Synthesis of NMP/RAFT Inifers and Preparation of Block Copolymers

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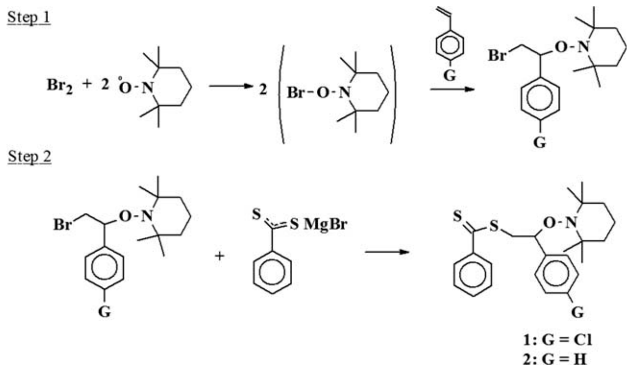
ABSTRACT: Two different initiator/transfer agents (inifers) containing an alkoxyamine and a dithiobenzoate were synthetized and used to trigger out either reversible addition-fragmentation chain transfer (RAFT) polymerization or nitroxide-mediated polymerization (NMP). α-Dithiobenzoate-ω-alkoxyamine-difunctional polymers were produced in both cases which were subsequently used as precursors in the formation of block copolymers. This synthetic approach was applied to *N*-isopropylacrylamide (NIPAM) or polyethylene oxide methacrylate (EOMA) to form α,ω-heterodifunctional homopolymers via RAFT at 60°C which were chain extended with styrene by activating the alkoxyamine moiety at 120°C. Under such temperature conditions, it is proposed that a tandem NMP/RAFT polymerization is initiated producing a simultaneous growth of polystyrene blocks at both chain-ends. Self-assembled nanostructures of these amphiphilic block copolymers were evidenced by scanning electron microscopy. © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 000: 000–000, 2012

KEYWORDS: block copolymers; dual controller; inifer; living polymerization; nitroxide-mediated polymerization; reversible addition fragmentation chain transfer (RAFT); reversible-deactivation radical polymerization

INTRODUCTION The reversible-deactivation radical polymerization (RDRP),[1]—vernacularly known as living free radical polymerization—is an ensemble of techniques commonly used for the synthesis of well-defined functional polymers with a predetermined molecular weight (MW) and narrow molar mass distribution ($Đ = M_w/M_n$). The general principle involved in the control of the chain propagation reaction is a temporal termination, or reversible-deactivation, induced by a variety of rapid equilibrium reactions between propagating radicals and dormant species. Albeit, in these processes, a small fraction of chains is irreversibly deactivated by radical–radical reactions, the living behavior of the polymerization is clearly observed by the MW increase with conversion and low $Đ$ values. RDRP includes degenerative-transfer polymerization methods as reversible addition-fragmentation chain transfer (RAFT)[2] and iodine-transfer polymerization (ITP/RITP)[3] and polymerizations based on reversible termination reactions as atom transfer radical polymerization (ATRP)[4] and nitroxide-mediated polymerization (NMP).[5]

These methods are based on different chemical reactions. For instance, RAFT polymerization depends on a well-known equilibrated interconversion of thiocarbonylthio compounds Z-(C=S)SR to a functional polymer Z-(C=S)SP in the early stages of the polymerization through the formation and fragmentation of intermediate radicals, whereas NMP relies on the reversible termination of propagating radicals with stable free radicals to form thermolabile alkoxyamines (P-ONR$_1$R$_2$).[6] Separately, RAFT and NMP offer the possibility to define accurately MW in the synthesis of complex polymer architectures with possible low $Đ$. Nevertheless, limitations associated with each system proscribe the use of some monomers and functionalities. For instance, the synthesis of a triblock copolymer entirely by RAFT with three different monomers has been only rarely applied, as a single RAFT agent cannot effectively control the polymerization of all three monomers at the same level. Conversely, the list of monomers that can be used in NMP is rather limited. The principle of formation of chains in RAFT and NMP entirely differs, therefore, it is of no use mixing a RAFT chain transfer agent (Z-(C=S)SR) with an alkoxyamine to carry out combined RDRPs. This particular combination NMP/RAFT could turn out to be interesting if a single molecule can be prepared with both functional groups, *v.gr.* a dithiobenzoate bearing an alkoxyamine in the Z or R group (T-Ph(C=S)S-R) and Ph(C=S)S-R-T, respectively, where T = alkoxyamine). The last compound is more interesting, as it can be used as chain transfer agent in a RAFT polymerization to prepare α,ω-heterodifunctional polymers (Z-(C=S)S-polymer-T). Afterward, an AB diblock copolymers can be formed

Additional Supporting Information may be found in the online version of this article.



SCHEME 1 Synthesis of 2-(4-chlorophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)ethyl-dithiobenzoate (1) and 2-phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)ethyl-dithiobenzoate (2).

via RAFT without altering the alkoxyamine group, which can be lastly used to initiate NMP to achieve an additional chain extension with monomer C. Alternatively, *Z*-(C=S)S-polymer-T can be heated in the presence of a monomer B to activate the scission of T establishing the NMP equilibrium. In such conditions a tandem NMP/RAFT polymerization would be produced, as the ω-thiocarbonylthio moiety could react with propagating radicals leading straightforward to ABA block copolymer.

The combination of two RDRP methods as mentioned above for the synthesis of block copolymers has been described earlier. For instance, a Br-containing alkoxyamine was synthetized and used as ATRP/NMP initiator to prepare self-assembled monolayers on silicon wafers.[7] The combination of an ATRP initiator and a RAFT chain transfer agent has been also succeeded. For instance, a dibromotrithiocarbonate was prepared and used to conduct, independently or concurrently, ATRP and RAFT polymerization.[8] Several chloro-xanthates were synthesized to combine RAFT polymerization of *N*-vinyl pirrolidone (NVP) with ATRP of styrene and (meth)acrylates to prepare well-defined NVP[9] or vinyl acetate[10] block copolymers. More recently, a multiheterofunctional inifer was prepared and used to prepare multihydrophilic block copolymers.[11] In these examples, heterodifunctional molecules (containing two different groups) were applied to prepare block copolymers from mechanistically incompatible monomers, independently and selectively, without the need of chain end transformation[12] or protection steps. This unimolecular approach differs of the use of thiocarbonylthio compounds as pseudohalogen initiators in ATRP.[13]

In this article, we present the synthesis of inifers **1** and **2** to introduce the concept of NMP/RAFT dual controllers. We demonstrate that such inifers are effective in the preparation of heterodifunctional polymers, which were used forming multiblock copolymers via tandem NMP/RAFT polymerization using water soluble monomers as *N*-isopropylacrylamide (NIPAM) or polyethylene oxide methacrylate (EOMA). At our best knowledge, it is the first report on the application of a NMP/RAFT inifer which clearly expand the possibilities of macromolecular design.

RESULTS AND DISCUSSION

As shown in Scheme 1, the strategy for the synthesis of inifer **1** comprises two steps: (a) the formation of the bromo adducts[14] by treating the oxoaminium bromide with 4-chlorostyrene or styrene and, (b) the formation of the dithiobenzoate group by treatment of bromo adducts with bromomagnesiumdithiobenzoate. The overall yield after column purification was estimated to be 21%. Compounds differ by the presence of chlorine atom in **1**, which might provide a greater stability and better control to polymerizations in comparison with the nonsubstituted inifer **2.** It should be noted that **1** and **2** (seeing it as RAFT agents with R = primary alkyl), would not anticipated to be effective because primary alkyl radicals are considered as poor homolytic leaving groups. However, the use of disubstituted monomers as trans-β-methyl styrene instead of styrene or 4-chloro styrene in the synthesis of more active chain transfer agents resulted in unstable intermediaries giving low yields in step 1 or undetectable formation of corresponding dithiobenzoates. Figure 1 and Supporting Information, Figure S1, show the ^{1}H NMR and ^{13}C NMR of **1** and **2,** respectively. Protons *d*, *e*, correspond to diastereotopic protons adjacent to the thiocarbonyl group, whereas signals at 5.1 (*f*) ppm correspond to benzylic protons; carbon *m* was assigned to the thiocarbonyl group. The fragmentation pattern and M$^+$ in the GC/MS spectrum (not shown in figures) gives a second piece of evidence about the successful and unprecedented synthesis of

