Macromolecules

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Cyclodextrin-Complexed RAFT Agents for the Ambient Temperature Aqueous Living/Controlled Radical Polymerization of Acrylamido Monomers

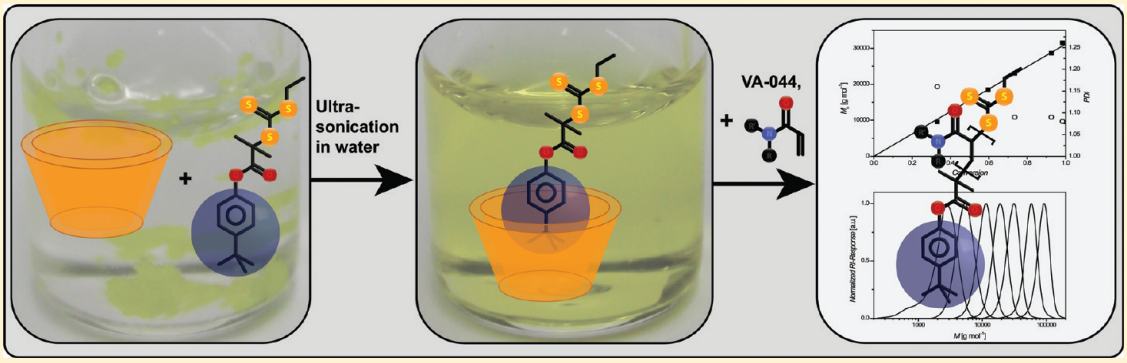
Bernhard V. K. J. Schmidt,[†] Martin Hetzer,[‡] Helmut Ritter,[*,‡] and Christopher Barner-Kowollik[*,†]

[†]Preparative Macromolecular Chemistry, Institut für Technische Chemie und Polymerchemie, Karlsruhe Institute of Technology (KIT), Engesserstr. 18, 76128 Karlsruhe, Germany

[‡]Lehrstuhl für Präparative Polymerchemie, Institut für Organische Chemie und Makromolekulare Chemie, Heinrich-Heine Universität, Universitätsstrasse 1, Geb. 26.33.00, 40225 Düsseldorf, Germany

Supporting Information

ABSTRACT:



The first aqueous reversible addition−fragmentation transfer (RAFT) polymerization of *N*,*N*-dimethylacrylamide (DMAAm), *N*,*N*-diethylacrylamide (DEAAm), and *N*-isopropylacrylamide (NIPAAm) utilizing host/guest complexes of cyclodextrin and hydrophobic chain transfer agents (CTAs) at 25 °C is described. Three novel guest-functionalized CTAs, namely 4-(*tert*-butyl)phenyl 2-(((ethylthio)carbonothioyl)thio)-2-methylpropanoate, bis(4-*tert*-butyl)benzyl carbonotrithioate, and benzyl (3-((4-(*tert*-butyl)phenyl)amino)-3-oxopropyl)carbonotrithioate, were synthesized and employed in aqueous RAFT polymerizations. The presented technique allows for the facile preparation of hydrophilic polymers with hydrophobic end groups in aqueous environments. The living/controlled radical polymerization afforded high molecular masses ($7500 \leq M_n \leq 116\,000$ g mol^{-1} for poly(DMAAm), $2500 \leq M_n \leq 150\,000$ g mol^{-1} for poly(DEAAm), and $4000 \leq M_n \leq 50\,000$ g mol^{-1} for poly(NIPAAm)) with low PDIs ($1.06 \leq$ PDI ≤ 1.54 for poly(DMAAm), $1.05 \leq$ PDI ≤ 1.39 for poly(DEAAm), and $1.15 \leq$ PDI ≤ 1.46 for poly(NIPAAm)). To confirm the living character of the polymerizations, kinetic measurements were undertaken that evidence a linear evolution of molecular weight with conversion. Furthermore, chain extensions were carried out that indicate a very high reinitiation efficiency (poly(DMAAm): from 10 500 to 97 500 g mol^{-1}, PDI = 1.08; poly(DEAAm): from 8500 to 83 000 g mol^{-1}, PDI = 1.13; poly(NIPAAm): from 9000 to 90 000 g mol^{-1}, PDI = 1.11). The resulting polymers were thoroughly characterized via *N*,*N*-dimethylacetamide (DMAc) size exclusion chromatography, ^{1}H NMR, and electrospray ionization-mass spectrometry (ESI-MS).

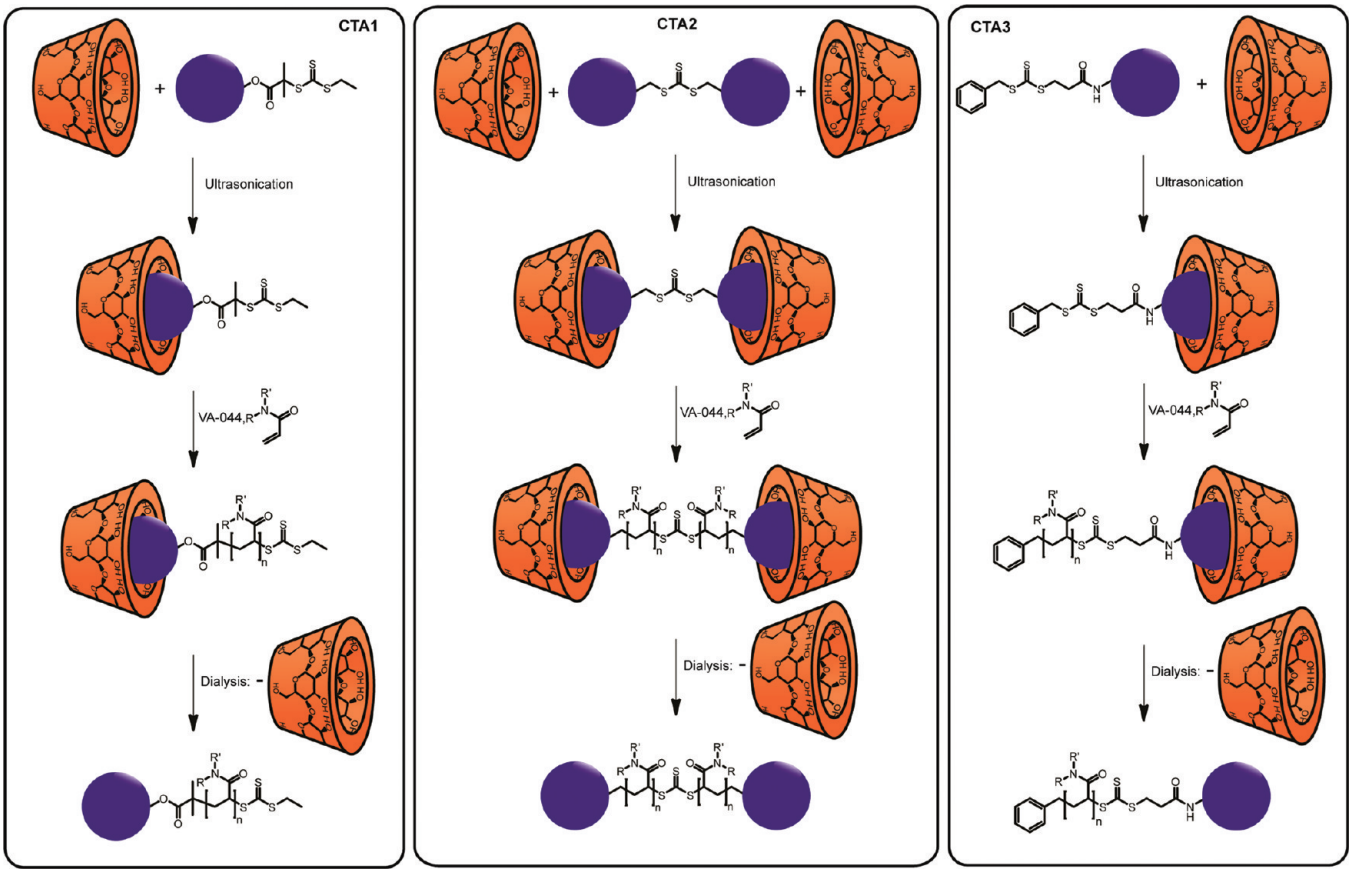
INTRODUCTION

Cyclodextrins play a significant role in current polymer research.[1,2] The ability of cyclodextrins to form supramolecular host/guest complexes with hydrophobic recognition sites such as adamantyl, 4-*tert*-butylphenyl, or isobornyl in aqueous solution leads to broad opportunities for the synthesis of complex macromolecular architectures. Recent examples are supramolecular block copolymers,[3,4] the connection of cyclodextrin-centered stars with guest endfunctionalized polymers,[5] cyclodextrin/guest networks,[6] or supramolecular grafting.[7] A variety of applications are proposed for macromolecular systems containing cyclodextrins including drug delivery,[8] supramolecular hydrogels,[9] supramolecular polymers,[10] polymer/enzyme conjugates,[11] or optical receptors.[12] Furthermore, cyclodextrins are obtained from starch making it a renewable resource, and its applications are thus highly interesting from the point of sustainability.[1]

Controlled/living radical polymerization is a versatile tool for the preparation of complex macromolecular architectures, e.g.,

Received: May 26, 2011
Revised: August 12, 2011
Published: August 25, 2011

Scheme 1. Procedure for the RAFT Polymerization of Acrylamido Monomers with Cyclodextrin-Complexed CTAs[a]



[a] DMAAm: R = R′ = Me; DEAAm: R = R′ = Et; NIPAAm: R = *i*-Pr, R′ = H: R-approach (**CTA1**), Z-approach (CTA3), and combined approach (**CTA2**). The guest substituent, e.g. 4-*tert*-butylphenyl, is depicted in blue.

brushes, block copolymers, and bioconjugates. Molecular weight control and low polydispersity as well as control over the polymer end groups can be accomplished via nitroxide-mediated radical polymerization,[13,14] atom transfer radical polymerization,[15,16] or the reversible addition−fragmentation transfer (RAFT) process.[17−21] In particular, RAFT polymerization has emerged as a very efficient tool for the synthesis of water-soluble polymers due to its high tolerance of functional monomers.[22−25] The polymerization itself can be conducted directly in water with a broad range of water-soluble monomers that include methacrylates,[26] methacrylamides,[27] styrenics,[28] acrylates,[29] and acrylamides[30−32] so far. Furthermore, the utilization of water is interesting from an environmental and economic point of view as water is nontoxic, nonflammable, and readily available. Thus, it is easy to handle safely and low priced.

