Supporting Information

for

Functionalizable Hydrophilic Polycarbonate, Poly(5-methyl-5-(2-hydroxypropyl)aminocarbonyl-1,3-dioxan-2-one), Designed as a Degradable Alternative for PHPMA and PEG

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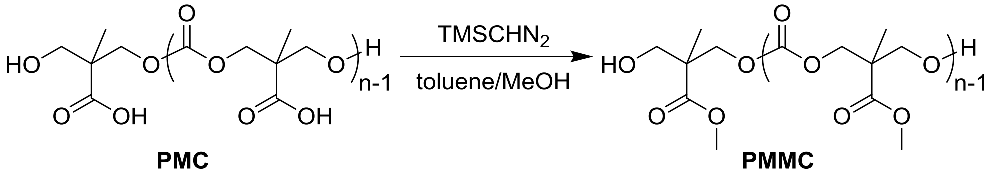
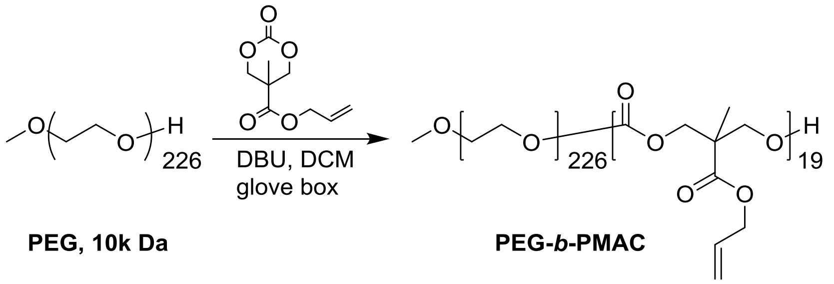
Experimental Section

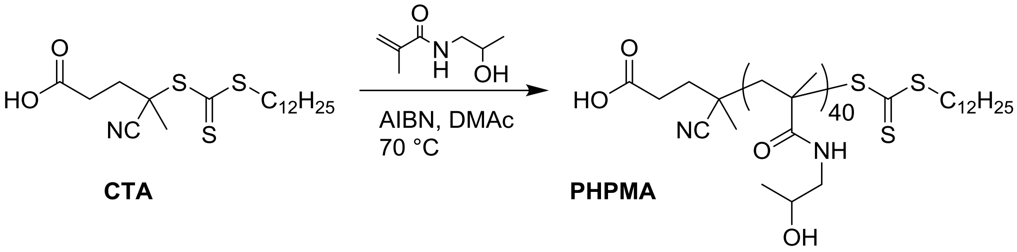


Methylation of Carboxylic Acid Functionalities[1] in PMC (synthesis of PMMC, 3). To a stirred solution of PMC$_{27}$ (50 mg, 0.012 mmol) in 1 mL of toluene:MeOH (3:2), an etheric solution (2 M in diethyl ether) of (trimethylsilyl)diazomethane (TMSCHN$_2$) was added dropwise until the yellow color persisted (~250 μL). The mixture was stirred for 30 min at RT and concentrated *in vacuo* to give poly(5-methyl-5-methyloxycarbonyl-1,3-dioxan-2-one), PMMC$_{27}$ (**3**). $M_{\mathrm{n,NMR}}$ = 4700 g/mol; $M_{\mathrm{n,GPC}}^{\mathrm{THF}}$ = 6700 g/mol; PDI = 1.09. ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.35-4.23 (m, -OC(O)OC$\boldsymbol{H}_2$-), 3.73 (s, -OC$\boldsymbol{H}_3$), 1.25 (s, -C(C$\boldsymbol{H}_3$)(CH$_2$O-)$_2$), 1.20 (s, -C(C$\boldsymbol{H}_3$)CH$_2$OH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 172.7, 154.5, 69.0, 52.7, 48.4, 46.6, 17.6. IR (neat, cm^{-1}): 3100–2800, 1736, 1458, 1389, 1227, 1142, 972, 872, 787, 733.

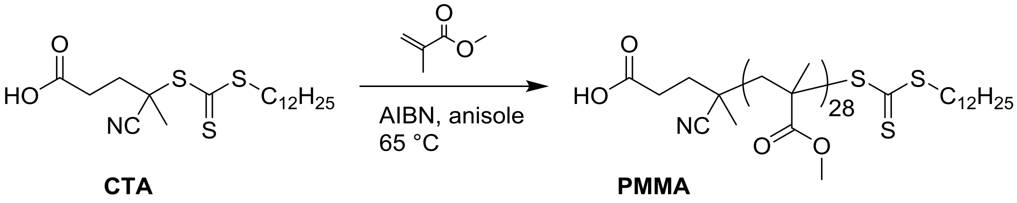
PEG 6kDa (12). T_{g} = -12.5 °C (-17 °C, as reported[2]), T_{m} = 57.8 °C. TGA in Ar: 320–430 °C, 92% mass loss; 8% mass remaining above 500 °C.



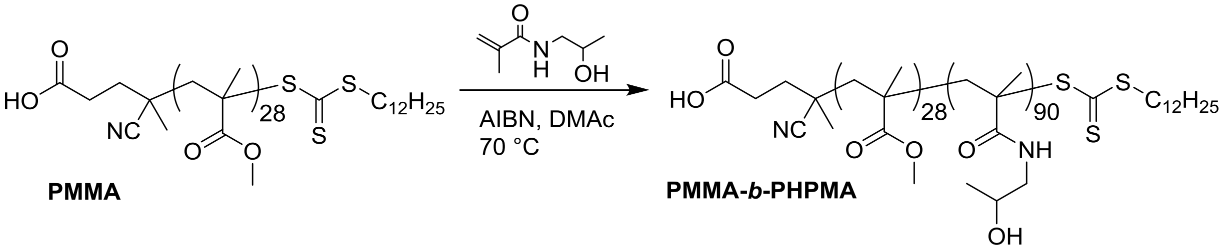
Synthesis of PEG-*b*-PMAC (14). mPEG (10 kDa, 100 mg, 0.010 mmol) and MAC (160 mg, 0.80 mmol) were dissolved in dry DCM (1.6 mL, [MAC] = 0.5 M). DBU (1.5 μL, 0.010 mmol) was added to the monomer/initiator solution. After the desired time, the polymerizations were quenched by addition of a DCM solution of benzoic acid (1.8 mg, 0.015 mmol in 200 μL DCM) and precipitated directly into cold diethyl ether to yield PEG-*b*-PMAC (**14**) as a white powder. Yield = 130 mg, 95% based upon 25% conversion. $M_{\mathrm{n,NMR}}$ = 13800 g/mol; $M_{\mathrm{n,GPC}}^{\mathrm{DMF}}$ = 12000 g/mol; PDI = 1.05. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.86 (m, -CH$_2$C$\boldsymbol{H}$CH$_2$), 5.33-5.18 (m, -CH$_2$CHC$\boldsymbol{H}_2$), 4.61 (d, J = 5.6 Hz, -OC$\boldsymbol{H}_2$CHCH$_2$), 4.33-4.24 (m, -OC(O)OC$\boldsymbol{H}_2$-), 3.80-3.46 (br, -OC$\boldsymbol{H}_2$C$\boldsymbol{H}_2$-), 3.36 (s, C$\boldsymbol{H}_3$O-), 2.50 (t, J = 6.8 Hz, -CH$_2$O$\boldsymbol{H}$), 1.25 (s, -C(C$\boldsymbol{H}_3$)(CH$_2$O-)$_2$), 1.21 (s, -C(C$\boldsymbol{H}_3$)CH$_2$OH). ^{13}C NMR (75 MHz, CDCl$_3$): δ 171.8, 154.5, 131.7, 118.6, 70.7, 68.7, 66.0, 46.6, 17.6. IR (neat, cm^{-1}): 3100–2700, 1751, 1466, 1342, 1234, 1096, 957, 841, 787. T_g = -18.5 °C; T_m = 48.5 °C. TGA in Ar: 200–300 °C, 24% mass loss; 300–420 °C, 65% mass loss; 7% mass remaining above 500 °C.



