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ARTICLE

Influence of End Groups on the Stimulus-Responsive Behavior of Poly[oligo(ethylene glycol) methacrylate] in Water

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ABSTRACT: The influence of the chemical structure of both end groups onto the lower critical solution temperature (LCST) of poly[oligo(ethylene glycol) monomethyl ether methacrylate] (POEGMA) in water was systematically investigated. POEGMA of M_n = 3550 g/mol and M_w/M_n = 1.14 prepared by reversible addition−fragmentation chain transfer (RAFT) polymerization was equipped with two different functional end groups in a one-step postpolymerization reaction combining activated esters, functional amines, and functional methane thiosulfonates. As end groups, *n*-propyl, *n*-hexadecyl, di(*n*-octadecyl), poly(ethylene glycol)-550 (PEG), 1*H*,1*H*-perfluorononyl, azobenzene, and trimethylethylammonium groups were systematically combined with methyl, *n*-hexadecyl, and 1*H*,1*H*,2*H*,2*H*-perfluorooctyl groups. Polymers were characterized by gel permeation chromatography, dynamic light scattering, and turbidimetry. Hydrophobic end groups at either end of the polymer chain decreased the LCST. For hydrophobic groups at both ends of the chain their influence was additive. Two large hydrophobic end groups allowed micelle formation below the LCST and an LCST higher than to be expected from nonaggregated polymers. The strongest hydrophobic effect was found for rigid aromatic end groups, which was attributed to their incompatibility with the flexible polymer chain. Charged end groups increased the LCST and could compensate for the effect of hydrophobic end groups at the opposite end group. PEG end groups could mask a hydrophobic influence of the opposite end group and stabilized the LCST.

Introduction

Stimulus responsive polymers that have a lower critical solution temperature (LCST) in water are gaining an increasing interest in recent research. Below the LCST, the polymers are well soluble in water and adopt an extended chain conformation. At the LSCT, the polymers become hydrophobic and undergo a chain collapse. Above the LCST, the polymers are insoluble in water. If the concentration of polymer is sufficiently high, a clouding and eventual precipitation of the material can be observed upon heating a clear solution above the LCST. This enables precise measurements of LCSTs through turbidimetry. Usually, the transition occurs quite sharp within a very small temperature range and is fully reversible. Because of this abrupt and well inducible change from a swollen coil to a hydrophobic collapsed globule, polymers with an LCST are often termed "smart" materials and are employed and probed in a variety of applications such as thermosensitive bioconjugates,[1−4] molecular actuators,[5] drug delivery,[6,7] tunable optical devices,[8] or chromatographic separation.[9,10] Although LCST values found in the literature for a given polymer are usually in unison, measured LCST values of that polymer can vary depending on concentration, molecular weight,[11−13] salt concentration,[14,15] tacticity,[16,17] or incorporation of comonomers.[14,18]

In many applications, stimulus responsive polymers are conjugated to proteins,[19,20] fluorescent dyes,[21,22] or surfaces[23] with their end groups. In these setups, and especially when the polymer is intended to change a distance between both of its end groups through its chain collapse, it is important to know the influence of both (modified) end groups onto the LCST. The end groups may also be used to adjust the LCST, for instance for micellar drug carrier applications.[24] Furyk et al. attributed the molecular weight influence onto the LCST solely onto the influence of the end groups, which is stronger the lower the molecular weight is.[25] Several studies, including theoretical ones,[26] have thus elucidated the influence of end groups on the LCST.[11,13,27−29] The most investigated stimulus responsive polymer in water is poly[*N*-isopropylacrylamide] (PNIPAM),[24,25,30−32] from which also thermoresponsive bioconjugates have been prepared through end-group modification.[4,33,34]

Nonlinear PEG analogues, such as poly[oligoethylene glycol monomethyl ether methacrylate] (POEGMA), have recently been receiving a lot of interest as stimulus responsive polymers relevant for biomedical applications.[18,35] Precision in the polymerization of OEGMA has been achieved for example by anionic polymerization[36,37] and atom transfer radical polymerization.[38−42] As a consequence, POEGMA polymers and especially copolymers proved to feature an adjustable thermoresponsive behavior that is comparable to that of PNIPAM,[39,40] which can also be utilized in hydrogels[41] and molecular brushes.[42]

However, a systematic survey of the influence of the end groups on its thermoresponsive behavior has not been conducted yet.

The synthesis of polymers with two different functional end groups is challenging, and as a consequence, some studies have investigated the influence of only one functional end group onto the LCST.[13,27,28] Stimulus responsive polymers with two different functional end groups have been prepared by living

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cationic ring-opening polymerization,[29] atom transfer radical polymerization (ATRP),[13,28] free radical polymerization,[24,25,30] living cationic polymerization,[43] or reversible addition−fragmentation chain transfer (RAFT) polymerization[44] in combination with functionalized initiators,[13,28,29,43] terminating agents,[29,43] or chain transfer agents.[24,44] These approaches, however, require a separate polymerization procedure, with distinct initiation and termination reactions, for each end group combination of interest. It is therefore not possible to completely eliminate influences of the molecular weight or the molecular weight distribution onto the LCST. Many reports on end group influences deal with the effect of hydrophobic end groups, which generally reduce the LCST, similar to the incorporation of hydrophobic comonomers.[24,30,45,46]

Preparing various heterotelechelic polymers with identical degrees of polymerization and polydispersity indices may be achieved by postpolymerization end-group modifications of a polymer with two separately addressable reactive end groups. Examples following the concept of click chemistry include thiol−ene/thiol−yne reactions,[31] activated esters,[47] azide with acetylene cycloaddition,[27,48,49] thiocarbonyl with dienophile cycloaddition,[50] pyridyl disulfides,[48] methane thiosulfonates,[51] or Michael addition.[49]

In this study, we investigate the influence of both end groups of heterotelechelic POEGMA (M_n = 3550 g/mol) synthesized via RAFT polymerization. The use of a pentafluorophenyl (PFP) ester modified chain transfer agent (CTA) afforded a polymer with a PFP ester and a dithioester end group. Postpolymerization functionalization by combining functional amines and functional methane thiosulfonates (MTS) enabled to selectively modify both end groups in a single step with very high conversions. This way, a library of polymers differing only in their end groups but with the same degree of polymerization and same polydispersity indices could be obtained. The influence of the end groups including different hydrophobic, charged, fluorophilic, and uninfluential moieties and combinations thereof onto the LCST was systematically investigated.

