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Aqueous RAFT Polymerization: Recent Developments in Synthesis of Functional Water-Soluble (Co)polymers with Controlled Structures†

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ABSTRACT

Reversible addition−fragmentation chain transfer (RAFT) polymerization has been the focus of intensive research over the past few years since this methodology allows the synthetic tailoring of macromolecules with complex architectures including block, graft, comb, and star structures with predetermined molecular weight, terminal functionality, and narrow molecular weight distribution. In this paper we recount significant milestones in achieving controlled free radical homopolymerization and block copolymerization of water-soluble and amphiphilic monomers including nonionic, cationic, anionic, and zwitterionic species. It is shown that under aqueous conditions, control of homopolymerization and further blocking to extend the molecular weight or to produce precisely structured block copolymers require not only careful selection of reagents (initiator, chain transfer agent, and monomer) but also regulation or elimination of hydrolysis of the ω-terminal thiocarbonylthio functionality. The technological potential of such systems is illustrated for the stimuli (pH) reversible micellization of amphiphilic block copolymers and for stabilization and stimuli responsive aggregation of gold nanoparticles bearing covalently tethered co(polymers). Given the advantages of RAFT over other controlled free radical techniques for preparation of water-soluble architectures, it may be anticipated that this technology will be at the forefront of nano- and microscale self-assembly in electronics and biotechnology.

Introduction

One of the most technologically challenging yet potentially rewarding areas of polymer chemistry is the synthesis of amphiphilic macromolecules with precisely structured architectures (controlled molecular weights and compositions). Appropriately tailored polymers are capable of spontaneous or stimuli-induced supramolecular self-assembly in aqueous media or at interfaces to yield micro- or nanostructured entities with a virtually unlimited number of potential applications in pharmaceutics, medical diagnostics, personal care, and biotechnology.

In this Account we recount strategic discoveries in our laboratories, and others, which now allow facile synthesis of homopolymers, block copolymers, and polymers with intricate structures directly in ***aqueous*** solution utilizing a controlled free radical polymerization technique given the acronym RAFT (reversible addition-fragmentation chain transfer) by its discoverers. It is our intent not only to illustrate the important structural types synthesized for the first time in a controlled manner, but to discuss some of the advantages and limitations of this synthetic method, including the necessity of reducing or effectively eliminating a competing hydrolysis mechanism, which becomes important at extended polymerization times and affects both kinetics and control of molecular weight and molecular weight distribution of the resulting macromolecules.

RAFT Polymerization. RAFT is a relatively new, so-called, controlled/"living" free radical polymerization technique discovered by researchers at CSIRO in Australia.[1] It is arguably the most versatile of such techniques being applicable to the widest range of monomers under a large number of experimental conditions. Unlike atom transfer radical polymerization or stable free radical polymerization, RAFT operates on the principle of degenerative chain transfer. Rizzardo et al.[1,2] proposed a mechanism for RAFT polymerization as outlined in Scheme 1. The RAFT process involves conventional free radical polymerization of a substituted monomer in the presence of a suitable chain transfer agent (CTA). The CTA **1** typically possesses a thiocarbonylthio group (S═C−S) with substituents R and Z that impact the reaction kinetics and, importantly, the degree of structural control. A wide range of CTAs has been reported including dithioesters,[1] trithiocarbonates,[3] dithiocarbamates,[4,5] xanthates (dithiocarbonates)[6,7] and phosphoryl-/thiophosphoryldithioformates.[8] Initiation is accomplished utilizing conventional thermal, photochemical, redox, or γ-irradiation methods. Unlike conventional polymerization in which all growing chains, P•, begin by addition of initiator-derived radicals to

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Andrew B. Lowe received his B.Sc. (Hons) degree in Chemistry (1993) and D.Phil degree (1997) with Professors Norman C. Billingham and Steven P. Armes from the University of Sussex. After a one-year postdoctoral appointment, he moved to the Department of Polymer Science at the University of Southern Mississippi as a Senior Research Fellow in the McCormick Group. In June 2002 he was appointed as Assistant Professor in the Department of Chemistry and Biochemistry at the University of Southern Mississippi. He is a recent recipient of the Ralph E. Powe Junior Faculty Award. His current research interests include the application of controlled polymerization techniques, specifically RAFT, ATRP, and ROMP, for the preparation of novel "smart" multifunctional water-soluble polymers, supramolecular self-assembly, and the synthesis of biocompatible/bioactive monomers/polymers.

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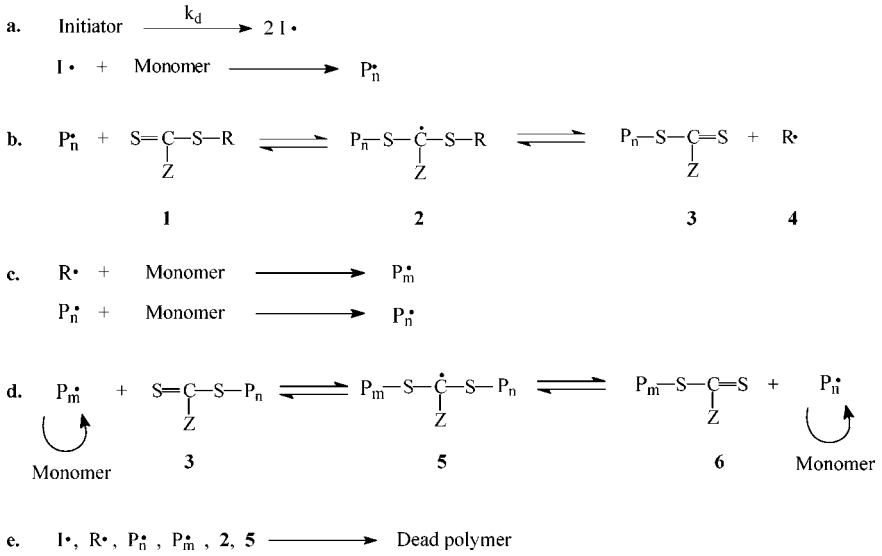
Scheme 1. Proposed RAFT Mechanism



monomer (Scheme 1, eq a), RAFT yields almost exclusively CTA-derived chains, $P_m^•$ (Scheme 1, eqs b and c). The latter originate from R• (**4**), a fragmentation product of intermediate **2**. In most controlled RAFT polymerizations, the concentration of initiator is kept low relative to CTA and the reactivity of the CTA is usually substantially higher than that of monomer, favoring initiation by R• (**4**) fragments. The consumption of CTA **1** and reversible fragmentation of species **2** to yield the reinitiating R• fragment are often referred to as the "pre-equilibrium" shown in eq b of Scheme 1. Eventually, the "main" equilibrium (eq d) is reached in which active (kinetic) radical chain ends add to monomer or reversibly to dormant chains (termed macro-CTAs). The narrow molecular weight distribution, an important feature of controlled RAFT polymerization, is apparently due to rapid establishment of the pre-equilibrium, efficient reinitiation by the R• fragment, and attainment of the main equilibrium in which the population of dormant chains (macro-CTAs) and/or intermediate radicals **5** (not reactive enough to add to monomers) is much higher than the total number of propagating chains $P_n^•$ and $P_m^•$. Indeed, the pseudo-first-order kinetics, the linear evolution of molecular weight with time, narrow molecular weight distributions, and the ability to prepare block copolymers under appropriate conditions attest to significant elimination of chain termination events such as radical coupling and chain transfer common to conventional free radical polymerization shown in **e** of Scheme 1.

It should be mentioned that an alternative, though controversial, amendment to the RAFT process includes coupling of intermediate **2** or **5** with other radical species (these could be primary initiator-derived radicals or $P_n^•$/$P_m^•$, for example). A complete discussion of kinetics, modeling, and ESR studies is reviewed elsewhere.[9]

Figure 1a–c illustrates behavior diagnostic of traditional living and controlled/"living" free radical polymerizations. Figure 1a shows typical size exclusion chromatographic traces of polymer molecular weight evolution with time; Figure 1b shows a kinetic plot with monomer concentration changes with time. Ideally, pseudo-first-order kinetics is observed due to establishment of a steady-state concentration of radicals during the "main" equilibrium shown in Scheme 1, eq d. In some instances, this is preceded by an initial induction/retardation period (also illustrated in Figure 1b). Figure 1c shows characteristic plots of molecular weight and polydispersity (M_w/M_n) vs conversion.

Results and Discussion

Even though the major controlled free radical polymerizations, best exemplified by nitroxide-mediated polymerization (NMP)[10] and atom transfer radical polymerization (ATRP),[11,12] have been practiced longer than RAFT, these have several limitations. The former usually requires relatively high temperatures, while the latter often is limited by monomer functionality and solvent selection for proper catalyst activity. RAFT, on the other hand, appears to be extremely versatile with respect to monomer functionality and is conducted under simple conditions, not requiring vacuum lines, inert conditions, or highly dry/pure reagents. Significantly, utilizing RAFT, researchers in our laboratories, and elsewhere, have developed synthetic procedures and analytical testing protocol that now allow (co)polymerization of a wide variety of nonionic, anionic, cationic, and zwitterionic monomers (Figure 2) and the subsequent extensive characterization of the resulting polymers directly in aqueous media.

