Macromolecules **2007,** *40,* 2503−2508

About the Phase Transitions in Aqueous Solutions of Thermoresponsive Copolymers and Hydrogels Based on 2-(2-methoxyethoxy)ethyl Methacrylate and Oligo(ethylene glycol) Methacrylate

Jean-François Lutz,* Katja Weichenhan, Özgür Akdemir, and Ann Hoth

Research Group Nanotechnology for Life Science, Fraunhofer Institute for Applied Polymer Research, Geiselbergstrasse 69, Potsdam 14476, Germany

Received December 20, 2006; Revised Manuscript Received February 5, 2007

ABSTRACT: The phase transitions in water of well-defined copolymers of 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) and oligo(ethylene glycol) methacrylate (OEGMA, $M_n = 475$ g mol^{-1}) were studied by means of ^1H NMR, dynamic light scattering (DLS) and turbidimetry. These copolymers were synthesized by atom transfer radical polymerization (ATRP) in order to obtain macromolecules with a homogeneous chain-to-chain comonomer composition and therefore with a narrow phase transition. As previously reported, copolymers containing 10 mol % of OEGMA per chain ($M_n = 20\,100$ g mol^{-1}; $M_w/M_n = 1.35$) exhibited a sharp LCST in water around 40 °C, whereas copolymers having 20 mol % of OEGMA per chain ($M_n = 19\,500$ g mol^{-1}; $M_w/M_n = 1.32$) precipitated slightly above 50 °C. DLS indicated that these phase transitions are most likely due to a reversible coil-to-globule transition. Moreover covalently cross-linked networks of MEO_2MA and OEGMA were synthesized by ATRP in the presence of the cross-linker ethylene glycol dimethacrylate. These hydrogels were thermoresponsive and exhibited LCST values comparable to those measured for their single-chains analogues (e.g., hydrogels containing 20 mol % of OEGMA within the network underwent phase transitions at approximately 51−53 °C).

Introduction

Synthetic macromolecules undergoing rapid conformational change in response to an external stimulus such as pH, temperature, ionic strength or irradiation became lately very important in applied material science.[1−3] For example, thermoresponsive polymers exhibiting a lower critical solution temperature (LCST) in aqueous medium are very promising materials for bioapplications such as enzyme recycling, protein chromatography, controlled bioadhesion, hyperthermia-induced drug delivery or tissue engineering.[4−9] Such polymers are soluble in water below the LCST but precipitate at temperatures above it. Hence, temperature can be used as a simple external trigger for controlling the hydrophilicity and therefore the structural shape of these macromolecules.[10−12] Classic examples of synthetic polymers exhibiting an aqueous LCST include poly(*N*,*N*′-diethyl acrylamide),[1] poly(dimethylaminoethyl methacrylate),[1] poly(*N*-acryloylpyrrolidine),[13] poly(2-isopropyl-2-oxazoline),[14] elastin-like artificial polypeptides,[15] poly(vinyl methyl ether),[16] and poly(*N*-isopropylacrylamide) (PNIPAM).[17] The latter has been by far the most studied and applied thermoresponsive polymer and therefore can be considered as the gold standard in this research area. However, despite its widespread popularity in material science, PNIPAM has inherent disadvantages such as an irreversible phase transition and, for short polymers, a significant influence of end groups on the thermal behavior.[18−22]

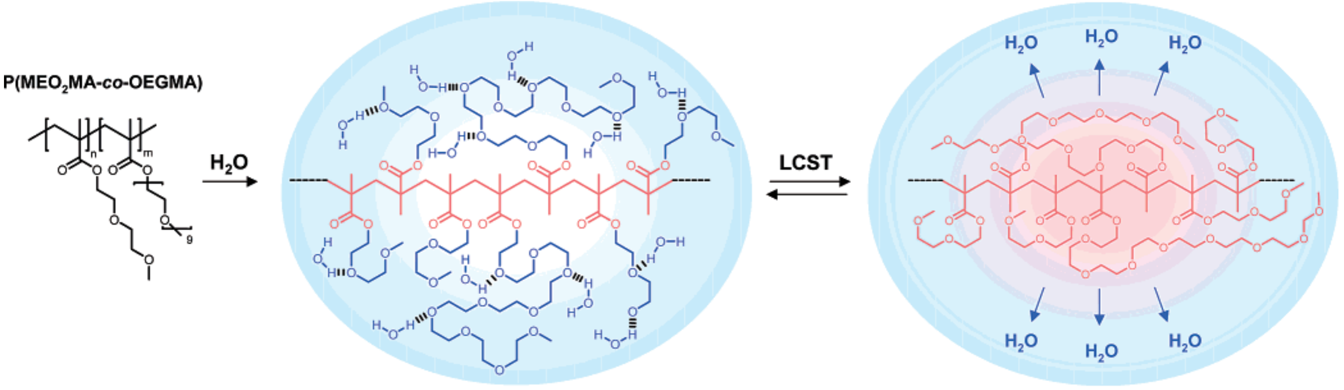
Thermoresponsive polymers containing short oligo(ethylene glycol) side chains were recently proposed as an attractive alternative to PNIPAM.[23−29] In particular, we reported last year the synthesis by atom transfer radical polymerization (ATRP) of well-defined thermoresponsive copolymers based on oligo(ethylene glycol) macromonomers of different chain-lengths n (i.e., of different hydrophilicity but similar chemical nature).[30−32] For example, random copolymers of 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA, $n = 2$) and oligo(ethylene glycol) methacrylate (OEGMA, $n \sim 9$) exhibit LCST values in between 26 °C and 90 °C, which can be precisely adjusted by varying the comonomer composition (Scheme 1). For example, cloud points of either 37, 39, or 49 °C were observed in pure water for copolymers possessing in average respectively 8, 10, or 20% of OEGMA units per chain.[31] These novel thermosensitive macromolecules are very promising for biomedical applications since they are principally composed of biocompatible oligo(ethylene glycol) segments.[33−35] Moreover, the phase transitions measured for the copolymers P(MEO_2MA-*co*-OEGMA) were found to be reversible and relatively insensitive to important parameters such as concentration of the copolymer in water, ionic strength and chain-length.[30,31] Hence, copolymers P(MEO_2MA-*co*-OEGMA) appear as promising alternative to conventional PNIPAM for bioapplications and more generally for building any kind of thermosentive materials. For instance, the fact that P(MEO_2MA-*co*-OEGMA) can be synthesized using the versatile ATRP method suggests that such thermoresponsive segments can be potentially easily connected to a wide variety of synthetic polymers, biological structures and inorganic surfaces.[36−42] However, our previous reports focused primarily on the synthesis of these novel copolymers while many aspects of their physicochemical properties still have to be explored. Hence, the goal of the present article is to shed more light on the thermoresponsive behavior of P(MEO_2MA-*co*-OEGMA). In particular, the nature of the phase transitions of these copolymers in dilute aqueous solutions was investigated using ^1H NMR, light scattering and turbidimetry. Moreover, since thermoresponsive hydrogels are of particular importance for several applications (vide supra), the physico-chemistry of macroscopic hydrogels based on MEO_2MA and OEGMA was preliminary

