Supporting Information

One-pot Double Modification of p(NIPAAm): A Tool for Designing Tailor-Made Multiresponsive Polymers

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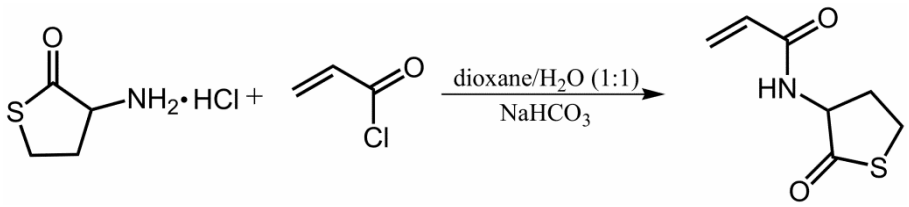
Materials

Tetrahydrofuran (Aldrich, HPLC grade) was purified by distillation over sodium/benzophenone and kept under nitrogen before usage. *N*-Isopropyl acrylamide (NIPAAm) (Aldrich, 97 %) was recrystallized from a mixture of toluene/*n*-hexane (1:1 v/v). 2,2'-Azobis(isobutyronitrile) (AIBN) (Aldrich) was recrystallized twice from methanol. *N*,*N*-dimethyl acrylamide (DMA) (Aldrich, 99 %) was passed over a column filled with activated, basic alumina (Aldrich, Brockmann I) before usage. 2-{[(Butylsulfanyl)-carbonothioyl]sulfanyl}propanoic acid was synthesized according to a recipe described elsewhere.[1] 3-(Aminopropyloxy)azobenzene was synthesized from 4-phenylazophenol and 3-aminopropylbromide hydrobromide in *N*,*N*-dimethyl formamide (DMF) in the presence of NaOH according to the procedure published by Freitag et al.[2] The synthesis of 1-ethoxyethyl acrylate (EEA) is also described elsewhere.[3] The following chemicals were used as received: chloroform (Aldrich, HPLC grade), 1,4-dioxane (Acros, 99+ %), DMF (Aldrich, 99.8 %, water free), ethyl acetate (Aldrich, HPLC grade), D,L-homocysteinethiolactone hydrochloride (Acros, 99 %), acryloylchloride (ABCR, 96 %), benzylamine (Aldrich, 99.5 %), *n*-octylamine (Aldrich, 99 %), 4-fluorobenzylamine (Acros, 97 %), ethanolamine (Fluka, ≥ 99 %), *N*,*N*-dimethylethylenediamine (Aldrich), furfurylamine (Acros, 99+ %), 3-morpholinopropylamine (Aldrich), *n*-propylamine (Fluka, ≥ 99 %), methyl acrylate (Fluka, ≥ 99 %), 2,2,2-trifluoroethyl acrylate (TCI, ≥ 98 %), 2-hydroxyethyl acrylate (TCI, ≥ 96 %), isobornyl acrylate (TCI, ≥ 93 %), 2-(2-ethoxyethoxy)ethyl acrylate (TCI, ≥ 98 %) and benzyl acrylate (ABCR, 95 %).

Synthesis of Thiolactone acrylamide (TlaAm)

