Tuning the Temperature Response of Branched Poly(*N*-isopropylacrylamide) Prepared by RAFT Polymerization

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ABSTRACT: Reversible addition-fragmentation chain transfer (RAFT) polymerization in the presence of a compound capable of both reversible chain transfer through a thiocarbonylthio moiety and propagation via a vinyl group led to highly branched copolymers by a method analogous to self-condensing vinyl copolymerization. An acryloyl trithiocarbonate prepared by copper-catalyzed azide-alkyne cycloaddition was copolymerized with *N*-isopropylacrylamide (NIPAM) in ratios selected to tune the distribution and length of branches in the resulting thermoresponsive polymers. The degree of branching increased with chain transfer agent (CTA) concentration, as proven by NMR spectroscopy, size exclusion chromatography, and viscometry. Retention of the thiocarbonylthio compound during the polymerization was evidenced by successful chain extension of a branched *N*-isopropylacrylamide (PNIPAM) macroCTA by RAFT polymerization of *N*,*N*-dimethylacrylamide. The branched polymers led to reduced lower critical solution temperatures as compared to linear PNIPAM, an effect attributed primarily to an increased contribution of hydrophobic end groups. End group cleavage by radical-induced reduction resulted in an increased transition temperature more similar to that expected for linear PNIPAM.

Introduction

The dramatically different bulk and solution behaviors of branched polymers as compared to linear analogs of similar molecular weight are primarily the result of a pronounced influence of chain ends, decreased chain entanglement, and reduced hydrodynamic volume.[1] To fully capitalize on these unique physical properties, it is generally beneficial to control the number of branch points and the length of the branches, such that the overall macromolecular properties can be tuned. One particularly useful method for the preparation of highly branched polymers is the copolymerization of vinyl monomers with another species capable of both propagation and initiation, a process often called *self-condensing vinyl copolymerization*.[2] Branching is typically accomplished by employing an AB* "inimer" that contains both a polymerizable double bond (A) and an initiating moiety (B*). Several reports have demonstrated the particular utility of combining this methodology with controlled radical polymerization (CRP) techniques to facilitate control over branch length and polydispersity. Hawker and Fréchet et al.[3] prepared hyperbranched styrenic polymers via nitroxide-mediated radical polymerization,[4,5] and Matyjaszewski and co-workers employed atom transfer radical polymerization[6−10] to prepare hyperbranched polystyrene[11] and polyacrylates.[12−14]

Reversible addition-fragmentation chain transfer (RAFT)[15−17] has also proven to be a versatile CRP technique for creating well defined and highly functional[18,19] macromolecular topologies[20] under a variety of reaction conditions, including homogeneous[21−25] and heterogeneous aqueous media,[26−28] from essentially any monomer capable of radical polymerization. RAFT has recently been employed to synthesize highly branched (co)polymers by employing AB* chain transfer agents,[29−31] divinyl (co)monomers,[32−34] and pendant xanthate copolymers.[35] Wang and co-workers reported RAFT polymerization mediated by a chain transfer agent (CTA) containing a polymerizable styrenic group and a benzyl dithiobenzoate moiety.[29] Rimmer et al.[30,36−39] prepared a variety of highly branched temperature-responsive polymers with a polymerizable CTA that instead contained an imidazole thiocarbonylthio RAFT moiety. These polymers proved useful for protein purification[39] and temperature dependent phagocytosis[40] and clearly demonstrated the effect of end group polarity on the corresponding solution properties. We recently communicated the preparation of highly branched poly(*N*-isopropylacrylamide) (PNIPAM) and polystyrene by RAFT polymerization with a novel acryloyl trithiocarbonate.[41] By capitalizing on the orthogonality and efficiency of click chemistry techniques,[42] specifically copper-catalyzed azide-alkyne cycloaddition,[43,44] this CTA was prepared in high yield and was demonstrated to successfully control the distribution of branches and branching points in the resulting polymers.

Herein, we focus specifically on the preparation of branched PNIPAM by RAFT and describe the dramatic influence of chain architecture on the resulting responsive solution behavior. By varying molecular weight and degree of branching, we verify the pronounced effect of end group polarity and multiplicity on the temperature-susceptibility of branched PNIPAM. The presence of multiple CTA-derived hydrophobic end groups led to dramatic reduction in lower critical solution temperature (LCST). Additionally, because the resulting branched polymers contained active trithiocarbonate end groups, block copolymerization led to copolymers with temperature-responsive branched cores and linear hydrophilic exteriors.

