Thermogelation of PEG-Based Macromolecules of Controlled Architecture

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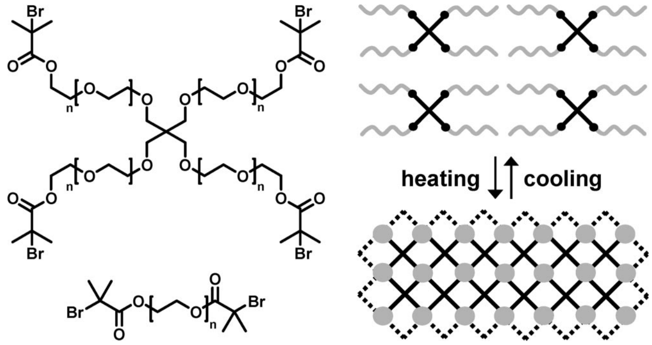
Graft (co)polymers with oligo(ethylene glycol) side chains emerged lately as a promising new class of thermoresponsive polymers.[1] Indeed, these macromolecules exhibit, for the most part, a defined lower critical solution temperature (LCST) in aqueous or physiological medium.[2−5] This thermoresponsive behavior is believed to be related to the amphiphilic character of these polymers.[6] Indeed, the hydrophilic oligo(ethylene glycol) side chains form H-bonds with water, whereas the backbones, which are usually less polar in nature, lead to a competitive hydrophobic effect. For instance, oligo(ethylene glycol)-grafted polymers based on poly(vinyl ether),[2] poly(norbornene),[7] polyester,[8] polystyrene,[9] poly(acrylate),[10] or poly(methacrylate)[4,11] backbones were all reported to exhibit a LCST in water. Still, the latter category has been progressively more studied in recent years. Indeed, most of the oligo(ethylene glycol) methyl ether methacrylates are commercially available and moreover can be readily polymerized using versatile polymerization techniques such as atom transfer radical polymerization (ATRP) or reversible addition−fragmentation transfer polymerization (RAFT).[12] For example, we recently reported that the atom transfer radical copolymerization of two oligo(ethylene glycol) methacrylates of different chain lengths, namely 2-(2-methoxyethoxy)ethyl methacrylate (MEO_2MA) and oligo(ethylene glycol) methacrylate ($OEGMA_{475}$, $M_n = 475$ g mol^{-1}), leads to the formation of thermoresponsive copolymers with a precisely tunable LCST in water.[5] 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.[4] Hence, these novel polymers appear as promising candidates for building advanced stimuli-responsive materials. For example, several recent reports described the preparation of oligo(ethylene glycol)-based thermoresponsive materials such as dendrimers, microgels, silica particles, gold particles, block copolymer aggregates, carbon nanotubes, and planar surfaces.[13]

In the present work, P(MEO_2MA-*co*-OEGMA) segments were studied for preparing thermoreversible hydrogel networks. Biocompatible scaffolds with switchable properties between room temperature and physiological temperature are materials of high interest for biotechnological applications such as regenerative medicine, cell engineering, transdermal patches, and implants. Some synthetic and biological polymers have already been shown to exhibit a thermogelation behavior in aqueous medium.[14,15] In particular, hydrophilic copolymers (i.e., random, block, graft, or star copolymers) containing thermoresponsive poly(*N*-isopropylacrylamide) (PNIPAM) segments usually display a sol−gel transition in water.[16,17] In such cases, the physical cross-linking is induced by the collapse of the PNIPAM chains above LCST. Herein, comparable materials based on P(MEO_2MA-*co*-OEGMA) were synthesized and characterized. The goal of this communication is to demonstrate that oligo(ethylene glycol) methacrylates constitute a unique platform for preparing biorelevant thermogels with optimal properties under near physiological conditions.

Scheme 1. (left) Molecular Structures of the 4-Arm Star (top) and Linear (bottom) PEG Macroinitiators Used in the Present Study; (right) Schematic Representation of the Thermogelation of the Star Polymers[a]



[a] Dark gray and black segments represent the thermoresponsive P(MEO_2MA-*co*-OEGMA) chains and the permanently hydrophilic PEG star cores, respectively.

