Synthesis of α,ω-Dimercapto Poly(*N*-isopropylacrylamides) by RAFT Polymerization with a Hydrophilic Difunctional Chain Transfer Agent

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ABSTRACT: A new hydrophilic difunctional reversible addition−fragmentation chain transfer (RAFT) agent, diethylene glycol di(2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate) (DEGDIM**)** was synthesized and shown to be effective in imparting living characteristics to the radical polymerization of *N*-isopropylacrylamide (NIPAM), providing a route to telechelic poly(*N*-isopropylacrylamides) (PNIPAM) of predictable molecular weights and narrow molecular weight distributions. The thiocarbonylthio end groups were transformed into thiol groups via aminolysis with near quantitative yields, as determined by a thiol-specific quantitative UV absorbance assay. By using a pyrene-substituted initiator, bis(*N*-(1-pyrenylbutyl))-4,4′-azobis-(4-cyanopentanamide) (BPAC), it was found that the amount of initiator-derived polymer chains in the DEGDIM mediated polymerization of NIPAM was negligible (∼1%) compared to the amount of polymer chains derived from DEGDIM, the difunctional chain transfer agent. These results support the theoretical calculations and confirm the high purity of α,ω-dithiol telechelic hydrosoluble polymers prepared by the RAFT polymerization process.

Introduction

Living free radical polymerization (LFP) methodologies provide tools for the preparation of complex macromolecules of precise architecture with techniques readily amenable for large-scale production and, as such, they have expanded the realm of commodity polymers. Also, in conjunction with the tools of combinatorial chemistry, they lend themselves readily to the creation of polymer libraries. Among the LFP techniques, the reversible addition−fragmentation chain transfer (RAFT) polymerization offers a number of practical advantages, as it is remarkably tolerant toward a wide range of functional groups, including hydroxyl, carboxyl, and ionic groups and it can be carried out in organic solvents as well as in water.[1−3] In a RAFT polymerization, a reversible chain transfer agent (CTA or RAFT agent) is added to the polymerization medium. In the presence of (macro)radicals, the CTA induces reversible addition−fragmentation transfer reactions to create an equilibrium between "active" propagating radicals and "dormant" CTA-terminated chains that can become active again. This equilibrium reaction is responsible for the control of the polymerization. The number-average molecular weight (M_n) of RAFT-generated polymers can be adjusted by selecting the appropriate ratio of monomer to CTA concentration, while the polydispersity index is controlled by the chain transfer constant of the CTA. The most effective RAFT agents are thiocarbonylthio compounds of general structure Z−C(═S)-S−R, where Z is the activating group and R is the leaving group. As a consequence of the RAFT process, nearly all polymer chains bear a thiocarbonylthio group at one chain end and the R substituent at the other end.[4,5]

Difunctional CTAs of general structure Z−(C═S)-S−R−S-(C═S)−Z, such as 1,4-bis(2-(thiobenzoylthio)prop-2-yl)benzene, also function as effective RAFT agents.[6,7] Depending on the ratio of initiator to CTA, it is possible to adjust the ratio of difunctional to monofunctional polymers while maintaining control over M_n and over the polydispersity index.[8] Since such CTA molecules have two reinitiating centers, polymerization propagates in two directions and each polymer chain bears a unit originating from the CTA. The difunctional CTAs reported so far introduce an aromatic group into each chain. This group is innocuous when incorporated into hydrophobic polymers such as polystyrene, poly(lauryl methacrylate), or poly(methyl methacrylate), the polymers prepared in the previous studies, but it may affect the solution properties of water-soluble polymers, in particular for samples of low molar masses.

Polymers prepared with difunctional CTAs possess two thiocarbonylthio termini that can be further manipulated by postpolymerization reactions. Aminolysis of the thiocarbonylthio end groups transforms them into thiol functionalities under mild conditions and in one step.[9−11] Mercapto-functionalized polymers have found numerous applications in material sciences, electronics, optics, and nanotechnology[12−15] due to the specific interaction of the thiol group with gold, silver, and other metals. For these applications, it is important to ensure that the transformations occur quantitatively. In addition, thiol groups provide a handle toward further functionalization via Michael addition to α,β-unsaturated carbonyl compounds[9,16] or via nucleophilic substitution.[17]

We report here a simple and efficient procedure for the synthesis of a new difunctional CTA in which the two thiocarbonylthio groups are linked by a diethylene glycol residue, thus better suited to the preparation of telechelic hydrophilic polymers than previously reported symmetrical CTAs. We demonstrate the effectiveness of this CTA in the synthesis of α,ω-dithiocarbonylthio-poly(*N*-isopropylacrylamides) (PNIPAM). Several reasons prompted us to prepare PNIPAM, the prototype of "intelligent polymers".[18] The behavior of NIPAM under RAFT conditions has been investigated by several research groups and, consequently, it is well characterized under a variety of experimental conditions.[19−23] The RAFT polymerization of NIPAM has been used to prepare NIPAM-based diblock copolymers,[24] star, and branched polymers.[25−28] We present experimental procedures allowing the near quantitative conversion of α,ω-dithiocarbonylthio-

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PNIPAMs into the corresponding α,ω-dimercapto polymers, as determined by analysis of end group functionalities. Using a pyrene-labeled initiator in conjunction with the difunctional CTA, we determine the fraction of α-thiocarbonylthio-ω-pyrenyl-PNIPAM chains that are formed by fragmentation of the initiator of polymerization. The number of such chains is small (<1.5%) under desired polymerization conditions and in agreement with theoretical predictions. The techniques presented should be readily applicable to the preparation of a variety of hydrophilic α,ω-dimercapto homopolymers and copolymers.

Experimental Section

Materials. All chemicals were purchased from Sigma-Aldrich Chemicals Co. unless otherwise specified. Azobisisobutyronitrile (AIBN, 98%) and 4,4′-azobis-(4-cyanopentanoic acid) (ACPA, 97%) were recrystallized from methanol prior to use. 4-(1-Pyrene)-butylamine hydrochloride was prepared from 4-(1-pyrene)butanoic acid (98%) as described earlier.[29] *N*-Isopropylacrylamide (NIPAM, 99%) was obtained from Acros Organics and recrystallized from an acetone/hexanes (4:6, v/v) mixture. 2-Methyl-1-propanethiol (92%), carbon disulfide (99.9%), sodium hydroxide (97%+), 1,1′-carbonyldiimidazole (97%), triethylamine (99.5%), and tricaprylylmethylammonium chloride were used as received. Dimethyl sulfoxide (DMSO, >99.9%) was used without purification. 1,4-Dioxane and tetrahydrofuran (THF) were purified by a solvent purification system with two packed columns of activated alumina provided by Innovative Technology Inc. All other solvents were of reagent grade and used as received. Water was deionized using a Millipore MilliQ system.

