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Effects of Substitution Groups on the RAFT Polymerization of *N*-Alkylacrylamides in the Preparation of Thermosensitive Block Copolymers

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ABSTRACT: Reversible addition−fragmentation chain transfer (RAFT) polymerization was used to prepare a series of homo- and copolymers of *N*-alkyl-substituted acrylamides. The acrylamide monomers have similar chemical structures, but they all exhibit difference in reactivities, especially between *N*-monosubstituted and *N*,*N*-disubstituted acrylamides during the RAFT process. Results from size exclusion chromatography and matrix-assisted laser desorption ionization time-of-flight mass spectrometry indicate chain transfers to monomers are easier to occur for *N*-monosubstituted polyacrylamides, with negative deviations of the molecular weights from the theoretical values. The high transfer activity makes them good macro-chain transfer agents (CTAs). The stronger electron-donating conjugative effect renders the disubstituted acrylamides more reactive, meaning that they can react more readily with monosubstituted polyacrylamide−CTAs to form a sequent block. Tri- and tetrablock copolymers with multiple thermosensitivity have been successfully prepared and tested following these guiding principles.

Introduction

Thermosensitive polymers can manifest significant changes in their properties at a lower critical solution temperature (LCST) and have attracted much research interest because of their rheological and technological importance and potential biomedical applications.[1,2] *N*-Alkyl-substituted polyacrylamides are representative of these polymers,[3−6] and the structure of the *N*-substitution groups and the molecular weight of the polymers are important to determine the thermosensitivity and solution behavior of the polymers.[4,7,8] Chemical modifications of the polymers can also lead to a change in their LCST behavior.[9,10] We have shown previously that the LCST of *N*-alkyl-substituted acrylamide polymers can be easily tuned by a radical random copolymerization of appropriate comonomers.[11,12]

The *N*-alkyl-substituted polyacrylamides obtained from conventional free radical polymerizations are usually polydispersed with broadened thermal transitions.[9,13] Polymers of a well-defined structure and molecular weight are desired and can be prepared by controlled radical polymerization methods, the most used of which include nitroxide-mediated polymerization, atom transfer radical polymerization, and reversible addition−fragmentation chain transfer (RAFT) polymerization. Block copolymers responding to multiple external stimuli may also be obtained.[14,15] RAFT polymerization has a good tolerance for functional groups of monomers and has been successfully applied to the preparation of selected *N*-alkyl-substituted polyacrylamides.[16,17] The groups of McCormick and others have reported the RAFT polymerization of several acrylamide monomers under different conditions using various chain transfer agents (CTAs).[18−24] The polymerization of *N*-isopropylacrylamide mediated by RAFT has been extensively studied.[25−29] Other *N*-substituted acrylamides have not yet drawn as much attention. Most studies have focused on the reaction conditions of RAFT techniques, including the adoption of different RAFT reagents, initiators, and solvents.[17−30]

In this work, we intended to prepare multiblock copolymers from various mono- and disubstituted acrylamides by the RAFT technique. In a conventional radical polymerization, the difference in reactivity caused by the substitution groups in the acrylamides may be negligible, but we found that the number and nature of the *N*-alkyl substitution groups are important to determine the reactivity of the monomers in the RAFT process and the solution properties of the final polymers. The effect of the substitution groups on the kinetics and the control in the RAFT polymerization of these acrylamides have been studied by analyzing the living degree of the polymerization and the structure of the end groups.

Experimental Section

Materials. All chemicals were purchased from Aldrich (Milwauke, WI) and were of analytical grade quality. They were used without further purification unless otherwise stated. 2,2′-Azoisobutyronitrile (AIBN) was recrystallized from methanol. Water was purified with a Millipore Mill-Q system. *N*-Isopropylacrylamide (iPA) was recrystallized from toluene/hexane (3:2, v/v). *N*,*N*-Dimethylacrylamide (DMA) was vacuum-distilled prior to use. *N*-*tert*-Butylacrylamide (tBA) (Aldrich, 97%) was used without further purification. Other *N*-substituted acrylamide monomers including *N*,*N*-ethylmethylacrylamide (EMA), *N*,*N*-diethylacrylamide (DEA), *N*-*n*-propylacrylamide (nPA), *N*-*n*-butylacrylamide (nBA), *N*-*sec*-butylacrylamide (sBA), and *N*-isobutylacrylamide (iBA) were prepared from the corresponding alkylamines and acryloyl chloride (analytical grade), according to a procedure as reported by Shea et al.[31] A trithiocarbonate (2-dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionic acid, DMP) was used as the RAFT reagent and prepared according to a previously reported procedure.[32]

General RAFT Polymerization. With AIBN as the initiator and DMP as the RAFT reagent, all polymerizations were conducted in

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dimethyl sulfoxide (DMSO) at 70, 80, or 90 °C in septa-sealed vials that were bubbled with nitrogen for 20 min before the reaction. The typical [DMP]/[AIBN] ratio was 5:1. Samples were periodically withdrawn from reaction mixtures for analyses. A typical procedure (for nPA) is described here. DMP (0.284 g, 0.779 mmol), AIBN (25.6 mg, 0.156 mmol), and nPA (13.2 g, 0.117 mol) were added along with 30 mL of DMSO to a 100 mL flask equipped with a magnetic stirring bar. After purging with N_2 for 20 min, the flask was immersed in a preheated oil bath at 70 °C, and the polymerization proceeded at 70 °C for 50−60 min before the product (PnPA) was purified by precipitation in distilled water (conversion $= 64.4\%$, $M_n = 8100$, PDI $= 1.07$). The RAFT polymerization for selected polymers such as PnPA, PiPA, and PDEA was repeated several times (at least three times), and the results were reproducible as long as the purity of the monomers was guaranteed.

