

Synthesis of Degradable Copolymer Networks Containing Hemiacetal Components and Well-Defined Backbones

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Received 10 June 2010; accepted 11 October 2010

DOI 10.1002/app.33589

Published online 10 March 2011 in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: A novel copolymer network was prepared using divinyl ether bis[4-(vinylloxy)butyl] (4-methyl-1,3-phenylene) biscarbamate (BECT) as crosslinking agent. First, the backbone chains were synthesized by the copolymerization of acrylic acid (AA) and methyl methacrylate (MMA) using reversible addition-fragmentation chain-transfer technique. The molecular weight of poly(AA-co-MMA) was well-controlled, and the polydispersity was low. Carboxyl group on the poly(AA-co-MMA) chains then reacted with BECT in the presence of pyridinium

p-toluenesulfonate, generating a copolymer network with hemiacetal component in the crosslinking segment. After being treated in strong acid, this copolymer network was able to be degraded owing to the hemiacetal structure, but the backbone chains remained intact. The copolymer network was stable in basic or neutral environment. © 2011 Wiley Periodicals, Inc. *J Appl Polym Sci* 121: 1860–1865, 2011

Key words: copolymerization; networks; degradation

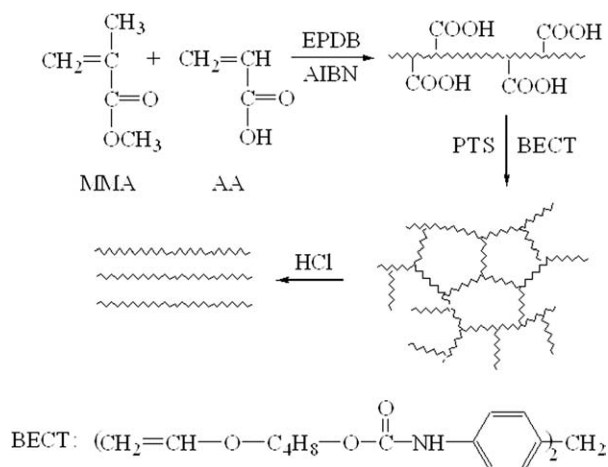
INTRODUCTION

Polymer networks prepared by free radical polymerization possess a wide application in dental materials, protective and decorative coatings, contact lenses, superabsorbent materials, and hydrogels for biomaterials.¹ Multifunctional monomers are frequently used in free radical polymerizations to generate polymer networks by two methods. In the first way, when a divinyl crosslinking agent was used in the free radical polymerization, a network could be obtained directly.² In the second way, a linear polymer with functional sites, such as hydroxyl group, was synthesized previously and then crosslinked by a special multifunctional reagent, such as diisocyanate, to generate a polymer network in two steps.³ The intelligent gels, such as pH-sensitive gels, had been widely investigated because of their special characteristics. The general pH-sensitive polymer gels exhibit swelling or deswelling behavior as pH changes, but their chemical compositions and molecular structures remain intact.^{4–6} Thus, pH-sensitive polymer gels with special components that will decompose in selective media attracted great attention for the biomedical materials, such as controlled drug delivery and tissue engineering,^{7–9} and for electronics industry.^{10,11}

The addition reaction between alkyl vinyl ether and carboxylic acid to generate hemiacetal ester has been used as a protecting method for carboxyl group in the anionic (co)polymerization of (meth)acrylic acid.¹² Divinyl ethers and dicarboxylic acids underwent polyaddition reaction to synthesize thermally degradable polymers with a weak covalent bond in the main chain.¹³ Ruckenstein reported a pH-sensitive copolymer network containing acetal component that degraded in acid environment via combination of polyaddition and anionic polymerization.¹⁴

In the past decades, techniques for controlled/living free-radical polymerization, including nitroxide-mediated polymerization (NMP),^{15,16} atom transfer radical polymerization (ATRP),^{17,18} and reversible addition-fragmentation chain transfer polymerization (RAFT),¹⁹ have attracted great attention because of their ability to synthesize polymers with well-controlled molecular weights and low polydispersities,²⁰ well-defined architectures such as block,^{21,22} comb,^{23,24} graft,²⁵ and star²⁶ structures. However, the use of NMP and ATRP methods has been limited by their incompatibilities with certain monomers or reaction conditions. The NMP merely appeared utility for styrene and derivative systems, whereas ATRP was not suitable for monomers or initiators with acid functionality.²⁷ The RAFT polymerization has been well developed because of its adaptability of a wide range of nonfunctional and functional monomers, such as (meth)acrylic acid which has been vastly used in amphiphilic block copolymers,²⁸ miniemulsion polymerization,^{29,30} and

