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Exchange of Substituents between (Macro)Alkoxyamines and (Macro)RAFT Agents (ESARA): A Bridge between Nitroxide-Mediated and RAFT Controlled Radical Polymerization Techniques

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ABSTRACT: Developing new tools to combine different polymerization techniques significantly extends the possibilities in terms of polymer design. Here, we report on a radical process abbreviated ESARA that creates a bridge between two controlled radical polymerization (CRP) techniques, nitroxide-mediated polymerization (NMP) and reversible addition−fragmentation chain transfer polymerization (RAFT). Proof of concept was first obtained with low molecular weight compounds. Alkoxyamine and thiocarbonylthio control agents were shown to exchange their respective substituents in selected experimental conditions, opening the way for the synthesis of new original control agents. The ESARA process was then implemented at the macromolecular level. Polystyryl macroalkoxyamines were converted to the corresponding polystyryl macroRAFT agents using thiocarbonylthio compounds. In addition, polystyryl macroRAFT agents were converted back to polystyryl macroalkoxyamine after reaction with an alkoxyamine. The bridge created between the two CRP techniques offers an access to a large number of well-defined polymer architectures such as block copolymers that would be difficult to obtain by only one technique.

Introduction

Advanced polymer applications from optoelectronics to biotechnologies contribute to the high demand of tailored macromolecular systems. The ability to synthesize well-defined complex architectures and functional polymers is thus of great importance. For instance, segmented polymers such as block copolymers are particularly attractive to improve the mechanical properties of polymeric materials or to prepare nanosized objects for drug/gene delivery purposes. In addition, polymers bearing site-specific functional groups presents numerous advantages for the synthesis of polymer (bio)conjugates.

To address these challenges, controlled polymerization techniques were developed during the last decades. Among them, controlled radical polymerizations (CRP) techniques[1] became increasingly popular since they are easy to process and applicable to a wide range of monomers. They proved to be very powerful tools to access to a large library of tailor-made macromolecules. Moreover, polymers bearing various specific terminal entities were synthesized from functional control agents (initiators or chain transfer agents, CTA) since the latter are governing the nature of the chain-ends.

The main CRP techniques include atom transfer radical polymerization (ATRP),[2,3] stable free radical polymerization (SFRP), especially nitroxide-mediated polymerization (NMP)[4−6] and the reversible addition−fragmentation (RAFT) process.[7−9] Each one is based on a different chemistry but all offer the possibility to control the molecular weight (MW) and molecular weight distribution (MWD) and to synthesize complex polymer architectures such as block copolymers. Nevertheless, in each case, limitations associated with the control systems proscribe the use of some monomers and functionalities. Then, finding pathways to combine the CRP techniques is highly desirable since it would widen even more the possibilities both in terms of polymer functionalization and macromolecular design.[10−15]

Here, we describe an original radical process abbreviated ESARA for exchange of substituents between (macro)alkoxyamines and (macro)RAFT agents that enables one to switch reversibly from NMP to RAFT techniques: Alkoxyamines are initiators used to promote the control free radical polymerization via NMP, resulting in the production of nitroxide-terminated macromolecules, i.e. macroalkoxyamines, and RAFT agents are thiocarbonylthio CTAs that promote the control of free radical polymerization via the RAFT process, resulting in thiocarbonylthio-terminated macromolecules, i.e., macroRAFT agents.

Radical-based reactions were shown to be efficient to remove the nitroxyl- or thiocarbonylthio-ω-ends of polymer chains produced respectively by NMP and RAFT.[16,17] In addition, reactions between TEMPO-based alkoxyamines and thiocarbonylthio compounds were used to functionalize polymer end-groups or to study the RAFT process. Beyou et al. obtained dithiocarbamate-terminated PS chains from TEMPO-terminated ones after reaction at high temperature with thiuram disulfide iniferters.[16] On the other hand, in their Monte Carlo simulation study, Ao et al. used reactions between low molecular weight TEMPO-based alkoxyamines and dithiobenzoates, generally bearing identical substituents, in order to probe the RAFT mechanism.[18] In this article, we show that radical chemistry, via a careful selection of experimental conditions, allows to efficiently and reversibly convert NMP agents and living polymer chains into RAFT ones.

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As proof of concept, the ESARA process was first tested with low molecular weight (MW) compounds. The carboxylic acid-functionalized tertiary substituent from the commercially available MAMA−SG1 alkoxyamine was transferred onto various benzyl-substituted RAFT agents, and other functional tertiary RAFT agents were synthesized from an alkoxyamine bearing an activated ester moiety. Then, this was extended at the macromolecular level. We show that polystyryl macroalkoxyamines can be transformed to polystyryl macroRAFT agents and *vice versa*. As it will be emphasized, this process opens the way to the synthesis of a large number of original and functional control agents, polymers and complex macromolecular architectures.

Experimental Section

Materials. Dibenzyl trithiocarbonate (DBzTTC) and *N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*O*-(2-carboxylprop-2-yl)hydroxylamine (MAMA−SG1, BlocBuilder) were kindly provided by Arkema. The *N*-hydroxysuccinimidyl ester of MAMA−SG1 (MAMA−NHS−SG1) was synthesized according to a previously published procedure.[19] Benzyl dithiobenzoate (BzDB) was obtained in quantitative yield and high purity following the previously published synthetic procedure[20] and using benzyl mercaptan (Aldrich, 99%). Polystyryl−SG1 macroalkoxyamines and polystyryl macroRAFT agents were synthesized in bulk following the previously described procedures[21,22] and using the control agents indicated in the text. *tert*-Butanol, *tert*-butyl benzene, and ethyl benzene were purchased from Aldrich and used without further purification. 4,4′-Azobis(isobutyronitrile) (AIBN) (Fluka, 98%) was purified by recrystallization from ethanol.

Characterization of Alkoxyamines, RAFT Agents, and Polymer Samples. NMR experiments were performed using $CDCl_3$ as solvent and a Bruker AC300 spectrometer (^{1}H 300 MHz, ^{13}C 75.48 MHz, and ^{31}P 121.59 MHz) at the Spectropole of Marseille, France. Chemical shifts are given relative to tetramethylsilane (TMS) (internal reference).

Polymers were precipitated in a large volume of methanol, recovered by filtration, washed several times with the same solvent, and finally dried under vacuum up to constant weight.

Molecular weight distributions (MWD) were determined by size exclusion chromatography (SEC). SEC analyses were performed using a Waters 515 HPLC pump, three Styragel columns (HR 3 (4.6 mm × 300 mm, separation between 500 and 30 000 g·mol^{-1}), HR 4 (4.6 mm × 300 mm, separation between 5 000 and 600 000 g·mol^{-1}), and HR5 (4.6 mm × 300 mm, separation between 2 000 and 4×10^6 g·mol^{-1})) and two detectors: UV/visible (Waters 486) set at $\lambda = 254$ nm or $\lambda = 304$ nm and differential refractometer (RI) (Waters 2414). Measurements were performed by injection of 10 μL of polymer solution (5 mg·g^{-1}) in tetrahydrofuran (THF) that was previously filtered through a 0.22 μm Millipore membrane and also used as eluent at a flow rate of 1 mL·min^{-1} (25 °C). Number average molecular weights (M_n) and polydispersity indices (PDI) of the samples were determined using the Waters Millenium software. Calibration was based on polystyrene standards.

High-resolution electrospray ionization mass spectrometry (ESI−MS) analyses were performed at the Spectropole of Marseille (France) using a Qstar Elite apparatus (Applied Biosystems SCIEX) equipped with an atmospheric pressure ionization source (API). Samples were ionized in a positive electrospray mode: electrospray tension (ISV), 5500 V; nebulization air pressure, 20 psi. High resolution spectra and exact mass were obtained in triplicate with a time of flight analyzer (ToF) and with a double internal calibration. Samples were dissolved in 300 μL of dichloromethane and diluted to 1/10^3 with a 3 mol·L^{-1} ammonium acetate solution in methanol. The pseudo molecular ion $[M + H]^+$ and the ammonium adduct $[M + NH_4]^+$ of a poly(ethyleneglycol) (PEG300) oligomer, with an expected m/z at 327.2013 and 344.2278, respectively, were used as internal references. Sample solutions were doped with the internal standard before introduction in the ionization source by infusion at 10 μL·mn^{-1}. For clarity, only the m/z values of the pseudo molecular ion $[M + H]^+$ will be given for the synthesized compounds.

Liquid chromatography at the critical conditions (LC−CC) experiments were performed on a Varian PL-GPC 120 apparatus, a fully thermostated system composed of an Agilent 1100 series pump, a degasser and a RI detector. The following columns were used: Macherey & Nagel 250 × 4.6 mm Nucleodur C_{18} gravity, pore diameter 110 Å, particle size 3 μm; Macherey & Nagel 250 × 4.6 mm Nucleodur C_{18} gravity, pore diameter 110 Å, particle size 5 μm. *N*,*N*-Dimethylformamide (DMF) was used as eluent after filtration on a 0.2 μm Nylon Alltech membrane. Samples were solubilized in DMF at 0.5 wt %. before being filtered on a 0.2 μm Nylon Alltech filter. Flow rate was set at 0.8 mL.min^{-1} and temperature of the oven containing the columns and the RI detector at 72 °C.