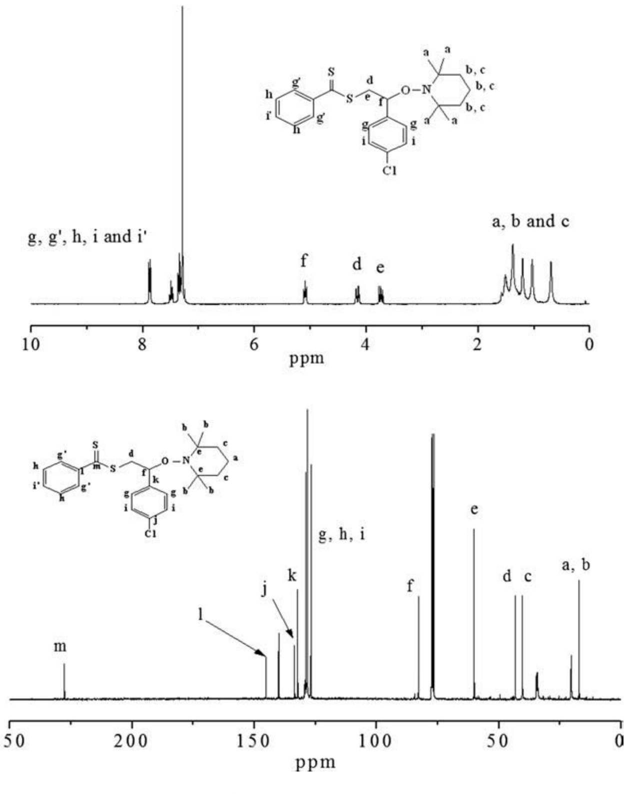


FIGURE 1 ^{1}H (top) and ^{13}C (bottom) NMR spectra of 2-(4-chlorophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)ethyl-dithiobenzoate (**1**).

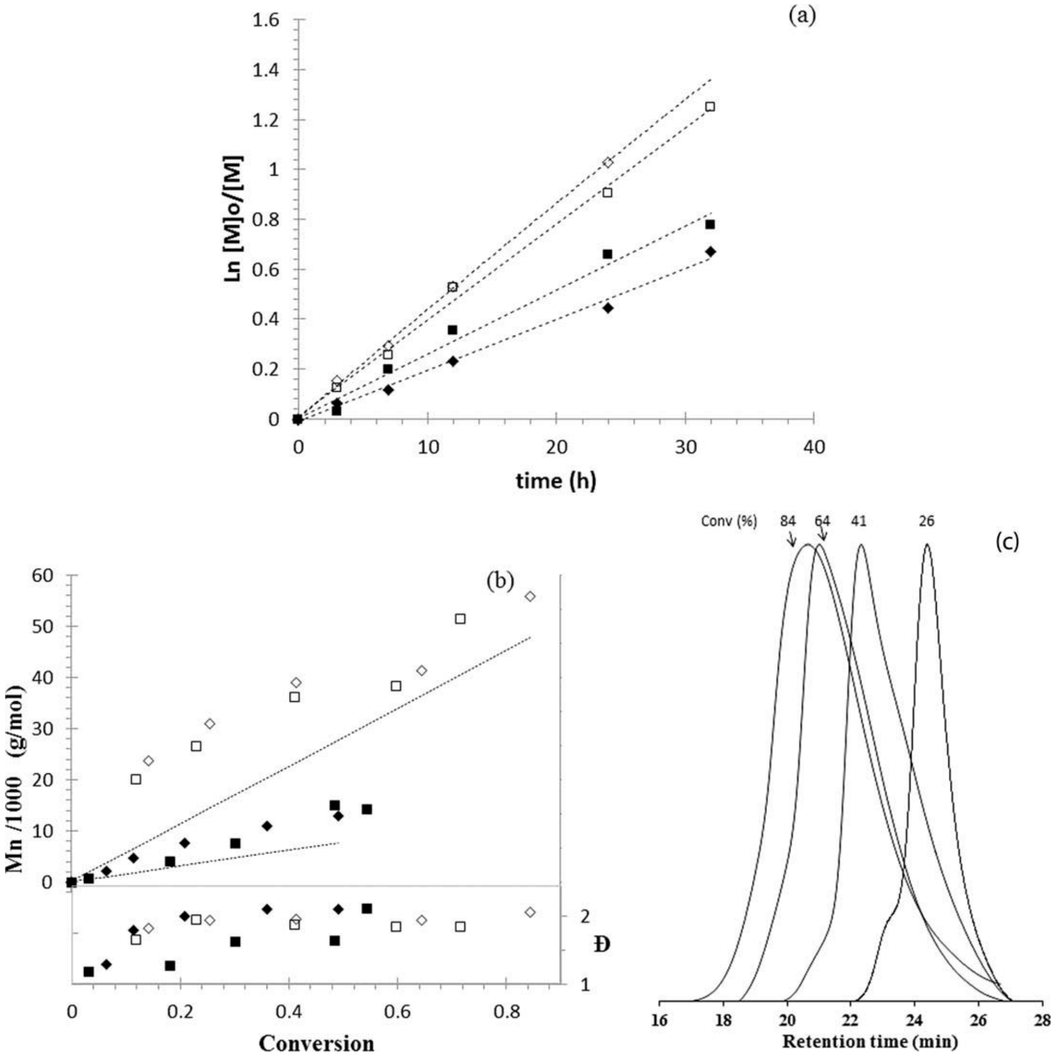
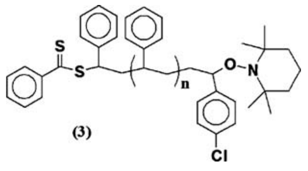


FIGURE 2 (a) Time dependence of Ln([M]$_0$/[M]), (b) Mn versus monomer conversion for RAFT polymerizations of styrene ([S]/[**1**]/[AIBN] = 150/1/0.5; (◆), [S]/[**2**]/[AIBN] = 150/1/0.5; (■), [S]/[**1**]/[AIBN] = 650/1/1; (◇) and [S]/[**2**]/[AIBN] = 650/1/1 (□), $T = 60°C$), and (c) SEC traces for the bulk RAFT polymerization of styrene in the presence **2**; ([S]/[**2**]/[AIBN]=150/1/0.5 $T = 60°C$).

such inifers. These compounds were subsequently evaluated for the controlled polymerization of S and in the formation of block copolymers composed of butyl acrylate (BA), *t*-butyl acrylate (*t*-BA), acrylic acid (AA), NIPAM, and EOMA.

RAFT Polymerization of Styrene with Inifers 1 and 2 as Chain Transfer Agents

The reaction conditions and results of the RAFT polymerization of styrene with a molar ratio[S]/[Inifer]/[2,2′-azobis(isobutyronitrile), AIBN] = 150/1/0.5 and 650/1/1 are summarized in Figure 2 (see also Supporting Information, Tables S1 and S2). A linear development of Ln([M]$_0$/[M])-vs.-time and a gradual shift of size exclusion chromatography (SEC) traces to higher MW was observed in all polymerizations indicating the living character of the process. However, the molar mass distribution (*Đ*) increases with conversion and $M_{n_{SEC}}$ is higher than the theoretical values determined from the molar ratio of consumed monomer to inifer. These results reflect the fact that the dithiobenzoate moiety does not have a good homolytical leaving group (R group) relative to the attacking polystyryl macroradical. That may imply a low fragmentation rate for the intermediate radical and a greater possibility for side reactions. High *Đ* values also reflect the fact that an equimolar ratio of inifer to initiator was used to increase the polymerization rate when it was targeted high MW ([S]/[Inifer]/[AIBN] = 650/1/1). As it is anticipated that the alkoxyamine group remains untouched during the RAFT polymerization; the product of the RAFT polymerization should be a heterodifunctional polystyrene (PS) (**3**).



(3)

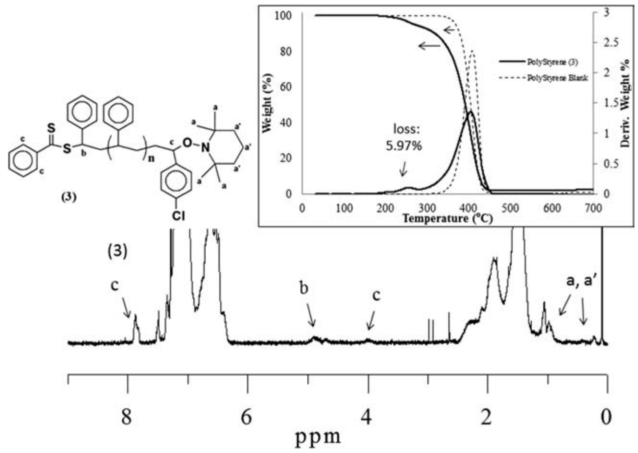


FIGURE 3 ^{1}H NMR of a PS (**3**) prepared by RAFT polymerization in the presence of inifer **1** at 60°C [S]/[**1**]/[AIBN] = 150/1/0.5. M_n = 5130 g/mol (conversion = 30%) and its corresponding TGA thermogram (solid line) compared with an anionic PS of comparable MW (dotted line).

