Macromolecules

Article

pubs.acs.org/Macromolecules

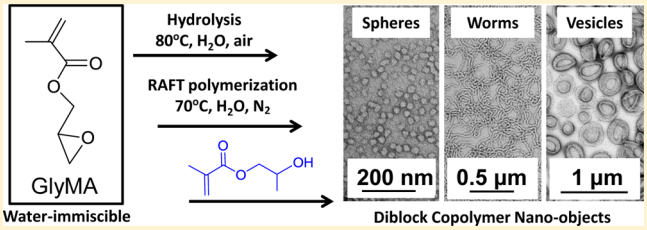
From a Water-Immiscible Monomer to Block Copolymer Nano-Objects via a One-Pot RAFT Aqueous Dispersion Polymerization Formulation

L. P. D. Ratcliffe, A. J. Ryan, and S. P. Armes*

Dainton Building, Department of Chemistry, The University of Sheffield, Brook Hill, Sheffield, South Yorkshire S3 7HF, U.K.

Supporting Information

ABSTRACT: We describe the facile atom-efficient synthesis of diblock copolymer nano-objects via a one-pot RAFT aqueous dispersion polymerization protocol starting from a water-immiscible methacrylic monomer. More specifically, an aqueous emulsion of glycidyl methacrylate (GlyMA) is quantitatively converted into a 10% w/w aqueous solution of glycerol monomethacrylate (GMA) at 80 °C in air within 9 h in deionized water. ^{1}H NMR spectroscopy studies indicate no evidence for either methacrylic ester hydrolysis or polymerization during this ring-opening reaction. Kinetic analysis indicates that a significant rate acceleration occurs as the reaction mixture switches from a two-phase emulsion to a single aqueous phase. This observation is fully consistent with the GlyMA–GMA–water ternary phase diagram determined at 80 °C. The 10% w/w aqueous solution of GMA can be polymerized using RAFT chemistry to produce a near-monodisperse PGMA macromolecular chain-transfer agent (macro-CTA), which indicates that relatively little dimethacrylate impurity is produced during the conversion of GlyMA into GMA. This PGMA macro-CTA can be subsequently chain-extended using 2-hydroxypropyl methacrylate (HPMA) via a RAFT aqueous dispersion polymerization formulation. The resulting PGMA–PHPMA diblock copolymers can form well-defined spheres, worms, or vesicles depending on the relative block compositions, since this dictates the copolymer curvature and hence the self-assembly behavior. Bearing in mind that GMA is a relatively expensive specialty monomer and GlyMA is a commodity monomer, this appears to be a highly cost-effective, purely aqueous one-pot route to diblock copolymer nano-objects.



INTRODUCTION

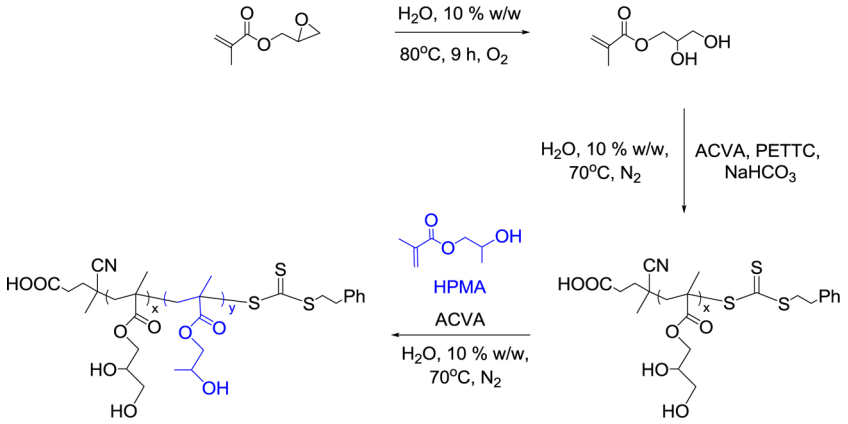
Glycerol monomethacrylate (GMA) is a hydrophilic nonionic methacrylic monomer that is used commercially for the manufacture of soft contact lenses.[1] In academic studies it has also been utilized as a comonomer to prepare highly biocompatible cross-linked hydrogels.[1−4] GMA is usually synthesized from glycerol, using acetone to protect two of its three hydroxyl groups, prior to transesterification of the third hydroxyl group with methyl methacrylate and finally selective removal of the acetyl protecting group. This multistep route makes GMA a relatively expensive specialty monomer and also leads to a mixture of 1,3- and 2,3-hydroxy isomers.[5]

In principle, well-defined PGMA-based block copolymers can be prepared using anionic polymerization. However, protecting group chemistry is required for the hydroxyl groups, which necessitates a three-step synthesis.[6,7] More recently, a range of controlled-structure GMA-based copolymers, including homopolymers,[5] diblock and triblock copolymers,[8−11] and macromonomers,[12] have been synthesized directly using living radical polymerization. For example, atom transfer radical polymerization (ATRP)[13−16] has been used to prepare well-defined sterically stabilized latex particles that (i) adsorb reversibly onto cellulose fibers via phenylboronic acid-mediated binding,[17] (ii) act as model Pickering emulsifiers,[18] and (iii) can be covalently stabilized to produce colloidosomes.[19]

In 2010, Li and Armes[20] reported the synthesis of amphiphilic diblock copolymers based on GMA and 2-hydroxypropyl methacrylate (HPMA) using reversible addition–fragmentation chain transfer (RAFT) polymerization.[21−23] First, GMA was homopolymerized to produce a water-soluble macromolecular chain transfer agent (macro-CTA). Then chain extension was conducted using HPMA under aqueous dispersion polymerization conditions (HPMA is water-miscible up to 10% w/w at 70 °C but forms a water-insoluble homopolymer). Using a fixed mean degree of polymerization of the macro-CTA and working at an overall concentration of 10% solids, a series of near-monodisperse sterically stabilized PGMA–PHPMA diblock copolymer nanoparticles of controllable size in the 26–105 nm range were produced simply by varying the target DP of the core-forming PHPMA block. Moreover, a polydisperse vesicular morphology was produced at 20% solids, and a one-pot protocol was briefly explored. However, block copolymer polydispersities were relatively high (M_w/M_n > 3.5) when targeting longer DP values for the core-forming block due to the presence of a dimethacrylate impurity in the HPMA monomer, which

Received: September 12, 2012
Revised: January 4, 2013
Published: January 17, 2013

Scheme 1. Conversion of Glycidyl Methacrylate (GlyMA) to Glycerol Monomethacrylate (GMA) in Water at 80 °C, Followed by the *in Situ* Preparation of a near-Monodisperse PGMA Macro-CTA via RAFT Aqueous Solution Polymerization, Followed by the Synthesis of a Well-Defined PGMA–PHPMA Diblock Copolymer via RAFT Aqueous Dispersion Polymerization[a]



[a]Systematic variation of the mean degree of polymerization of the core-forming hydrophobic PHPMA block enables either spheres, worms, or vesicles to be obtained using this atom-efficient one-pot aqueous formulation.

