Macromolecules **2005,** *38,* 3601−3614

New Water Soluble Agents for Reversible Addition−Fragmentation Chain Transfer Polymerization and Their Application in Aqueous Solutions

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Received August 23, 2004; Revised Manuscript Received February 10, 2005

ABSTRACT: A series of nonionic, anionic, and cationic water-soluble monomers bearing the (meth)acrylate, (meth)acrylamide, or styrene moiety were polymerized in water by free-radical polymerization via reversible addition−fragmentation chain transfer (RAFT). Several new water-soluble RAFT agents based on dithiobenzoate were employed that are water soluble independently of the pH. One of them bears a fluorophore, enabling unsymmetrical double end-group labeling as well as the preparation of fluorescent-labeled polymers. The temperature-dependent stability of the new RAFT agents against hydrolysis was studied. Controlled polymerization in aqueous solution was possible with styrenic, acrylic, and methacrylic monomers; molar masses increase with conversion, and polydispersities are relatively low. But RAFT polymerization failed for an anionic itaconate. Whereas polymerizations of methacrylamides were slow at temperatures below 60 °C, such conditions proved favorable for the RAFT polymerization of acrylates and methacrylates, to minimize hydrolysis of the dithioester end-group functionality, and to improve the preparation of block copolymers.

1. Introduction

The recent methods of controlled free-radical polymerization[1] enable the synthesis of new homopolymers and block copolymers with predetermined molar masses, low polydispersities, and well-defined end groups, which are more difficult to obtain or even not accessible by other synthetic methods. Controlled radical polymerization is more tolerant to functional groups on the monomers than classical “living polymerization” methods and can be run in many conventional solvents over a wide range of temperatures. Controlled radical polymerization also provides a facile access to complex polymer architectures such as star, graft, and hyperbranched polymers under milder conditions. The mostly used controlled radical polymerization methods have been “nitroxyl-mediated polymerization” (NMP),[2−4] “atom transfer radical polymerization” (ATRP),[5−7] and more recently, “reversible addition−fragmentation chain transfer polymerization” (RAFT).[8−10]

With the growing interest in water as a solvent, the implementation of controlled radical polymerization methods in an aqueous environment became a focus of interest. Controlled radical polymerization is still a challenge in aqueous solution because of a number of practical problems (e.g., solubility and stability of the reagents needed in water) as well as because of inherent difficulties to characterize properly the water-soluble polymers obtained (as needed to evaluate the controlled radical polymerization process). Within the various controlled radical polymerization methods, RAFT seems the most promising one for aqueous systems.[11] “nitroxyl-mediated polymerization” often needs relatively high temperatures and high monomer concentrations, while many ATRP catalysts tend to bind strongly to typical hydrophilic groups in the monomers and polymers. Though hydrolysis and aminolysis reactions may interfere with the aqueous RAFT polymerization process,[11] it seems that these side reactions can be minimized by adjusting the pH of the reaction medium to appropriate values.[12−15] Examining the stability of some water-soluble RAFT agents for dependence on temperature and pH,[14,15] the RAFT agents were found to be relatively stable in neutral and acidic conditions but to be sensitive to base. Their stabilities differed depending on the neighboring groups next to active centers. Some examples for aqueous controlled radical polymerization of water soluble styrenic,[15,16] acrylate,[17] and (meth)acrylamide-based[12,13,18,19] monomers via RAFT in water have been reported to yield homopolymers with increasing molar masses with ongoing conversion and with low polydispersities.[11−18] However, the number of reports and detailed data is still limited, and the choice of useful water-soluble RAFT agents even more so. Also, when polymers made by RAFT in water were employed as macroRAFT agents and their blocking ability was tested, they failed in some cases.[16] The failure was attributed to preferential fragmentation of the intermediate radical formed during the preequilibrium of the blocking copolymerization, apparently particular to the use of an aqueous reaction medium.[16]

To learn more about the feasibility of the RAFT process for successful controlled radical polymerization in a homogeneous aqueous solution, we studied the polymerization of several typical water-soluble monomers, such as nonionic (**M1**− **M3**), anionic (**M4**−**M7**), cationic (**M8**−**M12**), and zwitterionic (**M13**) ones with different polymerizable groups (Figure 1) under typical conditions, i.e., in semidilute solution at moderate temperatures and preferentially at ambient pH (pH ≈ 6). For this purpose, we extended a series of pH-independent water-soluble RAFT agents reported recently[15] by two new water-soluble RAFT agents, namely,

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10.1021/ma048268o CCC: $30.25

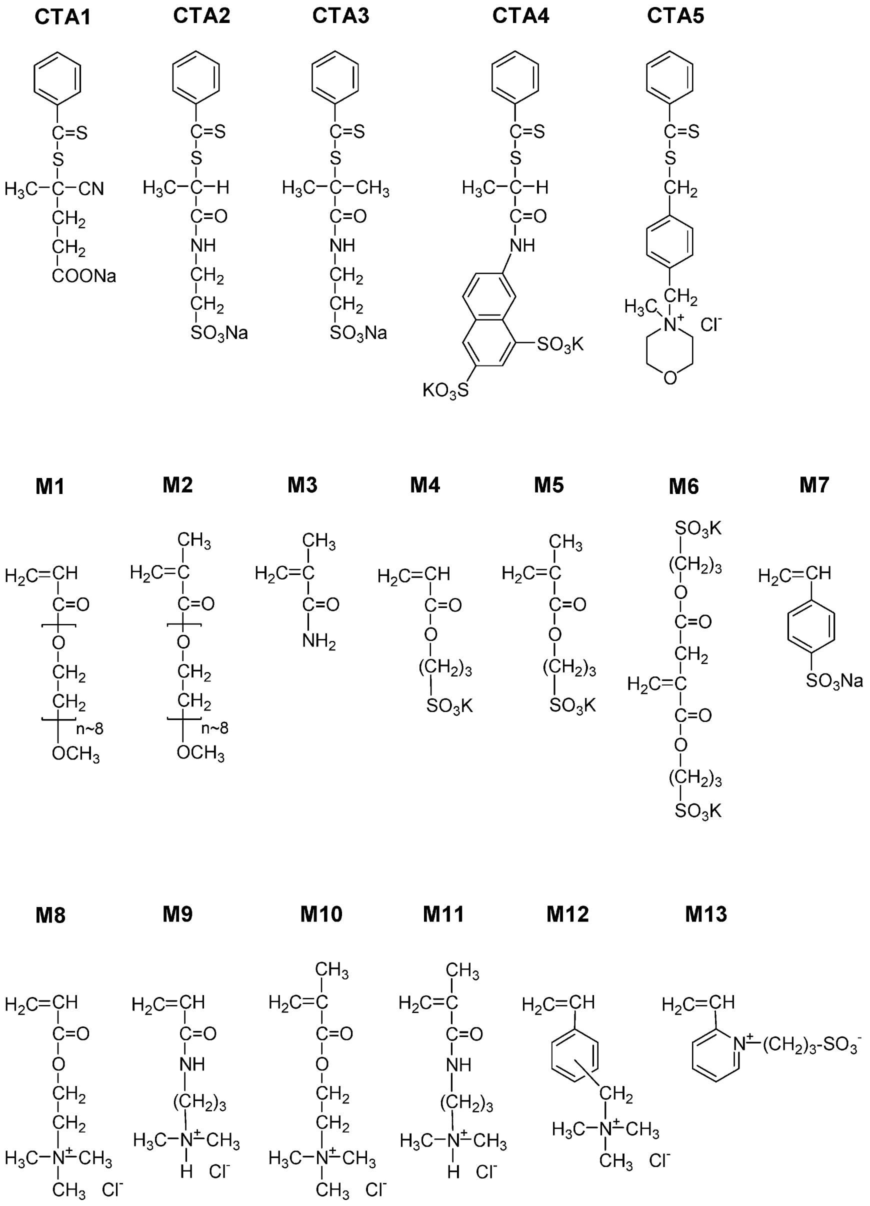

Figure 1. Chemical formulas of used RAFT agents (**CTA1**−**CTA5**), monomers (**M1**−**M13**), and initiators (**V-50**, **V-545**).

CTA3 and **CTA4**, which bear permanently charged anionic sulfonates (Figure 1). **CTA3** was synthesized as an analogue of the recently reported **CTA2**.[15] Different from the latter that is useful for acrylic and styrenic monomers, **CTA3** should be suited to polymerize methacrylic monomers such as **M2**, **M3**, **M5**, **M10**, and **M11**. **M3** and **M11** are known to require relatively low pH values for successful RAFT polymerization.[12,13] **CTA4** is a functional analogue of **CTA2** that bears a fluorophore. Beside the use of this fragment as fluorescent label for various polymer investigations, the use of **CTA4** should facilitate the analysis of the polymers produced (vide infra). The frequently used carboxylic acid **CTA1** was employed as a reference compound as it is equally suited for controlling the polymerization of acrylates, acrylamides, methacrylates, methacrylamides, and styrene derivatives.[8,11]

2. Experimental Section

2.1. Materials. Poly(ethylene glycol) methyl ether acrylate (M_r = 454) (**M1**), (2-acryloyloxyethyl)trimethylammonium chloride (80% aq soln) (**M8**), *N*-(3-(dimethylamino)propyl) acrylamide (97%) (**M9**), *N*-(3-(dimethylamino)propyl) methacrylamide (99%) (**M11**), KI (99+%), 2-naphthylamino-6,8-disulfonic acid monopotassium salt (85%), carbon disulfide (99.9+%), and phenylmagnesium chloride (2 M in THF) were used as received from Aldrich. Poly(ethylene glycol) methyl ether methacrylate (M_r = 430) (Bisomer MPEG350 MA, **M2**) was obtained from Laporte (UK). Methacrylamide (98+%) (**M3**), vinylbenzyltrimethylammonium chloride (97%, 60:40 para/meta mixture) (**M12**), 4,4′-azobis(4-cyanovaleric acid), and D_2O (99.8 atom % D) were purchased from Acros Organics. 3-(Acryloyloxy)propanesulfonate potassium salt (**M4**), 3-(methacryloyloxy)propanesulfonate potassium salt (**M5**), 2-methylenesuccinic acid bis(3-sulfopropyl) ester dipotassium salt (**M6**), and 3-(2-vinylpyridinio)propanesulfonate (**M13**) were gifts from Raschig AG (Ludwigshafen, Germany). Taurine (99+%), α-bromoisobutyryl bromide (97+%), sodium styrene sulfonate (90+%) **(M7)**, and 2-bromopropionyl bromide (99%) were used as received from Fluka. (2-Methacryloyloxyethyl)trimethylammonium chloride (80% aq soln) was obtained from Degussa-Röhm (Germany) (**M10**). Inhibitor 4-methoxyphenol was removed from monomers **M1**, **M2**, and **M11** by passing through basic aluminum oxide. **M9** was diluted by twice the volume of 0.5 M of aqueous KCl, then it was brought to pH 3 by addition of concentrated HCl while cooling, thus protonating the amine moiety of the monomer. After adding the initiator and the RAFT agent, the mixture was extracted thrice with diethyl ether. The inhibitor 4-methoxyphenol was removed analogously from the polymerization solutions of **M8** and **M10**. 2,2′-Azobis(2-methylpropionamidine) dihydrochloride (**V-50**) and 2,2′-azobis(2-methyl-*N*-phenylpropionamidine) dihydrochloride (**V-545**) were gifts of Wako Pure Chemical Industries. Solvents used for synthesis and purification were all analytical grade. Silicagel 60 (0.040−0.063 mm) for column chromatography and aluminum oxide (basic, activity *I*, 0.063−0.200 mm) were from Merck. Buffer solution potassium hydrogen phthalate/HCl pH $= 4.01 \pm 0.02$ (pH at 25 °C) was purchased from Roth. Buffer solution pH = 6 was prepared from citric acid monohydrate (Fluka, +99.5%) and Na_2HPO_4 (Riedel-deHaën, puriss). Polymers were dialyzed in water with tubes "Zellu Trans" (nominal molar mass cutoff 3500) from Roth (Germany).

