Synthesis of Model Primary Amine-Based Branched Copolymers by Pseudo-Living Radical Copolymerization and Post-polymerization Coupling of Homopolymers

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Received December 12, 2008; Revised Manuscript Received January 7, 2009

ABSTRACT: Two synthetic routes to highly branched primary amine-based methacrylic copolymers are described. One route involves statistical copolymerization of 2-aminoethyl methacrylate (AMA) monomer in its hydrochloride salt form with a disulfide-based dimethacrylate (DSDMA) comonomer via RAFT copolymerization, while the other route involves statistical coupling of near-monodisperse PAMA homopolymer chains using bifunctional reagents that react with primary amines. Both intermolecular branching and intramolecular cyclization occur in each route, with the former being favored at high PAMA concentration and the latter being favored at low PAMA concentration, as expected. In the former case, cleavage of the disulfide bonds in the DSDMA branch points confirms that the highly branched, polydisperse copolymers simply comprise randomly linked, near-monodisperse primary chains. In the latter case, the final product is highly dependent on the type of branching reagent that is used. In the case of divinyl sulfone (DVS), the coupling chemistry is both fast and irreversible, leading to permanently branched copolymer chains. On the other hand, using poly(ethylene glycol) diacrylate (PEGDA) *initially* leads to branched copolymer chains, but the remaining primary amine groups subsequently catalyze hydrolysis of the β-aminoester bonds in the PEGDA branch points, leading to slow regeneration of linear chains. No hydrolytic degradation occurs if *N,N′*-methylenebis(acrylamide) is used as a brancher, but this reagent is significantly less reactive than DVS.

Introduction

There is increasing interest in the synthesis and properties of highly branched vinyl copolymers, particularly when prepared by pseudo-living radical polymerization.[1−5] This can be achieved without causing gelation by simply copolymerizing a monofunctional monomer with a bifunctional comonomer, provided that there is on average less than one fully reacted bifunctional comonomer per primary chain. For example, both Sherrington's group[3] and Zhu and co-workers[6,7] have reported the synthesis of branched methacrylic copolymers via atom transfer radical polymerization (ATRP), while Matyjaszewski's group has recently published on the analogous branched acrylic copolymers via ATRP.[8] We have shown that branching occurs relatively late in such copolymerizations[9,10] and that, at least under ATRP conditions, almost ideal behavior is observed. In other words, gelation invariably occurs if there is more than one fully reacted bifunctional comonomer per primary chain, whereas gelation is suppressed if there is less than one fully reacted bifunctional comonomer per chain. In contrast, the synthesis of branched vinyl copolymers using reversible addition−fragmentation chain transfer (RAFT) polymerization appears to be fundamentally different. Previously reported data suggest that nonideal behavior is typically observed in the analogous RAFT syntheses, with significantly more than one bifunctional comonomer per chain being required in order to induce gelation.[11−13] The obvious explanation for this discrepancy is that intramolecular cyclization, which naturally leads to "wastage" of the bifunctional comonomer, is much more favored under RAFT conditions.

Herein we report the synthesis of new branched methacrylic copolymers based on 2-aminoethyl methacrylate (AMA). Homopolymerization of AMA via ATRP and RAFT has been recently reported by our group.[14] In principle, branched PAMA polymers can be readily prepared by two methods, either (1) by pseudo-living radical copolymerization of AMA with a bifunctional comonomer or (2) by the random coupling of preformed near-monodisperse PAMA homopolymer chains via Michael addition, using various small molecule reagents such as diacrylates or divinyl sulfone. In both cases the resulting branched PAMA (co)polymers are relatively well-defined, cationic, and water-soluble. As such, they are expected to be interesting model systems for understanding the behavior of the structurally complex, but nevertheless commercially successful, branched copolymers based on polyethylenimine.

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Experimental Section

Materials. AMA monomer,[14] DSDMA comonomer,[10] and the RAFT chain transfer agent, 4-cyanopentanoic acid dithiobenzoate (CTP),[15] were synthesized according to previously reported protocols. 4,4′-Azobis(4-cyanopentanoic acid) (V-501), tris(2-carboxyethyl)phosphine (TCEP), divinyl sulfone (DVS), *N,N′*-methylenebis(acrylamide) (MBAA), and poly(ethylene glycol) diacrylate (PEGDA; M_n = 700) were all purchased from Aldrich and were used as received. All other chemicals were purchased from either Fisher or Aldrich at the highest available purity and were used as received.

RAFT Synthesis of $PAMA_{39}$ Homopolymer. RAFT polymerizations of AMA were conducted at 70 °C, employing V-501 as the radical initiator and CTP as the RAFT chain transfer agent. A typical protocol was as follows. AMA (3.00 g, 18.1 mmol), CTP (0.092 g, 0.33 mmol), and V-501 (0.0183 g, 0.066 mmol) were added along with 1,4-dioxane (2.26 mL) and deionized water (6.80 mL) to an ampule. The solution was sparged with nitrogen for ∼30 min and then placed in a preheated oil bath at 70 °C. The reaction was terminated after 5 h by cooling the reaction tube in an ice bath, followed by exposure to air. The crude product was purified by dialysis against water to remove unreacted AMA monomer and 1,4-dioxane and then freeze-dried overnight from water.