Experimental Section

Materials. *N*,*N*,*N*′,*N*″,*N*″-Pentamethyldiethylenetriamine (PMDETA, Aldrich 99%), propargyl acrylate (Aldrich 98%), *N*,*N*-dimethylformamide (DMF, Aldrich 99.9%), tris(2-carboxyethyl)phosphine hydrochloride (TCEP-HCl, Calbiochem 100%), *N*-ethylpiperidine hypophosphite (EPHP, Aldrich 95%), ethanolamine (Acros 99%), toluene (Aldrich 99.5%), tetrahydrofuran (THF, Aldrich 99%), DMSO-d_6 (Cambridge Isotope, 99.9 atom% D) and $CDCl_3$ (Aldrich 99.8 atom% D) were used as received. 2-Dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionic acid 3-azidopropyl ester (**1**) was prepared as previously reported.[45] Prior to use, 1,4-dioxane (Alfa Aesar 99+%) and *N*,*N*-dimethylacrylamide (DMA, TCI Tokyo Kasei) were passed through a small column of basic alumina, *N*-isopropylacrylamide (NIPAM, TCI Tokyo Kasei) was recrystallized from hexane, 2,2-azobisisobutryonitrile (AIBN,

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Table 1. Synthesis of Branched Poly(*N*-Isopropylacrylamide) by Reversible Addition−Fragmentation Chain Transfer (RAFT) Copolymerization with an Acryloyl Trithiocarbonate (2)[a]

entry	monomer/CTA	[M]:[CTA]:[I][b]	time (h)	M_n (g/mol)[c]	M_w/M_n[c]	DB[d]	DP_n per branch[e]
A	NIPAM/**2**	50:1:0.5	4	12300	1.48	0.045	22
B	NIPAM/**2**	25:1:0.5	4	8300	1.68	0.072	14
C	NIPAM/**2**	50:1:0.1	24	11600	1.42	0.045	22
D	NIPAM/**2**	25:1:0.1	24	8800	1.69	0.089	11
E	NIPAM/**2**	10:1:0.1	24	5100	2.04	0.16	6
F	-/**2**	0:5:0.1	72	8740	2.29		
G[f]	DMA/**A**	500:1:0.1	18	35500	2.10		

[a] NIPAM = *N*-isopropylacrylamide. **2** = 1-[3-(2-methyl-2-dodecylsulfanylthiocarbonylsulfanylpropionyloxy)propyl]-1*H*-[1,2,3]triazol-4-ylmethyl acrylate. DMA = *N*,*N*-dimethylacrylamide. Temperature = 70 °C. Entries **A**-**E**: [NIPAM] = 3 M in 1,4-dioxane, conversion of NIPAM = 0.99. Entry **F**: [CTA] = 0.5 M in toluene, conversion of **2** = 0.64. [b] Molar ratio of monomer, chain transfer agent **2**, and 2,2-azobisisobutyronitrile. [c] Determined by size exclusion chromatography. [d] DB: Average degree of branching determined by ^{1}H NMR spectroscopy by comparing the end group (0.88 ppm, -C**H**$_3$), branched unit (4.42 ppm, −CH$_2$−C**H**$_2$-triazole), and linear monomer unit (4.0 ppm, -C**H**-(CH$_3$)$_2$ signals according to the equation DB = $[n_{\text{end groups}} + n_{\text{branched units}}]/[n_{\text{end groups}} + n_{\text{branched units}} + n_{\text{linear units}}]$ [e] Number average degree of polymerization (DP_n) per branch = DB^{-1}. [f] Chain extension of PNIPAM macroCTA (entry **A**) with DMA. Temperature = 70 °C; [DMA] = 3 M in *N*,*N*-dimethylformamide; conversion of DMA = 0.76.

Aldrich 98%) was recrystallized from ethanol, and CuBr (Aldrich 98%) was stirred for 12 h in glacial acetic acid and isolated by filtration and drying under vacuum.

