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Synthesis of novel branched polymers for enhanced oil recovery
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Synthesis of RAFT Agents for Aqueous Polymerisation of Acrylamide

CHAPTER 2. SYNTHESIS OF RAFT AGENTS

Abstract

The facile synthesis of three different reversible addition fragmentation chain transfer (RAFT) agents, i.e. 3-(((benzylthio)carbonothioyl)thio) propanoic acid (BCPA), 4-(((2-carboxyethyl)thio)carbonothioyl)thio)methy) benzoic acid (CABCPA), and 3-(((4-vinylbenzyl)thio)carbonothioyl)thio) propanoic acid (ViBCPA), containing a polymerisable double bond) was demonstrated. The RAFT agents were evaluated for the aqueous polymerisation of acrylamide, yielding polymers with experimental molecular weights ranging from 2,686 to 136,100 Da. Control over the polymerisations was displayed by linear first order kinetic plots and agreement between experimental and theoretical molecular weight. Polydispersity indices (PDIs) were found to vary for each RAFT agent, whereby CABCPA displayed the lowest values (≤ 1.23) for molecular weights up to 132,500 Da.

2.1 Introduction

Despite the number of applications in which polyacrylamide (PAM) finds its way,\(^1\)\(^-\)\(^4\) only limited work on RAFT polymerisation of AM is available. Recently, the reactivity ratios of AM and acrylic acid (AA) in DMSO were investigated. Nevertheless, molecular weights of the copolymers were limited to 15,000 Da.\(^5\) Regarding the synthesis of PAM up to higher molecular weight values, water or an aqueous buffer is required as solvent. Several dithiocarbonates were evaluated, however, reported molecular weights are limited to 100,000 Da.\(^6\)\(^-\)\(^8\) The best control over the polymerisation was obtained with a trithiocarbonate RAFT agent,\(^6\) or xanthate O-ethyl-S-1-(methyloxycarbonyl)ethylxanthate (MCEX)\(^9\)\(^,\)\(^10\). Trithiocarbonate dibenzyl carbonothioate (DBTTC) was successfully applied in methanol,\(^11\) presenting molecular weights of 50,000 Da with polydispersity indices (PDIs) up to 1.20. \(S,S'\)-bis (\(\alpha, \alpha'\)-dimethylacetic acid)
trithiocarbonate (BDAT) was applied in water yielding molecular weights of 17,000 Da with a low PDI, and up to 72,000 Da with PDIs below 1.25. 3-(((benzylthio)carbonothioyl)thio)propanoic acid (BCPA) was applied in water/acetone, obtaining PAM with molecular weights up to 37,000 Da and a low PDI. Higher molecular weights of approximately 1,000,000 Da were reported with xanthate MCEX in water, however, the RAFT agent required polymerisation with AM in a mixture of ethanol and water up to a low degree of polymerisation (DP), in order to obtain water solubility. This imperative step makes the polymerisation complex and undesirable from an industrial perspective.

Of specific interest is trithiocarbonate BCPA, because of its reported results and facile synthesis, in one pot under mild conditions. Next to AM (vide supra), BCPA was employed in the polymerisation of several monomers, i.e. 2-hydroxyethyl acrylate, acrylic acid (AA), NIPAM, 2-acrylamido-2-methylpropane sulfonic acid, and DMA. Furthermore, BCPA was employed in the synthesis of a 7 arm multifunctional RAFT agent by coupling of BCPA to cyclodextrin (core as part of the Z-group). This core was polymerised with styrene (St) in bulk at 60 – 120 °C initiated by α, α’-Azoisobutyronitrile (AIBN) to yield star shaped polymers. Another multifunctional RAFT agent based on BCPA (12 arms) was synthesised with a polyester core and applied in the polymerisation of butyl acrylate (BA) and St. On top of that, poly(ethylene glycol) monomethyl ether methacrylate (PEGMA) was polymerised with BCPA in acetonitrile. Polymers were coupled upon reaction with a bifunctional monomer, yielding monodisperse star polymers. More branched polymers containing AM were synthesised by copolymerising AM with bifunctional monomer N,N’-methylenbis (acrylamide) (BisAM). Obtained polymers had molecular weights up to 1,280,000 Da, however, PDIs were ranging from 4.7 to 8.6. The feeding protocol of the monomers was evaluated in a more recent report. Star-polymers were prepared by an arm first (AF) and core first (CF) procedure. In the AF approach, arms were polymerised before the addition of BisAM, yielding molecular weights up to 715,000 Da and PDIs below 2.2. The CF approach involved the synthesis of a branched core, followed by chain extension with AM, leading to molecular weights up to 579,000 Da and PDIs below 2.4. A third approach involved direct copolymerisation of AM and BisAM, limiting the molecular weight to 204,000 Da with a PDI of 1.9, resulting from progressing gelation. Finally, BisAM was fed continuously to the mixture, yielding molecular weights up to 1,290,000 Da with PDIs up to 9.4.

