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Simplification of the synthesis of the reversible addition–fragmentation chain transfer agent 2-(2-cyanopropyl)-dithiobenzoate

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Abstract: The general literature procedure for the preparation of the reversible addition–fragmentation chain transfer (RAFT) agent 2-(2-cyanopropyl)-dithiobenzoate (CPDB) was modified by omitting the recrystallisation of the intermediate di(thiobenzoyl)disulphide. The yield of the CPDB in the simplified synthesis was increased four times compared to the standard one. The behaviour of the CPDB obtained by the modified procedure and by the standard one in the polymerisation of methyl methacrylate was investigated. The CPDB synthesized by the simplified procedure showed itself to be a good RAFT agent, giving excellent control over the polymerisation of methyl methacrylate and it behaved in the same manner as the CPDB prepared by the literature method. The obtained poly(methyl methacrylate) had a narrow molecular weight distibution (PD = 1.1).

Keywords: 2-(2-cyanopropyl)-dithiobenzoate; preparation; reversible addition–fragmentation chain transfer; poly(methyl methacrylate).

INTRODUCTION

In recent years, much effort has been focused on the synthesis of polymers with controlled molar masses and very narrow molar mass distributions. With the development of several methods of controlled radical polymerisation, well-defined polymers with complex architectures, including block,[1,2] graft[3] and star[4,5] structures, could be prepared. The development of these methods was promoted by the growing need for truly living radical polymerisation systems that would offer all the benefits of ionic polymerisations without the serious disadvantages inherent to such systems. Among them, RAFT (reversible addition–fragmen-

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tation chain transfer) polymerisation has proven itself to be the most versatile one, since it is applicable to a wide range of monomers and can be performed in a wide variety of solvents over a broad range of experimental conditions. RAFT polymerisations are now being used successfully by an ever-growing number of research groups around the world. The key to successful RAFT polymerisations is the presence of a highly efficient dithioester chain transfer agent. Among numerous RAFT agents, only a few are commercially available (carboxymethyl dithiobenzoate, for example). Regarding the importance of the synthesis of RAFT agents of different structures, a large number of procedures for the synthesis of dithioester compounds have been developed. As the syntheses of these RAFT agents are usually costly and require multi-step reactions, the loss of polymerisation mediator throughout the RAFT polymerisation process may be an issue when scaling-up the process. A simple reaction that leads to the full removal of the thiocarbonyl-thio end group from the polymeric chains and recovery of the chain transfer agent has already been reported.[6] In addition, simplifications of the syntheses of RAFT agents would promote scaling-up the RAFT polymerisation processes.

This study focused on the synthesis of 2-(2-cyanopropyl)-dithiobenzoate (CPDB) which, together with cumyl dithiobenzoate, is one of the most frequently employed RAFT agents. CPDB was reported to be an efficient RAFT agent in the polymerisation of a number of monomers.[7–10] 2-(2-Cyanopropyl)-dithiobenzoate can be synthesized in two ways. One method is a single-step procedure, by reaction of Davy reagent or P_4S_{10} with benzoic acid. The obtained CPDB was used to control *in situ* the free-radical polymerisation of styrene and alkyl (meth)acrylates.[11] The isolation of pure CPDB demands a multi-step procedure.[12] One of the steps in this preparation is the synthesis of dithiobenzoic acid. Dithiobenzoic acid is unstable and should be stored at low temperatures (< –20 °C)[13] or used immediately. For this reason, it is usually transferred into di(thiobenzoyl)disulphide. Di(thiobenzoyl)disulphide is used not only for the synthesis of CPDB, but also for the syntheses of many different RAFT agents.[14]

In the present study, the standard procedure for the preparation of CPDB was modified and simplified by omitting the intermediate step of the recrystallisation of di(thiobenzoyl)disulphide in order to avoid great loss of material in this step. The behaviour of the CPDB synthesized by the simplified procedure in the polymerisation of methyl methacrylate was investigated and compared with that of the CPDB synthesized by the standard method.

EXPERIMENTAL

Methyl methacrylate, MMA, (Fluka) was distilled under reduced pressure after removal of the inhibitor with a 10 % aqueous NaOH solution. Azobis(isobutyronitrile), AIBN, (Aldrich), was purified by recrystallisation from methanol. Benzene, thiophene free, (Fluka) was distilled before use.