2.2. Synthesis of RAFT Agents. Sodium 2-(2-thiobenzoylsulfanylpropionylimino)ethansulfonate (**CTA2**) and *N*-methyl-*N*-(thiobenzoylsulfanylmethylenephenylmethyl) morpholinium chloride (**CTA5**) were synthesized as described before.[15] 4-Thiobenzoylthio-4-cyanopentanoic acid (**CTA1**) was synthesized as described by Thang et al.[20] **CTA1** was converted into the sodium salt by dissolution in CH_2Cl_2, followed by extraction into aqueous phase via slow addition of 1 M of NaOH (pH always < 7) and subsequent lyophilization.

Synthesis of Sodium 2-(2-Methyl-2-thiobenzoylsulfanylpropionylimino)ethansulfonate (**CTA3**). α-Bromoisobutyryl bromide (10.01 g, 43.1 mmol) in CH_2Cl_2 (50 mL) was added dropwise to taurine (5.42 g, 42.9 mmol) in aqueous NaOH (1 M, 86.5 mL). The resulting two-phase system was stirred vigorously for 15 h at ambient temperature. After separation of the organic phase, the aqueous phase was adjusted to pH 2 and extracted twice with diethyl ether then adjusted to pH 6 by aqueous NaOH (1 M) and diluted to 100 mL. 30 mL of this solution of sodium 2-(2-bromo-2-methylpropionylamino)-ethanesulfonate (12.9 mmol) was added to an aqueous solution of sodium dithiobenzoate (14 mmol, pH 6) and KI (0.10 g, 0.6 mmol). The mixture was stirred at 57 °C for 18 h under nitrogen atmosphere, adjusted to pH 2, and extracted twice with diethyl ether. The aqueous phase was separated, the pH adjusted to 6 by aqueous NaOH (1 M), diluted with ethanol, and evaporated, keeping the temperature below 40 °C to minimize hydrolysis or alcoholysis. The residue was redissolved in the minimum amount of ethanol/$CHCl_3$ (25:75 by volume), and insoluble impurities were filtered off. Column chromatography (silicagel, eluent: ethanol/$CHCl_3$ 25:75 by volume) gave the product as hygroscopic powder (yield 0.95 g, 20%). ($C_{13}H_{16}NNaO_4S_3$, $M_r = 369.46$ g mol^{-1}): Calcd: C 42.26, H 4.37, N 3.79, S 26.04. Found: C 41.05, H 4.32, N 3.50, S 22.54. MS (ESI, negative ions) signal at 345.9 ($M-Na^+$). ^1H NMR (300 MHz in D_2O): $\delta_H = 1.64$ (s, 6H, CH_3), 2.96 (t, 2H, $-CH_2SO_3$), 3.48 (t, 2H, $-CON-CH_2-$), 7.37 (m, 2H, =CH aryl-(meta)), 7.55 (m, 1H, =CH aryl(para)), 7.82 (m, 2H, =CH aryl-(ortho)) ppm. ^{13}C NMR (75 MHz in D_2O): $\delta_C = 24.8$ ($-CH_3$), 36.4 ($-NH-CH_2-$), 50.1 ($-CH_2-SO_3$), 56.5 ($S-C-$), 127.1 (aryl CH(2)), 129.2 (aryl CH(3)), 133.6 (aryl CH(4)), 145.4 (aryl C(1)), 175.5 ($-CON-$), 228.7 ($-C=(S)S-$). FT-IR (KBr, selected bands): 1635 (vs broad, superposed sec. amide I and ν C=C aryl), 1538 (s, sec. amide II), 1214 (vs broad, superposed ν_{as} SO_3, ν C=S), 1049 (ν_s SO_3), 761 (δ_{oop} CH, monosubstituted phenyl) cm^{-1}. UV−vis (in water): band at $\lambda_{max} = 483$ nm ($\epsilon = 130$ L mol^{-1} cm^{-1}).

Synthesis of Potassium 2-(2-Thiobenzoylsulfanylpropionylimino)naphthalene-6,8-disulfonate (**CTA4**). 2-Bromopropionyl bromide (14.93 g, 67.1 mmol) in CH_2Cl_2 (30 mL) was added dropwise to 2-naphthylamino-6,8-disulfonic acid monopotassium salt (15.00 g, 37.3 mmol) in aqueous KOH (1 M, 135 mL), while cooling with ice. The two-phase system was stirred vigorously for 12 h at ambient temperature. The aqueous phase was separated and precipated into ethanol. The precipitate was filtered off, washed with ethanol, and dried under reduced pressure to yield 21.13 g of crude 2-(2-bromo-propionylamino)-naphthalene-6,8-disulfonic acid dipotassium salt (containing 7% KBr determined by elemental analysis). This intermediate (6.49 g, 11.7 mmol) and KI (0.126 g, 7.5×10^{-4} mol) were dissolved in an aqueous solution of potassium dithiobenzoate (25 mmol in 60 mL, pH 6). The solution was rapidly adjusted to pH 6 and stirred at ambient temperature for 13 h, then precipitated in acetone. The precipitate was dissolved in the minimum amount of water and precipitated again by adding acetone. Removing the first precipitated fractions (1.29 g) contaminated by inorganic salt, the product was obtained as hygroscopic solid (yield 3.94 g, 55%). Elemental analysis ($C_{20}H_{15}K_2NO_7S_4$, $M_r = 587.79$ g mol^{-1}): Calcd: C 40.87, H 2.57, N 2.38, S 21.82; C/N = 17.17, C/S = 1.87. Found: C 39.07, H 2.81, N 2.24, **S** 20.77; C/N = 17.44, C/S = 1.88. MS (FAB, matrix glycerol, negative ions) signal at 548.0 (M−K). ^1H NMR (300 MHz in D_2O,): $\delta_H = 1.62$ (d, 3H, CH_3), 4.53 (q, 1H, CH), 7.22 (t, 2H, =CH phenyl), 7.41 (t, 1H, =CH phenyl, 7.61 (d, 1H, =CH naphthyl), 7.71 (d, 2H, =CH phenyl), 7.91 (d, 1H, =CH naphthyl), 8.31 (s, 2H, =CH naphthyl), 8.72 (s, 1H, =CH naphthyl) ppm. ^{13}C NMR (75 MHz in D_2O): $\delta_C = 16.3$ (CH_3), 51.4 (S−CH), 116.2 (naphthyl CH (7)), 122.9 (naphthyl CH (1)), 123.4 (naphthyl CH (3)), 127.1 (phenyl CH-(2)), 129.1 (phenyl CH(3)), 130.0 and 130.2 (naphthyl C (9 + 10)), 131.3 and 131.6 (naphthyl O_3S-C (6 + 8)), 133.8 (phenyl CH(4)), 138.3 (naphthyl CH (5)), 138.5 (naphthyl CH (4)), 139.8 (naphthyl N−C(2)), 141.1 (phenyl C(1)), 173.0 ($-CONH-$), 228.7 ($-C=(S)S-$) ppm. FT-IR (KBr, selected bands): 1623 (vs broad, superposed sec. amide I and ν C=C aryl), 1538 (s sec. amide II), 1194 (vs broad, superposed ν_{as} SO_3, ν C=S), 1106 (s, δ_{ip} CH, naphthyl ?), 1039 (vs, ν_s SO_3), 761 (δ_{oop} CH, monosubstituted phenyl), 665 (s, ring deformation aryl), 615 (s, ring deformation aryl) cm^{-1}. UV−vis (in water): bands at $\lambda_{max} = 483$ nm ($\epsilon = 110$ L mol^{-1} cm^{-1}), $\lambda_{max} = 301$ nm ($\epsilon = 25.0 \times 10^3$ L mol^{-1} cm^{-1}), and $\lambda_{max} = 251$ nm ($\epsilon = 47.1 \times 10^3$ L mol^{-1} cm^{-1}).

2.3. Polymerization. Reaction mixtures were deoxygenated by bubbling N_2 for 30 min. In kinetic studies, samples were collected from the reaction mixture at given time intervals by a syringe through a septum. Polymerizations were stopped by the addition of an aqueous solution of 4-methoxyphenol. All polymer samples were dialyzed against water with tubes having nominal molar mass cutoff of 3500 and then lyophilized. Conversions were determined on the basis of recovered polymers after lyophilization of the dialyzed samples. The type and the amounts of monomer, RAFT agent, and initiator engaged in the polymerization media, and temperatures are listed in Table 1. In a typical polymerization procedure, monomer **M12** (5.22 g, 23.9 mmol) was added to **CTA4** (84 mg, 1.35×10^{-4} mol) and initiator **V-545** (11.5 mg, 2.72×10^{-5} mol) in 0.5 M aqueous NaBr solution (50 mL) in a flask equipped with a magnetic stirrer and closed by a rubber septum. After deoxygenation by bubbling with N_2 for 30 min, the flask was placed in a thermostated oil bath (48 °C). Samples were taken at different time intervals with a syringe through the septum. The amounts of collected polymer samples were in the range between 0.1 and 1 g. No polymer formation during the induction period was found by ^1H NMR in cross-checking experiments.

For the synthesis of **poly-M12**-*block*-polydimethylacrylamide, macroRAFT agent **poly-M12-CTA** was isolated after 185 min of ongoing polymerization of **M12** in the presence of **CTA4** (cf. Table 1, $M_n = 27\,000$, determined by end-group analysis via absorbance at 490 nm). **Poly-M12-CTA** (134.4 mg, 5.00×10^{-6} mol), dimethylacrylamide (0.501 g, 5.00 mmol), and initiator **V-545** (1.2 mg, 2.75×10^{-6} mol) in 4 mL of deionized water were polymerized for 5 h at 48 °C. The reaction mixture was dialyzed (nominal molar mass cutoff 3500) and lyophilized (yield 0.525 g, 85% conversion of DMA). The refractive index increment was determined as 0.166 mL/g in 1 wt % aqueous acetic acid/0.2 M of Na_2SO_4.

