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SHORT COMMUNICATION

Unsymmetrical bifunctional trithiocarbonate as unexpected by-product in the synthesis of a dithioester RAFT agent

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Abstract The trithiocarbonate 2-(benzylsulfanylthiocarbonylsulfanyl) propanoic acid is formed as minor by-product in the synthesis of the dithioester 2-((2-phenylthioacetyl) sulfanyl) propanoic acid via the Grignard route. The mechanism for this side reaction is not clear. The isolated trithiocarbonate may act as unsymmetrical but bifunctional RAFT agent in the aqueous polymerization of *N*,*N*-dimethyl acrylamide. Therefore, it is important to separate it completely from the dithioester before engaging the latter in controlled free radical polymerization to guarantee a maximum control.

Keywords Reversible addition fragmentation chain transfer · Controlled free radical polymerization · Aqueous polymerization

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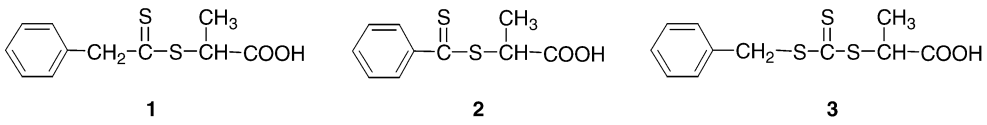
Introduction

The reversible addition–fragmentation chain transfer (RAFT) method [1] has evolved as a powerful technique in the past years, e.g., to prepare polymers with controlled molar mass, relatively low polydispersities, well-defined end groups, or of complex architecture such as block copolymers. The method performs particularly well in comparison to other methods of controlled polymerization, when monomers or reaction media are involved, which contain acid or strongly polar groups, or ligands. Accordingly, our interest has focused on the use of the RAFT method for the synthesis of water-soluble polymers [2, 3] or for polymerization reactions in aqueous media [4–6]. In the search for suited RAFT agents, we were attracted by reports on the dithioester 2-((2-phenylthioacetyl)sulfanyl) propanoic acid **1** (Fig. 1) [7], as this agent enables relatively fast polymerizations with only short induction periods compared to its analogue 2-[thiobenzoylsulfanyl] propionic acid **2** and other dithiobenzoates [8, 9], which, so far, have been used much more frequently [10]. Moreover, the 2-propionyl leaving group enables the synthesis of telechelic polymers bearing a carboxyl end group [11, 12].

The success of the controlled polymerization techniques depends crucially on the minimization of side reactions. This is true not only for side reactions that are inherent to the system but also to such that result from impurities in the reagents, in our case, e.g., of the RAFT agent used, or from side products formed in the course of the reaction. Therefore, there is a growing awareness to identify possible contaminants or side reactions of the most widespread classes of RAFT agents, namely, dithioesters and trithiocarbonates, which may interfere with the success of the RAFT process. For instance, hydrolysis [5, 6, 13, 14] or aminolysis [11] of dithioesters is a particular threat. The

Fig. 1 Dithioesters and trithiocarbonates discussed



(partial) loss of RAFT active end groups under these circumstances is even aggravated by the formation of thiols that are known to act as efficient classical chain transfer agents. Another example is the oxidative degradation of the thiocarbonyl group to the carbonyl group [15]. Also, thermal *cis*-elimination of the dithioacid fragment was described recently [16]. Concerning disturbing impurities, possible residual thiols left over from the synthesis of dithioesters and trithiocarbonates must be removed carefully for the reasons mentioned above. Depending on the synthetic procedures chosen, the contamination of dithioesters by the analogous thioesters must be taken into account, although the latter seem to have only little effect on the polymerization [5]. The latter example is rather exceptional in the sense that the occurring impurities were identified. Otherwise, the synthesis of RAFT agents is generally troubled by the occurrence of colored impurities, which must be removed by extensive recrystallization or by chromatography, but whose chemical nature stays obscure, as they generally are not identified.