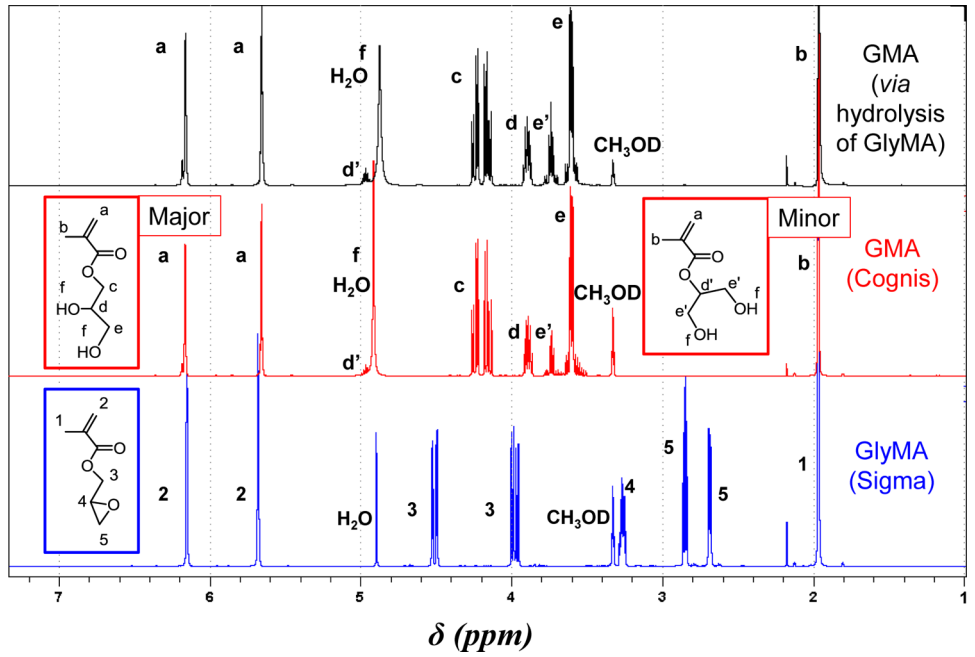


Figure 1. ^{1}H NMR spectra (CD_3OD) of glycerol monomethacrylate (GMA) monomer prepared via hydrolysis of glycidyl methacrylate (GlyMA) at 10% w/w (upper spectrum), commercial GMA monomer donated by Cognis (middle spectrum), and commercial glycidyl methacrylate monomer (lower spectrum).

inevitably led to branching. Moreover, blocking efficiencies were relatively poor: GPC analyses typically revealed the presence of significant levels (10–20%) of PGMA macro-CTA as a contaminant.

This prototype RAFT aqueous dispersion polymerization formulation was subsequently optimized by Blanazs et al.[24] Very high HPMA conversions were achieved within 2 h at 70 °C, with good blocking efficiencies and relatively low final polydispersities (M_w/M_n < 1.20). In particular, detailed phase diagrams were constructed that enable three distinct diblock copolymer morphologies (spheres, worms, or vesicles) to be reliably targeted.[25] Moreover, the worm phase forms free-standing aqueous gels due to inter-worm contacts.[26] Such worm gels are soft, shear-thinning, highly biocompatible, and thermo-responsive, with a reversible worm-to-sphere transition (and hence degelation) being observed on cooling.[26,27] This unusual behavior allows facile sterilization via cold ultrafiltration, with the original gel being reformed at ambient temperature.

Herein we describe the synthesis of well-defined PGMA–PHPMA diblock copolymers starting from glycidyl methacrylate (GlyMA). In principle, this commodity monomer is an ideal starting material, since literature precedent suggests that it should react with 1 equiv of water to produce GMA with no side products.[28−30] In practice, GlyMA is water-immiscible, and the only literature reports of such an approach involves the use of glacial acetic acid or H_2SO_4 as a catalyst.[31] However, we show that a 10% w/w aqueous emulsion of GlyMA is quantitatively converted into a 10% w/w aqueous solution of GMA simply on heating at 80 °C for 8–9 h in the absence of

dx.doi.org/10.1021/ma301909w | *Macromolecules* 2013, 46, 769–777

any catalyst (see Scheme 1 and Figure 1). Once formed, GMA is directly polymerized *in situ* via RAFT aqueous solution polymerization to produce a PGMA macro-CTA, which can be subsequently chain-extended with HPMA to generate a range of diblock copolymer nano-objects with controllable morphologies via a highly convenient and atom-efficient one-pot protocol.

EXPERIMENTAL SECTION

Materials. Glycidyl methacrylate (GlyMA; 97%), 2-hydroxypropyl methacrylate (HPMA; 97%), and 4,4′-azobis(4-cyanopentanoic acid) (ACVA; V-501; 99%). HPLC analysis of the HPMA monomer[24] indicated a dimethacrylate impurity of around 0.10 mol %. Glycerol monomethacrylate (GMA; 99.8%) was kindly donated by Cognis Performance Chemicals (Hythe, UK) and used without further purification. Deuterated methanol (CD_3OD) was purchased from Goss Scientific (Nantwich, UK). Sodium hydrogen carbonate (Laboratory Reagent grade) was purchased from Fisher Scientific (Loughborough, UK). All solvents were of HPLC quality and were purchased from Fisher Scientific (Loughborough, UK). Deionized water (pH 6.3 at 21 °C) was used for all aqueous polymerizations.

Synthesis of Glycerol Monomethacrylate (GMA) from Glycidyl Methacrylate (GlyMA). In a typical experiment, glycidyl methacrylate (4.96 g, 35 mmol) was added to water (44.78 g, 2.49 mol, 10% w/w solution) in a round-bottomed flask fitted with a condenser. The initial emulsion was stirred for 9 h at 80 °C and eventually became a homogeneous aqueous solution, with 99% conversion to glycerol monomethacrylate as judged by ^{1}H NMR. ^{1}H NMR (400.13 MHz, CD_3OD, 298 K): δ 1.97 (s, 3H, $-CH_3$), 3.55−3.65 (m, 2H, $-CH_2$), 3.68−3.78 (m, 2H, $-CH_2$), 3.86−3.92 (m, 1H, −CH), 4.12−4.28 (m, 2H, $-CH_2$), 4.93−5.0 (m, 1H, −CH), 5.63−5.69 (m, 1H, $=CH_2$), 6.14−6.2 (m, 1H, $=CH_2$).

PGMA$_x$ Macro-CTA Synthesis Starting from GlyMA. A typical protocol for the synthesis of $PGMA_{56}$ is as follows. To a round-bottomed flask containing 4-cyano-4-(2-phenylethane sulfanylthiocarbonyl)sulfanylpentanoic acid (PETTC) RAFT agent (0.222 mmol, 0.075 g, synthesized using the method described by Semsarilar et al.[32]), an aqueous solution of GMA monomer (10 mmol, 1.60 g in 14.42 mL, prepared as described above) was added to target a mean degree of polymerization (DP) of 45, assuming a CTA efficiency of 100%. Further water (0.79 g, to afford a 10% w/w solution), ACVA initiator (0.044 mmol, 12.5 mg, CTA/ACVA molar ratio = 5.0), and $NaHCO_3$ (0.225 mmol, 18.9 mg) were then added to this solution, which was stirred until all of the PETTC had dissolved. The resulting yellow solution was degassed via a nitrogen sparge for 30 min, before the sealed flask was immersed into an oil bath set at 70 °C. After 4.5 h (final GMA conversion exceeded 99%, as judged by ^{1}H NMR), the RAFT polymerization was quenched by immersion in ice and the reaction solution was exposed to air. A small aliquot was removed, freeze-dried, and then dissolved in methanol before precipitation into a 10-fold excess of chloroform. The precipitated PGMA macro-CTA was washed three times with chloroform before being dried in a vacuum oven overnight at 40 °C. ^{1}H NMR analysis indicated a DP of 56 for this PGMA macro-CTA as judged by end-group analysis. This indicates a CTA efficiency of ∼80%. DMF GPC (refractive index detector, using a series of near-monodisperse poly(methyl methacrylate) calibration standards) indicated an M_n of 17 600 g mol^{-1} and an M_w/M_n of 1.10.