An ice-cooled solution of D,L-homocysteine thiolactone hydrochloride (7.0 g, 45.6 mmol) in H_2O/1,4-dioxane (1/1, 100 mL) was treated with $NaHCO_3$ (19.15 g, 227.9 mmol) and stirred for 30 minutes at 0 °C. Acryloyl chloride (8.3 g, 91.2 mmol) was added to the mixture dropwise. The reaction mixture was allowed to reach room temperature overnight. Brine (100 mL) was added and the mixture was extracted with EtOAc (3 x 200 mL). The collected organic fractions were dried (Na_2SO_4) and subsequently the solvent was removed. The crude residue was purified by recrystallization from dichloromethane, yielding TlaAm as a white, crystalline solid (6.4 g, 37.3 mmol, 82 %). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) (Figure S1) δ 8.45 (*d*, 1 H, 8.2 Hz), 6.23 (*dd*, 1 H, 17.1, 9.7 Hz), 6.12 (*dd*, 1 H, 17.1, 2.6 Hz), 5.65 (*dd*, 1 H, 9.7, 2.6 Hz), 4.70 (*ddd*, 1 H, 15.3, 8.2, 7.1 Hz), 3.42 (*app dt*, 1 H, 11.3, 5.3 Hz), 3.30 (*ddd*, 1 H, 10.9, 6.9, 1.4 Hz), 2.44 (*m*, 1 H), 2.09 (*m*, 1 H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 205.3 (C), 164.6 (C), 131.0 (CH), 126.2 (CH_2), 58.2 (CH), 30.3 (CH_2), 26.8 (CH_2).



Scheme S1. One step synthesis of TlaAm.

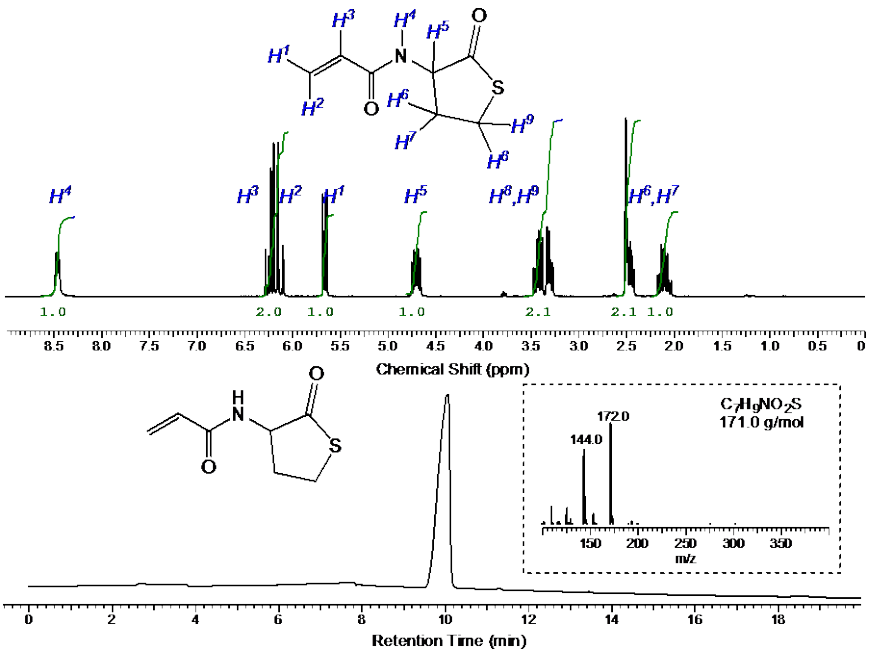
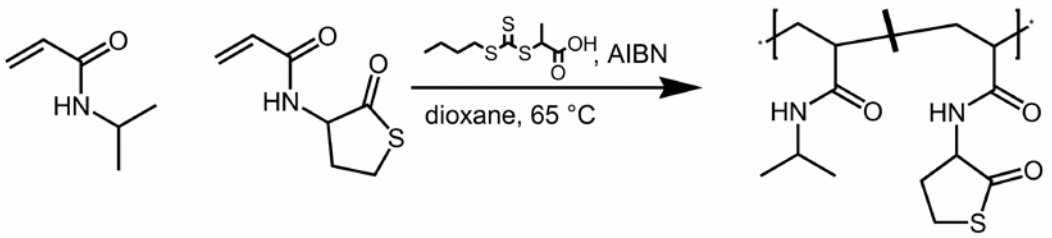


Figure S1 - ^{1}H-NMR spectrum (300 MHz, DMSO-d_6) with peak assignment and integration (*top)* and HPLC trace with MS analysis (positive mode) of the dominant species (*bottom*) of the purified TlaAm.