Synthesis of PHPMA$_{40}$ (13). To a flame-dried Schlenk flask (10 mL) equipped with a magnetic stir bar under N_2 atmosphere was added 4-cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid (CTA, 8.5 mg, 0.020 mmol), HPMA (300 mg, 2.1 mmol), AIBN (1.0 mg, 6.3 μmol) and 2.5 mL of dimethylacetamide (DMAc). The mixture was stirred for 10 min at RT, deoxygenated through three cycles of freeze-pump-thaw and back-filled with N_2. After the last cycle, the reaction mixture was stirred for 15 min at RT and immersed into a pre-heated oil bath at 70 °C to start the polymerization. After 5 h, the polymerization was quenched by cooling the reaction flask with liquid N_2. The polymer was purified by precipitation into cold diethyl ether twice. The yellow precipitate was collected through centrifugation and kept under vacuum overnight to remove residual solvents. Yield 110 mg of product, 92% yield based upon ~40% conversion. $M_{n,NMR}$ = 6100 g/mol; $M_{n,GPC}^{DMF}$ = 2100 g/mol; PDI = 1.30. ^1H NMR (300 MHz, DMSO-d_6): δ 7.40-7.04 (br, -C(O)N$\boldsymbol{H}$-), 4.80-4.64 (br, $-CH_2CH(CH_3)(O\boldsymbol{H})$), 3.74-3.60 (br, $-CH_2C\boldsymbol{H}(CH_3)(OH)$), 3.28-3.20 (br, $-SC\boldsymbol{H}_2-$), 3.04-3.28 (br, $-C\boldsymbol{H}_2CH(CH_3)(OH)$), 2.35-2.26 (m, $-CH_2C\boldsymbol{H}_2C(O)OH$), 2.02-1.37 (m, $-C\boldsymbol{H}_2C(CH_3)(C(O)-)-$), 1.37-1.20 (m, $-SCH_2CH_2(C\boldsymbol{H}_2)_9CH_3$), 1.20-0.60 (m, $-CH_2C(C\boldsymbol{H}_3)(C(O)-)-$, $-CH_2CH(C\boldsymbol{H}_3)(OH)$ and $S(CH_2)_{11}C\boldsymbol{H}_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.1, 65.0, 64.9, 64.8, 54.6, 47.6, 45.1, 44.6, 31.3, 29.0, 21.6, 21.4, 17.8, 16.5, 15.2, 14.02. IR (neat, cm^{-1}): 3650-3100, 3050–2700, 1751, 1636, 1528, 1466, 1342, 1242, 1103, 957, 841, 787. T_g = 157.0 °C. TGA in Ar: 220–475 °C, 92% mass loss; 6% mass remaining above 500 °C.

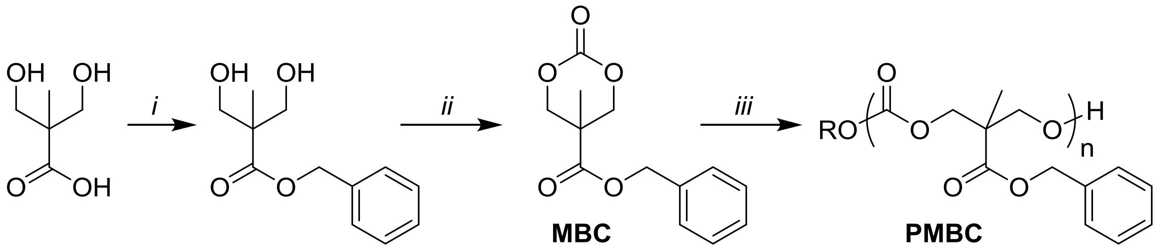


Synthesis of PMMA$_{28}$. To a flame-dried Schlenk flask (10 mL) equipped with a magnetic stir bar under N_2 atmosphere was added CTA (202 mg, 0.50 mmol), MMA (3.00 g, 30 mmol), AIBN (8.2 mg, 0.050 mmol) and 1.5 mL of anisole. The mixture was stirred for 10 min at RT, deoxygenated through three cycles of freeze-pump-thaw and back-filled with N_2. After the last cycle, the reaction mixture was stirred for 15 min at RT and immersed into a pre-heated oil bath at 65 °C to start the polymerization. After 4 h, the polymerization was quenched by cooling the reaction flask with liquid N_2. The polymer was purified by precipitation into a methanol:water (4/1) mixture twice. The yellow precipitate was collected through centrifugation and kept under vacuum overnight to remove residual solvents. Yield 1.3 g of product, 87% yield based upon ~47% conversion. $M_{n,NMR}$ = 3200 g/mol; $M_{n,GPC}^{THF}$ = 4500 g/mol; PDI = 1.11. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70-3.52 (br, -OC$\boldsymbol{H}_3$), 3.21 (t, J = 7.3 Hz, -SC$\boldsymbol{H}_2$CH$_2$-), 2.61-2.46 (m, -C$\boldsymbol{H}_2$C(O)OH), 2.38-2.06 (m, -CH$_2$C$\boldsymbol{H}_2$C(O)OH), 2.06-1.74 (br, -C$\boldsymbol{H}_2$C(CH$_3$)(C(O)O-)-), 1.68 (s, -C(CN)(C$\boldsymbol{H}_3$)-), 1.62 (m, -SCH$_2$C$\boldsymbol{H}_2$-), 1.48-1.10 (m, -SCH$_2$CH$_2$(C$\boldsymbol{H}_2$)$_9$CH$_3$), 1.09-0.70 (m, -CH$_2$C(C$\boldsymbol{H}_3$)(C(O)O-)- and -S(CH$_2$)$_{11}$C$\boldsymbol{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.2, 177.9, 177.1, 105.1, 60.1, 59.8, 54.5, 53.0, 51.9, 45.6, 45.1, 45.0, 44.6, 37.0, 34.2, 32.0, 29.7, 29.6, 29.5, 29.4, 29.2, 29.0, 27.1, 22.8, 18.8, 16.5, 14.2. IR (neat, cm^{-1}): 3100–2800, 1728, 1443, 1389, 1242, 1150, 988, 841, 810, 748. T_g = 96.0 °C. TGA in Ar: 160–210 °C, 34% mass loss; 210–300 °C, 9% mass loss; 300–370 °C, 19% mass loss; 370–430 °C, 29% mass loss; 8% mass remaining above 500 °C.



Synthesis of PMMA$_{28}$-*b*-PHPMA$_{90}$ (15). To a flame-dried Schlenk flask (10 mL) equipped with a magnetic stir bar under N_2 atmosphere was added PMMA$_{28}$ (45 mg, 14 μmol), HPMA (300 mg, 2.1 mmol), AIBN (1.0 mg, 6.3 μmol) and 2.5 mL of DMAc. The mixture was stirred for 10 min at RT, deoxygenated through three cycles of freeze-pump-thaw and back-filled with N_2. After the last cycle, the reaction mixture was stirred for 15 min at RT and immersed into a pre-heated oil bath at 70 °C to start the polymerization. After 7 h, the polymerization was quenched by cooling the reaction flask with liquid N_2. The copolymer was purified by precipitation into cold diethyl ether twice. The yellow precipitate was collected through centrifugation and kept under vacuum overnight to remove residual solvents. Yield 210 mg of product, 93% yield based upon ~60% conversion. $M_{n,NMR}$ = 16100 g/mol; $M_{n,GPC}^{DMF}$ = 3400 g/mol; PDI = 1.56. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.40-7.04 (br, -C(O)N$\boldsymbol{H}$-), 4.80-4.64 (br, -

$CH_2CH(CH_3)(O\boldsymbol{H})$), 3.74-3.61 (br, $-CH_2C\boldsymbol{H}(CH_3)(OH)$), 3.61-3.48 (br, $-C(O)OC\boldsymbol{H}_3$), 3.04-3.28 (br, $-C\boldsymbol{H}_2CH(CH_3)(OH)$), 2.37-2.26 (m, $-CH_2C\boldsymbol{H}_2C(O)OH$), 2.02-1.37 (m, $-C\boldsymbol{H}_2C(CH_3)(C(O)-)-$), 1.37-1.20 (m, $-SCH_2CH_2(C\boldsymbol{H}_2)_9CH_3$), 1.20-0.60 (m, $-CH_2C(C\boldsymbol{H}_3)(C(O)-)-$, $-CH_2CH(C\boldsymbol{H}_3)(OH)$ and $S(CH_2)_{11}C\boldsymbol{H}_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.4, 177.1, 177.0, 104.5, 64.9, 64.8, 64.7, 54.4, 53.7, 51.8, 47.6, 47.4, 45.0, 44.5, 44.3, 43.9, 21.5, 21.4, 18.5, 17.9, 16.5, 15.2. IR (neat, cm^{-1}): 3650-3050, 3050–2700, 2361, 1728, 1636, 1520, 1458, 1250, 1196, 1134, 949, 841. T_g = 105.5 and 162.0 °C. TGA in Ar: 250–390 °C, 37% mass loss; 390–480 °C, 49% mass loss; 12% mass remaining above 500 °C.



Scheme S1. Synthesis and ring-opening polymerization (ROP) of 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one, MBC. *Conditions*: (i) benzyl bromide, TEA, THF, 70 °C, overnight; (ii) ethyl chloroformate, TEA, THF, 0 °C to RT, overnight; (iii) ROH, DBU, DCM, 29 °C in the glovebox.

