Combining Atom Transfer Radical Polymerization and Disulfide/Thiol Redox Chemistry: A Route to Well-Defined (Bio)degradable Polymeric Materials

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ABSTRACT: Linear well-defined degradable polymethacrylates with internal disulfide link were prepared by atom transfer radical polymerization (ATRP) of methyl, *tert*-butyl, and benzyl methacrylate using bis[2-(2-bromoisobutyryloxy)ethyl] disulfide as the initiator and CuBr/2,2'-bipyridine as the catalyst at 50 °C. The disulfide bond was cleaved to thiol by reduction with tributylphosphine, yielding polymers of half the molecular weight of the starting materials. Degradable gels were prepared by the copolymerization of methyl methacrylate and a disulfide-containing difunctional methacrylate, bis(2-methacryloyloxyethyl) disulfide, using similar reaction conditions. The produced gels were reduced with tributylphosphine to form soluble, low molecular weight linear poly(methyl methacrylate) fragments containing thiol groups at the chain end and along the backbone, originating from the disulfide difunctional initiator and monomer, respectively. The disulfide-cross-linked gels were further used as "supermacroinitiators" for the bulk ATRP of styrene at 90 °C, employing CuBr/N,N,N'',N'',Pentamethyldiethylenetriamine as the catalyst. The length of the polystyrene pendant chains could be controlled by varying the reaction time. The prepared gels with segmented structure swelled more than the starting polymethacrylate gels in both THF and toluene. Degradation experiments confirmed the high degree of chain-end bromine functionalization of the "supermacroinitiators".

Introduction

The development of "green" methods is an ongoing effort in chemistry, materials science, and industry. The term "green" implies the use of environmentally friendly (nontoxic and reusable) reagents and solvents in the processes, or the development of active catalysts, and technologies consuming less energy.¹ In polymer synthesis, the preparation of recyclable and (bio)degradable materials is particularly important for prevention of environmental pollution.² Such polymeric materials contain, as part of their backbones, weak chemical links which can be easily cleaved chemically or photochemically at ambient conditions. The produced lower molecular weight polymeric fragments can be further degraded by microorganisms. Degradable polymers are also of significant interest in soil treatment, tissue engineering, and (drug) delivery, which has further stimulated the research in the field.³⁻⁵ Cleavable links such as ester, amide, polysulfide, etc., can be generated in the backbone during the polymerization, which is typical for polymers prepared by polycondensation processes. Radical polymerization, which has wide application in industry, can also be used to synthesize degradable polymers. The incorporation of the cleavable functional group can be achieved by the use of functional initiators or monomers. However, because of fast irreversible chain-breaking reactions, such as radical coupling or disproportionation and/or transfer, conventional radical polymerization is not suitable for the preparation of well-defined structures.

Materials produced by radical polymerization with controlled molecular weight, narrow molecular weight distribution, and high degree of chain-end functionalization have only become accessible with the development of the various methods for controlled/"living" radical polymerization (CRP) that rely upon an equilibrium between active (radicals) and dormant species.^{6–10} The past decade has witnessed the flourishing of several methods of CRP, among which atom transfer radical polymerization (ATRP),¹¹⁻¹⁴ reversible addition-fragmentation chain transfer (RAFT),^{15,16} nitroxide-medi-ated polymerization,^{17,18} and degenerative transfer with alkyl iodides¹⁹ are the most widely applicable. This is due to the simple experimental setup, the use of inexpensive or easy to prepare and purify reagents, in addition to the typical for the radical polymerization tolerance toward functional groups, solvents and impurities. ATRP has been successfully used to prepare a wide variety of well-defined polymeric materials including functional polymers,²⁰ gradient,²¹ and segmented copolymers²² as well as hybrid materials.²³ This CRP technique was recently employed to synthesize welldefined degradable polymers by the incorporation of hydrolytically, photochemically,²⁴ or electrochemically²⁵ labile chemical bonds in the polymer backbone.

