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Acrylamide-Based Copolymers Bearing Photoreleasable Thiols for Subsequent Thiol−Ene Functionalization

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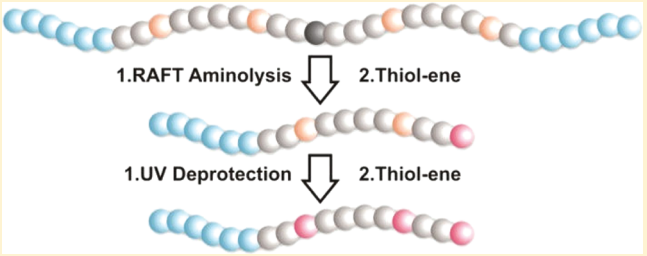
S *Supporting Information*

ABSTRACT: A new set of monomers is presented in order to incorporate thiols into radical polymers using a protecting chemistry/photocleavage route. The (co)polymerization kinetics of an *o*-nitrobenzyl thioether-containing acrylamide derivative are reported. The presence of the *o*-nitrobenzyl moiety is found to strongly affect the polymerization. Nevertheless, water-soluble copolymers with *N*,*N*-dimethylacrylamide (DMAAm) as a comonomer are obtained either by free radical polymerization ($10\,000 \leq M_n \leq 17\,500$ g mol^{-1}; $1.5 \leq$ PDI ≤ 1.8) or by reversible addition−fragmentation transfer (RAFT)-mediated controlled/living radical polymerization ($2000 \leq M_n \leq 5700$ g mol^{-1}; $1.1 \leq$ PDI ≤ 1.2). Deprotection under UV light ($\lambda = 366$ nm) at ambient temperature is followed by UV/vis monitoring of the protecting group release, which proceeds to completion between 40 min and 2 h within the studied range of concentration as demonstrated by ^{1}H NMR spectroscopy. Thiol−maleimide addition is subsequently carried out and found to proceed with a nearly quantitative yield (ca. 90%) as measured by ^{1}H NMR. Different block copolymers ($9400 \leq M_n \leq 16\,500$ g mol^{-1}; $1.3 \leq$ PDI ≤ 1.4) with a PDMAAm water-soluble block, a polystyrene hydrophobic block, or a poly(*N*-isopropylacrylamide) thermosensitive block as the first segment and possessing the photoreleasable thiol moieties in the second block are subsequently synthesized by RAFT-mediated polymerization. We finally demonstrate the orthogonal sequential deprotection and reaction with benzyl maleimide of two different thiol species originating from the thiocarbonylthio functionality and the *o*-nitrobenzyl protected lateral groups, respectively.



INTRODUCTION

The past 5 years have witnessed a significant growth of interest in the use of *click* methodologies in polymer and materials chemistry.[1] Since macromolecules are difficult to quantitatively modify and bear multiple functional groups, the efficiency and orthogonality of *click* reactions has indeed very often proven to be useful.[2] Although the most prominent technique was initially the azide−alkyne cycloaddition,[3] its generally required use of copper as a catalyst has led to a gradual shift of attention toward copper-free chemistries such as thiol−ene and thiol−yne additions,[4] (hetero) Diels−Alder [4 + 2] cycloaddition,[5] some very efficient nucleophilic substitutions,[6] oxime formation,[7] nitrile oxide−alkyne cycloaddition,[8] or ring-opening of epoxides.[9] Copper-free synthetic methods are particularly interesting when bio-related applications are envisioned. Thiol-based *click* conjugations have shown to be very powerful in various fields of application.[10] Thiols can react very efficiently with themselves to form disulfide bridges and with electron-withdrawing group-substituted enes such as (meth)-acrylates or maleimides via a radical pathway or Michael addition.[4] Furthermore, they are also able to strongly bind to a wide range of metal surfaces, for instance, silver or gold.[11]

Radical polymerization is arguably the most versatile polymerization technique since it is tolerant to most functional groups. However, there are some exceptions and thiols are one of them due to their large transfer constants in the polymerization of vinyl monomers.[12] Indeed, they are regularly employed to reduce the molecular weight or introduce a specific functionality in radically prepared macromolecules.[13] Consequently, sulfhydryl groups need to be introduced after the polymerization or to be protected (or masked) when they are initially present. For example, the pyridyl disulfide group (PyDS) has been often incorporated—especially when bioapplications were targeted—by using functional monomers,[14] initiators,[15] or RAFT agents.[16] PyDS has also been attached by amidation to amino-containing polymers using *N*-succinimidyl 3-(2-pyridyldithio)propionate.[17] Matyjaszewski

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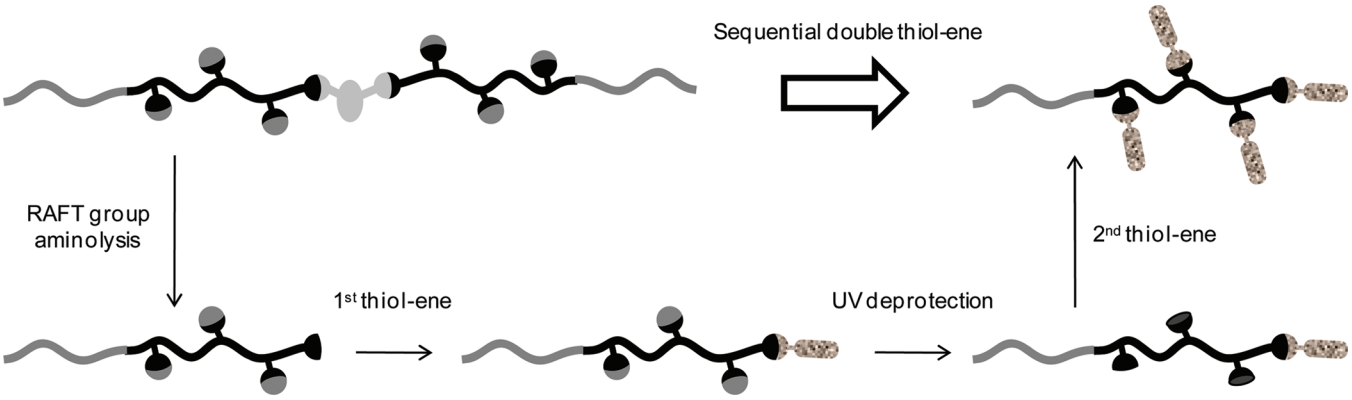
Scheme 1. General Sequential Deprotection/Thiol−Ene Functionalization Strategy Applied to a RAFT Polymerization-Made Block Copolymer Possessing the Protected Thiol Groups as a Comonomer Unit in One Block



and colleagues employed a bifunctional ATRP initiator composed of a disulfide linker to obtain midchain-functionalized polystyrene (PS) which was eventually reduced by DTT to yield PS-SH.[18] Li et al. also introduced thiols using an alkyl disulfide yet as a lateral group.[19] Classical protecting-group chemistry has also been employed to prepare ATRP initiators[20−22] or nitroxides[23] bearing a thiol group which was subsequently activated after functioning to mediate the polymerization. In the case of RAFT-mediated controlled/living polymerization thiocarbonylthio compounds are used as controlling agent, but they can also be regarded as masked thiols since methods such as aminolysis, hydrolysis, and metal hydride reduction will lead to the mercapto-end-functionalized chains.[24]

In the context of pure postpolymerization (i.e., the incorporation of previously absent sulfur atoms), alkyl halides such as ATRP-made polymers have been substituted using thiourea to form isothiouronium salts which were subsequently hydrolyzed to give thiol-capped polymers.[25,26] Very recently, Boyer et al. reported a nucleophilic substitution of Br-capped polymers employing methanethiosulfonate followed by basic hydrolysis[27] while Paris and co-workers used potassium thioacetate to obtain end-thiolated polymers via hydrolysis of the intermediate thioester-capped chains.[28]

Protecting group chemistry is very often employed in pure organic chemistry, particularly when complex structures are targeted.[29] It consists in the reversible protection of one or several functional groups which can potentially react while performing a modification meant to occur on another part of the molecule. It also allows in some applications the activation of specific functions when desired. While chemically driven deprotections have been employed to a high extent in polymer chemistry, the use of light-induced deprotection has been the subject of much less attention. The phototriggered release of chemical groups is very attractive as it allows not only for temporal control of the reaction but also for its spatial control. For instance, the *o*-nitrobenzyl group and its methoxy-substituted derivatives have been often used, e.g., for polymer functionalization,[30] reversible bioconjugation,[31] or surface photopatterning.[32]

In the current study, we introduce two novel functional monomers which bear a light-cleavable protected-thiol substituent. The polymerizability of the acrylamide monomer via a free radical mechanism is studied. Subsequently, the ability of the so-formed copolymers to release thiols and undergo Michael addition is evidenced. The RAFT process is then used to generate well-defined block copolymers incorporating the masked thiols in one block. Finally, sequential Michael addition reactions are performed at the chain end after aminolysis of the thiocarbonylthio moiety and along the chain after photodeprotection (Scheme 1).