A typical procedure of the RAFT copolymerization of the second block is quite similar and is described here for the addition of iPA to a PnPA macro-CTA prepared above. The macro-CTA PnPA (3.0 g, 0.37 mmol), AIBN (9.14 mg, 0.056 mmol), iPA (6.28 g, 0.056 mol), and DMSO (40 mL) were added to a 100 mL round-bottomed flask. The mixture was purged with N_2 for 20 min, and the copolymerization was allowed to proceed in an oil bath at 70 °C for 40 min before termination by exposure to air. The product was then dialyzed in distilled water for more than 3 days and isolated by lyophilization (for reaction time of 40 min: conversion $= 85.8\%$, $M_n = 20\,900$, PDI $= 1.14$).

Triblock and tetrablock copolymers were prepared similarly with the diblock and triblock copolymers, respectively, as the macro-CTAs to chain extend with the appropriate comonomers. The products were purified by dialysis and then isolated by lyophilization in the same way.

Polymer Characterization. The NMR spectra of the monomers and polymers in $CDCl_3$ were recorded on a Bruker-AV400 spectrometer operating at 400 MHz for protons. Monomer conversions were determined by comparing the integration of the NMR signals (5.0−6.5 ppm) of the protons of the vinyl group of the residual monomers with the integration of the characteristic NMR signals of the polymer.

The molecular weights and the polydispersity index (PDI) of the samples were obtained by size exclusion chromatography (SEC) on a Waters 1525 system equipped with three Waters Styragel columns (HR3, HR4, and HR6; each 7.8 mm × 300 mm, 5 μm particle size, providing an effective molecular weight range from 500 to 10^7 g mol^{-1}) equilibrated at 30 °C and a refractive index detector (Waters 2410). Tetrahydrofuran (THF) was used as the mobile phase (1.0 mL min^{-1}), and the system was calibrated with polystyrene standards from 200 to 10^6 g mol^{-1}.

Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) of the polymers was performed on an AutoFlex MALDI-TOF (Bruker Daltonics) equipped with a nitrogen laser (337 nm) and an accelerating potential of 20 kV. Samples were prepared by mixing a solution of the polymer in THF (10 mg/mL) and a solution of 3-β-indole acrylic acid (IAA) matrix in THF (10 mg/mL) with a ratio of 1:20. Then, the resulting mixture (1 μL) was deposited onto the sample plate, and the solvent was evaporated at room temperature. Spectra were recorded in the reflector mode with external calibration.

LCST was measured on a Cary 300 Bio UV−vis spectrophotometer equipped with a temperature-controlled sample holder. The transmittance of the aqueous solution of the polyacrylamides was measured at 500 nm at a heating rate of 0.1 °C/min from 10 to 75 °C.[7]

Results and Discussion

Scheme 1. Reversible Addition−Fragmentation Chain Transfer (RAFT) Polymerization of *N*-Alkyl-Substituted Acrylamides in Dimethyl Sulfoxide (DMSO) with 2,2′-Azoisobutyronitrile (AIBN) as the Initiator

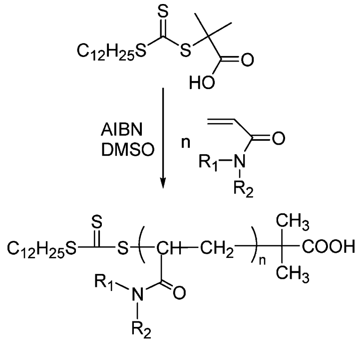
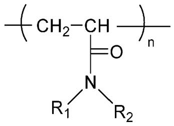


Table 1. Chemical Structures and Aqueous Solution Properties of Poly(*N*-alkylacrylamide)s

	R_1	R_2	abbrev	LCST (°C)[a]
poly(*N*,*N*-dimethylacrylamide)	Me	Me	PDMA	soluble
poly(*N*,*N*-ethylmethylacrylamide)	Me	Et	PEMA	70
poly(*N*,*N*-diethylacrylamide)	Et	Et	PDEA	32
poly(*N*-isopropylacrylamide)	H	iPr	PiPA	36
poly(*N*-*n*-propylacrylamide)	H	nPr	PnPA	25
poly(*N*-*n*-butylacrylamide)	H	nBu	PnBA	insoluble
poly(*N*-isobutylacrylamide)	H	iBu	PiBA	insoluble
poly(*N*-*sec*-butylacrylamide)	H	sBu	PsBA	insoluble
poly(*N*-*tert*-butylacrylamide)	H	tBu	PtBA	insoluble

[a] Measured by UV−vis spectrophotometry at 50% transmittance with a heating rate of 0.1 °C/min. Polymer molecular weight about 10 kDa, 1 g/L solution in water.

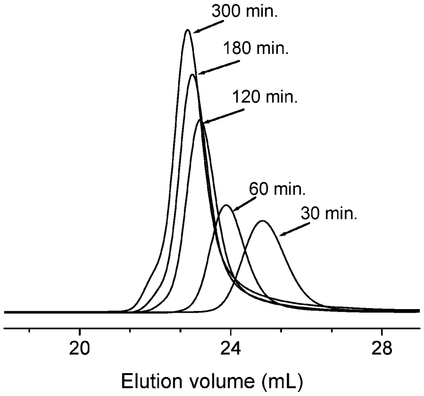


Figure 1. Size exclusion chromatographic traces of poly(*N*-*n*-propylacrylamide) (PnPA) obtained by RAFT homopolymerization by the use of 2-dodecylsulfanylthiocarbonyl-sulfanyl-2-methylpropionic acid) (DMP) as the RAFT reagent, and 2,2′-azoisobutyronitrile (AIBN) as the initiator, in dimethyl sulfoxide (DMSO) at different reaction times at 70 °C.