Diethylene Glycol Di(2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate) (DEGDIM). This compound was synthesized by coupling the precursor trithiocarbonate, 2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methyl propionic acid (synthesized according to ref 10) to diethylene glycol according to a procedure reported by Mahanthappa et al. with slight modification.[6] Oxalyl chloride (8.0 mL, 100 mmol) was added while stirring to solid of 2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methyl propionic acid (2.54 g, 10 mmol) kept under nitrogen at room temperature. At the end of the addition, the mixture was warmed up to 40−50 °C for 1−2 h, resulting in the formation of a dark-red solution. The excess oxalyl chloride was then removed in vacuo to yield 2-(1-isobutyl)-sulfanylthiocarbonylsulfanyl-2-methyl propionyl chloride. A solution of diethylene glycol (0.42 g, 4.0 mmol) in THF (5 mL) was added dropwise to the product, and the resulting solution was kept at 40−50 °C for 6 h. At the end of the reaction, the solution was cooled to room temperature, and ethanol (1 mL) was added to quench the remaining acyl chloride. Excess ethanol was removed under reduced pressure to yield a reddish oil, which was eluted through a silica gel column using dichoromethane/hexanes (3:1, v/v) as eluent to separate the difunctional CTA, diethylene glycol di(2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate) (DEGDIM, 1.6 g, 60%) from the monofunctional CTA, ethyl 2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate (EIM, 0.42 g, 15%) obtained as a byproduct. DEGDIM: MS (MH^+) found: 575.1116 *m/z*, calcd for $C_{22}H_{38}O_5S_6$: 574.93 *m/z*. ^{1}H NMR ($CDCl_3$) ppm, δ 1.01 (d, 12H, $-CH(CH_3)_2$), 1.70 (s, 12H, $-SC(CH_3)_2C(=O)$), 1.96 (septet, 2H, $-CH(CH_3)_2$), 3.19 (d, 4H, $-SCH_2$), 3.66 (t, 4H, $-OCH_2$), 4.22 (t, 4H, $-C(=O)OCH_2$); UV (chloroform): λ_{max}= 310 nm; ϵ = 28 600 M^{-1} cm^{-1}. EIM: MS (MH^+) found: 280.0617 *m/z*, calcd for $C_{11}H_{20}O_2S_3$: 280.47 *m/z*. H: ^{1}H NMR ($CDCl_3$) ppm, δ 1.01 (d, 6H, $-CH(CH_3)_2$), 1.24 (t, 3H, $-OCH_2CH_3$), 1.69 (s, 6H, $-SC(CH_3)_2(C=O)$), 1.96 (septet, 1H, $-CH(CH_3)_2$), 3.19 (d, 2H, $-SCH_2$), 4.15 (q, 2H, $-OCH_2CH_3$).

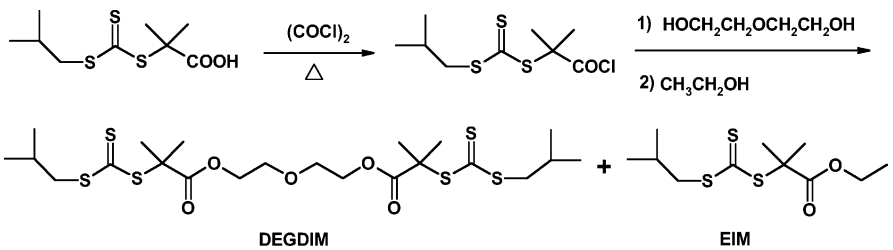
Bis(*N*-(1-pyrenylbutyl))-4,4′-azobis-(4-cyanopentanamide) (BPAC). A solution of 4,4′-azobis-(4-cyanopentanoic acid) (280 mg, 1.0 mmol) and 1,1′-carbonyldiimidazole (324 mg, 2.0 mmol) in dimethylsulfoxide (DMSO, 5 mL) was stirred at room temperature for 6 h. A solution of 4-(1-pyrene)-butylamine hydrochloride (682 mg, 2.2 mmol) and triethylamine (222 mg, 2.2 mmol) in DMSO (5 mL) was then added into the reaction mixture, which was kept at room temperature for 12 h. The product was recovered by precipitation in cold diethyl ether. The precipitate was dissolved in THF and precipitated in hexanes. It was further purified by flash chromatography using THF/hexanes (1:1) as eluent. Yield: 480 mg, 61%. ^{1}H NMR (DMSO-d_6) ppm, δ 1.60 (t, 4H, $-CH_2CH_2$-Py), 1.69 (s, 6H, $=NC(CN)CH_3$), 1.83 (quintet, 4H, $-NHCH_2CH_2$), 2.11−2.24 (t, 4H, $=NC(CN)CH_2$), 2.34 (t, 4H, $-C(=O)CH_2$), 3.18 (t, 4H, $-NHCH_2$), 3.38 (t, 4H, $-CH_2CH_2$Py), 8.00−8.40 (m, 18H, −Py).

Polymerization. The following procedure leading to PNIPAM-7k is typical. A solution of the chain transfer agent (DEGDIM, 115 mg, 0.2 mmol), the initiator (AIBN, 3.28 mg, 0.02 mmol), and the monomer (NIPAM, 1.47 g, 13 mmol) in 1,4-dioxane (10 mL) was placed in a round-bottom flask with rubber septa. The solution was deoxygenated by bubbling nitrogen for 30 min at room temperature. The reaction flask was placed in an oil bath preheated to 65 °C. The polymerization was allowed to proceed for 3 h under constant magnetic stirring. At the end of this polymerization, the solution was cooled to room temperature. The polymer was isolated by precipitation in diethyl ether. It was purified further by two consecutive reprecipitations from THF into diethyl ether. Yield: 1.30 g, 88%. ^{1}H NMR ($CDCl_3$) ppm, δ 1.02 (d, $-CH_2CH(CH_3)_2$), 1.16 (s, $-NHCH(CH_3)_2$), 1.20−2.40 (multipeaks, polymer backbone protons), 3.28 (s, $-SCH_2$), 3.66 (s, $-OCH_2$), 4.02 (s, $-NHCH$), 4.22 (s, $-C(=O)OCH_2$), 6.40 (bs, $-C(=O)NH$).