$M_{n_{NMR}}$ estimated from the ^{1}H NMR spectra[15] of samples obtained at moderated or high conversion are rather close to the $M_{n_{SEC}}$ (See Supporting Information, Table S2). This result strongly suggests that a major fraction of chains ($[M_{n_{NMR}}/M_{n_{SEC}}]_{avg} \times 100 = 90\%$) is functionalized with the dithiobenzoate group and validates the structure of **3**.

The structure of PS (3) was confirmed by the characteristics signals of ortho protons in the thiobenzoate group and the methyl protons in the alkoxyamine group as can be seen in the ^{1}H NMR spectrum of a sample prepared with a molar ratio [S]/[1]/[AIBN] = 150/1/0.5 at 60°C (Fig. 3). The assignments of resonances were confirmed by comparing the chemical shifts of inifer **1**. To further validate the sample structure, we performed a TGA analysis. The inset in Figure 3, shows the corresponding thermogram obtained under nitrogen atmosphere and the weight loss associated with the first degradation event at 206°C. The weight loss between 206 and 254°C is 5.97%, which is consistent with the of chain-ends content [(308/5130) × 100 = 6.0% (w/w)]. The thermal stability of this samples is compared with an anionic PS (M_n = 5300 g/mol, $Đ$ = 1.07). As can be seen, the heterodifunctional PS is less stable than the reference PS, with thermal decomposition starting at about 300°C, being complete by 450°C.

As an additional evidence for the retention of the RAFT-end groups, matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF-MS) analysis for a PS (**3**) (M_n = 4,620; $Đ$ = 1.6), prepared in the presence of **1** at 60°C [S]/[1]/[AIBN] = 150/1/0.3) was conducted as shown in Figure 4. Three main ion series can be distinguished [Fig. 4(a)] with various head and end-groups and a repeat unit of 104.06 Da corresponding to the molar mass of the styrene.

To assign the polymer structure to these series, the molar mass calculation of many possible structures combining different terminal groups (including the dithiobenzoate, alkoxyamine, 2-(methyl)-propionitrile groups as well as other produced during the MALDI-TOF-MS analysis as $CH_2{=}CPh$—, $CHPh{=}CH$—, chlorostyrene) were evaluated. The major peak indicated in expanded region shown in Figure 4(b) correspond to the series: $CH_2{=}CHPh{-}(CH_2{-}CHPh)_n{-}CH_2{-}CH(C_9H_{18}NO)(PhCl)\ Na^+$; consistent with the polymer being capped with an alkoxyamine (detailed structure see ○ in Table 1). The MW given by MALDI-TOF-MS for this series is M_n = 3597.98; M_w = 3804.95; $Đ$ = 1.06. For n = 29, the experimental peak centered at 3453.19 m/z fits with the calculated molar mass with Na^+ (3453.04 g/mol). The small series indicated with symbol ⌂ corresponds to the counterpart, that is, a polymer end-capped by the dithiobenzoate group. The molar mass calculated for n = 32 is 3505.98 which is consistent with the experimental m/z = 3505.69. The structures assigned to series indicated with symbols •, □, △, ◇ also contains the dithiobenzoate group and the experimental molar mass is in good agreement with the calculated (see Table 1 and Fig. 4). For instance, the series identified with the symbol "□" can be assigned to the structure $S{=}C(Ph)S{-}(CHPh{-}CH_2)_n{-}CH_2{-}CH(C_9H_{18}NO)(PhCl)\quad Na^+$. The peak at m/z = 3465.4 is attributed to this structure with n = 29, which fits with the calculated m/z = 3464.96. The MALDI-TOF-MS spectrum provides with a definitive evidence of the structure of PS (**3**) prepared with inifer **1**, even though the degree of functionality cannot be assessed precisely. Nevertheless, on the base of the apparent intensity area of the series "•, ○, □," it can be reasonably stated the

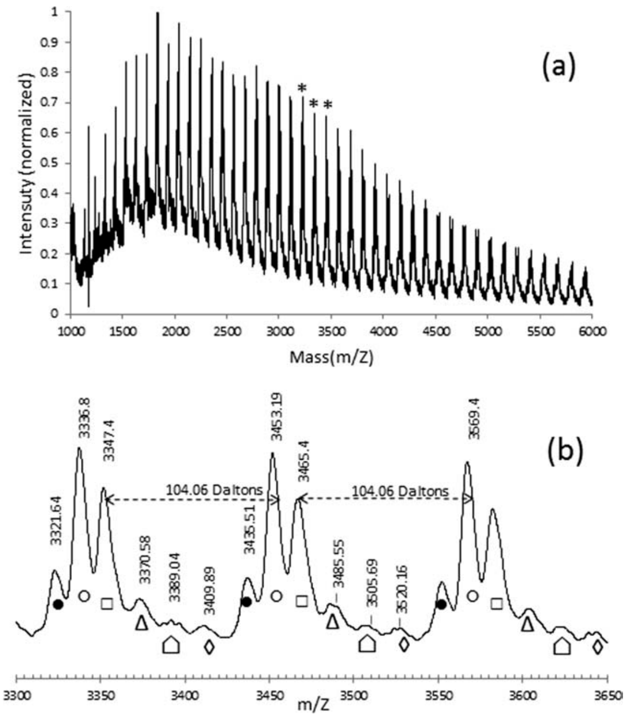
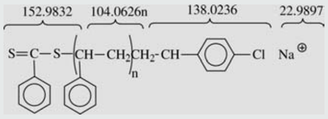
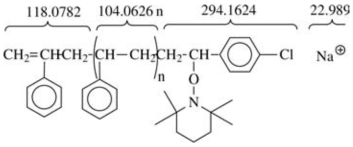
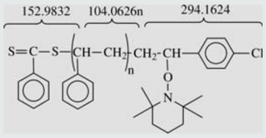
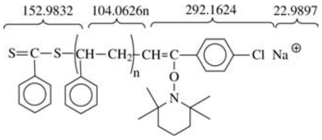
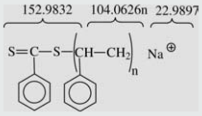
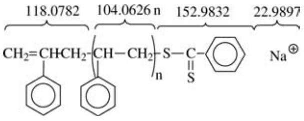


FIGURE 4 (a) MALDI-TOF-MS spectrum of a PS (**3**) (M_n = 4620; $Đ$ = 1.6), prepared in the presence of **1** at 60°C [S]/[**1**]/[AIBN]=150/1/0.3). (b) Expanded region of the spectrum (a). The peaks are labeled with their measured MW. The detailed structures are shown in Table 1.

TABLE 1 PS (**3**) with Various End-Groups Estimated by MALDI-TOF-MS in Figure 4

Symbol in Figure 4	Polymer Structure	Formula weight (*Na)
●		Mass (exp) = 3435.23 Mass (calc) = 3435.87 $n = 30$
○		Mass (exp) = 3453.19 Mass (calc) = 3453.04 $n = 29$
□		Mass (exp) = 3465.40 Mass (calc) = 3464.96 $n = 29$
△		Mass (exp)= 3485.55 Mass (calc) = 3485.95 $n = 29$
⌂		Mass (exp)= 3505.69 Mass (calc) = 3505.98 $n = 32$
◇		Mass (exp) = 3520.16 Mass (calc) = 3519.99 $n = 31$

end-functionality is even higher that that calculated by ^{1}H NMR (>95%).

Further evidence about the structure of PS (**3**) was obtained from ESR measurements. Carefully purified samples were dissolved in fresh distilled toluene, placed in an ESR tube, degassed, sealed, and heated in an ESR spectrometer to dissociate 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) and its accumulated concentration was followed in the medium (see Fig. 5). The signal intensity increased rapidly to reach a maximum ($[T]_{\max}$). After this point, TEMPO concentration decay was observed suggesting that side reactions occur involving the macroradical **4** and TEMPO (see Scheme 2). A reshuffling of the dithiobenzoate groups is also possible to form **5** and **6** during this treatment involving the formation of an intermediate free radical PS-S-C°-S-PS. Various kinetic models were tested to simulate the TEMPO evolution and decay assuming the reversible dissociation of TEMPO furthermore, different side reactions were assumed at elevated temperature. $[T]_{\max}$ was calculated to be 1.411, whereas the initial concentration of alkoxyamine $[PT]_0$ was 1.90 (arbitrary units). The decay is a second-order process described by $-d[T]/dt = 2k_2[T] \times [S]$, where S stands for an unknown reductive substance. We obtained excellent fit for the kinetic curves by adjusting k_2, $[PT]_0$, and $[S]$. The impact of reactions between TEMPO and **3**, as well as, TEMPO and *p*-chloride atom were also tested but their contribution was found not significant. The half-life time, for PT and TEMPO was calculated to be 4.2 and 23.7 min, respectively. Interestingly, no chain coupling was produced as evidenced by the comparison of SEC traces of samples before and after heating (not