EXPERIMENTAL SECTION

Materials. Cysteamine hydrochloride (98%, ABCR), 2-nitrobenzyl bromide (98%, ABCR), lithium hydroxide (98%, Alfa Aesar), acryloyl chloride (96%, Alfa Aesar), methacryloyl chloride (97%, ABCR), triethylamine (TEA, 99+%, Merck), sodium hydrogen carbonate ($NaHCO_3$, 99%, Roth), 2-aminoethanol (99%, Fluka), tri-*n*-butylphosphine (TBP, ≥90%, Fluka), dimethylphenylphosphine (DMPP, 99%, Sigma-Aldrich), 1,4-dioxane (99+%, Acros), and acetonitrile (HPLC grade, Acros) were used as received. Ethanol, methanol, chloroform, ethyl acetate, toluene, and *n*-hexane were of all from VWR (Normapur grade) and also used as received. 2,2′-Azobisbutyronitrile (AIBN, 98%, Sigma-Aldrich) was recrystallized twice from methanol and stored at −19 °C. *N*,*N*-Dimethylacrylamide (DMAAm, 99%, Sigma-Aldrich) and styrene (99%, Acros) were passed through a column of basic alumina (VWR) to remove the inhibitor and stored at −19 °C. *N*-Isopropylacrylamide (NiPAAm) was recrystallized twice from toluene/*n*-hexane 1:1 v/v. Dichloromethane (VWR, Normapur) was dried on 4 Å molecular sieves. Dibenzyltrithiocarbonate (DBTTC)[33] and benzyl maleimide[34] were synthesized according to previously reported procedures.

*Monomer Synthesis. 2-((2-Nitrobenzyl)thio)ethanamine (**1**).* **1** was synthesized according to a previously reported procedure.[35] In a 150 mL beaker, lithium hydroxide (1.2506 g, 51.2 mmol) was dissolved in deionized water (25 mL) and ethanol (75 mL) was added. The resulting suspension was subsequently introduced into a 250 mL double-necked round-bottom flask containing cysteamine hydrochloride (2.9141 g, 25.1 mmol). A 150 mL dropping funnel was connected and filled with a solution of 2-nitrobenzyl bromide (5.5214 g, 25.0 mmol) in ethanol (100 mL). The solution was subsequently added dropwise to the cysteamine mixture over a period of 15 min at ambient temperature. The mixture was further stirred at 35 °C for 40 min. Ethanol was removed by rotary evaporation, and 100 mL of deionized water was added. The heterogeneous mixture was poured into a separating funnel and extracted with dichloromethane (3 × 150 mL). The organic fractions were combined, dried over sodium sulfate, filtered, and evaporated. The residue was subsequently purified by flash column chromatography using dichloromethane/methanol 4:1 to give the pure product as a yellow viscous oil (3.5365 g, 67%). The compound was rapidly used for further reactions since limited degradation was observed upon storage. ^{1}H NMR ($CDCl_3$, 250 MHz, δ): 7.96 (d, 1H), 7.26−7.59 (m, 3H), 4.07 (s, 2H), 2.85 (t, 2H), 2.57 (t, 2H), 1.67 (s, 2H) ppm.

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*N-(2-((2-Nitrobenzyl)thio)ethyl)acrylamide (**2**).* In a 250 mL double-necked round-bottom flask, **1** (3.5365 g, 16.7 mmol) and triethylamine (2.80 mL, 19.8 mmol) were dissolved in dry dichloromethane (150 mL). A dropping funnel was connected to the flask and filled with a solution of acryloyl chloride in dry dichloromethane (20.2 mmol in 30 mL). The flask was cooled to 0 °C, and the acryloyl chloride solution was added dropwise under vigorous stirring over a period of 30 min. The mixture was then allowed to warm to ambient temperature and left to stir for another 15 h. After washing with 2 × 40 mL of brine and 40 mL of a $NaHCO_3$-saturated solution, the organic phase was dried over magnesium sulfate, filtered, and evaporated. The residue was purified by flash column chromatography using chloroform/ethyl acetate 9:1 as an eluent to give an opaque yellow oil which gave a yellow solid upon standing (3.5143 g, 79%). ^{1}H NMR ($CDCl_3$, 250 MHz, δ): 7.91 (d, 1H), 7.32–7.54 (m, 3H), 6.17 (dd, 1H), 6.10–5.90 (broad, 1H), 6.03 (dd, 1H), 5.59 (dd, 1H), 4.02 (s, 2H), 3.42 (q, 2H), 2.58 (t, 2H) ppm.

*N-(2-((2-Nitrobenzyl)thio)ethyl)methacrylamide (**3**).* The same procedure as for **2** was employed, except that methacryloyl chloride was used instead of acryloyl chloride. Briefly, **1** (0.8278 g, 3.9 mmol) and triethylamine (0.53 mL, 4.0 mmol) were dissolved in dry dichloromethane (70 mL). Subsequently, a solution of methacryloyl chloride in dichloromethane (4.1 mmol in 15 mL) was slowly added. After purification by flash column chromatography using chloroform/ethyl acetate 9:1 as an eluent, **3** was obtained as a viscous yellow oil (0.5542 g, 51%). ^{1}H NMR ($CDCl_3$, 250 MHz, δ): 7.91 (d, 1H), 7.54–7.32 (m, 3H), 6.37–6.17 (broad, 1H), 5.64 (m, 1H), 5.27 (m, 1H), 4.02 (s, 2H), 3.40 (q, 2H), 2.59 (t, 2H), 1.90–1.88 (m, 3H) ppm.

*Polymerizations. (Co)polymerizations of **2** and DMAAm.* In a 10 mL round-bottom flask, monomer(s), AIBN, and—if necessary—DBTTC were dissolved in 1,4-dioxane. For a collation of all polymerization conditions, please refer to Table 1. The mixture was deoxygenated by purging with nitrogen over a period of 30 min. The polymerization was triggered by immersing the flask into an oil bath preheated to 70 °C. Samples were periodically withdrawn to follow the reaction kinetics. A portion was diluted in $CDCl_3$ to determine the conversion by ^{1}H NMR. Another portion was evaporated and dissolved in DMAC (+ 1 wt % LiBr) for size-exclusion chromatography analysis.

Table 1. Experimental Conditions of the (Co)polymerizations at 70 °C in 1,4-Dioxane of *N*-(2-((2-Nitrobenzyl)thio)ethyl) Acrylamide 2 and DMAAm Reported in the Present Study

entry	symbol[c]	[M]/[AIBN]	2:DMAAm (mol/mol)	[DBTTC]/[AIBN]
A[a]		20	100:0	
B[a]		20	15:85	
C[b]	●	100	15:85	
D[b]	×	50	15:85	
E[b]	■	50	0:100	
F[b]	♦	50	39:61	
G[b]	○	50	59:41	
H[b]	▲	50	15:85	2
I[b]	□	50	15:85	1

[a][M] = 2.6 M. [b][M] = 0.5 M. [c]The symbols noted in the Table refer to Figures 1 and 2.