Exchange of Substituents between SG1-Based Alkoxyamines and RAFT Agents. *Synthesis of 2-Carboxylprop-2-yl Dithiobenzoate (MAMA−DB).* In a 150 mL Schlenk tube, BzDB (2.44 g; 1×10^{-2} mol) and a small excess of MAMA−SG1 (5.72 g; 1.5×10^{-2} mol; 1.5 equiv) were dissolved in 20 mL of *tert*-butanol. The red solution was then deoxygenated by nitrogen bubbling for 20 min before being heated at 90 °C in a thermostated oil bath for 20 h. 2-Carboxylprop-2-yl dithiobenzoate (MAMA−DB) was extracted from the resulting reaction medium with a 1 mol·L^{-1} NaOH aqueous phase. The basic orange solution was then neutralized with HCl in the presence of a diethyl ether phase which became purple. The ether phase was washed two times with a 10% NaCl aqueous solution and dried over anhydrous magnesium sulfate. MAMA−DB was obtained as a purple oil after purification by silica gel chromatography (kieselgel-60) with pentane/ethyl acetate/acetic acid (80/19/1 vol %) as the eluent (Yield: 40%; purity > 99%).

NMR (ppm): ^{1}H: 1.80 (s, 6H, CH_3); 7.34 (t, 2H, Ar−H); 7.50 (t, 1H, Ar−H); 7.95 (d, 2H, Ar−H); 8.79 (broad peak; 1H; COOH); ^{13}C: 24.82 (2C, CH_3); 54.97 (1C, C); 126.77 (2C, Ar CH); 128.36 (2C, Ar CH); 132.56 (1C, Ar CH); 144.52 (1C; aryl C); 178.77 (1C, COOH); 225.72 (1C; C(=S)S).

High resolution MS, $[C_{11}H_{12}O_2S_2]$: characteristic ion $[M + H]^+$ m/z theoretical value, 241.0351; found, 241.0347.

Synthesis of 2-Carboxylprop-2-yl Benzyl Trithiocarbonate (MAMA−BzTTC). Similar synthetic and purification pathways than for MAMA−DB were used with DBzTTC as the RAFT agent (2.9 g; 1×10^{-2} mol). However, since such trithiocarbonates can be seen as difunctional RAFT agents, the molar excess of MAMA−SG1 (11.4 g; 3.0×10^{-2} mol) was adjusted. The purification procedure led to a yellow solid corresponding to 2-carboxylprop-2-yl benzyl trithiocarbonate (MAMA−BzTTC) (Yield: 50%; purity > 99%). When a 10-fold excess of MAMA−SG1 was used the reaction yield was increased to 90%.

NMR (ppm): ^{1}H: 1.74 (s, 6H, CH_3); 4.52 (s, 2H, CH_2); 7.30 (m, 5H, Ar−H); 10.76 (broad peak; COOH) ^{13}C: 25.28 (2C, CH_3); 41.68 (1C; CH_2); 55.94 (1C, C); 127.90 (1C, Ar CH); 128.82 (2C, Ar CH); 129.38 (2C, Ar CH); 134.74 (1C; Aryl C); 179.13 (1C, COOH); 220.03 (1C; C(=S)S).

High resolution MS, $[C_{12}H_{14}O_2S_3]$: characteristic ion $[M + H]^+$ m/z theoretical value, 287.0229; found, 287.0224.

No significant amount of di(2-carboxylprop-2-yl) trithiocarbonate (DMAMA−TTC) could be isolated.

Synthesis of N-Hydroxysuccinimidyl Ester of 2-Carboxylprop-2-yl Dithiobenzoate (MAMA−NHS−DB). In a 150 mL Schlenk tube, MAMA−DB (0.29 g; 1.2×10^{-3} mol) and a small excess of MAMA−NHS−SG1 (0.86 g; 1.8×10^{-3} mol; 1.5 equiv) were dissolved in 20 mL of *tert*-butanol. The red−purple solution was then deoxygenated by nitrogen bubbling for 20 min before being heated at 40 °C in a thermostated oil bath for 20 h. MAMA−NHS−DB was isolated by precipitation in pentane and obtained as a pink solid after purification by silica gel chromatography

(kieselgel-60) with pentane/ethyl acetate (75/25 vol%) as the eluent (Yield: 50%; purity >99%).

NMR (ppm): ^{1}H: 1.94 (s, 6H, CH_3); 2.80 (m, 4H, CH_2); 7.35 (t, 2H, Ar−H); 7.51 (t, 1H, Ar−H); 7.97 (d, 2H, Ar−H); ^{13}C: 24.11 (2C, CH_2); 24.58 (2C, CH_3); 52.68 (1C, C); 125.67 (2C, Ar CH); 127.38 (2C, Ar CH); 131.66 (1C, Ar CH); 142.78 (1C; Aryl C); 167.76 (2C, C(=O)N); 167.83 (1C, C(=O)O); 225.72 (1C; C(=S)S).

High resolution MS, [$C_{15}H_{15}NO_4S_2$]: characteristic ion $[M + H]^+$ m/z theoretical value, 338.0515; found, 338.0511.

Table 1. Reaction Yields for the Exchange of Substituents between Low Molecular Weight SG1-Based Alkoxyamines and RAFT Agents

initial RAFT agent	initial alkoxyamines	alkoxyamines excess (equiv)	resulting compound	yield (%)
BzDB	MAMA-SG1	1.5	MAMA-DB	40
DBzTTC	MAMA-SG1	3	MAMA-BzTTC	50
DBzTTC	MAMA-SG1	10	MAMA-BzTTC	90
Bz-OEtX	MAMA-SG1	1.5	MAMA-OEtX	<5
BzDB	MAMA-NHS-SG1	1.5	MAMA-NHS-DB	<5
MAMA-DB	MAMA-NHS-SG1	1.5	MAMA-NHS-DB	50

Exchange of Substituents between Polystyryl−SG1 Macro Alkoxyamines and Benzyl RAFT Agents. *Synthesis of Polystyryl Dithiobenzoate (PS−DB).* In a 150 mL Schlenk tube, 1 g of white polystyryl−SG1 (PS−SG1) (M_n = 2910 g·mol^{-1}; PDI = 1.12; living fraction = 95% as determined by ESR[21]) and BzDB (1.22 g; 5×10^{-3} mol; 10 equiv) were dissolved in 20 mL of ethyl benzene. The red solution was then deoxygenated by nitrogen bubbling for 20 min before being heated at 90 °C in a thermostated oil bath for 20 h. The resulting pink polystyryl−dithiobenzoate (PS−DB) was purified by precipitation in cold methanol (M_n = 2920 g·mol^{-1}; PDI = 1.12).

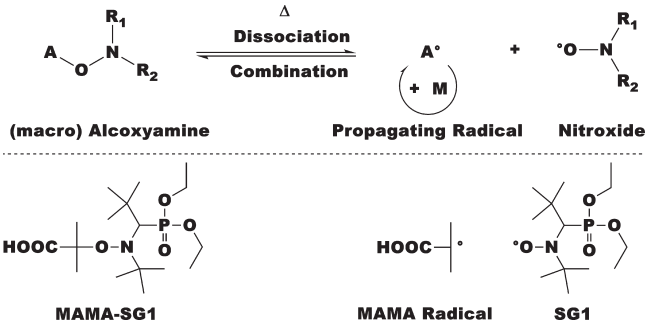
Synthesis of Polystyryl Benzyl Trithiocarbonate (PS−BzTTC). In a 150 mL Schlenk tube, 1 g of white polystyryl−SG1 (M_n = 2910 g·mol^{-1}; PDI = 1.12; living fraction = 95% as determined by ESR) and DBzTTC (1.45 g; 5×10^{-3} mol; 10 equiv) were dissolved in 20 mL of ethyl benzene. The yellow solution was then deoxygenated by nitrogen bubbling for 20 min before being heated at 90 °C in a thermostated oil bath for 20 h. The resulting light yellow polystyryl−benzyl trithiocarbonate (PS−BzTTC) was purified by precipitation in cold methanol (M_n = 3072 g·mol^{-1}; PDI = 1.14).

Exchange of Substituents between Polystyryl MacroRAFT Agent (PS−RAFT) and MAMA−SG1. *Exchange of Substituents between PS−DB and MAMA−SG1.* In a 150 mL Schlenk tube, 1 g of pink PS−DB synthesized in the presence of MAMA−DB (M_n = 12 860 g·mol^{-1}; PDI = 1.15) and MAMA−SG1 (0.298 g; 7.8×10^{-4} mol; 10 equiv) were dissolved in 20 mL of ethyl benzene. The pink solution was then deoxygenated by nitrogen bubbling for 20 min before being heated at 65 °C in a thermostated oil bath for 20 h. The resulting white PS−SG1 was purified by precipitation in cold methanol (M_n = 12 260 g·mol^{-1}; PDI = 1.16).

