H₂O₂ Enables Convenient Removal of RAFT End-Groups from Block Copolymer Nano-Objects Prepared via Polymerization-Induced Self-Assembly in Water

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Supporting Information

ABSTRACT: RAFT-synthesized polymers are typically colored and malodorous due to the presence of the sulfur-based RAFT end-group(s). In principle, RAFT end-groups can be removed by treating molecularly dissolved copolymer chains with excess free radical initiators, amines, or oxidants. Herein we report a convenient method for the removal of RAFT end-groups from aqueous dispersions of diblock copolymer nano-objects using H₂O₂. This oxidant is relatively cheap, has minimal impact on the copolymer morphology, and produces benign side products that can be readily removed via dialysis. We investigate the efficiency of end-group removal for various diblock copolymer nano-objects prepared with either dithiobenzoate- or trithiocarbonate-based RAFT chain transfer agents. The advantage of using UV GPC rather than UV spectroscopy is demonstrated for assessing both the kinetics and extent of end-group removal.

INTRODUCTION

Over the past two decades reversible addition−fragmentation chain transfer (RAFT) polymerization 1−4 has become a well-established route for the synthesis of a wide range of controlled-structure functional copolymers for various potential applications. 5−10 RAFT polymerization enables good control over target molecular weight, molecular weight distribution, and copolymer architecture, while also providing access to a wide range of specific end-groups. 11−18 The recent development of polymerization-induced self-assembly (PISA) has been based largely on RAFT-mediated polymerization conducted in heterogeneous media. 19−26 PISA has enabled the rational design of a wide range of bespoke block copolymer nanoparticles (e.g., spheres, worms, vesicles, framboidal vesicles, platelets, etc.), 27−30 and certain formulations appear to be promising for potential biomedical applications. For example, poly(glycerol monomethacrylate)−poly(2-hydroxypropyl methacrylate) diblock copolymer worm gels are readily sterilizable via cold ultrafiltration and induce stasis in human embryonic stem cells. 31 Closely related disulfide-functional worm gels are sufficiently robust to enable 3D cell culture for extended periods in plastic matrices. 32 Targeting diblock copolymer vesicles via PISA has enabled encapsulation (and, in some cases, the subsequent release) of various model payloads such as fluorescently labeled water-soluble polymers, silica nanoparticles, or globular proteins, which augurs well for drug delivery applications. 12,33,34

In the context of potential biomedical and cosmetics applications, one of the main drawbacks of RAFT-synthesized (co)polymers is the color, malodor, and possible toxicity conferred by the sulfur-based end-groups; whether they be dithioesters, trithiocarbonates, or xanthanes, 4 RAFT end-group cleavage via hydrolysis 35,36 (or other chemistries) results in the formation of low molecular weight byproducts that may be preferentially internalized within mammalian cells, apparently without inducing toxicity in at least some cases. 37

In practice, such problems are often circumvented by preemptive removal of the RAFT end-group under controlled conditions. Not surprisingly, this approach works rather better for acrylic (or styrenic) polymers compared to more sterically congested methacrylic polymers. 38,39 Numerous chemistries have been employed, such as aminolysis using either primary

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amines or hydrazine,\textsuperscript{40} ozonolysis,\textsuperscript{41} bond cleavage using radicals derived from addition of excess initiator, thermolysis,\textsuperscript{45,46} or, more recently, light-mediated removal.\textsuperscript{47} However, as far as we are aware, there is only one literature report of using H$_2$O$_2$ for removing RAFT end-groups, and this brief study was restricted to the derivatization of soluble poly(N-vinylpyrrolidone) chains in aqueous solution at 80 $^\circ$C.\textsuperscript{48} A radical mechanism was proposed, whereby hydroxyl radicals generated at elevated temperature replaced each RAFT end-group with a terminal alcohol.

Herein we revisit the use of H$_2$O$_2$ as a means of removing RAFT end-groups from various examples of methacrylic diblock copolymer nanoparticles in aqueous solution. In this context, the nonionic nature and relatively low molecular weight of H$_2$O$_2$ might be expected to offer a significant advantage in terms of its faster ingress within the nanoparticle interior. Moreover, it is emphasized that H$_2$O$_2$ is relatively cheap and produces only water and oxygen as byproducts. It is perhaps also noteworthy that relatively few RAFT end-group derivatization studies have focused on methacrylic copolymers, rather than the more reactive acrylic or styrenic copolymers.