RAFT Homopolymerization of *N*-Substituted Acrylamides. Scheme 1 shows the synthetic pathway for the RAFT polymerization of all the momoners listed in Table 1. DMP is a trithiocarbonate with very high chain transfer efficiency and was selected as the RAFT reagent.[29,32,33] Table 1 shows a list of *N*-substituted polyacrylamides prepared in this study and their solution properties in water. The monomers include both *N*-monosubstituted and *N*,*N*-disubstituted acrylamides. It is known that the thermosensitivity and solution behavior of the polymers depend on the *N*-alkyl substitution group of the acrylamide monomers. For the acrylamide substituted with methyl groups, the polymer (PDMA in Table 1) is freely soluble in water, while polymers with more hydrophobic alkyl groups (such as *n*-, *iso*-, *sec*-, and *tert*-butyl groups) are rather insoluble in water at a molar mass of ca. 10 kDa.

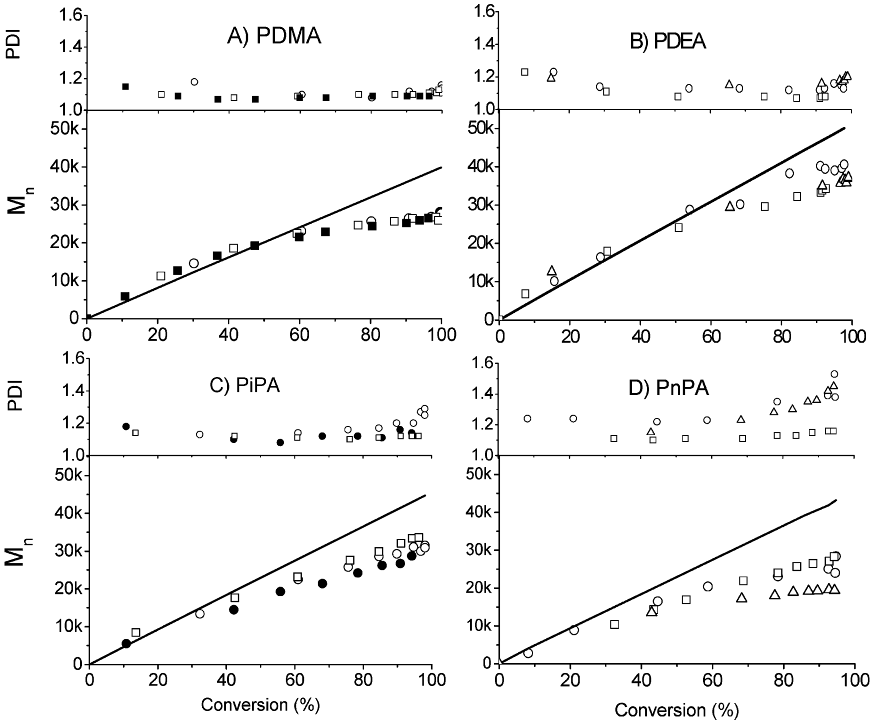


Figure 2. Number-average molecular weight (M_n) and polydispersity index (PDI) vs conversions for (A) poly(*N*,*N*-dimethylacrylamide) (PDMA), (B) poly(*N*,*N*-diethylacrylamide) (PDEA), (C) poly(*N*-isopropylacrylamide) (PiPA), and (D) poly(*N*-*n*-propylacrylamide) (PnPA) prepared by RAFT homopolymerizations: open symbols, [monomer]/[DMP]/[AIBN] = 400/1/0.2; closed symbols, [monomer]/[DMP]/[AIBN] = 400/1/0.1; squares, 70 °C; circles, 80 °C; triangles, 90 °C. Solid lines are the fitted theoretical values from eq 1.

Figure 1 shows the SEC elution curves for the homopolymerization of nPA at 70 °C. The RAFT polymerization of nPA was well controlled at this temperature with PDI values lower than 1.2 (Figure 2D, though the PDI values showed an increase at higher reaction temperatures). No shoulders or tails are observed in the SEC traces until the reaction time reached 180 min. A small high-molecular-weight shoulder seems to appear at a reaction time of 300 min. Other *N*-alkylpolyacrylamides prepared have shown similar results. For the samples of low molecular weights, results obtained from MALDI-TOF agreed well with the SEC results.

The M_n and PDI (M_w/M_n) of the polymers of *N*-alkylacrylamides obtained under different reaction conditions have been studied by the use of NMR, MALDI-TOF (for samples of lower molecular weights), and SEC. The conversion of the monomers was also obtained from NMR experiments as described in the Experimental Section. In many cases, the reactions were repeated to confirm the experimental data and to optimize the reaction conditions. Typical examples of the polymers of mono- and disubstituted acrylamides are shown in Figure 2, in which the respective M_n and PDI values are plotted as a function of conversion for PDMA, PDEA, PiPA, and PnPA under different reaction conditions (different temperatures and ratios of [DMP]/[AIBN]). The RAFT polymerizations of DMA and DEA (Figure 2A,B) are quite well controlled. The PDI values throughout the RAFT process are below 1.2, even at high conversions. Changing the ratio of [DMP]/[AIBN] or reaction temperature has little influence on the molecular weight of the polymers. Elevated temperatures may cause a slightly broader distribution of molecular weights (Figure 2B,D, PDI values are above 1.2 at 90 °C). The observed molecular weights are consistent with the theoretical values (solid line) initially, with a negative deviation at high conversions. The theoretical molecular weight ($M_{n,th}$) can be calculated from

$$\bar{M}_{n,th} = M_{CTA} + \frac{[\text{monomer}]}{[\text{CTA}]} \times M_{\text{monomer}} \times \text{conversion (\%)} \quad (1)$$

where M_{CTA} and M_{monomer} are the molecular weights of RAFT agent and monomers, respectively, and [monomer] and [CTA] are the initial monomer and CTA concentrations. It is to be noted that $M_{n,th}$ was calculated from eq 1 without considering the number of radicals derived from the initiator,[16] which can be a possible cause of the negative deviation (discussed in more detail later).

