

Libraries of Methacrylic Acid and Oligo(ethylene glycol) Methacrylate Copolymers with LCST Behavior

C. REMZI BECER,^{1,2,3} SABINE HAHN,^{1,3} MARTIN W. M. FIJTEN,^{1,2} HANNEKE M. L. THIJIS,^{1,2}
RICHARD HOOGENBOOM,^{1,2} ULRICH S. SCHUBERT^{1,2,3}

¹Laboratory of Macromolecular Chemistry and Nanoscience, Eindhoven University of Technology, Den Dolech 2, 5612 AZ Eindhoven, The Netherlands

²Dutch Polymer Institute (DPI), John F. Kennedylaan 2, 5612 AB Eindhoven, The Netherlands

³Laboratory of Organic and Macromolecular Chemistry, Friedrich-Schiller-University Jena, Humboldtstrasse 10, 07743 Jena, Germany

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ABSTRACT: Homopolymers of methacrylic acid (MAA), monoethyleneglycol methyl ether methacrylate (MEOMA), diethyleneglycol methyl ether methacrylate (MEO₂MA), oligo(ethyleneglycol) methyl ether methacrylate (OEGMA₄₇₅ and OEGMA₁₁₀₀) and oligo(ethyleneglycol) ethyl ether methacrylate (OEGEMA₂₄₆) were synthesized with various chain lengths via reversible addition fragmentation chain transfer (RAFT) polymerization. The homopolymers of MAA, MEOMA and OEGMA₁₁₀₀ did not show any cloud point (CP) in the range of 0–100 °C, whereas at a pH value of 7, the CPs were found to be 20.6, 93.7, and 20.0 °C for p(MEO₂MA), p(OEGMA₄₇₅) and p(OEGEMA₂₄₆), respectively, with an initial monomer to initiator ratio of 50. Furthermore, statistical copolymer libraries of MAA with OEGMA₄₇₅ and OEGMA₁₁₀₀ were prepared. The cloud points of the random copolymers of MAA and OEGMA₄₇₅ were found to be in the range of 20–90 °C; surprisingly, even though the homopolymers of MAA and OEGMA₁₁₀₀ did not exhibit any LCST behavior, the copolymers of these monomers at certain molar ratios (up to 40% OEGMA₁₁₀₀) revealed a double responsive behavior for both temperature and pH. Finally, the cloud points were found to be in the range of 22–98 °C, measured at pH values of 2, 4, and 7, while no cloud point was detected at pH 10. © 2008 Wiley Periodicals, Inc. *J Polym Sci Part A: Polym Chem* 46: 7138–7147, 2008

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INTRODUCTION

Responsive polymeric structures with well-defined macromolecular composition, functionalities and topology, so-called “smart” materials, have become the interest of many researchers.¹

Correspondence to: U. S. Schubert (E-mail: ulrich.schubert@uni-jena.de)

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Intelligence of these “smart” materials is mostly based on their response to the environmental changes or external stimulation. Small organic compounds as well as polymeric structures can exhibit a phase transition from soluble to insoluble upon heating. This phenomenon is called lower critical solution temperature (LCST) behavior and is based on the existence of hydrogen bonding between the water molecules and the polymer chain. The polymers with LCST behavior show a sudden and (mostly) reversible change from hydrophilic to hydrophobic behavior that makes them attractive for usage as “smart” switchable materials in applications ranging from, i.e., drug delivery systems, soft actuators or valves, coatings and even in textile materials.^{2–6}

Controlled/“living” radical polymerization techniques had a rapid development in the last decade since they allow the straight-forward synthesis of well-defined polymers.⁷ The accuracy and the reproducibility of LCST transitions can be tailored by utilizing living and controlled polymerization techniques, such as anionic,⁸ radical⁹ and cationic^{10,11} polymerizations. These techniques have enabled the synthesis of advanced structures with a targeted length of the polymer. Moreover, the architecture as well as the desired monomer composition and distribution along the backbone can be controlled in an excellent manner. The reversible addition fragmentation chain transfer (RAFT) polymerization mechanism is one of the most successful controlled radical polymerization techniques because of its tolerance to various functionalities and ease of application.¹² Besides, the recently significantly improved characterization techniques allow to gain more information from the materials (see, e.g., MALDI-TOF MS/MS) and commercialization of high-tech automated parallel synthesis platforms has opened up possibilities for the screening of a wide range of materials in a relatively short period with high reproducibility.¹³

