Available online at www.sciencedirect.com
SCIENCE DIRECT
Polymer 47 (2006) 1011–1019
polymer
www.elsevier.com/locate/polymer

Effect of an added base on (4-cyanopentanoic acid)-4-dithiobenzoate mediated RAFT polymerization in water

Luca Albertin [1], Martina H. Stenzel, Christopher Barner-Kowollik, Thomas P. Davis *

School of Chemical Engineering and Industrial Chemistry, Centre for Advanced Macromolecular Design, The University of New South Wales, Sydney, NSW 2052, Australia

Received 24 June 2005; received in revised form 12 December 2005; accepted 13 December 2005

Abstract

The effect of an added base on the aqueous reversible addition–fragmentation chain transfer polymerization of a methacrylic glycomonomer with (4-cyanopentanoic acid)-4-dithiobenzoate was investigated. When sodium carbonate or sodium bicarbonate were used to dissolve the RAFT agent in aqueous solution at room temperature, an inhibition period of 60–90 min was observed at the beginning of the polymerization together with a marked decrease in the overall polymerization rate. Also, experimental M_n values were much higher than the calculated ones in both cases. When sodium carbonate was used, control over the polymerization process was lost within 43% conversion. Better results were obtained with sodium bicarbonate, in which case the molecular weight distribution remained narrow and unimodal up to 81% conversion. At that point, a higher molecular weight shoulder developed that kept growing in intensity at the proceeding of the reaction. Dramatically improved results were obtained by adding circa 10% ethanol to the polymerization mixture to facilitate the dissolution of (4-cyanopentanoic acid)-4-dithiobenzoate. Following this protocol, narrow polydispersity poly(methyl 6-*O*-methacryloyl-α-D-glucoside) was obtained possessing a molecular weight close to the predicted value.

Keywords: Aqueous RAFT polymerization; RAFT agent; Living radical polymerization

1. Introduction

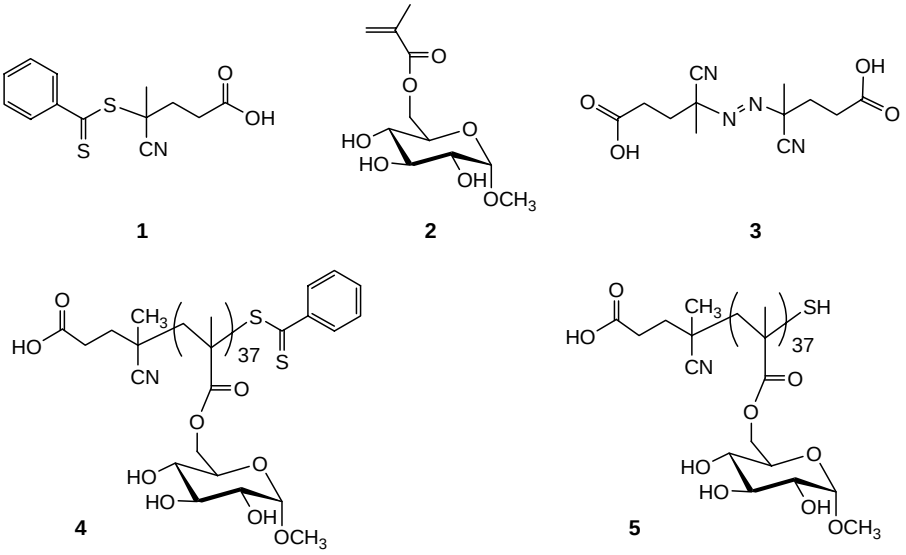
Reversible addition–fragmentation chain transfer (RAFT) polymerization [1] in homogeneous aqueous media is a fairly new and largely unexplored field of research that owes most of its progress to the groups led by Charles McCormick and Andrew Lowe [2–10]. The appeal of this technique stems from the possibility to directly polymerize ionic and highly hydroxylated monomers in a living fashion and in a solvent (water) which is cheap, non-toxic, stable over time, readily available in high purity from commercial or in-house sources and that can be easily removed by freeze–drying.

One of the challenges posed by aqueous RAFT is the need to design water soluble RAFT agents that are stable under the various conditions of pH, temperature and ionic strength that will be used. In this context (4-cyanopentanoic acid)-4-dithiobenzoate (CPADB, compound **1** in Scheme 1) is by far the most commonly used chain transfer agent, its synthesis and application being described in the original RAFT patents [11,12]. In our experience though, under neutral conditions CPADB is virtually insoluble in pure water at room temperature and only sparingly soluble at 60–70 °C [13]. In fact, in all reports describing its use in homogeneous aqueous solution the compound is either used in its salt form [5,11], or the pH of the solution is increased by addition of a base [8], or again the RAFT agent dissolution is facilitated by a high concentration of amphiphilic monomer [9].

We have previously described the successful aqueous RAFT polymerization of a methacryloyl-derived glycomonomer up to quantitative conversion [14] as well as the first synthesis of a narrow-polydispersity poly(vinyl ester)-like glycopolymer in methanol and water [15]. As part of our ongoing interest in macromolecular design [16], we now describe the reversible addition–fragmentation chain transfer polymerization of methyl 6-*O*-methacryloyl-α-D-glucoside (6-*O*-MAMGlc, compound **2** in Scheme 1) in water and water/ethanol mixtures according to three different polymerization protocols and discuss the influence of the additive (base or ethanol) used to help the RAFT agent dissolution on the polymerization kinetics

* Corresponding author. Fax: +61 2 9385 5966.
E-mail address: camd@unsw.edu.au (T.P. Davis).
[1] Now at the joint research unit CNRS-bioMérieux, Ecole Normale Supérieure de Lyon, 46 allée d'Italie, 69007 Lyon, France.

0032-3861/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.polymer.2005.12.069



Scheme 1. Structure of the RAFT agent (**1**), monomer (**2**), initiator (**3**), macroRAFT agent (**4**) and macrothiol (**5**) used in this study.

and on the molecular weight distribution of the resulting polymer.

