Macromolecules **2004,** *37,* 1735−1741

Hydrolytic Susceptibility of Dithioester Chain Transfer Agents and Implications in Aqueous RAFT Polymerizations[†]

**David B. Thomas,[‡] Anthony J. Convertine,[‡] Roger D. Hester,[‡]
Andrew B. Lowe,[§] and Charles L. McCormick*,[‡,§]**

*Department of Polymer Science, University of Southern Mississippi,
Hattiesburg, Mississippi 39406-0076, and Department of Chemistry and Biochemistry,
University of Southern Mississippi, Hattiesburg, Mississippi 39406-5043*

Received October 17, 2003; Revised Manuscript Received December 15, 2003

ABSTRACT: The controlled radical polymerization (CRP) technique reversible addition−fragmentation chain transfer (RAFT) has potential for preparing functional (co)polymers directly in an aqueous environment. Hydrolysis and aminolysis can eliminate the active end groups necessary for maintaining "livingness" in water. These reactions have not previously been evaluated with respect to their effect on aqueous RAFT polymerizations. Herein we determine rate constants of hydrolysis and aminolysis for representative water-soluble chain transfer agents (CTAs) cyanopentanoic acid dithiobenzoate (CTP) and the macro-chain-transfer agents (macro-CTAs) of poly(sodium 2-acrylamido-2-methylpropanesulfonate) ($AMPS_X$) and poly(acrylamide) (AM_X) at selected pH values. Rates of hydrolysis and aminolysis both increase with increasing pH and decrease with increasing molecular weight of the dithioester. On the basis of these rate constants, mathematical relationships have been developed to predict the number of living chain ends and the molecular weight with competitive hydrolysis. Utilizing this approach, predictions of molecular weight at specific conversions are in agreement with experimental values determined by SEC/MALLS.

Introduction

Of the polymerization techniques commonly used for the polymerization of vinyl monomers, free radical polymerization has long been recognized as the most robust.[1] As a result, a wide variety of functional monomers have been successfully polymerized over a range of reaction conditions. The recent advent of controlled radical polymerization[2] (CRP) techniques including atom transfer radical polymerization,[3,4] nitroxide-mediated polymerization,[5,6] and reversible addition−fragmentation chain transfer (RAFT)[7−10] polymerization has greatly expanded the utility of radical polymerization. Utilizing these techniques, it is possible to prepare polymers of controlled molecular weight and molecular weight distribution as well as advanced architectures such as block, comb, and star copolymers.[11] The RAFT process, in particular, is distinguished by its versatility with respect to both monomer choice and polymerization conditions. This control is achieved through a complex series of reactions and intermediates, which must be understood in order to select the appropriate combination of monomer(s), chain transfer agent (CTA), and polymerization conditions.

For successful homogeneous aqueous RAFT polymerization,[12−26] an additional layer of complexity must be addressed. Water may promote undesirable side reactions[17] including hydrolysis of the CTA, thereby diminishing the control of a polymerization. Thiocarbonyl compounds have long been known to be thermodynamically unstable toward hydrolysis. The difference in energy between the C=O functionality and the C=S functionality has been calculated to be 180 kJ mol^{-1}.[27] The kinetic barrier to hydrolysis, however, is significant. Accordingly, a strong temperature dependence is observed in the hydrolysis rates of dithioesters.[28] Levesque et al. found that at 20 °C 5−25% hydrolysis was observed in 24 h while at 35 °C 40−60% hydrolysis was observed over the same period depending on pH.

Recently, a second deleterious side reaction, aminolysis of the dithioester, was proposed as the failure mechanism in the aqueous RAFT polymerization of acrylamide at pH = 7.[17] The reaction of dithioesters with primary and secondary amines has been known for more than 50 years[29−31] and has recently been demonstrated to be an effective method for the modification of proteins through thioacylation.[28] The reaction is known to be first order with respect to dithioester concentration with a low energy of activation.[32] Amines are also known to catalyze the reaction, resulting in a second-order dependence on amine concentration.[28,32] Further, only unprotonated amines react with dithioesters, causing the aminolysis rate to be a strong function of solution pH.[28,33] Primary and secondary amines react rapidly with dithioesters at pH values above 7 but are essentially unreactive below pH = 7.

The impact of dithioester hydrolysis and/or aminolysis on aqueous RAFT polymerizations is a particularly important issue because both result in loss of active chain ends, diminish control, and increase polydispersity; however, these have not been specifically addressed in prior literature. In fact, the only publication that specifically discusses CTA stability as it relates to polymerization control is concerned with photolysis of the dithioesters.[34]

In this contribution, we seek to better quantify the effects of hydrolysis and aminolysis reactions on aqueous RAFT polymerizations. The most widely utilized water-soluble CTA, sodium 4-cyanopentanoic acid dithiobenzoate (CTP), and macro-chain-transfer agents

---

[†] Paper No. 96 in a series entitled "Water-Soluble Polymers".
[‡] Department of Polymer Science.
[§] Department of Chemistry and Biochemistry.
* To whom correspondence should be addressed.

10.1021/ma035572t CCC: $27.50

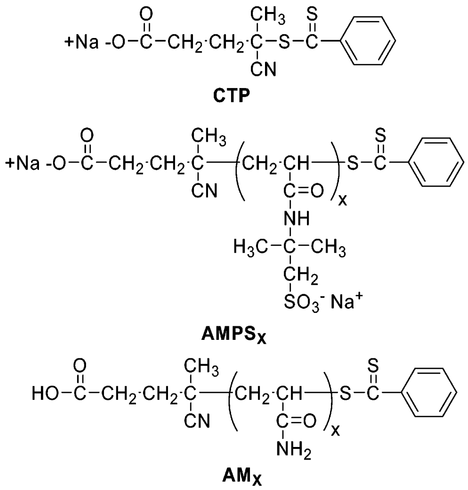


Figure 1. Dithioester compounds: 4-cyanopentanoic acid dithiobenzoate (CTP) and macro-CTAs of sodium 2-acrylamido-2-methylpropanesulfonate (AMPS$_X$) and acrylamide (AM$_X$).