Experimental section

Materials and methods

Benzyl magnesium chloride (1.3 M in tetrahydrofurane (THF) from Fluka), carbon disulfide (99% from Aldrich), 2-bromopropionic acid (99% from Fluka), 4,4′-azobis(4-cyanovaleric acid) (97% from Acros Organics), and trioxane (99.5% from Acros Organics) were used as obtained. Tetrahydrofurane (99% from Fluka) was distilled over sodium/potassium metal under nitrogen. A 1,4-dioxane (99% from Merck) and *N*,*N*-dimethyl acrylamide (99% from Aldrich, stabilized with hydroquinone monomethylether) were purified before polymerization by column filtration (aluminium oxide, basic, 50–200 μm mesh from Acros Organics).

^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR were performed on a Varian Bruker 300 MHz and 75 MHz, respectively. UV–Vis analysis was performed on a Cary 1 Varian UV–Vis spectrophotometer. Aqueous size exclusion chromatography (SEC) was performed using a Spectra

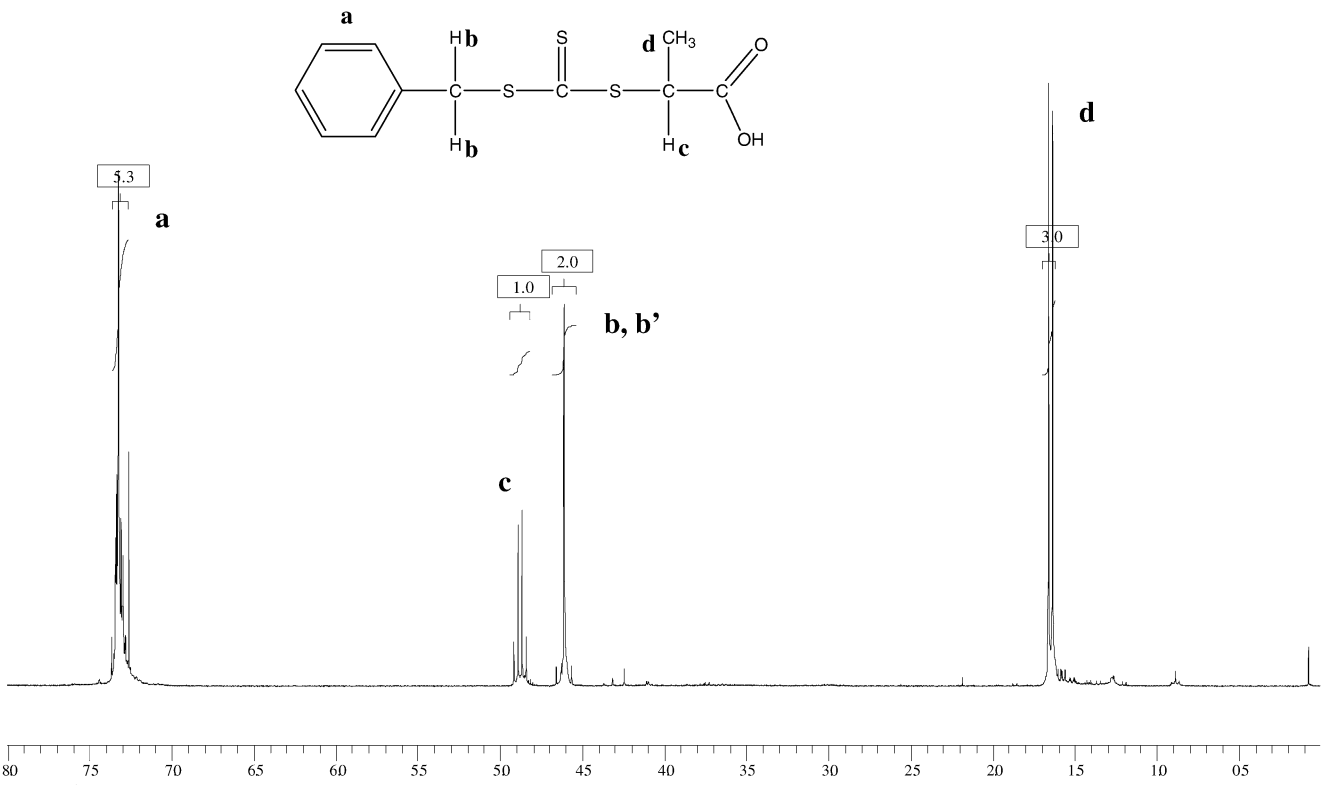


Fig. 2 ^{1}H NMR spectrum of 3 in $CDCl_3$

Physics P 1000 isocratic pump equipped with a Wyatt Optilab DSP refractive index detector, a Spectra Physics UV 2000 UV/VIS detector, and a set of four TSK-GEL® polyglycidyl(meth)acrylate gel columns [6,000 (7.5× 300 mm); 5,000 (7.5×300 mm); 3,000 (7.5×300 mm), Hema Bio (hydroxyethylmethacrylate gel); 40 (8.0× 300 mm)] from Tosoh Biosep (Montgomeryville, USA). A 0.2 M Na_2SO_{4+} 1% acetic acid in deionized water was used as an eluent (1.0 ml·min^{-1}) at 23 °C. Calibration was performed with poly(vinylpyrrolidone) standards.

Synthesis of 2-(benzylsulfanylthiocarbonylsulfanyl) propanoic acid **3**