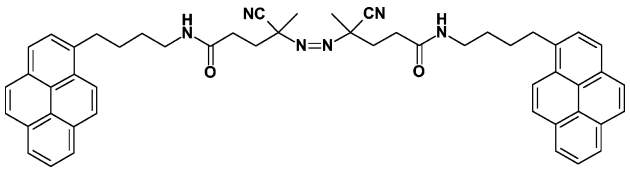
The polymerization kinetics and the absolute molecular weights of the polymers were determined by extracting aliquots (0.5 mL) from the polymerization solution at the desired time interval. The extracted solutions were immediately quenched by cooling in a dry ice−acetone slurry. Most of the solvent was removed under a gentle stream of nitrogen. The resulting solid was dissolved in 1 mL of $CDCl_3$ for ^{1}H NMR measurements or 2 mL of DMF for GPC measurements. The degree of conversion was evaluated from the areas of the signals due to the vinyl proton resonance at 5.60 ppm and the sum of the areas of the isopropyl methine proton resonance signals at δ 4.02 ppm and δ 4.10 ppm, corresponding, respectively, to PNIPAM and to remaining NIPAM monomer.

Preparation of α,ω-Dimercapto Poly(*N*-isopropylacrylamides). The following procedure is typical. *n*-Butylamine (0.146 g, 2 mmol, 10-fold molar excess of thiocarbonylthio moiety) and a small amount of the reducing agent, tris(2-carboxyethyl) phosphine hydrochloride (TCEP, catalytic amount), were added to a solution of α,ω-dithiocarbonylthio poly(*N*-isopropylacrylamide) (PNIPAM-7k, 0.70 g 0.2 mmol of thiocarbonylthio moieties) in THF (10 mL). The resulting solution was stirred for 1 h at room

Scheme 1. Synthesis and Structure of Diethylene Glycol Di(2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate) (DEGDIM) and Structure of the Side Product Ethyl 2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate (EIM)



Scheme 2. Structure of bis(*N*-(1-pyrenylbutyl))-4,4′-azobis-(4-cyanopentanamide) (BPAC)



BPAC

temperature under a N_2 atmosphere. The product was recovered by precipitation in diethyl ether and purified by two consecutive reprecipitations from THF into diethyl ether. Yield: 0.66 g, 95%. ^{1}H NMR ($CDCl_3$) ppm, δ 1.16 (s, $-NHCH(CH_3)_2$), 1.20−2.40 (multiplets, polymer backbone protons), 3.66 (s, $-OCH_2$), 4.02 (s, $-NHCH$), 4.22 (s, $-C(=O)OCH_2$), 6.40 (bs, $-C(=O)NH$).

Quantitative Thiol Analysis by the Ellman Method. The thiol content of the polymers was determined by colorimetric analysis according to Ellman's procedure.[30] The Ellman reagent was prepared by dissolving 5,5′-dithiobis(2-nitrobenzoic acid) in 0.1 M phosphate buffer (pH 8.0) at the concentration of 0.4 mg/mL (1.0 mmol/mL). A thiol substituted polymer (2−10 mg depending on M_n to obtain a thiol group concentration of ∼0.67 mmol) was dissolved in 3.0 mL of deionized water, and the resulting solution was brought to pH 8.0 by addition of an aqueous pH 8.0 phosphate buffer (6.0 mL). Both the deionized water and the phosphate buffer were deoxygenated by bubbling with N_2 for 30 min before use. An aliquot of Ellman's reagent (1.0 mL) was added to the polymer solution. The resulting solution was mixed by swirling and kept in the dark at room temperature for ∼15 min. The absorbance of the solution at 412 nm was recorded. A solution prepared by adding 1.0 mL of Ellman's reagent to a solution obtained by mixing 3.0 mL of deionized water (3.0 mL) and an aqueous pH 8.0 phosphate buffer solution (6 mL) was used as a blank. All the measurements were performed in triplicate.

Determination of the M_n Values by UV−Vis Absorbance Spectroscopy. To determine the M_n values of α,ω-dithiocarbonylthio-PNIPAMs by UV−vis absorbance, we used eq 1, which takes into account the presence of initiator-derived chains:

$$M_n = \frac{w}{c_{CTA} + c_{IPC}} \quad (1)$$

where w is the weight of polymer sample in the solution analyzed (in g), c_{CTA} is the amount of thiocarbonylthio residues in the polymer sample (in mol) determined experimentally by application of Beer's law and using the molar extinction coefficient of DEGDIM in chloroform ($\epsilon_{310} = 28\,600\ M^{-1}\ cm^{-1}$). Because each DEGDIM molecule has two thiocarbonylthio moieties (chromophores) and each DEGDIM generates one polymer chain with thiocarbonylthio moiety at both ends, the number of c_{CTA} represents the amount (in mol) of CTA-derived polymer chains in the sample. The number of c_{IPC} (in mol) is the amount of initiator-derived polymer chains (IPC) present in the polymer sample. This equation hypothetically assumes that the polymer chains are either endcapped with thiocarbonylthio moieties or initiator residues at both ends, although most of the actual IPCs are terminated with an initiator residue at one end and a thiocarbonylthio moiety at the other end.

To determine c_{CTA}, a known amount of α,ω-dithiocarbonylthio poly(*N*-isopropylacrylamide) (2 − 5 mg) was dissolved in $CHCl_3$ (10 mL). The absorbance of each solution at 310 nm was recorded and the concentration of c_{CTA} was calculated using the molar extinction coefficient of DEGDIM determined above. All measurements were performed in duplicate. To determine c_{IPC}, the pyrene-substituted initiator BPAC was used instead of AIBN to initiate the polymerization under the same conditions. The polymers obtained were aminolyzed to remove the thiocarbonylthio end groups, thus allowing precise determination of the content of pyrenyl end groups, using the absorbance at 342 nm and a molar extinction coefficient of $2 \times \epsilon_{342}$ ($\epsilon_{342,MeOH} = 32\,800\ M^{-1}\ cm^{-1}$ for 4-(1-pyrene)butylamine chloride employed as model compound).[31] Two such samples, namely α,ω-SH-PNIPAM(py)-7k and α,ω-SH-PNIPAM(py)-11k (Table 2), were prepared with polymerization times of 3 and 4 h. The c_{IPC} values determined experimentally for polymers prepared with BPAC were also used to determine the M_n value of polymers prepared with AIBN of similar polymerization time.