(macro-CTAs) of poly(sodium 2-acrylamido-2-methylpropanesulfonate) (AMPS$_X$) and poly(acrylamide) (AM$_X$) have been studied under aqueous conditions similar to those used for polymerization (Figure 1). Specific goals of this work include the development of an understanding of the effects of molecular weight and solution pH on the rate of CTA hydrolysis and quantification of the relative importance of aminolysis and hydrolysis under specified conditions. Given relative rates of hydrolysis and aminolysis, it is now possible to the predict molecular weight of polymers produced under aqueous RAFT conditions.

Experimental Section

Materials. All chemicals were purchased from Aldrich at the highest purity available and used as received unless otherwise noted. 4-Cyanopentanoic acid dithiobenzoate (CTP) was prepared according to a published proceedure.[12] Deionized water (DI H_2O) was obtained from a Barnstead NANO-Pure reverse osmosis filtration unit (resistivity >18 MΩ). Buffers (0.02 M, pH = 5.5, 7.0, 9.0, 10.0) were prepared by dissolving the tetrasodium salt of ethylenediaminetetraacetic acid (EDTA) in DI H_2O and adjusting the pH with concentrated HCl. A buffer solution of pH = 2.0 was prepared by diluting concentrated HCl to a concentration of 0.01 M with DI H_2O. Macro-chain-transfer agents (macro-CTAs) of poly(sodium 2-acrylamido-2-methylpropanesulfonate) (AMPS$_X$)[13,22] ($M_n = 8900$, $M_w/M_n = 1.11$; $M_n = 2400$, $M_w/M_n = 1.20$) and poly(acrylamide)[25] ($M_n = 58\,000$, $M_w/M_n = 1.17$; $M_n = 1200$, $M_w/M_n = 1.20$) were prepared according to published procedures.

Hydrolysis Solutions. A stock solution of CTP was first prepared by dissolving 505.3 mg (1.8 mmol) of CTP in diethyl ether and adding DI H_2O so that a phase-separated mixture resulted. Small amounts of 6 M NaOH were then added at 0 °C with frequent agitation until all of the red color was in the aqueous phase. The solution was then purged with N_2 for 30 min to remove the ether, resulting in a final stock solution of 9.11 wt %, pH = 7. An appropriate amount of the stock solution was diluted with the buffer of the appropriate pH so that the final concentration of CTA in solution was 5.0×10^{-3} M. Solutions of AMPS$_X$ and AM$_X$ were prepared from the freeze-dried polymer by direct dissolution in the appropriate buffer so that the final concentration of end groups was 5.0×10^{-3} M. All solutions were placed in septa-sealed vials and purged with N_2 for 20 min prior to reaction at 70 °C. Aliquots were removed at selected times for analysis.

Aminolysis Solutions. Samples were prepared in the same manner as the hydrolysis solutions, except that ammonium hydroxide was added to the buffered solutions (pH = 5.5 and 7.0) such that the final ammonia concentration was 5.0×10^{-3} M. The pH of the solution was then adjusted one last time by addition of 0.1024 N HCl. All solutions were placed in septa-sealed vials and purged with N_2 for 20 min prior to reaction at 70 °C. Aliquots were removed at selected times for analysis.

Hydrolysis Solutions for NMR Spectroscopy. A sample of CTP in EDTA/D_2O was prepared by dissolving 11 mg (0.029 mmol) of ethylenediaminetetraacetic acid, tetrasodium salt (EDTA), in 1 mL of D_2O and adjusting the pH to ~7 with DCl. CTP (80 mg) (0.286 mmol) was then added to the solution with rapid stirring. Small amounts of NaOD were added to maintain the pH ~7 as the CTP dissolved. Finally, the solution pH was adjusted to 9.0. A sample of macro-CTA was dissolved directly in the EDTA/D_2O buffer at pH = 9.0. The samples were then purged with N_2 for 15 min, transferred to an NMR tube, and sealed under a N_2 atmosphere. The samples were heated at 70 °C, and ^{1}H NMR spectra were obtained at 0, 2, 4, and 6 h.

Aqueous Size Exclusion Chromatography (ASEC). Absolute molecular weights and polydispersities of the polymers were determined by ASEC using Viscotek TSK Viscogel (G3000PW$_{XL}$, 200 Å) and TosoBiosciences TSK-GEL (G2500PW$_{XL}$, <200 Å) columns and 0.05 M Na_2SO_4/acetonitrile, 80/20 (v/v), as the eluent at a flow rate of 0.5 mL/min. Detection was achieved via a Polymer Labs LC1200 UV/vis detector, a Wyatt Optilab DSP interferometric refractometer, and a Wyatt DAWN EOS multiangle laser light scattering detector ($\lambda = 690$ nm). The dn/dc values were determined using a Wyatt Optilab interferrometric refractometer and the Wyatt ASTRA SEC/LS software package at 690 nm and 25 °C in the above eluent. AMPS$_X$ and AM$_X$ hydrolysis samples were analyzed directly utilizing ASEC to separate the polymer from any small molecules in solution. The fraction of the dithioester functionality that remained on the chain end was determined by comparison of the area of the UV signal of the polymer ($\lambda = 300$ nm) at t_x to that at $t = 0$.

Other Analytical Techniques. CTP hydrolysis and aminolysis aliquots were separated by high-pressure liquid chromatography (HPLC) using YMC-Pack ODS-Al (250 × 4.6 mm) and Agilent ZORBAX Eclipse XDB-C8 (150 × 4.6 mm) columns with methanol as the eluent at a flow rate of 0.15 mL/min. The disappearance of CTP was followed by monitoring the integrated intensity of the UV signal (300 nm) and comparing the area at t_x to that at $t = 0$. NMR spectra were obtained on a Varian 200 MHz (CTP) or 500 MHz (macro-CTA) spectrometer using D_2O as the solvent and the residual solvent peak as the internal reference.