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Scheme 1 Preparation and degradation of copolymer network.

ab initio emulsion polymerization.^{31,32} Patrickios,³³ for the first time, reported amphiphilic model co-networks via RAFT polymerization based on *n*-butyl methacrylate and 2-(dimethylamido)ethyl methacrylate crosslinked with ethylene glycol dimethacrylate, but there is no research on the synthesis of degradable polymer networks by RAFT.

The aim of this study was using RAFT technique to synthesize a well-defined copolymer with pending carboxyl group and then to prepare pH-sensitive copolymer network via the addition reaction between carboxyl and vinyloxy groups. As shown in Scheme 1, the acid functionalized copolymer was synthesized via RAFT copolymerization of methyl methacrylate (MMA) and acrylic acid (AA) using 2,2'-azobisisobutyronitrile (AIBN) as initiator and 2-(ethoxycarbonyl)prop-2-yl dithiobenzoate (EPDB) as RAFT agent. After copolymerization, BECT and pyridinium *p*-toluenesulfonate (PTS) were added into the polymerization system, generating a copolymer network that possessed stability in basic and neutral environments but decomposed in acid condition.

EXPERIMENTAL

Materials

Tetrahydrofuran (THF) was dried with CaH_2 under reflux for more than 24 h and distilled. 1,4-Dioxane (DOX) was dried with CaH_2 under reflux for more than 24 h and distilled. AA was distilled under reduced pressure. MMA was washed with 5% NaOH aqueous solution and deionized water until neutralization, dried overnight with anhydrous MgSO_4 , and then distilled under reduced pressure. 4-Hydroxybutyl vinyl ether (HBVE, Chongqing Research Institute of Chemical Industry, 95%) was dried with CaO and doubly distilled under reduced pressure. Diphenylmethane diisocyanate (MDI,

Beijing Keju Chemical Material) was distilled under reduced pressure. Pyridinium *p*-toluenesulfonate (PTS, Aldrich, 98%) was used as received. 2,2'-Azobisisobutyronitrile (AIBN) was recrystallized from ethanol and dried under vacuum. 2-(Ethoxycarbonyl)prop-2-yl dithiobenzoate (EPDB) was prepared according to literature,³⁴ δ_H (600 MHz, CDCl_3) 7.93 (2H, *o*-Ar-H), 7.51 (1H, *p*-Ar-H), 7.35 (2H, *m*-Ar-H), 4.15 (2H, $-\text{COO}-\text{CH}_2-$), 1.75 (6H, $-\text{C}(\text{CH}_3)_2-$), 1.23 (3H, CH_3-CH_2-).

Synthesis of BECT

In a well-dried round-bottom flask with magnetic stirring, MDI and HBVE with molar ratio of 1 : 2 were dissolved in purified THF under the protection of nitrogen. The reaction was performed at 50°C and the content of isocyanate group in the system was monitored by treating the sample with an excess of di-*n*-butylamine in acetone, and then the excess di-*n*-butylamine was determined by back-titration with standard hydrochloric acid.³⁵ The conversion of isocyanate group reached 99% for 12 h. Then, white solid BECT powder was obtained by twice precipitation in a large amount of hexane from THF solution, dried under vacuum, and stored at room temperature. The chemical structure of BECT was determined by $^1\text{H-NMR}$ analysis, δ_H (600 MHz, CDCl_3) 7.28, 7.10 (8H, Ar-H), 6.58 (2H, Ar-NH), 6.47 (2H, $\text{CH}_2=\text{CH}-$), 4.18 (4H, $\text{COO}-\text{CH}_2$), 4.16, 3.99 (4H, $\text{CH}_2=\text{CH}-$), 3.88 (2H, Ar- CH_2 -Ar), 3.71 (4H, $\text{O}-\text{CH}_2-\text{CH}_2$), 1.65, 1.77 (8H, $\text{CH}_2-(\text{CH}_2)_2-\text{CH}_2$).

