DOI: 10.1002/masy.200750856

A Study of Simple RAFT Transfer Agents for the Polymerization of (Meth-)acrylates and Acrylamides

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Summary: Within this work we aimed to study different RAFT agents for the potential use in coupled block copolymerization. Starting from S-(thiobenzoyl)thioglycolic acid as a commercial available CTA it should easily be possible to modify the substituent due to the thiocarboxylic group. Different chain transfer agents CTA's were synthesized and RAFT polymerizations of methyl methacrylate, butyl acrylate, *N*,*N*-dimethyl acrylamide, *N*,*N*-diethyl acrylamide, and *N*-isopropyl acrylamide were carried out and compared with each other.

Keywords: acrylamides; block copolymers; RAFT; reversible addition–-fragmentation chain transfer polymerisation

Introduction

Since microgels and microparticles are implement in a large range of applications synthesis and characterization of them have attracted much attention in the last decades.[1–3] Microgels can be synthesized conventionally through emulsion polymerisation. Within this method it is necessary to use a cross-linker (e.g. *N*,*N*-methylenbisacrylamid (BIS) besides monomer, initiator, and surfactant.[4,5] However, with this approach inhomogeneous cross-linking densities were obtained. Another method to generate microgels is photo cross-linking of well defined polymer structures.[6] For this purpose amphiphilic block copolymers, which are able to produce micelles in a proper solution, are used. Depending on which part of the micelle, the core, the corona, or both the core and the corona should be cross-linked a photo sensitive monomer (e.g. 2-(dimethylmaleimido)-*N*-ethylacrylamide (DMIAAm)) has to be integrated randomly in this part of the block copolymer. To synthesize well defined block copolymers with controlled molecular weight and low polydispersity for the mentioned purpose living polymerization techniques would be beneficial. Various living radical methods including nitroxide-mediated polymerisation (NMP),[7] atom transfer radical polymerisation (ATRP),[8,9] and reversible addition–fragmentation chain transfer polymerisation (RAFT)[10,11] have all been successfully adapted for this purpose. In order to obtain end functionalized block copolymers RAFT polymerization has some advantages compared to other techniques. In contrast to NMP and ATRP RAFT chemistry has a high tolerance to functional monomers and to mild reaction conditions (e.g. reaction in the presence of oxygen, low reaction temperature) under which the polymerizations can be carried out.[12–14]

Controlled behaviour is achieved through a dithiocarbonyl component, which is used as a chain transfer agent (CTA) and induces equilibrium of dormant and living chains (Figure 1). CTA activity is mainly influenced by two components, R-group and Z-group. While the Z-group is stabilising the intermediate state of the dithiocarbonyl group, the R-group should be a good leaving group and otherwise able to react with monomers to start new polymer chains.[15] RAFT polymerization enables also the introduction of functionalized

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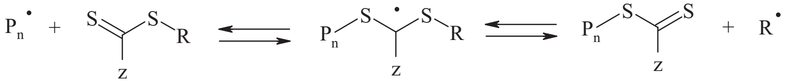

Figure 1.
Basic reaction steps in the RAFT process.

endgroups into the polymer chain. This is possible when the R-group of the CTA is modified with the desired functional group. Block copolymers with defined end functionalities are important with respect to the applications of the microgels they may build. They can exhibit linkages to proteins and also to certain drugs for a potential use in controlled drug delivery.[16,17]

Within this work we aimed to study different RAFT agents for the potential use in coupled block copolymerization. Starting from *S*-(thiobenzoyl)thioglycolic acid as a commercial available CTA it should easily be possible to modify the R-group due to the thiocarboxylic group (Figure 2). Different CTA's were synthesized and RAFT polymerizations of methyl methacrylate, butyl acrylate, *N*,*N*-dimethyl acrylamide, *N*,*N*-diethyl acrylamide, and *N*-isopropyl acrylamide were carried out and compared with each other.