*Synthesis of P(DMAAm-co-**2**) (**4**).* Test polymer **4** was produced to evaluate the possibility of thiol photodeprotection followed by thiol–maleimide addition. The mixture was prepared according to entry B (Table 1): In a 10 mL round-bottom flask, monomer **2** (0.2063 g, 0.77 mmol), DMAAm (0.4345 g, 4.34 mmol), and AIBN (0.0423 g, 0.26 mmol) were dissolved in 1,4-dioxane (2 mL). The mixture was deoxygenated by purging with nitrogen for 30 min and then immersed in an oil bath preheated to 70 °C. After 21 h, the flask was cooled to ambient temperature. The polymer was recovered as a slightly yellow powder by 2-fold precipitation in *n*-hexane at ambient temperature (^{1}H NMR, acetone-d_6) $([\mathbf{2}]/[M])_{polymer}$ = 14 mol % (30 wt %).

*Synthesis of the PDMAAm-TTC-PDMAAm MacroRAFT Agent (**7**).* In a 50 mL round-bottom flask, DMAAm (3.9607 g, 39.6 mmol), DBTTC (0.2320 mg, 0.80 mmol), and AIBN (0.0522 g, 0.32 mmol) were dissolved in 1,4-dioxane (15.9 mL). The mixture was deoxygenated by purging with nitrogen over a period of 1 h. The polymerization was triggered by immersing the flask into an oil bath preheated to 70 °C. After 40 min, the polymerization was stopped by cooling the flask to ambient temperature. ^{1}H NMR analysis of the raw mixture in $CDCl_3$ indicated a conversion of 35%. The reaction mixture was concentrated by rotary evaporation, and the polymer was obtained as a yellow powder by 2-fold precipipation in *n*-hexane followed by filtration on a glass filter. (SEC/DMAC) M_n = 3000 g mol^{-1}; PDI = 1.10 (^{1}H NMR, acetone-d_6) M_n = 2600 g mol^{-1}.

*Synthesis of PDMAAm-b-P(DMAAm-co-**2**)-TTC-P(DMAAm-co-**2**)-b-PDMAAm (**8**).* In a 10 mL round-bottom flask, macroRAFT agent **7** (0.1081 g, 0.04 mmol), DMAAm (0.2153 g, 2.15 mmol), monomer **2** (0.1018 g, 3.82 mmol), and AIBN (0.0083 g, 0.05 mmol) were dissolved in 5 mL of 1,4-dioxane. The mixture was deoxygenated by purging with nitrogen over a period of 30 min. The polymerization was triggered by immersing the flask into an oil bath preheated to 70 °C. After 16.5 h, the polymerization was stopped by cooling the flask down to ambient temperature. ^{1}H NMR analysis of the raw mixture in $CDCl_3$ indicated a conversion of 86%. The reaction mixture was slightly concentrated under vacuum, and the polymer was obtained as a light-yellow powder by 2-fold precipipation in *n*-hexane at ambient temperature followed by filtration on a glass filter. (SEC/DMAC) M_n = 8200 g mol^{-1}; PDI = 1.32. (^{1}H NMR, acetone-d_6) $([\mathbf{2}]/[M])_{polymer}$ = 11 mol % (25 wt %); M_n = 9400 g mol^{-1}.

*Synthesis of the PS-TTC-PS MacroRAFT Agent (**9**).* In a 10 mL round-bottom flask, AIBN (0.0420 g, 0.26 mmol) and DBTTC (0.1483 g, 0.51 mmol) were dissolved in styrene (4.0083 g, 38.1 mmol). The mixture was deoxygenated by purging with nitrogen over a period of 30 min. The polymerization was triggered by immersing the flask into an oil bath preheated to 60 °C. After 7 h, the polymerization was stopped by cooling the flask down to ambient temperature. ^{1}H NMR analysis of the raw mixture in acetone-d_6 indicated a conversion of 33%. The reaction mixture was diluted with a small volume of THF, and the polymer was obtained as a yellow powder by 2-fold precipipation in cold methanol followed by filtration on a glass filter. (SEC/DMAC) M_n = 3800 g mol^{-1}; PDI = 1.12.

*Synthesis of PS-b-P(DMAAm-co-**2**)-TTC-P(DMAAm-co-**2**)-b-PS (**10**).* In a 10 mL round-bottom flask, macroRAFT agent **9** (0.1567 g, 0.04 mmol), DMAAm (0.2153 g, 2.15 mmol), monomer **2** (0.1018 g, 3.82 mmol), and AIBN (0.0083 g, 0.05 mmol) were dissolved in 5 mL of 1,4-dioxane. The mixture was deoxygenated by purging with nitrogen over a period of 30 min. The polymerization was triggered by immersing the flask into an oil bath preheated to 70 °C. After 16.5 h, the polymerization was stopped by cooling the flask down to ambient temperature. ^{1}H NMR analysis of the raw mixture in $CDCl_3$ indicated a conversion of 77%. The reaction mixture was slightly concentrated under vacuum, and the polymer was obtained as a light-yellow powder by 2-fold precipipation in *n*-hexane at ambient temperature followed by filtration on a glass filter. (SEC/DMAC) M_n = 6500 g mol^{-1}; PDI = 1.27. (^{1}H NMR, acetone-d_6) M_n = 9950 g mol^{-1}.

*Synthesis of the P(DMAAm-co-**2**)-TTC-P(DMAAm-co-**2**) macroRAFT Agent (**11**).* In a 10 mL round-bottom flask, monomer **2** (0.2805 g, 1.05 mmol), DMAAm (0.6125 g, 6.12 mmol), DBTTC (0.0404 g, 0.14 mmol), and AIBN (0.0262 g, 0.16 mmol) were dissolved in 1,4-dioxane (13.7 mL). The mixture was deoxygenated by purging with nitrogen for 1 h and then immersed in an oil bath preheated to 70 °C. After 5.5 h, the flask was cooled down to ambient temperature. A monomer conversion of 50% was determined by ^{1}H NMR. The polymer was recovered as a light-yellow powder by 2-fold precipitation in *n*-hexane at ambient temperature. (SEC/DMAC) M_n = 3800 g mol^{-1}; PDI = 1.10. (^{1}H NMR, acetone-d_6) M_n = 3800 g mol^{-1}.

*Synthesis of the P(DMAAm-co-**2**)-b-PNiPAAm-TTC-PNiPAAm-b-P(DMAAm-co-**2**) (**12**).* In a 10 mL round-bottom flask, macroRAFT

agent **11** (0.0385 g, 0.01 mmol), NiPAAm (0.2187 g, 1.93 mmol), and AIBN (0.7 mg, 4 μmol) were dissolved in 1,4-dioxane (3 mL). The mixture was deoxygenated by purging with nitrogen over a period of 30 min. The polymerization was triggered by immersing the flask into an oil bath preheated to 70 °C. After 14 h, the polymerization was stopped by cooling the flask down to ambient temperature. ^{1}H NMR analysis of the raw mixture in $CDCl_3$ indicated a conversion of about 90%. The reaction mixture was concentrated by rotary evaporation, and the polymer was obtained as a yellow powder by 2-fold precipitation in *n*-hexane followed by filtration on a glass filter. (SEC/DMAC) M_n = 16 500 g mol^{-1}; PDI = 1.36.

Polymer-Analogue Modifications. Photodeprotection Kinetics. Copolymer **4** was dissolved in acetonitrile at different concentrations and transferred to a 1 cm square quartz cell. The cell was placed 5 mm in front of a hand-held TLC lamp (8 W) and irradiated at 366 nm at ambient temperature. At timed intervals the cuvette was placed in a UV spectrometer to monitor the absorbance of the solution at 345 nm, corresponding to the maximum of absorption of photoreleased *o*-nitrosobenzaldehyde.

*Synthesis of Fully Deprotected P(DMAAm-co-**2**) **4** (**5**).* Copolymer **4** (0.1044 g, 0.12 mmol protected thiol groups) was dissolved in acetonitrile (39 mL). The solution was transferred in three 15 mL headspace vials (Pyrex, diameter 20 mm), which were airtight crimped employing SBR seals with PTFE inner linear. The mixture was deoxygenated by purging with nitrogen for 30 min. The vials were placed 5 mm in front of a hand-held TLC lamp (8 W) and irradiated at 366 nm at ambient temperature for 2.5 h. Polymer **5** was recovered by precipitation in cold *n*-hexane (0.7740 g, 89%). ^{1}H NMR in acetone (see Figure 4) showed no trace of residual protecting groups.