---

* Corresponding author. E-mail: lutz@iap.fhg.de.

10.1021/ma062925q CCC: $37.00

Scheme 1. Proposed Mechanism for the Temperature-Induced Phase Transition of Copolymers P(MEO_2MA-*co*-OEGMA) in Aqueous Solutions



studied and compared to the behavior of individual copolymer chains.

Experimental Part

Chemicals. 2-(2-Methoxyethoxy)ethyl methacrylate (Aldrich, 95%), poly(ethylene glycol) methyl ether methacrylate (Aldrich, $M_n = 475$ g·mol^{-1}), ethylene glycol dimethacrylate (Aldrich, 98%), methyl 2-bromopropionate (MBP) (Aldrich, 98%) and 2,2′ bipyridyl (Bipy) (Fluka, 98%) were used as received. Copper(I) bromide (Aldrich, 98%) and copper(I) chloride (Acros, 95%) were washed with glacial acetic acid in order to remove any soluble oxidized species, filtered, washed with ethanol, and dried.

Preparation of Single Chain Copolymers by Atom Transfer Radical Copolymerization of MEO_2MA and OEGMA. Copper chloride (1 equiv) and 2,2′ bipyridyl (2 equiv) were added to a Schlenk tube sealed with a septum. The tube was purged with dry argon for a few minutes. Then, a degassed mixture of 2-(2-methoxyethoxy)ethyl methacrylate (90 equiv), oligo(ethylene glycol) methyl ether methacrylate (10 equiv), and ethanol (monomers/ethanol ~ 1:1.25 v/v) was added through the septum with a degassed syringe. Last, methyl 2-bromopropionate (1 equiv) was added with a microliter syringe. The mixture was heated at 60 °C in an oil bath for several hours. The experiment was stopped by opening the flask and exposing the catalyst to air. The final mixture was diluted in ethanol and passed through a short silica column (60−200 mesh) in order to remove copper catalyst. Then, the filtered solution was diluted with deionized water and subsequently purified by dialysis in water (Roth, ZelluTrans membrane, molecular weight cutoff: 4000−6000). Last, water was removed by azeotropic distillation with ethanol. The purified polymer appeared as a clear oil.

Preparation of Covalently Cross-Linked Hydrogels by Atom Transfer Radical Copolymerization of MEO_2MA and OEGMA. Monolithic hydrogels were molded into capillary tubes having an internal diameter of 4 mm. Typically, 4 capillaries, copper bromide (1 equiv), 2,2′ bipyridyl (2 equiv), and a stir-bar were added to a Schlenk tube. Capillaries were stabilized in a separate compartment above the stir-bar for avoiding them to break by stirring. The tube was sealed with a septum and purged with dry argon for a few minutes. Then, a degassed mixture of 2-(2-methoxyethoxy)ethyl methacrylate (90 equiv), oligo(ethylene glycol) methyl ether methacrylate (10 equiv), ethylene glycol dimethacrylate (1 equiv), and ethanol (monomers/ethanol ~ 1:1.25 v/v) was added through the septum with a degassed syringe. The capillaries were fully immersed in this monomer/solvent solution. Last methyl 2-bromopropionate (1 equiv) was added with a microliter syringe. The mixture was heated overnight at 60 °C. The experiment was stopped by opening the flask and exposing the catalyst to air. The hydrogels were extracted from the capillaries by breaking carefully the glass. The resulting cylindrical monoliths were washed several times with pure ethanol in order to extract the copper catalyst. After such treatment (i.e., approximately 24 h in ethanol), the initially green gels appeared as transparent materials in ethanol solution, which indicated complete catalyst removal. Afterward, the hydrogels were dried under vacuum at 35 °C for several days. The purified polymers appeared as transparent gels.

