Macromolecules

ARTICLE

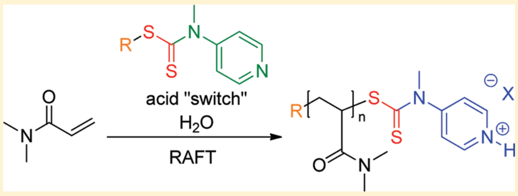
pubs.acs.org/Macromolecules

Switchable Reversible Addition−Fragmentation Chain Transfer (RAFT) Polymerization in Aqueous Solution, *N*,*N*-Dimethylacrylamide

Daniel J. Keddie,* Carlos Guerrero-Sanchez, Graeme Moad,* Ezio Rizzardo, and San H. Thang

CSIRO Materials Science and Engineering, Bag 10, Clayton South, VIC 3169, Australia

S *Supporting Information*



ABSTRACT: Reversible addition−fragmentation chain transfer (RAFT) polymerization of a "more activated monomer" (MAM), *N*,*N*-dimethylacrylamide (DMAm), has been successfully achieved in aqueous solution using an acid/base switchable pyridyl-substituted dithiocarbamate RAFT agent. The effect of strength (pK_a) and stoichiometry of the acid used to switch the RAFT agent on the molecular weight and dispersity of poly(*N*,*N*-dimethylacrylamide) (PDMAm) were examined, making use of high-throughput protocol. Best control was achieved with a stoichiometric amount of the strongest acid investigated, *p*-toluenesulfonic acid monohydrate. Use of weaker acids (higher pK_a) or less than stoichiometric amounts of acid with respect to RAFT agent resulted in broader molecular weight distributions. These results can be rationalized in terms of the extent of protonation of the pyridine nitrogen of the RAFT agent (pK_a ~ 3.13). The preparation of unimodal low dispersity block copolymers of PDMAm with the "less-activated" monomers (LAMs) *N*-vinylcarbazole (NVC), vinyl acetate (VAc), and *N*-vinylpyrrolidone (NVP) demonstrated the fidelity of the RAFT end group in these experiments and provides a further example of the utility of switchable RAFT polymerization.

INTRODUCTION

Reversible addition−fragmentation chain transfer (RAFT) polymerization,[1−4] mediated by thiocarbonylthio chain transfer agents (or RAFT agents, **1**) (Scheme 1), possesses several advantages over other forms of reversible deactivation radical polymerization (RDRP),[5] such as atom transfer radical polymerization (ATRP)[6] and nitroxide mediated polymerization (NMP).[7,8] These include the ability to control the polymerization of a broad range of functional monomers (including vinyl esters and amides) and the absence of potentially toxic transition metal catalysts. RAFT polymerizations are simple to implement, because experimental conditions can mirror those of conventional radical polymerization; differing only by the addition of a RAFT agent.[2−4]

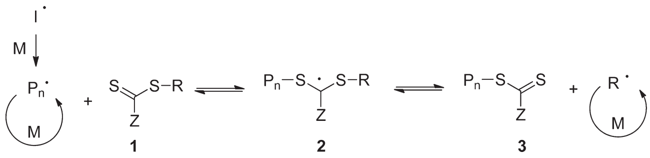
To achieve optimal control over a RAFT polymerization, addition of the monomer derived propagating radical ($P_n^\bullet$) to the thiocarbonyl of a RAFT agent **1** and subsequent fragmentation of the RAFT intermediate **2** must occur efficiently. To facilitate this, the selection of a RAFT agent suitable for the monomer system is critical. Because propagating radicals of "more-activated" monomers (MAMs) (e.g., methacrylic, acrylic and styrenic monomers) are somewhat stabilized by conjugation, they are less reactive than propagating radicals derived from the "less-activated" monomers (LAMs) (e.g., vinyl esters and vinylamides). As such, these two classes of monomer require RAFT agents that are tailored to their differing reactivity. For effective control over polymerization of MAMs, dithioesters (Z = alkyl or aryl) or trithiocarbonates (Z = SR) are generally used. When these RAFT agents are used in the polymerization of LAMs, inhibition/retardation is observed, as fragmentation of the more reactive LAMs derived propagating radical is slow with respect to propagation.[9] The presence of O or N as the "Z" group adjacent to the thiocarbonyl, as is the case with xanthates (Z = OR) or dithiocarbamates (Z = NR_2), both slows addition of radicals to the RAFT agent and promotes the subsequent fragmentation such that it is not the rate determining step in chain transfer. Hence, these RAFT agents are regularly used for control over LAMs polymerization. Generally, xanthates and dithiocarbamates are relatively unreactive toward MAM derived propagating radicals,[10] making them ineffective control agents for these monomers. However, they may be effective for MAMs when the substituent is part of an aromatic heterocycle[10] or when highly electron withdrawing groups are present on the heteroatom.[11] As the reactivity of commonly used RAFT agents are tailored to either MAMs or LAMs, preparation of low dispersity polyMAM-*block*-polyLAM is not possible using the conventional RAFT process. While some RAFT agents, such as the *N*,*N*-diaryldithiocarbamates, have been reported by Destarac et al.[12] and Malepu et al.[13] for the homopolymerization of both MAMs and LAMs, these RAFT agents give only moderate control with both monomer classes.[12,13] When they were used for the preparation of poly(methyl acrylate)-*block*-poly(vinyl acetate), Malepu et al.[13] achieved a polymer of relatively high dispersity (M_w/M_n = 1.37).

Recently, we reported new acid/base "switchable" dithiocarbamate[14−16] and trithiocarbonate[17] RAFT agents. The dithiocarbamates offer good control over polymerization of both MAMs and LAMs and provide a route to polyMAM-*block*-polyLAM copolymers of low dispersity. To prepare well controlled copolymers, with unimodal molecular weight distributions, the polyMAM propagating radical must add effectively to the LAM. In organic solution, optimum control of MAMs was achieved in the presence

Received: April 1, 2011
Revised: July 28, 2011
Published: August 15, 2011

dx.doi.org/10.1021/ma200760q | *Macromolecules* 2011, 44, 6738–6745

Scheme 1. Simplified Mechanism of RAFT Polymerization



of 1 equiv of a strong acid (with respect to the RAFT agent), such as trifluoromethanesulfonic acid or *p*-toluenesulfonic acid monohydrate (TsOH).[14] Weaker acids were less effective presumably due to the weak basicity of the pyridyl functionality (pK_a of pyridinium = 5.23).[18] This requirement has implications for the use of these RAFT agents in aqueous polymerization because dissociation of the strong acid with quantitative formation of hydronium ion (H_3O^+) in aqueous solution will decrease the effective acid strength. Furthermore, competitive acid–base equilibria due to the comparatively high concentration of water has the potential to reduce the efficiency of "switching" via protonation, when compared with that observed in organic solution and reduce the level of control achievable.