RAFT Aqueous Dispersion Polymerization of a $PGMA_{56}$−$PHPMA_{373}$ Diblock Copolymer. A typical protocol for the synthesis of a $PGMA_{56}$−$PHPMA_{373}$ diblock copolymer is as follows: HPMA monomer (3.90 g, 27.05 mmol; target DP = 373) and water (35.15 g, to produce 10% w/w solids) were added in turn to a solution of $PGMA_{56}$ macro-CTA (0.65 g, 4.06 mmol dissolved in 5.85 g water) in a 100 mL round-bottomed flask. ACVA was then added (6.04 mg, 0.022 mmol, CTA/ACVA molar ratio = 4.0), and the solution was degassed via a nitrogen sparge for 30 min. The reaction flask was then sealed and immersed in an oil bath set at 70 °C. The reaction solution was then sampled at various time intervals to obtain a series of diblock copolymers of varying PHPMA DPs at a fixed PGMA DP. Finally, the reaction was quenched by cooling to 0 °C and exposure to air.

Construction of Ternary Phase Diagram. An aqueous solution of GMA and an aqueous emulsion of GlyMA were prepared at the same monomer concentration (10.0% w/w) at 21 °C. The GMA solution was gradually added to the GlyMA emulsion (3.00 g) in known proportions (determined gravimetrically using a four-figure balance) and shaken vigorously until the GMA−GlyMA aqueous mixture became homogeneous, as judged by visual inspection. This protocol was repeated several times and at various GMA and GlyMA concentrations to obtain a ternary phase diagram. This phase diagram protocol was repeated at 80 °C using a temperature-controlled oil bath.

Copolymer Characterization. *^{1}H NMR Spectroscopy.* All NMR spectra were recorded using a 400 MHz Bruker Avance-400 spectrometer in CD_3OD. At least 64 scans were recorded per spectrum in each case.

Gel Permeation Chromatography (GPC). Polymer molecular weights and polydispersities were determined using a DMF GPC instrument operating at 60 °C that comprised two Polymer Laboratories PL gel 5 μm Mixed C columns and one PL polar gel 5 μm guard column connected in series to a Varian 390 LC multidetector suite (only the refractive index detector was utilized) and a Varian 290-LC pump injection module. The GPC eluent was HPLC grade DMF containing 10 mM LiBr and was filtered prior to use. The flow rate was 1.0 mL min^{-1}, and DMSO was used as a flow-rate marker. Calibration was conducted using a series of 10 near-monodisperse poly(methyl methacrylate) standards (M_n = 625−618 000 g mol^{-1}, K = 2.094 × 10^{-3}, α = 0.642). Chromatograms were analyzed using Varian Cirrus GPC software.

Transmission Electron Microscopy (TEM). Copper TEM grids (Agar Scientific, UK) were surface-coated in-house to yield a thin film of amorphous carbon. The grids were then plasma glow-discharged for 40 s to create a hydrophilic surface. Each aqueous diblock copolymer dispersion (0.20% w/w, 11 μL) was placed onto a freshly glow-discharged grid for 1 min and then blotted with filter paper to remove excess solution. To stain the deposited nanoparticles, a 0.75% w/w aqueous solution of uranyl formate (9 μL) was placed via micropipet on the sample-loaded grid for 20 s and then carefully blotted to remove excess stain. Each grid was then carefully dried using a vacuum hose. Imaging was performed at 100 kV using a Phillips CM100 instrument equipped with a Gatan 1k CCD camera.

Dynamic Light Scattering (DLS). Intensity-average diameters were calculated via the Stokes−Einstein equation for dilute aqueous dispersions of diblock copolymer nano-objects at 25 °C using a Malvern Zetasizer NanoZS instrument at a scattering angle of 173°.

RESULTS AND DISCUSSION

A wide range of stimulus-responsive block copolymers can be prepared using RAFT polymerization.[33−41] In particular, bespoke diblock copolymer nano-objects can be readily prepared by polymerization-induced self-assembly (PISA) using this chemistry.[25,42−49] In addition to the examples discussed in the Introduction, well-known literature reports include the polymerization of *N*-isopropylacrylamide using a poly(*N*,*N*′-dimethylacrylamide) macro-CTA via RAFT aqueous dispersion polymerization[50] and the polymerization of either styrene[51,52] or benzyl methacrylate[45,46,53] or cholesteryl-based monomers[47] in either alcohol or alcohol/water mixtures via RAFT dispersion polymerization. Similarly, An et al.[54−56] have reported a successful aqueous RAFT formulation for the polymerization of acrylic monomers such as 2-methoxyethyl acrylate.

Recently, we reported the elucidation of detailed phase diagrams for PGMA−PHPMA diblock copolymer nano-objects prepared via RAFT aqueous dispersion polymerization.[24] We regard this formulation as a convenient prototypical model to

dx.doi.org/10.1021/ma301909w | *Macromolecules* 2013, 46, 769−777

develop our understanding of such systems. Moreover, in view of the well-documented biocompatibility of both PGMA and PHPMA,[3,26,57,58] such formulations are expected to have potential biomedical applications. Important goals of the present study were (i) to address the relatively high cost of using GMA and (ii) to develop a convenient one-pot aqueous protocol that was sufficiently robust to allow access to each of the three known morphologies (spheres, worms, and vesicles).[24,25]

According to Shaw and co-workers, GlyMA can be converted into GMA via forced hydrolysis in aqueous solution in the presence of acetic acid at 80 °C.[31a] However, there is some literature precedent to suggest that an acid catalyst may not be required. For example, Wang et al.[28] reported that epoxy ring-opening reactions can be achieved for a wide range of water-immiscible compounds (e.g., styrene oxide or cyclohexene oxide) with good selectivity simply by heating an aqueous suspension of the starting material to either 60 or 100 °C in the absence of any other reagents. Since the dissociation constant of water increases at elevated temperatures,[59] Wang et al.[28] suggested that water acted as both a reagent and a (very) mild acid catalyst. However, epoxy-based vinyl monomers such as GlyMA were not examined in this earlier study. Similarly, Greenwood and co-workers[60] have shown that the forced hydrolysis of 3-glycidoxypropyltrimethoxysilane in dilute aqueous solution at 60 °C allows the *in situ* synthesis of glycerol-functionalized silica sols.[29]