Experimental Section

Methods. Gel permeation chromatography (GPC) was performed on 2 mg/mL THF solutions on MZ-Gel SDplus columns to determine the polystyrene equivalent molecular weight and the polydispersity index (PDI) M_w/M_n. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured on a 400 MHz instrument by Bruker on $CDCl_3$ solutions at room temperature. Cloud points were determined using 10 mg/mL aqueous solutions (Millipore grade) and were observed by optical transmittance at a wavelength of λ = 632 nm through a 1 cm quartz cell using a Jasco V-630 photospectrometer with a Jasco ETC-717 Peltier element with a heating rate of 1 °C/min. The transmitted light was recorded versus the temperature, and the LCST given is the temperature at 50% transmittance. Dialysis membranes were purchased from Roth (Germany) and had a molecular weight cutoff of 3500 g/mol. Dynamic light scattering was measured on a Malvern Zetasizer Nano in a low volume glass cuvette (45 μL) at 20 °C on 1 g/L solutions in Millipore water at an angle of 90°.

α-*Pentafluorophenyl*, ω-*dithioester poly*[*oligo*(*ethylene glycol*) *monomethyl ether methacrylate*], *PFP-POEGMA-DTE* (***P1***), was prepared by RAFT polymerization of commercial oligoethylene glycol monomethyl ether methacrylate with a molecular weight of about 300 g/mol utilizing pentafluorophenyl-(4-phenylthiocarbonylthio-4-cyanovalerate) (PFP-CTA) as a chain transfer agent, as described elsewhere.[52] M_n (GPC, polystyrene equivalent) = 3550 g/mol, PDI = 1.14, M_n (NMR) = 3800 g/mol.

Dioctadecylamine was prepared according to the literature.[53]

Amino-terminated poly(*ethylene glycol*) (*PEG-NH$_2$*) was prepared according to a literature procedure from PEG monomethyl ether with a molecular weight of 550 g/mol.[54]

N-(*2-Aminoethyl*)*-4-*(*2-phenyldiazenyl*)*benzamide* was synthesized as described in the literature.[55]

Sodium methanethiosulfonate was synthesized according to a literature procedure from sodium methylsulfinate and sulfur.[56]

S-1H,1H,2H,2H-Perfluorooctyl methanethiosulfonate. 3.15 g (23.5 mmol) of sodium methanethiosulfonate was dissolved in 5 mL of dry DMF. 5 g (11.7 mmol) of 1*H*,1*H*,2*H*,2*H*-perfluorooctyl bromide was separately dissolved in 2 mL of dry DMF. Both solutions were combined and stirred at 40 °C. Upon mixing, some precipitation occurred. After 3 h, two liquid phases had formed. Stirring at 40 °C was however continued overnight. After that time, there was one liquid phase. The solvent was removed at reduced pressure, and the light-yellow residue was extracted with diethyl ether. By removing the diethyl ether, 4.51 g (84.2%) of product was obtained which could be used without further purification. ^{1}H NMR, $CDCl_3$, 300 MHz, δ /ppm = 3.35 (m, 5 H, −CH_3 and −SCH_2−), 2.64 (m, 2 H, −CF_2CH_2−). ^{13}C NMR, $CDCl_3$, 75 MHz, δ = 50.47 (*C*H_3−), 32.32 (t, J = 16.5 Hz, −CF_2*C*H_2−), 27.03 (t, J = 3.5 Hz, −S*C*H_2−). ^{19}F NMR, $CDCl_3$, 376 MHz, δ = −81.3 (3 F), −114.7, −122.3, −123.2, −123.7, −126.5 (2 F each). MS (FD) m/z (%): 457.59 (100.00), 458.60 (12.59), 459.60 (9.43).

S-Hexadecyl methanethiosulfonate was prepared in analogy to the above procedure from 2.66 g (8.71 mmol) of hexadecyl bromide and 2.39 g (17.8 mmol) of sodium methanethiosulfonate. 2.26 g (77.2%) of product was obtained. ^{1}H NMR, $CDCl_3$, 300 MHz, δ = 3.28 (s, 3 H, −SO_2CH_3), 3.13 (t, J = 7 Hz, 2 H, −CH_2S−), 1.76 (m, 2 H, −CH_2−CH_2S−), 1.21 (m, 24 H −CH_2−), 0.84 (t, J = 7 Hz, 3 H, CH_3−CH_2−).

General Procedure for α,ω-Functionalization of Polymers. In a typical run, 76 mg (20 μmol) of PFP-POEGMA-DTE (**P1**) was dissolved in 1 mL of chloroform. 20 equiv (400 μmol) of the respective MTS reagent (methyl, hexadecyl or 1*H*,1*H*,2*H*,2*H*-perfluorooctyl methanethiosulfonate) dissolved in 1 mL of chloroform was added, and the mixture was stirred for 1 min. Then, 50 equiv (1 mmol) of the respective amine (*n*-propyl, *n*-hexadecyl, dioctadecyl, poly(ethylene glycol), or 1*H*,1*H*-perfluorononyl) was injected. The mixture was stirred overnight at room temperature. For (2-aminoethyl)trimethylammonium chloride and *N*-(2-aminoethyl)-4-(2-phenyldiazenyl)benzamide as amines, the reactions were performed in DMF instead of chloroform. For (2-aminoethyl)trimethylammonium chloride, triethylamine (0.5 mL) was additionally added as auxiliary base and cosolvent.