2. Experimental

2.1. Materials and methods

Unless otherwise specified, all chemicals were reagent grade and used as received. 4,4′-Azobis(cyanopentanoic acid) (98%, Fluka), deuterium oxide (99.9%, Cambridge Isotopes), *N,N*-dimethylacetamide (HPLC grade, Aldrich), *N,N*-dimethylformamide (HPLC grade, Fischer), ethanol (spectroscopic grade, Aldrich) and water (HPLC grade, Riedel de Haën) were used as received. (4-Cyanopentanoic acid)-4-dithiobenzoate **1** and methyl 6-*O*-methacryloyl-α-D-glucoside **2** were prepared according to the published methods (Scheme 1) [9,14,17]. A stock solution of methyl 6-*O*-methacryloyl-α-D-glucoside in water (1.00 M, HPLC grade, pH 7) was used for all experiments. Accurate volumes were measured with an automatic pipettor (Eppendorf Research, 200–1000 μL) calibrated with distilled water (22 °C, d_{H2O} = 0.9878, mean error = 0.05%). Dialysis purifications were performed with Slide-A-Lyzer Dialysis Cassettes (3–13 mL, 3.5 kDa MWCO, Pierce Biotechnology).

2.2. Analysis

Molecular weights and molecular weight distributions were measured by size exclusion chromatography (SEC) using a Shimadzu modular LC system comprising a DGU-12A solvent degasser, a LC-10AT pump, a SIL-10AD auto injector, a CTO-10A column oven and a RID-10A refractive index detector. The system was equipped with a 50×7.8 mm guard column and four 300×7.8 mm linear columns (Phenomenex 500, 10^3, 10^4 and 10^5 Å pore size; 5 μm particle size). *N,N*-Dimethylacetamide (0.03% w/v LiBr, 0.05% w/v BHT) was used as eluant at a flow rate of 1 mL min^{-1} while the columns temperature was maintained at 40 °C. Polymer solutions (3–5 mg mL^{-1}) were injected in 50 μL volumes. Calibration was performed with narrow polydispersity polystyrene standards (Polymer Laboratories) in the range 0.5–1000 kDa and SEC traces were analysed with Cirrus 2.0 software (Polymer Laboratories). Conversions were calculated directly from the refractive index traces according to published method [14]. Macroradical reaction experiments were monitored with a SEC instrument consisting of a GBC LC1110 HPLC pump, a Viscotek VE5111 manual injector port, and a Viscotek TriSEC Model 302 triple detector array comprising a 90° angle laser light scattering detector and a differential refractometer operating at the same wavelength (λ = 670 nm). The system was equipped with a 50×7.5 mm guard column and three 300×7.5 mm linear columns (PLgel 500, 10^3 and 10^4 Å pore size; 5 μm particle size). *N,N*-Dimethylformamide (0.1% w/v LiBr, 0.05% w/v BHT) was used as eluant at a flow rate of 1 mL min^{-1} while the columns temperature was maintained at 60 °C. Polymer solutions (2–3 mg mL^{-1}) were injected in 100 μl volumes. SEC traces were analysed with OmniSEC 4.0 software (Viscotek). A d*n*/d*c* value of 0.0902 mL/g was used for molecular weight calculations, that was determined from repeated injections of poly(methyl 6-*O*-methacryloyl-α-D-glucoside) dithiobenzoate solutions of known concentration (DMF eluant, 60 °C, M_n (SEC) 17,500; PDI 1.06).

2.3. Polymerization experiments

All experiments were conducted in Schlenk tubes sealed with rubber septa. The polymerization solutions were degassed with 3–4 freeze–evacuate–thaw cycles and transferred to an oil bath pre-heated to 70 °C. At consecutive reaction times, aliquots of solution (100–200 μL) were drawn from the reaction mixture using a gas-tight syringe pre-purged with nitrogen and fitted with a 0.72 mm OD needle. The sampled solution was quenched in ice–water for 10 s. and diluted with DMAc eluant (2.00 mL) for SEC analysis.

Table 1
Summary of RAFT polymerization experiments

Run no.	Monomer (M)	RAFT agent (mM)	Reaction time (min)	Conv. (%)[a]	M_n (Da) theory	M_n (Da) SEC[b]	M_w/M_n SEC
1	**2** (0.80)	CPADB (7.8)	375	97	26,200	327,150	3.67
2	**2** (0.77)	CPADB (7.6)	280	99	26,100	174,000	1.75
3	**2** (0.87)	CPADB (8.1)	232	100	28,300	26,300	1.14

CPADB is (4-cyanopentanoic acid)-4-dithiobenzoate. Temperature, 70 °C. Solvent (initiator concentration): run 1, water/Na_2CO_3 (3.6 mM); run 2, water/$NaHCO_3$ 0.1 M (3.5 mM); run 3 water/ethanol 87:13 (3.8 mM).

[a] Size exclusion chromatography, calculated from the relative area of monomer and polymer peaks.

[b] Polystyrene equivalents.

2.4. Sodium carbonate protocol

Run 1 in Table 1. 4,4′-Azobis-(4-cyanopentanoic acid) (0.0206 g, 7.20×10^{-5} mol) and (4-cyanopentanoic acid)-4-dithiobenzoate (0.0434 g, 1.55×10^{-4} mol) were dissolved in 2.00 mL each of Na_2CO_3 solution prepared by adding three tips of a small spatula of salt to 2.00 mL of HPLC grade water. The monomer solution (4.00 mL, 4.00×10^{-3} mol) was introduced in a Schlenk tube and mixed with a calculated amount of initiator (7.20×10^{-2} M, 500 μL, 1.80×10^{-5} mol) and RAFT agent (7.77×10^{-2} M, 500 μL, 3.88×10^{-5} mol) aqueous solutions. Total reaction time: 375 min. Final conversion: 97%. M_n (SEC) 327,000; PDI 3.67.

2.5. Sodium hydrogen carbonate protocol

Run 2 in Table 1. 4,4′-Azobis-(4-cyanopentanoic acid) (0.0174 g, 6.08×10^{-5} mol) and (4-cyanopentanoic acid)-4-dithiobenzoate (0.0555 g, 1.99×10^{-4} mol) were dissolved in 2.00 and 3.00 mL, respectively, of 0.1 M $NaHCO_3$ water solution (HPLC grade). The monomer solution (4.00 mL, 4.00×10^{-3} mol) was introduced in a Schlenk tube and mixed with a calculated amount of the initiator (3.04×10^{-2} M, 600 μL, 1.83×10^{-5} mol) and RAFT agent (6.62×10^{-2} M, 600 μL, 3.97×10^{-5} mol) aqueous solutions. Total reaction time: 280 min. Final conversion: 99%. M_n (SEC) 174,000; PDI 1.75.

