Synthesis and Chemical Degradation of Branched Vinyl Polymers Prepared via ATRP: Use of a Cleavable Disulfide-Based Branching Agent

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ABSTRACT: Highly branched poly(2-hydroxypropyl methacrylate) has been prepared by atom transfer radical polymerization (ATRP) in methanol at 20 °C using a disulfide-based dimethacrylate (DSDMA) branching agent. The mean degree of polymerization of the primary chains was fixed at 50; since ATRP has reasonably good living character, the molecular weight distribution of these primary chains is relatively narrow, which allows significantly better control than conventional radical polymerization. Varying the proportion of the DSDMA produced a series of soluble branched polymers, provided that there was on average less than one branching agent per primary chain. However, higher levels of DSDMA lead to macrogelation, as expected. The soluble branched polymers were characterized using triple detector gel permeation chromatography (GPC). The most highly branched copolymers had weight-average molecular weights of up to 540 000, with polydispersities of around 8.0 and Mark–Houwink α parameters as low as 0.21 being obtained. ¹H NMR spectroscopy confirmed that very high monomer conversions were obtained (>99%), and the final branched copolymers contained little or no unreacted pendent vinyl groups. The disulfide bond in the DSDMA branching agent was readily cleaved using either dithiothreitol or benzoyl peroxide. GPC studies confirmed the progressive decrease in molecular weight and polydispersity during the chemical degradation of one of the branched copolymers with reaction time. Eventually, the final polydispersity of this degraded branched copolymer was comparable to that of linear poly(2-hydroxypropy) methacrylate) prepared in the absence of any disulfide-based dimethacrylate branching agent. Thus, all the disulfide bonds had been cleaved, reducing the branched copolymer to its near-monodisperse primary chains

Introduction

Branched polymers have recently received much attention due to their interesting solution properties and their ease of preparation as compared to dendrimers.¹ Branched polymers can be prepared by condensation polymerization,² ring-opening polymerization,³ free radical polymerization, ^{4,5} nitroxide-mediated radical polym-erization,⁶ atom transfer radical polymerization (ATRP),^{7–11} reversible addition fragmentation chain transfer (RAFT) polymerization,¹² oxyanionic polymerization,¹³ and group transfer polymerization.¹⁴ The synthesis of branched vinyl polymers can be achieved by self-condensing vinyl polymerization (SCVP) reported by Frechet and co-workers¹⁵ or by the bifunctional vinyl comonomer route favored by Sherrington and coworkers.^{4,5,16–18} One advantage of the latter route is that syntheses can be carried out using cheap, readily available monomers and branching agents, whereas the former route usually requires the prior synthesis of monomer-initiator precursors or related adducts.

ATRP is a type of living radical polymerization that was independently developed by Wang and Matyjaszewski and also by Sawamoto and co-workers in 1995.^{19,20} ATRP involves an alkyl halide initiator and a transition metal catalyst; the latter complex is used to add or remove terminal halogen atoms from the polymer chain ends.^{21–23} This rapid, reversible capping leads to suppression of the instantaneous concentration of propagating polymer radicals, which in turn minimizes

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termination and allows relatively good control over the molecular weight distribution. Typically, copper(I) halide is used in conjunction with a nitrogen-based complexing ligand,^{24,25} and ATRP is usually conducted in organic solvents.²¹ Elevated temperatures are often selected for styrenic²⁵ or methacrylic monomers²⁶ so as to offset their relatively sluggish rates of polymerization, although the choice of suitable ligands can sometimes alleviate this problem. Alternatively, Armes and coworkers have recently shown that ATRP can be used to polymerize a wide range of hydrophilic methacrylates with good control under surprisingly mild conditions, provided that protic solvents such as lower alcohols (e.g., methanol) are selected.²⁷⁻³¹ The most relevant example in the context of the present study is that low polydispersity linear poly(2-hydroxypropyl methacrylate) can be obtained in very high yield within a few hours at ambient temperature via methanolic ATRP.³²

In principle, the pseudo-living character of ATRP offers a number of advantages for the synthesis of branched polymers via the Sherrington route. First, the primary chain length is readily controlled by adjusting the monomer/initiator molar ratio. Second, relatively narrow polydispersities are obtained (typically $M_w/M_n < 1.30$). This means that the probability of unwanted macrogelation due to cross-linking caused by a minor population of higher molecular weight chains is significantly reduced. Thus, it is of considerable interest to evaluate the use of ATRP for the synthesis of branched vinyl polymers, and indeed, preliminary results have been very encouraging.³³



Figure 1. Schematic representation of the synthesis of branched poly(2-hydroxpropyl methacrylate) via methanolic ATRP at 20 °C using a disulfide-based dimethacrylate branching agent (DSDMA).