For work-up, one of two different procedures was applied. For reactions with amines and MTS reagents soluble in diethyl ether (all except poly(ethylene glycol) amine, *N*-(2-aminoethyl)-4-(2-phenyldiazenyl)benzamide, and (2-aminoethyl)trimethylammonium chloride), the completed reactions were dried in vacuum, and water was added to the residue. After several extractions with diethyl ether to remove any side products, the aqueous phase was extracted with chloroform to transfer the polymeric product into the organic phase. Upon removal of the chloroform, pure end-group-functionalized polymers were obtained in 50−80% yields. An alternative work-up procedure applicable to all reactions was dialysis against methanol through 3500 g/mol molecular weight cutoff membranes for 3 days with solvent changes twice a day. This afforded pure polymers in 40−80% yields.

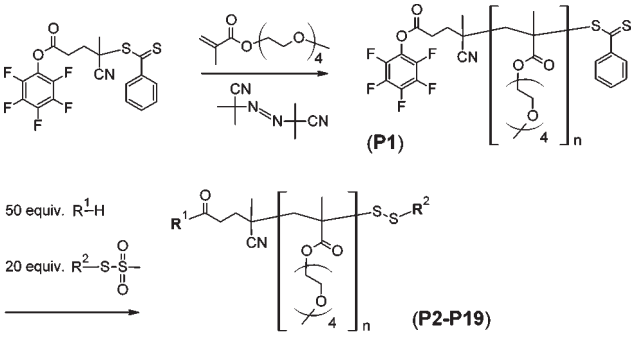
GPC data (polystyrene equivalent molecular weight and polydispersity index M_w/M_n) are summarized in Table 1 together with the LCST value of each polymer. NMR, $CDCl_3$, 400 MHz, δ/ppm: poly[oligoethylene glycol methacrylate]: ^{1}H, 4.07 (−COOCH_2−), 3.64, 3.60, 3.52 (−OCH_2CH_2O−), 3.36 (−OCH_3), 1.96−1.65 (−CH_2−), 1.00, 0.81 (−CH_3). ^{13}C, 177.2 (−COO−), 71.8, 70.4, 68.3 (−OCH_2CH_2O−), 63.8 (−COO-CH_2−), 59.0 (−OCH_3), 54.5 (−CH_2−), 44.6 (−(CH_3)*C*-(COO−)−), 18.5, 16.2 (−CH_3). α-(Trimethylammonium)ethyl amide: ^{1}H, 3.79 (−CH_2NHCO−), 3.73 ((CH_3)$_3$N$^+$CH_2−), 3.30 ((CH_3)$_3$N$^+$−), 2.41 (−NHCOCH_2−). ^{13}C, 65.5 ((CH_3)$_3$-N$^+$*C*H_2−), 54.5 ((CH_3)$_3$N$^+$−), 34.4 (−*C*H_2NHCO−), 30.9

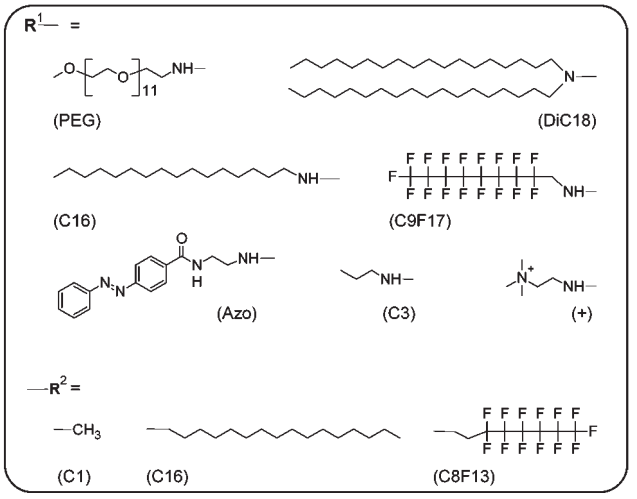
Table 1. End Groups, Measured Polystyrene Equivalent and Theoretical Molecular Weights, Polydispersity Indices, LCSTs, and Hydrodynamic Radii of Polymers Synthesized

	α end group ($\mathbf{R^1}$)	ω end group ($\mathbf{R^2}$)	$M_{n,GPC}$[a]/g mol^{-1}	$M_{n,theor}$[b]/g mol^{-1}	PDI[a]	LCST/°C	R_H[c]/nm
P1	C_6F_5O-	$-SCSPh$[d]	3550	3550	1.14	42.8	3.28
P2	$CH_3(OCH_2CH_2)_{11}NH-$	$-CH_3$	3270	3840	1.11	62.7	3.57
P3	$CH_3(OCH_2CH_2)_{11}NH-$	$-C_{16}H_{33}$	3270	4050	1.11	62.4	
P4	$CH_3(OCH_2CH_2)_{11}NH-$	$-CH_2CH_2C_6F_{13}$	3100	4180	1.13	62.1	
P5	C_3H_7NH-	$-CH_3$	3230	3350	1.14	58.3	3.31
P6	C_3H_7NH-	$-C_{16}H_{33}$	3370	3560	1.12	50.1	
P7	C_3H_7NH-	$-CH_2CH_2C_6F_{13}$	3440	3680	1.10	49.7	
P8	$C_{16}H_{33}NH-$	$-CH_3$	3590	3530	1.13	53.6	3.77
P9	$C_{16}H_{33}NH-$	$-C_{16}H_{33}$	3900	3740	1.11	45.8	
P10	$C_{16}H_{33}NH-$	$-CH_2CH_2C_6F_{13}$	3820	3870	1.13	44.7	4.28
P11	$(CH_3)_3N^+CH_2CH_2NH-$	$-CH_3$	3480	3390	1.16	66.3	3.28
P12	$(CH_3)_3N^+CH_2CH_2NH-$	$-C_{16}H_{33}$	3620	3600	1.12	62.5	
P13	$(CH_3)_3N^+CH_2CH_2NH-$	$-CH_2CH_2C_6F_{13}$	3620	3720	1.17	62.1	
P14	$C_8F_{17}CH_2NH-$	$-CH_3$	3590	3740	1.14	50.9	
P15	$C_8F_{17}CH_2NH-$	$-C_{16}H_{33}$	3660	3950	1.13	51.7	8.51
P16	$C_8F_{17}CH_2NH-$	$-CH_2CH_2C_6F_{13}$	4020	4070	1.14	50.3	8.62
P17	$(C_{18}H_{37})_2N-$	$-CH_3$	4330	3810	1.15	48.9	
P18	$(C_{18}H_{37})_2N-$	$-CH_2CH_2C_6F_{13}$	4800	4150	1.14	48.9	7.83
P19	$C_6H_5N{=}NC_6H_4CONH(CH_2)_2NH-$	$-CH_3$	3400	3650	1.16	49.1	