Copolymerization of AA and MMA

In a typical experiment, 8 g of AA and MMA mixture with molar ratio of 1 : 9, 0.055 g (0.33 mmol) of AIBN, and 0.268 g (1.0 mmol) of EPDB were dissolved in 20 mL of DOX in a round-bottom flask equipped with a magnetic stirrer. The system was degassed with three freeze-evacuate-thaw cycles. The polymerization was performed under argon atmosphere at 65°C in an oil bath. After certain reaction time, trace amount of samples were taken out with dry syringes for determining the monomer conversions, molecular weights, and polydispersities. The copolymer samples for $^1\text{H-NMR}$ analysis were further purified by precipitation in hexane, removing the unreacted monomers and then vacuum-dried over night at 50°C.

Preparation of copolymer network

When the monomer conversion reached above 99%, the polymerization was stopped by cooling the mixture to room temperature. Half molar amount of BECT relative to AA with a trace amount of PTS

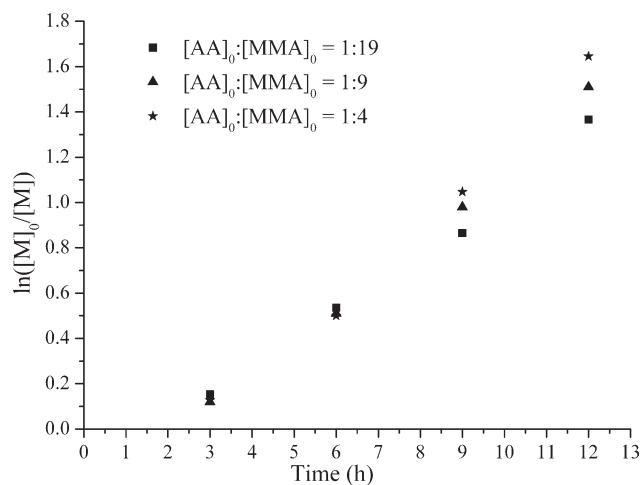


Figure 1 Plots of $\ln([M]_0/[M])$ versus time for the copolymerization of AA and MMA.

was then added into the mixture under the protection of nitrogen with magnetic stirring. The cross-linking reaction took place at 30°C. After the stirrer failing in running, the gel was washed by THF in a Soxhlet extractor for 24 h, and no polymer was detected in the extracting solvent.

pH Response of the copolymer network

At room temperature, 4 g of dried copolymer gel was swelled in 30 mL of THF and 2 mL of hydrochloric acid (0.1M), 2 mL of NaOH aqueous solution (0.1M), and 2 mL of deionized water were then added, respectively. The time needed to form a clear solution was recorded. The clear solution obtained was then neutralized to pH 7, followed by being poured into a large excess of hexane, and the precipitated polymer

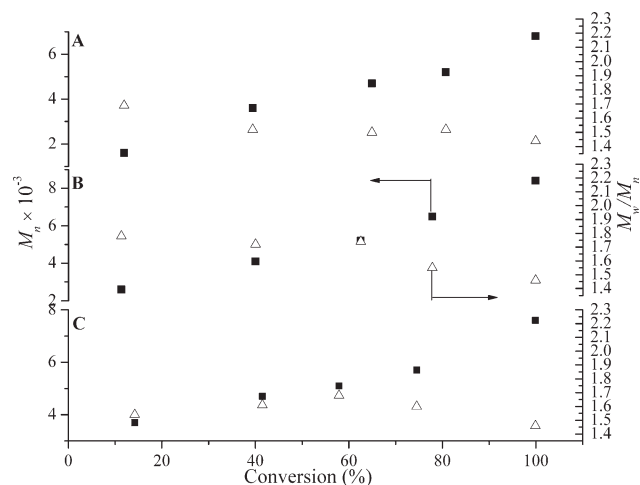


Figure 2 M_n and M_w/M_n versus monomer conversion for the RAFT copolymerization of AA and MMA in DOX at 65°C: (A) $[AA]_0 : [MMA]_0 = 1 : 4$; (B) $[AA]_0 : [MMA]_0 = 1 : 9$; (C) $[AA]_0 : [MMA]_0 = 1 : 19$.