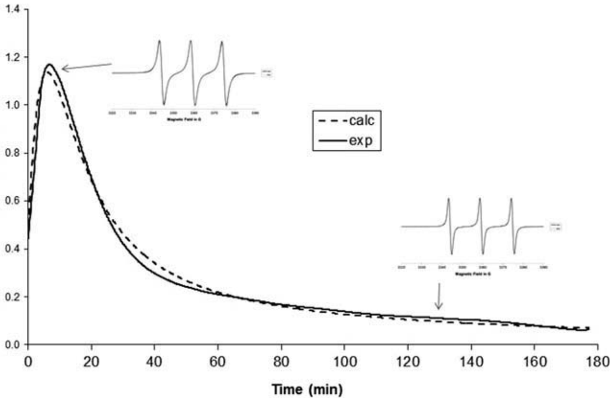
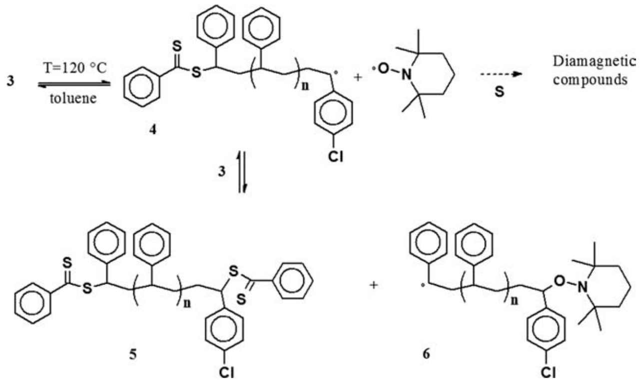


FIGURE 5 Experimental and simulated concentration of TEMPO during the decomposition of PS prepared via RAFT at 120°C.



SCHEME 2 Dissociation of difunctional PS (**3**) at 120°C.

shown in figures). This may suggest that the radical–radical termination of **4** and **6** is prevented by the high dilution and/or retarded by the RAFT equilibrium.

Even though styrene RAFT polymerization performed in the presence of inifers **1** or **2** yielded heterodifunctional PS (**3**) with broad molar mass distribution ($Đ$ = 1.3–2.1), the method is suitable for the preparation of block copolymers via RAFT or, via a concurrent NMP/RAFT polymerization. Thus, it was also interesting to test the ability of such inifers for the preparation of PS using the typical conditions for NMP polymerization at high temperature in the absence of a thermal initiator.

Styrene NMP Polymerization with 1 or 2

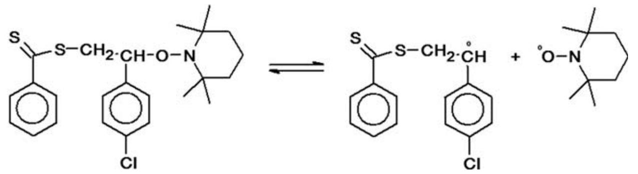
Inifers **1** and **2** were also tested as alkoxyamines in a bulk polymerization of styrene at 120°C using a degassed solution containing a molar ratio $[S]/[\text{inifer}] = 200/1$. Polymers were precipitated twice in methanol obtaining reddish product that give us a qualitative indication about its dithiobenzoate functionalization. The thermal decomposition of inifers generates TEMPO and its corresponding carbon centered radical as shown in Scheme 3. It was hypothesized that the styrene initiation and the reversible cross-coupling of TEMPO with polymeric radicals belonging to a NMP mechanism took place. However, the addition of the dithiobenzoate moiety to growing radicals cannot be excluded which can also activate the RAFT process. Therefore, under NMP conditions, that is, temperatures around 120°C, a tandem NMP/RAFT polymerization occurs. Obviously, this combined process might be affected by secondary reactions such as coupling of intermediate RAFT radicals with TEMPO and a partial loss of the dithiobenzoate group through thermal degradation.[16]

Results of bulk styrene polymerization in the presence of inifers **1** and **2** at 120°C are summarized in Figure 6 (see Supporting Information, Table S3). MWs increased with conversion and the molecular mass distributions remained narrow throughout the polymerization ($Đ$ = 1.2–1.5). The pseudo-first-order kinetic plot exhibited a consistent consumption of monomer as a function of time [Fig. 6(a)] but deviation from linear first-order behavior is observed after 8 h of reaction, likely due to the aforementioned side reactions. The M_n vs. conversion plot [Fig. 6(b)] is approximately linear for both inifers. However, experimental M_n values are higher than those predicted all along. This deviation can be explained by the fact that radical–radical coupling reactions of ω-dithiobenzoate or ω-TEMPO propagating macroradicals (**4** and **6**, respectively) leads up to new dormant polymers capable to increase its size subsequently. This is a key difference with monofunctional dormant species that increases the MW progression slope and $Đ$. In fact, chains might propagate at both extremities and the coupling reactions may occur unavoidably. High temperature can also be a potential drawback for conducting RAFT polymerizations, as temperature may favor dithiobenzoate decomposition. Nevertheless, the degree of thiocarbonylthio functionalization of samples calculated by NMR was again very high ($[M_{n_{NMR}}/M_{n_{SEC}}]_{avg} \times 100 = 92\%$) indicating that the thermal degradation of dithiobenzoate is indiscernible. It is worth mentioning that the effect of electron-withdrawing substituent in inifer**1** is revealed, as the $M_{n_{SEC}}$ of samples prepared with this compound is closer to the theoretical values compared with samples 17–22 prepared with inifer **2**.

The SEC chromatograms of polystyrenes prepared with **1** (corresponding to entries 11–16 in Supporting Information, Table S3) are presented in Figure 6(c) to show the entire shift of traces up to high MW. The tandem polymerization described above might also yield heterodifunctional polymers, which are suitable for applying in subsequent RAFT or NMP/RAFT processes to prepare block copolymers. To test its capability for reacting either as RAFT chain transfer agent or as alkoxyamine, we performed preliminary chain extension reactions to prove its difunctionality. The results are described below.

Chain Extension

Heterodifunctional polystyrenes (**3**) prepared by RAFT in the presence of **1** were retaken in styrene and heated at 120°C without any kind of initiator. For instance, a PS having a M_n = 12,960 g/mol and $Đ$ = 1.8 was extended to M_n = 26,330 g/mol, ($Đ$ = 1.5) in 3 h with a yield of 44%. This experiment demonstrates that the alkoxyamine group contained in PS (**3**) is still active. However, admitting that the RAFT process is activated, it is impossible to determinate the degree of extension at the α and ω ends. To understand the possible interferences between the RAFT and NMP, a PS (**3**) (M_n = 10,980 g/mol) was treated with AIBN/PPh$_3$ in THF to transform the thiocarbonylthio end group into a hydroxyl function.[17] The PS was then chain extended via NMP activating the remaining alkoxyamine group at 120°C and compared with the product prepared under the same conditions from the unmodified PS (**3**). Unexpectedly, the monomer



SCHEME 3 Thermal decomposition of inifer 1.