[a] Polystyrene equivalent molecular weight and polydispersity index determined by GPC. [b] Theoretical molecular weight determined from the M_n(GPC) of **P1** and the molecular weight of the end groups assuming 100% conversion. [c] Hydrodynamic radius in water at 20 °C measured by dynamic light scattering. [d] For **P1**, no disulfide bridge between polymer chain and $\mathbf{R^2}$ end group; structure given in Scheme 1.

Scheme 1. Synthesis of α,ω-Heterotelechelic Polymers Based on Pentafluorophenyl Esters and Functional Methane Thiosulfonates Together with Structures and Abbreviations of End Groups





(−NHCOCH_2−). α-*n*-Propylamide: ^{1}H, 3.15 (−CH_2NHCO−), 0.87 (CH_3−). α-Hexadecylamide: ^{1}H, 3.15 (−CH_2NHCO−), 2.27 (−NHCOCH_2−), 1.45 (−CH_2CH$_2$NHCO−), 1.24 (−CH_2−), 0.85 (CH_3−). ^{13}C, 39.5 (−*C*H$_2$NHCO−), 31.7, ($CH_3CH_2CH_2$−), 31.4 (−NHCO*C*H$_2$−), 29.6 (−CH_2−), 29.5 (−*C*H$_2$CH$_2$NHCO−), 26.7 (−*C*H$_2$CH$_2$CH$_2$NHCO−), 22.5 (CH_3CH_2−), 14.0 (CH_3−). α-1*H*,1*H*-Perfluorononylamide: ^{19}F, −80.6 (3 F), −118.1 (2 F), −121.8 (6 F), −122.6 (2 F), −123.3 (2 F), −126.0 (2 F). α-Dioctadecylamide: ^{1}H, 3.24 ((−CH_2)$_2$NCO−), 2.45 ((−CH_2)$_2$-NCOCH_2−), 1.28 (CH_3CH_2−), 1.25 (−CH_2−), 0.89 (CH_3−). ^{13}C; 47.1 ((−*C*H$_2$)$_2$NCO−), 31.7 ($CH_3CH_2CH_2$−),29.6 (−CH_2−), 22.5 (CH_3CH_2−), 14.1 (CH_3−). α-2-[4-(Phenyldiazenyl)benzoylamino]-ethylamide: ^{1}H, 7.96, 7.91, 7.50. ω-methyl disulfide: ^{1}H, 2.36 (−SCH_3). ^{13}C, 24.2 (−SCH_3). ω-Hexadecyl disulfide: ^{1}H, 2.61 (−SCH_2−), 1.55 (−SCH_2CH_2−), 1.25 (−CH_2−), 0.86 (CH_3−). ^{13}C, 39.5 (−SCH_2−), 32.1 ($CH_3CH_2CH_2$−), 29.7 (−CH_2−), 28.8 (−SCH_2*C*H$_2$−), 22.5 (CH_3CH_2−), 14.1 (CH_3−). ω-1*H*,1*H*, 2*H*,2*H*-Perfluorooctyl disulfide: ^{1}H, 2.78 (−SCH_2−), 2.40 (−SC-H$_2$CH_2−) ^{13}C, 31.1 (−SCH_2*C*H$_2$−), 28.5 (−SCH_2−). ^{19}F, −81.1 (3 F), −114.1, −122.2, −123.2, −123.6, −126.5 (2 F each).

End-group conversions as calculated from NMR integrations were between 90% and 97% for α end-group conversions and between 89% and 98% for ω end-group conversions, based on the presence of terminal phenyl dithioester in the starting polymer PFP-POEGMA-DTE.

Results and Discussion

Synthesis. Starting from POEGMA with α pentafluorophenyl (PFP) ester and ω dithioester end groups,[47] the synthesis of polymers with two different functional end groups proceeded via a one-pot, one-step reaction employing an excess of a functional primary or secondary amine and a functional methane thiosulfonate (MTS)[51] (see Scheme 1). In the following, the amide residues ($\mathbf{R^1}$) are termed α end group, whereas the disulfide residues ($\mathbf{R^2}$) will be referred to as ω end groups. Commercially available methyl-MTS was used. MTS reagents with hexadecyl and 1*H*,1*H*,2*H*,2*H*-perfluorooctyl residues were synthesized in two steps from sulfur, sodium methylsulfinate, and the respective alkyl bromides, adopted from the literature (see Scheme 2).[57] Because of a simple purification through either extraction or dialysis, a library of heterotelechelic polymers could easily be obtained. In order to systematically assess the influence of the end groups on the LCST of POEGMA, such of different sizes and of different polarities, including fluorophilic residues were probed. Perfluorinated alkyl chains are very hydrophobic,[58] but fluorocarbon blocks[59,60] or chains with 15[61] or 17[62−64] F atoms have been shown to phase separate from regular alkyl chains. A 1*H*,1*H*-perfluorononylamide (with 17 F atoms, C9F17) and a 1*H*,1*H*,2*H*,2*H*-perfluorooctyl disulfide (with 13 F atoms, C8F13) were thus included