Experimental Part

Materials

The monomers, methyl methacrylate (MMA, Merck-Schuchardt), butyl acrylate (BA, Aldrich), and *N*,*N*-dimethyl acrylamide (DMAAM, Aldrich) were purified by vacuum distillation prior to use. *N*-isopropyl acrylamide (NIPAAM, Acros) was recrystallised from *n*-hexane. *N*,*N*-diethyl acrylamide (DEAAM) was synthesised as described in literature.[18] *S*-(thiobenzoyl) thioglycolic acid (Aldrich), *tert*-butanethiol (Aldrich), polyethyleneglycol methylether ($M_n = 5000$ g/mol) (Aldrich), and 2,2′-azobisisobutyronitrile (AIBN, Merck-Schuchardt) were used as received. $CHCl_3$, 1,4-dioxane, and *n*-hexane were distilled over $CaCl_2$ or KOH before use.

Characterization

Molecular weight and molecular weight distribution (MWD) were obtained by size exclusion chromatography (SEC) using a PL-120 equipped with two GRAM columns (GRAM 10^3 Å and GRAM 10^2 Å) and RI detector. The measurements were carried out in *N*,*N*-dimethyl acetamide (DMAc) with 0.42 wt% LiBr at 50 °C with a flow rate of 1.0 mL/min. PMMA standards were used for calibration. The ^{1}H NMR spectra were recorded on a BRUKER DRX 500 spectrometer (500 MHz).

Synthesis of S-(Thiobenzoyl)thioglycolic acid ethylester (2)

5.0 g (0.024 mol) of *S*-(thiobenzoyl) thioglycolic acid (1), 100 mL chloroform, 1.9 g (0.04 mol) ethanol, and two drops of H_2SO_4 conc. were added into a 250 mL round-bottomed flask. The mixture was boiled in a thermostated oil bath for 5 h under reflux. After cooling to room temperature the reaction solution was washed

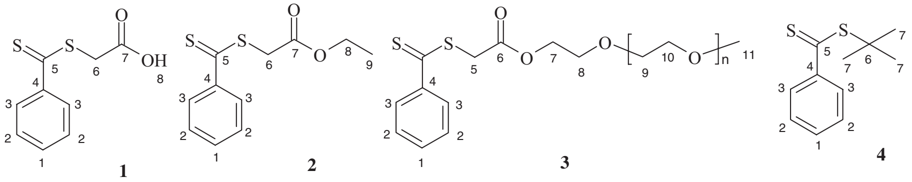

Figure 2.
Chain transfer agents for RAFT - polymerization.

with saturated $NaHCO_3$ to absorb H_2SO_4. The organic phase was washed with deionized water twice and the aqueous phases were extracted twice with $CHCl_3$. Organic phases were dried with Na_2SO_4 and solvent was removed under reduced pressure. The resulted product was dried under vacuum for 1 d at 50 °C. 5.47 g of an oily, red solid were obtained (yield = 94 %).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.29 (t, J = 7.14 Hz, 3H, H-9); 4.20 (dd, J = 7.05 Hz, 4H, H-6,H-8); 7.39 (t, J = 7.98 Hz, 2H, H-3); 7.54 (t, J = 7.42 Hz, 1H, H-1); 8.01 (dd, J = 8.21 Hz, 2H, H-2).

Synthesis of S-(thiobenzoyl)thioglycolic acid-(polyethyleneglycol methylether) ethylester (3)

A 500 ml round-bottomed flask with magnetic stirring bar was filled with 40 g (0.008 mol) polyethyleneglycol methylether, 300 mL $CHCl_3$, 4.2 g (0.02 mol) *S*-(thiobenzoyl)thioglycolic acid, and two drops of H_2SO_4 conc. The reaction mixture was boiled in a thermostated oil bath for 6 h under reflux. After cooling to room temperature the reaction mixture was diluted with 200 mL $CHCl_3$ and washed three times with a saturated $NaHCO_3$ solution and with deionized water twice. The organic phase was dried with Na_2SO_4 and the solvent was removed under reduced pressure. 38.2 g of an oily, red product were obtained.