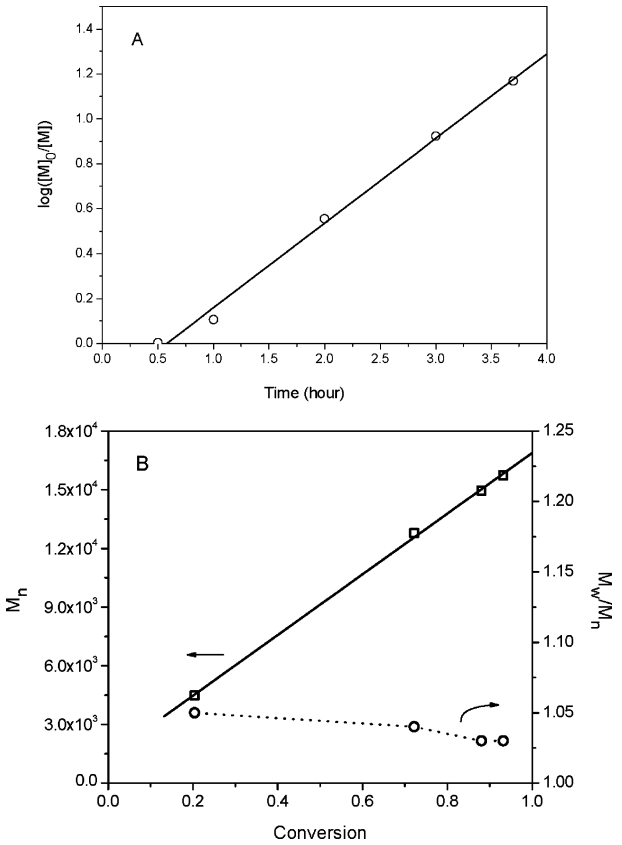


Figure 1. Pseudo-first-order kinetic plot (A) and evolution of the number-average molecular weight (M_n, from 4k to 15k, open squares) and polydispersity (M_w/M_n), open circles) with conversion (B) for polymerization of *N*-isopropylacrylamide (NIPAM) mediated by the reversible addition−fragmentation chain transfer agent diethylene glycol di(2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate) (DEGDIM) and initiated by azobisisobutyronitrile (AIBN) at 65 °C in 1,4-dioxane.

Instrumentation. ^{1}H NMR spectra were recorded on a Bruker AMX-400 (400 MHz) instrument. The chemical shifts are referenced to tetramethylsilane (TMS). Mass spectra were recorded on a Micromass Autospec TOF instrument equipped with a LSIM source (Centre Régional de Spectrométrie de Masse, Université de Montréal, Montréal, QC, Canada). Gel permeation chromatography (GPC) was performed with a GPC system consisting of an Agilent 1100 isocratic pump, a set of TSK-gel α-M (particle size 13 μm, exclusion limit 1×10^7 Da for polystyrene in DMF) and a TSK-gel α-3000 (particle size 7 μm, exclusion limit 1×10^5 Da for polystyrene in DMF) (Tosoh Biosep) columns, a Dawn EOS multiangle laser light scattering detector, $\lambda = 690$ nm (Wyatt Technology Co.), and an Optilab DSP interferometric refractometer $\lambda = 690$ nm (Wyatt Technology Co.) under the following conditions: injection volume, 100 μL; flow rate, 0.5 mL/min; eluent, DMF; temperature, 40 °C. The d*n*/d*c* value of PNIPAM was determined to be 0.0738 mL/g at 690 nm in DMF at 40 °C using an Optilab DSP interferometric refractometer (Wyatt Technology Corp).

Results and Discussion

Synthesis of the Difunctional CTA and the Pyrene-Modified Initiator. The difunctional thiocarbonylthio RAFT

Table 1. Number-Average Molecular Weights (M_n) and Polydispersities (M_w/M_n) for Poly(*N*-isopropylacrylamide) (PNIPAM) Obtained by Polymerization of *N*-Isopropylacrylamide (NIPAM) in Dioxane in the Presence of the Reversible Addition−Fragmentation Chain Transfer Agent Diethylene Glycol Di(2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate) (DEGDIM) and the Initiator Azobisisobutyronitrile (AIBN) at 65 °C

sample	polymerization time (h)	$[NIPAM]_0/[DEGDIM]_0$	M_n (kg mol^{-1}) MALLS[a]	M_n (kg mol^{-1}) theoretical[b]	M_w/M_n (GPC)[c]	conversion (%)
PNIPAM-1h	1.0	130	4.2	3.6	1.05	20.4
PNIPAM-2h	2.0	130	12.7	11.2	1.04	72.2
PNIPAM-3h	3.0	130	14.7	13.4	1.03	87.5
PNIPAM-4h	3.8	130	15.8	14.3	1.03	93.2

[a] Multiangle laser light scattering [b] M_n = conversion × $([NIPAM]_0)/([DEGDIM]_0) \times M_0 + M_{CTA}$ [c] From GPC data recorded on a system equipped with a MALLS detector and a refractive index detector (see Experimental Section).

Table 2. Number-Average Molecular Weights (M_n) and Polydispersities (M_w/M_n) for Poly(*N*-isopropylacrylamide) (PNIPAM) Obtained by Polymerization of *N*-Isopropylacrylamide (NIPAM) in Dioxane in the Presence of the Reversible Addition−Fragmentation Chain Tranfer Agent Diethylene Glycol Di(2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate (DEGDIM) and Either Azobisisobutyronitrile (AIBN) (Entries 1−4) or Bis(*N*-(1-pyrenylbutyl))-4,4′-azobis-(4-cyanopentanamide) (BPAC) as Initiator (Entries 5 and 6) at 65 °C

sample name	polymerization time (h)	$[NIPAM]_0/[DEGDIM]_0$	M_n (kg mol^{-1}) MALLS[a]	M_n (kg mol^{-1}) NMR[b]	M_n (kg mol^{-1}) UV−vis	M_w/M_n (GPC)[d]	conversion (%)
PNIPAM-7k	2.0	66	7.8	6.7	7.0	1.03	92.5
PNIPAM-13k	3.0	120	14.7	12.8	13.7	1.04	94.1
PNIPAM-15k[c]	3.8	130	15.8	13.7	15.1	1.03	93.2
PNIPAM-23k	4.5	210	24.4	22.3	23.5	1.08	96.3
PNIPAM(py)-6k	3.0	60	7.6	6.2	6.8	1.02	85.3
PNIPAM(py)-11k	4.0	100	13.7	10.5	11.8	1.04	92.5

[a] Multiangle laser light scattering. [b] $M_n = ([H3])/([H2]) \times 4 \times M_0 + M_{CTA}$ [c] PNIPAM-15k in Table 2 and PNIPAM-4h in Table 1 are the same polymer. [d] From GPC data recorded on a system equipped with a MALLS detector and a refractive index detector (see Experimental Section).

