# A general synthetic strategy to prepare poly(ethylene glycol)-based multifunctional copolymers

Swati De, Carol Stelzer and Anzar Khan*

Department of Materials, Swiss Federal Institute of Technology, CH-8093 Zürich, Switzerland

## General Methods and Materials

Polyethylene glycol monomethyl ether ($M_n$ = 5 kDa), 2-bromoisobutyryl bromide, 2-bromo-2-methylpropanoic acid ethyl ester, 4,4′-dinonyl-2,2′-dipyridyl, Cu(I)Br, glycidyl methacrylate, lithium hydroxide (LiOH), 4-methoxybenzyl mercaptan, poly(ethylene glycol) methyl ether acrylate ($M_n$ = 480), 1-naphthylacetic acid, adamantane-1-carbonyl chloride, and decanoyl chloride were purchased from commercial sources. 2-(2-(2-Methoxyethoxy)ethoxy)ethane thiol, **5**, was synthesized as described in; C. Hass.; B. Kirste.; H. Kurreck.; G. Schloemp. J. Am. Chem. Soc. 1983, 105, 7375. NMR spectra were recorded on Bruker AV500 MHz spectrometers, using $CDCl_3$ as the solvent. UV-visible spectroscopic analysis was performed on JASCO V-670 UV-Vis-NIR spectrophotometer using 2.0 mm path length and 0.3 mL volume quartz cuvette. Analytical GPC measurements were performed using a Viscotek GPC system equipped with a pump and a degasser (GPCmax VE2001, flow rate 1.0 mL/min), a detector module (Viscotek 302 TDA) and three columns (2×PLGel Mix-C and 1×ViscoGEL GMHHRN 18055, 7.5 × 300 mm for each).

## Synthesis

**General Comments:**

1. For ATRP polymerizations, 4,4′-dinonyl-2,2′-dipyridyl ligand seems to be the best choice (considering PDI of the resulting polymers) perhaps due to its unreactivity towards epoxide group. Moreover, solution polymerization yield polymers with better PDI than bulk polymerization.
2. If a polymer is soluble in the thiol-reactant then the reaction can be carried out under solvent-less conditions. However, if needed, an organic solvent such as THF can be used.
3. LiOH can be replaced by triethylamine, if required.
4. After the thiol-epoxy reaction, a water wash removes the inorganic salts and LiOH. However, if the polymer produced is highly water soluble, then the reaction mixture can directly be precipitated into a non-solvent. In the case of direct precipitation, the triethylamine salts may stay with the polymer. This is not an issue, as the subsequent reaction is carried out in the presence of triethylamine.

5. The esterification reaction can be carried out at elevated temperatures, espacially in the cases where the comonomer presents significant steric issues.

6. Choice of the solvents (for reactions) and non-solvents (for precipitations) depend upon the chemical nature of the polymer produced.

7. Water solubility of the polymers depends upon the block lengths, chemical nature of the functional groups introduced, length of the PEG-macromonomer, ratio of the PEG-macromonomer to glycidyl methacrylate monomer, and can be tuned. Hence, the information provided in Table **1** is specific to the materials prepared during this study.

8. If required, the dual-functional polymers can be purified by passing through a silica gel or neutral alumina plug. In the case of silica gel, material loss is observed espacially with polymers with high content of PEG-macromonomer.