Despite the above literature reports, it is not at all obvious that such an approach would work well for epoxy-based methacrylic monomers such as GlyMA. This is because prolonged heating in water at high temperature is likely to cause ester hydrolysis and perhaps also background polymerization as well as the desired ring-opening of the epoxide group. Moreover, at intermediate conversions it is also feasible that the hydroxyl groups of the initially generated GMA might react with the epoxide ring of the remaining GlyMA, which would lead to the unwanted production of dimethacrylate impurities. Nevertheless, we decided to explore the feasibility of converting GlyMA into GMA in deionized water at 80 °C in the absence of any catalyst (see Scheme 1). Since oxygen is a well-known inhibitor, this reaction was conducted in air in order to prevent *in situ* polymerization using an initial GlyMA concentration of 5, 10, or 15% w/w. The solubility of GlyMA in water was estimated by visual inspection to be 1.4−1.5% w/w at 21 °C and 2.4−2.5% w/w at 80 °C. Thus, each initial reaction mixture was a two-phase GlyMA-in-water emulsion, rather than a homogeneous aqueous solution. Conversion of GlyMA into GMA was monitored by ^{1}H NMR spectroscopy: the two epoxy proton signals (**5**, see Figure 1) at 2.68 and 2.85 ppm due to GlyMA gradually disappeared (see Figure S1 in the Supporting Information), while new GMA signals assigned to the two protons of the 2,3-hydroxy isomer (**e**) and the four protons of the 1,3-hydroxy isomer (**e′**) appeared at 3.6 and 3.75 ppm, respectively. This approach generated the representative kinetic data shown in Figure 2 (see Figure S2 for the corresponding conversion vs time curves).

There are several features of interest. First, the rate of hydrolysis of GlyMA for the initial emulsion is relatively slow due to the limited aqueous solubility of this monomer. However, this rate clearly increases dramatically after a certain characteristic time period. This corresponds to the point at which the initial two-phase aqueous emulsion becomes a homogeneous aqueous solution. This is because, for a given set

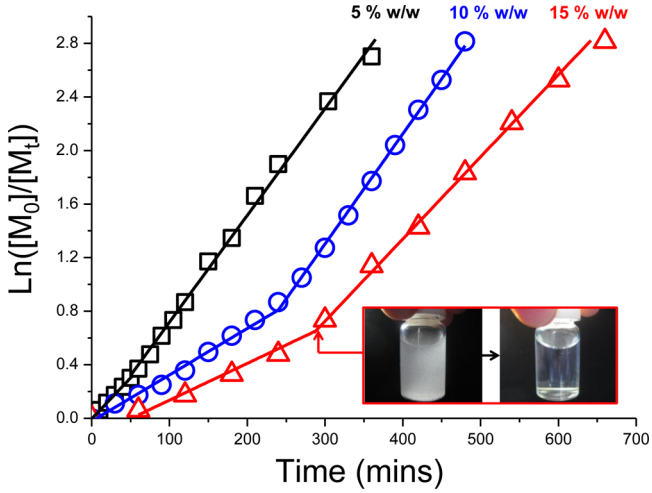


Figure 2. Rate of hydrolysis of glycidyl methacrylate (GlyMA) to form glycerol monomethacrylate (GMA) in water at 80 °C in the presence of air at three different GlyMA concentrations, as judged by ^{1}H NMR spectroscopy. A significant rate enhancement is observed in each case, the onset of which corresponds to the point in the reaction at which sufficient GMA is generated to transform the initial two-phase emulsion into a homogeneous aqueous solution (see inset).

of conditions, there will be a critical concentration of GMA product that solubilizes all of the remaining water-immiscible starting material to produce a single-phase reaction mixture, which contains a higher GlyMA concentration than the limiting aqueous solubility of this reactant. This hypothesis is supported by visual inspection of the reaction solution, which changes from a turbid emulsion to a transparent solution (see inset digital photographs in Figure 2) at approximately the same characteristic time at which the onset of the rate acceleration is observed. This phase change occurs at approximately 1, 4, or 5 h for initial GlyMA concentrations of 5.0, 10.0, or 15.0% w/w, respectively (see Figure 2 and Table 1).

Second, it is clear that the overall rate of conversion of GlyMA into GMA is actually faster at a lower initial GlyMA concentration (see Table 1). At first sight, this observation appears to be counterintuitive: water is always present in large excess (~50 M for a 10% w/w formulation) in each experiment, so the rate of reaction might be expected to be simply pseudo-first-order with respect to the GlyMA concentration. This classical assumption is valid for many reactions conducted in homogeneous solution but requires modification due to the heterogeneous (two-phase) nature of the initial reaction mixture. Essentially, two pseudo-first-order rate constants are required to describe the overall kinetics: a relatively low rate constant is observed for the initial hydrolysis conducted under heterogeneous conditions, whereas a significantly higher value is obtained once the reaction solution becomes homogeneous. Thus, the conversion of GlyMA into GMA at 5.0% w/w is significantly faster than at 10.0% w/w (or 15.0% w/w) *because rather less GMA is required to solubilize the remaining GlyMA if the latter is present at a lower concentration*. As a result, the characteristic time period required for the initially heterogeneous reaction mixture to become homogeneous is minimized, *which leads to a faster overall rate of reaction at a lower reagent concentration*. This may also explain why the acetic acid-catalyzed transformation of GlyMA into GMA was conducted under relatively dilute conditions (~7% w/w) by Shaw et al.[31a]

dx.doi.org/10.1021/ma301909w | *Macromolecules* 2013, 46, 769−777

Table 1. Heterogeneous and Homogeneous Rate Constants for the Conversion of Glycidyl Methacrylate (GlyMA) into Glycerol Monomethacrylate (GMA) in Water at 80 °C in the Presence of Air at Three Different GlyMA Concentrations, As Judged by ^{1}H NMR Spectroscopy[a]

initial [GlyMA], % w/w	two-phase rate const, $\times 10^4$ s^{-1}	one-phase rate const, $\times 10^4$ s^{-1}	estd time required for a single phase reaction soln, h	react time for conv of GlyMA into GMA	[GlyMA] at point of formation of single phase, % w/w	[GMA] at point of formation of single phase, % w/w
5.0	1.02	1.33	1	8 h (96%)	2.5	2.5
10.0	0.58	1.37	4	9 h (99%)	4	6
15.0	0.46	1.02	5	14 h (99%)	6	9

[a]The actual GlyMA and GMA concentrations at the point of formation of a homogeneous reaction solution are also estimated from the ^{1}H NMR data.

In view of this unusual situation, a GlyMA−GMA−water ternary phase diagram was constructed at both ambient temperature (21 °C) and also at the reaction temperature used for the conversion of GlyMA to GMA (80 °C). This tenary phase diagram is shown in Figure 3. The phase space for the homogeneous (single phase) aqueous solution is clearly larger at 80 °C than at 21 °C. This is consistent with the higher water solubility observed for GlyMA at 80 °C but may also indicate that the cosolvency effect of the GMA is greater at this temperature. As anticipated, the critical compositions required for the formation of a homogeneous GlyMA−GMA−water solution indicated by this phase diagram correspond closely to those estimated from the intermediate GlyMA conversions (calculated from the ^{1}H NMR data; see blue triangles) at the characteristic times required for an upturn in the reaction rate (see Table 1). This indicates that a self-consistent set of physicochemical data has been obtained for this GlyMA-to-GMA transformation. The initial GlyMA-in-water emulsions were also characterized by optical microscopy at 21 °C. Relatively unstable and rather polydisperse droplets of approximately 5−200 μm were observed (see Figure S3), with laser diffraction studies suggesting volume-average diameters of 10−20 μm, regardless of the GlyMA concentration (see Figure S4). This suggests that hydrolysis does not primarily occur at the droplet surface during the initial two-phase regime. Otherwise, a faster rate of hydrolysis would be expected at higher GlyMA concentrations which is inconsistent with the kinetic data shown in Figure 2. Instead, it is believed that hydrolysis primarily occurs in the aqueous solution phase at a rate that depends on the relatively low concentration of dissolved GlyMA monomer (2.4 to 2.5% w/w), with the emulsion droplets simply acting as GlyMA reservoirs.