Close examination of Scheme 1 for homopolymerization and extension to block copolymerization reveals certain requirements for successful implementation of RAFT in aqueous media. Monomers, initiators, and CTA should be soluble and the rates of initiation, fragmentation, reinitiation, propagation, and reversible addition to CTA appropriate for establishing the "main equilibrium". For optimal block copolymerization, the product macro-CTA from homopolymerization is typically isolated, dissolved in water, and reactivated with an appropriate water-soluble initiator. Obviously, only those homopoly-

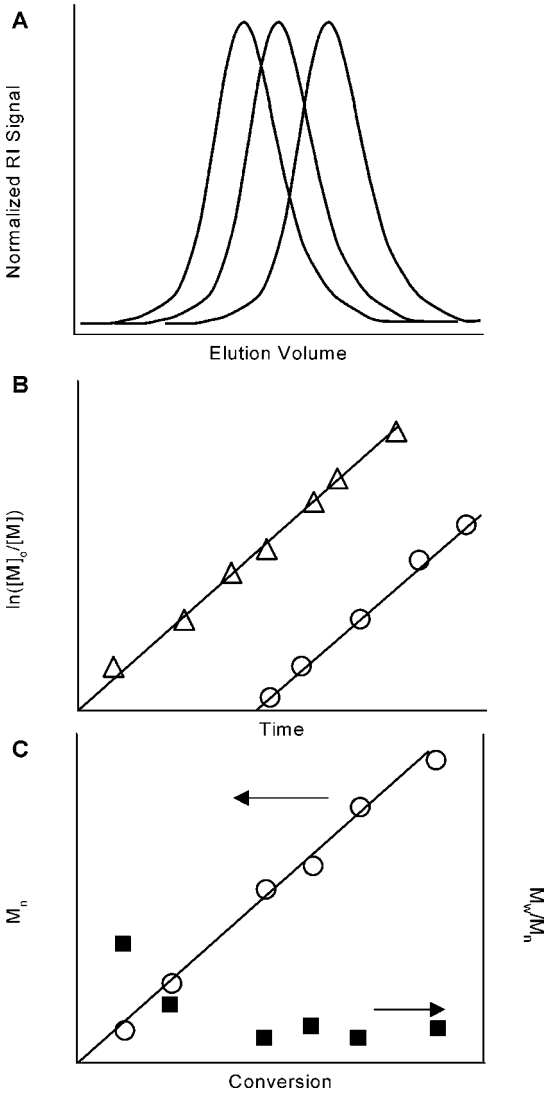


FIGURE 1. Diagnostics of traditional living or controlled/"living" free radical polymerizations. (a) Size exclusion chromatography traces of polymer evolution with time, (b) pseudo-first-order kinetic plot illustrating polymerization with (circles) and without (triangles) an induction/retardation period, and (c) plots of M_n and polydispersity as a function of conversion.

mers with thiocarbonylthio end groups can be chain extended into block copolymers. As will be experimentally demonstrated later, the efficiency of block formation for two monomers is often dependent on the order of addition; for example, a macro-CTA of monomer A may be more efficient in adding monomer B than the macro-CTA of B adding monomer A. This phenomenon is due to differences in bond scission efficiency of the intermediate radicals and selectivity in subsequent reinitiation by respective fragmented kinetic chains. Also, both homopolymer (macro-CTA) and the resulting block copolymer should remain soluble in water throughout the polymerization for best results.

Perhaps the most concerning issue of aqueous RAFT polymerization is the potential for competitive hydrolysis of CTA or macro-CTA during polymerization. Hydrolytic products from monomer or polymer can also react adversely with CTA functionality. Chain extension and blocking in RAFT, and thus control of undesired termination events, depend critically on the availability of thiocarbonylthio groups on every chain end.

Experimental verification of molecular weight control can be gained by comparison of the actual molecular weight, as determined by size exclusion chromatography (light scattering/refractive index detection), with the number average molecular weight, $M_{n,Th}$, predicted by eq 1. This equation assumes initiation by CTA-derived R-group radicals only.

$$M_{n,Th} = \left\{\frac{[\text{monomer}]}{[CTA]}[M_w \text{ of monomer}]\cdot\rho\right\} + M_{wCTA} \quad (1)$$

The molar concentrations of the monomer and CTA and their formula weights are known. Conversion, ρ, can be determined spectroscopically by NMR or UV analysis of aliquots, for example, or gravimetrically. Recent advances in aqueous size exclusion chromatography and on-line detection via multiple angle laser light scattering (MALLS) now allow rapid analysis and data reduction.

First Examples of Aqueous RAFT. The first successful aqueous RAFT polymerization was reported by the Australian CSIRO group in December of 1998.[1] They polymerized the sodium salt of 4-styrenesulfonate, NaSS, **M1** (Figure 2), at 70 °C in the presence of the water-soluble CTA sodium 4-cyanopentanoic acid dithiobenzoate, **CTA1**, and 4,4′-azobis(4-cyanopentanoic acid), **I1** (Figure 3), obtaining a homopolymer with $M_n = 8000$ and a polydispersity index (PDI) of 1.13. There were no reports in that study, or previous literature to our knowledge, of successful block copolymerization or chain extension. We therefore embarked on a research program building on these intriguing results and our extensive water-soluble polymer background.

Our first experiments with a variety of water-soluble monomers indicated that in order to have any success we would have to (a) control relative selectivity of propagating radicals for the thiocarbonylthio groups and monomer, (b) consider further intermediate chain scission and reinitiation rates with more reactive monomers (simultaneously, other groups were also working on the effects of varying R$^\bullet$ and Z for nonwater-soluble monomers),[13,14] and (c) eliminate or reduce hydrolysis of thiocarbonylthio groups (see Scheme 1). Later, we discovered that even low degrees of hydrolysis of monomer side-chain functionality could be fatal to RAFT if not controlled or eliminated.

Mitsukami in our group conducted preliminary hydrolysis experiments[15] clearly demonstrating that lowering pH could reduce hydrolysis in two dithioester CTAs, CTP (**CTA1**) and carboxymethyl dithiobenzoate (**CTA2**). Since NaSS, **M1**, is soluble over the entire useful pH range, it seemed possible to adjust pH to significantly retard CTA hydrolysis and yet maintain initiator and CTA solubility, both critical to reaction control. The strategy brought immediate success. Homopolymerization of **M1** with **CTA1** conducted at 70 °C in water under these conditions

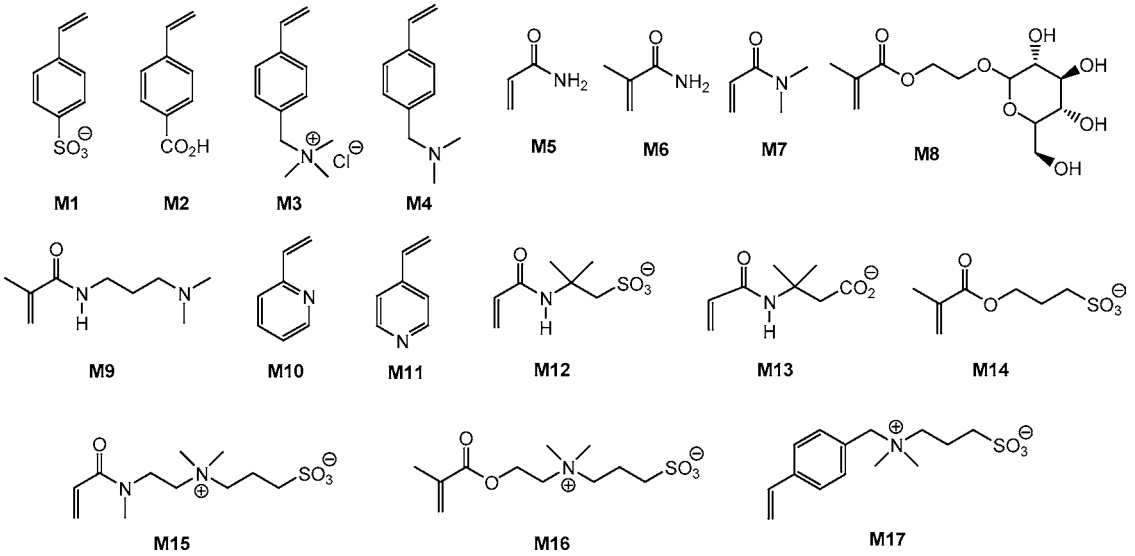


FIGURE 2. Hydrophilic/water-soluble monomers susceptible to aqueous RAFT polymerization.

