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Comblike Polymethacrylates with Poly(ethylene glycol) Side Chains via Nitroxide-Mediated Controlled Free-Radical Polymerization

Julien Nicolas,*,† Patrick Couvreur,† and Bernadette Charleux‡

Laboratoire de Physico-Chimie, Pharmacotechnie et Biopharmacie, UMR CNRS 8612, Faculté de Pharmacie, Univ. Paris-Sud, 5 rue Jean-Baptiste Clément, FR 92296 Châtenay-Malabry, France, and Laboratoire de Chimie des Polymères, UMR CNRS 7610, UPMC Paris 6, 4 place Jussieu, FR 75252 Paris cedex 05, France

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Nitroxide-mediated controlled free-radical polymerization (NMP)[1] is one of the so-called controlled free-radical polymerization (CRP) techniques, which are commonly used for the synthesis of well-defined, functional macromolecules. NMP is based on a reversible activation−deactivation equilibrium in which the nitroxide reversibly deactivates the growing radical into an alkoxyamine dormant end-functionality. Compared to other CRP methods, namely atom-transfer radical polymerization (ATRP)[2,3] and reversible addition−fragmentation chain transfer (RAFT),[4,5] NMP has the advantage of being only governed by a thermal process and does not require any catalyst or bimolecular exchange. However, one of the weak points of this technique is its relatively limited range of controllable monomers, mainly styrenics,[6] acrylates,[7] and acrylic acid,[8] even with the second generation of nitroxides such as the *N*-*tert*-butyl-*N*-(1-diethylphosphono-2,2-dimethylpropyl) nitroxide, also called SG1[7] (Figure 1a), or the 2,2,5-trimethyl-4-phenyl-3-azahexane 3-nitroxide (TIPNO).[9]

Apart from the synthesis of a specific nitroxide exclusively devoted to methacrylates,[10] to circumvent this limitation and to open the door to SG1-mediated polymerization of methyl methacrylate (MMA) and methacrylic acid (MAA), it has been recently reported[11−14] that a very small amount of styrene (S) in the polymerization medium (typically 4.4−8.8 mol % with respect to the monomer) along with the *N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*O*-(2-carboxylprop-2-yl) hydroxylamine (also called BlocBuilder or MAMA) as the initiator (Figure 1b) allowed (i) high conversions to be reached, (ii) well-defined PMMA- or PMAA-rich copolymers to be obtained, and (iii) high proportions of living chains to be recovered, leading to block copolymers after further chain extension. This is explained by a dramatic reduction of the concentration of propagating radicals (due to a reduction of the average activation−deactivation equilibrium constant, $\langle K \rangle$),[11,15] leading to a decrease of the irreversible termination rate. The method led to the formation of macroalkoxyamines with a methacrylate−styrene−SG1 terminal sequence (Figure 1c) able to dissociate into a propagating radical and a free nitroxide at low temperature (typically below 90 °C).[12]

Poly(ethylene glycol) (PEG), also called poly(ethylene oxide) (PEO) or poly(oxyethylene) (POE), is a hydrophilic and flexible polymer deeply employed in the pharmaceutical area, especially for drug delivery purposes such as polymer−protein/peptide bioconjugates (termed PEGylation)[16−21] or "stealth" long-circulating nanoparticles.[22−25] Indeed, PEG gives rise to several potential beneficial effects including increased bioavailability and plasma half-lives, biocompatibility/decreased immunogenicity, reduced proteolysis, and enhanced solubility and stability, thus being considered as a key material in this field.[16] Whereas linear PEGs are commonly obtained by ring-opening polymerization of ethylene oxide, in the context of CRP, poly(ethylene glycol)-based acrylate and methacrylate monomers can be successfully polymerized via ATRP[26−30] and RAFT.[31−33] However, to the best of our knowledge, no example has been reported using NMP of poly(ethylene glycol) methacrylates. Only few studies dealing with NMP of poly(ethylene glycol) styrene[34] and acrylate[35] monomers mediated by the TIPNO nitroxide are available, but they are limited to low conversions (typically below 50%). Indirect pathways have been also investigated leading to PEG-macroalkoxyamines based on TIPNO[36] or SG1,[37] both deriving from the functionalization of linear PEGs. The scope of the present study is directly related to this point where the viability of the copolymerization method described above will be investigated with the commercially available, bulky poly(ethylene glycol) methyl ether methacrylate (MePEGMA, M_n = 300 g mol^{-1}) (Figure 1d).