2.6. Ethanol protocol

In a typical experiment (run 3, Table 1) the monomer solution (3.00 mL, 3.00×10^{-3} mol) was introduced in a Schlenk tube and mixed with ethanol solutions of 4,4′-azobis-(4-cyanopentanoic acid) (5.98×10^{-2} M, 220 μL, 1.32×10^{-5} mol) and (4-cyanopentanoic acid)-4-dithiobenzoate (1.20×10^{-1} M, 235 μL, 2.81×10^{-5} mol). All collected samples were freeze–dried for 2 h before re-dissolving them in DMAc eluant for SEC analysis. The remaining polymer was recovered (159 mg) by precipitation in excess methanol followed by centrifugation and freeze–drying. Total reaction time: 103 min. Final conversion: 98%. M_n (SEC) 26,300; PDI 1.14. ^{1}H NMR (300 MHz, D_2O, 50 °C) δ (ppm): 0.97 and 1.13 (H-11), 1.91 (CH_2 chain), 3.40 (4-H), 3.46 (H-7), 3.60 (2-H), 3.70 (3-H), 3.82 (5-H), 4.10 and 4.37 (6-H), 4.82 (H-1), 7.56 (H_{meta} arom), 7.73 (H_{para} arom), 7.97 and 8.00 (H_{ortho} arom). ^{13}C NMR (126 MHz, D_2O, 40 °C) δ (ppm): 17.38 (C-11), 45.5 (C-9), 54.5 (C-10), 55.75 (C-7), 65.22 (C-6), 69.78 (C-5), 70.62 (C-4), 71.89 (C-2), 73.82 (C-3), 99.86 (C-1), 179.5 (C-8).

2.7. Synthesis of poly(methyl 6-O-methacryloyl-α-D-glucoside) dithiobenzoate (*4*)

The title compound was prepared according to the ethanol protocol but without sampling at intermediate reaction times. After quenching the reaction, two aliquots (50 and 100 μL) of solution were drawn for analysis. Both aliquots were freeze–dried overnight and re-dissolved in DMF eluant (2.00 mL) and D_2O (0.700 mL) for SEC and proton NMR analysis, respectively. The remaining solution was dialysed against purified water (dark, 24 h, two changes of water) followed by freeze–drying (dark, 5 days): the product compound was recovered as pink powder. Total reaction time: 50 min. Final conversion: 87%. Yield: 1.861 g, 55%. M_n (NMR) 8400; M_n (SEC) 9900; PDI (SEC) 1.09.

2.8. Synthesis of poly(methyl 6-O-methacryloyl-α-D-glucoside) thiol (*5*)

Poly(methyl 6-*O*-methacryloyl-α-D-glucoside) dithiobenzoate **4** (0.200 g, 2.4×10^{-5} mol) was dissolved in aqueous NaOH (1.9×10^{-2} M, 4.00 mL) and the resulting solution was stirred initially at room temperature (16 h) and then at 60 °C (4 h) in the dark. The solution was hence dialysed against purified water (dark, 18 h, two changes of water) and the title compound recovered as peach–white powder by freeze–drying (dark, 2 days). Yield: 0.120 g, 60%. M_n (SEC) 10,000; PDI (SEC) 1.10.

2.9. Macroradical reaction experiments

The general procedure was the same as for polymerization experiments according to the ethanol protocol, but the sampled solutions were quenched in liquid nitrogen for 10 s, freeze–dried overnight and diluted with DMF eluant (2.00 mL) for SEC analysis.

2.10. Reaction of a macro-RAFT agent with a macro-thiol

Poly(methyl 6-*O*-methacryloyl-α-D-glucoside) dithiobenzoate **4** (0.0425 g, 5.1×10^{-6} mol) and poly(6-*O*-methacryloyl-α-D-glucoside) thiol **5** (0.0429 g, 5.1×10^{-6} mol) were introduced in a Schlenk tube, dissolved in water (1.00 mL,

HPLC grade), and mixed with an ethanol solution of 4,4′-azobis-(4-cyanopentanoic acid) (2.81×10^{-2} M, 155 μL, 4.36×10^{-6} mol). Total reaction time: 92 min. M_n (SEC) 10,000; PDI (SEC) 1.08.

2.11. Reaction between macro-thiols

Poly(methyl 6-*O*-methacryloyl-α-D-glucoside) thiol **5** (0.0767 g, 9.1×10^{-6} mol) was introduced in a Schlenk tube, dissolved in water (1.00 mL, HPLC grade), and mixed with an ethanol solution of 4,4′-azobis-(4-cyanopentanoic acid) (2.81×10^{-2} M, 155 μL, 4.36×10^{-6} mol). Total reaction time: 94 min. M_n (SEC) 10,200; PDI (SEC) 1.09.

3. Results and discussion

For the RAFT polymerization of methacrylic glycomonomer **2** (Scheme 1), we initially dissolved both the initiator and the RAFT agent in slightly basic water solutions containing either Na_2CO_3 (sodium carbonate protocol) or $NaHCO_3$ (sodium hydrogen carbonate protocol). We then added a calculated amount of the resulting solutions to an aqueous monomer mixture and ran the polymerizations at 70 °C. For both protocols, the initial concentrations of monomer, initiator and RAFT agent were similar (run 1 and 2 in Table 1).

The first order kinetic plot for the RAFT polymerization experiments carried out in basic solution are shown in Fig. 1 (■ and ▲). In both cases, after an initial inhibition period the reaction appears to proceed under pseudo-first order rate kinetics up to quantitative monomer consumption. Clearly, a higher pH results in a longer induction period (~90 min for the sodium carbonate protocol vs. ~60 min for the sodium hydrogen carbonate protocol) and in a slower overall rate of polymerization.