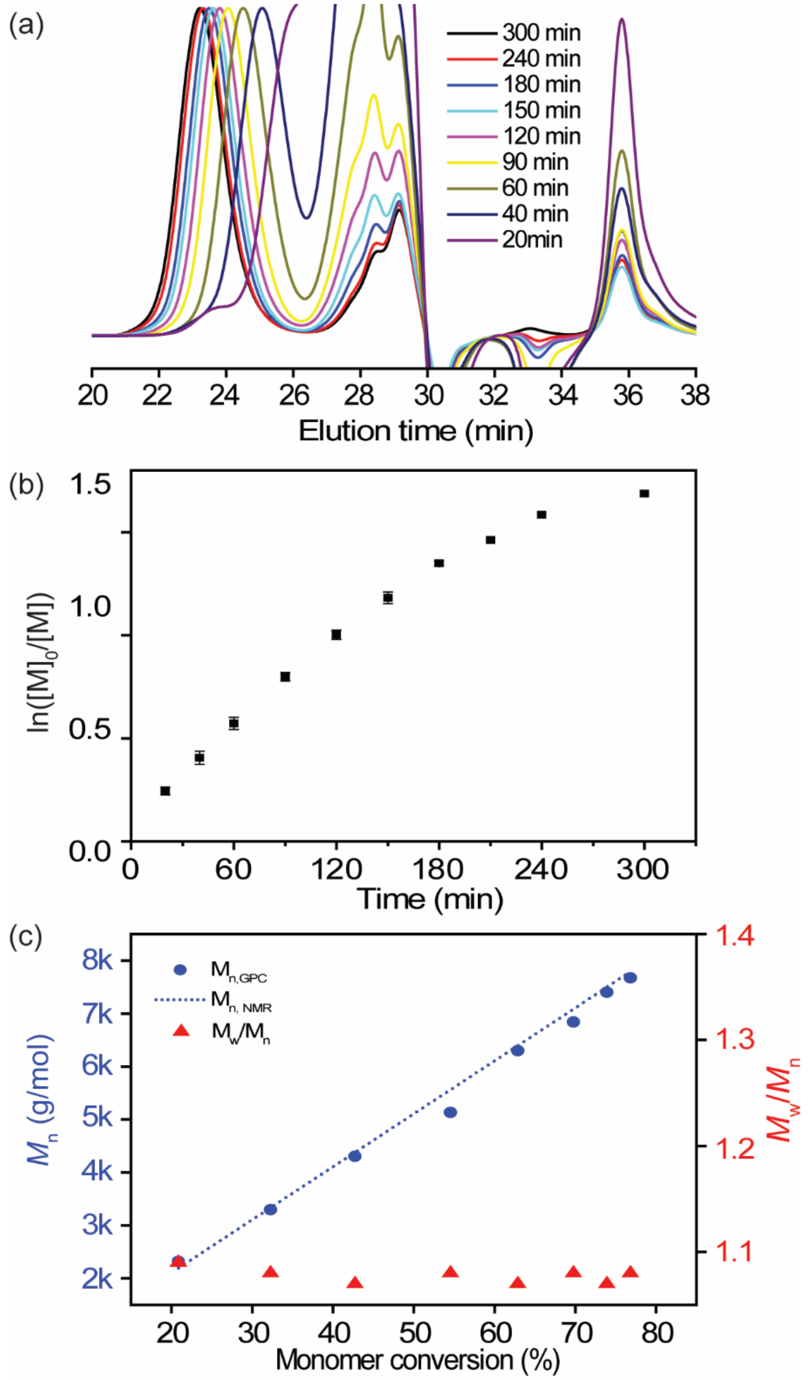


Figure S1. (a) GPC profiles (THF as an eluent, 1 mL/min) as a function of polymerization time, for the ROP of MBC; (b) Plot of $\ln([M]_0/[M])$ against time, obtained from ^1H NMR spectroscopy data; (c) Plot of number-average molecular weight (M_n) and polydipersity (M_w/M_n) against % monomer conversion in the ROP of MBC. *Conditions*: $[MBC]_0 = 0.5$ M in DCM at 29 °C in the glovebox, [MBC] : [BnOH] : [DBU] = 40 : 1 : 1.

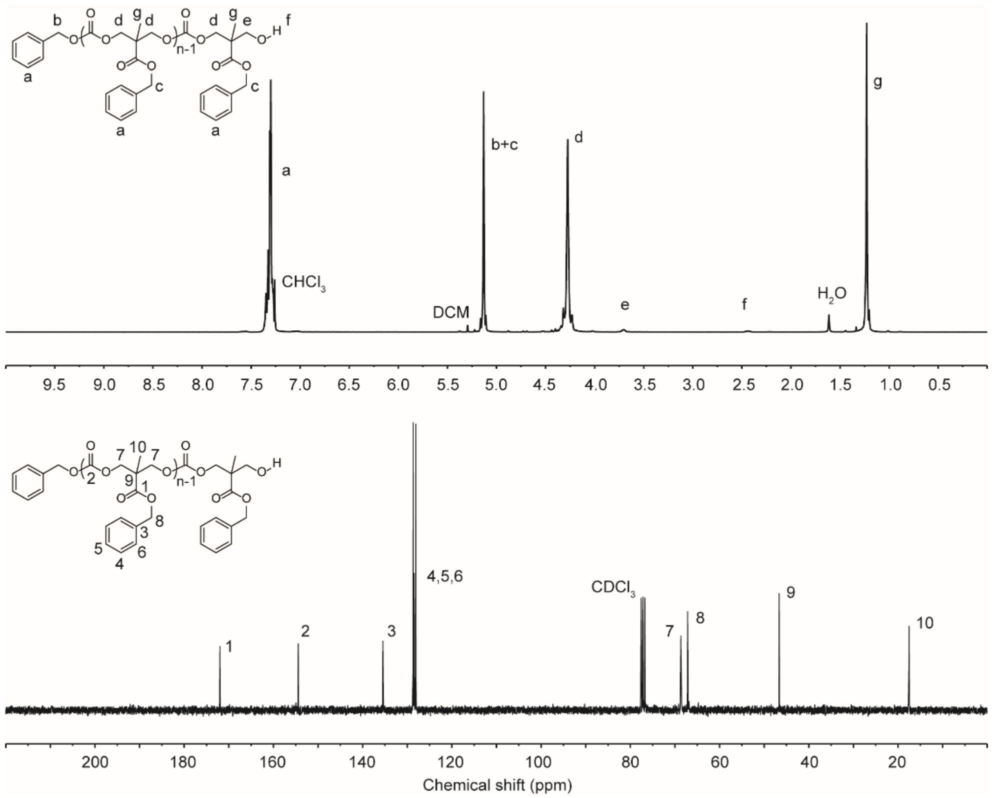


Figure S2. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) of PMBC$_{27}$ (**1**) initiated from benzyl alcohol using DBU. *Conditions*: $[MAC]_0$ = 0.5 M in DCM at 29 °C in the glovebox, $[MBC]_0$: [BnOH] : [DBU] = 40 : 1 : 1.

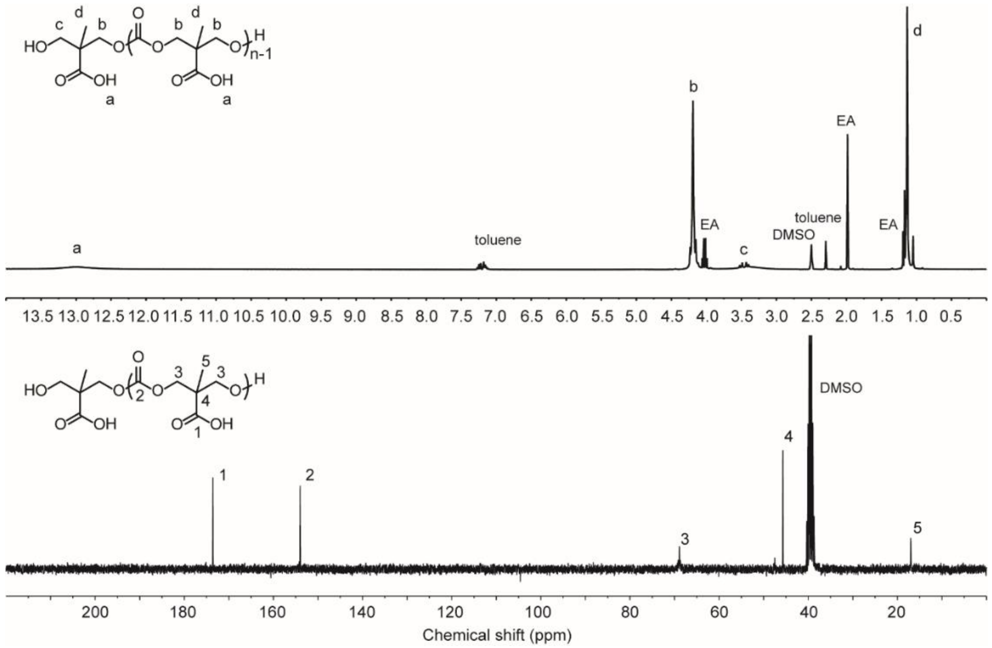


Figure S3. ^{1}H and ^{13}C NMR spectra (DMSO-d_6) of PMC$_{27}$ (**2**). EA = ethyl acetate.

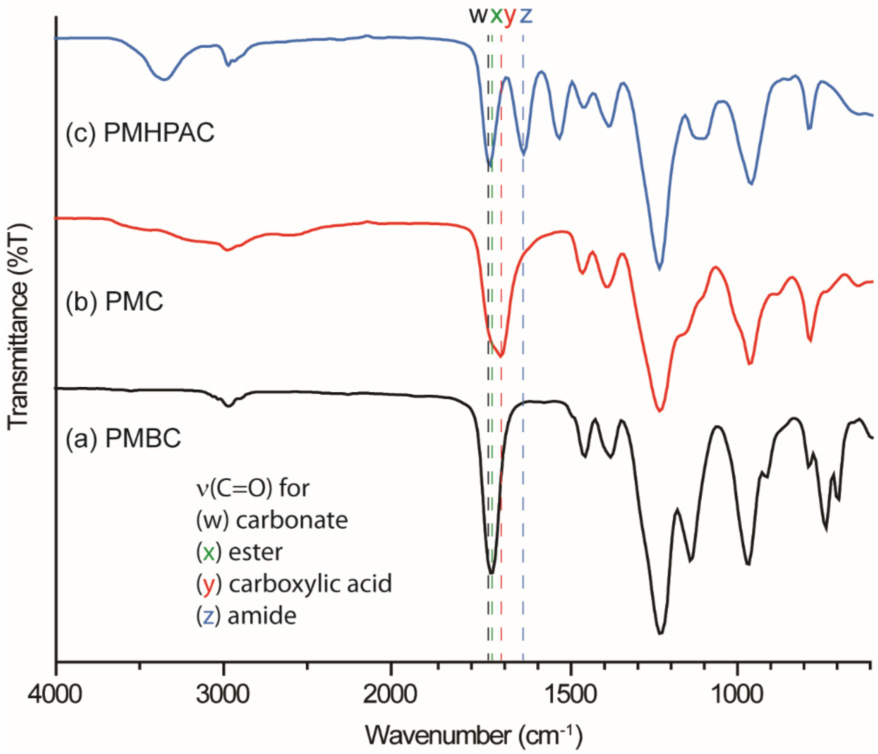


Figure S4. FTIR spectra of (a) PMBC_{27} (**1**), (b) PMC_{27} (**2**), and (c) PMHPAC_{27} (**4**).