\section*{Experimental Section}

Materials. Glycerol monomethacrylate (GMA, 99.8%), 2-hydroxypropyl methacrylate (HPMA, 99.3%), and benzyl methacrylate (BzMA, 99.2%) were donated by GEO Specialty Chemicals (Hythe, UK) and used without further purification. The synthetic route used to obtain HPMA results in the production of two isomeric forms.\textsuperscript{49} The isomeric composition was confirmed by $^1$H NMR spectroscopy. The "HPMA" monomer actually contained 75 mol % HPMA, with the remainder being its closely related isomer, 2-hydroxyisopropyl methacrylate [HIPMA].

4-Azobis(4-cyanopentanoic acid) (ACVA, 99%) and dichloromethane were purchased from Sigma-Aldrich (UK) and were used as received. 2-Cyano-2-propylthiobenzozate (CPDB) was purchased from Strem Chemicals Ltd. (Cambridge, UK) and was used as received. 4-Cyano-4′-(2-phenylethenesulfanylthiocarbonyl)sulfanyl-pentanoic acid (PETTC) RAFT agent was synthesized as previously reported.\textsuperscript{50} For the sake of brevity, the acronyms DB and TTC are used to denote dithiobenzozate and triithiocarbonate end-groups for the various copolymers prepared in this study. Deuterated DMF and methanol were purchased from Goss Scientific Instruments Ltd. (Crewe, UK). All other solvents were purchased from Fisher Scientific (Loughborough, UK) and used as received. Deionized water was used for all experiments.

\textbf{Protocol for the Synthesis of PGMA Macro-CTAs.} Synthesis of a dithiobenzozate-functionalized poly(glycerol monomethacrylate) PGMA$_2$ chain transfer agent is representative of all dithiobenzozate-functionalized macro-CTAs and was prepared as follows. GMA monomer (25.0 g, 156.1 mmol) and CPDB RAFT agent (0.864 g, 3.9 mol), HPMA monomer (1.70 g, 11.8 mmol; target DP = 600) and ACVA initiator (1.84 mg, 6.55 μmol) were weighed into a flask equipped with a stirrer, a condenser, and a drying tube. The flask was purged with N$_2$ for a further 5 min. Deionized water (18.3 mL) and methanol were added into the flask under N$_2$ atmosphere, producing a 20.0% w/w aqueous solution. After 30 min, the reaction solution was stirred for 3 h before the polymerization was quenched by exposure to air. The resulting red solution was degassed for a further 10 min. The flask was subsequently sealed and immersed into an oil bath set at 70 $^\circ$C. After 100 min, the GMA polymerization was quenched by exposure to air. A yellow powder was then obtained.

\begin{table}[h]
\centering
\caption{Summary of Molecular Weight Data Obtained Using DMF GPC (Refractive Index Detector; vs Poly(methyl methacrylate) Calibration Standards) before and after H$_2$O$_2$ Treatment for the Series of Diblock Copolymer Nano-Objects Used in This Study}
\begin{tabular}{|c|c|c|c|c|}
\hline copolymer composition & copolymer morphology & M$_w$/g mol$^{-1}$ & M$_w$/M$_n$ before & after \\
\hline G$_{52}$-DB & dissolved chains & 15 700 & 1.18 & 1.19 \\
G$_{52}$-H$_{135}$-DB & worms & 35 600 & 1.12 & 1.16 \\
G$_{52}$-H$_{135}$-TTC & worms & 37 400 & 1.15 & 1.20 \\
G$_{52}$-B$_{200}$-DB & spheres & 15 600 & 1.26 & 1.29 \\
G$_{104}$-H$_{50}$-DB & spheres & 58 600 & 1.19 & 1.24 \\
G$_{104}$-H$_{600}$-DB & spheres & 79 100 & 1.24 & 1.28 \\
G$_{104}$-H$_{600}$-DB & spheres & 136 100 & 1.46 & 1.46 \\
G$_{248}$-DB & vesicles & 101 700 & 1.32 & 1.40 \\
\hline
\end{tabular}
\end{table}

The crude copolymer was purified via precipitation from methanol into excess dichloromethane to yield a yellow powder. $^1$H NMR analysis indicated a mean degree of polymerization of 52 for this PGMA-TTC macro-CTA (M$_w$ = 13 700, M$_w$/M$_n$ = 1.26; see Table 1). This suggests a CTA efficiency of around 74%.