In 2002, Tsarevsky and Matyjaszewski reported the synthesis of a bifunctional ATRP initiator derived from bis(2-hydroxyethyl) disulfide.³⁴ This initiator was used to prepare low polydispersity polystyrene containing a disulfide bond located in the middle of the chain. This disulfide unit was cleaved using excess dithiothreitol (DTT) in THF at 60 °C to produce thiol-terminated polystyrene chains with half the molecular weight of the original polymer. In the present study, we have used the same bis(2-hydroxyethyl) disulfide starting material to prepare a model disulfide-based branching agent that is readily cleavable under mild conditions. A similar approach has been used to prepare hydrogels that can be degraded to produce soluble polymers.³⁵⁻³⁷ In one recent proof-of-concept study, various hydrogels were successfully reconstructed from the soluble thiol-functionalized polymer products obtained by degradation of the original hydrogel.³⁵ Inspired by this work, we designed a disulfide-based dimethacrylate (DSDMA, see Figure 1) to learn more about the nature of the branched vinyl polymers that are obtained using the approach described by Sherrington and co-workers.¹⁸ In their original paper, the Strathclyde group used an ozonecleavable cross-linker to gain insight into the nature of branched poly(methyl methacrylate) prepared by conventional radical polymerization.¹⁸ In contrast, the present study is devoted to understanding the nature of a branched vinyl polymer, poly(2-hydroxyethyl methacrylate), that is synthesized by controlled radical polymerization, namely, ATRP.

Experimental Procedures

Materials. 2-Hydroxypropyl methacrylate (HPMA, 97%) was kindly donated by Cognis Performance Chemicals (Hythe, UK). Benzoyl peroxide (BPO, 97%), bis(2-hydroxyethyl) disulfide (technical grade), methacryloyl chloride (97%), dithio-threitol (DTT; 99%), Cu(I)Br (99.999%), 2,2'-bipyridine (bpy, 99%), and methanol (99%) were purchased from Aldrich and used as received. The ME-Br initiator was synthesized by esterification of 4-(2-hydroxyethyl)morpholine (ME) with 2-bromoisobutyryl bromide, as described previously.³⁸ Water was deionized and doubly distilled prior to use. The silica used for removal of the ATRP copper catalyst was column chromatography grade silica gel 60 (0.063-0.200 mm) purchased from E. Merck (Darmstadt, Germany).

Synthesis of the Disulfide-Based Dimethacrylate Branching Agent. Bis(2-hydroxyethyl) disulfide (BHEDS, 7.70 g, 50 mmol, 1.0 equiv) and triethylamine (50 mL, 40 mmol, 8.0 equiv) were dissolved in 150 mL of anhydrous THF. The flask containing the solution was then immersed in an ice bath, and methacryloyl chloride (21.0 g, 200 mmol, 4.0 equiv) was added dropwise to the stirred THF solution. The resulting heterogeneous mixture was stirred at 20 °C for 24 h and then filtered to remove the triethylamine hydrochloride byproduct. The solvent was removed by evaporation, and the crude product was dissolved in chloroform. This solution was washed three times with an aqueous solution of 0.1 M Na₂- CO_3 , followed by three washings with water. The purified organic solution was dried using anhydrous MgSO₄, and the chloroform was removed under reduced pressure. The final disulfide-based dimethacrylate (DSDMA) product was obtained as a slightly yellow liquid (10.0 g, 69%) and was stored in a freezer under nitrogen in the absence of light prior to use. ¹H NMR spectroscopy indicated a mean degree of esterification of at least 97%. $^{1}\!\mathrm{H}$ NMR: δ 5.6 and 6.2 ppm (4 H, singlet, $CH_2C(CH_3)COO$; 4.4 ppm (4 H, triplet, $CH_2C(CH_3)COOCH_2$ -CH₂); 3.0 ppm (4 H, triplet, COOCH₂CH₂SS); 1.95 ppm (6 H, singlet, CH₂C(CH₃)COO). An assigned ¹H NMR spectrum of this compound is shown in the Supporting Information.

Homopolymerization of 2-Hydroxypropyl Methacrylate Using Conventional Free Radical Chemistry. The HPMA monomer (5.04 g, 35 mmol) was introduced into a dry 100 mL Schlenk flask containing 6.0 mL of THF and a magnetic stir bar. After purging with nitrogen for 30 min, the AIBN initiator (0.05 g) was added to this flask under nitrogen. The flask was then immersed in a preheated (60 °C) oil bath. After approximately 60 min, ¹H NMR analysis indicated that about 40% of the HPMA had been polymerized (the vinyl signals between δ 5.5 and 6.0 were compared to that of the CH_3 group of the methacrylate backbone at δ 0.5–1.5). The crude homopolymer was then dissolved in a small amount of THF and precipitated into a large excess of water to remove the unreacted monomer. The purified HPMA homopolymer was dried under vacuum to remove traces of solvent and finally isolated in 33% yield.