There has been recent focus on RAFT polymerization performed in aqueous media, partially due to potential economic benefits.[19] The use of water as the reaction solvent also facilitates control in the polymerization of monomers containing highly polar functionalities, which include cationic, anionic, zwitterionic and neutral polar groups,[19] which have low solubility in organic media. To this end, we investigated the applicability of the switchable RAFT protocol being performed in aqueous media.

In this investigation we illustrate the importance of the strength (pK_a) and stoichiometry of the switching acid for aqueous polymerization in the presence of switchable *N*-alkyl-*N*-pyridyldithiocarbamate RAFT agents, utilizing the MAM, DMAm, as the example case. Subsequent neutralization of the PDMAm macro-RAFT agent and block copolymer formation with the LAMs, NVC, VAc, and NVP is also presented.

EXPERIMENTAL SECTION

Materials. All solvents were of analytical reagent (AR) grade unless otherwise stated. Tetraethyleneglycol, 4-(methylamino)pyridine, bromoacetonitrile, 2-bromopropionyl bromide, *n*-butyllithium (*n*-BuLi, 1.6 M in hexanes), TsOH, trifluoroacetic acid (CF_3CO_2H), chloroacetic acid ($ClCH_2CO_2H$), acetic acid (AcOH), DMAm, VAc, NVP, and NVC were purchased from Sigma-Aldrich and used as received unless otherwise stated. 2,2′-Azobis[2-methyl-*N*-(2-hydroxyethyl)propionamide] (VA 086) was purchased from Wako chemicals and used as received. DMAm and VAc were filtered through neutral alumina (70–230 mesh) and fractionally distilled under reduced pressure immediately before use. NVP was filtered through neutral alumina and purified by fractional thawing of frozen sample (zone refining)[20] immediately before use. Milli-Q water (18.2 MΩ cm) was used for all aqueous polymerization reactions. Cyanomethyl methyl(pyridin-4-yl)carbamodithioate (**4**) and methyl 2-((methyl(pyridin-4-yl)carbamothioyl)thio)propanoate (**5**) were prepared by the reported literature procedures.[14] Analytical thin layer chromatography (TLC) was performed on Merck Silica Gel F_{254} TLC plates. Preparative column chromatography was performed using Merck Silica Gel 60 (mesh 230–400).

Characterization. Nuclear magnetic resonance (NMR) spectra were obtained with a Bruker Avance 200 or 400 MHz spectrometer (^{1}H 200 or 400 MHz, ^{13}C 50 MHz). High resolution electron impact (HR-EI) mass spectra recorded using a ThermoQuest MAT95XP operating at 70 eV using perfluorokerosene (PFK) as a reference. High resolution electrospray ionization (HR-ESI) mass spectra were recorded using a Waters Q-TOF-II using 35 eV cone voltage, employing lock spray and sodium iodide as a reference sample. High resolution gel permeation chromatography (GPC) was performed on a system comprising a Waters 590 HPLC pump and a Waters 410 refractive index detector equipped with 3 × Waters Styragel columns (HT2, HT3, HT4, each 300 mm ×7.8 mm providing an effective molecular weight range of 100–600 000). The eluent was *N,N*-dimethylformamide (DMF) (containing 0.45% w/v lithium bromide (LiBr)) at 80 °C (flow rate: 1 mL min^{-1}). Number-average (M_n) and weight-average (M_w) molecular weights were evaluated using Waters Millennium software. High-throughput GPC measurements were performed on a Shimadzu system equipped with a CMB-20A controller system, a SIL-20A HT autosampler, a LC-20AT tandem pump system, a DGU-20A degasser unit, a CTO-20AC column oven, a RDI-10A refractive index detector, and a PL Rapide (Varian) column at 70 °C. *N,N*-Dimethylacetamide (DMAc) (with 2.1 g L^{-1} of lithium chloride (LiCl)) was used as eluent at a flow rate of 1 mL min^{-1}. The GPC columns were calibrated with low dispersity polystyrene standards (Polymer Laboratories) ranging from 3100 to 650 000 g mol^{-1}, and molecular weights are reported as polystyrene equivalents. A third-order polynomial was used to fit the log M_p vs time calibration curve, which was linear across the molecular weight ranges.

RAFT Agent Synthesis. *Synthesis of 2-(2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)ethyl 2-Bromopropanoate.* A solution of tetraethylene glycol (188 g, 968 mmol, 10.1 equiv) and pyridine (7.90 g, 8.1 mL, 100 mmol, 1.05 equiv) in dry tetrahydrofuran (THF) (100 mL) had a solution of 2-bromopropionyl bromide (20.6 g, 10 mL, 95.5 mmol) in dry THF (50 mL) added dropwise over 1 h after which the reaction mixture was allowed to warm to room temperature (RT) and stirred for a further 16 h. Aqueous hydrochloric acid (HCl) (1 M, 500 mL) was added and the resulting mixture extracted with dichloromethane (DCM, 6 × 100 mL). The combined organics were washed with water (2 × 100 mL) and dried (anhydrous sodium sulfate (Na_2SO_4)), and solvent was removed under reduced pressure to give 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl 2-bromopropanoate as a colorless liquid (23.34 g, 70.9 mmol, 74%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.73 (d, J = 6.9 Hz, 3H, CH_3), 3.19 (br s, 1H, OH), 3.46–3.70 (m, 14H, OCH_2CH_2O), 4.23 (m, 2H, CO_2CH_2), 4.32 (q, J = 6.9 Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5 (CH_3), 39.9 (CH), 61.5 (CH_2OH), 64.9 (CO_2CH_2), 68.6 (OCH_2), 70.2 (OCH_2), 70.4 (OCH_2), 70.5 (OCH_2), 72.4 (OCH_2), 170.1 (C=O). MS (HR-ESI) 351.0417 m/z [M + Na]$^+$ ($C_{11}H_{21}BrO_6Na$ requires 351.0419).