Results and Discussion

Our recent efforts to polymerize acrylamide and *N*-[3-(dimethylamino)propyl]methacrylamide directly in aqueous media clearly highlight the importance of pH in aqueous RAFT polymerizations and acrylamido polymerizations in particular.[17,18,24,25] It was of interest, therefore, to examine more closely the hydrolytic stability of dithioesters useful in RAFT polymerization as a function of solution pH and molecular weight. Further, the comparison of the rates of hydrolysis to those of aminolysis (the proposed failure mechanism in the polymerization of acrylamide at ambient pH)[17] would allow the evaluation of the relative importance of these two processes in aqueous RAFT polymerization. Finally, we desired to develop a model to predict the effect of dithioester hydrolysis on the resultant polymer molecular weights and polydispersities. To this end, we studied the most widely used water-soluble chain transfer agent, CTP, as well as representative water-soluble macro-CTAs, AMPS$_X$ and AM$_X$ (Figure 1), at selected pH values. EDTA was selected as the buffering species due the large number of ionizable moieties, allowing buffers to be prepared at pH = 5.5, 7.0, 9.0, and 10.0.

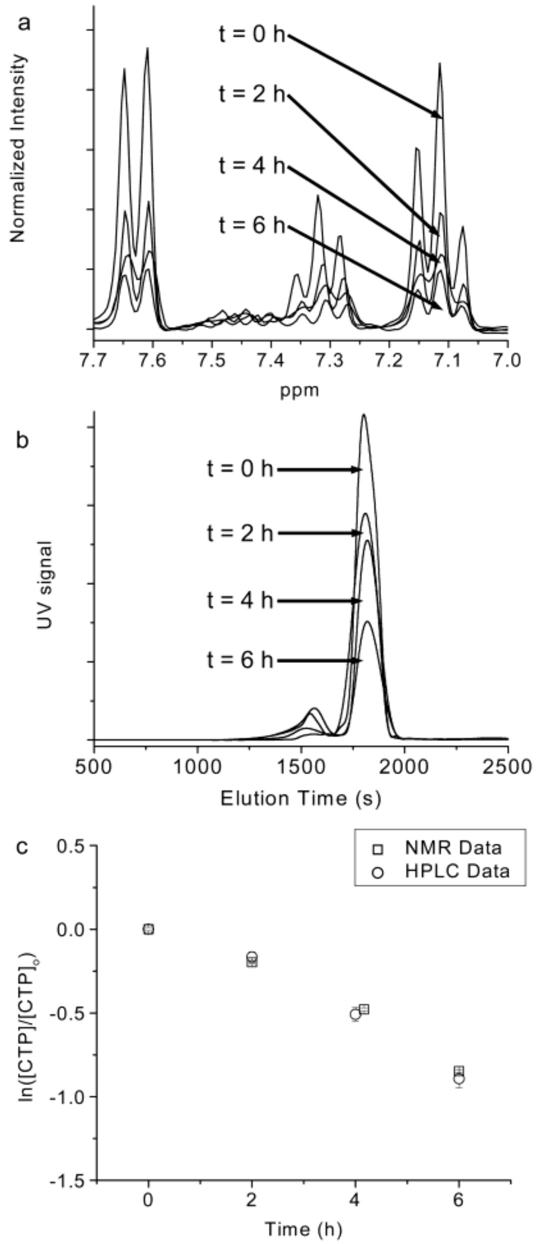


Figure 2. (a) ^{1}H NMR spectra, (b) HPLC chromatograms, and (c) the pseudo-first-order rate plots for the hydrolysis of CTP at pH = 9.0.

Solutions at pH = 2.0 were prepared with HCl due to the insolubility of EDTA at this low-pH condition.

The disappearance of dithioester with time was followed with ^{1}H NMR. No attempt was made to identify the various hydrolysis and aminolysis products, since the concentration of the dithioester remaining in solution was of primary concern. Successful quantification of the amount of dithioester remaining necessitated the separation of the dithioester from both the buffering species and the reaction products. For CTP this was achieved via HPLC using C_{18} and C_8 functionalized columns in series with methanol as the eluent. The HPLC method was verified by comparison of the ^{1}H NMR spectra of a sample of CTP hydrolyzed in D_2O buffered at pH = 9.0 (Figure 2a) with the chromatographs of a separate sample hydrolyzed at the same pH (Figure 2b). In ^{1}H NMR spectroscopy, the triplet at 7.12 ppm and the doublet at 7.63 ppm correspond to aromatic protons in CTP.[12] These signals proved ideal for following the disappearance of CTP due to the absence of any overlapping signals from the reaction products. The excellent agreement between the data obtained by NMR and HPLC (Figure 2c) confirmed the efficient separation of CTP by HPLC. The ASEC method to separate the macro-CTAs from hydrolysis products was confirmed in a similar manner.

Table 1. Rates of Hydrolysis (k_{hyd}) and Aminolysis (k_{a}) at 70 °C for Different CTAs as a Function of pH

CTA	pH	$k_{\mathrm{hyd}} \times 10^5$ (s^{-1})	$k_{\mathrm{a}} \times 10^2$ ($L^2\ mol^{-2}\ s^{-1}$)
CTP	5.5[a]	1.8 ± 0.4	0
CTP	7.0[a]	2.5 ± 0.2	44 ± 5
CTP	9.0[a]	4.2 ± 0.4	
CTP	10.0[a]	15 ± 1	
$AMPS_9$	2.0[b]	0.15 ± 0.03	
$AMPS_9$	5.5[a]	0.29 ± 0.05	
$AMPS_9$	7.0[a]	0.19 ± 0.04	
$AMPS_9$	9.0[a]	0.57 ± 0.04	
$AMPS_9$	10.0[a]	1.1 ± 0.1	
$AMPS_{38}$	2.0[b]	0.15 ± 0.03	
$AMPS_{38}$	5.5[a]	0.14 ± 0.02	
$AMPS_{38}$	7.0[a]	0.20 ± 0.03	0.6 ± 0. 3
$AMPS_{38}$	9.0[a]	0.360 ± 0.004	
$AMPS_{38}$	10.0[a]	0.84 ± 0.06	
AM_{17}	5.5	0.88 ± 0.03	
AM_{816}	5.5	0.44 ± 0.03	

[a] Buffered with EDTA. [b] 0.01 M HCl(aq).