MePEGMA was first homopolymerized in bulk at 80 °C under SG1-based BlocBuilder alkoxyamine initiation (Table 1, expt 1). Unfortunately, the polymerization was too fast and exothermic (isothermal conditions could not be maintained), leading to a poor control. As expected, when a small amount of styrene (f_{S0} = 0.088) was initially added in the reaction medium under identical experimental conditions (Table 1, expt 2), the polymerization was drastically slowed down due to the formation of more thermally stable S−SG1 alkoxyamine bonds during the activation−deactivation process. The first-order kinetic plot was linear, accounting for a constant number of propagating radicals and molar masses increased linearly with monomer conversion (Figure 2). Even though the polydispersity index (PDI = M_w/M_n) was rather low (∼1.4) below 25−30% conversion due to an efficient decrease of the average activation−deactivation equilibrium constant, it increased rapidly to more than 2.2 at 60% conversion, indicating a complete loss of control.

This poor control was possibly due to the important increase of the polymerization medium viscosity when the monomer conversion increased. Besides, a too fast consumption of styrene during the copolymerization, leading to a significant deviation of the instantaneous monomer ratio from the initial value, might also be at the origin of this loss of control. Indeed, from the ^{1}H NMR spectra of the raw mixtures of expt 2, it was calculated that f_S was 0.050, 0.030, and only 0.014 at 37, 55, and 69% conversion, respectively.

Even though a very small addition of styrene to the SG1-mediated bulk polymerization of MePEGMA significantly helped to fit the criteria of a controlled system, the sharp increase of the PDI was not satisfying and needed further improvements. The idea was then to perform the reaction in diluted medium using an environmentally friendly solvent. Ethanol was selected as a good solvent of the monomers, the corresponding (co) polymers, the initiator, and the nitroxide, and the polymerizations were performed at various concentrations in monomer(s):

* Corresponding author: Tel +33 1 46 83 58 53; fax +33 1 46 61 93 34; e-mail julien.nicolas@u-psud.fr.
† Univ. Paris-Sud.
‡ UPMC Paris 6.

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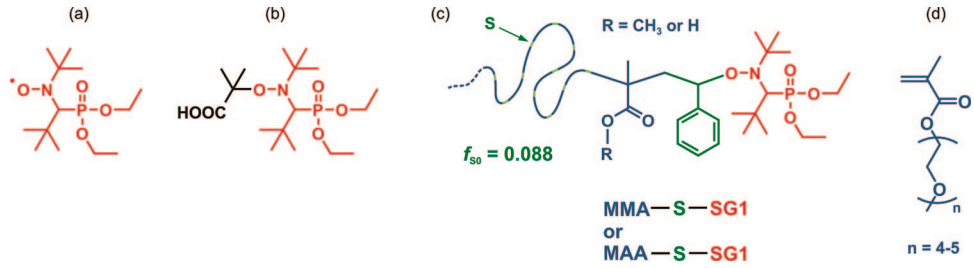

Figure 1. (a) SG1 nitroxide, (b) BlocBuilder alkoxyamine initiator (also called MAMA), (c) schematic representation of SG1-mediated copolymerization of methacrylic esters and styrene (f_{S0} is the initial molar fraction of styrene in the copolymerization mixture), and (d) poly(ethylene glycol) methyl ether methacrylate (MePEGMA).

Table 1. Experimental Conditions for the SG1-Mediated Homopolymerization of Poly(ethylene glycol) Methyl Ether Methacrylate (MePEGMA) and Its Copolymerization with Styrene (S)

expt	solvent[a]	monomers,[b] wt %	MePEGMA,[c] mol L^{-1}_{org}	S, mol L^{-1}_{org}	initial molar fraction of S (f_{S0})	BlocBuilder alkoxyamine, mol L^{-1}_{org}
1	bulk	100	3.50	0	0	3.5×10^{-2}
2	bulk	100	3.37	0.33	0.088	3.5×10^{-2}
3	ethanol	50	1.50	0	0	1.5×10^{-2}
4	ethanol	50	1.50	0.15	0.088	1.5×10^{-2}
5	ethanol	30	0.84	0.08	0.088	8.6×10^{-3}
6	ethanol	15	0.40	0.04	0.088	4.2×10^{-3}
7	ethanol	30	0.83	0.08	0.088	1.8×10^{-2}
8	ethanol	30	0.83	0.08	0.088	4.3×10^{-3}

[a] $T = 80$ °C (bulk) or $T = 78.5$ °C (ethanol). [b] Overall weight fraction of monomers. $[SG1]_0/[alkoxyamine]_0 = 0.10$. [c] $M_n = 300$ g mol^{-1} and polydispersity index was 1.07 as determined by size exclusion chromatography (SEC).