The possibility to solubilize hydrophobic molecules in water is another interesting application of cyclodextrins. In this context hydrophobic monomers were solubilized in water with cyclodextrins, e.g., in radical polymerization,[33,34] living radical polymerization,[35−37] enzymatic polymerization,[38] and rhodium-catalyzed polymerization.[39] To connect the solubilizing effect of cyclodextrins with RAFT polymerization, we investigated the aqueous RAFT polymerization of three acrylamido monomers, namely *N,N*-dimethylacrylamide (DMAAm), *N,N*-diethylacrylamide (DEAAm), and *N*-isopropylacrylamide (NIPAAm), in the presence of a hydrophobic chain transfer agent (CTA) that is solubilized via a host/guest complex. The employed hydrophobic CTAs bear the 4-*tert*-butylphenyl group that is well-known for its stable host/guest complexes with β-cyclodextrins.[40,41] Three novel CTAs were synthesized, which contain the guest group in regions of variable reactivity within the molecule. The guest group can be incorporated in the R group, the Z group, or both. As the CTA allows control over the chain-end functionality in RAFT polymerization, hydrophobic chain ends are obtained directly (as depicted in Scheme 1).

The hydrophobic chain ends may have further use as guests in complex self-assemblies with cyclodextrin-functionalized polymers or surfaces e.g. to construct supramolecular block copolymers[3,4] or to obtain supramolecular grafting, e.g. on cellulose.[7] In the case of thermoresponsive polymers that show lower critical solution temperature (LCST) behavior such as poly(NIPAAm) or poly(DEAAm), it is well-known that hydrophobic end groups can induce a change in the observed LCST.[42−44] Therefore, a modulation of the thermoresponsivity of these polymers is possible. Furthermore, most water-soluble CTAs contain carboxylic acid or sulfonic acid groups which lead to acid-functionalized polymers.[23,30,45] In cases where acid-functionalized water-soluble polymers—e.g., because of unspecific interactions in biological systems—are undesirable, a polymer analogous removal/modification is required which can be complicated depending on the reaction type. Therefore, it is interesting to study the polymerization via hydrophobic guest-functionalized CTA/cyclodextrin

complexes in water. Our current approach provides the opportunity to create hydrophilic polymers without acidic end groups in one step.

In the current contribution we thus describe the first aqueous RAFT-mediated polymerization of hydrophilic monomers employing a supramolecular cyclodextrin/CTA host/guest complex utilizing 4-*tert*-butylphenyl-substituted CTAs. The presented approach is the first methodology that leads to hydrophilic polymers with hydrophobic end groups in one step via aqueous RAFT polymerization. High molecular weights and conversions were reached at 25 °C with good control over polydispersity and molecular weight as determined via *N*,*N*-dimethylacetamide (DMAc) size exclusion chromatography. Furthermore, we describe the first—to the best of our knowledge—living radical polymerization of DEAAm in aqueous solution. The structure of the synthesized polymers was confirmed via electrospray ionization-mass spectrometry (ESI-MS) and ^{1}H NMR spectroscopy. The living character of the polymer chains was proven via chain extension experiments and the recorded evolution of the full molecular weight distribution with conversion. In addition, several methods for the postpolymerization removal of the cyclodextrins were studied.

EXPERIMENTAL PART

Materials. 2-Bromoisobutyric acid (Sigma-Aldrich, 98%), 3-bromopropionyl chloride (ABCR, 90%), 4-*tert*-butylbenzyl bromide (Acros, 97%), 4-*tert*-butylphenol (Sigma-Aldrich, 99%), 4-*tert*-butylaniline (Acros, 99%), 4-*tert*-butylbenzylmercaptan (Sigma-Aldrich, 99%), acetone (VWR, normapur), benzylmercaptan (Merck, synth. grade), carbon disulfide (Acros, 99.9%), dichloromethane (DCM, Acros extra dry over molecular sieves), ethanethiol (Acros, 99%), ethyl acetate (VWR, normapur), hydroquinone (Fluka, 99%), $K_3PO_4 \cdot H_2O$ (Sigma-Aldrich, puriss.), randomly methylated β-cyclodextrin (Me-β-CD, average methylation grade 1.8 per glucose unit, pharmaceutical grade was a gift from Wacker), *n*-hexane (VWR, normapur), *N*,*N*′-dicyclohexylcarbodiimide (DCC, ABCR, 99%), *N*,*N*-(dimethylamino)pyridine (DMAP, Sigma-Aldrich, 99%), silica gel (Merck, Geduran SI60. 0.063−0.200 mm), Taka-Diastase from *Aspergillus oryzae* (Sigma-Aldrich, 126 u mg^{-1}), tetrahydrofuran (THF, Acros extra dry over molecular sieves), triethylamine (Acros, 99%), and trifluoroacetic acid (ABCR, 99%) were used as received. 2,2′-Azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044, Wako, 99%) was recrystallized twice from methanol. *N*,*N*-diethylacrylamide (DEAAm, TCI, 98%), *N*,*N*-dimethylacrylamide (DMAAm, TCI, 99%), and 1,4-dioxane (VWR, HPLC-grade) were passed over a short column of basic alumina prior to use. *N*-isopropylacrylamide (NIPAAm, Acros, 99%) was recrystallized twice from *n*-hexane. Acetic acid/acetate buffer had a pH of 5.2 with an acetic acid (Roth, 99%) concentration of 0.27 mol L^{-1} and a sodium acetate (Roth, 99%) concentration of 0.73 mol L^{-1}.

Synthesis of 2-(((Ethylthio)carbonothioyl)thio)-2-methylpropanoic Acid (EMP). In a 100 mL round-bottom flask ethanethiol (1.4 mL, 18.91 mmol, 1.2 equiv) was dissolved in a suspension of $K_3PO_4 \cdot H_2O$ (4.27 g, 18.57 mmol, 1.1 equiv) in acetone (60 mL) at ambient temperature. After stirring for 20 min at ambient temperature carbon disulfide (3.0 mL, 49.69 mmol, 3.0 equiv) was added, and the solution turned yellow. 2-Bromoisobutyric acid (2.74 g, 16.41 mmol, 1.0 equiv) was added after 20 min, and the mixture was stirred at ambient temperature overnight. HCl (200 mL, 1 mol L^{-1}) was added, and the aqueous phase was extracted with DCM (2 × 150 mL). The combined organic extracts were washed with deionized H_2O (75 mL) and brine (75 mL), dried over Na_2SO_4, and filtered. After evaporation of the solvent the yellow oily residue was purified via column chromatography on silica gel with *n*-hexane:ethyl acetate 1:2 as eluent. The yellow fractions were combined and evaporated, and the residue was recrystallized from *n*-hexane at 40 °C to give the product as yellow crystals (2.71 g, 12.09 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): [δ, ppm] = 1.27 (t, 3H, CH_3), 1.66 (s, 6H, C−(CH_3)$_2$), 3.23 (q, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): [δ, ppm] = 11.9 (CH_3), 24.2 (C−(CH_3)$_2$), 30.3 (CH_2), 54.6 (C−(CH_3)$_2$), 177.9 (C═O), 219.6 (C═S). ESI-MS: $[M + Na^+]_{exp}$ = 247.09 *m*/*z* and $[M + Na^+]_{calc}$ = 246.990 *m*/*z*.

Synthesis of 4-(*tert*-Butyl)phenyl 2-(((Ethylthio)carbonothioyl)thio)-2-methylpropanoate (CTA1). In a 50 mL Schlenk flask 2-(((ethylthio)carbonothioyl)thio)-2-methylpropanoic acid (1.02 g, 4.55 mmol, 1.0 equiv), 4-*tert*-butylphenol (1.71 g, 11.38 mmol, 2.5 equiv), and DMAP (0.22 g, 1.80 mmol, 0.4 equiv) were dissolved in anhydrous DCM (20 mL). At 0 °C, a solution of DCC (1.90 g, 9.21 mmol, 2.0 equiv) in anhydrous DCM (12 mL) was added. After 1 h the solution was warmed to ambient temperature, stirred overnight, filtered, and concentrated under reduced pressure. The residual yellow oil was purified via column chromatography on silica gel with *n*-hexane:ethyl acetate 20:1 as eluent. The product was obtained as yellow oil which solidified upon cooling (1.54 g, 4.32 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): [δ, ppm] = 1.30 (s, 9H, (CH_3)$_3$), 1.34 (t, 3H, *J* = 7.4 Hz, CH_2−CH_3), 1.83 (s, 6H, C−(CH_3)$_2$), 3.32 (q, 2H, *J* = 7.4 Hz, CH_2), 7.00 (d, 2H, *J* = 8.8 Hz, C*H*−C−O), 7.37 (d, 2H, *J* = 8.8 Hz, *CH*−C−C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): [δ, ppm] = 12.9 (CH_3), 25.4 ((CH_3)$_2$), 31.3 ((CH_3)$_3$), 31.4 (CH_2), 34.5 (C−CH_3)$_3$), 55.8 (C−(CH_3)$_2$), 120.7 (CH−C−O), 126.2 (CH−C−C−(CH_3)$_3$), 148.7 (CH−C−O; C−C(CH_3)$_3$), 171.8 (C═O), 221.1 (C═S). ESI-MS: $[M + Na^+]_{exp}$ = 379.11 *m*/*z* and $[M + Na^+]_{calc}$ = 379.039 *m*/*z*.

Synthesis of Bis(4-*tert*-butyl)benzyl) Carbonotrithioate (CTA2). In a 50 mL round-bottom flask, 4-*tert*-butylbenzylmercaptan (1.0 mL, 5.36 mmol, 1.0 equiv) was dissolved in a suspension of $K_3PO_4 \cdot H_2O$ (1.39 g, 6.02 mmol, 1.1 equiv) in acetone (20 mL) at ambient temperature. After stirring for 10 min at ambient temperature carbon disulfide (1.0 mL, 16.56 mmol, 3.1 equiv) was added, and the solution turned yellow. 4-*tert*-Butylbenzyl bromide (1.0 mL, 5.44 mmol, 1.0 equiv) was added after 10 min, and the mixture stirred at ambient temperature overnight. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The yellow oily residue was purified via column chromatography on silica gel with *n*-hexane as eluent. A yellow oil was obtained which solidified upon cooling (1.82 g, 4.52 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): [δ, ppm] = 1.30 (s, 18H, C−(CH_3)$_3$), 4.59 (s, 4H, CH_2−S), 7.25−7.29 (m, 4H, *CH*), 7.31−7.36 (m, 4H, *CH*). ^{13}C NMR (100 MHz, $CDCl_3$): [δ, ppm] = 31.3 (CH_3), 34.6 (C−(CH_3)$_3$), 41.3 (CH_2), 125.7 (CH), 129.0(CH), 131.8 (C−C−(CH_3)$_3$), 150.8 (C−CH_2), 223.2 (C═S). ESI-MS: $[M + Na^+]_{exp}$ = 424.99 *m*/*z* and $[M + Na^+]_{calc}$ = 425.141 *m*/*z*.