The challenges to obtain a material for a specific application might be overcome by mapping the structure-property relationships of a wide range of polymeric structures that allows a subsequent prediction of polymer properties and a targeted design of materials with the desired properties. Such an approach requires the preparation of libraries of well-defined polymers having systematical changes in, e.g., polymer molecular weight, length and/or architecture to be able to determine quantitative structure-property relationships.^{14,15} The synthesis and screening of

such polymer libraries can be accelerated by the use of high-throughput synthesis and screening equipment.^{16,17} In addition, the use of automated parallel synthesis platforms increases the comparability of the different copolymers based on the elimination of handling errors.^{13(a)}

Poly(*N*-isopropyl acrylamide) (PINAM) is the most widely investigated thermoresponsive polymer because its LCST is close to the body temperature under physiological conditions while the thermal transition is not affected by variations in concentration or ionic strength.^{18–20} Alternatively, poly(oligo (ethyleneglycol) methacrylate) based polymers have attracted great attention in the last couple of years due to their tunable LCST behavior.²¹ Polymerization of the commercially available OEGMA type of monomers yields comb-shaped polymers that can be used for many biomedical purposes, i.e., PEGylation of proteins.²² These comb-shaped polymers have several advantages over linear PEG for *in vivo* applications. For instance, the excretion of linear PEG (with an M_n above 20,000 Da) from the body is much harder in comparison to comb-shaped PEG (with an M_n of 300–2000 Da per “teeth”) since it is linked to the backbone with a cleavable ester bond.²³

In this contribution, the synthesis and characterization as well as cloud point determination of mono-, di- and oligo- (ethyleneglycol) methacrylate (OEGMA) homopolymers with various degree of polymerization will be discussed. Furthermore, the investigation of random copolymers of OEGMAs with the pH sensitive monomer, methacrylic acid (MAA), will be discussed, resulting in double responsive copolymers.

EXPERIMENTAL

Materials

Methacrylic acid (MAA, Aldrich) was purified by treating the monomer with inhibitor-remover (Aldrich). Mono(ethyleneglycol) methyl ether methacrylate (MEOMA, Aldrich), di(ethylene glycol) methyl ether methacrylate (MEO₂MA, Aldrich), oligo(ethyleneglycol) methyl ether methacrylate (OEGMA₄₇₅, $M_n \sim 475$ g/mol, Aldrich) and oligo(ethyleneglycol) ethyl ether methacrylate (OEGEMA₂₄₆, $M_n = 246$ g/mol, Aldrich) were purified by passing over a neutral aluminum oxide column. Oligo(ethyleneglycol) methyl ether methacrylate (OEGMA₁₁₀₀, $M_n \sim 1100$ g/mol, Aldrich) was dissolved in dichloromethane, passed

over a neutral aluminum oxide column and dried under vacuum. Azobis(isobutyronitrile) (AIBN, Aldrich) was recrystallized from methanol. 2-Cyano-2-butyl dithiobenzoate (CBDB, chain transfer agent) was kindly provided by AGFA. Solvents were purchased from Biosolve and buffer solutions from Merck.