\textbf{Synthesis of PGMA$_{52}$-PHPMA$_{60}$ Diblock Copolymer Spheres.} These diblock copolymer nanoparticles were prepared via RAFT aqueous dispersion polymerization, as reported by Blanazs et al.\textsuperscript{3} As a typical example, PGMA$_{52}$-PHPMA$_{60}$ spheres were synthesized as follows. PGMA$_{52}$-DB macro-CTA (0.322 g, 19.7 μmol), HPMA monomer (1.7 g, 11.8 mmol; target DP = 600) and ACVA initiator (1.84 mg, 6.55 μmol; macro-CTA/ACVA molar ratio = 3.0) were weighed into a 50 mL round-bottomed flask and dissolved in deionized water (18.3 mL). The resulting solution was purged under N$_2$ for 30 min before being sealed and immersed in an oil bath at 70 $^\circ$C for 5 h. The HPMA polymerization was quenched by exposure to air. A final HPMA conversion of more than 99% was determined by $^1$H NMR analysis. These copolymer spheres were characterized by DMC GPC without further purification and used directly for RAFT end-group removal experiments (M$_w$ = 79 100, M$_w$/M$_n$ = 1.24; see Figure S2).

\textbf{Synthesis of PGMA$_{52}$-PMA$_{135}$ Diblock Copolymer Worms.} These diblock copolymer nanoparticles were prepared via RAFT aqueous dispersion polymerization, as reported by Blanazs et al.\textsuperscript{3} A typical protocol used for the PISA synthesis of PGMA$_{52}$-PMA$_{135}$ worms was as follows. PGMA$_{52}$ macro-CTA (3.60 g, 0.395 mmol; CTA/ACVA molar ratio = 5.0) and CPDB RAFT agent (target degree of polymerization, DP = 55) instead of CPDB via the same general protocol as that described above. A final GMA conversion of 70% was determined by $^1$H NMR analysis. The crude copolymer was purified via precipitation from methanol into excess dichloromethane to yield a yellow powder. $^1$H NMR analysis indicated a mean degree of polymerization of 52 for this PGMA-TTC macro-CTA (M$_w$ = 13 700, M$_w$/M$_n$ = 1.26; see Figure S1). This suggests a CTA efficiency of around 74%.
monomer (0.90 g, 6.2 mmol; target DP = 400), and ACVA initiator (1.46 mg, 5.20 μmol, CTA/ACVA molar ratio = 3.0) were weighed into a 25 mL round-bottomed flask and dissolved in deionized water (9.31 mL). The resulting solution was purged under N2 for 30 min before being sealed and immersed in an oil bath at 70 °C for 4 h. The HPMA polymerization was quenched by exposure to air, and a final HPMA conversion of more than 99% was determined by 1H NMR analysis. These copolymer vesicles were characterized without further purification and used directly for RAFT end-group removal experiments (Mn = 101 700, Mw/Mn = 1.32; see Figure S3).

Synthesis of PGMA61−PBzMA100 Diblock Copolymer Spheres. These diblock copolymer nanoparticles were prepared via RAFT aqueous emulsion polymerization, as reported by Cunningham et al.52 PGMA61−DB macro-CTA (0.368 g, 36.9 μmol), BzMA monomer (0.65 g, 3.69 mmol; target DP = 100), and ACVA initiator (3.45 mg, 12.3 μmol; macro-CTA/ACVA molar ratio = 3.0) were weighed into a 25 mL round-bottomed flask and dissolved in deionized water (9.19 mL). The resulting solution was purged under N2 for 30 min before being sealed and immersed in an oil bath at 70 °C for 4 h. The BzMA polymerization was quenched by exposure to air and a final BzMA conversion of more than 99% was determined by 1H NMR analysis. These copolymer spheres were characterized without further purification and used directly for RAFT end-group removal experiments (Mn = 15 600, Mw/Mn = 1.26; see Figure S3).