*Michael Addition on Fully Deprotected P(DMAAm-co-**2**) **5** (**6**).* Copolymer **5** (60 mg, 81 μmol thiol groups), benzyl maleimide (0.2046 g, 1.29 mmol), and DMPP (0.1 mg, 0.7 μmol) were dissolved in acetonitrile (4 mL). The mixture was deoxygenated by purging with nitrogen for 30 min, after which deoxygenated TEA (100 μL, 0.72 mmol) was added using a nitrogen-purged syringe. After 15 h, polymer **6** was recovered by precipitation in cold *n*-hexane. ^{1}H NMR in acetone (see Figure 4) revealed a functionalization yield of 92%.

*Synthesis of PDMAAm-b-P(DMAAm-co-**2**)-SH (**13**).* In a 10 mL round-bottom flask, **8** (0.5996 g, ca. 64 μmol according to M_n determined by ^{1}H NMR) was dissolved in acetonitrile (9.7 mL) together with TBP (21 μL, 85 μmol). The resulting yellow mixture was deoxygenated by purging with nitrogen for 30 min. Using a nitrogen-purged syringe, deoxygenated 2-aminoethanol (49 μL, 0.81 mmol) was added. After stirring 18 h at ambient temperature, a pale yellow solution was obtained. Polymer **13** was recovered by precipitation in cold *n*-hexane. (SEC/DMAC) M_n = 7200 g mol^{-1}; PDI = 1.37.

*Synthesis of ω-((1-Benzyl-2,5-dioxopyrrolidin-3-yl)thio)-PDMAAm-b-P(DMAAm-co-**2**) (**14**).* In a 10 mL round-bottom flask, **13** (0.4200 g, ca. 89 μmol end-chain thiol groups according to M_n(**8**) determined by ^{1}H NMR) and benzyl maleimide (0.1029 g, 0.55 mmol) were dissolved in acetonitrile (11.1 mL). The resulting slightly yellow solution was deoxygenated by purging with nitrogen for 40 min. Using a nitrogen-purged syringe, deoxygenated TBP (12 μL, 49 μmol) was added, followed 20 min later by TEA (45 μL, 0.33 mmol). After 18 h polymer **14** was recovered by precipitation in cold *n*-hexane. ^{1}H NMR in acetone (see Figure 6) revealed a functionalization yield of 95%. (SEC/DMAC) M_n = 8000 g mol^{-1}; PDI = 1.24.

*Synthesis of Fully Deprotected ω-((1-Benzyl-2,5-dioxopyrrolidin-3-yl)thio)-PDMAAm-b-P(DMAAm-co-**2**) **14** (**15**).* Copolymer **14** (90.7 mg, 85 μmol protected thiol groups) was dissolved in acetonitrile (30 mL). The solution was transferred into three 15 mL headspace vials (Pyrex, diameter 20 mm), which were airtight crimped employing SBR seals with PTFE inner linear. The mixture was deoxygenated by purging with nitrogen for 30 min. The vials were placed 5 mm in front of a hand-held TLC lamp (8 W) and irradiated at 366 nm at ambient temperature for 2.5 h. Polymer **15** was recovered by precipitation in cold *n*-hexane. ^{1}H NMR in acetone (see Figure 6) showed no trace of residual protecting groups. (SEC/DMAC) M_n = 6200 g mol^{-1}; PDI = 1.17.

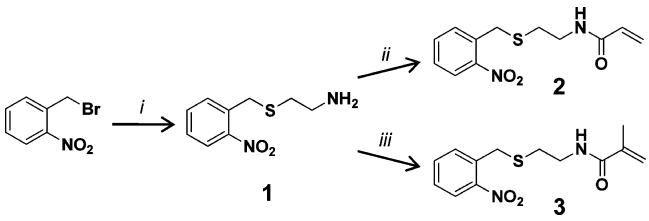
*Michael Addition on Fully Deprotected ω-((1-Benzyl-2,5-dioxopyrrolidin-3-yl)thio)-PDMAAm-b-P(DMAAm-co-**2**) **15** (**16**).* Copolymer **15** (32.7 mg, 35 μmol thiol groups), benzyl maleimide (0.0818 g, 0.44 mmol), and DMPP (0.04 mg, 0.3 μmol) were dissolved in acetonitrile (3 mL). The mixture was deoxygenated by purging with nitrogen for 30 min, after which deoxygenated TEA (40 μL, 0.29 mmol) was added using a nitrogen-purged syringe. After 15 h, copolymer **16** was recovered by precipitation in cold *n*-hexane. ^{1}H NMR in acetone (see Figure 6) revealed a functionalization yield of 89%. (SEC/DMAC) M_n = 8200 g mol^{-1}; PDI = 1.35.

Characterizations. ^{1}H NMR spectroscopy was carried out on either a Bruker AM 250 or a Bruker AM 400 spectrometers at 250 or 400 MHz, respectively. The δ-scale is referenced to tetramethylsilane (δ = 0.00 ppm) as internal standard. Size-exclusion measurements were performed on a Polymer Laboratories/Varian PLGPC 50 Plus system comprising a Polymer Laboratories 5.0 mm bead-size guard column (50 × 7.5 mm^2), followed by three PL columns and a differential refractive-index detector. The eluent was *N*,*N*′-dimethylacetamide (DMAc) at 50 °C with a flow rate of 1 mL min^{-1}. The SEC system was calibrated using linear poly(styrene) (PS) standards ranging from 160 to 6 × 10^6 g mol^{-1} and linear poly(methyl methacrylate) standards ranging from 700 to 2 × 10^6 g mol^{-1}. The resulting molecular weight distributions were determined by universal calibration using Mark–Houwink parameters for PS (K = 14.1 × 10^{-5} dL g^{-1}, α = 0.70).[36] Molecular weights relative to PS are reported in the current contribution. UV/vis spectra were recorded on a Varian Cary 300 Bio spectrophotometer.

RESULTS AND DISCUSSION

Monomer Synthesis. When a statistical copolymerization is conducted, one usually prefers to use comonomers of a rather similar electronic and steric structure. For the sake of versatility, we thus synthesized two monomers starting from the same substituent building block: one acrylamide for copolymerizations with other acrylamides or acrylates and one methacrylamide to use together with other methacrylamides or methacrylates (see Scheme 2). It could be verified that these

Scheme 2. Synthetic Routes to Photocleavable Protected Thiol-Containing Monomers[a]



[a]Reagents and conditions: (i) LiOH, cysteamine hydrochloride, H_2O/EtOH, 35 °C; (ii) acryloyl chloride, triethylamine, DCM, 0 °C → ambient temperature; (iii) methacryloyl chloride, triethylamine, DCM, 0 °C → ambient temperature.

two monomers were photosensitive since a clear change in their UV–vis spectra was observed after irradiation at 366 nm (see Figure S3). In the current study, we will focus on the incorporation of these photoreactive monomers into various macromolecular architectures.