*Synthesis of 2-(2-(2-(2-Hydroxyethoxy)ethoxy)ethoxy)ethyl 2-((Methyl(pyridin-4-yl)carbamothioyl)thio)propanoate (**6**).* To a solution of 4-(methylamino)pyridine (1.08 g, 10 mmol) in dry THF (60 mL) under nitrogen was added *n*-BuLi (6.25 mL, 1.6 M, 10 mmol, 1 equiv) in hexanes dropwise, and the reaction mixture was left to stir at RT for 1 h. Subsequently, carbon disulfide (CS_2) (0.9 mL, 1.14 g, 15 mmol, 1.5 equiv) was added dropwise, and the reaction mixture was stirred at RT for 2 h under nitrogen. Afterward, 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl 2-bromopropanoate (3.62 g, 11 mmol, 1.1 equiv) was added and the resultant solution was stirred at RT for a further 4 h. Saturated sodium bicarbonate solution ($NaHCO_3$) was added, and the solution extracted with DCM (2 × 100 mL) washed with saturated $NaHCO_3$ (2 × 100 mL) and brine (1 × 100 mL). The combined organics were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure to give an orange liquid. Purification by column chromatography (SiO_2, eluent: 95% chloroform ($CHCl_3$)/5% methanol (MeOH)) gave 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl 2-((methyl(pyridin-4-yl)carbamothioyl)thio)propanoate **6** as a viscous yellow liquid (3.93 g, 91%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53 (d, J = 7.5 Hz 3H, CH_3), 2.68 (br t, 1H, OH), 3.56–3.79 (m, 14H, OCH_2CH_2O), 3.71 (s, 1H, NCH_3), 4.28 (m, 2H, CO_2CH_2), 4.64 (q, J = 7.5 Hz, 1H, CH), 7.26 (m, 2H, pyridyl ArH), 8.75 (m, 2H, pyridyl ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.8 ($CHCH_3$), 45.2 (NCH_3) 49.8 ($CHCH_3$), 61.7 (CH_2OH), 64.9 (CO_2CH_2), 68.9 (OCH_2), 70.3 (OCH_2), 70.5 (OCH_2), 70.6 (OCH_2), 70.6 (OCH_2), 72.6 (OCH_2), 121.8 (pyC-3), 151.6 (pyC-2), 151.9 (pyC-4), 171.8

(C═O), 196.9 (C═S); MS (HR-ESI) 455.1293 m/z $[M + Na]^+$ ($C_{18}H_{28}N_2O_6S_2Na$ requires 455.1287).

Polymerization of *N*,*N*-Dimethylacrylamide. *Ampule Experiments.* The polymerization of DMAm was performed by preparing stock solutions of known concentration, which were placed in ampules, degassed via three freeze−evacuate−thaw cycles, flame-sealed, and heated for the designated time period. An example is shown below.

*Preparation of Low Dispersity Poly(N,N-dimethylacrylamide) Using Cyanomethyl Methyl(pyridin-4-yl)carbamodithioate (**4**) at 80 °C.* Stock solution I of VA 086 (27 mg) in a volume of 5 mL of water was prepared in a volumetric flask. A mixture of cyanomethyl methyl(pyridin-4-yl)carbamodithioate (**4**) (40.8 mg), TsOH (35.4 mg), DMAm (1.81 g), stock solution I (1 mL), and water to a volume of 10 mL was prepared in a volumetric flask. Aliquots (5 mL) of this stock solution were transferred to ampules that were degassed by three repeated freeze−evacuate−thaw cycles and sealed. The ampules were heated at 80 °C for specified times (see Supporting Information for details of additional polymerizations).

High-Throughput Experiments. High-throughput RAFT polymerization experiments were performed using a Chemspeed Swing-SLT automated synthesizer following procedures similar to those described elsewhere.[21,22] The synthesizer was equipped with a glass reactor block consisting of 16 reaction vessels (13 mL) with thermal jackets connected in series through the reaction block and connected to a heating/cooling system (Hüber, −90 to +140 °C). In addition, all reaction vessels were equipped with coldfinger reflux condensers (∼7 °C). Mixing was achieved by vortex agitation (up to 1400 rpm). Liquid transfers were handled by a 4-needle head (4-NH) capable of four simultaneous sample transfers. The 4-NH was connected to a reservoir bottle (degassed water) for needle rinsing after each liquid transfer step. This solvent reservoir was degassed by continuously sparging with nitrogen and was also utilized to prime the tubing lines of the 4-NH. When experiments were carried out, the synthesizer was maintained under an inert atmosphere by supplying a constant flow of nitrogen into the hood of the synthesizer. A nitrogen atmosphere was also applied to reactors and stock solutions at all times. Prior to the polymerizations, an "inertization process" was undertaken in which the reaction vessels were heated to 135 °C and subjected to 10 cycles of vacuum (2 min) and filling with nitrogen (2 min) to ensure the elimination of oxygen.

Stock solutions were prepared, degassed by sparging with nitrogen for 15 min, and placed inside the automated synthesizer. Stock solutions of RAFT agent **6**, acid (TsOH, CF_3CO_2H, $ClCH_2CO_2H$, and AcOH) and VA 086 in water were prepared. Aliquots of stock solutions and water from the reservoir were transferred into the reactors with the automated liquid handling system to provide the desired concentrations of reagents (see Supporting Information for more details). After the liquid transfers were completed, pH measurements were performed using a pH needle in the 4-NH of the automated synthesizer. The pH needle was calibrated with standard buffer solutions (pH = 2, 4, 7, 9, 10). The reaction solutions were degassed through three freeze−evacuate−thaw cycles carried out as follows: The reaction mixtures were cooled to −35 °C while vortex was applied to the reaction block (200 rpm, 2 min). Vacuum (∼10 mbar) was then applied to the reactor block while the reactors were heated to −10 °C with vortex (600 rpm, 2 min). The reactors were then filled with nitrogen. The effectiveness and reproducibility of this degassing procedure, conducted within this type of automated parallel synthesizer, is reported elsewhere.[23] After the degassing procedure, the reactors were sealed under a nitrogen atmosphere and heated to desired reaction temperature (80 °C) while vortex was applied to the reaction block (150 rpm); the temperature of the reflux condensers on top of the reactors was set to 7 °C. Time zero (t_0) for kinetic data was taken to be the moment the reactors reached 80 °C. At pre-established times, monomer conversions and molecular weights of the formed polymers were followed by sampling 75 μL from the reaction mixtures with the automated liquid handling system into NMR tubes and GPC vials. GPC and NMR samples for analysis were prepared with the automated liquid handling system of the synthesizer at the end of the experiment by adding the corresponding GPC and NMR solvents. All GPC samples from the automated synthesizer were measured using a high-throughput GPC instrument (DMAc) to obtain kinetic trends in data. GPC for the highest conversion sample of each reaction mixture was also performed using by high-resolution GPC (DMF).

Block Copolymers. The synthesis of block copolymers of DMAm and LAMs were performed by preparing stock solutions of known concentration, which were placed in ampules, degassed via three freeze−pump−thaw cycles, flame-sealed and heated for the designated time period. An example is shown below (see Supporting Information for the experimental conditions for the preparation of the PDMAm macro-RAFT agent B and additional block copolymers).