Because of the high relevance of tailoring the RAFT agent to the designated reaction (Chapter 1), the first step towards the industrially relevant synthesis of polyacrylamide with well-defined macromolecular properties lies in the selection of a RAFT agent that offers sufficient control over the polymerisation. By developing a straightforward synthetic procedure, the successful polymerisation of linear polyacrylamide paves the way for the synthesis of more complex architectures. In the
current work we present the synthesis of BCPA (RAFT agent A) and two derivatives, containing a carboxylic group on the benzylic position (RAFT agent B) and a vinyl group on the benzylic position (RAFT agent C), respectively. RAFT agent B and C can be synthesised by a synthetic procedure similar to that of RAFT agent A, with starting materials that are readily available. RAFT agent B is foreseen to offer a higher water solubility, whereas RAFT agent C contains a double bond to introduce branching. These RAFT agents are envisioned to be used in the polymerisation of AM, whereby the RAFT agent has to offer a certain level of control over the reaction. The latter is evaluated by kinetic plots of the polymerisations. Moreover, the presented synthetic strategy has to be suitable for the polymerisation up to high molecular weight, in order to render the process relevant from an application point of view. Therefore, initial aqueous polymerisations with different DPs are performed and illustrate the potential for their use in the industrially relevant aqueous polymerisations of acrylamide.

2.2 Experimental

2.2.1 Chemicals

Acrylamide (AM, electrophoresis grade, ≥ 99%), 4,4’-Azobis(4-cyanvaleric acid) (ACVA, ≥ 98.0%), 3-mercaptpropionic acid (≥ 99%), CS₂ (≥ 99.9%), Benzyl bromide (98%), 4-(bromomethyl) benzoic acid (97%). Sodium thiosulfate, pentahydrate (≥ 99.5%), and 4-vinylbenzyl chloride (≥ 90%) were purchased from Sigma-Aldrich and used as received. Ammonium persulfate (APS, ≥ 99%) was obtained from Acros Organics and used without further purification.

2.2.2 Synthesis of RAFT agent A (BCPA)

3-mercaptopropionic acid (2.2 mL, 25 mmol) was added to an aqueous solution of potassium hydroxide (2.8 g, 50 mmol of KOH in 25 mL demineralised water). CS₂ was cooled for 30 minutes in ice before opening the bottle and added drop wise (2.6 mL, 52.5 mmol) in more than 40 min to the reaction mixture under vigorous stirring. The clear solution turned orange and was stirred for 2 h at room temperature. Benzyl bromide (3 mL, 25 mmol) was added and the reaction mixture was stirred at 80°C overnight. In order to obtain the RAFT agent, the reaction mixture was cooled down and chloroform and HCl were added. The organic and aqueous layer were separated in a separation funnel and the aqueous layer was extracted twice with chloroform. The organic layer was washed with NaCl solution and subsequently with water. After drying over Na₂SO₄, the solvent was evaporated at the rotary evaporator. The yellow oil was subsequently recrystallised from dichloromethane, in order to obtain the product as a yellow solid (4.5 g,
16.6 mmol, 66% yield). The NMR spectra and structures with labelled atoms are available in the supplementary information.