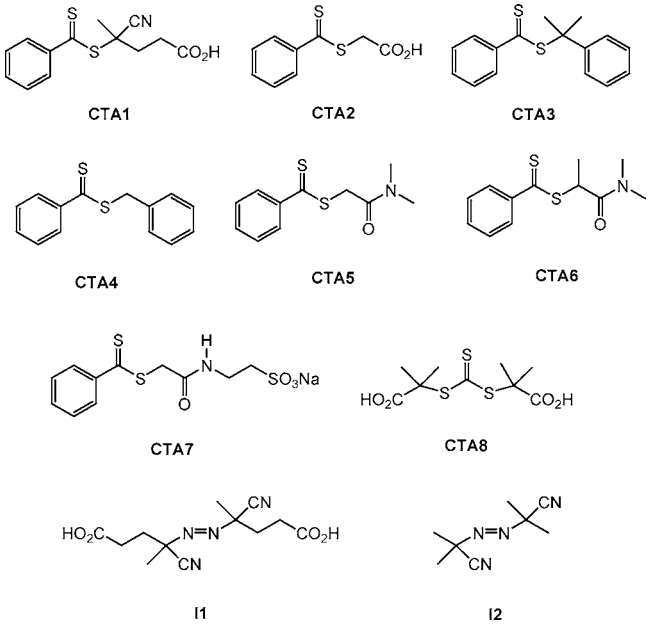


FIGURE 3. Examples of chain transfer agents and initiators used for aqueous-based RAFT polymerizations.

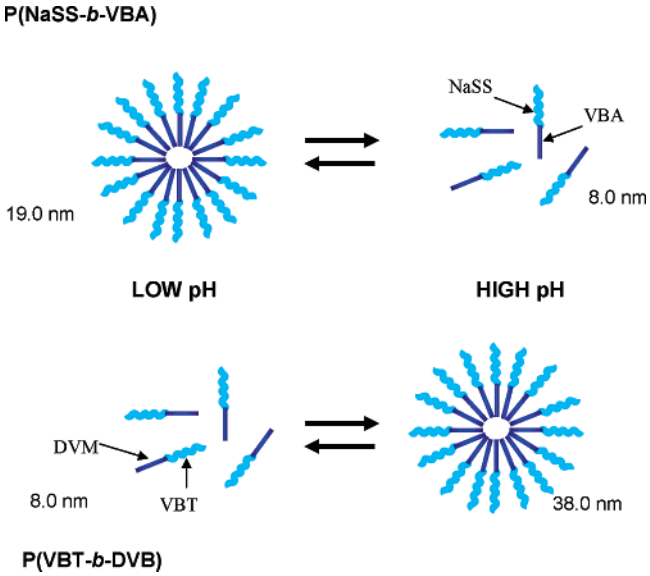


FIGURE 4. Schematic representation of AB diblock aggregation with changes in solution pH.

led to near-quantitative monomer conversion in 1−1.5 h as determined by ^{1}H NMR spectroscopy. The best molecular weight control and lowest polydispersity was found at 70% conversion, where the theoretical and experimental molecular weights were in close agreement and a PDI of 1.12 was obtained.[16]

Having established suitable conditions for the RAFT polymerization of **M1** to yield a macro-CTA with a dithioester end group, we subsequently prepared block copolymers with 4-vinylbenzoic acid (VBA) **M2**. These block copolymers proved to be stimuli responsive and thus capable of supramolecular self-assembly, since the hydrophilicity of the VBA block can be altered simply by changing the solution pH. At low pH, the protonated VBA segments of the AB block copolymer are hydrophobic while the NaSS units remain ionized and hydrophilic. It was demonstrated that the AB block copolymer undergoes self-assembly into spherical micelles (Figure 4) with average hydrodynamic diameters of ca. 19.0 nm. This process can be reversed by increasing pH, resulting in unimers of ca. 8 nm in which both blocks are ionized, hydrophilic, and nonassociative.

By using a similar synthetic strategy, block copolymers of the permanently cationic *ar*-vinylbenzyltrimethylammonium chloride (VBT), **M3**, and *N*,*N*-dimethyl-benzylvinylamine (DVB), **M4**, a proton acceptor, were prepared. At low pH, the block copolymer exists in its unimeric state since both blocks are positively charged and thus hydrophilic. However, at higher pH, the DVB block is unprotonated, rendering it hydrophobic. Under these conditions, the block copolymers undergo self-assembly into micelle-like aggregates of ca. 38 nm, with the hydrophobic DVB blocks residing in the micellar core and the VBT blocks in the corona (Figure 4).

Homopolymers and Block Copolymers from Anionic Acrylamido Monomers. Extremely encouraged by the

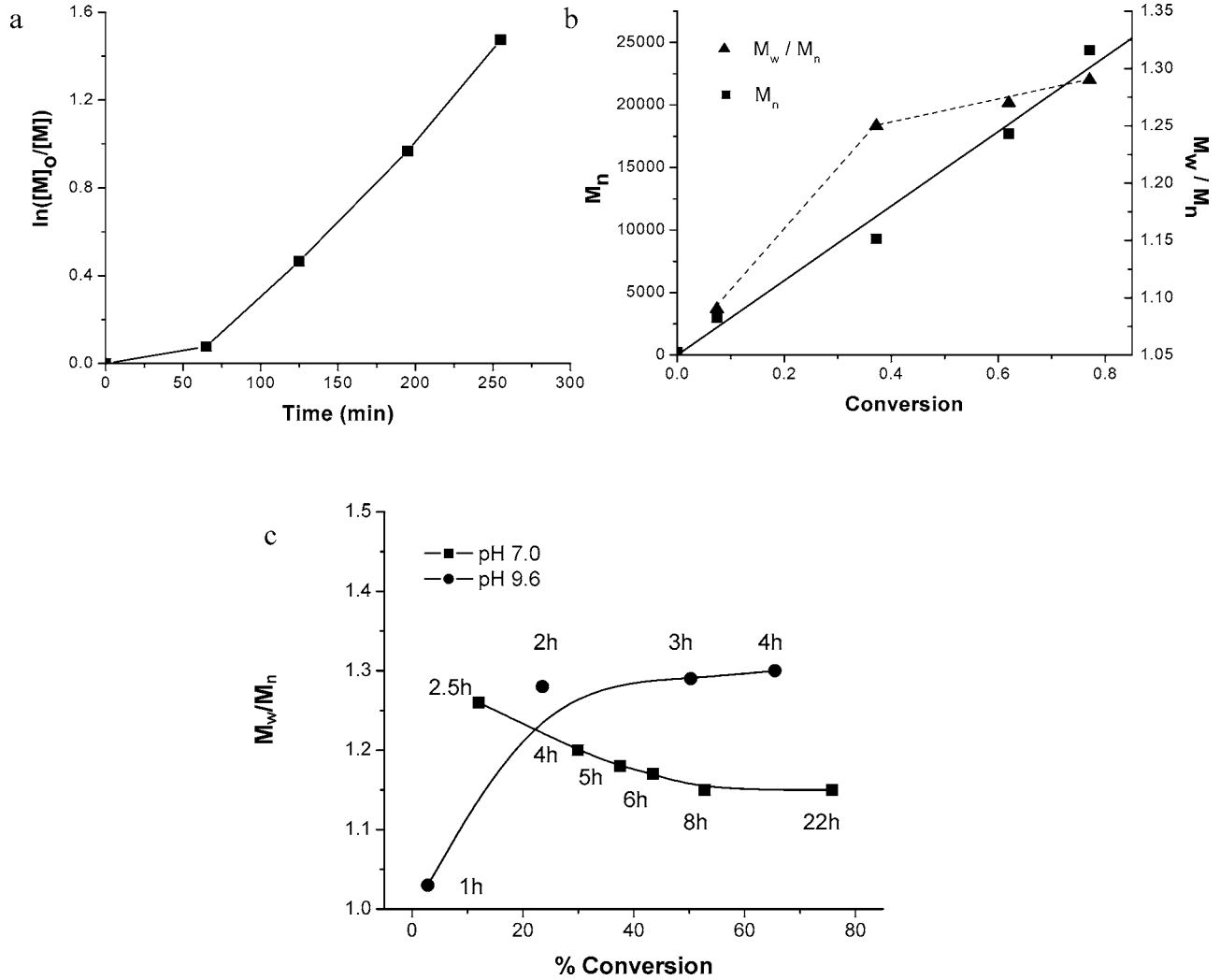


FIGURE 5. Kinetic plot for the homopolymerization of AMPS (a) M_n and M_w/M_n vs conversion (b) and M_w/M_n vs conversion at pH 7.0 and pH 9.6 (c).

success of our first aqueous RAFT studies with the styrenic-based monomers, **M1**−**M4**, we accepted the challenge of utilizing monomers that have historically proven problematic to polymerize via controlled/"living" free radical methods. Specifically, Sumerlin began a study of the acrylamido monomers **M12** and **M13**—these species were predicted to exhibit similar stimuli-induced aqueous solution behavior as the styrenic materials. At the time we were beginning this research, there were no literature reports detailing the controlled polymerization of *any* charged acrylamido monomers and only a handful describing the successful polymerization of neutral acrylamido species. As such, we envisioned that successful polymerization of **M12** or **M13** would pose significant problems. Fortuitously, both of these species homopolymerized readily in a controlled manner directly in water at 70 °C, pH ≈ 9.6 using **CTA1** with **I1** in a molar ratio of 5:1 (Figure 5).[17,18]

Molecular weights were controlled by varying the reaction times (conversions). Linear pseudo-first-order rate plots were obtained (Figure 5a) after an initial induction/retardation period of ∼60 min. M_n/conversion plots were also linear (Figure 5b). The effect of pH on the molecular weight distribution at selected conversions during **M12** homopolymerization is shown in Figure 5c. M_w/M_n increased with conversion at pH 9.6 but decreased with conversion at pH 7.0. We attribute this difference to CTA hydrolysis; evidently, hydrolysis at the lower pH is minimal (see later text). The macro-CTAs of **M12** and **M13** were subsequently reinitiated in the presence of the companion monomer to yield AB diblock copolymers. The SEC traces (not shown) indicate quantitative reinitiation, with the experimental molecular weights (Table 1) being in close agreement with those calculated utilizing eq 1.

