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Copolymerization of 2-Hydroxyethyl Acrylate and 2-Methoxyethyl Acrylate via RAFT: Kinetics and Thermoresponsive Properties

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ABSTRACT: Kinetic studies of the (co)polymerization of 2-hydroxyethyl acrylate (HEA) and/or 2-methoxyethyl acrylate (MEA) via reversible addition−fragmentation chain transfer polymerization (RAFT), using dibenzyltrithiocarbonate (DBTTC) as chain-transfer agent, resulting in well-defined copolymers, are presented. Both monomers were found to have equal reactivity revealing the formation of ideal random (azeotropic) copolymers. The thermoresponsive properties of aqueous solutions of the copolymers at 5 mg/mL, depending on the polymer composition, the chain length, and the end-groups, were investigated. The cloud point (CP) of the synthesized copolymers increases with the content of HEA and decreases with the decreasing chain length. Exchanging one of the hydrophobic benzylic end-groups of the copolymers by isobutyronitrile resulted in more hydrophilic copolymers with significantly higher CP-temperatures. Thus, new potential biomaterials with an adjustable cloud point between 0 and 60 °C, showing a small hysteresis between heating and cooling, were successfully prepared.

Introduction

Thermoresponsive polymers have gained significant interest in biomedical applications[1−3] due to their manifold uses in different areas such as controlled drug delivery,[4−6] biomolecule separation,[7,8] sensors,[9,10] and switchable cell adhesion.[11,12] Many of these thermoresponsive materials are based on polymers exhibiting a lower critical solution temperature (LCST), meaning that they undergo an abrupt change in solubility at a certain temperature in aqueous solutions; i.e., increasing the environmental temperature leads to precipitation of the polymer.[13] Currently, poly(*N*-isopropylacrylamide) (PNIPAM) is the most studied LCST polymer showing a robust transition close to body temperature,[14,15] and is relatively insensitive to changes in concentration and pH. Nevertheless, an increasing number of polymers has recently been introduced as potential alternatives to PNIPAM including poly(methoxy oligoethylene glycol methacrylate)s[16,17] and poly(2-oxazoline)s.[18−20]

Tanaka et al. synthesized a biocompatible polyacrylate, poly(2-methoxyethyl acrylate) (PMEA) and reported that it has an excellent blood compatibility featuring a significantly low adsorption of plasma protein and low platelet adhesion in comparison with other poly(acrylate)s.[21] PMEA is expected to be a promising biomaterial and is now commercially used as coating material for artificial organs.[22] In combination with more hydrophilic monomers such as *N,N*-dimethylacrylamide, 2-methoxyethyl acrylate is known to exhibit a LCST transition in water.[23]

In addition, the synthesis of 2-hydroxyethyl acrylate (HEA) based thermoresponsive copolymers with the more hydrophobic vinyl butyl ether, *n*-butyl acrylate, or 2-hydroxyethyl methacrylate has been reported in the literature.[24−27] In fact, PHEA is a biocompatible material[26−30] with similar properties as the widespread poly(2-hydroxyethyl methacrylate), used for example as material for contact lenses.

Many of the investigations performed with these materials dealt with ill-defined polymers due to the fact that they were prepared by free radical polymerization and copolymerization. Recently, we reported the nitroxide mediated copolymerization of 2-hydroxypropyl acrylate with a variety of comonomers, including HEA, resulting in well-defined thermoresponsive copolymers.[31,32]

The preparation of well-defined polyacrylates with controlled microstructures end-functionalities is a basic requirement for the development of functional biomaterials with thermoresponsive properties. To achieve this aim, controlled radical polymerization techniques, such as atom transfer radical polymerization (ATRP),[33,34] reversible addition−fragmentation chain transfer (RAFT)[35,36] and nitroxide-mediated radical polymerization (NMP),[37−39] were used. Even though it is known that HEA and MEA can both be polymerized in a controlled manner, their copolymerization has not been reported so far.[40−44]

In the present study we investigated the (co)polymerization of MEA and HEA via reversible addition−fragmentation chain transfer (RAFT) polymerization and obtained well-defined copolymers with tunable cloud point temperatures. The polymerization kinetics as well as the reactivity ratios were determined providing insight in the polymer microstructure. Furthermore, the influence of the polymer microstructure and the influence of the end groups on the cloud points of the copolymers was determined and the effect of both the ratio of hydrophilic and hydrophobic monomers and the effect of the end-groups on the cloud points are discussed.

Experimental Section

Materials and instrumentation. *N,N*-Dimethylformamide (DMF), 2-hydroxyethyl acrylate (HEA) and 2-methoxyethyl acrylate (MEA) were obtained from Sigma-Aldrich. HEA and MEA were passed through a neutral aluminum oxide column before use to remove the inhibitor. Dibenzyltrithiocarbonate (DBTTC) was kindly provided by Arkema and used as received. 2,2′-Azobis(isobutyronitrile) (AIBN) was obtained from Aldrich and purified by double recrystallization in methanol.

^{1}H NMR spectra were recorded on a Bruker DPX-400 FT-NMR spectrometer at 400 MHz, using deuterated dimethyl

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sulfoxide (DMSO-d_6) as solvent, and tetramethylsilane (TMS) served as an internal standard. The overall monomer conversions for the HEA and MEA homopolymerizations were calculated from the ^{1}H NMR spectra using the integral of the acrylate signals (δ = 6.4−5.8 ppm) and the integral of the CH_2− units next to the hydroxy- or methoxy-groups (δ = 3.7−3.5 ppm), respectively. For the copolymerizations, the overall conversions were calculated as described for the homopolymerizations. Thus, the MEA conversion was calculated using the ratio of the acrylate signals of the monomer (δ = 3.38−3.36 and 6.33−6.30 ppm) and the methyl signal of the methoxy-group (δ = 3.2−3.3 ppm). The HEA conversion was calculated using the ratio of the acrylate signals of the monomer (δ = 3.40−3.38 and 6.36−6.33 ppm) and the integral of the CH_2− units next to the hydroxy- or methoxy-group (δ = 3.7−3.5 ppm) and subtraction of the integral of the CH_2− units next to the methoxy-group of PMEA.