Synthesis of 1-[3-(2-Methyl-2-dodecylsulfanylthiocarbonylsulfanylpropionyloxy)propyl]-1*H*-[1,2,3]triazol-4-ylmethyl Acrylate (2). A solution of **1** (1.00 g, 2.24 mmol), propargyl acrylate (494 μL, 4.47 mmol), and PMDETA (233 μL, 1.12 mmol) in DMF (89.5 mL) was purged with nitrogen and transferred via cannula to a 100 mL round-bottom flask containing CuBr (160.4 mg, 1.12 mmol) and a magnetic stir bar under a nitrogen environment. The reaction mixture was stirred at room temperature in the absence of oxygen. After 11 h, the reaction mixture was exposed to air, the solution was passed through a column of neutral alumina, and the column was rinsed with tetrahydrofuran (90 mL × 2). The resulting solution was dried under vacuum to give a residual oil in 99% yield. ^{1}H NMR (δ (ppm), DMSO-d_6): 8.16 (s, 1H, triazole), 6.34 (d, 1H, CH_2═CH), 6.19 (q, 1H, CH$_2$═C*H*), 5.98 (q, 1H, CH_2═CH), 5.21 (s, 2H, *O*═C−O−CH_2−triazole), 4.40 (t, 2H, −CH$_2$−CH_2−triazole), 4.04 (t, 2H, -CH$_2$−CH_2−O−C═O), 3.24 (t, 2H, −CH$_2$−CH_2−S−C═S), 2.12 (t, 2H, −CH_2−CH$_2$−triazole), 1.67−1.40 (m, 8H, −CH_2−CH$_2$−S−C═S and −S−C(CH_3)$_2$−CO), 1.40−1.20 (m, 18H, CH$_3$−C$_9H_{18}$−CH$_2$−CH$_2$S−C═S), 0.87−0.82 (t, 3H, CH_3−C$_9$H$_{18}$−CH$_2$−CH$_2$S−C═S). Anal. Calcd: C, 55.98; H, 7.77; N, 7.53. Found: C, 55.94; H, 8.04; N, 7.20.

RAFT Polymerizations of NIPAM with CTA 2. An example RAFT polymerization procedure was as follows.[46,47] NIPAM (3.095 g, 27.34 mmol), CTA **2** (290.0 mg, 0.547 mmol) and AIBN (44.8 mg, 0.273 mmol) were placed in a sealed 20 mL vial equipped with a magnetic stir bar. After the vial was purged with nitrogen for 20 min, nitrogen-purged 1,4-dioxane (9.39 mL) was added, and the reaction vial was placed in a preheated reaction block at 70 °C. Samples were removed periodically by syringe to determine monomer conversion by ^{1}H NMR spectroscopy and molecular weight by size exclusion chromatography (SEC). The polymerization was quenched after 4 h by cooling and exposing the reaction mixture to air. The resulting PNIPAM (M_n = 12 300 g/mol; M_w/M_n = 1.48) was isolated by precipitating into ether and drying under vacuum.

Hyperbranched Homopolymerization of 2. CTA **2** (0.278 g, 0.525 mmol) and AIBN (1.70 mg, 0.011 mmol) were placed in a sealed 4 mL vial equipped with a magnetic stir bar. After the vial was purged with nitrogen for 20 min, nitrogen-purged toluene (1.07 mL) was added, and the reaction vial was placed in a preheated reaction block at 70 °C. Samples were removed periodically by syringe to determine monomer conversion by ^{1}H NMR spectroscopy and molecular weight by SEC. The polymerization was quenched after 72 h by cooling and exposing the reaction mixture to air. The resulting hyperbranched poly(**2**) (M_n = 8740 g/mol; M_w/M_n = 2.29) was isolated by drying under vacuum.

Chain Extension of Branched PNIPAM Macro-CTA with DMA. Branched PNIPAM macro-CTA (**A**, Table 1) (159 mg, 0.013 mmol) was placed in a sealed 4 mL vial equipped with a magnetic stir bar. After purging the vial with nitrogen for 20 min, nitrogen purged DMF (2.16 mL), DMA (0.67 mL, 6.46 mmol), and a concentrated solution of AIBN in DMF (0.25 mL of 5.12 mM solution, 0.0013 mmol) were added. The vial was placed in a preheated reaction block at 70 °C. Samples were removed periodically by syringe to determine monomer conversion by ^{1}H NMR spectroscopy and molecular weight by SEC. The polymerization was quenched after 18 h by cooling and exposure to air. The resulting polymer was isolated by dialyzing against deionized water and freeze-drying.

