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Synthesis and characterization of innovative well-defined difluorophosphonylated-(co)polymers by RAFT polymerization

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Reversible addition-fragmentation chain-transfer (RAFT) polymerization of a methacrylate derivative bearing a difluorophosphonylated moiety, namely diisopropyl 1,1-difluoro-5-methacryloyloxy-pentylphosphonate, was successfully achieved for the first time in the presence of 4-cyano-4-(thiobenzoylthio)pentanoic acid as chain transfer agent. Polymers with various molecular weights and low dispersities were obtained in a controlled way. Additionally, a new chain transfer agent containing a difluorophosphonated moiety (pCF_2-CTA) was successfully prepared to control the polymerization of methyl methacrylate and to create pCF_2 functionality at the poly(methyl methacrylate) chain-end by RAFT polymerization. The dealkylation of phosphonate esters polymers was performed with excellent yields using bromotrimethylsilane.

Introduction

Phosphorus-based polymers have found diversified applications such as proton exchange membrane[1,2] (PEM), anticorrosion[3-5] and nanomaterials[6-9]. Over the last decade, they have been widely studied as biomaterials[10-13] in tissue-engineering and dental applications[10, 14-17] due to their specific properties such as strong binding onto oxide metal surfaces and biocompatibility. Most of the phosphorous synthetic materials have been obtained by the incorporation of phosphate or phosphonate groups.[10, 18-22] Phosphates are easily hydrolyzed and the low pKa_2 value of phosphonates can be a major drawback for various applications. To improve the resistance against hydrolysis and enzymatic degradation as well as the pKa values, the difluoromethylene phosphonate (pCF_2) group is considered the best candidate to mimic the phosphonate function in medicinal chemistry.[23-25] The introduction of two highly electronegative fluorine atoms adjacent to the phosphonate group could dramatically change the physical and biological properties of these compounds.[24-26] Therefore, we are particularly interested in the difluoromethylene phosphonate (pCF_2) group due to its aqueous stability. Moreover, the conversion of phosphonate esters into their phosphonic acid analogues can be easily performed by dealkylation. It is clearly established that difluorophosphonic acids are more acidic (pKa_2 = 5.4) than the corresponding phosphonic (pKa_2 = 7.6) or phosphoric (pKa_2 = 6.4) acids.[23] It is therefore expected that difluorophosphonic acids would be mainly diionic at physiological pH (pH = 7.4). They would be capable of forming stronger bindings with calcium ions, the main inorganic component of the dental hard tissue hydroxyapatite (HAp) and oxide surfaces than phosphate group.[27] Thanks to their good adhesive and biocompatible properties, we have successfully demonstrated that pCF_2-functionalized (meth)acrylate monomers can be used as etching adhesive-primer for dental applications.[27-29] Besides, polymers bearing difluorophosphonic groups show a high proton conductivity for replacing perfluorosulfonic acid based polymer such as Nafion.[30, 31] However, up to now, only a few examples of pCF_2 group introduction in materials science were reported in the literature. Although thermal-initiated and photo-initiated free-radical polymerization of pCF_2-monomers have been previously reported,[29, 31] the synthesis of well-defined polymers containing the pCF_2 moiety with controlled architectures have not been previously investigated. Canniccioni *et al.*[32] reported the reversible addition-fragmentation chain-transfer (RAFT) polymerization of dimethyl(methacryloyloxy)methyl phosphonate (MAPC1) using dithioester-based chain transfer agent and trithiocarbonate-based chain transfer agent to afford well-defined phosphorous polymers with low dispersities ($Đ_M$ = 1.23-1.35). Well-defined phosphorous block copolymers having a thermo-responsive poly[*N*-(*n*-propyl)acrylamide] block have been prepared with potential value for drug delivery.[33] In the medical field, phosphorous based poly(oligoethyl glycol acrylate)s (POEGA) block copolymers stabilizing magnetic iron oxide nanoparticles could be employed as contrast agents in magnetic resonance imaging (MRI) technique.[34] The

versatility of the RAFT polymerization technique leading to polymers containing phosphorous groups either as side groups by direct RAFT polymerization of a phosphorous monomer or either at the chain end of polymer using a phosphorous chain transfer agent was studied by Boyer *et al*. for stabilization of magnetic iron oxide nanoparticles.[35]