RAFT Synthesis of $PAMA_{329}$ Homopolymer. AMA (1.49 g, 9.0 mmol), CTP (0.005 g, 0.018 mmol), and V-501 (0.0010 g, 0.004 mmol) were added along with methanol (3.0 g) and deionized water

10.1021/ma802750x CCC: $40.75
Published on Web 01/30/2009

(3.0 g) to an ampule. The ampule was sparged with nitrogen for ~30 min and then placed in a preheated oil bath at 70 °C. The reaction was terminated after 24 h by cooling the reaction tube in an ice bath, followed by exposure to air. The crude product was purified by dialysis against water and then freeze-dried overnight from water.

RAFT Syntheses of Branched PAMA Copolymers Using DSDMA Brancher. A typical protocol was as follows. AMA (0.60 g, 3.62 mmol), CTP (0.0204 g, 0.072 mmol), DSDMA (0.0383 g, 0.132 mmol), and V-501 (0.0044 g, 0.016 mmol) were added along with methanol (0.45 mL) and deionized water (0.45 mL) to an ampule. The ampule was sparged with nitrogen for ~30 min and then placed in a preheated oil bath at 70 °C. The reaction was terminated after 90 h by cooling the reaction tube in an ice bath followed by exposure to air. Samples were analyzed by aqueous GPC and ^{1}H NMR in order to assess the evolution of the molecular weight distribution and the extent of reaction, respectively. The crude product was purified by dialysis against water and then freeze-dried overnight from water.

Branched Copolymer Syntheses via Postpolymerization Coupling of PAMA Homopolymer. A typical procedure was as follows: 0.10 g of PAMA homopolymer was added to 2.0 mL of deionized water, and the solution pH was adjusted to pH 9.0 using 1.0 M NaOH solution. Bifunctional coupler (either PEGDA or DVS or MBAA) was then added to this dilute aqueous PAMA solution. Samples were periodically withdrawn and immediately analyzed by aqueous GPC and ^{1}H NMR in order to assess the evolution of the molecular weight distribution and the extent of reaction, respectively.

Cleavage of Disulfide-Containing Branched Copolymers by Reduction with TCEP. In a typical procedure, the disulfide-containing branched PAMA copolymer (0.100 g) was dissolved in 10 mL of deionized water, and TCEP (0.020 g; TCEP/disulfide molar ratio = 4.26) was added. The reaction mixture was stirred at room temperature for 5 h. Samples were analyzed by aqueous GPC to determine the extent of cleavage of the disulfide branch sites within the copolymer.

Copolymer Characterization. All ^{1}H NMR spectra were recorded in D_2O using a 250 MHz Bruker ACF-250 spectrometer. The molecular weights and polydispersities of all the homopolymers and branched copolymers were determined by aqueous GPC at 35 °C using a PL Aquagel-OH 40 and a Aquagel-OH 30 column connected in series to a triple detection detector. The eluent was a pH 3.0 buffer comprising 0.30 M NaH_2PO_4 and 1.0 M acetic acid at a flow rate of 1.0 mL min^{-1}. The data were analyzed using PL Cirrus GPC software (version 2.0) supplied by Polymer Laboratories.

Results and Discussion

Synthesis of Branched Polymers via RAFT Copolymerization. In a recent communication,[16] one of us reported that 4-cyanopentanoic acid dithiobenzoate (CTP) is a suitable chain transfer agent for the RAFT polymerization of primary amine-based methacrylamide monomers in aqueous solution. The same chain transfer agent was used for the RAFT synthesis of AMA homopolymers in the present study. However, it was found that a water-miscible organic solvent such as methanol or 1,4-dioxane is required as a cosolvent to improve the solubility of the CTP. This is important because a relatively large amount of CTP is required to target lower molecular weight PAMA homopolymers. The CTP:initiator molar ratio was fixed at 5:1, which is quite typical for RAFT polymerizations.[17−19] The solution pH was kept relatively low (pH 4−5) so as to avoid hydrolysis and/or aminolysis of the CTP.[20] Figures 1 and 2 show kinetic data obtained for the homopolymerization of AMA in a 1:1 water/methanol mixture at 70 °C. The semilogarithmic plot was reasonably linear up to 90%, and the molecular weight versus conversion plot was linear; such results suggest that the polymerization is well controlled under these conditions.

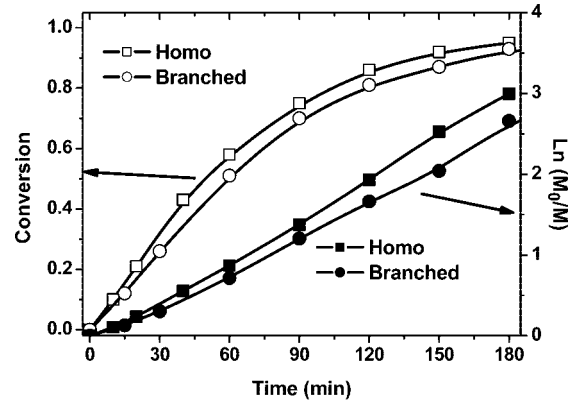


Figure 1. Conversion vs time curves and semilogarithmic plots of monomer concentration vs time for the homopolymerization of AMA and branched copolymerization of AMA with DSDMA in a 1:1 w/w water/methanol mixture at 70 °C. Homopolymerization conditions: 40% w/v AMA; target DP = 50; the relative molar ratios were AMA:CTP:V501 = 50:1:0.2. The relative molar ratios of AMA:CTP:DSDMA:V501 used for the branched copolymerizations were 50:1:1.5:0.2.