2.4. Methods. NMR spectra were taken with a Bruker Avance 300 (300 MHz, 32 scans for ^1H, 1500 scans for ^{13}C). 1,4-Dioxane was used as an internal reference at 67.4 ppm for ^{13}C NMR measurements in D_2O.[15] For stability tests, followed by ^1H NMR, RAFT agents were dissolved directly in D_2O, and the integrated signal of added dioxane was used as an internal reference. pH measurements were done with an Erbo PHT 3140 pH meter. IR spectra were taken from KBr pellets by a FT-IR spectrometer (Bruker IFS 66/s). IR peak assignments were made according to tabulated values.[21] Mass

Table 1. Polymerization Conditions Used for the Experiments

monomer (mmol)	RAFT agent (mol × 10^{-5})	initiator (mol × 10^{-5})	polym temp	solvent	polym time (h)
M1 (29.1)	CTA4 (18.8)	V-545 (3.8)	48 °C	70 mL 0.5 M (aq) KCl	ks[a]
M2 (30.9)	CTA1 (20.0)	V-50 (5.3)	55 °C	25 mL water	ks
M3 (125.0)	CTA3 (20.0)	V-50 (4.0)	55 °C	95 mL water	ks
M4 (55.6)	CTA1 (12.2)	V-50 (3.2)	55 °C	75 mL water	ks
M4 (52.3)	CTA4 (15.1)	V-545 (3.0)	48 °C	75 mL 0.5 M (aq) KCl	ks
M5 (64.4)	CTA1 (14.8)	V-50 (4.0)	55 °C	75 mL water	ks
M6 (6.5)	CTA1 (15.0)	V-50 (3.0)	50 °C	25 mL buffer soln pH = 6	17
M6 (2.2)	CTA3 (5.0)	V-50 (1.0)	55 °C	15 mL water	20
M6 (2.2)	CTA5 (5.0)	V-50 (1.0)	55 °C	5 mL water	4
M7 (21.8)	CTA4 (22.5)	V-545 (4.5)	55 °C	30 mL 0.5 M (aq) NaBr	7
M8 (50.4)	CTA4 (13.9)	V-545 (2.8)	48 °C	55 0.5 M (aq) KCl	ks
M9 (69.6)	CTA4 (21.7)	V-545 (4.3)	48 °C	60 mL 0.5 M (aq) KCl	ks
M10 (38.5)	CTA3 (20.0)	V-50 (4.0)	55 °C	45 mL water	ks
M11 (44.2)	CTA3 (13.5)	V-50 (3.0)	55 °C	60 mL water	ks
M12 (23.9)	CTA4 (13.6)	V-545 (2.7)	48 °C	50 mL 0.5 M (aq) NaBr	ks
M13 (4.4)	CTA3 (5.0)	V-50 (1.0)	55 °C	15 mL water	22
M13 (4.4)	CTA3 (5.0)	V-50 (1.0)	55 °C	15 mL buffer soln pH = 4	22
M13 (24.5)	CTA4 (17.0)	V-545 (3.0)	55 °C	25 mL 0.5 M (aq) NaBr	6
M13 (4.4)	CTA5 (4.0)	V-50 (1.0)	55 °C	5 mL water	4

[a] ks = kinetic study performed.

Table 2. d*n*/d*c* Values of Polymers (Measured at 30 °C, 632 nm)

polymer	solvent	d*n*/d*c*
poly-M1	1 wt % acetic acid/0.2 M Na_2SO_4 (aq)	0.125 mL/g
poly-M2	1 wt % acetic acid/0.2 M Na_2SO_4 (aq)	0.132 mL/g
poly-M4	0.1 M $NaNO_3$	0.123 mL/g
poly-M5	0.1 M $NaNO_3$	0.125 mL/g
poly-M8	1 wt % acetic acid/0.2 M Na_2SO_4 (aq)	0.152 mL/g
poly-M9	1 wt % acetic acid/0.2 M Na_2SO_4 (aq)	0.182 mL/g
poly-M10	1 wt % acetic acid/0.1 M Na_2SO_4 (aq)	0.146 mL/g
poly-M11[a]	1 wt % acetic acid/0.1 M Na_2SO_4 (aq)	0.194 mL/g
poly-M12	1 wt % acetic acid/0.2 M Na_2SO_4 (aq)	0.188 mL/g

[a] Value taken from ref 13.

spectra were recorded by a TSQ7000 (Thermo Finnigan) spectrometer. Elemental analysis was done with a model EA 1110 (CHNS−O) from CE Instruments. UV−vis spectra were recorded with a UV−vis spectrophotometer Cary-1 (Varian) equipped with a temperature controller (Julabo F-10). Extinction coefficients of the polymers in water were determined from polymer samples polymerized without the use of a RAFT agent. Turbidimetry used a temperature-controlled turbidimeter model TP1 (E. Tepper, Germany). Refractive index increments d*n*/d*c* of the polymers were determined at 30 °C at 632 nm by ScanRef from PSS GmbH (Mainz, Germany), and are listed in Table 2.

Aqueous size-exclusion chromatography (ASEC) was run at 30 °C using Spectra Physics instruments for cationic and nonionic polymers (column combination: TSK-GEL [polyglycidyl(meth)acrylate-Gel] from TOSOH: PWH guard column 12 μm, G6000 17 μm (operating range < 2 × 10^8), G5000 PW 17 μm (operating range < 1 × 10^7), G3000 10 μm (operating range 500−800 000), and HEMA Bio [Hydroxyethylmethacrylate-Gel] from PSS: Hema Bio 40 10 μm (operating range 100−20 000)). Evaluation was by multi-angle light scattering (MALLS) (Wyatt DAWN DSP, Wyatt, Santa Barbara, CA, wavelength 632 nm) and by calibration with poly(2-vinylpyridine) (P2VP) standards (PSS GmbH, Mainz, Germany). Aqueous size-exclusion chromatography for polyanions was done using the pump Thermoquest P100 with eluent: aqueous 0.1 M of $NaNO_3$ (3 columns: Polymer Laboratories aquagel-OH 50, 8 μm (operating range 50 000−1 000 000), PL aquagel-OH 40, 8 μm (operating range 10 000−200 000), PL aquagel-OH 30, 8 μm (operating range 100−30 000), RI detection). Wyatt Optilab DSP interferometric refractometer, flow rate of 0.800 mL/min, using multi-angle light scattering (MALLS) (Wyatt DAWN EOS, Wyatt, Santa Barbara, CA, DAWN EOS 30 mW GaAs laser, wavelength 690 nm). Size-exclusion chromatography (SEC) with *N*-methylpyrrolidone (NMP) at 70 °C was performed using a TSP (Thermo Separation Products from Thermo-Finnigan, Dreiech, Germany) equipped with a Shodex RI-71 refractive index detector, a TSP UV detector, eluent 0.05 M of LiBr in NMP (Columns: PSS GRAM [polyester columns] 10 μm (operating range 100−1 × 10^7)) at a flow rate of 0.800 mL/min; calibration by polystyrene standards (PSS, Mainz, Germany). Size-exclusion chromatography in tetrahydrofuran at 25 °C used a Waters 515 HPLC isocratic pump equipped with a Waters 2414 refractive index detector, a Waters 2487 UV detector and a set of Styragel columns (HR 5, HR 45, HR 3, molar mass range 500−100 000) from Waters. Eluent: THF (HPLC, from Roth), flow rate 1.0 mL/min^{-1}, calibration by poly(styrene) standards (PSS, Mainz, Germany).

3. Results

3.1. Synthesis and Properties of the RAFT Agents. The new dithiobenzoates **CTA3** and **CTA4** are synthesized by reacting a functional alkyl halide with the sodium salt of dithiobenzoate. The latter was prepared via the Grignard route because the method of Becke and Hagen[22] leads to some contamination by thiobenzoate, which is virtually impossible to separate.[15] This approach is known to work well for primary and secondary alkyl halides,[8] but in the case of **CTA3** and **CTA4**, the solubility of the respective intermediate halides requires their coupling to dithiobenzoate in water. Still, **CTA4** was accessible via this approach at ambient temperature, analogous to the synthesis of **CTA2**.[15] A most recent report describes a similar strategy to **CTA2**,[19] though some analytical data seem inconsistent. The synthesis of **CTA3** was more difficult, as tertiary alkyl halides require thermal activation for the coupling reaction to compensate for the increased steric restrictions. However, higher temperatures favor decomposition of the dithioesters by hydrolysis. Coupling in aqueous reaction media at about 60 °C proved the best compromise; while no coupling was observed at ambient temperature, hydrolysis is too fast at 70 °C. Different from the carboxylic acid **CTA1** that has been frequently employed in aqueous RAFT polymerization but is only soluble at neutral or basic pH, RAFT agents **CTA3** and **CTA4** are soluble in water in the full pH range like **CTA2** and **CTA5.**[15]

Note that in **CTA4**, the 2-naphthylamino-6,8-disulfonate fragment imparts not only water solubility to the RAFT agent, but may serve also as an analytical tool. The UV−vis absorption spectrum exhibits three char-

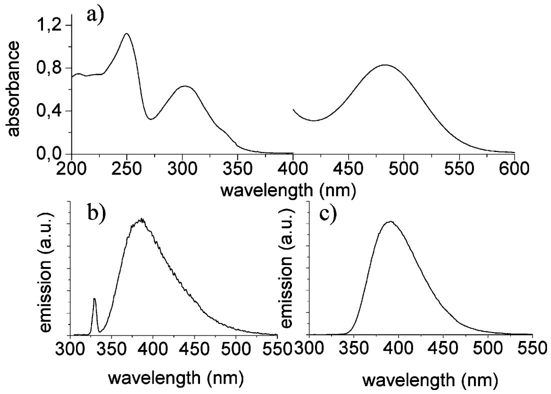

Figure 2. Optical spectra of **CTA4** in water. (a) UV−vis absorption spectra (conc 2.39×10^{-6} M (200−400 nm) and 7.5×10^{-3} M (400−600 nm). (b) Fluorescence emission spectra, excitation at 300 nm. (c) Fluorescence emission spectra of **poly-M7** polymerized using **CTA4**, excitation at 300 nm (M_n = 22 000 according to end-group analysis via the visible band of the dithioester unit at 488 nm and the naphthalene band at 251 nm).

acteristic absorption maxima, at 251, 301, and 483 nm (Figure 2a). The maximum at 483 nm is the $n \rightarrow \pi^*$ transition of the C=S group, i.e., it is indicative of intact dithioester end groups. As this transition is forbidden, the extinction coefficient is low, being on the order of 10^2 L mol^{-1} cm^{-1} (Table 3). The comparison of **CTA4** with the other dithiobenzoates demonstrates that the absorbance maxima as well as the molar extinction coefficient of the C=S group depend somewhat on the chemical structure of the thiol fragment of the dithioester. Increasing substitution on the α-C seems to induce a bathochromic shift of the band, i.e., the C=S bond becomes easier to activate. The absorption band of **CTA4** at 301 nm has, according to the comparison with the extinction coefficients of **CTA1** and **CTA3** at this wavelength, contributions from both the dithiobenzoate moiety and the naphthalene chromophore, with the naphthalene fragment accounting for almost half of the molar extinction (Table 3). Note that, for **CTA1** and **CTA3**, the contributions of the thiol fragments to the absorbance at 301 nm are negligibly low. The absorption band at 251 nm is characteristic for the naphthalene chromophore of **CTA4** (Table 3) and, therefore, may serve for its specific detection. The extinction coefficients of **CTA1** and **CTA3** at this wavelength are much lower (no specific band). Furthermore, **CTA4** exhibits fluorescence as its precursor 2-naphthylamino-6,8-disulfonate. Consequently, polymers prepared in the presence of **CTA4** become inherently labeled with a fluorescent end group. The fluorescence emission spectra of the RAFT agent and of such polymers are exemplified in Figure 2b and c, demonstrating that the spectra of **CTA4** and of the polymers derived from it are virtually identical.