**PEG macroinitiator 1:** Polyethylene glycol monomethyl ether ($M_n$ = 5000) (5 g, 1.0 mmol) and freshly distilled triethylamine (131 mg, 1.3 mmol) were taken in dry THF (30 mL) in a round-bottom flask. The solution was cooled with an ice bath. Then, 2-bromoisobutyryl bromide (360 mg, 1.2 mmol) in 20 mL of dry THF was slowly added via a dropping funnel. After the addition was complete, the mixture was stirred at 50 °C for 12 h. The precipitated salts were filtered off, and the filtrate was evaporated in vacuum. Then 1 M HCl (30 mL) was added and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water (50 mL), saturated $Na_2CO_3$ (30 mL), and brine (30 mL), dried with $MgSO_4$, filtrated, and concentrated under reduced pressure. Then the product was recrystallized from ethanol to yield 4.85 g of macroinitiator **1** (Yield = 94 %). $^1$H-NMR (δ, ppm, 500 MHz, $CDCl_3$): 1.94 (s, 6H, C(**$CH_3$**)$_2$Br), 3.38 (s, 3H, O**$CH_3$**), 3.42 (t, 2H, O**$CH_2$**), 3.64 (br s, O**$CH_2CH_2$**O), 3.87 (t, O**$CH_2$**), 4.33 (t, 2H, COO**$CH_2$**); $^{13}$C-NMR (δ, ppm, 125 MHz, $CDCl_3$): 30.7, 59.1, 65.5, 69.1, 70.76, 72.1, 172.3; GPC ($CHCl_3$): $M_n$ = 6300, $M_w$ = 7800, PDI ($M_w/M_n$) = 1.23.

**PEG-*b*-poly(glycidyl methacrylate) 2:** PEG-macroinitiator **1** (1 g, 0.19 mmol), glycidyl methacrylate (2.92 g, 20.5 mmol), and 4,4′-dinonyl-2,2′-dipyridyl (192 mg, 0.47 mmol) were taken in 5 mL anisole in a schlenk tube and purged with $N_2$ gas for 40 min. Cu(I)Br (28 mg, 0.19 mmol) was added and nitrogen purging was continued for another 5 mins. The reaction mixture was then stirred under nitrogen atmosphere in a preheated oil bath at 60 °C for 1 h. Then, the reaction was stopped by cooling to room temperature and opening the vessel to air. The reaction mixture was precipitated into isopropanol, filtered, and dried. The resulting solid was then dissolved in minimum amount of $CH_2Cl_2$ and passed through silica gel plug and then re-precipitated from isopropanol to give 1.3 g of PEG-*b*-PGMA polymer **2**. $^1$H-NMR (δ, ppm, 500 MHz, $CDCl_3$): 0.94-1.15 (m, 3H, $C\mathbf{H_3}$), 1.90-1.97 (m, 2H, $\mathbf{CH_2}CCH_3$), 2.64 (broad signal, 1H, $COOCH_2CH\mathbf{CH_2}O$), 2.84 (broad signal, 1H, $COOCH_2CH\mathbf{CH_2}O$), 3.24 (broad signal, 1H, $CH_2\mathbf{CH}CH_2O$), 3.38 (s, 3H, $O\mathbf{CH_3}$), 3.42 (t, 2H, $O\mathbf{CH_2}CH_2O$), 3.64 (broad signal, $O\mathbf{CH_2CH_2}O$), 3.83 (broad signal, 1H, $COO\mathbf{CH_2}$), 4.28 (broad signal, 1H, $COO\mathbf{CH_2}$); $^{13}$C-NMR (δ, ppm, 125 MHz, $CDCl_3$): 17.0, 19.0, 44.8-45.3, 48.9, 54.0-54.3, 65.8-66.0, 70.7, 176.3-177.4; GPC ($CHCl_3$): $M_n$ = 41100, $M_w$ = 53300, PDI ($M_w/M_n$) = 1.29.