The disulfide group is an example of (bio)degradable group, which can be cleaved in the presence of reducing agents,^{26,27} nucleophiles, electrophiles,^{28,29} or photochemically.^{30,31} Since the redox potential of the disulfide (R-S-S-R')/thiol couple depends on the nature of the substituents R and R' and the reaction medium composition (solvent polarity, pH, presence of complexforming ions, etc.),^{27,32} a polymeric disulfide can be designed in such a way that the reductive scission of the sulfur-sulfur bridge will occur at sufficient rate only in a given environment. Copious amount of work has been published on the disulfide/thiol interchange^{27,33,34} due to its relevance to various phenomena occurring in living cells including protein structure stabilization,³⁵

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enzyme catalytic activity, and redox cycles.^{27,36,37} Of special interest is the fact that tumors are often hypoxic, and polymeric materials that degrade in reductive environment can be envisioned to degrade therein, releasing a preliminarily incorporated drug, which provides an opportunity for cancer tissue-selective therapy.³⁸

Disulfide groups can be introduced in a polymer using an appropriate initiator or monomer. A disulfide-based ATRP initiator densely attached or patterned to a gold surface was used to graft several methacrylate monomers from the surface in controlled fashion.³⁹ The preparation of degradable well-defined polystyrene by ATRP was recently reported in which the disulfide/thiol reversible interconversion was utilized to obtain loweror higher-molecular-weight polymers.²⁵ Poly(2-hydroxyethyl methacrylate) containing 2-pyridyl disulfide end group was synthesized by ATRP and was used to modify proteins having free thiol groups.⁴⁰ Because of its attractiveness, the reversible reductive degradation of polymeric materials containing one or more disulfide groups has been studied and exploited, although by no means extensively. Some examples of materials include disulfide-cross-linked cellulose (modified cotton),41-43 polyoxazolines,44 and linear polymers with one or more di- or polysulfide links.^{25,45}

Herein, we report the ATRP of methyl, *tert*-butyl, and benzyl methacrylate (MMA, tBuMA, and BnMA, respectively) using bis[2-(2-bromoisobutyryloxy)ethyl] disulfide ((BiBOE)₂S₂) as a difunctional initiator containing the cleavable disulfide link. Degradable gels with disulfide bridge cross-links were synthesized as well using the same initiator and a mixture of MMA and disulfide-containing dimethacrylate (bis(2-methacryloyloxyethyl) disulfide (MAOE)₂S₂). The modification of the gels by chain-extension reactions with styrene (Sty), i.e., their use as ATRP "supermacroinitiators", is also described. Finally, the reversible redox cleavage of the internal disulfide bond of the synthesized polymeric materials is demonstrated.

Experimental Section

Materials. Prior to use, the neat monomer (MMA, tBuMA, BnMA, or Sty) was passed through a column filled with basic alumina in order to remove the polymerization inhibitor. CuBr (98%, Aldrich) was purified by a modified literature procedure: washing with glacial acetic acid followed by 2-propanol.⁴⁶ The conventional radical initiator V-70 (Wako) was recrystallized from methanol. All other reagents (bis(2-hydroxyethyl) disulfide (BHEDS; 98%, TCI), dicyclohexylcarbodiimide (DCC), 4-(N,N-dimethylamino)pyridine (4-DMAP), 2-bromoisobutyric acid, methacryloyl chloride, 2,2'-bipyridine (bpy), tributylphosphine (Bu₃P)) and the solvents were used as received. N,N,N',N'',N''-Pentamethyldiethylenetriamine (PMDETA)⁴⁷ was deoxygenated prior to the experiments by nitrogen bubbling for 2–3 h.

Synthetic Procedures. a. Synthesis of Disulfide Initiator (BiBOE)₂S₂. 20.09 g (0.13 mol) of BHEDS was dissolved in 350 mL of THF. A solution of 43.4 g (0.26 mol) of 2-bromoisobutyric acid in 50 mL of THF was added, and the solution was cooled in an ice-water bath. A solution of 53.65 g (0.26 mol) of DCC in 50 mL of THF was added upon stirring followed by a solution of 3.2 g of 4-DMAP in 50 mL of THF. The reaction mixture was kept in the ice-water bath for 5 min and then for 18 h at room temperature. The precipitated dicyclohexylcarbamide was filtered off and washed with 50 mL of THF on the filter. The solvent was evaporated, and the formed suspension was kept in refrigerator for several hours and then at room temperature for 3 days. The impurities crystallized and were removed by filtration. The obtained viscous oil (86% yield) was analyzed by NMR (acetone- d_6 ; δ , ppm): 4.46 (t, 2H, CH₂OOC), 3.09 (t, 2H, CH₂S), and 1.94 (s, 6H, (CH₃)₂C). 2–3% of unreacted hydroxy groups were present in the product. 1 mL of the oil weighs approximately 1.48 g. Prior to polymerization experiments, this initiator was deoxygenated by bubbling with nitrogen for 2–3 h.