*Preparation of Poly(N,N-dimethylacrylamide) Macro-RAFT Agent A Using Cyanomethyl Methyl(pyridin-4-yl)carbamodithioate (**4**) at 80 °C.* A mixture of cyanomethyl methyl(pyridin-4-yl)carbamodithioate (**4**) (102 mg), TsOH (88.5 mg), DMAm (4.53 g), VA 086 (13.5 mg), and water to a volume of 25 mL was prepared in a volumetric flask. Aliquots of this stock solution were transferred to 2 ampules that were degassed by three repeated freeze−evacuate−thaw cycles and flame-sealed. The ampules were heated at 80 °C for 30 min, cooled, isolated, and combined. The resultant solution was neutralized with excess sodium bicarbonate (pH ∼7−8) and the water removed by lyophilization. The isolated residue was dissolved in a minimal amount of DCM and filtered to remove inorganic salts. Precipitation three times into diethyl ether gave the purified PDMAm macro-RAFT agent A (2.27 g, $M_{n,NMR}$ = 7060, $M_{n,GPC}$ = 10 000, M_w/M_n = 1.17).

Preparation of Low Dispersity Poly(N,N-dimethylacrylamide)-block-poly(N-vinylcarbazole) at 60 °C. A stock solution I of 2,2′-azobis(2-methylpropionitrile) (AIBN, 66.5 mg) in a volume of 5 mL of 1,4-dioxane was prepared in a volumetric flask. A mixture of PDMAm macro-RAFT agent A (615 mg, $M_{n,NMR}$ = 7060, $M_{n,GPC}$ = 10 000, M_w/M_n = 1.17), NVC (1.67 g), stock solution I (0.5 mL), and 1,4-dioxane to a volume of 5 mL was prepared in a volumetric flask. Aliquots of this stock solution were transferred to ampules that were degassed by three repeated freeze−evacuate−thaw cycles and sealed. The ampules were heated at 60 °C for specified times (see Supporting Information for details of additional polymerizations).

Measurement of the Acid Dissociation Constant (pK_a) of RAFT Agent 6-H$^+$. Measurements of pH for the ^{1}H NMR titration of RAFT agent **6** with TsOH were directly obtained from NMR tubes containing RAFT agent **6** at different levels of protonation, as previously prepared from stock solutions using the liquid handling system of the automated synthesizer. The pH needle of the synthesizer was calibrated with standard buffer solutions (pH = 2, 4, 7, 9, 10) prior to the measurements. ^{1}H NMR was taken of each solution and the chemical shift of the hydrogen atoms adjacent to the pyridine nitrogen of **6** were plotted against pH with the point of inflection giving the pK_a (see Supporting Information for pH and chemical shift data).

Estimation of the Equilibrium Concentration of 6-H$^+$. The equilibrium concentration of the RAFT agent **6-H$^+$** present in the high-throughput polymerization reaction mixtures was estimated with CurTiPot pH and Acid−Base Titration, version 3.5.4 for Excel,[24] using the initial concentrations of the reagents and literature pK_a values of TsOH (∼−1.5),[25] CF_3CO_2H (0.52),[18] $ClCH_2CO_2H$ (2.87),[18] AcOH (4.76),[18] an approximation of the pK_a of DMAm-H$^+$ (∼−0.5),[26] and the calculated pK_a of **6-H$^+$** (see Supporting Information for details).

■ RESULTS AND DISCUSSION

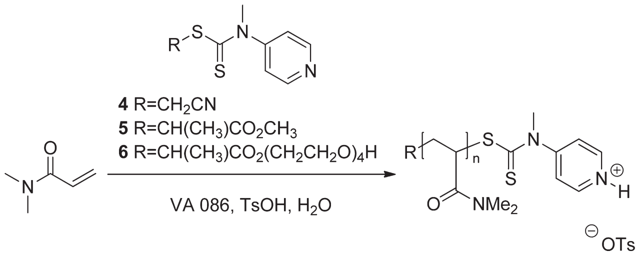
Aqueous Polymerization of *N*,*N*-Dimethylacrylamide. Aqueous RAFT polymerization of DMAm has been previously reported for the synthesis of homopolymers[27] and block copolymers.[28] Polymerization of acrylamido monomers, such as DMAm, are often undertaken using acidic pH in an attempt to reduce hydrolysis of the acrylamido monomer[29] and in turn limit RAFT agent aminolysis. This has been done via the use of buffered solutions[30] or alternatively by employing RAFT agents[28] and/or initiators[27,28] that contain acidic functionality.

For the polymerization of DMAm using switchable RAFT the reaction conditions were adapted from those reported previously by the McCormick group.[27] The nonacidic VA 086 was used as the radical initiator so as not to affect the state of the switchable RAFT agent in solution. Initially, we employed the cyanomethyl RAFT agent **4**[14] with a polymerization temperature of 80 °C in water and a target molecular weight of 10 000 (Scheme 2). In the presence of TsOH ([TsOH]/[RAFT] = 1) polymers of low dispersity were obtained (entry 1, Table 1).

Polymerizations performed at 70 °C targeting different molecular weights gave broader dispersity as the targeted molecular weight increased. This is conceivably due to a decrease in equilibrium concentration of the protonated RAFT agent, when the RAFT agent and acid concentrations in the polymerization solution are reduced (entries 2 and 3, Table 1). Similar results were obtained with the secondary ester RAFT agent **5**[14] at either 70 or 80 °C (entries 4 and 5, Table 1). These RAFT agents (**4** and **5**) are not soluble in water in the absence of acid preventing a control reaction with the neutral nonprotonated RAFT agent.

To allow for aqueous polymerization of DMAm in absence of acid and to illustrate any differences between the neutral and the acidified (switched) forms, a new RAFT agent (**6**) containing a water-solubilizing "R" group based on tetraethylene glycol (TEG) was prepared. The TEG was converted to 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl 2-bromopropanoate (74% yield) by reaction with the corresponding bromoacyl bromide. This was subsequently converted to the desired RAFT agent **6** (91% yield) by reaction with the methyl(pyridin-4-yl)carbamodithioate salt, derived from 4-(methylamino)pyridine and CS_2, via the routine methodology.[4,14] As expected, the dispersity and the control of molecular weight for PDMAm synthesis, using the water-soluble RAFT agent **6**, were significantly improved in the presence of 1 equiv of acid when compared to experiments conducted in the absence of acid (Table 1, entries 6−9). These results illustrate the effect of acidification upon switchable pyridyl-substituted dithiocarbamate RAFT agents in relation to their ability to control of the polymerization of DMAm. Analogous results for the polymerization of *n*-butyl acrylate, another MAM, with and without acid were previously observed in organic solution.[14]

Scheme 2. RAFT Polymerization of Dimethylacrylamide in Water



High Throughput Polymerization. High-throughput experimentation and automated parallel synthetic techniques have been demonstrated to be valuable tools for rapid kinetic measurements in polymerization reactions (even in oxygen and moisture sensitive reactions, such as anionic polymerization), for the rapid preparation of well-defined polymeric materials, and for experiments where a large parameter space must be explored.[31−34] Use of these experimental techniques has obvious advantages over the "classical" lab-scale synthesis. These include a reduction in time and resources, acceleration of research and enhanced accuracy and reproducibility, as parallel experiments are performed concurrently under the same conditions. For these reasons we made use of automated parallel polymerization techniques to systematically study the effect of different acids and stoichiometries upon the switchable RAFT polymerization of DMAm.