^{1}H-NMR (400 MHz, DMSO-d_{6}) \( \delta \)_{H18} = 12.36 (s, 1H), \( \delta \)_{H2,4} = 7.35 (dd, \( J \) = 7.5, 1.7 Hz, 2H), \( \delta \)_{H1,5} = 7.30 (t, \( J \) = 6.9 Hz, 2H), \( \delta \)_{H6} = 7.27 - 7.24 (m, 1H), \( \delta \)_{H7} = 4.64 (s, 2H), \( \delta \)_{H13} = 3.55 - 3.48 (t, \( J \) = 3.52 Hz, 2H), \( \delta \)_{H15} = 2.68 - 2.61, (t, \( J \) = 2.64 Hz, 2H). ^{13}C-NMR (400 MHz, DMSO-d_{6}) \( \delta \)_{C10} = 223.77, \( \delta \)_{C16} = 172.98, \( \delta \)_{C3} = 135.53, \( \delta \)_{C1,2} = 129.87, \( \delta \)_{C4,6} = 129.66, \( \delta \)_{C5} = 128.12, \( \delta \)_{C7} = 40.85, \( \delta \)_{C13} = 33.01, \( \delta \)_{C15} = 32.33. HRMS (ESI+, \( m/z \)): calculated for C_{11}H_{12}O_{2}S_{3}-H [M-H]^+: 273.00777; found: 273.00722. FT-IR: 1690 (C=O stretch), 1493, 1452, 1423, 1398, 1372, 1342, 1290, 1260, 1198, 937, 837, 799, 770, 702, 692, 658, cm\(^{-1}\). CHS results (C_{11}H_{12}O_{2}S_{3}, 272.406): Calculated (C%: 48.50, H%: 4.44, S%: 35.31), found (C%: 49.06, H%: 4.62, S%: 35.75). Melting point: 83.5 – 86.8 °C.

### 2.2.3 Synthesis of RAFT agent B (CABCPA)

3-mercaptopropionic acid (2.2 mL, 25 mmol) was added to an aqueous solution of potassium hydroxide (2.8 g, 50 mmol of KOH in 25 mL demineralised water). CS₂ was cooled for 30 minutes in ice before opening the bottle and added drop wise (2.6 mL, 52.5 mmol) in more than 40 min to the reaction mixture under vigorous stirring. The clear solution turned orange and was stirred for 2 h at room temperature. 4-(bromomethyl)benzoic acid (5.376 g, 25 mmol) was added to an aqueous solution of potassium hydroxide (2.8 g, 50 mmol in 25 mL demineralised water). After addition of HCl, the mixture was filtered over a Büchner funnel with a sintered glass disc. The solid product was dissolved in THF and dried over Na₂SO₄, followed by evaporation of the solvent. The yellow solid was subsequently recrystallised from THF and pentane in order to obtain the product as a yellow crystalline solid (4.05 g, 12.8 mmol, 51% yield).

^{1}H-NMR (400 MHz, DMSO-d_{6}) \( \delta \)_{H2,4} = 12.36 (s, 1H), \( \delta \)_{H9} = 11.3 (s, 1H) \( \delta \)_{H1,5} = 7.88 (d, \( J \) = 8 Hz, 2H), \( \delta \)_{H2,4} = 7.47 (d, \( J \) = 7.9 Hz, 2H), \( \delta \)_{H10} = 4.72 (s, 2H), \( \delta \)_{H16} = 3.52 (t, \( J \) = 6.8 Hz, 2H), \( \delta \)_{H18} = 2.66 (t, \( J \) = 6.8 Hz, 2H). ^{13}C-NMR (400 MHz, DMSO-d_{6}) \( \delta \)_{C13} = 222.39, \( \delta \)_{C19} = 172.87, \( \delta \)_{C7} = 167.38, \( \delta \)_{C3} = 140.97, \( \delta \)_{C6} = 130.42, \( \delta \)_{C1,5} = 130, \( \delta \)_{C2,6} = 129.89, \( \delta \)_{C10} = 40.24, \( \delta \)_{C16} = 32.74, \( \delta \)_{C18} = 32.31. HRMS (ESI+, \( m/z \)): calculated for C_{12}H_{12}O_{2}S_{3}H [M-H]^+: 316.99705; found: 316.99705. FT-IR: 1688 (C=O stretch), 1609 (C=O stretch), 1574, 1423, 1404, 1314, 1277, 1200, 1175, 1121, 1055, 1018, 924, 822, 783, 762, 723, 648, cm\(^{-1}\). CHS results (C_{12}H_{12}O_{2}S_{3}, 316.416): Calculated (C%: 45.55, H%: 3.82, S%: 30.40), found (C%: 46.60, H%: 4.44, S%: 27.80). Melting point: 179.1 – 207.3 °C.