b. Synthesis of Disulfide Monomer (MAOE)₂S₂. The diester was prepared from the corresponding diol, BHEDS, and methacryloyl chloride in the presence of pyridine since the previously reported procedure;⁴⁸ namely, the reaction of 2-chloroethyl methacrylate with sodium disulfide is more laborious, and the overall monomer yield is low. In a 500 mL roundbottomed flask, cooled in ice-water bath, 29 mL (0.3 mol) of methacryloyl chloride was dissolved in 200 mL of methylene chloride dried over sodium sulfate. 0.06 g of hydroquinone was added, followed by 24.3 mL of pyridine, dried over sodium sulfate. A heterogeneous mixture was thus obtained, to which, upon stirring, 15.4 g (0.1 mol) of BHEDS was added over a period of 10 min. The mixture was stirred in the cooling bath for another 30 min and then at room temperature for 17 h. The methylene chloride solution was extracted with three 150 mL portions of water, twice with 150 mL of 10% solution of sodium carbonate in water, and again with 3 portions of water. The solution was then dried over sodium sulfate, and the solvent was evaporated. 13.62 g of crude product was thus obtained. To remove the excess of methacrylic acid, the product was dissolved in 200 mL of ether, and the solution was passed through a column filled with basic alumina, covered with a 1-2 cm layer of sodium carbonate. The absorbent was washed with 30-40 mL of ether, and the solvent was removed from the combined solution. 11.0 g (38%) of product was thus obtained as a yellowish oil. The NMR spectrum in acetone- d_6 consists of the following signals: 6.09 ppm (d, 1H, =CH), 5.65 ppm (d, 1H, =CH), 4.42 ppm (t, 2H, CH₂OOC), 3.08 ppm (t, 2H, CH_2S), and 1.92 ppm (s, 3H, $CH_3C=$). On the basis of NMR and IR spectral analysis, the product thus obtained contained no unreacted methacrylic acid or alcohol.

c. Preparation of Degradable Linear Polymethacrylates by ATRP. MMA (5 mL, 0.0467 mol) was mixed with 3 mL of acetone and 0.2 mL of Ph₂O (internal standard for GC). The mixture was degassed by six freeze-pump-thaw cycles, and the flask was filled with nitrogen. CuBr (0.0666 g, 0.464 mmol) and bpy (0.1449 g, 0.929 mmol) were then added to the frozen mixture, and the flask was closed, evacuated, and backfilled with nitrogen. This vacuum-nitrogen cycle was repeated twice, and the mixture was warmed to let it thaw. The reaction flask was heated to 50 °C, and the deoxygenated initiator, (BiBOE)₂S₂ (99 μ L, 0.32 mmol, 1/145 vs monomer), was injected. Samples were taken out periodically to check the conversion and molecular weights. The same conditions were used for the polymerization of tBuMA and BnMA.