ATRP of 2-Hydroxypropyl Methacrylate in the Presence of the DSDMA Branching Agent. A typical protocol for the synthesis of branched HPMA-based copolymers via methanolic ATRP using the DSDMA branching agent was as follows. ME-Br (0.1939 g, 0.70 mmol, 1.0 equiv), DSDMA (0.0903 g, 0.35 mmol, 0.50 equiv), and HPMA (5.04 g, 35 mmol, 50.0 equiv) were codissolved in methanol (6.0 mL). After purging with nitrogen for 30 min, the Cu(I)Br catalyst (0.1001 g, 0.70 mmol, 1.0 equiv) and the bpy ligand (0.2184 g, 1.4 mmol, 2.0 equiv) were added to this stirred solution under nitrogen. The reaction mixture immediately became dark brown and progressively more viscous, indicating the onset of polymerization. After approximately 16 h, ¹H NMR analysis indicated that more than 99% of the HPMA had been polymerized (disappearance of vinyl signals between δ 5.5 and 6.0). The reaction solution was diluted with methanol and turned blue on exposure to air, indicating aerial oxidation of the Cu-(I) catalyst. The resulting branched HPMA-DSDMA copolymer (isolated yield = 85%). **Cleavage of the Disulfide-Containing Branched Polymers by Reduction with Dithiothreitol.** In a typical procedure, the disulfide-containing ME-HPMA₅₀-DSDMA_{0.95} branched copolymer (0.100 g, 0.0164 mmol of disulfide units) was dissolved in 6 mL of deoxygenated THF solvent, and dithiothreitol (DTT; 0.0192 g, 0.125 mmol) was added. The reaction mixture was stirred under nitrogen at 40 °C. Samples were periodically withdrawn, diluted with THF at ambient temperature, and analyzed by THF GPC immediately to determine the extent of cleavage of the disulfide branch sites in the copolymer.

Cleavage of the Disulfide-Containing Branched Polymers by Oxidation with Benzoyl Peroxide. In a typical procedure, the disulfide-containing ME-HPMA₅₀-DSDMA_{0.95} branched copolymer (0.100 g, 0.0164 mmol of disulfide units) was dissolved in 6 mL of deoxygenated THF solvent, and benzoyl peroxide (BPO; 0.121 g, 0.50 mmol) was added. The reaction mixture was stirred under nitrogen at 60 °C. Samples were periodically withdrawn, diluted with THF at ambient temperature, and analyzed by THF GPC immediately to determine the extent of cleavage of the disulfide branch sites in the copolymer.

Copolymer Characterization. All ¹H NMR spectra were recorded using a Bruker AC 250 MHz spectrometer. A Polymer Laboratories PL-GPC50 integrated GPC system was used to analyze the branched polymers. Linear and branched HPMAbased polymers were characterized by GPC using THF (containing 2% triethylamine) as an eluent at a flow rate of 1.0 mL min⁻¹ at 30 °C equipped with two 5 μ m (30 cm) mixed C columns, a WellChrom K-2301 refractive index detector operating at 950 \pm 30 nm, a Precision detector PD 2020 light scattering detector (at scattering angles of 90 and 15 °C), and a BV400RT viscosity detector. Molecular weights of the branched copolymers were determined by the triple detection method using PL Cirrus Multi online software (version 2.0) supplied by Polymer Laboratories. A series of near-monodisperse linear PMMA standards (purchased from Polymer Labs) was used to construct the calibration curve. The refractive index increments (dn/dc) of the branched copolymers were determined in THF using an Optilab differential refractometer operating at 633 nm. One reviewer has pointed out that it is possible that our branched copolymers may contain microgel fractions. All GPC samples were analyzed directly from the polymerizing solution after ultrafiltration (i.e., silica was not used to remove the ATRP catalyst from these aliquots). In most cases, the recovery of the branched copolymer after silica treatment was fairly efficient. However, significant loss of copolymer was observed during silica treatment of the ME-HPMA₅₀-DSDMA_{0.95} branched copolymer, which may indicate the presence of a microgel fraction in this particular sample.

Results and Discussion

Choice of Monomer. 2-Hydroxypropyl methacrylate (HPMA) was chosen as the monomer in this study for several reasons. First, Save et al. had already studied the kinetics of polymerization of this monomer via ATRP and shown that very high conversions could be obtained within a few hours at ambient temperature.³² Second, poly(2-hydroxypropyl methacrylate) is sufficiently hydrophobic to be soluble in THF, which is the preferred eluent for our triple detection GPC system. Third, although not a feature of the present study, the secondary hydroxyl groups in HPMA polymers can be readily esterified by reaction with excess succinic anhydride to produce well-defined polyacids.³⁹ In this context, it is noteworthy that Sherrington and co-workers recently reported that branched architectures can lead to very interesting aqueous solution properties, such as the suppression of the well-known polyelectrolyte effect.⁴⁰



Figure 2. GPC traces recorded using (a) the refractive index detector and (b) the light scattering detector for the series of branched copolymers obtained by ATRP of HPMA in the presence of increasing amounts (mol %) of the disulfide-based dimethacrylate (DSDMA) branching agent. See Table 1 for detailed polymerization conditions.

