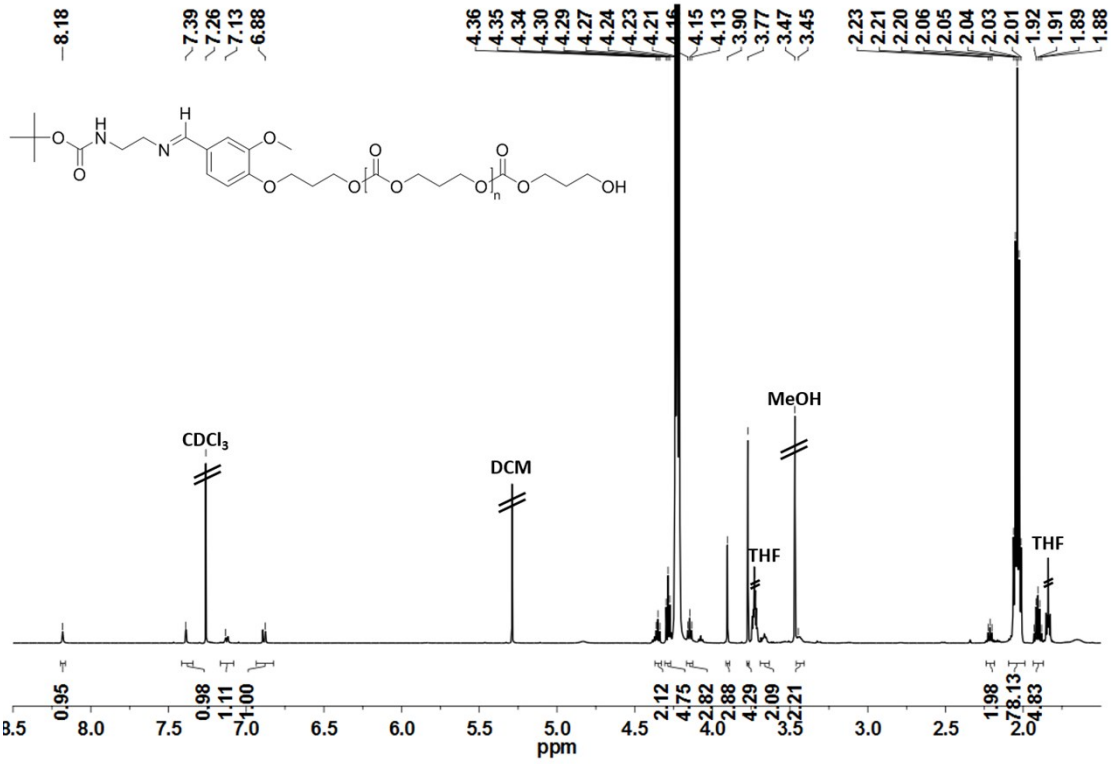


Figure S18. ^{1}H NMR spectrum of PTMC-Imine-Boc in $CDCl_3$-*d*

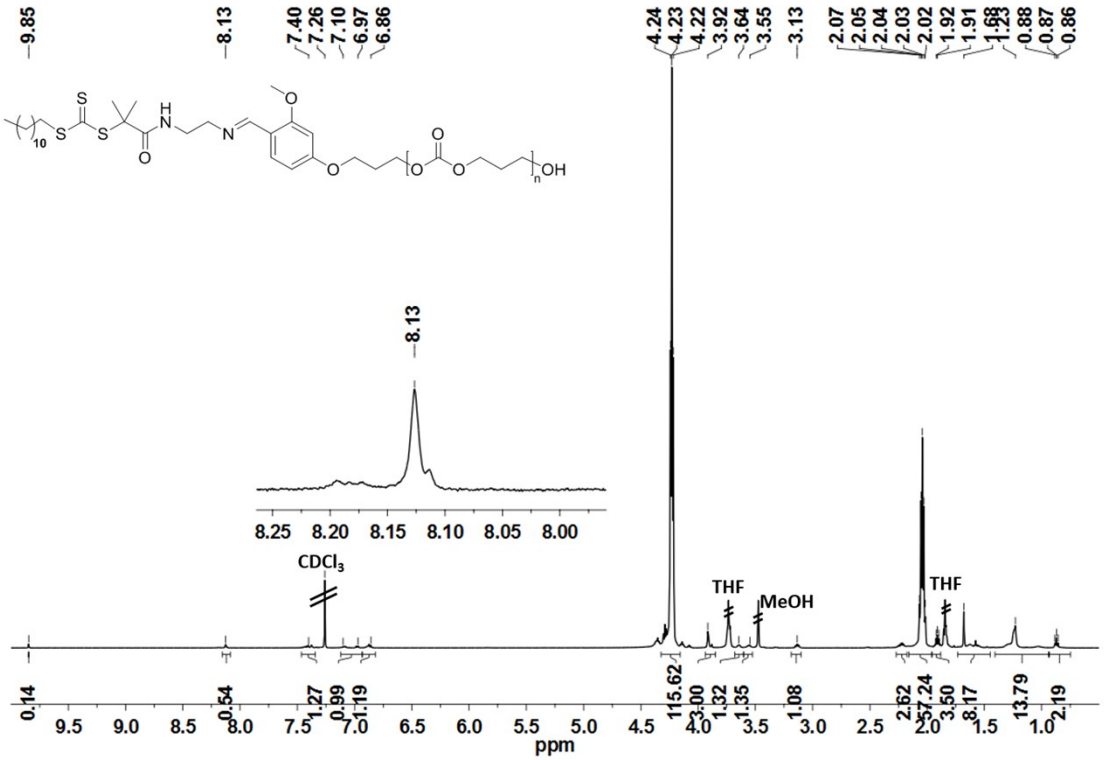


Figure S19. ^{1}H NMR spectrum of PTMC-CTA in $CDCl_3$-*d*