**Thiol-functionalized polymer 3:** To a stirred and ice-cold solution of PEG-*b*-PGMA **2** (0.3 g, 0.006 mmol) and 4-methoxybenzyl mercaptan (0.556 g, 3.6 mmol), LiOH (37.9 mg, 0.9 mmol) was added slowly, the cooling was removed and the resulting reaction mixture was stirred at room temperature for 3 h. Then, water (5 mL) was added, and the polymer was extracted into $CH_2Cl_2$ (2 × 10 mL). The resulting organic solution was then concentrated and precipitated into isopropanol three times and dried. 0.43 g (87%). $^1$H-NMR (δ, ppm, 500 MHz, $CDCl_3$): 0.95-1.08 (m, 3H, $CC\mathbf{H_3}$), 1.80-1.96 (m, 2H, $\mathbf{CH_2}CCH_3$), 2.55 (broad signal, 2H, $CH(OH)\mathbf{CH_2}S$), 3.62 (broad signal, 1H, $CH(\mathbf{OH})CH_2S$), 3.67 (broad signal, $O\mathbf{CH_2CH_2}O$), 3.70 (broad signal, 2H, $\text{-}S\mathbf{CH_2}Ph$), 3.78 (broad signal, 3H, $\text{-}Ph\mathbf{CH_3}$), 3.93 (broad signal, 2H, $COO\mathbf{CH_2}$), 4.08 (broad signal, 1H, $\mathbf{CH}(OH)CH_2S$), 6.84 (d, $J$ = 8.1 Hz, 2H, $\text{-}SCH_2\mathbf{Ph}$), 7.22 (d, $J$ = 7.9 Hz, 2H, $\text{-}SCH_2\mathbf{Ph}$); $^{13}$C-NMR (δ, ppm, 125 MHz, $CDCl_3$): 18.0, 19.8, 34.8, 36.2, 45.2, 55.5, 67.8-68.0, 70.7, 114.2, 129.9, 130.2, 158.9, 177.0-177.5; GPC ($CHCl_3$): $M_n$ = 93200, $M_w$ = 118100, PDI ($M_w/M_n$) = 1.26.

**Bifunctional polymer 4:** Polymer **3** (0.1 g, 0.0008 mmol) was taken in dry THF (5 mL) and stirred in ice-water bath for 5 min. Then, $Et_3N$ (0.11 g, 1.1 mmol) was added drop wise. After 10 mins, 1-naphthylacetyl chloride (0.22 g, 1.1 mmol) and catalytic amounts of DMAP in dry THF (5 mL) was added drop wise. The reaction mixture was stirred at room temperature for 12 h. After the reaction was complete, contents were poured into acidic ice-cold water and extracted with $CH_2Cl_2$. The resulting solution was then concentrated and precipitated into isopropanol three times to give 0.140 g of polymer **4** (yield = 88%). $^1$H-NMR (δ, ppm, 500 MHz, $CDCl_3$): 0.99-1.20 (m, 3H, $CC\mathbf{H_3}$), 1.76-1.88 (m, 2H, $\mathbf{CH_2}CCH_3$), 2.41 (broad signal, 2H, $CH(OH)\mathbf{CH_2}S$), 3.36-4.20 (broad signal, $O\mathbf{CH_2CH_2}O$ and $COO\mathbf{CH_2}CH(OCO\mathbf{CH_2}Nap)CH_2S$ $\mathbf{CH_2}PhO\mathbf{CH_3}$), 5.15 (broad signal, 1H, $\mathbf{CH}(OCOCH_2Nap)CH_2S$), 6.62-8.10 (multiple broad signals, 11H, $CH(OCOCH_2\mathbf{Nap})CH_2S\mathbf{Ph}$). $^{13}$C-NMR (δ, ppm, 125 MHz, $CDCl_3$): 18.0, 19.8, 31.5, 34.9-

36.1, 39.0, 45.2, 55.4, 65.8-68.2, 70.8, 114.1, 124.1-133.9, 158.8, 171.0, 177.0-177.5; GPC ($CHCl_3$): $M_n$ = 151700, $M_w$ = 189700, PDI ($M_w/M_n$) = 1.25.

**Polymer 6:** 2-(2-(2-Methoxyethoxy)ethoxy)ethane thiol, **5**, was allowed to react with polymer **2**, according to the procedure described above. After the reaction, the crude reaction mixture was directly precipitated into a mixture of ether:toluene (2:1) without any water washing. $^1$H-NMR (δ, ppm, 500 MHz, MeOD): 0.95-1.08 (m, 3H, C$\mathbf{H_3}$), 1.80-1.96 (m, 2H, $\mathbf{CH_2}CCH_3$), 2.78 (broad signal, 4H, CH(OH)$\mathbf{CH_2}$S$\mathbf{CH_2}$Ph), 3.31 (broad signal, 1H, CH(**OH**)$CH_2$S), 3.37 (br s, O$\mathbf{CH_3}$), 3.52-3.69 (broad signal, O$\mathbf{CH_2CH_2}$O), 3.98 (broad signals, 3H, COO$\mathbf{CH_2}$**CH**(OH)$CH_2$S); $^{13}$C-NMR (δ, ppm, 125 MHz, MeOD): 16.9, 19.1, 32.0, 35.8, 44.9, 58.1, 67.6-71.8,177.0-177.5; GPC (DMF): $M_n$ = 77600, $M_w$ = 104000, PDI ($M_w/M_n$) = 1.34.