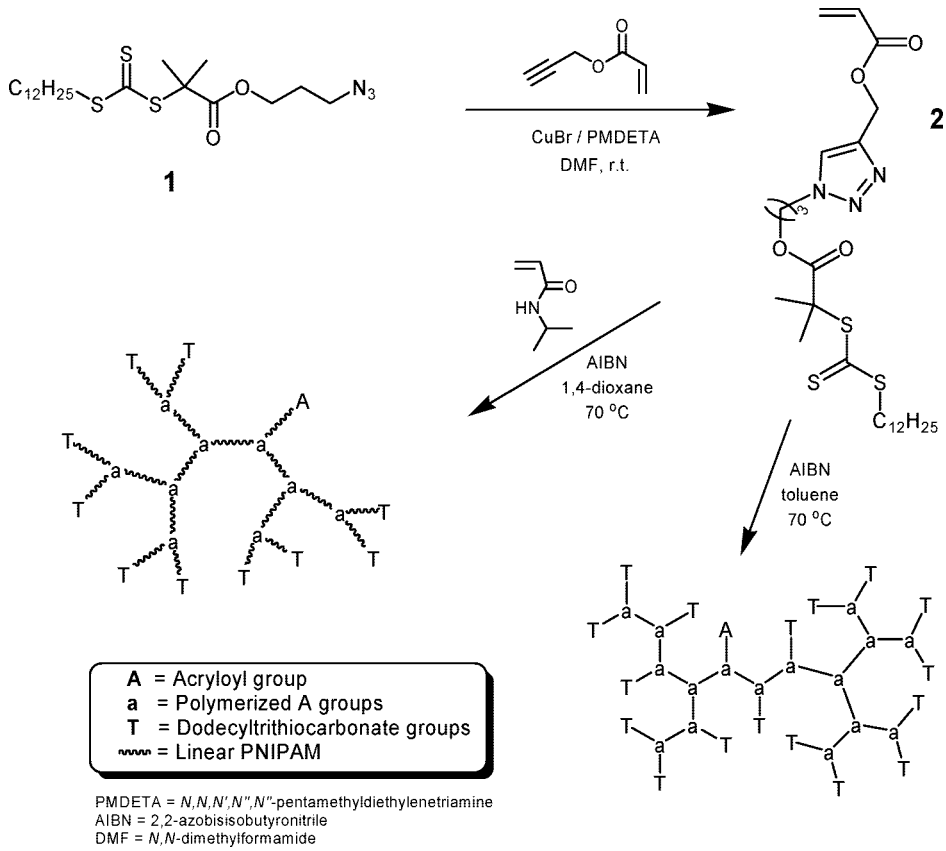
Trithiocarbonate End Group Reduction. Reduction of the thiocarbonylthio groups was accomplished according to a method derived from Chong et al.[48] PNIPAM (**B**, Table 1) (1.082 g, 0.070 mmol), AIBN (4.6 mg, 0.028 mmol), and EPHP (0.250 g, 1.395 mmol) were placed in a sealed 20 mL vial equipped with a magnetic stir bar, and the mixture was purged with nitrogen for 20 min. Nitrogen purged toluene (15 mL) was added, and the reaction vial was placed in a preheated reaction block at 110 °C. After 4 h the vial was opened to air and allowed to cool. The product was isolated by precipitating into ether, drying under vacuum, dialyzing against deionized water, and freeze-drying.

Analyses. SEC was conducted in 0.05 M LiBr in DMF at 55 °C with a flow rate of 1.0 mL/min (Viscotek VE 2001 GPCmax; Columns: ViscoGel I-Series G3000 and G4000 mixed bed columns: molecular weight range 0−60 × 10^3 and 0−400 × 10^3 g/mol, respectively). Detection consisted of a Viscotek VE 3580 refractive index detector operating at λ = 660 nm and a Viscotek Model 270 Series Platform, consisting of a laser light scattering detector (operating at 3 mW, λ = 670 nm with detection angles of 7° and 90°) and a four capillary viscometer. Molecular weights were determined by the triple detection method. ^{1}H NMR spectroscopy was conducted in $CDCl_3$ or DMSO-d_6 with a Bruker Avance 400 spectrometer operating at 400 MHz. The sample was analyzed on a ThermoFinnigan CE Elantech Model Flash EA1112 elemental analyzer, which was initially 5-point calibrated with atropine, acetanilide, nicatinamide, and cyclohexanone-2,4-dinitrophenylhydrazine. Samples were run in duplicate, or triplicate. Dynamic light scattering was conducted with a Malvern Zetasizer Nano-S equipped with a 4 mW, 633 nm He−Ne laser, and an Avalanche photodiode detector at an angle of 173°. To determine temperature-dependent solution size, sizes were measured at increments of 1 °C with an equilibration time of 30 min between each sample. UV−vis spectroscopy was conducted with an Ocean Optics USB2000 USB-ISS-UV/vis spectrophotometer.