After the initial success using TsOH as the acid switch, we undertook experiments with varying acid concentration and acid strength, as the degree of protonation of the RAFT agent has a marked effect on the level of control achieved during polymerization. It was postulated that, if proton transfer occurred at a much higher rate than that of addition−fragmentation, then less than 1 equiv of acid with respect to RAFT agent concentration may give similar control to that observed when the ratio is 1:1. This was not the case for these systems. The use of less than 1 equiv of acid ([TsOH]/[RAFT] = 0.5 or 0.2) gave broader molecular weight distributions than that of 1 equiv. The equilibrium between the protonated and neutral forms of the RAFT agent effectively results in a RAFT agent with activity somewhere between active and nonactive forms in the presence of less than 1 equiv of acid. This results in broader molecular weight distributions, as shown in the example below using TsOH (Figure 1). While the dispersities of the polymers prepared with less than 1 equiv of acid to RAFT agent are broader than those prepared with equimolar acid, there appears to be a preference for the propagating radical to attack the switched fraction of the RAFT agent in solution in these reactions, as evidenced by the molecular weight distributions being significantly narrowed (0.5 equiv, M_w/M_n = 1.21; 0.2 equiv,

Table 1. Details of Polymer Syntheses Using Standard Experimental Methods[a]

entry	RAFT agent	[RAFT] (10^{-2} M)	[TsOH] (10^{-2} M)	[I] (10^{-4} M)	T (°C)	M_n[b]	M_n (theory)[c]	M_w/M_n[b]	time (h)	conv (%)
1	**4-H**$^+$	1.83	1.83	18.3	80	11500	9500	1.11	1	95
2	**4-H**$^+$	1.83	1.83	18.3	70	13000	9600	1.09	3	96
3	**4-H**$^+$	0.915	0.915	18.3	70	22500	19000	1.13	3	95
4	**5-H**$^+$	0.915	0.915	18.3	80	25700	19800	1.15	4	>99
5	**5-H**$^+$	0.457	0.457	9.15	70	36100	38400	1.30	3	96
6	**6-H**$^+$	0.915	0.915	18.3	70	21000	17000	1.21	1	85
7	**6**	0.915	0	18.3	70	27800	17800	1.48	1	89
8	**6-H**$^+$	0.915	0.915	0.29	80	22700	17800	1.20	6	89
9	**6**	0.915	0	0.29	80	20800	14000	1.64	6	70

[a] [M] = 1.83 M. [b] GPC DMF eluent, PS equivalents. [c] M_n (theory) = $[([M]_0/[RAFT]_0) \times MW_{monomer}] \times$ % conversion.

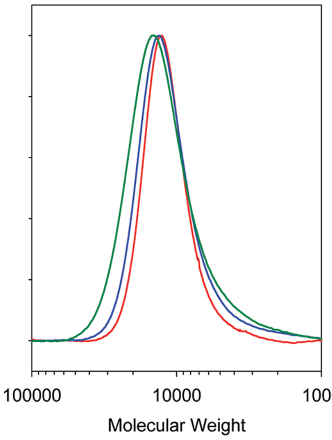


Figure 1. GPC chromatograms of PDMAm **6-H**$^+$ ([TsOH]/[**6**] = 1; M_n = 11 500, M_w/M_n = 1.10) (red curve), PDMAm **6**−**0.5H**$^+$ ([TsOH]/[**6**] = 0.5; M_n = 10 600, M_w/M_n = 1.21) (blue curve), and PDMAm **6**−**0.2H**$^+$ ([TsOH]/[**6**] = 0.2; M_n = 10 900, M_w/M_n = 1.29) (green curve).

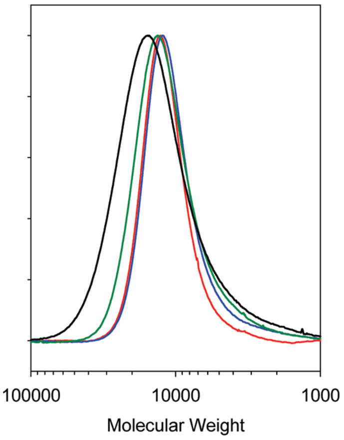


Figure 2. GPC chromatograms of PDMAm **6-H**$^+$ ([TsOH]/[**6**] = 1; M_n = 11 500, M_w/M_n = 1.10) (red curve), PDMAm **6-H**$^+$ ([CF_3CO_2H]/[**6**] = 1; M_n = 10 000, M_w/M_n = 1.18) (blue curve), PDMAm **6-H**$^+$ ([$ClCH_2CO_2H$]/[**6**] = 1; M_n = 10 300, M_w/M_n = 1.26) (green curve), and PDMAm **6-H**$^+$ ([AcOH]/[**6**] = 1; M_n = 11 100, M_w/M_n = 1.38) (black curve).

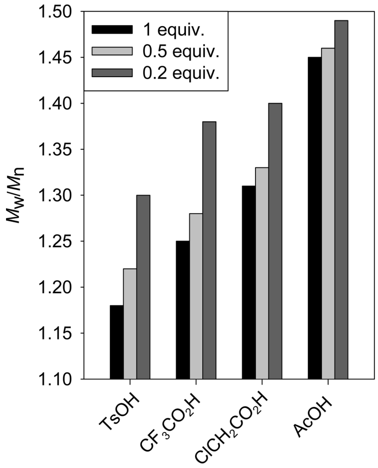


Figure 3. Dispersity (M_w/M_n) dependence on acid strength and concentration at high monomer conversion (NB: data shown for high-throughput GPC with DMAc eluent).