Synthesis of 3-Bromo-*N*-(4-(*tert*-butyl)phenyl)propanamide. In a 100 mL Schlenk flask 4-*tert*-butylaniline (1.5 mL, 9.42 mmol, 1.0 equiv) and triethylamine (1.9 mL, 13.60 mmol, 1.4 equiv) were dissolved in anhydrous THF (30 mL). At 0 °C, 3-bromopropionyl chloride (1.3 mL, 13.14 mmol, 1.4 equiv) in anhydrous THF (15 mL) was added dropwise and stirred at ambient temperature overnight. Saturated $NaHCO_3$ solution (180 mL) was added and extracted with DCM (2 × 180 mL). The combined organic extracts were washed with deionized H_2O (180 mL) and brine (180 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The solid residue was recrystallized twice from *n*-hexane:ethyl acetate 5:1 to give the product as pale yellow crystals (1.37 g, 4.83 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): [δ, ppm] = 1.30 (s, 9H, (CH_3)$_3$), 2.92 (t, 2H, *J* = 6.6 Hz, CH_2−C═O), 3.71 (t, 2H, *J* = 6.6 Hz, CH_2Br), 7.34, (d, 2H, *J* = 8.5 Hz, C*H*−C−(CH_3)$_3$), 7.38 (N*H*), 7.44 (d, 2H, *J* = 8.5 Hz, C*H*−CNH). ^{13}C NMR (100 MHz, $CDCl_3$): [δ, ppm] = 27.2 (CH_2−Br), 31.3 (C−(CH_3)$_3$), 34.4 (C−(CH_3)$_3$), 40.7 (CH_2−C═O), 119.9 (CH−C−NH), 125.9 (CH−C−C−(CH_3)$_3$),

134.8 (*C*−NH), 147.8 (*C*−C−$(CH_3)_3$), 167.9 (*C*═O). ESI-MS: $[M + Na^+]_{exp}$ = 306.12 *m*/*z* and $[M + Na^+]_{calc}$ = 307.182 *m*/*z*.

Synthesis of Benzyl (3-((4-(*tert*-butyl)phenyl)amino)-3-oxopropyl) Carbonotrithioate (CTA3). In a 50 mL round-bottom-flask benzylmercaptan (498 μL, 4.23 mmol, 1.0 equiv) was dissolved in a suspension of $K_3PO_4 \cdot H_2O$ (1.08 g, 4.69 mmol, 1.1 equiv) in 25 mL of acetone at ambient temperature. After stirring for 10 min at ambient temperature carbon disulfide (766 μL, 12.69 mmol, 3.0 equiv) was added, and the solution turned yellow. 3-Bromo-*N*-(4-(*tert*-butyl)-phenyl)propanamide (1.20 g, 4.23 mmol, 1.0 equiv) was added after 10 min, and the mixture was stirred at ambient temperature overnight. HCl (160 mL, 1 mol L^{-1}) was added and extracted twice with DCM (2 × 160 mL). The combined organic extracts were washed with deionized H_2O (160 mL) and brine (160 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The solid residue was recrystallized from *n*-hexane:ethyl acetate 1:1 to give the product as a yellow solid in two fractions (1.21 g, 3.00 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): [δ, ppm] = 1.30 (s, 9H, $(CH_3)_3$), 1.60 (s, 1H, N*H*), 2.79 (t, 2H, *J* = 7.0 Hz, C═O−CH_2), 3.73 (t, 2H, *J* = 7.0 Hz, S−CH_2−CH_2), 4.61 (s, 2H, CH_2), 7.25−7.45 (m, 9H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): [δ, ppm] = 31.3 (C−$(CH_3)_3$), 32.0 (CH_2−C═O), 34.4 (*C*−$(CH_3)_3$), 36.1 (CH_2−CH_2−S), 41.5 (CH_2), 119.8 (*C*H−C−NH), 125.9 (CH−C−C$(CH_3)_3$), 127.8 (*C*H), 128.7 (CH−*C*H−C−CH_2), 129.3 (CH−C−CH_2), 134.8, 134.9 (*C*−NH, *C*−CH_2), 147.6 (*C*−C−$(CH_3)_3$), 168.5 (*C*═O), 223.7 (*C*═S). ESI-MS: $[M + Na^+]_{exp}$ = 426.27 *m*/*z* and $[M + Na^+]_{calc}$ = 426.100 *m*/*z*.

Exemplary Procedure for the Polymerization of DMAAm (Refer to the Supporting Information for the Polymerization Procedure of DEAAm and NIPAAm). **CTA1** (4.9 mg, 0.014 mmol, 1.0 equiv) and Me-β-CD solution (40 wt % in deionized water, 228 mg, 0.070 mmol, 5.0 equiv) were added into a Schlenk tube. The two-phase mixture was ultrasonicated until a clear yellow solution was obtained. Subsequently, a stirring bar, DMAAm (274 mg, 2.77 mmol, 198.9 equiv), VA-044 (1.0 mg, 0.003 mmol, 0.2 equiv), and deionized H_2O (0.8 mL) were added. After three freeze−pump−thaw cycles the tube was sealed and placed into an oil bath at 25 °C and removed after 6 h. The tube was subsequently cooled with liquid nitrogen to stop the reaction. An NMR sample was withdrawn for the determination of conversion, inhibited with a pinch of hydroquinone (∼5 mg) and D_2O was added. A conversion of 88% was calculated based on the NMR data (see the Characterization Methods section for details of the calculation). The residue was dialyzed with a SpectraPor3 membrane (MWCO = 3500 Da) for 3 days at ambient temperature and for 2 days at 45 °C. The solvent was removed in vacuo to yield the polymer as a yellow solid (96 mg, 39%, GPC(DMAc): $M_{n,GPC}$ = 17 000 g mol^{-1}, PDI = 1.09).

In the case of short-chain polymers (with targeted M_n below 3500 g mol^{-1}) the reaction mixture was dialyzed with a SpectraPor3 membrane (MWCO = 1000 Da) for 3 days at ambient temperature. The polymer sample was subsequently diluted with acetic acid/acetate buffer, the α-amylase containing enzyme mixture Taka-Diastase was added to degrade the residual cyclodextrins, and the mixture was incubated at 37 °C for 24 h and boiled for 10 min.[46,47] Finally, the mixture was dialyzed against water for 3 days at ambient temperature, and the solvent was removed in vacuo.

For the other polymerizations the Me-β-CD/CTA/initiator ratio was kept constant at 5/1/0.2. The DMAAm/CTA ratio was altered, and water was added to keep the concentration constant at 3.0 mol L^{-1}. The experiments with **CTA2** and **CTA3** were conducted in an analogous fashion.

Exemplary Procedure for the Chain Extension of Poly(DMAAm) (Refer to the Supporting Information for the Chain Extension of Poly(DEAAm) and Poly(NIPAAm)). Poly(DMAAm) ($M_{n,GPC}$ = 10 500 g mol^{-1}, PDI = 1.17, 20.0 mg, 0.002 mmol, 1.0 equiv) as macro-CTA, DMAAm (183 mg, 1.85 mmol, 925.0 equiv), VA-044 (0.3 mg, 0.001 mmol, 0.5 equiv), and deionized H_2O (0.6 mL) were added into a Schlenk tube. After three freeze−pump−thaw cycles the tube was placed into an oil bath at 25 °C and kept there for 24 h. The reaction mixture was cooled with liquid nitrogen, subjected to air, and dialyzed for 3 days at ambient temperature. The solvent was removed in vacuo to give the polymer as a yellow solid (197 mg, 97%, GPC(DMAc): $M_{n,GPC}$ = 97 500 g mol^{-1}, PDI = 1.08).

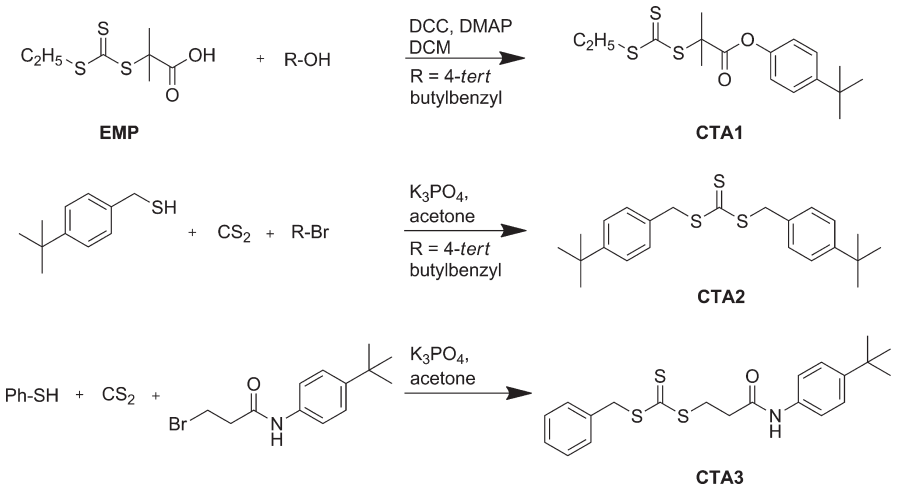
Exemplary Procedure for Kinetic Measurements (Refer to the Supporting Information for the Kinetic Measurements for DEAAm and NIPAAm). **CTA1** (12.2 mg, 0.034 mmol, 1.0 equiv) and Me-β-CD solution (40 wt % in deionized water, 551 mg, 0.168 mmol, 4.9 equiv) were added to a Schlenk tube. The two-phase mixture was ultrasonicated until a clear yellow solution was obtained. Subsequently, DMAAm (1.00 g, 10.10 mmol, 297.1 equiv), VA-044 (2.2 mg, 0.007 mmol, 0.2 equiv), and deionized H_2O (2.7 mL) were added. The solution was separated into several tubes with a stirring bar, and three freeze−pump−thaw cycles were applied. Subsequently, the tubes were sealed and placed into an oil bath at 25 °C. After specific time intervals the tubes were cooled with liquid nitrogen. Samples for NMR analysis were withdrawn, a pinch of hydroquinone (∼5 mg) was added to inhibit further polymerization, and D_2O was added. The conversion was calculated via comparison of the vinyl proton integrals with the appropriate integrals of the backbone or side chains of the polymers (see Characterization Methods for details). The residual sample in each tube was purified by dialysis for 3 days at ambient temperature and 1 day at 45 °C. The solvent was removed in vacuo and the polymer subjected to SEC analysis.