Size exclusion chromatography (SEC) was measured on a combined SEC system with a high pressure liquid chromatography pump (Bischoff HPLC), a Jasco 2035-plus RI detector and four MZ-DVB gel columns (30, 100, and 2 × 3000 Å) in series at 30 °C. A solution of DMF containing 1.0 g LiBr/L was used as eluent at a flow rate of 1.0 mL/min. SEC of the polymers was performed in DMF (as mentioned above) or in THF with 0.25 g 2,6-di-*tert*-butyl-4-methylphenol/L using a high-performance liquid chromatography pump (ERC HPLC 64200) equipped with a RI Jasco detector. Adequate molecular weight separation was achieved using five MZ gel columns in series at a flow rate of 1.0 mL/min and a temperature of 20 °C. The diameter of each column was 8 mm, the nominal pore width were 50, 50, 100, 1000, and 10000 Å, respectively. The molecular weights were calculated using a poly(methyl methacrylate) (PMMA) calibration and the PSS WinGPC Unity software.

Cloud points of aqueous polymer solutions were determined by turbidity measurements in a Crystal 16 by Avantium Technologies. Four blocks of four parallel temperature controlled sample holders are connected to a Julabo FP40 cryostat allowing 16 simultaneous measurements. Turbidity of the solutions was measured by the transmission of red light through the sample vial as a function of the temperature. Solutions of the polymers were prepared in deionized water and were stirred at room temperature until all polymer was dissolved or dispersed. Two heating/cooling cycles were applied from 0 to 80 °C at 1.0 °C/min with hold steps of 5 min at the extreme temperatures. The cloud points are given as the 50% transmittance point during the second heating ramp.

Polymerizations. Synthesis of Poly(2-hydroxyethyl acrylate) as a Representative Example. 2-Hydroxyethyl acrylate (2.91 g, 25 mmol) and dibenzyltrithiocarbonate (0.07 g, 0.25 mmol) were dissolved in DMF (12.5 mL). After degassing the solution three times by freeze-vacuum-thaw cycles, the mixture was immersed in an oil bath thermostated at 70 °C while stirring. The polymerization was started by adding AIBN (0.01 g, 0.05 mmol) and proceeded for 3 h at 70 °C. Poly(2-hydroxyethyl acrylate) was isolated and purified by triple precipitation in *n*-hexane/diethyl ether (1:1), collected and dried under reduced pressure at room temperature.

PHEA: $M_{n,SEC}$(DMF) = 8000 g/mol; M_w/M_n = 1.2 monomodal. ^{1}H NMR (DMSO-d_6): δ 1.2−2.0 (b, −C*H*$_2$−CH−(−C(O)OR)−), 2.1−2.4 (b, −CH$_2$−C*H*−(−C(O)OR)−), 3.4−3.7 (b, −C(O)O−*C*H$_2$−*CH*$_2$−OH), 3.8−4.2 (b, −C(O)O−*CH*$_2$−CH$_2$−OH), 4.7−4.9 (b, −O*H*), 7.1−7.4 (m, Ar−*H*) ppm. PMEA: $M_{n,SEC}$(DMF) = 12100 g/mol; M_w/M_n = 1.3 monomodal. ^{1}H NMR (DMSO-d_6): δ 1.3−1.9 (b, −C*H*$_2$−CH−(−C(O)OR)−), 2.2−2.4 (b, −CH$_2$−C*H*−(−C(O)OR)−), 3.2−3.3 (b, −O−*CH*$_3$), 3.4−3.6 (b, −C(O)O−*C*H$_2$−*CH*$_2$−O−CH$_3$), 4.0−4.2 (b, −C(O)O−*CH*$_2$−CH$_2$−O−CH$_3$), 7.1−7.4 (m, Ar−*H*) ppm.

Poly(2-methoxyethyl acrylate) and HEA/MEA random copolymers with different content of HEA were synthesized according to the above-described procedure using different molar ratios of the comonomers in the feed (Table 1). Polymers with various degrees of polymerization were obtained using a ratio of [M]:[DBTTC]:[I] = 100:1.0:0.2 and different reaction time. The results are summarized in Table 2.

For the kinetic investigations, samples (200 μL) were taken from the polymerization mixture after 15, 30, 60, 120, 240, 300, 360, 540, 720, and 1440 min. The obtained polymers were characterized using SEC and ^{1}H NMR spectroscopy.

Table 1. Conditions for the Homo- and Copolymerizations of 2-Hydroxyethyl Acrylate and 2-Methoxyethyl Acrylate via RAFT in DMF at 70 °C Using DBTTC as RAFT Agent and AIBN as Initiator ([M]:[DBTTC]:[I] = 100:1.0:0.2).[a]

	comonomers			
monomer mixture	HEA [g]/[mmol]	MEA [g]/[mmol]	C_0 ΣM [mol/L]	t/T [h]/[°C]
M1	-	3.26/25.05	1.59	3/70
M2	0.30/2.58	2.93/22.51	1.59	3/70
M3	0.29/2.50	2.92/22.44	1.58	3/70
M4	0.58/5.00	2.61/20.06	1.59	3/70
M5	0.87/7.49	2.28/17.52	1.59	3/70
M6	0.87/7.49	2.27/17.44	1.59	3/70
M7	1.17/10.08	1.95/14.98	1.60	3/70
M8	1.45/12.49	1.63/12.52	1.60	3/70
M9	1.74/14.98	1.30/9.99	1.60	3/70
M10	2.03/17.48	0.98/7.53	1.61	3/70
M11	2.03/17.48	0.98/7.53	1.61	3/70
M12	2.32/19.98	0.66/5.07	1.61	3/70
M13	2.62/22.56	0.33/2.54	1.62	3/70
M14	2.91/25.06	-	1.62	3/70
M15	-	3.25/24.97	1.58	1/70
M16	0.58/4.99	2.60/19.98	1.62	1/70
M17	1.74/14.98	1.31/10.07	1.61	1/70
M18	1.74/14.98	1.30/9.99	1.60	1/70
M19	2.03/17.48	0.98/7.53	1.61	1/70
M20	2.32/19.98	0.65/4.99	1.61	1/70
M21	2.61/22.48	0.33/2.54	1.62	1/70
M22	2.90/24.97	-	1.62	1/70

[a] DMF: 12.5 mL; DBTTC: 0.07 g (0.25 mmol); AIBN: 0.01 g (0.05 mmol).