CHAPTER 2. SYNTHESIS OF RAFT AGENTS

2.2.4 Synthesis of RAFT agent C (ViBCPA)

3-mercaptopropionic acid (2.2 mL, 25 mmol) was added to an aqueous solution of potassium hydroxide (2.8 g, 50 mmol of KOH in 25 mL demineralised water). CS₂ was cooled for 30 minutes in ice before opening the bottle and added drop wise (2.6 mL, 52.5 mmol) in more than 40 min to the reaction mixture under vigorous stirring. The clear solution turned orange and was stirred for 2 h at room temperature. 4-vinylbenzyl chloride (3.5 ml, 25 mmol) was added and the reaction mixture was stirred at 90°C for 75 min. HCl (5 mL, 12 molar) and ethyl acetate were added in order to dissolve solids and the mixture was separated in a separation funnel. The organic layer was washed with brine and dried over Na₂SO₄. Afterwards, the solvent was evaporated at the rotary evaporator to obtain a yellow oil. The product was purified by column chromatography (6:1 heptane:ethyl acetate with 2.5% toluene and 2.5% acetic acid). The product was a yellow crystalline solid (2.69 g, 9 mmol, 36% yield).

¹H-NMR (400 MHz, DMSO-d₆) δ_H2O = 12.36 (s, 1H), δ_H4,2,5,1 = 7.41 - 7.30 (m, 4H), δ_H7 = 6.61 - 6.62 (m, 1H), δ_H8 = 5.79 (dd, J = 17.7, 1.1 Hz, 1H), δ_H8' = 5.22 (d, J = 10.9 Hz, 1H), δ_H9 = 4.63 (s, 2H) δ_H15 = 3.54 (t, 2H), δ_H17 = 2.68 - 2.61 (t, 2H). ¹³C-NMR (400 MHz, DMSO-d₆) δ_C12 = 223.68, δ_C18 = 172.89, δ_C7 = 136.98, δ_C6 = 136.63, δ_C3 = 135, δ_C2 = 130.3, δ_C4 = 130.17, δ_C1,5 = 126.76, δ_C8 = 115, δ_C9 = 39.92, δ_C15 = 32.75, δ_C16 = 32.12. HRMS (ESI+, m/z): calculated for C₁₃H₁₄O₂S₃-H [M-H]⁺: 299.02342; found: 299.02287. FT-IR: 1686 (C=O stretch), 115, 908, 812, 764, 733, 710, 660, cm⁻¹. CHS results (C₁₃H₁₄O₂S₃): Calculated (C%: 52.32, H%: 4.73, S%: 32.23), found (C%: 53.59, H%:5.12, S%: 29.82). Melting point: 69.3 - 83.1°C.