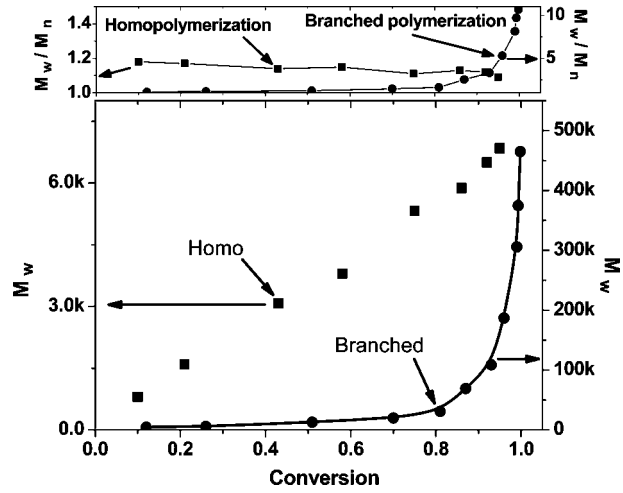


Figure 2. Molecular weight vs conversion data for AMA homopolymerization and branched copolymerization of AMA with DSDMA in a 1:1 w/w water/methanol solution at 70 °C using a V501 azo-initiator. Homopolymerization conditions: 40% w/v AMA; target DP = 50; relative molar ratios were AMA:CTP:V501 = 50:1:0.2. Branched copolymerization conditions: relative molar ratios were AMA:CTP:DSDMA:V501 = 50:1:1.5:0.2.

Having established suitable polymerization conditions for the RAFT homopolymerization of AMA, a cleavable disulfide-based dimethacrylate, DSDMA, was introduced into such polymerizations so as to induce branching (see Scheme 1). According to Flory, if the system behaves ideally and only intermolecular cross-linking occurs, just one fully reacted divinyl comonomer per primary chain is sufficient for gelation.[21] This theory has been verified for the synthesis of branched methacrylic copolymers via ATRP, which is normally conducted at relatively high monomer concentration (45−55%). However, according to Gao et al., a significant degree of intramolecular cyclization can also occur during such branching copolymerizations, especially when the monomer (and hence polymer) concentration is relatively low.[22] These findings are supported by our recent results obtained for a model branching system: quaternization of near-monodisperse poly(2-(dimethylamino)ethyl methacrylate) using 1,2-bis(2-iodoethoxy)ethane (BIEE).[23] More specifically, we found that intramolecular cyclization is favored if the polymer concentration is below the critical coil−coil overlap concentration, c^*, whereas intermolecular branching is favored if the polymer concentration is substantially above c^*. In the present

Scheme 1. Schematic Representation for the Synthesis of Branched PAMA Copolymer via RAFT Copolymerization of AMA with DSDMA Using CTP at 70 °C

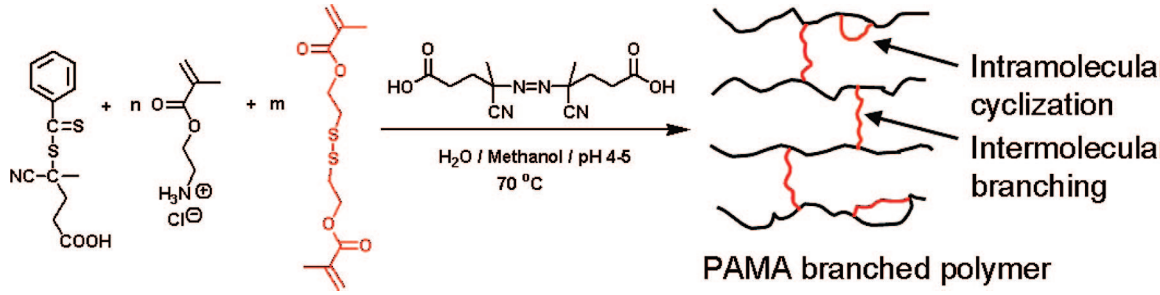


Table 1. Summary of the PAMA Homopolymer and Various Branched PAMA Copolymers Synthesized via RAFT Chemistry at 70 °C

entry no.	DSDMA:CTP molar ratio	AMA concn (% w/v)	time (h)	conversion (%)	M_n	M_w	M_w/M_n
1	0.00	20	24	98.0	12 100	13 300	1.10
2	1.00	26	24	96.0	12 400	17 700	1.43
3	1.11	10	90	95.0	12 200	16 700	1.37
4	1.11	20	90	99.5	13 900	34 800	1.83
5	1.11	40	90	99.9	19 000	69 200	3.64
6	1.50	20	90	99.9	31 600	59 900	1.90
7	1.50	40	90	99.9	56 200	767 000	13.65
8	1.76	20	90	99.5	36 200	82 100	2.27
9	1.76	40	90	macroscopic gelation			

work, we estimate c^* to be approximately 15% w/v and 2.8% w/v for PAMA homopolymer with mean degrees of polymerization of 39 and 329, respectively (see Supporting Information for these two calculations).