Exchange of Substituents between Dipolystyryl Trithiocarbonate (DPS−TTC) and MAMA−SG1. In a 150 mL Schlenk tube, 1 g of DPS−TTC synthesized in the presence of DBzTTC (M_n = 5760 g·mol^{-1}; PDI = 1.22) and MAMA−SG1 (0.636 g; 1.7×10^{-3} mol; 10 equiv) were dissolved in 20 mL of ethyl benzene. The yellow solution was then deoxygenated by nitrogen bubbling for 20 min before being heated at 65 °C in a thermostated oil bath for 20 h. The resulting light yellow polymer was purified by precipitation in cold methanol (M_n = 3870 g·mol^{-1}; PDI = 1.20).

Chain Extension Experiments. *Polymerization of Styrene in the Presence of PS−DB MacroRAFT Agent.* First, 0.25 g of PS−DB (M_n = 2920 g·mol^{-1}; PDI = 1.12) and AIBN (2.1×10^{-3} g, 1.7×10^{-5} mol) were dissolved in styrene (4.2 g, 4.0×10^{-2} mol). The pink solution was then deoxygenated by nitrogen bubbling for 20 min before being heated at 70 °C in a thermostated oil bath for 20 h. The resulting pink polymer was purified by precipitation in cold methanol (M_n = 16 050 g·mol^{-1}; PDI = 1.16).

Scheme 1. General Mechanism of Nitroxide-Mediated Polymerization (NMP) and Structure of MAMA−SG1 Alkoxyamine and SG1 Nitroxide



Polymerization of Styrene in the Presence of PS−BzTTC MacroRAFT Agent. First, 0.125 g of PS−BzTTC (M_n = 3070 g·mol^{-1}; PDI = 1.14) and AIBN (1.34×10^{-3} g, 8.1×10^{-6} mol) were dissolved in styrene (2.0 g, 1.95×10^{-2} mol). The yellow solution was then deoxygenated by nitrogen bubbling for 20 min before being heated at 70 °C in a thermostated oil bath for 20 h. The resulting yellow polymer was purified by precipitation in cold methanol (M_n = 18 400 g·mol^{-1}; PDI = 1.18).

Results and Discussion

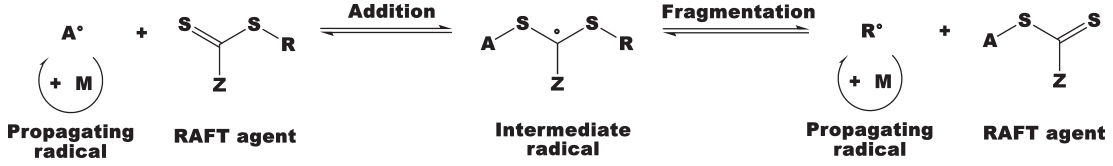
Nitroxide-mediated and RAFT polymerization are based on two distinct radical mechanisms:

NMP is based on the thermally induced reversible termination reactions of propagating radicals with nitroxide stable free radicals (Scheme 1). The kinetics of the polymerization and control of the resulting polymer molecular weight (MW) and molecular weight distribution (MWD) greatly depend on the dissociation and recombination rate coefficients of the various (macro)alkoxyamines formed during polymerization, hence on the nature of the nitroxide and the propagating radicals. For instance, the crowded *N-tert*-butyl-*N*-(1-diethylphosphono-2,2-dimethylpropyl) nitroxide (also called SG1) (Scheme 1), that was developed in our laboratory, has shown to be very efficient concerning the polymerization of a wide range of styrenic and acrylate monomers.[23] In addition, it was recently shown that the polymerization of methacrylates such as methyl methacrylate (MMA) could be also controlled using 2,2-diphenyl-3-phenylimino-2,3-dihydroindol-1-yloxyl nitroxide (DPAIO).[24]

NMP is commonly initiated by thermolabile alkoxyamines (Scheme 1) that have a pivotal role on the control of the polymerization.[21] The nature of leaving radical A$^{\bullet}$ influences the dissociation rate constant of the corresponding alkoxyamines A−nitroxide and also governs the α-functionalization of the polymer chains. The more stabilized/sterically hindered A is, the faster the dissociation. From previous studies, the use of new tertiary SG1-based alkoxyamines has shown to significantly improve the quality of the polymerization control of both styrenic and acrylate monomers. In addition, A is retained after polymerization at the α-end of the chains, thus, if it bear a reactive/functional group such as a carboxylic acid (e.g., MAMA−SG1 (Scheme 1)), numerous possibilities are offered both in terms of polymer functionalization and macromolecular design.[19]

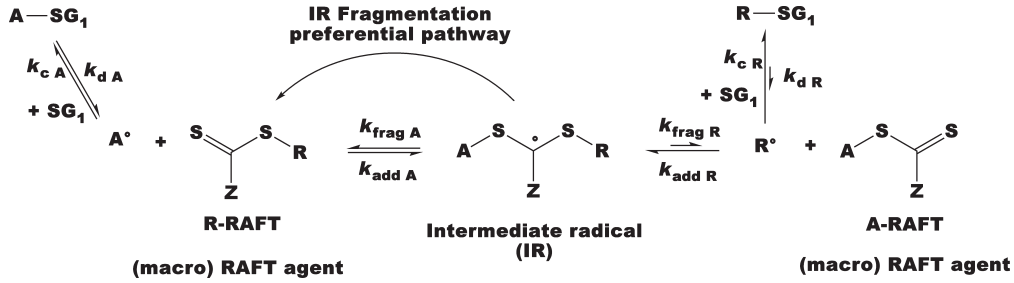
Regarding RAFT polymerization (Scheme 2), polymerization control is based on a reversible transfer mechanism induced by thiocarbonylthio CTAs (RAFT agents). Kinetics and quality of the control of the polymerization greatly depend on the transfer constant of the RAFT agents which is a composite of the addition and fragmentation rate coefficients. They thus depend on the nature of the (macro)RAFT agents (Z and R substituents) and

Scheme 2. General Mechanism of RAFT Polymerization



Scheme 3. General Mechanism of the ESARA Process

Scheme 4. ESARA Process Mechanism and Preferential Fragmentation Pathway of the Intermediate Radicals[a]



[a] k_d and k_c are respectively the dissociation and combination rate coefficients of the (macro)alkoxyamines. k_{add} and k_{frag} are respectively the addition and fragmentation rate coefficients associated with the (macro)RAFT agents.

the propagating radicals[25] (Scheme 2). Again, the initial RAFT agent has a pivotal role on the control of the polymerization. The most widely used are dithioesters, especially dithiobenzoates, trithiocarbonates, dithiocarbamates and xanthates and the polymerization of a wide range of monomers from vinyl esters to methacrylics can be controlled.

The radical source in a RAFT polymerization is identical than in conventional radical polymerization (e.g., thermoinitiators such as AIBN). However, chain initiation is mainly governed by the R group of the initial RAFT agent. For an efficient control, the latter should (i) be a good leaving group (as a general rule, the more substituted and the more stabilized $R^\bullet$, the faster the fragmentation rate) and (ii) ensure nonetheless a fast and selective reinitiation of polymer chains. If those requirements are fulfilled, the majority of the chains retains the R group as their α-end. The use of functional or reactive R groups thus offers numerous possibilities for the synthesis of α-functional macromolecules and for macromolecular design. Finally, from the above remarks, it could be noted that accessing to RAFT agents bearing tertiary and/or functional R groups is highly desirable.

The ESARA Process. The ESARA process described here enables one to exchange the A and R substituents between (macro)alkoxyamines and (macro)RAFT agents using radical chemistry. From a general perspective and considering SG1-based alkoxyamines as an example, the A group of A−SG1 is transferred to R−RAFT to form a new (macro)-RAFT agent A−RAFT and a new (macro)alkoxyamine R−SG1 (Scheme 3).

This requires the $R^\bullet$ radical to be less stabilized/sterically hindered than $A^\bullet$, although, in this case, the selectivity of the fragmentation reaction during the reversible addition−fragmentation process do not favor the formation of A−RAFT.[25] As already mentioned by numerous authors, the fragmentation of the intermediate radicals (IR) (Scheme 4) is indeed very selective and largely displaced toward the formation of the more stabilized/sterically hindered radical ($A^\bullet$ in this case).

The originality of the ESARA process however lays on (i) the use of alkoxyamines as the radical source and (ii) a careful selection of A and/or R substituents:

(i) Due to the lower stabilization/steric hindrance of $R^\bullet$ compared to $A^\bullet$, a temperature range can be defined where the dissociation rate of A−SG1 is significant whereas the dissociation rate of R−SG1 is very low.