M_w/M_n = 1.29) from those in the absence of acid (ca. M_w/M_n ~1.50). This would be expected to occur to some degree if the rate of proton transfer is indeed faster than that of addition−fragmentation. While these results may suggest the use of excess acid ([TsOH]/[RAFT] > 1) may further improve the control over the polymerization of DMAm, preliminary experiments using RAFT agent **4** showed no significant improvement in dispersity, when compared to stoichiometric acid concentrations ([TsOH]/[RAFT] = 1). Further to this, inhibition of polymerization was observed, increasing the probability of unwanted side reactions (see Supporting Information for details).

Unsurprisingly, polymers of lower dispersity were also obtained with increasing acid strength, whereby TsOH (pK_a ~ −1.5)[25] gave PDMAm with the lowest dispersity followed by CF_3CO_2H (0.52),[18] $ClCH_2CO_2H$ (2.87),[18] and AcOH (4.76)[18] (see Figure 2).

The combined effects of acid concentration and acid strength on RAFT polymerization of DMAm can be appreciated by examining Figure 3 (also Table 2), which clearly shows the trends for lower dispersity with an increase in either parameter (further details of polymer syntheses available in Supporting Information).

Acid Dissociation Constant (pK_a) of RAFT Agent 6-H$^+$.

The results obtained when the polymerization of DMAm is performed in the presence of various acids can be rationalized by calculating the acid dissociation constant (pK_a) of the switchable RAFT agent **6-H**$^+$ and therefore the extent of protonation in solution. This was achieved by ^{1}H NMR titration of **6** with TsOH in 20% dimethylsulfoxide (DMSO)-d_6/80% water (v/v) (Scheme 3), following the protocol of Grycova et al.,[35] in which the chemical shift of hydrogen atoms at the 2 and 6 positions of the pyridine ring is observed with changing pH. From the titration curve (Figure 4) the pK_a of **6-H**$^+$ was calculated to be 3.13. It has been previously reported that concentrations of DMSO need to be upward of 26% (v/v) to see appreciable changes (>±0.2) in pK_a from those in pure water, as the molar ratio of DMSO to water is significantly lower than the volume ratio (ca. 6% at 20% v/v).[36]

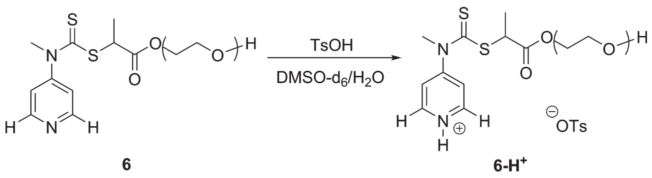
Upon protonation of **6**, the apparent transfer constant increases, leading to polymers with lower dispersity in the polymerization of DMAm. The extent of protonation ([**6-H**$^+$]$_{eq}$/[**6**]$_0$) is dictated by the pK_a of the acid compared to that of the RAFT agent **6-H**$^+$ (~3.13), where dispersity is decreased significantly with increasing acid strength (refer to Table 2). Acid concentration also affects [**6-H**$^+$]$_{eq}$/[**6**]$_0$ and therefore the dispersity of the resultant polymer. This can be seen by the decreasing dispersity of PDMAm with increasing amounts of acid in the case of TsOH, CF_3CO_2H, and $ClCH_2CO_2H$. In the case of AcOH there is negligible difference in the dispersity with increasing acid concentration. This can be rationalized by the fact that the pK_a of AcOH is higher than that of the RAFT agent **6-H**$^+$ and is therefore AcOH is unable to protonate the RAFT agent **6** to any appreciable amount. This effect on the apparent transfer constant can also be seen in Figure 5, where narrowing of dispersity is more pronounced in the presence of CF_3CO_2H and $ClCH_2CO_2H$ when compared with that of TsOH. A decrease in transfer constant results in addition of more monomer units per active cycle, induced by less efficient protonation of the RAFT agent **6**. As the polymerization proceeds, the dispersity decreases as the variation between chains becomes less significant. In the presence of AcOH, the narrowing of dispersity in less pronounced due to the RAFT agent **6** not being protonated to any appreciable amount, and hence behaving as a poorer control agent.

Table 2. Details of Polymer Syntheses Using High-Throughput Methods[a]

entry	acid	[acid]/[**6**]	pH (t_0)[b]	M_n[c]	M_n (theory)[d]	M_w/M_n[c]	time (min)	conv (%)	[**6**-H$^+$]$_{eq}$/[**6**]$_0$ (%)[e]
1	TsOH	1.0	2.77	11500	8500	1.10	74	85	78
2	TsOH	0.5	3.47	10600	8400	1.21	76	84	45
3	TsOH	0.2	4.14	10900	8200	1.29	78	82	19
4	CF_3CO_2H	1.0	1.88	10000	8000	1.18	66	80	77
5	CF_3CO_2H	0.5	2.92	10400	8000	1.19	68	80	45
6	CF_3CO_2H	0.2	3.45	10300	8000	1.31	70	80	19
7	$ClCH_2CO_2H$	1.0	3.12	10300	8200	1.25	66	82	56
8	$ClCH_2CO_2H$	0.5	3.48	11300	8600	1.23	68	86	36
9	$ClCH_2CO_2H$	0.2	3.99	10800	8500	1.35	70	85	17
10	AcOH	1.0	3.86	11100	8300	1.38	71	83	13
11	AcOH	0.5	4.17	11700	8700	1.37	73	87	9
12	AcOH	0.2	4.54	11000	7900	1.41	75	79	6

[a] [M] = 1.83 M, [**6**] = 1.83 × 10^{-2}, target MW = 10 000. [b] pH at t_0 measured before degas cycles. [c] GPC DMF eluent, PS equivalents. [d] M_n (theory) = $[([M]_0/[RAFT]_0) \times MW_{monomer}] \times$ % conversion. [e] Calculated using equilibrium concentrations, estimated from pK_a values and the initial concentrations of acid, **6** and DMAm using CurTiPot pH and Acid−Base Titration 3.5.4 for Excel.[24]

Scheme 3. ^{1}H NMR Titration of 6 with TsOH, Illustrating Hydrogen Atoms at the 2 and 6 Positions on the Pyridine Ring



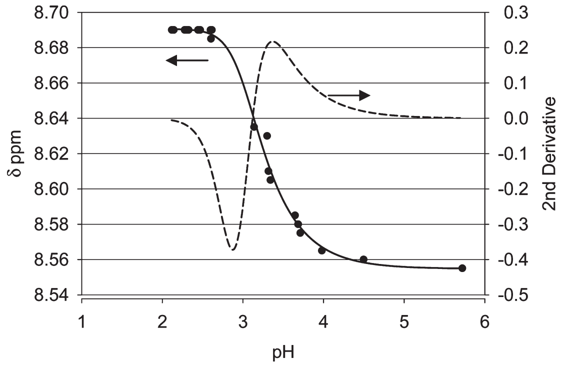


Figure 4. ^{1}H NMR titration curve of **6** with TsOH in 20% DMSO-d_6/80% water (v/v) (NB: chemical shift of H atoms on 2 and 6 position observed with changing pH) (solid line) and the second derivative (dotted line) showing the pK_a of **6-H**$^+$ as 3.13.