**Polymer 7:** Reaction of decanoyl chloride, with polymer **6**, according to the procedure described above (precipitation from methanol), gave polymer **7**. $^1$H-NMR (δ, ppm, 500 MHz, $CDCl_3$): 0.88 (t, 6H), 1.26 (broad signal, 12H), 1.62 (broad signal, 4H), 2.32 (broad signal, 2H), 2.76 (broad signal, 4H), 3.38 (s, 3H), 3.54-3.64 (broad signals, O$\mathbf{CH_2CH_2}$O), 4.10 (broad signal, 2H), 5.15 (broad signal, 1H); $^{13}$C-NMR (δ, ppm, 125 MHz, $CDCl_3$): 8.7, 16.9, 19.1, 22.9-34.3, 45.9, 58.8, 70.4-72.1, 171.5, 177.0-177.5; GPC (DMF): $M_n$ = 134000, $M_w$ = 177000, PDI ($M_w/M_n$) = 1.32.

**Polymer 9:** Glycidyl methacrylate (1.8 g, 13 mmol), di(ethylene glycol) methyl ether methacrylate (4.8 g, 26 mmol) together with initiator 2-bromo-2-methylpropanoic acid ethyl ester (0.50 g, 0.26 mmol), ligand 4,4'-dinonyl-2,2'-bipyridine (0.21 g,0.51 mmol) and solvent THF (4 ml) were taken in a schlenk tube and purged with $N_2$ gas for 40 min. After adding copper(I) bromide (38 mg, 0.26 mmol) the solution was stirred for 20 h at room temperature. The polymerization mixture was diluted with dichloromethane and precipitated into diethyl ether, washed twice with fresh diethyl ether, and passed through a small plug of silica gel to give 5.3 g of the polymer after drying under vacuum. $^1$H-NMR (δ, ppm, 300 MHz, $CDCl_3$): 0.55-2.35 (multiple signals from the backbone-H), 2.56 (broad signal, 1H, $COOCH_2CH\mathbf{CH_2}O$), 2.77 (broad signal, 1H, $COOCH_2CH\mathbf{CH_2}O$), 3.14 (broad signal, 1H, $COOCH_2\mathbf{CH}CH_2O$), 3.33 (s, 3H, O$\mathbf{CH_3}$), 3.45-3.68 (broad signal, 6H, $COOCH_2\mathbf{CH_2}O\mathbf{CH_2CH_2}OCH_3$), 3.73 (broad signal, 1H, $COO\mathbf{CH}_2CHCH_2O$), 3.90-4.14 (broad signals, 2H, $COO\mathbf{CH_2}CH_2OCH_2CH_2OCH_2$), 4.14-4.35 (multiple broad signals, $COO\mathbf{CH}_2CHCH_2O$+$CH_3C\mathbf{H_2}O$); GPC ($CHCl_3$): $M_n$ = 42100, $M_w$ = 71800, PDI ($M_w/M_n$) = 1.70.