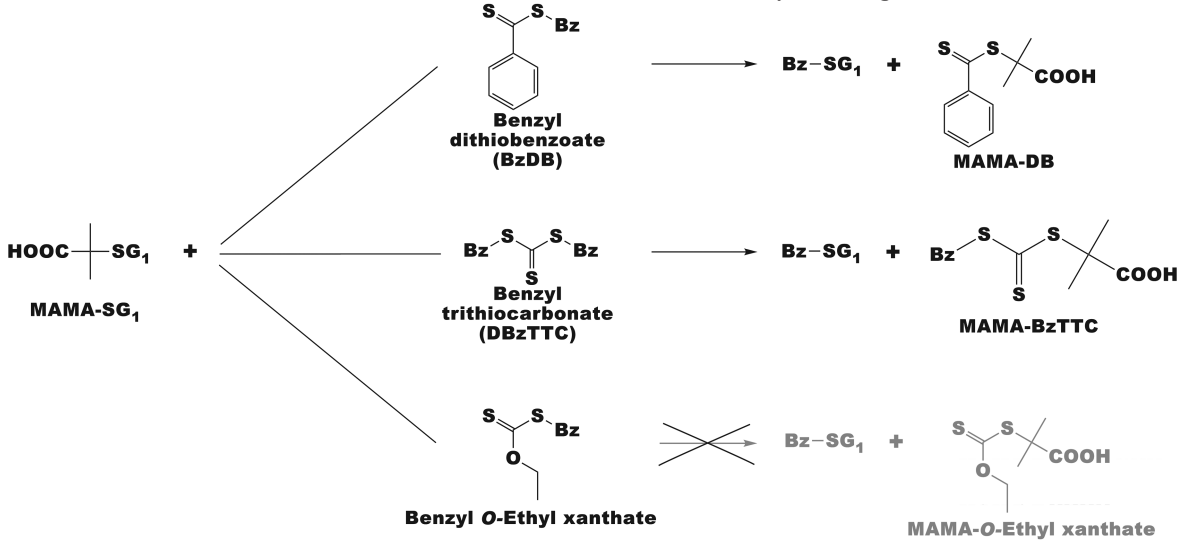
(ii) A and/or R groups are selected such as the selectivity of the fragmentation reaction of IRs allows the release of the $R^\bullet$ fragment radical.

If both conditions are fulfilled, $R^\bullet$ radicals are rapidly and irreversibly trapped by the SG1 nitroxide formed following the dissociation of A−SG1. The trapping reaction of $R^\bullet$ is favored by both the high combination rate coefficient of SG1 with alkyl radicals and the higher concentration of SG1 compared to $R^\bullet$ due to the persistent radical effect.[6] The global reaction equilibrium is thus displaced toward the unfavorable formation of the new A−RAFT and R−SG1 due to the very low dissociation rate of the latter at the selected reaction temperature (Scheme 4).

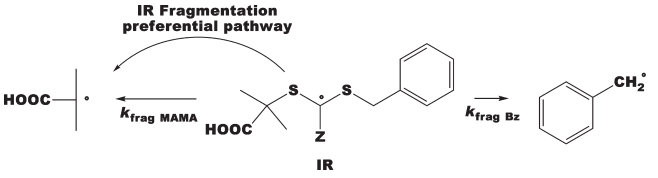
Proof of Concept with low MW Compounds. The ESARA process was first tested with low MW compounds for the synthesis of RAFT agents with R substituents bearing functional/reactive groups and/or corresponding to stabilized/sterically hindered $R^\bullet$ fragment radicals (Table 1). For this purpose, the new generation of alkoxyamines exhibiting low dissociation temperatures developed in our laboratory were used since their versatility can lead to a large number of structure/functionalities.

As an example, the commercial MAMA−SG1 alkoxyamine (BlocBuilder) bearing a tertiary and functional (carboxylic acid function) A group was reacted at 90 °C with various benzyl RAFT agents, such as benzyl dithiobenzoate

Scheme 5. Reaction of MAMA−SG1 with Various Benzyl RAFT Agents



Scheme 6. Structure and Fragmentation Preferential Pathway of Intermediate Radicals (IR) Formed during the Reaction between MAMA Radicals and Benzyl RAFT Agents[a]



[a] $k_{\text{frag MAMA}}$ and $k_{\text{frag Bz}}$ are respectively the fragmentation rate coefficients for the MAMA and Bz leaving groups.

(BzDB) and dibenzyl trithiocarbonate (DBzTTC) (Scheme 5). These benzyl RAFT agents were chosen because they are easily synthesized in a high yield or even commercial and because the two requirements for an efficient ESARA process are met: (i) The dissociation of MAMA−SG1 is much faster than the benzyl−SG1 (Bz−SG1) alkoxyamine (at 90 °C, $k_{\text{d MAMA−SG1}} = 1.6 \times 10^{-2}$ s^{-1}; $k_{\text{d Bz−SG1}} = 1.1 \times 10^{-5}$ s^{-1}).[26] Between 60 and 100 °C, the dissociation of MAMA−SG1 is significant whereas the dissociation of Bz−SG1 is negligible. (ii) Benzyl radical is rather stabilized and may fragment from the IRs formed during the reaction (Scheme 6).

First, the reaction of MAMA−SG1 with BzDB led to the formation of MAMA−DB. The main side products were untransformed BzDB and MAMA−SG1, Bz−SG1, the MAMA−MAMA coupling product and SG1. It appears from these results that the formation rate of MAMA−DB is slow because of the difference in leaving group ability between MAMA and benzyl radicals. This was further confirmed by simulation using the PREDICI software (see Supporting Information). They suggested that fragmentation from IR of the MAMA substituent exhibits a rate coefficient, $k_{\text{frag MAMA}}$, about 2 orders of magnitude higher than the one corresponding to the benzyl substituent, $k_{\text{frag Bz}}$. In addition, an improvement of the reaction yield was predicted when increasing the temperature up to 100 °C, increasing reaction time, and increasing the MAMA−SG1 excess even if the amount of free SG1 increases concomitantly.

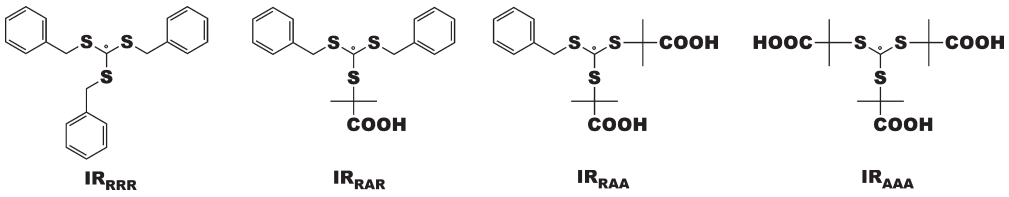
Regarding the trithiocarbonate RAFT agent DBzTTC, reaction with MAMA−SG1 led mainly to the formation of the monosubstituted trithiocarbonate MAMA−BzTTC and almost no disubstituted DMAMA−TTC was obtained. Again the side products were untransformed DBTTC and MAMA−SG1, Bz−SG1, MAMA−MAMA coupling product, and SG1.

In this case, the system was particular due to the nature and structure of DBzTTC. First, for trithiocarbonates, the addition and the fragmentation rate coefficients are respectively lower and higher compared to the corresponding dithiobenzoates[9] (irreversible termination reactions involving the intermediate radicals are also less likely). Second, DBzTTC can be considered as a difunctional RAFT agent (with only one thiocarbonyl) since the two benzyl substituents are potential leaving groups. The latter particularity implies the formation of intermediate radicals with 3 potential leaving groups (Scheme 7). For IRs possessing two different types of substituents, either one MAMA and two benzyl substituents (IR_{RAR}) or two MAMA and one benzyl substituents (IR_{RAA}), the probability of fragmentation of a benzyl group is very different. The release of the benzyl radical is indeed much less likely from IR_{RAA} than from IR_{RAR} and thus the formation of DMAMA−TTC is largely unfavored.

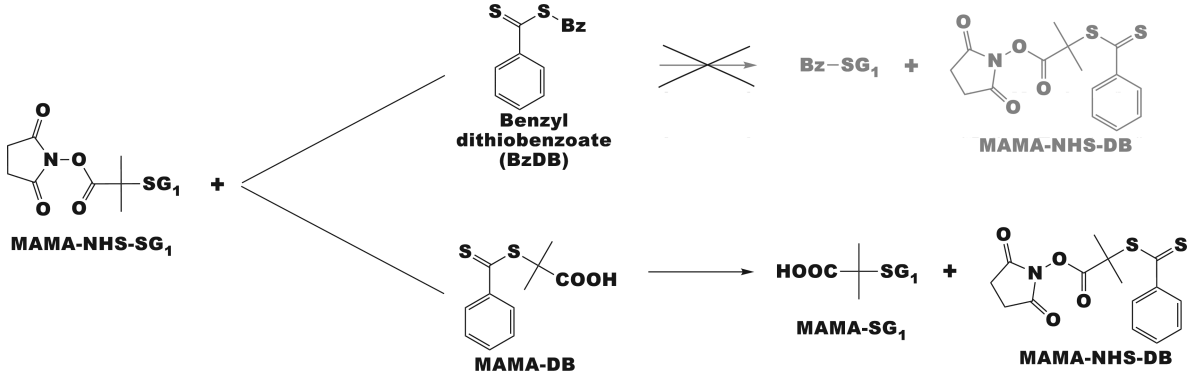
These results were first confirmed by PREDICI simulations (see Supporting Information). The formation of MAMA−BzTTC is much favored than the one of DMAMA−TTC. DBzTTC is first rapidly converted to MAMA−BzTTC. Then, a low amount of DMAMA−TTC may be formed but with a very slow rate (yield $< 5\%$). Second, experimentally, a sample of MAMA−BzTTC was isolated and subsequently reacted with 1.5 equiv of MAMA−SG1. Again, no DMAMA−TTC could be isolated, confirming that the release of the benzyl radical from IR_{RAA} is very unlikely. To favor the formation of DMAMA−TTC and generally to increase the rate and the yield of the synthesis, phenylethyl RAFT agents may be used instead of benzyl ones.