Synthesis

Most of the polymerizations were performed in a Chemspeed AcceleratorTM SLT106 automated synthesizer. The robot was equipped with a four-needle head and an array of 16 parallel 13 mL glass reactors. All reactors were connected to a Huber Unistat Tango (heating range: -40 – 145 °C) and were equipped with a cold-finger reflux condenser in which the temperature can be controlled from -5 °C to 40 °C. A double inert atmosphere was maintained by applying a 1.1 bar flow over the reactors and a 1.5 bar argon flow through the hood of the Accelerator. The inert atmosphere in the hood of the Accelerator SLT106 was obtained by flushing with argon for at least 90 min prior to the experiments. In addition, the reaction vessels were heated to 120 °C, evacuated for 15 min, and then filled with argon. This procedure was repeated three times to be able to perform the reactions under inert atmosphere. Different amounts of the RAFT agent (CBDB in toluene), AIBN (in toluene) and the desired monomers were transferred into the reaction vessels. The ratio of RAFT to AIBN was 1:0.25. The reaction volume was 4 mL for each reaction. The kind of monomers, the ratio of monomers and the monomer to CBDB ratio were varied in the experiments. The polymerization mixtures were heated to 70 °C and vortexed at 600 rpm. After 10 h stirring at 70 °C, the reaction vessels were cooled to room temperature. The products were purified by precipitating into an appropriate nonsolvent, i.e., *n*-hexane or diisopropylether, whereas chloroform was used in the case of the poly(methacrylic acid) homopolymers. After removal of the solvents and residual monomers, the polymers were dried in a vacuum oven at 40 °C overnight prior to analysis. Some polymerization experiments were performed in the oil bath using the same reagent ratios and experimental conditions as in the automated synthesis platform. Initial aliquots from each reactor and the final aliquots were withdrawn into small vials to determine the monomer conversion and the molecular weight data.

GC measurements were performed on an Inter-science Trace GC with a Trace Column RTX-5 connected to a PAL autosampler. GPC measurements were performed on a Shimadzu system equipped with a SCK-10A system controller, a LC-10A pump, a RID-10A refractive index detector, and a PL gel 5 μ m Mixed-D column at 50 °C, using *N,N*-dimethylacetamide (with 2.1 g/L LiCl) as eluent at a flow rate of 1 mL/min. Turbidimetry measurements were performed in a Crystal 16 from Avantium Technologies. Four blocks of parallel temperature-controlled sample holders were connected to a Julabo FP40 cryostat, allowing 16 simultaneous measurements. Turbidity of the solutions at a concentration of 5 mg/mL 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 (Laborpure, Behr Labor Technik) and were stirred at room temperature until all polymeric material was dissolved or dispersed. Two heating cycles were applied from 0 to 100 °C at 1 °C/min with hold steps of 5 min at the most extreme temperatures. The cloud points are given as the 50% transmittance point during the first heating ramp of the aqueous polymer solutions.

RESULTS AND DISCUSSION

The schematic representation of the RAFT process is depicted in Scheme 1. Initiation is followed by an equilibrium reaction between the radical species B and the active chain radical A formed during the initiation step or a new radical formed from the leaving group of the chain transfer agent (CTA) D. These radicals can subsequently react with monomer to form the new propagating species, A and E, respectively. In step IV, the equilibrium step between the dormant polymeric CTA species F and G and the polymer radicals P_y and P_z is depicted. The transfer step between active and dormant species is important to obtain the “controlled” character of the polymerization. Termination via disproportionation or combination (step V) are always operative to some extent, but can be largely eliminated by maintaining appropriate conditions that control the radical concentration.

In the present contribution the reversible addition fragmentation chain transfer polymerization (RAFT) technique was employed for the controlled radical polymerization of the monomers shown in Scheme 2.