Measurements and Analysis. Size Exclusion Chromatography, SEC. Molecular weights and molecular weight distributions were determined by SEC performed at 25 °C in tetrahydrofuran (THF) as eluent (flow rate: 1 mL·mn^{-1}), using three SDV columns (Polymer Standards Service GmbH) with a particle size of 5μ and a porosity of 10^3, 10^5, and 10^6 Å (the porosity values do not correspond to real pore diameters but to manufacturer standards). The detection was performed with a RI detector (Shodex RI-71) and a UV detector (TSP UV 1000; 260 nm). For calibration, linear polystyrene standards (PSS, Germany) were used.

Cloud Point Measurements. The cloud points of the polymer solutions in water were measured on a Tepper TP1 photometer (Mainz, Germany). Transmittance of polymer solutions in deionized water at 670 nm was monitored as a function of temperature (cell path length, 12 mm; one heating/cooling cycle at rate of 1 °C·min^{-1}).

Dynamic Light Scattering (DLS). Dynamic light scattering was performed with a High Performance Particle Sizer (HPPS-ET 5002, Malvern Instruments, UK) using a light scattering apparatus equipped with a He−Ne ($\lambda = 632.8$ nm) laser and a thermoelectric Peltier temperature controller (temperature control range: 10−90 °C). The measurements were made at the scattering angle $\theta = 173°$ ("backscattering detection"). For each measurement, the optimal measurement position, i.e., the optimal distance of the focal point from the cuvette wall, and the optimal attenuator was automatically determined by the HPPS software (Dispersion Technology Software 4.0). The autocorrelation functions were analyzed with the CONTIN method. The apparent hydrodynamic radius R_H of the polymer aggregates were calculated according to the Stokes−Einstein equation, $R_H = kT/6\pi\eta D_{app}$, with D_{app} apparent diffusion coefficient and η viscosity of the solution. The R_H values discussed herein are the mean sizes of the volume distribution. Prior to measurement, the polymer solutions were filtered using a WICOM OPTI-Flow 0.45 μm disposable filter and were placed in a 12.5 × 12.5 mm polystyrene disposable cuvette. Temperature-dependent DLS experiments were run with a heating or cooling program using steps of 2 °C. An equilibration time of 10 min was used at each step.

^{1}H NMR. ^{1}H NMR spectra were recorded in $CDCl_3$ or D_2O on a Bruker DPX-400 operating at 400.1 MHz. A polymer concentration of 10 mg·mL^{-1} was used for each measurement (32 scans).

Swelling/Deswelling Experiments. Swelling ratios were estimated gravimetrically. Dried hydrogels cylindrical monoliths with a length of 10 mm and an initial weight W_d of approximately 100 mg were placed in an excess of deionized water at room temperature. The weight of the swollen hydrogels W_s was then measured as a function of time. Prior to each measurement, the surfaces of the monoliths were shortly dried with a hygroscopic filter paper. The swelling ratio Q were then calculated according to eq 1.

Table 1. Properties of Copolymers of OEGMA and MEO$_2$MA Prepared by ATRP[a]

	[MEO$_2$-MA]$_0$, equiv	[OEGMA]$_0$, equiv	[EGDM]$_0$, equiv	catalyst	M$_n$	M_w/M_n
1	90	10		1 equiv CuCl/Bipy$_2$	20 100	1.35
2	80	20		1 equiv CuCl/Bipy$_2$	19 500	1.32
3	90	10	1	1 equiv CuBr/Bipy$_2$	gel	gel
4	80	20	1	1 equiv CuBr/Bipy$_2$	gel	gel

[a] Experimental conditions: 60 °C; in ethanol solution (monomers/ethanol = 1:1.25 (v/v)) and in the presence of 1 equiv of the initiator MBP.

$$Q = (W_s - W_d)/W_d \qquad (1)$$

When the swelling ratio reached a plateau at room temperature, the samples were heated at a temperature above LCST (i.e., 60 °C) and the evolution of the swelling ratio was further monitored as a function of time at this higher temperature.

Results and Discussion

Nature of the Phase Transitions for P(MEO$_2$MA-*co*-OEGMA) Single Chains. Well-defined copolymers of MEO$_2$-MA and OEGMA were synthesized by atom transfer radical copolymerization in ethanol solutions (Table 1). Two different comonomer compositions MEO$_2$MA/OEGMA were investigated in the present work: 90:10 and 80:20. As reported previously, the former leads to copolymers exhibiting a sharp LCST at approximately 40 °C in pure water (e.g., a cloud point of 39 °C was observed at a concentration of 3 mg·mL^{-1}), whereas the latter leads to copolymers having an aqueous LCST around 50 °C (e.g., a cloud point of 49 °C was observed at a concentration of 3 mg·mL^{-1}).[31] Since the molar fraction of OEGMA in the copolymers is the main factor influencing the LCST, such defined phase transitions can only be observed if the copolymers have an uniform chain-to-chain composition (i.e., are synthesized using a living or pseudo-living polymerization technique such as ATRP).[30,31]

Scheme 1 shows the mechanism proposed for explaining the thermoresponsiveness of P(MEO$_2$MA-*co*-OEGMA) copolymers. For most of the macromolecules exhibiting an aqueous LCST, the thermoresponsive behavior generally results from a subtle balance between favorable and unfavorable interactions in water. In the case of PNIPAM for example, amide functions form stabilizing H-bonds with water, whereas apolar regions such as the alkyl backbone or the isopropyl substituents lead to a competitive hydrophobic effect.[17] Above LCST, this balance is disrupted and polymer−polymer interactions are thermodynamically favored as compared to polymer−water interactions. In the present case, hydrogen bonding with surrounding water molecules is also the driving-force, which promotes the aqueous solubilization of P(MEO$_2$MA-*co*-OEGMA) at room temperature. Indeed, the conformationally favored formation of H-bonds between the ether oxygens of poly(ethylene glycol) and water hydrogens is believed to be one of the key factors responsible for the unusual water solubility of this poly(ether).[43−45] However for P(MEO$_2$MA-*co*-OEGMA) copolymers, this favorable effect is counterbalanced by the hydrophobicity of the apolar backbone. To confirm this hypothesis the macromolecular structure of P(MEO$_2$MA-*co*-OEGMA) was investigated by ^{1}H NMR in various deuterated solvents. For instance, Figure 1 compares the spectra measured for the copolymer containing 20 mol % of OEGMA (Table 1, entry 2) in CDCl$_3$ and D$_2$O.