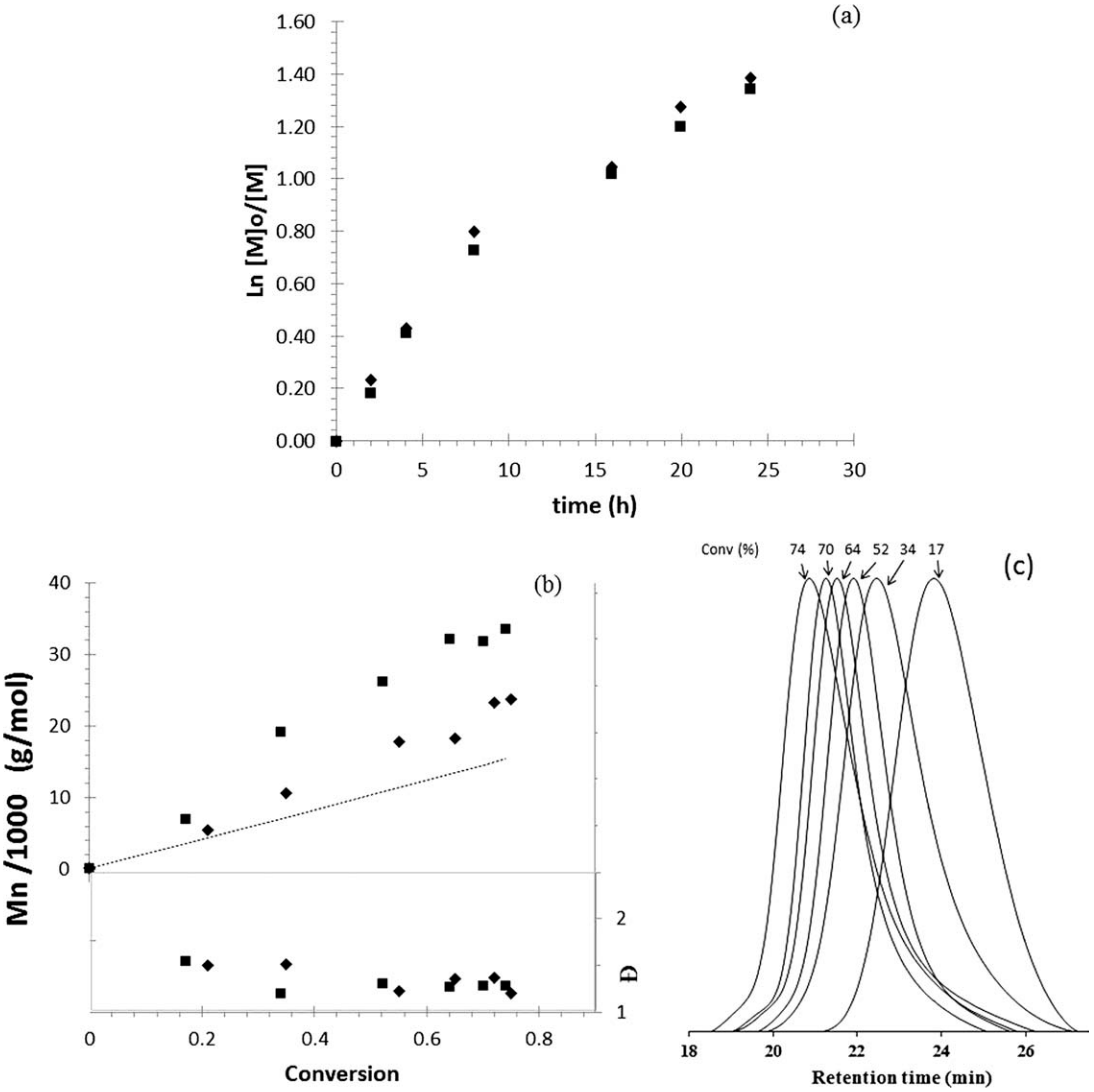


FIGURE 6 (a) Time dependence of Ln([M]$_0$/[M]), (b) Mn versus monomer conversion for a NMP/RAFT polymerizations of styrene ([S]/[**1**]/ = 200/1; (◆), [S]/[**2**]/ = 200/1; (■), T = 120°C), and (c) SEC traces for the samples obtained in the series ([S]/[**1**]/=200/1.

conversion is substantially higher for the modified PS and its MW increased twice as the PS (**3**) (See SEC traces in Supporting Information, Fig. S3). These results indicate that the NMP polymerization is altered by the presence of the dithiobenzoate chain-end; however, this interference is not destructive because $Đ$ is unaffected.

Conversely, a PS prepared using NMP conditions in the presence of **1** (M_n = 10,630 g/mol and $Đ$ = 1.5) was chain extended at 60°C using AIBN. This RAFT polymerization yielded a PS with M_n = 12,240 g/mol after 8 h of reaction. As in this case, only the dithiobenzoate group could cause such a chain growth and is put forward that the dithiobenzoate group is well-preserved during NMP at 120°C. SEC traces of chain-extended polymers and their corresponding prepolymers are presented in Supporting Information, Figures S2, S3 and data are quoted in Table S4. The results above suggest that synthesis of block copolymers is possible by alternating RAFT and NMP/RAFT polymerization; however, it is challenging to determinate the size of chain extension at each individual polymer end.

A possible way to clarify this issue is to prepare a heterodifunctional polymer based on an appropriate diene (*v.gr.* isoprene) under RAFT conditions. The chain extension with styrene and further oxidation (digestion) with OsO_4 of polydiene central block may provide valuable information about the size of outer blocks. Some model molecules representing chain ends in PS (**3**) has been prepared and used as a mixture in the styrene polymerization to determinate the effect on MW and $Đ$. The results will be developed in more detail in a forthcoming communication.

Block Copolymers

Once we studied the formation of PS using RAFT or NMP conditions, we sought to explore the use of inifers **1** and **2** for the synthesis of block copolymers composed of acrylic, methacrylic, or acrylamide derivatives monomers. The

TABLE 2 Conditions and results for the synthesis of BAB block copolymers through RAFT polymerization at 60°C and tandem NMP/RAFT polymerization at 120°C

Entry	Polymer	Inifer/M	Ratio[e,f]/inifer/AIBN			T (°C)	Conv (%)	t (h)	$M_{n_{SEC}}$ (g/mol)	M_{nth} (g/mol)	Đ
1[a]	PEOMA	**2**/EOMA[e]	84	1.0	0.3	60	74	4	38,140	6,110	1.2
2[b]	P(S-*b*-EOMA-*b*-S)	PEOMA/S	84	16.0	0.0	120	44	5	63,820	52,460	1.4
3[c]	PNIPAM	**1**/NIPAM	270	1.0	0.5	60	15	15	5,480	4,710	1.3
4[d]	P(S-*b*-NIPAM-*b*-S)	PNIPAM/S	88	12.0	0.0	120	36	7	38,700	19,930	1.8

[a] Methanol 50% (w/w).
[b] DMF 50% (w/w).
[c] Benzene 50% (w/w).
[d] THF 50% (w/w).
[e] Molar ratio for entries 1 and 3.
[f] Weight ratio for entries 2 and 4.

"RAFT-first" or the "NMP-first" approaches were the two possible routes to form the α,ω-heterodifunctional polymer, that is, the first block. For the second block, the RAFT or NMP conditions could lead to a structure AB or ABA, respectively, provided that a tandem polymerization is produced at 120°C. From an AB copolymer prepared entirely by RAFT polymerization, we can use the alkoxyamine group extending with a styrenic monomer to obtain a CABC tetrablock copolymer. The experimental conditions and results of different copolymers prepared using some of these synthetic possibilities are summarized in Tables 2 and 3.

We can see in Table 2 that polyEOMA (PEOMA) (Entry 1) and Poly(N-isopropylacrylamide) (PNIPAM) (Entry 3) prepared by RAFT polymerization using **2** and **1**, respectively, exhibit low *Đ* suggesting that in these cases the control is favored by the use of appropriate [inifer]/[AIBN] molar ratio and solvents. Measured M_n's are significantly higher than the calculated values, which might be explained by the fact that it is expressed in PS equivalents. These polymers should be α,ω-heterodifunctionals, that is, at the ω-end, they hold an alkoxyamine, whereas at the α-end they should have dithiobenzoate group. As it is known, the successful synthesis of block copolymers via a living free radical process is precluded if the end-group fidelity is not secured in each block formation step. As for most RDRP methods, it has been established that the end-group fidelity continually decreases during the polymerization process, the fact of having two functional groups makes more versatile these homopolymers forming complex structures. In the case of homopolymers quoted in Tables 2 and 3, it is also crucial to maintain high dithiobenzoate-group fidelity, but if the second block is prepared via NMP, the degree of functionality is less relevant.

Chain extension can be produced either at one or two extremities depending of the selected experimental conditions. For instance, chain extension of PNIPAM or PEOMA with styrene using typical NMP conditions resulted in amphiphilic block copolymers with excellent assembly behavior (see Entries 2 and 4 in Table 2). Indeed, clear evidence for vesicular structures was obtained by scanning electron microscopy (SEM) observation, as shown in Figure 7(a) for the P(S-*b*-NIPAM-*b*-S). Aggregation of these polymers was induced via the dropwise addition of water to THF solutions (a nonselective solvent) of the amphiphilic block polymers forming spherical vesicles with sizes in the range of 300–400 nm. The presence of holes in a number of the particles clearly demonstrates the hollow nature of the particles and their vesicular structure. Similar "open-mouth" vesicles were recently reported by Davis and coworkers[18] and Changez et al.[19] When P(S-*b*-EOMA-*b*-S) was self-assembled in the mixed THF/water solvents, supramolecular associations were also observed. However, in this case, small micelles sized between 16 and 42 nm were formed as shown in Figure 7(b). Further investigations on the formation of nano-objects are now in progress considering the effect of copolymers composition, experimentally determined MW, *Đ*, and hydrophobic/hydrophilic ratios to clarify the potential of inifers.