agent, diethylene glycol di(2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionate, was synthesized by a two-step procedure (Scheme 1) involving first, the preparation of 2-(1-isobutyl)sulfanylthiocarbonylsulfanyl-2-methylpropionic acid (IMA), according to the one-pot synthesis reported by Lai et al.,[32] and second, diesterification of diethylene glycol with IMA activated by conversion to the corresponding acyl chloride prior to coupling. A 1.2-fold molar excess of acyl chloride was added relative to the hydroxyl groups of diethylene glycol to ensure complete conversion of the diethylene glycol end groups. The excess acyl chloride was quenched with ethanol added in excess at the end of the reaction. As a result, some ethyl 2-(1-isobutyl)-sulfanylthiocarbonylsulfanyl-2-methylpropionate (EIM, Scheme 1) was obtained as a byproduct. Flash chromatography allowed us to separate the monofunctional CTA EIM, which eluted first, from the major product, the difunctional CTA DEGDIM. The purity of both products was ascertained by high-resolution mass spectrometry and ^{1}H NMR spectroscopy. The RAFT polymerization of NIPAM was carried out with DEGDIM in conjunction with a free radical initiator, either AIBN or bis(*N*-(1-pyrenebutyl))-4,4′-azobis(4-cyanopentanamide) (BPAC, Scheme 2), designed as a tool to quantify the fraction of PNIPAM chains bearing an initiator residue at one chain end, taking advantage of the strong absorbance of the pyrenyl group at 342 nm. The pyrene-substituted initiator was obtained by reaction of 2 equiv of 4-(1-pyrenyl)-butyl amine chloride with azobis(4-cyanopentanoic acid) in the presence of 1,1′-carbonyldiimidazole.[33]

Polymerization of *N*-Isopropylacrylamide in the Presence of DEGDIM. All polymerizations of NIPAM were carried out in dioxane at 65 °C. First, we monitored the progress of the polymerization with time, setting the monomer to CTA molar ratio at 130 and the initiator to CTA molar ratio at 1/10 to minimize the fraction of chains derived from AIBN. Aliquots of the polymerization mixture were taken at regular time intervals and subjected to gel permeation chromatography (GPC) and ^{1}H NMR analysis. The ability of the difunctional CTA DEGDIM to control the polymerization of NIPAM is demonstrated by the linear increase of M_n with conversion (Figure 1B). The polydispersity index decreases slightly from 1.05 to 1.03 as the polymerization progresses, concomitant with an increase of M_n from 4000 to 15 000 g mol^{-1} (Figure 1A and Table 1). A kinetic plot of the polymerization (Figure 1B) displays an induction period of ∼30 min, followed by a linear pseudo-first-order regime up to a monomer conversion of 93%. The occurrence of an induction period in RAFT polymerizations has been observed previously.[19,20]

Next, we polymerized NIPAM under the same conditions (dioxane, 65 °C, AIBN) but varied the NIPAM/CTA molar ratio. All polymerizations were left to proceed to high conversion (92−96%). The polymers were isolated and purified. The polymers have very low polydispersities as determined by GPC (Table 2), and the elution profiles were monomodal and symmetrical, except in the case of the polymer of highest molar mass for which the GPC trace presents a small shoulder on the high-molar-mass side (Figure 2). This minor component may be diagnostic of the formation of dimers by combination of two polymer chains under the conditions of very high monomer conversion (96%). We carried out DEGDIM-mediated polymerizations of NIPAM initiated by the bis(pyrenyl) initiator BPAC and confirmed that the resulting α,ω-thiocarbonylthio-PNIPAM(py)s have similar characteristics as the polymers prepared via AIBN initiation under identical conditions (Table 2).

Further proof of the success of the RAFT polymerization was obtained by analysis of the ^{1}H NMR spectra of the polymers, which present resonances at δ 1.02 and 3.28 ppm, originating, respectively, from the isobutyl methylene protons H_1 and the methyl protons H_2 (see Figure 3 for numbering of the protons of the polymer) of the isobutylsulfanylthiocarbonylsulfanyl [$(CH_3)_2CH-CH_2-S-(C=S)-S-$] moiety at each chain end, as well as signals ascribed to protons of the NIPAM units, in particular, a broad singlet centered at δ 4.02 ppm due to the isopropyl methine proton (H_3), as exemplified in Figure 3, where we present the ^{1}H NMR spectrum of a polymer of $M_n \sim 7000$ g mol^{-1}. The ^{1}H NMR spectrum also displays two weak broad singlets at δ 4.22 and 3.66 ppm, assigned to the methylene protons H_4 and H_5 of the diethylene glycol fragment originating from DEGDIM, providing further evidence of the ability of

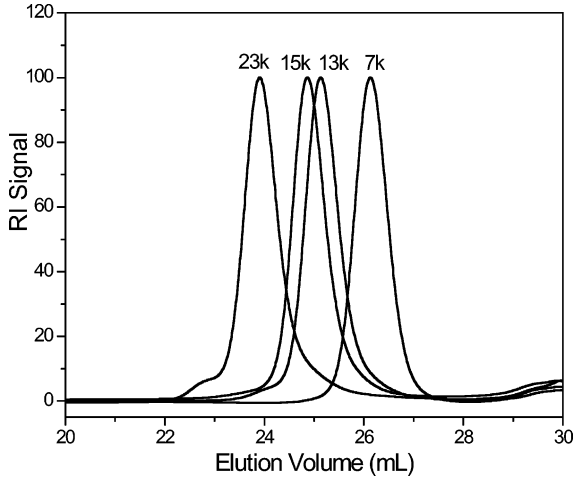


Figure 2. Normalized gel permeation chromatography (GPC) traces of poly(*N*-isopropylacrylamides) (PNIPAM) prepared by polymerization of *N*-isopropylacrylamide (NIPAM) in the presence of the reversible addition−fragmentation chain transfer agent diethylene glycol di(2-(1-isobutyl)sulfanylthiocarbonyl-sulfanyl-2-methylpropionate) (DEGDIM) and with the initiator azobisisobutyronitrile (AIBN) at 65 °C in 1,4-dioxane starting with the [NIPAM]/[DEGDIM] ratios listed in Table 2.

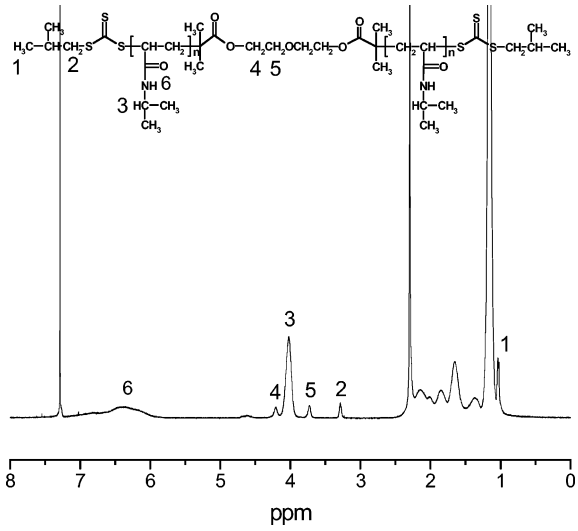


Figure 3. ^{1}H NMR spectrum of α,ω-di(isobutylthiocarbonylthio)-poly(*N*-isopropylacrylamide) (PNIPAM-7k) (solvent: $CDCl_3$).

