

Ambient temperature transition metal-free
dissociative electron transfer reversible addition-
fragmentation chain transfer polymerization (DET-
RAFT) of methacrylates, acrylates and styrene

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Abstract

Inorganic sulfites as reducing agents were successfully used in combination with typical reversible addition-fragmentation chain transfer (RAFT) agents, for the controlled DET-RAFT (DET: dissociative electron transfer) of methacrylates, methyl acrylate (MA) and styrene (Sty) near room temperature (30 °C). The polymerizations were first-order in respect to monomer conversion and polymers with narrow molecular weight distributions ($\bar{D} < 1.2$) and “living” features were obtained. MALDI-TOF experiments demonstrate the integrity of the chain ends and clearly show the absence of SO₂ in the polymer chains. Kinetic studies revealed that an increase of either temperature or concentration of sulfites provided faster reactions, without loss of control. *Ab initio* quantum chemistry calculations suggested that in the presence of the reducing agent, the RAFT agent undergoes one electron reduction to a stable radical anion that can then undergo fragmentation to yield the initiating carbon-centered radical. The new metal-free DET-RAFT developed proved to be versatile and robust, as it could be also used for the polymerization of different relevant monomers, such as glycidyl methacrylate (GMA), 2-(diisopropylamino)ethyl methacrylate (DPA) and 2-(dimethylamino)ethyl methacrylate (DMAEMA).

Introduction

Reversible deactivation radical polymerization (RDRP) methods have gained increasing attention by many research groups, in both academia and industry, as they allow the synthesis of polymers with predetermined molecular weights, low dispersity (\mathcal{D}), well-defined architectures (*e.g.*, block and graft copolymers) and with a high percentage of active chain-end functionality, which could not be achieved via conventional free radical polymerization.¹⁻⁴ RDRP methods can be used for the polymerization of a wide range of vinyl monomers under different reaction conditions and even in the presence of some impurities.^{4,5} The different RDRP techniques rely on the same principle, which is based on a reversible equilibrium between dormant and active (propagating radicals) chains.^{1-3,6} Reversible addition-fragmentation chain transfer (RAFT) is one of the most studied RDRP techniques and it is based on a degenerative chain transfer process.^{1,7} In RAFT (Scheme 1), a conventional initiator is used to generate the initial chains ($P_n\bullet$), which are rapidly trapped in an equilibrium with a RAFT agent, typically a thiocarbonylthio ($R-S-(C=S)-Z$) compound.^{1,7,8} The polymer chains become dormant while, at the same time, a leaving group ($R\bullet$) is released by the RAFT agent, and in turn adds to monomer leading to a new propagating radical. These new chains ($P_m\bullet$) can then propagate before being transferred back to the RAFT agent (dormant chain). The main addition-fragmentation equilibrium between dormant and propagating chains is then established and mediated by the RAFT agent moieties.⁸

of the fact that RDRP methods have some degree of interchangeability (i.e., one can switch from one method to another, or use two methods simultaneously), by combining a single electron transfer living radical polymerization (SET-LRP)¹⁴ initiation system with the RAFT control mechanism provided by the RAFT agent.^{11, 12} In opposition to RAFT, in the SET-LRP the activation of dormant species is achieved by single electron transfer, usually in the presence of a Cu(0)/ligand catalytic complex.¹⁵ Other transition metal-based catalysts have been used in SET-RAFT processes. For instance, Boyer's research group reported a similar SET-RAFT process using some iridium/ruthenium-based transition metal catalysts,¹⁶⁻¹⁸ which operated under photochemical activation with visible light. These approaches can serve as low temperature replacements for conventional thermal initiators used in RAFT, in the new SET-RAFT. However, it is still unclear which process dictates the control during propagation, as it may be either SET-LRP or RAFT or even a combination of both.¹² Nevertheless metal-catalyzed SET-RAFT has proven to be a very versatile technique and has been successfully used to polymerize styrene (Sty),¹¹ methyl methacrylate (MMA),^{12, 15} glycidyl methacrylate (GMA),¹⁹ cyclohexyl methacrylate (CHMA)²⁰ and *N*-vinylcarbazole²¹ (NVK) at room temperature giving polymers with low \bar{D} values.

Recently, while this work was on progress, a tertiary amine catalyzed ambient temperature SET-RAFT process was reported²² for the polymerization of MMA under UV irradiation (photo-induced process). In this work, the authors proposed tertiary amine-catalyzed photo-induced decomposition of RAFT agents under dissociative electron transfer conditions (DET). To date, no detailed mechanistic studies have been reported for either tertiary amine or transition metal catalyzed processes.

Although the metal-catalyzed SET-LRP process makes room temperature feasible in the SET-RAFT, it is highly desirable to keep the concentration of metal species as low as possible or even

avoid their use, since copper and many other transition metals are known to be toxic.^{2, 23, 24} The use of metal catalysts can potentially hinder the application of the SET-RAFT in the biomedical field or even increase the cost of production since the techniques used to purify the polymers are usually quite expensive.^{24, 25} Moreover, the visible or UV light-induced photochemical redox systems using tertiary amine or transition metal catalysts might be not suitable from the practical point of view, for example when scaling up the SET-RAFT process.

Our research group has demonstrated that inorganic sulfites, such sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$) can replace Cu(0) as an activator in the supplemental activator and reducing agent atom transfer radical polymerization (SARA ATRP).^{23, 26-28} Inorganic sulfites are extensively used as reducing agents in the food, beverage, paper and chemical industries, and are relatively inexpensive, safe and approved by the US Food and Drug Administration (FDA).²⁶

In this work we present a transition metal-free SET-RAFT system in which sodium sulfites were used as a replacement for the conventional catalytic systems currently employed in SET-RAFT polymerizations, to afford well-defined polymers. Three common sodium sulfites were tested (sodium dithionite, $\text{Na}_2\text{S}_2\text{O}_4$; sodium metabisulfite, $\text{Na}_2\text{S}_2\text{O}_5$ and sodium bisulfite, NaHSO_3) and different monomers families and reaction conditions were investigated, in order to assess the robustness and versatility of this new system. The mechanism of this new process is believed to involve dissociative electron transfer of the RAFT agent (formation of a stable radical anion from the RAFT agent and its fragmentation into di (or tri)thiocarboxylic acid anion, initiating free radicals. In order to distinguish this process from the metal-catalyzed SET-RAFT process, we have named this new process as dissociative electron transfer RAFT (DET-RAFT).