Following the procedure of d'Agosto et al. [7] for the synthesis of 2-((2-phenylthioacetyl)sulfanyl) propanoic acid (or 2-[(2-phenyl-1-thioxoethyl)thio]-propanoic acid as named in [7]), 1.3 M benzyl magnesium chloride in THF (31.0 ml, 40 mmol) and dry tetrahydrofurane (40.0 ml) were placed under nitrogen in a 250-ml three-necked flask fitted with a condenser. While cooling the flask in an ice bath, dry carbon disulfide (4.0 ml, 66 mmol) was added dropwise under stirring to yield a deep orange mixture. After 30 min, 2-bromopropionic acid (3.6 ml, 40 mmol) was added slowly. After 52 h, the mixture was poured into 200 ml of ethylacetate, washed with water (3×100 ml) and with saturated brine (100 ml). The organic extract was dried over magnesium sulfate. Solvents were evaporated under reduced pressure. The excess of bromopropionic acid was removed by micro-distillation at 160 °C and 0.5 mbar. The residue was dissolved in diethyl ether (200 ml) and extracted with a 50:50 (*v/v*) mixture of saturated sodium hydrogen carbonate with water (1×100 ml). The aqueous phase was washed with diethyl ether (1×50 ml) and acidified to pH<1 with 1 M hydrochloric acid. The milky solution was extracted with ethyl acetate (2×100 ml); the combined organic extracts were washed with water (2×50 ml) and saturated aqueous sodium chloride (50 ml) and dried with magnesium sulfate. Evaporation of the solvent gave a red oily product. By repeated crystallization from a mixture of hexane/benzene 10:1 (*v/v*), a colored by-product **3** could be separated from the main fraction of 2-((2-phenylthioacetyl)