TABLE 3 Conditions and results for the synthesis of CABC block copolymers through RAFT polymerization at 60°C and tandem NMP/RAFT polymerization at 120°C

Entry	Polymer	Inifer/M	Ratio[d,e]/inifer/AIBN			T (°C)	Conv (%)	t (h)	$M_{n_{SEC}}$ (g/mol)	Mn_{th} (g/mol)	*Đ*
1[a]	PAA	1/AA	307	1	0.3	60	33	4	18,540	16,900	1.7
2[b]	P(AA-*b*-BA)	PAA/BA	83.5	16.3	0.14	60	42	5	80,400	67,210	2.1
3[b]	P(S-*b*-AA-*b*-BA-*b*-S)	P(AA-*b*-BA)**/**S	81	19	0	120	32	2	97432	107,870	1.8
4	P*t*BA	2/*t*BA	217	1	0.9	65	24	4	19,670	7,380	2.0
5	P(*t*BA-*b*-S)	P*t*BA **/**S	83.3	16.2	0.01	65	39	8	30,800	37,480	1.8
6[c]	P(CIS-*b*-*t*BA-*b*-S-b-CIS)	P(*t*BA-*b*-S)CIS	80	20	0	120	55	2	47930	43,657	2.3

[a] Methanol 50% (w/w).
[b] DMF 50% (w/w).
[c] Toluene 50% (w/w).
[d] Molar ratio for entries 1 and 4.
[e] Weight ratio for entries 2,3,5 and 6.

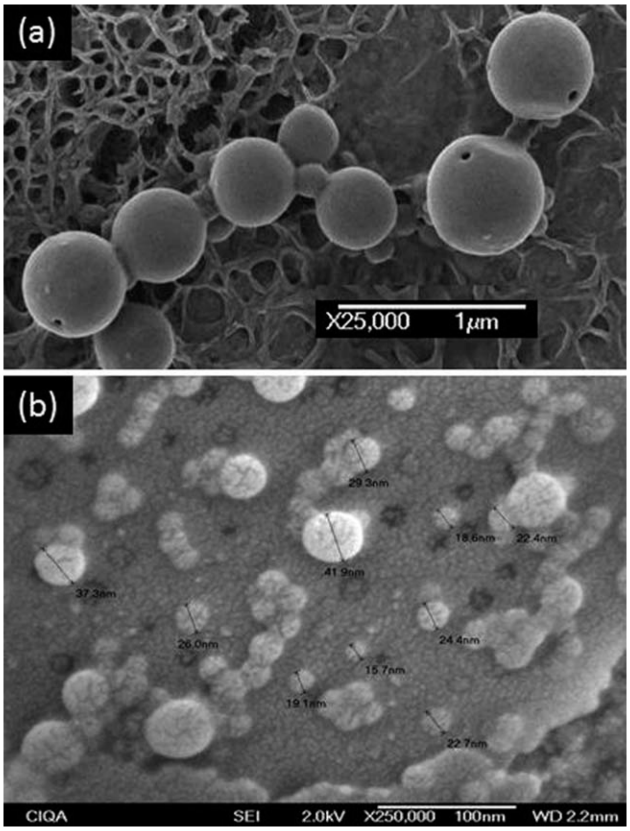


FIGURE 7 (a) SEM micrograph of self-assembled P(S-*b*-NIPAM-*b*-S) vesicles and (b) P(S-*b*-EOMA-*b*-S) micelles prepared by RAFT (central block) and NMP/RAFT polymerization (external blocks).

The accurate structure of block copolymers cannot be specified easily, but it is thought that the structure is probably a nonsymmetrical triblock because both the alkoxyamine and the dithiobenzoate groups can be activated simultaneously at 120°C producing propagation at different rates. The SEC traces of triblock copolymers are shown in Figure 8(a,b). It can be seen an entire shift in the chromatograms of the block copolymers to higher MW without ostensible formation of shoulders or tails.

The results for the synthesis of two diblock copolymers; P(AA-*b*-BA) and P(*t*BA-*b*-S) prepared by RAFT polymerization are summarized in Table 3. These AB copolymers exhibit a large dispersity due to the low chain transfer constant of **1** and **2**; however, the behavior in water of hydrolyzed materials suggests that the block copolymer structure has been formed. The extension of these diblock copolymers at 120 °C in the presence of styrene increases MW indicating the formation of CABC tetrablock copolymers.

The SEC traces in Figure 9(a,b) correspond to P(ClS-*b*-*t*BA-*b*-S-*b*-ClS) or P(S-*b*-AA-*b*-BA-*b*-S) and their corresponding precursors, respectively. It can be seen a shift to higher MW without the buildup of shoulders indicating the successful formation of CABC diblock copolymer. These examples show how the versatility of RAFT polymerization is enhanced by presence of the alkoxyamine group, which allows the extension with a further block afterward the preparation of a specific A or AB precursor.

Inifers **1** and **2** were initially intended to be used in the preparation of amphiphilic block copolymers (*in situ* formation of surfactants) in miniemulsion polymerization above 100°C. However, the results presented here show that such

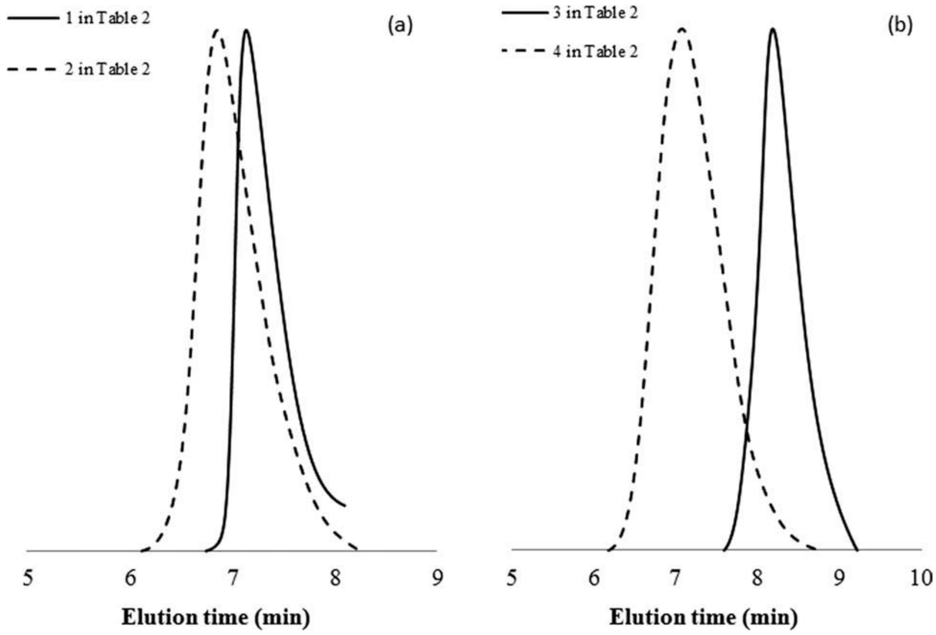


FIGURE 8 (a) SEC traces for the PEOMA (M_n = 38,140 g/mol; $Đ$ = 1.2) and its corresponding block copolymer P(S-*b*-EOMA-*b*-S) in dashed line (M_n = 63,820 g/mol; $Đ$ = 1.4); (b) SEC traces for the PNIPAM (M_n = 5480 g/mol; $Đ$ = 1.3) and its corresponding block copolymer P(S-*b*-NIPAM-*b*-S) in dashed line (M_n = 38,700 g/mol; $Đ$ = 1.8).

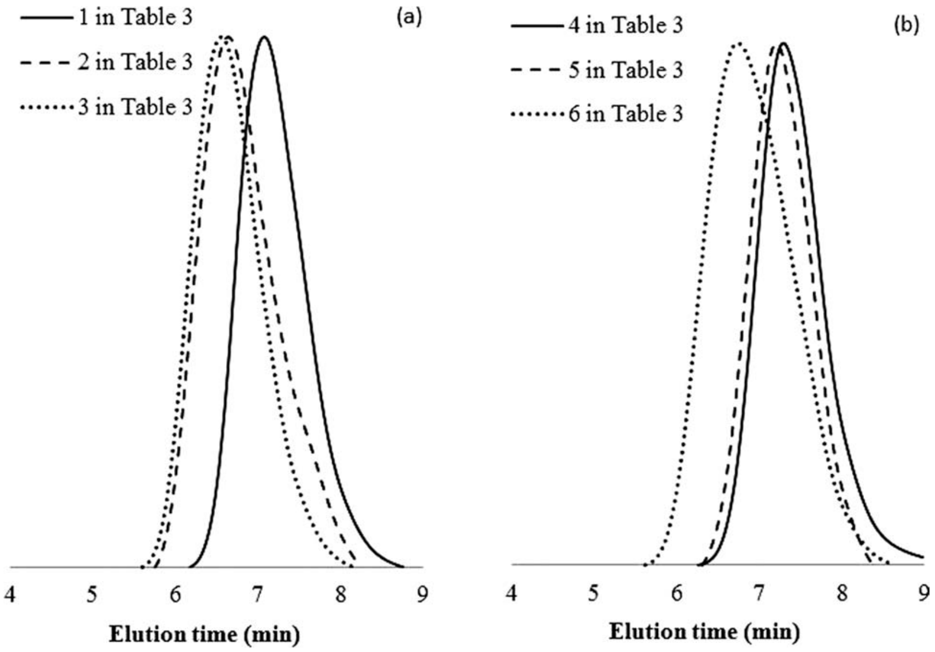


FIGURE 9 (a) SEC traces for polymers described in Entries 1–3 in Table 3 corresponding to the synthesis of P(ClS-*b*-*t*BA-*b*-S); (b) SEC traces for polymers described in Entries 4–6 in Table 3 corresponding to the synthesis of P(S-*b*-AA-*b*-BA).

compounds can be also used to prepare a wide range of new multiblock copolymers to form vesicles or micelles in a variety of sizes. For instance, it is quite appealing to create vesicles from water soluble block polymers and then form a cross-linked shell using surface initiated NMP. Our procedure is now being extended to other block copolymers that will be reported in due time. We also continue our efforts for developing advanced methods for the synthesis of new heterofunctional compounds for RDRP.