Synthesis of P(NIPAAm-*co*-TLaAm) and P(NIPAAm-*co*-DMA-*co*-TlaAm)

In a typical procedure 4.96 g (43.9 mmol) NIPAAm, 1.87 g (10.9 mmol) TlaAm, 11.8 mg (0.07 mmol) AIBN and 176 mg (0.74 mmol) 2-{[(butylsulfanyl)-carbonothioyl]sulfanyl}propanoic acid were dissolved in 20 mL dioxane ($[M]_0$/[CTA]/[AIBN] = 75/1/0.1). The solution was transferred into a Schlenk tube and degassed by 4-5 freeze-pump-thaw cycles. After that, the tube was immersed in a thermostated oil bath set to 65 °C and the solution was stirred for 4 hours. The polymerization was stopped by immersing the Schlenk tube in an ice/water bath followed by exposure of the polymerization solution to air. The final polymer was obtained by repeated precipitation into diethyl ether. P(NIPAAm-*co*-DMA-*co*-TlaAm) was synthesized in an analogue procedure. Table 1 (see main manuscript) summarizes all synthesized polymers including molecular characteristics.



Scheme S2. RAFT copolymerization of NIPAAm and TlaAm.

Preliminary observations from kinetic measurements (not shown here) revealed that the TlaAm content increases with increasing conversion, which means that the resulting polymers exhibit a compositional gradient along the chain. However, we expect this gradient to be limited, since all synthesized polymers (except the water insoluble P3, Table 1) still show a rather sharp coil-to-globule transition in water upon heating (Figure S8).

P(NIPAAm-*co*-TlaAm) with TlaAm contents of at least 50 mol% can be easily synthesized. , However, controlled homopolymerization *via* RAFT of TlaAm is not possible due to solubility issues.

Double modification of p(NIPAAm-*co*-TlaAm)

In a typical procedure, 100 mg of P1 was dissolved in 1 mL $CHCl_3$ followed by the addition of 133 µl (0.88 mmol) benzyl acrylate. After addition of 78 µL (0.88 mmol) furfurylamine, the solution was stirred for at least 3 hours and the product was finally obtained by repeated precipitation in diethyl ether. Products which were not precipitating were purified by dialysis in acetone using a SpectraPor™ regenerated cellulose membrane (MWCO = 3500). Polymers

modified with ethanolamine were dialysed in water using the same membrane. Typical yields were in the range of 60-70%. Figure S2 shows different reaction solutions being poured into diethylether after the modification reaction. The different precipitation behavior is a first indication for a successful modification of the polymer precursor.

Figure S2. Different batches after modification being poured into diethyl ether after 3 hours reaction time. The amine/acrylate combinations used are: 1) 4-fluorobenzylamine/ 2,2,2-trifluoroethyl acrylate; 2) ethanolamine/ hydroxyethyl acrylate; 3) *n*-octylamine/ isobornyl acrylate; 4) ethanolamine/ isobornylacrylate; 5) *n*-octylamine/ hydroxyethyl acrylate. In each case, P1 (see Table S1) was used as polymer precursor.

LC-MS analysis

An Agilent technologies 1100 series LC/MSD system equipped with a diode array detector and single quad MS detector (VL) with an electrospray source (ESI-MS) was used for classic reversed phase LC-MS (liquid chromatography mass spectroscopy) and MS analysis. Analytic reversed phase HPLC was performed with a Phenomenex C_{18} (2) column (5 µ, 250 x 4.6 mm) using a solvent gradient (0 → 100% acetonitrile in H_2O in 15 min) and the eluting compounds were detected *via* UV-detection (λ = 214 nm).