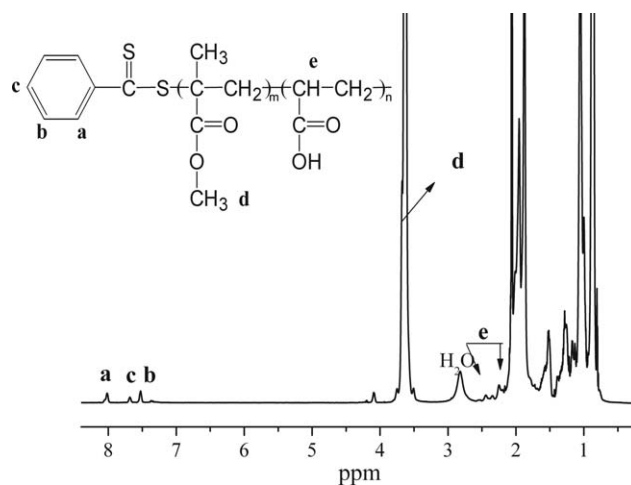


Figure 3 $^1\text{H-NMR}$ spectrum (in acetone- d_6) of P(AA-co-MMA) via RAFT technique ($[AA]_0 : [MMA]_0 = 1 : 4$, in DOX at 65°C for 24 h).

was washed with water and then with methanol, vacuum-dried at room temperature overnight.

Characterization

$^1\text{H-NMR}$ spectra were recorded in CDCl_3 or acetone- d_6 on a Bruker AV 600 MHz NMR spectrometer; M_n and M_w/M_n were estimated by gel permeation chromatography (GPC) on a Tosoh HLC 8320 GPC (column: TSK-Gel Super HZM-M \times 2) on the basis of a polystyrene calibration curve, using THF as solvent with a 0.35 mL/min flow rate at 40°C.

RESULTS AND DISCUSSION

Copolymerization of AA and MMA

The random copolymer P(AA-co-MMA) was obtained via RAFT polymerization of AA and MMA in DOX in the presence of EPDB. Figure 1 shows the linear relationship between $\ln([M]_0/[M])$ and time for the copolymerization of AA and MMA at different molar ratios, indicating that the copolymerization performed in first-order kinetics in each case. An introduction period was observed and might be caused by the starting RAFT agent consumed with slow fragmentation, retardation, and impurities.³⁶ The polymerization rate was enhanced with the increase of AA ratio in the feeding. And the monomer conversions were all above 99% in 24 h.

Figure 2 shows the evolution of M_n and M_w/M_n with the monomer conversion at various feeding ratios. In each case, M_n increased linearly with monomer conversion, and the polydispersity of the polymer was relatively low. This shows that the copolymerization of AA and MMA proceeded a living free-radical polymerization. Figure 3 depicts the $^1\text{H-NMR}$ spectrum of a typical well-purified

TABLE I
Copolymers of AA and MMA

PAM ^a	f^b	n/m^c	$M_{n,th}^d$	$M_{n,NMR}^e$	M_n^f	M_w/M_n^f
PAM-1	1 : 4	1/4.9	8200	11000	6800	1.44
PAM-2	1 : 9	1/9.3	8200	14100	9400	1.46
PAM-3	1 : 19	1/17	8200	10500	7600	1.46

^a P(AA-*co*-MMA).

^b Feeding ratio of AA and MMA.

^c Molar ratios of AA and MMA in copolymers determined by ¹H-NMR with the equation

$$\frac{n}{m} = \frac{I_e}{I_d/3}$$

^d M_n calculated by conversion with equation

$$M_{n,th} = \frac{[AA]_0 \times 72.06 + [MMA]_0 \times 100.12}{[EPDB]_0} \times 99\% + 268.43$$

^e M_n calculated by ¹H-NMR with the equation

$$M_{n,NMR} = \frac{72.06 \times I_e + 100.12 \times I_d/3}{(I_a + I_b + I_c)/5}$$

^f Determined by GPC.

P(AA-*co*-MMA) sample. The singlets at $\delta = 7.53$ – 8.01 ppm (peak a–c) correspond to the aromatic protons of EPDB units, demonstrating that the dithioester EPDB consequentially reacted with the initiating or propagating free-radicals and located at the ends of copolymer chains. The peaks at $\delta = 3.63$ ppm (peak d) and 2.20–2.50 ppm (peak e) result from MMA and AA units, respectively. The molecular weight of copolymers and molar ratios of AA and MMA in the copolymer chains could be calculated by ¹H-NMR spectra, and the results are listed in Table I. The molecular weights calculated by ¹H-NMR spectra ($M_{n,NMR}$) were larger than the theoretical values ($M_{n,th}$). It may be caused by the fact that not all polymer chains were terminated with a RAFT end group in the RAFT polymerization.³⁷ The molar ratio of AA and MMA (n/m) was calculated by the intensity ratio of peaks according to the characteristic protons for AA (I_e) and MMA (I_d). In all cases, n/m almost coincided as that in the feeding, indicating that the content of AA in the copolymer could be regulated by the feeding ratio of the monomers. Thus, the content of the carboxyl side groups as crosslinking functional sites could be controlled.