CTA Hydrolysis. With the large excess of water present under the experimental conditions, the hydrolysis reaction can be considered to be zero-order with respect to water. The rate of CTA hydrolysis can, therefore, be expressed in terms of an apparent rate constant of hydrolysis, k_{hyd}, and the CTA concentration, [CTA] (eq 1).

$$-\frac{\mathrm{d[CTA]}}{\mathrm{d}t} = k_{\mathrm{hyd}}[\mathrm{CTA}] \qquad (1)$$

The pseudo-first-order rate plots for the hydrolysis of CTP, $AMPS_{38}$, and $AMPS_9$ are presented in parts a, b, and c of Figure 3, respectively. Reasonably good fits are obtained, allowing estimates of the rate constants. The rate constants for hydrolysis are compiled in Table 1. It is apparent that both pH and CTA molecular weight have a strong influence on the rate of hydrolysis. Consistent with trends reported earlier,[28] the magnitude of k_{hyd} for CTP increases by nearly 1 order of magnitude from 2.5×10^{-5} to 15×10^{-5} s^{-1} as the pH increases from 7.0 to 10. Also, very little change in k_{hyd} was observed as the pH was reduced from 7.0 to 2.0.

The effect of degree of polymerization can be observed by comparing the values of k_{hyd} for $AMPS_{38}$, $AMPS_9$ and CTP. $AMPS_{38}$ hydrolyzes much more slowly than CTP and a little more slowly than $AMPS_9$. At pH = 9.0 values of k_{hyd} were determined as 4.2×10^{-5} s^{-1}, 0.57×10^{-5} s^{-1}, and 0.360×10^{-5} s^{-1} for CTP, $AMPS_9$, and $AMPS_{38}$ respectively. This behavior can be attributed to steric hindrance to the attack of water molecules on the dithioester, analogous to the well-known steric effects observed for carboxylic ester hydrolysis.[35] Macro-CTAs of acrylamide showed a similar trend in values of k_{hyd}.

CTA Aminolysis. The fraction of CTP remaining under aminolysis conditions as a function of time at pH = 5.5 and 7.0 is presented in Figure 4. It is important to note that the decreasing concentrations of CTP result from a combination of hydrolysis and aminolysis. This

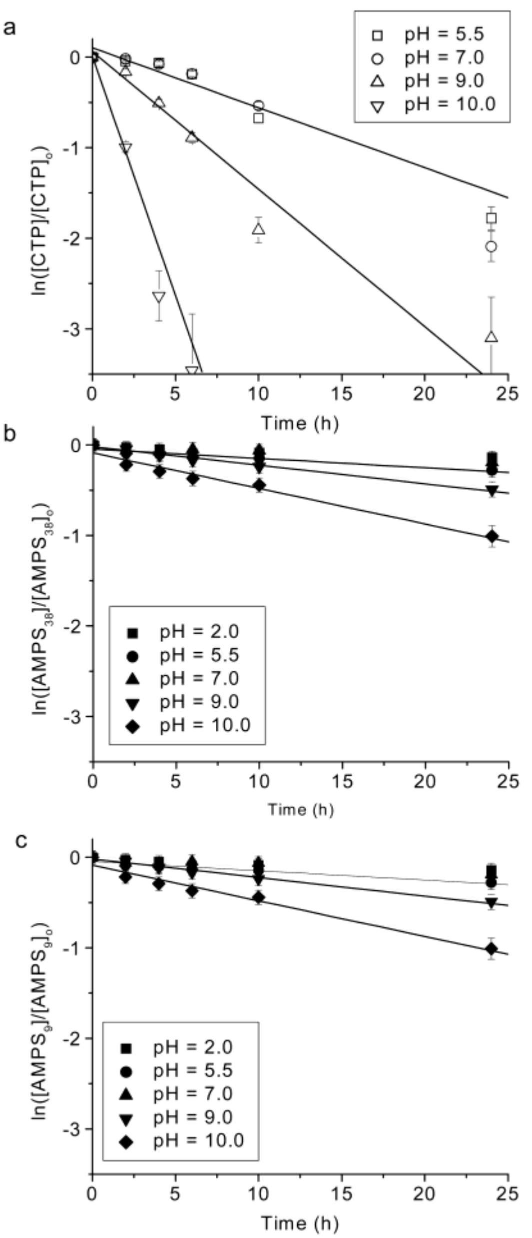


Figure 3. Pseudo-first-order rate plots for the hydrolysis of (a) CTP, (b) $AMPS_{38}$, and (c) $AMPS_9$ at 70 °C.

is described in eq 2

$$-\frac{d[CTA]}{dt} = k_{hyd}[CTA] + k_a[CTA][NH_3]^2 \qquad (2)$$

where k_a is the third-order rate constant for aminolysis and $[NH_3]$ is the concentration of ammonia in solution. (Here we use the order indicated in the literature report of Levesque et al.[28,32]) Applying the stoichiometric condition used in the experiments, $[CTA] = [NH_3]$, and integrating yields the relationship for k_a in eq 3, where $[CTA]_0$ is the initial concentration of CTA.

$$k_a = -k_h \frac{[CTA]^2 e^{2k_h t} - [CTA]_0^{\,2}}{(e^{2k_h t} - 1)[CTA]_0^{\,2}[CTA]^2} \qquad (3)$$

At pH = 5.5, all of the loss of CTP can be attributed to hydrolysis, but at pH = 7.0 aminolysis is also a significant process. The rate of aminolysis on a polymeric dithioester was determined in a similar manner utilizing $AMPS_{38}$ as the dithioester. The values of k_a are given in Table 1.