Choice of Branching Agent. In their first paper describing the synthesis of branched vinyl copolymers, Sherrington and co-workers used ozonolysis at -78 °C to chemically degrade branched poly(methyl methacrylate).⁴ These conditions led to efficient cleavage of the double bond in the but-2-ene-1,4-diacrylate branching agent. However, the workup of the ozonolyzed copolymer was acknowledged to be difficult and time-consuming. Moreover, it involved a precipitation step in methanol, which is a marginal solvent for low molecular weight poly(methyl methacrylate).⁴¹ Thus, although discounted by Sherrington et al., it seems likely that some fractionation most likely occurred during workup: this would account for the relatively low isolated yields of copolymer (only 20-50%) and also would explain why the polydispersity of one of the ozonolyzed copolymers is lower than the theoretical minimum value of 1.50 expected for materials prepared by conventional free radical copolymerization. In view of these perceived difficulties, we decided to explore the use of an alternative disulfide-based branching agent since it is wellknown that disulfide bonds can be readily and selectively cleaved using various reagents.^{34–37}

Copolymer Characterization. GPC chromatograms obtained for the branched HPMA copolymers using varying levels of the DSDMA branching agent are shown in Figure 2. GPC curves recorded using the refractive index detector (Figure 2a) show pronounced tailing to shorter retention times (higher molecular weights) with increasing DSDMA, but the main peak is not significantly shifted from that of the linear HPMA homopolymer prepared in the absence of any DSDMA. On the other hand, the light scattering detector (Figure 2b) is significantly more sensitive to the presence of

 Table 1. Summary of the Reaction Conditions for the Methanolic ATRP of HPMA in the Presence of the Disulfide-Based

 Dimethacrylate Brancher (DSDMA) at 20 °C

entry no.	target copolymer structure (subscripts refer to Dp)	DSDMA (mol %)	time (h)	conversion (%)	$M_{ m n}$	$M_{ m w}$	$M_{ m w}/M_{ m n}$	α
1	AIBN-initiated PHPMA	0.0	1.0	40	301 000	489 700	1.63	0.80
2	HPMA ₅₀ homopolymer	0.0	16.0	100	$14\ 100$	$17\ 300$	1.23	0.79
3	HPMA ₅₀ /DSDMA _{0.20}	0.4	16.0	>99.9	19 100	$27\ 100$	1.42	0.45
4	HPMA ₅₀ /DSDMA _{0.50}	1.0	16.0	>99	$22\ 600$	46 400	2.05	0.29
5	HPMA ₅₀ /DSDMA _{0.80}	1.6	16.0	>99	$30\ 400$	$91\ 400$	3.01	0.25
6	HPMA ₅₀ /DSDMA _{0.95}	1.9	16.0	>99	$67\ 300$	$540\ 000$	8.03	0.21
7	HPMA ₅₀ /DSDMA _{1.05}	2.1	16.0	macrogelation				

higher molecular weight chains. With this latter detector, the GPC peak maxima, and indeed each molecular weight distribution, are systematically shifted to lower retention times with increasing levels of DSDMA. The molecular weight and polydispersity data shown in Table 1 are those calculated from the light scattering detector analyses. For a fixed target degree of polymerization of 50, the DSDMA content of 1.9 mol % (see entry 6 of Table 1) corresponds to just less than one DSDMA brancher per chain. Under these conditions, a high molecular weight, relatively polydisperse branched HPMA-DSDMA copolymer is obtained ($M_{\rm w} = 540\ 000$ and $M_{\rm w}/M_{\rm n} = 8.03$). According to Sherrington's hypothesis, these conditions correspond to just below the gel point.³³ This simple approximation appears to be correct because increasing the DSDMA content to 2.1% causes macrogelation due to cross-linking (see entry 7 in Table 1). Mark-Houwink α values for this series of branched copolymers are also summarized in Table 1. These α values decrease monotonically from 0.80 for the linear polydisperse HPMA homopolymer (prepared as a reference material by conventional free radical polymerization using an AIBN initiator) to less than 0.30 for branched copolymers with the highest DSDMA contents. A very high conversion (typically >99%) was obtained in each copolymerization, which is due to the facile nature of the ATRP of HPMA in methanol under these conditions. Such high conversions are very important in living polymerizations because the target degree of polymerization (which is dictated by the monomer/ initiator molar ratio) is only achieved at the end of the polymerization. This is a fundamentally different situation to that found for conventional free radical polymerization, where high molecular weight chains are generated even at low conversions. This means that, if conversions are incomplete, soluble branched copolymers can be obtained from living radical polymerization formulations that might otherwise be expected to form chemical gels. Thus, in the event of incomplete polymerization, we believe that the precise monomer conversion should be cited as an important caveat for soluble branched copolymers prepared by living radical polymerization. It is noteworthy that other workers have also expressed this opinion, albeit in the context of insoluble copolymer gels rather than soluble branched copolymers.^{36,42}