**Polymer 11:** Glycidyl methacrylate (1.9 g, 14 mmol), poly(ethylene glycol) methyl ether acrylate ($M_n$ = 480) (6.3 g, 13 mmol) together with initiator 2-Bromo-2-methylpropanoic acid ethyl ester (62 mg, 0.32 mmol), ligand 4,4'-Dinonyl-2,2'-bipyridine (0.23 g, 0.55 mmol) and solvent THF (8 mL) were taken in a schlenk tube and purged with $N_2$ gas for 40 min. After adding copper(I) bromide (43 mg, 0.3 mmol) the solution was stirred overnight at room temperature. The polymerization mixture was diluted with dichloromethane and precipitated into diethyl ether, washed twice with fresh diethyl ether, and passed through a small plug of silica gel to give 3 g of the polymer after drying under vacuum. $^1$H-NMR (δ, ppm, 300 MHz, $CDCl_3$): 0.7-2.45 (broad multiple signals from backbone-H), 2.57 (broad signal, 1H, $COOCH_2CH\mathbf{CH_2}O$), 2.77 (broad signal, 1H, $COOCH_2CH\mathbf{CH_2}O$), 3.16 (broad signal, 1H, $COOCH_2\mathbf{CH}CH_2O$), 3.31 (broad signal, 3H, $O\mathbf{CH_3}$), 3.44-3.70 (broad signal, 32H, $O\mathbf{CH_2CH_2}O$), 3.72 (broad signal, 1H, $COOC\mathbf{H}_2CH(O)CH_2$), 3.91-4.45 (broad multiple signals, 3H, $COO\mathbf{CH_2}CH_2OCH_2$+$COOC\mathbf{H}_2CH(O)CH_2$). Please see Figure S1.

**Polymer 12:** To PEG-*r*-poly(glycidyl methacrylate) (1.5 g, 0.13 mmol) dissolved in dry THF (4 ml), thiophenol (0.86 g, 7.8 mmol) and triethylamine (15 mg, 0.14 mmol) were added and were stirred in a round bottom flask for 3 h at room temperature. The polymerization mixture was diluted with dichloromethane and precipitated into diethyl ether, washed twice with fresh diethyl ether, and passed through a small plug of silica gel to give 1.2 g of the polymer after drying under vacuum. $^1$H-NMR (δ, ppm, 300 MHz, $CDCl_3$): 0.7-2.55 (broad multiple signals from backbone-H), 3.05 (broad signal, 2H, $\mathbf{CH_2}SPh$), 3.37 (broad signal, 3H, $O\mathbf{CH_3}$), 3.5-3.8 (multiple broad signals, $O\mathbf{CH_2CH_2}O$+$CH(\mathbf{OH})CH_2SPh$), 3.8-4.40 (multiple broad signals), 7.11-7.5 (m, 5H, S**Ph**). Please see Figure S1.

**Polymer 13:**

Reaction of polymer **12** with adamantane-1-carbonyl chloride was carried out in a similar fashion as described for polymer **4**. The polymer was purified by passing through a short plug of silica gel using dichloromethane/methanol (75/15) solvent mixture. $^1$H-NMR (δ, ppm, 300 MHz, $CDCl_3$): 0.65-2 (broad multiple signals from backbone-H and adamantane moiety), 3.04 (broad signal, 2H, $\mathbf{CH_2}SPh$), 3.37 (broad signal, 3H, $O\mathbf{CH_3}$), 3.47-3.80 (broad signal, $O\mathbf{CH_2CH_2}O$), 3.80-4.50 (multiple broad signals, 4H, $COO\mathbf{CH_2}$), 5.11 (broad signal, 1H, $OCH_2C\mathbf{H}(OCO)CH_2SPh$), 7.0-7.5 (multiple broad signals, 5H, S**Ph**). Please see Figure S1.

Table 1. Solubility behaviour of the copolymers.

| Polymer | Heptane | Toluene | $CHCl_3$ | $CH_2Cl_2$ | $CH_3OH$ | $H_2O$ |
|---|---|---|---|---|---|---|
| **2** | - | - | + | + | - | -[a] |
| **3** | - | - | + | + | - | - |
| **4** | - | - | + | + | - | - |
| **6** | - | - | + | + | + | + |
| **7** | + | + | + | + | - | - |
| **9** | - | + | + | + | - | - |
| **11** | - | + | + | + | + | + |
| **12** | - | + | + | + | + | + |
| **13** | - | + | + | + | + | + |

- = insoluble, + = soluble

[a] Solubility of the scaffold **2** is governed by the length of the PGMA block. Hence, if required, water-soluble scaffolds can be obtained by reducing the length of the second block (i.e., via decreasing the polymerization temperature and/or time). Please also see comment 8 in General Comments.