SEC analysis

Size exclusion chromatography (SEC) was performed on a Waters instrument with a Waters 2414 Refractive Index Detector, equipped with 3 PSS serial columns (GRAM Analytical 30 and 1,000 Å, 10 µm particle size) at 35 °C. Poly(methyl methacrylate) standards were used for calibration and DMA containing LiBr (0.42 g/L) was used as an eluent at a flow rate of 1 mL/min. Molecular weights and dispersities (Đ) were determined using the Empower software. Figure S3 shows the SEC-traces of a representative selection of modified polymers, clearly indicating a molecular weight shift while Đ is maintained (see also Table 1).

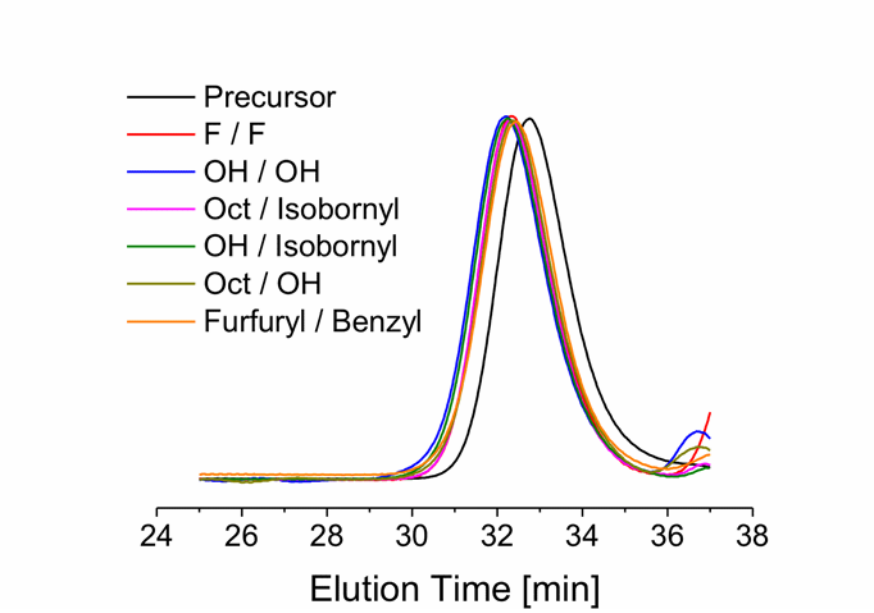


Figure S3. SEC-traces of P1 (Table 1) and a selection of corresponding modified polymers. Codes: F / F - 4-fluorobenzylamine/ 2,2,2-trifluoroethyl acrylate (entry #2, Table 2); OH / OH - ethanolamine/ hydroxyethyl acrylate (entry #3, Table 2); Oct / Isobornyl - *n*-octylamine/ isobornyl acrylate (entry #4, Table 2); OH / Isobornyl - ethanolamine/ isobornylacrylate (entry #5, Table 2); Oct / OH - octylamine/ hydroxyethyl acrylate; Furfuryl (entry #6, Table 2) / Benzyl – furfurylamine/ benzyl acrylate (entry #10, Table 2).

Figure S4 shows the SEC traces of P1 being functionalized with the combination benzylamine / methyl acrylate in untreated THF and in THF dried over sodium. One can clearly see the influence of peroxides present in the untreated THF, which act as oxidation agent and therefore accelerate the oxidation of the thiol groups into disulfide bridges. Consequently a dominant high molecular weight shoulder appears.