In this contribution, we investigated the RAFT polymerization of a methacrylate bearing a difluorophosphonylated group. Homopolymers bearing a pCF_2 group directly incorporated in the polymer backbone were synthesized *via* RAFT polymerization using diisopropyl-1,1-difluoro-5-methacryloyloxy-pentylphosphonate monomer with 4-cyano-4-(thiobenzoylthio)pentanoic acid as the chain transfer agent (CTA) and azobisisobutyronitrile (AIBN) as the initiator. Additionally, difluorophosphonylated end-functionalized polymers based on methyl methacrylate (MMA) were successfully obtained by RAFT polymerization using a new difluorophosphonated-CTA (pCF_2-CTA) to control the polymerization of MMA. The difluorophosphonate ester polymers were converted to their phosphonic acid analogues for potential applications in metal oxides functionalization and (bio)materials. To the best of our knowledge, the present study represents the first example of the RAFT polymerization of difluorophosphonylated monomers.

Experimental

Materials

Unless otherwise stated, all reagents were purchased from Sigma-Aldrich (Sigma-Aldrich SARL, Lyon, France) and were used without further purification. Sodium bicarbonate ($NaHCO_3$), magnesium sulfate ($MgSO_4$), sodium chloride (NaCl), aluminum oxide (neutral), acetone (99.5%), dichloromethane (DCM, 99.9%), chloroform ($CHCl_3$, 99.9%), ethyl acetate (99.9%), diethyl ether (Et_2O, 99.5%), *N,N*-dimethylformamide (DMF, 99.8%), methanol (CH_3OH, 99.6%), *n*-pentane (95.0%), bromotrimethylsilane (TMSBr, 97%), 4-cyano-4-(thiobenzoylthio)pentanoic acid (CTP, 97%), 4-(*N,N*-dimethylamino)pyridine (DMAP, 97%), triethylamine (TEA, 99%) and methacryloyl chloride (97%) were used as received. Methyl methacrylate (MMA, 99%), bromotrimethylsilane, and triethylamine were distilled prior to use. Azobisisobutyronitrile (AIBN, 98%) was recrystallized in ethanol. Dichloromethane was purified with a Puresolv™ apparatus (Innovative Technology, Newburyport, MA, USA). Diisopropyl(1,1-difluoro-5-hydroxypentyl) phosphonate (pCF_2OH) was synthesized following the previously described procedure[36] (see ESI).

Column chromatography was performed on silica gel Si 60 (40–63 µm). Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (Merck Chemicals, Darmstadt, Germany). All reactions were carried out under a dry argon atmosphere in oven-dried glassware.

Characterization

New products were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, ^{31}P NMR and by high resolution mass spectroscopy (HRMS).

The ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR spectra were recorded on a 400 MHz AC 400 spectrometer (Brucker Optics GmbH, Ettlingen, Germany), with TMS as internal reference for ^{1}H-NMR and ^{13}C-NMR chemical shifts, and with H_3PO_4 (85%) as external reference for ^{31}P-NMR chemical shifts.

High-resolution mass spectra (HRMS) were obtained with a Q-TOF Micro instrument (Waters Corporation, Milford, MA, USA) in electrospray ionization positive (ES+) or negative (ES-) mode and lockspray with orthophosphoric acid. These analyses were performed with an infusion introduction of 10 µL.min^{-1}, a source temperature of 80 °C, a desolvation temperature of 120 °C and an external calibration with NaI.