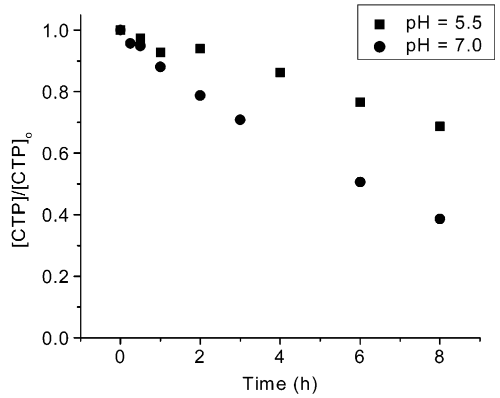


Figure 4. Fraction of CTP remaining under conditions where both hydrolysis and aminolysis may be significant.

Table 2. Kinetic Data from Aqueous RAFT Polymerizations Performed at 70 °C with a Dithiobenzoate as the CTA

monomer	t_{ind} (min)	$k_p^* \times 10^5$ (s^{-1})
AMPS[13]	51	12
acrylamide[17]	0	0.36

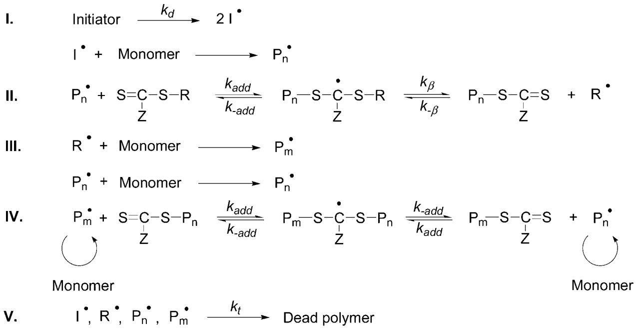
Effect of Dithioester Hydrolysis and Aminolysis on Aqueous RAFT Polymerizations. Under aqueous polymerization conditions, hydrolysis and aminolysis combine to reduce the concentration of CTA in solution below that which was originally introduced. The relative importance of these reactions, however, depends on the concentrations of monomer and amine as well as the magnitudes of k_{hyd}, k_a, and the apparent rate constant of propagation, k_p^*. Further, the length of the induction period, t_{ind}, in aqueous polymerizations is obviously very important because it extends the length of time that the more hydrolytically susceptible, low molecular weight CTA is exposed to the aqueous environment. Values of k_p^* and t_{ind} obtained from the literature are compiled in Table 2. In this section we develop the equations necessary to quantify the effects of these various processes in real aqueous RAFT polymerizations.

In an aqueous polymerization, the ammonia in solution arises from the hydrolysis of monomer and is depleted by reaction with [CTA]. Under this condition $[NH_3] \neq [CTA]$, but assuming a steady-state concentration of ammonia, the integrated form of eq 2 may be written as eq 4, which describes the time dependent concentration of CTA.

$$[CTA] = [CTA]_0\, e^{-(k_{hyd} + k_a[NH_3]^2)t} \qquad (4)$$

However, the RAFT process is comprised of *two* distinct phases (II and IV, Scheme 1). During the first, termed the preequilibrium (II, Scheme 1), the low molecular weight CTA is converted to macro-CTA. Experimentally, this process may be observed in the pseudo-first-order kinetic plot of the polymerization as an induction period, t_{ind}.[36,37] Values of t_{ind} ranging from 0 up to 10 h have been reported, after which successful RAFT polymerization was possible.[16,37,38] Since low molecular weight CTAs are only present in the system during this period, it is appropriate to use the value of k_{hyd} and k_a obtained for CTP ($k_{hyd,CTP}$ and $k_{a,CTP}$) and t_{ind} in eq 4 to describe the amount of CTA left at the

Scheme 1. Proposed RAFT Mechanism



end of the induction period, $[\mathrm{CTA}]_{\mathrm{ind}}$ (eq 5).

$$[\mathrm{CTA}]_{\mathrm{ind}} = [\mathrm{CTA}]_0\ \mathrm{e}^{-(k_{\mathrm{hyd,CTP}}+k_{\mathrm{a,CTP}}[\mathrm{NH_3}]^2)t_{\mathrm{ind}}} \tag{5}$$

At polymerization times significantly longer than the induction period, however, the hydrolysis of the macro-CTA must also be considered. Since the rate of hydrolysis was found to decrease sharply as the CTA was converted to a macro-CTA with 9-mer units, but much more gradually between 9- and 38-mer units, the rate constant of hydrolysis of the macro-CTA can be assumed to be constant, $k_{\mathrm{hyd,macro}}$. Similarly, the rate constant for aminolysis of the macro-CTA, $k_{\mathrm{a,macro}}$, may be used. The equation that describes the CTA concentration during the main equilibrium (IV, Scheme 1) can be obtained from eq 4 by substituting $[\mathrm{CTA}]_{\mathrm{ind}}$ for $[\mathrm{CTA}]_0$, $k_{\mathrm{hyd,macro}}$ for k_{hyd}, $k_{\mathrm{a,macro}}$ for k_{a}, and the time during the main equilibrium, $(t - t_{\mathrm{ind}})$, for t (eq 6).

$$[\mathrm{CTA}] = [\mathrm{CTA}]_{\mathrm{ind}}\ \mathrm{e}^{-(k_{\mathrm{hyd,\,macro}}+k_{\mathrm{a,macro}}[\mathrm{NH_3}]^2)(t-t_{\mathrm{ind}})} \tag{6}$$