50, 30, and 15 wt % (Table 1, expts 3−6). When no styrene was initially added in the reaction medium for a concentration of 50 wt % of MePEGMA in ethanol (expt 3), the polymerization was fast in the very first minutes but stopped at 55% conversion to give a P(MePEGMA) of $M_n = 15\,000$ g mol^{-1} with $M_w/M_n = 1.8$ (Figure 2), in agreement with previous results obtained with MMA in bulk.[11] A too large activation−deactivation equilibrium constant, K, led to a high concentration of propagating radicals, promoting their self-termination. However, when a small amount of styrene was added to target $f_{S0} = 0.088$ (expt 4), the polymerization rate was strongly slowed down and molar masses increased linearly with monomer conversions following theoretical values. Compared to its counterpart in bulk (Table 1, expt 2), PDIs were drastically lowered (Figure 2). For instance at ∼55% conversion, PDI was 1.45 in 50 wt % ethanol whereas it was 1.87 in bulk, even though it still slowly increased at high conversions.

To investigate the effect of dilution over the kinetics and the molar mass distribution, further experiments at 30 and 15 wt % in ethanol (Table 1, expts 5 and 6, respectively) were performed. This was at the expense of the polymerization rate which was significantly reduced upon dilution due to a possible effect of the polymerization medium (polarity and/or viscosity) (Figure 2). A better control was however noticed and PDIs (1.40−1.45 at ∼62% conversion) were significantly below those obtained at 50 wt % in ethanol. These satisfying results were also emphasized by the continuous shift of the SEC chromatograms toward higher molar masses (see Figure S1 in the Supporting Information). As a consequence, a judicious compromise has to be found between acceptable polymerization rates (governed by the dilution) and narrow enough molar mass distributions.

With 8.8 mol % of styrene based on the monomers at constant monomer concentration, the initial alkoxyamine concentration was then varied (Table 1, expts 6−8), while keeping a constant

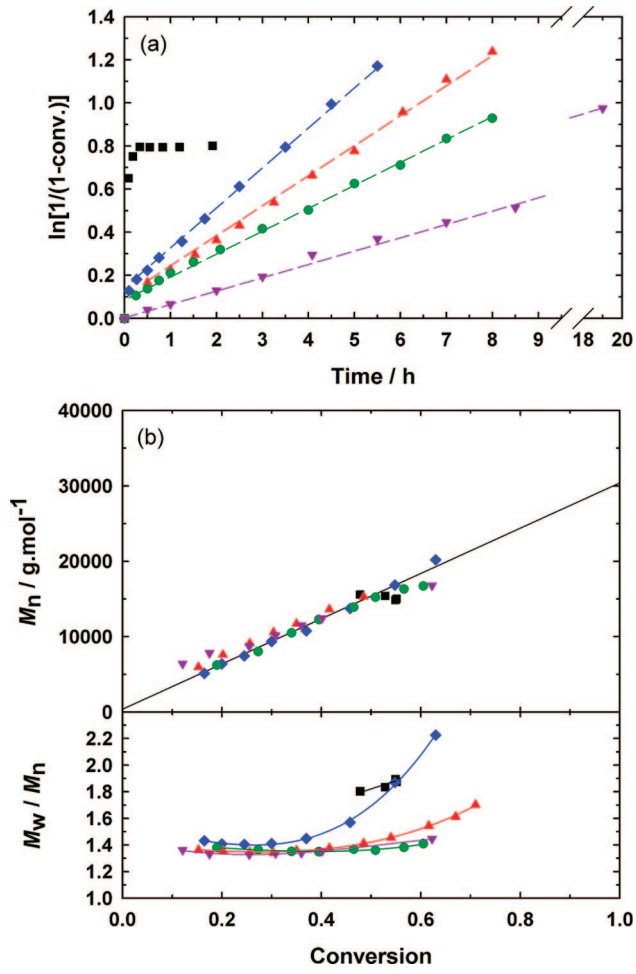

Figure 2. SG1-mediated controlled free-radical polymerization of MePEGMA initiated by the BlocBuilder alkoxyamine as a function of the monomer concentration, the reaction temperature, and the initial molar fraction of styrene (f_{S0}): ◆, expt 2 (bulk, $T = 80$ °C, $f_{S0} = 0.088$); ■, expt 3 (50 wt % in ethanol, $T = 78.5$ °C, $f_{S0} = 0$); ▲, expt 4 (50 wt % in ethanol, $T = 78.5$ °C, $f_{S0} = 0.088$); ●, expt 5 (30 wt % in ethanol, $T = 78.5$ °C, $f_{S0} = 0.088$); ▼, expt 6 (15 wt % in ethanol, $T = 78.5$ °C, $f_{S0} = 0.088$). (a) ln[1/(1 − conv)] vs time (conv = MePEGMA conversion); (b) number-average molar mass, M_n, and polydispersity index, M_w/M_n, vs conversion; the full line represents the theoretical M_n.

nitroxide/alkoxyamine molar ratio, in order to target different molar masses. In all three experiments, first-order kinetic plots were linear (Figure 3). For high concentrations of alkoxyamine (expts 6 and 7), molar masses increased linearly, following predicted values while exhibiting low PDIs around 1.4 at 64% conversion. When a high molar mass was targeted (expt 8), the macromolecular characteristics of the obtained copolymer were