Table 2. Characterization of Homo- and Copolymers of 2-Hydroxyethyl Acrylate and 2-Methoxyethyl Acrylate Synthesized via RAFT in DMF at 70 °C Using DBTTC as RAFT Agent and AIBN as Initiator ([M]:[DBTTC]:[I] = 100:1.0:0.2)

polymer	monomer mixture	F_{HEA}[a]	P_n[a]	M_n[b]/ [g/mol]	PDI[b]	CP/[°C][c]
P1	M1	0.00	91	12 100	1.3	-
P2	M2	0.10	90	10 100[d]	1.3[d]	n.d.
P3	M3	0.12	88	11 400	1.3	5.7
P4	M4	0.20	94	11 900	1.3	4.8
P5	M5	0.31	93	11 100	1.4	7.0
P6	M6	0.31	95	9100[d]	1.3[d]	n. d.
P7	M7	0.42	86	10 800	1.3	10.6
P8	M8	0.50	94	11 700	1.4	15.9
P9	M9	0.59	87	11 400	1.3	20.5
P10	M10	0.70	78	9900	1.3	29.0
P11	M11	0.69	86	6800[d]	1.3[d]	n.d.
P12	M12	0.80	93	10 000	1.3	56.8
P13	M13	0.91	90	9100	1.3	-
P14	M14	1.00	96	8000	1.2	-
P15	M15	0.00	35	4400[d]	1.3	-
P16	M16	0.27	45	5300[d]	1.3	-
P17	M17	0.49	35	3600[d]	1.3	-
P18	M18	0.61	34	3400[d]	1.3	-
P19	M19	0.71	36	3100[d]	1.3	6.0
P20	M20	0.81	35	2400[d]	1.3	9.5
P21	M21	0.91	43	1900[d]	1.2	-
P22	M22	1.00	39	1100[d]	1.1	-

[a] Determined using ^{1}H NMR spectroscopy. [b] Determined by SEC (DMF) using PMMA standards. [c] CP (cloud point) determined by turbidimetry with $c_{polymer}$ = 5 mg/mL in water (second heating cycle). [d] Determined by SEC (THF) using PMMA standards.

Table 3. Conditions for the Cleavage of Poly(2-hydroxyethyl acrylate-*co*-2-methoxyethyl acrylate) Using AIBN in DMF at 100 °C for 3 h with [P]:[AIBN] = 1.0:100

	starting polymer			
	M_n[a] [g/mol]	[g]/[mmol]	AIBN [g]/[mmol]	DMF [mL]
P2	11 500	0.50/0.04	0.68/4.14	13.5
P4	12 000	0.30/0.03	0.80/4.87	10.0
P6	11 900	0.50/0.04	0.68/4.14	13.6
P7	10 600	0.50/0.05	0.76/4.63	10.0
P8	11 600	0.50/0.04	0.79/4.81	10.0
P9	10 600	0.42/0.04	0.76/4.63	10.0
P11	10 400	0.51/0.05	0.77/4.69	15.4
P12	11 000	0.42/0.04	0.73/4.45	10.0

[a] Determined and calculated using ^{1}H NMR spectroscopy.

Table 4. Characterization Data of Cleaved Poly(2-hydroxyethyl acrylate-*co*-2-methoxyethyl acrylate) Using AIBN in DMF at 100 °C with [P]:[AIBN] Ratios of 1.0:100

	starting polymer			cleaved polymer			
cleaved polymer	no.	M_n[a] [g/mol]	PDI[a]	$P_n/2$[b]	M_n[c] [g/mol]	PDI[c]	CP [°C][d]
CP2	P2	10 100[c]	1.3[c]	53	6800	1.3	5.2
CP4	P4	11 900	1.2	52	7000	1.3	7.6
CP6	P6	9100[c]	1.3[c]	52	6400	1.3	15.4
CP7	P7	10 800	1.3	52	6200	1.3	18.2
CP8	P8	11 700	1.5	55	6600	1.4	23.2
CP9	P9	11 400	1.4	53	5800	1.4	30.8
CP11	P11	6800[c]	1.3[c]	51	3800	1.4	40.8
CP12	P12	10 000	1.3	47	2900	1.4	-

[a] Determined by SEC (DMF) using PMMA standards. [b] Determined using ^{1}H NMR spectroscopy. [c] Determined by SEC (THF) using PMMA standards. [d] CP (cloud points) determined by turbidimetry with $c_{polymer}$ = 5 mg/mL in water (2nd heating cycle).

General Procedure for the Synthesis of Poly(2-hydroxyethyl acrylate-*co*-2-methoxyethyl acrylate) with $P_n/2$ by Cleavage with AIBN. Poly(2-hydroxyethyl acrylate-*co*-2-methoxyethyl acrylate) (Table 2, P11; 0.51 g, 0.05 mmol) was dissolved in DMF (15.4 mL). After the mixture was immersed in an oil bath and thermostated at 100 °C while stirring, the reaction was started by adding AIBN (0.77 g, 4.69 mmol) and proceeded for 3 h at 100 °C. The resulting copolymer was isolated and purified by precipitation in *n*-hexane/diethyl ether (1:1), collected and dried in vacuum at room temperature.

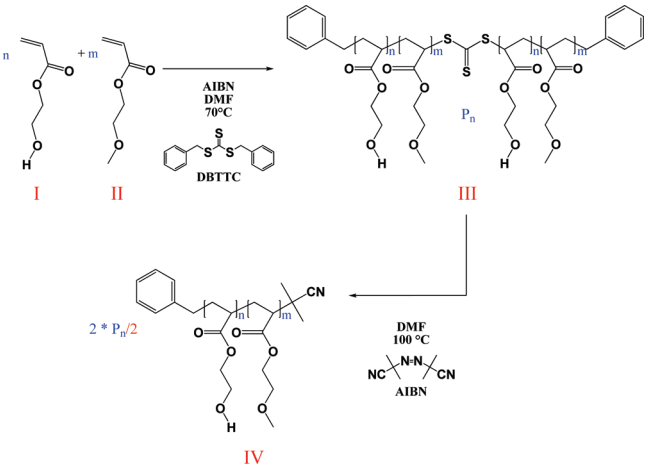
$M_{n,SEC}$(THF) = 3800 g/mol; M_w/M_n = 1.4 monomodal. ^{1}H NMR (DMSO-d_6): δ 1.2−2.0 (b, $-CH_2-CH-(-C(O)OR)-$), 2.1−2.4 (b, $-CH_2-CH-(-C(O)OR)-$), 3.2−3.3 (b, $-O-CH_3$), 3.4−3.7 (b, $-C(O)O-CH_2-CH_2-OH$ and $-C(O)O-CH_2-CH_2-O-CH_3$), 3.8−4.2 (b, $-C(O)O-CH_2-CH_2-OH$ and $-C(O)O-CH_2-CH_2-O-CH_3$), 4.7−4.9 (b, $-OH$), 7.1−7.4 (m, Ar−*H*) ppm.