Block Copolymer Synthesis. The significance of switchable RAFT is the ability to control a much wider range of monomers than conventional RAFT process. This is exploited to greatest effect in the preparation of block copolymers incorporating both MAMs and LAMs. To illustrate this capacity, block copolymers of PDMAm and the less-activated monomers NVC, VAc, and NVP were prepared (see Supporting Information for full details of polymerization conditions). All block copolymers were successfully prepared in organic solution. Although NVP is water-soluble, a block copolymer of NVP could not be prepared in aqueous solution. We attribute this to hydrolytic instability in water of the hemithioaminal group formed (arising from the dithiocarbamate end-group with a terminal NVP unit) in a reaction similar to that described by Pound et al.[37] for the decomposition of a xanthate end group of PNVP. As this hydrolysis occurs at the terminal carbon of the NVP chain,[37] dithiocarbamates, xanthates, and other types of RAFT agents can be expected to behave similarly in this context. To the best of our knowledge there are no reports in the literature pertaining to the RAFT polymerization of LAMs (vinyl esters, vinyl amides, etc.) in aqueous media. Nevertheless, PDMAm-*block*-PNVC (Figure 6a), PDMAm-*block*-PVAc (Figure 6b), and PDMAm-*block*-PNVP (Figure 6c) of low dispersity were successfully prepared from PDMAm utilizing the switchable RAFT protocol.

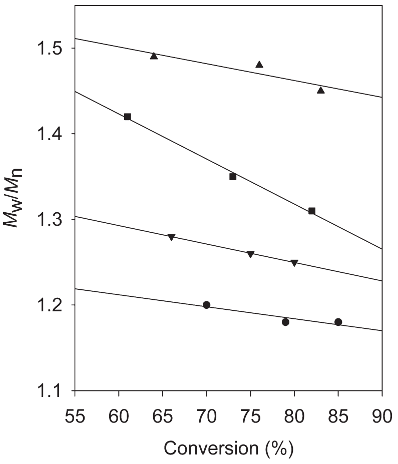


Figure 5. Progression of dispersity with monomer conversion (between 55 and 90%) with respect to acid strength ([acid]/[**6**] = 1): TsOH (●); CF_3CO_2H (▼); $ClCH_2CO_2H$ (■); AcOH (▲).

For successful preparation of these block copolymers it is important to purify the initial PDMAm macro-RAFT agent to remove any residual monomer, as this is incompatible with the RAFT group upon switching and will lead to poor control in the polymerization of the second block. Neutralization, by the addition of excess sodium bicarbonate, is preferred during this purification process rather than alternately using the addition of stoichiometric base directly to the block extension reaction mixture containing the protonated macro RAFT agent. This is due the difficulty of adding exactly 1 equiv of base to switch the RAFT

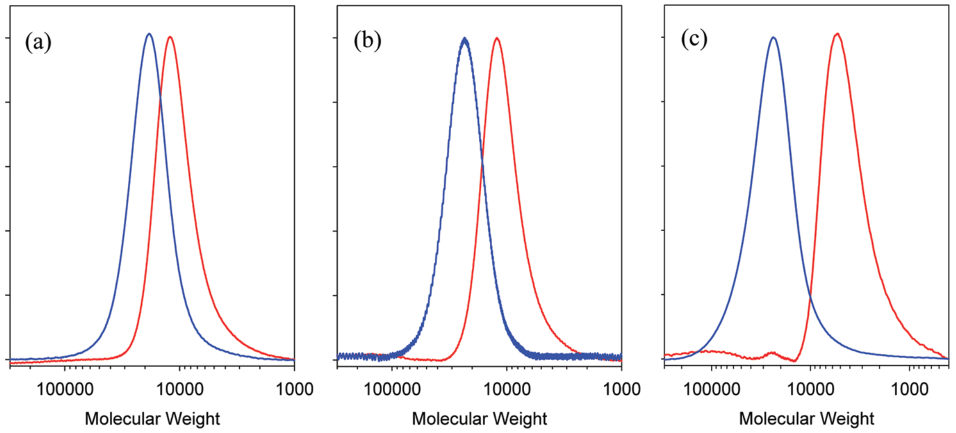


Figure 6. GPC chromatograms of (a) PDMAm **4-H**$^+$ (M_n = 10 000, M_w/M_n = 1.17) (red curve) and PDMAm-*block*-PNVC **4** (M_n = 16 400, M_w/M_n = 1.13) (blue curve), (b) PDMAm **4-H**$^+$ (M_n = 10 000, M_w/M_n = 1.17) (red curve) and PDMAm-*block*-PVAc **4** (M_n = 20 100, M_w/M_n = 1.15) (blue curve), and (c) PDMAm **4-H**$^+$ (M_n = 3660, M_w/M_n = 1.27) (red curve) and PDMAm-*block*-PNVP **4** (M_n = 16 000, M_w/M_n = 1.19) (blue curve).

end-group, preventing the presence of excess acid or base. Due to the hydrolytic instability of the RAFT end-group upon incorporation of LAMs any excess acid (or base) results in diminished control of the polymerization and broader molecular weight distributions in the final product. For the polymerization of NVC or NVP block copolymers, or homopolymers for that matter, removal of all acid is essential as its presence degrades the monomer to carbazole or pyrrolidone respectively, with acetaldehyde also being produced (among other degradation products).[38,39]

■ CONCLUSION

We have demonstrated that switchable RAFT polymerization can be implemented in aqueous media, by the preparation of low dispersity PDMAm. Acid strength and concentration have a marked effect on the degree of control over the polymerization. TsOH, at equimolar concentration to RAFT agent, gave polymers of lowest dispersity in the polymerization of DMAm. Similar results are expected with the use of any acid with p$K_a < 0$. As the extent of protonation of the RAFT agent is reduced, through the use of either a weaker acid or a lower concentration of acid, the dispersity of the resulting polymer increases. Block copolymers of PDMAm were successfully prepared with the LAMs NVC, VAc, and NVP, following neutralization of the RAFT end group, illustrating the utility of the switchable RAFT protocol in the preparation of new polymeric materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Full details of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: daniel.keddie@csiro.au (D.J.K.), graeme.moad@csiro.au (G.M.).