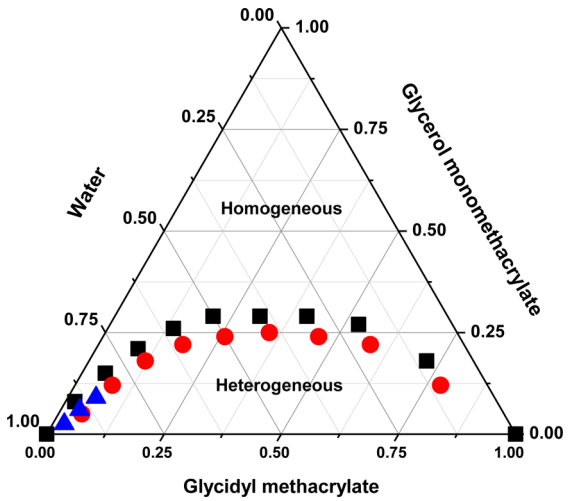


Figure 3. Ternary phase diagram obtained for various mass fractions of glycidyl methacrylate, glycerol monomethacrylate, and water obtained at 21 °C (black squares) and 80 °C (red circles). The blue triangles represent the three critical ternary compositions corresponding to the observed phase change from an initial aqueous emulsion to a homogeneous aqueous solution for glycidyl methacrylate concentrations of 5.0, 10.0, or 15.0% w/w, as judged by ^{1}H NMR spectroscopy (see Figure 2).

In principle, at least three side reactions may occur during the transformation of GlyMA into GMA. First, ester hydrolysis of either GlyMA or GMA to produce methacrylic acid (and the corresponding alcohol) might be expected. Second, polymerization of either monomer could occur, although this is less likely if the reaction is conducted in air because oxygen acts as an effective inhibitor. Third, epoxy groups can be ring-opened with primary or secondary alcohols; thus, GlyMA could react with GMA to produce a dimethacrylate impurity. In practice, the ^{1}H NMR spectrum recorded for an aqueous solution of GMA monomer produced after heating a 10.0% w/w aqueous emulsion of GlyMA for 9 h at 80 °C is remarkably clean, with no evidence for any of these side reactions (see Figure 1). In fact, the main difference between this ^{1}H NMR spectrum and that of commercial GMA synthesized via the acetone protecting group strategy (kindly donated by Cognis) is simply the relative proportions of the major and minor isomers, which are 2,3-dihydroxypropyl methacrylate and 1,3-dihydroxypropyl methacrylate, respectively (see inset chemical structures in Figure 1). The commercial route to GMA produces a 92:8 isomeric ratio, whereas the GlyMA route to GMA utilized in the present work generates an 87:13 isomeric ratio. As a comparison, Shaw et al. obtained a 75:25 isomeric ratio for the synthesis of GMA from GlyMA using an acetic acid catalyst; these workers also suggested a mechanism to account for the formation of the minor isomer.[31] Despite this subtle variation in isomeric composition, the GMA produced by forced hydrolysis of GlyMA in the present study appears to behave identically to the GMA provided by Cognis monomer when used for the *in situ* synthesis of PGMA−PHPMA diblock copolymer nanoparticles (see below).

The 10% w/w aqueous GMA solution obtained after the hydrolysis of GlyMA at 80 °C for 9 h is a convenient starting point for the one-pot synthesis of a PGMA macro-CTA via RAFT chemistry. Thus, the aqueous GMA solution was cooled to 20 °C and deoxygenated using a nitrogen sparge, and the RAFT CTA (PETTC), free radical initiator (ACVA; [PETTC]/[ACVA] molar ratio = 5.0), and $NaHCO_3$ were added prior to conducting the RAFT polymerization of GMA at 70 °C, as shown in Scheme 1. A trithiocarbonate was preferred for this aqueous solution polymerization since such CTAs are known to be less susceptible to hydrolysis than dithiobenzoates.[22] $NaHCO_3$ was utilized to ensure water

dx.doi.org/10.1021/ma301909w | *Macromolecules* 2013, 46, 769−777

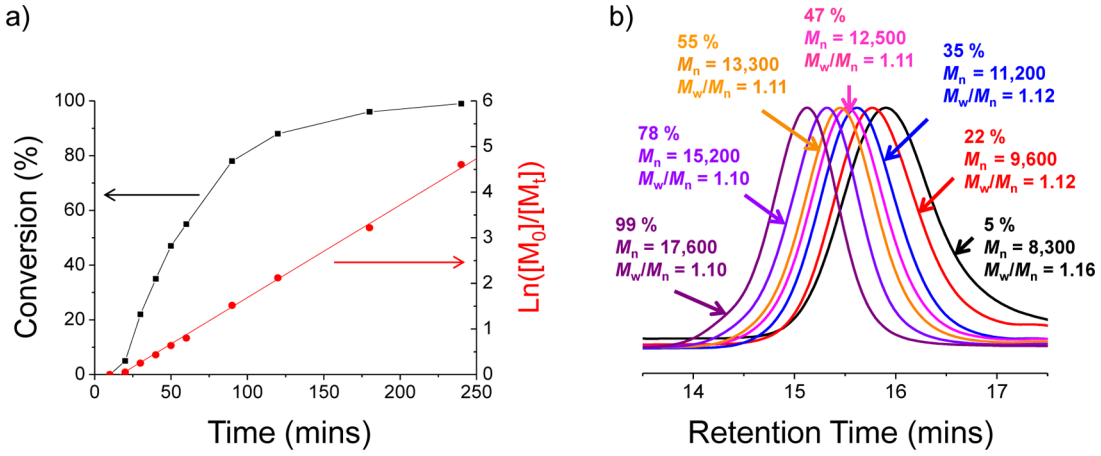


Figure 4. Kinetic data obtained for the synthesis of PGMA macro-CTA. A DP of 45 was targeted and a CTA/initiator molar ratio of 5.0 was utilized at 70 °C in aqueous solution: (a) conversion vs time curve (black squares) and the corresponding semi-logarithmic plot (red circles); (b) DMF GPC curves obtained with corresponding conversions, as judged by ^{1}H NMR spectroscopy.