The different absorbance maxima in the visible and in the UV range can be used to determine the number of average molar masses M_n of the polymers prepared by **CTA4** via end-group analysis at different wavelengths. This is a valuable analytical option as the molar mass analysis of water-soluble polymers, in particular, of polyelectrolytes, requires mostly the use of expensive equipment and even so is notoriously troubled with difficulties, including artifacts due to association and adsorption phenomena.

Each absorbance band has some advantages and inconveniences for end-group determination. The band at 483 nm, in the visible range, is useful to determine the dithioester functionality. This band is generally applicable to polymers produced via RAFT using dithioesters.[15] But the extinction coefficient is small (cf. Table 3), implying that high polymer concentrations are necessary to obtain a sufficient absorbance signal when the molar mass increases. Not all polymers are sufficiently soluble in water, or they give cloudy solutions, thus limiting this method. Moreover, the extinction coefficient may vary somewhat in the course of polymerization with the changing neighboring groups (cf. entries for **CTA1** to **CTA5** in Table 3), thus reducing the precision. Often this is accompanied by a slight shift of the absorbance maximum. The high extinction at 301 nm of all dithiobenzoates allows end-group determination to be carried out with small amounts of polymer for many acrylic and methacrylic polymers, and even for some styrenic polymers (such as **poly-M7** and **poly-M12**) as the absorbance of these polymers at this wavelength is still very low (see Table 3). However, this absorbance value is less reliable for end-group determination as the absorbance at this wavelength is a superposition of two independent bands (naphthyl core and dithiobenzoate core) when using **CTA4**. For instance, possible environmental effects on the spectrum will add up, and the extinction coefficient may change more with ongoing polymerization than that discussed for the extinction coefficient of the weak visible band.

In the case of **CTA4**, the additional naphthalene chromophore gives rise to a third specific intense maximum at 251 nm. The inherent absorbance of some styrenic polymers at this wavelength interferes with this band of the RAFT agent, but the 251 nm band of the naphthalene chromophore is very useful for end-group analysis of acrylic polymers (cf. Table 3). When used together, the three different absorbance bands allow not only a simple cross check on the reliability of the end-group analysis of the M_n values, but enable also a facile estimation of the amount of active polymer chain ends. Whereas the band at 251 nm is a measure for the amount of initiating fragments “R” of the RAFT agent in the polymers, the band at 483 nm is a measure for the amount of dithioester groups present, i.e., of “dormant” chain ends. The band at 301 nm with mixed contributions from the dithiobenzoate group and the “R” group can serve to cross check the reliability of this comparison though being inherently less precise. If the dithioester groups are consumed by whatever side reaction (such as recombination of growing chains, hydrolysis, etc.), this will result in a mismatch of the M_n values calculated from the different absorbance bands. This information is hard or impossible to deduce from other techniques employed to determine molar mass, but it is most valuable, e.g., when employing polymers made by RAFT as macroRAFT agents in a second polymerization reaction, to synthesize block copolymers.

Before employing the new RAFT agents **CTA3** and **CTA4** in aqueous polymerization mixtures, their stability against hydrolysis was tested in D_2O by ^{1}H NMR at different temperatures (Figure 3), similar to a method used previously,[15] and compared to the behavior of **CTA2** (which is considerably more stable than **CTA1**).[15] The stability of **CTA3** was measured by following the decay of the integrated proton signal of the $-C(=S)-S-C-CH_3$ fragment at 1.67 ppm that is sensitive to the loss of the dithioester group. Analogously, the decom-

Table 3. Characteristic Absorbance Bands of RAFT Agents and Polymers in Aqueous Solution

	ϵ at 251 nm		ϵ at 301 nm		visible band	
compound	[L mol^{-1} cm^{-1}]	[L g^{-1} cm^{-1}]	[L mol^{-1} cm^{-1}]	[L g^{-1} cm^{-1}]	λ_{max} [nm]	ϵ [L mol^{-1} cm^{-1}]
CTA1	2.29×10^3	7.60	11.7×10^3	38.87	497	115
CTA3	2.98×10^3	8.06	13.0×10^3	35.17	489	130
CTA4	47.1×10^3	80.13	25.0×10^3	42.43	483	110
CTA5[a]					480	97
poly-M1		< 0.02		< 0.01	489	
poly-M2					509	
poly-M3					494	
poly-M4		0.182		0.022	483	
poly-M5					490	
poly-M7		1.30		0.020	488	
poly-M8		0.084		0.025	485	
poly-M9		0.044		0.023	485	
poly-M10					497	
poly-M11					493	
poly-M12		1.22		0.023	490	

[a] Data taken from ref 15.

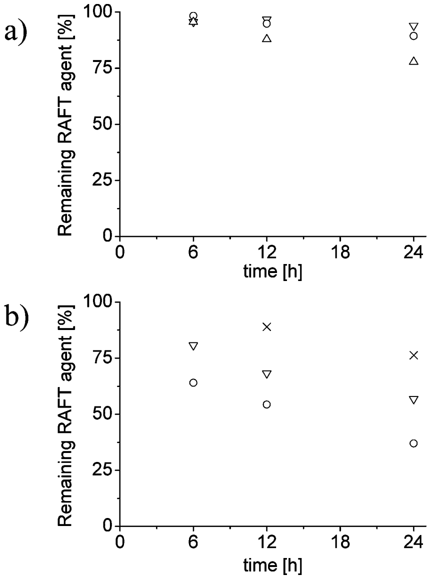

Figure 3. Stability of RAFT agents in D_2O at 50 °C (×), 60 °C (▽), 70 °C (○), and 80 °C (△) as followed by ^{1}H NMR spectroscopy of (a) **CTA3** and (b) **CTA4**.

position of compound **CTA4** is followed by the decay of the proton peak at 1.71 ppm. Whereas reference samples stored at 4°C did not show any decay over 24 h, storage at elevated temperatures leads to some degradation (Figure 3). Comparing the data from Figure 3a with the reported data on **CTA2**,[15] **CTA3** is the more stable compound. The situation is different in **CTA4**. Whereas **CTA2** is yet hardly decomposed at 60 °C after 24 h, almost half of **CTA4** is decomposed under the same conditions. In summary, the stability of the RAFT agents increases in the series **CTA1** < **CTA4** < **CTA2** < **CTA3**. In fact, **CTA3** is the most stable RAFT agent we have tested up to now, even surpassing the very stable **CTA5**;[15] only 25% of the compound was decomposed after 24 h at 80°C. These findings might be explained by hydrophobic shielding of the dithioester moiety by the two β-methyl groups of **CTA3** against the attack by water. However, not only the close vicinity of the dithioester group (which is identical for **CTA2** and **CTA4**) is of importance for hydrolytic stability. Putatively, the reduced stability of **CTA4** may be attributed to the increased hydrophilic environment around the molecule caused by the naphthalene disulfonate fragment.

Note that a part of the degradation of **CTA4** is due to the conversion of the dithioester group to the thioester according to the NMR spectra of partially decomposed mixtures, as reported previously for other dithioesters,[15] and is not only due to full hydrolysis of the $-C(=S)-S$ moiety. Therefore, some other reported stability tests for dithiobenzoates in aqueous solution based on UV detection[14] may have overestimated the stability of such dithioester end groups on polymer chains because the eventual conversion of the dithioester to a thioester moiety (as found in our tests with **CTA2** and **CTA4**) would not have been noticed.

Since the stability of the low molar mass RAFT agents can be problematic at temperatures above 60 °C depending on structure, similar problems may exist for growing macroRAFT agents. Therefore, it seems wise to work at lower temperatures in an aqueous medium for RAFT polymerizations when possible to not reduce end-group functionality. Consequently, the polymerization experiments in this study were conducted at 55 °C or even at lower temperatures (Table 1).

3.2. Aqueous RAFT Polymerization of Acrylic Monomers. The anionic acrylic ester **M4** was chosen for initial aqueous polymerization studies as its polymer is a well-behaved, water-soluble polymer at ambient pH using the established RAFT agent **CTA1** as well as the new, labeled **CTA4** (Figure 4). As shown in Figure 4a, the polymerization of **M4** in the presence of **CTA1** at 55 °C reached 90% conversion after 5 h and follows pseudo-first-order kinetics after an initial retardation period of about 60 min. The ASEC traces of samples taken at increasing reaction times present basically unimodal peaks with decreasing elution volumes and reducing width as expected for controlled polymerization. At short elution volumes, a small band indicative of an additional high molar mass polymer (>1 000 000) is detected, too, whose relative importance decreases with conversion. This peak was always present in the samples of **poly-M4** (with or without RAFT agents present) and is attributed to uncontrolled polymerization of the destabilized monomer before the reaction. Neglecting this high molar mass impurity, the number of the average molar mass M_n increases steadily with conversion, according to analysis by MALLS as well as by end-group determination using the visible dithioester band at 483 nm (Figure 4c). Both M_n values match well and are close to the M_n value expected theoretically for the given ratio of monomer to RAFT agent. The polydispersities according to MALLS are very narrow (M_w/

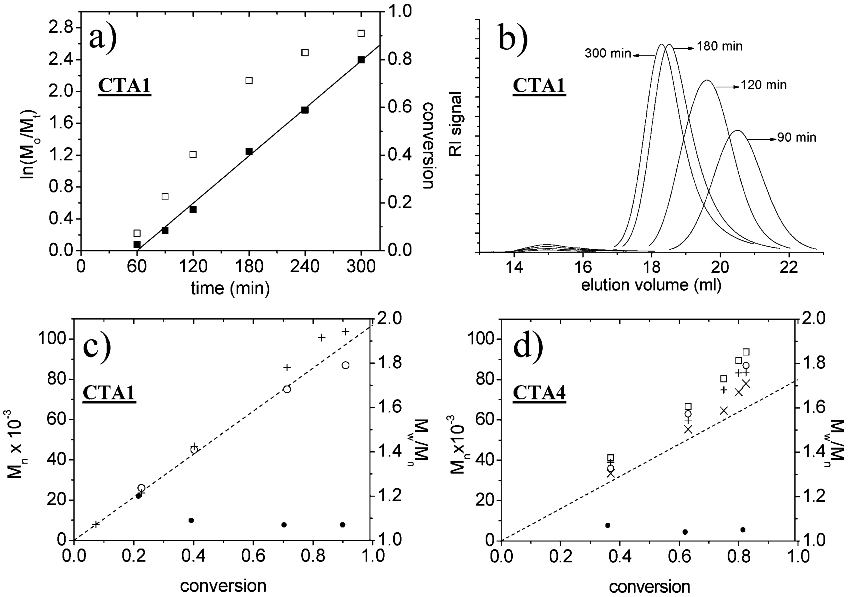

Figure 4. Polymerization of **M4** in water using initiator **V-50** and RAFT agent **CTA1** at 55 °C ([CTA]/[*I*] = 3.8). (a) (□) Conversion determined by gravimetry vs time, (■) $\ln(M_0/M_t)$ vs time, the solid line is the linear fit of $\ln(M_0/M_t)$ vs time data. (b) Evolution of ASEC elugrams with polymerization time (eluent: 0.1 M of aq $NaNO_3$). (c) Evolution of M_n and PDI (M_w/M_n) with conversion, (○) M_n according to MALLS, (+) M_n estimated by the visible band of the dithioester end group, (●) polydispersity of sample determined with MALLS. The dashed line (- - -) is the theoretically calculated evolution of M_n. (d) Polymerization of **M4** in water using initiator **V-545** and RAFT agent **CTA4** at 48 °C ([CTA]/[*I*] = 5/1), (□) M_n estimated by using the UV band at λ_{max} = 301 nm, (×) M_n estimated by using the UV band at λ_{max} = 251 nm. The meaning of symbols (○), (+), (●), and (- - -) is the same as in (c).