The evolution of the molecular weight distribution with conversion is informative of the activity of CPADB under the tested conditions: When sodium carbonate was used to dissolve the initiator and the RAFT agent (Fig. 2), control over the molecular weight of the resulting polymer was lost within the first 135 min of reaction (43% conversion). In fact, a bimodal MWD is observed that shifts to higher molecular weights until exceeding the upper resolution limit of the SEC system (~10^6 Da, PS standards). Better results were obtained when a 0.1 M solution of sodium hydrogen carbonate was used (sodium hydrogen carbonate protocol, Fig. 3). In this case, the resulting MWD curves remain quite narrow and unimodal up to 81% conversion and 130 min of reaction: at that point a higher molecular weight shoulder becomes visible that grows in intensity at the proceeding of the reaction.

With both protocols, the experimental M_n of the obtained polymer is much higher than the corresponding theoretical value calculated from the formula:

$$M_n = M_M x \frac{[M]_0}{[RAFT]_0} + M_{RAFT} \quad (1)$$

where M_M and M_{RAFT} are the molecular weights of monomer and RAFT agent, respectively, x is conversion and $[M]_0$ and $[RAFT]_0$ are the initial concentrations of monomer and RAFT agent (Fig. 4) [11]. For instance, at 81% conversion the experimental values are 7 and 4 times bigger than the calculated ones. The magnitude of the observed deviation is such that it cannot be simply explained with the error intrinsic to the use of PS equivalent molecular weights.

A possible explanation for the described loss of control is the degradation of the RAFT agent and of the end-of-chain dithiobenzoyl groups, caused by the basic pH of the solution. This hypothesis would also account for discoloration of the polymerization mixture observed at the end of run 1 (sodium carbonate protocol, Table 1) and is consistent with the findings of a recent publication by Thomas et al. [4]. Through an NMR study, the authors demonstrate how the use of a non-neutral pH accelerates the hydrolysis of (4-cyanopentanoic acid)-4-dithiobenzoate and, depending on the specific system investigated, can lead to a loss of control over the polymerization process and higher than expected molecular

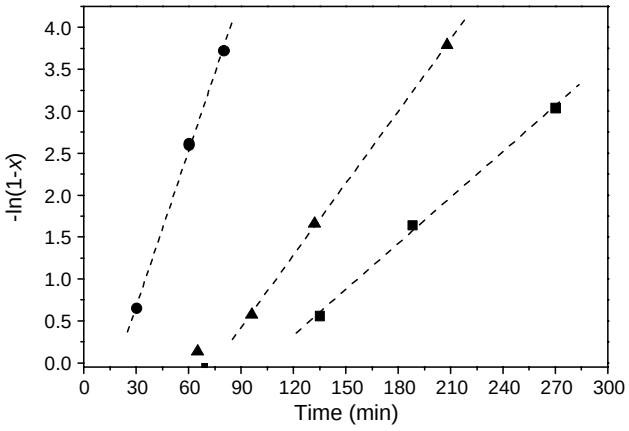


Fig. 1. First order plot for the RAFT polymerization of **2** in water solution containing Na_2CO_3 (■), $NaHCO_3$ (▲) or ethanol (●). Dashed line: linear regression of the linear portion of the plot.

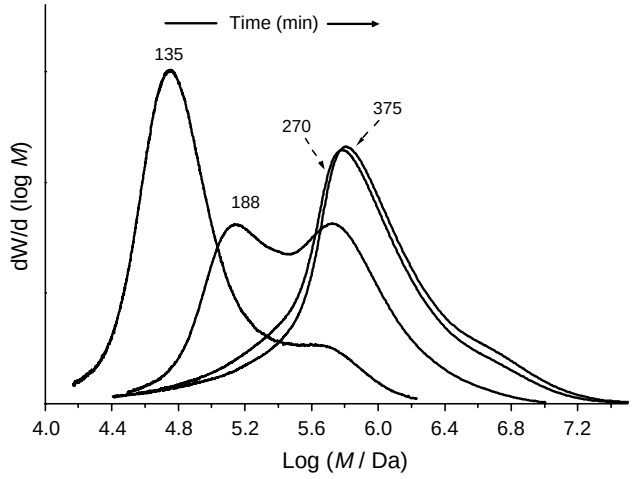


Fig. 2. Evolution of the molecular weight distribution with conversion for the RAFT polymerization of **2** according to the sodium carbonate protocol (run 1 in Table 1). From left to right, each curve corresponds to 43, 81, 95 and 97% conversion, respectively. Normalized areas; size exclusion chromatography, polystyrene equivalents.

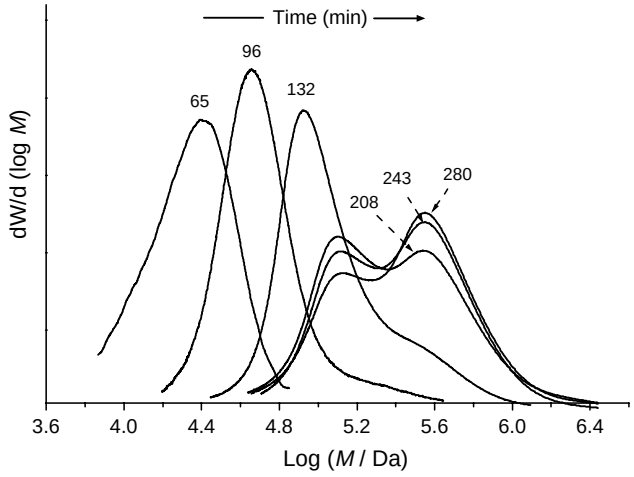


Fig. 3. Evolution of the molecular weight distribution with conversion for the RAFT polymerization of **2** according to the sodium hydrogen carbonate protocol (run 2 in Table 1). From left to right, each curve corresponds to 13, 44, 81, 98, 98 and 99% conversion, respectively. Normalized areas; size exclusion chromatography, polystyrene equivalents.

weights. For instance at pH = 10 and 70 °C, about 90% of the RAFT agent is hydrolysed in 2.5 h.

