



Communication

Macro-RAFT Synthesis by Single Unit Monomer Insertion (SUMI) into Dithiobenzoate RAFT Agents – Towards Biological Precision

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Abstract: Achieving well defined control over the monomer sequence in polymers remains a long standing challenge in polymer chemistry. Sequence control by single unit monomer insertion (SUMI), ‘one at a time’, into dithiobenzoate RAFT agents has been explored. Macro-RAFT [(CH₃)₃C(CN)-(M)-SC(=S)-phenyl] synthesis by SUMI of styrene and N-isopropylacrylamide (NIPAm) into 2-cyano-2-propyl dithiobenzoate was successful. However, attempted SUMI of maleic anhydride (MAH) gave low yield consistent with the low reactivity of MAH towards 2-cyano-2-propyl radicals. Insertion of methyl methacrylate (MMA) provided an oligomeric insertion product due to the low transfer constant of the dithiobenzoate in MMA polymerization. Next, A step towards the controlled synthesis of macro-RAFT [(CH₃)₃C(CN)-(M₁)-(M₂)-SC(=S)-phenyl] was taken. The insertion of MAH, styrene and NIPAm into the styrene SUMI product has been investigated. Insertion of MAH into the macro-RAFT was fast, however, reactions with styrene and NIPAm were slow attributed both to the low concentration of monomer used and the poor leaving group ability of the propagating species. This study demonstrates the potential of RAFT for the synthesis of a new generation of synthetic polymers.

Keywords: Macro-RAFT agent; single unit monomer insertion (SUMI), sequence control

1. Introduction

Precisely controlled compositions, well-defined architectures and narrow molecular weight distributions are basic requirements for functional polymers utilized in biomedical, biotechnology and nanotechnology. These requirements can be achieved by applying techniques for reversible-deactivation radical polymerization (RDRP) [1], such as reversible addition fragmentation chain transfer (RAFT) [2-4]. However, radical processes are still limited when it comes to sequence control. Achieving well defined control over the monomer sequence in polymers, as e.g. proteins in nature or polynucleotide biosynthesis, remains a long standing challenge in polymer chemistry in particular radical polymerization [5]. Sequence controlled materials are very promising for performing various advanced tasks such as selective transport, signal transduction or catalytic reactions [6].

Zard and coworkers [7] first investigated single unit monomer insertion (SUMI) using xanthate transfer chemistry by inserting a single unit of less-activated monomer (LAM) [5,7]. Shadi *et al.* explored the scope and limitations for performing successive SUMI for styrene or NIPAm into a trithiocarbonate RAFT agent [8]. Mcleary, Klumperman and colleagues [9] observed that complete conversion of the initial RAFT agent to a species incorporating a single monomer unit is common to many well-behaved RAFT polymerizations, a behaviour termed selective initiation. Moad *et al.* [10] argued that the critical factors for such a selective initialization phenomena are a high chain transfer constant for the RAFT agent in combination with a fast addition of the radical ($R\cdot$) to monomer relative to propagation. Recently Vandenberg and coworkers [11] synthesized sequence controlled acrylate oligomers via four consecutive RAFT single monomer additions whereby they made use of automated recycling GPC to provide purification after each SUMI step, which poses the biggest problem when several monomer units are consecutively added.

In this paper, firstly, single unit insertion of styrene, N-isopropylacrylamide (NIPAm), methyl methacrylate and maleic anhydride (MAH) into 2-cyanopropan-2-yl dithiobenzoate (**1**) were explored. Secondly, insertion of styrene NIPAm and MAH into the so-formed styrene single unit insertion product were examined.