To study the hypothesized pH-induced self-assembly, series of well-defined AB diblock and statistical copolymers of **M12** and **M13** were prepared (Table 2). At pH values below 5, the carboxylate functionality in **M13** is protonated, rendering it hydrophobic. In contrast, the **M12** units remain hydrophilic at both low and high pH. We expected these block copolymers to exhibit similar aqueous solution properties to the styrenic polymers prepared by Mitsukami. Indeed, a combination of NMR spectroscopy, dynamic light scattering, and fluorescence measurements confirmed reversible pH-induced micelle formation. Hydrodynamic diameters of the unimers and

Table 1. Conversion, Molar Mass, and Polydispersity Data for Aqueous RAFT AMPS (M12) and AMBA (M13) Block Copolymerizations

sample	comp (theory) (AMPS/AMBA)	comp (expt)[a] (AMPS/AMBA)	M_n (theory)[a] (g/mol)	M_n (expt)[a] (g/mol)	M_w/M_n[a]
PAMPS macro-CTA				33 900	1.14
P(AMPS-*b*-AMB A)	45/55	46/54	68 500	69 700	1.14
PAMBA macro-CTA				31 300	1.14
P(AMBA-*b*-AMP S)	47/53	49/51	64 400	57 900	1.16

[a] As determined by ASEC, calibrated with NaPSS standards in 20% CH_3CN/80% 0.1 $NaNO_3$ eluent.

Table 2. Data for the RAFT Polymerization of AMBA (M13) Employing a PAMPS (PM12) Macro-CTA in Water (pH 8) at 70 °C

sample	conv (%)[a]	M_n (theory)[b] (g/mol)	M_n (expt)[c] (g/mol)	M_w/M_n[c]	DP_{AMPS}	DP_{AMBA}	comp ASEC[c] (AMPS/AMBA)	comp NMR[e] AMPS/AMBA	D_h (nm) pH 9.0	D_h (nm) pH 1.0
P($AMPS_{70}$-*b*-$AMBA_{62}$)	87	28 300	29 000	1.15	70[c]	62[c]	53/47	50/50	6.0	25.0
P($AMPS_{70}$-*b*-$AMBA_{40}$)	85	24 200	24 500	1.10	70[c]	40[c]	64/36	64/36	5.0	24.0
P($AMPS_{70}$-*b*-$AMBA_{25}$)	84	21 300	21 300	1.15	70[c]	25[c]	75/25	77/23	6.0	21.0
P($AMPS_{70}$-*b*-$AMBA_{16}$)	94	19 600	19 700	1.21	70[c]	16[c]	82/19	82/19	6.0	18.0
P($AMPS_{106}$-*stat*-$AMBA_{40}$)	84	28 700	32 000	1.15	106[d]	40[d]		73/27	11.0	7.0
P($AMPS_{35}$-*stat*-$AMBA_{112}$)	89	27 100	29 800	1.14	35[d]	112[d]		24/76	11.0	9.0
P($AMPS_{79}$-*stat*-$AMBA_{89}$)	87	29 400	35 300	1.13	79[d]	89[d]		47/53	13.0	9.0

[a] Determined from the residual monomer concentration obtained from the RI detector during ASEC. [b] Determined using M_n(theory) = $[M] \times [M_{wmon}]$ x conversion/[CTA] + $M_{WMacro-CTA}$. [c] Determined by ASEC. [d] Determined by using the M_n determined from ASEC and the copolymer composition determined by ^{1}H NMR spectroscopy. [e] Determined using ^{1}H NMR spectroscopy.

multimeric micelles are given in Table 2. The sequestration/release potential of these stimuli-responsive micelles was demonstrated by observing relative fluorescence intensity of the I_1 and I_3 bands of pyrene added to the aqueous solutions at low and high pH.[18] Recently, similar diacid AB diblock copolymers were also shown to undergo pH-induced self-assembly.[19]

Homopolymers and Block Copolymers from Neutral Acrylamido Monomers. Important targets for synthetic polymer chemists are segments of block, graft, or star copolymers comprised of nonionic, hydrophilic monomers. Homo- and copolymers containing industrially important acrylamide (AM), **M5**, and *N*,*N*-dimethylacrylamide (DMA), **M7**, are especially useful for pharmaceutical, personal care, medical diagnostics, and biotechnology applications due to their biocompatibility. Concurrently with the studies being performed by Sumerlin, Donovan explored the RAFT polymerization of **M7** in organic, aqueous, and mixed *N*,*N*-dimethylformamide (DMF)/water mixtures.[20,21]

Initial studies revolved around the polymerization of **M7** in benzene using **CTAs 3**−**6**. We designed and synthesized **CTA5** and **CTA6** for the RAFT polymerization of **M7** choosing R-groups structurally and electronically similar to the propagating chain end of **M7**. **CTA6**, as anticipated, proved to be a highly efficient species, yielding **M7** homopolymers with unimodal, narrow molecular weight distributions. However, it was at this point that we first observed some differences in behavior when compared to the ionic styrenic and acrylamido monomers. While the **M7** homopolymerizations bore many of the characteristics of controlled polymerization, we observed poor molecular weight control. Experimentally determined molecular weights 30−50% higher than those predicted by eq 1 were not uncommon. Similar observations were made when **M7** was polymerized in aqueous media or DMF/water mixtures with **CTA1** and **CTA6** with **I1**.

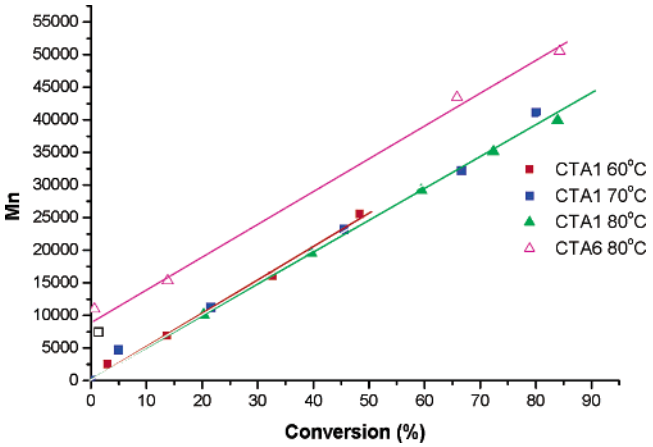


FIGURE 6. Plots of molecular weight versus conversion for PDMA synthesized at 60, 70, and 80 °C in the presence of CTP (**CTA1**) and at 80 °C in the presence of TBP (**CTA6**).

A comparative study of the effectiveness of **CTA1** and **CTA6** in controlling the polymerization of DMA (**M7**) was performed at CTA/initiator (**I1**) ratios of 5:1 at 60, 70, and 80 °C in water or DMF/water solution (Figure 6).

The M_n vs conversion plots in water alone utilizing **CTA6** at 80 °C and **CTA1** at 60, 70, and 80 °C, respectively, are linear and exhibit identical slopes, though the former shows a nonzero intercept. We subsequently found that addition of a critical concentration of DMF to the aqueous solution resulted in coincidence of the experimental data points for **CTA6** with those of **CTA1**. Given the efficiency of **CTA6** in benzene, it appears that elevated temperature and a cosolvent are needed to solvate and assist in the production of the R$^\bullet$ fragment necessary for controlling the RAFT process (Scheme 1). The radical from fragmentation of **CTA1** is readily solubilized and sufficiently energetic for monomer addition.