Size Exclusion Chromatography (SEC): Polymers were characterized on a SEC system operating in DMF eluent at 60 °C fitted with a guard column (PL Gel 5 µm) and two Polymer Laboratories PL Mixed D columns, a Waters 410 differential refractometer and a Waters 481 UV detector operating at 309 nm. The instrument operated at a flow rate of 1.0 mL.min^{-1} and was calibrated with narrow linear poly(methyl methacrylate) (PMMA) standards ranging in molecular weight from 4100 g.mol^{-1} to 160800 g.mol^{-1}. Molecular weights and dispersity ($Đ_M$) were calculated using Waters EMPOWER software.

FTIR absorption spectra were recorded on a Perkin Elmer Spectrum One FTIR Spectrometer with an ATR accessory. The IR absorptions were observed as strong bands and are given in cm^{-1}.

Synthesis of diisopropyl (1,1-difluoro-5-methacryloyloxypentyl)phosphonate (pCF_2MA)

Under an inert argon atmosphere, diisopropyl(1,1-difluoro-5-hydroxypentyl)phosphonate (pCF_2OH, 1.20 g, 4.17x10^{-3} mol), triethylamine (0.70 mL, 5.20x10^{-3} mol) and dichloromethane (DCM, 6.00 mL) were added to a round bottom flask. The mixture was then stirred and cooled at 0 °C for 10 min. Methacryloyl chloride (0.42 mL, 4.30x10^{-3} mol) was subsequently added dropwise under stirring at 0 °C. The reaction mixture was then stirred at 0 °C for 2 h and at room temperature for 24 h. The reaction mixture was quenched by adding diethyl ether (10.0 mL) and $NaHCO_3$ (saturated solution, 5.0 mL). After stirring for 15 min, the mixture was extracted with Et_2O/CH_2Cl_2 (50/50: v/v) and the combined organic layers were washed with a NaCl saturated solution, dried over $MgSO_4$ and filtered. After evaporation of the volatiles under reduced pressure, the crude product was purified by column chromatography with a mixture of ethyl acetate/pentane (20/80: v/v) to give pCF_2MA monomer (0.89 g) as a colorless oil. Yield = 60%.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.35 (dd, J = 6.2 Hz, J = 5.3 Hz, -CH(C**H**$_3$)$_2$), 1.54-1.75 (m, -CF_2CH_2(C**H**$_2$)$_2$$CH_2$-), 1.93 (s, CH_2=C(C**H**$_3$)-), 1.99-2.15 (m, -CF_2C**H**$_2$-), 4.15 (t, J = 6.2 Hz, -COOC**H**$_2$-), 4.80-4.88 (m, -OC**H**(CH$_3$)$_2$), 5.49 and 6.03

(CH_2=C(CH_3)). ^{13}C NMR (100.62 MHz, $CDCl_3$. δ ppm): 18.30 (-COOCH$_2$CH$_2$**C**H$_2$-), 23.70-24.10 [-OCH(**C**H$_3$)$_2$], 28.30 (-COOCH$_2$**C**H$_2$-), 33.30-33.50 (-**C**H$_2$-CF$_2$-), 64.10 (-COO**C**H$_2$-), 73.50-73.50 [-O**C**H(CH$_3$)$_2$], 118.90-124.00 (-**C**F$_2$-), 125.40 [**C**H$_2$=C(CH$_3$)-], 136.30 [CH$_2$=**C**(CH$_3$)-], 167.40 (-**C**OO-). ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): -113.07 (dt, J = 108.8 Hz, J= 19.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$, δ ppm): 5.48 (t, J = 108.8 Hz). HR-MS : $[M]^+_{cal}$ = 356.1608 g.mol^{-1}, $[M]^+_{found}$ = 356.1601 g.mol^{-1}.