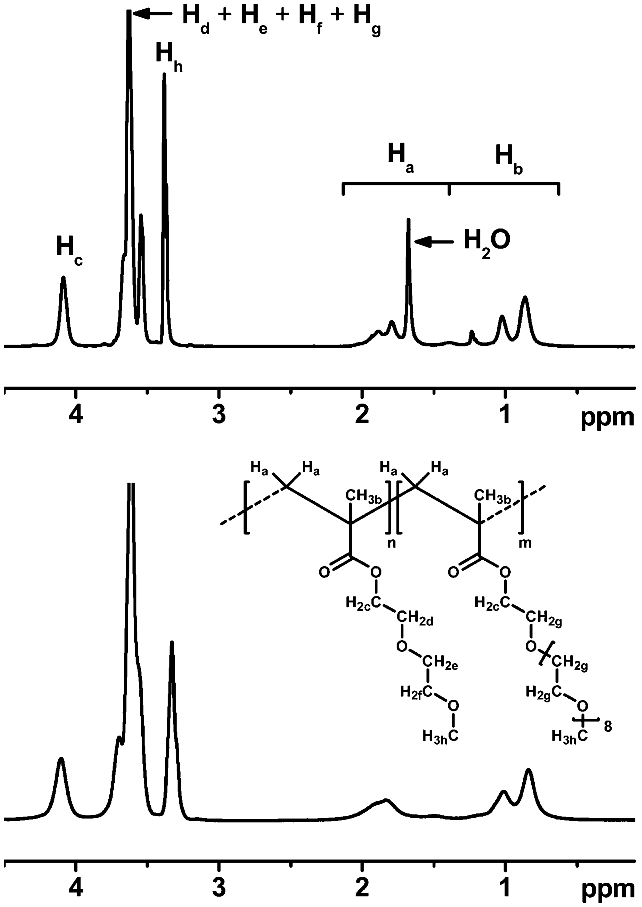


Figure 1. ^{1}H NMR spectra of a copolymer P(MEO$_2$MA-*co*-OEGMA) containing 20 mol % of OEGMA per chain (Table 1, entry 2) recorded in either CDCl$_3$ (top) or D$_2$O (bottom).

In deuterated chloroform, all the protons of this copolymer lead to sharp and intense signals, which suggests that the macromolecule is uniformly molecularly dissolved. This observation was corroborated by the integration of the different regions of the spectrum, which fit almost perfectly to the theoretical values (Table 2). Rather different results were observed in deuterated water (Figure 1). In D$_2$O, the peaks corresponding to the protons of the oligo(ethylene glycol) side chains remain sharp, but the signals of the protons belonging to the backbone or located in close proximity of the backbone (e.g., the CH$_2$ neighboring the ester functions) are considerably reduced and broadened as compared to those observed in CDCl$_3$. The integration values additionally reveal that the hydration of these macromolecules is not uniform (Table 2). Some authors reported that the hydrophilic/hydrophobic balance of oligo(ethylene glycol) macromonomers and corresponding polymers is sufficiently marked to induce their aggregation in water.[46−49] Ito and co-workers demonstrated that comb polymers with multiple PEG side chains generally adopt a compact coil conformation in water (i.e., single-chain entities).[47] However, the existence of intermolecular associations, resulting in the formation of larger aggregates such as polymer vesicles, was also recently suggested.[49] Thus, in the present case, it was important to study the exact conformation of P(MEO$_2$MA-*co*-OEGMA) copolymers in aqueous solutions above and below the LCST. Figure 2 shows the typical size distributions measured by dynamic light scattering (DLS) for an aqueous solution (3 mg·mL^{-1}) of the copolymer containing 20 mol % of OEGMA

Table 2. Integration Values Measured by ^{1}H NMR for a Copolymer P(MEO$_2$MA-*co*-OEGMA) Containing 20 mol % of OEGMA (Table 1, Entry 2)[a]

	3.95−4.30 ppm of H_c	3.45−3.85 ppm of $H_d + H_e + H_f + H_g$	3.20−3.45 ppm of H_h	1.35−2.25 ppm of H_a	0.50−1.30 ppm of H_b
theory	200	1120[b]	300	200	300
$CDCl_3$	190	1136	300[c]	*d*	310
D_2O	175	1114	300[c]	124	262

[a] Experimental conditions: 25 °C, 32 scans, polymer concentration = 10 mg mL^{-1}. [b] As commercial OEGMA macromonomers are not monodisperse, this theoretical value was calculated assuming an average number of 32 H_g protons per OEGMA unit. [c] Set as a reference, assuming that these methoxy protons are well-soluble in all the investigated solvents. [d] Not quantifiable due to the presence of the peak of irremovable water at 1.68 ppm.