Results and Discussion

Synthesis and Analysis of Branching. Copper-catalyzed azide−alkyne cycloaddition[42−44] has proven to be a near-ideal method for efficient polymer modification.[49−55] RAFT polymerization with CTA **1** allows the synthesis of azido-terminated polymers capable of subsequent transformations with alkynes to obtain a variety of functional telechelics.[45,46,56] While postpolymerization modification with alkynyl (meth)acrylates provides a route to well-defined (meth)acryloyl macromonomers,[57] prepolymerization functionalization of the azido portion

Scheme 1. Synthesis of Acryloyl Trithiocarbonate Chain Transfer Agent (1-[3-(2-Methyl-2-dodecylsulfanylthiocarbonylsulfanylpropionyloxy)propyl]-1*H*-[1,2,3]triazol-4-ylmethyl Acrylate (2)) and Subsequent Preparation of Branched Poly(*N*-isopropylacrylamide) (PNIPAM) Copolymers and Hyperbranched Poly(2) by Reversible Addition−Fragmentation Chain Transfer Polymerizations



of the low molecular weight CTA with propargyl acrylate yields an AB* acryloyl trithiocarbonate (**2**) (Scheme 1). This species can participate in RAFT polymerization by both reversible chain transfer and propagation via the thiocarbonylthio and acryloyl groups, respectively. Therefore, radical polymerization in the presence of **2** gives rise to hyperbranched polymers with thiocarbonylthio end groups, while copolymerization with a conventional vinyl monomer yields branched copolymers with an average degree of branching (DB) and branch length determined by the polymerization stoichiometry.

NIPAM and CTA **2** were copolymerized by RAFT as outlined in Scheme 1. Selected ratios of [monomer]/[**2**]/[AIBN] afforded PNIPAM with $M_n \approx (5-12) \times 10^3$ g/mol (Table 1). RAFT copolymerization was expected to occur by rapid addition of the initiator-derived radical (or oligomeric radical) to **2**, and after fragmentation of the RAFT adduct radical, the resulting acryloyl-functionalized CTA-fragment should initiate copolymerization of NIPAM and **2** to yield acryloyl-terminated oligomers with pendant trithiocarbonate moieties. As the polymerization proceeded, essentially every chain should contain a terminal acryloyl group and trithiocarbonate moieties on each branch termini. As the terminal acryloyl groups were incorporated into other chains, molecular weight was expected to increase with both chain and step growth characteristics, eventually leading to increasingly broadened molecular weight distributions with multiple chain populations.[58] As seen from the example in Figure 1A, SEC analysis confirmed both an increase in molecular weight and polydispersity with conversion, though the broad and complex molecular weight distributions that resulted from the hybrid chain/step growth mechanism prohibited the typical M_n versus conversion diagnostic of polymerization control that is typical for RAFT.

Retention of the trithiocarbonate moieties on each end group of the branched PNIPAM was demonstrated by chain extension with a second monomer. DMA was polymerized via RAFT by employing branched PNIPAM with M_n = 12 300 g/mol as a macroCTA. SEC of the resulting copolymer demonstrated the expected increase in molecular weight (M_n = 35 500 g/mol), while maintaining the complex molecular weight distribution characteristic of the branched macroCTA at intermediate conversion levels (Figure 1B). As the polymerization proceeded, a more unimodal molecular weight distribution was observed, perhaps the result of decreased chromatographic resolution at higher molecular weights. Because of the polymerizable acryloyl groups expected to persist on each macroCTA, extension of the PNIPAM branches with DMA was likely accompanied by a simultaneous step-growth type process, accounting for the increase in polydispersity index (PDI) (Table 1).

In accordance with the model proposed above for the polymerization of NIPAM with **2**, the DB and average branch lengths were tunable by varying the reaction stoichiometry. DB was calculated from the molar ratio of branched and terminal units to the total number of units,[59] as determined by ^{1}H NMR spectroscopy (Table 1). A ratio of [NIPAM]/[**2**] = 50/1 (Table 1, entry **C**) led to DB = 0.045, corresponding to branches with average length of 22 repeat units. Doubling the concentration of branching agent ([NIPAM]/[**2**] = 25/1, Table 1, entry **D**) led to a 2-fold increase in the degree of branching (DB = 0.089) and a halving of the average branch length to 11 repeat units. A further increase in [**2**] to yield [NIPAM]/[**2**] = 10/1 (Table 1, entry **E**) led to DB = 0.16 and average branch lengths of 6 repeat units. SEC of the polymerization products confirmed an increase in PDI with the concentration of branching agent (**2**), as expected (Table 1). Homopolymerization of **2** led to