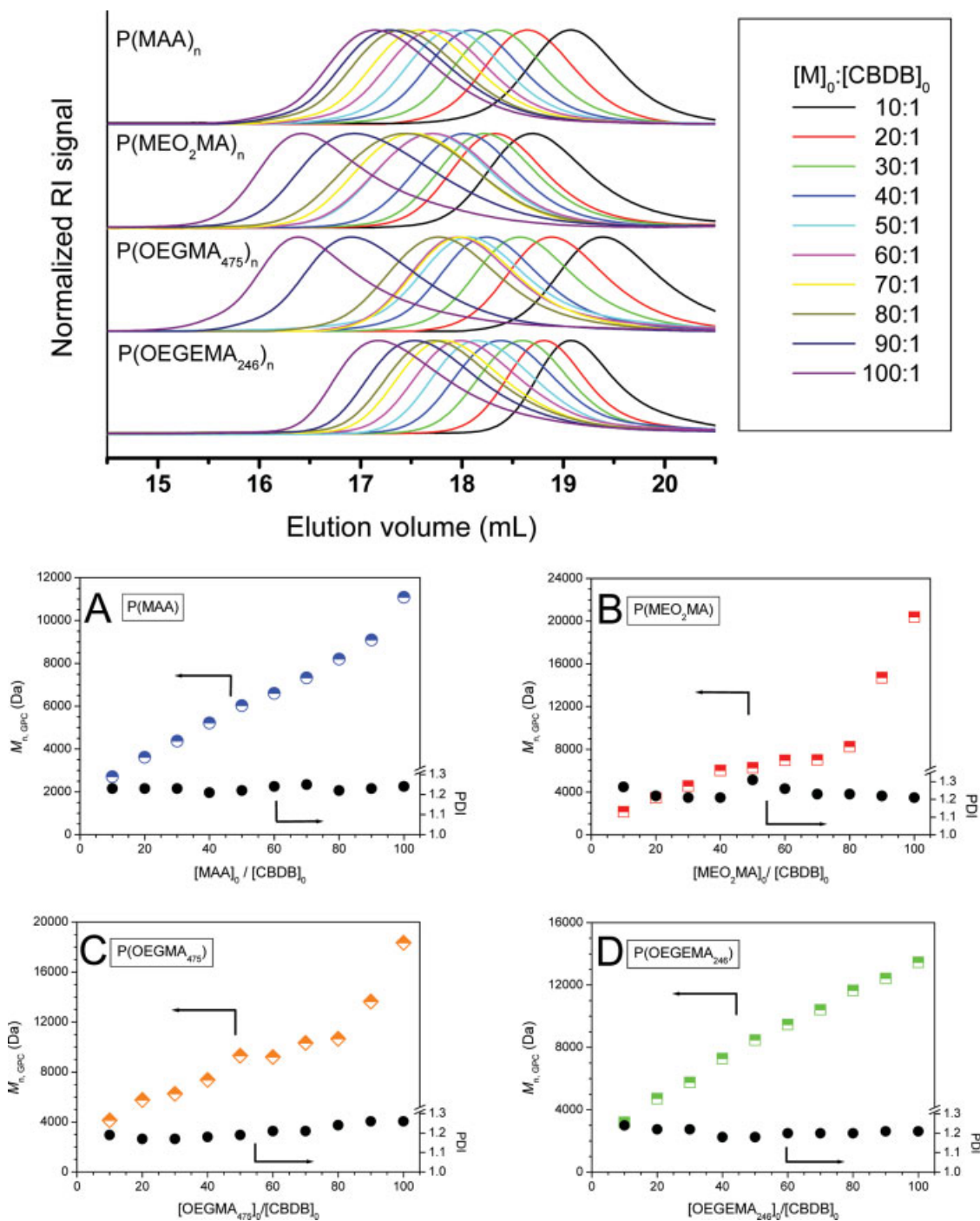


Figure 1. Size exclusion chromatography traces (top) as well as $M_{n, GPC}$ and PDI values as function of monomer to CTA ratio for the homopolymerizations of (A) MAA, (B) MEO₂MA, (C) OEGMA₄₇₅ and (D) OEGEMA₂₄₆ with different monomer to CTA feed ratios changing from 10:1 to 100:1 with steps of 10.

to investigate the LCST behavior. The structural characterization of these homopolymers is listed in Table 1. The cloud points of the purified homopolymers were determined in a parallel turbidim-

etry instrument (Crystal 16TM from Avantium) at a polymer concentration of 5 mg/mL at pH 4, 7, and 10, respectively. There is no cloud point observed for the homopolymers of p(MAA),