Characterization Methods. NMR measurements were conducted on a Bruker AM250 spectrometer at 250 MHz for hydrogen nuclei for kinetic measurements, a Bruker Avance III 300 spectrometer at 300 MHz for hydrogen nuclei for kinetic measurements, and a Bruker AM400 spectrometer at 400 MHz for hydrogen nuclei and at 100 MHz for carbon nuclei for structure verification. 2D ROESY (rotating frame nuclear Overhauser effect spectroscopy) NMR spectra were measured on a Bruker Avance III 300 spectrometer at 300 MHz. For the determination of the conversion of DMAAm the integrals of one vinylic proton (5.78−5.89 ppm) and the methyl side chain protons (2.87−3.28 ppm) were employed (refer to the Supporting Information Figure S11). The conversion of DEAAm was determined with the integral of one vinylic proton (5.57−5.73 ppm) and with the integral of the side chain methyl groups and backbone protons (0.81−1.97 ppm) (see also Figure S17 in the Supporting Information). The calculation of the NIPAAm conversion was carried out with the integrals of one vinylic proton (5.47−5.59 ppm) and the integral of the side chain methyl groups and the backbone protons (0.92−1.95 ppm) (refer to the Supporting Information Figure S23).

Size exclusion chromatography (SEC) was performed on a Polymer Laboratories PL-GPC 50 Plus Integrated System, comprising an autosampler, a PLgel 5 μm bead-size guard column (50 × 7.5 mm) followed by three PLgel 5 μm MixedC columns (300 × 7.5 mm), and a differential refractive index detector using *N*,*N*-dimethylacetamide (DMAc) containing 0.3 wt % LiBr as eluent at 50 °C with a flow rate of 1.0 mL min^{-1}. The SEC system was calibrated against linear poly(styrene) standards with molecular weights ranging from 160 to 6 × 10^6 g mol^{-1}. All SEC calculations were carried out relative to poly(styrene) calibration (Mark−Houwink parameters *K* = 14.1 × 10^{-5} dL g^{-1}; α = 0.7).[48]

ESI-MS spectra were recorded on a LXQmass spectrometer (ThermoFisher Scientific, San Jose, CA) equipped with an atmospheric pressure ionization source operating in the nebulizer-assisted electrospray mode. The instrument was calibrated in the *m*/*z* range 195−1822 Da using a standard containing caffeine, Met-Arg-Phe-Ala acetate (MRFA), and a mixture of fluorinated phosphazenes (Ultramark 1621) (all from Aldrich). A constant spray voltage of 4.5 kV was used, and nitrogen at a dimensionless sweep gas flow rate of 2 (∼3 L min^{-1}) and a dimensionless

Scheme 2. Synthetic Routes to the Utilized Complexable CTAs



sheath gas flow rate of 12 (~1 L min^{-1}) were applied. The capillary voltage, the tube lens offset voltage, and the capillary temperature were set to 60 V, 110 V, and 275 °C, respectively.

Theoretical molecular weights were calculated with the following equation:

$$M_{n,theo} = \text{conversion} \times M_w(\text{monomer}) \times \frac{[\text{monomer}]_0}{[\text{CTA}]_0} + M_w(\text{CTA})$$

RESULTS AND DISCUSSION

Our approach for the utilization of hydrophobic CTAs in aqueous RAFT polymerizations via cyclodextrin inclusion complexes includes the synthesis of novel hydrophobic CTAs that are subjected to complex formation with randomly methylated cyclodextrin (Me-β-CD) and are subsequently used in the RAFT polymerization of DMAAm, DEAAm, and NIPAAm.

Design and Synthesis of the Chain Transfer Agents. Several trithiocarbonate-CTAs for the aqueous RAFT-polymerization of hydrophilic monomers are mentioned in the literature.[23,30,45,49] As R-group usually the benzyl or a tertiary-α-carbonyl group are employed. The synthesis of trithiocarbonates can be carried out via the deprotonation of thiols, their nucleophilic attack on carbon disulfide, and nucleophilic attack of the resulting trithiocarbonate salt on bromo compounds. O'Reilly and co-workers recently presented an elegant way to synthesize trithiocarbonate-CTAs utilizing potassium phosphate as base in acetone.[50] This synthetic route was employed for all of the CTAs described in the current work. As guest group the 4-*tert*-butylphenyl motif was chosen due to its high complexation constant with β-cyclodextrin ($K \approx 18\,000-25\,000$ L mol^{-1}).[40] From an earlier publication of Wenz and co-workers a similar complexation constant of Me-β-CD with the 4-*tert*-butylphenyl group can be anticipated from a close analogue (heptakis(2,6-di-*O*-methyl)-β-cyclodextrin).[41]

As depicted in Scheme 2, the synthesis of the guest-functionalized CTAs was accomplished either directly or in two stages to include guest groups for β-cyclodextrin complexes into the CTAs. The guest group was incorporated in the R group (**CTA1**), Z group (**CTA3**), or both (**CTA2**). One possibility was the use of DCC-coupling after the synthesis of a precursor CTA (e.g., synthesis of **CTA1**). An alternative route was the synthesis of a guest-functionalized molecule containing a bromine leaving group (e.g., **CTA3**). The direct route utilized guest-functionalized thiols and bromides (e.g., **CTA2**). The synthesized CTAs were characterized via NMR spectroscopy (refer to the Supporting Information Figures S1−S6) and ESI-MS.

Complexation of Chain Transfer Agents with Me-β-Cyclodextrin. For the utilization of the guest-functionalized CTAs in aqueous RAFT polymerizations host/guest complexes have to be formed with cyclodextrin. Me-β-CD was chosen as host compound due to its increased water solubility compared to β-cyclodextrin.[51] The complexation was accomplished via mixing the guest-functionalized CTAs with aqueous 40 wt % Me-β-CD solution and ultrasonication until a clear yellow solution was obtained. Depending on the structure of the CTA the suspension had to be ultrasonicated for variable times, as the ultrasonication time depends on the complex stability and the possibility to disperse the CTA in the aqueous solution.

Figure 1 shows CTA/Me-β-CD solutions and as control CTA/water solutions before ultrasonication and after ultrasonication at ambient temperature. From the yellow color in the solution after ultrasonication it is obvious that the CTA/Me-β-CD complex was formed. In contrast, the solution in the control experiment shows no yellow color. To ensure complete inclusion, a 5-fold excess was used for all CTAs. For **CTA1** a homogeneous solution was obtained after 35 min; for **CTA2** and **CTA3** a homogeneous solution was obtained after 100 min of ultrasonication.

A further method to characterize the CTA/Me-β-CD complexes is the two-dimensional ROESY (rotating frame nuclear Overhauser effect spectroscopy) NMR technique.[3,52] In general, there are two modes for the formation of the inclusion complex. The guest can insert into the hydrophobic cavity via the primary, i.e., the side with the smaller opening, or the secondary face of the cyclodextrin, i.e., the side with the bigger opening. From the resonances in the ROESY spectrum it is in principle possible to assign the formed type of the complex. The complexation of **CTA1** with Me-β-CD could be evidenced via the resonance of the *tert*-butyl protons at 1.33 ppm with the inner protons of Me-β-CD (signal between 3.27 and 3.87 ppm) in D_2O at 25 °C as depicted in Figure 2. Furthermore, the signal of the *tert*-butyl protons is shifted from 1.30 to 1.33 ppm, thus changing place

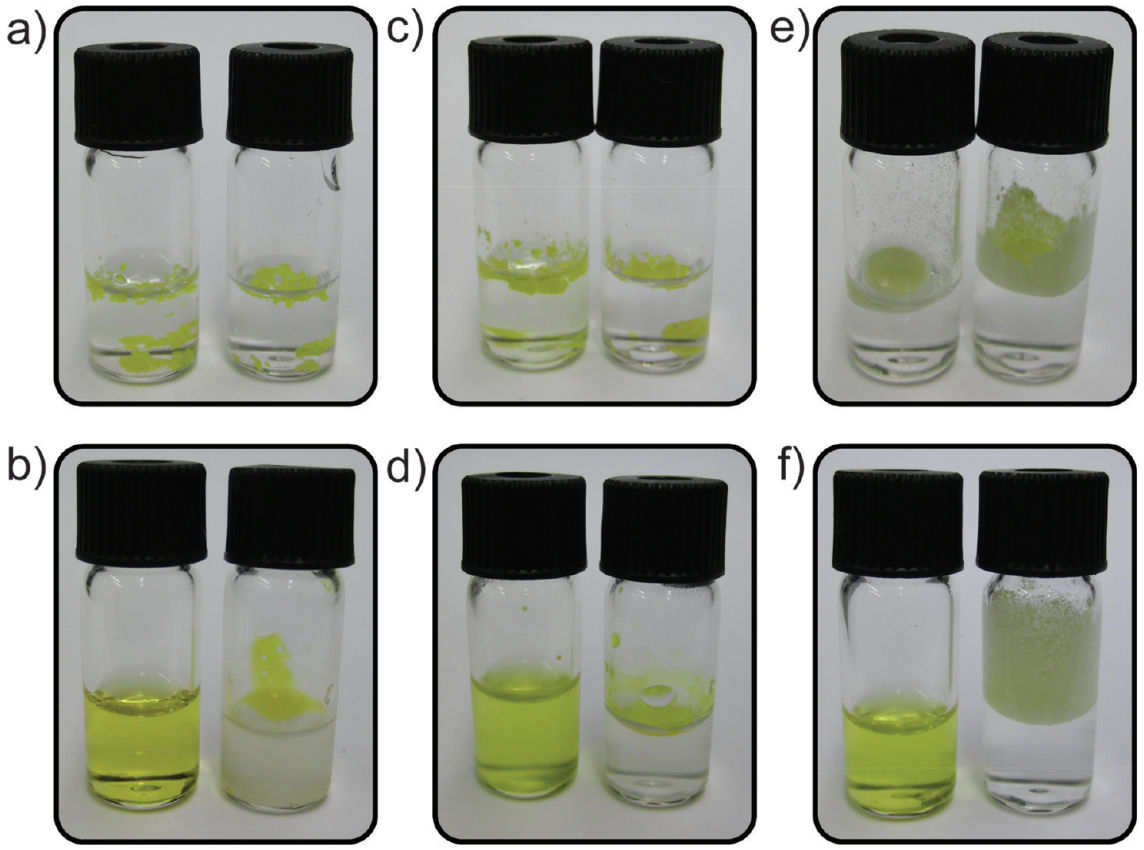


Figure 1. Mixtures of **CTA1** (a, b), **CTA2** (c, d), and **CTA3** (e, f) with aqueous 40 wt % Me-β-CD solution (left) and deionized water (right). Top: before ultrasonication, bottom: after ultrasonication.