Compared with PDMA and PDEA, PiPA (Figure 2C) and especially PnPA (Figure 2D) have larger negative deviations of molecular weight and larger PDI values at high conversions. Changing the reaction conditions affected the RAFT polymerization of iPA and nPA. Elevated reaction temperatures caused more significant negative deviations of the molecular weights as well as larger PDI values (over 1.3, Figure 2D). It is important to mention that similar effects of temperature and of initiator concentration were obtained with all monomers in the family, although only specific examples are shown in Figure 2 for selected monomers.

The reaction kinetics of the RAFT polymerization process have been studied with the molecular weight data obtained at various reaction times (and under different conditions), as discussed above. The reactions with the monomers listed in Table 1 all show a similar general trend. Typical examples of a mono- and dialkyl-substituted acrylamide are shown in Figure 3. The kinetic data for the polymerization of DMA and nPA under different reaction conditions are shown in parts A and B of Figure 3, respectively. Linear plots are obtained at lower conversions, but deviations from the linearity are observed at long reaction times, especially for PnPA at higher temperatures. Higher temperatures and higher initiator concentrations resulted

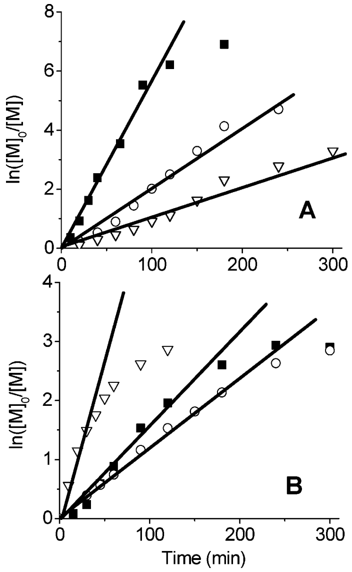


Figure 3. Pseudo-first-order rate plot for the RAFT homopolymerization of (A) *N*,*N*-dimethylacrylamide) (DMA): (▽) [DMA]/[DMP]/[AIBN] = 400/1/0.1, 70 °C; (○) [DMA]/[DMP]/[AIBN] = 400/1/0.2, 70 °C; (■) [DMA]/[DMP]/[AIBN] = 400/1/0.2, 80 °C; (B) *N*-*n*-propylacrylamide (nPA) with [nPA]/[DMP]/[AIBN] = 400/1/0.2: (▽) 90 °C; (■) 80 °C; (○) 70 °C. The solid lines show the general trends.

in higher rates of polymerization. Under the same reaction conditions, the polymerization rates of PDMA are much higher than those of PnPA, indicating the higher reactivity of the DMA monomers. It seems obvious that the RAFT polymerizations of *N*,*N*-dialkyl-substituted acrylamides were better controlled than those of *N*-monoalkyl-substituted monomers. PDMA and PDEA have lower PDI values, less negative deviations of molecular weight, and faster polymerization rates. Compared with *N*-monosubstituted acrylamides, *N*,*N*-disubstituted monomers may have a higher reactivity and form more stable radicals because of their stronger electron-donating conjugative effect in their molecular structure, which also accounts for the diminished influence of temperature on RAFT polymerization of *N*,*N*-disubstituted monomers.

Negative deviations of molecular weight for RAFT polymerization of *N*-alkyl-substituted acrylamides have been reported previously.[14,21] In the block copolymerization of acrylic acid with iPA, the molecular weight of copolymers measured by MALDI-TOF was somewhat lower than the theoretical values.[14] According to the classic RAFT mechanism, the negative deviations may be an indication of the existence of other sources of radicals than the CTA-derived ones, such as initiator-derived chains.[16] McCormick and co-workers have reported the good agreement between observed and theoretical molecular weights for the RAFT polymerization of acrylamide in DMSO utilizing a trithiocarbonate as the CTA, but the M_n vs conversion plot still showed a slight negative deviation of molecular weight at higher conversions.[22] The use of other trithiocarbonates as CTAs also caused the negative deviation of molecular weights.[34] Better agreements between the SEC results and $M_{n,th}$ were obtained when the RAFT reactions proceeded at room temperature.[29] A more precise form of eq 1 can be used by taking into account the initiation of chains by the initiator:

$$\bar{M}_{n,th} = M_{CTA} + \frac{[\text{monomer}]}{[\text{CTA}] + df\,[\text{AIBN}](1 - e^{-k_d t})} \times M_{\text{monomer}} \times \text{conversion (\%)} \quad (2)$$

where d is the number of chains produced from radical−radical termination ($1 < d < 2$), f the initiator efficiency ($0 < f < 1$), t the reaction time, and k_d the decomposition rate constant for the initiator (the value for AIBN is ca. 6.2×10^{-5} s^{-1} in dimethylformamide at 71.2 °C). Since the k_d value is usually small, the second term in the denominator in eq 2 often becomes negligible, even when the maximum values for d and f are taken ($d = 2$ and $f = 1$, respectively). The consideration of the radicals formed by the initiator and the initiator efficiency (taken as 0.5) may help to explain the negative deviations to a certain extent.[16,22,35,36] In our experiments, using a decreased amount of AIBN (therefore lower [AIBN]) failed to correct the deviations (shown in Figure 2A,C). This indicates that initiator-derived radicals, if any, may not be the principal cause of the molecular weight deviations in this case. For PiPA and PnPA (Figure 2C,D), lower reaction temperature can correct this negative deviations to a certain extent, indicating that a lower temperature may decrease the number of other radicals formed. In the cases of *N*,*N*-disubstituted PDMA and PDEA, however, changing the temperature had little effect on the molecular weight of the polymers. Thus, the negative deviations of molecular weight seem to be related to the structure of monomers.