Table 1. Structural Characterization and the Cloud Points of the Homopolymers

Code	Monomer	[M] ₀ /[CBDB] ₀	M _{n,GPC} ^a (g/mol)	PDI	Yield ^b (%)	CP ^c (°C)		
						pH 4	pH 7	pH 10
H1	MAA	50:1	6,020	1.22	86	–	–	–
H1	MAA	100:1	11,080	1.24	67	–	–	–
H2	MEOMA	50:1	7,480	1.19	n.d.	n.s.	n.s.	n.s.
H3	ME ₂ OMA	50:1	6,280	1.31	56	n.s.	20.6	21.6
H4	ME ₂ OMA	100:1	20,380	1.21	37	n.s.	21.8	23.1
H5	OEGMA ₄₇₅	50:1	9,310	1.19	35	97.0	93.7	96.6
H6	OEGMA ₄₇₅	100:1	18,340	1.26	19	93.2	89.8	92.8
H7	OEGMA ₁₁₀₀	50:1	14,560	1.19	50	–	–	–
H8	OEGEMA ₂₄₆	50:1	8,470	1.18	49	28.3	20.0	21.3
H9	OEGEMA ₂₄₆	100:1	13,450	1.21	44	27.6	21.6	22.8

n.s., not soluble.

^a Number average molecular weights were calculated according to polystyrene standards.

^b Gravimetric yield calculated from the mass of the polymer after purification.

^c Cloud points were determined at 5 mg/mL in the range of 0–100 °C.

p(MEOMA), p(OEGMA₁₁₀₀) in the range of 0–100 °C. In the case of p(MEOMA) the polymer is not soluble in water since the single ethyleneglycol unit is insufficient to solubilize the hydrophobic polymer backbone. As shown in Table 1, p(MEO₂MA) and p(OEGMA₂₄₆) homopolymers exhibited cloud points close to room temperature (20–29 °C) at pH 4, 7, and 10, whereas p(MEO₂MA) could not be dissolved at the acidic pH value. It is obvious that the number of ethyleneglycol units on each repeating unit has an effect on the cloud point of the polymer. OEGMA₂₄₆ has in average three repeating units of ethyleneglycol, whereas MEO₂MA has only two. The possible reason for their similar cloud points might be due to the difference in their end groups of the ethyleneglycol repeating units, which is methyl in case of MEO₂MA and ethyl for OEGMA₂₄₆. These results indicate that the number of ethyleneglycol units is increasing the cloud point while the additional aliphatic units cause a decrease.

The homopolymers of p(MAA) were soluble in water because of the hydrophilicity of the carboxylic acid groups that form hydrogen bonds with the surrounding water molecules. As a consequence, there is no LCST behavior observed for p(MAA) up to 105 °C. P(OEGMA₁₁₀₀) has a very similar structure to linear PEG since each methacrylate repeating unit bears 22 ethyleneglycol units in average. These side chains are sufficiently long to shield the methacrylate backbone from water making the polymer fully soluble in aqueous solution. The ratio of the ether groups to the methacrylate backbone is lower in

p(OEGMA₄₇₅) in comparison to the p(OEGMA₁₁₀₀) homopolymers. As a result, the hydrophilicity of the p(OEGMA₄₇₅) homopolymers is lower and a cloud point is observed close to 100 °C.

Furthermore, the effect of the chain length on the LCST behavior of the p(OEGMA₄₇₅) and p(MEO₂MA) homopolymers was investigated and polymers with different chain lengths exhibited cloud points in the range of 80–98 °C and 15–25 °C, respectively. The measured cloud points are depicted in Figure 2. There is no strong influence of the chain length on the LCST behavior for this class of polymers. Even though, these monomers can not be protonated or deprotonated, the turbidimetry measurements were performed in buffer solutions at four different pH values, which are 2, 4, 7, and 10, to allow a detailed comparison to their corresponding double responsive copolymers with methacrylic acid (see below).

