POLYMERIZATION OF A PHOSPHONATED METHACRYLATE VIA RAFT LIVING RADICAL POLYMERIZATION

Benjamin Canniccioni, Sophie Monge, Ghislain David, Jean-Jacques Robin

Institut Charles Gerhardt Montpellier UMR 5253 CNRS-UM2-ENSCM-UM1
Equipe Ingénierie et Architectures Macromoléculaires,
Université Montpellier II cc1702, Place Eugène Bataillon
34095 Montpellier Cedex 5, France

Introduction

Phosphorus containing polymers are very promising compounds as their range of applications is broad. For example, they can improve flame resistance[1,2] and are used as adhesion promoters for paints, and adhesives.[3] There are also employed in the composition of glasses fibers and films with high mechanical resistance or as synthetic ion-exchangers. More recently, these materials were involved for applications in the biomedical field,[4] especially as agents for controlled drug release.[5] For such purpose, polymer structures have to be well-known, notably in terms of molecular weight, and architecture. In that context, Reversible Addition Fragmentation Transfer (RAFT) polymerization appears as in interesting tool as it allows the synthesis of polymers with well-controlled architecture, predictable molecular weight, and narrow polydispersity without using such drastic conditions as in ionic polymerizations.

In this contribution, we report on the controlled polymerization of a phosphonated monomer, namely dimethyl(methacryloyloxy)methyl phosphonate ($MAPC_1$), in 1,4-dioxane using cyanoisopropyl dithiobenzoate as chain transfer agent. The reported results open the way to the synthesis of block copolymers involving phosphonated moieties which could be used for biomedical applications.

Experimental

Materials. AIBN (Sigma Aldrich) was recrystallized from methanol. 1,4-dioxane (99%, Sigma Aldrich) was organic synthesis grade. Dimethyl(methacryloyloxy)methyl phosphonate ($MAPC_1$) and cyanoisopropyl dithiobenzoate (CIDB) were synthesized as already reported.[6,7]

Instrumentation. Molecular mass distribution and polydispersity index were determined by size exclusion chromatography (SEC) on a system equipped with a Showa Denko KK Model RI 101 refractive index detector and PLgel columns using DMF at 1 $mL.min^{-1}$ as the eluent. PMMA standards were used for calibration. All polymerization kinetics was followed using a NMR BRUKER 200 MHz spectrometer.

Synthesis of Dimethyl(methacryloyloxy)methyl phosphonate $MAPC_1$. Paraformaldehyde (3.6 g, 0.12 mol) was added to dimethyl hydrogenophosphonate (11g, 0.1mol), anhydrous K_2CO_3 (0.7 g, 5 mmol) and methanol (50 mL). Reaction occurred during one hour at room temperature. Then, the reactional mixture was filtered and methanol was removed under reduced pressure. The obtained phosphonated alcohol was dissolved in chloroform under inert atmosphere. Triethylamine and methacryloyl chloride were added dropwise at 0 °C. Temperature was maintained during one hour and then reaction occurred at room temperature for 12 hours. Targeted product was finally obtained by liquid-liquid extraction using chloroform and sodium chloride (saturated solution). The product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (20:3, v/v) as the eluent.

Typical RAFT polymerization of $MAPC_1$. $MAPC_1$ (2 g, 9.6 mmol), cyanoisopropyl dithiobenzoate (22.1 mg, 0.1mmol), AIBN (3.3 mg, 0.02 mmol) were added in a schlenk tube under nitrogen in 1,4-dioxane (10 mL). The mixture was degazed by four freeze-pump-thaw cycles and then heated at 75 °C under nitrogen in a thermostated oil bath during appropriate time. Samples were taken periodically for conversion and molecular weight analysis. The reaction was stopped by quenching the solution in liquid nitrogen. The resulting poly(dimethyl(methacryloyloxy)methyl phosphonate) was precipitated in cold hexane (M_n=8300 $g.mol^{-1}$, PDI=1.23).

Results and Discussion

Polymerization of Dimethyl(methacryloyloxy)methyl phosphonate. The synthesis of poly(dimethyl(methacryloyloxy)methyl phosphonate) is depicted in **Figure 1**. Polymerizations were carried out in 1,4-dioxane using cyanoisopropyl dithiobenzoate as chain transfer agent and AIBN at 75 °C. Different molecular weights were targeted. **Figure 2** describes the results obtained in the case of a molecular weight equal to 16000 $g.mol^{-1}$ at 80 % conversion.

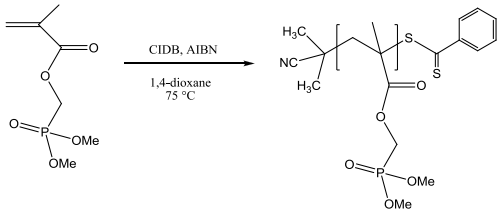

Figure 1. Synthesis of poly(dimethyl(methacryloyloxy)methyl phosphonate).

The figure also shows the control of the RAFT polymerization of $MAPC_1$. Conversion was determined by ^1H NMR comparing acrylic protons of the double bond and methylene in α of the ester function. Polymerization was stopped about 70 % conversion. $Ln([M]_0/[M])$ showed linear variation as a function of time indicating that the concentration of active species remained fairly constant during the polymerization, and that termination reaction could then be neglected. Moreover, linear variation of the molecular weight as a function of the conversion indicated that transfer as well as irreversible termination reactions were not significant. Thus, all chains grew simultaneously with time of the polymerization. Polydispersity indexes remained low during all the reaction (values between 1.16 and 1.26).