solubility of the PETTC in its anionic carboxylate form. The mean degree of polymerization (DP) of the PGMA chains was targeted to be 45, since we have recently shown that such DP values enable a range of diblock copolymer morphologies to be accessed when conducting RAFT syntheses under such conditions.[20,24,25] After a brief induction period of around 20 min (a common feature of RAFT polymerizations according to the literature[61−64]), essentially full conversion (>99%) was achieved within 4 h (see Figure 4a). DMF GPC chromatograms were unimodal, and the evolution of molecular weight with conversion was linear (see Figure 4b), which is characteristic of such pseudo-living polymerizations. The near-monodisperse nature of the PGMA chains (M_w/M_n = 1.10 at full conversion) suggests that the dimethacrylate content of the GMA monomer is relatively low, since this impurity would inevitably lead to extensive branching if present at an appreciable concentration.[65,66] However, it is perhaps noteworthy that such branching can be difficult to detect when relatively low DP values are targeted (see Figure S5 in the Supporting Information and accompanying text for RAFT syntheses of PGMA conducted in homogeneous solution when targeting a higher DP of 200). After 4.5 h, a small sample of the PGMA macro-CTA was extracted, freeze-dried from water, and precipitated into excess chloroform for ^{1}H NMR and GPC studies. The mean DP was estimated to be 56, which suggests a CTA efficiency of around 80%. GPC analysis (vs poly(methyl methacrylate) standards) indicated an M_n of 17 600 and an M_w/M_n of 1.10.

Two different protocols were explored for the chain extension of this $PGMA_{56}$ macro-CTA. First, a deoxygenated aqueous solution of HPMA and ACVA was added to the aqueous $PGMA_{56}$ solution while still under a nitrogen atmosphere at 70 °C, thus allowing *in situ* polymerization of HPMA to produce PGMA−PHPMA diblock copolymer nano-objects. Alternatively, the $PGMA_{56}$ aqueous solution was exposed to air, cooled to 20 °C, and stored at 5 °C prior to subsequent use. Such aqueous macro-CTA solutions could be efficiently chain-extended with HPMA under RAFT aqueous dispersion polymerization conditions up to 3 weeks after their original synthesis to produce comparable results to those achieved with the macro-CTA used immediately for *in situ* PGMA−PHPMA diblock copolymer syntheses.

The reaction conditions used for the RAFT aqueous dispersion polymerization of HPMA at 10.0% w/w solids are indicated in Scheme 1. A diblock composition of $PGMA_{56}$−$PHPMA_{373}$ was targeted, since our previous studies indicated that such a formulation leads to the *in situ* evolution of copolymer morphology.[24,25] The polymerizing solution was periodically sampled at various time intervals in order to monitor both the monomer conversion and any change in copolymer morphology. More than 99% conversion was achieved within 1.5 h, as judged by ^{1}H NMR studies.[24] Diblock copolymers with relatively low final polydispersities (M_w/M_n < 1.33) were produced that contained only modest levels of macro-CTA contamination and the theoretical M_n values were comparable to those given by the GPC data (see Figure 5). Moreover, polydispersities increased with conversion, which suggests some degree of branching due to low levels of dimethacrylate impurity, as described elsewhere.[20,24,67]

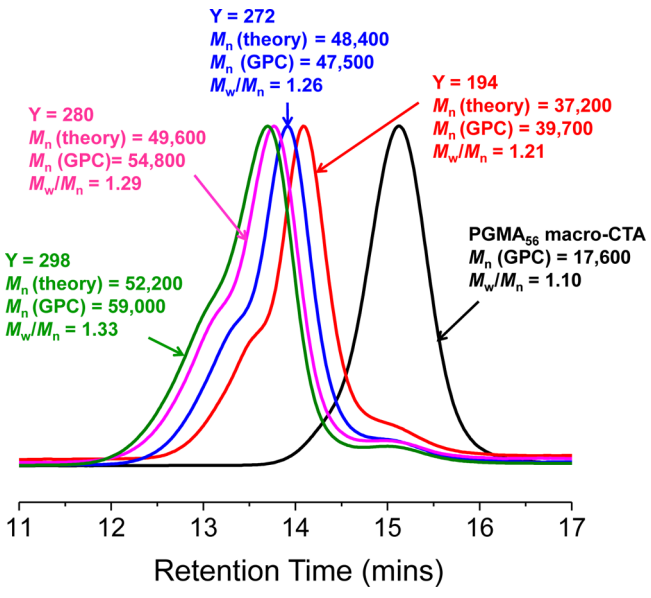


Figure 5. DMF GPC curves obtained for a series of $PGMA_{56}$−$PHPMA_y$ diblock copolymers (where *y* varies from 194 to 298) and the corresponding $PGMA_{56}$ macro-CTA.

dx.doi.org/10.1021/ma301909w | *Macromolecules* 2013, 46, 769−777

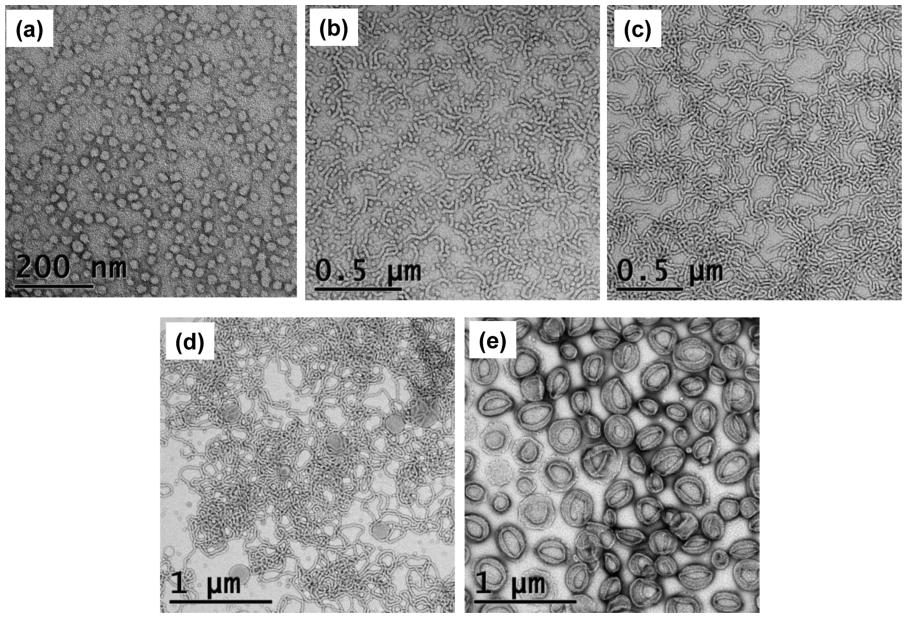


Figure 6. Representative TEM images obtained at various reaction times for the RAFT aqueous dispersion polymerization of HPMA at 70 °C using a $PGMA_{56}$ macro-CTA when targeting a final diblock copolymer composition of $PGMA_{56}$–$PHPMA_{373}$ at 10% w/w solids. (a) $PGMA_{56}$–$PHPMA_{194}$ spheres (at 52% HPMA conversion) (b) $PGMA_{56}$–$PHPMA_{272}$ sphere/worm mixed phase (at 73% HPMA conversion), (c) $PGMA_{56}$–$PHPMA_{280}$ worms (at 75% HPMA conversion), (d) $PGMA_{56}$–$PHPMA_{298}$ worm/vesicle mixed phase (at 80% HPMA conversion), and (e) $PGMA_{56}$–$PHPMA_{336}$ vesicles (at 90% HPMA conversion).