H2O2 Protocol for Cleavage of RAFT End-Groups. The dithiobenzoate end-groups within PGMA104−PHPMA600 spheres were cleaved as follows: A 10% w/w copolymer dispersion (3.0 mL) was diluted to 7.5% w/w by addition of deionized water (1.0 mL). H2O2 (1.48 μL, 14.5 μmol; H2O2/CTA molar ratio = 5.0) was added to this dispersion as a 30% w/w aqueous solution. The resulting reaction solution was immersed in an oil bath at 70 °C and left exposed to air. The intrinsic pink coloration disappeared after around 7 h as judged by visual inspection. The trithiocarbonate end-groups on PGMA52−PHPMA135 worms were cleaved using the same protocol. Visual inspection indicated that the initial yellow coloration almost completely disappeared after 8 h. Preliminary experiments were conducted at pH 6, but subsequent more detailed studies were conducted at pH 3−4, with these lower values arising from the presence of the carboxylic acid-functionalized ACVA initiator and RAFT CTA (PETTC).

NMR Spectroscopy. All 1H NMR spectra were recorded in either deuterated methanol (for the PGMA macro-CTAs and PGMA−PHPMA diblock copolymers) or deuterated DMF (for the PGMA−PBzMA diblock copolymers) using a 400 MHz Bruker Avance-400 spectrometer (64 scans averaged per spectrum).

Gel Permeation Chromatography (GPC). Copolymer molecular weights and polydispersities were determined using an Agilent 1260 Infinity GPC system equipped with both refractive index and UV−vis detectors. Two Agilent PL gel 5 μm Mixed-C columns and a guard column were connected in series and maintained at 60 °C. HPLC-grade DMF containing 10 mM LiBr was used as eluent, and the flow rate was set at 1.0 mL min−1. DMSO was used as a flow-rate marker. The refractive index detector was used for calculation of molecular weights and polydispersities by calibration using a series of ten near-monodisperse poly(methyl methacrylate) standards (with Mn values ranging from 625 to 618 000 g mol−1). UV GPC chromatograms were obtained simultaneously by detection at a fixed wavelength of 309 nm which corresponds to the absorption maximum assigned to the dithiobenzoate or trithiocarbonate RAFT end-groups.

UV−Vis Absorption Spectroscopy. Absorption spectra were recorded between 200 and 800 nm using a Shimadzu UV-1800

Scheme 1. Reaction Schemes for (a) the Synthesis of a Gx−Hy−DB Diblock Copolymer via RAFT Aqueous Dispersion Polymerization, (b) the Synthesis of a Gx−Hy−TTC Diblock Copolymer via RAFT Aqueous Dispersion Polymerization, and (c) the Synthesis of a Gx−By−DB Diblock Copolymer via RAFT Aqueous Emulsion Polymerization
For kinetic studies, 0.10 mL aliquots were diluted ten-fold by addition of methanol (0.90 mL). Measurements were also conducted on purified freeze-dried copolymers after redispersing in water at either 0.25 or 0.50 mg mL\(^{-1}\) in order to observe absorption maxima at 309 and 550 nm, respectively.

**Transmission Electron Microscopy (TEM).** Copolymer dispersions were diluted fifty-fold at 20 °C to generate 0.20% w/w dispersions. Copper/palladium TEM grids (Agar Scientific, UK) were coated in-house to produce a thin film of amorphous carbon. These grids were then treated with a plasma glow discharge for 30 s to create a hydrophilic surface. Each aqueous diblock copolymer dispersion (12 μL; 0.20% w/w) was placed on a freshly treated grid for 1 min and then blotted with filter paper to remove excess solution. To stain the deposited nanoparticles, an aqueous solution of uranyl formate (9 μL; 0.75% w/w) was placed on the sample-loaded grid via a micropipet for 20 s and then carefully blotted to remove excess stain. Each grid was then carefully dried using a vacuum hose. Imaging was performed using a FEI Tecnai Spirit TEM instrument equipped with a Gatan 1kMS600CW CCD camera operating at 120 kV.

**Oscillatory Rheology Experiments.** An AR-G2 rheometer equipped with a variable temperature Peltier plate, a 40 mL 2° aluminum cone, and a solvent trap was used for all experiments. Temperature sweeps were conducted at an angular frequency of 1.0 rad s\(^{-1}\) and a constant strain of 1.0%. The temperature was increased by 1.0 °C between each measurement, allowing an equilibration time of 2 min in each case. A solvent trap was required to prevent evaporation of water over the time scale of these experiments.