MALDI-TOF MS Analyses of the Polymers. MALDI-TOF mass spectrometry was used to examine the end groups of the polymers prepared including PnPA, PiPA, PDEA, and PDMA to further deduce the causes of molecular weight deviations. Figure 4 shows the MALDI-TOF spectra of PnPA and PDMA obtained at different conversions (reaction times 40 min and 4 h), showing in general the distribution of the molecular weights of the polymers. In Figure 4A (for PnPA with a conversion of 50.7%), each repeating sequence consists of four obvious peaks; in Figure 4B (for PnPA with a conversion of 92.8%), each repeating sequence consists of two extra peaks with a total of six peaks (listed in Table 2). Figure 4A,B shows that the expected dormant chains are CTA-derived (peaks 1−3) and are more intense. Peak 3 (1646.8 g/mol in Figure 4A and 2891.4 g/mol in Figure 4B) may also be assigned to dead polymers since the combined chains with methylpropionic acid groups of AIBN have the same mass (1646.3 g/mol for sample A and 2891.1 g/mol for sample B) (Table 2). At the early stage of polymerization (40 min), very few dead polymers were produced. The very intense signal of peak 3 may be assigned to products of CTA-derived living chains ionized with K$^+$. Peak 4 at 1672.5 g/mol (Figure 4A) or 2800.5 g/mol (Figure 4B) may be assigned to disproportionation chains (transfer to monomer nPA). This peak was observed on all MALDI-TOF spectra for all samples and changed little even when the samples were different or under different conditions. Moreover, considering the good control of molecular weight and high transfer efficiency of polymers at the early stage of reactions, the irreversible transfer and disproportionation reactions were not likely to occur. Thus, the disproportionation products (peak 4) are believed to be formed by fragmentation during ionization inside the mass spectrometer, as reported previously.[25,37]

Peaks 5 and 6 were nearly undetectable in Figure 4A (PnPA, conversion = 50.7%) but were prominent in Figure 4B (PnPA, conversion = 92.8%). Similar results were observed for other samples such as PiPA. The intensities of these peaks increased for the samples with higher conversions or longer reaction times. Therefore, with time, some living chains may have been terminated by either disproportionation or transfer to monomers to form dead chains. This should lead to a negative deviation at the late stage of RAFT polymerization. The elevated temperature may accelerate the monomer transfer, resulting in larger deviations of molecular weights (shown in Figure 2C,D).

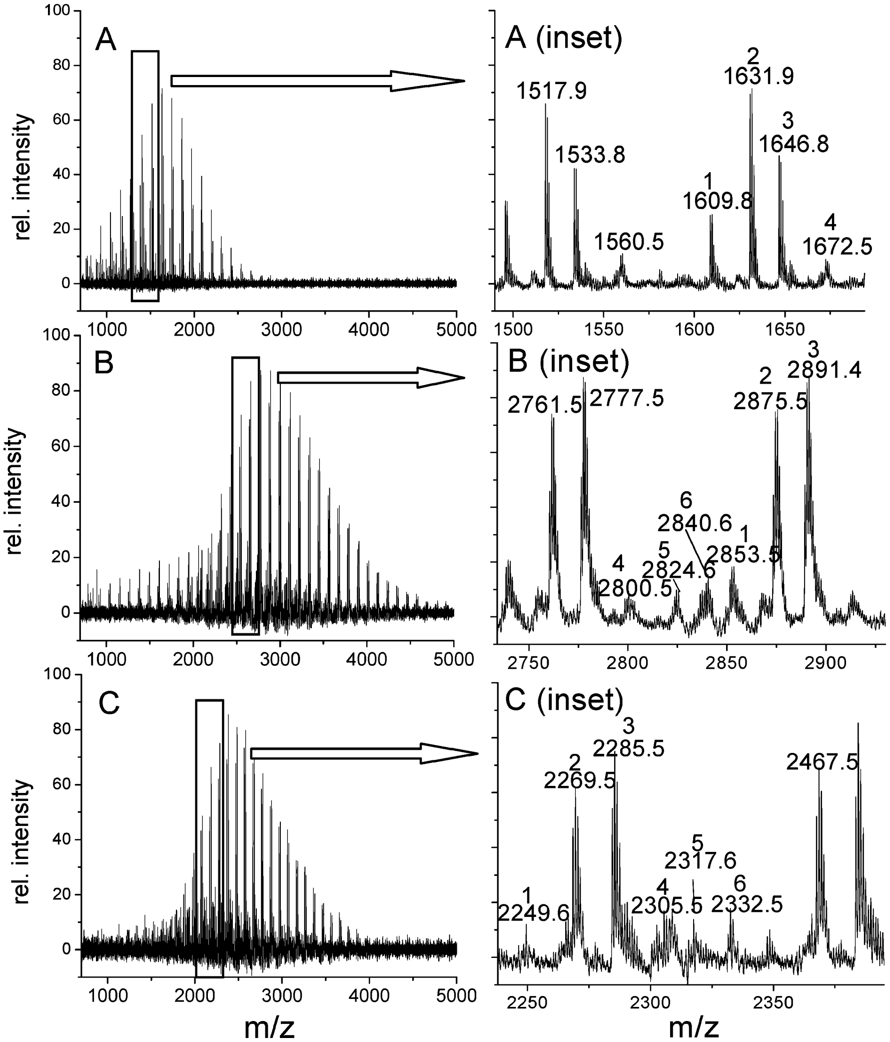


Figure 4. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra (reflector mode, IAA matrix) of poly(*N*-*n*-propylacrylamide) (PnPA) and poly(*N*,*N*-dimethylacrylamide) (PDMA) obtained by RAFT homopolymerization at 70 °C with [monomer]/[DMP]/[AIBN] = 30/1/0.1 under different conversions. (A) PnPA, conversion = 50.7%, reaction time 40 min, M_n = 1750, PDI = 1.04; (B) PnPA, conversion = 92.8%, reaction time 4 h, M_n = 3030, PDI = 1.04; (C) PDMA, conversion = 78.3%, reaction time 40 min, M_n = 2650, PDI = 1.02. Spectrum C inset: peak 5: $NC-C(CH_3)_2-DMA_{23}-C(CH_3)_2-CN\ H^+$; peak 6: $NC-C(CH_3)_2-DMA_{23}-S-CSSR\ H^+$.