d. Preparation of Degradable Gels with Disulfide Groups. MMA (5 mL, 0.0467 mol) and the disulfide-containing dimethacrylate (MAOE)₂S₂ (0.15 mL, 0.57 mmol) were dissolved in 2 mL of acetone, and the mixture was degassed as described above. The catalyst consisted of 0.0334 g (0.233 mmol) of CuBr and 0.0727 g (0.4667 mmol) of bpy. The reaction mixture was heated to 50 °C, and 50 μL (0.164 mmol, 1/285 vs MMA) of deoxygenated $(BiBOE)_2S_2$ was added. Gel was formed after ca. 250 min (ca. 80% monomer conversion, determined by gravimetry). The obtained gel was washed repeatedly with acetone (4-5 times with 500 mL portions, keeping the gel in the solvent for ca. 12 h) to remove any free polymer. In another experiment, the amount of the initiator (BiBOE)₂S₂ was increased 3-fold (to 0.491 mmol, i.e., 1/95 vs MMA), while keeping the amounts of the other reagents constant, to check the influence of the monomer-to-initiator ratio on the kinetics of the polymerization. Gelation was observed in ca. 150 min (93% monomer conversion). In a control experiment, a mixture of 5 mL (0.0467 mol) of MMA and 0.15 mL (0.57 mmol) of $(MAOE)_2S_2$ in 2 mL of acetone was copolymerized at 50 °C (after deoxygenation) using 0.04 g (0.12 mmol) of V-70. Gelation occurred after 43-45 min at 47% monomer conversion.



Figure 1. Synthesis and reductive degradation of polymethacrylates with internal disulfide link (R = methyl, *tert*-butyl, or benzyl).

e. Chain Extension of the Disulfide-Containing PolyM-MA-Based "Supermacroinitiator" Gel with Sty. 0.3 g of the dried gel described above was mixed with 8 mL (0.070 mol) of Sty, and the mixture was kept in a refrigerator overnight and then at room temperature for 2 h to allow for sufficient gel swelling. The mixture was degassed as described above, and 0.0286 g (0.20 mmol) of CuBr was added, followed by injection of $42 \,\mu\text{L}$ (0.20 mmol) of deoxygenated PMDETA. The reaction was carried out for 2.5 h at 90 °C. The product was washed repeatedly with THF to remove any free polymer. To obtain a gel with higher molecular weight of the pendant polySty chains, the reaction time was increased to 5 h.

f. Reductive Degradation of the Disulfide-Containing Linear Polymers and Gels. 0.04 g of the linear polymer was dissolved in 1 mL of 50 mM solution of LiBr in DMF (same solution as the eluent for SEC) containing 0.05 mL of Ph₂O (SEC standard), and 0.05 mL of Bu₃P was added. The degradation was complete within several minutes. The gels were degraded in similar fashion: 0.04 g of the gel was kept in 6 mL of THF containing 0.10 mL of Ph₂O for 1 h to let it swell, and 0.10 mL of Bu₃P was added. The degradation accompanied by complete dissolution took several hours to days depending on the cross-link density.

Analyses. NMR spectra were recorded on a Bruker instrument operating at 300 MHz. Monomer conversions were determined on a Shimadzu GC-14A gas chromatograph equipped with a flame ionization detector and a capillary column (30 m \times 0.53 mm \times 1.0 μ m CEC-Wax column, Chrom Expert Co.) using diphenyl ether as the standard or by gravimetry. Molecular weight distributions were determined by SEC using a series of Styrogel columns (10⁵ Å, 10³ Å, 100 Å, PSS) and THF (30 °C) or DMF containing 50 mM LiBr (50 °C) as the eluent and polyMMA calibration using diphenyl ether as internal standard. The swelling ratios of gels were determined by immersing the gels in a solvent (THF or toluene) and keeping them in closed vials at room temperature for 3-4 days. The swollen material was taken out, quickly dried with filter paper, and weighed. Then, it was dried at 60-65 °C under vacuum to constant weight and weighed again. The swelling is expressed as the mass of solvent absorbed by 1 g of dry gel.

Results and Discussion

Synthesis of Disulfide-Containing Linear Polymethacrylates. The preparation of degradable linear polySty with one or more disulfide groups by ATRP and its reversible redox cleavage/coupling was recently described. The Sty ATRP was carried out in bulk at 90 °C and was initiated by the 2-bromopropionate ester of BHEDS and catalyzed by CuBr/PMDETA.²⁵

For the ATRP of methacrylates, a 2-bromoisobutyrate initiator was used (Figure 1). The kinetics and the evolution of the molecular weight distributions with conversion for the solution ATRP of three methacrylates, MMA, tBuMA, and BnMA, initiated by $(BiBOE)_2S_2$ are shown in Figure 2. The first-order kinetic plots were practically linear, indicating a constant radical concentration throughout the polymerization. The volume of the reaction mixture and the targeted degree of polymerization at complete monomer conversion were kept constant, but due to the different molecular weights and densities of the three monomers, the catalyst and