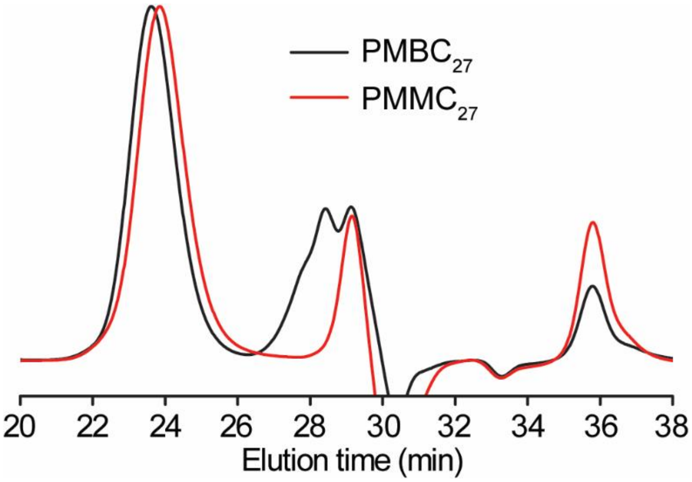


Figure S5. GPC profiles (THF as eluent, 1 mL/min) of before (PMBC, **1**) and after hydrogenolysis, followed by methylation (PMMC, **3**). The carboxylic acids of intermediate PMC (**2**) after hydrogenolysis of **1** were converted to methyl esters (PMMC, **3**) using $\mathrm{TMSCH_2N_2}$ for GPC analysis.

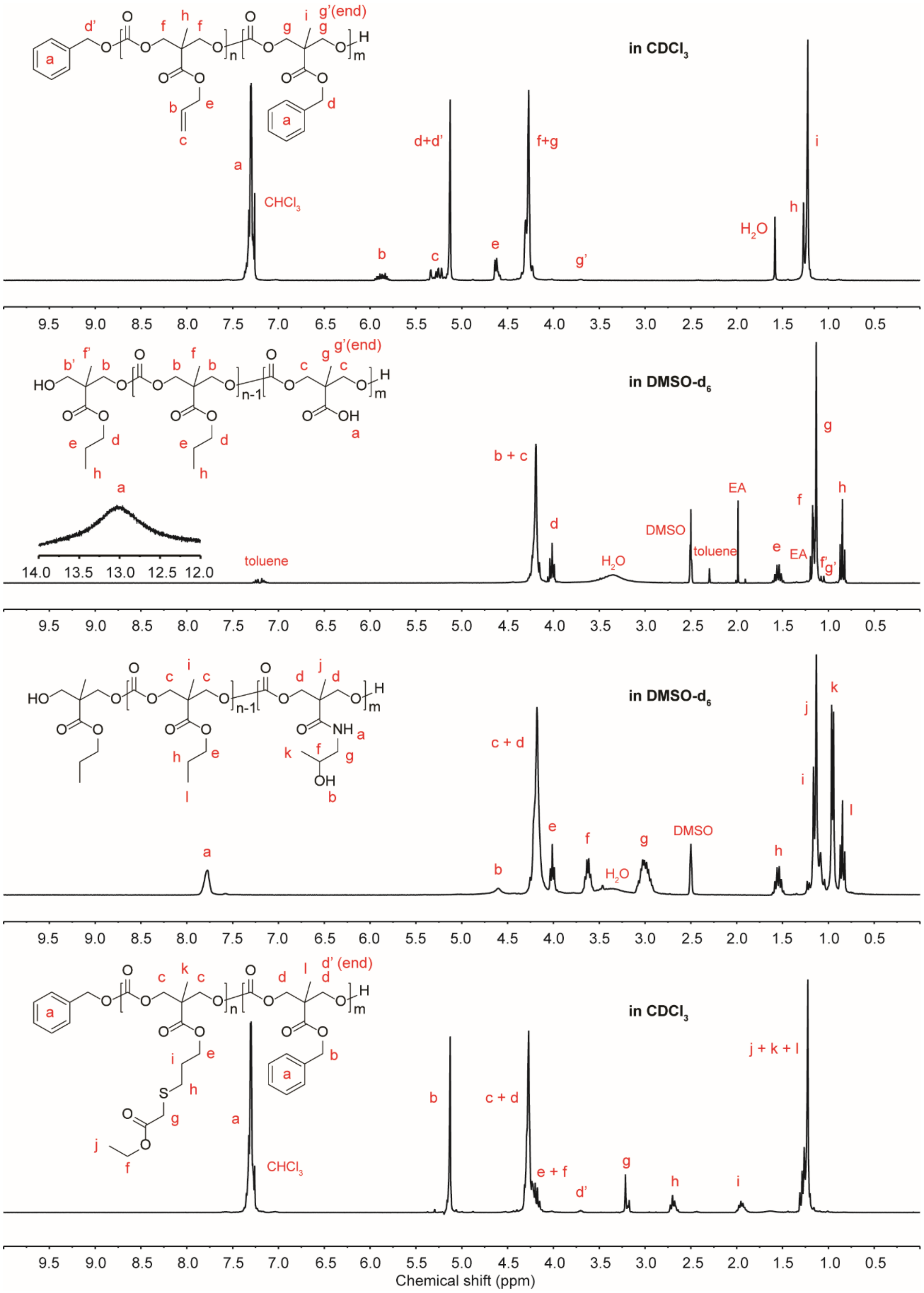


Figure S6. ^{1}H NMR spectra of PMAC$_{20}$-*b*-PMBC$_{70}$ (**8**), PMPC$_{20}$-*b*-PMBC$_{70}$ (**9**), PMPC$_{20}$-*b*-PMHPAC$_{70}$ (**10**) and **11**. EA = ethyl acetate.

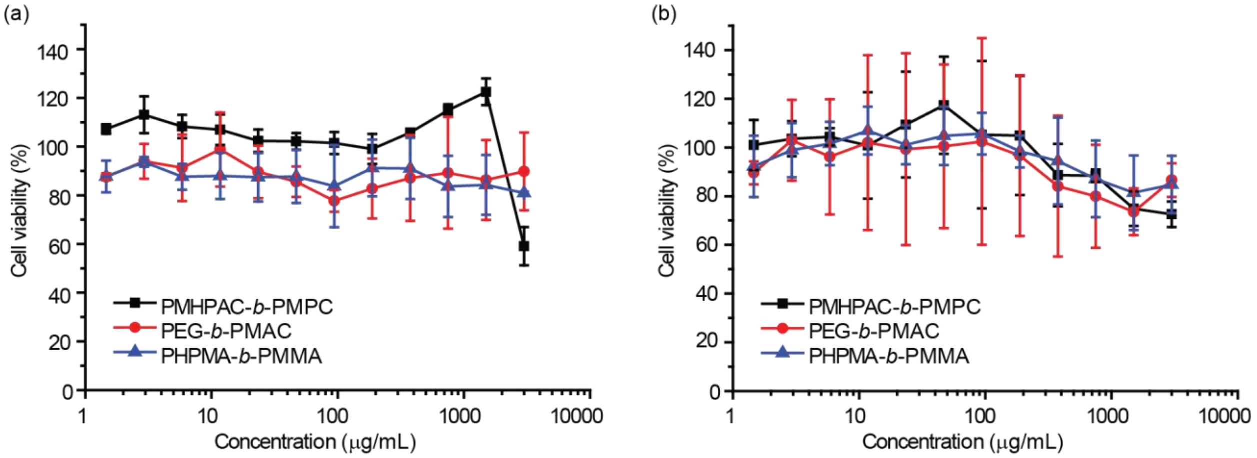


Figure S7. Cytotoxicity of PMHPAC-*b*-PMPC (**10**), PEG-*b*-PMAC (**14**), and PHPMA-*b*-PMMA (**15**) incubated with (a) RAW 264.7 mouse macrophages and (b) OVCAR-3 cells.