2. Results and Discussion

2.1. Single unit monomer insertion (SUMI) into 2-cyanopropan-2-yl dithiobenzoate (**1**)

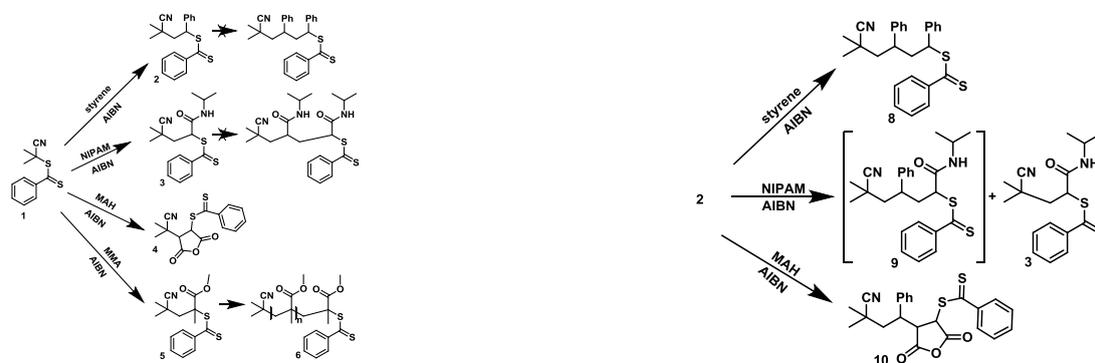
The initial RAFT agent utilized in the present work is 2-cyanopropan-2-yl dithiobenzoate (**1**), azobis(isobutyronitrile) (AIBN) was used as an initiator to ensure there would be no initiator derived insertion products. In situ NMR experiments with styrene, NIPAm, MMA and MAH were performed. SUMI of styrene or NIPAm into **1** provided **2** or **3** (Scheme I) analogously to similar reactions previously carried out with dodecyl 2-cyanopropan-2-yl trithiocarbonate [8]. Dimers or higher monomer insertion products were not observed in these experiments. Initiator derived by-products from cage reaction of initiator derived radicals were observed in the expected amounts. For SUMI experiments of MAH into **1** (Scheme I), the RAFT agent and MAH monomer were almost unchanged after 24 h and only small amounts of single inserted macro-RAFT (**4**) was formed, even though the proper amount of AIBN had been converted into initiator derived by-products. This was ascribed to the low reactivity of the electron deficient monomer MAH towards the initiator derived 2-cyanopropan-2-

yl radical. However, this was unexpected since MAH is described as reactive in literature [12]. In the experiments with MMA (Scheme I) only low amounts of the SUMI product **5** was observed. An oligomeric product **6** with degree of polymerization ~ 4 was formed observed by ESI-MS analysis (with $m/z = 221.03 + (n \times 100) + 1$) and oligomers formed from **6** by elimination of dithiobenzoic acid (with $167.09 + (n \times 100) + 1$).

Several further oligomer series were observed in minor amounts, these are not yet fully identified but might correspond to the products from “missing step” reactions and oligomers with thionoketone or sulfine ends.

The oligomer formation rather than SUMI can be understood by the relatively low transfer constant of 2-cyanopropan-2-yl dithiobenzoate RAFT agent in MMA polymerization [14] such that multiple units of MMA can be inserted per activation cycle under the reported conditions.

Scheme I (a) Schematic representation of SUMI of styrene, NIPAm, MAH and MMA into 2-cyanopropan-2-yl dithiobenzoate (**1**) **(b)** Schematic representation of SUMI of styrene, NIPAm and MAH into 3-cyano-3-methyl-1-phenylbutyl dithiobenzoate (**2**) macro-RAFT agent.



2.1. Single unit monomer insertion into 3-cyano-3-methyl-1-phenylbutyl dithiobenzoate (**2**) macro-RAFT agent

The SUMI product **2** was utilized for further SUMI experiments, in these experiments the appropriate monomer was added directly to the reaction mixture after 7.5 h, which was degassed and heated at 70 °C for 6, 12, 18 h (see experimental section). A monomer to **2** ratio of $\sim 2:1$ was used to compensate for the low reaction rate, no initial initiator was added.