M_n < 1.1) but may underestimate somewhat the true values.[15] By replacing RAFT agent **CTA1** by the new labeled **CTA4**, polymerization of **M4** behaves very similarly. The initial retardation period is about 60 min, kinetics are equally fast, the number of the average molar mass M_n increases steadily with conversion, and polydispersities are very narrow (Figure 4d). Exploiting the multiple absorption bands introduced into the system by **CTA4**, M_n values calculated by end-group determination via the dithioester band at 483 nm and via the UV naphthalene band at 251 nm match well. Estimating M_n values by analyzing the (less reliable) combined band at 301 nm also shows a reasonable agreement of the data, though the values seem to overestimate the true values somewhat. Clearly, the use of the labeled RAFT agent is an attractive method to complement molar mass data by a simple and low-cost analytical method such as UV–vis spectroscopy.

Having established the usefulness of **CTA4** in aqueous solution polymerization for monomer **M4**, we studied its use for the nonionic macromonomer **M1** (Figure 5). **M1** (and equally **M2**, vide infra) is a versatile monomer with interesting properties, such as being soluble in many organic solvents and in water or being nontoxic and biocompatible, with a high potential for biomedical applications. Figure 5a shows that polymerization of **M1** proceeds about as fast as for **M4** and follows pseudo-first-order kinetics up to 85% conversion after an initial retardation period of about 60 min. But for longer reactions (>240 min), kinetics slow down. This suggests that the radical concentration in the reaction medium is reduced. The ASEC elugrams show a continuous shift to lower elution volumes, indicating a steady growth in molar mass. Evaluation by online MALLS gives a linear increase in the molar mass close to the theoretically expected one and low polydispersities of about 1.3 (Figure 5b). Cross checking the ASEC data for **poly-M1** by SEC in NMP and calibrating with polystyrene standards, polydispersities are low (about 1.15) and molar masses increase linearly with increasing conversions, too. But the apparent M_n values are lower by a factor of 3, indicating that calibration with polystyrene is not appropriate for the polymerized macromonomer because of the strong structural differences. However, when calculating M_n values from the dithioester band at 489 nm and the naphthalene band at 251 nm as well as from the mixed band at 301 nm, the numbers for the bands are close to each other as well as to the theoretically expected value (Figure 5b), corroborating the usefulness of the labeled RAFT agent.

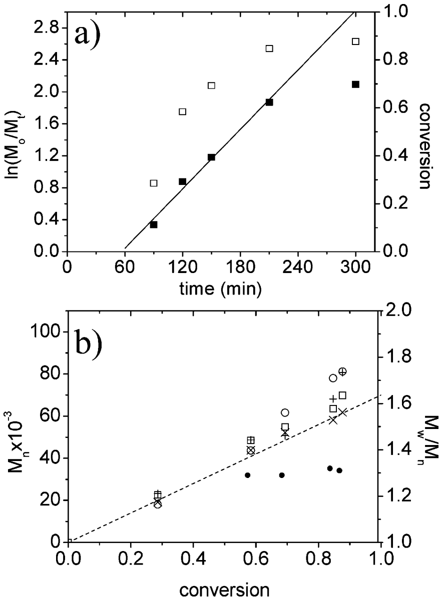

Figure 5. Polymerization of **M1** in water using initiator **V-545** and RAFT agent **CTA4** at 48 °C ([CTA]/[*I*] = 5/1). (a) (□) Conversion determined by gravimetry vs time, (■) $\ln(M_0/M_t)$ vs time, the solid line is the linear fit of $\ln(M_0/M_t)$ vs time data (without point at 300 min). (b) Evolution of M_n and M_w/M_n with conversion; meaning of symbols as in Figure 4c and d.

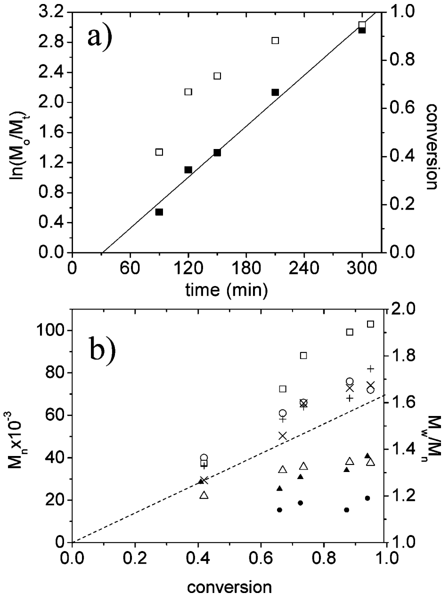

Figure 6. Polymerization of **M8** in water using initiator **V-545** and RAFT agent **CTA4** at 48 °C ([CTA]/[*I*] = 5/1). (a) (□) Conversion determined by gravimetry vs time, (■) ln(M_0/M_t) vs time, the solid line is the linear fit of ln(M_0/M_t) vs time data. (b) Evolution of M_n and M_w/M_n with conversion, (△) M_n according to calibration with **P2VP** standards, (▲) polydispersity according to calibration with **P2VP** standards; meaning of other symbols as in Figure 4c and d.

For the last sample taken after 300 min of polymerization (which does not fit to first-order kinetics any more), the M_n value calculated from the 489 nm band is somewhat higher than that derived from the 251 nm band as well as that of the theoretical value. This discrepancy may reflect a partial loss of dithioester end groups at extended reaction times, e.g., because of hydrolysis.

The cationic acrylate **M8** was polymerized at 48 °C in water by employing **CTA4** and **V-545** (Figure 6). The polymerization proceeds to 90% conversion within a few hours and follows pseudo-first-order kinetics up to high conversion after an initial retardation period of about 30 min (Figure 6a). Again, the ASEC elugrams shift steadily to lower elution volumes with increasing conversion. Evaluation of the MALLS data (Figure 6b) shows a linear increase in the molar mass, close to that theoretically expected, and low polydispersities of about 1.15. An attempted calibration of the ASEC with poly(2-vinylpyridine) standards indicated rather low polydispersities (about 1.35) and molar masses increasing linearly with the conversion, too. However, the apparent M_n values are considerably lower than the values derived from MALLS (by a factor of 2), as the polymer standard is not appropriate. In contrast, M_n values calculated by end-group analysis both from the dithioester band at 485 nm and the naphthalene band at 251 nm, agree well with the ASEC and theoretical numbers (Figure 6b), indicating good preservation of the dithioester end group during the polymerization process. In the case of **poly-M8**, however, the UV data for the absorbance of the mixed band at 301 nm give only approximate M_n values that exceed systematically the ones derived from the other analytical data. This may be explained by the observed slight broadening of this mixed band in the polymer, which probably reduces the apparent extinction coefficient at the maximum wavelength of 301 nm somewhat, thus pretending higher molar masses.

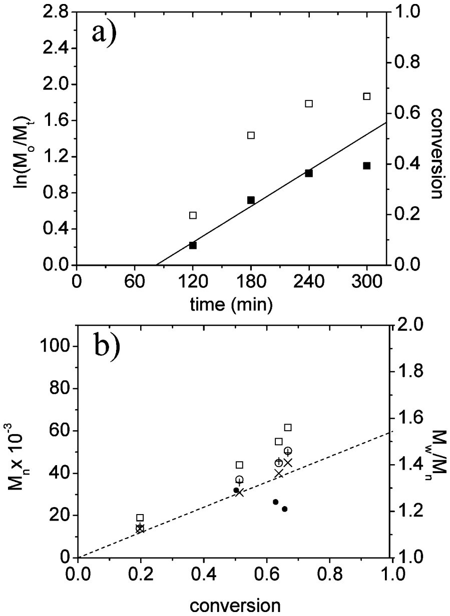

Figure 7. Polymerization of **M9** in water using initiator **V-545** and RAFT agent **CTA4** at 48 °C ([CTA]/[*I*] = 5/1). (a) (□) Conversion determined by gravimetry vs time, (■) ln(M_0/M_t) vs time, the solid line is the linear fit of ln(M_0/M_t) vs time data (without data point at 300 min). (b) Evolution of M_n and M_w/M_n with conversion; meaning of symbols as in Figure 4c and d.

The aqueous RAFT polymerization of cationic acrylamide **M9** using **CTA4** and **V-545** at 48 °C was attempted at pH = 6 and pH = 3.2, adjusting the pH of the solutions by addition of small quantities of NaOH and HCl, respectively. No polymer could be obtained at pH 6, even after 300 min of reaction, but the polymerization carried out at pH 3.2 was successful. After a retardation period of around 70 min, polymerization goes up to about 70% conversion within 5 h (Figure 7a). The kinetics deviate from pseudo-first-order beyond 60% conversion. The ASEC traces show a shift of the peak to lower elution volumes, i.e., a steady evolution of molar mass with conversion until 240 min, after which the molar masses stagnate. Nevertheless, the evaluation of the data in Figure 7b shows a linear increase in the molar mass, close to the theoretically expected one, according to MALLS and to end-group analysis using the dithioester band at 485 nm and the naphthalene band at 251 nm, with polydispersities of 1.2 according to MALLS. As for the cationic polyacrylate **poly-M8**, an attempted calibration of the ASEC with poly(2-vinylpyridine) standards exhibited a linear increase of the molar masses of **poly-M9** with conversion. However, the apparent M_n values are lower by a factor of 2 than the values derived from MALLS, indicating that the polymer standard is not appropriate. The apparent polydispersity is relatively high at about 1.5. Also, analogous to the polyacrylate **poly-M8**, the UV data for the less-reliable mixed band at 301 nm provided in the case of **poly-M9** values for M_n that exceed systematically the ones derived from the other analytical data. Once more, the extinction coefficient seems to differ in the RAFT agent and in the polymer, presumably because of broadening of the mixed band (vide supra).