In conclusion, the ESARA process showed to be efficient using low MW model compounds. It is anticipated to be applicable to various RAFT agents such as dithioesters, trithiocarbonates and dithiocarbamates. Nevertheless, in the specific case of symmetric trithiocarbonates (e.g., DBzTTC), it appeared that the exchange of the two R substituents of the RAFT agent is challenging due to structure of the IRs that are formed during the reaction. This particularity could however be used to synthesize original asymmetric trithiocarbonates (e.g., MAMA−BzTTC).

Scheme 7. Various Intermediate Radicals (IR) Potentially Formed during the Reaction of MAMA−SG1 with DBz−TTC



Scheme 8. Reaction of MAMA−NHS−SG1 with BzDB and MAMA−DB



Limits of the Process. Although the previous results clearly validate the initial concept, we also explored eventual limitations associated with the ESARA process that may restrict its applicability.

Process efficiency depends on the nature and the structure of both the starting (macro)alkoxyamines and (macro)-RAFT agents:

Concerning the (macro)alkoxyamines, to displace the reaction equilibrium, the resulting R−nitroxide (macro)-alkoxyamines should be more stable than the starting A−nitroxide one. The use of tertiary A substituents is hence very interesting.

Concerning the (macro)RAFT agents, to displace favorably the addition−fragmentation equilibrium toward the formation of A−RAFT (macro)agents, Z and R groups of the initial R−RAFT (macro)agent should have appropriate characteristics to obtain efficient addition and fragmentation steps.

First, the Z group, which regulates the rate of the addition reaction, should activate sufficiently the thiocarbonyl function to ensure a fast transfer rate of A$^{\bullet}$ radicals onto the initial R−RAFT agent. The more stabilized A$^{\bullet}$ the more activating Z should be.[25] To illustrate this first point, the reaction between the tertiary MAMA−SG1 with benzyl *O*-ethyl xanthate (Bz−OEtX) was investigated (Scheme 5). In this case, no formation of MAMA *O*-ethyl xanthate (MAMA−OEtX) (yield $< 5\%$) was observed probably because of the low transfer activity of the xanthate agent toward the stabilized MAMA radical. The latter mainly recombines with the nitroxide SG1 or another MAMA radical rather than adding to the *O*-ethyl xanthate agent. It should be noted that this observation is consistent with the fact that *O*-ethyl xanthate is not able to control of polymerization of methacrylic monomers. It is however anticipated that the ESARA process can be successfully used to modify xanthate agents but with substituents corresponding to less stabilized/sterically hindered thus more reactive radicals (requiring higher reaction temperature).

Second, the R substituent, which regulates the selectivity of the fragmentation reaction, should correspond to a fragment radical R$^{\bullet}$ less stabilized/sterically hindered than A$^{\bullet}$ but still be a sufficiently good leaving group able to fragment from the IRs. The fragmentation rate coefficient of R, k_{fragR}, should not be too low compared to the fragmentation rate coefficient of A, k_{fragA}, to ensure the formation of R$^{\bullet}$ (rough estimation from PREDICI simulations indicates that the ratio $k_{\mathrm{fragA}}/k_{\mathrm{fragR}}$ should be at least $< 10^3$). To illustrate this second point, the reaction between the tertiary MAMA−NHS−SG1 with BzDB or DBzTTC was investigated (Scheme 8). No formation of MAMA−NHS−DB nor MAMA−NHS−BzTTC (yield $< 5\%$) was observed probably due to a much higher fragmentation rate coefficient of the MAMA−NHS leaving group ($k_{\mathrm{frag\ MAMA-NHS}}$) compared to the benzyl one. The release of Bz$^{\bullet}$ fragment radicals from the IRs is very unlikely in these cases. Actually, the radical stabilization of A$^{\bullet}$ significantly increases coming from the MAMA radical to its activated-ester counterpart, MAMA−NHS. This is consistent with the significantly higher dissociation rate of MAMA−NHS−SG1 than MAMA−SG1 itself.[19] In addition, different authors already showed that MAMA−RAFT agents have a low efficiency concerning the control of the polymerization of methyl methacrylate (MMA). In the latter case, the low efficiency is ascribed to the poorer leaving group ability of the MAMA radical compared to the MMA propagating radical.[9,27]

According to the above discussion, MAMA−NHS−DB could however be obtained from MAMA−NHS−SG1 by using a dithiobenzoate bearing a better R leaving group than the benzyl one. A similar reaction was therefore performed by substituting BzDB by MAMA−DB (Scheme 8). Indeed, this time, MAMA−NHS−DB was successfully obtained in good yield because the leaving group ability of MAMA is much closer than the one of MAMA−NHS.

It is worth mentioning that the latter strategy can be used to synthesize a wide range of functional (macro)RAFT agents using either different ester derivatives of MAMA−SG1 or the activated ester function of MAMA−NHS−SG1 for the coupling of various entities.[28,19]

Combination of Nitroxide-Mediated and RAFT Polymerizations. An important application of the ESARA process is the reversible conversion of macroalkoxyamines to macro-RAFT agents, i.e., the living polymer chains obtained

respectively by NMP and RAFT controlled radical polymerization techniques. This would indeed provide an interesting tool to combine both techniques and to obtain complex macromolecular architectures such as original block copolymers.

This ability was illustrated here in the case of polystyrene (PS). First, polystyryl−SG1 macroalkoxyamine (PS−SG1) were converted to polystyryl−dithiobenzoate (PS−DB) using BzDB and to polystyryl−trithiocarbonate (PS−TTC) using DBzTTC. Second, polystyryl−RAFT macroagents (PS−RAFT) were converted back to PS−SG1 using MAMA−SG1 (Scheme 9).[29]

1. Switching from Macroalkoxyamines to MacroRAFT Agents. A white colored PS−SG1 sample (M_n = 2910 g·mol^{-1}; PDI = 1.12) synthesized by NMP using MAMA−SG1 was reacted with (a) BzDB or (b) DBzTTC at 90 °C ($k_{d\ PS-SG1}$ = 3.1 × 10^{-4} s^{-1}).[21]

(a) Reaction with BzDB resulted after precipitation in a pink colored PS (M_n = 2920 g·mol^{-1}; PDI = 1.12) that suggested the substitution of SG1 chain-ends by the dithiobenzoate chromophores and the formation of PS−DB (Scheme 10). Besides the absence of peaks corresponding to SG1 chain-ends on the ^{31}P NMR spectra, this was confirmed using size exclusion chromatography (SEC), liquid chromatography at the critical condition (LC−CC) and performing a chain extension experiment with the resulting PS−DB sample.[30]

On SEC chromatograms (i) no peak corresponding to PS−PS coupling events was observed and the MWD of the PS−DB remained identical to that of the initial PS−SG1 (Figure 1, parts A and B) and (ii) the presence of dithiobenzoate chain-end chromophores was evidenced using a UV detector set at λ = 304 nm. Thiocarbonylthio moieties indeed exhibit a strong absorption at this wavelength conversely to the styryl repetitive units and SG1 that do not absorb. Whereas no peaks corresponding to the starting PS−SG1 was detected, a significant peak corresponding to the resulting PS−DB was observed (Figure 1C).

Liquid chromatography at the critical conditions (LC−CC) enables to access the end-group distribution of a polymer blend.[31] Under those particular conditions, the elution of homopolymer chains becomes independent from their molecular weight and only depends on the chemical nature of their terminal moieties. The technique is therefore particularly adapted to determine the efficiency of chain-end chemical modification.

Here we used the experimental conditions that were developed in our laboratory for the characterization of functional PS.[32] Analyses showed in this case a quantitative shift of the peak corresponding to the starting PS−SG1 toward lower elution volume. This is consistent with the formation of PS−DB bearing a terminal dithiobenzoate moiety that is more polar than the nitroxyle one (Figure 2A).