Figure 2. Kinetics (a) and molecular weight evolution (b) for the ATRP of MMA, tBuMA, and BnMA in acetone (5:3 by volume) initiated by $(BiBOE)_2S_2$ at 50 °C using CuBr/bpy as the catalyst. [Monomer]/[$(BiBOE)_2S_2$]/[CuBr]/[bpy] = 145:1:1.5: 3.

initiator concentration differed in the three studied systems, causing unequal polymerization rates. The ratio of polymerization rate to the sum of concentrations of catalyst and initiator was the highest for BnMA. This was most likely due to the highest value of the propagation rate constant of this monomer ($k_p(BnMA, 50 \text{ °C}) = 1224-1510 \text{ L mol}^{-1} \text{ s}^{-1}$, while $k_p(MMA, 50 \text{ °C}) = 648 \text{ L} \text{ mol}^{-1} \text{ s}^{-1}$).⁴⁹ In all three cases, the molecular weights increased with conversion in a linear fashion, and the polydispersities remained relatively low ($M_w/M_n < 1.4$), indicating the controlled/"living" nature of the polymerization.

Reductive Cleavage of the Disulfide-Containing Linear Polymers. The produced polymers contained a disulfide link in the middle of the chain, which could be cleaved either reversibly (by reduction to thiol that can be reoxidized to disulfide) or irreversibly (i.e., by oxidation with performic acid to the corresponding sulfonic acid⁵⁰). Numerous methods for the chemical reduction of disulfides to thiols are known and used in biochemistry, mostly to cleave the cystine disulfide bridge in polypeptides and proteins.²⁶ Since the redox potential of the thiol/disulfide couple depends on the



Figure 3. Reductive degradation of disulfide-containing (a) polyMMA, (b) polytBuMA, and (c) polyBnMA with Bu_3P in DMF at room temperature for 1 h. The SEC traces of the starting and the cleaved polymer are shown with solid and dashed lines, respectively.



Figure 4. Preparation of degradable polyMMA-based gels by ATRP and their use as "supermacroinitiators". The disulfide and thiol groups originating from the functional initiator are shown in italics and the ones from the functional monomer in regular font. PolyMMA and polySty chains are represented with solid and dotted lines, respectively.

polarity and composition of the reaction medium, the decomposition rate of the polymers can be controlled by changes in the medium. In addition, the nature and polarity of the polymeric backbone should also influence the degradation rate.^{27,32} In our previous work,²⁵ the disulfide bond in polystyrene prepared by ATRP was cleaved to mercapto groups using dithiothreitol (DTT) in THF or DMF under a nitrogen atmosphere to avoid air oxidation of both the polymeric thiol and DTT. The reaction in DMF was faster and more efficient than in THF but was still relatively slow: 50 h at 60 °C was required to fully reduce the disulfide bonds in the polymer. Phosphines such as triphenylphosphine⁵¹ and especially Bu_3P^{52} in the presence of water (or moisture) reduce the disulfide group significantly more efficiently. Bu₃P transforms disulfides to thiols very rapidly and has been widely used in the study of proteins.⁵³ Its major advantages (as opposed to DTT) are relative stability toward autooxidation and high affinity to disulfide groups, meaning that large excess of this reagent is not needed for complete reduction.²⁶ Moreover, Bu₃P does not interfere with reagents typically used to bind to the formed thiol groups, which is especially important in protein analysis. It can be used, for instance, in conjunction with 1,3-propane sultone⁵⁴ or ω -toluene sultone,⁵⁵ which trap very effectively the formed thiol groups by alkylation, thus preventing backoxidation to disulfide after exposure to air.

In the current study, Bu_3P was used to cleave the disulfide-containing polymethacrylates converting them to thiol-terminated polymers of lower molecular weight. The reduction (Figures 1 and 3) was carried out at room temperature in DMF or THF under ambient atmosphere and was complete in several minutes. The number-averaged molecular weight of the products of degradation was approximately twice lower than the starting materials, since the labile disulfide link was in the middle of the polymer chains.