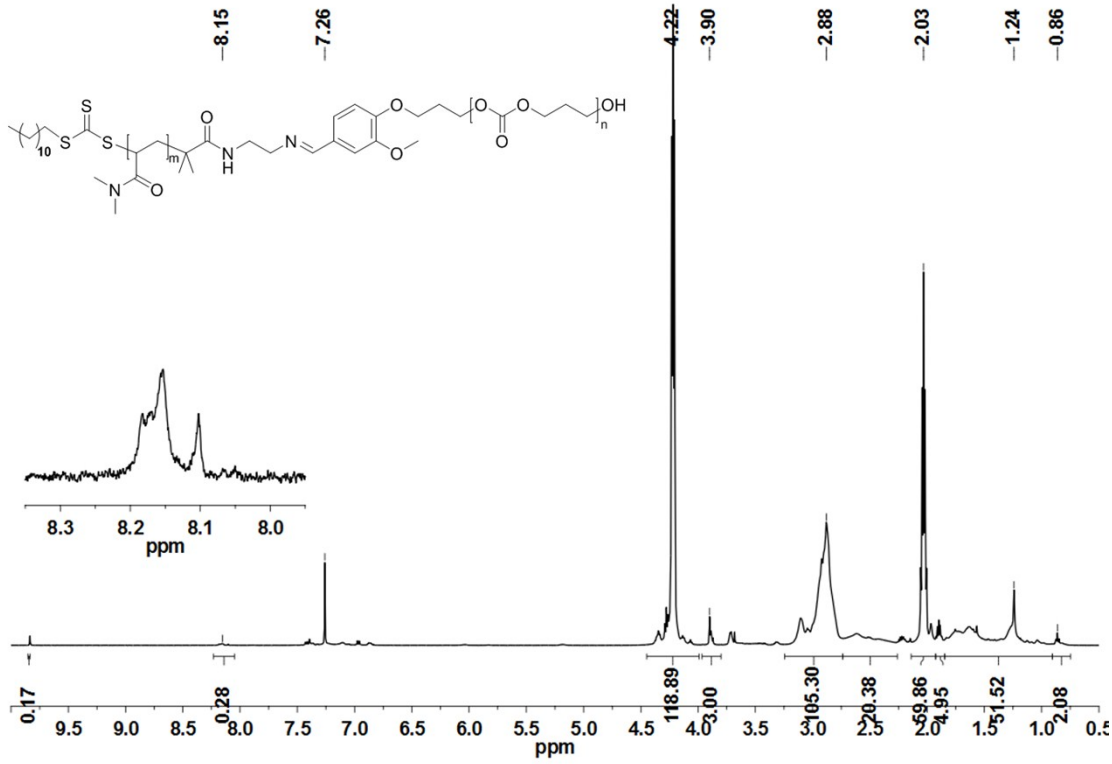


Figure S20. ^{1}H NMR spectrum of PDMAAm-*b*-PTMC 1 in $CDCl_3$-*d*

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