^{1}H-NMR ($CDCl_3$) δ (ppm): 3.35 (s, 3H, H-11); 3.61 (m, H-10, H-9, H-8,); 4.19 (s, 2H, H-5); 4.21 (t, 2H, H-7); 7.37 (t, J = 7.82 Hz, 2H, H-3); 7.53 (t, J = 7.51 Hz, 1H, H-1); 7.99 (dd, 2H, J = 7.63 Hz, H-2).

Synthesis of S-thiobenzoyl-tert-butyl thioester (4)

To a solution of 3.30 g (0.016 mol) *S*-(thiobenzoyl)thioglycolic acid in 150 mL diethylether 2.6 g (0.029 mol) *tert*-butanethiol in 100 mL 1 N NaOH was added. The red solution was stirred continuously for 5 h and colour changed to purple. The reaction mixture was washed twice with 500 mL 1 N NaOH and 10 % NaCl each. After drying with $MgSO_4$ organic layer was evaporated under reduced pressure. A deep purple liquid product remained (yield 86 %).

^{1}H-NMR ($CDCl_3$) δ (TMS, ppm): 1.67 (s, 9H, H-7); 7.33 (t, J = 7.52 Hz, 2H, H-3); 7.46 (t, J = 7.46 Hz, 1H, H-1); 7.83 (dd, J = 7.51 Hz, 2H, H-2).

General Procedure of RAFT; Preparation of PMMA, PBA, PDMAAM, PDEAAM, PNIPAAM

The polymers were obtained by RAFT polymerization using different CTA's and monomers. A typical procedure to obtain PMMA with CTA 1 with a CTA/AIBN ratio of 5/1 was as follows. Other samples were synthesized in a similar manner.

Into a two neck round-bottomed flask 4.44 g (0.044 mol) MMA, 0.055 g (0.26 mmol) S-(thiobenzoyl)thioglycolic acid, and 0.008 g (0.052 mmol) AIBN were added and dissolved in 20 mL 1,4-dioxane. The mixture was degassed with Argon for 50 min and the reaction was carried out at 80 °C for 25 h. After cooling to room temperature the polymer was precipitated drop wise into 200 mL pentane at 0 °C. The product was separated by filtration and reprecipitated from 1,4-dioxane in pentane and dried under vacuum for 24 h. Due to the CTA a pink-coloured polymer was received.

Results and Discussion

Starting from commercial available *S*-(thiobenzoyl)thioglycolic acid three chain transfer agents for the use in RAFT polymerization could be synthesized by means of esterification or transesterification. High yields and pure products were obtained except that CTA 3 is contaminated with non-functionalized PEG, which could not be separated. Oppositely an excess of compound 1 in the modification could not be removed from PEG-CTA because of the instability of the CTA at basic conditions.

The results of RAFT polymerization of MMA are summarized in Table 1. All reaction systems give polymers with comparable molecular weights, thus, we

Table 1.
Results of RAFT polymerization of methyl methacrylate (MMA).

CTA	t [h]	T [°C]	yield (α) [%]	$M_{th.}$ a) [10^3 g/mol]	M_n [10^3 g/mol]	$\frac{M_w}{M_n}$
1	25	80	26	21.0	50.0	1.53
2	25	80	35	28.2	55.6	1.56
3	48	80	36	33.8	59.3	1.82
4	24	80	68	54.6	61.9	1.68

[CTA]/[AIBN] = 5/1; [MMA]/[CTA] = 160/1; solvent: 1,4-dioxane.

a) $M_{th.} = \frac{[MMA]}{[AIBN]} \cdot \alpha \cdot M_{MMA} + M_{CTA}$.

Table 2.
Results of RAFT polymerization of butyl acrylate (BA).