Figure 4 shows the relationship of $M_{n,NMR}$ and n/m versus monomer conversion for the copolymerization of AA and MMA with feeding ratio of 1 : 4. The $M_{n,NMR}$ increased linearly with the monomer conversion, sharing a similar trend as M_n determined by GPC. The components of copolymer altered with the monomer conversion, because the reactivity ratio of MMA was larger than that of AA ($r_{MMA} > r_{AA}$) according to Q-e scheme.³⁸ At the

starting stage of copolymerization, the molar ratio of AA ($n/m = 1/7.4$, for 2 h) in the polymer chains was smaller than that in feeding. The n/m value increased as the polymerization proceeded and was nearly equal to the feeding ratio at the final stage. Thus, it would be considered that the copolymerization of AA and MMA underwent a random mechanism in the presence of RAFT agent.

Preparation of copolymer network

BECT and PTS were added into the DOX solution under the protection of nitrogen after the

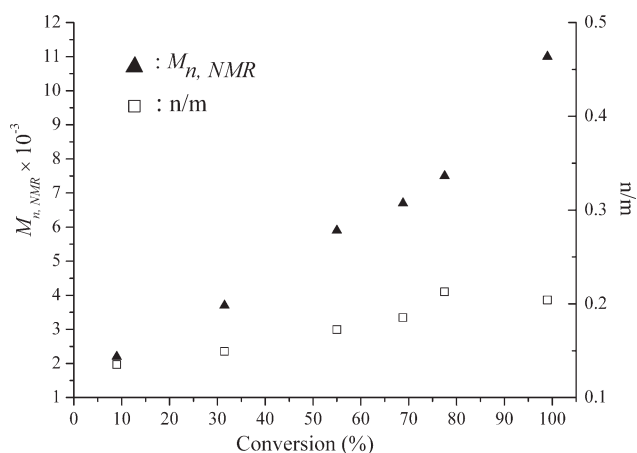


Figure 4 $M_{n,NMR}$ and n/m versus monomer conversion ($[AA]_0 : [MMA]_0 = 1 : 4$): $M_{n,NMR}$, molecular weight determined by ¹H-NMR data; n/m , molar ratio of AA and MMA calculated by ¹H-NMR data.

TABLE II
Synthesis and Hydrolysis of Copolymer Gels

PAM	Crosslinking time (h)	Hydrolyzing time (h) ^a
PAM-1	1	1
PAM-2	2	1
PAM-3	–	–

^a Treated with HCl.

copolymerization terminated at room temperature. The reaction of carboxyl and vinyl group took place immediately, generating a graft copolymer at the first stage and then network. A trace amount of sample was taken out with a dry syringe before the gel formation for a GPC measurement, and it was further purified by precipitation in hexane for ¹H-NMR analysis. As shown in Table II, in both PAM-1 and PAM-2 systems, the magnetic stirrers failed in working within 2 h, indicating that copolymer gels with hemiacetal components were obtained in the flasks. The copolymer gels were washed by THF in a Soxhlet extractor for 24 h. And no polymer was detected in the extracting solvent, confirming that a complete gel formation occurred via the addition reaction of linear copolymers with BECT. The crosslinking time needed to form copolymer gels depended on the feeding ratio of MMA and AA. As shown in Table II, the crosslinking process was delayed by decreasing the content of AA units in the copolymer chains, but no visible gel was obtained in PAM-3 system because of much less crosslinking sites in polymer chains when a lower AA feeding ratio was used.