Recently, Perrier and co-workers reported the synthesis of soluble branched poly(methyl methacrylate) using RAFT polymerization.¹² The Leeds group claimed that RAFT is superior to ATRP for such vinyl branched polymer syntheses since significantly lower polydispersities were obtained. This work can be criticized on two counts. First, it is not possible to make a meaningful comparison between the GPC data reported by Perrier and co-workers and that reported by the Sherrington/ Armes groups since the Leeds group only used a refractive index detector. On the basis of the previous discussion regarding Figure 2, it is absolutely clear that

this approach is flawed for branched polymers since refractive index detection significantly underestimates $M_{\rm w}$ and hence $M_{\rm w}/M_{\rm n}$. Moreover, Perrier and co-workers reported final monomer conversions of around 96%. Although these values are relatively high, this still leaves open the possibility that their formulations would have gelled if they had been allowed to attain their final target degrees of polymerization. In this context, it is unfortunate that Perrier et al. chose not to carry out any control experiments in the absence of any bifunctional comonomer (in their case, ethylene glycol dimethacrylate), so it was not possible to assess the initiator efficiencies in their syntheses. We also note that these RAFT syntheses of branched copolymers required relatively long reaction times (40-60 h) and elevated temperatures (60 °C), even for incomplete monomer conversions. Nevertheless, we acknowledge that RAFT polymerization is an important, and perhaps potentially more attractive, route to soluble branched copolymers using the Sherrington approach.

It is well-known that branched polymers have more compact structures in solution as compared to linear polymers of the same molecular weight since higher levels of branching lead to smaller hydrodynamic volumes. GPC analysis is only sensitive to changes in hydrodynamic volume. This means that linear polymer chains of a given molecular weight cannot be distinguished from higher molecular weight branched chains since in principle these species could elute at the same retention volume. Figure 3 shows the relationship between log (molecular weight) and retention volume for the branched HPMA-DSDMA statistical copolymers prepared by ATRP. For a given retention volume, each of the branched copolymers has higher molecular weights than the polydisperse linear HPMA homopolymer reference prepared using the AIBN initiator (entry 1 in Table



Figure 3. Relationship between log (molecular weight) and retention volume for the branched copolymers obtained by the ATRP of 2-hydroxypropyl methacrylate in the presence of increasing levels (mol %) of the DSDMA branching agent.



Figure 4. Mark–Houwink plot and light scattering signal obtained for the branched ME-HPMA₅₀-DSDMA_{0.95} copolymer obtained by ATRP (see entry 6 in Table 1).



Figure 5. Evolution of ¹H NMR spectra recorded during the synthesis of the ME-HPMA₅₀-DSDMA_{0.50} branched copolymer (entry 4 in Table 1) by ATRP in d_4 -methanol at 20 °C. Conditions: 5.04 g of HPMA and 6.0 mL of methanol; relative molar ratios of initiator, catalyst, and ligand (ME-Br/CuBr/bpy) are 1:1:2.

1). Moreover, the molecular weight increases monotonically with increasing DSDMA brancher content. These results strongly suggest a systematic increase in the degree of branching of these HPMA-DSDMA copolymers with increasing DSDMA content.

A double log plot of intrinsic viscosity versus molecular weight is shown in Figure 4 for the HPMA-DSDMA statistical copolymer prepared at the highest level of DSDMA branching agent that did not cause macrogelation (entry 6 in Table 1). The GPC curve obtained for the same copolymer using the light scattering detector is also shown. The Mark–Houwink α value calculated for this copolymer is 0.21, which indicates a heavily branched architecture and is significantly lower than the α values of 0.50–0.56 reported by Sherrington and co-workers.^{4,5}

¹H NMR spectroscopy was used (i) to determine monomer conversions by periodically sampling the polymerizing solutions and (ii) to assess the presence (or absence) of semi-reacted DSDMA pendent groups in the final isolated branched copolymers. A series of ¹H NMR spectra is depicted in Figure 5 for the HPMA₅₀/ DSDMA_{0.50} branched copolymer (entry 4 in Table 1). The vinyl signals due to the HPMA monomer at 5.4–6.3 ppm decrease progressively with time as the polymer signals