CTA	t [h]	T [°C]	yield (α) [%]	$M_{th.}$ a) [10^3 g/mol]	M_n [10^3 g/mol]	$\frac{M_w}{M_n}$
1	40	80	69	70.9	24.7	1.49
2	40	80	38	39.2	24.5	1.31
3	40	80	22	27.5	12.6	1.35
4	40	80	72	73.9	28.6	1.22

[CTA]/[AIBN] = 5/1; [BA]/[CTA] = 160/1; solvent: 1,4-dioxane;

a) $M_{th.} = \frac{[BA]}{[AIBN]} \cdot \alpha \cdot M_{BA} + M_{CTA}$.

can conclude that the rates of polymerization are of the same magnitude. The slight changes between the chemical structures of the CTA's do not effect the RAFT of MMA in 1,4-dioxane and molecular weight distributions (MWD) are also similar. However, MWD of the sample which was synthesized in the presence of CTA 3 is broader due to the presence non-functionalized PEG. The best results were obtained with CTA 4. The structure of this CTA is more appropriate for the RAFT polymerization of MMA and less reactive to undergo side reactions.

RAFT polymerizations of MMA with aromatic CTA show similar molecular weights but narrower MWD in benzene.[19] However, these CTA's are only useful for specific solvents. RAFT polymerization of MMA in 2-butanone gives narrow MWD but only low molecular weight even after 24 h. Other CTA's give similar results as described here.[20]

RAFT polymerization of BA yields nearly the same molecular weights for reaction with CTA 1, 2, and 4 but lower molecular weight with CTA 3 (see Table 2). The MWD of RAFT polymerization with CTA 3 exhibits that a narrowly distributed block copolymer was obtained. Great differences in the yields of RAFT prepared with CTA's 1 and 2 were found. This leads us to the conclusion that CTA's with acid functionality are more reactive than

Table 3.
Kinetic studies of RAFT of BA using CTA 1 and CTA 4.

CTA	t [h]	T [°C]	yield (α) [%]	$M_{th.}$ a) [10^3 g/mol]	M_n [10^3 g/mol]	$\frac{M_w}{M_n}$
1	20	80	37	38.1	29.0	1.29
1	30	80	45	46.3	46.7	1.24
1	40	80	69	71.0	36.9	1.49
4	20	80	52	53.5	19.5	1.24
4	30	80	66	67.8	26.6	1.20
4	40	80	72	73.9	28.6	1.22

[CTA]/[AIBN] = 5/1; [BA]/[CTA] = 160/1; solvent: 1,4-dioxane.

a) $M_{th.} = \frac{[BA]}{[AIBN]} \cdot \alpha \cdot M_{BA} + M_{CTA}$.

Table 4.
Results of RAFT polymerization of *N*,*N*-dimethyl acrylamide (DMAAM).

CTA	t [h]	T [°C]	yield (α) [%]	$M_{th.}$ [a] [10^3 g/mol]	M_n [10^3 g/mol]	$\frac{M_w}{M_n}$
1	40	80	45	35.8	11.8	1.49
2	40	80	15	12.1	7.9	1.62
3	40	80	61	53.3	14.2	1.80
4	40	80	65	51.7	12.0	1.21

[CTA]/[AIBN] = 5/1; [DMAAM]/[CTA] = 160/1; solvent: 1,4-dioxane.
[a] $M_{th.} = \frac{[DMAAM]}{[AIBN]} \cdot \alpha \cdot M_{DMAAM} + M_{CTA}$.

without for polymerization of BA. However, the increasing MWD is an evidence for the lost of control of the polymerization.

Kinetic studies of RAFT of BA with CTA 1 show that molecular weight increases and MWD decreases by increasing the reaction time (Table 3). After 40 h MWD becomes broader and conversion increases without increase of molecular weight. RAFT of BA is not longer controlled because longer chains lost their end groups. However, if the same kinetic studies were done with the tert-butyl chain transfer agent (4) molecular weights and conversions increase until a reaction time of 40 h. For all samples MWD's close to 1.2 were obtained. The obtained molecular weights with RAFT polymerization of butyl acrylate are determined in a dimension where end-functionality should still be present. Thus, the synthesized polymers should be convenient to prepare di- or tri block copolymers.