The RAFT agent, 2-(2-cyanopropyl)-dithiobenzoate (CPDB), was prepared by a standard method described in the literature.[15] To a thoroughly dried, three-necked round-bottomed flask equipped with a magnetic bar, addition funnel, thermometer and condenser was added elemental sulphur (6.4 g, 0.20 mol), 25 % sodium methoxide solution in methanol (40 g) and anhydrous methanol (40 g). Benzyl chloride (12.6 g, 0.10 mol) was the added dropwise *via* an addition funnel over a period of 90 min at room temperature. The resulting violet-brown solution was then heated and allowed to reflux overnight. After cooling to room temperature, the mixture was filtered to remove the white solid (sodium chloride) which was formed as a by--product during the reaction. The methanol was removed by rotary evaporation at 40 °C. The resulting violet-brown solid was then re-dissolved in distilled water (100 ml) and transferred to a separation funnel. The crude sodium dithiobenzoate solution was washed with diethyl ether (3×50 ml). A final layer of ether (50 ml) was added to the solution and the two-phase mixture was then acidified with 32 % aqueous HCl until the aqueous layer lost its characteristic violet-brown colour and the top, ether, layer was deep purple. The ether layer containing dithiobenzoic acid was extracted. Deionized water (120 ml) and 1.0 M NaOH (240 ml) were added, and sodium dithiobenzoate was extracted into the aqueous layer. This washing process was repeated two times more to yield a final solution containing sodium dithiobenzoate (360 ml).

The next step was the synthesis of di(thiobenzoyl)disulphide. Potassium ferricyanide (13.17 g, 0.040 mol) was dissolved in deionized water (200 ml). Potassium ferricyanide solution (140 ml) was transferred to a conical flask equipped with a magnetic bar. Potassium ferricyanide solution was added dropwise to the sodium dithiobenzoate *via* an addition funnel over a period of 1 h under vigorous stirring. The red precipitate was filtered and washed with deionized water until the washings become colourless. The solid was dried under vacuum at room temperature. The product was recrystallized from anhydrous ethanol.

The target compound was prepared in the reaction of di(thiobenzoyl)disulphide with azobisisobutyronitrile (AIBN). A solution of AIBN (2.90 g, 0.018 mol) and di(thiobenzoyl)disulphide (3.60 g, 0.012 mol) in ethyl acetate (70 ml) was heated at reflux for 18 h. The ethyl acetate was removed under vacuum. The crude product, CPDB-1, was subjected to column chromatography on a 25×2.6 cm column filled with silica gel (Woelm mesh size 0.063–0.2 mm, ICN Pharmaceuticals, Germany) as the stationary phase and ethyl acetate: *n*-hexane (0.2:0.98) as the eluent, at a flow rate of 1.0 mL min^{-1}.

Due to the large loss of di(thiobenzoyl)disulphide in the recrystallisation step, the synthesis of di(thiobenzoyl)disulphide was repeated but this time it was used in the subsequent reaction without recrystallisation to yield CPDB-2.

The structure of the CPDB from the both synthesis was confirmed by ^{13}C-NMR spectroscopy using a Varian-Gemini-200 (200 MHz) instrument.

In order to determine whether CPDB-2 was equally effective as a RAFT agent as CPDB-1, methyl methacrylate was polymerised using both RAFT agents.

The polymerisations of methyl methacrylate, MMA, were performed in a three-necked round-bottomed flask equipped with a magnetic stirring bar, a condenser, a thermometer, an inlet for nitrogen and a rubber septum for removing samples. The flask was charged with MMA (30 ml, 0.28 mol), benzene (10 ml, 0.11 mol), AIBN (40 mg, 0.24 mmol) and CPDB (104 mg, 0.470 mmol). Nitrogen was bubbled through the reaction mixture for 15 min at room temperature before starting the polymerisation, while during the polymerisation the nitrogen stream was directed over the top of the condenser, thus keeping the reaction mixture under a nitrogen atmosphere. A preheated oil bath was employed to commence the polymerisations. The polymerisations were performed at 60 °C. Samples were removed from the flask every 2 h

via a needle and syringe and precipitated into methanol. The polymer samples were reprecipitated from chloroform solution into methanol and dried to constant mass at room temperature under vacuum.