While still puzzled over the lack of molecular weight control observed for **M7**, we began a series of failed attempts at RAFT polymerization of the commercially

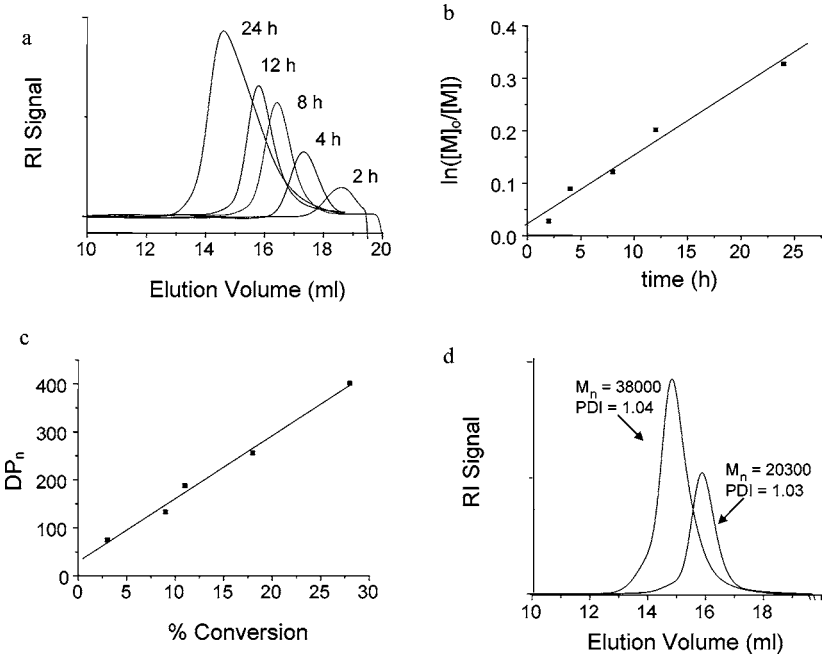


FIGURE 7. Experimental data showing (a) the evolution of molecular weight during homopolymerization of **M5**; (b, c) the linear kinetic and DP_n/conversion plots, and (d) demonstration of successful block copolymer formation.

important monomer acrylamide (**M5**). As with **M12** and **M13**, **M5** represented a species that had never previously been polymerized in a controlled fashion by any technique. Eventually, Thomas was successful in controlling the synthesis of poly(AM) (PAM) homopolymers and block copolymers in water.[22,23] This feat required not only appropriate CTA choice, but careful selection of reaction conditions. The homopolymerization was successfully performed in an aqueous acetic acid/sodium acetate buffer (pH = 5.0) solution utilizing 2-(2-thiobenzoylsulfonylproponylamino)ethanesulfonic acid (STPE) **CTA7**, a CTA designed by our group to be soluble over a wide pH range and to have steric and electronic characteristics for facile fragmentation. A [CTA]/initiator ratio of 1.15, [**M5**] = 2.0 M, and [initiator] = 2.17×10^{-3} were utilized. Figure 7 shows the SEC chromatograms demonstrating the evolution of molecular weight during homopolymerization (a) along with the linear kinetic and DP_n/conversion plots (b and c). Finally, the controlled extension (blocking) of the macro-CTA is evidenced by SEC traces after sequential addition of **M5** and reinitiation (d). That chain extension occurs for virtually all molecules is clear from SEC since there is no evidence from either refractive index or light scattering (not shown) detection of nonextended polymer. The resulting molecular weight distributions are also exceptionally narrow. However, as with **M7**, we found very large differences in the observed and theoretical molecular weights, with the measured values being approximately 50% higher than theory. Also like **M7**, and in contrast to the ionic monomers, the polymerization of **M5** was very slow, reaching only ~30% conversion in 24 h. These results reinforced our growing concerns regarding the possibility of deleterious side reactions such as monomer and/or CTA hydrolysis, as well as aminolysis in the case of **M5**, and prompted us to initiate a study of CTA and macro-CTA stability.

Hydrolytic Stability of CTA1 and Macro-CTAs of Poly(M12) and Poly(M5). The impact of CTA hydrolysis and/or aminolysis (a result of **M5** hydrolysis liberating ammonia which subsequently reacts with CTA) is an extremely important issue since both events result in a loss of active chain ends, diminish control, and increase the polydispersity of the resulting materials. We chose to examine the most widely employed CTA for aqueous RAFT, specifically **CTA1**, along with macro-CTAs of poly(**M12**) and poly(**M5**).[24] Studies involving the polymerization of **M5** highlighted the importance of solution pH in attaining and maintaining control. Initial experiments focused on the hydrolytic stability of **CTA1** as monitored by a combination of NMR spectroscopy and high-pressure liquid chromatography (Figure 8).

In ^{1}H NMR spectroscopy (Figure 8a), the triplet at 7.12 ppm and the doublet at 7.63 ppm correspond to aromatic protons in **CTA1**. These signals proved ideal for following the disappearance of **CTA1**. The excellent agreement between the data obtained by NMR spectroscopy and HPLC (Figure 8c) confirmed the efficient separation of **CTA1** by HPLC. These data clearly demonstrate CTA hydrolysis, at pH = 9.0. Figure 9a−c shows the effect of pH on the rates and extents of hydrolysis for **CTA1**, poly(**M12**) with a degree of polymerization (DP_n) = 38, and poly(**M12**) with DP_n = 9.

It is clear that both pH and CTA molecular weight have strong influences on the rate of hydrolysis. The magnitude of the apparent rate constant of hydrolysis, k_{hyd}, for **CTA1** 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 10.0. Also, very little change in k_{hyd} was observed as the pH was

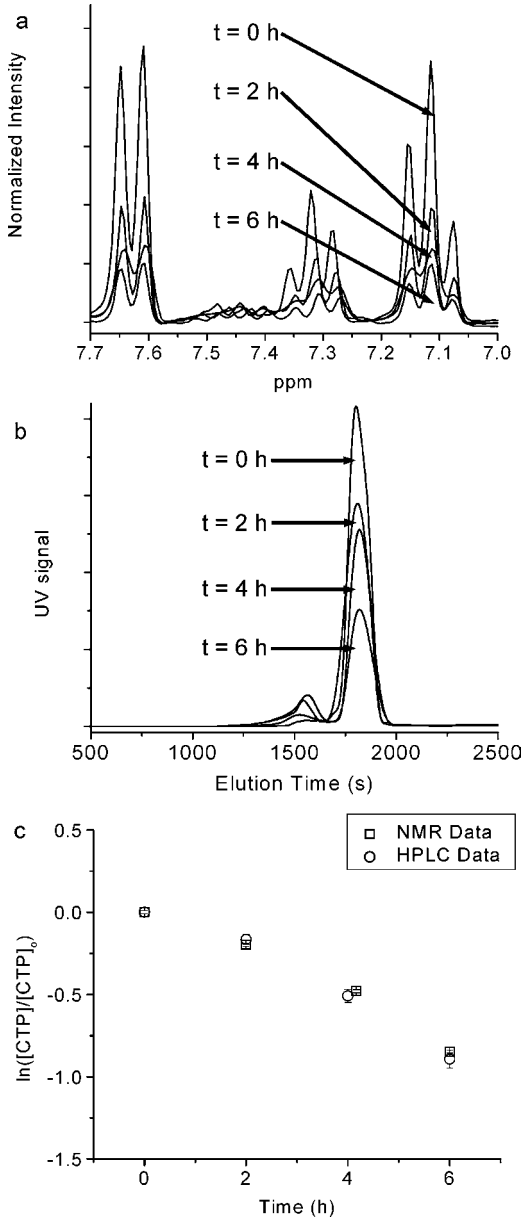


FIGURE 8. (a) ^{1}H NMR spectra, (b) HPLC chromatograms, and (c) pseudo-first-order rate plots for the hydrolysis of **CTA1** at pH = 9.0.

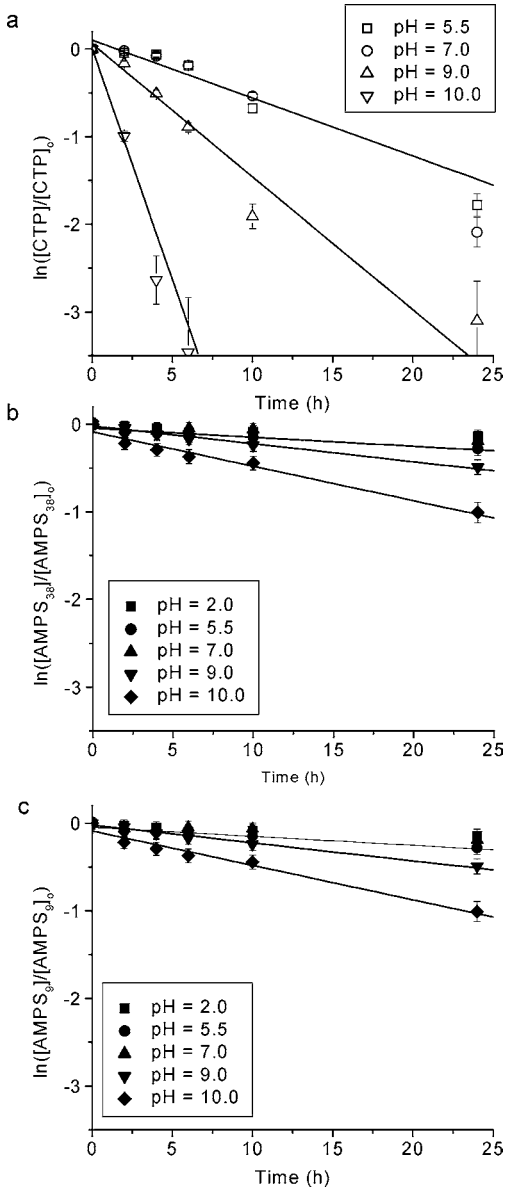


FIGURE 9. Pseudo-first-order rate plots for the hydrolysis of (a) **CTA1**, (b) poly(**M12**)$_{38}$, and (c) poly(**M12**)$_9$ at 70 °C.