For PAM-1, while BECT was grafted onto the copolymer backbone chain, the changes of molecular weight and polydispersity were detected by GPC

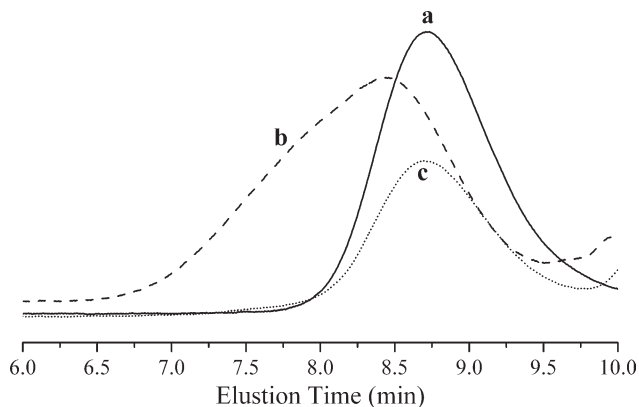


Figure 5 GPC chromatograms of (a): PAM-1, $M_n = 6800$, $M_w/M_n = 1.44$; (b) graft copolymer obtained by addition reaction of PAM-1 with BECT for 40 min, $M_n = 13,600$, $M_w/M_n = 2.01$; and (c) hydrolyzed product of copolymer gel, $M_n = 7800$, $M_w/M_n = 1.39$.

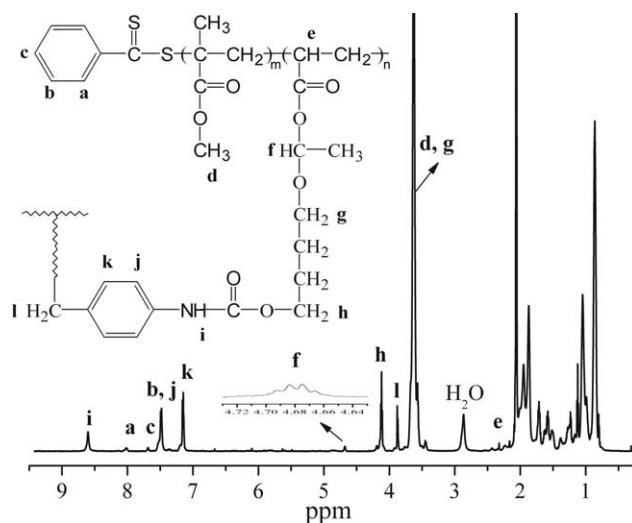


Figure 6 ¹H-NMR spectrum (in acetone-d₆) of graft copolymer obtained by addition reaction of PAM-1 with BECT for 40 min.

curves as shown in Figure 5. M_n shifted from 6800 (a) to 13,600 (b) and M_w/M_n increased from 1.44 to 2.01. Figure 6 depicts ¹H-NMR spectrum of the graft copolymer. The characteristic peak of the hemiacetal methine proton was present at $\delta = 4.69$ ppm (peak f), while the absorptions corresponding to aromatic protons of EPDB units (peaks a–c) and protons of both backbone (peaks e) and side chains (peaks d, g–l) were present, demonstrating that the crosslinking process via the addition reaction between carboxyl group and BECT had no obvious effect on the polymer backbone chains with RAFT end groups attached.

pH Response of the copolymer network

The copolymer network exhibits pH response because of the crosslinking segment consisting acetal molecular structure.³⁹ When a series of certain mass of copolymer network were well swelled in THF in beakers, equal volume of hydrochloric acid (0.1M), NaOH aqueous solution (0.1M), and deionized water were added into the beakers, respectively. The copolymer gels that were treated with strong alkali and water remained unchanged. However, after being treated with strong acid, the gels became smaller. Within a short time (see Table II), the network disappeared completely and a clear solution formed finally. The products of hydrolysis were obtained by precipitation in a large amount of hexane and then subjected to GPC measurement. As shown in Figure 5(c), the M_n and M_w/M_n of the recovered polymer ($M_n = 7800$, $M_w/M_n = 1.39$) were close to its precursor PAM-1 (Fig. 5(a), $M_n = 6800$, $M_w/M_n = 1.44$),

indicating that a complete degradation of the hemiacetal component occurred in the presence of a strong acid but no decomposition happened to the backbone chains.

CONCLUSIONS

A well-defined structure copolymer of AA and MMA with controlled molecular weight and low polydispersity was synthesized via RAFT polymerization. This acid functionalized copolymer underwent addition reaction with divinyl ether BECT in the presence of PTS to generate copolymer network. Because of the hemiacetal structure, a weak covalent bond, in the crosslinking segment, this copolymer network exhibited the ability to be degraded in strong acid. Meanwhile, the backbone chains were unchanged during the hydrolysis process. Thus, this copolymer network might have potential applications in reworkable materials.

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