It is also known from the literature that there is an influence of the end group on the cloud point of the polymers, which becomes more distinct at lower molecular weights.²⁴ Indeed, there is a slight increase in the cloud point of p(OEGMA₄₇₅) for the shortest chain lengths ([M]/[I] = 10–40), which may be attributed to the hydrophobic character of the chain transfer agent attached to the chain end. There is no strong difference in the cloud point for different pH values. Nevertheless, the cloud points are 1–2 °C lower at pH 7 in comparison to acidic or basic solutions, which is most likely due to slightly stronger interactions between the PEG chains and hydroxide ions or hydronium protons compared to water. A similar

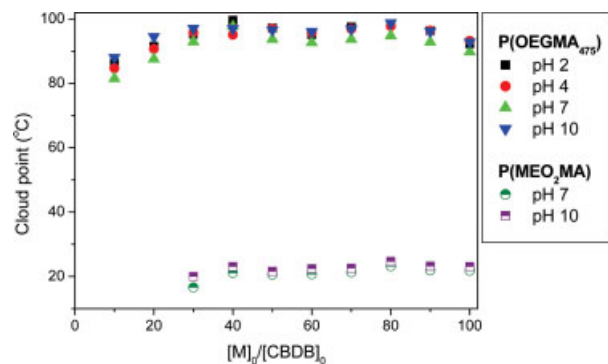


Figure 2. Cloud points of p(OEGMA₄₇₅) and p(MEO₂MA) homopolymers as a function of monomer to CTA feed ratio at different pH values. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

behavior was observed for the homopolymers of MEO₂MA at pH values of 7 and 10. However, the CPs of p(MEO₂MA) were found in the range from 15 to 25 °C, which is far below the CPs of p(OEGMA₄₇₅). This is caused by the changed hydrophilic/hydrophobic balance shifted to more hydrophobic. By taking advantage of this behavior, it is possible to tune the LCST of the polymers by simply altering the MEO₂MA and OEGMA₄₇₅ content, as was previously demonstrated by Lutz et al.²⁵ However, our interest is focused on double responsive polymers that are switchable both by temperature and pH, which can be achieved by the incorporation of an acidic or a basic monomeric unit. Therefore, copolymers of MAA and OEGMA₄₇₅ or OEGMA₁₁₀₀ were prepared with a systematic variation of the monomer content in