Results of RAFT polymerization of DMAAM in 1,4-dioxane are summarized in Table 4. Molecular weights between 8000 g/mol and 14200 g/mol were obtained. As expected the highest molecular weights were achieved with CTA 3. However, MWD of RAFT product with CTA 3 was relatively broad because of unmodified PEG-molecules in the mixture. Variation of the three carbonic acid derivates used as CTA 1-3 causes no significant difference in the polymer products. Highest yields and narrowest MWD were achieved with the *tert*-butylthioester CTA 4. When the expected molecular weights are compared with the obtained ones there is a clear disagreement. Lower experimental M_n values would mean that more polymer chains are grown than generated from initiator. Differences might also be due to that the PMMA-calibration is not appropriate for the analysed polymers.

RAFT polymerization of DEAAM produced similar molecular weights with the used CTA systems (Table 5). Narrow MWD were obtained with CTA 2 and 4. PDEAAM synthesised with CTA 3 showed a broader MWD analogous to RAFT polymerization of DMAAM. The obtained yields of PDEAAM are higher as the ones of PDMAAM. Table 5 also shows kinetic studies of DEAAM RAFT polymerization with CTA 2. After 20 h the obtained

Table 5.
Results of RAFT Polymerization of *N*,*N*-diethyl acrylamide (DEAAM).

CTA	t [h]	T [°C]	yield (α) [%]	$M_{th.}$ [a] [10^3 g/mol]	M_n [10^3 g/mol]	$\frac{M_w}{M_n}$
1	40	80	50	51.0	13.6	1.45
2	20	80	53	54.1	14.0	1.28
2	30	80	58	59.2	15.4	1.23
2	40	80	60	61.2	16.6	1.27
3	40	80	62	86.0	7.4	1.72
4	40	80	70	71.3	15.0	1.10

[CTA]/[AIBN] = 5/1; [DEAAM]/[CTA] = 160/1; solvent: 1,4-dioxane.
[a] $M_{th.} = \frac{[DEAAM]}{[AIBN]} \cdot \alpha \cdot M_{DEAAM} + M_{CTA}$.

Table 6.
Results of RAFT Polymerization of N-isopropyl acrylamide (NIPAAM).

CTA	t [h]	T [°C]	yield (α) [%]	$M_{th.}$ [a] [10^3 g/mol]	M_n [10^3 g/mol]	$\frac{M_w}{M_n}$
1	20	80	36	32.8	13.3	1.50
2	20	80	10	9.3	13.0	1.45
3	20	80	48	48.4	11.8	1.99
3	48	80	64	62.9	13.1	1.69
4	20	80	12	11.1	5.5	1.24
4	30	80	26	23.7	8.2	1.18

[CTA]/[AIBN] = 5/1; [NIPAAM]/[CTA] = 160/1; solvent: 1,4-dioxane.

[a] $M_{th.} = \frac{[NIPAAM]}{[AIBN]} \cdot \alpha \cdot M_{NIPAAM} + M_{CTA}$.

molecular weight was 14000 g/mol. After 40 h molecular weight and yield increases only about 16600 or rather 60 %, thus, one can conclude that reaction almost stopped (maybe by a loss of active sites). However, narrow MWD after 40 h supports a controlled RAFT polymerisation of DEAAM with CTA 2.

Table 6 presents the results of RAFT polymerization of NIPAAM with different CTA's. There are only small differences of molecular weight and MWD between RAFT with CTA's 1 and 2, but yield with CTA 2 is only 10 %. The reaction with CTA 4 gives the best results as well as at the other studied monomers. RAFT with PEG-CTA was carried out for 20 h as well as for 48 h. The distinction of molecular weight is insignificant but yield increases, hence RAFT polymerization of NIPAAM with the PEG-CTA is less controlled. However, RAFT with CTA 4 shows linear increase in yield and molecular weight with longer reaction time.

Conclusion

S-(thiobenzoyl)thioglycolic acid and two derivatives (ethyl and PEG ester) could successfully be used for the polymerisation of (meth)acrylates and *N*-substituted acrylamides under standardized conditions. By the use of CTA 3 amphiphilic block copolymers could be obtained. However, due to difficulties in the purification of CTA 3 most block copolymers were contaminated with PEG. The later might be removed by dialysis. Based on these results the preparation of stimuli responsive particles should be possible.

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