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New chain transfer agents for reversible addition-fragmentation chain transfer (RAFT) polymerisation in aqueous solution

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Abstract

New chain transfer agents for free radical polymerisation via reversible addition-fragmentation chain transfer (RAFT) were synthesised that are particularly suited for aqueous solution polymerisation. The new compounds bear dithioester and trithiocarbonate moieties as well as permanently ionic groups to confer solubility in water. Their stability against hydrolysis was studied, and compared with the one of a frequently employed water-soluble RAFT agent, using UV–Vis-spectroscopy and ^{1}H-NMR measurements. An improved resistance to hydrolysis was found for the new RAFT agents compared to the reference one, providing good stabilities in the pH range between 1 and 8, and up to temperatures of 70 °C.

Keywords: Reversible addition fragmentation chain transfer; Polymer synthesis; Polyelectrolytes

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1. Introduction

Free radical polymerisation has got new impetus in the past years due to the up-rise of the so-called 'controlled polymerisation' methods. Compared to the classical free radical process, these methods enable the synthesis of homo- and copolymers with predictable molar masses, low polydispersities, and well-defined end-groups. Also, the synthesis of complex polymer architectures is facilitated such as of stars, graft and block copolymers. The mostly used methods are the so-called 'nitroxide mediated polymerisation' (NMP) [1–3], 'atom transfer radical polymerisation' (ATRP) [4–6], and more recently 'reversible addition-fragmentation chain transfer polymerisation' (RAFT) [7–9] and, as special case, 'macromolecular design via the interchange of xanthates' (MADIX) [10]. Each of the methods presents inherent advantages and inconveniences.

Although a prominent advantage of free radical polymerisation is the tolerance to electrophilic and nucleophilic compounds, in particular to the presence of water, controlled free radical polymerisation studies in aqueous solution are minority [10–18]. On the one hand, this is due to the need of modifying the necessary additives to confer water-solubility to them. On the other hand, this is due to the high temperatures of above 100 °C, as often needed for NMP, or to the sensitivity of the 'controlling agents' to the presence of water, as for many ATRP catalysts. In this context, the use of the RAFT method appears particularly appealing for aqueous polymerisation systems [12]. Still, the number of reports on the use of the RAFT method in aqueous systems is limited [18–30], and surprisingly little has been reported concerning the stability of the RAFT agents under such polymerisation conditions. However, the commonly used classes of dithioester and trithiocarbonate compounds are known to be sensitive to hydrolysis [31]. Therefore, new designed RAFT agents are needed as well as more information about the water stability of RAFT agents, in order to explore to which extent RAFT polymerisations enable a

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controlled free radical polymerisation in aqueous solution.

In this general context, we synthesised some new dithioester and trithiocarbonate derivatives suitable for RAFT polymerisations (Fig. 1), that are specially designed for water-solubility independent of the pH, by virtue of a permanently ionic group, and studied their stability towards hydrolysis in dependence on the pH and the temperature. The results were compared with the behaviour of 4-(thiobenzoylthio)-4-cyanopentanoic acid **4**, i.e. the RAFT agent that is the most frequently used one for aqueous polymerisation systems up to now [19,21,26,27,29].

RAFT agents **1–3** bear the permanently charged cationic quaternary ammonium group, or the anionic sulfonate group, respectively. In contrast, the hydrophilicity of the carboxyl group in **4** depends on the pH controlled protonation/deprotonation equilibrium. As for **4**, the active fragment ('Z-group') for the RAFT process is dithiobenzoic acid in **1** and **3**, while **2** bears the trithiocarbonate group. The potential leaving groups in the addition fragmentation process are the benzyl group in **1** and **2**, and the propionate-2-yl group in **3**. Both groups are known to be suited for controlling the polymerisation of styrenic and acrylic monomers [7,8]. However, the second substituent of the trithiocarbonate group in **2** is an *n*-alkyl group that is not expected to participate in the addition fragmentation process due to the stronger C–S bond [24]. Accordingly, RAFT agent **2** is not bifunctional, as most other trithiocarbonates used for RAFT so far, but acts a monofunctional RAFT agent only [8,18,24,25], as do compounds **1**, **3** and **4**.

2. Experimental

2.1. Materials

N-methylmorpholine (99.5 + %), α,α′ dichloro-*p*-xylene (98%), carbon disulfide (99.9 + %) and phenyl magnesium chloride (2 M in THF) were used without further purification from Aldrich. Anhydrous magnesium sulfate (98 + %), sodium 2-mercaptoethanesulfonate (98 + %), taurine (99 + %) and 2-bromopropionyl bromide (+97%) were used as received from Fluka. Solvents used for synthesis were all analytical grade (Riedel de Haën and Fluka). 2,2′Azobis(2-methylpropionamidine)dihydrochloride (**V-50**) was a gift of Wako Pure Chemical Industries. Vinylbenzyltrimethylammoniumchloride (**VBAC**), 60:40 para:meta mixture (97%), deuterium oxide (99.8 Atom % D) and thiobenzoic acid (90%) were purchased from Acros Organics. Buffer solutions 'A' potassium hydrogen phthalate/HCl (pH = 4.01 ± 0.02 at 25 °C), 'D' potassium dihydrogen phosphate/sodium hydrogen phosphate (pH = 7.01 ± 0.01 at 25 °C) and 'G' sodium hydrogen carbonate/sodium carbonate (pH = 10.01 ± 0.01 at 25 °C) were purchased from Roth. Buffer solution 'B' pH = 5.00 ± 0.02 potassium hydrogen phthalate/NaOH was purchased from Aldrich. Buffer solution 'C' pH = 6 was prepared from citric acid monohydrate (Fluka +99.5) and sodium hydrogen phosphate (Riedel de Haën, puriss). Buffer solutions 'E' and 'F' with pH = 8.0 and 9.0 were made with borax/HCl. Column chromatography was performed on Silicagel 60 (0.040–0.063 mm, Merck).

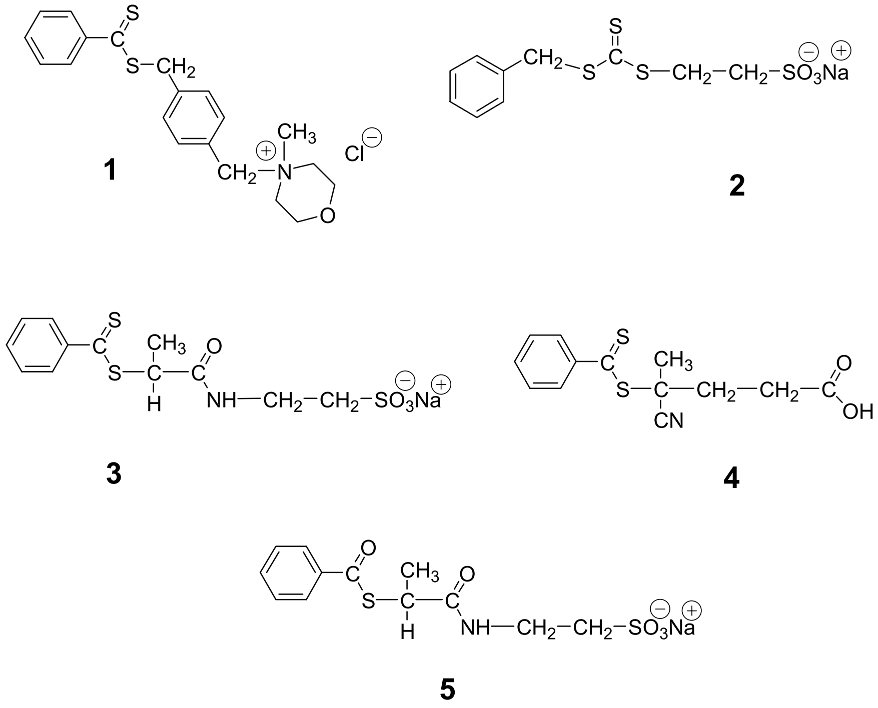

Fig. 1. RAFT agents synthesized and used in this study.