Degradation Study of PMHPAC. Degradation of PMHPAC in aqueous base was monitored by ^{1}H NMR spectroscopy. $PMHPAC_{27}$ (15 mg, 2.6 μmol) was dissolved in 700 μL of D_2O and transferred to a NMR tube. Upon injection of 6 μL of 40 % $NaOD/D_2O$ (~0.1 M) into the NMR tube, the first scan was recorded at 2 min. Then, the tube was dipped in an oil bath adjusted to 60 °C and ^{1}H NMR spectra were collected at desired times. Within 2 min, the polycarbonate backbone was severed and the polymer was fragmented to monomer, MHPAC, which was observed by disappearance of the polycarbonate backbone proton (labelled as m in Figure S8d) and the appearance of the corresponding protons of MHPAC (labelled as b−g in Figure S8a). In addition, bubbles were observed in the NMR tube, which was considered to be due to the production of CO_2. As time progressed, the monomer was further degraded and formed 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) as the appearance of the corresponding protons (labelled as h and i in Figure S8a). The relative ratio of bis-MPA *vs* MHPAC, calculated from ^{1}H NMR proton resonance intensities, increased (Figure S9). Further, MHPAC and bis-MPA were confirmed by ESI-MS (negative-ion mode) as 190.1112 and 133.0547 peaks, corresponding to $C_8H_{16}NO_4^-$ (calculated, 190.1085) and $C_5H_9O_4^-$ (calculated, 133.0506), respectively, in the solution at the time of 9 days after $NaOD_{(aq)}$ addition (Figure S10). It is uncertain why the MS data did not agree with the expected deuterated products, $C_8H_{14}D_2NO_4^-$ and $C_5H_7D_2O_4^-$, which would have been observed at $^+2$ amu higher values, 192.1210 and 135.0632, respectively. In a separate experiment, degradation of PMHPAC was facilitated in high base concentration and at higher temperature. After incubation of $PMHPAC_{27}$ in 1.0 M $NaOH_{(aq)}$ at 100 °C overnight, the resulting aqueous solution was washed with DCM (×3) and lyophilized. The lyophilized products contained bis-MPA and amino-2-propanol, as determined by comparing the ^{1}H NMR spectrum of the lyophilized product (Figure S8c) with ^{1}H NMR spectrum of the solution of bis-MPA and amino-2-propanol in 0.1 M NaOD/D_2O (Figure S8b).

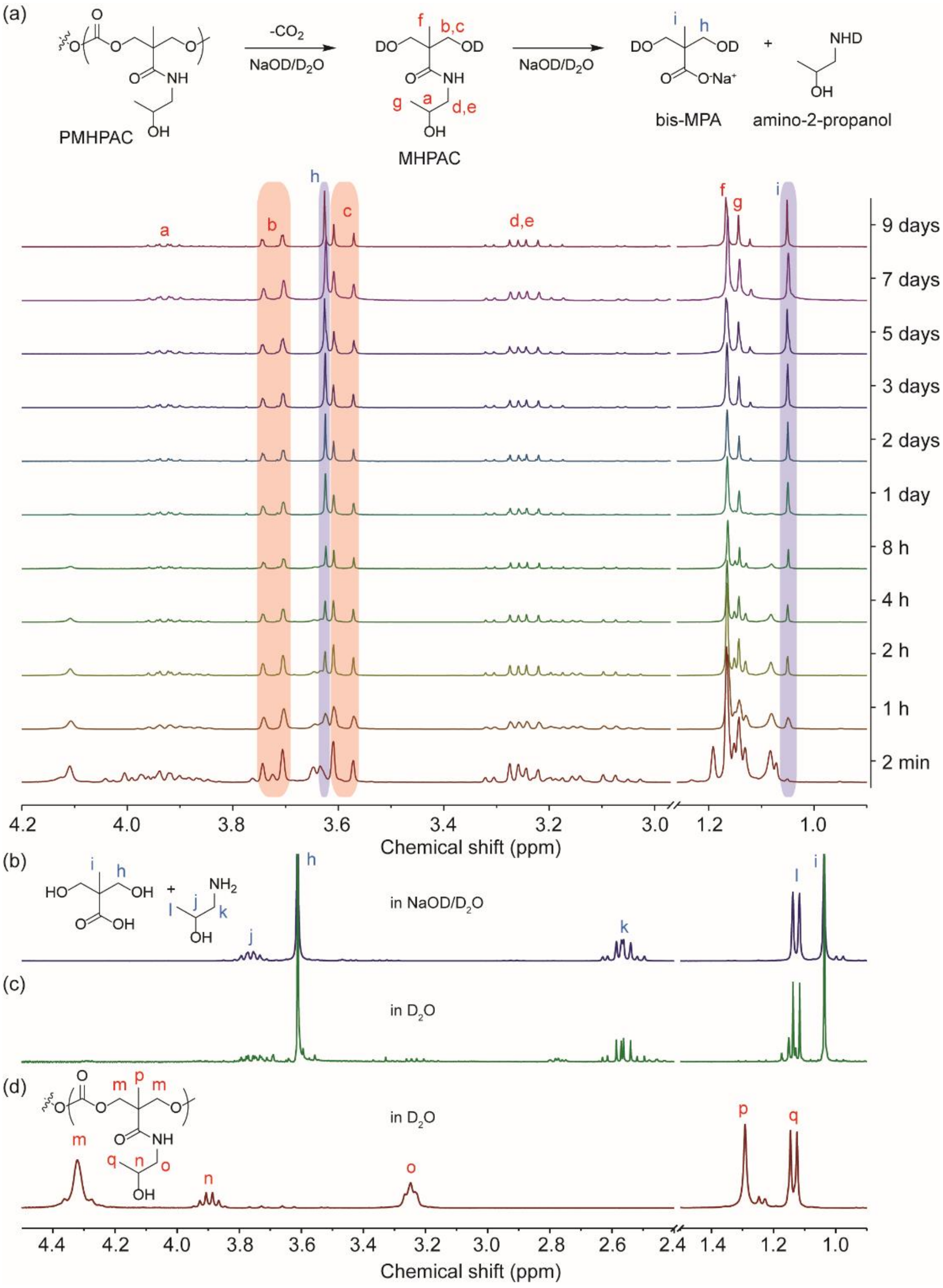


Figure S8. ^{1}H NMR spectra of (a) $PMHPAC_{27}$ in 0.1 M NaOD/D_2O at 60 °C at various time points, (b) a mixture of bis-MPA and amino-2-propanol co-dissolved in 0.1 M NaOD/D_2O, (c) the lyophilized products of $PMHPAC_{27}$ after incubation in 1.0 M $NaOH_{(aq)}$ overnight at 100 °C and dissolved in D_2O, and (d) $PMHPAC_{27}$ in D_2O.

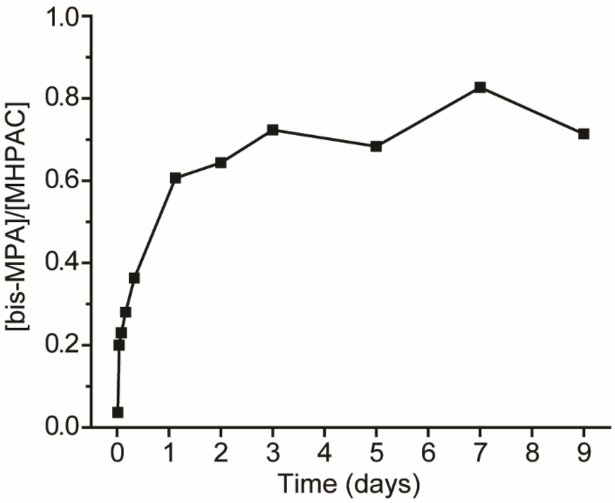


Figure S9. Relative molar ratios of bis-MPA *vs* MHPAC by the time interval in the solution of PMHPAC in 0.1 M NaOD/D_2O at 60 °C, calculated by [(the integration of i)/3]/[(the integration of b and c)/4] in Figure S8a.