2.2.5 RAFT polymerisation of AM with RAFT agent A and B

AM (e.g. entry CABCBA-PAM197: 0.45 g, 6.3 mmol) was dissolved in a buffer of acetic acid and sodium acetate (3 mL, pH = 5) and charged to a three-neck flask, equipped with a stirring magnet. The RAFT agent (B, 0.0102 g, 0.03 mmol) was added and the mixture was degassed by purging with N₂ under vigorous stirring for at least 30 min. The reaction mixture was subsequently heated to the designated temperature (80°C) and initiated by addition of ACVA (0.0026 g, 0.01 mmol). After the polymerisation time (330 min) the reaction mixture was exposed to air and diluted with demineralised water in order to terminate the reaction. Polymers were precipitated in methanol, dried at 70°C up to constant weight and subsequently characterised. An overview of the reaction conditions is listed in table 1.
Table 1: RAFT polymerisation of AM & NIPAM with RAFT agent A, B, and C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>CTA</th>
<th>[CTA]</th>
<th>[I]</th>
<th>[M]</th>
<th>M:solv (w:vol)</th>
<th>T (°C)</th>
<th>t (min)</th>
<th>Conv. (%)</th>
<th></th>
<th>M[n,thor.</th>
<th>M[n,GPC</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCPA-PAM30</td>
<td>A</td>
<td>1</td>
<td>0.49</td>
<td>32</td>
<td>0.23</td>
<td>70</td>
<td>120</td>
<td>94</td>
<td>2,412</td>
<td>2.843</td>
<td>1.24</td>
<td></td>
</tr>
<tr>
<td>BCPA-PAM778</td>
<td>A</td>
<td>1</td>
<td>0.19</td>
<td>905</td>
<td>0.14</td>
<td>80</td>
<td>30</td>
<td>86</td>
<td>55,775</td>
<td>47,540</td>
<td>1.27</td>
<td></td>
</tr>
<tr>
<td>BCPA-PAM1738</td>
<td>A</td>
<td>1</td>
<td>0.19</td>
<td>1,810</td>
<td>0.14</td>
<td>80</td>
<td>112</td>
<td>96</td>
<td>123,943</td>
<td>85,610</td>
<td>1.53</td>
<td></td>
</tr>
<tr>
<td>CABCPA-PAM197</td>
<td>B</td>
<td>1</td>
<td>0.29</td>
<td>197</td>
<td>0.15</td>
<td>80</td>
<td>330</td>
<td>100</td>
<td>14,316</td>
<td>18,810</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>CABCPA-PAM200</td>
<td>B</td>
<td>1</td>
<td>0.17</td>
<td>220</td>
<td>0.25</td>
<td>80</td>
<td>43</td>
<td>91</td>
<td>14,481</td>
<td>24,410</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td>CABCPA-PAM1570</td>
<td>B</td>
<td>1</td>
<td>0.38</td>
<td>1,963</td>
<td>0.22</td>
<td>80</td>
<td>66</td>
<td>80</td>
<td>112,508</td>
<td>132,500</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>ViBCPA-PAM524</td>
<td>C</td>
<td>1</td>
<td>0.16</td>
<td>535</td>
<td>0.15</td>
<td>80</td>
<td>145</td>
<td>98</td>
<td>37,748</td>
<td>50,560</td>
<td>1.84</td>
<td></td>
</tr>
<tr>
<td>ViBCPA-PAM1311</td>
<td>C</td>
<td>1</td>
<td>0.33</td>
<td>1,410</td>
<td>0.16</td>
<td>80</td>
<td>127</td>
<td>93</td>
<td>93,894</td>
<td>113,600</td>
<td>1.59</td>
<td></td>
</tr>
<tr>
<td>ViBCPA-PAM2058</td>
<td>C</td>
<td>1</td>
<td>0.32</td>
<td>2,100</td>
<td>0.16</td>
<td>80</td>
<td>128</td>
<td>98</td>
<td>146,274</td>
<td>136,100</td>
<td>1.82</td>
<td></td>
</tr>
<tr>
<td>BCPA-PNIPAM21</td>
<td>A</td>
<td>1</td>
<td>0.25</td>
<td>25</td>
<td>0.17</td>
<td>25</td>
<td>885</td>
<td>82</td>
<td>2,571</td>
<td>2,686</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

a) CTA-polymer:monomeric units in polymer
b) 50:50 vol% mixture of buffer and EtOH
c) Redox initiation with ammonium persulphate and sodium thiosulphate in a 5:4 ratio
d) Determined gravimetrically
e) Determined by 1H-NMR

2.2.6 RAFT polymerisation of AM with RAFT agent C

Because of to lower hydrophilicity of RAFT agent C compared to RAFT agent A and B, 2 mL ethanol was used to dissolve the RAFT agent, prior to the addition of monomer. After addition of the monomer dissolved in a buffer of acetic acid and sodium acetate (pH = 5), the reaction mixture was degassed and the procedure was continued similarly to RAFT agent A and B.

2.2.7 Kinetic experiments

The general polymerisation procedure was followed, however, at certain time intervals aliquots of 0.3 ml were taken from the reaction mixture and immediately precipitated in acetone. The conversion of samples was determined, followed by drying of the samples and characterisation by GPC.

2.2.8 Characterisation

Conversion of AM was measured using GC. Samples of reaction mixtures were dissolved in acetone containing 1,000 ppm pentadecane (reference) and injected on a Hewlett-Packard 5890 GC equipped with an Elite-Wax ETR column. Polymer samples were dissolved in deionised water containing 0.05 M sodium nitrate and subjected to GPC. An Agilent 1200 system was equipped with Polymer Standard Service (PSS) columns (100 Å and 3,000 Å, 8 x 300 mm) and an aqueous 0.05 M
sodium nitrate solution was used as the eluent. Column temperature was maintained at 40 °C and detection of polymers was conducted with a refractive index (RI) detector, operated at 40 °C. AM-based calibration and WinGPC software (GPC) were used to calculate the apparent molecular weight and PDI of the samples. Proton nuclear magnetic resonance (1H-NMR) and carbon nuclear magnetic resonance (13C-NMR) spectra were recorded using a Varian Mercury Plus spectrometer operating at 400 MHz, using DMSO-d6 as solvent. Mass spectra were recorded using an LTQ Orbitrap XL spectrometer (ThermoFisher Scientific) with ESI ionisation in positive mode. FT-IR spectra were recorded on a Shimadzu IRTracer-100 FT-IR spectrophotometer. Shimadzu LabSolutions IR software was used to record the spectra at a resolution of 4 cm⁻¹ by averaging 32 scans for each sample and background scan. Elemental Analysis of the RAFT agents for the elements S, C, and H was performed on a EURO EA analyser.