HEA/MEA random copolymers with different content of HEA and polymerization degree of $P_n/2$ were synthesized according to the above-described procedure with different copolymers in the feed (Table 3). All of the cleavage reactions with AIBN were performed according to the literature in degassed DMF (purged with argon for 1 h).[46] The results are summarized in Table 4.

Results and Discussion

The RAFT (co)polymerization of HEA (I) and MEA (II) was investigated using dibenzyltrithiocarbonate (DBTTC) as RAFT agent and AIBN as the initiator with [M]:[DBTTC]:[AIBN] ratios of 100:1.0:0.2. The (co)polymerizations were performed for 3 h at 70 °C and ~1.6 M monomer concentration in DMF leading to copolymers of the general microstructure III and a degree of polymerization of P_n (Scheme 1). The polymerization was stopped at a conversion of ~80%, which suppresses the occurrence

Scheme 1. Synthesis of P(HEA-*co*-MEA) (III) with Degrees of Polymerization of P_n via RAFT, Followed by Treatment of the Copolymers III with AIBN Leading to P(HEA-*co*-MEA) (IV) with $P_n/2$



of undesired termination reactions that become more likely when less monomer is present. In a second step the copolymers III were treated with AIBN, which generates copolymers (IV) with a polymerization degree of $P_n/2$, the same microstructure, and a converted end-group.

First of all the kinetics of the homopolymerizations were investigated by analyzing samples that were withdrawn from the polymerization mixtures at different time intervals. The first order kinetic plot for the homopolymerizations of HEA or MEA revealed a linear dependence indicating a constant free radical concentration indicative for the absence of significant termination reactions (Figure 1, left; dashed and dotted lines). The linear increase of molecular weight with conversion as well as the relatively narrow molecular weight distributions (polydispersity index (PDI) ≤ 1.40) further demonstrate the control over the polymerization of HEA and MEA (Figure 1, right). Furthermore, the homopolymerization of HEA was reproducibly found to be at a lower rate than the polymerization of MEA, which is not understood at this moment.

The copolymerization of HEA and MEA with 20, 40, 60, and 80 mol % MEA was investigated next. Figure 1 left, clearly demonstrates that the monomer composition does not influence the overall monomer conversion as could be expected from a slightly lower reactivity observed for HEA homopolymerization. The similar polymerization rates for all copolymerizations of HEA and MEA suggest that both monomers have equal reactivity under the applied reaction conditions. A linear increase of M_n with $M_{n,th}$ and low PDI values (Figure 1, right) were observed for all copolymerizations demonstrating that these proceeded in a controlled manner. [An example of the obtained SEC elugrams of the kinetic study of the copolymerization of 2-hydroxyethyl acrylate (HEA; f_{HEA} = 0.6) with 2-methoxyethyl acrylate (MEA; f_{MEA} = 0.4) in THF is given in Figure S3 (Supporting Information)].

The evolution of monomer composition with overall monomer conversion was determined by ^{1}H NMR spectroscopy and is depicted in Figure 2, left. The incorporated HEA fraction (F_{HEA}) is close to the HEA fraction in the feed (dotted lines) for all four copolymerizations at all conversions indicating an ideal random (azeotropic) copolymerization of both monomers. The exception on the close proximity of F_{HEA} with f_{HEA} are the copolymerizations containing 40 and 60 mol % of MEA at low conversions (< 20%), showing a larger scatter of F_{HEA} around the theoretical composition, which can be ascribed to inaccuracies in the peak deconvolution in the ^{1}H NMR spectra. To be able to determine the reactivity ratios, F_{HEA} was calculated at ~10% monomer

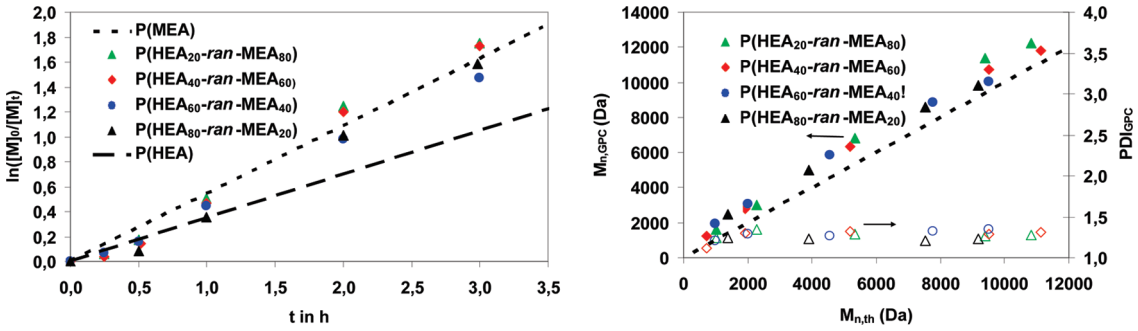


Figure 1. Left: Kinetic plot of $\ln([M]_0/[M]_t)$ versus time in the RAFT polymerizations of 2-hydroxyethyl acrylate (HEA) and 2-methoxyethyl acrylate (HEA). Right: Plot of the experimental number-average molecular weight (M_n) and polydispersity index (PDI) versus theoretical number-average molecular weight ($M_{n,th}$; calculated from the monomer to initiator ratio and monomer conversion). The dashed line represents the ideal situation where $M_n = M_{n,th}$.