Polymers were dialysed in water with tubes ‘Zellu Trans’ (Roth, Germany), nominal cut off molar mass 4000–6000.

2.2. Synthesis of RAFT agents

*2.2.1. N-methyl-N-(thiobenzoylsulfanylmethylenephenylmethyl) morpholinium chloride (**1**)*

Under argon flow, 1.52 g of CS_2 (27 mmol) were added at ambient temperature over 15 min to 10 ml of phenylmagnesium chloride 2 M in THF (20 mmol). 7.00 g of α,α' dichloro-*p*-xylene (40 mmol) in THF were added at 25 °C over a period of 15 min. Then, the reaction was maintained at 60 °C during 4 h. The reaction mixture was washed with 250 ml water and the organic products were extracted with 250 ml diethyl ether. The ether phase was washed with 250 ml brine and dried over magnesium sulfate. The organic phase was concentrated and purified by column chromatography (silicagel, eluent: cyclohexane). The red fraction was collected, and the solvents removed under reduced pressure. The residue was dissolved in 20 ml of DMSO and 5.06 g of *N*-methylmorpholine (50 mmol) were added under argon flow. The temperature was raised to 60 °C for 48 h. After cooling, the reaction mixture was dissolved in 100 ml of water. The less polar compounds were extracted with diethyl ether. The dication salt 1,4-(bis-(*N*-methyl morpholinio) benzene) dichloride formed as side-product was removed by precipitation in acetone and filtration. Storage of the filtrate at -4 °C produced red needles of **1**. Yield: 1.5 g (19%). Elemental analysis ($C_{20}H_{24}NOS_2Cl$, $M_r = 393.99$ g mol^{-1}): Calc: **C** 60.96, **H** 6.13, **N** 3.55, **S** 16.27; Found: **C** 60.75, **H** 6.23, **N** 3.48, **S** 15.87. MS (FAB, *m*-nitrobenzylalcohol, positive ions) signal at 358.3 $(M-Cl)^+$. ^{1}H NMR (200 MHz in D_2O, δ in ppm): 2.80 (s, 3H, CH_3-N^+), 3.05 and 3.26 (m, 2H + 2H, $-CH_2-N^+R^1R^2-CH_2-$, *cis* and *trans* position to the methyl group on the heterocycle), 3.80 (m, 4H, $-CH_2-O-$), 4.32 and 4.36 (2s, 2H + 2H, $-CH_2-\Phi-CH_2-$), 7.00–7.30 and 7.60–7.70 (m and d, 7H + 2H, aromatic $=CH-$). ^{13}C NMR (75 MHz in D_2O) $\delta = 41.4$ (aryl $-CH_2-S-$), 46.1 (CH_3-N^+), 59.2 ($-CH_2-O-$), 60.7 ($-CH_2-N^+$ heterocycle), 67.6 (aryl-CH_2-N^+), 126.1, 127.4, 129.1, 130.4, 133.6, 134.0, 138.5, 144.4 (C aryl), 227.3 ($C(=S)-S-$). FT–IR (selected bands in cm^{-1}): 3020 (aromatic $=CH-$, ν), 2959 (aliphatic $-CH-$, ν), 2876 (aliphatic N^+-C-H, ν), 1222 and 1039 ($C=S$, ν). UV–Vis (in water): bands at $\lambda_{max1} = 305$ nm ($\varepsilon = 99200$ l mol^{-1} cm^{-1}), $\lambda_{max2} = 480$ nm ($\varepsilon = 97$ l mol^{-1} cm^{-1}).

*2.2.2. Sodium S-benzyl-S′-2-sulfonatoethyl trithiocarbonate (**2**)*

1.92 g (11.4 mmol) of sodium 2-mercaptoethansulfonate and 25 ml of deoxygenated 0.5 M NaOH were stirred for 30 min under N_2 atmosphere at ambient temperature, before injecting 3.00 ml (50.5 mmol) of carbon disulfide. The mixture was stirred for 4 h at ambient temperature, before the excess of CS_2 was removed in vacuo. Then, 3.85 g (30.4 mmol) of benzylchloride were added to the flask, and the solution was stirred vigorously for 12 h at ambient temperature. Heating the suspension obtained to 70 °C for 20 min gave a clear solution from which yellow crystals precipitated after allowing to cool to ambient temperature. Best results were obtained when stopping precipitation after 1 h, as prolonged crystallisation times resulted in co-crystallisation of impurities, which are difficult to separate though increasing the yield. The formed yellow precipitate was filtered off. The filter cake was washed with 50 ml of diethyl ether. The product was dried over P_2O_5 under reduced pressure to yield 1.48 g (39%) of yellow crystal sheets. **2** can be re-crystallised from water if further purification is necessary. Decomposition before melting starts at about 300 °C. Elemental analysis ($C_{10}H_{11}NaO_3S_4$, $M_r = 330.45$ g mol^{-1}): Calc: **C** 36.35, **H** 3.36, **S** 38.82; Found: **C** 36.74, **H** 3.13, **S** 38.25. MS (FAB, thioglycerol, negative ions) signal at 307.0 $(M-Na)^-$. ^{1}H-NMR (300 MHz, in DMSO-d_6): $\delta = 2.73-2.79$ (m, 2H, $-CH_2SO_3$), 3.55–3.60 (m, 2H, $-CH_2-C-SO_3$), 4.67 (s, 2H, $\Phi-CH_2-SC(=S)S-$), 7.25–7.41 (m, 5H, aromatic $=CH-$). ^{13}C NMR (75 MHz in DMSO-d_6) $\delta = 32.70$ ($-S\mathit{C}H_2CH_2SO_3$), 40.19 ($\Phi-\mathit{C}H_2-SC(=S)S-$), 48.86 ($CH_2SO_3$), 127.52 (aryl CH(4)), 128.49 (aryl CH(2)), 129.08 (aryl CH(3)), 135.05 (aryl C(1)), 223.42 ($-SC(=S)S-$). FT–IR (KBr, selected bands): 3060, 3025, 1229, 1207, 1177, 1118, 1063, 833, 798, 772, 705, 596 cm^{-1}. UV–Vis (in water): band at $\lambda_{max} = 425$ nm ($\varepsilon = 55$ l mol^{-1} cm^{-1}).

*2.2.3. Sodium 2-(2-thiobenzoylsulfanyl propionylimino) ethanesulfonate (**3**)*

5.62 g (44.9 mmol) of taurine and 3.57 g (89.7 mmol) of NaOH were dissolved in 70 ml of water. 10.01 g (44.9 mmol) of 2-bromopropionylbromide dissolved in 60 ml of CH_2Cl_2 were added drop-wise. The resulting two-phase system was stirred vigorously for 10 h. After separation of the organic phase, the aqueous phase was extracted twice with 50 ml of diethyl ether. The aqueous phase was separated, and the pH was adjusted by 1 M NaOH to a value of 6, and the solution was freeze-dried. 8.52 g (22.1 mmol) of the solid obtained were added to 0.15 g (0.9 mmol) of KI and 150 ml of an about 0.4 M aqueous solution of sodium dithiobenzoate. The solution was stirred at room temperature for 5 h. Then, it was filtered, acidified with 1 M HBr and extracted thrice with 100 ml of diethyl ether. The pH was readjusted to value of 6.5 with 1 M NaOH. The solution was freeze-dried. Yield of crude **3**: 14.03 g (69.7%) (containing according to elemental analysis 61 wt% of inorganic salt: Found: **C** 15.92, **H** 1.40, **N** 1.95, **S** 10.78, **Br** 46.4, **Cl** 0.90). The crude product can be used as RAFT agent without further purification. The pure compound free from salt can be obtained by fractionate precipitation of a saturated solution in methanol by adding successive aliquots of acetone, rejecting the first and the last fractions. Elemental analysis of purified **3** ($C_{12}H_{14}NNaO_4S_3$, M_r =355.43 g mol^{-1}): Calc: **C** 40.55, **H** 3.97, **N** 3.94, **S** 27.07. Found: **C** 39.94, **H** 3.90, **N** 3.98, **S** 26.51. ^{1}H-NMR (300 MHz in D_2O): $\delta = 1.58$ (d, 3H, CH_3), 3.00 (t, 2H, $-CH_2SO_3$), 3.54 (t, 2H, $-CH_2-C-SO_3$) 4.51 (q, 1H, CH), 7.40 (m, 2H, aryl =CH(meta)), 7.58 (m, 1H, aryl =CH(para)), 7.88 (m, 2H, aryl =CH(ortho)). ^{13}C NMR (75 MHz in D_2O): $\delta = 16.55$ (S–C–CH_3–), 36.07 (–NH–CH_2–), 50.13 (–CH_2–SO_3Na), 50.45 (S–CH(CH_3)–), 127.27 (aryl CH(2)), 129.15 (aryl CH(3)), 133.71 (aryl C(4)), 144.53 (aryl CH(1)), 173.63 (–CONH–), 228.34 (–C=(S)S–).