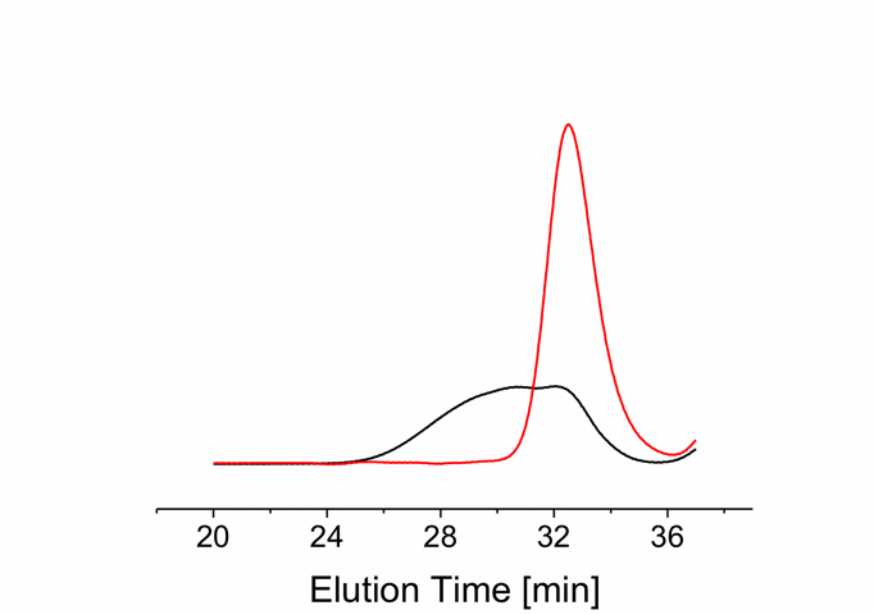


Figure S4. SEC traces of P1 functionalized with the combination benzylamine/ methyl acrylate in untreated THF (black curve) and in THF dried over sodium.

NMR analysis

^{1}H- and ^{13}C-NMR (Attached Proton Test, APT) spectra were recorded in $CDCl_3$ (Eurisotop) on a Bruker AM500 spectrometer at 500 MHz or on a Bruker Avance 300 at 300 MHz. Chemical shifts are presented in parts per million (d) relative to $CDCl_3$ (7.26 ppm in ^{1}H- and 77.23 ppm in ^{13}C-NMR) as the internal standard. All ^{19}F NMR experiments were performed on a Bruker Avance 300 spectrometer equipped with a 5 mm BBO gradient probe, by tuning the ^{1}H channel (300.13 MHz) to the nearby ^{19}F frequency (282.40 MHz).

Figure S5 shows excerpts of the ^{1}H-NMR spectra of P1 (Table 1) and modification batch #7 (Table 2), clearly demonstrating the full disappearance of the doublet signal originating from the thiolactone ring after modification.

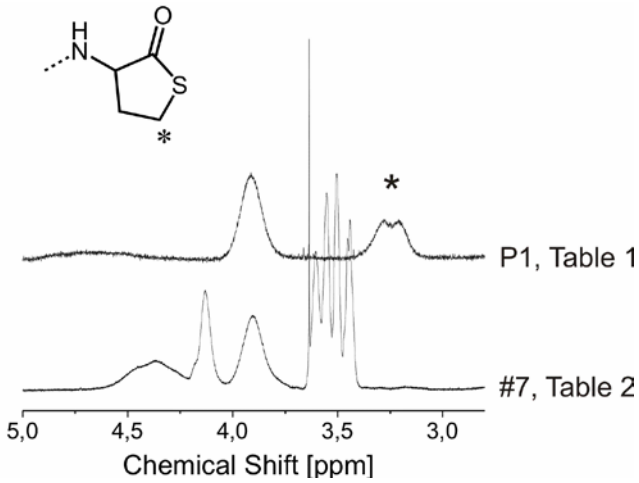


Figure S5. Excerpts of ^{1}H-NMR traces of P1 (Table 1) and P1 being functionalized with benzylamine/ 2-(2-ethoxyethoxy)ethyl acrylate (entry #7, Table 2); 300 MHz, $CDCl_3$.

Figure S6 shows the ^{19}F-NMR spectrum of P1 being functionalized with the combination 4-fluorobenzylamine/2,2,2-trifluoroethyl acrylate. The detected ratio of the integrals of both peaks is 2.9/1 fitting well with the theoretical value of 3/1.