## RESULTS AND DISCUSSION

A series of PISA-synthesized diblock copolymer nano-objects were examined in this study. These nano-objects were carefully selected in order to enable various comparisons to be made. In particular, we wished to explore (i) the effect of varying the particle diameter for a series of spherical nanoparticles, (ii) the effect of copolymer morphology (i.e., spheres vs. worms vs vesicles), (iii) the extent to which a more hydrophobic core-forming block retarded ingress of the H\(_2\)O\(_2\) reagent, and (iv) whether trithiocarbonate end-groups could be removed as readily as dithiobenzoate end-groups from otherwise identical nano-objects. For the sake of brevity, the three PGMA, PHPMA, and PBzMA blocks investigated in this study are abbreviated to G, H, and B in all of the figures and tables, with the mean degrees of polymerization of each block being indicated in subscript.

Recently, we have designed a range of thermoresponsive PGMA−PHPMA worm gels for various biomedical applications, including highly biocompatible 3D cell culture matrices,

\(32,53\) induction of stasis in human stem cell colonies\(34\) and the cryopreservation of red blood cells.\(54\) For such biomaterials, the removal of RAFT end-groups is likely to be important for FDA approval, so in our initial experiments we focused on one such system.

For the preparation of the PGMA−PHPMA−DB worm gel examined in this study, HPMA was polymerized using a well-defined PGMA\(_{52}\)−DB macro-CTA to almost full conversion (>99%, see Scheme 1a), as indicated by the disappearance of the vinyl proton signals at 5.5 and 6.2 ppm. According to \(^1\)H NMR spectroscopy, the mean diblock copolymer composition was calculated to be PGMA\(_{52}\)−PHPMA\(_{135}\)−DMF GPC analysis (refractive index detector against poly(methyl methacrylate))− standards indicated that this diblock copolymer had an \(M_n\) of 35 600 g mol\(^{-1}\) and an \(M_n/M_w\) of 1.12.

Initial attempts to cleave RAFT end-groups involved treating a 7.5% w/w PGMA\(_{52}\)−PHPMA\(_{135}\)−DB worm gel with various amounts of H\(_2\)O\(_2\) in the presence of air at 70 °C (see Scheme 2). In each case, UV−vis absorption spectra were recorded after diluting the aqueous dispersion ten-fold with methanol to produce 9:1 methanol/water solutions. Normalized absorbance vs time plots (see Figure 1) indicated that more than 90% of dithiobenzoate end-groups could be removed using a H\(_2\)O\(_2\)/dithiobenzoate molar ratio of either 5.0 or 10.0. Lower molar ratios required rather long reaction times, whereas higher molar ratios led to the evolution of a high molecular weight shoulder in the GPC chromatogram (see Figure S4) and also produced subtle differences in the copolymer worm rheology (see Figure S5). On the basis of these preliminary experiments, a H\(_2\)O\(_2\)/dithiobenzoate molar ratio of 5.0 was selected for more detailed studies.

End-group removal for a 7.5% w/w aqueous dispersion of PGMA\(_{52}\)−PHPMA\(_{135}\)−DB worms using a H\(_2\)O\(_2\)/dithiobenzoate molar ratio of 5.0 was repeated on a gram scale to enable full characterization. Visual inspection indicated almost complete removal of the initial pink coloration, producing a white dispersion after 2 h at 70 °C. After purification by dialysis, \(^1\)H NMR studies indicated disappearance of the aromatic signals at 7.5−8.0 ppm assigned to the dithiobenzoate group (see Figure 1a), suggesting successful end-group removal. Comparison of the remaining integrated copolymer signals suggests little effect on the overall copolymer composition. DMF GPC chromatograms obtained for

![Scheme 2. Proposed Reaction Scheme for the Removal of Dithiobenzoate End-Groups from PGMA−PHPMA, Diblock Copolymer Nano-Objects Using H2O2 in Water](Image)
PGMA$_{52}$−PHPMA$_{135}$ before and after H$_2$O$_2$ treatment are similar, although a weak high molecular weight shoulder becomes slightly more prominent (see Figure 2b). However, there is only a minimal change in $M_n$ (from 35,600 to 35,700 g mol$^{-1}$) and $M_w/M_n$ (from 1.12 to 1.16), suggesting that the original copolymer molecular weight distribution is essentially unaffected.