3.3. Aqueous RAFT Polymerization of Styrenic Monomers. RAFT agents that are effective in the

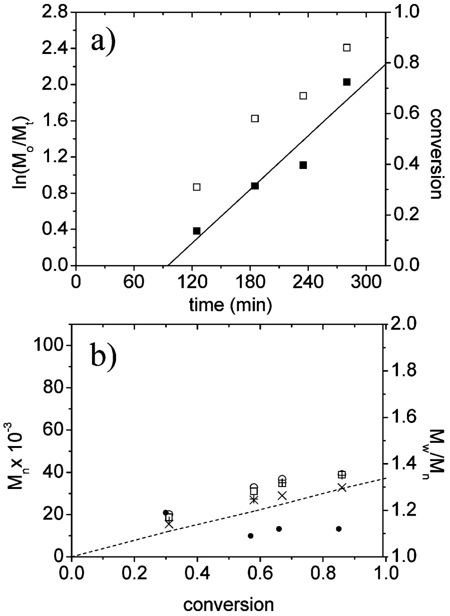

Figure 8. Polymerization of **M12** in water using initiator **V-545** and RAFT agent **CTA4** at 48 °C ([CTA]/[*I*] = 5/1). (a) (□) Conversion determined by gravimetry vs time, (■) ln(M_0/M_t) vs time, the solid line is the linear fit of ln(M_0/M_t) vs time data. (b) Evolution of M_n and PDI (M_w/M_n) with conversion; meaning of symbols as in Figure 4c and d.

polymerization of acrylates are generally effective in the polymerization of styrene derivatives, too. Therefore, controlled radical polymerization of the cationic styrene **M12** was investigated in aqueous solution with **CTA4** and **V-545** at 48 °C (Figure 8). Note that successful aqueous RAFT polymerization of **M12** has been reported before with **CTA1** and **CTA5**[15,16,23] but at higher temperatures. Though the polymerization is retarded by ~90 min, it follows pseudo-first-order kinetics later on, the conversion reaching about 90% after 5h. The ASEC traces show the continuous shift to smaller elution volumes with increasing time, and the derived M_n values grow linearly with conversion with good agreement of the values calculated from theory, from MALLS data, and from UV−vis bands at 490, 251, and 301 nm, respectively (Figure 8b). Polydispersities are about 1.1 even at high conversions, according to MALLS.

Similar to **M12**, the RAFT polymerization of the anionic styrene sulfonate **M7** proceeded smoothly in aqueous solution using **CTA4** and **V-545** at 55 °C, corroborating previous studies on the RAFT polymerization of **M7** employing **CTA1**.[23,24] Figure 2c exemplifies the usefulness of the naphthalene end group as a fluorescence label that is incorporated into the polyelectrolyte via the initiating group "R". In good agreement with the theoretically expected value, molar mass determination by end-group analysis gave identical M_n values when using both the visible band of the dithioester unit at 488 nm and the band at 251 nm of the naphthalene chromophore even at high conversions of 90%, demonstrating the good preservation of the dithioester end group.

The smooth RAFT polymerization of **M12** stimulated us to use **poly-M12** as a macro chain transfer agent for the synthesis of double-hydrophilic block copolymers. In a preliminary experiment, we studied the blocking of dimethylacrylamide because dimethylacrylamide was successfully blocked on polystyrene macro chain transfer agents by RAFT in organic solvents.[25,26] However, **poly-M12** was reported to act only poorly as a macro chain transfer agent for adding a second block of dimethylacrylamide in aqueous solution.[16] The failure was attributed to a preferential fragmentation of the intermediate radical formed during the preequilibrium of the blocking copolymerization.[16] Therefore, a sample obtained from the kinetic study of **M12** (**poly-M12-CTA**, M_n = 27 000, polydispersity 1.1) was used as a macroRAFT agent for the polymerization of dimethylacrylamide. The second polymerization step was conducted for 6 h to achieve high conversion, to increase the molar mass by the blocking experiment substantially, and thus, simplify polymer analysis. According to elemental analysis, the polymer product is composed of 25 wt % of **M12** and 75 wt % of dimethylacrylamide; the integration of the signals of the ^{1}H NMR spectrum is in good agreement.

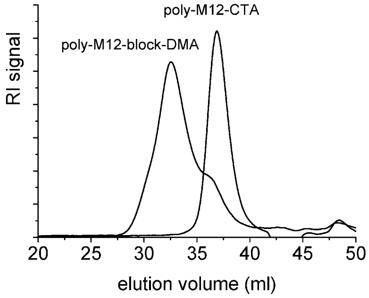

Figure 9. ASEC traces (eluent: 0.2 M of Na_2SO_4 in 1 wt % aq acetic acid) of macroRAFT agent **poly-M12-CTA** (sample from kinetic study 185 min M_n MALLS = 33 000, PDI MALLS = 1.13, M_n estimated as 27 300 by end-group analysis using the visible band absorption at λ_{max} = 490 nm of the dithioester end group) and **poly-M12**-*block*-poly(dimethylacrylamide) with M_n = 125 000 (by MALLS) and polydispersity of PDI 1.39 (MALLS).

Figure 9 compares the ASEC traces of the macroRAFT agent and block polymer. The signal of the polymer after the blocking experiment is shifted to lower elution volumes (V_e = 32.6 mL) compared to the signal of the macroRAFT agent **poly-M12-CTA** (V_e = 37.1 mL) but shows a shoulder at intermediate elution volume (V_e = 36.4 mL). The nearly complete disappearance of the signal of the original macroRAFT agent, together with the high UV signal of the new peak that is characteristic for the **poly-M12** block (but not for poly(dimethylacrylamide)), indicates a high blocking efficiency. The shoulder in the elugram is putatively attributed to a small amount of inactive **poly-M12** homopolymer because of termination reactions by combination. Evaluation of the GPC elugrams by MALLS gave a nominal M_n of 124 000 for the synthesized diblock with a polydispersity of 1.39, keeping in mind that molar mass determination of block copolymers by light scattering is a critical issue. Assuming that the molar mass of the **poly-M12** block has not changed during reaction and work up, the block copolymer should have a molar mass of M_n = 107 000 on the basis of elemental analysis (25 wt % of **poly-M12** block, 75 wt % of poly(dimethylacrylamide) block). The evaluation of the block copolymer by end-group determination via the UV band at 251 nm (naphthyl chromophore), made possible by using the labeled **CTA4** in the synthesis of the macroRAFT agent, gives a value of 93 000 for M_n. In contrast, end-group analysis via the dithiobenzoate end group was not possible because the prolonged polymerization conditions had led to marked discoloration of the polymers, i.e., to a marked loss of the

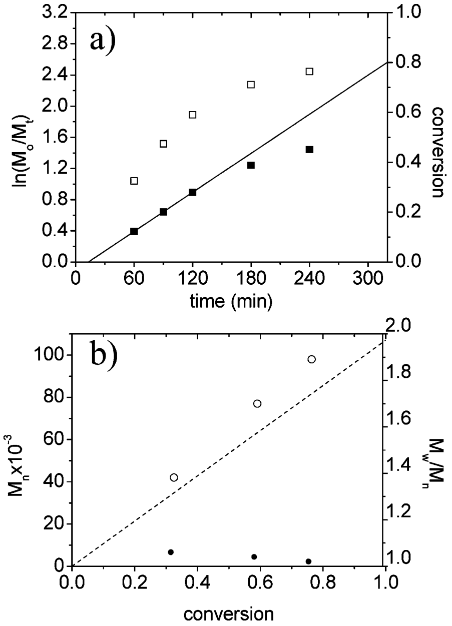

Figure 10. Polymerization of **M5** in water using initiator **V-50** and RAFT agent **CTA1** at 55 °C ([CTA]/[*I*] = 3.7). (a) (□) Conversion determined by gravimetry vs time, (■) ln(M_0/M_t) vs time, the solid line is the linear fit of ln(M_0/M_t) vs time data. (b) Evolution of M_n and M_w/M_n with conversion; meaning of symbols as in Figure 4c.

dithiobenzoate end groups. In light of the inherent difficulties to evaluate GPC/MALLS data from copolymers, the agreement of the M_n values derived from the various analytical methods is good.

3.4. Aqueous RAFT Polymerization of Methacrylic Monomers. Whereas dithioesters with leaving groups R such as benzyl (as in **CTA5**) or propion-2-yl (as in **CTA2** or in **CTA4**) are known as efficient RAFT agents for styrenic and acrylic monomers, they are much less efficient in the case of methacrylic monomers.[1] Therefore, we investigated the usefulness of classical **CTA1** as well as of the new, permanently anionic dithiobenzoate **CTA3** for aqueous polymerizations at relatively low temperatures.

As the anionic methacrylate **M5** was mentioned briefly in successful RAFT polymerizations using **CTA1** at 70 °C before,[17] we performed the polymerization of **M5** at a lower temperature (55 °C) by using **CTA1** and **V-50** to see the effect of temperature (Figure 10). After a short retardation period of about 15 min, the polymerization of **M5** is relatively fast at 55 °C and follows pseudo-first-order kinetics until ~70% conversion but then deviates from this behavior (Figure 10a). The ASEC traces of the polymers obtained shift to lower elution volumes with increasing conversion as expected for controlled radical polymerization, and the evaluation by MALLS in Figure 10b shows linear growth of the molar mass close to the theoretically calculated values and low polydispersities (down to 1.05).

Having verified the basic usefulness of **CTA1** for the controlled radical polymerization of methacrylates in water even at lower temperatures than typically reported, nonionic macromonomer **M2** was polymerized in aqueous solution using **CTA1** and **V-50** at 55 °C, as shown in Figure 11. **M2** is the methacrylate analogue of the acrylate macromonomer **M1** studied above, and has a similar potential as a functional monomer. After a retardation of about 25 min, a rapid polymerization is observed following pseudo-first-order kinetics (Figure 11a). The SEC traces of the polymer samples in THF exhibit a continuous shift toward lower elution volumes with the reaction time. Evaluating the SEC data by calibration with polystyrene standards, polydispersities are about 1.1. The apparent M_n values increase linearly with increasing conversion but are smaller by a factor of 3 than the theoretically calculated ones. As found for the analogous polyacrylate **poly-M1** (vide supra), polystyrene is a poor standard for **poly-M2**. The molar mass M_n was, therefore, additionally determined by analysis of the dithioester end-group visible band using the visible band with λ_{max} = 509 nm, providing values (M_n = 56 000 at 73% conversion) that are close to the theoretically calculated ones.