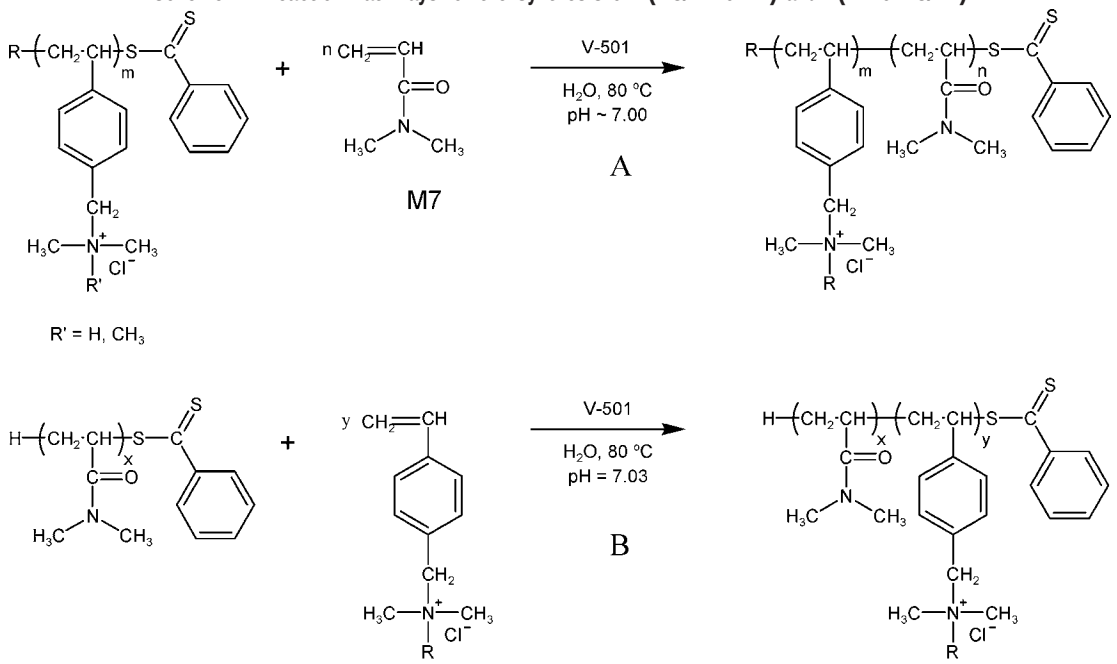
lowered from 7.0 to 2.0, demonstrating the enhanced stability of the dithioesters at low pH. The effect of degree of polymerization can be observed by comparing values of k_{hyd} for **CTA1** with poly(**M12**)$_{38}$ and poly(**M12**)$_9$ (Figure 9a−c). Poly(**M12**)$_{38}$ hydrolyzes much more slowly than **CTA1** and a little more slowly than poly(**M12**)$_9$. This can be attributed to steric hindrance to the attack of water molecules on the dithioester. In the case of **M5** the problem is compounded by the effect of aminolysis. NH_3 is liberated by the hydrolysis of **M5**. At pH ≈ 7.0 and higher, the loss of **CTA1** is due to both hydrolysis and aminolysis (dithioesters are known to be readily attacked by both 1° and 2° amines), whereas at pH ≈ 5.5, any loss is attributed solely to hydrolysis. This reinforces the conclusion that performing aqueous RAFT polymerizations at lower pH values is preferred.

Can this observed hydrolysis/aminolysis behavior help to explain the observed discrepancies between the experimentally determined and the theoretical molecular weights? We have shown that hydrolysis of **CTA1** and the macro-CTA from the RAFT polymerization of the anionic monomer **M12** occurs approximately 100 times slower than chain propagation in water at 70 °C in a pH 5 buffer. Acrylamide polymerization, via RAFT, is much slower, only twice as fast as CTA loss under the same conditions. As such, for **M12**, the polymerization is essentially complete before any significant (detectable) degree of CTA hydrolysis can occur, in contrast to **M5**. This readily explains our early successes with both **M12** and **M13**.

By following the extent of CTA hydrolysis, it is possible to predict the molecular weight from eq 2 for specific reaction times

$$M_n(t) = \frac{M_{MW} \times ([M]_o - [M]_o\, e^{-k_p^*(t-t_{ind})})}{[CTA]_{ind}\, e^{-(k_{hyd,macro}+k_{a,macro}[NH_3]_2)(t-t_{ind})}} \qquad (2)$$

Scheme 2. Reaction Pathways for the Synthesis of P(M3/M4-*b*-M7) and P(M7-*b*-M3/M4)



where, $M_n(t)$ = molecular weight of the living chains as a function of time, M_{MW} = monomer molecular weight, $[M]_o$ = initial monomer concentration, $[CTA]_{ind}$ = CTA concentration at the start of the polymerization, k_p^* = apparent rate constant for propagation, $k_{hyd,macro}$ = rate constant of hydrolysis of the macro-CTAs, $k_{a,macro}$ = third-order rate constant for aminolysis of the macro-CTAs, $[NH_3]$ = concentration of ammonia, t_{ind} = length of the induction period.

We now believe that part of the experimental overshoot of molecular weight (see, for example, the nonzero intercept in Figure 7) can be attributed to CTA hydrolysis during the induction/retardation period and then prior to the "main" equilibrium in RAFT (Scheme 1, eq c).[24]

RAFT Polymerization of Amine-Containing Monomers. Having established, in early studies, that RAFT is a superb technique for the controlled polymerization of functional monomers, we expanded our research to examine various amine-containing hydrophilic/water-soluble species. Following the initial success with the styrenic-based amine monomers, **M3** and **M4**, we examined (a) **M3**/**M4**-based block copolymers with **M7** as potential 'smart' materials, (b) the controlled synthesis of vinylpyridine-based polymers from **M9** and **M10**, and (c) the previously unreported controlled polymerization of an amine-containing methacrylamide species, **M8**.

Sumerlin and colleagues in our laboratories were responsible for the synthesis of the first examples the cationic/neutral **M3**/**M4**-**M7** AB diblock copolymers.[25] Generalized reaction pathways are shown in Scheme 2 for the addition of **M7** to the macro-CTAs of **M3** or **M4** (pathway A) or addition of the macro-CTA of **M7** to **M3** or **M4** (pathway B).

This particular study was especially enlightening since it clearly demonstrated the importance of the reaction sequence (termed "blocking") when preparing AB diblock copolymers from monomers which belong to different families (Figure 10).

The ASEC chromatograms (Figure 10a and b) clearly show poor blocking utilizing the styrenic homopolymers as macro-CTAs but excellent blocking (Figure 10c) when **M7** macro-CTAs are employed. The failure of the block copolymerization from the macro-CTA of **M4** is due to slow fragmentation of the intermediate radical and/or poor reinitiation efficiency of the produced poly (**M4**) macroradical. **M7**-*b*-**M4** copolymers prepared from an **M7** macro-CTA (degree of polymerization of 67) with **M4** block length varied from 34 to 74 showed reversible unimer-to-micelle transitions as the pH was raised to 10, as a result of the association of the hydrophobic **M4** blocks into cores and hydrophilic DMA blocks into coronas. Five- to ten-fold increases in hydrodynamic diameter were observed with self-assembly as determined by dynamic light scattering.

We recently extended our studies of amine-containing monomers to the vinylpyridine family (**M10** and **M11**).[26] Convertine examined the *bulk*, rather than solution, polymerization of 2- and 4-vinylpyridine utilizing AIBN (**I2**) as the source of free radicals and cumyl dithiobenzoate (CDB, **CTA3**) as the RAFT CTA using a molar ratio of 1:4.75 at 60 °C. This procedure allowed us to bypass the problems of spontaneous polymerization often observed in polar solvents for vinylpyridine monomers. The homopolymerizations of both **M10** and **M11** bore the characteristics expected of a controlled/"living" polymerization—linear evolution of M_n with conversion, low PDI, and a linear pseudo-first-order rate plot. The controlled characteristics were further demonstrated by the ability to prepare both 2VP-4VP and 4VP-2VP AB diblock copoly-