The samples were subsequently analyzed by TEM to assess their copolymer morphology, as shown in Figure 6. The first sample had an HPMA conversion of 53% as judged by ^{1}H NMR. This corresponds to a mean block composition of $PGMA_{56}$–$PHPMA_{194}$ which is a predominantly spherical phase. The second sample ($PGMA_{56}$–$PHPMA_{272}$) exhibited a mixed sphere/short worm phase, while a pure worm phase is observed at 75% conversion ($PGMA_{56}$–$PHPMA_{280}$). A predominantly vesicular phase was obtained at 90% conversion ($PGMA_{56}$–$PHPMA_{336}$), with pure vesicles being observed for all samples taken after this point. In general, the observed evolution in diblock copolymer morphology is consistent with that previously reported by Blanazs et al.[24,25] DLS analysis of the diluted reaction solutions corroborated these TEM studies. Thus, the spheres observed in Figure 6a had an intensity-average diameter of 32 nm and a relatively low polydispersity (0.085). The pure worm phase (Figure 6c) had a *sphere-equivalent* intensity-average diameter of 52 nm and a rather higher polydispersity of 0.133, while the vesicular phase shown in Figure 6e had an intensity-average diameter of 316 nm and a relatively broad size distribution (polydispersity = 0.215). Similar DLS observations have been previously reported by Blanazs and co-workers.[24,26]

Finally, it is perhaps worth emphasizing the complex phase behavior exemplified by this facile one-pot formulation. During the initial *in situ* hydrolysis of GlyMA, its rate of conversion into GMA is significantly enhanced by the switch from a two-phase emulsion to the formation of a single phase, since this increases the GlyMA concentration in the aqueous continuous phase. The GMA monomer is then polymerized in homogeneous aqueous solution to produce a water-soluble macro-CTA. During the subsequent RAFT polymerization of HPMA using this PGMA macro-CTA, the rate of polymerization of the hydrophobic monomer is enhanced by *phase separation*, since nucleation leads to a relatively high local HPMA concentration within the growing PHPMA-core micelles.[24]

■ CONCLUSIONS

A highly convenient atom-efficient one-pot synthesis of well-defined PGMA–PHPMA diblock copolymer nano-objects starting from glycidyl methacrylate (GlyMA) using RAFT aqueous dispersion polymerization is described. This water-immiscible commodity monomer is readily converted into glycerol monomethacrylate simply by heating a 10% w/w aqueous emulsion of GlyMA droplets at 80 °C in air for 9 h in the absence of any catalyst. Remarkably, ^{1}H NMR spectroscopy indicates that this transformation is highly selective, with no background evidence for either ester hydrolysis or polymerization and only a relatively low level of dimethacrylate impurity is produced. The kinetics of GlyMA hydrolysis is complex: a significant rate enhancement is observed when the initial two-phase aqueous emulsion eventually becomes a homogeneous aqueous solution. Since GMA acts as a cosolvent for GlyMA, this transformation occurs at a critical intermediate conversion that depends on both the initial GlyMA concentration and the reaction temperature. This leads to an unusual observation: the rate of hydrolysis is actually faster when conducted in more dilute solution. Construction of a GlyMA–GMA–water ternary phase diagram sheds useful light on this system. Once formed, the GMA is directly polymerized *in situ* via RAFT aqueous solution polymerization to produce a PGMA macro-CTA, which can be subsequently chain-extended with HPMA under aqueous dispersion polymerization conditions to generate a range of diblock copolymer nano-objects with well-defined morphologies (e.g., spheres, worms, or vesicles). This new approach augurs well for potential applications of these nano-objects, since it significantly reduces their overall cost by replacing the relatively expensive GMA monomer with a much cheaper feedstock (GlyMA). It also offers a potentially cost-

dx.doi.org/10.1021/ma301909w | *Macromolecules* 2013, 46, 769–777

effective solution for compliance with new legislation regarding the registration of chemicals in Europe (REACH).

■ ASSOCIATED CONTENT

Supporting Information

Typical intermediate ^{1}H NMR spectra and conversion vs time curves recorded for GlyMA hydrolysis at 80 °C; optical microscopy images and laser diffraction droplet size distributions for initial GlyMA-in-water emulsions; DMF GPC curves obtained for $PGMA_{200}$ homopolymers. This material is available. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail s.p.armes@shef.ac.uk.

Notes

The authors declare the following competing financial interest(s): We have filed a process patent application to protect the IP associated with this work.

■ ACKNOWLEDGMENTS

We thank the Scott Bader company (Wollaston, Northants, UK) for part-funding this EPSRC PhD studentship and also for permission to publish this work. Cognis (now GEO) is acknowledged for its generous supply of GMA and HPMA monomers. We thank Prof. N. C. Billingham of the University of Sussex, UK for useful comments on an early draft of this manuscript.