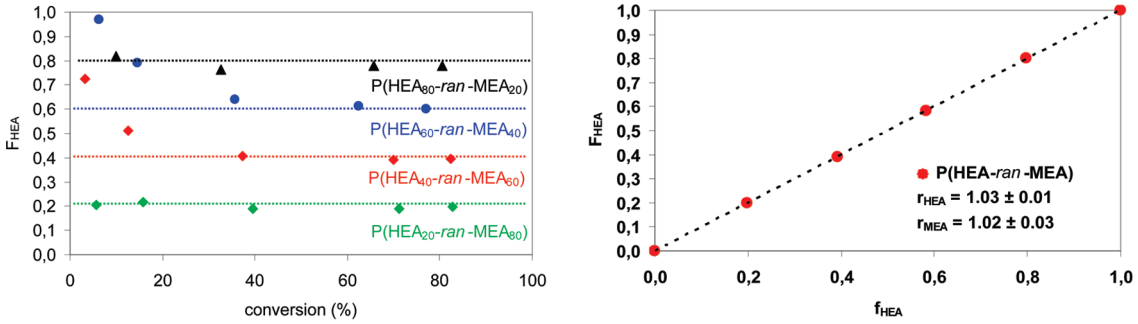


Figure 2. Left: Incorporated 2-hydroxyethyl acrylate (HEA) fraction (F_{HEA}; determined by ^{1}H NMR spectroscopy) as a function of total monomer conversion for the RAFT copolymerizations of 2-hydroxyethyl acrylate (HEA) with 2-methoxyethyl acrylate (MEA). Right: Corresponding plot of the calculated incorporated HEA fraction (F_{HEA} calculated from the kinetic plots) at ~10% total monomer conversion versus theoretical HEA fraction (f_{HEA}).

conversion using the MEA and HEA homopolymerization rates from the copolymerizations.[45] This calculated F_{HEA} at ~10% monomer conversion is plotted against the HEA fraction in the feed (f_{HEA}) in Figure 2, right. Least square nonlinear fitting of these data provided the reactivity ratios as $r_{HEA} = 1.03 \pm 0.01$ and $r_{MEA} = 1.02 \pm 0.03$. These reactivity ratios are both equal to one demonstrating the formation of azeotropic copolymers.

After determination of the copolymerization parameters, three series of HEA/MEA (co)polymers were prepared to investigate the effects of monomer composition and end-groups on the cloud points. The first two (co)polymer series with DP of 80 (Table 2, P1−14) and 40 (Table 2, P15−22) were prepared by simply changing the polymerization time (Table 1) resulting in (co)polymers with two benzyl end-groups (III). The third copolymer series was prepared by controlled cleavage of the copolymers with DP 80 using AIBN[46] resulting in copolymers with DP 40 with a benzyl group at one end and a isobutyronitrile group at the other (Table 4, CP2−12). These (co)polymers were purified by three times precipitation in diethyl ether/hexane mixtures (1:1) to remove unreacted monomer or AIBN, respectively. The molecular weight and PDI values of the purified (co)polymers are summarized in Tables 2 and 4. [^{1}H NMR characterizations of example copolymers with DP 80 and DP 40 are given in Figure S1 and Figure S2 (Supporting Information); SEC elugrams of the poly(2-hydroxyethyl acrylate-*ran*-2-methoxyethyl acrylate) ($F_{HEA,NMR} = 0.8$) before ($P_{n,NMR} = 93$; $M_n = 18100$ g mol^{-1}) and after the cleavage with AIBN ($P_{n,NMR} = 47$; $M_n = 13000$ g mol^{-1}) in DMF are given in Figure S4 (Supporting Information)]. The solubility behavior of the copolymers was investigated by turbidimetry. Aqueous polymer solutions ($c = 5$ mg/mL) were heated and cooled between 0 and 80 °C and cloud points were determined at 50% transmittance during polymer precipitation in the second heating run as well as dissolution in the second cooling run. The results are illustrated in Figure 3 showing that the cloud points increase with increasing F_{HEA} due to the higher hydrophilicity of HEA, as expected. All observed phase transitions were fully reversible showing only a small hysteresis between heating and cooling as indicated by the close proximity of the open and full symbols in Figure 3. The influence of the hydrophobic benzyl end-groups of the synthesized copolymers is much more pronounced with decreasing P_n resulting in lower CP-temperatures of the polymers with the lower degree of polymerization (Table 2). The hydrophobic benzyl end-groups decrease the solvation of the polymer chains while, in contrast, in the

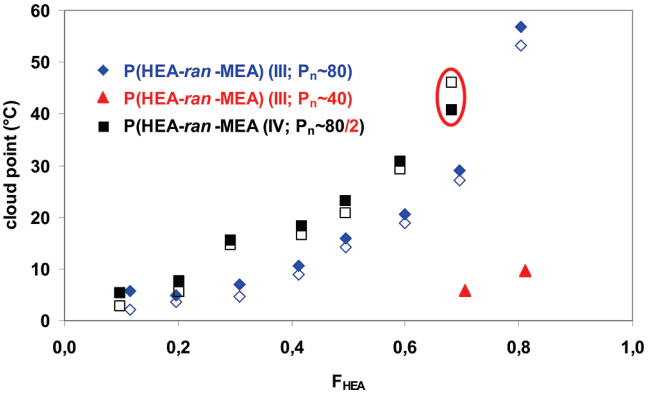


Figure 3. Cloud points (CP; full symbols: heating; open symbols: cooling; for P_n~40 the symbols perfectly overlap) of the poly(2-hydroxyethyl acrylate-*ran*-2-methoxyethyl acrylate) copolymers with different degrees of polymerizations and end-groups (III, $P_n \sim 80$: Table 2, P3−12; III, $P_n \sim 40$: Table 2, P19−20; IV, $P_n \sim 80/2$: Table 4, CP2−11) as a function of 2-hydroxyethyl acrylate fraction (F_{HEA}) determined in demineralized water with a polymer concentration of $c = 5$ mg/mL.