Experimental Section

Materials

2-(Diisopropylamino)ethyl methacrylate (DPA, Aldrich, 97 % stabilized), 2-(dimethylamino)ethyl methacrylate (DMAEMA, Aldrich, 98 % stabilized), glycidyl methacrylate (GMA, Sigma Aldrich, 97 % stabilized), methyl acrylate (MA, Acros, 99 % stabilized), methyl methacrylate (MMA, Sigma Aldrich, 99 % stabilized) and styrene (Sty, Sigma Aldrich, + 99 % stabilized) were passed through a sand/alumina column before use in order to remove the radical inhibitor.

4-Cyano-4-(phenylcarbonothioylthio) pentanoic acid (CTP, Sigma-Aldrich, > 97 %), cyclopentyl methyl ether (CPME, Sigma-Aldrich, inhibitor-free, anhydrous, +99.9 %), deuterated chloroform (CDCl_3) (Euriso-top, +1% TMS), dimethylformamide (DMF, Sigma-Aldrich, +99.8 %), 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid (DDMAT, Sigma-Aldrich, 98 %), ethanol (EtOH, Panreac, 99.5 %), isopropyl alcohol (IPA, Fisher Chemical), PS standards (Polymer Laboratories), sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$, 85 %, technical grade; Aldrich), sodium bisulfite (NaHSO_3 , Sigma-Aldrich, > 99 %), sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$, Sigma-Aldrich, > 99 %), and sulfolane (Acros, +99 %) were used as received.

Dimethyl sulfoxide (DMSO, Acros, 99.8+% extra pure) was treated with calcium hydride and distilled before use.

Purified water (Milli-Q®, Millipore, resistivity >18 M Ω .cm) was obtained by reverse osmosis.

Tetrahydrofuran (THF, Sigma, HPLC grade) and DMF (Sigma, HPLC grade) were filtered under reduced pressure before use.

Techniques

The chromatographic parameters of PMA, PMMA and PS were determined using a size exclusion chromatography (SEC) set-up from Viscotek (Viscotek TDMax) equipped with a differential viscometer (DV) and right-angle laser-light scattering (RALLS, Viscotek), low-angle laser-light scattering (LALLS, Viscotek) and refractive index (RI) detectors. The column set consisted of a PL 10 mm guard column ($50 \times 7.5 \text{ mm}^2$) followed by one Viscotek Tguard column ($8 \mu\text{m}$), one Viscotek T2000 column ($6 \mu\text{m}$), one Viscotek T3000 column ($6 \mu\text{m}$) and one Viscotek LT4000L column ($7 \mu\text{m}$). A dual piston pump was set with a flow rate of 1 mL/min. The eluent (THF) was previously filtered through a $0.2 \mu\text{m}$ filter. The system was also equipped with an on-line degasser. The tests were performed at 30°C using an Elder CH-150 heater. Before the injection ($100 \mu\text{L}$), the samples were filtered through a polytetrafluoroethylene (PTFE) membrane with $0.2 \mu\text{m}$ pore. The system was calibrated with narrow polystyrene (PS) standards. The dn/dc value was determined as 0.063 for PMA, 0.068 for PMMA and 0.185 for PS. Molecular weight (M_n^{SEC}) and dispersity ($\mathcal{D} = M_w/M_n$) of the synthesized polymers were determined by multidetector calibration using the OmniSEC software version: 4.6.1.354.

The chromatographic parameters of PGMA samples were determined by SEC, with refractive index (RI) (Knauer K-2301) detection. The column set consisted of a PL 10- μL guard column ($50 \times 7.5 \text{ mm}^2$), followed by two MIXED-B PL gel columns ($300 \times 7.5 \text{ mm}^2$, $10 \mu\text{L}$). The HPLC pump was set with a flow rate of 1 mL/min and the analyses were carried out at 60°C using an Elder CH-150 heater. The eluent was DMF, containing 0.3 % of LiBr. Before injection ($100 \mu\text{L}$), the samples were filtered through a PTFE membrane with $0.2 \mu\text{m}$ pore size. The system was calibrated with PMMA standards. The dn/dc value was determined as 0.087 for PGMA. Molecular weight (M_n^{SEC}) and dispersity ($\mathcal{D} = M_w/M_n$) of synthesized the polymers were determined by multidetectors calibration using the OmniSEC software version: 4.6.1.354.

The chromatographic parameters of PDPA and PDMAEMA samples were determined by a SEC system equipped with an online degasser, a refractive index (RI) detector and a set of columns: Shodex OHpak SB-G guard column, OHpak SB-804HQ and OHpak SB-804HQ columns. The polymers were eluted at a flow rate of 0.5 mL/min with 0.1 M Na₂SO₄ (aq)/1 wt % acetic acid/0.02 % NaN₃ at 40 °C. Before the injection (50 μ L), the samples were filtered through a PTFE membrane with 0.45 μ m pore. The system was calibrated with five narrow poly(ethylene glycol) (PEG) standards and the polymers molecular weights (M_n^{SEC}) and \bar{D} (M_w/M_n) were determined by conventional calibration using the Clarity software version 2.8.2.648.

400 MHz ¹H NMR spectra of reaction mixture samples were recorded on a Bruker Avance III 400 MHz spectrometer, with a 5-mm TIX triple resonance detection probe, in CDCl₃ with tetramethylsilane (TMS) as an internal standard. Conversions of the monomer were determined by integration of monomer and polymer peaks using MestRenova software version: 6.0.2-5475.

For matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF-MS) analysis, the PMA samples were dissolved in THF at a concentration of 10 mg·mL⁻¹ and 2-(4'-Hydroxybenzeneazo)benzoic acid (HABA) (20 mg·mL⁻¹ in THF) was used as a matrix and ionization agent. 10 μ L of the PMA solution was mixed with 10 μ L of the HABA solution in a 1 mL Eppendorf tube. The dried-droplet sample preparation technique was used; 2 μ L of the mixture was directly spotted on the MTP TF MALDI target, Bruker Daltonik (Bremen, Germany) and allowed to dry at room temperature, to allow matrix crystallization. The analysis was done in triplicate for each sample. External mass calibration was performed with a peptide calibration standard (Bruker Starter Kit) for 250 mass calibration points. Mass spectra were recorded using an Ultraflex III TOF/TOF MALDI-TOF mass spectrometer Bruker Daltonik (Bremen, Germany) operating in the linear positive ion mode, working under flexControl software (version 3.4, Bruker

Daltonik, Bremen, Germany). Ions were formed upon irradiation by a smart beam laser using a frequency of 200 Hz. Each mass spectrum was produced by averaging 2000 laser shots collected across the whole sample spot surface by screening in the range m/z 5-20 kDa. The laser irradiance was set to 50 % (relative scale 0-100) arbitrary units according to the corresponding threshold required for the applied matrix systems. Data analysis was done with flexAnalysis software (version 3.4, Bruker Daltonik, Bremen, Germany).

Procedures

Typical procedure for the DET-RAFT polymerization of MMA in DMSO at 30 °C with $[MMA]_0/[CTP]_0/[Na_2S_2O_4]_0 = 222/1/1$

The monomer (MMA) was purified in a sand/alumina column just before reaction. A mixture of MMA (4 mL, 37.6 mmol), CTP (48.7 mg, 0.169 mmol) and DMSO (2 mL previously bubbled with nitrogen for about 15 min) was placed in a Schlenk tube reactor. Next, $Na_2S_2O_4$ (33.9 mg, 0.169 mmol) was added to the reactor, which was sealed and frozen in liquid nitrogen. The Schlenk tube reactor containing the reaction mixture was deoxygenated with four freeze-vacuum-thaw cycles and purged with nitrogen. The Schlenk tube reactor was placed in a water bath at 30 °C with stirring (700 rpm). Different reaction mixture samples were collected during the polymerization by using an airtight syringe and purging the side arm of the Schlenk tube reactor with nitrogen. The samples were analyzed by 1H NMR spectroscopy in order to determine the monomer conversion and by SEC, to determine molecular weight and \bar{D} of the PMMA. The DET-RAFT of other monomers was done following the same procedure described above, just changing the reaction conditions.

Typical chain extension of a macro-RAFT PMA

A macro-RAFT PMA obtained at 50 % monomer conversion by a typical DET-RAFT reaction was precipitated in water. The polymer was then dissolved in THF and precipitated again in cold methanol. The polymer was dried under vacuum until constant weight. The MA (1.5 mL, 16.7 mmol) was purified in a sand/alumina column just before reaction and then added to the macro-RAFT PMA (118 mg, 0.014 mmol, $M_n^{SEC} = 8.5 \times 10^3$; $\bar{D} = 1.03$) in the Schlenk tube reactor. Sulfolane (3.0 mL previously bubbled with nitrogen for about 15 min) was added to the mixture (monomer/macro-RAFT PMA) in order to dissolve the macro-RAFT PMA. Next, $\text{Na}_2\text{S}_2\text{O}_4$ (11.1 mg, 0.056 mmol) was added to the reactor, which was sealed and frozen in liquid nitrogen. The Schlenk tube was deoxygenated with four freeze-pump thaw cycles and purged with nitrogen. The Schlenk tube reactor was placed in a water bath at 30 °C with stirring (700 rpm). The reaction was stopped after 70 h (monomer conversion = 96 %) and the mixture was analyzed by SEC.

Typical synthesis of a PMA-*b*-PS block copolymer

A macro-RAFT PMA obtained at 77 % monomer conversion by a typical DET-RAFT reaction was precipitated in water. The polymer was then dissolved in THF and precipitated again in cold methanol. The polymer was dried under vacuum until constant weight. The Sty (2.0 mL, 17.4 mmol) was purified in a sand/alumina column just before reaction and then added to the macro-RAFT PMA (393 mg, 0.025 mmol, $M_n^{SEC} = 15.8 \times 10^3$; $\bar{D} = 1.03$) in the Schlenk tube reactor. Sulfolane (1.0 mL previously bubbled with nitrogen for about 15 min) was added to the mixture (Sty/macro-RAFT PMA) in order to dissolve the macro-RAFT PMA. Next, $\text{Na}_2\text{S}_2\text{O}_4$ (5.0 mg, 0.025 mmol) was added to the reactor, which was sealed and frozen in liquid nitrogen. The Schlenk tube was deoxygenated with four freeze-pump thaw cycles and purged with nitrogen. The Schlenk tube reactor was placed in a water bath at 60 °C with stirring (700 rpm). The reaction was stopped

after 240 h (Sty conversion = 15%) and the mixture was analyzed by SEC. The PMA-*b*-PS block copolymer was precipitated in water, dissolved in THF and precipitated again in cold methanol. The structure of the pure PMA-*b*-PS was confirmed by ^1H NMR.

Results and discussion

Several inorganic sulfites have shown the ability to activate dormant polymer chains during the SARA ATRP of different monomer families.^{23, 26, 28} In this work, the use of these reducing agents in combination with 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (CTP, Figure 2) as the RAFT agent was investigated for the DET-RAFT of MMA as the model monomer. The results (Table 1) showed that it was possible to prepare well-defined PMMA ($\bar{D} < 1.2$), regardless of the inorganic sulfite used. Additionally, similarly to what was previously observed for a typical SARA ATRP reaction, the $\text{Na}_2\text{S}_2\text{O}_4$ afforded the fastest polymerization, whilst still retaining control.²⁶ Therefore, this reducing agent was selected to continue the study of this new metal-free DET-RAFT method developed.