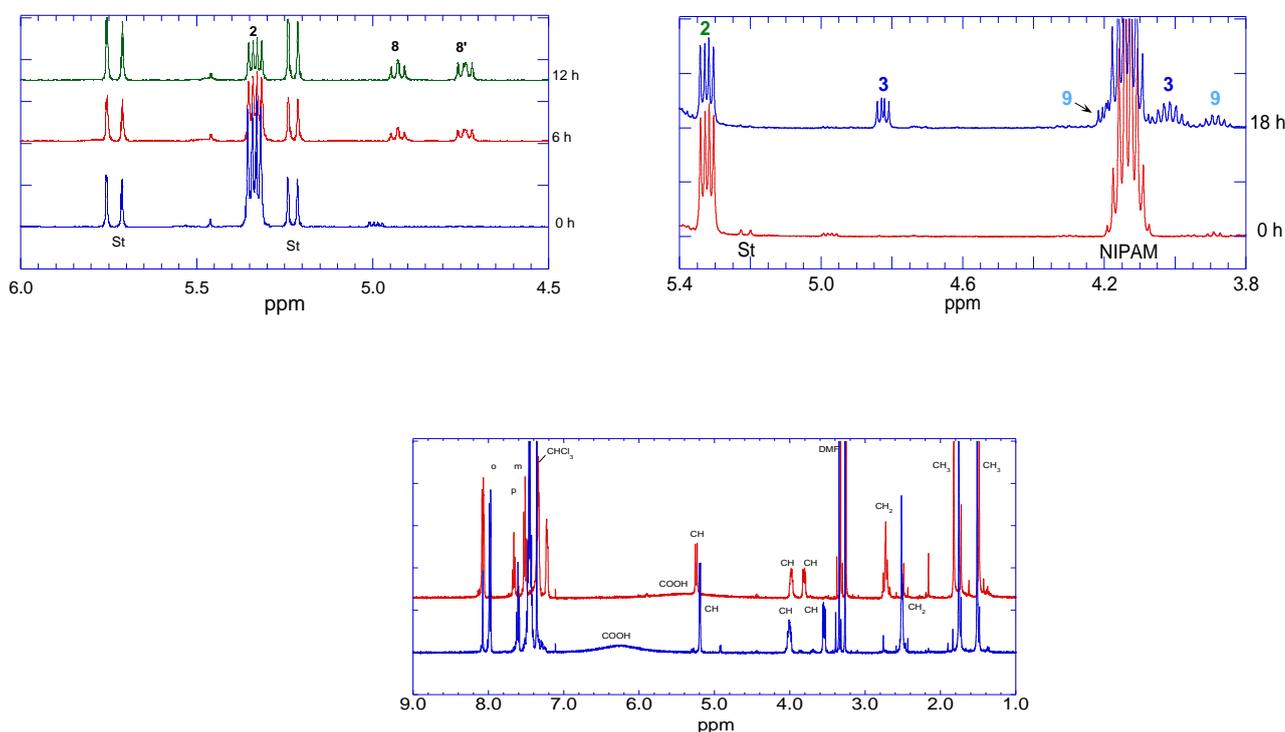
SUMI of styrene into **2** was observed as slow but successful providing about 50% conversion after 12 h (**8**, Scheme I). Since no additional initiator was added, the reaction was stopped before AIBN was consumed (dead end). Formation of higher oligomers was not observed in the $^1\text{H-NMR}$ spectra as shown (Figure 1).

SUMI of NIPAm into **2** (Scheme I) resulted in the desired styrene-NIPAm ‘co-dimer’ **9** and the initiator derived single unit insertion product **3**. The reaction outcome was ascertained by examining the region 4.1-4.3 ppm in $^1\text{H-NMR}$ (Figure 1). Signals attributable to the SCH(X)CH_2 and $(\text{CH}_3)_2\text{CHN-}$ hydrogens of **3** and **9** were assigned in Figure 1. The signals for the $\text{SCH(CONH(CH}_3)_2)\text{CH}_2$ hydrogens of **9** were largely obscured by those for the $(\text{CH}_3)_2\text{CHN-}$

NIPAm. The slow SUMI rate of styrene and NIPAm into **2** can be attributed to the poor leaving group ability of the propagating species *vs.* the 2-cyanopropan-2-yl radical.

SUMI of MAH into **2** (Scheme I) provided the two diastereomers of the desired product **10** in high yield after 6 h. This outcome is favored by several factors. Firstly, the 2-cyanopropan-2-yl is not very reactive towards MAH so there are only little to none initiator derived insertion products. Secondly, MAH propagates very slowly so that oligomeric products are not expected. The two diastereomers were isolated from the reaction mixture by preparative HPLC with CH₃CN/H₂O eluent, observed were two diastereomers of the maleic acid insertion product formed by hydrolysis of **10** as shown in ¹H-NMR (Figure 1).

Figure 1. (a) Region 4.5-6.0 ppm of ¹H-NMR spectra (CDCl₃) for reaction mixture at time 0 (lower) and after 6 and 12 h (middle and upper respectively) showing the signals corresponding to the SCH(X)CH₂ hydrogens corresponding to single unit styrene adduct **2** and to unit styrene adduct **8** (two diastereomers). Signals labeled 'St' are due to styrene monomer. **(b)** Region 3.8-5.5 ppm of the ¹H-NMR spectra (CDCl₃) for reaction mixture at time zero (lower) and after 18 h (upper) showing (from left to right) the signals corresponding to the SCH(X)CH₂ hydrogens corresponding to single unit styrene adduct **2** and the single unit NIPAm adduct **3**. Signals for the two diastereomers of the desired product **9** are largely obscured by the (CH₃)₂-CHN- of NIPAm. Signals in the region 3.8-4.0 ppm are attributable to the (CH₃)₂-CHN-hydrogens of **3** and **9** **(c)** region 1.0-9.0 ppm of the ¹H-NMR spectra (CDCl₃) of two diastereomers formed by hydrolysis of **10** isolated as the major products by preparative HPLC from insertion of MAH into single unit styrene insertion product **2**.