The building blocks of these controllable networks were synthesized by ATRP of MEO_2MA and $OEGMA_{475}$ in the presence of either linear or star-shaped PEG macroinitiators (Scheme 1, left). The formed copolymers possess permanently hydrophilic PEG inner blocks and thermoresponsive P(MEO_2MA-*co*-OEGMA) outer blocks. Below the LCST of the thermoresponsive segments, these (star)-block copolymers are expected to be double hydrophilic (i.e., fully soluble in aqueous medium), whereas above LCST, P(MEO_2MA-*co*-OEGMA) chains should precipitate, thus resulting in the formation of a defined hydrogel network (Scheme 1, right). At first glance, this concept may appear speculative, considering that these building blocks are principally composed of the same structural units (i.e., ethylene oxide). Yet, one objective of the present work is to demonstrate that a precise control over macromolecular architecture may induce strong thermothickening effects in water.

ATRP macroinitiators of different molecular weights were synthesized by reacting the terminal alcohol functions of either linear (i.e., 2 terminal OH groups) or 4-arm star (i.e., 4 terminal OH groups) commercial PEGs with 2-bromoisobutyryl bromide.[18] In all cases, quantitative esterification of the PEG chain ends was confirmed by ^{1}H NMR analysis. These structures were then used for initiating the copolymerization of MEO_2MA and $OEGMA_{475}$ at 60 °C, in ethanol solution and in the presence of copper(I) chloride and 2,2′ bipyridyl.[5] Various linear triblock copolymers P(MEO_2MA-*co*-OEGMA)-*b*-PEG-*b*-P(MEO_2MA-*co*-OEGMA) and 4-arm star block copolymers sPEG-*b*-P(MEO_2MA-*co*-OEGMA) were prepared under these experimental conditions (Table 1). Generally speaking, well-defined polymers with controlled molecular weight distribution, block lengths, and composition could be isolated in all cases. However, the molecular weights measured by SEC for the star-block copolymers were found to be much lower than expected. This aspect is not particularly surprising, taking into account the

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Table 1. Properties of the Thermoresponsive Linear and Star-Block Copolymers PEG-*b*-P(MEO_2MA-*co*-OEGMA) Prepared Using ATRP[a]

	initiator[b]	MEO_2MA/OEGMA	*t* (h)	$DP_{n,th}$[c]	conv[d]	DP_n[c]	M_n[e] (g mol^{-1})	M_w/M_n[e]	cloud point[f] in H_2O (°C)	cloud point [f] in PBS (°C)
1	L4000	90:10	20	50	0.86	43	19 400	1.22	42	38
2	L6000	90:10	20	50	0.84	42	19 300	1.1	47	44
3	L10000	90:10	20	50	0.80	40	18 500	1.2	–[g]	–[g]
4	S10000	90:10	20	50	0.99	49	18 300	1.26	60[g]	55[g]
5	S10000	90:10	20	100	0.62	62	25 400	1.22	56	40
6	S10000	90:10	44	150	0.62	93	24 800	1.38	50	37
7	S10000	90:10	64	200	0.59	118	34 600	1.18	52	36
8	S10000	95:5	64	150	0.70	105	36 900	1.23	40	31

[a] Experimental conditions: in ethanol solution (monomer/ethanol = 1:1.25 (v/v)), 60 °C, $[\text{initiator}]_0/[\text{CuCl}]_0/[\text{Bipy}]_0 = 1/1/2$. Entry 3 was performed in more dilute conditions. [b] The acronyms L and S denote linear and star PEG macroinitiators, respectively. [c] Average degree of polymerization per arm. [d] Overall monomer conversion calculated from ^{1}H NMR spectra. [e] Measured by SEC in THF. [f] Measured by turbidimetry for a concentration of 10 mg mL^{-1}; the presented values are the inflection points of the heating cycles. [g] Not possible or difficult to measure.