Table 1. Molecular weight and dispersity of PMMA obtained by DET-RAFT in DMSO at 60 °C, using different reducing agents as the activator. Conditions: $[\text{reducing agent}]_0/[\text{CTP}]_0/[\text{MMA}]_0 = 1/1/222$; $[\text{MMA}]_0/[\text{DMSO}] = 2/1$ (v/v).

Entry	Reducing agent	Time (h)	Conv. (%)	$M_n^{\text{SEC}} \times 10^{-3}$	\bar{D}
1	$\text{Na}_2\text{S}_2\text{O}_4$	23	54	20.0	1.08
2	$\text{Na}_2\text{S}_2\text{O}_5$	48	11	7.9	1.18
3	NaHSO_3	48	20	10.0	1.17

In order to understand the influence of the reducing agent in the polymerization features, different ratios $[\text{Na}_2\text{S}_2\text{O}_4]_0/[\text{CTP}]_0$ were investigated (Table 2 and Figure 1). As expected, the polymerization rate increased with the $\text{Na}_2\text{S}_2\text{O}_4$ concentration (Figure 1 (a) and Figure SF1 (a)), due to the faster activation of dormant chains. However, for the lowest concentration of $\text{Na}_2\text{S}_2\text{O}_4$ studied, the polymerization stopped at relatively low monomer conversion (40 - 60 %, black symbols in Figure 1 (a) and Figure SF1 (a)), probably due to an insufficient generation of radicals to maintain the RAFT equilibrium. It was also noticed that a high ratio $[\text{Na}_2\text{S}_2\text{O}_4]_0/[\text{CTP}]_0$ lead to a more pronounced deviation of the experimental molecular weights from the theoretical ones (Figure 1 (b) and Figure S1 (b)), suggesting the existence of some side reactions. Nevertheless, all the polymerizations were well-controlled in the range of $\text{Na}_2\text{S}_2\text{O}_4$ concentration studied, with polymers dispersity decreasing during the reaction ($\bar{D} < 1.2$).

The increase of the reaction temperature from 30 °C to 80 °C afforded faster polymerizations, however with a slightly higher deviation of the molecular weights (Figure SF2), probably due to an increase in the occurrence of side reactions. In addition, it should be noted that the polymerization performed at 80 °C achieved only a limited monomer conversion (≈ 25 %). This is possibly due to the fast generation of radicals from the $\text{Na}_2\text{S}_2\text{O}_4$, at the mentioned temperature, which would lead to early termination reactions. However, the same behavior was observed when the concentration of $\text{Na}_2\text{S}_2\text{O}_4$ was decreased by half (see Figure SF3). Therefore, more research is needed in order to clarify the reasons behind this behavior. Most probably, $\text{Na}_2\text{S}_2\text{O}_4$ could be decomposing at 80 °C which would lead to an inefficient generation of radicals during the polymerization. It should be stressed that at ambient temperature these issues were avoided.

As expected, there was no polymerization when using just the RAFT agent with no reducing agent (Table 2, entry 7), due to the lack of radical generation. In a second control experiment,

MMA was polymerized just in the presence of $\text{Na}_2\text{S}_2\text{O}_4$ (Table 2, entry 8). In this case there was formation of polymer, however with very high dispersity ($\bar{D} \approx 2$), since there was no RAFT agent to control the polymerization. This behavior has also been previously observed for the SARA ATRP of MA in the presence of just $\text{Na}_2\text{S}_2\text{O}_4$ and it was attributed to the formation of radicals by the reducing agent (SO_2^\bullet).²⁶ While $\text{Na}_2\text{S}_2\text{O}_4$ is capable of acting as a thermal initiator as shown in Table 2 (entry 8), this process is very slow (MMA conversion = 8% after 72h). Therefore, in the presence of RAFT agent at ambient temperature the direct initiation can be considered negligible, as confirmed by lack of SO_2 in the polymer chains (see Figure 6).

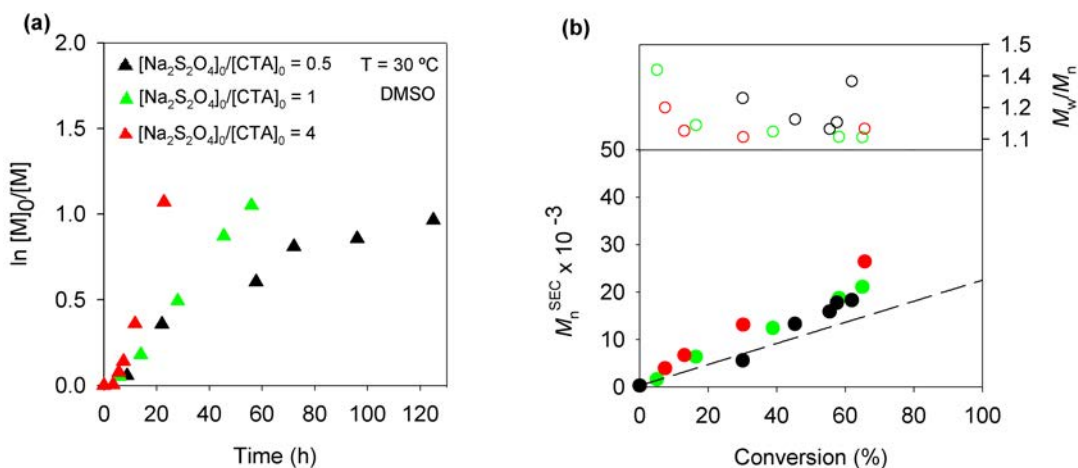


Figure 1. (a) Kinetic plots of $\ln[M]_0/[M]$ vs. time and (b) plot of the number-average molecular weights (M_n^{SEC}) and \bar{D} (M_w/M_n) vs. monomer conversion (the dashed line represents theoretical molecular weight at a given conversion) for the DET-RAFT of MMA at 30 °C in DMSO using different $[\text{Na}_2\text{S}_2\text{O}_4]_0/[\text{CTP}]_0$ ratios. Reaction conditions: $[\text{MMA}]_0/[\text{DMSO}] = 2/1$ (v/v); $[\text{CTP}]_0/[\text{MMA}]_0 = 1/222$.