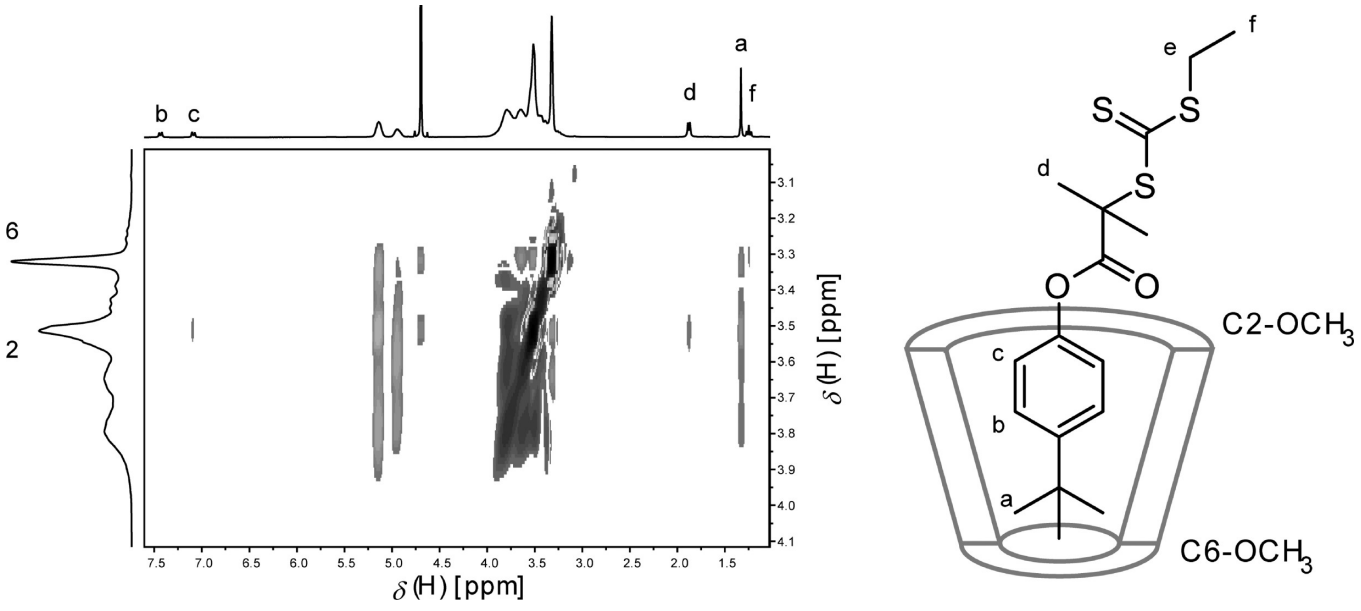


Figure 2. 2D ROESY NMR spectrum of a 1:1 molar mixture of **CTA1** and Me-β-CD in D_2O at 25 °C and a schematic illustration of the host−guest complex.

with the signal of the methyl protons from the ethyl group (refer to Figure S1 in the Supporting Information for a ^{1}H NMR spectrum of **CTA1**). Interestingly, the signal for the α-methyl protons of **CTA1** splits into two distinct signals due to chemical inequivalency after complex formation. This signal shows resonance with the C2-methoxy group which is due to a complex with an insertion from the secondary side as shown in Figure 2. Nevertheless, the unspecific resonances between the *tert*-butyl

dx.doi.org/10.1021/ma2011969 |*Macromolecules* 2011, 44, 7220–7232

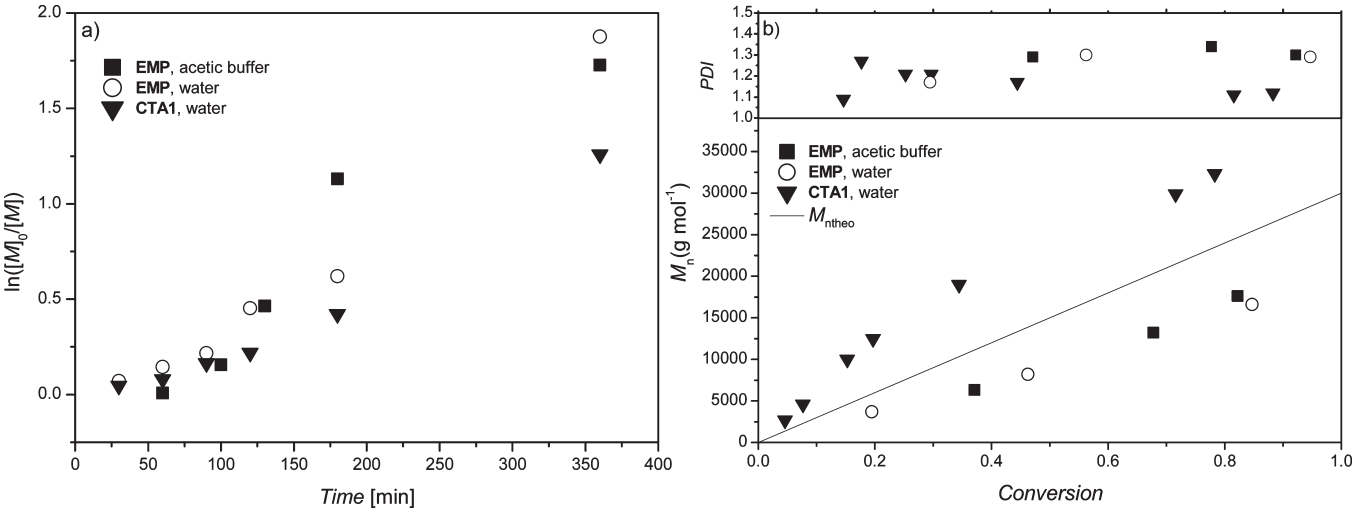


Figure 3. (a) Comparison between the kinetic plots of **EMP**-mediated polymerization in acetic acid/acetate buffer, **EMP**-mediated polymerization in water, or **CTA1**/cyclodextrin-mediated polymerization at 25 °C with a DMAAm/CTA/I ratio of 300/1/0.2 and a DMAAm concentration of 3.5 mol L^{-1}. (b) Comparison of the obtained molecular weights and PDIs as a function of monomer to polymer conversion.

groups with the C2-methoxy and the C6-methoxy group suggest a mixture of both inclusion modes.

The 2D ROESY spectra of **CTA2** and **CTA3** show the interaction between the CTA and Me-β-CD. The direction of the inclusion is not clearly assignable, although weak interaction of the aromatic protons with the C2-methoxy group indicates a complexation via the secondary face of Me-β-CD (refer to the Supporting Information Figures S7 and S8). For **CTA3** the resonances of the aromatic protons with the C6-methoxy and C2-methoxy protons indicate a complexation on both ends.

A comparison between the different CTAs shows several effects that have an influence on the complex stability upon monomer addition. One matter is the nature of the monomer, e.g., hydrophobicity and its ability to act as a guest, which is discussed below. An additional point is the hydrophobicity of the CTA with respect to the hydrophobicity of weak guest groups, e.g., dodecyl, hexyl, or butyl groups.[53,54] Although other CTAs exhibit the possibility to form inclusion complexes with Me-β-CD, e.g., the analogue of **CTA1** with dodecyl instead of ethyl group, addition of hydrophilic monomers leads to complete demixing due to the loss of the inclusion complex. Most likely, the hydrophobicity of the dodecyl group is too weakly masked by a β-cyclodextrin. Therefore, the complex is lost as competing guest molecules, e.g. monomers, are added, and the single host/guest complex with the 4-*tert*-butyl phenyl group is not strong enough to keep the whole CTA in solution. It is obvious that the stability of the host/guest complex is additionally correlated with the number of guest groups incorporated into the CTA. The more guest groups are incorporated, the more stable is the complex. As the host/guest complexes are in equilibrium with the free molecules, it is advantageous to have two complexed groups in one CTA molecule. If one of the two host/guest complexes is lost, the remaining one can keep the entire molecule in solution and accessible for the recreation of the second complex.

Polymerization with Complexed Chain Transfer Agents. For the polymerization of acrylamido monomers with Me-β-CD complexed CTA three steps were carried out as depicted in Scheme 1: First, the complex was formed via ultrasonication of the appropriate CTA in aqueous 40 wt % Me-β-CD solution. Second, monomer, water, and initiator were added, the reaction was degassed, and the polymerization subsequently commenced. Third, the polymerization mixture was subjected to dialysis to remove residual monomer, initiator and Me-β-CD.

As discussed by McCormick and co-workers, a major concern in aqueous RAFT polymerization of acrylamides is the hydrolysis/aminolysis of the CTA during the polymerization.[22,55,56] A solution for hydrolysis suppression/prevention is the use of acetic acid/acetate buffer as solvent and low-temperature initiators, e.g. VA-044.[49,55] Under these conditions, McCormick and colleagues showed that a controlled polymerization of acrylamide, DMAAm, and NIPAAm via the RAFT process in aqueous media is possible.[31,32,49] Furthermore, it is well-known that low temperatures favor the stability of β-CD complexes. For these reasons all polymerizations were conducted at 25 °C. As the CTA/Me-β-CD complexes were not soluble in acetic acid/acetate buffer, a series of DMAAm polymerizations—as a test system—were conducted in variable reaction media with **CTA1** or **EMP** to determine the effect of the reaction media on the polymerization. The results are summarized in Figure 3.

Figure 3a shows that the polymerization reaction with the complexed **CTA1** (triangles) proceeds slower than the polymerizations with **EMP** in acetic acid/acetate buffer (filled squares) or water (open circles), whereas the **EMP** mediated polymerizations show comparable reaction rates. Nevertheless, the reaction with **CTA1** leads to a conversion of 70% in 6 h while the reactions with **EMP** have a conversion of approximately 80% within 6 h. We propose that the difference in reaction rate is a result of the increasing steric hindrance associated with the bulky cyclodextrin complex. Although a slower reaction is observed a superior control over the polymerization with the **CTA1**/cyclodextrin complex can be noted. Lower PDIs were observed in these polymerizations as summarized in Figure 3b. In the case of **CTA1** (triangles) the observed molecular weight was higher than the theoretical molecular weight, whereas the molecular weight is lower than the theoretical molecular weight in the case of **EMP** (squares and open circles). As the polymerization has living/controlled character in both acetic acid/acetate buffer and pure

Table 1. Results for the Different Purification Methods

entry	purification procedure	residual Me-β-CD [% area]
1	no purification	29.1
2	CF_3COOH 2 h; dialysis 3 days, ambient temperature	7.5
3	dialysis 3 days, ambient temperature	8.4
4	dialysis 3 days, ambient temperature; dialysis 1 day, 45 °C	5.4
5	dialysis 3 days, ambient temperature; dialysis 2 days, 45 °C	3.3
6	dialysis 3 days, ambient temperature; Taka-Diastase acetate buffer 1 day, 37 °C; dialysis 3 days, ambient temperature	4.1

water with **EMP** as CTA at 25 °C, there is no need to carry out the polymerization at acidic pH in the case of complexed CTAs.