The DSDMA brancher was initially introduced into the copolymerization formulation at a DSDMA:CTP molar ratio of unity. The AMA monomer concentration was selected to be 26% w/v, which is a typical monomer concentration used for RAFT syntheses. It is emphasized that only *fully reacted* DSDMA brancher actually causes branching. Therefore, very high degrees of consumption of vinyl groups (>99%) are important in such syntheses.

The results shown in Table 1 (entry 2) indicate that the copolymer molecular weight and polydispersity obtained at a DSDMA:CTP molar ratio of unity are only slightly higher than that of the corresponding PAMA homopolymer prepared in the absence of any DSDMA brancher. This surprising result can be attributed to either the incomplete conversion of vinyl bonds (96%) or substantial intramolecular cyclization. Hence, the DSDMA:CTP molar ratio was increased to 1.11, and the reaction time was extended for a second series of copolymerizations. From Table 1 (entry 3) and Figure 3, the conversion was only 95% at 10% w/v AMA concentration, even after 90 h. However, increasing the AMA concentration to 20% w/v led to final conversions of 99.5% (Table 1, entry 4), suggesting that the copolymerization was essentially complete under these conditions. Nevertheless, the M_w of the isolated branched copolymer was 34 800, as compared to a PAMA homopolymer M_w of 13 300 obtained in the absence of DSDMA. Given that more than one brancher per primary chain has been introduced, these results strongly suggest that the extent of intramolecular cyclization remains significant at 20% w/v AMA. Increasing the AMA concentration up to 40% w/v under otherwise identical conditions led to a final copolymer M_w of 69 200, but macroscopic gelation still did not occur, which suggests that intramolecular cyclization is suppressed but not eliminated under these conditions (Table 1, entry 5).

Use of a DSDMA:CTP molar ratio of 1.50 led to more highly branched copolymers, as expected. Moreover, no macroscopic gelation was observed at AMA concentrations of either 20% w/v or 40% w/v (Table 1, entries 6 and 7). Gelation finally occurred at a DSDMA:CTP molar ratio of 1.76 when using 40% w/v AMA (Table 1, entry 9), but no gelation was observed under the same conditions with 20% w/v AMA (Table 1, entry 8). These results clearly demonstrate that rather nonideal branching behavior is obtained and that the extent of intramolecular cyclization is highly dependent on the monomer (and hence polymer) concentration. These results are in good agreement with a recent mathematical model developed for RAFT-synthesized branched copolymers which indicates that the gel point can be suppressed by intramolecular cyclization.[24]

Disulfide bonds can be efficiently cleaved either under reducing conditions (using either dithiothreitol or TCEP) or under oxidizing conditions (using benzoyl peroxide).[25−28] We have recently used this approach to selectively cleave disulfide bonds within branched poly(2-hydroxypropyl methacrylate)-based copolymers synthesized via ATRP.[10] The molecular weight distribution of fully degraded poly(2-hydroxypropyl methacrylate) was almost identical to a near-monodisperse linear poly(2-hydroxypropyl methacrylate) control synthesized by ATRP under the same conditions in the absence of any disulfide-based dimethacrylate branching agent. Since these branched copolymers comprise near-monodisperse primary chains, the branching process is not detrimental to the pseudo-living character of the ATRP chemistry. In the present study, the disulfide bonds within the branched PAMA copolymers were selectively cleaved using TCEP at room temperature. Figure 4 shows the GPC traces obtained for the branched copolymers (Table 1, entry 7) before and after cleavage. A GPC trace obtained for near-monodisperse PAMA homopolymer synthesized via RAFT in the absence of DSDMA brancher is also shown as a reference. Clearly, the molecular weight distribution

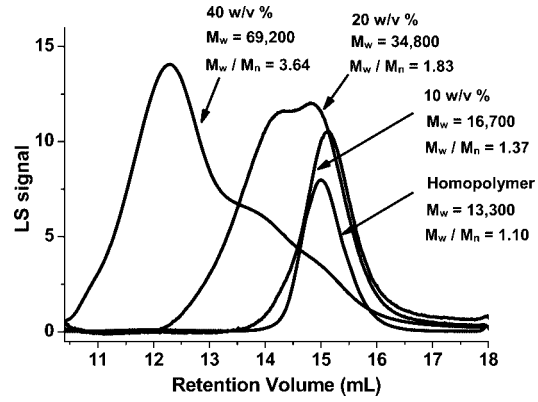


Figure 3. GPC traces for the branched PAMA copolymers synthesized via RAFT at either 10, 20, or 40% AMA monomer concentrations in the presence of the DSDMA brancher. Linear PAMA homopolymer prepared under the same conditions (20% AMA concentration) in the absence of any DSDMA brancher is also included as a reference. Conditions: target degree of polymerization of primary chains = 50; DSDMA:CTP molar ratio = 1.11, 70 °C for 24−96 h.