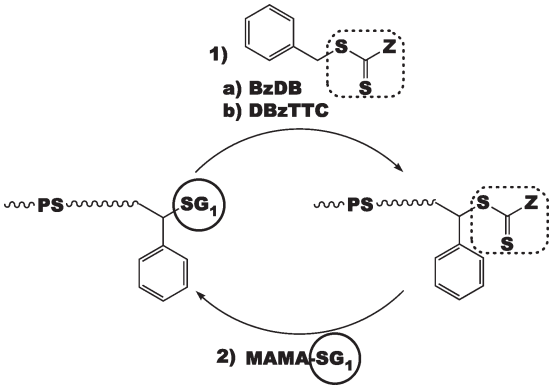
Finally, a chain extension test was performed using the resulting PS−DB sample (M_n = 2920 g·mol^{-1}; PDI = 1.12) as a macroRAFT agent for the bulk polymerization of styrene at 70 °C. In the presence of initiator, only the dithiobenzoate-ended chains are extended at this temperature. As a result, this experiment was used to evidence the eventual presence of dead PS and residual PS−SG1 chains in the PS−DB sample.

As shown in the Supporting Information, the MWD clearly shifted toward the high molecular weights (M_n = 16 050 g·mol^{-1}; PDI = 1.16). Only a very low proportion of polymer chains were not extended thus confirming the high yield of chain-end functionalization. The chromatograms obtained at λ = 304 nm indicated that the unextended chains did not bear a dithiobenzoate function. It is noteworthy that the latter chains may be formed during the ESARA process but they could also stem from the PS−SG1 initial sample for which the living fraction of SG1-terminated chains was not 100%.

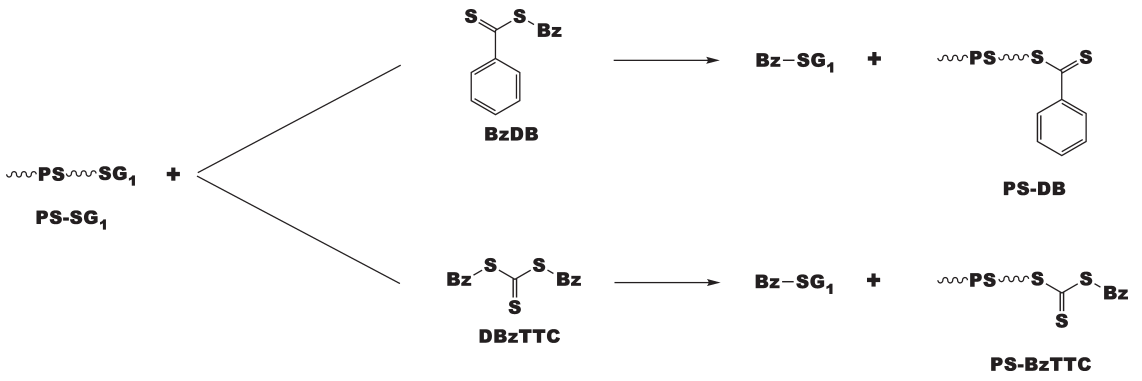
In conclusion, all these results converged toward a nearly quantitative conversion of the PS−SG1 macroalkoxyamine to the corresponding PS−DB macroRAFT agent.

(b) The same white colored PS−SG1 sample used previously (M_n = 2910 g·mol^{-1}; PDI = 1.12) was reacted with DBzTTC (Scheme 10). After precipitation, a yellow-colored polymer (M_n = 3070 g·mol^{-1}; PDI = 1.14) was recovered, indicating that the polymer chains did bear trithiocarbonate chromophores. Due to the difunctional nature of DBzTTC, dipolystyryl trithiocarbonate (DPS−TTC) might have been

Scheme 9. Switching Reversibly between Polystyryl Macroalkoxyamine to Polystyryl MacroRAFT Agent



Scheme 10. Reaction of PS−SG1 Macroalkoxyamine with (a) BzDB and (b) DBzTTC Resulting Respectively in the Formation of PS−DB and PS−BzTTC MacroRAFT Agents



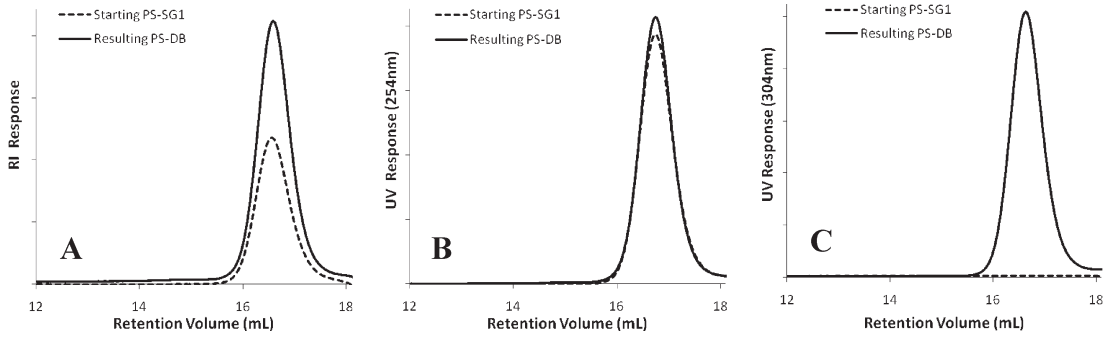


Figure 1. SEC chromatograms obtained for the starting PS−SG1 and the resulting PS−DB using (A) a refractometric detector, (B) a UV detector set at λ = 254 nm (absorption wavelength of the repetitive styryl units), and (C) a UV detector set at λ = 304 nm (absorption wavelength of the dithiobenzoate moiety).

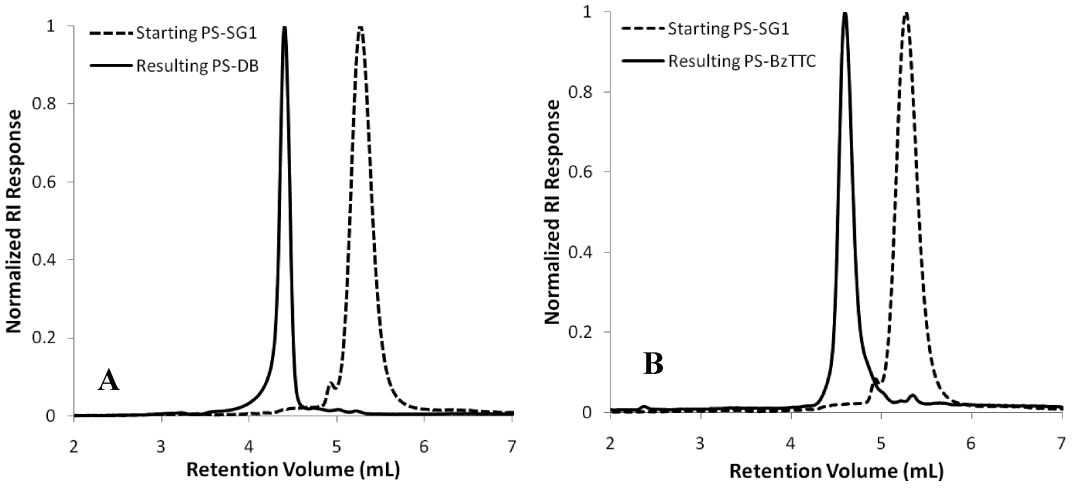


Figure 2. LC−CC chromatograms obtained after tranformation of a PS−SG1 macroalkoxyamine to (A) PS−DB and (B) PS−BzTTC macroRAFT agents.

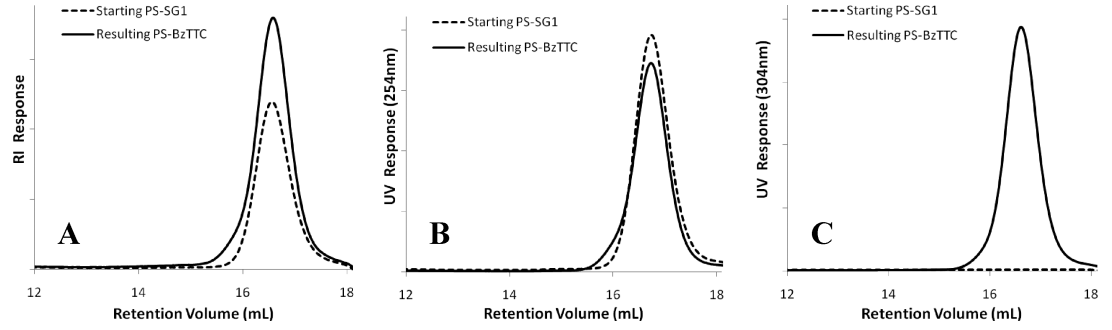


Figure 3. SEC chromatograms obtained for the starting PS−SG1 and the resulting PS−BzTTC using (A) a refractometric detector, (B) a UV detector set at λ = 254 nm (absorption wavelength of the repetitive styryl units), and (C) a UV detector set at λ = 304 nm (absorption wavelength of the trithiocarbonate moiety).

obtained. In this eventuality, the resulting polymer chains would exhibit a MW twice the one of the starting PS−SG1. However, no such chains were observed by SEC. Actually, although the leaving group ability of polystyryl and benzyl substituents might be close enough to allow the release of the benzyl group from the IR_{RAA} (Scheme 7), the excess of DBzTTC used for the reaction prevented the formation of DPS−TTC in this case. As a consequence, it was anticipated that the main product of the reaction was polystyryl benzyl trithiocarbonate (PS−BzTTC).