Table 2. Evolution of the Molecular Weight and Polydispersity Determined Using the Triple Detection Method during the Methanolic ATRP Synthesis of the Branched ME-HPMA₅₀-DSDMA_{0.50} Statistical Copolymer at 20 °C^a

ur 20° C							
entry no.	time (min)	conversion (%)	$M_{ m n}$	$M_{ m w}$	$M_{\rm w}/M_{\rm n}$	α	
1	5	14	$3\ 500$	3 900	1.10	b	
2	10	23	$5\ 000$	6 000	1.19	0.58	
3	20	31	$7\ 300$	8 800	1.20	0.50	
4	40	55	$10\ 800$	$13\ 100$	1.21	0.44	
5	80	76	$16\ 200$	$21\ 200$	1.31	0.43	
6	140	91	$21\ 000$	$29\ 700$	1.41	0.36	
7	260	97	$21\ 300$	$35\ 900$	1.68	0.35	
8	430	99	$23\ 100$	$43\ 600$	1.89	0.33	
9	1320	>99.9	$24\ 400$	$51\ 700$	2.12	0.29	

 a Conditions: 5.04 g of HPMA and 6.0 mL of methanol; ME-Br/CuBr/Bpy = 1:1:2; target copolymer structure was ME-HPMA₅₀/ DSDMA_{0.5}. b The molecular weight was too low (and the molecular weight distribution was too narrow) to allow reliable calculation of α in this case.

grow at 0.8–2.2 ppm. There is little or no evidence for any semi-reacted pendent vinyl groups at high conversion (>99%). GPC analyses were also carried out on the same aliquots that were extracted for the NMR studies, and these results are summarized in Table 2. The polydispersities and $M_{\rm w}$ values remain relatively low up to 50% conversion, with extensive branching only becoming evident in the latter stages. There is a progressive reduction in α with increasing conversion, with a final α value of 0.29 being attained under these particular conditions. The evolution of the molecular weight distribution with reaction time recorded using the refractive index detector during the synthesis of the same branched copolymer (entry 4 in Table 1) is shown in Figure 6. Under these conditions, the whole molecular weight distribution curve shifted progressively to higher molecular weight and remained more or less unimodal. Table 2 summarizes the GPC data obtained for the same copolymer calculated using the triple detection method. It is worth emphasizing that the $M_{\rm w}$ and polydispersity data change most noticeably in the latter stages of the polymerization, with significant differences being observed between 97 and 99.9% conversion. This observation supports our criticism of the RAFT syntheses of branched copolymers recently reported by Perrier et al.¹²

Chemical Degradation Using Dithiothreitol. Disulfide bonds can be readily cleaved using a well-known exchange reaction with dithiol compounds such as dithiothreitol (DTT)³⁴ or tributylphosphine.³⁶ This process is illustrated schematically in Figure 7. In principle, if all the disulfide bonds are cleaved, the branched HPMA-DSDMA statistical copolymer will be reduced to its primary chains (containing, on average, one or fewer randomly located thiol groups). First, we carried out a control experiment to confirm that no degradation of HPMA homopolymer occurs under the conditions used to cleave the disulfide bonds. Thus, the linear, polydisperse HPMA homopolymer prepared using the AIBN initiator was subjected to an excess of DTT in THF at elevated temperature. After DTT treatment, this HPMA homopolymer had an $M_{\rm n}$ of 307 000, an $M_{\rm w}$ of 491 000, and an M_w/M_n of 1.60, which is almost identical to that obtained for the HPMA precursor (see entry 1 in Table 1). Thus these conditions cause no discernible chemical degradation of HPMA homopolymer, as expected. In contrast, DTT treatment of the HPMA₅₀-DSDMA_{0.95} statistical copolymers leads to substantial chain scission and a concomitant reduction in both molecular weight



Figure 6. GPC chromatograms using (a) the refractive index detector and (b) the light scattering detector obtained after various polymerization times during the methanolic ATRP of the ME-HPMA₅₀-DSDMA_{0.50} branched copolymer (entry 4 in Table 1) at 20 °C. Conditions: 5.04 g of HPMA and 6.0 mL methanol; relative molar ratios of initiator, catalyst, and ligand (ME-Br/CuBr/bpy) are 1:1:2.

and polydispersity. This chemical degradation is conveniently monitored by GPC: typical data obtained for the DTT treatment of the ME-HPMA₅₀-DSDMA_{0.95} statistical copolymer are summarized in Table 3. Periodic sampling of the DTT-treated ME-HPMA₅₀-DS-DMA_{0.95} copolymer solution indicated a dramatic reduction in the molecular weight (particularly $M_{\rm w}$) and polydispersity, while the α value of the degraded copolymer increased monotonically up to 0.78 after 4 h at 40 °C, which is characteristic of a linear, rather than branched, polymer. According to the refractive index detector (see Figure 8a), the GPC curve for the final degraded copolymer has an almost identical appearance to that of a linear HPMA homopolymer (target degree of polymerization = 50) prepared via ATRP in the absence of any DSDMA. This suggests that the original ME-HPMA₅₀-DSDMA_{0.95} statistical copolymer has been degraded to its constituent primary chains (i.e., that every disulfide bond has been cleaved).