Removal of the Cyclodextrin after the Polymerization. For the removal of the cyclodextrin several methods were applied. A test polymerization with DMAAm and **CTA1** was carried out, divided into several samples, and purified in different ways. To compare the residual amounts of the cyclodextrin in the products, the peak area of the eluting cyclodextrin in the SEC analysis was calculated relatively to the peak area of the polymer. Dialysis was performed utilizing dialysis tubing with a MWCO of 3500 Da, but the treatment of the samples was varied. One purification method was the treatment of the crude polymerization solution with trifluoroacetic acid for 2 h as cyclodextrins are hydrolyzed by strong acids, and the solution was dialyzed for 3 days at ambient temperature afterward (entry 2 in Table 1). For comparison, the crude polymerization mixture was dialyzed for 3 days at ambient temperature (entry 3 in Table 1). Another method was dialysis for 3 days at ambient temperature and subsequently dialysis for 1 day or 2 days at 45 °C (entries 4 and 5 in Table 1). Furthermore, enzymatic treatment with Taka-Diastase in acetic acid/acetate buffer at 37 °C for 1 day was employed after dialysis for 3 days at ambient temperature and another dialysis for 3 days at ambient temperature after the enzymatic treatment (entry 6 in Table 1). The enzymatic treatment with Taka-Diastase from *Aspergillus oryzae* should lead to degradation of the cyclodextrins as it contains the enzyme α-amylase which is known to hydrolyze the α-1,4-glucosidic bond of the cyclodextrins.[46,47,57]

As listed in Table 1, dialysis at elevated temperatures, e.g. 45 °C, provides the best results with only 3.3% Me-β-CD remaining (entry 5 in Table 1). Nevertheless, enzymatic treatment has a very similar performance with 4.1% Me-β-CD remaining (entry 6 in Table 1; the corresponding elugrams can be found in the Supporting Information Figure S9). In the case of poly(DEAAm) and poly(NIPAAm), dialysis at elevated temperatures leads to the precipitation of the polymers that supports the removal of residual cyclodextrin. Generally, it should be noted that dialysis leads to a loss of low molecular weight polymers and oligomers. Especially in the case of low target molecular weights, the molecular weight distributions are thus to some extent affected.

Polymerization of *N,N*-Dimethylacrylamide with Complexed Chain Transfer Agents. DMAAm is very frequently employed in polymer science. In the living/controlled radical polymerization with complexed CTAs the best control is obtained with **CTA1** compared to **CTA2** and **CTA3** (see Table 2 and Tables S2, S3 in the Supporting Information). This can be attributed mostly to the complex stability and the tertiary α-ester R group in **CTA1**. A monomer concentration of 3.0 mol L^{-1} was chosen and the CTA/initiator ratio was held constant at 1/0.2. The complex of **CTA1** with Me-β-CD was stable throughout the reaction time and even at high monomer/CTA ratios up to 1000/1. Therefore, molecular weights ranging from 10 000 to 94 000 g mol^{-1} were obtained in good agreement with theoretical values. High conversion was reached in short reaction time even at the low polymerization temperature of 25 °C. The resulting PDIs lie between 1.06 and 1.17 (see Table 2 and Figure 4d). Although the polymers were purified according to the Experimental Part, a small residue of unremoved cyclodextrin (~0.4−5.5%) remained. Apart from residual cyclodextrin, the SEC traces are unimodal and show only minor low molecular weight tailing and no high molecular weight coupling products.

Table 2. Results for the Living/Controlled RAFT Polymerization of DMAAm at 25 °C in Aqueous Solution with CTA1

DMAAm/CTA/I	time/h	conv	$M_{n,theo}$/g mol^{-1}	$M_{n,GPC}$/g mol^{-1}	PDI
107/1/0.2	6	65	7 300	10 500	1.17
198/1/0.2	6	88	18 000	17 000	1.09
294/1/0.2	12	>99	29 500	36 500	1.08
585/1/0.2	12	94	55 000	62 000	1.06
1018/1/0.2	12	98	99 300	94 000	1.06

Time-resolved experiments with regard to conversion and molecular weight were carried out to confirm the living character of the polymerization (refer to Figure S10 in the Supporting Information for a collection of NMR spectra). As depicted in Figure 4, the kinetic first-order plot shows linearity, which confirms a constant radical concentration during the reaction; only a short induction period is observed (<30 min). The molecular weights are increasing linearly with conversion which evidence the living character of the polymerization, and the PDI is decreasing with increasing conversion. Further proof for the living radical polymerization comes from the chain extension of purified macro-CTAs with DMAAm. A quantitative reinitiation was observed that leads to a shift in molecular weight from 10 500 to 97 500 g mol^{-1} with a final PDI of 1.08. Nevertheless, small amounts of chain−chain coupling products were observed in the high molecular weight region.

The molecular structure of low molecular weight samples was confirmed via ESI-MS (M_n = 3000 g mol^{-1}) and ^1H NMR (M_n = 10 500 g mol^{-1}) (see Figures S12 and S13 in the Supporting Information), evidencing the incorporation of the hydrophobic end groups into the hydrophilic polymer. The mass spectrometric data show no signals from initiator-terminated polymer which is in accord with highly efficient chain-extension experiments.

With **CTA2** turbidity was observed on monomer addition that vanished in the beginning of the polymerization. In the polymerizations with **CTA3** turbidity was observed at monomer/CTA ratios exceeding 300/1. Nevertheless, molecular weights of 156 000 g mol^{-1} were reached with PDIs ranging from 1.31 to 1.54 (refer to the Supporting Information: Tables S2, S3 and Figures S14, S15) with high conversions in short reaction times. As stated above, less control over the polymerization is observed with **CTA2** and **CTA3**. The less stable complexes of Me-β-CD with **CTA2** and **CTA3** lead to partial demixing on monomer and

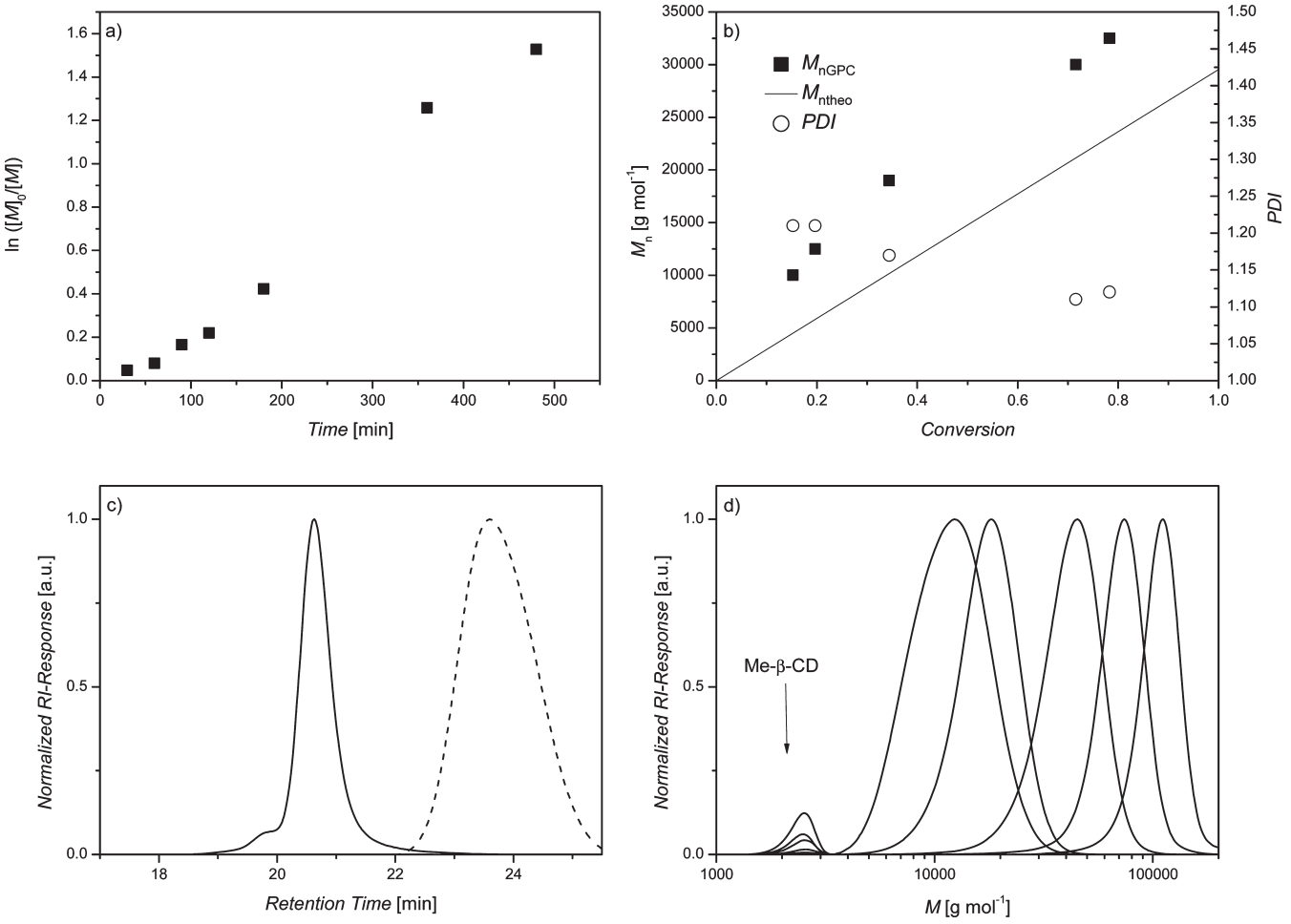


Figure 4. (a) Kinetic plot for the polymerization of DMAAm at 25 °C with **CTA1**. (b) Evolution of M_n with conversion at 25 °C with DMAAm/**CTA1**/I: 297/1/0.2. (c) Chain extension at 25 °C for 24 h. (d) Molecular weight distributions for different monomer/CTA ratios (DMAAm/**CTA1** (conversion) from left to right: 107/1 (65%); 198/1 (88%); 294/1 (>99%); 585/1 (94%); 1018/1 (98%)).

water addition as observed via a turbidity of the solution. Such a demixing explains the higher disagreement of experimental molecular weights compared to theoretical molecular weights, as fewer CTA molecules are accessible in the solution in the case of turbidity, thus leading to higher molecular weights. The broader polydispersity of the polymers prepared with **CTA2** and **CTA3** can be also attributed to the partial demixing as the undissolved CTA molecules react on a slower time scale. Therefore, low molecular weight tailing is observed which leads to higher PDIs. Nevertheless, chain-extension experiments were conducted that proof the living character of the polymerization based on a high reinitiation efficiency.