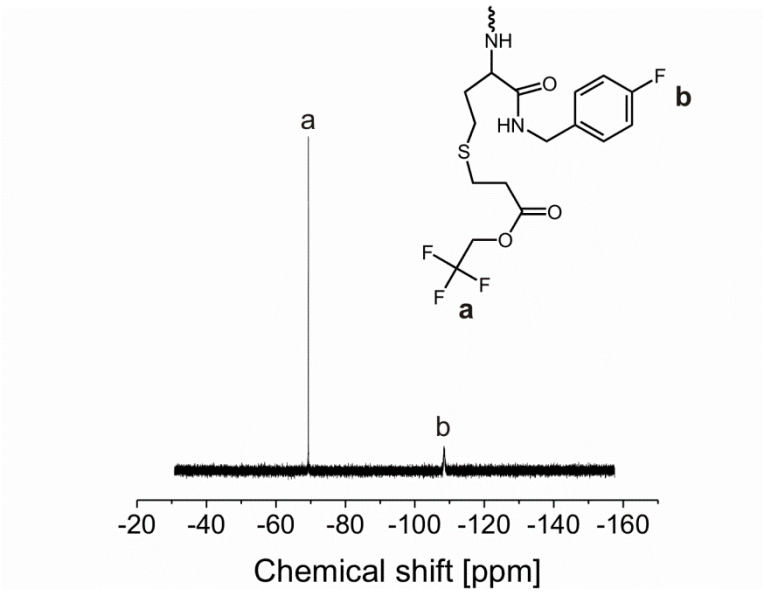


Figure S6. ^{19}F-NMR trace of P1 being functionalized with the combination 4-fluorobenzylamine/ 2,2,2-trifluoroethyl acrylate (500 MHz, $CDCl_3$)

Figure S7 shows excerpts of ^{1}H-NMR traces of P2 being functionalized with the combination *N*,*N*-dimethylethylenediamine / 2-(2-ethoxyethoxy)ethyl acrylate using varying (substoechiometric) amounts of the amine. Table S1 summarizes the detected degrees of functionalization in comparison with the composition of the reaction mixture. It is noted that a slight overlap of the signals of interest with others appearing in the NMR traces most probably causes some deviation from the real degrees of functionalization.

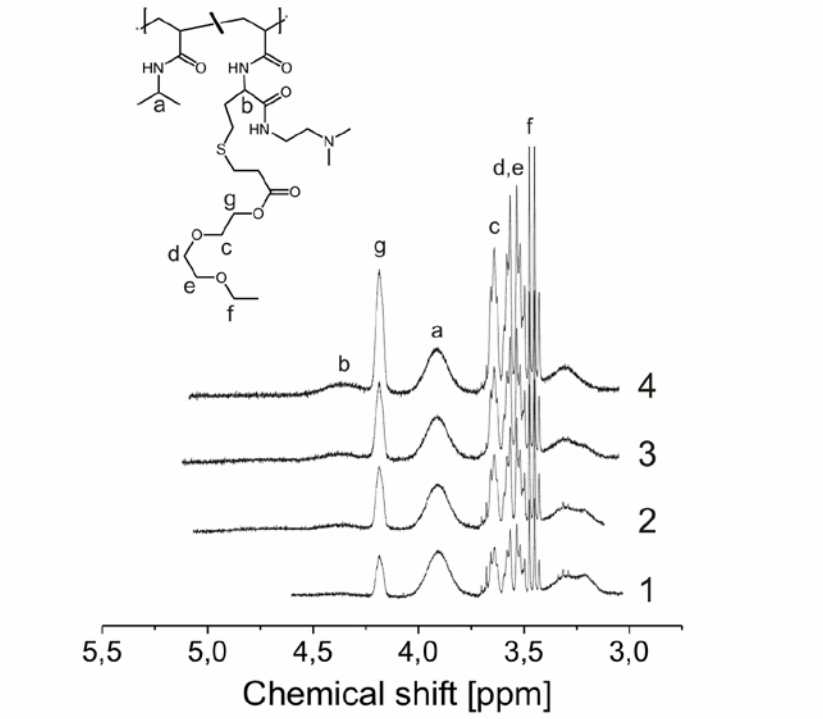


Figure S7. Excerpts of ^{1}H-NMR traces of P2 being functionalized with the combination N,N-diethylene diamine / 2-(2-ethoxyethoxy)ethyl acrylate using varying (substoechiometric) amounts of the amine (300 MHz, $CDCl_3$)

Table S1. Degrees of functionalization of P2 modified with N,N-dimethylethylene diamine/ 2-(2-ethoxyethoxy)ethyl acrylate in comparison with initial amine/ thiolactone ratios.