Since the concentration of living chains is equal to the concentration of CTA, eq 6 also represents the concentration of living chains in the reaction. Accordingly, the concentration of dead chains may be calculated from the difference between the CTA concentration at the start of polymerization, $[\mathrm{CTA}]_{\mathrm{ind}}$, and the time-dependent CTA concentration (eq 7).

$$[\text{dead chains}] = [\mathrm{CTA}]_{\mathrm{ind}} - [\mathrm{CTA}] \tag{7}$$

The time-dependent concentration of CTA may also be applied to describe the time-dependent molecular weight, $M_{\mathrm{n}}(t)$, of the living chains in an aqueous RAFT polymerization. The conventional equation used to predict the molecular weight, M_{n}, of polymers produced by RAFT depends on the molecular weight of the monomer, M_{MW}, the initial monomer concentration, $[\mathrm{M}]_0$, the conversion, p, the initial CTA concentration, and the molecular weight of the CTA, M_{CTA}, as described by eq 8.

$$M_{\mathrm{n}} = \frac{M_{\mathrm{MW}}[\mathrm{M}]_0 p}{[\mathrm{CTA}]_0} + M_{\mathrm{CTA}} \tag{8}$$

Substituting the time-dependent concentration of CTA from eq 6 for $[\mathrm{CTA}]_0$ and the pseudo-first-order relationship for polymerization (eq 9) into eq 8 yields an equation for the molecular weight of the living chains as a function of time, $M_{\mathrm{n}}(t)$ (eq 10).

$$[\mathrm{M}]_0 p = [\mathrm{M}]_0 - [\mathrm{M}]_0\ \mathrm{e}^{-k_{\mathrm{p}}^*(t-t_{\mathrm{ind}})} \tag{9}$$

$$[\mathrm{M}]_n(t) = \frac{M_{\mathrm{MW}}([\mathrm{M}]_0 - [\mathrm{M}]_0 \mathrm{e}^{-k_{\mathrm{p}}^*(t-t_{\mathrm{ind}})})}{[\mathrm{CTA}]_{\mathrm{ind}}\ \mathrm{e}^{-(k_{\mathrm{hyd,macro}}+k_{\mathrm{a,macro}}[\mathrm{NH_3}]^2)(t-t_{\mathrm{ind}})}} \tag{10}$$

It is important to note that eq 10 is only valid when (a) the RAFT mechanism is operational, (b) the rate of polymerization is greater than the rate of hydrolysis ($k_{\mathrm{p}}^*[\mathrm{M}] > k_{\mathrm{hyd}}[\mathrm{CTA}]$), and (c) k_{p}^* is constant. So long as $[\mathrm{M}]/[\mathrm{CTA}]$ is not too great (here we limit $[\mathrm{M}]/[\mathrm{CTA}] < 2000$) and monomer conversion is not too high, the first two criteria may be met. The third criterion dictates that eq 10 is only valid for real systems where the pseudo-first-order kinetic plot is linear. With these restrictions in mind, it was of interest to examine some experimental data from the literature in terms of these equations.

In our recent report of acrylamide polymerization, it was found that at pH = 7 all visible color was bleached from solution in 4 h, indicating the near-quantitative loss of CTA.[17] Applying eq 4 to this situation (utilizing the values of k_{hyd} and k_{a} obtained for CTP at pH = 7.0) indicates that 95% of the CTP is destroyed in 4 h when the steady-state concentration of ammonia $[\mathrm{NH_3}] = 0.02$ M. This represents just 1 mol % of the total monomer in solution and supports aminolysis as a reasonable failure mechanism for acrylamide polymerization at pH = 7. Further, the importance of performing the aqueous polymerization of hydrolytically susceptible acrylamido monomers in acidic conditions is underscored.[17,24]

Even when aminolysis is not a concern (e.g., when low-pH conditions are utilized) dithioester hydrolysis may seriously impact the control in an aqueous RAFT polymerization. Here two specific cases, acrylamide polymerization at pH = 5.5 and AMPS polymerization at pH = 7.0 (both at 70 °C), are examined.

The concentration of living and dead chain ends is plotted as a function of time in parts a and b of Figure 5 for acrylamide and AMPS polymerizations, respectively. For acrylamide, the apparent rate of RAFT polymerization is quite low, necessitating long reaction times (28% conversion was obtained in 1440 min).[17] During this time period, extensive CTA hydrolysis can occur, resulting in only 68% of the chains in solution retaining functional end groups. The polymerization of AMPS, on the other hand, proceeds at a much greater rate, reaching 76% conversion in just 250 min. During this relatively short time period, only limited hydrolysis occurs and 98% of the chains retain functional end groups.

The molecular weight control for these polymerizations was also examined using eq 10. The predicted molecular weights with and without hydrolysis are plotted as a function of conversion in parts c and d of Figure 5 for acrylamide and AMPS polymerizations, respectively. Once again hydrolysis has a greater effect on the acrylamide polymerization due to the slow rate of polymerization. At 27% conversion, the predicted molecular weight with hydrolysis is 22 000, while in the absence of hydrolysis the predicted molecular weight is 15 000. Further, it is clear from Figure 5c that disparity between the two values only increases with increasing conversion. For AMPS polymerization, on the other hand, there is relatively little difference between the two predicted values. At 76% conversion, molecular weights of 29 000 and 26 000 are predicted in the presence and absence of hydrolysis, respectively.

These predictions compare well with the experimental results for acrylamide and AMPS polymerizations.