Synthesis of 5-(diisopropoxyphosphoryl)-5,5-difluoropentyl-4-cyano-4-(thiobenzoylthio)pentanoate (pCF$_2$-CTA)

Under argon atmosphere, a solution of *N,N'*-dicyclohexyldicarbodiimide (DCC, 0.17 g, 8.25x10^{-4} mol) in dry DCM (2.0 mL) was added dropwise to a stirred solution of 4-cyano-4-(thiobenzoylthio)pentanoic acid (CTP, 0.18 g, 6.45x10^{-4} mol), pCF$_2$OH (0.23 g, 7.99x10^{-4} mol) and 4-(*N,N*-dimethylamino)pyridine (DMAP, 8 mg, 6.55x10^{-5} mol) in dry DCM (5.0 mL) and cooled at 0 °C. After complete addition, the solution was stirred under argon at 0 °C for 4 h then at room temperature for 2 days. The mixture was filtered and the white solid was washed with DCM. The filtrate was then washed with HCl (2M), saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography with a mixture of ethyl acetate/*n*-pentane (40/60: v/v) to give pCF$_2$-CTA (0.31 g) as a rose oil. Yield: 89%.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.37 [dd, J = 6.2 Hz, J = 3.6 Hz, -OCH(C**H**$_3$)$_2$], 1.56-1.80 (m, -(C**H**$_2$)$_2$CH$_2$CF$_2$-), 1.94 (s, -C(CN)C**H**$_3$), 2.01-2.15 (m, -CF$_2$C**H**$_2$-), 2.39-2.72 [-C(CN)CH$_3$-C**H**$_2$C**H**$_2$COO-], 4.12 (t, J = 6.2 Hz, -COOC**H**$_2$-), 4.80-4.89 [m, -OC**H**(CH$_3$)$_2$], 7.38-7.92 (C$_6$H$_5$-). ^{13}C NMR (100.62 MHz, $CDCl_3$, δ ppm): 17.40 (-**C**H$_2$CH$_2$CF$_2$-), 24.10 (-OCH(**C**H$_3$)$_2$), 28.20 (-COOCH$_2$**C**H$_2$-), 29.80 (-**C**H$_2$CH$_2$COO-), 33.50 (-**C**H$_2$COO-), 45.80 [-**C**(CN)CH$_3$], 64.60 (-COO**C**H$_2$-), 73.50 and 73.60 [-O**C**H(CH$_3$)$_2$], 118.50-144.60 (-**C**F$_2$- and **C**$_6$H$_5$-), 171.50 (**C**=O), 222.30 (**C**=S). ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): -113.02 (dt, J = 108.6 Hz, J = 19.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$, δ ppm): 5.39 (t, J = 108.6 Hz). FT-IR (ν cm^{-1}): 2936-2982 (CH), 1733 (C=O), 1265 (P=O), 984 (P-O). HR-MS: $[M+H]^+_{cal}$ = 550.1662 g.mol^{-1}, $[M+H]^+_{found}$ = 550.1671 g.mol^{-1}.

RAFT polymerization of diisopropyl (1,1-difluoro-5-methacryloyloxypentyl)phosphonate (pCF$_2$MA)

pCF$_2$MA monomer (0.920 g, 2.58x10^{-3} mol), 4-cyano-4-(phenylcarbonothioylthio) pentanoic acid (CTP, 0.018 g, 6.45x10^{-5} mol), AIBN (2.0 mg, 1.21x10^{-5} mol) and DMF (2.50 mL) were charged to a round bottom flask equipped with a magnetic stir bar. The mixture was deoxygenated by bubbling argon for 40 min then immersed in an oil bath thermostated at 70 °C. Samples were removed periodically by using a degassed syringe to perform size exclusion chromatography (SEC) analysis and to monitor monomer conversion by ^{1}H NMR spectroscopy. After 8 h, the polymerization was quenched by rapid cooling and exposure to air. DMF was removed under reduced pressure. The residue was then dissolved in DCM and precipitated in cold *n*-pentane, filtered and dried under vacuum. The polymer was obtained as a pink viscous gel with $M_{n,NMR}$ = 6687 g.mol^{-1} (DP$_{n,NMR}$ = 18), $M_{n,SEC}$ = 10600 g.mol^{-1}; $Đ_M$ = 1.19.