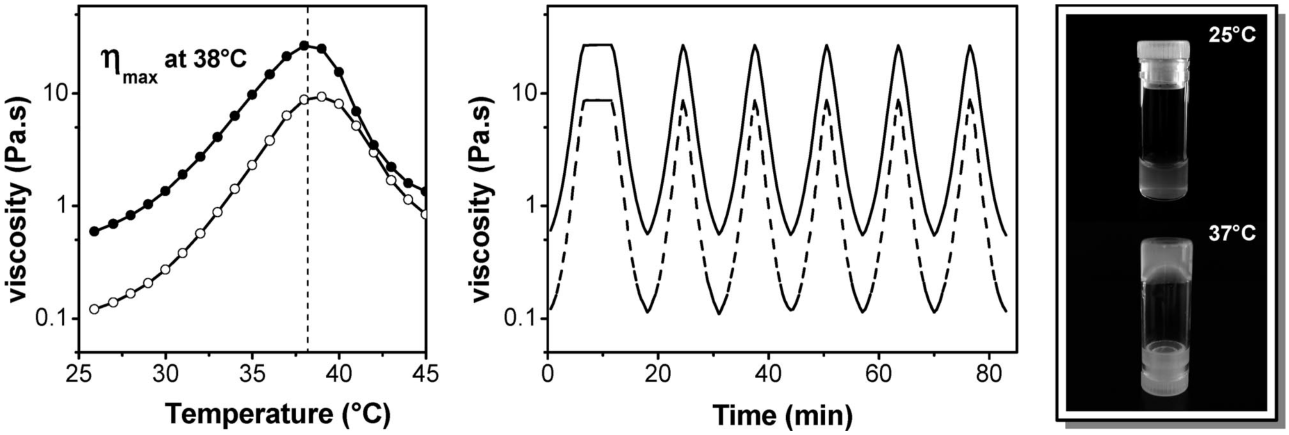

Figure 1. (left) Plots of viscosity as a function of temperature measured at a constant shear rate of 10 s^{-1} for a star-block copolymer sPEG-*b*-P(MEO_2MA-*co*-OEGMA) (Table 1, entry 8) in PBS solution at a concentration of 16 (empty symbols) or 23 wt % (full symbols). (middle) Plots of viscosity as a function of time and temperature (six heating/cooling cycles between 25 and 38 °C) for the same polymer in PBS buffer solution at a concentration of 16 (dashed line) or 23 wt % (full line). During the first heating/cooling cycle the temperature was kept constant at 38 °C for 5 min. The photographs on the right show the typical aspect of the polymer solutions below (top) and above (bottom) LCST (16 wt % in PBS).

differences in hydrodynamic volume between the analyzed star/graft architectures and the linear standards used for SEC calibration. Nevertheless, ^{1}H NMR allowed an accurate determination of the arm length for the star copolymers (Table 1).

The properties of the linear and star-block copolymers in aqueous medium were studied by turbidimetry, optical tests, and viscosimetry. Dilute aqueous solutions were first investigated in order to measure the cloud point of the P(MEO_2MA-*co*-OEGMA) outer blocks. All samples exhibited a reversible phase transition in pure deionized water and in phosphate buffered saline (PBS) solutions (Table 1).[19] However, the presence of a permanently hydrophilic PEG inner block complicates to some degree the turbidimetry measurements. Thus, relatively concentrated solutions are needed (i.e., 10 mg mL^{-1}) to determine correctly the cloud points. Moreover, the phase transitions of the P(MEO_2MA-*co*-OEGMA) outer blocks were found to be about 5−10 °C higher than those previously reported for their unbounded analogues.[5] This aspect is most certainly another direct consequence of the covalent attachment of the P(MEO_2MA-*co*-OEGMA) segments to internal hydrophilic PEG blocks.