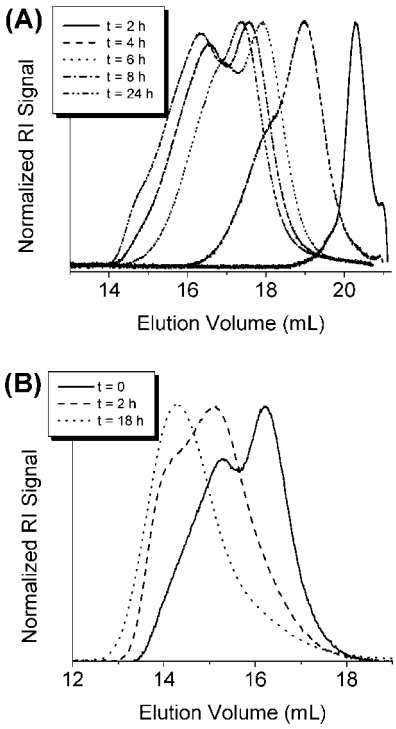


Figure 1. Size exclusion chromatography refractive index (RI) traces as a function of time for the polymerization of (A) *N*-isopropylacrylamide (NIPAM) (entry **D,** Table 1) with chain transfer agent (1-[3-(2-methyl-2-dodecylsulfanylthiocarbonylsulfanylpropionyloxy)propyl]-1*H*-[1,2,3]triazol-4-ylmethyl acrylate (**2**)) ([NIPAM]/[**2**]/[2,2-azobisisobutyronitrile] = 25/1/0.1; 70 °C; [NIPAM] = 3 M in 1,4-dioxane) and (B) *N,N*-dimethylacrylamide (DMA) (Entry **G**, Table 1) with a branched poly(*N*-isopropylacrylamide) Macro-chain transfer agent ([DMA]/[**A**]/[AIBN] = 500/1/0.1; 70 °C; [DMA] = 3 M in *N,N*-dimethylformamide).

hyperbranched polymers that demonstrated the highest PDI of the polymers considered. A corollary of this phenomenon is that as the initial concentration of **2** was decreased, the polymerizations began to more closely resemble typical RAFT polymerizations, leading to increasingly more linear polymers with narrower molecular weight distributions.[60]

The variable extent of branching was further confirmed by capitalizing on the distinctive solution properties of branched polymers as compared to their linear analogs. At a given molecular weight, branched polymers demonstrate a higher molecular density because of their more compact nature. Since molecular density is conveniently related to intrinsic viscosity ([η]), SEC viscometry in DMF at 55 °C was conducted to yield insight regarding the branched nature of the PNIPAM. According to the Mark−Houwink−Sakurada (MHS) equation ([η] = KM^a, where M is the molar mass and K and a are constants for a given polymer−solvent pair at a specified temperature), plotting log[η] versus log(molar mass) yields a line with slope = a. The value of a is expected to vary from 0 for spheres to 2 for rigid rods, with random coil polymers typically having $a \approx 0.5-0.8$.

To aid with comparisons, a linear PNIPAM reference was prepared by RAFT polymerization. Several important relationships were observed in the MHS plots of the linear and branched PNIPAM over a selected common molecular weight range (Figure 2). Both the intrinsic viscosities and the MHS a values of the branched polymers were less than that of the linear reference. The linear PNIPAM reference yielded $a = 0.79$, while the values of the branched sample were all considerably lower ($a = 0.33-0.54$). Moreover, in a comparison of the branched samples, the intrinsic viscosity and a decreased as the fraction

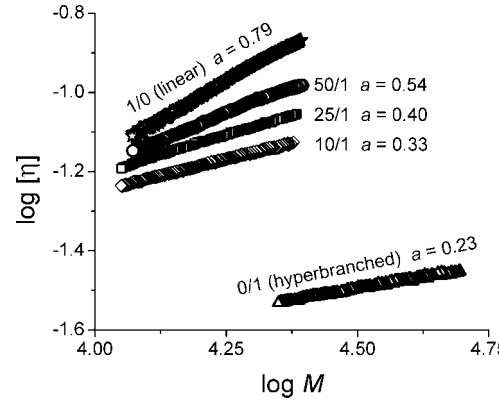


Figure 2. Mark−Houwink−Sakurada plot of log(intrinsic viscosity ([η])) versus log(molar mass (M)) (*N,N*-dimethylformamide, 55 °C) for poly(*N*-isopropylacrylamide) with varying degrees of branching. Data labels include the corresponding ratio of [*N*-isopropylacrylamide]/[chain transfer agent (1-[3-(2-methyl-2-dodecylsulfanylthiocarbonylsulfanylpropionyloxy)propyl]-1*H*-[1,2,3]triazol-4-ylmethyl acrylate (**2**))] and the resulting a values determined from the slope.