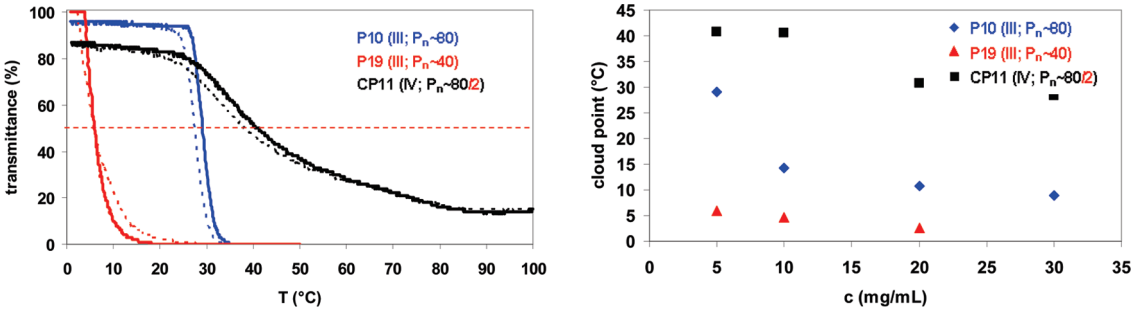


Figure 4. Left: Transmittance (full line: heating; dashed line: cooling) of the poly(2-hydroxyethyl acrylate-*ran*-2-methoxyethyl acrylate) copolymers with $F_{HEA} \sim 0.7$ and different degrees of polymerizations and end-groups as a function of temperature determined in demineralized water with a polymer concentration of $c = 5$ mg/mL. Right: Cloud points (CP; 2nd heating cycle) of the poly(2-hydroxyethyl acrylate-*ran*-2-methoxyethyl acrylate) copolymers with different degrees of polymerizations and end-groups (III, $P_n \sim 80$: Table 2, P10; III, $P_n \sim 40$: Table 2, P19; IV, $P_n \sim 80/2$: Table 4, CP11) as a function of 2-hydroxyethyl acrylate concentration determined in demineralized water.

presence of hydrophilic end-groups the CP normally increases with decreasing P_n.[20]

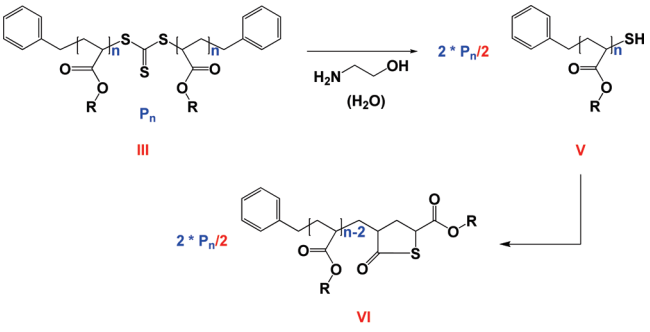
Exchanging one of the hydrophobic end-groups of the copolymers by isobutyronitrile using AIBN (Scheme 1; IV) resulted in copolymers with $P_n/2 \sim 40$ (Table 4, CP2−12) which are more hydrophilic than the corresponding precursor copolymers ($P_n \sim 80$; Table 2, P2−12) and much more hydrophilic than the copolymers with the comparable DP of 40 carrying benzylic groups at both ends (Table 2, P19−20), resulting in a significant increase of the CP-temperatures. The cloud points of the heating and cooling cycle of the cleaved copolymer highlighted (red ellipse) in Figure 3 are approximated cloud points, because the transmittance curve of the measurement never reached the expected 0% (Figure 4, left). Thus, the collapsed copolymer globules are assumed to be strongly hydrated resulting in a weaker tendency to aggregate and, thus, less scattering of light is observed.

The effects of polymer chain length as well as end-groups and concentration are clearly summarized in Figure 4. Figure 4, left, depicts representative transmittance versus temperature plots for the three different copolymers with $F_{HEA} \sim 0.7$. In addition, it demonstrates the absence of hysteresis for the heating and cooling curves even for the copolymer that does not form large aggregates upon precipitation and, therefore, never reaches 0% transmittance. The evolution of the cloud point temperatures with the concentration of the same copolymers with $F_{HEA} \sim 0.7$ is depicted in Figure 4, right. The decrease of CP with increasing concentration suggests the LCST of the copolymer with DP 40 (P19) below 0 °C and the LCST of the copolymers with DP 80 (P10) and 80/2 (CP11) will be somewhat lower but close to the lowest measured CP's of 8 and 28 °C, respectively, underlining the effect of the end-group and degree of polymerization on the LCST of each copolymer and not only on the CP's of the copolymers at the concentration of 5 mg/mL.

Since the turbidimetry is only sensitive to larger aggregates a second, different method for the cloud point determination was applied. Looking at the aggregation at the molecular level the dynamic light scattering (DLS) is more sensitive to the cloud point, thus the CP determined by DLS (~24 °C) is lower, but still in a good agreement with the cloud point determined using turbidimetry (~28 °C). For a direct comparison, a plot of the transmittance (%) and hydrodynamic diameters D_h (nm) as a function of the temperature (°C) of the solution of a representative copolymer ($c = 5$ mg/mL; $F_{HEA} = 0.7$) is given in the Figure S5 (Supporting Information), underlining the suitability for the cloud point determination of both methods, the turbidimetry and the dynamic light scattering (DLS).

Additional experiments were performed to cleave P(HEA-*co*-MEA) copolymers with DP 80 via aminolysis using 1,2-aminoethanol and to study the influence of the chain length and the end-groups on the thermoresponsive properties. Aminolysis of

Scheme 2. Cleavage of P(HEA-*co*-MEA) (III) with a Degree of Polymerization P_n via Aminolysis Using 1,2-Aminoethanol Leading to *SH* or Thiolactone Terminated P(HEA-*co*-MEA) (V or VI) with $P_n/2$



R: $-CH_2-CH_2-OH$ or $-CH_2-CH_2-O-CH_3$

polystyrene and poly(methyl methacylate) prepared by reversible addition−fragmentation chain transfer polymerization was investigated.[47] For polystyrene the dithiobenzoyl end-groups were cleaved via aminolysis and the resulting thiol was oxidized to form a disulfide bond; for poly(methyl methacylate) the resulting thiol end-group tends to cyclize through backbiting with formation of a thiolactone. Cleavage of the trithiocarbonate groups within P(HEA-*co*-MEA) is expected to result first in thiol groups which eventually cyclize via backbiting with formation of thiolactone end-groups (Scheme 2). However, this reaction was not studied in detail. ^{13}C NMR analysis did not reveal any signals characteristic for the carbonyl group of a five-membered thiolactone; this could be caused by the relatively high molecular weight of the polymer. Nevertheless the polymers with thiolactone or thiol end-groups should be more polar than the polymers with benzyl- or isobutyronitril end-groups, respectively, resulting in higher cloud points in comparison to these polymers.