Table 2. Kinetic data for the DET-RAFT of MMA in DMSO at 30 °C or 60 °C, using different $[\text{Na}_2\text{S}_2\text{O}_4]_0/[\text{CTP}]_0$ ratios. Conditions: $[\text{MMA}]_0/[\text{DMSO}] = 2/1$ (v/v); $[\text{CTP}]_0/[\text{MMA}]_0 = 1/222$.

Entry	$[\text{Na}_2\text{S}_2\text{O}_4]_0/[\text{RAFT agent}]_0$	T (°C)	k_p^{app} (h^{-1})	Time (h)	Conv. (%)	$M_n^{\text{SEC}} \times 10^{-3}$	\bar{D}
1	1/1	30	0.018	28	39	12.4	1.09
2	1/1	60	0.037	23	54	20.0	1.08
3	4/1	30	0.056	23	66	26.4	1.10
4	4/1	60	0.072	22	58	36.1	1.13
5	0.5/1	30	0.012	58	45	13.3	1.14
6	0.5/1	60	0.014	48	36	15.9	1.12
7 ^a	0/1	30	-	72	0	-	-
8 ^b	1/0	30	-	72	6	4.5	2.51

^a Control experiment without reducing agent; ^b Control experiment without RAFT agent.

The potential of the metal-free DET-RAFT method was explored through the polymerization of different relevant monomers (Table 3 and Figure 2). Both Sty and MA have a wide range of applications and are commonly investigated as model monomers for different RDRP systems.^{22, 25, 29, 30} GMA is particularly attractive since it possesses an epoxy ring which can be easily opened, affording different ways to functionalize the polymer and produce PGMA-based materials with distinct properties.¹⁹ Finally, both DPA and DMAEMA are functional monomers exhibiting a pH-responsive behavior and have been extensively studied for biomedical applications (*e.g.*, gene delivery).^{31, 32}

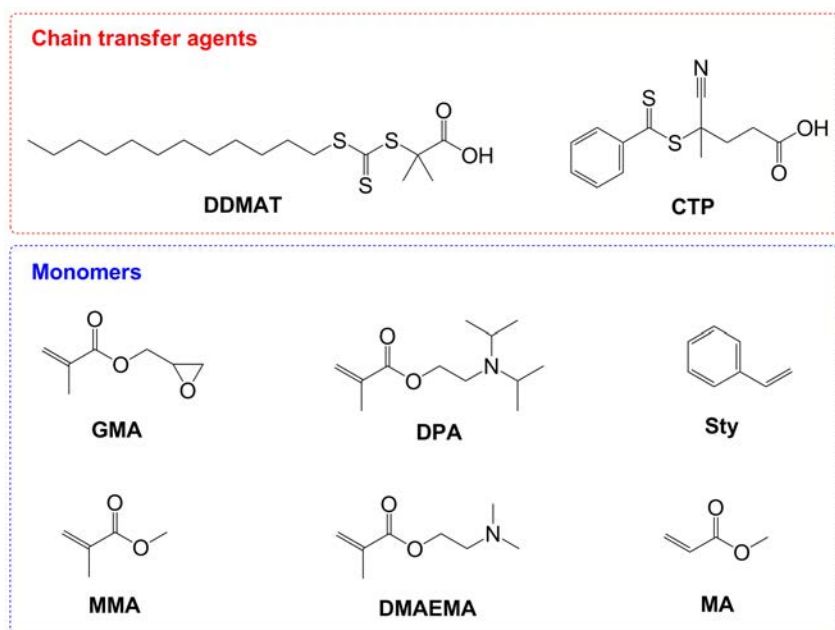


Figure 2. Chemical structure of the monomers and RAFT agents investigated for the metal-free DET-RAFT.

The type of RAFT agent, solvent and temperature were adjusted according to the structure of each monomer.^{28,33-35} The results presented in Table 3 suggest that this new developed DET-RAFT method is very robust, since it afforded well-defined polymers ($\bar{D} \leq 1.3$) near room temperature (with the exception of PS, which was polymerized at 60 °C to afford a reasonable reaction rate, since the k_p of PS is very low³⁶) for different monomer families (and different RAFT agents).

Table 3. Molecular weight parameters of different polymers prepared by DET-RAFT. Conditions: $[\text{monomer}]_0/[\text{RAFT agent}]/[\text{Na}_2\text{S}_2\text{O}_4]_0 = 222/1/1$ (v/v).

Entry	Monomer	RAFT agent	Solvent	S/M ^a (v/v)	T (°C)	Time (h)	Conv. (%)	$M_n^{\text{SEC}} \times 10^{-3}$	\bar{D}
1	GMA	CTP	DMF	1/1	30	48	38	15.4	1.14

2	DPA	CTP	IPA	2/1	40	120	53	20.8	1.06
3	DMAEMA	CTP	IPA	1/1	30	240	36	12.5	1.31
4	Sty	DDMAT	CPME	1/2	60	72	41	6.0	1.08
5	MA	DDMAT	CPME	1/2	30	72	50	8.5	1.03

^a S/M: solvent/monomer ratio (v/v)

The molecular weight distribution of the polymers was unimodal (Figure 3, Figures SF4 and SF5) and symmetric showing no signs of loss of chain-end functionality. Additionally, the chemical structure of the polymers, as well as the presence of the fragments derived from the RAFT agents, were confirmed by ¹H NMR spectroscopy (Figure 4 and Figures SF6 to SF10). Due to the overlapping of the signals derived from both the RAFT agent and the polymer, it was not possible to accurately determine the percentage of chain-end functionality of the polymers by this method.