Polymerizability of the *o*-Nitrobenzyl-Protected 2-Mercaptoethyl (Meth)acrylamides. The following part is dedicated to a study on the polymerizability of acrylamide **2**. Indeed, incorporating nitrobenzyl moieties via a prepolymerization approach does not seem straightforward since these groups

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are known to act as retarders or even inhibitors in free-radical polymerization.[37] Nevertheless, some examples can be found in the literature. For instance, although they were unable to obtain homopolymers, Voit and co-workers succeeded in incorporating *N*-nitroveratryloxycarbonyl-protected amines into methyl methacrylate-based polymers.[32a] Gohy and co-workers reported the successful controlled synthesis of homopolymers of nitrobenzyl methacrylate by ATRP, however, only up to 30% conversion.[38] Recently, Grubbs and colleagues successfully employed alkoxyamines bearing nitrobenzyl groups on both the nitroxide and the initiating fragment sides to efficiently control the free-radical polymerization of methyl methacrylate.[39]

We initially proceeded to homopolymerize **2** employing conditions similar to those reported by Voit and colleagues (Table 1, entry A). Contrary to their findings, we observed a conversion of 34% after 24 h at 60 °C (M_n = 22 500 g mol^{-1}; PDI = 1.8). The experiment proves the polymerizability of **2**, yet higher conversions are usually desirable. It was thus decided that a copolymerization approach was feasible, since in most applications (e.g., bioconjugation or surface grafting) the incorporation of few reactive groups along the polymer chain is sufficient for the final purpose. An alternative acrylamide was selected for this purpose, namely *N*,*N*-dimethylacrylamide (DMAAm). Indeed its polymer has the advantage of being organo- and water-soluble and to some extent biocompatible.[40] We initially employed a molar ratio **2**/DMAAm of 15:85 since it represents a reasonable minimal amount of incorporated groups. The copolymerizations were conducted at 70 °C in 1,4-dioxane with two initial AIBN concentrations. With [M]/[AIBN] = 100, the polymerization proceeded relatively slowly and only reached 50% after 8 h (refer to Figure 1): a value at which a conversion plateau was observed. Using a higher concentration of radical initiator ([M]/[AIBN] = 50) permitted to convert 92% of the monomer mixture into polymer in ca. 20 h (Figure 1). Subsequently, the initiator concentration was kept constant and the monomer mixture composition was varied (see Table 1). When DMAAm was reacted alone, the polymerization proceeded relatively rapidly with more than 90% of the monomer being consumed in 4 h.

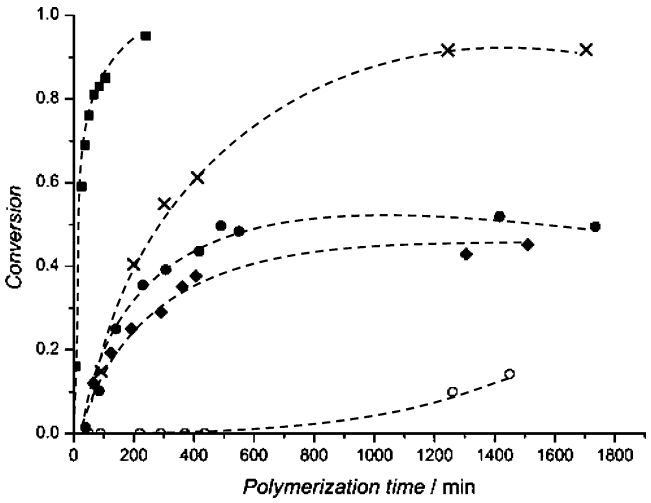

Figure 1. Evolution of the global monomer conversion vs time for the free-radical (co)polymerization of **2** with DMAAm at 70 °C in 1,4-dioxane with variable initiator concentrations and comonomer mixture compositions (see Table 1). The dashed lines are drawn to guide the eye.

Increasing the proportion of **2** and keeping the overall monomer concentration constant resulted in significantly decreased polymerization rates (refer to Figure 1). Examination of the macromolecular characteristics also revealed a strong impact of the nitrobenzene groups on the chain length. Indeed, while molecular weights ranging from ca. 65 and 40 kg mol^{-1} were obtained for the homopolymerization of DMAAm, 3−4 times lower molecular weights were found when 15 mol % of **2** was present in the copolymerization mixture. For a given conversion range, a continuous decrease of MW was observed for an increase in [**2**] (see Figure 2).

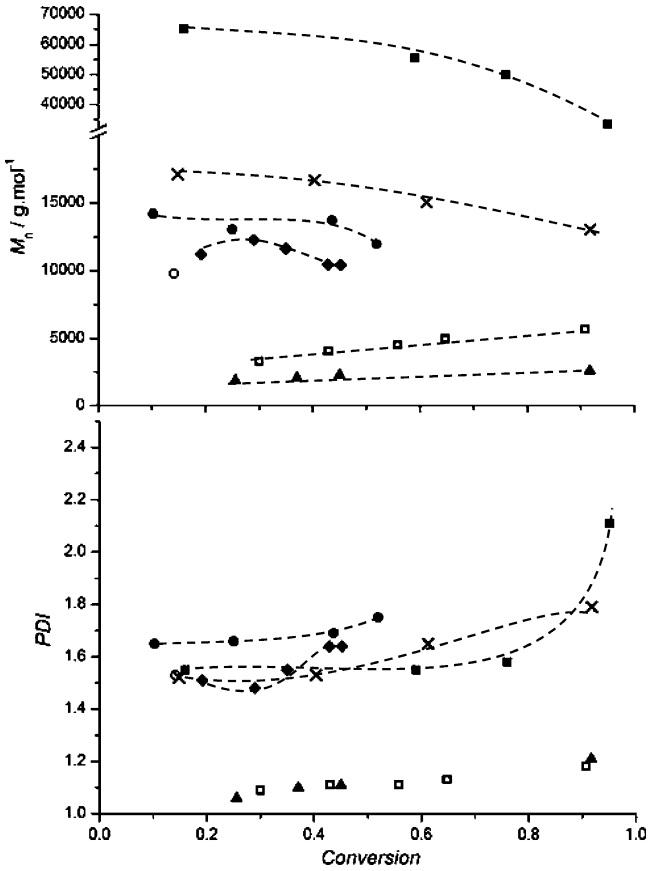

Figure 2. (top) Evolution of the number-average molar masses vs conversion for the free-radical and RAFT-mediated living/controlled radical (co)polymerizations of **2** with DMAAm at 70 °C in 1,4-dioxane with different initiator concentrations and comonomer mixture compositions (see Table 1). (bottom) Corresponding polydispersity indices. The dashed lines are drawn to guide the eye.

We additionally found that **3** was able to copolymerize with methyl methacrylate (see Figure S4). However, the remainder of our study will focus on the acrylamide derivative **2**. The use of **3** for obtaining polymethacrylamide-based polymers will be the subject of a future publication.

In addition to providing a means to calculate the overall monomer conversion, monitoring by ^{1}H NMR revealed that the incorporation of **2** was rather similar to that of DMAAm. Particularly, purified copolymer **4** (Scheme 3), obtained at the highest monomer conversion (92%, entry D), revealed that the *o*-nitrobenzyl thioether moieties remained intact throughout the polymerization and that the comonomer ratio in the copolymer was rather similar to the comonomer feed, 14:86 and 15:85, respectively (see Figure S5). Consequently, we

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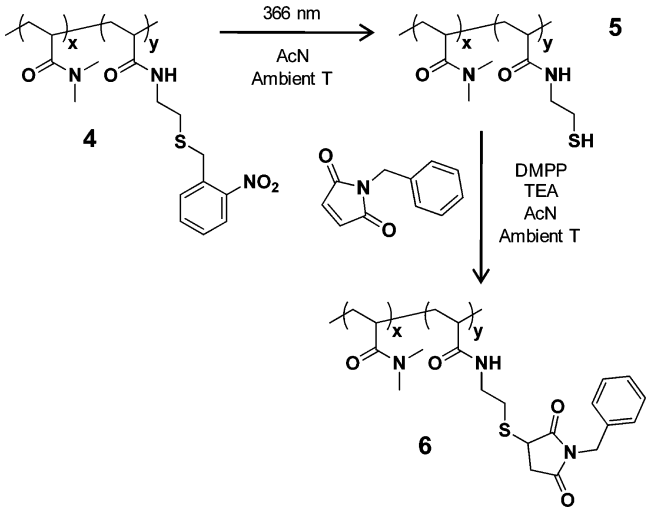
Scheme 3. Photodeprotection of P(DMAAm-*co*-2) Copolymer at 366 nm Followed by Base-Catalyzed Michael Addition with Benzyl Maleimide



evaluated the possibility of releasing thiols along the polymer chains and of subsequently reacting them with Michael acceptors such as maleimide derivatives.