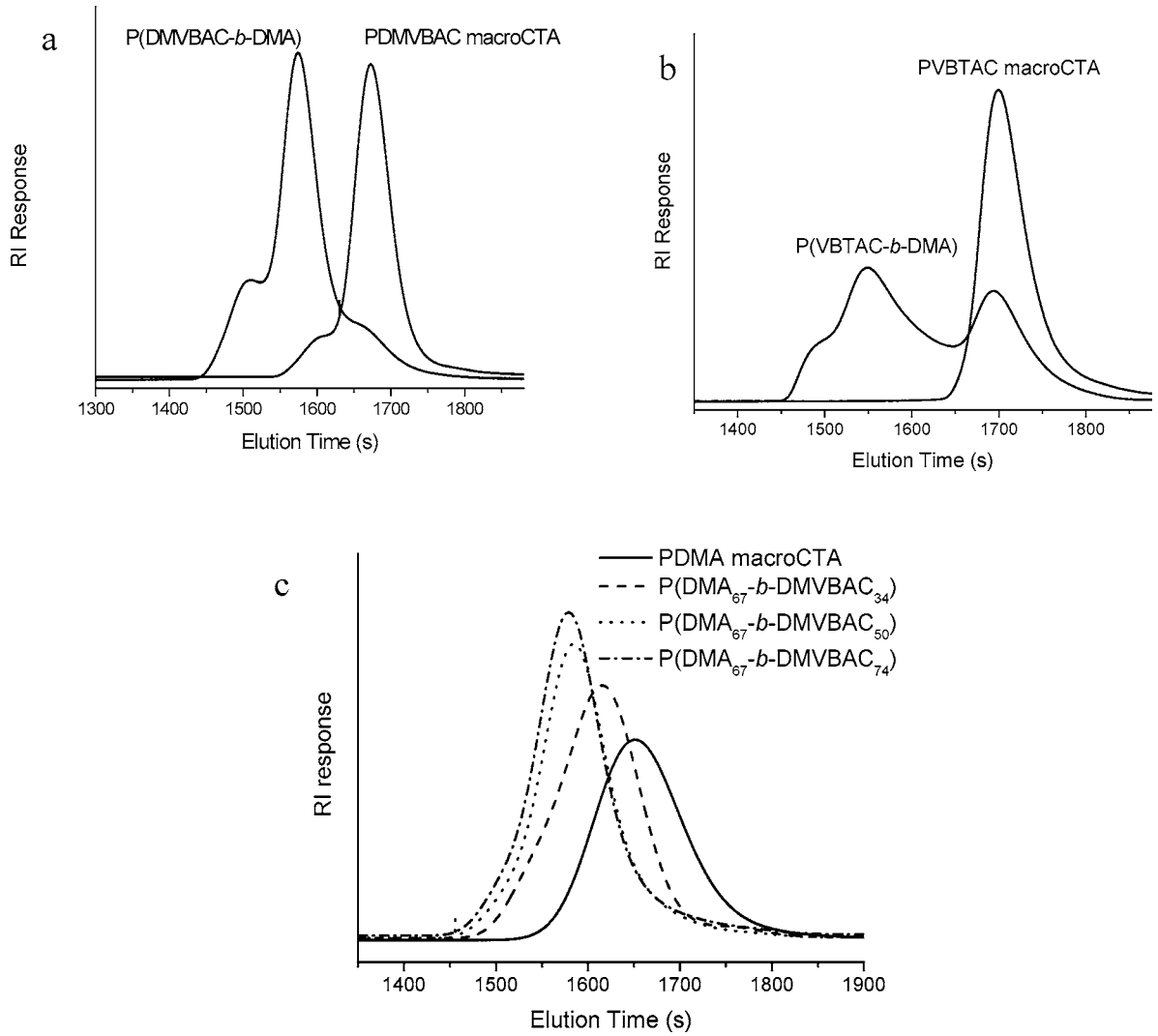


FIGURE 10. (a) ASEC chromatograms for block copolymerization of **M7** mediated with an **M4** macro-CTA, (b) an **M3** macro-CTA, and (c) ASEC chromatograms for the **M7** macro-CTA and three block copolymers with **M4**.

mers, i.e., employing either a P(**M11**) or P(**M12**) macro-CTA with quantitative reinitiation, as determined by SEC.

In addition to the styrenic-based amines and the vinylpyridines and following the hydrolysis study conducted earlier by Thomas and colleagues, Vasilieva examined the aqueous homopolymerization of **M9** utilizing **CTA1** in conjunction with **I1** under buffered conditions (pH = 5.0, 70 °C) (Figure 11).[27]

The reasonable correlation of theoretical and experimental molecular weights, the linearity of the M_w/conversion plots, the narrow M_w/M_n values, and the excellent SEC separation of the macro-CTA from the chain extended and block copolymer with **M7** illustrate excellent control with very limited competing hydrolysis.

Homopolymers from Zwitterionic Sulfobetaine Monomers. To further demonstrate the versatility of RAFT, we recently disclosed the first examples of controlled polysulfopropylbetaine homopolymers[28,29] and block copolymers.[30] Polybetaines are of considerable interest due to their anti-polyelectrolyte behavior[31,32] in aqueous media and their bio/hemocompatible properties.[33] The acrylamido **M15-**, methacrylic **M16-**, and styrenic **M17**-based sulfobetaine monomers, shown in Figure 2, were polymerized in aqueous salt solutions (0.5 M NaBr) at 70 °C using **CTA1** at a concentration of 9.98×10^{-2} mmol and initiator **I1** at a concentration of 2.02×10^{-2} mmol with the CTA/I ratio held constant at 5:1.

Figure 12 shows representative experimental results for monomer **M17** (similar results were obtained for both **M15** and **M16**). Table 3 shows the excellent agreement of the experimental values of molecular weight as determined by SEC MALLS and those calculated from eq 1. All polymerizations showed controlled evolution of molecular weight with time and linear kinetic and M_n vs conversion plots. M_w/M_n values approached 1.04−1.08 with higher conversion. **M17** exhibited the longest induction period of around 50 min as compared to 10 min for **M16** and 20 min for **M15**. The rates of polymerization were **M16** > **M17** > **M15**. The slowest kinetics, exhibited by **M15**, may indicate a lower rate constant for fragmentation of the macro-RAFT intermediate radical or a greater selectivity in adding to the macro-CTA relative to monomer.

RAFT Polymerization of Additional Nonionic Hydrophilic Monomers. In addition to the commercially im-

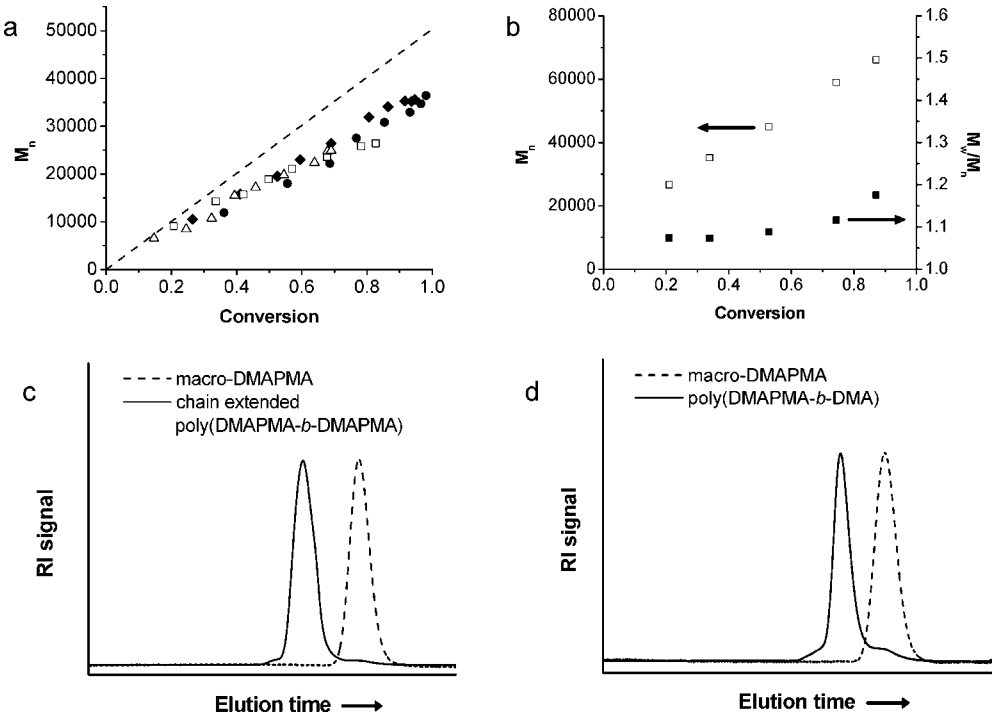


FIGURE 11. (a) M_n vs conversion in the homopolymerization of **M9** in an acetic acid/sodium acetate buffer, pH = 5, at 70 °C; [CTA]/[I] = 1.5/1 (circles), 3/1 (diamonds), 5/1 (squares), and 8/1 (triangles). (b) M_n and M_w/M_n vs conversion in the polymerization of **M9** using macro**M9** as the CTA. (c) ASEC traces of macro**M9** and successful chain extension with **M9** and (d) blocking of P(**M9**) with **M7**.

Table 3. Experimental Values of Molecular Weight As Determined by SEC MALLS and Those Calculated from Eq 1 for the Polysulfopropylbetaine Homopolymers

sample	conv on (%)[b]	d*n*/d*c*[c]	theoretical mol wt	obsd mol wt (M_n)[d]	M_w/M_n[d]
PMAEDAPS[a]	91	0. 1533 ± 0.0036	44 100	58 250	1.08
PDMAPS[a]	93	0.1293 ± 0.0008	45 700	47 500	1.04
PDMVBAPS[a]	90	0.1578 ± 0.0021	44 900	47 200	1.06

[a] Prepared using 4-cyanopentanoic acid dithiobenzoate, **CTA1**. [b] As determined by the residual monomer concentration employing the RI detector. [c] Measured using Wyatt's Optilab Differential Refractometer in 80% 0.5 M NaBr/20% acetonitrile. [d] As determined by aqueous size exclusion chromatography in 80% 0.5 M NaBr/20% acetonitrile using Wyatt's DAWN EOS multiangle laser light scattering detector.

portant **M5** and **M7** nonionic acrylamido monomers, we recently extended our studies to the methacrylate family, more specifically to the glycomonomer 2-methacryloxyethyl glucoside (MAGlu, **M8**).[34] The direct polymerization of glycomonomers without the need for protecting group chemistries had previously proven problematic, although several reports detailing the successful ATRP of sugar-containing monomers have recently appeared.[35,36] **M8** is readily polymerized with **I1** and **CTA1** as the initiator/CTA pair at a molar ratio of 1:5, directly in aqueous media at 70 °C. Polymerizations proceed smoothly and rapidly as evidenced by the SEC traces and the kinetic and M_n vs conversion plots. This is a significant result and will likely lead to the synthesis of previously unattainable sugar–polymer materials.