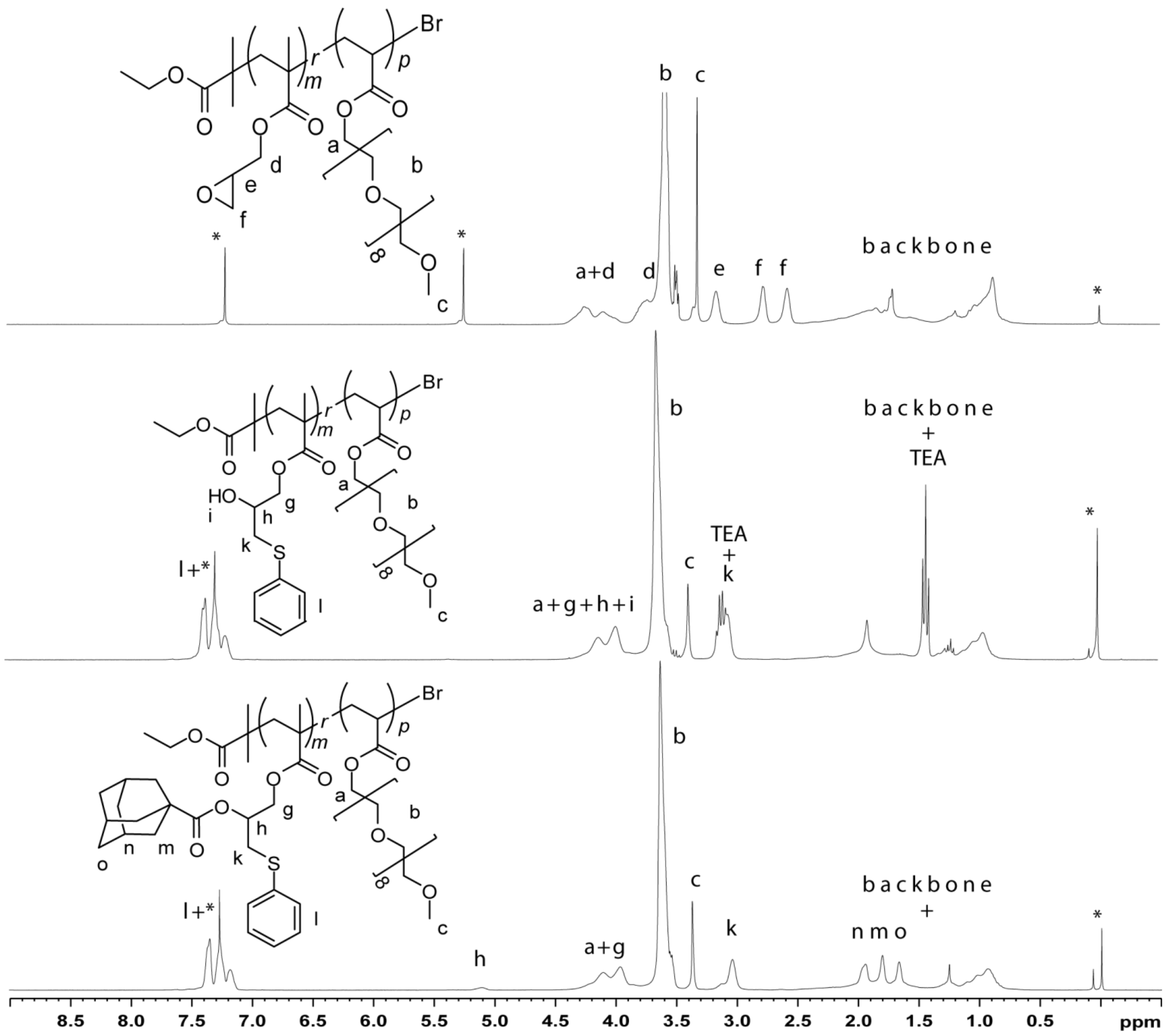

Figure S1. $^1$H-NMR of polymers **11**, **12**, and **13**. Signals from tetramethylsilane, dichloromethane, and chloroform are shown with the help of asterisks. TEA stands for triethylamine.