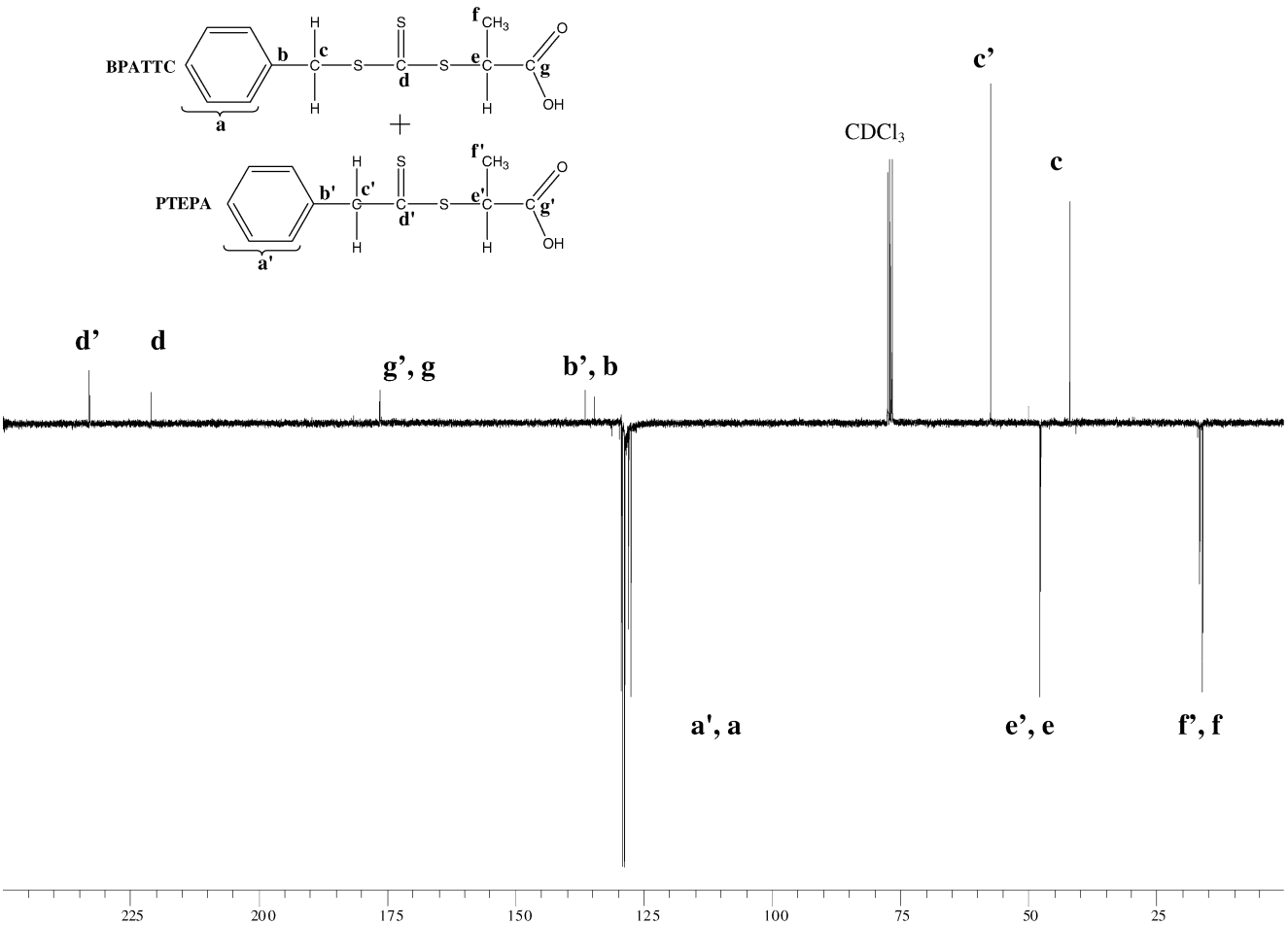


Fig. 3 ^{13}C NMR spectrum (75 MHz, spin-echo) of a mixture of **1** and **3** in $CDCl_3$. Peak assignments for **1** are according to literature [7]. Peak assignments for **3** are made due to increment calculations [24] and analogies to the spectrum of **1**

sulfanyl) propanoic acid **1**. Yield, 0.294 g (2.7%) of orange crystals of **3**.

Elemental analysis ($C_{11}H_{12}O_2S_3$, M_r=272.41 g·mol^{-1}): C 48.50, H 4.44, S 35.31; found C 49.28, H 4.42, S 34.19.

Mass spectrometry (Fast Atom Bombardment (FAB), matrix glycerol, positve ions) signal at (m/z): 272.6 (M+1), 123.1 (phenyl–CH_2–S), 91.2 (benzyl), 77.4 (phenyl).

^{1}H NMR (300 MHz in $CDCl_3$): δ_H=1.65 (d, 3H, –CH_3), 4.61 (d, 2H, –CH_2–), 4.88 (q, 1H, –CH–), 7.2–7.4 (m, 5H, Ar–H) ppm.

^{13}C NMR (75 MHz in $CDCl_3$) δ_C=16.59 (–CH_3), 41.90 (–CH_2–), 47.75 (–CH–), 127.44, 127.91, 128.75 (CH_{aryl}), 134.45 (C_{aryl}), 176.32 (–COOH), 220.92 (–C(=S)–S–) ppm.

Fourier transform infrared spectroscopy (KBr, selected bands): 3,645–2,351, 1,703, 1,450, 1,414, 1,313, 1,240, 1,063, 925, 823, 796, 708, 692 cm^{-1}.