More intriguing is the fact that when the sodium hydrogen carbonate protocol is used, not only a bimodal molecular weight distribution is obtained, but the relative intensity of the higher molecular weight peak keeps increasing even after quantitative monomer consumption is achieved (Fig. 3). This behaviour suggests that coupling reactions between formed macromolecules are taking place; indeed, as a living radical polymerization approaches 100% conversion, the residual monomer concentration becomes low enough to allow competition between propagation and termination reactions of the macro-radicals (Scheme 2). Hence, at high conversion bimolecular termination via coupling can reasonably produce dead polymer with twice the molecular mass of the living chains (reaction **ix** in Scheme 2). Nonetheless, our results appear to be incompatible with this explanation: in the bimodal

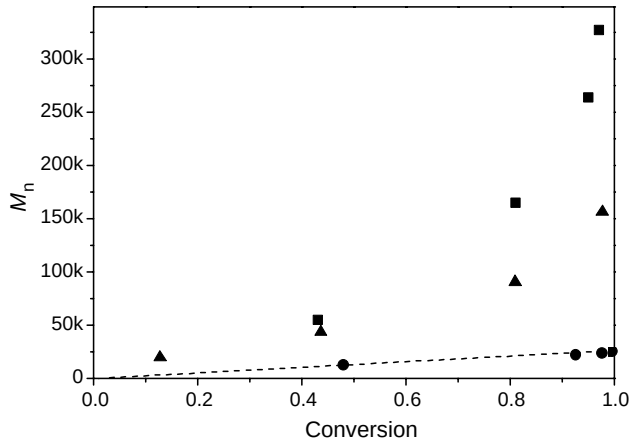
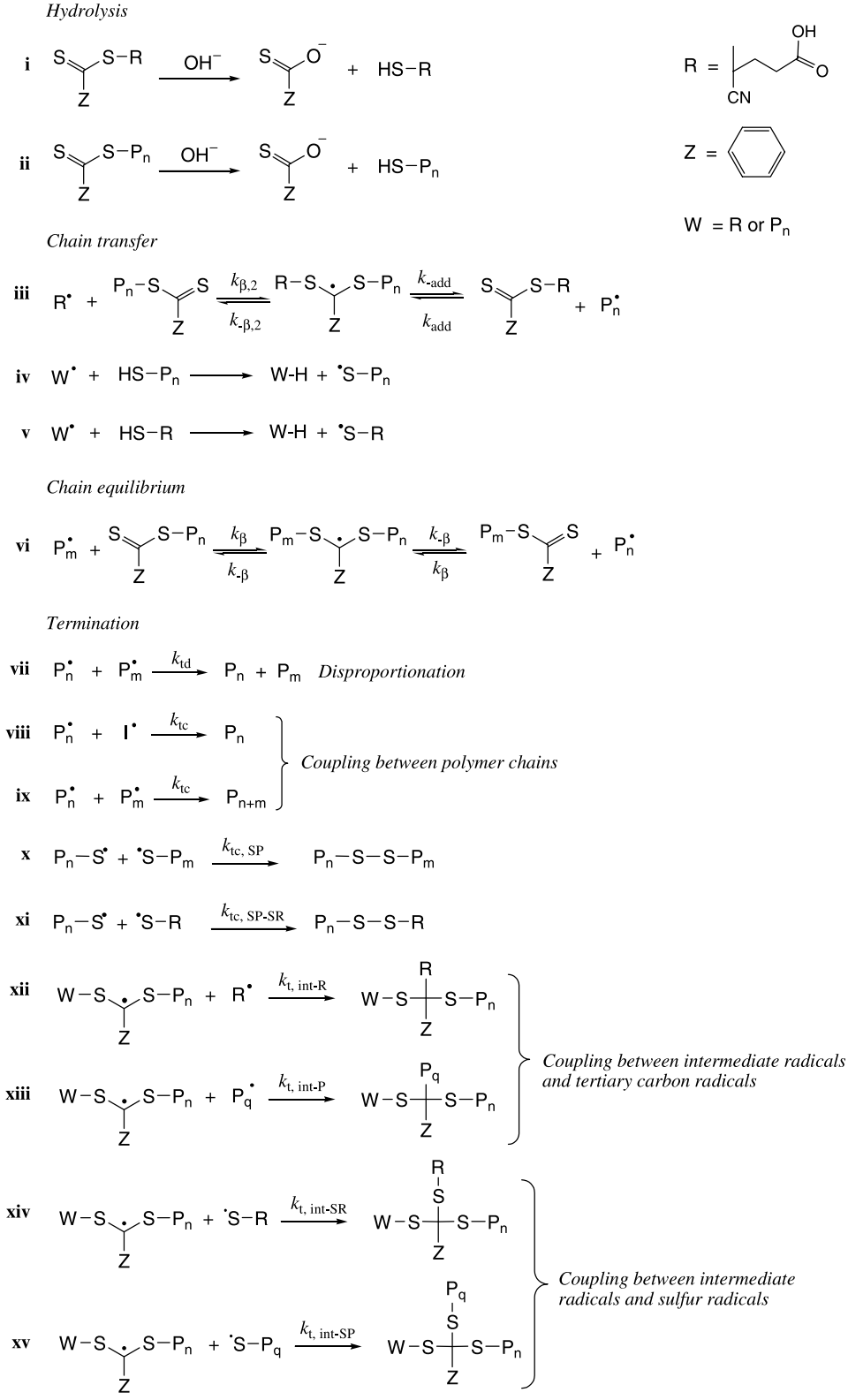


Fig. 4. Evolution of the molecular weight with conversion for the RAFT polymerization of **2** in water solution containing Na_2CO_3 (■), $NaHCO_3$ 0.1 M (▲) or ethanol (●). RAFT agent, initiator concentrations (mM): 7.8, 3.6 (■); 7.6, 3.5 (▲); 8.1, 3.8 (●). T = 70 °C. Dashed line: theoretical value.

distributions in Fig. 3 the higher molecular weight peak has its maximum at 2.8 times the lower molecular weight peak. An alternative explanation could be the coupling between an activate polymer chain and the intermediate RAFT radical (reaction **xiii** with $W = P_m$), as suggested by Fukuda et al. for styrene polymerization [18–20].