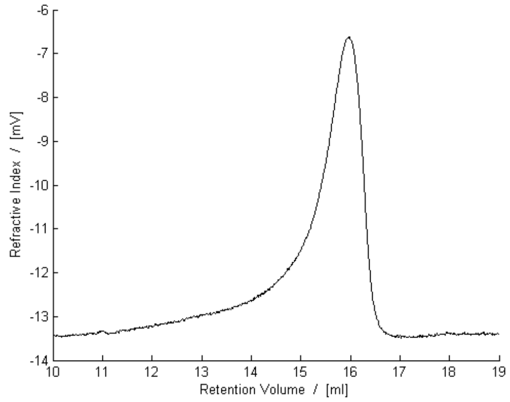

Figure S2. GPC trace of polymer **11** in chloroform.

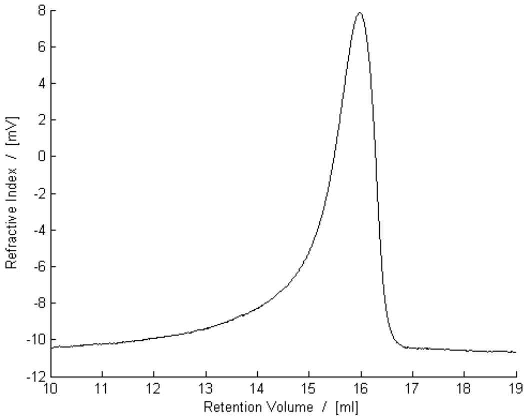

Figure S3. GPC trace of polymer **12** in chloroform.

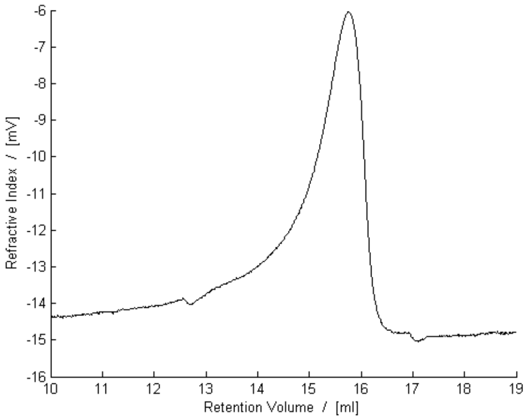

Figure S4. GPC trace of polymer **13** in chloroform.

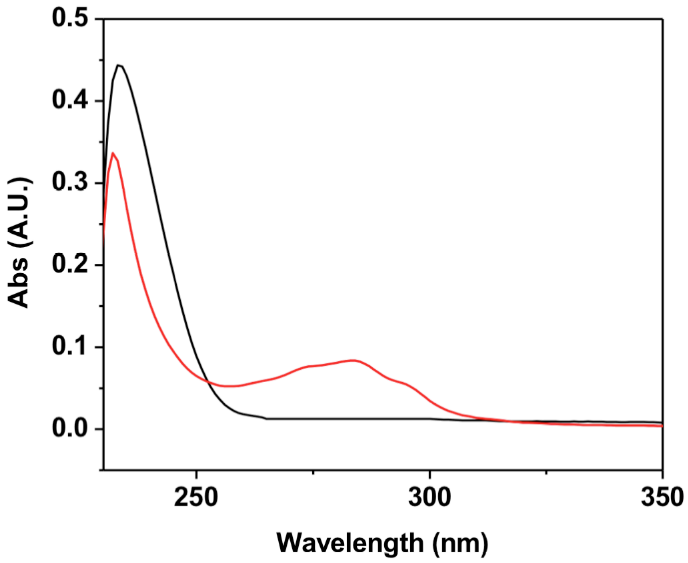

Figure S5. UV/Vis absorption spectra of polymers **3** (black) and **4** (red).