The white powder produced on freeze-drying the purified copolymer was dissolved in methanol and analyzed by UV−vis spectroscopy in order to assess the extent of end-group removal (see Figure 3a). Methanol is a good solvent for both the PGMA and PHPMA blocks; this protocol ensures molecular dissolution of the copolymer chains and hence eliminates any light scattering effects on the spectra. Dithiobenzoate end-groups exhibit a characteristic absorbance at 309 nm, which is clearly visible in the original PGMA$_{52}$−PHPMA$_{135}$ copolymer spectrum. H$_2$O$_2$ treatment of the aqueous copolymer dispersion ([H$_2$O$_2$]/[DB] molar ratio = 5.0; 70 °C for 160 min) leads to almost complete disappearance of this 309 nm signal. However, a relatively weak new absorption appears at approximately 270 nm, which prevents the absorbance at 309 nm falling to zero. The origin of this new spectral feature is currently unclear and probably warrants further studies. Similar observations are made in the corresponding visible region of the same spectra (Figure 3b): the much weaker absorption located at around 509 nm almost completely disappears. This is consistent with the digital images shown in Figure 3c, which confirm the complete removal of the pink coloration from the freeze-dried copolymer powder. Moreover, a tube inversion test indicated that thermoreversible degelation can still be induced on cooling a reconstituted H$_2$O$_2$-treated copolymer worm gel from 37 to 2 °C. These observations were confirmed using variable temperature oscillatory rheology studies (Figure 4). Moreover, such gel rheology studies are almost identical to the data set obtained for the original worm gel prior to H$_2$O$_2$ treatment. In particular, there is almost no change in the gel modulus, $G'$, at 37 °C or in the critical gelation temperature (CGT) for this worm gel.

**Figure 2.** (a) $^1$H NMR spectra recorded before and after removal of the dithiobenzoate (DB) end-group from a 7.5% w/w G$_{52}$−H$_{135}$ diblock copolymer aqueous dispersion by exposure to H$_2$O$_2$ for 160 min in water (pH 4−6, 70 °C) using a [H$_2$O$_2$]/[DB] molar ratio of 5.0; (b) Molecular weight distributions obtained via DMF GPC (refractive index detector, calibrated against poly(methyl methacrylate) standards) for a G$_{52}$-H$_{135}$ diblock copolymer before and after treatment with H$_2$O$_2$ under the conditions stated in (a).

**Figure 3.** (a) UV−vis absorption spectra recorded for 0.25 mg mL$^{-1}$ G$_{52}$−H$_{135}$ diblock copolymer solutions in methanol before and after dithiobenzoate end-group removal ([H$_2$O$_2$]/[DB] = 5.0, 70 °C, 160 min). (b) Visible absorption spectra obtained for the same copolymers at 5.0 mg mL$^{-1}$ in methanol indicating the disappearance of the relatively weak absorption band at approximately 500 nm (which corresponds to the intrinsic pink color conferred by the RAFT chain-end). (c) Digital image showing the freeze-dried G$_{52}$−H$_{135}$ copolymer before and after dithiobenzoate end-group removal.

**Figure 4.** Temperature-dependent oscillatory rheology studies on a 10% w/w G$_{52}$−H$_{135}$ worm gel before (G$_{52}$−H$_{135}$−DB) and after (G$_{52}$−H$_{135}$) treatment with H$_2$O$_2$ to remove the dithiobenzoate chain-ends. The freeze-dried powder was redispersed in cold 150 mM PBS at 2 °C. Inset digital images show a 10% w/w dispersion of the reconstituted G$_{52}$−H$_{135}$ copolymer after end-group removal as a free-flowing liquid at 2 °C and a free-standing gel at 37 °C.
The kinetics of dithiobenzoate end-group removal at 70 °C from H2O2-treated PGMA104−PHPMA135−DB spheres was conducted by extracting a series of aliquots from the 7.5% w/w copolymer dispersion after various time periods and subsequently diluting ten-fold with methanol (to produce a 9:1 methanol/water solution) prior to analysis by UV−vis spectroscopy at 20 °C. As expected, gradual attenuation in the 309 nm absorption band was initially observed (see Figure 5a). However, apparently no further reduction occurred after approximately 6 h. Inspecting the evolution in UV spectra more closely, this artifact appears to be the result of an additional spectral feature at 270 nm, which is associated with the formation of unknown low molecular weight degradation products (e.g. possibly benzoic acid). In order to circumvent this problem, further end-group removal studies were conducted using UV GPC analysis. By setting the UV detector to a fixed wavelength of 309 nm, it was possible to monitor the extent of end-group removal for copolymer chains bearing either a dithiobenzoate or a trithiocarbonate end-group. The decisive advantage of this approach is that fractionation of the copolymer chains from the small molecule impurities occurs in the GPC column prior to analysis. Thus, there is no longer any interference from the small molecule impurities absorbing at shorter wavelengths, which aids quantification. For this particular data set, an overall 96% reduction in the original UV signal was observed within 8 h (see Figure 5b). At this point, we examined whether full end-group removal could be achieved given a sufficiently long reaction time. Thus, the H2O2 treatment was extended from 8 to 24 h at 70 °C, which led to an overall reduction in the original UV GPC signal of 98% (see Figure S6).