2.2.4. 4-thiobenzoylsulfanyl-4-cyanopentanoic acid (4)

4 was synthesized by heating the mixture of 4.25 g (13.9 mmol) bis(thiobenzoyl) disulfide and 5.84 g (20.8 mmol) 4,4′ azobis(4-cyanopentanoic acid) in ethyl-acetate at 80 °C under inert atmosphere as described by Thang et al. [32].

2.2.5. Sodium 2-(2-benzoylsulfanylpropionylimino)ethanesulfonate (5)

An analogous procedure used for the synthesis of **3** was used also for the synthesis of **5**. Thiobenzoic acid was used instead of dithiobenzoic acid, and HCl was used instead of HBr. **5** was obtained as a white solid. Inorganic salt impurities (NaBr and NaCl) were not removed. Yield: 70% (corrected for the amount of 51 wt% of inorganic salt according to elemental analysis). Elemental analysis ($C_{12}H_{14}NNaO_5S_2$, M_r =339.37 g mol^{-1}): Calc: **C** 42.47, **H** 4.16, **N** 4.13, **S** 18.90; C/N = 10.28, C/S = 2.25. Found: **C** 21.68, **H** 1.92, **Br** 25.0, **Cl** 8.8, **N** 2.26, **S** 9.80; C/N = 9.59, C/S = 2.21. ^{1}H-NMR (300 MHz, in D_2O): $\delta = 1.51$ (d, 3H, $-CH_3$), 3.01 (t, 2H, $-CH_2SO_3$), 3.56 (t, 2H, N–CH_2–C–SO_3), 4.27 (q, H, –CSS–CH–), 7.49–7.93 (m, 5H, =CH– aryl). ^{13}C NMR (75 MHz in D_2O) $\delta = 16.9$ (S–CH–CH_3–), 36.0 (–NH–CH_2–), 43.2 (–S–CH(CH_3)–), 50.1 (–CH_2–SO_3Na), 127.7 (aryl CH(2)), 129.6 (aryl CH(3)), 135.1 (aryl CH(4)), 136.2 (aryl C(1)), 175.0 (–C(=O)H–), 194.5 (–C(=O)S–).

2.3. Polymerization of N-vinylbenzyl-N,N,N-trimethylammoniumchloride (VBAC)

VBAC was polymerised in water using initiator **V-50** and the RAFT agents **1** at 52 °C (7.8×10^{-5} mol of **1**, 3.2×10^{-5} mol of **V-50**, 27.4 mmol of **VBAC** and 14 ml of distilled water), or **2** at 55 °C (9.0×10^{-5} mol of **2**, 1.8×10^{-5} mol of **V-50**, 20.6 mmol of **VBAC** and 25 ml of distilled water), or **5** at 50 °C (9.0×10^{-5} mol of **2**, 1.8×10^{-5} mol of **V-50**, 7.40 mmol of **VBAC**). Solutions were deoxygenated by bubbling N_2 for 30 min before polymerisation.

2.4. Methods

NMR spectra were taken with an apparatus Bruker Avance 300 (32 scans for ^{1}H, 1500 scans for ^{13}C). 1,4-dioxane was used as an internal reference at 67.19 ppm for ^{13}C-NMR measurements in D_2O [33]. IR-spectra were taken from KBr pellets by a FT–IR spectrometer (Bruker IFS 66/s). Mass spectra were recorded by a spectrometer TSQ7000 (Thermo Finnigan). UV–Visible spectra were recorded with a UV–Vis spectrophotometer Cary-1 (Varian) equipped with temperature controller (Julabo F-10). Spectra were recorded every 30 min. After dissolution of the RAFT agent in the buffer solution, the quartz cell was immediately placed in the measurement compartment with thermostated control. Buffer solution were used for UV stability measurements at pH = 4, 5, 6, 7, 8, 9 and 10. For studies at pH = 1 and 2, RAFT agents were dissolved in water, and then pH was adjusted by addition of 1 M HCl (pH verified with pH-meter Erbo PHT 3140). In the ^{1}H-NMR stability tests followed by ^{1}H-NMR, dioxane was used as an internal reference. The pH of the solutions was adjusted to pH = 6. RAFT agent **4** was converted to the salt by addition of the necessary amount of 1 M NaOH in D_2O. Aqueous size exclusion chromatography (ASEC) was done with a Spectra Physics Instruments (Columns: TSK-GEL® [polyglycidyl(meth)acrylate-Gel] from TOSOH: Guard, 6000, 5000, 3000 and 40. Eluent: aqueous 0.2 M Na_2SO_4 containing 1 wt% of acetic acid), with calibration by poly(2-vinylpyridine) (**P2VP**) standards from PSS GmbH (Mainz, Germany), and by multi-angle light scattering MALLS (Wyatt DAWN DSP, Wyatt, Santa Barbara, CA/USA, laser wavelength 633 nm, d_n/d_c =0.188 ml/g [34]).

3. Results and discussion

The synthesis of new compounds **1**, **2** and of the only most recently mentioned **3** [30,35], follows classical pathways. The anionic trithiocarbonate **2** is particularly convenient to synthesise, by adding carbon disulfide on double salt of 2-mercapto ethane sulfonic acid, and alkylating the adduct with benzyl chloride. Anionic **2** has the additional advantage to be purified by crystallisation from water, thus removing the inorganic salts and other water-soluble side products easily and efficiently. The ^{1}H-NMR spectra of the pure compounds are shown in Figs. 2–4.

Cationic dithioester **1** is obtained as pure compound by successive alkylation of the dithiobenzoate anion and of *N*-methylmorpholine with α,α′-dichloro-*p*-xylene. The anionic dithioester **3** is analogously prepared by alkylation of the dithiobenzoate anion with 2-(2-bromo-propionylimino) ethanesulfonate. Testing different methods for the preparation of the dithiobenzoate anion in the synthesis of **1** and **3** (see Experimental part), both methods worked equally well in our hands to obtain the dithioesters. However, when

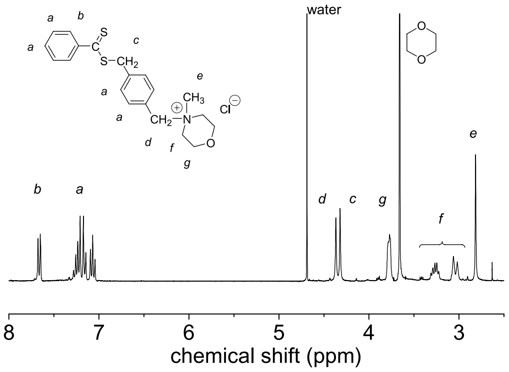

Fig. 2. ^{1}H-NMR spectra of **1** in D_2O.

the sodium salt of dithiobenzoate is synthesised by the method of Becke and Hagen [36], the dithioester **3** was always contaminated with a small quantity of impurity (about 5 mol% according to the integration of the ^{1}H-NMR signals) with very similar ^{1}H and ^{13}C-NMR spectra, that could not be separated efficiently from **3**, neither by crystallisation nor by extraction nor by column chromatography. The impurity was identified by its NMR spectra to be the thiobenzoate analog of **3**, namely **5**, as confirmed by separate synthesis and mixing experiments of **3** and **5**. In contrast, when the sodium salt of dithiobenzoate is synthesised via the Grignard method, **3** could be obtained free from **5**. Actually, during the course of our studies, the use of **3** for the RAFT polymerisation of acrylamide was reported [30,35]. But differing from our analytical data, the most recently reported analytical data for **3** [35] do not match fully the proposed structure and indicate the marked presence of impurities.