Polymerization of *N,N*-Diethylacrylamide with Complexed Chain Transfer Agents. DEAAm is a monomer that exhibits a very low LCST of around 30 °C.[58] At a reaction temperature of 25 °C, it should be possible to polymerize DEAAm in aqueous media via the RAFT process. Although the living radical polymerization in organic media has been described,[59] a living/controlled radical polymerization of this monomer in aqueous solution has not been accomplished yet. **CTA1**, **CTA2**, and **CTA3** were employed for the polymerization of DEAAm. The monomer concentration was held constant at 3.5 mol L^{-1}, the temperature at 25 °C, and the CTA/initiator ratio at 1/0.2. As with DMAAm, **CTA1** shows the best control over the polymerizations. No turbidity or demixing is noticed for monomer/CTA ratios up to 200/1, and only a slight turbidity is observed for higher CTA/monomer ratios in the case of **CTA1**. Molecular weights from 2500 up to 87 000 g mol^{-1} that were in good agreement with the theoretical values were reached in short reaction times, e.g., 12 or 18 h, with quantitative conversions and PDIs ranging from 1.05 to 1.11 (see Table 3 and Figure 5d). The resulting molecular weight distributions are unimodal and display no evidence for high molecular weight termination products or low molecular weight

Table 3. Results for the Living/Controlled RAFT Polymerization of DEAAm at 25 °C in Aqueous Solution with CTA1

DEAAm/CTA/I	time/h	conv	$M_{n,theo}$/g mol^{-1}	$M_{n,GPC}$/g mol^{-1}	PDI
12/1/0.2	12	>99	1 900	2 500	1.10
42/1/0.2	12	>99	5 800	5 000	1.11
80/1/0.2	12	>99	10 600	10 000	1.09
163/1/0.2	12	>99	21 100	18 000	1.08
248/1/0.2	12	>99	32 000	29 000	1.07
426/1/0.2	18	>99	54 600	55 000	1.06
813/1/0.2	18	>99	103 800	87 000	1.05

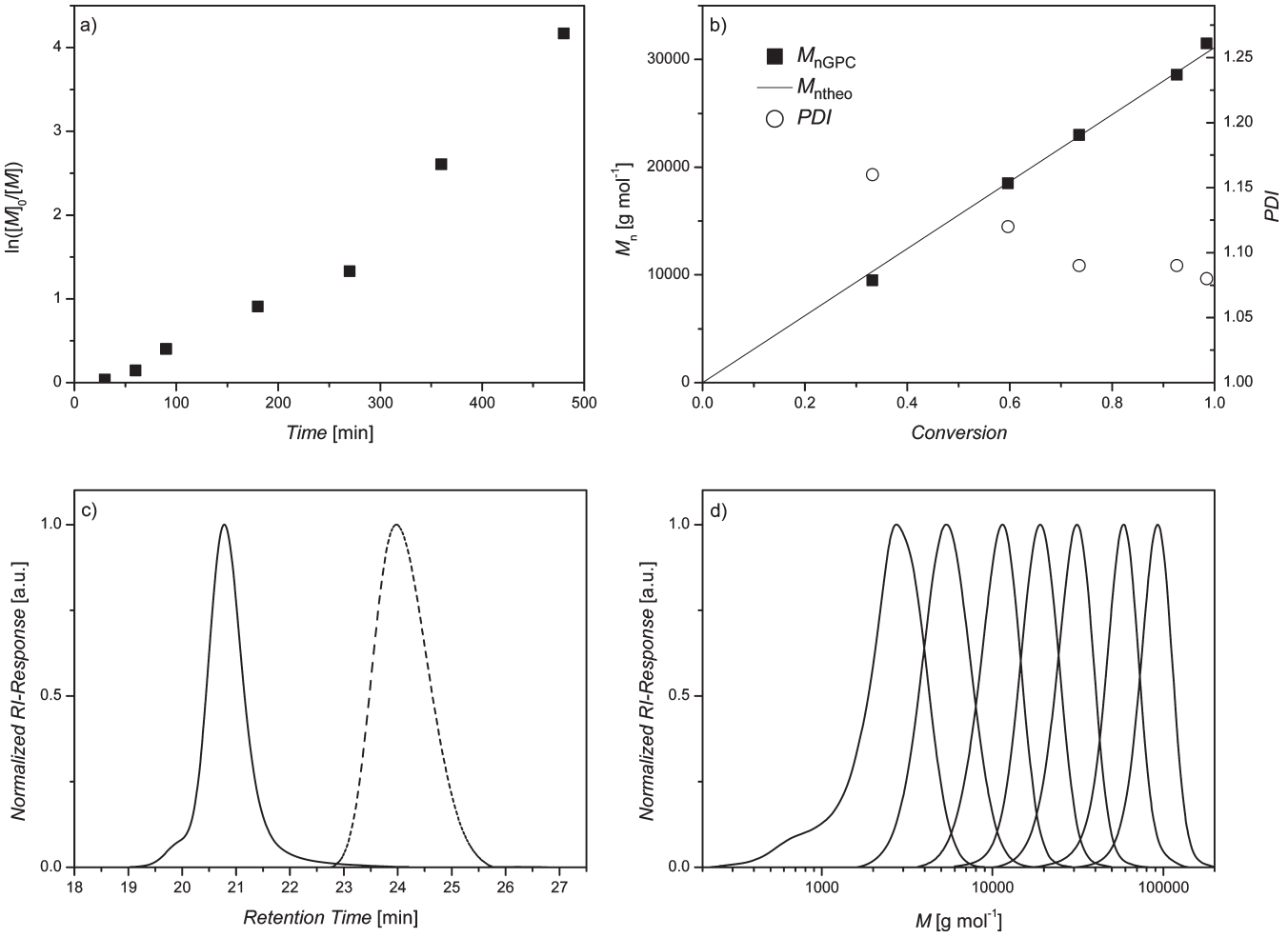


Figure 5. (a) Kinetic plot for the polymerization of DEAAm at 25 °C with **CTA1**. (b) Evolution of M_n with conversion at 25 °C with DEAAm/**CTA1**/I: 241/1/0.2. (c) Chain extension at 25 °C for 24 h. (d) Molecular weight distributions for different monomer/CTA ratios (DEAAm/**CTA1** from left to right (conversion > 99%): 12/1; 42/1; 80/1; 163/1; 248/1; 426/1; 813/1).

tailing, except for the lowest target molecular weight where low molecular weight (<1000 g mol^{-1}) species are observed.

To confirm the living character of the polymerization, time-resolved experiments with regard to conversion and molecular weight were carried out (refer to Figure S11 in the Supporting Information for a collection of NMR spectra) and chain extensions were performed as depicted in Figure 5. Besides a constant radical concentration as evidenced by a linear first-order plot with a short induction period under 30 min, the molecular weight grows linearly with conversion as expected for polymerizations with living character. Furthermore, the experimental molecular weights are in good agreement with the theory, and the PDIs are decreasing with increasing conversion. The chain extension affords a very high reinitiation efficiency with a growth in molecular weight from 8500 to 83 000 g mol^{-1} and a PDI of 1.13 for the resulting polymer with a small amount of chain−chain coupling products.

ESI-MS and ^{1}H NMR were recorded of a low molecular weight sample (M_n = 4000 g mol^{-1}) to confirm the structure of the synthesized polymers. The results are in agreement with the expected polymer structure proving the incorporation of the hydrophobic end groups into the hydrophilic polymer (refer to the Supporting Information: Figures S18 and S19). Furthermore, there is no indication of initiator derived chains in the ESI-MS spectrum which explains the high reinitiation efficiency.

Table 4. Results for the Living/Controlled RAFT Polymerization of NIPAAm at 25 °C in Aqueous Solution with CTA1

NIPAAm/CTA/I	time/h	conv	$M_{n,theo}$/g mol^{-1}	$M_{n,GPC}$/g mol^{-1}	PDI
15/1/0.2	18	>99	2100	4000	1.15
39/1/0.2	18	>99	4800	7500	1.29
44/1/0.2	18	>99	5500	9000	1.15
260/1/0.2	20	>99	30100	50000	1.46

For the other CTAs (**CTA2** and **CTA3**) turbid solutions were observed upon water addition. Nevertheless, high conversions were reached in short reaction times, and molecular weights ranging from 4000 to 116 000 g mol^{-1} were reached with PDI from 1.10 to 1.39 (see also Tables S5 and S6 in the Supporting Information). Similar to the polymerizations of DMAAm with **CTA2** and **CTA3**, a disagreement of the experimental molecular weights with those theoretically predicted was noted that could be due to the turbid nature of the solution at the beginning of the polymerization process. It is also worth noting that the polymers remained in solution throughout the entire reaction time with all