Applying this optimized analytical protocol to the PGMA52−PHPMA135−DB worms (see above) indicated a 95% reduction in RAFT end-group concentration within 2.5 h at 70 °C. Moreover, the rate of end-group removal achieved for this aqueous dispersion of copolymer worms was comparable to that achieved for a water-soluble dithiobenzoate PGMA52−DB homopolymer precursor under the same conditions (i.e., same molar concentration of dithiobenzoate groups) (see Figure 6). This indicates that the H2O2 reagent can readily access the dithiobenzoate end-groups within the weakly hydrophobic PHPMA cores, which is consistent with the partially hydrated nature of these core-forming chains. Essentially the same absorption band was observed within 5 h (see Figure 5b), at which point we examined whether full end-group removal could be achieved given sufficient reaction time. Thus, the H2O2 treatment was extended from 8 to 24 h at 70 °C, which led to an overall reduction in the original UV GPC signal of 98% (see Figure S6).
was used to prepare PGMA$_{51}$–PbzMA$_{100}$–DB spheres via RAFT aqueous emulsion polymerization (see Scheme 1c) according to a protocol recently reported by Cunningham and co-workers. This diblock composition was selected so that the mean diameter of these spheres was approximately 25 nm, which is comparable to the mean width of the dithiobenzoate-based PGMA$_{32}$–PHPMA$_{135}$ worms (as estimated by TEM studies). On treating these PGMA$_{32}$–PbzMA$_{100}$–DB spheres with H$_2$O$_2$, the rate of end-group removal was found to be very slow, with 60% of end-groups remaining after 8 h as judged by UV GPC (see Figure 6). This suggests that, despite its nonionic nature and relatively low molecular weight, diffusion of the H$_2$O$_2$ reagent into the PbzMA cores is severely retarded compared to PHPMA cores.

In a related series of experiments, three examples of PGMA$_{104}$–PHPMA$_{300}$–DB spheres (where $x = 300, 600, or 900$, corresponding to mean DLS hydrodynamic diameters of 54, 81, and 117 nm, respectively) were also subjected to H$_2$O$_2$ treatment followed by UV GPC analysis (see Figure 7). The purpose of these experiments was to examine whether particle size had any effect on the rate of end-group removal. Normally, slower H$_2$O$_2$ ingress might be expected for larger particles, but if the PHPMA cores are relatively hydrated, then in principle there might be no physical barrier to the diffusion of this reagent.

H$_2$O$_2$ treatment (using a H$_2$O$_2$/dithiobenzoate molar ratio of 5.0 at 70 ºC) of these PGMA$_{104}$–PHPMA$_{300}$–DB spheres at a fixed 7.5% w/w copolymer concentration led to a significant reduction in the rate of end-group removal with increasing PHPMA DP (see Figure 7). At first sight, this suggests a slower rate of H$_2$O$_2$ ingress into the larger spheres. However, targeting a higher DP at the same fixed copolymer concentration inevitably means a lower concentration of dithiobenzoate end-groups. Comparing the rate of end-group cleavage for PGMA$_{104}$–PHPMA$_{300}$ spheres at 7.5% w/w with that for PGMA$_{104}$–PHPMA$_{900}$ spheres at 18.0% w/w (i.e., at the same molar concentration of dithiobenzoate end-groups) indicates essentially no difference in kinetics (see Figure 7). This confirms that the partially hydrated PHPMA cores of this series of spheres offer no diffusional barrier to H$_2$O$_2$ ingress, at least for the particle size range investigated herein.