In order to probe the influence of the added base and the role of termination via coupling in our experiments, a polymerization was conducted in which the initiator and the RAFT agent were dissolved in ethanol before being added to the monomer (ethanol protocol), thus avoiding the addition of a base to the reaction mixture (run 3 in Table 1). Although all other parameters were virtually unchanged, the results of this experiment were dramatically different from what was previously observed. The reaction proceeded at a much faster rate and with an induction period of only ~20 min (Fig. 1); the experimental M_n of the obtained polymer was only slightly lower than its theoretical value (Fig. 4) and the molecular weight distribution remained narrow and unimodal up to quantitative monomer consumption (PDI 1.13–1.15). Addition of about 10% ethanol to the polymerization mixture did not significantly affect the solubility of the polymer formed, and the solution remained completely clear even after cooling to room temperature. Fig. 5 shows the evolution of the molecular weight distribution with time for a polymerization carried out according to the ethanol protocol. The first four curves from the front correspond to 48, 92, 98 and 99% monomer conversion, respectively. After all monomer had been used, the reaction was left proceeding for another 130 min in order to monitor the change in MWD with time. Neither the M_n value nor the shape of the distribution changed over this period, and the polydispersity index of the formed polymer remained unchanged to the second decimal digit (final PDI 1.14): coupling reactions involving macromolecular species had evidently taken place only to a small extent.

The results of the ethanol protocol experiment are consistent with the general behaviour of carbon-centred radicals: a methacrylate radical carrying a bulky substituent (a cyclic sugar), at fairly high temperature (70 °C), and in a polar solvent (water), will mainly terminate via disproportionation [21]. This will have no effect on the molecular weight and polydispersity of the polymer formed, although it will reduce its chain end functionality and ability to form copolymers [22]. Moreover, since termination is chain length dependent and its rate coefficient decreases with chain length [23,24,28,29], the majority of termination reactions will occur between activated macro-radicals and the primary radicals constantly supplied by the initiator decomposition. In this context, the effect on the molecular weight distribution of the polymer would be too small to be detected. Finally, steric hindrance considerations suggest that in the case of poly(methyl 6-*O*-methacryloyl-α-D-glucoside), the formation of three-arm stars like those resulting from reactions **xii** and **xiii** (Scheme 2) is unlikely. It is hence reasonable to expect the MWD of poly(methyl 6-*O*-methacryloyl-α-D-glucoside) produced via RAFT not change dramatically even in the presence of primary radicals supplied by the initiator; that is unless some other reaction takes place.



Scheme 2. Plausible radical reactions involving formed polymer chains for an aqueous RAFT polymerization conducted under basic conditions up to quantitative monomer conversion. P_n indicates a polymer chain with degree of polymerization 'n'.

So far we have only considered radical–radical reactions involving species normally present in a RAFT process. When hydrolysis of CPADB and of the end-of-chain dithiobenzoyl groups takes place though (reactions **i–ii**, Scheme 2), thiols and thionobenzoic acid are released into the system. Thiols in particular, can be involved in chain transfer reactions (**iv**) and transformed in sulphur-centred radicals; in their turn, these radicals could afford disulfides (**x**) and trithiocarbonates

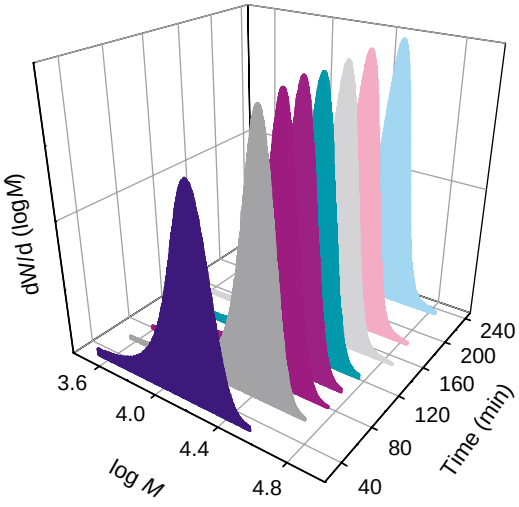


Fig. 5. Evolution of the molecular weight distribution with time for the RAFT polymerization of **2** according to the ethanol protocol (run 3 in Table 1). The first four curves from the front correspond to 48, 92, 98 and 99% conversion, respectively. All other curves correspond to 100% conversion. Normalized areas; size exclusion chromatography, polystyrene equivalents.

(**xiv** for W=P_m, **xv** for W=R) with twice the molecular weight of the starting macromolecules ($n \cong m$ for a narrow polydispersity polymer), or again trithiocarbonates with three times the molecular weight of the starting macromolecules (**xv** for W=P_m). In order to investigate this hypothesis, 1.86 g of dithiobenzoyl-terminated poly(methyl 6-*O*-methacryloyl-α-D-glucoside) were synthesised according to the ethanol protocol (**4** in Scheme 1; M_n 9900; PDI 1.09), and part of it was hydrolysed under basic conditions to afford the corresponding macro-thiol **5** (M_n 10,000; PDI 1.10). Fig. 6 shows the ^{1}H NMR spectra of both polymers after purification: as expected, they are identical in all but the three aromatic signals from the end-of-chain dithiobenzoyl group (7.56 H_{meta}, 7.73 H_{para} and 7.97 H_{ortho}), which are only visible for macro-RAFT agent **4**. Two model experiments where then performed in which the obtained polymers were reacted according to the ethanol protocol but in the absence of monomer (Table 2); samples were drawn at regular intervals over a period of 90 min and the evolution of the MWD with time was monitored via size exclusion chromatography.