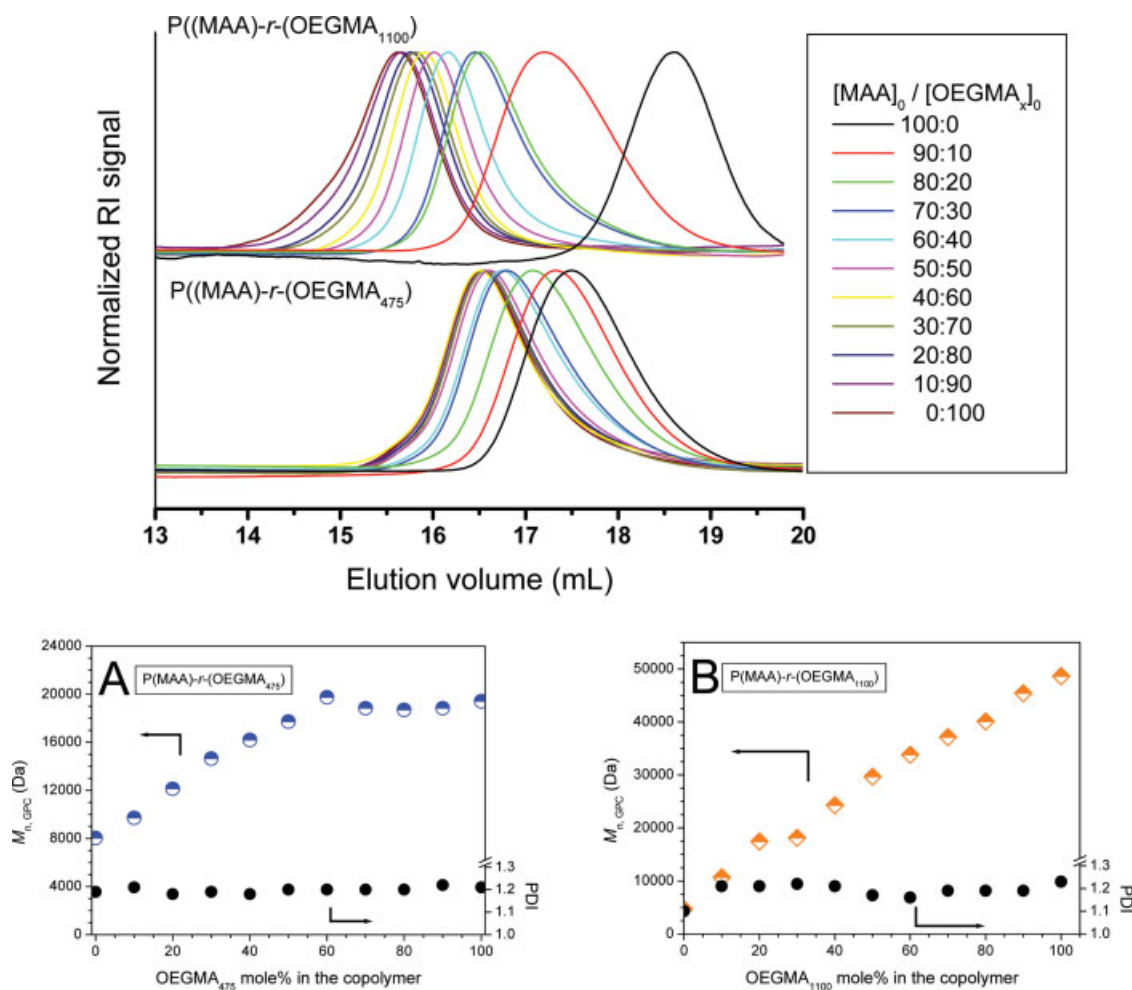


Figure 3. Size exclusion chromatography traces for the copolymerizations of MAA and OEGMA₄₇₅ or OEGMA₁₁₀₀ with different monomer ratios changing from 0:100 to 100:0 and the corresponding $M_{n, GPC}$ and PDI values. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

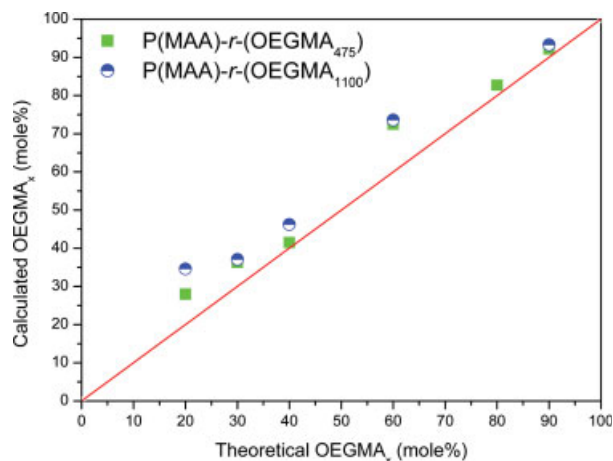


Figure 4. Theoretical composition versus the calculated composition of the MAA and OEGMA₄₇₅ or OEGMA₁₁₀₀ copolymers. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the polymers. The content of MAA in the copolymer was varied from 0 to 100% with steps of 10%. The molecular weight and the polydispersity indices of the polymers were determined by SEC measurement. As shown in Figure 3, the obtained SEC traces exhibited monomodal distribution for all polymers. Besides, the molecular weights increased linearly with the increasing content of OEGMA₁₁₀₀ in the copolymer, whereas the polydispersity indices remained below 1.3.

Furthermore, the copolymers were characterized with ¹H NMR spectroscopy to determine the incorporated monomer contents, as depicted in Figure 4. The content of OEGMA_x was found to be slightly higher than the theoretical ratios (diagonal line), which indicates that OEGMA_x has a slightly higher reactivity than MAA in the RAFT polymerization. Nevertheless, all copolymers were found to be well-defined consisting of monomer compositions close to the desired theoretical composition.