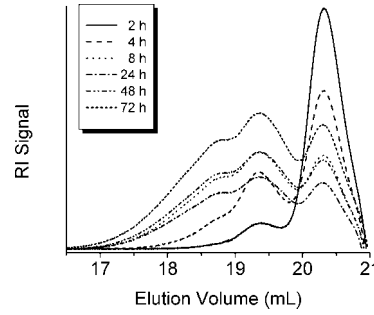


Figure 3. Size exclusion chromatography refractive index (RI) traces as a function of time for the self-condensing vinyl homopolymerization of chain transfer agent (1-[3-(2-methyl-2-dodecylsulfanylthiocarbonylsulfanylpropionyloxy)propyl]-1*H*-[1,2,3]triazol-4-ylmethyl acrylate (**2**)) (**F**, Table 1) ([*N*-isopropylacrylamide]/[**2**]/[2,2-azobisisobutyronitrile] = 0/5/0.1; 70 °C; [**2**] = 0.5 M in toluene).

of branching agent (**2**) was increased. These observations are consistent with the DB results obtained by NMR spectroscopy and offer further evidence that the branched nature of the PNIPAM was directly related to the amount of branching agent included during the polymerization.

Polymerization of the branching agent in the absence of a traditional monomer should lead to hyperbranched polymers with highly compact molecular dimensions. Homopolymerization of **2** was conducted in toluene at 70 °C with a ratio of [**2**]/[AIBN] = 5/0.1, leading to polymer with M_n = 8740 g/mol and PDI = 2.29 at 64% conversion. SEC analysis led to results typical for hyperbranched polymerizations, demonstrating traces with multimodal distributions indicative of highly branched topologies (Figure 3). Because the repeat unit structure of this polymer is significantly different from that of the branched PNIPAM examples, a direct comparison of its intrinsic viscosity with those of the other branched polymers is not entirely reliable. However, the MHS slope of $a = 0.23$ for the hyperbranched sample is clear indication of its more highly compact nature (Figure 2).

Aqueous Solution Behavior. Aqueous solutions of PNIPAM exhibit sharp phase transitions around 32 °C. Below this LCST, the polymer exists as molecularly dissolved unimers, but upon heating, chain dehydration and intermolecular aggregation leads to insolubility and eventual precipitation. Branched macromolecules often demonstrate significantly different solution behaviors as compared to their linear counterparts, a feature which is

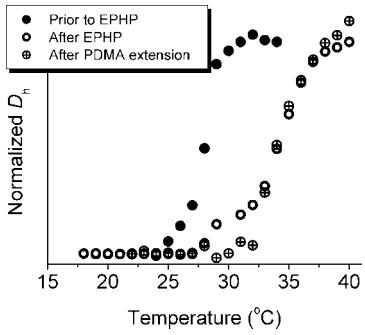


Figure 4. Hydrodynamic diameter (D_h) versus temperature for a 0.1 w/v % aqueous solution of branched poly(*N*-isopropylacrylamide) (prepared by [*N*-isopropylacrylamide]/[chain transfer agent (1-[3-(2-methyl-2-dodecylsulfanylthiocarbonylsulfanylpropionyloxy)propyl]-1*H*-[1,2,3]triazol-4-ylmethyl acrylate (**2**))] = 50/1) before and after *N*-ethylpiperidine hypophosphite (EPHP) reduction and after poly(*N*,*N*-dimethylacrylamide) (PDMA) extension. The size scale was normalized to allow better comparison of the transition temperatures for each sample.