Figure 4C is the MALDI-TOF mass spectra of PDMA (sample taken at 40 min at 78.3% conversion). Peaks 1−4 are ascribed to the similar structures in PnPA (shown in Table 2). Peaks 1, 2, and 3 are attributed to the living chains with transfer agent end groups as H^+, Na^+, and K^+ adducts, respectively. Peak 4 (2305.5 g/mol) is probably the result of fragmentation inside the mass spectrometer. There are two more sets of peaks with very low intensity in Figure 4C. They cannot be attributed to disproportionation or transfer to monomers as in PnPA samples. Peak 5, ascribed to combination with AIBN end groups, has the lowest intensity, suggesting few dead polymers were produced. Peak 6 corresponds to initiator-derived living chains which are not observed in the spectra of PnPA and PiPA. The PDMA sample taken at 4 h (99.6% conversion) was also analyzed, which has a similar repeating sequence peaks with higher intensity of peaks 5 and 6 (data not shown). PDEA has a similar MS spectrum as PDMA (not shown). No evidence of chain termination by disproportionation or transfer to monomers was observed on the MS spectra of PDMA or PDEA. During RAFT polymerizations, for *N*,*N*-disubstituted acrylamides, the termination may be prone to combination, while for *N*-monosubstituted acrylamides, disproportionation or transfer to monomers may be their preferred termination modes. The MALDI-TOF results show that most chains in the RAFT polymerization of DMA or DEA are living products including CTA-derived and initiator-derived chains, which demonstrates their homopolymerizations are under good control.

Compared with *N*,*N*-disubstituted acrylamides, as mentioned earlier, *N*-monosubstituted monomers are less reactive but form more active radicals, which are easier to transfer to monomers. As a consequence, PnPA or PiPA has significant negative deviations from the theoretical molecular weight. *N*,*N*-Disubstituted monomers such as DMA and DEA are more reactive but form more stable radicals, resulting in high polymerization rates and high monomer conversions. But the stable radicals may have difficulties to react with other monomers in subsequent copolymerizations, even in self-blocking experiments.

RAFT Copolymerization. Diblock copolymers can be made by using the homopolymer as a macro-CTA to react with a second monomer. PiPA was chain-extended with nPA to obtain the corresponding diblock copolymer P(iPA-*b*-nPA), which exhibits a monomodal SEC trace (Figure 5A). The clear shifts of the copolymer peaks away from the peak of macro-CTA PiPA (Figure 5A) confirm the formation of block copolymers. Similarly, PnBA was chain-extended with iPA to obtain the corresponding block copolymers. The copolymers P(nBA-*b*-iPA) also exhibit monomodal SEC traces. However, with nPA as the second comonomer, PnBA cannot convert completely

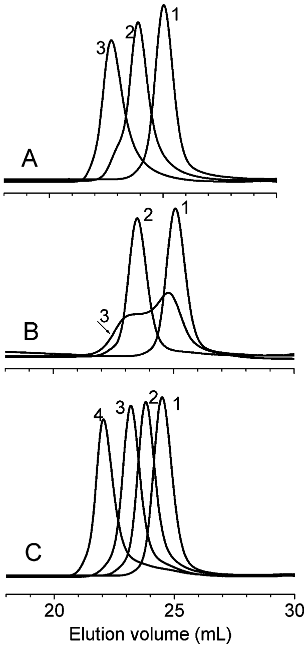
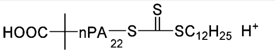
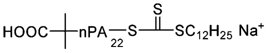
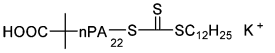
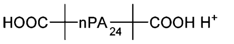
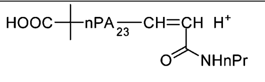
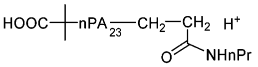
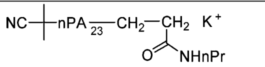
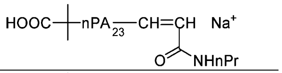
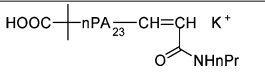


Figure 5. Size exclusion chromatographic traces for the macro-chain transfer agent (CTA) and the corresponding chain-extended block copolymers obtained by RAFT polymerization at 70 °C in DMSO: (A) trace 1: macro-CTA PiPA, M_n = 9600, PDI = 1.10; trace 2: P(iPA-*b*-nPA), M_n = 17 200, PDI = 1.15; trace 3: P(iPA-*b*-nPA), M_n = 28 900, PDI = 1.17; (B) trace 1: macro-CTA Poly(*N*-*n*-butylacrylamide) (PnBA), M_n = 9070, PDI = 1.11; trace 2: P(nBA-*b*-iPA), M_n = 20 900, PDI = 1.15; trace 3: P(nBA-*b*-nPA); (C) SEC traces for tetrablock copolymer poly(*N*-*n*-propylacrylamide-*b*-*N*-isopropylacrylamide-*b*-*N*,*N*-ethylmethylacrylamide-*b*-*N*,*N*-dimethylacrylamide) (P(nPA-*b*-iPA-*b*-EMA-*b*-DMA)) and the corresponding macro-CTAs: trace 1: PnPA, M_n = 14 600, PDI = 1.10; trace 2: P(nPA-*b*-iPA), M_n = 20 400, PDI = 1.12; trace 3: P(nPA-*b*-iPA-*b*-EMA), M_n = 27 600, PDI = 1.16; trace 4: P(nPA-*b*-iPA-*b*-EMA-*b*-DMA), M_n = 45 800, PDI = 1.25. The conversion of the last block was at 94% and of the beginning blocks at 72−73%.