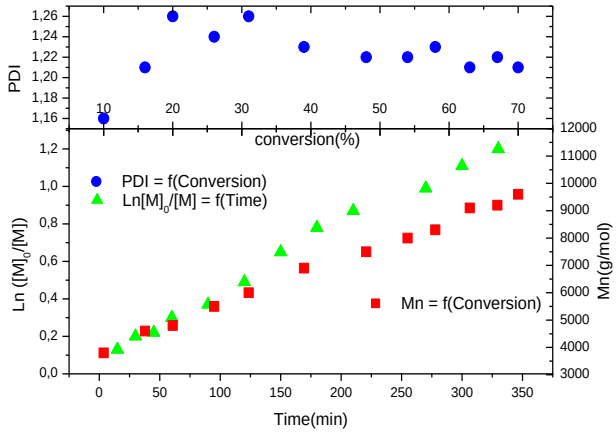

Figure 2. RAFT polymerization of $MAPC_1$.

Molecular weight distribution and polydispersity indexes were determined by size exclusion chromatography (SEC) (**Figure 3**). As expected, Gaussian type curves repartition of mass was observed as well as low polydispersity indexes (below 1.5). ^1H NMR spectroscopy (**Figure 4**) permitted a precise characterization of the poly(dimethyl(methacryloyloxy)-methyl phosphonate)s synthesized. Protons attributed to the phosphonated moiety were clearly identified at 3.7 ppm whereas methylene in α of the ester function showed a chemical shift at 4.3 ppm. We also checked the presence of aromatic protons brought by cyanoisopropyl dithiobenzoate chain transfer agent between 7.3 and 7.9 ppm. Moreover, obtained NMR spectrum showed that the precipitation in hexane led to complete removal of unreacted monomer, and confirmed that $PMAPC_1$ was obtained with good purity. The phosphonated polymer was achieved with a 40 % yield. Finally, ^1H NMR spectroscopy also allowed the determination of the molecular weight of the synthesized poly(dimethyl(methacryloyloxy)methyl phosphonate). The comparison between the polymer signals (phosphonated groups) and those of the chain transfer agent (aromatic protons) enabled to establish that the

experimental molecular weight was close to the one targeted ($M_{n(NMR)}$ = 14000 g.mol^{-1}).

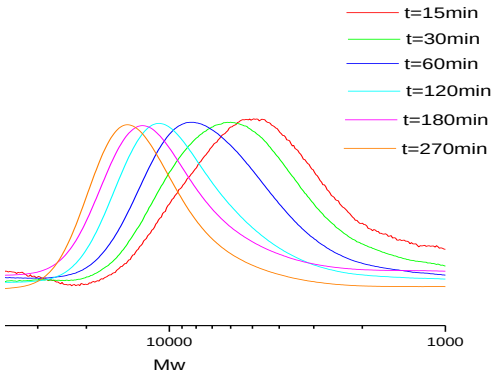

Figure 3. SEC traces of $PMAPC_1$ synthesized by RAFT polymerization.

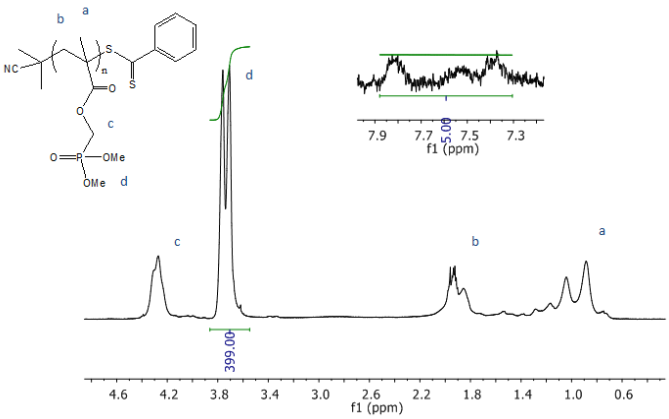

Figure 4. ^{1}H NMR (200 MHz, acetone-d6) for the polymerization of $MAPC_1$.

Polymerization of dimethyl(methacryloyloxy)methyl phosphonate was also carried out in other solvents than 1,4-dioxane to evaluate both the influence of the solvent on the polymerization kinetics and to determine broader experimental conditions as the obtaining of $PMAPC_1$-based block copolymers was also targeted, notably from poly(ethylene oxyde) macro-chain transfer agent. In this scope, experiments in N,N-dimethylformamide and dimethylacetamide was also carried out. The resulting poly(dimethyl(methacryloyloxy)methyl phosphonate)-*b*-poly(ethylene oxyde) will be evaluated as double hydrophilic copolymers.

Conclusion

RAFT polymerization of $MAPC_1$ have been achieved in 1,4-dioxane at 75 °C with a dithioester chain transfer agent and AIBN as initiator. Thanks to this method, it was possible to control the synthesis of $PMAPC_1$. To our knowledge, we described the controlled polymerization of phosphonated monomer by RAFT process. Thus, it could be used in a further step as macro chain transfert agent to build double hydrophilic block copolymers with exhibiting complexing properties. Micellar organizations of such diblock copolymers in water media are expected and evaluation of these copolymers for drug delivery could be evaluated.

References

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