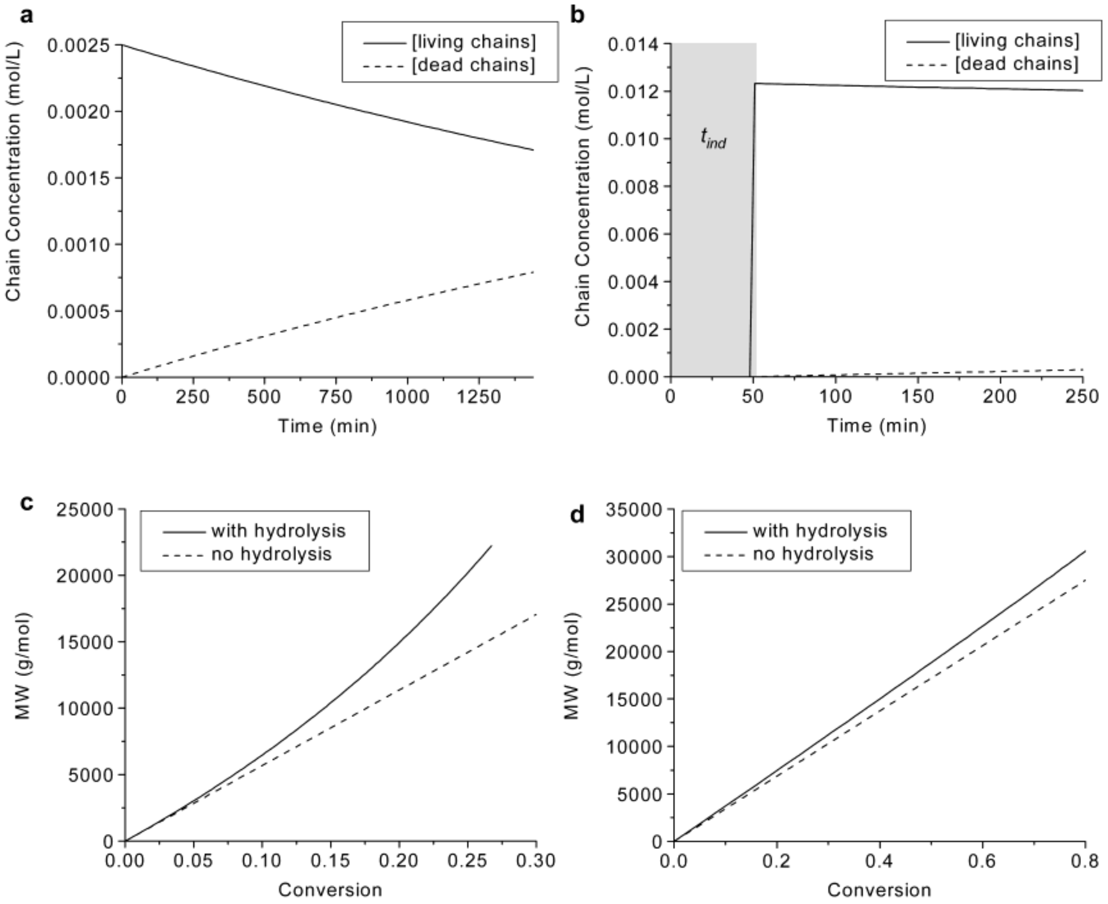


Figure 5. Theoretically predicted concentrations of living and dead chain ends for (a) acrylamide polymerization at pH = 5.5, 70 °C, and (b) AMPS polymerization at pH = 7, 70 °C. Molecular weights as a function of conversion for (c) acrylamide polymerization at pH = 5.5, 70 °C, and (d) AMPS polymerization at pH = 7, 70 °C. Molecular weights with and without hydrolysis were calculated utilizing eqs 10 and 8, respectively. (For acrylamide polymerizations $t_{\mathrm{ind}} = 0$ min, $k_{\mathrm{p}}{}^* = 0.36 \times 10^{-5}$ s^{-1}, $k_{\mathrm{a,macro}} = 0$, $[\mathrm{NH_3}] = 0.02$ M, $k_{\mathrm{hyd,CTP}} = 1.8 \times 10^{-5}$ s^{-1}, and $k_{\mathrm{hyd,macro}} = 0.44 \times 10^{-5}$ s^{-1}; for AMPS polymerizations $t_{\mathrm{ind}} = 51$ min, $k_{\mathrm{p}}{}^* = 12 \times 10^{-5}$ s^{-1}, $k_{\mathrm{a,macro}} = 0.6$, $[\mathrm{NH_3}] = 0$, $k_{\mathrm{hyd,CTP}} = 2.5 \times 10^{-5}$ s^{-1}, and $k_{\mathrm{hyd,macro}} = 0.2 \times 10^{-5}$ s^{-1}.)

Polymerization of acrylamide in water produces polymers with molecular weights substantially higher than predicted by eq 8. Further, the differences observed between molecular weights predicted with eqs 8 and 10 are in line with the differences observed in aqueous vs organic RAFT polymerizations of acrylamide mediated by a dithioester.[25] At 24 h, values predicted by eq 10 are 46% higher than those predicted by eq 8, while aqueous polymerizations produced polymers with molecular weights 38% higher than those in organic polymerization. Likewise, aqueous RAFT polymerizations of AMPS yielded polymers with molecular weights in reasonable agreement with values predicted by eq 8 (within 10%).[13,19] The reader should note that the molecular weights and conversions were obtained by direct aqueous SEC analysis using RI and MALLS detection so deviations are not due to inaccuracies common in utilizing SEC standards.

Conclusions

Clearly, hydrolysis and aminolysis can be important issues in aqueous RAFT polymerization. Through careful management of reaction conditions, however, it is possible to minimize their effects. Maintenance of appropriate solution pH is an important strategy. Hydrolysis may be minimized at neutral to moderately acidic solution pH values. When aminolysis may be an issue, however, acidic conditions are indicated. Also, management of the reaction kinetics is useful. Minimization of the induction period and maximization of the polymerization rate greatly improve the retention of chain end functionality. The rate constants and equations presented in this contribution should serve as a useful guide for evaluating the importance of hydrolysis and aminolysis in specific aqueous polymerization systems. Herein we successfully utilized them to predict molecular weights at specific conversions in aqueous polymerizations of acrylamide and AMPS.