DEGDIM to act as CTA in the RAFT polymerization of NIPAM. It is possible to extract M_n values from ^{1}H NMR spectra of α,ω-thiocarbonylthio-PNIPAMs, using the areas of the signal of H_3 (4.02 ppm) and of H_2 (3.28 ppm). As shown in Table 2, the NMR-derived M_n values were slightly lower than the corresponding values determined by GPC. The difference may be partially due the fact that the area of H_2 cannot be precisely integrated because of the very low content of polymer end groups.

The value of M_n can be determined more accurately from UV−vis spectroscopy by using the strong absorbance of the thiocarbonylthio moiety centered at 310 nm. The precise determination of M_n from UV spectra requires one to take into account the concentration (c_{IPC}) of chains derived from the initiator, which bear an initiator fragment at one chain end. Theoretically, this value can be estimated from the decomposition rate of the initiator from eq 2:[34]

$$c_{IPC} = af([I]_0 - [I]_t) = af[I]_0(1 - e^{-k_d t}) \qquad (2)$$

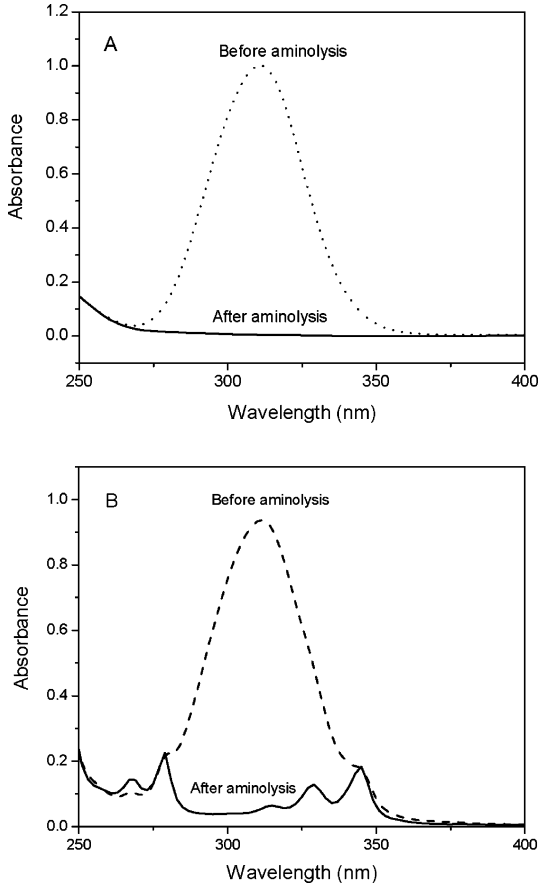


Figure 4. UV-absorbance spectra of (A) α,ω-di(isobutylthiocarbonylthio)-poly(*N*-isopropylacrylamide) (PNIPAM-13k) and α,ω-(dimercapto)-poly(N-isopropylacrylamide) (α,ω-SH-PNIPAM-13k) in $CHCl_3$ and (B) α,ω-di(isobutylthiocarbonylthio)-poly(*N*-isopropylacrylamide) (PNIPAM(py)-11k,) and α,ω-(dimercapto)-poly(*N*-isopropylacrylamide) (α,ω-SH-PNIPAM(py)-11k) in methanol.

where *a* is the mode of termination ($a = 1$ for termination by combination), *f* is the initiation efficiency, k_d is the decomposition rate of the initiator (for AIBN at 65 °C, $k_d = 1.925 \times 10^{-5}$ s^{-1}),[35] $[I]_0$ and $[I]_t$ are the initial initiator concentration and the remaining initiator concentration at polymerization time *t*. A more straightforward and meaningful expression is to take the ratio of c_{IPC} with respect to $[CTA]_0$. Assuming an initiator efficiency $f = 0.6$ and taking $[I]_0/[CTA]_0 = 0.1$, the term $c_{IPC}/[CTA]_0$ is calculated to be 0.40, 0.78, 1.13, and 1.45% for polymerization times of 1, 2, 3, and 4 h, respectively.

To obtain the experimental values of c_{IPC}, a pyrene-containing initiator BPAC was synthesized and used to initiate NIPAM polymerization under identical conditions. Because the pyrene chromophores chains absorb light in the same spectral range as the thiocarbonylthio group (from 310 to 345 nm), the polymers had to be converted to the corresponding α,ω-dimercapto-PNIPAMs prior to quantification of c_{IPC}. The α,ω-dithiol-PNIPAM sample has no absorption around 342 nm (Figure 4A). We carried out a UV analysis of the α,ω-dithiol-PNIPAM(py) samples obtained by aminolysis of polymers prepared in the presence of the pyrene-labeled initiator BPAC. Absorbance spectra of the sample PNIPAM(py)-11K before and after aminolysis are presented in Figure 4B. The absorbance maximum of 1-alkylpyrene at $\lambda = 342$ nm ($\epsilon_{342} = 32\,800$ M^{-1} cm^{-1} in methanol) is merely a shoulder to the long wavelength side of the thiocarbonylthio moiety in the spectrum of the α,ω-dithiocarbonylthio sample, and its value cannot be determined accurately. However, in the spectrum of the aminolyzed sample

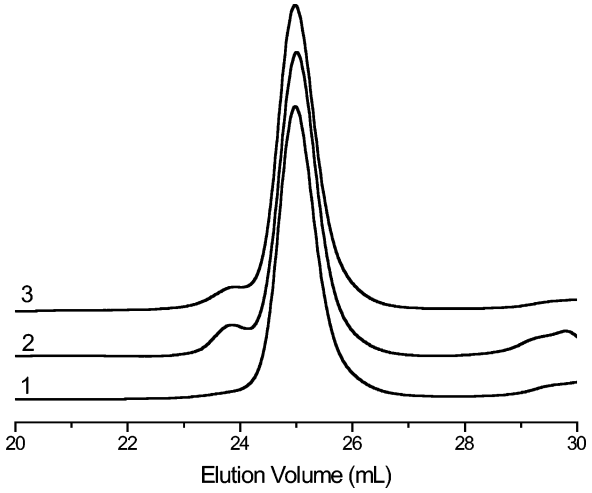


Figure 5. Normalized gel permeation chromatography (GPC) traces of (1) α,ω-di(isobutyl-thiocarbonylthio)-poly(*N*-isopropylacrylamide) (PNIPAM-15k), (2) α,ω-dimercapto)-poly(*N*-isopropylacrylamide) (α,ω-SH-PNIPAM-15k) prepared by aminolysis in the absence of the reducing agent tris(2-carboxyethyl) phosphine hydrochloride (TCEP) and (3) α,ω-(dimercapto)-poly(*N*-isopropylacrylamide) (α,ω-SH-PNIPAM-15k) prepared by aminolysis in the presence of the reducing agent tris(2-carboxyethyl) phosphine hydrochloride (TCEP).