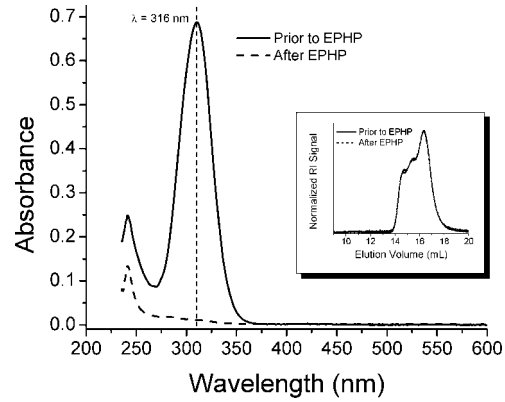


Figure 5. UV−vis spectra and size exclusion chromatography refractive index (RI) traces (inset) of branched poly(*N*-isopropylacrylamide) before and after trithiocarbonate reduction with *N*-ethylpiperidine hypophosphite (EPHP), (**A**, Table 1).

partially a result of increased molecular density.[61−65] Moreover, because branched polymers contain a multitude of chain termini, end group identity can have a dramatic influence on the solubility of the resulting polymers.

The temperature-dependent aqueous solution behavior of the branched PNIPAM was investigated by dynamic light scattering (DLS). In each case, the LCST values were significantly less than those typically associated with the linear polymer. For instance, the polymer prepared with [NIPAM]/[**2**] = 50/1 demonstrated an LCST (defined as the onset of the transition from unimers to larger multimolecular aggregates) of about 25 °C (Figure 4). A polymer with an increased degree of branching prepared with [NIPAM]/[**2**] = 25/1 led to a transition at approximately 20 °C. On the basis of our previous reports of the effect of CTA-derived end groups on the solubility behavior of polymers prepared by RAFT,[56] we attributed the reduced LCST values primarily to enhanced hydrophobicity resulting from increased concentration of the dodecyl chain termini that are derived from **2**. The number of these hydrophobic moieties is directly proportional to the degree of branching. Indeed, the most highly branched copolymer (prepared with [NIPAM]/[**2**] = 10/1) was not water-soluble at temperatures as low as 2 °C. Rimmer et al.[30] and Whittaker et al.[66] suggested similar end group effects for the atypical LCSTs of branched PNIPAM with hydrophobic chain termini.

While the reduction in LCST can also be partially attributed to the branched nature of the polymer, demonstrating the specific influence of the hydrophobic end groups was possible by their facile removal via reduction. The standard method of thiocarbonylthio end group cleavage is aminolysis, which leads to sulfhydryl-terminated chains. In this case, the multifunctional thiols were expected to be problematic as a result of their propensity to oxidatively disulfide couple, which could lead to macroscopic gelation. Instead, radical-induced reduction was accomplished via reaction with EPHP,[48] resulting in −H terminated polymers. UV−vis spectroscopy confirmed essentially quantitative disappearance of the trithiocarbonate absorbance at $\lambda = 316$ nm, while SEC analysis confirmed the molecular weight distribution remained constant after reduction (Figure 5). For the polymer prepared with [NIPAM]/[**2**] = 50/1, reduction with EPHP resulted in an increase in LCST from approximately 25 to 28 °C (Figure 4). This value was still slightly below that of typical linear PNIPAM, an effect that might be attributable to increased molecular density (decreased free volume) in the branched polymer and the hydrophobic acryloyl comonomer units derived from the CTA. The branched polymer extended with hydrophilic PDMA demonstrated an LCST that was slightly higher (30 °C) than the either the unmodified or reduced PNIPAM.

Conclusion

We have demonstrated that RAFT polymerization of NIPAM in the presence of a compound capable of both reversible chain transfer through a thiocarbonylthio moiety and propagation via a vinyl group allows the production of highly branched polymers in a method similar to self-condensing vinyl copolymerization. The average degree of branching and branch length were readily tuned by manipulation of the reaction stoichiometry, and the branched nature of the resulting polymers was confirmed by a variety of techniques, including NMR spectroscopy, viscometry, and light scattering. Retention of the thiocarbonylthio compound during the polymerization was evidenced by successfully employing the branched polymer as a macroCTA for the RAFT polymerization of a second monomer. Increased branching led to an increased contribution of end groups, and because these CTA-derived end groups were hydrophobic dodecyl moieties, the branched polymers demonstrated significantly reduced LCST values as compared to linear PNIPAM. End group modification by radical-induced reduction or chain extension with a hydrophilic monomer resulted in an increased LCST. This approach should be extendable to the synthesis of a variety of branched stimuli-responsive copolymers with a high concentration of sulfur-containing end groups that can facilitate polyvalent bioconjugation, surface immobilization, etc.

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Supporting Information Available: Figure showing dynamic light scattering results with absolute scaling. This information is available free of charge via the Internet at http://pubs.acs.org.

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