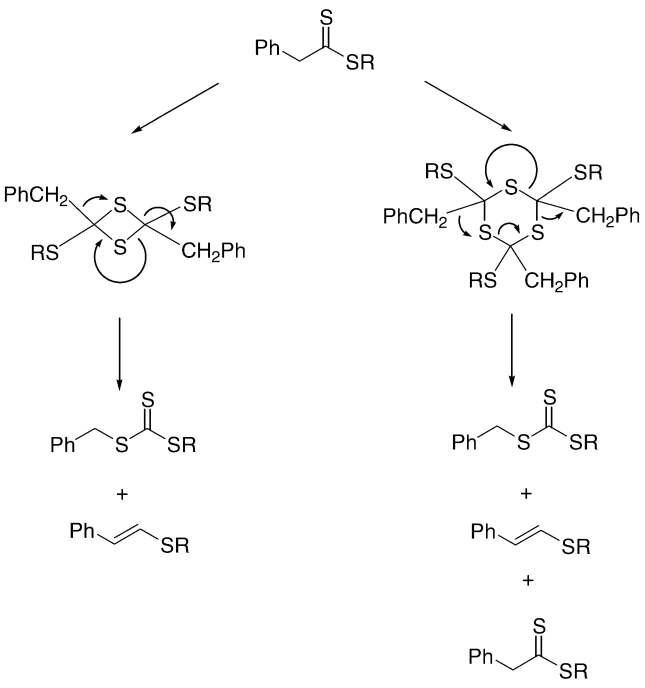
UV–Vis (in water): bands at λ_{max}=445 nm (ε= 110 l·mol^{-1}·cm^{-1}), λ_{max}=368 nm (ε=460 l·mol^{-1}·cm^{-1}), λ_{max}=310 nm (ε=10,400 l·mol^{-1}·cm^{-1}).

RAFT polymerization of N,N-dimethyl acrylamide in water

N,*N*-Dimethyl acrylamide was passed over basic aluminum oxide to remove the inhibitor hydroquinone monomethylether. Deionized water was boiled and cooled down under nitrogen. 2-(Benzylsulfanylthiocarbonylsulfanyl) propanoic acid **3** (0.0240 g, 1.10^{-4} mol), 4,4′-azobis(4-cyanovaleric acid) (0.0058 g, 2.10^{-5} mol), *N*,*N*-dimethyl acrylamide (2.00 g, 2.02.10^{-2} mol), and water (10.0 g) were placed in a two-necked 50-ml flask equipped with a magnetic stirrer. A pH level of 3 was adjusted to neutral by adding 0.1 M aqueous NaOH. The flask was closed by septa, and the mixture degassed by bubbling through N_2 for 30 min. The mixture was heated to 85 °C for 245 min. Every 20 min, 0.4-ml samples were withdrawn using a stainless steel syringe previously rinsed with N_2, and an equivalent amount of N_2 was introduced in the flask. Polymerization was stopped by freezing the samples in liquid N_2 and storing at +4 °C. SEC samples were prepared by adding 5 ml of the eluent to 0.2 g of each sample.

Results and discussion

In this context, we noticed that a small but varying amount of yellow-orange impurity was formed during the synthesis of dithioester **1** when synthesized from benzyl magnesium-chloride, CS_2, and 2-bromopropionic acid. This impurity showed a similar color to the desired product and proved difficult to remove, as for instance, it shows a very close retention factor in thin layer chromatography. By varying the work-up procedures, we succeeded to separate this product by repeated crystallization from hexane/benzene 10:1 (*v*/*v*) to give orange needles in low yield (<5%). The ^{1}H NMR spectrum (Fig. 2) shows an identical number of signals with very similar coupling patterns and chemical shifts to the reported spectrum of the target compound **1** [7]. Still, the slight differences are significant: whereas the signals attributed to the methyl and phenyl group show the same chemical shifts in the by-product and in **1** within experimental precision, the signals attributed to the protons in α positions to the thiocarbonyl moiety are shifted by 0.2–0.4 ppm to lower field in the by-product. Moreover, elemental analysis indicates a net chemical formula of $C_{11}H_{12}O_2S_3$ for the by-product instead of $C_{11}H_{12}O_2S_2$ for the target **1**. In agreement, FAB mass spectrometry indicates a molar mass of 272. The decisive clue comes from the ^{13}C spectrum of the by-product. Although the spectrum exhibits many similarities to the one of **1**, as found in the ^{1}H NMR spectra, most importantly, the signal at 57.3 ppm that is attributed to the benzylic carbon is replaced by a new signal at 41.9 ppm, whereas the 232.6-ppm signal of the C=S group in a dithioester is replaced by a signal at 220.9 ppm. The latter signal position is characteristic for the C=S group in trithiocarbonates. The differences are best illustrated in the spectrum of the mixed compounds (Fig. 3) when the amount of the side product exceeds a certain level (otherwise, the relatively weak thiocarbonyl signal will be easily missed).