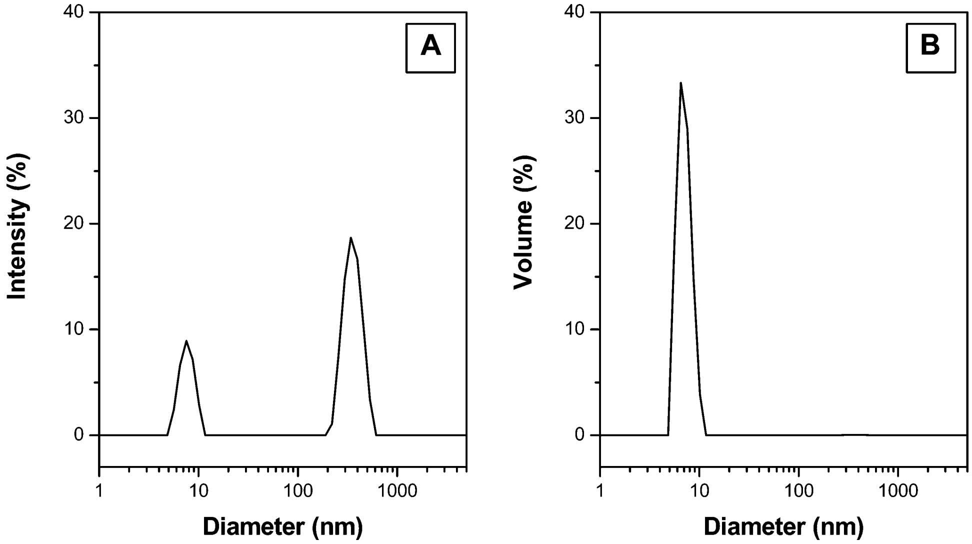


Figure 2. Intensity size distribution (A) and volume size distribution (B) measured by dynamic light scattering at room temperature (i.e., below LCST) for an aqueous solution (3 mg·mL^{-1}) of a copolymer P(MEO$_2$MA-*co*-OEGMA) containing 20 mol % of OEGMA per chain (Table 1, entry 2).

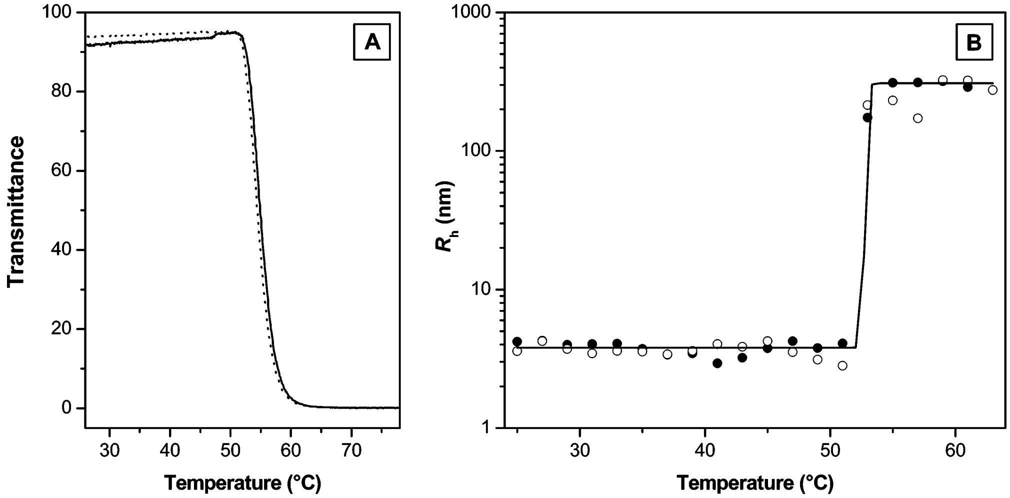


Figure 3. Plots of transmittance as a function of temperature (A) measured by turbidimetry (solid line, heating; dotted line, cooling) and plots of the hydrodynamic radius R_h as a function of temperature (B) recorded by dynamic light scattering (full symbol: heating, empty symbols; cooling) for an aqueous solution (1 mg·mL^{-1}) of a copolymer P(MEO$_2$MA-*co*-OEGMA) containing 20 mol % of OEGMA per chain (Table 1, entry 2); the full line represents a Boltzmann fit of the data.

(Table 1, entry 2). This solution was optically clear at room temperature but the DLS intensity distribution indicated the coexistence of small particles with a hydrodynamic radius (R_h) of approximately 3.7 nm and larger aggregates having a radius of roughly 150 nm.[50] The latter are indeed a negligible minority, as evidenced by the volume distribution shown in Figure 2B (these larger objects represent less than 0.01% of the overall volume distribution). Hence below LCST, P(MEO$_2$MA-*co*-OEGMA) adopts mostly a coiled conformation in water. It is important to note that this observation is independent of the mode of purification used for removing macroscopic dust from the samples. Two pathways were compared: (i) the direct dissolution of the raw polymer in prefiltered (0.45 μm) deionized water and (ii) the microfiltration (0.45 μm) of a premade aqueous solution of the copolymer. In both cases, comparable intensity and volume distributions were measured by DLS.