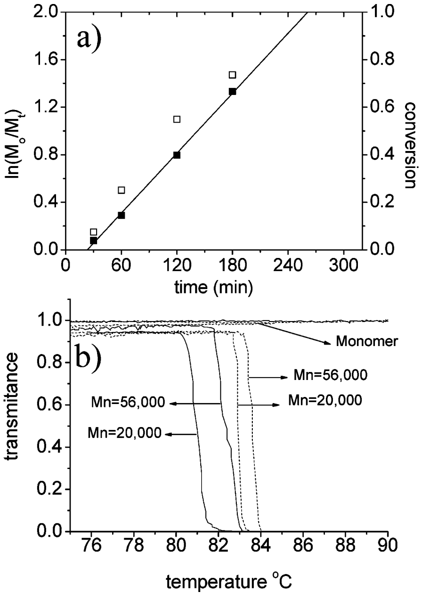

Figure 11. Polymerization of **M2** in water using initiator **V-50** and RAFT agent **CTA1** at 55 °C ([CTA]/[*I*] = 3.8). (a) (□) Conversion vs time (conversion values determined by using IR signal ratios of monomer and polymer obtained from SEC), (■) ln(M_0/M_t) vs time, the solid line is the linear fit of ln(M_0/M_t) vs time data. (b) Transmittance vs temperature curves (1 °C/min dotted line: heating; solid line: cooling) of 1 wt % aq solutions of of **poly-M2** with different molar masses according to end-group analysis.

When heating polymethacrylate **poly-M2**, we observed a cloud point at 83−84 °C (Figure 11b), in contrast to polyacrylate **poly-M1** that gives transparent aqueous solutions up to 95 °C. The thermal transition of **poly-M2** is reversible, with a small hysteresis in the heating and cooling cycles. The effect of the molar mass on the cloud point is small. This makes **poly-M2** attractive as an alternative thermally sensitive smart polymer.

The utility of the new, pH-independent water-soluble RAFT agent **CTA3** was investigated in the polymerization of the cationic methacrylate **M10** using initiator **V-50** at 55 °C. The polymerization is rapid after a short retardation period, reaching 80% conversion within less than 4 h. The plot of reaction time vs ln(M_0/M_t) and conversion in Figure 12a illustrates that the reaction follows pseudo-first-order kinetics. Although ASEC analysis of **poly-M10** samples that are produced by conventional free-radical polymerization works correctly, the ASEC analysis of the polymers obtained by controlled radical polymerization with **CTA3** failed. Under the conditions needed to make the polymers pass through the columns, very high apparent molar masses

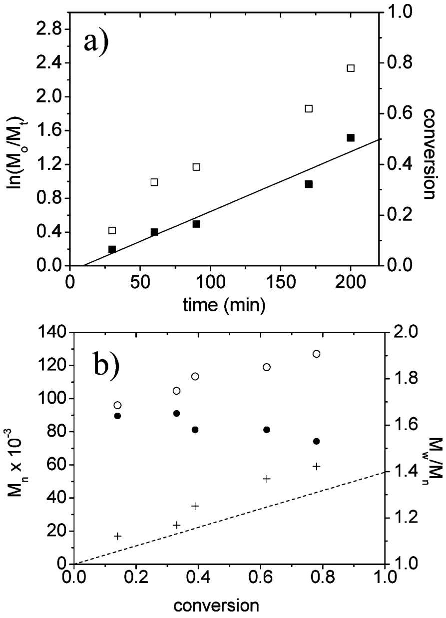

Figure 12. Polymerization of **M10** in water using initiator **V-50** and RAFT agent **CTA3** at 55 °C ([CTA]/[I] = 5/1). (a) (□) Conversion vs time, (■) ln(M_0/M_t) vs time, the solid line is the linear fit of ln(M_0/M_t) vs time data. (b) Evolution of M_n and M_w/M_n with conversion; meaning of symbols as in Figure 4c and d.

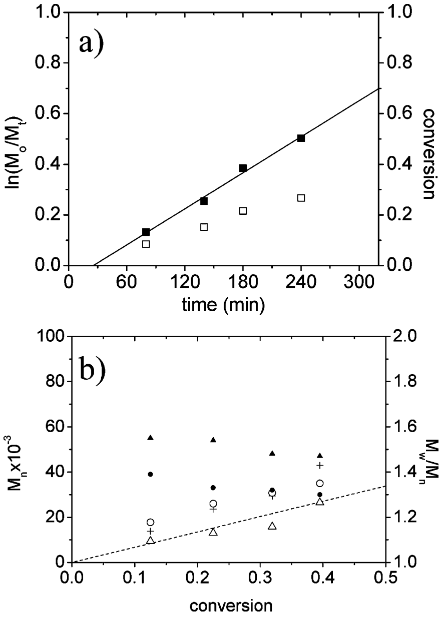

Figure 13. Polymerization of **M11** in water using initiator **V-50** and RAFT agent **CTA3** at 55 °C ([CTA]/[I] = 5/1). (a) (□) Conversion vs time, (■) ln(M_0/M_t) vs time, the solid line is the linear fit of ln(M_0/M_t) vs time data. (b) Evolution of M_n and M_w/M_n with conversion; meaning of symbols as in Figures 4c and 6b.

and relatively high apparent polydispersities were found, which changed only slightly with monomer conversion (Figure 12b). These findings are attributed to polymer aggregates in the high ionic strength eluent, presumably formed because of the electrostatic interaction of the anionic end groups with the cationic polymer. This aggregation is also evident by dynamic light scattering when changing the solvent from pure water to the ASEC eluent. In this situation, molar mass analysis by end-group determination proved most helpful; the M_n values derived from the absorbance of the dithioester band at 493 nm evolve linearly with conversion and are close to the theoretically calculated ones (Figure 12b).

The usefulness of the new RAFT agent **CTA3** was subsequently investigated in the aqueous polymerization of the cationic methacrylamide **M11** using initiator **V-50** at 55 °C. Similar to the polymerization of the analogous acrylamide **M9,** the polymer was only obtained when polymerizing at pH = 4 (Figure 13), but not at pH = 6. The reaction of **M11** shows a retardation time of ~30 min and is slow in comparison with the cationic methacrylate **M10**, reaching only 50% conversion after 4 h, while following pseudo-first-order kinetics (Figure 13a). The ASEC traces present a continuous shift to lower elution volumes. The evaluation of the data by MALLS gives a linear increase of the molar mass. The calculated M_n values are in good agreement with those determined by end-group analysis using the dithioester band at 497 nm (Figure 13b) with polydispersities between 1.3 and 1.4. However, the determined M_n values are systematically about 20% higher than the theoretically calculated values. Calibration of the ASEC with poly(2-vinylpyridine) standards corroborated the linear increase of the molar mass and gave good agreement of the apparent M_n values with the theoretically calculated ones and indicated polydispersities between 1.4 and 1.5.

CTA3 was also engaged in attempts to polymerize the unsubstituted methacrylamide **M3** using initiator **V-50** at 55 °C at pH values of 6.2, 5.4, and 3. As for acrylamide, **M3** is inherently difficult for RAFT polymerization because of the risk of slow hydrolysis of the primary amide and subsequent aminolysis of the dithioester group.[12,14,19] Indeed, even after 8 h of reaction, only traces of colorless polymers (conversion less than 2%) were obtained at a pH of 6.2 and 5.4. However, polymerization worked out at pH = 3, where **CTA3** is easily water soluble (different from **CTA1**), though rate of the reaction is slow compared to the other polymerizations conducted at 55 °C in our study. The reaction seems to follow pseudo-first-order kinetics for up to 6 h after a retardation period of ~50 min (Figure 14a). However, the ASEC traces are very close to each other, and there is only a small shift toward low elution volumes with conversion. The M_n values determined from MALLS and end-group analysis with the band at 494 nm show a continuous increase (Figure 14b) but deviate by a factor of 2 from the theoretical values, while the calculated polydispersities are about 1.4.

3.5. Attempted Aqueous RAFT Polymerization of Other Monomers. The parent compound 2-vinyl pyridine was reported to undergo successful controlled radical polymerization by RAFT, at least in bulk.[27] Therefore, controlled radical polymerization using RAFT agent **CTA4** and initiator **V-545** in an aqueous solution was attempted for monomer **M13**, the sterically demanding betaine derivative of 2-vinyl pyridine whose polymer is not soluble in standard organic solvents, at 55 °C. However, no polymer was obtained, although **M13** polymerizes in the absence of the RAFT agent under similar conditions. Additional attempts to polymerize the monomer in the presence of the RAFT agents **CTA3** and **CTA5** using the initiator **V-50** failed, too. Adjusting the pH to 4, as was found helpful in the case of acrylamide **M9**, did not improve the situation either. We noted that, in all cases, the reaction mixture became

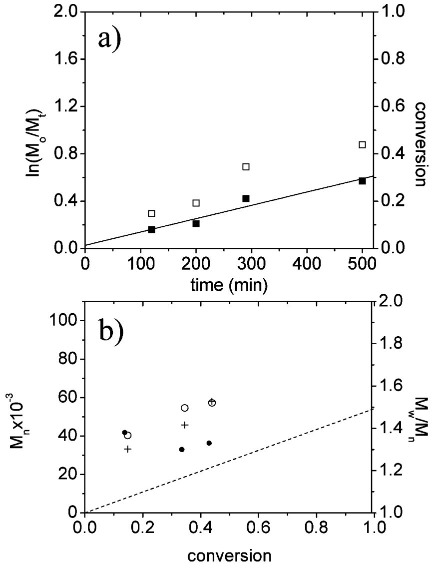

Figure 14. Polymerization of **M3** in water using initiator **V-50** and RAFT agent **CTA3** at 55 °C ([CTA]/[*I*] = 5/1). (a) (□) Conversion vs time, (■) $\ln(M_0/M_t)$ vs time, the solid line is the linear fit of $\ln(M_0/M_t)$ vs time data. (b) Evolution of M_n and M_w/M_n with conversion; meaning of symbols as in Figure 4c.

discolored after prolonged times, indicating the degradation of the dithiobenzoate group. We have no satisfactory explanation yet for this finding, as the RAFT agents were stable in the case of the other monomers studied under comparable conditions. The zwitterionic moiety as such cannot be responsible, as several zwitterionic monomers have been polymerized successfully by RAFT in the past.[28,29,30]

The itaconate **M6** bears two sulfonate groups and, thus, is an interesting speciality to confer high anionic charge density and hydrophilicity to polymers, but reports on **poly-M6** are scarce.[31−33] Therefore, the polymerization of **poly-M6** in water via RAFT was attempted using **CTA1**, **CTA3**, and **CTA5** at 55 °C (cf. Table 1), but none of these trials produced the polymer. In contrast to the attempted RAFT polymerization of **M13**, the red color of the solutions was not lost throughout the polymerization reactions, suggesting that hydrolysis, etc., of the RAFT agents cannot be blamed for the failure. In a control experiment, the classical free-radical polymerization of **M6** under comparable conditions (2.2 mmol of **M6,** 7.36×10^{-5} mol of **V-50**, but no RAFT agent in 15 mL water at 55 °C) gave 17% conversion after 22 h. Therefore, we assume that controlled radical polymerization of **M6** by employing dithiobenzoate-derived RAFT agents at reduced temperatures is not possible in solution because of strongly reduced rates of polymerization. Therefore, the claims made in patents[34] on the utility of itaconates for aqueous RAFT polymerization must be taken with caution. A most recent study[35] on RAFT polymerization of itaconate diesters at 65 °C using various RAFT agents revealed the sluggishness of such polymerizations even in bulk and the need to carefully fine tune the stabilizing group ("Z-group") as well as the leaving group ("R-group") simultaneously when controlled radical polymerization of such monomers is intended.