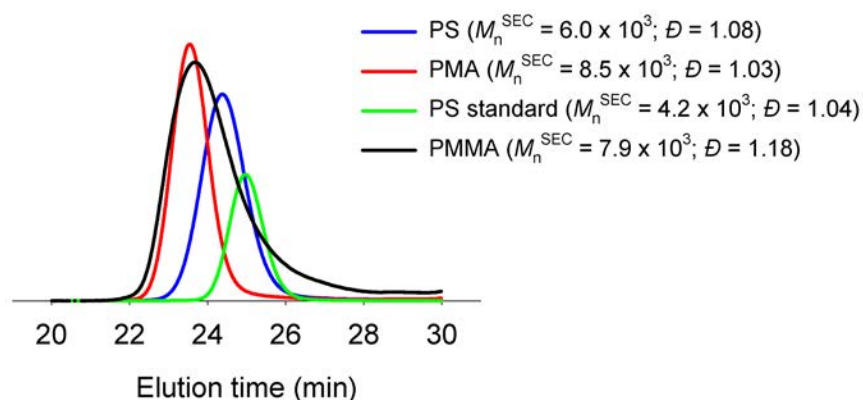


Figure 3. SEC traces (eluent: THF) of different samples (red, black and blue lines) prepared by DET-RAFT in comparison to a PS standard (green line).

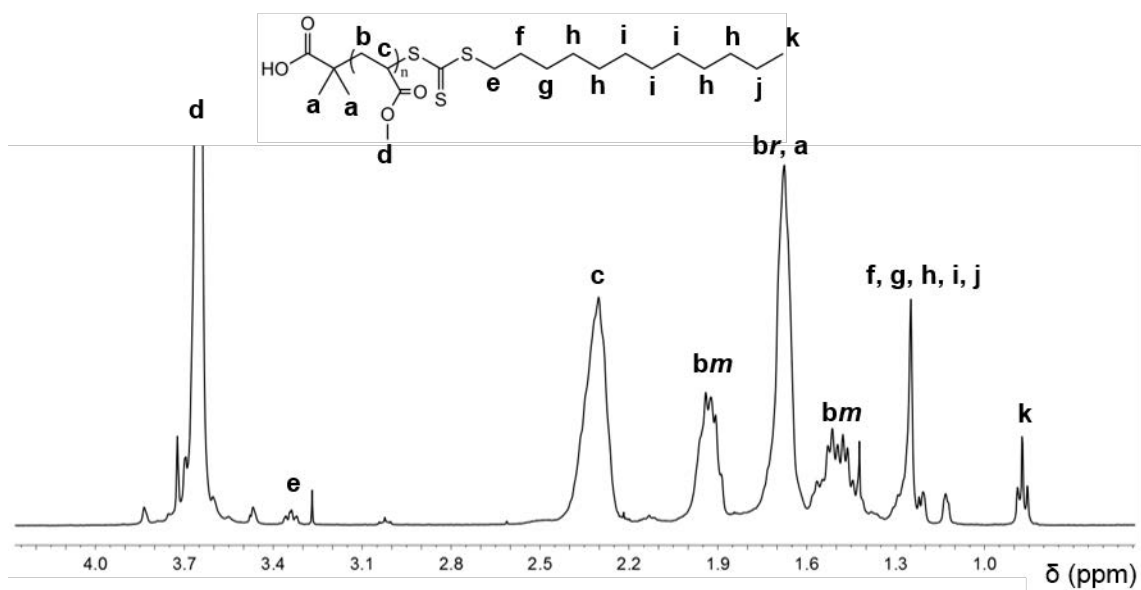


Figure 4. ^1H NMR spectrum (solvent: CDCl_3) of a PMA sample ($M_n^{\text{SEC}} = 8.5 \times 10^3$; $\mathcal{D} = 1.03$; $M_n^{\text{NMR}} = 5.7 \times 10^3$) prepared by DET-RAFT.

As alternative confirmation of the chain end integrity, a PMA sample obtained at 50 % monomer conversion ($[\text{MA}]_0/[\text{DDMAT}]_0/[\text{Na}_2\text{S}_2\text{O}_4]_0 = 222/1/1$) was purified and then used as a macro-RAFT agent in a chain extension experiment in order to evaluate the “living” character of the polymer. Figure 5 presents the normalized RI signals of the SEC analysis, which show the complete shift of the molecular weight distribution of the macro-RAFT PMA towards lower retention volumes (higher molecular weight), confirming the high chain-end functionality of the polymer. In addition, the second block was obtained at high monomer conversion (96 %) and the resultant extended polymer presented very low dispersity ($\mathcal{D} = 1.05$, red line in Figure 5). These results suggest that the method reported here could be useful for the preparation of well-defined block copolymers, which is extremely important for macromolecular engineering. To confirm that hypothesis, a well-defined block copolymer (Figure 6) PMA-*b*-PS was prepared by reinitiation of a Macro RAFT PMA sample obtained by DET-RAFT. It is also worth mentioning that, to the best

of our knowledge, this is the first metal/ligand-free DET-RAFT process, which is a clear advantage when considering the purification of the polymers.

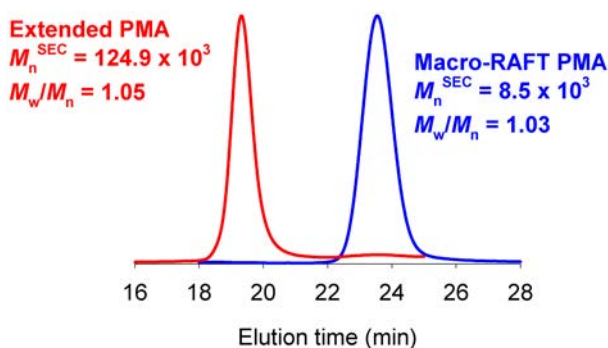


Figure 5. Normalized RI signal (SEC analysis) of a macro-RAFT PMA (blue line) and the respective extended PMA (red line) after chain extension experiment by DET-RAFT.