In fact, different from **1** and **2**, compound **3** proved difficult to purify, notably from the inorganic by-products. If no analytical pure samples are needed, the RAFT agent can be isolated as mixture with 2 mol equivalents of sodium halogenide, eventually also contaminated slightly with thioester **5** (depending on the synthetic pathway, as discussed above), and used as such. Preliminary tests indicated that the presence of these side products in **3** does not interfere with the chain transfer capacity of **3** in the RAFT polymerisation of styrene and acrylate derivatives, and that pure **5** is not an efficient RAFT agent (see below).

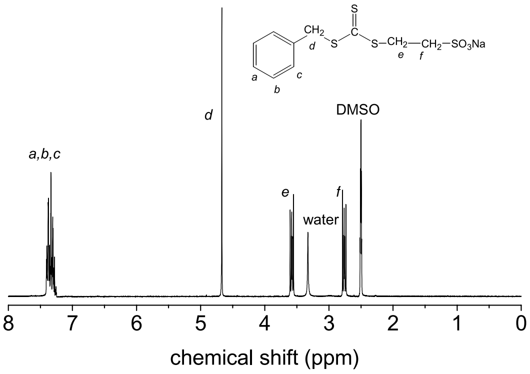

Fig. 3. ^{1}H NMR spectra of **2** in DMSO-d_6.

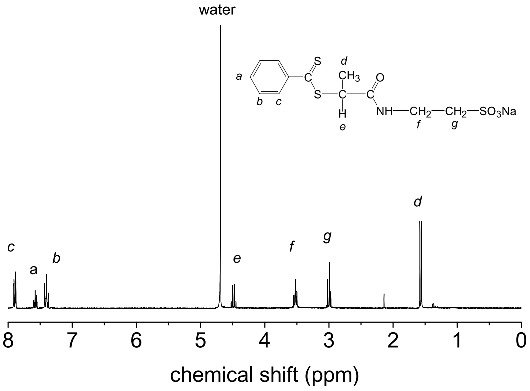

Fig. 4. ^{1}H NMR spectra of **3** in D_2O.

Because little information is available to which extent dithioesters and trithiocarbonates are sensitive to hydrolysis, we investigated the stability of the new compounds **1–3** in water, and compared their behaviour to the one of the frequently used RAFT agent **4** which is well water-soluble as sodium salt.

First, we elaborated the useful pH window for RAFT agents **1** to **4** (see Table 1). The degradation of the RAFT active dithioester in water seems to be easily tracked by the characteristic absorption peak of the forbidden $n \rightarrow \pi^*$ transition of the C=S group at (**1**: λ_{max} =480 nm; **2**: λ_{max} =425 nm; **3**: λ_{max} =483 nm; **4**: λ_{max} =497 nm). The onset of the degradation is sensitively indicated by following the evolution of the absorbance via Vis-spectrometry, but the measurements could not be exploited for quantitative kinetic studies because degradation results in at least two opposing effects. On the one hand, the absorbance is decreased due to loss of the chromophore, on the other hand, the solutions (at least in the case of **1** and **2**) become turbid as some of the degradation products are

Table 1
Stability of RAFT agents **1–4** at 40 °C in water, in dependence on pH

pH		RAFT Agents			
	Buffer	**1**	**2**	**3**	**4**
1	No	Stable	Stable	Stable	Insoluble
2	No	Stable	Stable	Stable	Insoluble
4	A	n.d[a]	n.d.[a]	n.d.[a]	Insoluble
5	B	Stable	Stable	Stable	Insoluble
6	C	Stable	Stable	Stable	Stable
7	D	Stable	n.d.[a]	n.d.[a]	n.d.[a]
8	E	O	O	O	O
9	F	–	–	–	–
10	G	=	=	=	=

Symbols ‘O’, ‘–’ and ‘ = ’ indicate increasing rates of decomposition as followed by the decrease of absorbance in the vis-spectrum, or by separation of decomposition products.

[a] n.d.: Cloudy solution with partial precipitation of the RAFT agent due to interaction with buffer components.

insoluble in water. Moreover, by comparing UV–Vis spectra with ^{1}H-NMR spectra, we found that hydrolysis results in degradation products (such as dithiobenzoic acid) with absorbance spectra in the visible that are similar to the ones of the parent RAFT agents. Therefore, considerable residual absorbance is still observed even when the compound is already completely hydrolysed according to ^{1}H-NMR. For instance, RAFT agent **3** is fully hydrolyzed after 3 h at 70 °C at pH 10, but the residual absorbance at λ_{max} =483 nm is still about 65% of the original value, pretending stability. Therefore, though UV–Vis studies are convenient for preliminary tests and may provide an upper estimation limit, a true evaluation of stability or instability, respectively, must be done by other methods, such as ^{1}H-NMR spectroscopy.

Combining Vis-spectroscopic studies with ^{1}H-NMR, hydrolysis was not observed at 40 °C over a period of 24 h in the range between pH 6 and pH 7. Concerning more acidic conditions, the established RAFT agent **4** is not soluble in water at lower pH values, but the new agents **1–3** are. When potassium hydrogen phthalate/HCl solution was used as a buffer solution of pH = 4, solutions of **1–3** become cloudy nearly instantaneously, or form precipitate in the case of **1**. The same problem occurred in the case of compounds **2–4**, for the buffer solution of pH = 7, containing potassium di-hydrogen phosphate/di-sodium hydrogen phosphate. These precipitates, however, are due to a specific interaction of the RAFT agents with the buffer ingredients rather than to acidic hydrolysis. Agents **1–3** did not decompose at pH = 1 and pH = 2 within 12 h at 40 °C according to ^{1}H-NMR, if the pH is adjusted by concentrated HCl (Table 1). Whereas the RAFT agents seem to be rather stable to acidic conditions, they are sensitive to base. While at pH = 8, Vis-spectroscopy indicated a slow onset of degradation after 10 h, more basic conditions led to accelerated degradation (cf. Table 1). Depending on the detailed structure of the compounds, the solution stayed transparent (for **3** and **4**) or produced precipitate (for **1** and **2**). Therefore, when employing typical RAFT agents in water, the pH is best maintained below a value of 8.

Having thus defined the most useful pH window, we investigated the hydrolytic stability of **1–4** at normal ambient pH, i.e. at pH = 6, for elevated temperatures, as most free radical polymerisations are performed with thermal initiators. In order to get some chemical information about eventual degradation products, ^{1}H-NMR spectroscopy in D_2O was used for these studies (Figs. 6–8; for full spectra of the pure compounds see Figs. 2–4).

The results of stability tests for cationic **1** in D_2O are summarised in Fig. 5(a). This RAFT agent shows no detectable decomposition by ^{1}H-NMR within 24 h up to 60 °C. Though at 80 °C, slow decomposition is observed. After 24 h, about 70% of the starting compound are still preserved, but degradation is clearly visible, as indicated most clearly by the loss of peaks attributed to aromatic protons at 7.00–7.30 ppm and to the benzylic protons at 4.32 and 4.36 ppm. The intensity of the signals of the protons attributed to the *N*-methyl morpholinium residue is reduced proportionally to the loss of the benzylic protons of **1**, too. Simultaneously, numerous new signals appeared. In particular, one can identify new multiplets of aromatic protons between 7.30 and 7.50 ppm, as well as new singulets at 4.15, 4.45, and 4.55 ppm, putatively attributed to new functional benzylic protons. Also, new multiplets between 3.85 and 4.0 ppm, and singulets at 2.93 and 3.02 ppm indicate changes in the chemical environment of the *N*-methylmorpholinium residue. Only the multiplet at 3.25 ppm, attributed to the $-CH_2-O-CH_2-$ fragment, is virtually unchanged. The various new peaks are difficult to attribute to particular degradation products on the base of the chemical shifts and coupling patterns only. In any case, the observations strongly suggest that hydrolytic degradation leads to several products.