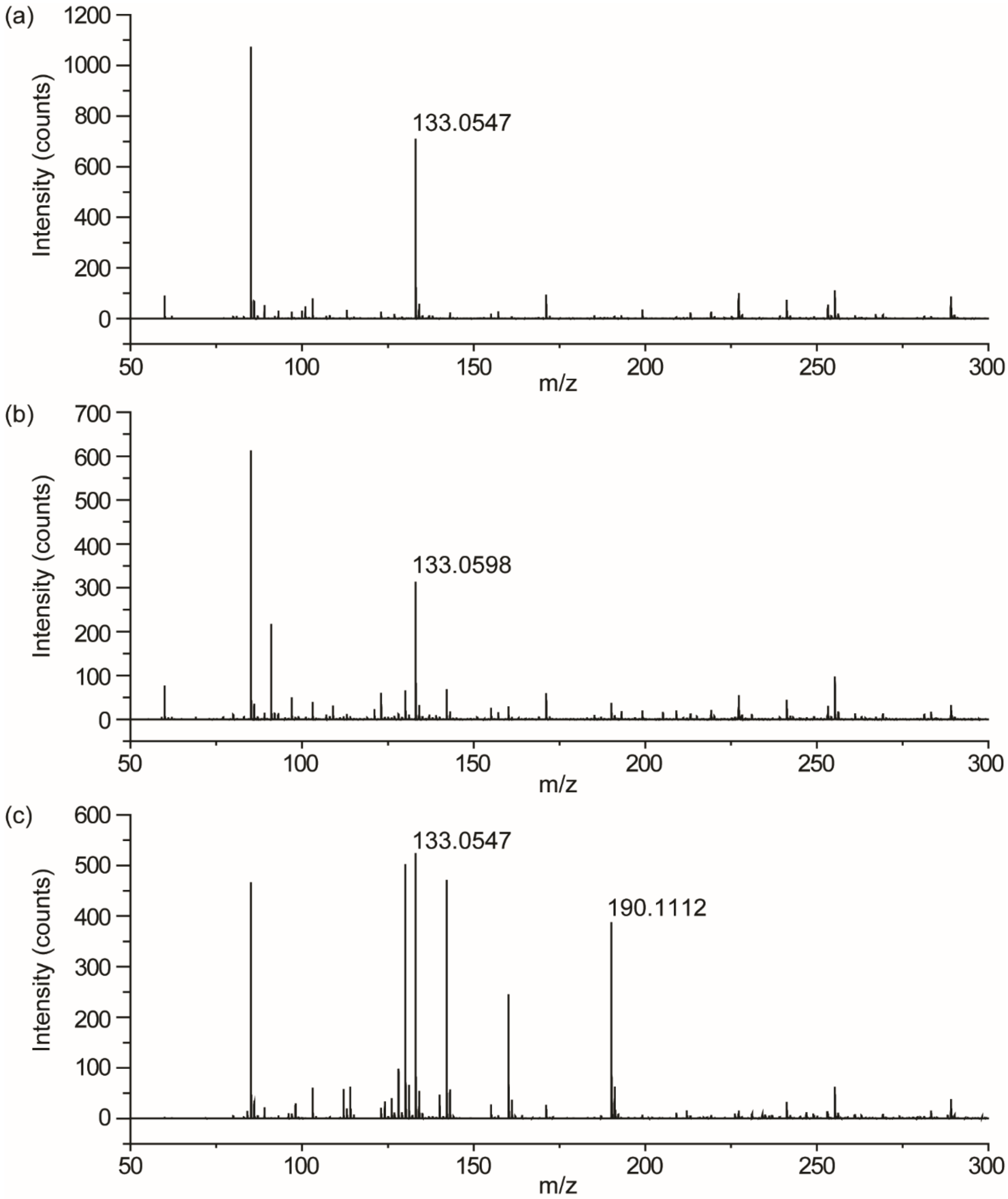
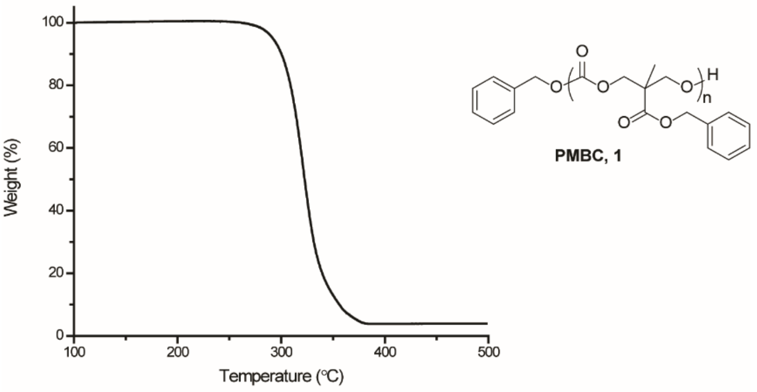


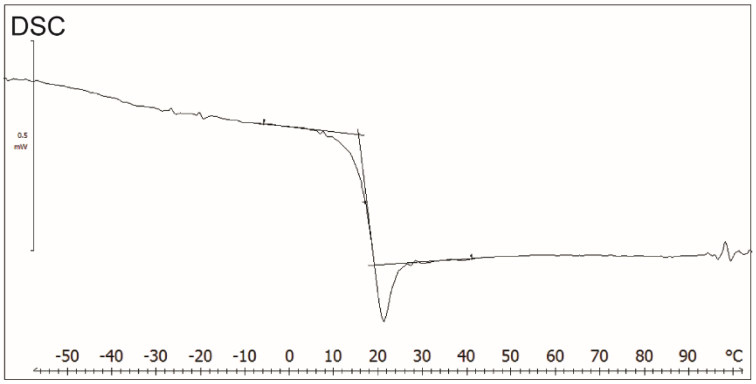
Figure S10. ESI MS spectra of (a) a mixture of bis-MPA and amino-2-propanol in 0.1 M NaOD/D_2O, (b) the lyophilized products of $PMHPAC_{27}$ after incubation in 1.0 M $NaOH_{(aq)}$ overnight at 100 °C and dissolved in D_2O, and (c) $PMHPAC_{27}$ in 0.1 M NaOD/D_2O at 60 °C for 9 days in negative mode; *m/z* range of 50–300.

TGA



PMBC, 1

DSC



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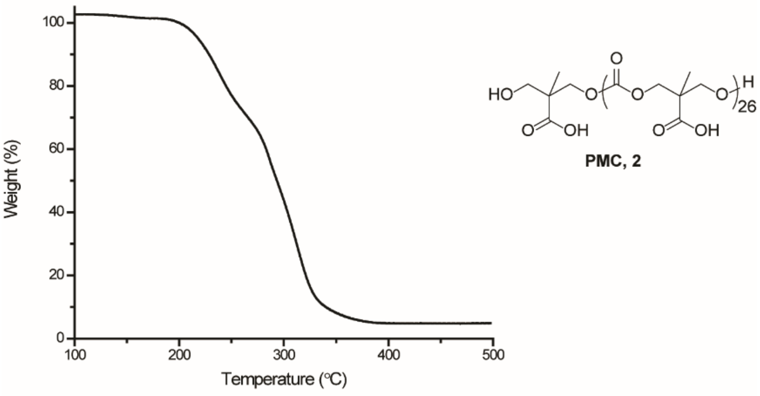
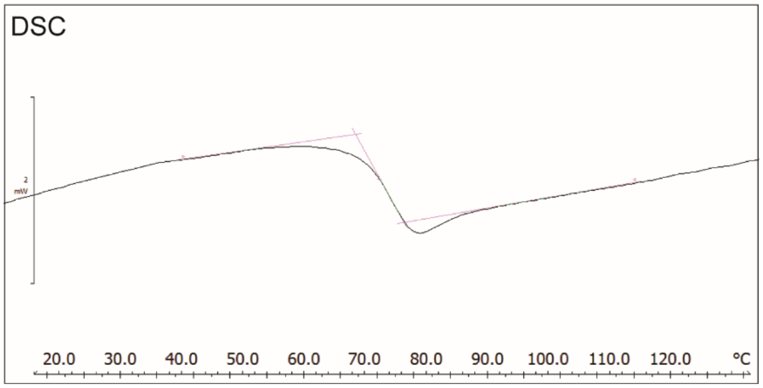
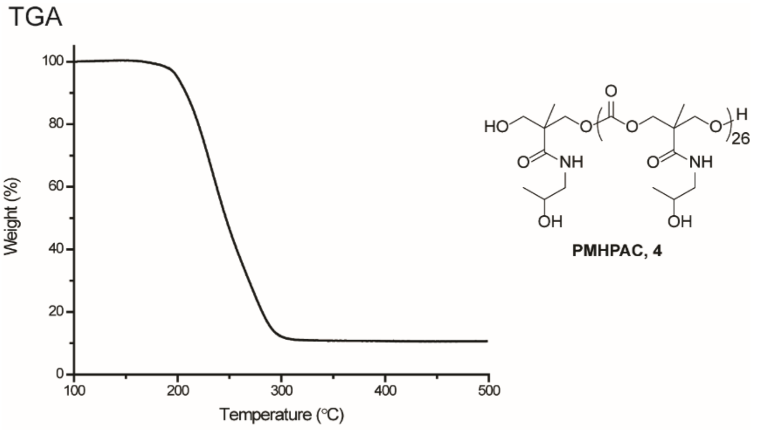