Aqueous RAFT-Prepared (Co)polymers and Facile Surface Modification. By virtue of the RAFT mechanism, (co)polymers prepared via this technique are α,ω-functionalized. One end is functionalized with the initiating fragment, while the other bears a thiocarbonylthio species. The thiocarbonylthio functionality may be readily reduced to a thiol under facile conditions with a mild reducing agent such as sodium borohydride. We have shown that, provided this reduction is performed in the presence of either a gold sol or a gold film, the resulting reduced thiol-functional (co)polymers will immediately anchor to the gold surface to yield either gold-functional nanoparticles or surface-modified films. This chemistry may be conducted in aqueous media (Figure 13).[37,38] Using this approach we tethered a variety of functional, water-soluble polymers to gold surfaces including anionic, cationic, and zwitterionic species.

Conclusions/Outlook and Future Directions

In this account of research utilizing RAFT technology for the synthesis of water-soluble amphiphilic (co)polymers, we attempted to present key mechanistic and experimental considerations for attaining precise control over (co)polymer composition, molecular weight, and end-chain functionality. Over the last two and one-half years, we have confirmed that the basic conceptual model first offered by Rizzardo, Moad, and colleagues in the CSIRO groups and later studied by other groups for RAFT polymerization in bulk or organic solvents is applicable to water-soluble monomers through careful selection of CTA, initiator, temperature, and solvent conditions. For polymerization directly in water, the apparent rate of

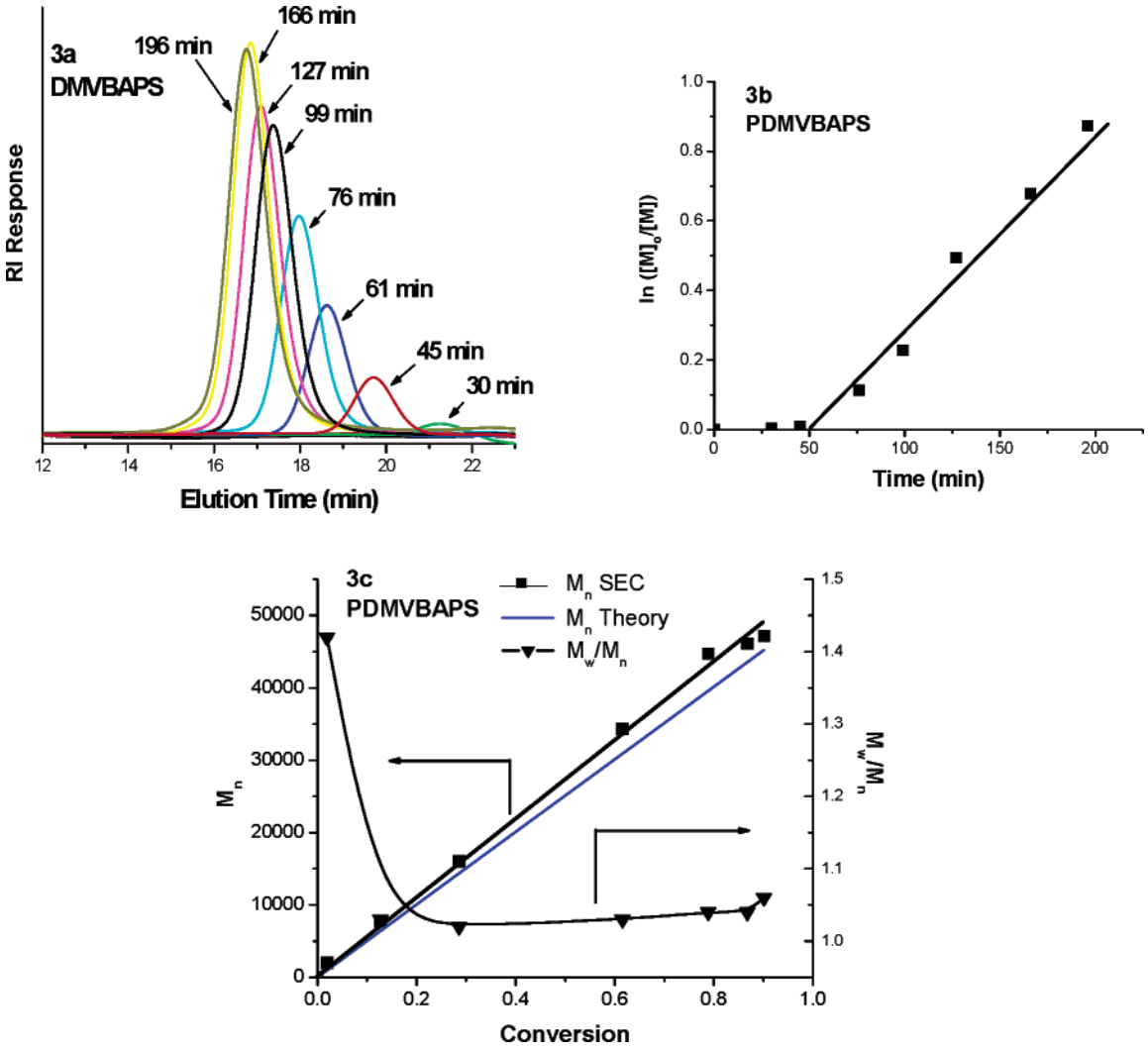


FIGURE 12. (a) Aqueous size exclusion chromatograms, (b) pseudo-first-order kinetic plots, and (c) the M_n and M_w/M_n vs conversion plots for the aqueous RAFT polymerization **M17**.

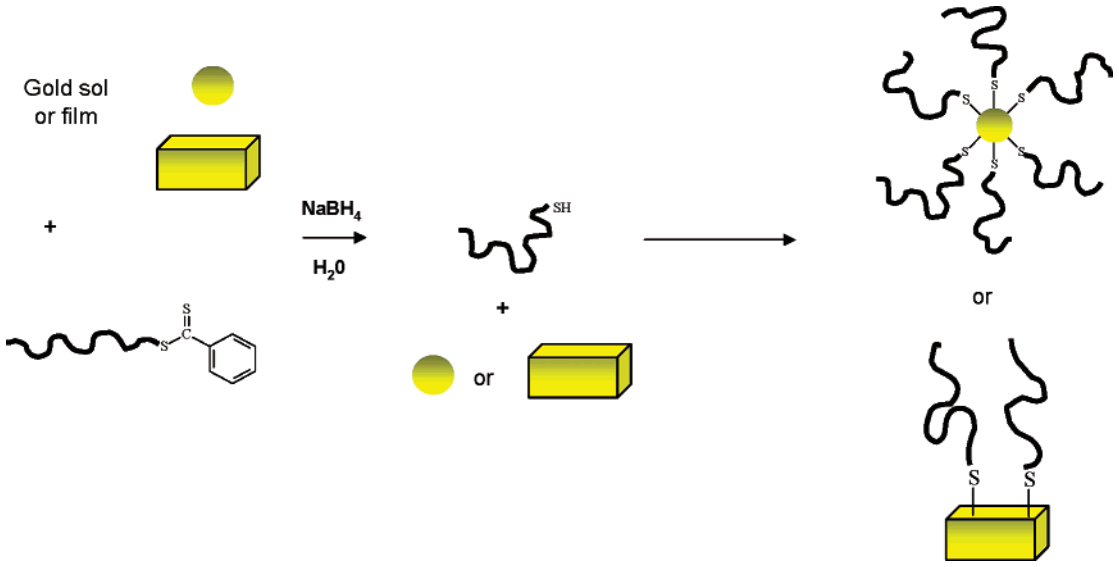


FIGURE 13. Facile modification of gold surfaces with RAFT-prepared (co)polymers.

monomer conversion to polymer should be orders of magnitude higher than hydrolysis of thiocarbonylthio functionality of the CTA and/or macro-CTA. The wide variability of propagation (conversion) rates for different monomer types (styrenic, acrylamido, acrylate, etc.) and differences in monomer and polymer (nonionic, cationic,

anionic, and zwitterionic) solvation present challenges to synthetic chemists for selection of proper RAFT conditions. To date and during our studies, relatively few examples of aqueous RAFT have been reported, probably due to difficulties in preparing appropriate water-soluble CTAs and improper selection of monomers, solvent, and other conditions. However, despite this slow start, we believe that the future of aqueous RAFT technology holds immense potential. The relative ease of preparing block copolymers which exhibit reversible self-assembly into micelles in response to pH has enormous implications in pharmaceutical science, controlled activity, and water remediation. The in situ formation of polymer-stabilized gold (and other noble metal) nanoparticles from macro-CTAs forecasts stimuli-mediated transport and delivery for nano- and macroscale applications including catalysis, lithography, electronics, diagnostics, and fluidics.

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