The thermogelation of these macromolecules was studied at higher concentrations in water. Interestingly, all the synthesized polymers exhibited reversible thermothickening properties in aqueous medium. Yet, the star-block copolymers showed stronger gelation behaviors than the linear triblock architectures. The latter did not lead to highly cohesive networks even at concentration as high as 30 wt %. On the other hand, the star-shaped copolymers exhibited observable sol−gel transitions at concentrations of 15 wt % or higher. These observations are in good agreement with earlier reports on PNIPAM-based block copolymers.[17]

Figure 1 (left) shows some plots of viscosity as a function of temperature for PBS solutions of a star-block copolymer with an outer-block composition $MEO_2MA/OEGMA_{475}$ of 95/5 (Table 1, entry 8). Above the LCST of the outer blocks (i.e., 31 °C), a clear increase of viscosity with temperature was observed. Additionally, the maximum viscosity η_{max} was found at 38 °C, thus rendering this material suitable for bioapplications. Above 40 °C, a decrease of viscosity due to gel syneresis was also observed, which is a typical behavior of thermogels.[15] Nevertheless, this sample displayed an observable gel phase (Figure 1, right) within a near physiological range of temperature (35−42 °C). Thus, the properties of this promising thermoreversible network were investigated further. For instance, Figure 1 (middle) shows the evolution of the viscosity of PBS solutions of the same sample (Table 1, entry 8) for repeated heating/cooling cycles between 25 and 38 °C (i.e., η_{max}). First, it is noteworthy that symmetric peaks were observed for each cycle, thus indicating fully reversible properties (i.e., no apparent hysteresis). Moreover, the maximum viscosity of the sample was studied at constant temperature (Figure 1, middle, first cycle). There was no noticeable change in η_{max} with time (i.e., no syneresis at constant temperature). Hence, hydrogels based on 4-arm star block copolymers sPEG-*b*-P(MEO_2MA-*co*-OEGMA) appear as materials of choice for repeated applications between room and body temperature.

In conclusion, linear triblock copolymers and 4-arm star-block copolymers, based on permanently hydrophilic PEG inner blocks and thermoresponsive P(MEO_2MA-*co*-OEGMA) outer blocks, exhibit thermothickening properties in aqueous medium. In particular, highly biorelevant thermogelation behaviors were evidenced for the star-block copolymers. Although essentially composed of the same biocompatible material (i.e., ethylene oxide units), these optimized architectures exhibit controllable sol−gel transitions at near physiological temperatures. Hence, these novel materials may find a variety of applications in cell biology and tissue engineering.

Experimental Part. Chemicals. 2-(2-Methoxyethoxy)ethyl methacrylate (Aldrich, 95%), oligo(ethylene glycol) methyl ether methacrylate (Aldrich, $M_n = 475$ g mol^{-1}), linear α−ω-dihydroxy-telechelic poly(ethylene glycol) (J.T. Baker, 4000 g mol^{-1}; Merck, 6000 and 10 000 g mol^{-1}), 4-arm star hydroxy-terminated poly(ethylene glycol) (4-arm-PEG-OH) (Jenkem Technology, 10 000 g mol^{-1}), 2-bromoisobutyryl bromide (Aldrich, 98%), and 2,2′-bipyridyl (Bipy) (Fluka, 98%) were used without further purification. Copper(I) chloride (Acros, 95%) was washed with glacial acetic acid in order to remove any soluble oxidized species, filtered, washed with ethanol, and dried.

Example of Synthesis of a PEG-Based ATRP Macroinitiator. 20 g (2 mmol) of 4-arm-PEG-OH (10 000 g mol^{-1}) was dissolved in 60 mL of freshly dried dichloromethane and degassed under argon. After full dissolution of the polymer, 2.23 mL (16 mmol) of triethylamine was added, and the reaction mixture was cooled at 0 °C in a dry ice/ethanol bath. Subsequently, 2-bromoisobutyryl bromide (1.98 mL, 16 mmol) was added dropwise for 20 min. The reaction mixture was slowly allowed to reach room temperature and stirred overnight. After reaction, a small amount of activated coal was added. The mixture was stirred, left for 1 h, and filtrated over silica gel. The filtrate was washed two times with 100 mL of hydrogen carbonate solution, concentrated, and then precipitated in 1.5 L of diethyl ether. The final product (4-arm-PEG-Br, 13.01 g, 61% yield) was then obtained as a white powder after filtration and drying at 40 °C under vacuum. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.90 (s, 24H, $CH_3{-}CBr$), 3.33 (s, 8H, $({-}C{-}CH_2)_4$), 3.40−3.70 (m, $CH_2{-}CH_2{-}O$), 3.84 (t, 8H, $CH_2{-}O{-}C{=}O$), 4.28 (t, 8H, $CH_2{-}CH_2{-}O{-}C{=}O$).