2.3 Results and discussion

2.3.1 Synthesis of RAFT agents

RAFT agent 3-(((benzylthio)carbonothioyl)thio)propanoic acid (A), 4-(((2-carboxyethyl)thio)carbonothioyl)thio)methyl)benzoic acid (B), and 3-(((4-vinylbenzyl)thio)carbonothioyl)thio)propanoic acid (C) were synthesised as outlined in figure 1. The synthesis of RAFT agent A has been previously reported in literature. Alternatively, in the present work, purification of RAFT agent A was performed by recrystallisation twice from dichloromethane. Because of the high reactivity of 4-(bromomethyl)benzoic acid compared with benzyl bromide, the reaction time for the second step in the synthesis of RAFT agent B was reduced from overnight to minutes, as the reaction mixture turned from liquid to solid instantaneously. Since RAFT agent B was not soluble in chloroform, solubility in several solvent was evaluated. The compound was not soluble in toluene, dichloromethane, diethyl ether, ethyl acetate, methanol, and ether. In THF, however, high solubility was obtained and THF was used for the dissolution of the RAFT agent, followed by drying over Na2SO4. In order to purify the compound, it was recrystallised from THF, followed by recrystallisation from pentane.

Because of the better leaving group ability of bromine compared with chlorine, the reaction temperature was increased from 80 to 90 °C in the synthesis of RAFT agent C, containing 4-vinylbenzyl chloride. Comparable to RAFT agent B, compound C was not soluble in chloroform. Therefore, several solvents were evaluated. Dichloromethane, toluene, and diethyl ether, however, did not solubilise the RAFT agent. THF, TFA and HCl, on the other hand, were capable of dissolving compound C. The obtained yield for RAFT agent C is relatively low, which is
attributed to the presence of a side product in the reaction mixture, namely 3-((2-mercaptop-2-(4-vinylphenyl)ethanethiol)thio)propanoic acid (figure 2).

According to elemental analysis, sulphur contents in the obtained RAFT agents were up to 8.6 % lower than their theoretical values. The latter is attributed to the presence of impurities and traces of solvent, as can also be seen in the $^1$H-NMR spectra depicted in the supplementary information and is further supported by the measured melting ranges.

### 2.3.2 Polymerisation with RAFT agent A, B, and C

In order to evaluate the suitability of RAFT agent A, B, and C in the polymerisation of AM, polymers were prepared according to the conditions outlined in table 1. Experimental molecular weights ranging from 2,800 to 136,000 Da were obtained with PDIs between 1.18 and 1.84, at polymerisation times of 30 to 330 min. The higher PDIs were mainly observed for RAFT agent C, which includes a vinyl group that can participate in the polymerisation, leading to a branched polymer. Similarly, relatively high PDIs were reported for RAFT polymerisation of galactose-based saccharide monomers in presence of a RAFT agent containing a vinyl group (inimer), especially at higher monomer to RAFT agent ratio. Other reports on syntheses with inimers include the polymerisation of NIPAM and DMA (PDI 1.42 - 2.10),$^{18}$ St (PDI 1.90 - 3.33),$^{19}$ St and NIPAM (PDI 1.44 - 2.46 and 1.23 - 1.71 respectively),$^{20}$ methyl methacrylate (MMA), methyl acrylate (MA),
tert-butyl acrylate (TBA), and St (PDI 1.16 - 9.18), as well as hyperbranched cores containing MA, chain-extended with St and TBA to give star-shaped polymers (PDI 1.12 - 1.88), vinyl acetate (VA) (PDI 1.71 - 4.59 and 2.35 - 2.92), and poly(ethylene glycol) methacrylate (PEGMA) (PDI approximately 2.0).

RAFT agent B, interestingly, offers lower dispersities over the targeted range of molecular weights than RAFT agent A. The difference between the two RAFT agents lays mainly in the solubility of the RAFT agent, more specifically that of the R-group. The toluene R-group of RAFT agent A is, especially in water, expected to be very reactive because of the high stability of the radical. The 4-carboxybenzyl benzoic acid R-group of RAFT agent B is more hydrophilic, as well as less stable, and thus less reactive. The combination of the latter two effects leads to a more controlled development of the RAFT pre-equilibrium.