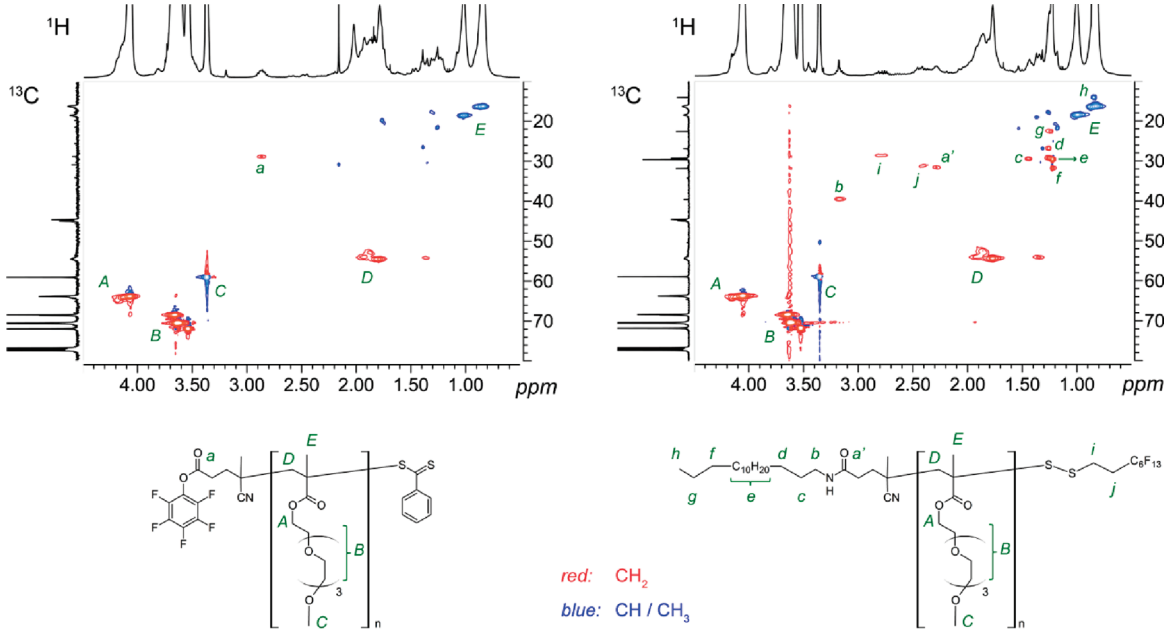
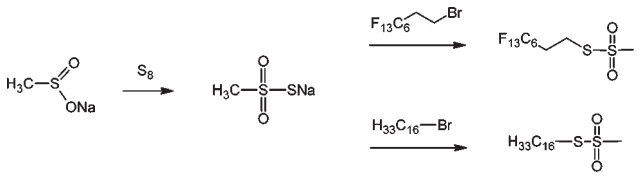


Figure 1. Exemplary $^{1}H/^{13}C$ HSQC NMR spectra of the starting polymer **P1** (left) and polymer **P10** with α C16, ω C8F13 end groups (right) showing the complete end-group conversions.

Scheme 2. Synthesis of *S*-Hexadecyl and *S*-1*H*,1*H*,2*H*,2*H*-Perfluorooctylmethanethiosulfonate



into the functional end groups of interest. Because of the postpolymerization strategy, all polymers had exactly the same average degree of polymerization and the same molecular weight distribution.

GPC traces of all product polymers **P2**−**P19** were monomodal, had a narrow molecular weight distribution, and did not differ in form or width from the trace of the starting polymer **P1**. Polystyrene equivalent molecular weights and PDIs are given in Table 1. Generally, the experimental molecular weights M_n were in good agreement (less than 8% deviation) with the theoretical M_n expected for quantitative end-group conversions, except for PEG α end groups, where the experimental M_n was significantly lower than expected, and for dioctadecyl α end groups, where the molecular weights found were higher than expected. Nevertheless, these shifted curves were monomodal and narrow. The divergence may be explained by the blocklike structure of the PEG-terminated polymers and the 3-arm-star-like structure of the dioctadecyl-terminated polymers.

UV−vis measurements (not shown) indicated a complete removal of the terminal dithioesters from each polymer **P2**−**P19** due to the absence of its strong absorbance band centered at 302 nm.

NMR spectroscopy could be used to quantify the conversions at each end group. Conversions were generally above 90% at each end group, yielding polymers with a high fraction of heterotelechelic chains. Generally, each end group produced characteristic signals in ^{1}H, ^{13}C, or ^{19}F NMR. Additionally, a quantitative shift of main-chain located protons directly influenced by the end groups, such as the methylene group adjacent to the α amide, was

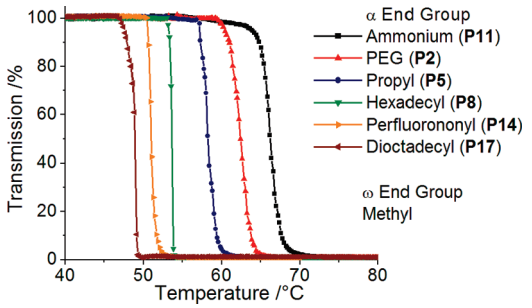


Figure 2. Transmission versus temperature plots recorded while heating 10 mg/mL aqueous polymer solutions at 1 °C/min.

generally observed. As example, the $^{1}H/^{13}C$ HSQC spectrum of polymer **P10** is presented in Figure 1, showing the quantitative (within NMR accuracy) conversions of the α PFP ester into a hexadecyl amide and the ω dithioester into a 1*H*,1*H*,2*H*,2*H*-perfluorooctyl disulfide.