The results of stability test of the RAFT agent **3** are exhibited in Fig. 5(b). Anion **3** is relatively stable at 60 °C and lower temperatures. But at higher temperatures, notable degradation is observed after 24 h: 15% of starting compound were decomposed at 70 °C, and 53% at 80 °C. According to the ^{1}H-NMR spectra taken at regular intervals (Fig. 6), and comparing the newly developing signals with the ones of reference compounds prepared, three major degradation products are found. The first one results from the conversion of the dithioester moiety to the thioester moiety. I.e., **3** is converted into **5** as indicated by the increase of the minor doublet at 1.51 ppm ($-CH_3$) with time, while the doublet at 1.60 ppm ($-CH_3$) of **3** decreases simultaneously. In parallel in the ^{13}C-NMR spectra, the signal at 228 ppm attributed to the $-C(=S)S-$ moiety is gradually replaced by a signal at 194 ppm attributed to the $-C(=O)S-$ moiety. This reaction is particularly notable at temperatures above 60 °C. The two other degradation products result from the hydrolysis of dithioester moiety, too (Fig. 6). The new two doublets rising at 1.36 and 1.41 ppm can be attributed to degradation products bearing the 2-(2-propionylimino) ethanesulfonate fragment (presumably the alcohol and the thiol). In contrast to the dithioester moiety, the amide bond is not affected by the storage in water under these conditions according to the NMR spectra, nor is the aromatic core.

Fig. 5(c) presents the decomposition tests of the reference compound 4-(thiobenzoylthio)-4-cyanopentanoic acid **4** at different temperatures. After 24 h, nearly 36% of the reagent have already decomposed at 50 °C, 84% have been degraded at 60 °C, and even 90% are lost at 70 °C. In the series of decomposition spectra at 70 °C (Fig. 7), two different types of decomposition could be observed. The new singulet at 1.857 ppm, showing up next to the singulet at 1.863 ppm that is attributed to the methyl group ($CH_3-C(CN)-SC(=S)-$), was only observed at reaction temperatures of 60 °C or more. In analogy to the findings for the degradation of **3**, this singulet is attributed to the conversion of the C=S into the C=O group, without

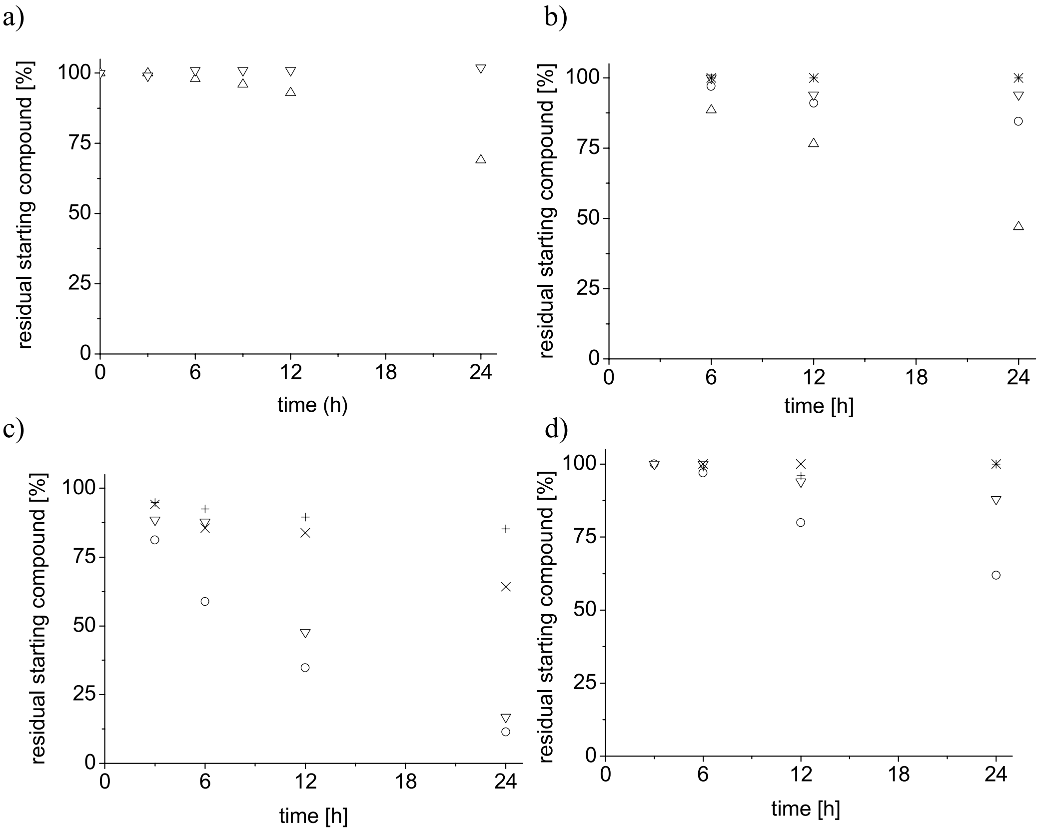

Fig. 5. Stability of RAFT agents in D_2O at pH 6 at different temperatures, followed by ^{1}H-NMR: 40 °C = (+), 50 °C = (×), 60 °C = (▽), 70 °C = (○), and 80 °C = (△): (a) agent **1**; (b) agent **3**; (c) agent **4**; (d) agent **2**.

cleavage of the C–S–C linkage. The latter reaction, however, is assumed to produce the newly rising singulet at 1.66 ppm, putatively attributed to the signal of the CH_3–C(CN)–S– moiety after hydrolysis.

Different from dithioesters **1**, **3** and **4**, the water-soluble anion **2** is a trithiocarbonate. The stability of **2** is summarised in Fig. 5(d). The compound is fully stable during 24 h storage in water up to 50 °C, but not at higher temperatures. Storage at 70 °C produces some turbidity. Following the decrease in the intensity of the singulet at 4.64 ppm (–S–C(=S)–S–CH_2Aryl) (Fig. 8), 12% of **2** were degraded at 60 °C, while 38% were decomposed at

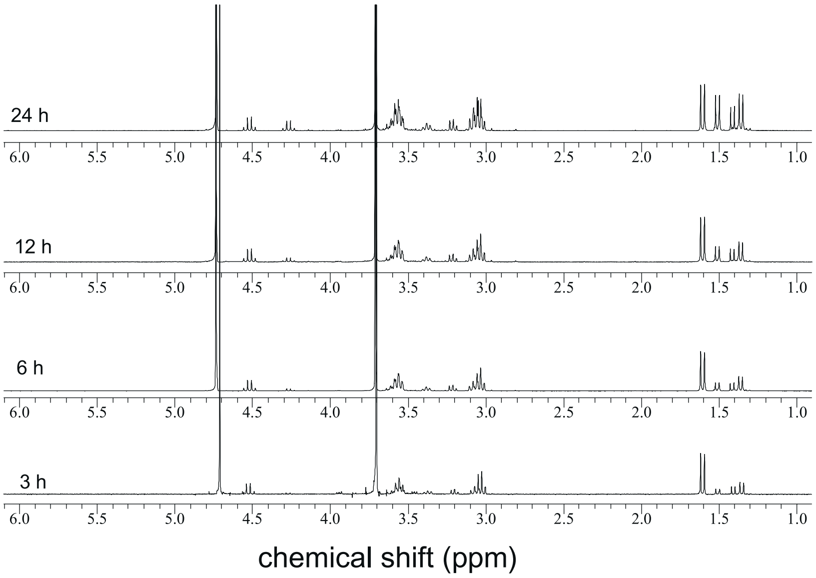

Fig. 6. Evolution of the ^{1}H NMR spectra of **3** in D_2O at pH = 6 with decomposition at 80 °C.