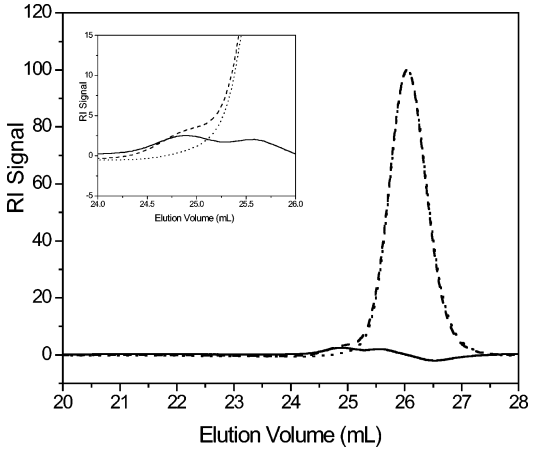


Figure 6. Gel permeation chromatography (GPC) traces of α,ω-di-(isobutyl-thiocarbonyl-thio)-poly(*N*-isopropylacrylamide) (PNIPAM-7k, dashed line), α,ω-(dimercapto)-poly(*N*-isopropylacrylamide) (PNIPAM-7k, dotted line), and the curve obtained by subtracting the dotted line from the dashed line (solid line); inset focuses on the elution volume corresponding to the disulfide elution.

this interference is removed, and the characteristic features of the pyrenyl chromophore are readily recognized. This absorbance is absent in the UV−vis spectrum of PNIPAM samples obtained in polymerizations initiated with AIBN (Figure 4A). The absorbance at 342 nm was used to determine accurately the pyrenyl content of the polymer and, consequently, the percentage of chains bearing an initiator fragment at one chain end. The percentages of pyrenyl-terminated chains in α,ω-SH-PNIPAM(py)-7K and α,ω-SH-PNIPAM(py)-11K were determined to be 0.92% and 1.23%, respectively, which are in close agreement with the values, 1.13% and 1.45%, calculated for polymers obtained via DEGDIM-mediated NIPAM polymerizations initiated with AIBN. Obviously, there are much fewer initiator-derived polymer (IPC) chains than dithiocarbonylthio endcapped polymer chains, which is in agreement with the criteria of ideal RAFT polymerization that the fraction of polymer chains derived from the initiator is negligible compared to CTA-terminated polymer chains.[36] As listed in Table 2, the M_n determined by UV is very similar to the corresponding molecular weight measured by GPC. The good agreement in molecular weight from UV, NMR, and GPC further confirmed the proposed polymer structure and the success of DEGDIM-mediated RAFT polymerization. In this connection, it should be noted that the decomposition rate of AIBN and ACPA, the precursor used in the preparation of BPAC, is slightly different. The 10 h half-life temperatures for AIBN and ACPA are 65 °C in toluene and 69 °C in water, respectively.

Functionality of α,ω-Dimercapto-PNIPAM. The thiocarbonylthio termini of the PNIPAM samples were converted to thiols by *n*-butyl amine induced aminolysis, following a slightly modified version of the procedure reported by Patton et al.[7] The reaction consumes 2 mol of amine per mol of thiocarbonylthio group, generating the desired thiol-terminated polymer, isobutylthiol, and a dialkylthiourea, in our case, di-*n*-butylthiourea. A 10 molar excess amine with respect to thiocarbonylthio groups was used to ensure completeness of the conversion. Under these conditions, aminolysis proceeds rapidly at room temperature, reaching near completion within 1 h,[16] and the excess *n*-butylamine can be removed effectively by reprecipitation of the aminolyzed polymers. In all cases, a small amount of the reducing agent tris(2-carboxyethyl) phosphine hydrochloride (TCEP) was added to the reaction mixture in order to minimize oxidative coupling of the α,ω-dithiol PNIPAMs to form disulfides. But even under these reductive conditions, the α,ω-dithiol PNIPAMs were contaminated with traces of the corresponding dimers, as seen for example in Figure 5, where we present GPC traces of PNIPAM-15K (trace 1) and the corresponding aminolyzed samples obtained in the absence of TCEP (trace 2) or in the presence of TCEP (trace 3). Trace 2 presents a small peak on the high-molar-mass side of the main eluting band, which cannot be seen in trace 1, and consequently is attributed to disulfide formation. This high-molar band can still be detected as a weak shoulder on the left of the eluting band, indicating that although the reducing agent suppressed significantly disulfide formation, the isolated α,ω-dithiol PNIPAMs still contains trace amounts of dimers, possibly formed during the reprecipitations carried out to purify the sample.

A quantitative analysis of the thiol content of the polymers was performed using the colorimetric test developed by Ellman,[30] which is based on the fact that free thiols react

Table 3. Percentages of Thiol End Groups in α,ω-Dimercapto-poly(*N*-isopropylacrylamides) (α,ω-SH-PNIPAM) Obtained after Aminolysis of the Corresponding α,ω-Diisobutylthiocarbonylthio-poly(*N*-isopropylacrylamides)

sample name	M_n (kg mol^{-1})[a]	% free [SH]	% disulfide	total % [SH]
α,ω -SH-PNIPAM-7k	6.7	94.0 ± 0.6	2.5	99.0
α,ω-SH-PNIPAM-13k	13.4	94.4 ± 0.5	2.2	98.8
α,ω-SH-PNIPAM-15k	14.8	94.5 ± 0.6	2.0	98.5
α,ω-SH-PNIPAM-23k	23.2	91.6 ± 1.2	1.7	95.0
α,ω-SH-PNIPAM(py)-6k	6.5	94.4 ± 0.4	2.0	98.4
α,ω-SH-PNIPAM(py)-11k	11.5	90.0 ± 0.2	2.5	95.0

[a] Values calculated from Table 2 by subtracting the molecular weight (266.5) of two isobutylthiocarbonylthio moieties from the corresponding M_n obtained by UV−vis determinations.

quantitatively with DTBN (5,5′-dithiobis(2-nitrobenzoic acid)) to form 1 equiv of 2-nitro-5-thiobenzoic acid (NTB)), which has a strong absorption centered at 412 nm ($\epsilon_{412} = 13\,600\ M^{-1}\ cm^{-1}$) in basic solution (pH > 7.0). Neither the α,ω-dithiol PNIPAMs, nor their α,ω-dithiocarbonylthio precursors absorb light of $\lambda > 400$ nm. The amounts of −SH groups determined by this method are listed in Table 3 as percentages of the thiocarbonylthio end groups of the precursor polymers (% free SH).