■ REFERENCES

(1) Iyer, R.; McKenna, P.; Smallridge, M.; Matthews, M.; Natesh, A.; Baker, J. Monomers and Macromers for Forming Hydrogels. WO2010102747, 2010.
(2) Compañ, V.; Tiemblo, P.; García, F.; García, J. M.; Guzmán, J.; Riande, E. *Biomaterials* **2005**, *26*, 3783−3791.
(3) Haigh, R.; Rimmer, S.; Fullwood, N. J. *Biomaterials* **2000**, *21*, 735−739.
(4) Rimmer, S.; Wilshaw, S.-P.; Pickavance, P.; Ingham, E. *Biomaterials* **2009**, *30*, 2468−2478.
(5) Save, M.; Weaver, J. V. M; Armes, S. P.; McKenna, P. *Macromolecules* **2002**, *35*, 1152−1159.
(6) Liu, F.; Liu, G. *Macromolecules* **2001**, *34*, 1302−1307.
(7) Mori, H.; Hirao, A.; Nakahama, S.; Senshu, K. *Macromolecules* **1994**, *27*, 4093−4100.
(8) Pilon, L. N.; Armes, S. P.; Findlay, P.; Rannard, S. P. *Langmuir* **2005**, *21*, 3808−3813.
(9) Fujii, S.; Cai, Y.; Weaver, J. V. M; Armes, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 7304−7305.
(10) Liu, S.; Weaver, J. V. M; Save, M.; Armes, S. P. *Langmuir* **2002**, *18*, 8350−8357.
(11) Yuan, J. J.; Armes, S. P.; Takabayashi, Y.; Prassides, K.; Leite, C. A. P.; Galembeck, F.; Lewis, A. L. *Langmuir* **2006**, *22*, 10989−10993.
(12) Thompson, K. L.; Armes, S. P.; York, D. W.; Burdis, J. A. *Macromolecules* **2010**, *43*, 2169−2177.
(13) Braunecker, W. A.; Matyjaszewski, K. *Prog. Polym. Sci.* **2007**, *32*, 93−146.
(14) Matyjaszewski, K. *Macromolecules* **2012**, *45*, 4015−4039.
(15) Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1995**, *28*, 1721−1723.
(16) Wang, J.-S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614−5615.
(17) Zhang, D.; Thompson, K. L.; Pelton, R.; Armes, S. P. *Langmuir* **2010**, *26*, 17237−17241.
(18) Reed, K. M.; Borovicka, J.; Horozov, T. S.; Paunov, V. N.; Thompson, K. L.; Walsh, A.; Armes, S. P. *Langmuir* **2012**, *28*, 7291−7298.
(19) Thompson, K. L.; Armes, S. P. *Chem. Commun.* **2010**, *46*, 5274−5276.
(20) Li, Y. T.; Armes, S. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 4042−4046.
(21) Moad, G.; Rizzardo, E.; Thang, S. H. *Acc. Chem. Res.* **2008**, *41*, 1133−1142.
(22) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2009**, *62*, 1402−1472.
(23) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559−5562.
(24) Blanazs, A.; Madsen, J.; Battaglia, G.; Ryan, A. J.; Armes, S. P. *J. Am. Chem. Soc.* **2011**, *133*, 16581−16587.
(25) Blanazs, A.; Ryan, A. J.; Armes, S. P. *Macromolecules* **2012**, *45*, 5099−5107.
(26) Blanazs, A.; Verber, R.; Mykhaylyk, O. O.; Ryan, A. J.; Heath, J. Z.; Douglas, C. W. I.; Armes, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 9741−9748.
(27) Verber, R.; Blanazs, A.; Armes, S. P. *Soft Matter* **2012**, *8*, 9915−9922.
(28) Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270−2274.
(29) Greenwood, P.; Lagnemo, H. Aqueous Silica Dispersion. WO/2004/035474, 2004.
(30) Cabrera, I.; Fichtner, T.; Krieger, S.; Ratering, M. Theodorus; Plasters and Renders and Paints, Copolymer Dispersions and Their Use. WO/2008/040464, 2008.
(31) (a) Shaw, S. E.; Russo, T.; Solomon, D. H.; Qiao, G. G. *Polymer* **2006**, *47*, 8247−8252. (b) Olszewski-Ortar, A.; Gros, P.; Fort, Y. *Tetrahedron Lett.* **1997**, *38*, 8699−8702.
(32) Semsarilar, M.; Ladmiral, V.; Blanazs, A.; Armes, S. P. *Langmuir* **2011**, *28*, 914−922.
(33) Mertoglu, M.; Garnier, S.; Laschewsky, A.; Skrabania, K.; Storsberg, J. *Polymer* **2005**, *46*, 7726−7740.
(34) Smith, A. E.; Xu, X.; McCormick, C. L. *Prog. Polym. Sci.* **2010**, *35*, 45−93.
(35) Lowe, A. B.; McCormick, C. L. *Prog. Polym. Sci.* **2007**, *32*, 283−351.
(36) McCormick, C. L.; Sumerlin, B. S.; Lokitz, B. S.; Stempka, J. E. *Soft Matter* **2008**, *4*, 1760−1773.
(37) Barner-Kowollik, C.; Perrier, S. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 5715−5723.
(38) Boyer, C.; Bulmus, V.; Davis, T. P.; Ladmiral, V.; Liu, J.; Perrier, S. b. *Chem. Rev.* **2009**, *109*, 5402−5436.
(39) LoPresti, C.; Lomas, H.; Massignani, M.; Smart, T.; Battaglia, G. *J. Mater. Chem.* **2009**, *19*, 3576−3590.
(40) Williams, R. J.; O'Reilly, R. K.; Dove, A. P. *Polym. Chem.* **2012**, *3*, 2156−2164.
(41) Ma, J.; Cheng, C.; Wooley, K. L. *Macromolecules* **2009**, *42*, 1565−1573.
(42) Charleux, B.; Delaittre, G.; Rieger, J.; D'Agosto, F. *Macromolecules* **2012**, *45*, 6753−6765.
(43) Boyer, C.; Stenzel, M. H.; Davis, T. P. *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 551−595.
(44) Cai, W.; Wan, W.; Hong, C.; Huang, C.; Pan, C.-Y. *Soft Matter* **2010**, *6*, 5554−5561.
(45) Jones, E. R.; Semsarilar, M.; Blanazs, A.; Armes, S. P. *Macromolecules* **2012**, *45*, 5091−5098.
(46) Semsarilar, M.; Jones, E. R.; Blanazs, A.; Armes, S. P. *Adv. Mater.* **2012**, *24*, 3378−3382.
(47) Zhang, X.; Boissé, S.; Bui, C.; Albouy, P.-A.; Brulet, A.; Li, M.-H.; Rieger, J.; Charleux, B. *Soft Matter* **2012**, *8*, 1130−1141.
(48) Sugihara, S.; Blanazs, A.; Armes, S. P.; Ryan, A. J.; Lewis, A. L. *J. Am. Chem. Soc.* **2011**, *133*, 15707−15713.
(49) Sugihara, S.; Armes, S. P.; Blanazs, A.; Lewis, A. L. *Soft Matter* **2011**, *7*, 10787−10793.

(50) An, Z.; Shi, Q.; Tang, W.; Tsung, C.-K.; Hawker, C. J.; Stucky, G. D. *J. Am. Chem. Soc.* **2007**, *129*, 14493−14499.
(51) Huang, C.-Q.; Pan, C.-Y. *Polymer* **2010**, *51*, 5115−5121.
(52) Wan, W.-M.; Pan, C.-Y. *Polym. Chem.* **2010**, *1*, 1475−1484.
(53) Zhang, X.; Rieger, J.; Charleux, B. *Polym. Chem.* **2012**, *3*, 1502−1509.
(54) Liu, G.; Qiu, Q.; Shen, W.; An, Z. *Macromolecules* **2011**, *44*, 5237−5245.
(55) Liu, G.; Qiu, Q.; An, Z. *Polym. Chem.* **2012**, *3*, 504−513.
(56) Shen, W.; Chang, Y.; Liu, G.; Wang, H.; Cao, A.; An, Z. *Macromolecules* **2011**, *44*, 2524−2530.
(57) Zhao, C.; Li, L.; Zheng, J. *Langmuir* **2010**, *26*, 17375−17382.
(58) Madsen, J.; Armes, S. P.; Bertal, K.; Lomas, H.; MacNeil, S.; Lewis, A. L. *Biomacromolecules* **2008**, *9*, 2265−2275.
(59) Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725−2750.
(60) Greenwood, P. *Pigm. Resin Technol.* **2011**, *40*, 275−284.
(61) Barner-Kowollik, C.; Quinn, J. F.; Morsley, D. R.; Davis, T. P. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 1353−1365.
(62) McLeary, J. B.; Tonge, M. P.; Klumperman, B. *Macromol. Rapid Commun.* **2006**, *27*, 1233−1240.
(63) Monteiro, M. J.; de Brouwer, H. *Macromolecules* **2001**, *34*, 349−352.
(64) Zhang, X.; Giani, O.; Monge, S.; Robin, J.-J. *Polymer* **2010**, *51*, 2947−2953.
(65) Rosselgong, J.; Armes, S. P.; Barton, W.; Price, D. *Macromolecules* **2009**, *42*, 5919−5924.
(66) Rosselgong, J.; Armes, S. P.; Barton, W. R. S.; Price, D. *Macromolecules* **2010**, *43*, 2145−2156.
(67) Ali, A. M. I.; Pareek, P.; Sewell, L.; Schmid, A.; Fujii, S.; Armes, S. P.; Shirley, I. M. *Soft Matter* **2007**, *3*, 1003−1013.