Scheme 1 Hypothetical mechanism for cyclodimerization or cyclotrimerization of the thiocarbonyl groups with subsequent rearrangement and fragmentation to yield trithiocarbonates from dithioesters/SCM

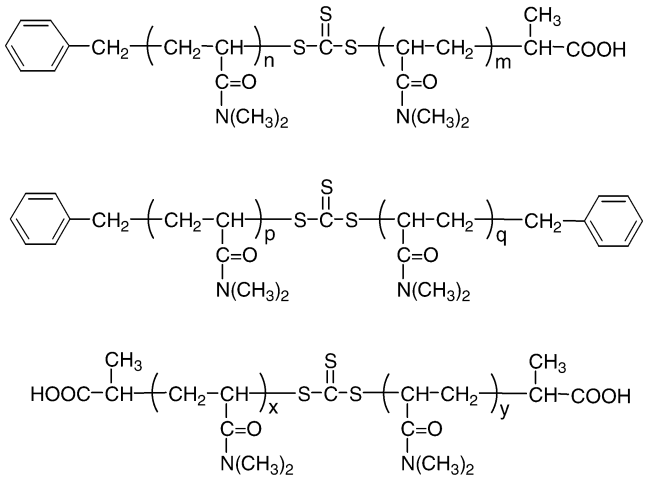


Fig. 4 Possible polymers obtained by RAFT polymerization when using RAFT agent **3**

Thus, to our surprise, the combined analytical data reveal that trithiocarbonate 2-(benzylsulfanylthiocarbonylsulfanyl) propanoic acid **3** (Fig. 1) is formed as the by-product in the synthesis of dithioester 1. This observation is not trivial to rationalize. Generally, the synthesis of **3** in the reaction mixture containing base and CS_2 would imply the presence of benzylmercaptane. However, the analysis of the starting compounds excluded such a contamination. Hence, we must conclude that **3** is formed due to a genuine side reaction of the target dithioester.

We can only speculate presently about the mechanism for the formation of the trithiocarbonate **3**, either instead of or from dithioester **1**. Possibly, the formation of by-product **3** is linked to the thermal stress applied during the distillation of the raw product in the work up. However, so far, thermal decomposition of dithioesters has been referred to olefin elimination with subsequent decomposition of the resulting dithioacid [16, 17]. Still, considering the high tendency of thioaldehydes and thioketones to form cyclic dimers and trimers already at ambient temperature due to the poor overlap of the C 2p and the S 3p orbitals of the thiocarbonyl moiety [18], the heating of **1** during distillation might possibly induce cyclodimerization or cyclotrimerization of the >C=S groups, with subsequent rearrangement and fragmentation, thus leading—within other by-products—to trithiocarbonate **3** (Scheme 1). This hypothetical reaction may be related to the known oligomerization of dithioformic acid upon storage [19], although this behavior has been considered as specific for this dithioacid due to its thioaldehyde-like character so far [20].

Whatsoever is the underlying reaction mechanism, the formation of trithiocarbonate **3** as side product may have important consequences. Trithiocarbonates can act as efficient RAFT agents, depending on the nature of the substituents. Trithiocarbonate **3** now bears two different fragments, namely, the 2-propionyl residue and the benzyl moiety, both of which are known to be good leaving groups in the RAFT polymerization of, e.g., styrenic and acrylic monomers [1, 10]. However, the reactivities of these two leaving groups differ [9], so that such a substitution pattern should complicate the RAFT process. For instance, the kinetics of the primary radical addition fragmentation steps will a priori not be identical. Also, the control on the end groups will be diminished, as degenerative chain transfer with **3** will result in a mixture of polymers with either two benzylsulfanyl, or with two 2-propionylsulfanyl, or with mixed end groups (Fig. 4).