The LCST behavior of the copolymer libraries with MAA and OEGMA₄₇₅ or OEGMA₁₁₀₀ was investigated at pH 2, 4, 7, and 10, respectively. The copolymer library of MAA and OEGMA₄₇₅ revealed LCST behavior in a relatively wide range between 20 and 90 °C, whereby the pure p(MAA) and p(MAA)_{0.1-r-(OEGMA₄₇₅)_{0.9} did not show cloud points. Surprisingly, the cloud point of p(OEGMA)₄₇₅ is lowered by the incorporation of the more hydrophilic MAA (Fig. 5). It should be noted that these copolymers are double responsive showing a LCST transition at pH 2 and 4 while}

they are fully soluble at pH 7 and 10. As mentioned previously in this contribution, homopolymers of MAA and also OEGMA₁₁₀₀ did not show any cloud point in the range from 0 to 100 °C at pH 2, 4, 7, and 10, respectively. However, the copolymers of these two monomers at certain ratios of MAA to OEGMA₁₁₀₀ (90:10, 80:20, 70:30, and 60:40) also show double responsive behavior. These polymers are found to be both thermoresponsive and pH-responsive. For instance, the copolymer of MAA:OEGMA₁₁₀₀ with a content of 90:10 revealed a cloud point at 24.1 °C in a buffer solution at pH 2 and at 37.8 °C at pH 4, while it is fully soluble at pH 7. This type of behavior might be beneficial for the development of drug delivery applications and biocompatible contrast agents for magnetic resonance imaging.²⁶ A possible explanation for this unexpected clouding behavior might be the intramolecular interactions between the ether groups and the carboxylic acid groups.^{21(d)}

CONCLUSIONS

We have described systematic and parallel polymerizations of various OEGMA_x monomers and MAA with the RAFT polymerization technique. Libraries of well-defined homopolymers (in total 60 polymers) were prepared and investigated regarding to their LCST behavior. The homopolymers with different degree of polymerization

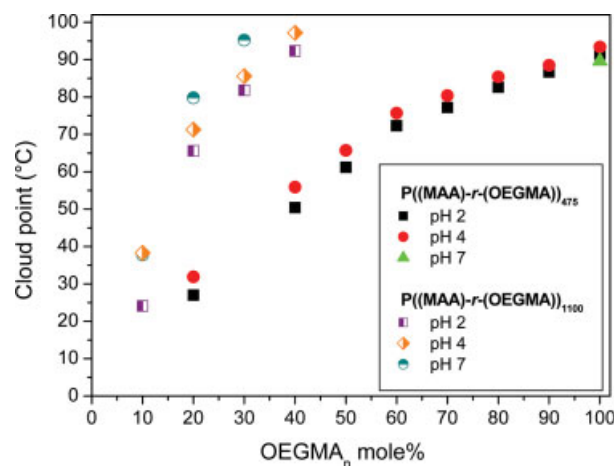


Figure 5. Cloud points of p((MAA)-r-(OEGMA₄₇₅)) and p((MAA)-r-(OEGMA₁₁₀₀)) copolymers as a function of OEGMA_n mole percentage at different pH values estimated by 50% transmittance points of the first heating curves. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

showed a slight effect on the LCST behavior, whereas the number of ethylene glycol units attached to each repeating unit revealed a strong decreasing trend with decreasing ethyleneglycol units. Furthermore, replacing the methoxy end group with ethoxy also significantly reduced the cloud points due to the higher hydrophobicity. In addition, well-defined copolymers of OEGMA_x's and methacrylic acid were synthesized with varying monomer contents. In the case of p(MAA)-*r*-(OEGMA₄₇₅) the cloud point could be tuned even in the range from 20 to 90 °C. Surprisingly, p(MAA)-*r*-(OEGMA₁₁₀₀) copolymers only showed a LCST behavior at certain compositions, although their homopolymers did not reveal any LCST behavior. Such unexpected properties could clearly only be identified by a library screening approach. A possible explanation for this behavior could be based on intramolecular hydrogen bonding interactions between the acid groups and the ethyleneglycol chains which is an additional driving force to expel the water from the hydration shell. Besides, the MAA-*r*-OEGMA_x copolymers presented a double responsive behavior, namely thermo- and pH-response. We believe that this systematic screening of LCST materials synthesized by controlled radical polymerization techniques represent a crucial step to identify structure-property relationships that will allow the development and the selection of the best suited material for a desired application in the future.

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