First, kinetic studies on the cleavage of the trithiocarbonate-containing copolymers using different amounts of 1,2-aminoethanol (10, 100, and 1000 equiv with respect to the trithiocarbonate-groups) were performed. The progress of the cleavage-reaction was followed by UV/VIS spectroscopy, monitoring the decrease of the absorption-intensity of the trithiocarbonate-group at 304 nm, (Figure 5, left). As expected, upon increasing the concentration of 1,2-aminoethanol in the reaction mixture the rate of the cleavage reaction increased: with 10 equiv of 2-aminoethanol a conversion of 56.1% of the trithiocarbonate-groups was obtained after 18 h, with 100 equiv the conversion increased to 88.8%, and with 1000 equiv a conversion of 93.4% was obtained.

Cloud point measurements with the copolymers obtained via aminolysis at 5 mg/mL revealed that no precipitation occurs up to

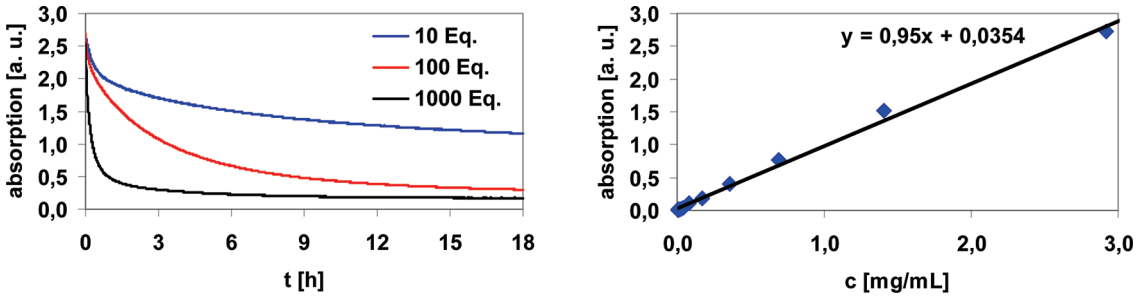


Figure 5. Left: Absorption vs time plot of the cleavage of trithiocarbonate groups in P(HEA-*co*-MEA) (P10, $F_{HEA} \sim 0.70$) via aminolysis with different amounts of 1,2-aminoethanol. Right: Calibration curve of the absorption at $\lambda = 304$ nm (absorbance vs concentration in H_2O at 25 °C).

100 °C demonstrating that the copolymers with DP 80/2 carrying *SH*-end-groups (or thiolactone end-groups) are more hydrophilic than the corresponding copolymers with benzyl- or isobutyronitril end-groups.

Additional cleavage experiments on the copolymers with DP 80, which will lead to different functional groups thereby influencing the cloud point behavior of the resulting copolymers with DP 80/2, will be part of the future work.

Conclusions

Well-defined (co)polymers were prepared by reversible addition−fragmentation chain transfer (RAFT) (co)polymerization of 2-hydroxyethyl acrylate (HEA) and/or 2-methoxyethyl acrylate (MEA), using dibenzyltrithiocarbonate (DBTTC) as chain transfer agent. Kinetic investigations revealed that the polymerizations proceeded in a controlled manner showing equal reactivity of the monomers during the copolymerizations resulting in the formation of azeotropic copolymers. The thermoresponsive properties of aqueous solutions of the copolymers at 5 mg/mL can be tuned by controlling the polymer composition, the chain length and end-groups. The CP of the synthesized copolymers increases with the content of HEA. The influence of the hydrophobic benzyl end-groups of the synthesized copolymers is more pronounced at lower degrees of polymerization resulting in lower CP-temperatures of the copolymers with $P_n \sim 40$ compared to $P_n \sim 80$. Exchanging one of the hydrophobic benzylic end-groups of the copolymers by isobutyronitrile using AIBN resulted in copolymers with $P_n/2$ ($P_n \sim 40$), which are more hydrophilic than the corresponding precursor copolymers ($P_n \sim 80$) and much more hydrophilic than the copolymers with the comparable chain length ($P_n \sim 40$) carrying benzylic groups at both ends, resulting in a significant increase of the CP-temperatures. New potential biomaterials with an adjustable cloud point between 0 and 60 °C, showing small hysteresis on heating and cooling, were thus successfully prepared.