The number and weight average molar masses, $\overline{M}_n$ and $\overline{M}_w$, respectively, and the polydispersity index, *PD*, of the obtained polymers were determined at 30 °C by gel permeation chromatography, SEC, using a Waters instrument fitted with four analytical columns (Waters HR 2, HR 3, HR 4 and HR 5E) and a refractive index detector. THF was used as the solvent at a flow rate of 1.0 ml min^{-1}. The obtained chromatograms were analyzed with Waters Breeze software using a calibration curve of narrow molar mass distribution PMMA standards (PSS Polymer Standards Service GmbH, Mainz, Germany).

RESULTS AND DISCUSSION

The RAFT agent, CPDB, was prepared in two syntheses which differed in the recrystallisation of the intermediate di(thiobenzoyl)disulphide. The final products (CPDB1 and CPDB2, with and without recrystallisation, respectively) from both syntheses were subjected to column chromatography with silica gel as the stationary phase and ethyl acetate:*n*-hexane (0.20:0.98) as eluent. The crude product made from the di(thiobenzoyl)disulphide recrystallized in ethanol gave seven fractions: green (which did not enter the column), yellow and pink which stayed on the column, and yellow (eluted first), pink, red and purple which eluted last. The main purple fraction gave 2-(2-cyanopropyl)-dithiobenzoate as a red--purple liquid after evaporation of the eluent. The yield of the CPDB-1 was extremely low when the pure substance was obtained (5 % of the theoretical yield).

The crude product from the second synthesis made from the di(thiobenzoyl)-disulphide without recrystallisation was reddish coloured, but after the column chromatography it gave the characteristic purple coloured fraction as the main product. The crude product from this synthesis gave four fractions: yellow and orange, which stayed on the column, and yellow and the main purple one, which eluted last. After evaporation of the eluent, the main purple fraction from the second synthesis gave CPDB-2 as a red-purple liquid.

The fact that more fractions were obtained during the column chromatography of CPDB-1 than during the chromatography of CPDB-2 indicates that during recrystallisation not only was di(thiobenzoyl)disulphide inherently lost, but also that it decomposed. It was observed that a resinous material was formed during the recrystallisation, which when removed was insoluble in ethanol. This could be the explanation of the green fraction which did not enter the column.

The ^{13}C-NMR spectrum and the numbering of the C atoms of the prepared CPDB-1 and CPDB-2 are shown in Figs. 1 and 2, respectively, from which it can be seen that all the expected peaks were present. One additional peak was found in the spectrum of the CPDB2 (at 23 ppm). This could arise by the recombination of primary radicals from the decomposition of AIBN, used in the last step of the synthesis. It was reported[12] that the highest level of impurity found in CPDB could be attributed to recombined radicals arising from the decomposition of

AIBN. This recombination compound was found to be difficult to remove from the RAFT agent, even after column chromatography, but it is inert to any radical reaction. The peak of the carbon atoms from the four equivalent CH_3 groups of such a compound is expected at 23 ppm in a ^{13}C-NMR spectrum. It is important to emphasise that the yield of the CPDB in the second synthesis was increased to 20 % of theoretical yield, which is four times more compared to the first one.

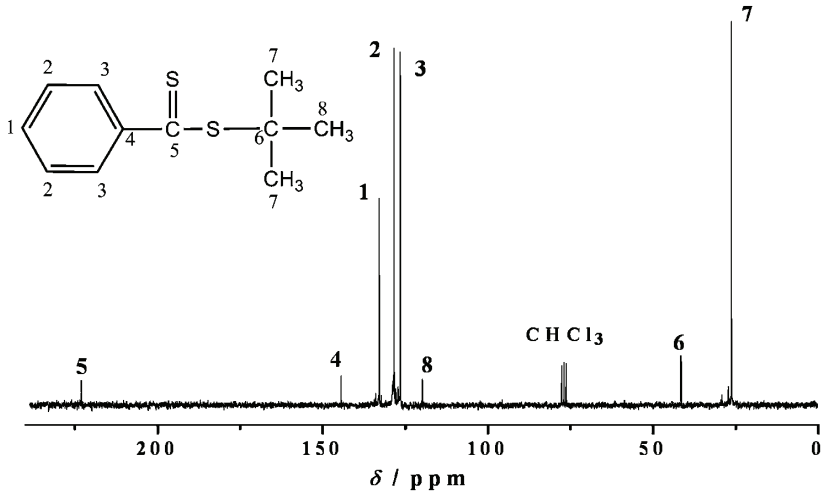

Fig. 1. ^{13}C-NMR Spectrum of CPDB-1 (inset: structure of CPDB with C atoms numbered).