4. Discussion

The results presented for the various representative water-soluble monomers and RAFT agents clearly demonstrate that controlled radical polymerization via RAFT is possible in aqueous solution for most systems with respect to polymerizable groups as well as hydrophilic moieties and including macromonomers such as **M1** and **M2**, which are attractive candidates for biomedical applications. Typically, molar masses follow pseudo-first-order kinetics up to reasonably high conversions, number average molar masses increase linearly with conversion, calculated M_n values are close to the theoretically expected ones, and polydispersities are low. Also, efficient synthesis of block copolymers is possible in aqueous solution using a macroRAFT agent. This implies that the known sensitivity of the $-C(=S)-S-$ moiety to hydrolysis is not an inherent obstacle to a versatile use of the RAFT method in aqueous solution. Concerning the choice of suited RAFT agents, all tested dithiobenzoates provided a priori reasonably well-controlled polymerization reactions, though retardation periods were observed in all cases. Still, for the controlled radical polymerization of a given monomer, the incorporation of an appropriate functionality on the initiating fragment ("R") or the active end group ("Z") in the RAFT agent may be important in addition to the appropriate choice of the active end group ("Z") that must match the polymerizable group to be effective. The use of RAFT agents bearing sulfonate groups has, for instance, the advantage to enable reactions even at low pH values as required for the polymerization of certain monomers, such as polymerizable tertiary amines.

In contrast to the analysis of standard polymers such as polystyrene, poly(methyl methacrylate), poly(butyl-acrylate), and the like, it is difficult to quantify precisely the perfection of the control on the aqueous polymerizations because the analysis of water-soluble polymers is troubled with problems and assumptions to be made. Therefore, the analytical data must be evaluated with care for detailed conclusions, and the analysis of each polymer system ought to be optimized individually. It is noteworthy that ASEC data evaluated by on-line MALLS analysis are not as reliable as often assumed because the various polymers of different structure may interact differently with the column material, thus modifying the elution behavior in an undesired way. Moreover, in model runs, MALLS seems to underestimate systematically the amount of low molar mass material in the ASEC instruments, giving apparently correct M_w values but too high M_n values.[15] Consequently, the apparent polydispersities in our studies are presumably somewhat too low (the true values are still very low compared to samples prepared without RAFT agent). Thus, subjecting our polymer samples to dialysis with a low molar mass cutoff membrane prior to ASEC to remove efficiently residual monomer that can interfere with the analysis virtually does not change the polydispersities determined. However, some polymer material may be lost by the work up of the polymerization mixtures so that the assumed conversions may be somewhat too low. Therefore, the small deviation of the obtained M_n values from the theoretically calculated molar mass frequently observed at high conversions may be at least partially apparent. In any case, as shown, the use of "general purpose" polymer standards for ASEC calibration or the switching to nonaqueous columns (if possible at all) does not improve the situation, but on the contrary, provides much less reliable figures of M_n, whereas they are useful for corroborating the polydispersities.

Keeping these analytical difficulties in mind, conclusions should be, therefore, on the basis of the combination of several analytical methods. In this respect, end-group analysis of the polymers in addition to the ASEC data proved to be most valuable, in particular when employing the chromophore labeled **CTA4**. The inherently present dithioester group is a useful label, too. Its visible band is in the range of 483−489 nm for acrylic polymers, about 490 nm for styrenic polymers, and 493−509 nm for methacrylic polymers (Table 3) and, thus, easy to follow. Despite some uncertainties about a strict constancy of the extinction coefficient of the C═S band in the visible due to a changing environment with ongoing polymerization, this specific end-group analysis of RAFT-made polymers works reasonably well for most systems up to 70% of conversion and beyond. The usefulness of end-group analysis is strikingly exemplified in the case of polycation **poly-M10**, obtained in the presence of the anionic **CTA3**, that forms big aggregates under our ASEC conditions. Aggregation is a widespread problem of polymers in aqueous solution but not always obvious. End-group analysis does not require molecular dissolution for determining the molar mass different from most other methods and, therefore, is still operative. When employing the chromophore-labeled **CTA4**, the combined end-group analysis of the initiating end group ("R") and the dithioester end group becomes possible and is most instructive; good agreement of both results and also with the theoretically expected molar mass indicates reliable meaningful data. In contrast, systematically higher values of M_n derived from analysis of the dithioester end group compared to the M_n values derived from analysis of the initiating end group ("R") and to the theoretical M_n values are a strong hint at an increasing loss of active dithioester chain ends. The utility of this test was exemplified by aminolyzing the dithioester end groups in the various samples obtained in the kinetic study of **M12** with **CTA4** by the addition of diethylamine. Whereas the M_n values calculated from the UV band at 251 nm (indicative of the naphthyl chromophore of the "R" group) stay constant, the apparent M_n values calculated from the mixed UV band at 301 nm, and even more the ones calculated from the visible dithioester band, increase steadily with increasing exposure to diethylamine.

Information on the extent of active end-group preservation is most valuable if the polymers made are intended to be used as macro-RAFT agents for the preparation of block copolymers. A closer look at the data exhibited in Figures 5b, 6b, and 7b suggests that, at prolonged reaction times, some dithioester end groups got lost. This underlines the advantageous use of low polymerization temperatures to minimize side reactions and the need of relatively fast polymerization rates. Within this reasoning, it is not surprising that (under the low-temperature conditions chosen) the slowly reacting methacrylamides **M3** and **M11** perform the least well in aqueous RAFT. In any case, the controlled radical polymerization of **M3** still needs optimization work concerning the best pH conditions, as additional problems due to hydrolysis of the primary amide moiety and subsequent aminolysis of the dithioesters under the conditions chosen might interfere (cf. work on poly(acrylamide) in ref 12).

In a preliminary experiment, we extended our homopolymerization studies to the aqueous synthesis of double-hydrophilic block copolymers using a macrochain transfer agent based on **poly-M12** onto which dimethylacrylamide was polymerized. The system was chosen because of apparently conflicting results in the literature. Whereas dimethylacrylamide was successfully blocked on polystyrene macro chain transfer agents by RAFT in organic solvents,[24,25] a recent report claimed that this very blocking sequence is troubled by inherent problems in aqueous systems. The difficulties were attributed to an unfavorable fragmentation equilibrium of the intermediate radicals formed by the addition of the growing polymer chain onto the RAFT agent in ref 16. It was concluded that only the reverse blocking sequence, namely poly(dimethylacrylamide)-*block*-**poly-M12**, using a macroRAFT agent poly(dimethylacrylamide)-**CTA** can be efficiently realized in water. But clearly, our results show that block copolymers **poly-M12**-*block*-poly(dimethylacrylamide) can be easily and efficiently prepared in aqueous solution using the macroRAFT agent **poly-M12-CTA**. This apparent contradiction of results is probably explained by a misinterpretation of the experiments.[16] In the study, the two macroRAFT agents employed were prepared differently; poly(dimethylacrylamide)-**CTA** was obtained by polymerization at 80°C for 3 h, whereas **poly-M12-CTA** was made by polymerization at 80°C for 24 h. Considering our findings concerning the sensitivity of the dithioester moiety toward hydrolysis, we believe that in the latter sample, many dithioester end groups had been hydrolyzed because of the prolonged polymerization time at high temperature. Evidently, this must result in poor blocking efficiency. In our study, **poly-M12-CTA** was made at 48 °C during about 3.5 h only, i.e., under conditions were hydrolysis is still negligible. This is evident from the double end-group analysis (via both the "R" and dithioester groups), indicating the virtually complete functionalization of the macroRAFT agent by the dithioester moiety. Consequently, successful blocking of dimethylacrylamide could be performed. Therefore, the hypothesis of a preferential fragmentation of intermediate RAFT radicals bearing an acrylic and a styrenic potential leaving group in favor of the styrenic group in aqueous solution[16] should be abandoned. The analysis of the block copolymer formed illustrates also that the use of simple and convenient polymerization conditions (high polymer yields, use of relatively small amounts of the precious macro-RAFT agent) convenes to obtain diblock copolymers. However, samples made in this way lose much of the RAFT end groups and, therefore, are no more suited for preparing triblock copolymers in a subsequent step.

5. Conclusions

A series of chain transfer agents, which are well-suited for RAFT polymerization of various types of monomers in aqueous solution, was synthesized. The new RAFT agents in this series bear permanent anionic groups so that they can be used at low pH values when necessary, i.e., under pH conditions where dithioester groups are most resistant to hydrolysis. Comparative stability tests suggest that the stability against hydrolysis of the dithioester moiety is improved by the presence of hydrophobic groups in the close vicinity. The various aqueous RAFT polymerizations performed present the typical features of controlled polymerization, such as pseudo-first-order kinetics up to high conversions, a linear increase of the number average molar mass with conversion, good agreement between experimentally determined and theoretically expected M_n values, low polydispersities, and efficient synthesis of block copolymers. Importantly, only analysis by several methods provided continuously reliable molar mass data. End-group analysis via the dithioester moiety works reasonably well. Moreover, when polymers are synthesized by using a RAFT agent that is labeled by a chromophore at the initiating end ("R"-group), both end groups can be quantified independently with simple UV−vis spectroscopic measurements. This allows the quantification of active, "dormant" end groups. High polymerization temperatures and prolonged reaction times increase the risk for hydrolysis of dithioester end groups of the dormant polymer chains. The RAFT polymerization in water yields well-defined polymers with (meth)acrylate-, acrylamide- and styrene-based water-soluble monomers at 48 and 55 °C. However, the rate of polymerization of methacrylamide-based monomers is very slow in the RAFT process at 55 °C. Since longer polymerization times are necessary to achieve high conversions, some termination reactions interfere with the polymerization in water. As a result, the control over methacrylamides is lower than that over methacrylate, acrylic, or styrenic analogues at 55 °C or lower temperatures in water.

Acknowledgment. We thank J. F. Baussard for the gift of **CTA5**. We gratefully acknowledge the help of J.-L. Habib-Jiwan (Université Catholique de Louvain) for taking FAB mass spectra, M. Kumke (University of Potsdam) for help with fluorescence measurements, S. Bruzzano (Fraunhofer IAP) for advice in aqueous SEC of polycations, and H. Schlaad, G. Rother, and M. Gräwert (Max-Planck-Institut für Kolloid- und Grenzflächenforschung, Potsdam) for help with SEC for polyanions and SEC in NMP. Financial support was provided by the Fraunhofer Society.

Supporting Information Available: ^{1}H NMR spectra of **CTA3** and **CTA4**; SEC elugrams of the data presented in Figures 5b−8b and 10b−14b. This material is available free of charge via the Internet at http://pubs.acs.org.

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MA048268O