All ω end groups surveyed in this study were connected to the polymer chain via disulfide links, which were stable under all synthetic and analytic conditions. The disulfide bridge did not have any significant influence onto the solubility behavior of the polymers as could be seen from a comparison of **P19** (α diazo, ω methyl disulfide POEGMA) with α diazo, ω isobutyronitrile POEGMA with the same degree of polymerization, as reported previously by us.[52] **P19** had an LCST of 49.1 °C, very close to 49.9 °C found for the isobutyronitrile analogue which had originated from the common method to remove the reactive dithioester end groups with AIBN.[65]

LCST Values. Representative cloud point heating plots of polymers **P2**, **P5**, **P8**, **P11**, **P14**, and **P17** (all with $\mathbf{R^2}$ = methyl) are shown in Figure 2. The curves showed sharp transitions from clear solutions (100% transmittance) to turbid mixtures (0% transmittance) within a narrow range of about 3 °C upon heating and only very small hystereses upon cooling (not shown). These observed phase separations were fully reversible for all polymers. The LCST values (50% transmittance) of all polymers are given in Table 1 and are plotted in Figure 3A,B. Both plots contain the same data;

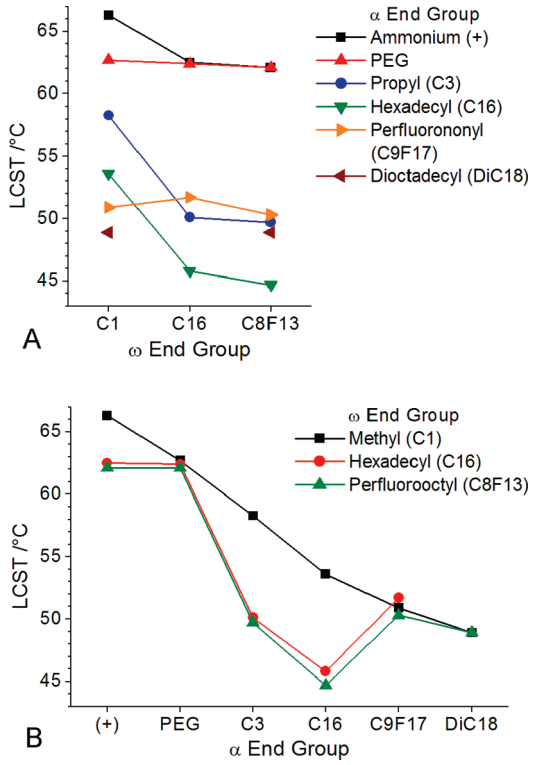


Figure 3. LCST values connected with lines according to (A) same α end groups with the *x*-axis giving the respective *ω* end groups and (B) same *ω* end groups with the *x*-axis giving the respective α end groups.

however, for clarity, in Figure 3A, the values are grouped according to same α (**R**^{1}) end groups, with the *x*-axis giving the respective *ω* (**R**^{2}) end groups, while in Figure 3B, each set of data points connected with lines represent polymers sharing the same *ω* end group. In the following the influence of the different end groups will be discussed.

Influence of PEG and Hydrophobic α *End Groups.* We first consider the case where only one end group was changed while the other remained the same. The black line in Figure 3b (and the transmittance plots in Figure 2) shows the change of LCST in a series with *ω* methyl end groups and varying α end groups. The LCST of polymer **P2** with an α PEG end group was 62.7 °C, very close to the literature value of about 64 °C,[18] presumably, because PEG is chemically very similar to the side chains of the oligo(ethylene glycol) methacrylate polymer and thus does not influence its solubility behavior. This was contrary to the end-group functionalization of poly[2-isopropyl-2-oxazoline] with oligo(ethylene glycol), which was reported to decrease the LCST.[29] As to be expected, the more hydrophobic the α end group became, the lower was the LCST. With an α propyl (C3) end group (**P5**), the LCST was 58.3 °C, 4.4 °C lower than with PEG. With an α hexadecyl (C16) end group (**P8**), the LCST was 53.6 °C, 4.7 °C lower than with C3, and with an α dioctadecyl (DiC18) end group (**P17**), the LCST was 48.9 °C, again 4.7 °C lower than C16. The ^{1}H,^{1}H-perfluorononyl (C9F17) α end group (**P14**), although shorter, had a stronger influence than the hexadecyl chain and caused an LCST of 50.9 °C, between those of hexadecyl and dioctadecyl residues, showing the higher impact of the perfluorinated end group.

Influence of Hydrophobic ω End Groups. The same effect was found for hydrophobic *ω* end groups. There was an LCST decrease of 8.2 °C when going from an *ω* methyl (C1) to an *ω* hexadecyl (C16) end group for the α C3 polymers **P5** (LCST 58.3 °C) and **P6** (LCST 50.1 °C) (blue curve in Figure 3a) and a 7.8 °C decrease for the same *ω* end group change for the α hexadecyl polymers **P8** (LCST 53.6 °C) and **P9** (LCST 45.8 °C) (green curve in Figure 3a). These differences are in good agreement with the LCST difference observed when going from an α PEG (**P2**) to an α C16 (**P8**) end group of 9.1 (4.4 + 4.7 °C). The perfluorooctyl (C8F13) *ω* end group had a very similar effect as the hexadecyl end group, with LCST for the perfluorinated group being in average 0.72 ± 0.50 °C lower for all five pairs compared (see red and green curves in Figure 3b).