^{1}H NMR (400 MHz, acetone D$_6$, δ ppm): 0.94-1.14 [-CH$_2$-C(C**H**$_3$)-]$_n$, 1.40 [-OCH(C**H**$_3$)$_2$], 1.50-2.25 [(-C**H**$_2$-C(CH$_3$)-]$_n$ and [-COOCH$_2$(C**H**$_2$)$_3$-], 4.04 (-COOC**H**$_2$-), 4.86 [-OC**H**(CH$_3$)$_2$], 7.47-7.91 (C$_6$**H**$_5$-). ^{13}C NMR (100.62 MHz, acetone D$_6$, δ ppm): 17.60, 23.20-23.50 [-OCH(**C**H$_3$)$_2$], 33.40-44.60, 64.30 [-COO**C**H$_2$(CH$_2$)$_3$CF$_2$-], 72.90-73.00 [-O**C**H(CH$_3$)$_2$], 116.70-128.50 (-**C**F$_2$-), 176.90 (-**C**OO-). ^{19}F NMR (376 MHz, acetone D$_6$, δ ppm): -113.16 (d, J =107.5 Hz). ^{31}P NMR (162 MHz, acetone D6, δ ppm): 5.14 (t, J =107.5 Hz). FT-IR (ν cm^{-1}): 2936-2982 (CH), 1727 (C=O), 1265 (P=O), 984 (P-O)$_{ester}$.

Typical procedure for the RAFT polymerization of methyl methacrylate using 5-(diisopropoxyphosphoryl)-5,5-difluoropentyl-4-cyano-4-(thiobenzoylthio)pentanoate (pCF$_2$-CTA) as the chain transfer agent

Methyl methacrylate (MMA, 0.704 g, 7.04x10^{-3} mol), pCF$_2$-CTA (0.0372 g, 6.78x10^{-5} mol), AIBN (2.0 mg, 1.19x10^{-5} mol) and DMF (2.0 mL) were charged to a round bottom flask equipped with a magnetic stir bar. The mixture was deoxygenated by bubbling argon for 30 min. The solution was then immersed in an oil bath thermostated at 60 °C. The mixture was quenched after 16 h by rapid cooling and exposure to air. DMF was removed under reduced pressure. The residue was then dissolved in DCM and precipitated in cold diethyl ether, filtered and dried under vacuum. The polymer was obtained as a pink powder with $M_{n,NMR}$ = 7749 g.mol^{-1} (DP$_{n,NMR}$ = 72), $M_{n,SEC}$ = 9500 g.mol^{-1}; $Đ_M$ = 1.18.

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.83-1.14 (-CH$_2$-C(C**H**$_3$)-)$_n$, 1.37 [-OCH(C**H**$_3$)$_2$], 1.50-2.53 [-C**H**$_2$-C(CH$_3$)-]$_n$, 2.39-2.72 [-C(CN)CH$_3$-C**H**$_2$C**H**$_2$COO-], 3.59 (-COOC**H**$_3$), 4.86 [-OC**H**(CH$_3$)$_2$], 4.11 [-COOC**H**$_2$(CH$_2$)$_3$CF$_2$-], 7.38-7.92 (C$_6$**H**$_5$-).^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): -113.08 (dt, J = 108.6 Hz, J = 19.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$, δ ppm): 5.40 (t, J = 108.6 Hz).

Typical procedure for ~~the~~ dealkylation of poly(pCF$_2$MA)

In a round bottom flask the poly(pCF$_2$MA)$_{16}$ (DP$_{n,NMR}$ = 16, $M_{n,MNR}$ = 5975 g.mol^{-1}, 60 mg, 1.00x10^{-5} mol) was dissolved in chloroform (1.0 mL). Bromotrimethylsilane (TMSBr, 0.25 mL, 1.89x10^{-3} mol) was then added at 0 °C. After completed addition, the reaction mixture was stirred for 48 h at room temperature. The excess of TMSBr and the solvent were then removed under reduced pressure. The crude polymer was dissolved in methanol (1.0 mL) and the mixture was stirred for 2 h at room temperature. The solution was then concentrated under vacuum to obtain a pink sticky polymer.