Figure 3 shows the thermal behavior of an aqueous solution (1 mg·mL^{-1}) of the copolymer containing 20 mol % of OEGMA (Table 1, entry 2), as monitored by dynamic light scattering (DLS) and turbidimetry. Both techniques reveal the temperature induced phase transition of P(MEO$_2$MA-*co*-OEGMA) in water. For instance, an abrupt transition was measured by DLS at a

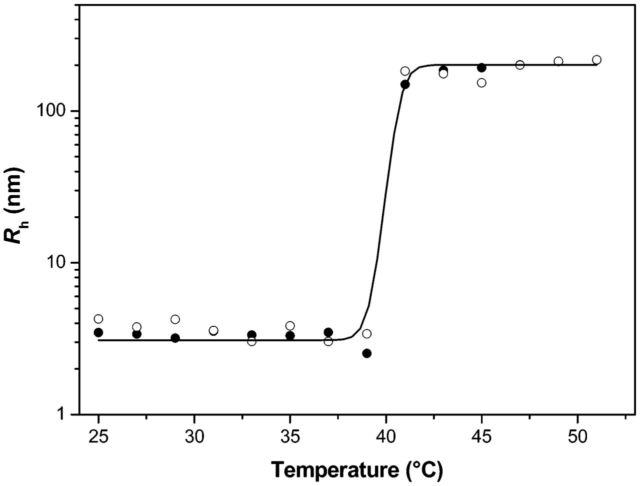


Figure 4. Plots of the hydrodynamic radius R_h as a function of temperature measured by dynamic light scattering (full symbol: heating, empty symbols; cooling) for an aqueous solution (1 mg·mL^{-1}) of a copolymer P(MEO$_2$MA-*co*-OEGMA) containing 10 mol % of OEGMA per chain (Table 1, entry 1); the full line represents a Boltzmann fit of the data.

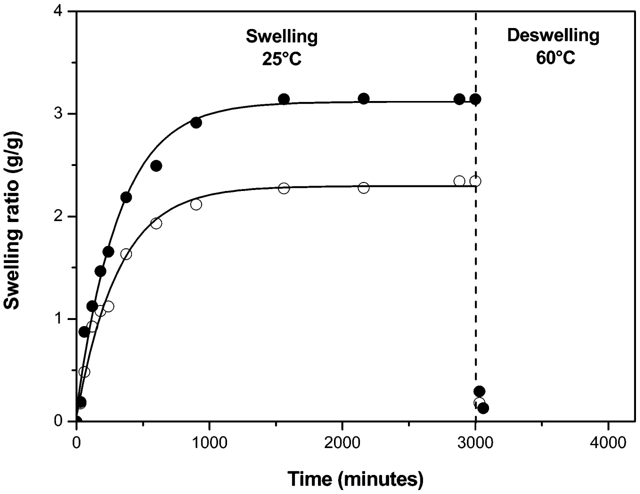


Figure 5. Evolution of the swelling ratio as a function of time for macroscopic hydrogels P(MEO$_2$MA-*co*-OEGMA) containing either 10% (Table 1, entry 3, empty symbols) or 20 mol % (Table 1, entry 4, full symbols) of OEGMA per chain. At $t = 3000$ min, the temperature of the aqueous medium was quickly raised from 25 °C to 60 °C.

temperature of approximately 53 °C (Figure 3B). Above this temperature, large aggregates with a hydrodynamic radius of approximately 300 nm were observed. Such large particles are comparable in size to what is usually observed above LCST for either PNIPAM, poly(*N*,*N*′-diethyl acrylamide) or poly(vinyl methyl ether).[51−53] It can be assumed by analogy that these objects are stable mesoglobules, which result from the aggregation of collapsed dehydrated chains.[17,52,53] However, as discussed in previous reports, the polymer−polymer interactions stabilizing these globules are probably not H-bonds like in PNIPAM (there is no strong H-bond donors in the molecular structure of P(MEO$_2$MA-*co*-OEGMA)) but weaker van der Waals interactions.[30] Thus, the phase transitions of P(MEO$_2$MA-*co*-OEGMA) copolymers are reversible (i.e., no hysteresis can be observed) as evidenced by turbidimetry and light scattering (Figure 3). Nevertheless, it is interesting to note that the cloud point measured by turbidimetry is slightly higher (i.e., approximately 1 °C) than the one measured by DLS.

Figure 4 shows the phase transition observed by DLS for an aqueous solution (1 mg·mL^{-1}) of P(MEO$_2$MA-*co*-OEGMA) containing 10 mol % of OEGMA (Table 1, entry 1). An abrupt transition can be clearly observed at approximately 40 °C, which is in good accordance with previously reported values.[31] Overall, the behavior of this copolymer in water is very comparable to what is described above for the copolymer with a higher OEGMA content. However, the DLS sizes displayed in Figure 4 are smaller than those shown in Figure 3. Below LCST, coils with a hydrodynamic radius of approximately 3 nm were observed, whereas above the LCST smaller mesoglobules with a hydrodynamic radius of approximately 200 nm were formed. Additionally, a slight shrinkage of the polymer coils could be observed shortly before the apparition of mesoglobules (i.e., 39 °C). Such behavior has been previously reported for other thermoresponsive polymers and could be a proof of coil dehydration (i.e., coil-to-globule transition) prior to aggregation.[18,51]

Phase Transitions of Covalently Cross-Linked Hydrogels. Macroscopic copolymer hydrogels composed of MEO$_2$MA and OEGMA were prepared using ethylene glycol dimethacrylate (EGDM) as a cross-linker (Table 1). Although such hydrogels could be easily synthesized by conventional radical polymerization, the ATRP methods was selected to ensure a homogeneous comonomer composition in each region of the macromolecular network. Indeed, in the ATRP process, all the chains constituting the network grow simultaneously and therefore consume homogeneously the comonomers.[54] Such precaution would not be necessary if one is only interested in the swelling of the hydrogel at room temperature. However, if a thermoresponsive gel is targeted, a defined composition of the network is probably essential. Two macroscopic gels with different MEO$_2$MA/OEGMA compositions were prepared: 90/10 and 80/20 (Table 1). Figure 5 shows the swelling/deswelling behavior measured for these two samples. Both hydrogels exhibited a satisfying swelling capacity in pure water and appeared as homogeneous transparent materials in the swollen state. However, the swelling rates and the maximum swelling ratios were found to be proportional to the fraction of OEGMA grafts in the network, which is a logical behavior previously observed for PEG grafted hydrogels.[55]