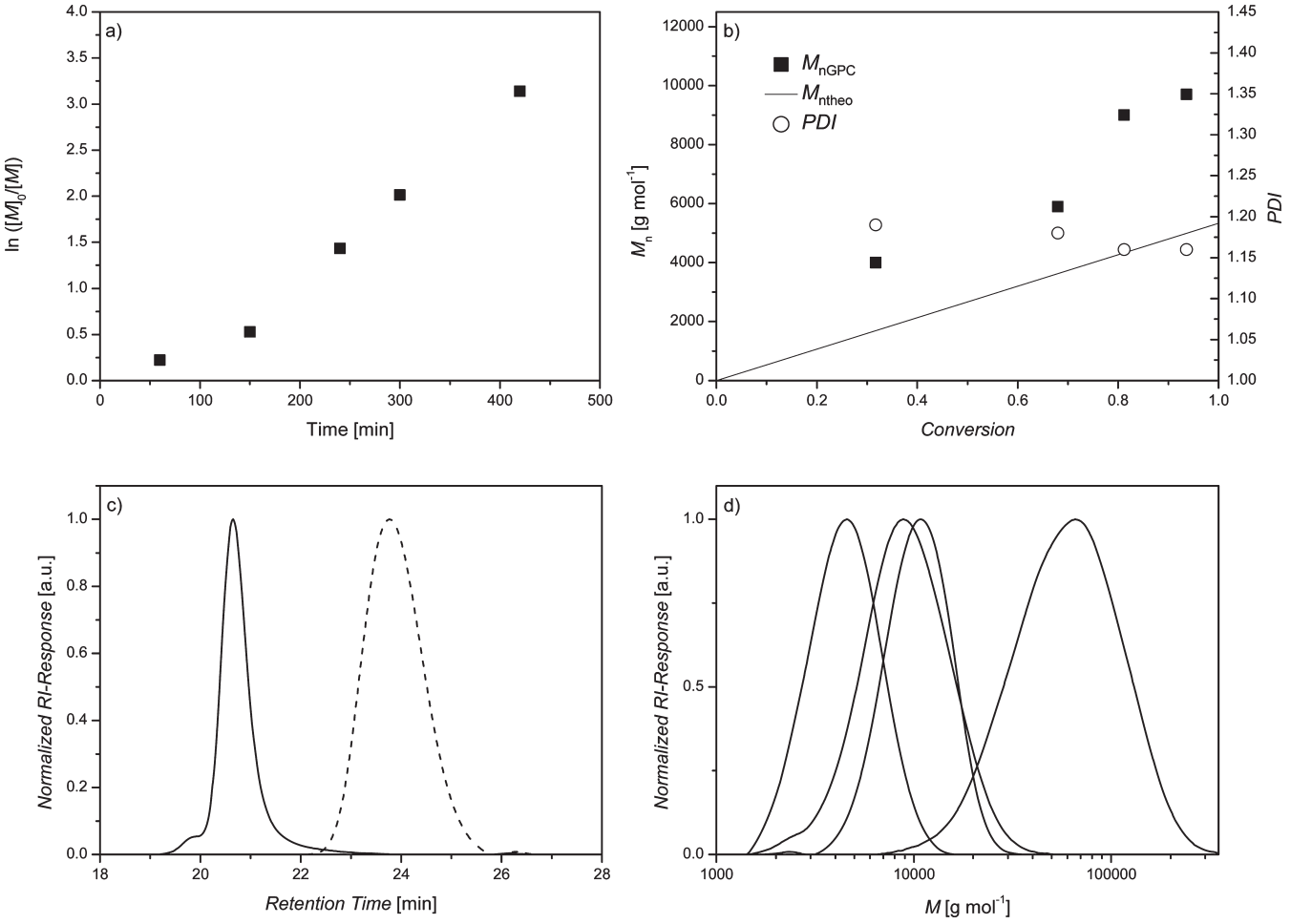


Figure 6. (a) Kinetic plot for the polymerization of NIPAAm at 25 °C with **CTA1**. (b) Evolution of M_n with conversion at 25 °C with NIPAAm/**CTA1**/I: 44/1/0.2. (c) Chain extension at 25 °C for 24 h. (d) Molecular weight distributions for different monomer/CTA ratios (NIPAAm/**CTA1** from left to right (conversion > 99%): 15/1; 39/1; 44/1; 260/1).

three CTAs although it is known from literature that hydrophobic end groups lead to a lower LCST in poly(DEAAm).[43]

Polymerization of *N*-Isopropylacrylamide with Complexed Chain Transfer Agents. Another important acrylamido monomer is NIPAAm. Because of the LCST of poly(NIPAAm) that is close to human body temperature, many efforts have been made in its synthesis.[25,44,49] As the LCST of poly(NIPAAm) is close to 31 °C,[60] which is comparable to the LCST of poly(DEAAm), a controlled polymerization of NIPAAm is feasible at 25 °C in aqueous media.[49] Therefore, it should be possible to polymerize NIPAAm with cyclodextrin-complexed CTAs at 25 °C in aqueous media as well.

In the case of NIPAAm a controlled polymerization was only possible for **CTA1**. The other CTAs showed complete demixing upon addition of the monomer and water, which is further discussed in the subsequent section. Nevertheless, with **CTA1** polymers up to 50 000 g mol^{-1} were synthesized with PDIs ranging from 1.15 to 1.46 with quantitative conversions in 18 or 20 h. The monomer concentration was held constant at 2.5 mol L^{-1}, the polymerization temperature at 25 °C, and the CTA/initiator ratio at 1/0.2. The results are summarized in Table 4. A significant excess of the experimental molecular weights compared to the theoretically predicted ones by a factor of 1.5−2.0 was evidenced that could be due to a partial disassembly of the CTA/cyclodextrin complex. The obtained polymers show unimodal molecular weight distributions with no significant tailing in the low molecular weight region. No high molecular weight termination products are visible.

A constant radical concentration was proven by a linear first-order plot also evidencing a short induction period of ~30 min. A confirmation of the living radical polymerization was accomplished via a chain-extension experiment and a time-resolved experiment that indicated a linear increase of molecular weight with conversion (see Figure 6). Higher experimental molecular weights compared to the theoretical molecular weights are observed, as discussed above. The chain extension shows that the amount of dead chains is neglible as chain extension from 9000 to 90 000 g mol^{-1} was performed with very high efficiency leading to a PDI of 1.11 showing only minor chain−chain coupling products.

Besides the kinetic studies, ESI-MS was performed to prove the structure of the obtained polymers. As depicted in Figure S24, the results fit very well to the expected values, indicating the incorporation of the hydrophobic end groups into the hydrophilic polymers. Furthermore, there is no indication of initiator-derived chains that matches with the observed high reinitiation efficiency. ^{1}H NMR was measured (refer to the Supporting Information Figure S25), indicating the incorporation of the hydrophobic end group in the aromatic region of the spectrum.

Effect of the Monomer Structure on the RAFT Polymerization with Complexed Chain Transfer Agents. Comparison of the studied monomers evidences that with increasing guest character the complexation of the CTAs decreases. With DMAAm no turbidity was observed for **CTA1** and only slight turbidity for **CTA2** and **CTA3**. This effect is also reflected in the control over molecular weights and PDIs as the best control is achieved with **CTA1**. In the polymerization of DEAAm, only slight turbidity was observed in the **CTA1** solution where DEAAm/**CTA1** ratios exceeded 300/1. With **CTA2** and **CTA3** turbidity was observed with DEAAm/CTA ratios from 13/1 to 813/1. In analogy to the polymerization of DMAAm the **CTA1**-mediated polymerizations of DEAAm show the best control over molecular weight and PDI. The overall trend is continuing in the polymerization with NIPAAm as it could only be conducted with **CTA1** and only short chains up to 50 000 g mol^{-1} could be synthesized with an increasing PDI toward longer chains. It appears that the substituents in the acrylamido monomers have a significant effect on the stability of the CTA/cyclodextrin complex. DMAAm disturbs the complex only weakly whereas DEAAm leads to a significant expulsion of CTA molecules from the cyclodextrin cavity. NIPAAm leads to expulsion in all cases with **CTA2** or **CTA3**, and complexes with **CTA1** were only stable up to a monomer/CTA ratio of 260/1. The complex stability is increasing from NIPAAm over DEAAm to DMAAm, which is in contrast to the ability of the substituent in the acrylamido monomer to act as a competing guest in the cyclodextrin. The more hydrophobic and bulky isopropyl group in NIPAAm has a bigger effect on the CTA/cyclodextrin complex stability than the ethyl group in DEAAm, which itself has a larger effect on the CTA/cyclodextrin complex than the methyl group in DMAAm. We propose that this effect is due to a shift in the host/guest equilibrium toward disassembly of the complex induced by additional guest molecules. These can be either monomers or additional water molecules. As monomers have to be employed in higher equivalents to synthesize high molecular weight polymers in controlled/living radical polymerizations, the possibility that the monomer leads to expulsion of the CTA from the Me-β-CD rises with increasing target molecular weights. An increasing amount of water may also lead to a loss of the CTA/cyclodextrin complex.[61] The amount of water increases with increasing target chain length as more water is needed to retain a solution polymerization. Therefore, the decrease in the complexation efficiency in the case of higher targeted molecular weights can be explained by the increasing employed amount of monomer and water molecules in these cases.

CONCLUSIONS

The utilization of cyclodextrins provides new opportunities for the synthetic methodology of living/controlled radical polymerization. Based on the concept of supramolecular chemistry, host/guest complexes seem to be attractive as controlling agents in living radical polymerizations. In the current contribution we report the first aqueous RAFT polymerization of acrylamido monomers, e.g. DMAAm, DEAAm, and NIPAAm, with a supramolecular complex of cyclodextrin and hydrophobic CTAs. The solubility of three novel guest-functionalized CTAs in water was enhanced drastically via a cyclodextrin/CTA inclusion complex. These complexes were thereafter utilized in living/controlled radical polymerizations at 25 °C in water, leading to hydrophilic polymers with hydrophobic end groups in one step. The polymerization leads to polymers with high molar masses and low PDIs ($7500 \leq M_n \leq 116\,000$ g mol^{-1}; $1.06 \leq$ PDI ≤ 1.54 for poly(DMAAm), $2500 \leq M_n \leq 150\,000$ g mol^{-1}; $1.05 \leq$ PDI ≤ 1.39 for poly(DEAAm) and $4000 \leq M_n \leq 50\,000$ g mol^{-1}; $1.15 \leq$ PDI ≤ 1.46 for poly(NIPAAm)). Furthermore, we described —to the best of our knowledge—the first living radical polymerization of DEAAm in water. The living character of the polymerizations was confirmed by a linear increase of the molecular weight with conversion, and chain extensions showed very high reinitiation efficiencies. ESI mass spectra and ^{1}H NMR spectra were in good agreement with the expectations evidencing the incorporation of hydrophobic end groups in the hydrophilic acrylamido polymers. Thus, we provide the first living/controlled polymerization of hydrophilic acrylamido monomers with hydrophobic CTA leading directly to hydrophobic end-functionalized polymers in aqueous solution.

ASSOCIATED CONTENT

Supporting Information. Analytical data of the chain transfer agents, experimental data on polymerizations with **CTA2** and **CTA3**, and additional data on polymerizations with **CTA1**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Tel (+49) 721 608-45642, Fax (+49) 721 608-45740, e-mail christopher.barner-kowollik@kit.edu (C.B.-K.);Tel (+49) 211 81-14760, Fax (+49) 211 81-15840, e-mail h.ritter@uni-duesseldorf.de (H.R.).

ACKNOWLEDGMENT

The authors acknowledge financial support for the current project from the German Research Council (DFG). C.B.-K. acknowledges financial support from the Karlsruhe Institute of Technology (KIT) in the context of the Excellence Initiative for leading German universities and the Ministry for Science and Arts of the state of Baden-Württemberg. The authors are additionally thankful to Prof. P. Roesky (KIT) for the measurement of a kinetic series of NMR samples.

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