Fig. 7 shows the evolution of SEC traces with time for the fist experiment (run 1 in Table 2), in which equimolar amounts of macroRAFT agent **4** and of macro-thiol **5** were used. Throughout the reaction, no significant change can be noticed in the refractive index traces (graph a), and the polydispersity index of the polymer mixture remains virtually unchanged (PDI_{final}=1.08). The formation of higher molecular weight species is only visible in the light scattering traces (graph b), where a new peak emerges at shorter retention times [25]. Similar results were obtained when only macro-thiol **5** was reacted (run 2, Table 2). Clearly, on this time scale radical

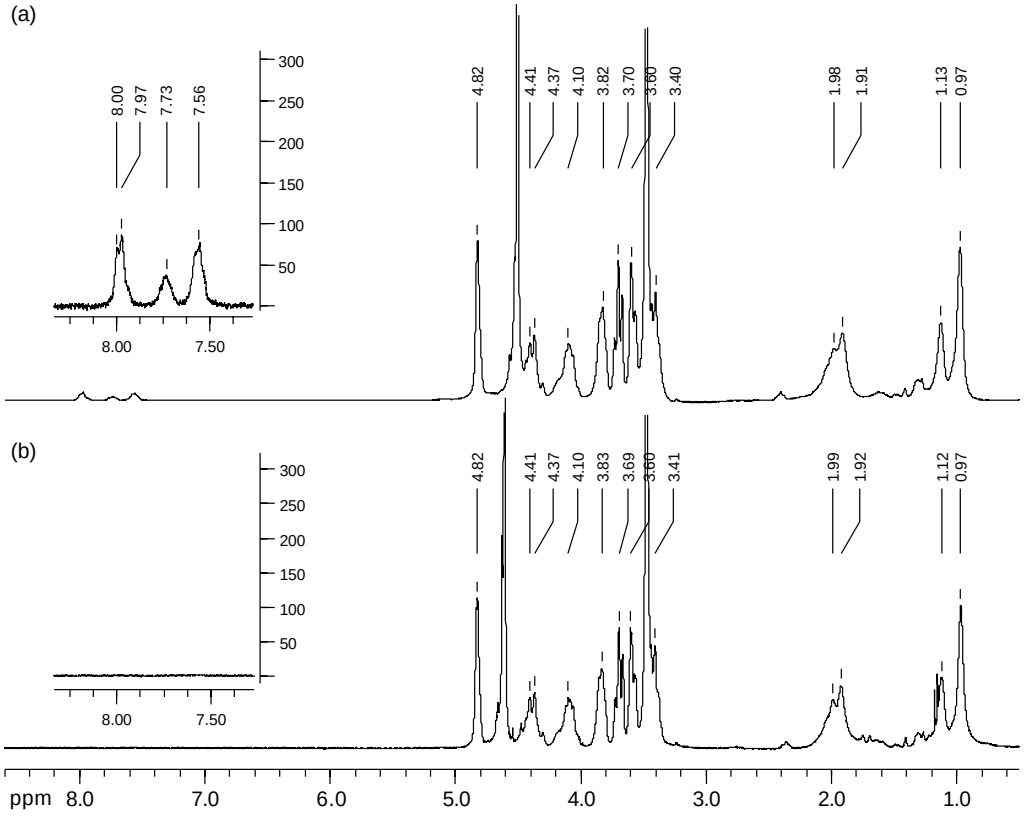


Fig. 6. ^{1}H NMR spectrum of (a) poly(methyl 6-*O*-methacryloyl-α-D-glucoside) dithiobenzoate **4** (50 °C) and (b) poly(methyl 6-*O*-methacryloyl-α-D-glucoside) thiol **5** (40 °C). Conditions: 300 MHz, D_2O. Note the disappearance of the dithiobenzoyl aromatic signals between 7.5 and 7.8 ppm.

Table 2
Summary of macroradical reaction experiments

Run no.	Macroraft (mM)	Macrothiol (mM)	Initiator (mM)	Reaction time (min)	M_n (Da)[a]		M_w/M_n[a]	
					Initial	Final	Initial	Final
1	4.4	4.4	3.8	92	9900	10,000	1.09	1.08
2	–	7.9	3.8	94	10,000	10,200	1.10	1.09

Temperature 70 °C; solvent: water/ethanol 87:13. [a]Size exclusion chromatography, calculated from the right angle light scattering signal with dn/dc = 0.0902.

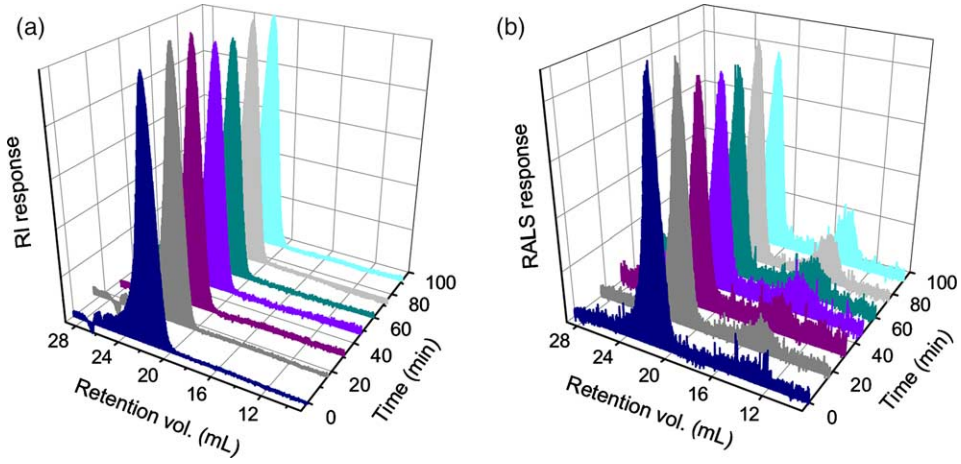


Fig. 7. Evolution of the size exclusion chromatography (a) refractive index (RI) and (b) right angle light scattering (RALS) trace with time for the reaction of poly(methyl 6-*O*-methacryloyl-α-D-glucoside) dithiobenzoate with poly(6-*O*-methacryloyl-α-D-glucoside) thiol in water/ethanol (run 1 in Table 2). Normalized areas.

reactions between partially (run 1) or totally (run 2) hydrolyzed RAFT-polymers cannot justify the change in molecular weight distribution observed for the sodium hydrogen carbonate protocol after quantitative monomer consumption was achieved.