Deprotection and Subsequent Functionalization. The deprotection reaction was performed using a simple hand-held UV lamp (8 W) generally used in laboratories to read TLC plates. The irradiation was carried out at ambient temperature in acetonitrile at 366 nm (refer to Scheme 3), where the absorbance of the polymer due to the presence of the *o*-nitrobenzyl groups is substantial (see Figure S6). Although irradiation at lower wavelengths (UV-C) would probably favor a faster deproctection due to a relatively higher absorbance, we reasoned that the employment of UV-A radiation was more promising in view of potential bioapplications. The drawback is that the photoreleased *o*-nitrosobenzaldehyde possesses a maximum of absorbance at 345 nm.[41] It is thus necessary to work under diluted conditions: a polymer concentration of a few g L^{-1}, which is in fact a typical concentration range in biochemistry.

For a concentration of 3 g L^{-1} of copolymer **4** (3.4 mM) the absorbance at 345 nm does not show any further change after being irradiated for ~2 h. ^{1}H NMR analysis of the purified polymer indicates that at this stage quantitative deprotection is achieved. Indeed, the spectrum of copolymer **5** (Figure 4, middle spectrum) shows no more distinct aromatic peaks, and the signal at ca. 4 ppm accounting for the methylene protons bound to the carbon bridging the sulfur atom and the benzyl ring in copolymer **4** completely disappeared.

Figure 3 clearly evidences the influence of the concentration on the deprotection kinetics. While quantitative deprotection was achieved in about 2 h at 3 g L^{-1}, only 25 min was sufficient to reach 97% deprotection at 0.35 g L^{-1}.

After purification by precipitation, the fully deprotected copolymer **5** was subsequently subjected to reaction with benzyl maleimide in presence of a catalytic amount of dimethylphenylphosphine—acting as a reducing agent to suppress disulfide bridging—and triethylamine as basic catalyst. The reaction was performed at ambient temperature overnight. After removal of the excess maleimide and catalysts, copolymer **6** was recovered and analyzed by ^{1}H NMR (Figure 4, see bottom spectrum). Two new peaks could be observed, both

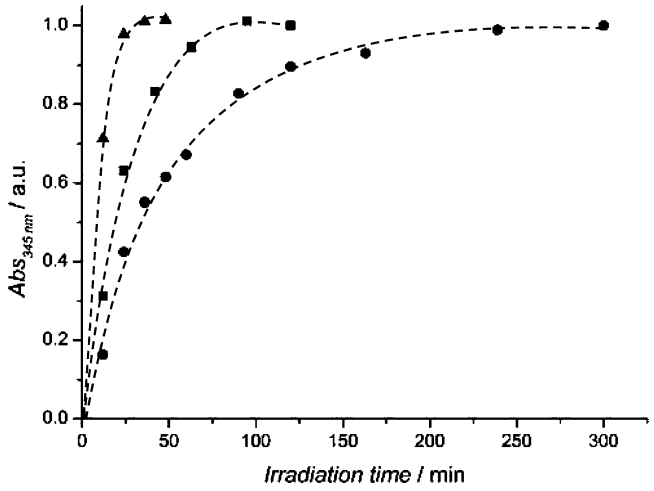


Figure 3. Normalized evolution of the absorbance at 345 nm of copolymer **4** (P(DMAAm$_{86}$-*co*-**2**$_{14}$)) solutions in acetonitrile vs time of irradiation at 366 nm at ambient temperature for different concentrations: 0.35 (▲), 1 (■), and 3 g L^{-1} (●). The dashed lines are drawn to guide the eye.

originating from the maleimide derivative: one at 4.65 ppm accounting for the methylene protons in the α-position of the benzyl ring and one between 7.15 and 7.45 ppm representing the aromatic protons. The absence of ethylenic protons at 6.65 ppm confirms that all excess maleimide was efficiently removed during purification and that the two aforementioned peaks are contributions solely due to grafted benzyl maleimide. Taking as a reference the side chain protons between 2.2 and 3.8 ppm and comparing the aromatic protons of **6** to those of the protected copolymer **4**, we calculate a global deprotection/functionalization sequence yield of 92%.

After having evidenced the efficiency of our system, we focused on obtaining better-defined architectures such as amphiphilic and thermosensitive block copolymers exhibiting the photocleavable group in the hydrophilic block, which could be of interest to construct surface-reactive nanoparticles,[42] nanovesicles,[43] or nanogels.[44]

Well-Defined Macromolecular Architectures. Although nitroxide-mediated polymerization could have been chosen since alkoxyamines are efficient controlling agents in radical polymerization of acrylamides,[45] we opted for reversible-addition−fragmentation transfer (RAFT) polymerization since we had in mind that the thiocarbonylthio moiety present at the end or in the middle of RAFT polymers could provide an additional and orthogonal source of thiols.[24] Furthermore, ATRP of acrylamide derivatives is not straightforward.[46] We employed dibenzyl trithiocarbonate (DBTTC) as RAFT agent since trithiocarbonates allow to efficiently mediate the radical polymerization of acrylamides.[47]

Two kinetic runs were performed using the best conditions found for the free-radical copolymerization of **2** and DMAAm, i.e., giving the highest conversion (entry D). Each experiment was performed with a different concentration of RAFT agent corresponding to [DBTTC]/[AIBN] = 2 or 1 respectively for entries H and I. As expected, in the case of an ideal chain transfer mechanism, the polymerization rate was not affected by the presence of the RAFT agent as conversion vs time plots for entries H and I were very similar to that of entry D (see Figure S8). However, the macromolecular characteristics were strongly altered (refer to Figure 2). Polymers with much lower

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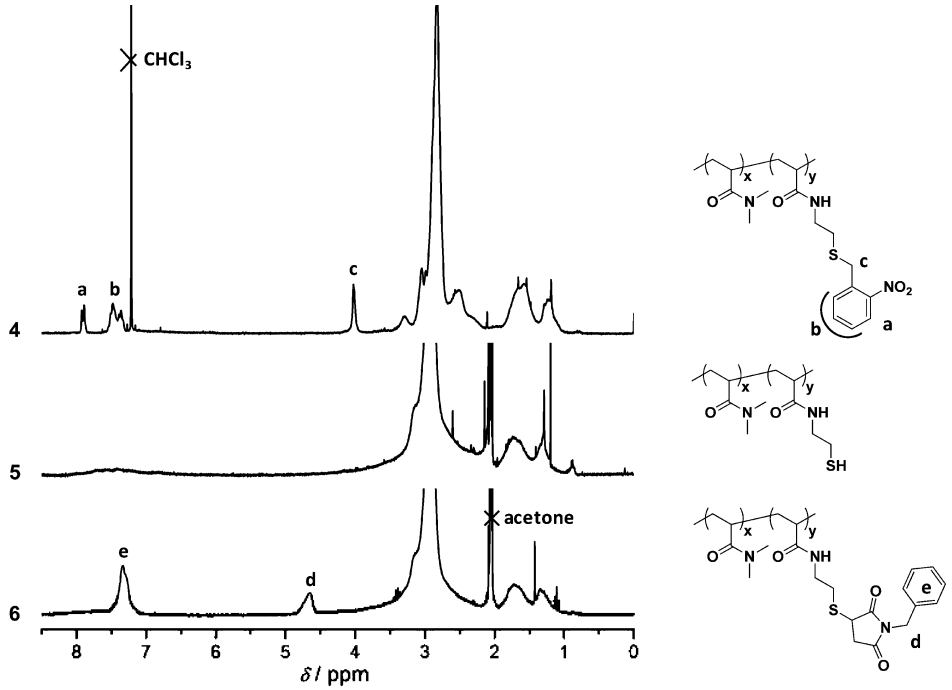

Figure 4. ^{1}H NMR spectra of purified copolymers after, from top to bottom, free-radical copolymerization of **2** with DMAAm (**4**), photodeprotection of a 3 g L^{-1} solution of **4** for 2 h (**5**), and reaction of **5** with benzyl maleimide (**6**).