Combination of Hydrophobic α *and ω End Groups.* The blue and green curves in Figure 3a (representing the LCST of α C3 polymers **P5**−**P7** and the α C16 polymers **P6**−**P10**, respectively) run parallel, with the differences between α C3 and α C16 end groups being 4.7, 4.3, and 5.0 °C for C1, C16, and C8F13 *ω* end groups, respectively. These similar differences show that the influence of two end groups appears to be additive; the introduction of an α C16 group for an α C3 end group caused an LCST decrease of 4.67 ± 0.35 °C in addition to a decrease caused by any of the three *ω* end groups. This observation suggests that LCST values may easily be tuned through a combination of two hydrophobic end groups. A goal would be to develop a quantitative model and an increment system based on this, from which LCST values could be predicted.

Large Hydrophobic ω End Groups. Combination of two hydrophobic end groups in order to reduce the LCST, however, was found to have certain limitations: When looking at the LCST data in Figure 3a,b, three temperatures stand out because they seem too high. The orange curve in Figure 3a, representing polymers **P14**−**P16** with α 1*H*,1*H*-perfluorononyl amide (C9F17) end groups, starting with polymer **P14** at an LCST of 50.9 °C, surprisingly rises when going from *ω* C1 to *ω* C16 to 51.7 °C for **P15**. The LCST of polymer **P16** with *ω* C8F13 end groups with 50.3 °C is lower than that of **P15**, but unexpectedly 5.6 °C higher than **P10** (with α C16 and *ω* C8F13 end groups) (see course of green curve in Figure 3b). The third temperature appearing at first glance too high is the LCST of **P18** with α dioctadecyl (DiC18) and *ω* C8F13 end groups of 48.9 °C, which is the same as for **P17** with α dioctadecyl (DiC18) and *ω* C1 end groups (brown triangles in Figure 3a and right side of Figure 3b). A reasonable explanation for this behavior is a microphase separation causing the large hydrophobic residues to form aggregates such as micelles. In that case, a single polymer chain does not have to provide solubility for its hydrophobic end group, but several polymer chains solubilize a collapsed sphere. The LCST of such systems has been known to be higher than of singly dissolved chains.[24,29] We thus employed dynamic light scattering (DLS) to measure the hydrodynamic radii of selected heterotelechelic polymers in water at 20 °C, at which all polymers gave clear solutions. The values are also given in Table 1. The sizes of polymers **P1**, **P2**, **P5**, **P8**, **P10**, and **P11** all showed hydrodynamic radii in the order of 3.3−4.3 nm, as to be expected from isolated polymers of around 3500 g/mol. Polymers **P15**, **P16**, and **P18**, which all had shown unexpectedly high LCST, all produced monodisperse size distributions around 7.8−8.6 nm, significantly larger than all other measured polymers. The aggregation behavior of triphilic (hydrophilic, lipophilic, and fluorophilic components) polymers into superstructures[66] has been the focus of various research projects. Kubowicz et al.[64] reported the formation of cylindrical micelles of poly(*N*-acylethylene imines) with both C8F17 and C16 end groups, while Kyerematen et al.[67] recently described that the formation of multicompartment

micelles[59,60,62,68,69] of triphilic polymers depends on the length of the hydrophilic block and its ability to form loops. The DLS results found here will require a further profound characterization of the exact composition of aggregates, which is beyond the scope of this paper. In short, the DLS measurements confirmed that the polymers that showed unexpectedly high LCST were not dissolved on a molecular level but formed aggregates already at room temperature. The influence of such phase-separated α C9F17 or α DiC18 end groups was in the same order of magnitude as the influence of solubilized α C3 end groups (**P6** and **P7**). Interesting is the direct comparison of α C16, ω C8F13 polymer **P10** (radius 4.28 nm; LCST 44.7 °C) with α C9F17, ω C16 polymer **P15** (radius 8.51 nm; LCST 51.7 °C), the main difference of which is that a methylene end group unit of **P10** is substituted with a $-CF_2CF_2-$ segment in **P15**. Because of this, the critical length of the perfluorinated block is exceeded, causing **P15** to form aggregates and have a higher LCST.

Rigid (*Aromatic*) *End Groups*. Within the series of polymers **P2**−**P19**, the lowest LCST of 44.7 °C was found for **P10** with two hydrophobic end groups, not large enough though to cause a phase separation. Surprisingly, the LCST of starting polymer **P1** with pentafluorophenyl ester and dithioester end groups was yet lower at 42.7 °C. We attributed this low value to the difficulty of the polymer to solubilize its end groups. In contrast to (perfluorinated) alkyl chain end groups, the aromatic groups are rigid and reduce the end group entropy because of limited possibilities for the rigid systems to respond to conformational polymer chain movements. In addition, aromatic rings generally prefer π−π stacking interactions both over contact with water and over interactions with the nonaromatic polymer chain. This further decreases the stability of the modified coil and favors a precipitation below the LCST of chains with nonaromatic end groups. In the series of polymers with ω C1 end groups, the α diazo end group of **P19** caused an LCST of 49.1 °C, only 0.2 °C above **P17** with an α DiC18 end group, showing the impact of the two aromatic rings. Inoue et al.[23] investigated the molecular weight dependent thermal response of poly[ethoxyethyl glycidyl ether] chains grafted onto gold surfaces. For characterization in aqueous solution, they reported an LCST decrease of 6.3−14.6 °C (depending on molecular weight) for (rigid) phenothiazine end groups as compared to butoxy end group. In a different study, where functional acetylenes were clicked to azide modified PNIPAM, the lowest LCST was found for 4-phenoxyphenyl end groups, when compared to phenyl, octyl, and butyl groups.[27] These results are in agreement with the findings of this study.