Preparation of Degradable Polymethacrylate Gels and Their Use as "Supermacroinitiators" for Further Chain Extension. The ATRP of a mixture of MMA and a difunctional monomer containing a disulfide bond, $(MAOE)_2S_2$ (1.2 molar % vs MMA), initiated by the disulfide initiator $(BiBOE)_2S_2$, yielded degradable gels (see the left-hand side of Figure 4). Both the initiator and the difunctional monomer served as sources of degradable disulfide groups in the gels.

Several kinetic samples were withdrawn from the reaction mixture during the synthesis, and conversion was determined by gravimetry. The gravimetric samples were then extracted with THF for 24 h, the solutions were filtered through a $0.2 \,\mu m$ PTFE membrane filter, and the molecular weights of the soluble polymer fractions were determined by SEC. The results from two experiments using different amounts of ATRP initiator (i.e., different numbers of propagating chains) are presented in Figure 5. With the higher [MMA]/[(Bi- $BOE_{2}S_{2}$] ratio (100/0.35 = 285; experiment MMA285gel) the reaction was slower, and complete gelation occurred at ca. 80% monomer conversion. When this ratio was decreased 3-fold (to 100/1.05 = 95), as expected, the polymerization rate increased (higher initiator concentration), and the reaction mixture gelled at around 93% monomer conversion. The differences in the behavior of the two studied systems are due to the different average numbers of difunctional monomer units per chain, which is determined by the ratio of [(MAOE)₂S₂] to [(BiBOE)₂S₂]. In experiment MMA285gel, the average number of difunctional monomer per chain was 3.5, and therefore the gel point was reached earlier than in experiment MMA95-gel, in which only about 1.2 (on average) cross-linking units were incorporated in each propagating chain. In the latter case, the formation of chains with more than one dimethacrylate units made the gelation possible. In conventional radical polymerization, the incorporation of the difunc-

 Table 1. Properties of Degradable Gels: PolyMMA "Supermacroinitiators" and the Products of Their Chain Extension with Sty^a

degradable gel	chain extension reaction time, h	$M_{ m n}$, b kg/mol	$M_{ m w}\!/\!M_{ m n}{}^b$	$swelling^c$ in	
				THF	toluene
MMA285-gel MMA285-Sty1-gel MMA285-Sty2-gel MMA95-gel	"supermacroinitiator" 2.5 5 "supermacroinitiator"	$14.9 \\ 66.4 \\ 119.3 \\ 10.0 \\$	1.60 1.38 1.70 1.52	9.6 23.4 24 16.5	5.7 22.3 23.4 13.1
MMA95-Sty1-gel	2.5	45.0	1.30	30.3	28.4

^{*a*} Conditions for the chain extension: [Sty]:[CuBr]:[PMDETA] = 350:1:1, disulfide-cross-linked gels as macroinitiators (0.3 g/8 mL of Sty), 90 °C, bulk. ^{*b*} SEC analysis of the products of reductive degradation with Bu_3P in THF for 25 h. No changes were observed if the reduction was carried out for an additional 40 h. ^{*c*} Expressed as grams of solvent absorbed by a gram of dry gel.



Figure 5. Kinetics of formation of polyMMA-based disulfidecross-linked gels by ATRP and evolution of molecular weights of the soluble polymer fraction extracted from the gels with reaction time. Conditions: $[MMA]/[(MAOE)_2S_2]/[(BiBOE)_2S_2]/[CuBr]/[bpy] = 100:1.22:0.35:0.5:1 (experiment MMA285-gel)$ or 100:1.22:1.05:0.5:1 (MMA95-gel), 50 °C in acetone (2:5 byvolume vs monomer).

tional monomer is far less uniform, and gel point is reached at markedly lower conversion than in ATRP. For instance, a polymerization mixture of MMA with 1.2 mol % of (MAOE)₂S₂, containing V-70 as radical initiator (used at a concentration close to the concentration of ATRP initiator in experiment MMA285-gel, with the same amounts of monomers and solvent and at the same temperature), gelled already at 47% monomer conversion. Similar differences were previously observed in the gelation of mixtures of Sty and 4,4'-divinylbiphenyl using nitroxide-mediated and conventional radical polymerization.⁵⁶

The molecular weights of the soluble polymer fractions increased with the reaction time due to both the living nature of the polymerization and the formation of branched structures via the incorporation of the dimethacrylate monomer in the backbone. The latter process was also reflected in the broad molecular weight distribution of the extractable soluble fraction ($M_w/M_n \approx 1.5-4.9$). The final products from the two reactions were isolated, thoroughly washed with acetone, and used for further experiments.