■ ACKNOWLEDGMENT

We acknowledge the Capability Development Fund of CSIRO Materials Science and Engineering for financial support. D.J.K. acknowledges the Office of the Chief Executive of CSIRO for an OCE postdoctoral fellowship.

■ REFERENCES

(1) 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.

(2) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2005**, *58*, 379–410.

(3) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2006**, *59*, 669–692.

(4) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2009**, *62*, 1402–1472.

(5) Jenkins, A. D.; Jones, R. G.; Moad, G. *Pure Appl. Chem.* **2010**, *82*, 483–491.

(6) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921–2990.

(7) Moad, G.; Rizzardo, E.; Thang, S. H. *Acc. Chem. Res.* **2008**, *41*, 1133–1142.

(8) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661–3688.

(9) Chiefari, J.; Mayadunne, R. T. A.; Moad, C. L.; Moad, G.; Rizzardo, E.; Postma, A.; Skidmore, M. A.; Thang, S. H. *Macromolecules* **2003**, *36*, 2273–2283.

(10) Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Chong, Y. K.; Moad, G.; Thang, S. H. *Macromolecules* **1999**, *32*, 6977–6980.

(11) Destarac, M.; Bzducha, W.; Taton, D.; Gauthier-Gillaizeau, I.; Zard, S. Z. *Macromol. Rapid Commun.* **2002**, *23*, 1049–1054.

(12) Destarac, M.; Charmot, D.; Franck, X.; Zard, S. Z. *Macromol. Rapid Commun.* **2000**, *21*, 1035–1039.

(13) Malepu, V.; Petruczok, C. D.; Tran, T.; Zhang, T.; Thopasridharan, M.; Shipp, D. A. In *Controlled/Living Radical Polymerization: Progress in RAFT, DT, NMP & OMRP*; Matyjaszewski, K., Ed.; American Chemical Society: Washington, DC, 2009; ACS Symposium Series Vol. 1024, pp 37–47.

(14) Benaglia, M.; Chiefari, J.; Chong, Y. K.; Moad, G.; Rizzardo, E.; Thang, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 6914–6915.

(15) Benaglia, M.; Chen, M.; Chong, Y. K.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **2009**, *42*, 9384–9386.

(16) Moad, G.; Benaglia, M.; Chen, M.; Chiefari, J.; Chong, Y. K.; Keddie, D. J.; Rizzardo, E.; Thang, S. H. In *Non-Conventional Functional Block Copolymers*; Theato, P., Kilbinger, A. F. M., Coughlin, E. B., Eds.; American Chemical Society: Washington, DC, 2011; ACS Symposium Series Vol. 1066, pp 81−102.

(17) Bicciocchi, E.; Chong, Y. K.; Giorgini, L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromol. Chem. Phys.* **2010**, *211*, 529–538.

(18) Lide, D. R., *CRC Handbook of Chemistry and Physics*, 84th ed.; CRC Press: Boca Raton, FL, 2003.

(19) Lowe, A. B.; McCormick, C. L. *Prog. Polym. Sci.* **2007**, *32*, 283–351.

(20) Bamford, C. H.; Schofield, E.; Michael, D. J. *Polymer* **1985**, *26*, 945–950.

(21) Guerrero-Sanchez, C.; Abeln, C.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 4151–4160.

(22) Guerrero-Sanchez, C.; Paulus, R. M.; Fijten, M. W. M.; de la Mar, M. J.; Hoogenboom, R.; Schubert, U. S. *Appl. Surf. Sci.* **2006**, *252*, 2555–2561.

(23) Guerrero-Sanchez, C.; Keddie, D. J.; Martinez, I.; Harrisson, S.; Saubern, S.; Thang, S. H.; Rizzardo, E.; Chiefari, J.; Moad, G. Manuscript in preparation, 2011.

(24) Gutz, I. G. R. *CurTiPot pH and Acid-Base Titration* 3.5.4 for Excel; http://www2.iq.usp.br/docente/gutz/Curtipot_.html.

(25) Berkowitz, B. J.; Grunwald, E. *J. Am. Chem. Soc.* **1961**, *83*, 2956.

(26) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 1985.

(27) Donovan, M. S.; Sanford, T. A.; Lowe, A. B.; Sumerlin, B. S.; Mitsukami, Y.; McCormick, C. L. *Macromolecules* **2002**, *35*, 4570–4572.

(28) Convertine, A. J.; Lokitz, B. S.; Vasileva, Y.; Myrick, L. J.; Scales, C. W.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2006**, *39*, 1724–1730.

(29) Lowe, A. B.; McCormick, C. L. In *RAFT polymerization in homogeneous aqueous media: initiation systems, RAFT agent stability, monomers and polymer structures*; Wiley-VCH Verlag GmbH & Co. KGaA: Berlin, 2008; pp 235—284.

(30) Thomas, D. B.; Sumerlin, B. S.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2003**, *36*, 1436–1439.

(31) Sciannamea, V.; Guerrero-Sanchez, C.; Schubert, U. S.; Catala, J. M.; Jerome, R.; Detrembleur, C. *Polymer* **2005**, *46*, 9632–9641.

(32) Bonilla-Cruz, J.; Guerrero-Sanchez, C.; Schubert, U. S.; Saldivar-Guerra, E. *Eur. Polym. J.* **2010**, *46*, 298–312.

(33) Guerrero-Sanchez, C.; Lohmeijer, B. G. G.; Meier, M. A. R.; Schubert, U. S. *Macromolecules* **2005**, *38*, 10388–10396.

(34) Guerrero-Sanchez, C.; Wouters, D.; Fustin, C.-A.; Gohy, J.-F.; Lohmeijer, B. G. G.; Schubert, U. S. *Macromolecules* **2005**, *38*, 10185–10191.

(35) Grycova, L.; Dommisse, R.; Pieters, L.; Marek, R. *Magn. Reson. Chem.* **2009**, *47*, 977–981.

(36) Holmes, D. L.; Lightner, D. A. *Tetrahedron* **1995**, *51*, 1607–22.

(37) Pound, G.; McKenzie, J. M.; Lange, R. F. M.; Klumperman, B. *Chem. Commun.* **2008**, 3193–3195.

(38) Kurov, G. N.; Afonin, A. V.; Svyatkina, L. I.; Dmitrieva, L. L.; Pal'chuk, E. G. *Russ. Chem. B* **1987**, *36*, 403–405.

(39) Ferguson, J.; Sundar Rajan, V. *Eur. Polym. J.* **1979**, *15*, 627–630.

■ NOTE ADDED AFTER ASAP PUBLICATION

This article posted ASAP on August 15, 2011. The second sentence in the abstract has been revised. The correct version posted on August 18, 2011.