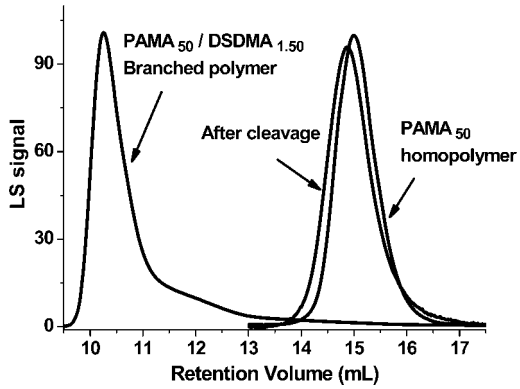
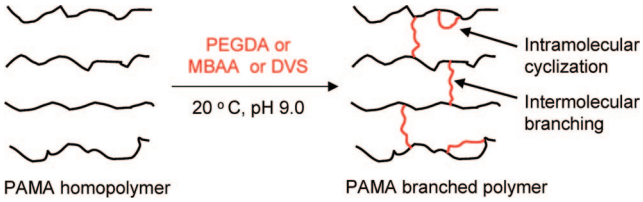


Figure 4. GPC traces obtained for branched $PAMA_{50}$ copolymer prepared using the DSDMA brancher before and after cleavage of its disulfide bonds using TCEP. $PAMA_{50}$ homopolymer is also shown as a reference.

Scheme 2. Reaction Scheme for the Postpolymerization Coupling of PAMA Homopolymer with Either PEGDA or DVS



of the disulfide-cleaved copolymer is very similar to that of the linear PAMA homopolymer, which confirms that the original branched PAMA copolymers simply comprised randomly linked near-monodisperse primary chains, as expected. In other words, the pseudo-living character of the RAFT chemistry is also preserved under branching conditions. This conclusion is also supported by our kinetics studies. As shown in Figure 1, the semilogarithmic plot was linear up to 90%, which suggests good living character for the branching copolymerization. From Figure 2, we can also see that the weight-average molecular weight increases very sharply when the polymerization conversion is higher than 90%; this characteristic is very similar to that of branched copolymer syntheses via ATRP.[9]

Synthesis of Branched Copolymers via Postpolymerization Coupling Reactions. Recently, we reported that highly branched copolymers can also be synthesized by a "postpolymerization coupling" approach.[23] In this approach, near-monodisperse PDMA homopolymers were first synthesized by group transfer polymerization, and then BIEE was used as a bifunctional reagent for the statistical quaternization of these chains. It was found that both intermolecular branching/cross-linking and intramolecular cyclization occurred, with the former process being favored at higher PDMA concentrations. However, one drawback of this PDMA/BIEE model system is that the rate of quaternization is relatively slow: depending on the initial PDMA concentration, reaction times varied from a few days to several weeks. A similar postpolymerization coupling approach can be used for the synthesis of branched PAMA copolymers from near-monodisperse PAMA homopolymer precursors (Scheme 2), but in this case the coupling chemistry involves Michael addition (rather than quaternization) and the rate of reaction is relatively fast. Three coupling reagents were examined: divinyl sulfone (DVS), poly(ethylene glycol) diacrylate (PEGDA), and *N,N′*-methylenebis(acrylamide). Each of these reagents reacts with the primary amine groups on the PAMA chains in aqueous solution at ambient temperature (see Scheme 2). The optimum solution pH for this Michael addition chemistry is ~9: below this pH, some of the primary amines are protonated and hence less reactive, while above pH 9 the PAMA chains are known to be prone to hydrolytic degradation.[29]

Table 2. Effect of Varying the Amount of Bifunctional DVS Branching Agent (Relative to PAMA Repeat Units) Added to Either 4.5% w/v or 2.8% w/v Aqueous Solution of Near-Monodisperse $PAMA_{39}$ Homopolymer at pH 9 and 25 °C for 5 days[a]

entry no.	$PAMA_{39}$ concn (%)	DVS:PAMA molar ratio	M_n	M_w	M_w/M_n
1		0	7 700	8 900	1.16
2	4.5	5	11 800	17 500	1.48
3	4.5	10	20 100	31 700	1.58
4	4.5	15	20 400	45 800	2.25
5	4.5	20	macroscopic gelation		
6	2.8	5	13 100	16 800	1.29
7	2.8	10	15 700	21 800	1.39
8	2.8	15	29 200	41 800	1.43
9	2.8	20	36 500	55 100	1.51
10	2.8	25	macroscopic gelation		

[a] Molecular weight data were obtained by aqueous GPC analysis using a light scattering detector. The increase in molecular weight is due to random coupling of the near-monodisperse $PAMA_{39}$ chains.

One obvious limitation of the "postpolymerization coupling" approach is that in situ adjustment of the solution pH to 9 requires stoichiometric quantities of base to neutralize the PAMA repeat units, which are initially present in their hydrochloride salt form. This is technically difficult to achieve for concentrated aqueous copolymer solutions of 20−40% w/v since addition of concentrated NaOH makes precise control over the solution pH somewhat problematic, while the high level of background salt that is generated can compromise the aqueous solubility of the PAMA chains. Thus, our initial syntheses were restricted to relatively dilute PAMA solutions (<5%). This is important because the estimated c^* for neutral PAMA chains of mean DP 39 is ~15% (see Supporting Information). Thus, there is a much greater probability that a significant proportion of the DVS or PEGDA coupling reagent will be "wasted" in forming intramolecular cycles rather than intermolecular branching.[23] With DVS, the Michael addition coupling reaction is very fast: branched copolymer is formed within 20 min, and the final conversion of DVS exceeded 99%. In order to achieve even higher conversion, the reaction was allowed to run for 5 days at 25 °C. Figures S1 and S2 in the Supporting Information show the series of GPC traces obtained for the final branched PAMA copolymers; the corresponding molecular weight distribution data are summarized in Table 2.