Table 3. Progressive Reduction in the Molecular Weight and Polydispersity Determined Using the Triple Detection Method for the Branched ME-HPMA₅₀-DSDMA_{0.95} Statistical Copolymer on Treatment with Excess Dithiothreitol in THF at 40 °C

entry no.	time (min)	$M_{ m n}$	$M_{ m w}$	$M_{\rm w}/M_{\rm n}$	α
1	0	67 300	$540\ 000$	8.03	0.21
2	5	$63\ 100$	$332\ 500$	5.27	0.28
3	10	$57\ 200$	$196\ 000$	3.43	0.34
4	20	$41\ 700$	93 000	2.23	0.42
5	40	$24\ 200$	$35\ 600$	1.47	0.58
6	140	$16\ 500$	$21\ 800$	1.32	0.72
7	240	$16\ 400$	$20\ 800$	1.27	0.78
8	N/A	$14\ 100$	$17\ 300$	1.23	0.79

In contrast, the light scattering GPC data indicate somewhat different results (see Figure 8b; only selected curves are shown for clarity). Although the original molecular weight distribution curve has changed significantly, a prominent molecular weight peak remains after DTT-induced chemical degradation at 40 °C for 4 h. This disparity simply reflects the much greater sensitivity of the light scattering detector toward higher molecular weight fractions. Once we recognized that degradation was incomplete, the same copolymer was treated for 4 h at 60 °C. At this higher temperature, the chemical degradation was much more efficient, and the high molecular weight feature disappeared (see Figure 8b). The light scattering GPC curve of the degraded copolymer corresponded closely to that of the linear HPMA homopolymer prepared in the absence of the DSDMA branching agent (see Figure 8b and Table 3). Thus, DTT can be used for the efficient cleavage of the disulfide bonds in the original ME-HPMA₅₀-DS-DMA_{0.95} branched copolymer, and the light scattering GPC detector is preferred for monitoring this degradation process.

It is perhaps also noteworthy that M_n and M_w data reported in Table 3 for the linear, near-monodisperse HPMA homopolymer prepared via ATRP in the absence of any DSDMA (see entry 8 in Table 3) are significantly higher than that reported by Save et al. under the same conditions.³² These apparent differences are primarily due to the type of GPC detector used. For example, entry 8 in Table 3 was analyzed using the light scattering detector. Reexamination of this same homopolymer using the refractive index detector gave an $M_{\rm p}$ of 9200 and an $M_{\rm w}$ of 11 500. These latter results are much closer to those reported by Save et al.,³² who used a refractive index detector exclusively in their work. Reanalysis of the chemically degraded HPMA homopolymer (entry 7 in Table 3) using the refractive index detector gave very similar data ($M_n = 9100$ and



Soluble, branched poly(2-hydroxypropyl methacrylate)

$M_w = 540,000; M_w/M_n = 8.03$

Linear, thiol-functionalized poly(2-hydroxypropyl methacrylate)

$$M_w = 20,800; M_w/M_n = 1.27$$

Figure 7. Schematic representation of the reduction of branched poly(2-hydroxypropyl methacrylate) using dithiothreitol (DTT). Cleavage of all the disulfide bonds in the DSDMA branching comonomer generates linear, thiol-functionalized primary chains of poly(2-hydroxypropyl methacrylate).



Figure 8. GPC traces recorded after various reaction times using (a) the refractive index detector and (b) the light scattering detector during the reductive degradation of the ME-HPMA₅₀-DSDMA_{0.95} branched copolymer (entry 6 in Table 1) with DTT. Conditions: 0.10 g of branched ME-HPMA₅₀-DSDMA_{0.95} statistical copolymer (1 disulfide equiv) and 0.0192 g of DTT (7.6 dithiol equiv) in 6 mL of THF at 40 °C (all refractive index curves) and either 40 or 60 °C (light scattering curves; see label on curve). The GPC curve obtained for linear, near-monodisperse poly(2-hydroxypropyl methacrylate) prepared via ATRP with a target degree of polymerization of 50 is included as a reference.