PMC, 2

DSC




TGA
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40
20
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100
200
300
400
500
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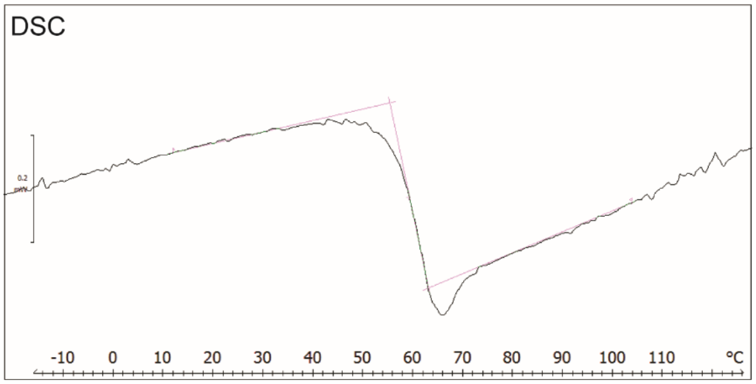
PMHPAC, 4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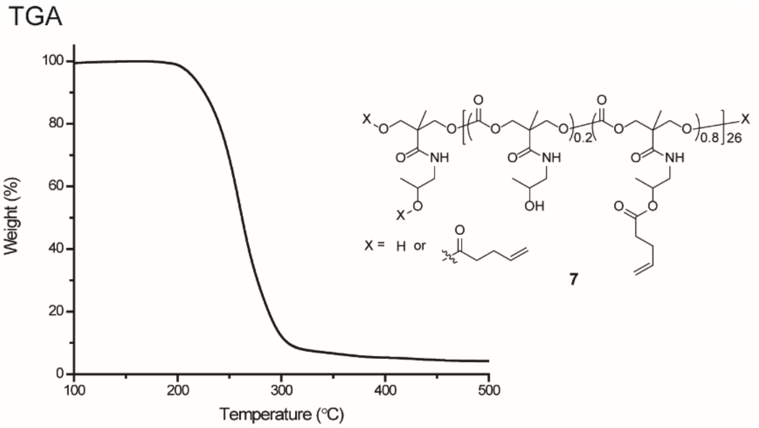
TGA
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40
20
0
100
200
300
400
500
Temperature (°C)
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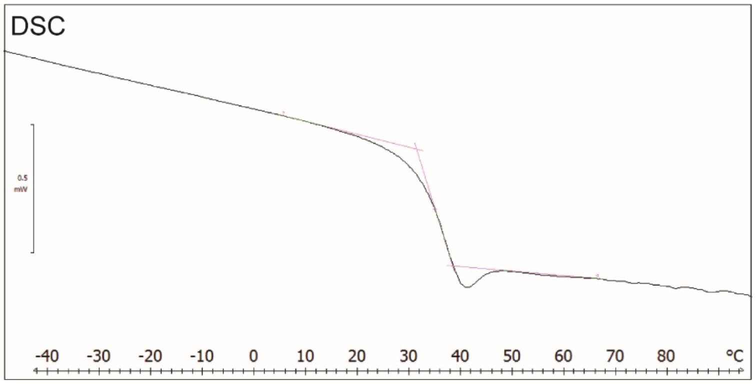
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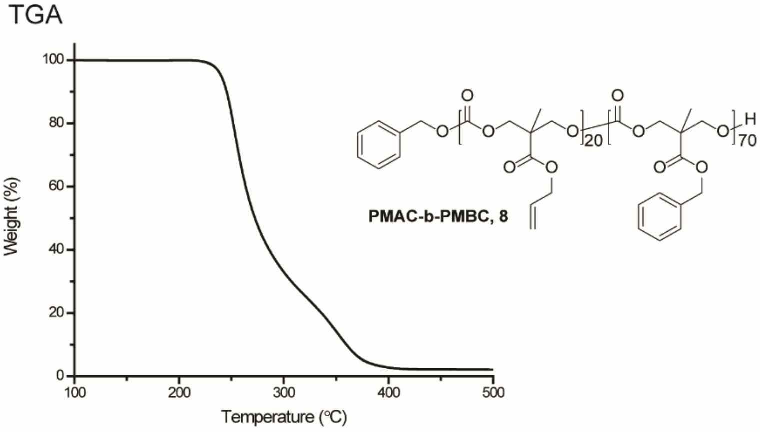
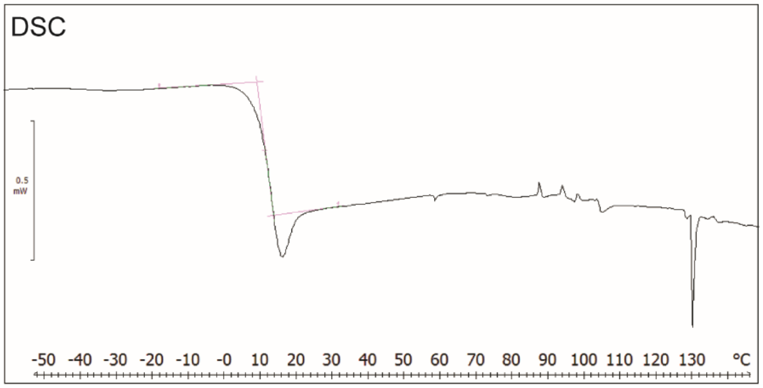
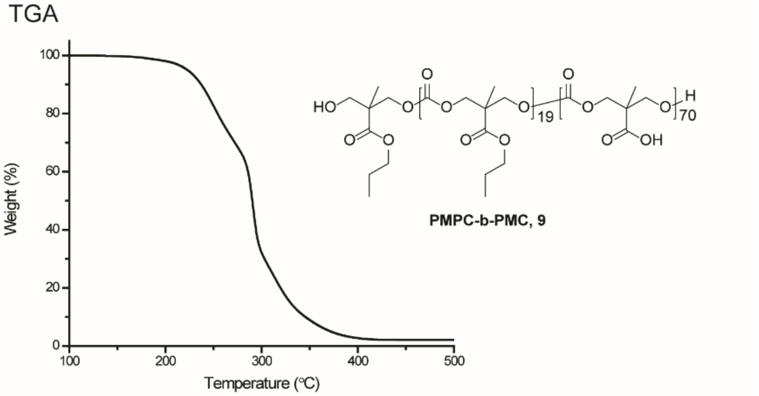
70
80
°C