Clearly, it is possible to obtain branched PAMA polymers using this approach (see entry 4, Table 2). However, it is emphasized that relatively high DVS/PAMA molar ratios are essential to ensure that branching occurs. In principle, if there were no intramolecular cyclization, just one DVS per PAMA primary chain should be sufficient to induce gelation. However, inspecting Table 2 and Figure S1, at a $PAMA_{39}$ concentration of 4.5%, more than 15 DVS molecules can react with each primary chain without causing gelation, while at a $PAMA_{39}$ concentration of 2.8% (Figure S2), more than 20 DVS molecules can react with each primary chain without causing gelation. From this series of experiments, it is clear that lower polymer concentrations strongly favor intramolecular cyclization over intermolecular branching. These observations are in good agreement with our previous studies of the quaternization of PDMA using 1,2-bis(2-iodoethoxy)ethane.[23]

In order to conduct such coupling reactions at higher PAMA concentrations, we utilized a 2:1 v/v water/pyridine mixture, rather than the addition of NaOH. Since pyridine is a stronger base than PAMA, this leads to in situ deprotonation to produce neutral PAMA chains. Using this approach, PAMA chains can be readily obtained in their reactive form at up to 28% w/w.

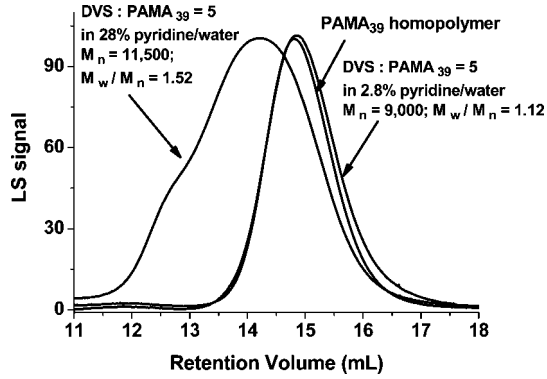


Figure 5. GPC traces recorded using a light scattering detector for the two branched PAMA polymers obtained after 5 days at 25 °C using a DVS:$PAMA_{39}$ molar ratio of 5.0 in a 2:1 v/v water/pyridine mixture conducted at both high (28%) and low (2.8%) PAMA concentration. A GPC trace obtained for the near-monodisperse $PAMA_{39}$ homopolymer precursor is included as a reference.

Table 3. Molecular Weight Data Obtained Using a Light Scattering GPC Detector for the Series of $PAMA_{329}$ Branched Polymers Obtained after 5 days at 25 °C in the Presence of Increasing Amounts of DVS Branching Agent Added to a 2.8% v/v Solution of $PAMA_{329}$ Dissolved in a 2:1 v/v Water/Pyridine Mixture

entry no.	DVS:$PAMA_{329}$ molar ratio	M_n	M_w	M_w/M_n
1	0	54 100	65 200	1.21
2	50	82 500	174 900	2.12
3	100	108 700	287 100	2.64
4	150	123 400	533 100	4.32
5	200	macroscopic gelation		

The DVS:PAMA molar ratio was held constant at 5:1, and the results are shown in Figure 5. Obviously, branched PAMA polymers of much higher molecular weight are obtained at 28% w/w than those synthesized at the same DVS/PAMA molar ratio at 2.8% w/w. Given that the estimated c^* for neutral PAMA chains of mean DP 39 is ~15%, these results clearly indicate intermolecular branching is favored when the PAMA concentration is higher than c^*, whereas intramolecular cyclization is favored when the PAMA concentration is lower than c^*.

The effect of varying the degree of polymerization of the PAMA homopolymer precursor was also examined. DVS was added in varying amounts to a 2.8% w/v solution of $PAMA_{329}$ dissolved in a 2:1 v/v water/pyridine mixture for 5 days at 25 °C to afford various DVS:PAMA molar ratios (see Table 3 and Figure 6). Clearly, the statistical coupling of much longer PAMA chains strongly favors intramolecular cyclization over intermolecular branching, since now as many as 150 DVS molecules per $PAMA_{329}$ chain can be tolerated without inducing gelation, whereas only ~25 DVS molecules were required to cause gelation under similar conditions using $PAMA_{39}$ homopolymer. It should be emphasized that the calculated c^* for $PAMA_{329}$ is about 2.8% w/v, which is identical to the experimental $PAMA_{329}$ concentration. In order to conduct our DVS coupling experiment at a significantly higher $PAMA_{329}$ concentration, a 2:1 v/v water/pyridine solvent mixture was utilized in order to ensure that the primary amine groups are fully deprotonated. At a $PAMA_{329}$ concentration of 28% w/v, i.e., well above our estimate for c^*, only 25 DVS molecules per PAMA chain can be tolerated, while addition of 50 DVS molecules per PAMA chain caused rapid macroscopic gelation. Using the same DVS:PAMA molar ratio, no changes in molecular weight are discernible when the $PAMA_{329}$ concentration was lowered to 2.8% (i.e., the same as the calculated c^*), since the vast majority of the DVS molecules are now wasted in intramolecular cyclization side reactions (see Figure 7). Compared to $PAMA_{39}$, the significantly higher

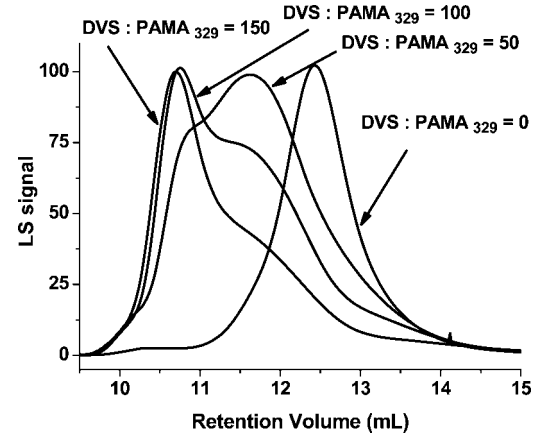


Figure 6. GPC traces recorded using the light scattering detector for the series of branched PAMA polymers obtained after 5 days at 25 °C in the presence of increasing amounts of DVS coupling agent per $PAMA_{329}$ chain at a [$PAMA_{329}$] of 2.8% w/v.