Entry	n_{amine}/ $n_{thiolactone}$ in the reaction mixture	Final degree of functionalization[a)]
1	0.25 / 1	39
2	0.5 / 1	54
3	0.75 / 1	65
4	2 / 1	94

a) Determined via ^{1}H-NMR by comparing the signals at 4.2 and 3.9 ppm (signals a and b in Figure S5).

Turbidity measurements

Turbidimetry measurements were performed on a CARY Bio 100 UV-VIS spectrophotometer equipped with a temperature controller, using a light source of 600 nm. The heating rate was set to 1 K/min for each measurement. In the case of azobenzene functionalized PNIPAAm, the freshly prepared solution was irradiated prior to the measurement with a 450 nm custom made LED device or 365 nm UV lamps (2 W/cm^2) positioned in a metal container for half an hour respectively. Figure S8 shows the transmittance as a function of temperature for P1 and P3 (Table 1). The low transmittance of P1 also at low temperatures can be attributed to an incomplete dissolution of the precursor. P2 was insoluble in water.

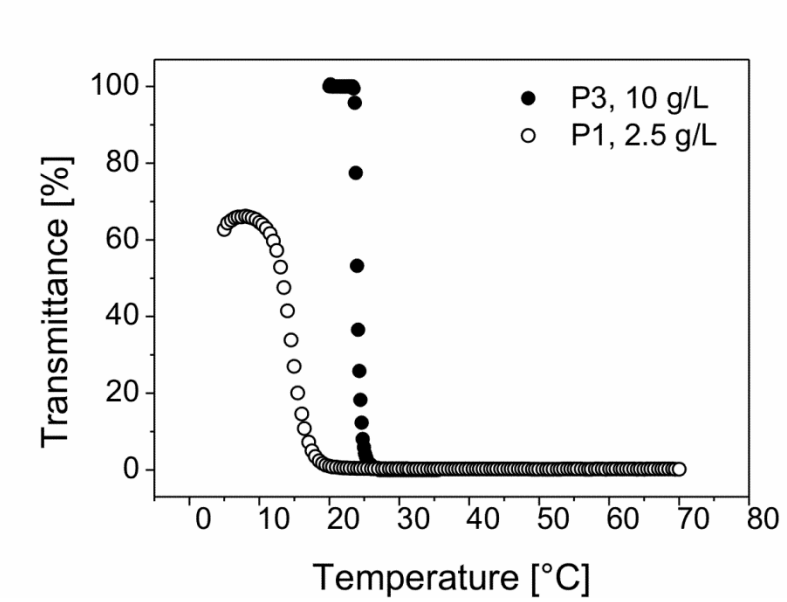


Figure S8. Transmittance as a function of temperature for aqueous solutions of the p(NIPAAm-*co*-TlaAm) precursors P1 and P3 (Table 1). The polymers were dissolved in Millipore water.

References

(1) Ferguson, C. J.; Hughes, R. J.; Nguyen, D.; Pham, B. T. T.; Gilbert, R. G.; Serelis, A. K.; Such, C. H.; Hawkett, B. S. *Macromolecules* 2005, *38*, 2191-2204.

(2) Desponds, A.; Freitag, R. *Langmuir* 2003, *19*, 6261-6270.

(3) Van Camp, W.; Du Prez, F. E.; Bon, S. A. F. *Macromolecules* 2004, *37*, 6673-6675.