This statement was confirmed both by SEC (Figure 3) and ^{1}H NMR. SEC chromatograms showed that the MWD of the resulting polymer remained identical to the one corresponding to the initial PS−SG1 (Figure 3, parts A and B). In addition, the presence of trithiocarbonate chain-ends was evidenced using a UV detector set at λ = 304 nm. Whereas no peaks corresponding to the starting PS−SG1 could be observed, a significant peak corresponding to the resulting PS−BzTTC was detected (Figure 3C).

Concerning NMR, no peak could be observed from ^{31}P NMR, indicating the absence of residual SG1 chain-ends. On the other hand, a significant distinctive singulet peak at 4.60 ppm corresponding to the methylene protons of the benzyl group in α of the trithiocarbonyl function was clearly observed by ^{1}H NMR. A number average MW $M_{n\ NMR}$ = 3770 g·mol^{-1} could then be calculated and the fact that this

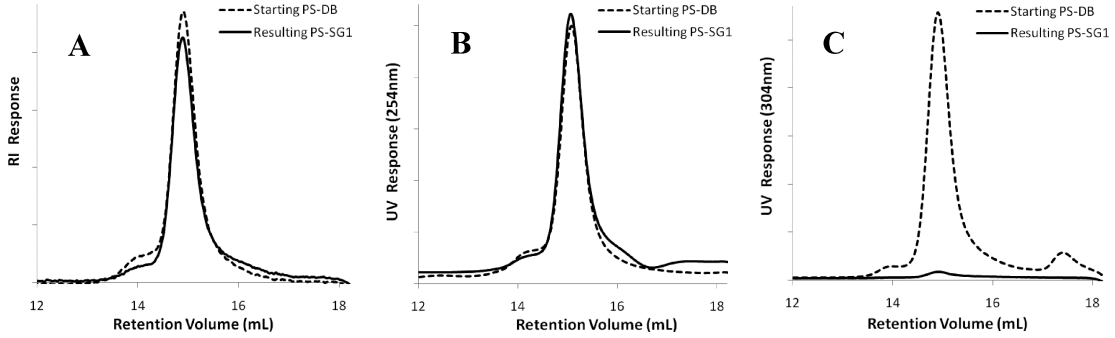
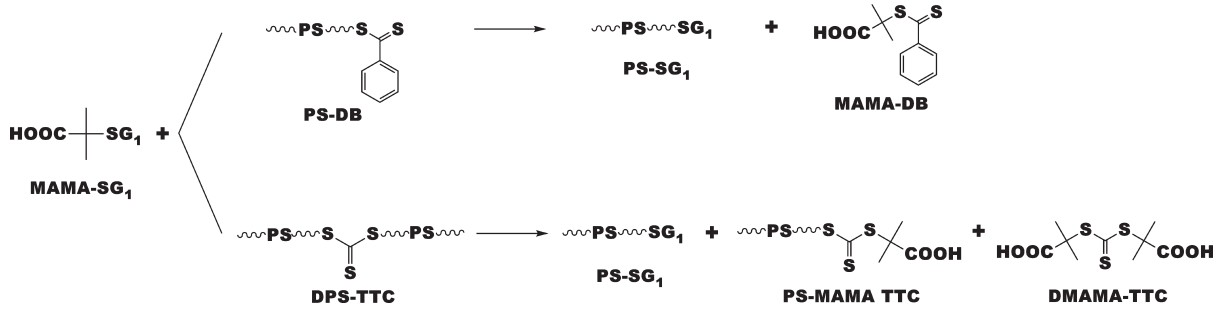


Figure 4. SEC chromatograms obtained for the starting PS−DB and the resulting PS−SG1 using (A) a refractometric detector, (B) a UV detector set at λ = 254 nm (absorption wavelength of the repetitive styryl units), and (C) a UV detector set at λ = 304 nm (absorption wavelength of the dithiobenzoate moiety).

Scheme 11. Reaction of PS macroRAFT agents (a) PS−DB and (b) DPS−TTC with MAMA−SG1 Resulted Respectively in the Formation of PS−SG1 and a Mixture of PS−MAMA TTC and PS−SG1



value is in close agreement with the SEC results confirmed that the main product was PS−BzTTC.

LC−CC analyses showed an almost quantitative shift (>95%) of the PS−SG1 peak toward lower elution volume given the greater polarity of the BzTTC moiety compared to SG1 (Figure 2B). The elution volume shift was however less important than in the case of PS−DB (Figure 2A).

Finally, a chain extension test was performed using the resulting PS−BzTTC sample (M_n = 3070 g·mol^{-1}; PDI = 1.14). Again, the MWD clearly shifted toward the high molecular weights (M_n = 18 400 g·mol^{-1}; PDI = 1.18) indicating that the large majority of the chains in the initial PS−BzTTC macroRAFT agent sample indeed bore a trithiocarbonate end-group that could be reactivated (see Supporting Information).

In conclusion, all these results converged toward a nearly quantitative conversion of the PS−SG1 macroalkoxyamine to the corresponding PS−BzTTC macroRAFT agent.

2. Switching from MacroRAFT Agents to Macroalkoxyamines. (a) First, a pink colored PS−DB (M_n = 12 860 g·mol^{-1}; PDI = 1.15) synthesized by RAFT polymerization using MAMA−DB as the CTA was reacted with MAMA−SG1 at 65 °C (Scheme 11). The reaction resulted, after precipitation, in a white colored polymer (M_n = 12 290 g·mol^{-1}; PDI = 1.16) indicating the removal of the dithiobenzoate chromophores and suggesting the formation of PS−SG1.

SEC chromatograms (Figure 4) revealed that no PS−PS chain−chain coupling events occurred since the MWD of the resulting PS−SG1 remained identical to that of the initial PS−DB (Figure 4, parts A and B).[33] In addition, the UV chromatograms obtained at λ = 304 nm confirmed the disappearance of the large majority of the dithiobenzoate chain-ends (Figure 4C). However, the presence of a small peak seemed to indicate that the reaction yield was not 100%. The difference in term of leaving ability between MAMA and polystyryl groups may indeed not be low enough to favor fast kinetics.

LC−CC analysis confirmed the SEC observations (Figure 5A). The PS−DB peak mostly shifted toward the higher elution volume corresponding to PS−SG1. However, this was only partial, indicating the presence of a low proportion of unreacted initial macroRAFT agent.

The formation of PS−SG1 was further confirmed by ^{31}P NMR. Indeed, spectra of the resulting polymer sample—conversely to the initial PS−DB—clearly showed the presence of the two characteristic peaks at 24.3 and 25.5 ppm corresponding to SG1 chain-ends.

In conclusion, the reaction between PS−DB macroRAFT agent with MAMA−SG1 led to the formation of PS−SG1 macroalkoxyamine. However, as evidenced by SEC and LC−CC, about 5 to 10% of the initial PS−DB remained unreacted using the experimental conditions described here. It could nonetheless be anticipated that a quantitative yield would be obtained by increasing the excess of MAMA−SG1 and/or increasing the reaction temperature and duration. Finally, it is noteworthy that MAMA−DB could be recovered and purified after precipitation of PS−SG1 for further utilization.

(b) Second, a similar reaction was performed with a yellow-colored dipolystyryl trithiocarbonate (DPS−TTC) synthesized by RAFT using DBzTTC as the CTA. DPS−TTC (M_n = 5760 g·mol^{-1}; PDI = 1.22) was reacted at 65 °C with either 1 or 10 equiv of MAMA−SG1 relatively to the trithiocarbonate function (Scheme 11).

By analogy to the reaction of MAMA−SG1 with the symmetric DBzTTC (see above), the fragmentation selectivity of IRs bearing two MAMA and one polystyryl substituents that are formed in this case may not favor the quantitative transformation of DPS−TTC to PS−SG1 and DMAMA−TTC (although the polystyryl substituent should

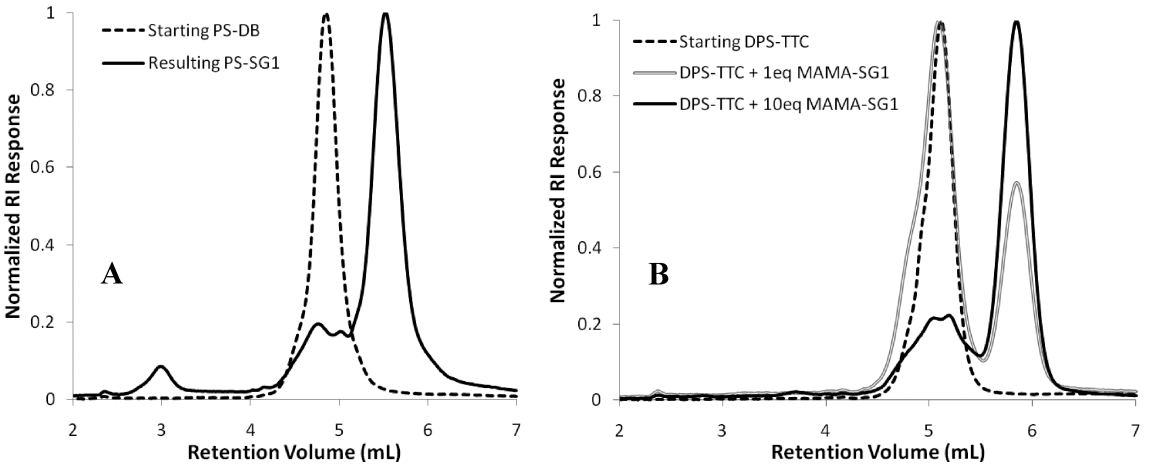


Figure 5. LC−CC chromatograms obtained after reaction of (A) PS−DB and DPS−TTC and (B) PS−BzTTC macroRAFT agents with MAMA−SG1.