EXPERIMENTAL

Materials

Styrene (S) (99%) was distilled under sodium at low pressure, *N*-isopopylacrylamide (NIPAM) was recrystallized twice in hexane before use. BA and *t*BA were purified under vacuum pressure using calcium hydride as drying agent. AA was distilled under reduced pressure. AIBN (98%) was recrystallized from methanol and stored in a refrigerator before use. TEMPO (Aldrich, 99%) was sublimated before application.

All other reagents, carbon tetrachloride (99.8%, ACS Reagent), carbon disulfide, (anhydrous $\geq$ 99%), THF, (anhydrous, $\geq$ 99.9%, Inhibitor free), bromobenzene, (99%), magnesium powder, (-50 mesh, 99 + %), magnesium sulfate, (anhydrous Reagent Plus), iodine, (ACS Reagent Plus, $\geq$ 99% Chips), bromide, (99.99%), CD_3Cl, and solvents, were purchased from Aldrich and was used as received. The polyethylene oxide methacrylate (EOMA) and 4-chlorostyrene were used as received.

Analyses

NMR spectra were recorded on a Bruker instrument operating at 500 MHz in $CDCl_3$. Monomer conversions were determined gravimetrically from precipitated and dried samples. MW and $Đ$ were determined by SEC. The SEC analysis was conducted with a Hewlett-Packard instrument (HPLC series 1100) equipped with UV light and refractive index detectors using a series of three PL-Gel columns (10^3, 10^5, and 10^6 Å) in THF as eluent at 40°C and at a flow rate of 1 mL/min. The apparent MWs (M_n and M_w) and $Đ$ were determined with a calibration based on linear poly(methyl methacrylate) or PS standards. SEM images were obtained using a JEOL equipment JSM-7401F, Cold type of FE-SEM field emission scanning electron microscope. The sample preparation for SEM measurements was done using the following procedure. The plate (copper) was cleaned with acetone and then air-dried. The block copolymer solution in THF/H_2O with a concentration of 1–3 mg/mL was drop-cast onto the surface of the plate. It was then allowed to dry at room temperature. The surface of the films was coated with gold and palladium alloy layer before recording the SEM images.

MALDI-TOF-MS

MALDI-TOF-MS measurements were performed on a Shimadzu Biotech AXIMA Performance equipped with a 337 nm nitrogen laser. Positive ion spectra were acquired in linear mode and 20 kV acceleration voltage. The mass scale was calibrated with Bradykinin (mass: 757.3997), P14R (mass: 1533.8582), and ACTH (mass: 2465.1989) with alpha-cyano-4-hydroxy-cinnamic acid. Samples were prepared from THF solution by mixing matrix (Dithranol [Fluka, >99% purity] 10 mg/mL), sodium trifluoroacetate (10 mg/mL) and sample (10 mg/mL) in a ratio 10:80:10. One microliter of the mixture was spotted on the Maldi plate. The spectrum shown in this article represents the original data without any filtering or background abstraction.

TGA measurements were performed on a computer controlled TGA model Q500 (TA Instruments). The sample was kept at a constant 25°C under a dry nitrogen atmosphere (40 mL/min) and then the same specimen was heated from ambient to 600°C at a rate of 10°C/min and from 600 to 800°C in oxygen atmosphere at a rate of 20°C/min.

ESR Measurements

The ESR spectra were recorded by an X-band Bruker EleXsys instrument using 100 kHz modulation frequency and 0.1 G modulation width. The applied microwave power was 1 mW, the scan time was 20.97 s, the number of points in the spectra was 1024, and the delay time between scans was 240 s. In the kinetical recording, the number of spectra was 36–48 for 2.5–3.5 h at temperature 120°C. The spectra were simulated by an automatic fitting program.[20] ESR parameters for low concentration $g = 2.0057$, AN = 15.41 G, width = 0.55 G. When the concentration was higher, broader lines (width = 1.5 G) were obtained and the nitrogen coupling was increased (AN = 15.25 G).

Synthesis of 2-(4-Chlorophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)ethyldithio benzoate (1)

The formation of chain transfer agents **1** was performed in two steps. First, TEMPO (1,6 g, 10.24 mmol) in 6 mL of CCl_4 was treated with bromide (0.81 g, 10.18 mmol) under magnetic stirring to form the oxoaminium bromide, a brown colored solid, that precipitates soon after the contact between both reactants. After completion of bromide addition, the solution was kept under agitation for 30 min. Then, 4-chlorostyrene (7.62 g, 54.58 mmol) diluted with 6 mL of CCl_4 was added and the temperature was raised to 50°C for 30 min producing a gradual consumption of oxoaminium bromide. The crude product was washed with 50 mL of water, taken up in hexane (30 mL), dried with magnesium sulfate, filtrated and evaporated to obtain an oily reddish product. This product was purified on neutral alumina oxide column using hexane/dichloromethane (9/1) as eluent. A colorless liquid (yield 45%), identified as 1-(4-chlorophenyl)etoxy)-2,2,6,6-tetramethylpiperidine (**1′**) or Br(4-chlorostyrene)-TEMPO adduct was obtained. The same procedure was repeated with styrene to obtain 1-(2-bromo-1-phenylethoxy)-2,2,6,6-tetramethylpiperidine (**2′**).

In a second step, an ice-bathed Grignard solution prepared from bromobenzene (0.93 g, 5.9 mmol) and magnesium powder (0.14 g, 5.9 mmol) in 5 mL of THF was vigorously stirred for 1 h, whereas a solution of carbon disulfide (0.45 g, 5.9mmol) in 5 mL of dry THF was dropped into the vessel under argon. The resulting dark red mixture was warmed at 50°C for 1 h before cooled to room temperature. A solution of **1′** (2 g, 59 mmol) in 10 mL of THF was then added while raising temperature at 50°C and maintaining it for 4 h. The crude product was treated with 50 mL of 10% aqueous solution of ammonium chloride and extracted in hexane (30 mL). The organic layer was dried on $MgSO_4$ and collected after rotary evaporation of solvent. This red oil product was purified twice by column chromatography using neutral aluminum oxide as stationary phase and hexane/ethyl acetate (9/1) as eluent. **1** was formed in a yield of 21% and with more than 96% purity (from ^{1}H NMR). The same procedure was repeated with **2′**.

1. ^{1}H NMR ($CDCl_3$, δ, ppm) 0.76–1.27 (m, 12H CH_3—CN), 1.31–1.72 (m, 6h CH_2—C(CH_3)—N), 3.74 (dd, 1H, CH_2—S, $J = 5$, $J = 8$, $J = 13$ Hz), 4.16 (dd, 1H CH_2—S, $J = 5$, $J = 8$, $J = 13$ Hz), 5.09 (dd, 1H CH—O, $J = 5$, $J = 8$ Hz), 7.31–7.62 (m, 7H Ph-*H*,), 7.88 (d, 2H,CH=C—CS, $J = 8$ Hz). ^{13}C NMR (65 MHz, $CDCl_3$): δ: 17.5–32.4 (C—$\underline{CH_2}$), δ: 18.7 (C—$\underline{CH_3}$), δ: 44.7 ($\underline{C}$—S—C=S), δ: 83.2 ($\underline{C}$—O—N), δ: 122.43 (C-Ph), δ: 135.2 ($\underline{C}$—Cl), δ: 141.60 ($\underline{C}$—C—O—N), δ: 147.2 ($\underline{C}$—C=S), δ: 226.7 (S—$\underline{C}$=S), GC-MS: m/z 448 (M+, 1%) 156 ($C_9H_{18}NO$, 45%), 138 (C_8H_7Cl, 40%), 105 (C_8H_7, 10%), 77 (C_6H_5, 25%).
2. ^{1}H NMR ($CDCl_3$, δ, ppm) 0.713–1.10 (m, 12H $\underline{CH_3}$—CN), 1.21–1.622 (m, 6h $\underline{CH_2}$—C(CH_3) —N), 3.78 (dd, 1H, $\underline{CH_2}$-S, $J = 5$, $J = 8$ Hz), 4.17 (dd, 1H $\underline{CH_2}$-S, $J = 5$, $J = 8$ Hz), 5.12 (dd, 1H $\underline{CH}$—O, $J = 3$, $J = 5$ Hz), 7.25–7.50 (m, 8H Ph-$\underline{H}$,), 7.865 (d, 2H,$\underline{CH}$=C—CS, $J = 9$ Hz). ^{13}C NMR (65 MHz, $CDCl_3$) δ: 17.5–32.4 (C—$\underline{CH_2}$); δ: 20.2 (C—$\underline{CH_3}$); δ: 44.7 ($\underline{C}$—S—C=S); δ: 83.6 ($\underline{C}$—O—N); δ: 122.43 (C-Ph); δ: 141.60 ($\underline{C}$—C—O—N); δ: 146 ($\underline{C}$—C=S); δ: 226.7 (S—$\underline{C}$=S). GC-MS: m/z 413 (M+, 1%), 156 ($C_9H_{18}NO$, 5%) 246 ($C_{16}H_{24}NO$, 20%), 105 (C_8H_7, 100%), 77 (C_6H_5, 35%).