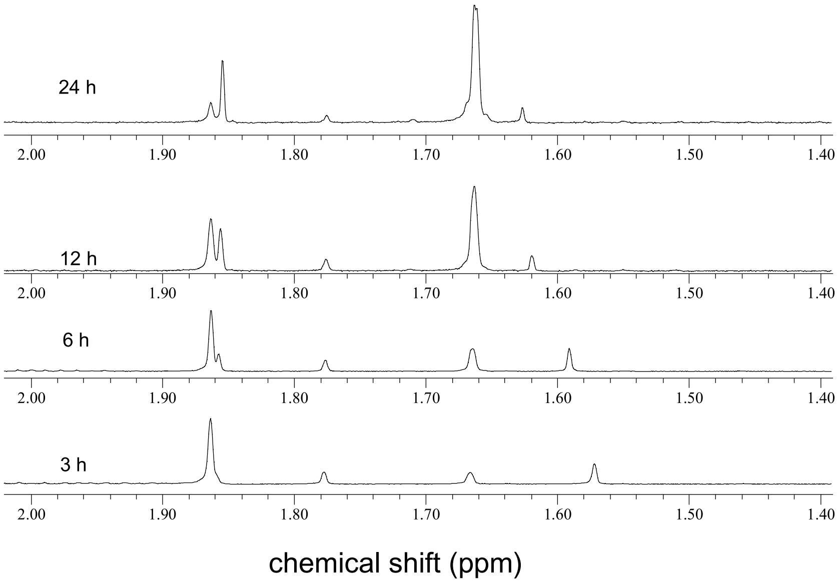

Fig. 7. Evolution of the ^{1}H NMR spectra of **4** in D_2O at pH = 6 with decomposition at 70 °C.

70 °C. The newly rising singulet at 4.05 ppm and the new multiplet at 6.70 ppm are difficult to attribute. Interestingly, the new ^{1}H-NMR signals give no indication for the formation of benzyl mercaptane or 2-mercaptoethanesulfonate resulting from the complete hydrolysis of the trithiocarbonate moiety.

Comparing the results for RAFT agents **1**–**4**, hydrolysis seems to be a danger for such compounds above 40 °C even under optimal pH conditions. The hydrolytic stability increases in the series **4** < **2** < **3** < **1**, i.e. the hitherto widely employed dithiobenzoate **4** is the least stable compound, while cationic **1** proved to be the most stable one. Whereas, the former exhibits already marked degradation at 50 °C, the latter shows virtually no decomposition at 60 °C. Even after 24 h of storage in water at 80 °C, 70% of the starting compound are still preserved. Compared to the different dithiobenzoates, trithiocarbonate **2** exhibits an intermediate resistance to hydrolysis.

According to the generally accepted mechanism of the RAFT process [8,9], the hydrolytic stability of a RAFT polymerisation system in aqueous media is only in parts given by the stability of the initial RAFT agent Z–C(=S)–S–R. The hydrolytic stability of the ‘dormant’ polymer chains, i.e. of the adducts of the growing radical chains and the Z–C(=S)–S– fragment of the RAFT agent employed, will play a crucial role, too. If the structure of the leaving

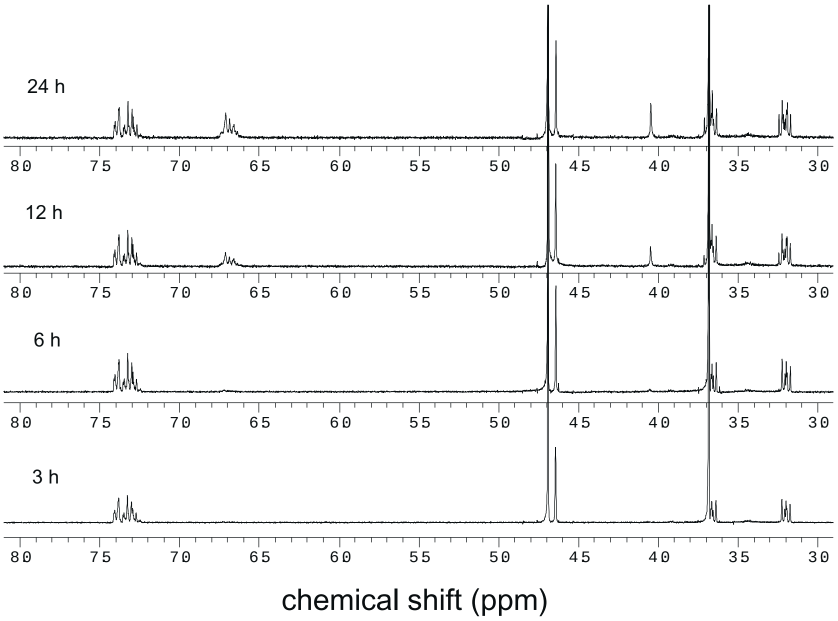

Fig. 8. Evolution of the ^{1}H NMR spectra of **2** in D_2O at pH = 6 with decomposition at 70 °C.

group in the RAFT agent is not a mimick of the growing polymer chain, a direct correlation cannot be expected. Nevertheless, it is obvious that for obtaining best results in controlling a polymerisation, attention should be paid to use a RAFT agent that provides good stability under the reaction conditions chosen. From the limited choice of examples in this study, and their various molecular differences, it is difficult to derive clear rules yet for improving the hydrolytic stability of eventual new RAFT agents. Possibly, the electron withdrawing CN group in α-position to the dithioester bond is responsible for the faster hydrolysis of **4**, while the more hydrophobic environment of the dithioester group in **1** improves the resistance.

In preliminary experiments, the usefulness of the new compounds **1** and **2** as RAFT agents was tested in the aqueous solution polymerisation of *N*-vinylbenzyl-*N,N,N*-trimethylammonium chloride **VBAC** initiated by the azo initiator **V-50** (Figs. 9 and 10). Fig. 9(a) and (b) present the aqueous size exclusion chromatography elugrams of the reaction mixtures with ongoing polymerisation. A continuous shift of the curves toward smaller elution volumes is observed, indicating continuously increasing molar masses and suggesting controlled free radical polymerisation. Fig. 9(c) presents the elugrams of the analogous polymerisation of **VBAC** in the presence of thioester **5**. In contrast to RAFT agents **1** and **2**, elution volumes are small from the very beginning of the reaction, and slightly move to higher ones with ongoing polymerisation. This means that the average molar masses are high already in the early polymerisation (after 30 min, $M_n = 6.2 \times 10^5$ according to **P2VP** standards, $M_w/M_n = 1.8$) and slowly decrease as the polymerisation proceeds (after 3 h, $M_n = 3.5 \times 10^5$ vs. **P2VP** standards, $M_w/M_n = 2.4$). These data compare very well to those obtained by polymerisation under the same conditions but in absence of any chain transfer agent (after 6 h, $M_n = 1.5 \times 10^5$ vs. **P2VP** standards, $M_w/M_n = 2.8$ [34]). Therefore, the data indicate an uncontrolled, 'normal' free polymerisation. This implies, that **5** which may be present as impurity in RAFT agent **3**, or may be formed by partial hydrolysis in situ, does neither contribute to the control of the polymerisation, nor inhibit the polymerisation process. Accordingly, the eventual formation of small amounts of thioesters at elevated temperatures from dithioesters during the controlled radical polymerisation in aqueous media should not be problematic (NB this may be different for thiols formed eventually).