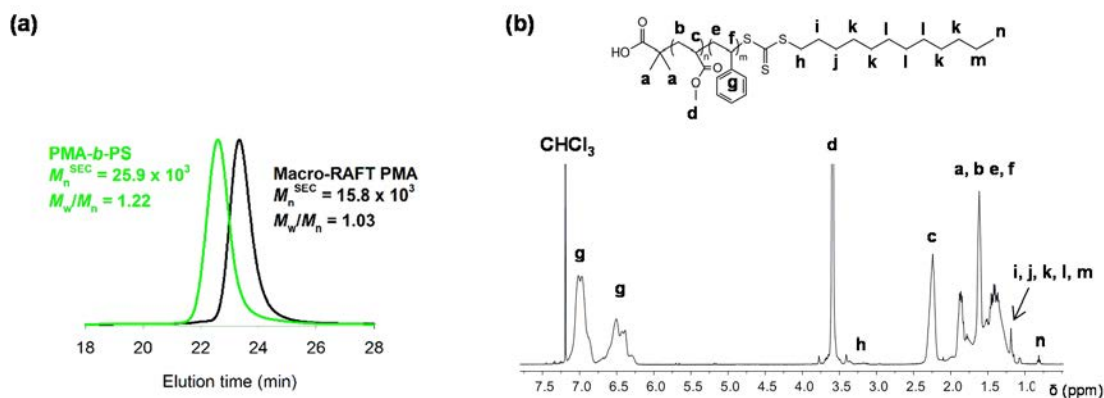


Figure 6. (a) Normalized RI signal (SEC analysis) of a macro-RAFT PMA (black line) and the PMA-*b*-PS block copolymer (green line) after chain extension experiment by DET-RAFT and (b) 1H NMR spectrum (solvent: $CDCl_3$) of a the PMA-*b*-PS block copolymer prepared by DET-RAFT.

Finally, to confirm the lack of SO_2 initiator fragments in the chain ends, the molecular structure of the PMA prepared by DET-RAFT was also studied by MALDI-TOF-MS (Figure 6). The enlargement of the spectrum (Figure 7 (b)) shows only one series of peaks, spaced by an

interval corresponding to the MA molar mass. According to the m/z values of the peaks, the polymer chains were found to be $[\text{RAFT agent}-(\text{MA})_n + \text{Na}^+]$ ($10029.7 = 364.63 + 86.09 \times 112 + 22.9$, where 364.63, 86.09 and 22.9 correspond to the molar mass of the RAFT agent, monomer and Na^+ , respectively). These results confirm that the PMA prepared by DET-RAFT presents a well-defined structure, free of initiator fragments (SO_2).

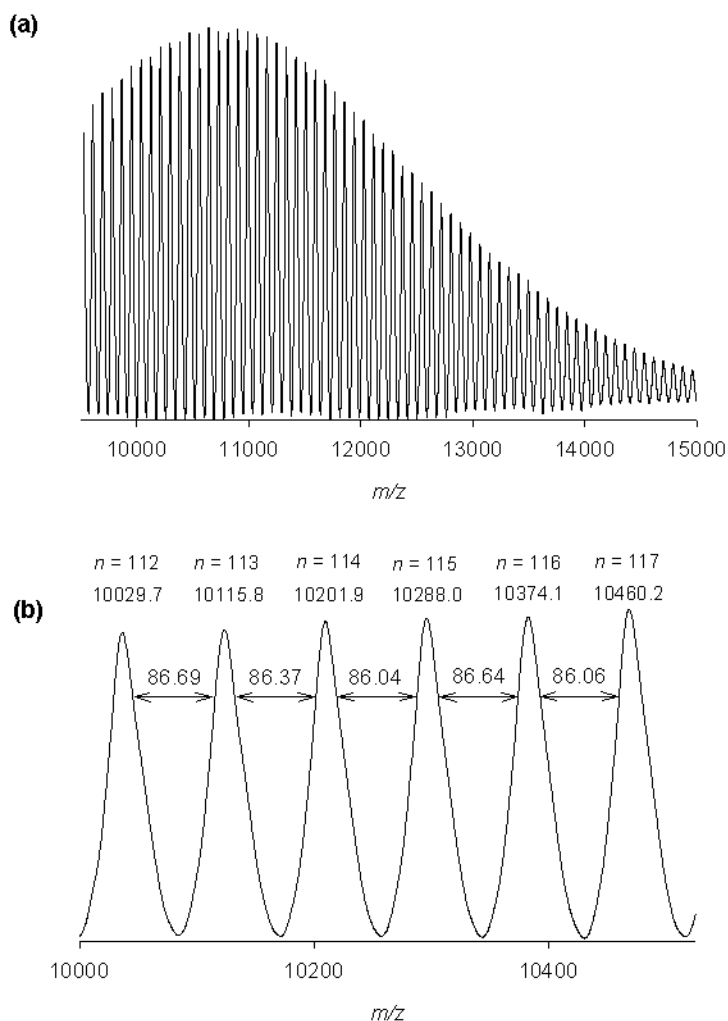
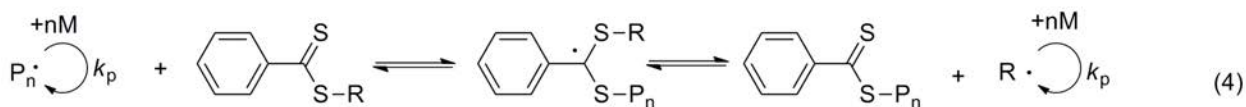
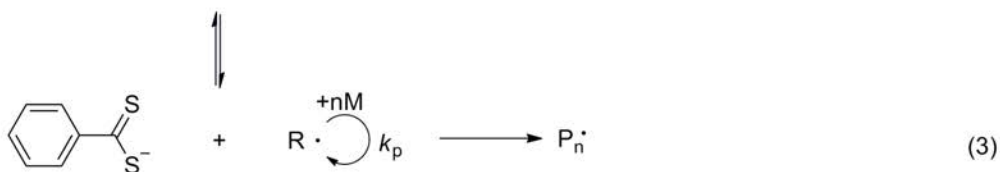
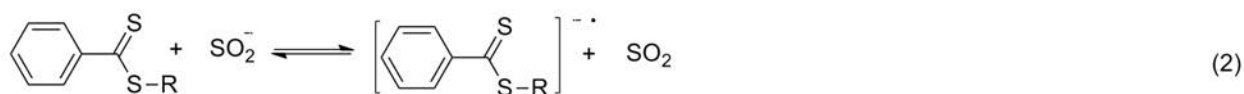


Figure 7. MALDI-TOF-MS (a) in the linear mode (using HABA as matrix) of a PMA ($M_n^{\text{SEC}} = 12.9 \times 10^3$, $D = 1.04$) sample prepared by DET-RAFT; (b) enlargement of the MALDI-TOF-MS spectrum from m/z 10000 to 10500.