General Procedure for the RAFT Polymerization of Styrene

Bulk styrene RAFT polymerization was performed at two distinct molar ratios: [*S*]/[1]/[AIBN] = 150/1/0.5 and 650/1/1. In typical experiment, a series of heavy-wall glass tubes were filled with the monomer solution degassed by three freeze–pump–thaw cycles and sealed. Then, tubes were heated at 60°C in thermostated oil bath and removed at predetermined times. All polymer samples were isolated by precipitation and characterized by SEC. Results are summarized in Supporting Information, Table S1 for the experiment performed with a molar ratio [*S*]/[inifer]/[AIBN] = 650/1/1 (see also Supporting Information, Table S2, for the experiment performed with a molar ratio [S]/[1]/[AIBN] = 150/1/0.5).

General Procedure for NMP of Styrene

To perform NMP experiments, the temperature and molar ratio were set at 120°C and S/**1** = 200/1, respectively. A solution containing 0.147 g of **1**, (0.356 mmol) and 7.42 g (71.3 mmol) of styrene was divided and placed in several ignition heavy-wall glass tubes. After degassing and sealing, tubes were immersed in the thermostated oil bath and removed at different time interval. SEC was used to determine MW and *Đ*. A similar procedure was performed with inifer **2**. Results are summarized in Supporting Information, Table S3.

Chain Extension

RAFT First Approach

In a heavy-wall glass tube were placed 4.32 g, (85 mmol) of styrene, 0.127 g(0.58 mmol) of **1** and 0.046 g (0.58 mmol) of AIBN. This mixture was degassed by three freeze–thaw pump cycles and then the tube was sealed and immersed in a thermostated oil bath for 8 h at 60°C. The polymer was isolated by precipitation in methanol and characterized by

SEC (M_n = 12,960 g/mol, $Đ$ = 1.8). 0.222 g, (0.017 mmol) of this polymer was placed into a heavy-wall glass tube and dissolved with 1.16 g (11 mmol) of styrene and 1.16 g of toluene. The mixture was degassed, sealed and heated for 3 h at 120°C. The polymer was isolated by precipitation in methanol and characterized by SEC (M_n = 26,330 g/mol, $Đ$ = 1.3). See Entry PS_2 in Supporting Information, Table S4.

NMP First Approach

The polymer prepared by NMP with **1** described in Entry 12 in Supporting Information, Table S3 (M_n = 10,630 g/mol and $Đ$ = 1.5) was retaken for this experiment. Thus, 0.105 g (0.0098 mmol) of this polymer was placed into a heavy-wall tube and mixed with 0.23 g (2.2 mmol) of styrene and 0.0017 g (0.0010 mmol) of AIBN. This mixture was degassed by three freeze–thaw pump cycles and the tube was sealed. The tube was immersed in a thermostated oil bath for 8 h at 60°C. The polymer was isolated by precipitation in methanol and characterized by SEC (M_n = 12,240 g/mol, $Đ$ = 1.8). See Entry 4, Supporting Information, Table S4 for detailed information. The same polymer was retaken (0.1356 g, 0.0127 mmol) in 0.905 g (8 mmol) of styrene in a heavy-wall glass tube. The tube was sealed after three freeze–thaw pump cycles and placed in an oil bath thermostated at 120°C for 2 h. After precipitation in methanol, MW was calculated by SEC (M_n = 27,150 g/mol and $Đ$ = 1.3). More detailed information is provided in the Supporting Information Section; see Entry PS_5, Table S4.

General Procedure for the Synthesis of Block Copolymers

Type BAB

The synthesis of BAB block copolymers was performed in two steps. First, a RAFT polymerization a monomer A was carried out followed by a tandem polymerization of a monomer B at 120°C as illustrated in the following example. For the synthesis of P(S-*b*-EOMA-*b*-S), 3.75 g (11.7 mmol) of EOMA (M_W = 321.43 g/mol) were mixed with 0.0595 g (0.132 mmol) of **1**, 0.0073 g (0.044 mmol) of AIBN, and 3.2 g of methanol and transferred in heavy-wall glass tube. The mixture was degassed by three freeze–thaw pump cycles and then sealed under vacuum. The tube was immersed in oil bath thermostated at 60°C for 3 h. The PEOMA obtained was dissolved in methanol and precipitate in petroleum ether. A reddish product was obtained with a yield of 74%. This isolated polymer was retaken (0.359 g, 0.00094 mmol) in a heavy-wall glass tube with 1.702 g (16 mmol) of S and 1.5 g of DMF. The mixture was degassed by freezing–pump–thaw three cycles and sealed. The tube was heated at 120°C for 5 h in a thermostated oil bath. The product was dissolved in THF and precipitated in a mixture methanol–water (yield 44%). The P(S-*b*-NIPAM-*b*-S) was prepared following the same procedure using NIPAM as monomer A and styrene as monomer B. Both BAB copolymers were characterized by SEC (Fig. 8) and results are described in Table 2.

Type CABC

The synthesis of CABC block copolymers involves the preparation of a diblock copolymer with monomer A and B entirely by RAFT polymerization followed by the chain extension with styrene using NMP/RAFT tandem polymerization. The P(S-*b*-AA-*b*-BA-*b*-S) was prepared as follows. In a heavy-wall glass tube were placed 2.03 g (28.2 mmol) of AA, 0.0411 g (0.092 mmol) of **1,** and 0.0054 g (0.033 mmol) of AIBN along with 1.98 g of methanol as dissolvent. The tube was degassed by three freeze–thaw pump cycles then sealed and heated in oil bath thermostated at 60°C for 3 h. After polymerization, the PAA was diluted in methanol and precipitate in petroleum ether to obtain a reddish product (yield 33%). This purified polymer (0.208 g, 0.01 mmol) was placed into a heavy-wall glass tube along with 1.06 g (8.3 mmol) of BA, 0.0019 g (0.01 mmol) of AIBN, and 0.99 g of DMF as solvent. The tube was degassed by three freeze–thaw pump cycles and sealed. The tube was then heated at 60°C for 5 h in a thermostated oil bath. The polymer was isolated by precipitation and characterized. The P(AA-*b*-BA) (0.32 g, 0.0059 mmol) was retaken with 1.33 g (13 mmol) of distilled S and 1.1 g of DMF in heavy-wall glass tube. The tube was degassed using the standard technique, sealed and heated at 120°C for 2 h. Quantitative methylation of the polyacrylic acid block was achieved using trimethylsilyldiazomethane[21] before SEC characterization. The same procedure was used to prepare P(ClS-*b*-*t*BA-*b*-S-*b*-ClS) by the intermediation of a diblock copolymer prepared by RAFT polymerization from *tert*-butylacrylate and styrene and then chain extended with 4-chlorostyrene (ClS) by NMP/RAFT tandem polymerization. A summary of experimental conditions and results is presented in the Table 3.

CONCLUSIONS

Inifers **1** and **2** were synthesized and used as RAFT or NMP agents in the polymerization of styrene. Both compounds were able to control the RAFT polymerization of styrene at conversions up to 71% and MWs up to 56,000 g/mol (vs. PS standards). Samples exhibit narrow molar mass distributions ($Đ$ = 1.3) at low conversion but the control is progressively loosed with conversion. Both inifers allow better control in the combined NMP/RAFT polymerization ($Đ$ = 1.2–1.5) but, as expected, polystyrenes prepared with **1** or **2** reveals large discrepancy between the theoretical and calculated MWs due to possible side reactions, likely the ineludible radical–radical termination of difunctional propagating species. NIPAM, butylacrylate, EOMA, and so forth were used to prepare homopolymers and block copolymers. The preparation of some multiblock copolymers was also achieved.

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