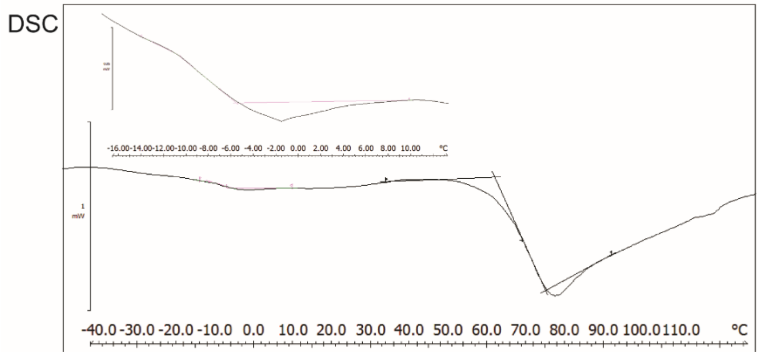


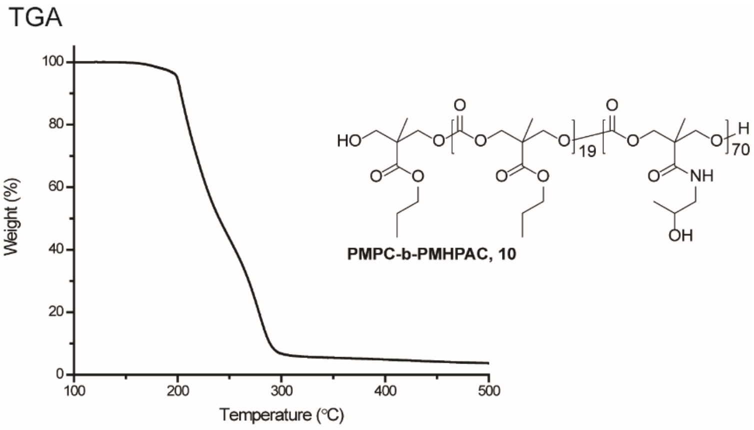
PMAC-b-PMBC, 8

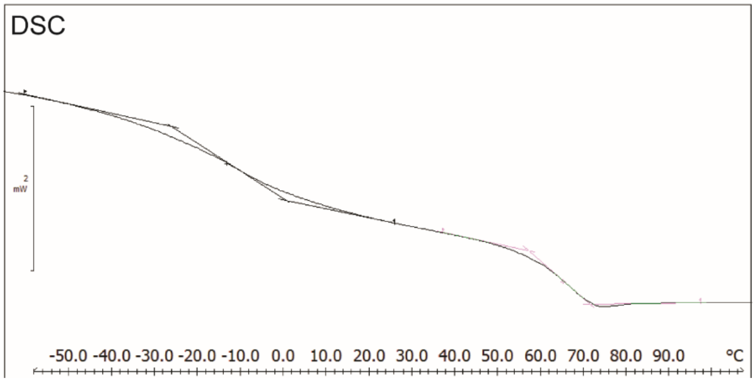


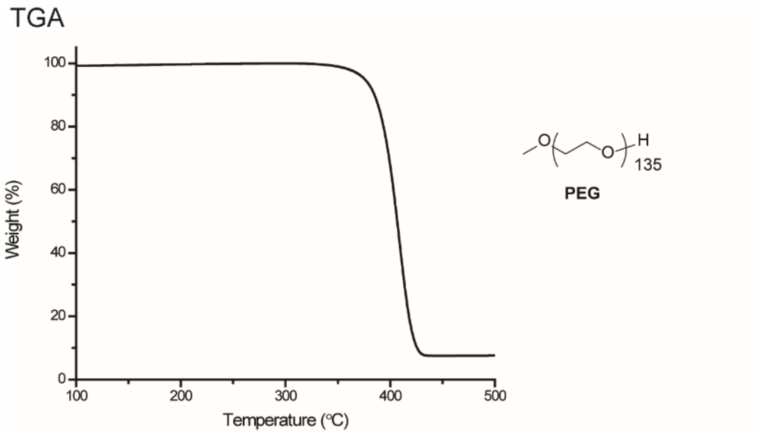


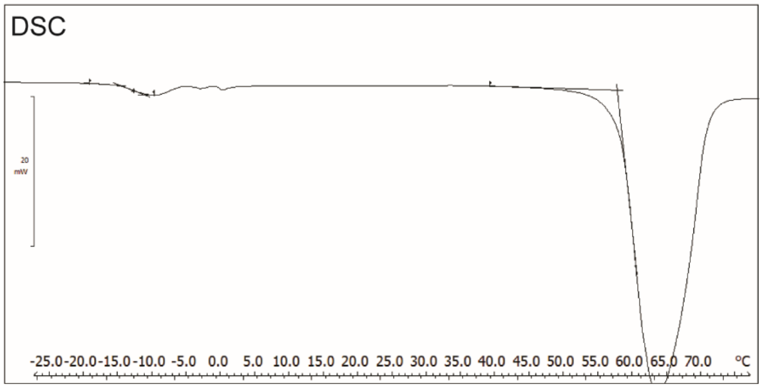
PMPC-b-PMC, 9

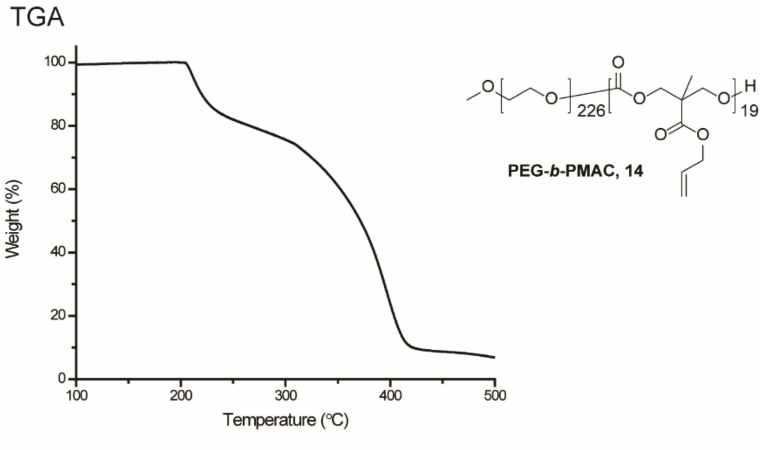



TGA
Weight (%)
100
80
60
40
20
0
100
200
300
400
500
Temperature (°C)
HO
O
19
70
H
NH
OH
PMPC-b-PMHPAC, 10

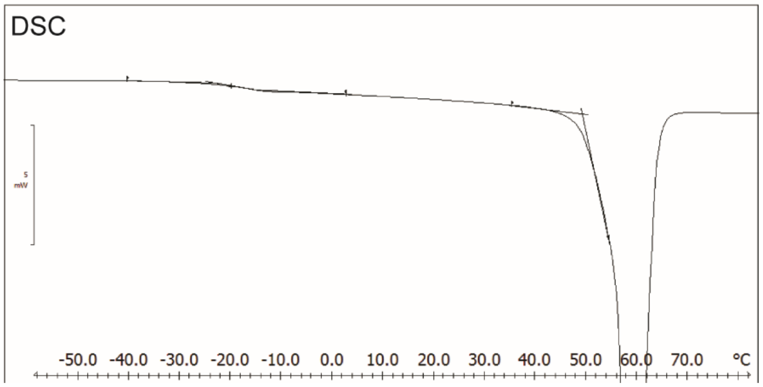

DSC
2 mW
-50.0 -40.0 -30.0 -20.0 -10.0 0.0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0 90.0
°C

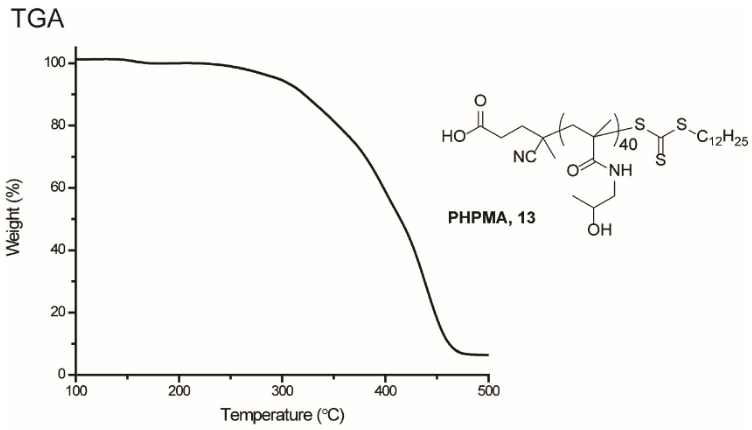

TGA
Weight (%)
100
80
60
40
20
0
100
200
300
400
500
Temperature (°C)
O
H
135
PEG


DSC
20 mW
-25.0 -20.0 -15.0 -10.0 -5.0 0.0 5.0 10.0 15.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0 55.0 60.0 65.0 70.0
°C

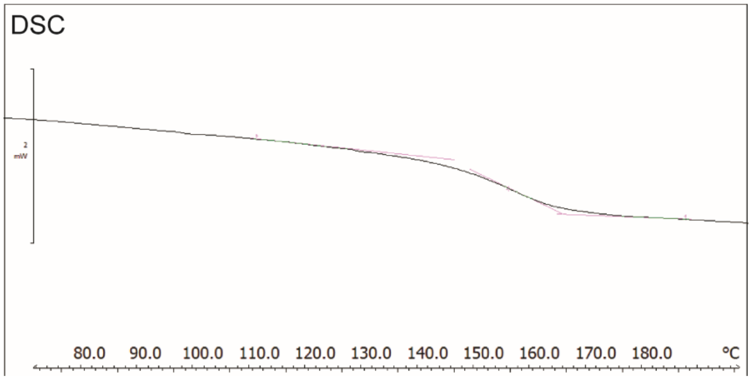


PEG-*b*-PMAC, 14

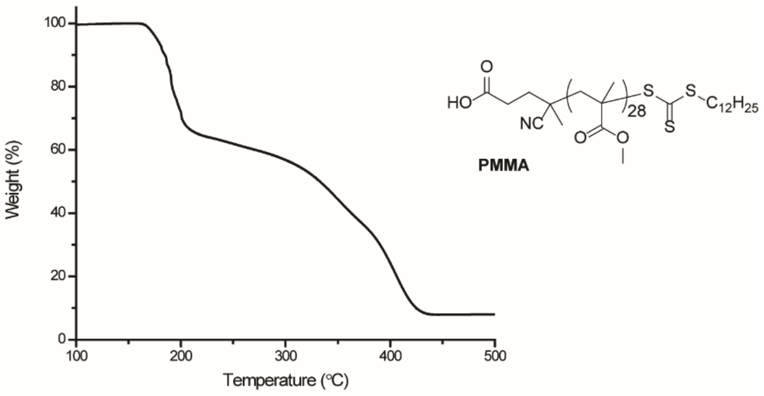




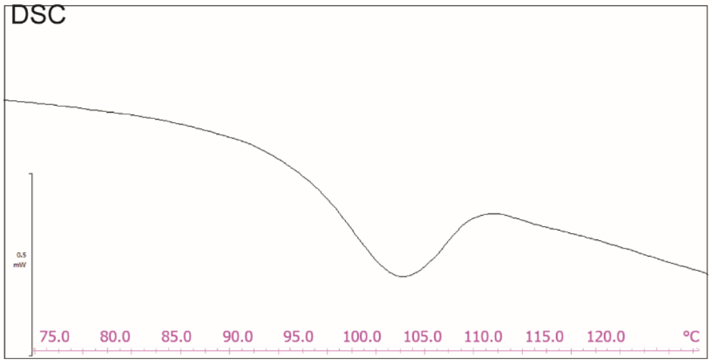
PHPMA, 13



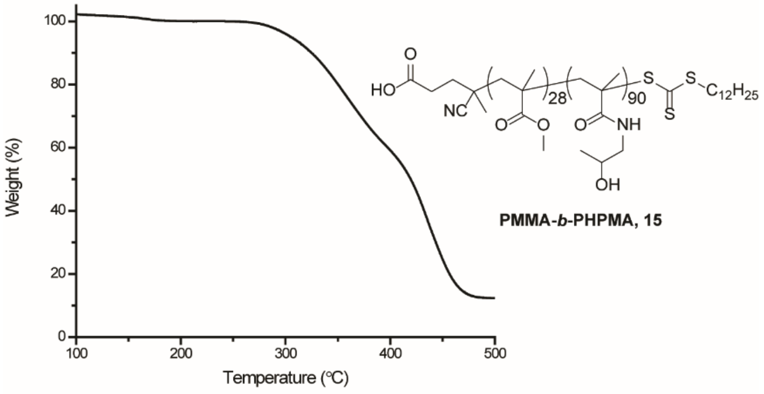
TGA



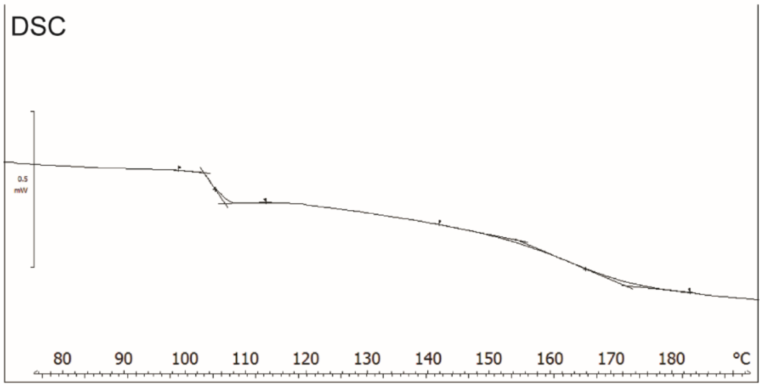
DSC



TGA



DSC



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2. Faucher, J. A.; Koleske, J. V.; Santee, E. R.; Stratta, J. J.; Wilson, C. W. *J. Appl. Phys.* **1966,** *37*(11), 3962-3964.