Moreover, GPC traces of polymers prepared with RAFT agent A display a small low molecular weight tail for both low and high molecular weight polymers (figure 3a). For equivalents prepared with RAFT agent B, both low and high molecular weight tailing is observed. However, when going to a higher degree of polymerisation (DP), tailing is found to disappear (figure 3b). RAFT agent C, containing a vinyl bond, displays a high molecular weight tail over the whole range of DPs (figure 4a).

\[
M_{n,\text{theo}} = \frac{[M]_0 \cdot \text{Conversion} \cdot M_w}{[CTA]_0} + M_{\text{CTA}} \quad (2.1)
\]

In figure 4b, the experimental molecular weight as function of its theoretical equivalent calculated according to Eq. 2.1 is displayed. As shown, RAFT agent A and B display a linear relationship between experimental and theoretical molecular weight. Gel permeation chromatography (GPC) traces of RAFT agent B
2.3. RESULTS AND DISCUSSION

![Figure 4](image1)

**Figure 4:** a) GPC traces obtained with RAFT agent C. b) Theoretical versus experimental molecular weight for polymers synthesised with RAFT agent A, B, and C.

![Figure 5](image2)

**Figure 5:** Kinetic plot of entry BCPA-PAM778 and BCPA-PAM1738, polymerised with RAFT agent A.

The results and discussion section of the text discuss the synthesis of RAFT agents and their performance in polymerisation reactions. GPC traces obtained with RAFT agent C are shown, demonstrating the high molecular weight tail observed over the whole range. RAFT agent B displays a linear relationship between experimental and theoretical molecular weight, while agent A shows a lower dispersity over the targeted range. The combination of these effects leads to a more controlled development of the RAFT pre-equilibrium.

Moreover, GPC traces of polymers prepared with RAFT agent A display a small low molecular weight tail for both low and high molecular weight polymers, whereas RAFT agent B offers lower dispersities over the targeted range. This is attributed to branching in the polymer (which confirms the pronounced high molecular weight tailing). The 4-carboxybenzyl benzoic acid R-group of RAFT agent B is more hydrophilic, as well as less stable, and thus less reactive. The combination of these effects leads to a more controlled development of the RAFT pre-equilibrium.

RAFT agent A and B display a linear relationship between experimental and theoretical molecular weight, whereas agent C offers lower dispersities over the targeted range. The difference between the two RAFT agents lays mainly in the solubility of the RAFT agent, more specifically that of the R-group. The toluene R-group of RAFT agent A is, especially in water, expected to be very reactive because of the high stability of the radical. The 4-carboxybenzyl benzoic acid R-group of RAFT agent B is more hydrophilic, as well as less stable, and thus less reactive. The combination of these effects leads to a more controlled development of the RAFT pre-equilibrium.

In figure 4b, the experimental molecular weight as a function of its theoretical value. For polymers obtained with RAFT agent C, the experimental molecular weight appears to decrease relatively to the theoretical molecular weight, at theoretical molecular weights above 110,000 Da. This latter effect can be ascribed to branching in the polymer (which confirms the pronounced high molecular weight tailing).

**Figure 4**: a) GPC traces obtained with RAFT agent C. b) Theoretical versus experimental molecular weight for polymers synthesised with RAFT agent A, B, and C.

**Figure 5**: Kinetic plot of entry BCPA-PAM778 and BCPA-PAM1738, polymerised with RAFT agent A.
weight tail in the GPC traces), leading to a decrease in hydrodynamic volume (in the dilute regime) and thus a discrepancy between experimental and theoretical molecular weight.\(^ {17,25-27}\)

Two kinetic experiments were performed, evaluating entry BCPA-PAM778 and BCPA-PAM1738 (table 1). As shown in figure 5, monomer consumption progresses linearly with reaction time, displaying first order kinetics. Both polymerisations do not display retardation. Interestingly, in literature both presence and absence of retardation is reported for RAFT polymerisation of acrylamide derivatives. For the cryopolymerisation of \(N,N\)-dimethylacrylamide (DMA) with a trithiocarbonate RAFT agent, retardation was observed, while for \(N\)-isopropylacrylamide (NIPAM) this effect was absent.\(^ {28}\) Applying a modified trithiocarbonate yielded retardation for both monomers, especially for NIPAM. The latter differences were left open to investigation. In similar polymerisations at 25 °C, no retardation was found for DMA and NIPAM.\(^ {29}\) Zhang et al, investigated the effect of solvent on the retardation of RAFT polymerisation of DMA with three different dithiobenzoates.\(^ {30}\) The retardation period was found to be highly dependent on the RAFT agent and the solvent conditions (dioxane, toluene, and bulk) were found to affect the induction period.