Ellman's reagent does not detect disulfide bonds, and, consequently, the fraction of thiol groups that underwent oxidative coupling during workup is not included in the % free SH listed in Table 3, which is lower than the total thiol termini generated by aminolysis. The fraction of dimers formed was estimated from GPC traces of thiocarbonylthio endcapped polymers and the corresponding α,ω-dithiol telechelic polymers, as exemplified in Figure 6, where we present GPC traces of the precursor polymer (dash), the corresponding α,ω-dithiol telechelic polymer (dot), and the difference between the two traces for which the maximum intensity was set at 100 (solid line). The maximum intensity of the small band detected in the solid trace was taken as the percentage of dimer contaminating the α,ω-dithiol telechelic polymer. Recalling that two thiol groups form one disulfide bond, we used this value to calculate the total content of SH-terminated polymers obtained by aminolysis of the thiocarbonylthio groups (Table 3). Quantitative conversion took place, except in the case of PNIPAM-23k, for which the conversion yield was ∼95%.

Conclusion

RAFT polymerization with a hydrophilic difunctional chain transfer agent, followed by aminolysis of the thiocarbonylthio chain ends, provides a facile and mild route to water-soluble α,ω-dithiol telechelic polymers with narrow molecular weight distributions and predictable molecular weights. Determination of end group concentration can be performed readily by a quantitative colorimetric assay of thiol groups. The effectiveness of the methodologies was demonstrated here in the case of α,ω-dithiol telechelic poly(*N*-isopropylacrylamide)s with high thiol functionality (∼95%), which offer an entry to a gamut of telechelic PNIPAMs and PNIPAM-decorated nanoparticles.

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References and Notes

(1) Favier, A.; Charreyre, M.-T. *Macromol. Rapid Commun*. **2006**, *27*, 653−692.
(2) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem*. **2005**, *58*, 379−410.
(3) McCormick, C. L.; Lowe, A. B. *Acc. Chem. Res.* **2004**, *37*, 312−325.
(4) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559−5562.
(5) Moad, G.; Chong, Y. K.; Postma, A.; Rizzardo, E.; Thang, S. H. *Polymer* **2005**, *46*, 8458−8468.
(6) Mahanthappa, M. K.; Bates, F. S.; Hillmyer, M. A. *Macromolecules* **2005**, *38*, 7890−7894.
(7) Patton, P. L.; Mullings, M.; Fulghum, T.; Advincula, R. C. *Macromolecules* **2005**, *38*, 8597−8602.
(8) Goh, Y. K.; Monteiro, M. J. *Macromolecules* **2006**, *39*, 4966−4974.
(9) Lima, V.; Jiang, X. L.; Brokken-Zijp, J.; Schoenmakers, P. J.; Klumperman, B.; Linde, R. V. D. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 959−973.
(10) Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Krstina, J.; Moad, G.; Postma, A.; Thang, S. H. *Macromolecules* **2000**, *33*, 243−245.
(11) Scales, C. W.; Convertine, A. J.; McCormick, C. L. *Biomacromolecules* **2006**, *7*, 1389−1392.
(12) McConnell, W. P.; Novak, J. P.; Brousseau, L. C.; Fuierer, R. R.; Tenent, R. C.; Feldheim, D. L. *J. Phys. Chem. B* **2000**, *104*, 8925−8930.
(13) Lowe, A. B.; Sumerlin, B. S.; Donovan, M. S.; McCormick, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 11562−11563.
(14) Kujawa, P.; Watanabe, H.; Tanaka, F.; Winnik, F. M. *Eur. Phys. J.* **2005**, *E17*, 129−137.
(15) Kujawa, P.; Segui, F.; Shaban, S.; Diab, C.; Okada, Y.; Tanaka, F.; Winnik, F. M. *Macromolecules* **2006**, *39*, 341−348.
(16) Qiu, X. P.; Winnik, F. M. *Macromol. Rapid Commun.* **2006**, *27*, 1648−1653.
(17) Xue, C. H.; Jog, S. P.; Murthy, P.; Liu, H. Y. *Biomacromolecules* **2006**, *7*, 2470−2474.
(18) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163−249.
(19) Convertine, A. J.; Ayres, N.; Scales, C. W.; Lowe, A. B.; McCormick, C. L. *Biomacromolecules* **2004**, *5*, 1177−1180.
(20) Convertine, A. J.; Lokitz, B. S.; Vasileva, Y.; Myrick, L. J.; Scales, C. W.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2006**, *39*, 1724−1730.
(21) Arotcarena, M.; Heise, B.; Ishaya, S.; Laschewsky, A. *J. Am. Chem. Soc.* **2002**, *124*, 3787−3793.
(22) Ray, B.; Isobe, Y.; Matsumoto, K.; Habaue, S.; Okamoto, Y.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **2004**, *37*, 1702−1710.
(23) Postma, A.; Davis, T. P.; Li, G.; Moad, G.; O'Shea, M. S. *Macromolecules* **2006**, *39*, 5307−5318.
(24) Schilli, C. M.; Zhang, M.; Rizzardo, E.; Thang, S. H.; Chong, Y. K.; Edwards, K.; Karlsson, G.; Muller, A. H. E. *Macromolecules* **2004**, *37*, 7861−7866.
(25) Feng, X.-S.; Pan, C.-Y. *Macromolecules* **2002**, *35*, 4888−4893.
(26) Zheng, G. H.; Pan, C.-Y. *Polymer* **2005**, *46*, 2802−2810.
(27) Chen, M.; Ghiggino, K. P.; Thang, S. H.; Wilson, G. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 4368−4372.
(28) Carter, S.; Rimmer, S.; Sturdy, A.; Webb, M. *Macromol. Biosci.* **2005**, *5*, 373−378.
(29) Winnik, F. M. *Macromolecules* **1990**, *23*, 233−242.
(30) Ellman, G. L. *Arch. Biochem. Biophys.* **1958**, *74*, 443−450.
(31) Browning, J. L.; Nelson, D. L. *J. Membr. Biol.* **1979**, *49*, 75.
(32) Lai, J. T.; Filla, D.; Shea, R. *Macromolecules* **2002**, *35*, 6754−6756.
(33) Winnik, F. M.; Adronov, A.; Kitano, H. *Can. J. Chem.* **1995**, *73*, 2030−2040.
(34) Chong, Y. K.; Krstina, J.; Le, T. P. T.; Moad, G.; Postma, A.; Rizzardo, E.; Thang, S. H. *Macromolecules* **2003**, *36*, 2256−2272.
(35) Moad, G.; Solomon, D.H. *The Chemistry of Free Radical Polymerization*; Pergamon: Oxford, 1995.
(36) Thomas, D. B.; Convertine, A. J.; Myrick, L. J.; Scales, C. W.; Smith, A. E.; Lowe, A. B.; Vasilieva, Y. A.; Ayres, N.; McCormick, C. L. *Macromolecules* **2004**, *37*, 8941−8950.

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