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Supporting Information Available: Figures showing 1H NMR spectra, SEC eluograms and a plot of the transmittance and hydrodynamic diameters as a function of temperature. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Gil, E. S.; Hudson, S. M. *Prog. Polym. Sci.* **2004**, *29*, 1173–1222.
(2) De las Heras Alarcón, C.; Pennadam, S.; Alexander, C. *Chem. Soc. Rev.* **2004**, *34*, 276–285.
(3) Schmaljohann, D. *Adv. Drug Delivery Rev.* **2006**, *58*, 1655–1670.
(4) Yoshida, R.; Sakai, K.; Okano, T.; Sakurai, Y. *Adv. Drug Delivery Rev.* **1993**, *11*, 85–108.
(5) Klouda, L.; Mikos, A. G. *Eur. J. Pharm. Biopharm.* **2008**, *68*, 34–45.
(6) Vertommen, M. A. M. E.; Cornelissen, H.-J. L.; Dietz, C. H. J. T.; Hoogenboom, R.; Kemmere, M. F.; Keurentjes, J. T. F. *J. Membr. Sci.* **2008**, *322*, 243–248.
(7) Costioli, M. D.; Fisch, I.; Garret-Flaudy, F.; Hilbrig, F.; Freitag, R. *Biotechnol. Bioeng.* **2003**, *81*, 535–545.
(8) Kikuchi, A.; Okano, T. *Prog. Polym. Sci.* **2002**, *27*, 1165–1193.
(9) Pietsch, C.; Hoogenboom, R.; Schubert, U. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 5653–5656.
(10) Gota, C.; Okabe, K.; Funatsu, T.; Harada, Y.; Uchiyama, S. *J. Am. Chem. Soc.* **2009**, *131*, 2766–2767.
(11) Okano, T.; Yamada, N.; Okuhara, M.; Sakai, H.; Sakurai, Y. *Biomaterials* **1995**, *16*, 297–303.
(12) Wischerhoff, E.; Uhlig, K.; Lankenau, A.; Börner, H. G.; Laschewsky, A.; Duschl, C.; Lutz, J.-F. *Angew. Chem., Int. Ed.* **2008**, *47*, 5666–5668.
(13) Taylor, L. D.; Cerankowski, L. D. *J. Polym. Sci.* **1975**, *13*, 2551–2570.
(14) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163–249.
(15) Aoshima, S.; Kanaoka, S. *Adv. Polym. Sci.* **2008**, *210*, 169–208.
(16) Lutz, J.-F.; Akdemir, O.; Hoth, A. *J. Am. Chem. Soc.* **2006**, *128*, 13046–10347.
(17) Neugebauer, D. *Polym. Int.* **2007**, *56*, 1469–1498.
(18) Hoogenboom, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 7978–7994.
(19) Diab, C.; Akiyama, Y.; Kataoka, K.; Winnik, F. M. *Macromolecules* **2004**, *37*, 2556–2562.
(20) Hoogenboom, R.; Thijs, H. M. L.; Jochems, M. J. H. C.; van Lankvelt, B. M.; Fijten, M. W. M.; Schubert, U. S. *Chem. Commun.* **2008**, 5758–5760.
(21) Tanaka, M.; Motomura, T.; Kawada, M.; Anzai, T.; Kasori, Y.; Shiroya, T.; Shimura, K.; Onishi, M.; Mochizuki, A. *Biomaterials* **2000**, *21*, 1471–1481.
(22) Mueller, X. M.; Jegger, D.; Augstburger, M.; Horisberger, J.; von Segesser, L. K. *Int. J. Artif. Organs* **2002**, *25*, 223–229.
(23) Bednarek, M.; Jankova, K.; Hvilsted, S. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 333–340.
(24) Mun, G. A.; Nurkeeva, Z. S.; Akhmetkalieva, G. T.; Shmakov, S. N.; Khutoyanskiy, V. V.; Lee, S. C.; Park, K. *J. Polym. Sci., Part B: Polym. Phys.* **2006**, *44*, 195–204.
(25) Mun, G. A.; Nurkeeva, Z. S.; Beissegul, A. B.; Dubolazov, A. V.; Urkimbaeva, P. I.; Park, K.; Khutoyanskiy, V. V. *Macromol. Chem. Phys.* **2007**, *208*, 979–987.
(26) Khutoryanskaya, A. V.; Mayeva, Z. A.; Mun, G. A.; Khutoryanskiy, V. V. *Biomacromolecules* **2008**, *9*, 3353–3361.
(27) Popescu, D.; Hoogenboom, R.; Keul, H.; Moeller, M. *Polym. Chem.* **2010**, DOI: 10.1039/c0py00051e.
(28) Chan, Y.; Wong, T.; Byrne, F.; Kavallaris, M.; Bulmus, V. *Biomacromolecules* **2008**, *9*, 1826–1836.
(29) Martinez-Ramos, C.; Lainez, S.; Sancho, F.; Esparza, M. A. G.; Planells-Cases, R.; Verdugo, J. M. G.; Ribelles, J. L. G.; Sanchez, M. S.; Pradas, M. M.; Barcia, J. A.; Soria, J. M. *Tissue Engin. A* **2008**, *14*, 1365–1375.
(30) Valles Lluch, A.; Campillo Frenandez, A.; Gallego Ferrer, G.; Monleon Pradas, M. *J. Biomed. Mater. Res. Part B: Appl. Biomater.* **2009**, *90*, 182–194.
(31) Eggenhuisen, T. M.; Becer, C. R.; Fijten, M. W. M.; Eckardt, R.; Hoogenboom, R.; Schubert, U. S. *Macromolecules* **2008**, *41*, 5132–5140.

(32) Hoogenboom, R.; Popescu, D.; Steinhauer, W.; Keul, H.; Möller, M. *Macromol. Rapid Commun.* **2009**, *30*, 2042–2048.
(33) Wang, J. S.; Matyjaszewski, K. *Macromolecules* **1995**, *28*, 7901–7910.
(34) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689–3746.
(35) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559–5562.
(36) Barner-Kowollik, C.; Davis, T. P.; Heuts, J. P. A.; Stenzel, M. H.; Vana, P.; Whittaker, M. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 365–375.
(37) Veregin, R. P. N.; Georges, M. K.; Hamer, G. K.; Kazmaier, P. M. *Macromolecules* **1995**, *28*, 4391–4398.
(38) Fukuda, T.; Terauchi, T.; Goto, A.; Ohno, K.; Tsujii, Y.; Miyamoto, T.; Kobatake, S.; Yamada, B. *Macromolecules* **1996**, *29*, 6393–6398.
(39) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661–3688.
(40) Lai, J. T.; Filla, D.; Shea, R. *Macromolecules* **2002**, *35*, 6754–6756.
(41) Lizotte, J. R.; Long, T. E. *Macromol. Chem. Phys.* **2004**, *205*, 692–698.
(42) Wang, Y.; Armitage, B. A.; Berry, G. C. *Macromolecules* **2005**, *38*, 5846–5848.
(43) Bian, K.; Cunningham, M. F. *Macromolecules* **2005**, *38*, 695–701.
(44) Clement, B.; Trimaille, T.; Alluin, O.; Gigmes, D.; Mabrouk, K.; Feron, F.; Decherchi, P.; Marqueste, T.; Bertin, D. *Biomacromolecules* **2009**, *10*, 1436–1445.
(45) Fijten, M. W. M.; Hoogenboom, R.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 4804–4816.
(46) Perrier, S.; Takolpuckdee, P.; Mars, C. A. *Macromolecules* **2005**, *38*, 2033–2036.
(47) Xu, J.; He, J.; Fan, D.; Wang, X.; Yang, Y. *Macromolecules* **2006**, *39*, 8616–8624.