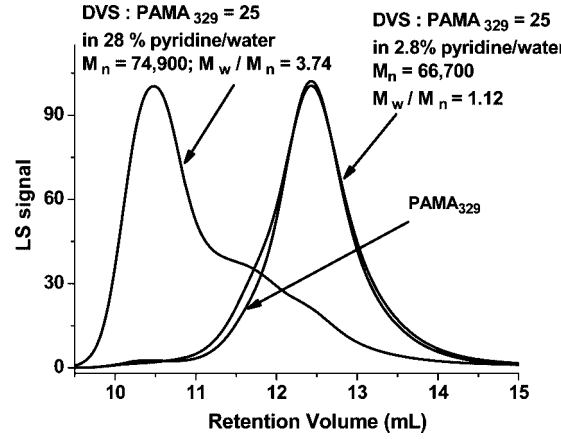


Figure 7. GPC traces recorded using a light scattering detector for the two branched PAMA polymers obtained after 5 days at 25 °C using a DVS:$PAMA_{329}$ molar ratio of 5.0 in a 2:1 v/v water/pyridine mixture conducted at both high (28%) and low (2.8%) PAMA concentration. A GPC trace obtained for the near-monodisperse $PAMA_{329}$ homopolymer precursor is included as a reference.

propensity toward intramolecular cyclization observed for $PAMA_{329}$ in dilute solution can be attributed to the much larger coil dimensions of the latter chains.

The PEGDA bifunctional coupling agent was reacted with a 3.8% w/v aqueous solution of $PAMA_{39}$ chains at pH 9 at a PEGDA/PAMA molar ratio of 2.73. A gradual buildup of molecular weight was observed within the first hour at 25 °C, with an M_w as high as 184 800 being obtained (see the first five entries in Table 4 and Figure S3). However, the molecular weight unexpectedly *decreased* over longer time periods (2−48 h), eventually producing only low molecular weight chains (and relatively low polydispersities) which are comparable to that of the original $PAMA_{39}$ homopolymer. This is because more than 90% of the primary amine groups remain unchanged and hence are available to catalyze the hydrolytic cleavage of the β-aminoester bonds within the PEGDA branch sites (see Scheme 3). In view of these remarkable and unexpected results, we undertook some small molecule model studies to examine the likelihood of such a degradation pathway. 2-Hydroxyethyl acrylate and ethanolamine were selected as small molecule analogues so as to better understand the proposed hydrolytic degradation mechanism. The ^{1}H NMR spectra shown in Figure S4 confirm that both Michael addition and hydrolytic degradation occurred as expected at pH 9: signals assigned to the β-aminoester adduct were observed after just 1 h, and the

Scheme 3. Postulated Hydrolytic Degradation Mechanism To Account for the Reduction in Molecular Weight Observed for Longer Reaction Times When Reacting PEGDA Brancher with Near-Monodisperse PAMA Chains

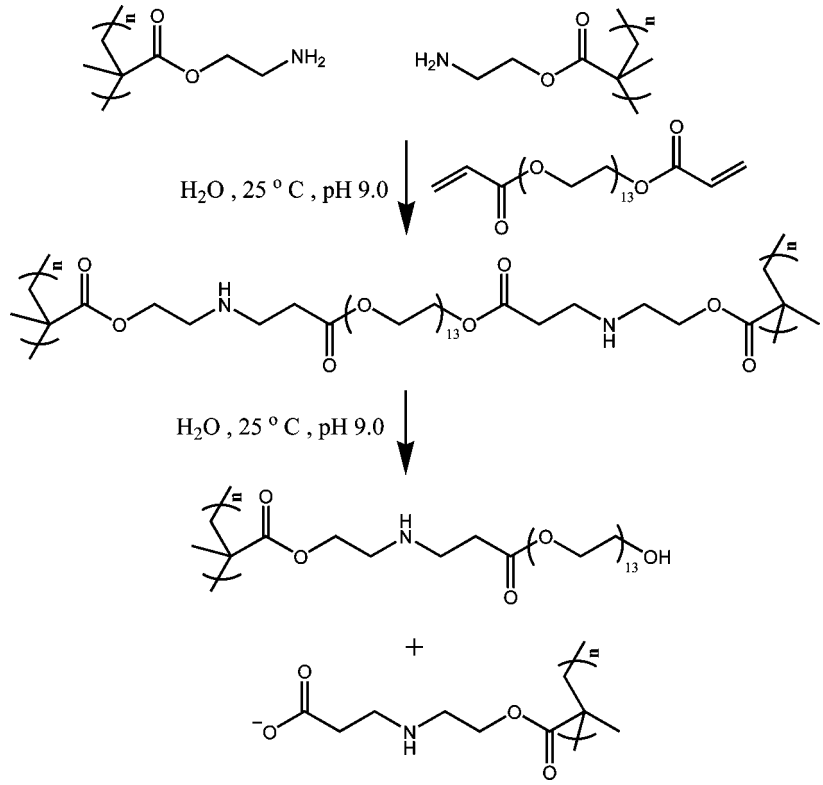


Table 4. Evolution of Molecular Weight Data Obtained by Aqueous GPC Using a Light Scattering Detector for the Addition of PEGDA to a 3.8% w/v Aqueous Solution of $PAMA_{39}$ Homopolymer Chains at pH 9 and 25 °C at a PEGDA/PAMA Molar Ratio of 2.73[a]