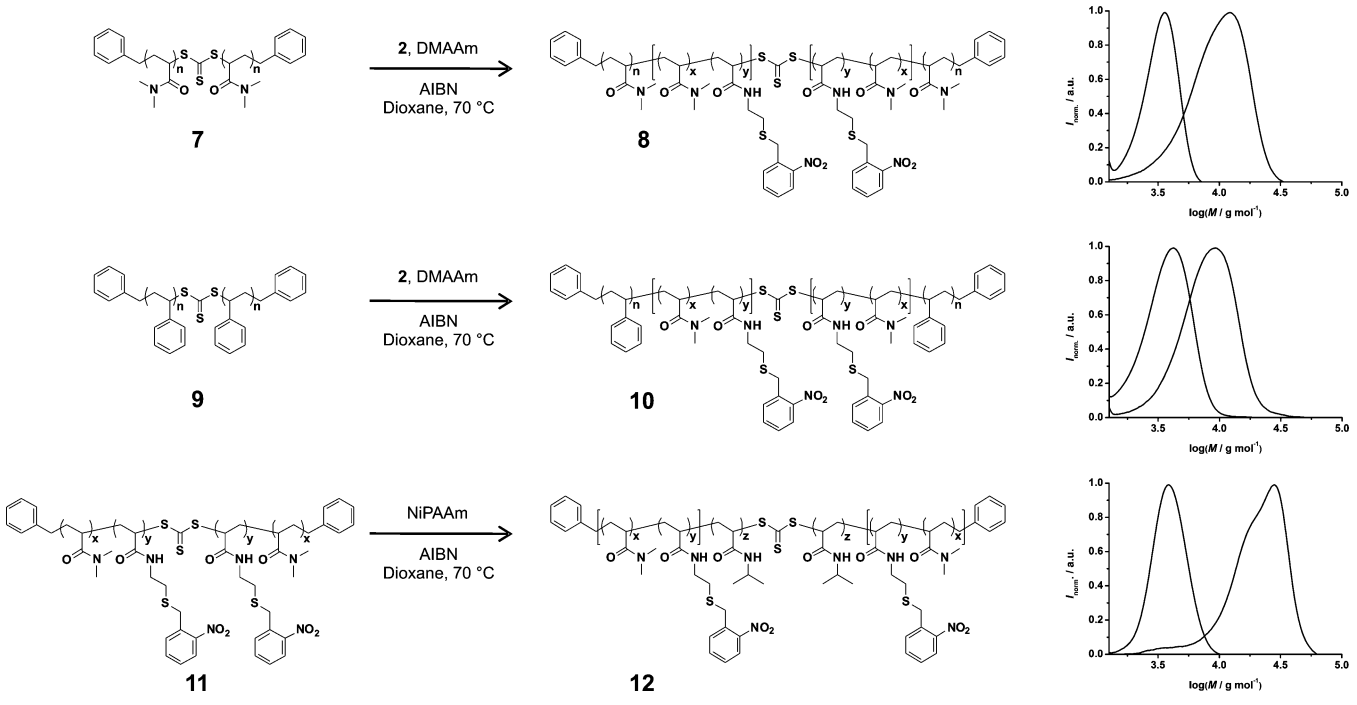

Figure 5. Synthesis of functional triblock copolymers by RAFT-mediated polymerization exhibiting the *o*-nitrobenzyl-protected thiols in either their inner (top and middle rows) or their outer (bottom row) block(s).

molecular weights ranging between 2000 and 5000 g mol^{-1} and polydispersity indices between 1.06 and 1.21 were identified by size-exclusion chromatography. Particularly, the progressive complete shift of the SEC traces with increasing monomer conversion demonstrated the controlled character of the polymerization (see Figure S9). Using PDMAAm or PS macromolecular RAFT agents **7** and **9**, respectively, allowed us to synthesize well-defined bishydrophilic and amphiphilic block copolymers, respectively (Figure 5). In each case, triblock copolymers comprising a middle block possessing the protected thiol units were obtained with rather low polydispersities, i.e., 1.32 and 1.27 for copolymers **8** and **10**, respectively. To further prove the living character of copolymers of **2** and DMAAm obtained in the presence of DBTTC, we synthesized P(DMAAm-*co*-**2**) macromolecular RAFT agent **11** using conditions similar to those of entry H (Table 1) and stopped the polymerization at a monomer conversion of 0.5 (Figure 5). We subsequently performed the RAFT polymerization of *N*-

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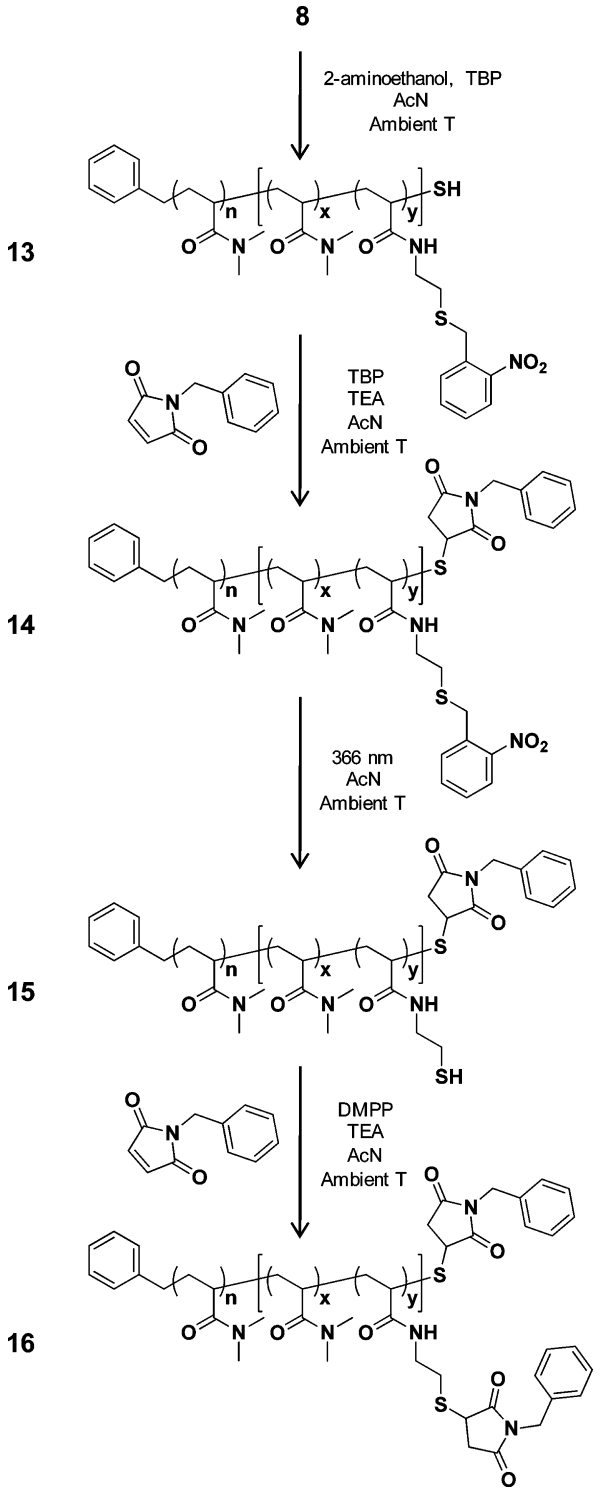
isopropylacrylamide (NiPAAm) in the presence of **11** and AIBN at 70 °C in 1,4-dioxane. The targeted degree of polymerization of the PNiPAAm block was purposely set at a high value (ca. 200) and the polymerization performed to a high monomer conversion (95%) to clearly evidence the consumption of **11**. The overlay of the SEC traces of **11** and of the corresponding product of the NiPAAm RAFT-mediated polymerization (Figure 5, bottom right) shows a distinct shift toward higher molecular weights together with a shoulder and a tail, both at lower molecular weights. The latter certainly originates from dead chains present in macroRAFT agent **11**, while the nonsymmetrical distribution may have arisen from irreversible termination by recombination, highly possible for polymerization of acrylamide derivatives at high conversion.