For entry BCPA-PAM778, the concentration of RAFT agent and initiator is doubled compared with entry BCPA-PAM1738. The latter translates to a reaction rate that is a factor two higher (k-value of \(1.2 \cdot 10^{-3}\) versus \(5.6 \cdot 10^{-3}\) with \(R^2\) values of the linear fit of 0.99 for both experiments), indicating a high dependence of the reaction rate on the concentration of radicals. In that respect, the reaction rate appears to be limited by the generation of radicals in the mixture.

In order to explore the versatility of the RAFT agents and their potential at lower reaction temperatures, a preliminary polymerisation of NIPAM was performed with RAFT agent A. Because of the lower critical solution temperature (LCST) of approximately 32 °C,\(^ {31}\) redox initiation was used at a reaction temperature of 25 °C. The molecular weight of the polymer was determined by \(^{1}H\)-NMR (see supplementary information). As can be seen from table 1, the experimental and theoretical molecular weight are in good correspondence.

### 2.4 Conclusions

3-(((benzylthio)carbonothioyl)thio) propanoic acid (BCPA), 4-(((((2-carboxyethyl)thio)carbonothioyl)thio)methyl)benzoic acid (CABCPA), and 3-(((4-vinylbenzyl)thio)carbonothioyl)thio) propanoic acid (ViBCPA) were successfully synthesised and characterised by \(^{1}H\)-NMR, \(^{13}C\)-NMR, FT-IR, mass spectrometry, and elemental analysis. The RAFT agents were applied in the aqueous polymerisation of acrylamide (AM), with short reaction times ranging from 30 to 330 min. The ob-
tained water soluble polymers showed molecular weights between 2,843 and 85,610 Da with polydispersity indices (PDIs) between 1.24 and 1.53 (BCPA), 18,810 and 132,500 Da with PDIs between 1.18 and 1.23 (CABCPA), and between 50,560 and 136,100 Da with PDIs between 1.59 and 1.84 (ViBCPA). The high PDIs for ViBCPA are ascribed to its inner character, intrinsically resulting in broader distributions. Experimental and theoretical molecular weight were found to be in good correspondence and control over the reaction was displayed in linear first order kinetics plots of the polymerisation with BCPA. The synthesised RAFT agents are a first step towards the industrial polymerisation of AM with control over the macromolecular properties, such as molecular weight.

2.5 Acknowledgement

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References

REFERENCES


2.5. **SUPPLEMENTARY INFORMATION CHAPTER 2**

Supplementary Information Chapter 2

**Figure S1:** FT-IR spectra of RAFT agent A, B, and C

**Figure S2:** $^1$H-NMR spectrum of RAFT agent A

The experimental molecular weight of PNIPAM (entry BCPA-PNIPAM21) was determined according to Eq. 2.2.
Figure S3: $^{13}$C-NMR spectrum of RAFT agent A

Figure S4: $^1$H-NMR spectrum of RAFT agent B
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Figure S5: $^{13}$C-NMR spectrum of RAFT agent B

Figure S6: $^1$H-NMR spectrum of RAFT agent C

\[
M_{n, \text{exp, PNIPAM}} = \frac{f_{19} + f_{20} + f_{24} + f_{25, 26}}{H_{19} + H_{20} + H_{24} + H_{25, 26}} \cdot M_M + M_{\text{CTA}} \quad (2.2)
\]
Figure S7: $^{13}$C-NMR spectrum of RAFT agent C

Figure S8: $^1$H-NMR spectrum of PNIPAM synthesised with RAFT agent A, recorded in DMSO-d$_6$

where $\int_X$ denotes the area of the integral of the protons X, $H_X$ the number of protons corresponding to atom X, $M_M$ the molar mass of NIPAM, and $M_{CTA}$ the molar mass of the RAFT agent.
Table S1: Integrals of protons for the calculation of the theoretical molecular weight of entry BCPA-PNIPAM21, according to the structural formula in figure S8

<table>
<thead>
<tr>
<th>Atom</th>
<th>Area</th>
<th>Protons</th>
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<tr>
<td>24</td>
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</tr>
<tr>
<td>25,26</td>
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<td>6</td>
</tr>
</tbody>
</table>

molar mass of the RAFT agent.