Finally, 10% w/w aqueous dispersions of PGMA$_{104}$–PHPMA$_{600}$–DB spheres, PGMA$_{48}$–PHPMA$_{135}$–DB worms, and PGMA$_{58}$–PHPMA$_{400}$–DB vesicles were each subjected to H$_2$O$_2$ treatment (H$_2$O$_2$/dithiobenzoate molar ratio = 5.0; 70 ºC for 3 h). In each case a high degree of decolorization was observed, indicating almost complete cleavage of the dithiobenzoate end-groups (see digital images shown in Figure 8). Moreover, it is perhaps worth emphasizing that if any loss of RAFT end-groups did occur during such PISA syntheses, then the relatively low levels (2–5% in most cases) of residual RAFT end-groups determined by UV GPC analysis actually represent upper limit values. TEM studies confirmed that this derivatization protocol produced no discernible effect on the copolymer morphology, with comparable images being obtained before and after H$_2$O$_2$ treatment in each case (Figure 8).

Although a hydroxyl radical mechanism was proposed by Pfukwa and co-workers, the following observations indicate that an oxidation mechanism may be more likely, at least under the end-group cleavage conditions described herein. Two identical batches of the same dithiobenzoate-functionalized PGMA$_{32}$–PHPMA$_{135}$ copolymer were subjected to end-group removal using H$_2$O$_2$ (H$_2$O$_2$/dithiobenzoate molar ratio = 5.0; 7.5% w/w copolymer dispersion; 70 ºC). One batch was degassed for 30 min using N$_2$ prior to end-group removal, with UV–vis spectroscopy studies indicating that dithiobenzoate cleavage was complete within about 240 min. In contrast, the second batch was not degassed and remained exposed to air during the H$_2$O$_2$ reaction. In this case, dithiobenzoate cleavage was complete within 150 min (see Figure S9). This rate acceleration in the presence of oxygen is consistent with an oxidative mechanism. Moreover, oxygen is a well-known retarder of radical-based reactions (e.g., free radical polymerizations or RAFT polymerizations). In summary, we suggest that H$_2$O$_2$-mediated end-group removal may proceed via an oxidative mechanism rather than a radical mechanism. Further studies are required to establish the precise nature of the end-groups that are formed after H$_2$O$_2$ treatment, although Pfukwa and co-workers present some indirect evidence that terminal hydroxyl groups may be formed, at least in the case of poly(N-vinylpyrrolidone) prepared using a xanthate-based RAFT agent.

**CONCLUSIONS**

H$_2$O$_2$ can be utilized as a relatively cheap reagent for the convenient and efficient removal of dithiobenzoate end-groups from PGMA$_{x}$–PHPMA$_{y}$ diblock copolymer nano-objects in concentrated aqueous solution. The original spherical, worm-like, or vesicular copolymer morphologies are retained after this chemical derivatization, and UV GPC analysis indicates that...
approximately 96% of dithiobenzoate end-groups can be removed within 8 h at 70 °C when using a H$_2$O$_2$/dithiobenzoate molar ratio of 5.0. Moreover, H$_2$O$_2$ treatment of a series of PGMA$_{104}$−PHPMA$_x$−DB spheres indicates that the rate of end-group removal was both independent of particle size and comparable to that observed for a water-soluble PGMA$_{52}$−DB homopolymer under the same conditions. This suggests that the highly hydrated nature of the weakly hydrophobic PHPMA core-forming chains does not inhibit H$_2$O$_2$ diffusion.

Oscillatory rheology studies confirm that removal of dithiobenzoate end-groups does not adversely affect the thermoresponsive gelation behavior exhibited by PGMA$_{52}$−PHPMA$_{135}$ worms in aqueous solution. However, end-group removal is much less effective for dithiobenzoate-functionalized PGMA$_{58}$−PBzMA$_{100}$ spheres, with less than 40% of these RAFT chain-ends being cleaved within 8 h at 70 °C using the same H$_2$O$_2$/dithiobenzoate molar ratio. This marked difference simply reflects the retarded diffusion of the H$_2$O$_2$ reagent into the relatively dehydrated hydrophobic PBzMA cores. It is also clear from this study that trithiocarbonate end-groups are significantly more resistant to H$_2$O$_2$ cleavage than dithiobenzoate end-groups under the same conditions. Finally, it is emphasized that UV GPC analysis in DMF is much more useful than UV−visible spectroscopy analysis of aqueous dispersions for monitoring the rate of RAFT end-group removal. This is because the former technique separates the copolymer chains from small molecule impurities prior to analysis, which eliminates spectral interference from the latter species.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.macromol.6b01963.

Figures S1–S9 (PDF)

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**Notes**

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