3. Experimental Section

Materials. Monomers were obtained from Aldrich. Styrene and MMA were purified by stirring with inhibitor remover and flash distillation before use. NIPAm was purified by recrystallization from Hexane/Et₂O 4:1. MAH was used as received. 2-cyanopropan-2-yl dithiobenzoate (**1**) was obtained from Aldrich and, with purity confirmed by ¹H-NMR, was used without purification. AIBN (VAZO64) was obtained from DuPont and was recrystallized from methanol/chloroform.

SUMI into 2-cyanopropan-2-yl Dithiobenzoate by Real Time Nuclear Magnetic Resonance. ¹H-NMR spectra for SUMI experiments in real time experiments were recorded on a Bruker BioSpin Av500 NMR spectrometer with a 5 mm inverse ¹³C/¹⁵N resonance probe operating at 500.13 MHz for ¹H.

Synthesis of 3-Cyano-3-methyl-1-phenylbutyl dithiobenzoate (2). A stock solution of 3-cyano-3-methyl-1-phenylbutyl dithiobenzoate (**2**) was prepared as follows. A 15 mL ampoule was charged with a solution of AIBN (156.7 mg, 0.954 mmol), styrene (496 mg, 4.77 mmol) and RAFT agent **1** (1.056 g, 4.77 mmol) in dichloroethane (2.40 mL). (The ratio AIBN:styrene determined by ¹H-NMR was 0.23:1.06:1 which compares with 0.2:1:1 based on the amounts reagents added) The solution was degassed through four freeze-pump-thaw cycles and flame sealed. The ampoule was placed in an oil bath at 70 °C for 7.5 h. At this time conversions of AIBN, styrene and **1** determined by NMR were 36, 93 and 100% respectively. This reaction solution was used directly as the stock solution of **2** in the second unit insertion experiments. ¹H-NMR (400MHz, CDCl₃, signals attributable to **2**): δ7.88-7.86 (2H, m, Ar-H), 7.58-7.10 (m, Ar-H), 6.30 (1H, d, J = 7.35 Hz, N-H), 4.85-4.80 (1H, dd, J = 5.00; 8.12 Hz, S-H), 4.07-3.96 (1H, septet, J = 6.65 Hz, (CH₃)₂-CH), 3.13-3.04 (1H, m, CH₂-CH-CH₂), 3.03-2.96 (2H, m, CH-CH₂-CH), 2.69-2.60 (2H, m, Cquat-CH₂), 1.41, 1.24 (2 x 3H, s, Cquat-CH₃), 1.17, 1.15 (2 x CH₃, s, (CH₃)₂-CH).

SUMI into 3-cyano-3-methyl-1-phenylbutyl dithiobenzoate (2). The following procedure is typical. Three 5 mL ampoules charged with the above reaction solution (0.4 mL) and styrene (60.22 mg, 0.578 mmol) which were degassed through four freeze-pump-thaw cycles and flame sealed. The ampoules were placed in an oil bath at 70 °C for 6, 12 and 18 h.

4. Conclusions

SUMI of styrene and NIPAm into 2-cyanopropan-2-yl dithiobenzoate (**1**) was successful. High yields were obtained and no evidence for oligomer formation was found. Attempted SUMI of MMA into **1** under similar conditions provided an oligomeric products which is attributed to the much lower transfer constant of **1** in MMA polymerization. SUMI of MAH into **1** was unsuccessful due to the low reactivity of MAH towards 2-cyanopropan-2-yl radicals. SUMI of styrene, NIPAm and MAH into the styrene SUMI product formed above was rapid and efficient for MAH, however, slow and selective for styrene and NIPAm. In the case of NIPAm an initiator derived by-product was formed.

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work were originally presented at the 246th ACS meeting in Indianapolis in 2013 and the studies are documented in greater detail [15].

Conflicts of Interest

"The authors declare no conflict of interest".

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