Table 2. Structures Corresponding to the Various MALDI-TOF MS Peaks in Figure 4B

peak	monoisotopic mass		structure
	experimental	theoretical	
1	2853.5	2855.1	 $HOOC-(nPA)_{22}-S-\overset{S}{\|}-SC_{12}H_{25}\ H^{+}$
2	2875.5	2877.1	 $HOOC-(nPA)_{22}-S-\overset{S}{\|}-SC_{12}H_{25}\ Na^{+}$
3	2891.4	2893.1 2891.1	 $HOOC-(nPA)_{22}-S-\overset{S}{\|}-SC_{12}H_{25}\ K^{+}$  $HOOC-(nPA)_{24}-COOH\ H^{+}$
4	2800.5	2802.9 2804.9	 $HOOC-(nPA)_{23}-CH{=}\underset{C(=O)NHnPr}{\underset{\mid}{CH}}\ H^{+}$  $HOOC-(nPA)_{23}-CH_2-\underset{C(=O)NHnPr}{\underset{\mid}{CH_2}}\ H^{+}$
5	2824.6	2823.9 2824.9	 $NC-(nPA)_{23}-CH_2-\underset{C(=O)NHnPr}{\underset{\mid}{CH_2}}\ K^{+}$  $HOOC-(nPA)_{23}-CH{=}\underset{C(=O)NHnPr}{\underset{\mid}{CH}}\ Na^{+}$
6	2840.6	2840.9	 $HOOC-(nPA)_{23}-CH{=}\underset{C(=O)NHnPr}{\underset{\mid}{CH}}\ K^{+}$

to block copolymers during copolymerization (Figure 5B, trace 3). This indicates the reactivity difference among the acrylamide derivatives although they have similar chemical structures.

We investigated the controlled nature of copolymerizations using three *N*-alkyl-monosubstituted polyacrylamides (PiPA, PnPA, and PnBA) and three *N*,*N*-disubstituted polyacrylamides (PDEA, PEMA, and PDMA) as macro-CTAs to copolymerize with nine acrylamide monomers as listed in Table 3 to prepare diblock copolymers (including self-blocking experiments). In all cases, we used the same polymerization conditions: the polymerization of macro-CTAs proceeded at 70 °C for 50−60 min, and the block copolymerization was allowed to proceed for 2 h before termination. Obviously, polymers of *N*-monosubstituted acrylamides (PiPA, PnPA, and PnBA) are more active macro-CTAs than the *N*,*N*-disubstituted ones (PEMA, PDMA, and PDEA) and can chain extend with other acrylamide monomers to form block copolymers, indicating their relative high chain transfer constants. Among them, PiPA is the best macro-CTA and can block copolymerize with all monomers on the list.

In most cases, the use of disubstituted PDEA, PEMA, and PDMA as macro-CTAs often results in mixture products of copolymers and unreacted homopolymers as exemplified by SEC trace 3 in Figure 5B. Exceptionally, PEMA can react successfully with DEA or DMA to form a diblock copolymer. The disubstituted DEA and DMA monomers reacted easily with other macro-CTAs to form a second block, but PDEA may be the worst macro-CTA on this list. Self-blocking of PDMA and PDEA may be successful with macro-CTAs of low molecular weights but was unsuccessful under the conditions used in these experiments (50−60 min reaction time during the preparation of CTAs). It is clear from the results in Table 3 that the number of *N*-alkyl substitution groups has a significant effect. The steric effect of the alkyl groups (length or size) is of secondary importance. For example, the RAFT polymerization of iPA seems to be better controlled than that of nPA and nBA.

These results further indicate that difference of reactivity exists among nearly all *N*-alkylacrylamide monomers due to the differences in the number and structure of the substitution groups. Between *N*-monosubstituted and *N*,*N*-disubstituted acrylamides, the difference of reactivity is more obvious. The stronger electron-donating conjugative effect renders the disubstituted acrylamides more reactive, along with the formation of more stable radicals, which are poor leaving groups with respect to the propagating radicals of *N*-monosubstituted ones. The MALDI-TOF results demonstrate that PnPA or PiPA is easy to chain transfer during RAFT polymerization. Thus, macro-CTAs of *N*-monosubstituted polyacrylamides have relative high transfer constants and are good leaving groups in the subsequent step of copolymerization.

It was reported that PDMA could be used as a macro-CTA for the RAFT polymerization of iPA.[27,38] Indeed, we found that the block copolymerization could be improved if the reaction time was shortened during the synthesis of the macro-CTAs. Our kinetic data show that DMA has a fast polymerization rate. At relatively long reaction times (50−60 min) for the samples in Table 3, the macro-CTA of PDMA may include some dead polymer chains, as shown by the MALDI-TOF mass spectrum (sample taken at 40 min). All reasons mentioned above may contribute to the problems (a mixture of copolymer and homopolymer) encountered in the blocking experiments. Generally, in addition to the relative reactivity of macro-CTA and the comonomer, other factors may also influence the success of a RAFT blocking copolymerization, including the purity of the monomer, the choice of CTA and initiator, the reaction conditions (N_2, temperature, reaction time), and even the process of purification of the macro-CTAs such as the dialysis conditions

Table 3. RAFT Block Copolymerization of *N*-Alkyl-Substituted Acrylamides[a]

	second comonmer								
macro-CTA	iPA	nPA	nBA	EMA	DMA	DEA	iBA	sBA	tBA
PiPA	√	√	√	√	√	√	√	√	√
PnPA	√	√	M	√	√	√	√	√	√
PnBA	√	M	√	√	√	√	√	√	√
PEMA	M	M	M	*b*	√	√	M	M	M
PDMA	M	M	M	M	M	√	M	M	M
PDEA	M	M	M	M	M	M	M	M	M

[a] The preparation of macro-CTAs: reaction at 70 °C for 50−60 min in DMSO; block copolymerization: reaction at 70 °C for 2 h in DMSO. √ = copolymerization occurs successfully; M = mixture of the copolymer and the homopolymer (macro-CTA). [b] Data not available.