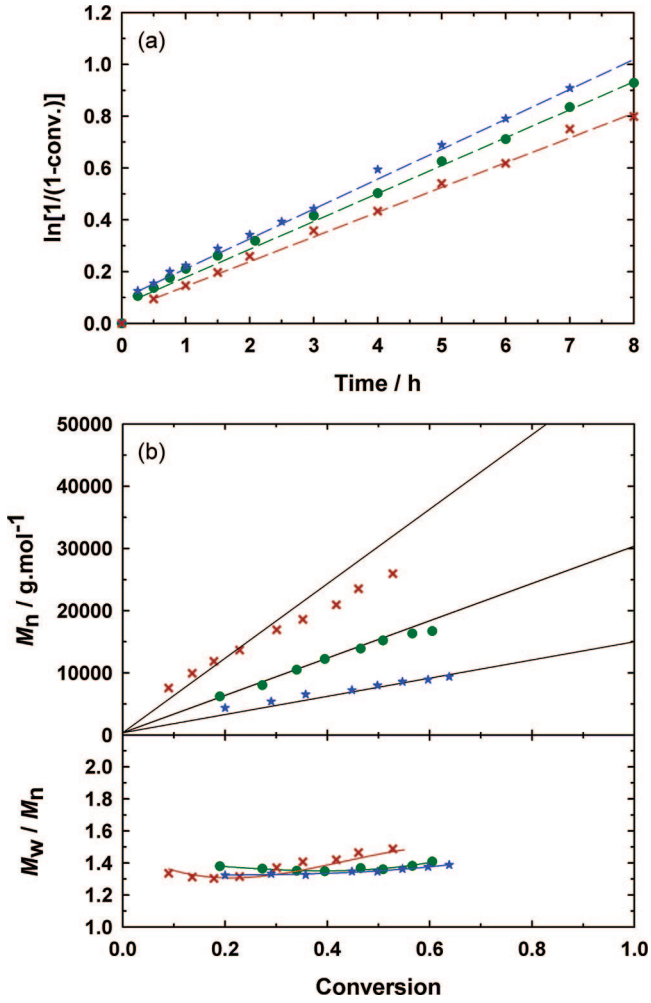

Figure 3. SG1-mediated controlled free-radical copolymerization of MePEGMA and styrene (initial molar fraction of styrene: $f_{S0} = 0.088$) at 30 wt % in ethanol initiated by the BlocBuilder alkoxyamine as a function of the alkoxyamine concentration: ★, expt 7 ($[alkoxyamine]_0 = 1.8 \times 10^{-2}$ mol L^{-1}_{org}); ●, expt 5 ($[alkoxyamine]_0 = 8.6 \times 10^{-3}$ mol L^{-1}_{org}); ×, expt 8 ($[alkoxyamine]_0 = 4.3 \times 10^{-3}$ mol L^{-1}_{org}). (a) ln[1/(1 − conv)] vs time (conv = MePEGMA conversion); (b) number-average molar mass, M_n, and polydispersity index, M_w/M_n, vs conversion; the full line represents the theoretical M_n.

still satisfying even though M_ns linearly deviated from theoretical values together with higher PDIs around 1.5 at 55% conversion.

All synthesized P(MePEGMA-*co*-S) copolymers were purified by a simple precipitation step in diethyl ether and analyzed by ^{1}H NMR spectroscopy (see Figure S2 in the Supporting Information). The incorporation of styrene in the polymer chain was determined in very good agreement with the initial feed ratio (in contrast to bulk where a strong deviation was observed). For instance for expt 4 ($f_{S0} = 0.088$), ^{1}H NMR gave ∼12 mol % of styrene in the copolymer isolated at 71% conversion. It is also worth mentioning that those copolymers were fully water-soluble at room temperature, demonstrating that such a small amount of styrene had no effect on the solubility of the resulting materials.

In summary, SG1-mediated copolymerization of MePEGMA with a very small addition of styrene (8.8 mol %) was investigated. In bulk, well-defined copolymers were only obtained at low monomer conversion. In ethanol solution, it was demonstrated that the obtained PMePEGMA-rich copolymers exhibited all the features of a controlled system, which proved the nearly universal character of the SG1-mediated copolymerization method applied to methacrylic esters. This study can be considered not only as another controlled monomer by NMP but also as an efficient way to create both organo- and water-soluble P(MePEGMA-*co*-S)-SG1 macroalkoxyamines, having the capability to dissociate at low temperature due to the penultimate unit effect (what an acrylate counterpart cannot do), thus laying the foundation for a forthcoming study concerning the synthesis of PEG-based amphiphilic block copolymers in homogeneous and aqueous dispersed media.

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Supporting Information Available: Experimental procedures and characterizations on prepared (co)polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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