Example of Atom Transfer Radical Copolymerization of MEO_2MA and OEGMA. Copper(I) chloride (1.8 mg, 0.018 mmol), 2,2′-bipyridyl (5.5 mg, 0.035 mmol), and 4-arm-PEG-Br macroinitiator (175.6 mg, 0.018 mmol) were added to a Schlenk tube sealed with a septum. The tube was purged with dry argon. Then, a degassed mixture of 2-(2-methoxyethoxy)ethyl methacrylate (1.88 g, 9.99 mmol), oligo(ethylene glycol) methyl ether methacrylate (250.5 mg, 0.527 mmol), and 2.3 mL of ethanol was added through the septum with a degassed syringe. The mixture was heated at 60 °C in an oil bath for several hours. After this time, 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 ($M_n = 36\,900$ g mol^{-1}; $M_w/M_n = 1.23$).

Measurements and Analysis. *Size Exclusion Chromatography (SEC).* Molecular weights and molecular weight distributions were determined by SEC performed at 25 °C in THF (flow rate 1 mL min^{-1}), using four 5 μm SDV columns (one guard column and tree columns of 4×10^3, 3×10^5, 2×10^6 Å). The detection was performed with a RI (DN-1000, WGE Dr. Bures) and a UV/vis detector (UV 2000; 260 nm). For calibration, linear polystyrene standards (PSS, Germany) were used.

^{1}H NMR. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker DPX-400 operating at 400.1 MHz. Monomer conversions were calculated from ^{1}H NMR spectra. For MEO_2MA and OEGMA, an overall monomer conversion was calculated since the double bonds of both monomers have a nearly identical NMR signature. In this case, the conversion was calculated by comparing the integrations of the vinyl protons of the remaining monomers (5.53 and 6.07 ppm) to the overall integration of the region 3.90−4.40 ppm where resonate 2 protons of the remaining monomers, 2 protons of the formed polymers, and 4−8 protons of the PEG macroinitiators.

Cloud Point Measurements. The cloud points of the polymer solutions in deionized water or PBS buffer were measured on a Tepper TP1 photometer (Mainz, Germany). Transmittance of polymer solutions 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}).

Viscosity Measurements. The viscosity of the polymer solutions as a function of time and temperature were measured using an AR-G2 Rheometer from TA Instruments equipped with a cone-and-plate geometry (cone angle: 1°00′22″, diameter: 40 mm; truncation: 30 μm). The evolution of viscosity against temperature (2 °C min^{-1}) was measured at a constant shear rate $\dot{\gamma} = 10$ s^{-1}. The polymer solutions were prepared in deionized water or in PBS buffer. Each sample was first heated to determine the temperature (T_{max}) to which the viscosity is maximum (η_{max}) and then cooled to reach 25 °C. Then several heating and cooling periods were conducted between 25 °C and T_{max}. During the first cycle, the sample was heated for 5 min at T_{max} to determine the stability of the gel at this temperature.

Optical Observation of the Sol−Gel Transitions. The sol−gel behaviors of the hydrogels were first screened using the tube inversion method. Standardized vials containing 1 mL of the polymer solutions (various concentrations in deionized water or PBS buffer) were immersed in a water bath at a given temperature for 10 min. After this time, the tubes were rapidly removed from the water bath and turned upside down to allow a visual assessment of the gel viscosities.

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(19) Due to a weak salting-out effect, the LCST values measured in PBS are always lower than in pure deionized water. This aspect is discussed in detail in refs 4 and 10c.

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