Both hydrogels were found to be thermoresponsive. Their phase transitions were visually evaluated (i.e., the formation of a skin layer on the surface of the hydrogels was examined as a function of temperature) and found to be in the range 42−45 °C for the gel with 10 mol % OEGMA (Table 1, entry 3) and 51−53 °C for the gel with 20 mol % OEGMA (Table 1, entry 4), which roughly correspond to the phase transitions observed for single-chain copolymers (vide supra). Preliminary evaluation of the deswelling kinetics of these thermoresponsive hydrogels indicated that their thermally induced shrinkage is extremely fast (Figure 5). Such a behavior could be a consequence of the presence of the long OEGMA grafted chains, which can potentially act as water release channels within the network and therefore boost the deswelling kinetics.[56] A comprehensive study of these promising materials is currently under investigation.

Conclusion

The thermal behavior of well-defined copolymers of 2-(2-methoxyethoxy)ethyl methacrylate and oligo(ethylene glycol) methacrylate P(MEO$_2$MA-*co*-OEGMA) was investigated in dilute aqueous solutions. As previously reported, these copolymers exhibit a sharp and reversible LCST in water. ^{1}H NMR and DLS measurement indicated that, similarly to PNIPAM, the observed phase transitions are probably due to a coil-to-globule transition. Shortly after dehydration, the collapsed macromolecules rearrange by collision into stable mesoglobules with an average hydrodynamic diameter of approximately 200−300 nm. Nevertheless, these particles are stabilized by weak intermolecular associations (i.e., van der Waals interactions) and therefore redissolve readily upon cooling without any noticeable hysteresis.

Additionally, covalently cross-linked hydrogels P(MEO$_2$MA-*co*-OEGMA) were prepared by atom transfer radical polymerization in the presence of small amounts of the difunctional cross-linker ethylene glycol dimethacrylate. Such cross-linked networks exhibited a thermoresponsive behavior in water and their LCST were found to be roughly comparable to those observed for their single-chains counterparts. Moreover their swelling/deswelling kinetics in water were found to be very appropriate for biomedical applications such as drug release or tissue engineering. A detailed investigation of these promising hydrogels is currently under investigation.

Acknowledgment. Fraunhofer society and Deutsche Forschungsgemeinschaft (LU 1195/1-1) are greatly acknowledged for financial support. Moreover, J.F.L. thanks professor André Laschewsky (Universität Potsdam) and Reinhard Sigel (MPIKG Golm) for fruitful discussions.