Fig. 10 presents the results of the aqueous solution polymerisation of **VBAC** in the presence of RAFT agents **1** (Fig. 10(a)) and **2** (Fig. 10(b)) in more detail. The elugrams were evaluated by on-line MALLS measurements, but also by calibration with **P2VP** polymer standards, as **poly-VBAC** standards were not available. The continuous, linear increase of molar mass with conversion is clearly visible for both polymerisation systems. Also, independently whether the GPC data were evaluated by MALLS or by help of a polymer standard, the polydispersity indices M_w/M_n are low for a free radical polymerization (between 1.1 and 1.5). Both features are commonly considered characteristic for a controlled free radical polymerization [3–6]. In agreement, the M_n values estimated from end group analysis by vis-spectroscopy of the $n-\pi^*$ transition of the dithioester chromophore at λ_{max} =480 nm (Fig. 10(a)) as well as of the trithiocarbonate chromophore at λ_{max} =425 nm (Fig. 10(b)) agree very well with the theoretically calculated values for a controlled polymerization (calculated from the ratio of monomer to RAFT agent weighed by the conversion). The latter finding suggests also that at least the majority of the polymer chains still bears an active dithioester end group or trithiocarbonate end group, respectively.

A more detailed analysis of the data is somewhat hampered by analytical difficulties (a widespread problem in the characterization of polyelectrolytes). In fact, the absolute molar mass values for M_n derived by three independent methods, namely from MALLS, from end group analysis, and from standard calibration, do not match. Strikingly in Fig. 10, while the M_n values estimated from end group analysis agree well with the theoretically expected ones, calibration by **P2VP** standards provides much lower values for M_n, whereas evaluation by MALLS provides much higher values for M_n. Moreover, the values for polydispersity index M_w/M_n derived from the two last methods differ notably (1.1–1.2 by MALLS, and 1.2–1.4 by standard calibration for high conversions).

The deviation of the M_n values estimated by standard calibration with **P2VP** is not unexpected, but the marked discrepancy between M_n derived from end group analysis and MALLS is worrying. Let alone from the systematic agreement between the theoretically expected M_n values and the ones determined by end group analysis (Fig. 10) that is difficult to assume as fortuitous, any deviation from a controlled polymerisation should result in too high apparent molar masses by end group analysis (the molar mass distribution is too narrow for termination by recombination being able to have an important effect). Therefore, end group analysis should provide correct values in the cases studied in Fig. 10. A thorough discussion of this severe problem is beyond this contribution. But we have good reason to believe that the low molar mass fraction is underestimated by MALLS [34]. Thus, the M_n values are too high, though the M_w values determined are correct. Consequently, the polydispersities obtained from MALLS analysis are underestimating the true values. The polydispersities estimated from standard calibration seem more credible. It is clear that the polydispersity index of the standard polymer is not necessarily identical to the true polydispersity index of the sample, as the elution time of a polymer on SEC columns is rarely a strictly linear function of the molar mass. Still, the polydispersity index derived from the calibration with a standard polymer is generally a much better approximation of the true value than the relative molar mass is. The above considerations

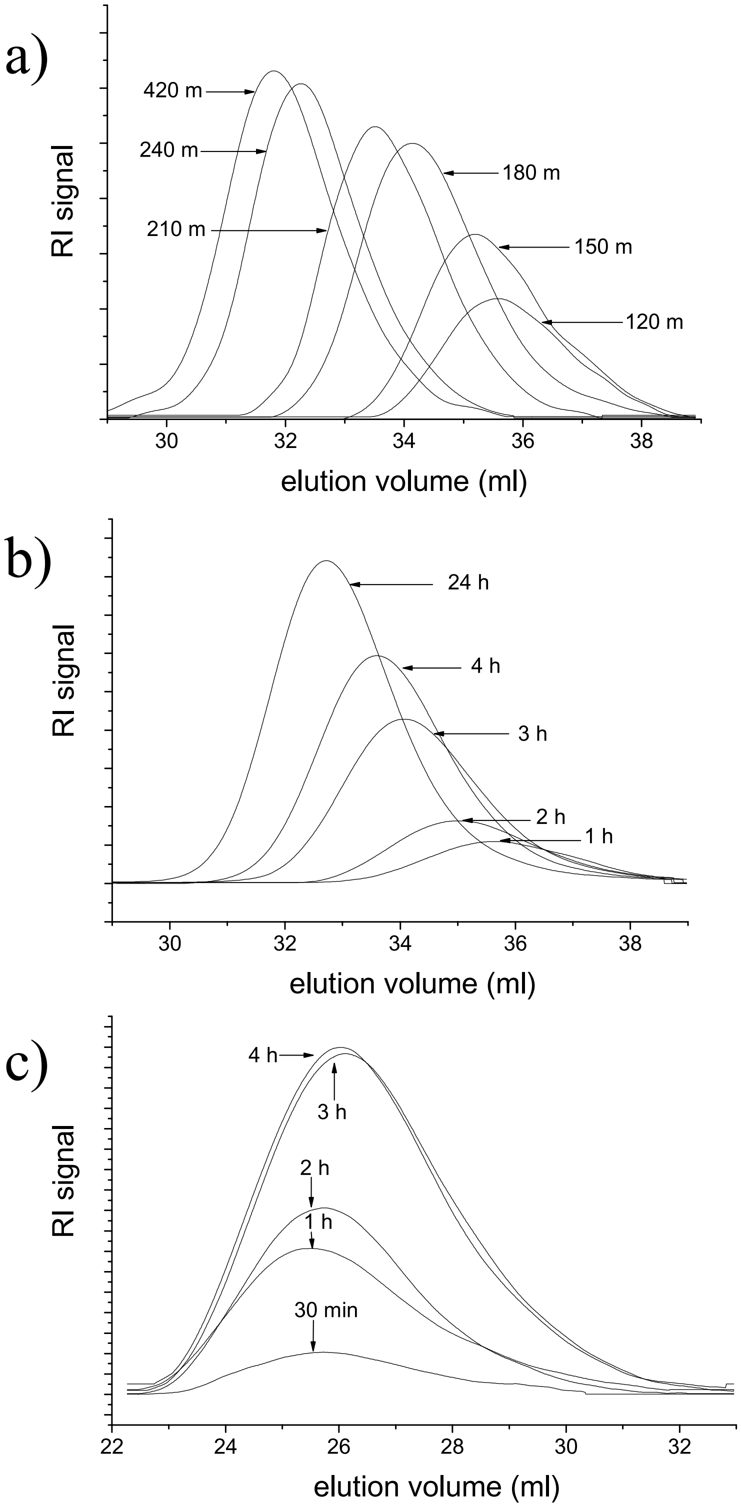

Fig. 9. Plots of the evolution of the aqueous size exclusion chromatograms with polymerisation time in the aqueous solution polymerisation of **VBAC** (cf. Fig. 10), using dithioester **1** (a), trithiocarbonate **2** (b) and thioester **5** (c).

are supported by the fact that when combining the M_w values obtained from MALLS with the polydispersities obtained by calibrating with **P2PV** standards, the thus calculated M_n values match closely the theoretically expected ones.

In any case, the preliminary results on the polymerization of cationic **VBAC**, namely continuous increase of molar mass, relatively low polydispersities, and high degree of end group functionalisation, exemplify the potential of compounds **1** and **2** as RAFT agents for aqueous solution