With the synthesis of copolymers by RAFT-mediated polymerization, we had not only in mind to produce well-defined (block) copolymers but also to introduce an additional masked thiol moiety. Indeed, aminolysis of the thiocarbonylthio compounds eliminates the RAFT end or middle group to yield ω-mercapto polymers (see Introduction). We envisaged that it should be possible to orthogonally deprotect/functionalize both types of thiols in a sequential manner. We thus reacted the block copolymer **8** with 2-aminoethanol in acetonitrile at ambient temperature in presence of tri-*n*-butylphosphine as a reducing agent (see Scheme 4). The effectiveness of the reaction can be assessed via both SEC and UV/vis spectroscopy. Although the number-average molecular weight of polymer **13** was not the half of that **8**—which can be explained by a nonsymmetrical structure or potential disulfide coupling as suggested by the increase in polydispersity—the successful removal of the trithiocarbonate moiety could be evidenced by disappearance of its characteristic UV absorbance maximum at ~310 nm (see Figure S10). ^{1}H NMR performed on the purified diblock copolymer **13** showed that the *o*-nitrobenzyl protecting group was insensitive to the aminolysis process (Figure 6, second row).

The released end-chain thiol functionality present in copolymer **13** was subsequently reacted with benzyl maleimide employing conditions previously described for the Michael addition on the deprotected thiol lateral groups of free-radical polymer **4** to produce benzyl maleimidothioether-capped copolymer **14**. A similar yield of 95% was calculated by ^{1}H NMR (refer to Figure 6). The purified copolymer **14** was then subjected to the same treatment as copolymer **4**, i.e., UV irradiation at 366 nm for 2 h to quantitatively produce copolymer **15** bearing multiple lateral thiol groups followed by triethylamine-catalyzed Michael addition with benzyl maleimide at ambient temperature to yield copolymer **16**. Again, a similar thiol−ene reaction yield of 89% was calculated from the relative integration of the aromatic protons signal to that of other lateral group protons between 2.2 and 3.8 ppm. Finally, it is important to note that the integrity of the well-defined polymeric backbones was maintained throughout all the consecutive modifications as demonstrated by similar molecular weight distributions ($1.17 \leq \text{PDI} \leq 1.25$) within a similar molecular weight range ($7200 \leq M_n \leq 8200$ g mol^{-1}) for copolymers **13**, **14**, **15**, and **16**. However, it remains difficult to draw any numerical interpretation due to the different nature of these copolymers and thus a different hydrodynamic behavior in size-exclusion chromatography.

Scheme 4. Synthetic Strategy for the Orthogonal Double Thiol-Maleimide Michael Addition via Sequential Aminolysis of the Thiocarbonylthio Moieties and *o*-Nitrobenzylthioether UV Deprotection



CONCLUSIONS

The synthesis of two new (meth)acrylamide derivatives bearing a UV-sensitive *o*-nitrobenzyl protected thiol group is reported. Despite the disturbing nature of the *o*-nitrobenzyl group in free-radical processes which retards the polymerization, it was possible to obtain statistical copolymers with *N*,*N*-dimethyla-

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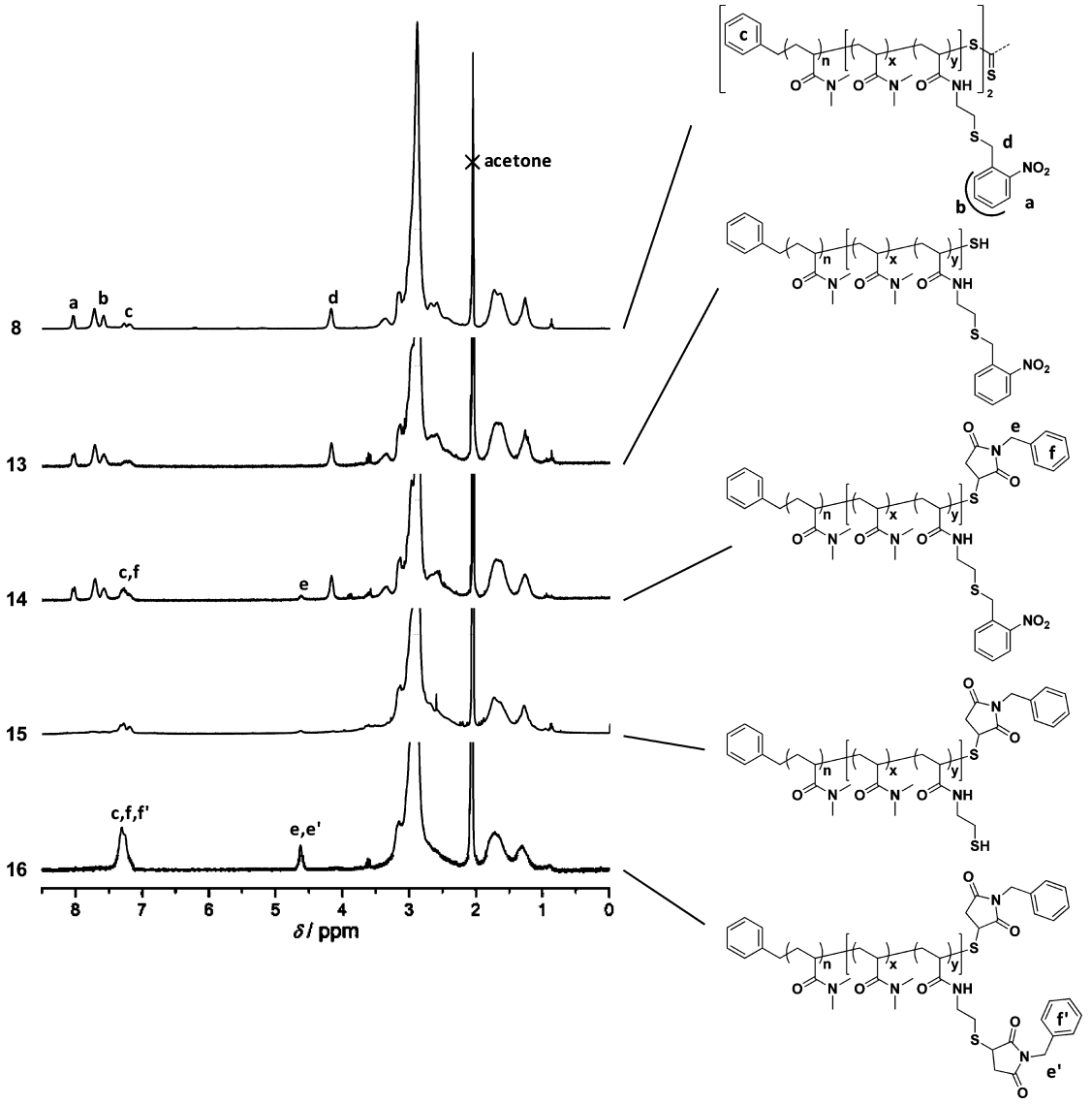

Figure 6. ^{1}H NMR spectra of purified copolymers after, from top to bottom, RAFT-mediated copolymerization of **2** with DMAAm (**8**), aminolysis of **8** (**13**), capping of end-chain released thiol by benzyl maleimide (**14**), photodeprotection of **14** for 2 h (**15**), and reaction of **15** with benzyl maleimide (**16**).

crylamide (DMAAm) in relatively high yields with an appropriate design of the reaction conditions. The protecting group remained intact throughout the polymerization process and could thus be used to trigger the release of multiple thiol groups along polymeric chains by UV irradiation. The deprotection rate was found to be concentration-dependent, probably due to the strongly absorbing nature of the photoreleased caging group in the irradiation wavelength domain. Nevertheless, full deprotection and close-to-quantitative subsequent thiol-maleimide functionalization (92%) could be achieved. In a further effort to create well-defined functional polymeric materials, RAFT-mediated polymerization was utilized to produce block copolymers possessing one statistical block consisting of DMAAm units and the protected thiol acrylamide derivative as a first segment and hydrophilic PDMAAm, hydrophobic polystyrene, or thermosensitive poly(*N*-isopropylacrylamide) as a second one. Importantly, a PDMAAm-based block copolymer was employed to demonstrate the effective orthogonal double deprotection/Michael addition of thiols originating from aminolyzed RAFT thiocarbonylthio midchain group and light-cleavable *o*-nitrobenzylthioether lateral groups, with high efficiency (95 and 89%, respectively).

■ ASSOCIATED CONTENT

Supporting Information

Additional NMR spectra, UV/vis absorption curves, and SEC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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