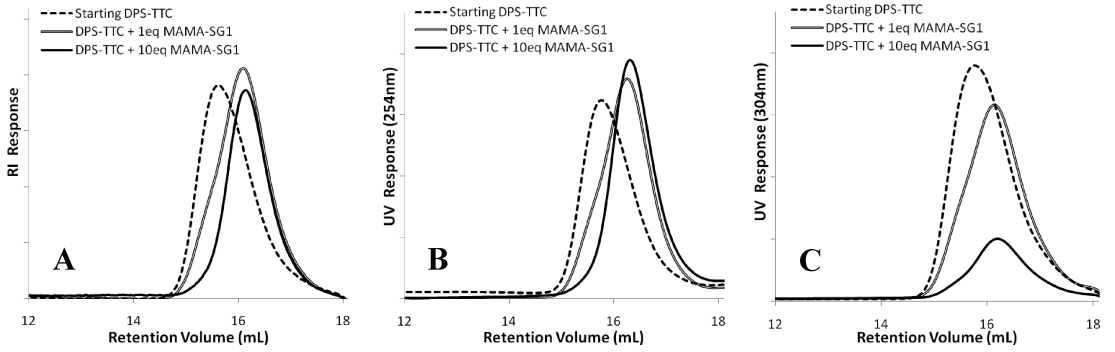


Figure 6. Chromatograms obtained for the starting DPS−TTC and the resulting polymer after reaction with either one or 10 equiv of MAMA−SG1 relatively to the trithiocarbonate functions using (A) a refractometric detector, (B) a UV detector set at $\lambda = 254$ nm (absorption wavelength of the repetitive styryl units), and (C) a UV detector set at $\lambda = 304$ nm (absorption wavelength of the trithiocarbonate moiety).

be a better leaving group than the benzyl substituent). The final polymer product of the reaction was then expected to be a mixture of PS−SG1 and PS−MAMA−TTC (Scheme 11). It was also anticipated that the resulting PS chains would exhibit a MW half the one of the starting DPS−TTC after cleavage of the chains at the level of their central trithiocarbonate group.

When performing the reaction with an excess of MAMA−SG1 (10 equiv), the results were consistent with these hypotheses. SEC chromatograms (Figure 6, parts A and B, solid black line) indeed showed a narrow peak corresponding PS chains with a MW ($M_n = 3870$ g·mol^{-1}; PDI = 1.20) that was close to half the one of the starting DPS−TTC chains (considering the increase in the chain-end molecular weight). No significant shoulder corresponding to the initial DPS−TTC was observed. In addition, chromatogram obtained with the UV detector set at $\lambda = 304$ nm (Figure 6C) indicated that a significant amount of the cleaved chains still bear a trithiocarbonate chain-end.

The LC−CC experiments confirmed the formation of PS−SG1 (Figure 5B). In addition, in agreement with the SEC chromatograms obtained with the UV detector set at $\lambda = 304$ nm, they also showed that some PS chains retained a trithiocarbonate function.

Now, when the same reaction was performed with only one equivalent of MAMA−SG1 relatively to the trithiocarbonyl functions of DPS−TTC, the results showed that a blend of DPS−TTC, PS−SG1 and PS−MAMA−TTC was obtained. A shoulder on the high MW side of the SEC chromatograms of the resulting polymer indicated that a proportion of the starting DPS−TTC remained unreacted (Figure 6, solid gray line). The majority of the chains were however cleaved and exhibited a MW about half the one of the starting DPS−TTC chains. The chromatogram obtained with the UV detector set at $\lambda = 304$ nm revealed that part of the latter, probably corresponding to PS−MAMA−TTC, retained the thiocarbonylthio chromophore (Figure 6C). Finally, LC−CC chromatograms confirmed the formation of PS−SG1 chains. It was however not possible to clearly discriminate between the DPS−TTC and PS MAMA−TTC chains.

In conclusion, the reaction between DPS−TTC macroRAFT agent with MAMA−SG1 led to the formation of PS−SG1 macroalkoxyamine exhibiting a MW half of the starting material. This further confirmed the proposed mechanism that implies the cleavage of the DPS−TTC chains at the level of their central trithiocarbonate group. Similarly to what was observed with low MW symmetric trithiocarbonates, complete conversion to PS−SG1 and DMAMA−TTC was not reached starting from the initial symmetric trithiocarbonate. Some PS−MAMA−TTC was evidenced and its proportion in the final polymer samples varied with the initial amount of MAMA−SG1. This may be taken into profit for some applications to obtain bipopulated blend of well-defined polymers.

Conclusions

The ESARA process proved to provide an efficient pathway linking nitroxide-mediated and RAFT controlled radical polymerization. The two mechanisms on which these two CRP

techniques are based were combined to enable (macro)-alkoxyamines and (macro)RAFT control agents to exchange their respective substituents.

The strategy was first validated with low MW compounds. The carboxylic acid-containing substituent of MAMA−SG1 alkoxyamine was successfully exchanged with the benzyl substituent of dithiobenzoate and trithiocarbonate RAFT agents, as was the activated ester containing substituent of MAMA−NHS−SG1 alkoxyamine with the MAMA substituent of MAMA−DB. The ESARA process can thus be seen as a synthetic tool for the preparation of original and functional control agents that are challenging to obtain by other mean. This is particularly true for the synthesis of RAFT agents bearing tertiary and/or functional substituents, such as MAMA−DB and MAMA−NHS−DB. The latter are indeed highly desirable to efficiently control the polymerization of a large number of monomers and for the synthesis of well-defined α-functional polymers.

The outcome of the ESARA process, kinetics and yield, greatly depends on the selection of the experimental conditions. The choice of the respective A and/or R substituents of the (macro)alkoxyamines and the (macro)RAFT agents is crucial as well as the reaction temperature: (i) the R group of the RAFT agent should exhibit a lower but sufficiently good leaving group ability compared to A substituent coming from the alkoxyamine and (ii) the dissociation rate of the initial alkoxyamine should be significant whereas that of the resulting alkoxyamine should be very low at the chosen temperature. If both conditions are fulfilled, the expected product is formed and the reaction yield can be optimized by increasing the excess of initial reagent and increasing the reaction time.

The efficiency of the ESARA process was then tested at the macromolecular level using preformed polystyryl macroalkoxyamines and macroRAFT agents. It enabled to exchange reversibly the chain-ends of these living polymer chains that are respectively obtained by NMP and RAFT polymerization. The ESARA process can therefore be used to combine these two CRP techniques, opening a wide range of possibilities for the synthesis of well-defined polymer architectures, such as block copolymers.

Finally, the ESARA process appears to be a very interesting tool not only for the design of complex and functional macromolecular systems but also in the field of radical chemistry. Indeed, it can be used to compare the leaving group abilities of various kinds of substituents and to gain some insights into the mechanism of NMP and RAFT polymerizations. In particular, the ESARA process could be used to study the eventual side reactions, e.g., irreversible termination involving the dithiobenzoate-derived IRs, which may occur during RAFT polymerization.

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Supporting Information Available: Text discusssing PREDICI simulations with a table of rate coefficients used and figures showing ESARA simulated kinetics and SEC chromatograms for the chain extension tests. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) For this macromolecular application, it should be noted that since the concentration of chain-ends in polymer samples is generally low, the reacting alkoxyamines or RAFT agents could be used in large excess to optimize the functionalization yield without any prohibitive added cost. In addition, this excess can also be recovered and "recycled" after isolation of the polymer.
(30) In this case, despite the low MW of the PS−DB sample, ^{1}H NMR could not be used for the quantification of the dithiobenzoate chain-ends and thus for the determination a number average MW since the peaks corresponding to the dithiobenzoate chain-ends overlapped the broad peaks of PS (7−8 ppm).
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(33) Interestingly, the small peak observed at high molecular weight (low retention volume) in the SEC chromatograms—which is usually observed for PS synthesized via dithiobenzoate-mediated RAFT polymerization and that can be ascribed[34] to (i) irreversibly

terminated chains via combination, (ii) intermediate radicals, or (iii) irreversible termination products of IR—did appear on the UV chromatograms of the starting PS−DB. It means that at least part of these chains contains a chromophore absorbing at $\lambda = 304$ nm, unlike terminated PS chains. In addition, it seemed that the former lost their chromophore upon reaction with MAMA−SG1.

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