(to avoid the possible hydrolysis of the trithiocarbonate group, especially for the more hydrophilic polymers).

RAFT Synthesis of Multiblock Copolymers. Knowing the difference of chain transfer efficiency of *N*-alkylacrylamides and the properties of the homopolymers, we can design and prepare well-defined block copolymers, even multiblock copolymers. We have synthesized ABC triblock copolymers, such as P(nPA-*b*-iPA-*b*-EMA), by a three-step sequential RAFT polymerization. As shown in Figure 5C, no obvious shoulders or tails were observed on the SEC traces of triblock copolymers, and the PDI is still low (1.16), suggesting most of triblock copolymers retained the trithiocarbonate end groups. Therefore, we tried to use this triblock copolymer as the macro-CTA to chain extend further with a fourth comonomer DMA. The reaction time of the first three steps of the RAFT process was limited to 50 min, and the reaction time of the last step was about 2 h. As expected, a tetrablock copolymer P(nPA-*b*-iPA-*b*-EMA-*b*-DMA) was successfully synthesized with a large increase in the molecular weight (45 800, PDI = 1.25) though there is a small low-molecular-weight tail shown in SEC trace. In the preparation of block copolymers, the conversion of the final block was usually higher (over 90%, due to a longer reaction time) and that of the beginning blocks much lower (72−73%). We have calculated the average number of polymer chains ($[\text{monomer}]_0 \times \text{conversion} \times M_{\text{monomer}})/M_n$) after the blocking experiment. The number remained more or less the same as the number of initial CTAs within experimental error at lower conversions and showed a small increase at higher conversions, indicating a loss of control when the conversion was high. For example, the conversion of last step of the tetrablock copolymer was quite high at 94%, and the number of polymer chains showed an increase of ca. 15%. The PDI of the tetrablock copolymer was correspondingly higher at 1.25.

Thermosensitivity of Multiblock Copolymers. These multiblock copolymers would exhibit interesting multiple thermosensitivity since the three blocks of nPA, iPA, and EMA present different cloud points related to those of the corresponding homopolymers. Results from the turbidimetry experiments of copolymers P(nPA_{129}-*b*-iPA_{52}-*b*-EMA_{63}) and P(nPA_{129}-*b*-iPA_{52}-*b*-EMA_{63}-b-DMA_{184}) are shown in Figure 6. The triblock copolymer showed a three-step phase transition at about 28.0, 47.5, and 63.4 °C for each step, corresponding to the LCSTs of each individual block. It can be expected that, when the temperature rises above the first LCST, the copolymers may aggregate to form micelles consisting of a core of the insoluble block surrounded by a corona of the remaining soluble blocks. When the temperature continues to rise, the other two blocks become insoluble step by step to form the outer shell of the aggregates. For tetrablock copolymers nPA_{129}-*b*-iPA_{52}-*b*-EMA_{63}-b-DMA_{184}, however, only one LCST was observed. The observation is somewhat surprising but quite understandable. The long sequence of DMA added as the final block increased the overall hydrophilicity of the whole copolymer and masked the effect of the other blocks macroscopically. Because of this increased overall hydrophilicity, the change in transmittance also became much smaller when compared to the triblock copolymer and indeed to other thermosensitive polymers in the family. It shows that much care must be taken in the design of a multiblock copolymer of this kind to obtain the desired solution and physical properties.

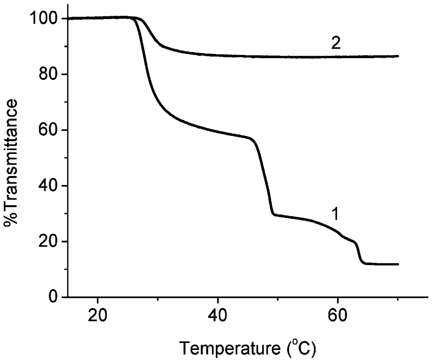


Figure 6. Changes in spectral transmittance observed at 500 nm for 1 g/L aqueous solutions of the tri- and tetrablock copolymers at a heating rate of 0.1 °C/min: (1) P(nPA_{129}-*b*-iPA_{52}-*b*-EMA_{63}) and (2) P(nPA_{129}-*b*-iPA_{52}-*b*-EMA_{63}-b-DMA_{184}).

Conclusion

RAFT polymerizations of various *N*-alkyl-substituted acrylamides can be carried out by the use of a trithiocarbonate as the chain transfer agent, but reactivity differences exist among nearly all these monomers due to the number and type of the *N*-alkyl substitution groups. It is important to notice the marked difference between *N*-monosubstituted and *N,N*-disubstituted acrylamides. RAFT polymerizations of *N,N*-disubstituted acrylamides can be better controlled than those of *N*-monosubstituted monomers (lower PDI values, less negative deviations of molecular weight from theoretical values and faster polymerization rates) because the higher reactivity of the monomers and the formation of more stable radicals. The obvious negative deviations of molecular weight of *N*-monosubstituted polyacrylamides results from chain transfer to monomers or disproportionation with prolonged reaction times. Compared with *N,N*-disubstituted acrylamides, *N*-monosubstituted monomers are less reactive but, once reacted, form more active radicals, resulting in high transfer constants of the propagating chains since they are good leaving groups. In general, the *N*-monosustituted polyacrylamides are better macro-CTAs. The stronger electron-donating conjugative effect renders the disubstituted acrylamide monomers more reactive, and they can react readily with macro-CTAs of *N*-monosubstituted polyacrylamides to form a sequent block.

The understanding of the difference of chain transfer efficiency and radical stabilization of *N*-alkyl-substituted acrylamides serves as a useful guide in the design of appropriate sequence of monomers for the preparation of complicated and well-defined block copolymers with multiple thermosensitivity, even tetrablock copolymers. The detailed solution properties of more-refined block copolymers are being studied, and the results should appear in a separate report.

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