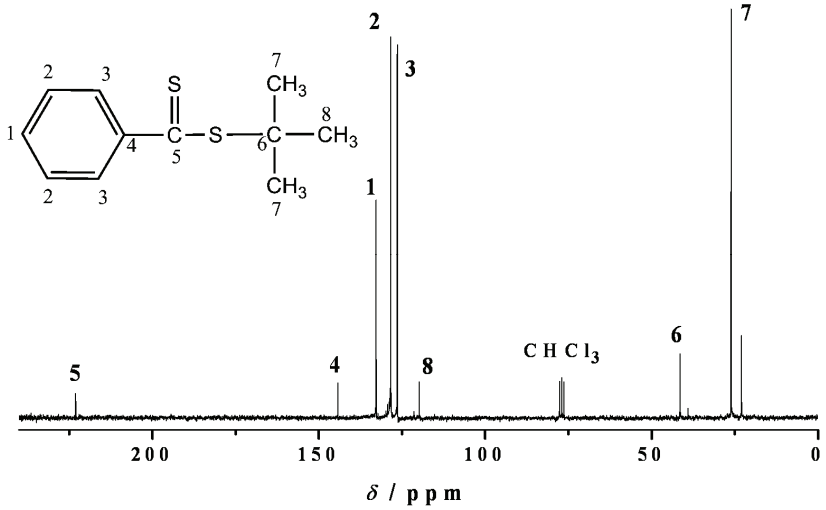

Fig. 2. ^{13}C-NMR Spectrum of CPDB-2 (inset structure of CPDB with C atoms numbered).

A change in the standard method of preparation of CPDB was previously reported in the literature.[16] The alteration concerned of the same step in the

procedure of CPDB synthesis to which attention was paid in this study. The purification di(thiobenzoyl)disulphide by the recrystallisation in ethanol was substituted by column chromatography using ethyl acetate/petroleum ether (1:1) as the eluent. The yield of CPDB was 50 % of the theoretical one, which is 2.5 times larger than one obtained in the present study. However, it must be emphasised that the purification di(thiobenzoyl)disulphide was completely avoided in synthesis procedure employed in this study, which is extremely important for laboratory or industrial scale-ups.

Two RAFT polymerisation of methyl methacrylate were performed using CPDB from the two different syntheses. Samples were taken from the reaction flask every 2 h. The polymer obtained after the RAFT polymerisation was pink due to the attachment of CPDB to the chain ends. Two series of PMMA samples were obtained: PMMA-1 from the polymerisation using the CPDB-1 and PMMA-2 from the polymerisation using the CPDB-2. The number and weight average molar masses, M_n and M_w, and the polydispersity index, *PD*, of the obtained polymers are given in Table I. The polymerisations mediated by CPDB-1 and CPDB-2 exhibited very similar kinetics, *i.e.*, the polymerisation rates were very similar (Fig. 3a).

TABLE I. Number and weight average molar mass and polydispersidity index, *PD*, of the PMMA-1 and PMMA-2 samples

Time, h	PMMA-1			PMMA-2		
	M_n / g mol^{-1}	M_w / g mol^{-1}	*PD*	M_n / g mol^{-1}	M_w / g mol^{-1}	*PD*
2	16625	18415	1.108	15161	16674	1.100
4	19481	21676	1.112	20872	23001	1.102
6	25126	27972	1.113	26071	28901	1.109
8	30436	34062	1.119	31958	35648	1.115
10	37271	41800	1.122	39412	44310	1.124

A comparison of $\overline{M}_w$ of PMMA-1 and PMMA-2 samples as a function of polymerisation time is shown in Fig. 3b, from which it can be seen that the molar mass increased with polymerisation time, as is to be expected for RAFT-controlled polymerisations, and that the rate of increases were very similar. The SEC chromatograms revealed good control of the CPDB-mediated polymerisations with narrow molar mass distributions. The comparison of An SEC chromatogram of a PMMA sample obtained using CPDB-2, is compared with that of the corresponding PMMA sample prepared using CPDB-1, in Fig. 4. As can be seen, the chromatograms are very similar.