The efficiency of trithiocarbonate **3** in aqueous RAFT polymerization was tested for the model monomer *N*,*N*-dimethyl acrylamide in aqueous solution (Fig. 5). As for many other RAFT systems [6, 14, 21–23], an inhibition period was found (in our case of about 25 min) before notable amounts of polymer were formed. Analysis of the data shows a linear evolution of the plot of $\ln([M_0]/[M])$ vs reaction time, indicating a constant concentration of active centers up to high conversions. The SEC data show the

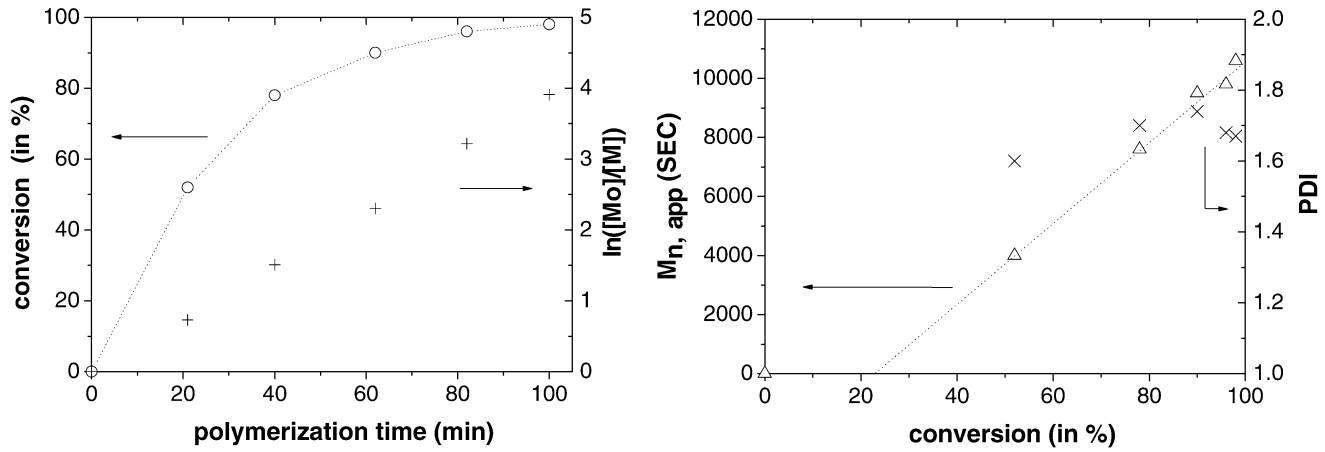


Fig. 5 SEC monitored aqueous polymerization of *N*,*N*-dimethyl acrylamide in the presence of RAFT agent **3**. The *lines* are guides to the eye

linear increase in the (apparent) number molar mass average $M_{n,app}$ with conversion, as is characteristic for controlled polymerizations. All these observations suggest that controlled polymerization takes place in the presence of **3**. Still, the apparent polydispersity was determined to be about 1.6–1.7. This value is high for polymers made by RAFT. The effect could be merely due to the calibration of the SEC by poly(vinylpyrrolidone) standards, i.e., by a polymer of different chemical nature than the analyte. But the finding rather suggests a reduced control of the polymerization process, alternatively, due to the two different leaving groups present in RAFT agent **3**. Clarification of this point will require a detailed polymerization study, but in any case, end group control is decreased in this system.

Conclusions

The synthesis of the dithioester 2-((2-phenylthioacetyl) sulfanyl) propanoic acid via the Grignard route produces the closely related trithiocarbonate 2-(benzylsulfanylthiocarbonylsulfanyl) propanoic acid as by-product. Preliminary tests demonstrate that a contamination of samples of the dithioester by some trithiocarbonate will not be inert in RAFT polymerizations. As the latter is able to act as RAFT agent by itself, such impurities will not endanger the basic RAFT polymerization process, but they may reduce the extent of polymerization control. Our findings, therefore, underline the importance of careful analysis and purification of the reactants employed in addition to the optimization of the polymerization conditions, for the optimization of controlled free radical polymerization systems.

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