4. Conclusions

The effect of an added base on the aqueous reversible addition–fragmentation chain transfer polymerization of a methacrylic glycomonomer with (4-cyanopentanoic acid)-4-dithiobenzoate was investigated. When sodium carbonate or sodium bicarbonate were used to dissolve the RAFT agent in aqueous solution, an inhibition period of 60–90 min was observed at the beginning of the polymerization together with a marked decrease of the overall polymerization rate. Also, experimental M_n values were much higher than the calculated ones in both cases. When sodium carbonate was used, control over the polymerization process was lost within 43% conversion, with a bimodal molecular weight distribution developing that eventually shifted outside the upper resolution limit of the SEC system. Better results were obtained with sodium bicarbonate, in which case the molecular weight distribution remained narrow and unimodal up to 81% conversion. At that point, a higher molecular weight shoulder began to develop that kept growing in intensity even after quantitative monomer consumption was achieved. Dramatically improved results were instead obtained when dissolution of (4-cyanopentanoic acid)-4-dithiobenzoate was facilitated by simple addition of circa 10% ethanol to the polymerization mixture. Following this protocol, narrow polydispersity poly(methyl 6-*O*-methacryloyl-α-D-glucoside) was obtained (PDI = 1.14) possessing a molecular weight (26,300 Da) close to the predicted value (28,300 Da).

The deviation from a well-controlled RAFT process observed for the polymerizations under basic conditions is most probably due to hydrolysis of the RAFT agent and of the end-of-chain dithiobenzoyl groups caused by the high pH of the solution. In this context, the generation of thiols and thionobenzoic acid will account for the strong inhibition and retardation observed. Thionobenzoate esters have in fact been described as chain transfer agents functioning via a radical addition–fragmentation mechanism [26,27]. In the absence of a leaving group though, thiobenzoic acid could either act as a radical scavenger (by forming non-propagating radicals) or as a retarder (by forming slowly re-initiating radicals). Finally, both the ethanol protocol experiment and model experiments involving a pre-formed macroRAFT agent and a macro-thiol indicate that, in the absence of a base and of thionobenzoic acid, coupling reactions between macroradicals cannot explain the change in molecular weight distribution after complete monomer conversion observed with the sodium hydrogen carbonate protocol. Further investigation is needed to elucidate the origin of this phenomenon.

Acknowledgements

L.A. acknowledges financial support from the Australian Department of Education, Training and Youth Affairs through

an International Postgraduate Research Scholarship. T.P.D. acknowledges the award of an Australian Professorial Fellowship.

References

[1] Moad G, Rizzardo E, Thang SH. Aust J Chem 2005;58(6):379–410.
[2] Donovan MS, Lowe AB, Sanford TA, McCormick CL. J Polym Sci, Part A: Polym Chem 2003;41(9):1262–81.
[3] McCormick CL, Lowe AB. Acc Chem Res 2004;37(5):312–25.
[4] Thomas DB, Convertine AJ, Hester RD, Lowe AB, McCormick CL. Macromolecules 2004;37(5):1735–41.
[5] Donovan MS, Sumerlin BS, Lowe AB, McCormick CL. Macromolecules 2002;35(23):8663–6.
[6] Lowe AB, McCormick CL. Aust J Chem 2002;55(6–7):367–79.
[7] Donovan MS, Sanford TA, Lowe AB, Sumerlin BS, Mitsukami Y, McCormick CL. Macromolecules 2002;35(12):4570–2.
[8] Sumerlin BS, Donovan MS, Mitsukami Y, Lowe AB, McCormick CL. Macromolecules 2001;34(19):6561–4.
[9] Mitsukami Y, Donovan MS, Lowe AB, McCormick CL. Macromolecules 2001;34(7):2248–56.
[10] Lowe AB, Sumerlin BS, McCormick CL. Polymer 2003;44(22):6761–5.
[11] Le TP, Moad G, Rizzardo E, Thang SH. Polymerization with living characteristics. WO 98/01478; 1998.
[12] Rizzardo E, Thang SH, Moad G. Synthesis of dithioester chain transfer agents and use of bis(thioacyl) disulfides or dithioesters as chain transfer agents. WO 99/05099; 1999.
[13] Albertin L. Well defined glycopolymers from RAFT polymerization: a chemoenzymatic approach. PhD Thesis. Sydney: The University of New South Wales; 2004.
[14] Albertin L, Stenzel M, Barner-Kowollik C, Foster LJR, Davis TP. Macromolecules 2004;37(20):7530–7.
[15] Albertin L, Kohlert C, Stenzel M, Foster LJR, Davis TP. Biomacromolecules 2004;5(2):255–60.
[16] Barner-Kowollik C, Davis TP, Heuts JPA, Stenzel MH, Vana P, Whittaker M. J Polym Sci, Part A: Polym Chem 2003;41(3):365–75.
[17] Thang SH, Chong YK, Mayadunne RTA, Moad G, Rizzardo E. Tetrahedron Lett 1999;40(12):2435–8.
[18] Kwak Y, Goto A, Tsujii Y, Murata Y, Komatsu K, Fukuda T. Macromolecules 2002;35(8):3026–9.
[19] Kwak Y, Goto A, Komatsu K, Sugiura Y, Fukuda T. Macromolecules 2004;37(12):4434–40.
[20] Kwak Y, Goto A, Fukuda T. Macromolecules 2004;37(4):1219–25.
[21] Vana P, Barner-Kowollik C, Davis TP, Matyjaszewski K. The encyclopedia of polymer science and technology. New York: Wiley; 2003.
[22] Matyjaszewski K. In: Matyjaszewski K, Davis TP, editors. Handbook of radical polymerization. Hoboken, USA: Wiley; 2002. p. 361–406.
[23] Russell GT, Gilbert RG, Napper DH. Macromolecules 1992;25(9):2459–69.
[24] Vana P, Davis TP, Barner-Kowollik C. Macromol Rapid Commun 2002;23(16):952–6.
[25] This is possible because the intensity of scattering is proportional to the square of the molecular mass of the dissolved polymer. See for example Johnson CS, Gabriel DA. Laser light scattering. New York: Dover Publications Inc.; 1994.
[26] Rizzardo E, Meijs GF, Thang SH. Macromol Symp 1995;98:101–23.
[27] Meijs GF, Rizzardo E, Le TPT, Chen Y-C. Die Makromolekulare chemie 1992;193(2):369–78.
[28] Theis A, Davis TP, Stenzel MH, Barner-kowollik C. Macromolecules 2005;38(24):10323–27.
[29] Johnston-Hall G, Theis A, Monteiro MJ, Davis TP, Stenzel MH, Barner-Kowollik C. Mocromol Chem Phys 2005;206(20):2047–53.