The polydispersities of the PMMA samples from both series (Table I) were also very similar for the same polymerisation time, indicating that CPDB-1 and CPDB-2 affected the same polymerisations.

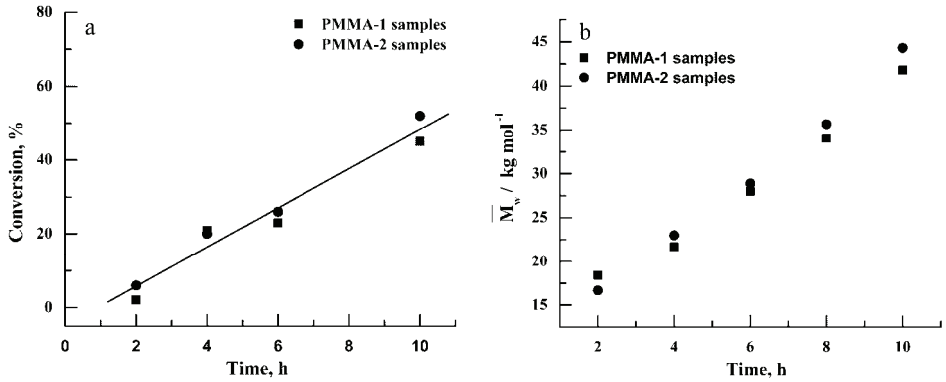

Fig. 3. a) MMA Conversion *vs.* polymerisation time in the presence of CPDB-1 and CPDB-2. b) Weight average molar mass of the PMMA-1 and PMMA-2 samples *vs.* polymerisation time.

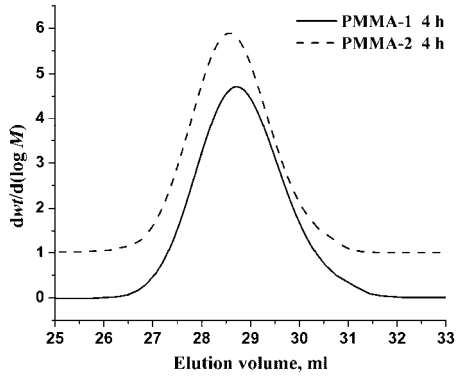

Fig. 4. SEC Chromatogram of PMMA samples obtained by polymerisation of MMA in the presence of CPDB-1 and in the presence of CPDB-2 for 4 h.

As can be seen, the CPDB obtained by the simplified procedure exerted the same effects in the polymerisation of PMMA as that obtained by the literature procedure.

CONCLUSIONS

The procedure of CPDB preparation was modified and simplified by omitting the recrystallisation of the intermediate di(thiobenzoyl)disulphide. The yield of the CPDB in the simplified synthesis was increased by a factor of four comparing to the literature method. The CPDB synthesized by the simplified procedure provided very good control of the polymerisation of methyl methacrylate, yielding PMMA samples with narrow molar mass distibutions, and behaved in the same manner as the CPDB prepared by the standard literature procedure. The simplification of the synthesis of CPDB introduced in this study is very important from the points of view of time, scale-up and amounts of solvents necessary.

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И З В О Д

ПОЈЕДНОСТАВЉЕЊЕ ПОСТУПКА СИНТЕЗЕ RAFT АГЕНСА 2-(2-ЦИЈАНОПРОПИЛ)-ДИТИОБЕНЗОАТА

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Стандардни поступак синтезе 2-(2-цијанопропил)-дитиобензоата (CPDB) агенса из литературе за RAFT полимеризацију, односно за реверзибилну адиционо-фрагментациону трансфер полимеризацију, је модификован изостављањем прекристализације међупроизвода бис-(тиобензоил)дисулфида. Принос CPDB-а синтетисаног поједностављеним поступком је четири пута већи у односу на принос CPDB-а синтетисаног стандардним поступком. Испитано је понашање CPDB-а добијеног модификованим и оног добијеног стандардним поступком у полимеризацији метил метакрилата. CPDB добијен поједностављеним поступком показао се као добар RAFT агенс који успоставља одличну контролу полимеризације метил метакрилата и који се понаша на исти начин као CPDB синтетисан стандардним поступком. Добијени поли(метил метакрилат) има уску ширину расподеле молских маса (*PD* = 1.1).

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