Acknowledgment. Support from the Department of Energy DE-FC26-01BC15317, GelTex Pharmaceuticals Inc., and the MRSEC program of the National Science Foundation (DMR-0213883) is gratefully acknowledged.

References and Notes

(1) Odian, G. *Principles of Polymerization*, 3rd ed.; Wiley-Interscience: New York, 1991.

(2) Darling, T.; Davis, T. P.; Fryd, M.; Gridnev, A.; Haddleton, D. M.; Ittel, S.; Matheson, R.; Moad, G.; Rizzardo, E. *J. Polym. Sci., Polym. Chem.* **2000**, *38*, 1706.

(3) Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimuro, T. *Macromolecules* **1995**, *28*, 1721.

(4) Wang, J. S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614.

(5) Solomon, D. H.; Rizzardo, E. US Patent 4,581,429, 1986.

(6) Georges, M. K.; Veregin, R. P. N.; Kazmaier, K. M.; Hamer, G. K. *Macromolecules* **1993**, *26*, 2987.

(7) 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.
(8) Quinn, J. F.; Rizzardo, E.; Davis, T. P. *Chem. Commun.* **2001**, 1044.
(9) Goto, A.; Sato, K.; Tsujii, Y.; Fukuda, T.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **2001**, *34*, 402.
(10) Vana, P.; Quinn, J. F.; Davis, T. P.; Barner-Kowollik, C. *Aust. J. Chem.* **2002**, *55*, 425.
(11) *Handbook of Radical Polymerization*; Matyjaszewski, K., Davis, T. P., Eds.; Wiley: Hoboken, 2002.
(12) Mitsukami, Y.; Donovan, M. S.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2001**, *34*, 2248.
(13) Sumerlin, B. S.; Donovan, M. S.; Mitsukami, Y.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2001**, *34*, 6561.
(14) Donovan, M. S.; Sumerlin, B. S.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2002**, *35*, 8663.
(15) Donovan, M. S.; Sanford, T. A.; Lowe, A. B.; Sumerlin, B. S.; Mitsukami, Y.; McCormick, C. L. *Macromolecules* **2002**, *35*, 4570.
(16) Donovan, M. S.; Lowe, A. B.; Sanford, T. A.; McCormick, C. L. *J. Polym. Sci., Polym. Chem.* **2003**, *41*, 1262.
(17) Thomas, D. B.; Sumerlin, B. S.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2003**, *36*, 1436.
(18) McCormick, C. L.; Donovan, M. S.; Lowe, A. B.; Sumerlin, B. S.; Thomas, D. B. Chain Transfer Agents for RAFT Polymerization in Aqueous Media. US Application No. 10/073,820.
(19) Sumerlin, B. S.; Lowe, A. B.; Thomas, D. B.; McCormick, C. L. *Macromolecules* **2003**, *36*, 5982.
(20) Lowe, A. B.; McCormick, C. L. *Aust. J. Chem.* **2002**, *55*, 367.
(21) Lowe, A. B.; Sumerlin, B. S.; Donovan, M. S.; Thomas, D. B.; Hennaux, P.; McCormick, C. L. In *Advances in Controlled/Living Radical Polymerization*; Matyjaszewski, K., Ed.; ACS Symposium Series 852; American Chemical Society: Washington, DC; p 586.
(22) Sumerlin, B. S.; Lowe, A. B.; Thomas, D. B.; McCormick, C. L. *Macromolecules* **2003**, *36*, 5982.
(23) Yusa, S.-I.; Shimada, Y.; Mitsukami, Y.; Yamamoto, T.; Morishima, Y. *Macromolecules* **2003**, *36*, 4208.
(24) Vasilieva, Y. A.; Thomas, D. B.; Scales, C. W.; McCormick, C. L., submitted to *Macromolecules*.
(25) The buffer for the polymerization of acrylamide is an acetic acid/sodium acetate buffer as described in a recently submitted manuscript: Thomas, D. B.; Convertine, A. J.; Myrick, L. J.; Scales, C. W.; Lowe, A. B.; Ayres, N.; McCormick, C. L., submitted to *Macromolecules*.
(26) Sumerlin, B. S. Ph.D. dissertation, 2003.
(27) Bonnans-Plaisance, C.; Gressier, J. C.; Levesque, G.; Mahjoub, A. *Bull. Soc. Chim. Fr.* **1985**, 891.
(28) Levesque, G.; Arsène, P.; Fanneau-Bellenger, V.; Pham, T.-N. *Biomacromolecules* **2000**, *1*, 400.
(29) Kjaer, A. *Acta Chem. Scand.* **1950**, *4*, 1347.
(30) Kjaer, A. *Acta Chem. Scand.* **1952**, *6*, 327.
(31) Kjaer, A. *Acta Chem. Scand.* **1952**, *6*, 1374.
(32) Delêtre, M.; Levesque, G. *Macromolecules* **1990**, *23*, 4733.
(33) Scheithauer, S.; Mayer, R. Thio and Dithiocarboxylic Acids and Their Derivaties. In *Topics in Sulfur Chemistry*; Senning, A., Ed.; G. Thieme Verlag: Stuttgart, Germany, 1979; Vol. 4.
(34) Quinn, J. F.; Barner, L.; Barner Kowollik, C.; Rizzardo, E.; Davis, T. P. *Macromolecules* **2002**, *35*, 7620.
(35) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; Wiley-Interscience: New York, 1992; p 285.
(36) Vana, P.; Davis, T. P.; Barner-Kowollik, C. *Macromol. Theory Simul.* **2002**, *11*, 823.
(37) Stenzel, M. H.; Cummins, L.; Roberts, E. G.; Davis, T. P.; Vana, P.; Barner-Kowollik, C. *Macromol. Chem. Phys.* **2003**, *204*, 1160.
(38) Thomas, D. B.; Convertine, A. J.; Myrick, L. J.; Scales, C. W.; Lowe, A. B.; McCormick, C. L., submitted to *Macromolecules*.

MA035572T