As dithioesters are very typical RAFT end groups, it is of interest to consider the influence of PFP esters and dithioesters separately. In a previous paper, we reported the LCST of POEGMA of the same molecular weight with α PFP ester and ω isobutyronitrile end groups to be 46.1 °C.[52] This temperature was 3.8 °C lower than the LCST of α diazo, ω isobutyronitrile POEGMA, showing that the PFP ester has a stronger hydrophobic effect than the diazo end group. This is further supported by the even lower LCST of 39.5 °C of α PFP, ω PFP POEGMA.[52] This observation was in contrast to contact angle measurements of glass surfaces exhibiting PFP esters, which were less hydrophobic than dioctadecylamide, octadecylamide, or even octylamide surface groups of the same concentration.[70] α PFP, ω isobutyronitrile POEGMA having an LCST of 46.1 °C and α PFP, ω dithioester POEGMA (**P1**) having an LCST of 42.8 °C showed the hydrophobic contribution of the dithioester; its removal via the AIBN method could increase the LCST for 3.3 °C in this case.

Influence of Charged End Groups. An effect described in the literature is an LCST increase of PNIPAM[24,27,30] or poly[2-isopropyl-2-oxazoline][29] through the introduction of hydrophilic end groups, such as azides,[27] hydroxyl groups,[24,30] or amines.[24] Except for PEG, which produced nearly the literature LCST of POEGMA, the end groups discussed so far had all caused an LCST decrease. We therefore next investigated, whether a charged end group, α-(trimethylammonium)ethylamide (abbreviated "(+)" or "ammonium"), would also result in a higher LCST of POEGA. Polymer **P11**, with an α ammonium and an ω methyl end group, had an LCST of 66.3 °C. This showed that the charged end group with a higher hydrophilicity than the polymer chain could indeed provide water solubility until 2.3 °C above the literature LCST of 64 and 3.6 °C above the LCST of α PEG, ω methyl-terminated polymer **P2**.

Combination of Charged and Hydrophobic End Groups. Of special interest was then the combination of two end groups with opposite effects—one raising and one lowering the LCST. The LCST of the α ammonium polymers **P12** and **P13**, with ω C16 and ω C8F13 end groups, had LCST of 62.5 and 62.1 °C, respectively (black curve in Figure 3a and first column in Figure 3b). These temperatures were lower than for ω methyl end groups (**P11**), showing an influence of both end groups of these heterotelechelic polymers. Coincidently, the LCST of α ammonium polymers **P12** and **P13** were very close to those found for the α PEG polymers **P3** and **P4**. However, the difference between ω methyl and ω C16 of 3.8 °C was significantly lower than 8.0 ± 0.2 °C observed for the uncharged C3 and C16 α end groups. Apparently, for end groups of conflictive influences, a simple addition of increments for each end group in order to determine the LCST of a system composed of a chain and two end groups is not possible. This shows that a complex quantitative model would be required to predict the effect of a chemical structure on the LCST. However, such a model is not available at present but would clearly be desirable. Still, this series showed that two end groups with opposite effects can compensate each other. In this case, the influence of the charged α ammonium group dominated the influences of hydrophobic ω C16 or ω C8F13 end groups, with the latter two having a smaller impact than they do in combination with hydrophobic α end groups.

Combination of PEG and Hydrophobic End Groups. Finally, we consider the combination of PEG with hydrophobic end groups. Surprisingly, the LCST drop of 8.0 ± 0.2 °C for ω C16 as compared to ω C1 end groups, as discussed above, was not found, when the polymer contained α PEG groups. Instead, only a decrease from 62.7 °C (**P2**) to 62.4 °C (**P3**) of 0.3 °C was measured. In addition, the difference between ω C8F13 and ω C16 end groups was lowest for α PEG end groups, with another decrease of 0.3 to 62.1 °C of polymer **P4** (see red curve in Figure 3a). In sum, the LCST values of all α PEG polymers were nearly the same, independent of the ω end group (red curve in Figure 3A), indicating an ability of PEG to mask the influence of a hydrophobic group at the opposite end of the polymer chain onto the LCST. This suggests that PEGylation, which is already employed for enhancing the therapeutic potential of peptides, proteins,[71] and drugs,[72] or improving the contents release behavior of copolymer modified liposomes,[73] may also be applied for LCST stabilization of poly[oligo(ethylene glycol) methacrylate], thereby broadening the potential of this biocompatible polymer through highly functional materials with well-predictable thermal responses.

Conclusion

The combination of pentafluorophenyl ester α end groups and aminolysis of ω dithioesters in the presence of functional MTS reagents allowed the synthesis of α,ω heterotelechelic poly[oligo-(ethylene glycol) methacrylate] (POEGMA) in one-pot, one-step reactions. A library of polymers all with the same degree of polymerization but with two end groups of variable sizes and polarities could thus be obtained. These polymers were used to systematically investigate the influence of the end groups on the thermoresponsive behavior of POEGMA. As expected, the introduction of one hydrophobic end group caused an LCST decrease, with perfluorinated alkyl chains being more hydrophobic than regular alkyl chains. With two hydrophobic end groups, the influences of both were additive. Oligo(ethylene glycol) with a molecular weight 550 g/mol as one end group led to an LCST very close to the literature value due to the chemical similarity to the polymer. The influence of PEG was strong enough to mask the influence of hydrophobic groups on the opposite end of the polymer, thus stabilizing the LCST. Charged end groups increased the LCST. In the combination of charged with hydrophobic end groups, their influences compensated each other, with the charge having a higher contribution. With two large hydrophobic end groups, aggregates were formed at room temperature, which led to LCST higher than to be expected from the added influences of each individual end group. For perfluorinated alkyl chains, a chain with 13 F atoms did not phase separate, while a chain with 17 F atoms did cause aggregation, with the resulting system having an LCST in the same order than with dissolved propyl end groups. The strongest LCST decrease was found for rigid aromatic end groups, due to an incompatibility with both water and the flexible polymer chain.

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