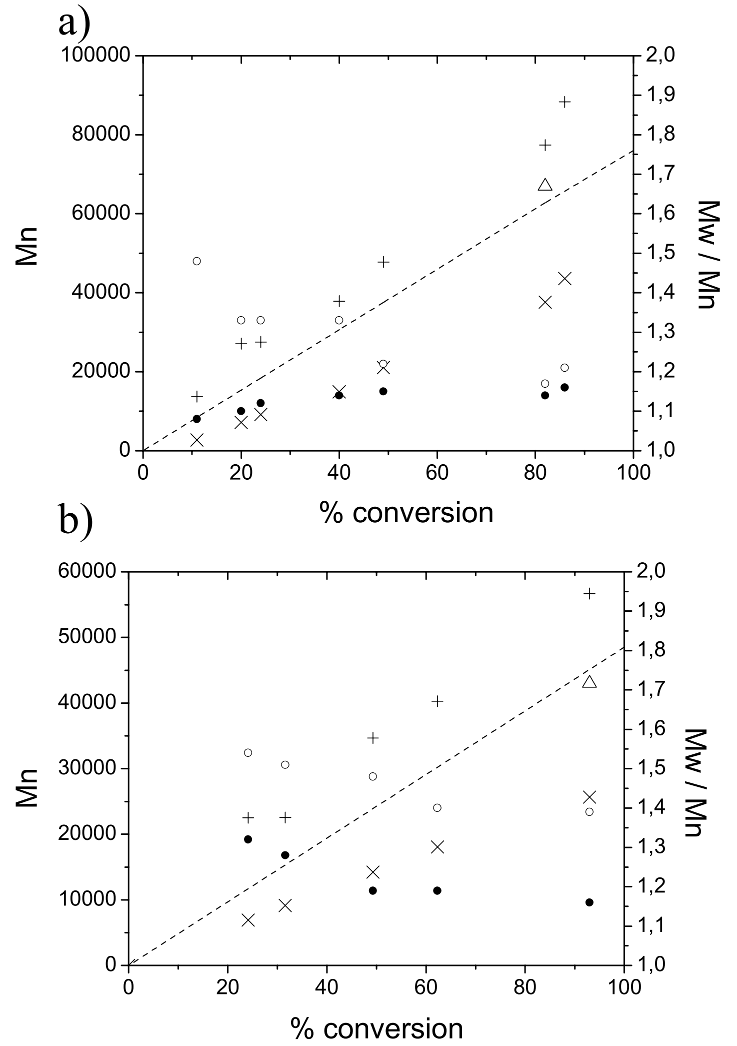

Fig. 10. Plots of the evolution of number-average molar mass M_n and of polydispersity index M_w/M_n with conversion in the polymerization of **VBAC** in aqueous solution, using RAFT agents **1** at 50 °C (a), and **2** at 55 °C (b): (+) M_n according to MALLS, (×) M_n according to calibration with **P2VP** standards, (△) M_n estimated by using the visible band at (a) $\lambda_{max} = 480$ nm of the dithioester end group, or (b) at $\lambda_{max} = 425$ nm of the trithiocarbonate end group (○) polydispersity according to calibration with **P2VP** standards, (●) polydispersity of sample determined with MALLS. The dashed line (- - -) indicates the theoretically calculated evolution of M_n.

polymerisation. But the results underline, too, that numbers calculated from ASEC data have to be taken with care, and considerable efforts are necessary to obtain reliable absolute data on molar masses as well as on polydispersities [34].

4. Conclusions

New chain transfer agents for the RAFT process bearing dithioester and trithiocarbonate moieties as well as permanently ionic groups to confer solubility in water in the full pH range were synthesised. The new compounds are well suited for the use aqueous solution polymerisation. They are long-term stable in the pH range between 1 and 8 up to 40 °C, and show improved resistance to thermal hydrolysis compared to 4-thiobenzoylthio-4-cyanopentanoic acid, which is hitherto the mostly employed RAFT agent for aqueous polymerisation systems. Whereas the best stability was observed for the cationic dithiobenzoate *N*-methyl-*N*-(thiobenzoyl sulfanyl methylene phenylmethyl) morpholinium chloride, the anionic agent sodium *S*-benzyl-*S*′-2-sulfonatoethyl trithiocarbonate with an intermediate resistance to hydrolysis is characterised by its convenient synthesis and facile purification.

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References

[1] Solomon DH, Rizzardo E, Cacioli P. 1986; US patent 4,581429.

[2] Georges MK, Veregin RPN, Kazmaier PM, Hamer GK. Macromolecules 1993;26:2987–8.

[3] Hawker CG, Bosman AW, Harth E. Chem Rev 2001;101:3661–88.

[4] Matyjaszewski K. Macromol Symp 2000;152:29–42.

[5] Coessens V, Pintauer T, Matyjaszewski K. Prog Polym Sci Symp 2001;26:337–77.

[6] Kamigaito M, Ando T, Sawamoto M. Chem Rev 2001;101: 3689–746.

[7] Le TPT, Moad G, Rizzardo E, Thang SH. Intern Pat Appl 1998: PCT WO9801478 [CA 1998: 115390].

[8] Moad G, Mayadunne RTA, Rizzardo E, Skidmore M, Thang SH. Macromol Symp 2003;192:1–12.

[9] Barner-Kowollik C, Davis TP, Heuts JPA, Stenzel MH, Vana P, Whittaker M. J Polym Sci Polym Chem 2003;A41:365–75.

[10] Charmot D, Corpart P, Michelet D, Zard SZ, Biadatti T. Intern Pat Appl 1998; PCT WO9858974.

[11] Cunningham MF. Prog Polym Sci 2002;27:1039–67.

[12] Lowe AB, McCormick CL. Aust J Chem 2002;55:367–79.

[13] Gabaston LI, Furlong SA, Jackson RA, Armes SP. Polymer 1999;40: 4505–14.

[14] Wang XS, Jackson RA, Armes SP. Macromolecules 2000;33:255–7.

[15] Wang XS, Malet FLG, Armes SP, Haddleton DM, Perrier S. Macromolecules 2001;34:162–4.

[16] Percec V, Popov AV, Ramirez-Castillo E, Monteiro M, Barboiu B, Weichold O, Asandei AD, Mitchell CM. J Am Chem Soc 2002;124: 4940–1.

[17] Huang W, Charleux B, Chiarelli R, Marx L, Rassat A, Vairon JP. Macromol Chem Phys 2002;203:1715–23.

[18] Lai JT, Filla D, Shea R. Macromolecules 2002;35:6754–6.

[19] Chiefari J, Chong YK, Ercole F, Krstina J, Jeffery J, Le TPT, Mayadunne RTA, Meijs GF, Moad CL, Moad G, Rizzardo E, Thang SH. Macromolecules 1998;31:5559–62.

[20] Ladavière C, Dörr N, Claverie JP. Macromolecules 2001;34:5370–2.

[21] Mitsukami Y, Donovan MS, Lowe AB, McCormick CL. Macromolecules 2001;34:2248–56.

[22] Taton D, Wilczewska AZ, Destarac M. Macromol Rapid Commun 2001;22:1497–503.

[23] Shim SE, Shin Y, Jun JW, Lee K, Jung H, Choe S. Macromolecules 2003;36:7994–8000.

[24] Ferguson CJ, Hughes RJ, Pham BTT, Hawkett BS, Gilbert RG, Serelis AK, Such CH. Macromolecules 2002;35:9243–5.

[25] Mayadune RTA, Rizzardo E, Chiefari J, Moad G, Postma A, Thang SH. Macromolecules 2000;33:243–5.

[26] Donovan MS, Sanford TA, Lowe AB, Sumerlin BS, Mitsukami Y, McCormick CL. Macromolecules 2002;35:4570–2.

[27] Donovan MS, Sumerlin BS, Lowe AB, McCormick CL. Macromolecules 2002;35:8663–6.

[28] Donovan MS, Lowe AB, Sanford TA, McCormick CL. J Polym Sci Part A Polym Chem 2003;41:1262–81.

[29] Sumerlin BS, Lowe AB, Thomas DB, McCormick CL. Macromolecules 2003;36:5982–7.

[30] Thomas DB, Sumerlin BS, Lowe AB, McCormick CL. Macromolecules 2003;36:1436–9.

[31] Janssen MJ. In: Patai S, editor. The Chemistry of Carboxylic Acids and Esters. New York: Interscience; 1969. p. 706–64. Chapter 15.

[32] Thang SH, Chong YK, Mayadune RTA, Moad G, Rizzardo E. Tetrahedron Lett 1999;40:2435–8.

[33] Gottlieb HE, Kotlyar V, Nudelman A. J Org Chem 1997;62:7512–5.

[34] Bruzzano S, Laschewsky A, Mertoglu M, Wieland C. in preparation.

[35] McCormick CL, Lowe AB, Sumerlin BS, Thomas DB. 2003; PCT WO 03/066685 A2 Chain Transfer Agents for RAFT Polymerization in Aqueous Media.

[36] Becke F, Hagen H. 1968; German patent DE 1274121(CA 1969; 70: 322, 3573v).