 $M_{\rm w} = 11$ 700), thus providing further evidence that the original branched copolymer had been efficiently converted into its primary chains, as intended. Moreover, since chemical degradation yields the primary chains almost exclusively, the chain transfer to polymer must be negligible during the ATRP synthesis of these branched copolymers. One of the reviewers of this manuscript has suggested that termination by coupling should be expected in the final stages of the ATRP copolymerization (i.e., under monomer-starved conditions). The effect of this side reaction would be to double the $M_{\rm w}$, but of course this cannot be readily distinguished from the random branching processes that are occurring. Moreover, there is no evidence for significant coupling during the linear homopolymerization of HPMA carried out under the same ATRP conditions.

Chemical Degradation Using Benzoyl Peroxide. DTT is a relatively expensive reagent. However, it is well-documented that alkyl disulfides can also be efficiently cleaved under oxidative conditions using reagents such as peroxides, hydroperoxides, or peroxyacids.^{43,44} According to Allen and Book, the oxidation of



Figure 9. GPC traces recorded after various reaction times using (a) the refractive index detector and (b) the light scattering detector during the oxidative degradation of the ME-HPMA₅₀-DSDMA_{0.95} branched copolymer (entry 6 in Table 1) using benzyl peroxide at 60 °C. Conditions: 0.1 g (1 disulfide equiv) of branched ME-HPMA₅₀-DSDMA_{0.95} copolymer and 0.121 g (30.5 peroxide equiv) of benzoyl peroxide in 6 mL of THF. Only selected light scattering curves are shown for clarity. The GPC curve obtained for linear, near-monodisperse poly(2-hydroxypropyl methacrylate) prepared via ATRP with a target degree of polymerization of 50 is included as a reference.

disulfides is complex: a range of functional groups, including sulfoxides and sulfonic acids, can be generated depending on the precise conditions.⁴⁵ Thus we explored the use of benzoyl peroxide to cleave the disulfide bonds in the DSDMA branch sites. Our THF GPC results obtained using this reagent at 60 °C under a nitrogen atmosphere are summarized in Table 4 and Figure 9 (only selected curves are shown for clarity). Under these conditions, complete chemical degradation is also readily achieved within 160 min, as evidenced by the light scattering GPC curves shown in Figure 9.

In principle, it should be possible to reconstitute the original branched ME-HPMA₅₀-DSDMA_{0.95} copolymer from the degraded primary chains by reacting the pendent thiol groups with a disulfide compound such as bis(2-hydroxyethyl) disulfide. This possibility will be explored in future work. However, such reconstruction will most likely not be possible if benzoyl peroxide is

Table 4. Progressive Reduction in the Molecular Weight and Polydispersity Determined Using the Triple **Detection Method for the Branched**

ME-HPMA₅₀-DSDMA_{0.95} Statistical Copolymer on Treatment with Excess Benzoyl Peroxide in THF at 60 °C

entry no.	time (min)	$M_{ m n}$	$M_{ m w}$	$M_{ m w}/M_{ m n}$	α
1	0	$67\ 300$	$540\ 000$	8.03	0.21
2	10	$61\ 100$	$279\ 000$	4.57	0.33
3	40	41200	91000	2.21	0.42
4	80	31600	$49\ 600$	1.57	0.55
5	160	$14\ 200$	$17\ 900$	1.26	0.77
6	N/A	$14\ 100$	$17\ 300$	1.23	0.79

employed to cleave the disulfide bonds since this degradation chemistry does not generate thiol groups. According to the recent results reported by Hamilton and co-workers for insoluble copolymer gels,³⁵ the final degree of branching of the reconstituted branched copolymer should depend on the precise conditions (e.g., copolymer concentration) selected for the thiol/disulfide exchange reaction.

Conclusions

A chemically cleavable disulfide-based dimethacrylate branching agent has been used to gain considerable insight into the nature of branched vinyl polymers obtained using the Sherrington route via methanolic ATRP of 2-hydroxypropyl methacrylate under mild conditions. The disulfide bonds can be efficiently cleaved either under reducing conditions using dithiothreitol or under oxidizing conditions using benzoyl peroxide. In both cases, GPC analyses confirm that fully degraded poly(2-hydroxypropyl methacrylate) has almost the same molecular weight distribution as a linear poly(2hydroxypropyl methacrylate) sample synthesized by ATRP under the same conditions in the absence of any disulfide-based dimethacrylate branching agent. Thus, the primary chains of these branched copolymers are well-defined and have $M_{\rm n}$ and $M_{\rm w}$ values predicted for a well-controlled ATRP synthesis. Moreover, incorporation of the disulfide-based dimethacrylate branching agent is clearly the sole reason for the high molecular weights and degrees of branching observed for these materials; possible side reactions such as chain transfer to polymer or termination by combination, which might be expected to occur to some extent under monomerstarved conditions, appear to be negligible.

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Supporting Information Available: Assigned ¹H NMR spectrum of the disulfide-based dimethacrylate (DSDMA) branching agent. This material is available free of charge at the Internet at http://pubs.acs.org.

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