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.* **2005**, (3), 276−285.
(3) Lutz, J.-F. *Polym. Int.* **2006**, *55*, 979−993.
(4) Okano, T.; Yamada, N.; Okuhara, M.; Sakai, H.; Sakurai, Y. *Biomaterials* **1995**, *16*, 297−303.
(5) Stayton, P. S.; Shimoboji, T.; Long, C.; Chilkoti, A.; Ghen, G.; Harris, J. M.; Hoffman, A. S. *Nature (London)* **1995**, *378*, 472−474.
(6) Galaev, I. Y.; Mattiasson, B. *Trends Biotech.* **1999**, *17*, 335−340.
(7) Kikuchi, A.; Okano, T. *Prog. Polym. Sci.* **2002**, *27*, 1165−1193.
(8) Cunliffe, D.; de las Heras Alarcon, C.; Peters, V. S. J. R.; Alexander, C. *Langmuir* **2003**, *19*, 2888−2899.
(9) Hoffman, A. S.; Stayton, P. *Macromol. Symp.* **2004**, *207*, 139−151.
(10) Yoshida, R.; Uchida, K.; Kaneko, Y.; Sakai, K.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Nature (London)* **1995**, *374*, 240−242.
(11) Arotçaréna, M.; Heise, B.; Ishaya, S.; Laschewsky, A. *J. Am. Chem. Soc.* **2002**, *124*, 3787 -3793.
(12) Hua, F.; Jiang, X.; Zhao, B. *Macromolecules* **2006**, *39*, 3476−3479.
(13) Mertoglu, M.; Garnier, S.; Laschewsky, A.; Skrabania, K.; Storsberg, J. *Polymer* **2005**, *46*, 7726−7740.
(14) Park, J.-S.; Kataoka, K. *Macromolecules* **2006**, *39*, 6622−6630.
(15) Mart, R. J.; Osborne, R. D.; Stevens, M. M.; Ulijn, R. V. *Soft Matter* **2006**, *2*, 822−835.
(16) Maeda, Y. *Langmuir* **2001**, *17*, 1737−1742.
(17) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17* (2), 163−249.
(18) Wang, X.; Qiu, X.; Wu, C. *Macromolecules* **1998**, *31*, 2972−2976.
(19) Wang, X.; Wu, C. *Macromolecules* **1999**, *32*, 4299−4301.
(20) Cheng, H.; Shen, L.; Wu, C. *Macromolecules* **2006**, *39*, 2325−2329.
(21) Kujawa, P.; Segui, F.; Shaban, S.; Diab, C.; Okada, Y.; Tanaka, F.; Winnik, F. M. *Macromolecules* **2006**, *39*, 341−348.
(22) Xia, Y.; Burke, N. A. D.; Stover, H. D. H. *Macromolecules* **2006**, *39*, 2275−2283.
(23) Han, S.; Hagiwara, M.; Ishizone, T. *Macromolecules* **2003**, *26*, 8312−8319.
(24) Ali, M. M.; Stöver, H. D. H. *Macromolecules* **2004**, *37*, 5219−5227.
(25) Kitano, H.; Hirabayashi, T.; Gemmei-Ide, M.; Kyogoku, M. *Macromol. Chem. Phys.* **2004**, *205*, 1651−1659.
(26) Jones, J. A.; Novo, N.; Flagler, K.; Pagnucco, C. D.; Carew, S.; Cheong, C.; Kong, X. Z.; Burke, N. A. D.; Stöver, H. D. H. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 6095−6104.
(27) Sugihara, S.; Kanaoka, S.; Aoshima, S. *Macromolecules* **2005**, *38*, 1919−1927.
(28) Zhang, D.; Macias, C.; Ortiz, C. *Macromolecules* **2005**, *38*, 2530−2534.
(29) Zhao, B.; Li, D.; Hua, F.; Green, D. R. *Macromolecules* **2005**, *38*, 9509−9517.
(30) Lutz, J.-F.; Akdemir, O.; Hoth, A. *J. Am. Chem. Soc.* **2006**, *128*, 13046−13047.
(31) Lutz, J.-F.; Hoth, A. *Macromolecules* **2006**, *39*, 893−896.
(32) Skrabania, K.; Kristen, J.; Laschewsky, A.; Akdemir, O.; Hoth, A.; Lutz, J.-F. *Langmuir* **2007**, *23*, 84−93.
(33) Duncan, R. *Nature Rev. Drug Discov.* **2003**, *2*, 347−360.
(34) Lutz, J.-F.; Stiller, S.; Hoth, A.; Kaufner, L.; Pison, U.; Cartier, R. *Biomacromolecules* **2006**, *7*, 3132−3138.
(35) Pasut, G.; Veronese, F. M. *Adv. Polym. Sci.* **2006**, *192*, 95−134.
(36) Davis, K.; Matyjaszewski, K. *Adv. Polym. Sci.* **2002**, *159*, 1−157.
(37) Pyun, J.; Kowalewski, T.; Matyjaszewski, K. *Macromol. Rapid Commun.* **2003**, *24*, 1043−1059.
(38) Lele, B. S.; Murata, H.; Matyjaszewski, K.; Russell, A. J. *Biomacromolecules* **2005**, *6*, 3380−3387.
(39) Lutz, J.-F.; Börner, H. G.; Weichenhan, K. *Macromol. Rapid Commun.* **2005**, *26*, 514−518.
(40) Mantovani, G.; Lecolley, F.; Tao, L.; Haddleton, D. M.; Clerx, J.; Cornelissen, J. J. L. M.; Velonia, K. *J. Am. Chem. Soc.* **2005**, *127*, 2966−2973.
(41) Matyjaszewski, K. *Prog. Polym. Sci.* **2005**, *30*, 858−875.
(42) Lutz, J.-F.; Börner, H. G.; Weichenhan, K. *Macromolecules* **2006**, *39*, 6376−6383.
(43) Israelachvili. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 8378−8379.
(44) Begum, R.; Matsuura, H. *J. Chem. Soc. Faraday Trans.* **1997**, *93*, 3839−3848.
(45) Tasaki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8459−8469.
(46) Ito, K.; Tanaka, K.; Tanaka, H.; Imai, G.; Kawaguchi, S.; Itsuno, S. *Macromolecules* **1991**, *24*, 2348−2354.
(47) Ito, K.; Tomi, Y.; Kawaguchi, S. *Macromolecules* **1992**, *25*, 1534−1538.
(48) Kawaguchi, S.; Yekta, A.; Duhamel, J.; Winnik, M. A.; Ito, K. *J. Phys. Chem.* **1994**, *98*, 7891−7898.
(49) Li, X.; Ji, J.; Shen, J. *Macromol. Rapid Commun.* **2006**, *27*, 214−218.
(50) Comparable bimodal intensity distributions were also measured for several other water soluble polymers (e.g., PNIPAM) with the same instrument (same concentration) and may be artifacts of this commercial built-in light scattering setup.
(51) Lessard, D. G.; Ousalem, M.; Zhu, X. X.; Eisenberg, A.; Carreau, P. J. *J. Polym. Sci., Part B: Polym. Phys.* **2003**, *41*, 1627−1637.
(52) Aseyev, V.; Hietala, S.; Laukkanen, A.; Nuopponen, M.; Confortini, O.; Du Prez, F. E.; Tenhu, H. *Polymer* **2005**, *46*, 7118−7131.
(53) Kujawa, P.; Aseyev, V.; Tenhu, H.; Winnik, F. M. *Macromolecules* **2006**, *39*, 7686−7693.
(54) Wang, A. R.; Zhu, S. *Polym. Eng. Sci.* **2005**, *45*, 720−727.
(55) Lee, W.-F.; Lin, Y.-H. *J. Appl. Polym. Sci.* **2003**, *90*, 1683−1691.
(56) Kaneko, Y.; Nakamura, S.; Sakai, K.; Aoyagi, T.; Kikuchi, A.; Sakurai, Y.; Okano, T. *Macromolecules* **1998**, *31*, 6099−6105.

MA062925Q