ATRP has an important advantage for the preparation of degradable gels compared to conventional radical polymerization: the bromine atoms are preserved in the product, and therefore the gel can be functionalized by attachment of various functional groups or more complex molecules such as dyes, drugs, etc. A simple way to demonstrate the high chain-end functionality of the gels prepared by ATRP is to use them as "supermacroinitiators" in ATRP chain extension reactions with other monomers followed by analysis of the products (vide



Figure 6. SEC traces of the products of degradation of MMA285-gel and two gels prepared from this "supermacroinitiator" by chain extension with Sty. The notation and reaction conditions are explained in Table 1.

infra). Chain extension reaction of polyMMA-based gels was performed using Sty as the second monomer and CuBr/PMDETA as the catalyst at 90 °C. The "supermacroinitiator" had been repeatedly washed prior to the experiment to remove any free polyMMA chains that could also initiate the polymerization of Sty. Two different polyMMA gels were studied, namely, the final products from the reactions presented in Figure 5 (MMA285-gel and MMA95-gel). Schematically, the block formation and the degradation of the gels are sketched in Figure 4. The physical properties such as swellability of the gels with "blocky" structure differed significantly from those of the parent "supermacroinitiators". Table 1 lists the swelling ratios of the two polyMMAhomopolymer degradable gels and the gels derived therefrom by chain extension in both THF and toluene.

Demonstration of the Degree of Functionalization of PolyMMA-Based Gels by Reductive Degradation of Gels with Segmented Structure Prepared Therefrom. The polyMMA-based gels were successfully degraded in THF using Bu₃P as the disulfide reducing agent, forming linear soluble polyMMA chains containing at least one thiol end group originating from the disulfide initiator and potentially one or more attached to the backbone originating from the disulfide-containing cross-linker $(MAOE)_2S_2$ (Figure 4). The soluble polymers formed by the reduction were analyzed by SEC. After the chain extension, the gel with pendant polymeric chains was washed repeatedly with THF to remove any free polySty, generated by thermal initiation, and degraded using Bu₃P. The formed block copolymer was analyzed by SEC. The results from the chain extension experiments are summarized in Table 1. The molecular weights of the products of reductive degradation of the gels, given in Table 1, demonstrate the efficient initiation from the polyMMA-based "su-

permacroinitiators". This is further verified from the symmetrical shift observed in the SEC traces of the soluble linear polymers formed after the reduction of the gels (Figure 6).

Figure 6 shows that no significant amount of homopolymer of MMA was observed in the products of degradation of the gels with segmented structures, indicating the high degree of functionalization of the gel prepared by ATRP.

Conclusions

Bis[2-(2-bromoisobutyryloxy)ethyl] disulfide was employed as initiator for the ATRP of methyl, tert-butyl, and benzyl methacrylate, catalyzed by CuBr/2,2'-bipyridine, to yield well-defined linear polymers with internal disulfide bond. The reductive cleavage of the latter with tributylphosphine was fast and efficient and produced polymers of lower molecular weight than the starting materials.

Mixtures of methyl methacrylate (MMA) and a difunctional methacrylate monomer with internal disulfide bond were copolymerized by ATRP using disulfidecontaining initiator and the formed gels were successfully degraded upon reduction to form soluble, low molecular weight linear polyMMA fragments containing thiol groups at the chain ends and along the backbone (originating from the disulfide difunctional initiator and monomer, respectively). The disulfide-cross-linked gels contained alkyl bromide end groups and were used as "supermacroinitiators" in chain extension reactions with styrene, producing degradable gels with pendant polystyrene chains that had higher swelling ratios in THF and toluene than the original polyMMA-based "supermacroinitiators".

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