Mechanistic considerations

We believe that the initiation process of the RAFT polymerization reported here is based on the reductive cleavage of the RAFT (or poly-RAFT) compound.¹⁴ One electron injection from the sulfite electron donor leads to the formation of stable radical anions from the RAFT agent, that can then fragment into the initiating radical R and the Ph-C(S)-S(-) anion. The simplified proposed mechanism is shown in the Scheme 2. The initial dissociation of dithionite anions into SO_2^\bullet appears to be thermally driven and not photochemically, as it was demonstrated by the similar results obtained from polymerizations conducted in the presence or absence of light (see Figure SF11 and Table ST1).



Scheme 2. General mechanism of SET-promoted formation and decomposition of radical anion from the dithioester-based RAFT agent.

To support the proposed reaction mechanism, *ab initio* quantum chemistry calculations were used to predict the reduction potential of the RAFT agent and the stability of the resulting radical

anion. Calculations were performed at a high level theory following standard protocols¹³ used in our previous studies.^{16-18, 37, 38} Full details of our methodology are provided in the Supporting Information. Our calculated reduction potential of the RAFT agent in DMSO solvent was -0.61 V *versus* SHE, while the SO₂/SO₂⁻ couple was calculated to have a potential of -0.52 V under the same conditions. Whilst this is slightly higher than the RAFT agent potential, the difference falls within the range of error expected for these types of calculations.¹³ The free energy profile shown in Figure 8 reveals that the addition of an electron to the RAFT agent produces a stable radical anion with a barrier to dissociation of 46 kJ mol⁻¹ at 298 K. Indeed stable radical anions have previously been identified for related phenylcarbonothioylthio RAFT agents by electron paramagnetic resonance (EPR).¹⁴ However, the overall dissociation process is predicted to be only slightly endergonic (9 kJ mol⁻¹), consistent with the reaction being kinetically driven in a polymer context.

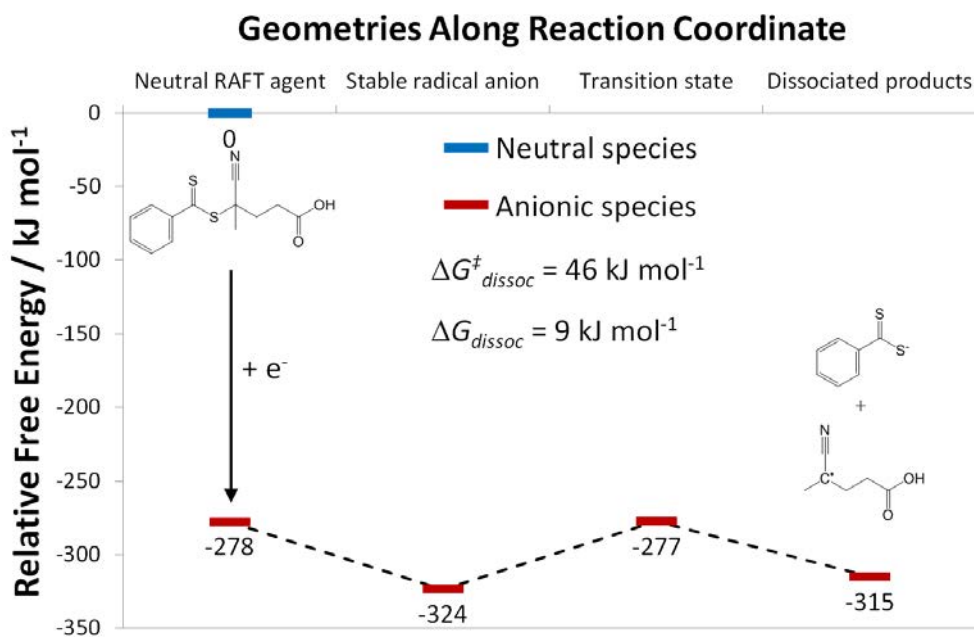


Figure 8. The free energy profile for the reductive cleavage of the RAFT agent.

Conclusions

A new metal-free DET-RAFT method, which avoids both conventional radical initiators and photo redox processes, was developed for the polymerization of different monomer families near room temperature. It is based on the use of inorganic sulfites in combination with common RAFT agents employed in RAFT. The polymerizations show typical “living” features and produce polymers with controlled molecular weights ($\bar{D} \leq 1.3$), and high end-group fidelity.

Supporting Information. Kinetic data, SEC chromatograms, NMR spectra and detailed theoretical methodology. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENT

The ^1H NMR data were obtained at the Nuclear Magnetic Resonance Laboratory of the Coimbra Chemistry Centre (<http://www.nmrccc.uc.pt>), University of Coimbra, supported in part by the Grant REEQ/481/QUI/2006 from FCT, POCI-2010 and FEDER, Portugal. MLC gratefully acknowledges generous allocations of supercomputing time on the National Facility of the Australian National Computational Infrastructure and financial support from the Australian Research Council Centre of Excellence for Electromaterials Science. The authors would like to thank Dr. Anatoliy Popov for the MALDI analysis.

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Table of Contents

Ambient temperature transition metal-free dissociative electron transfer reversible addition- fragmentation chain transfer polymerization (DET- RAFT) of methacrylates, acrylates and styrene

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