entry no.	time (h)	M_n	M_w	M_w/M_n
1	0	10 100	11 700	1.16
2	0.08	24 300	42 700	1.76
3	0.16	30 200	75 400	2.50
4	0.33	37 350	131 500	3.52
5	0.83	41 600	184 800	4.44
6	2.33	36 500	132 900	3.64
7	4.33	32 000	85 600	2.68
8	7.33	27 200	55 000	2.02
9	24	16 500	21 900	1.32
10	48	14 600	19 100	1.31
11	120	12 300	15 700	1.28

[a] The initial increase in molecular weight is due to random branching, and the eventual reduction in molecular weight is due to slow hydrolysis of the β-aminoester groups within the PEGDA branch points.

signals due to 2-hydroxyethyl acrylate completely disappeared within 24 h. More importantly, a sharp peak was observed at 3.63 ppm, which is assigned to the four equivalent oxyethylene protons of ethylene glycol. The elimination of this small molecule indicates that Michael addition is followed by based-catalyzed hydrolytic cleavage of the β-aminoester group, as suggested by the prior work of Lynn and Langer.[30] Thus, this control experiment is fully consistent with our suggested degradation pathway mechanism for PAMA branched copolymers prepared using PEGDA (see Scheme 3).

In principle, the slow hydrolytic degradation observed for these branched PAMA polymers can be avoided by using bisamides such as *N,N′*-methylenebis(acrylamide) rather than bisacrylate branchers. Although the branching reaction is relatively slow (it is well-known that acrylamides are less reactive than acrylates in Michael addition-type reactions), no reduction in molecular weight is observed on longer time scales because the amide bonds in the branch sites are much more stable than ester bonds (see Figure S5 and Table S1 in the Supporting Information).

We believe that our results, which clearly demonstrate the effect of c^* on the branching efficiency, should also be relevant to the synthesis of branched copolymers using conventional radical copolymerization. In this context, it is noteworthy that Sherrington and co-workers have observed that gelation can be significantly suppressed under more dilute conditions when copolymerizing methyl methacrylate with ethylene glycol dimethacrylate using AIBN initiator at 80 °C.[31]

Conclusions

Two synthetic routes to highly branched primary amine-based methacrylic copolymers are described. The first route involves statistical copolymerization of 2-aminoethyl methacrylate (AMA) monomer in its hydrochloride salt form with a disulfide-based dimethacrylate comonomer via RAFT, while the second route involves coupling of near-monodisperse PAMA homopolymer chains using various bifunctional reagents that react with primary amines. In the former case, cleavage of the disulfide bonds in the DSDMA branch points confirms that the highly branched polydisperse copolymers simply comprise randomly linked near-monodisperse primary chains. In the latter case, the final product depends on the chemical nature of the bifunctional reagent. If divinyl sulfone (DVS) is used, the coupling chemistry is both fast and irreversible, leading to permanently branched copolymer chains. In contrast, using poly(ethylene glycol) diacrylate (PEGDA) initially leads to highly branched chains, but the remaining primary amine groups subsequently catalyze hydrolysis of the β-aminoester bonds in the PEGDA branch points, leading to slow regeneration of linear chains. No hydrolytic degradation is observed if *N,N′*-methylenebis(acrylamide) is used as a bifunctional reagent, but this brancher reacts much more slowly than DVS. Intermolecular cross-linking and intramolecular cyclization occur in both these routes: the former is

favored at high PAMA concentration, and the latter is favored at low PAMA concentration, as expected.

Acknowledgment. S.P.A. is the recipient of a five-year Royal Society-Wolfson Research Merit Award. EPSRC is thanked for postdoctoral funds to support Y.T.L. (Platform Grant: EP/E012949/1).

Supporting Information Available: Calculation of the critical overlap concentration calculation; GPC traces for the series of branched PAMA polymers obtained using increasing amounts of DVS per $PAMA_{39}$ chain in dilute aqueous solution at pH 9; GPC traces for the series of PAMA branched copolymers obtained by the addition of PEGDA branching agent to a dilute aqueous solution of $PAMA_{39}$ homopolymer at pH 9; suggested reaction of 2-hydroxyethyl acrylate with ethanolamine at pH 9; assigned ^{1}H NMR spectra for the reaction of 2-hydroxyethyl acrylate with ethanolamine at pH 9; GPC traces and molecular weight data for a series of branched PAMA polymers obtained by the addition of MBAA to a dilute aqueous solution of $PAMA_{39}$ homopolymer at pH 9. This material is available free of charge via the Internet at http://pubs.acs.org.

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MA802750X