^{1}H NMR (400 MHz, CD_3OD, δ ppm): 0.89-1.29 [-CH$_2$-C(C**H**$_3$)-]$_n$, 1.50-2.43 [(-C**H**$_2$-C(CH$_3$)-]$_n$ and [-COOCH$_2$(C**H**$_2$)$_3$CF$_2$-)], 4.01 [-COOC**H**$_2$(CH$_2$)$_3$CF$_2$-], 7.46-8.02

(C_6H_5-). ^{19}F NMR (376 MHz, CD_3OD, δ ppm): -114.80 (d, J = 107.5 Hz). ^{31}P NMR (162 MHz, CD_3OD, δ ppm): 5.97 (t, J = 107.5 Hz).

Typical procedure for dealkylation of pCF_2-poly(methyl methacrylate) (pCF_2-PMMA)

In a round bottom flask, pCF_2-$PMMA_{72}$ ($DP_{n,NMR}$ = 72, $M_{n,NMR}$ = 7749 g.mol^{-1}, 20 mg, 2.58x10^{-6} mol) was dissolved in $CHCl_3$ (0.50 mL) and TMSBr (0.02 mL, 1.52x10^{-4} mol) was then added at 0 °C. After completed addition, the reaction mixture was stirred for 48 h at room temperature. The excess of TMSBr and the solvent were then removed under reduced pressure. The crude polymer was dissolved in $CHCl_3$/methanol (v/v 1/1; 1.0 mL) and stirred for 2 h at room temperature. After removing the volatiles and drying the residue under vacuum, the polymer was isolated.

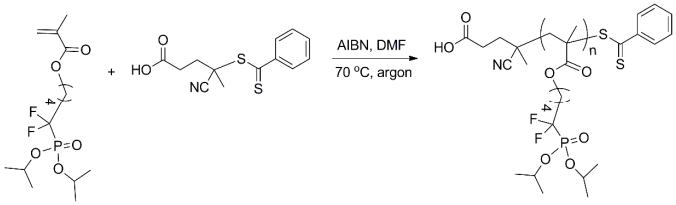
^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.82-1.14 [-CH_2-C(C**H**$_3$)-]$_n$, 1.50-2.22 [-C**H**$_2$-C(CH_3)-]$_n$, 2.39-2.72 [-C(CN)CH_3-(CH_2)$_2$COO-], 3.59 (-COOC**H**$_3$), 4.12 [t, -COOC**H**$_2$(CH_2)$_3$$CF_2$-], 7.44-8.05 ($C_6H_5$-). ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): -113.50 (d, J = 107.5 Hz). ^{31}P NMR (162 MHz, $CDCl_3$, δ ppm): 8.67.

Results and discussion

In order to introduce the pCF_2 groups within the polymer backbone, the RAFT polymerization of pCF_2MA was first considered.

RAFT polymerization of pCF_2MA

The synthesis of well-defined poly(pCF_2MA) was first reported by using the RAFT polymerization of the pCF_2MA monomer. 4-Cyano-4-(thiobenzoylthio)pentanoic acid (CTP) was chosen due to its high efficiency to control the polymerization of methacrylates.[37, 38]



Scheme 1: RAFT polymerization of pCF_2MA.

The homopolymerization of pCF_2MA was carried out in DMF at 70 °C using CTP as the chain transfer agent and AIBN as the initiator **(Scheme 1).** The samples were periodically taken to monitor monomer conversion, number average molecular weight and dispersity. The monomer conversion was determined by ^{1}H NMR spectroscopy of samples in deutered chloroform by comparing the integration area value of the vinyl proton signals (5.49-6.03 ppm) with the integration area value of the -OC**H**(CH_3)$_2$ signals of the phosphonate ester (4.80-4.88 ppm). Number-average molecular weights ($M_{n,SEC}$) and dispersities ($Đ_M$) were determined by size exclusion chromatography (SEC) in DMF. First experiments using a molar ratio pCF_2MA/CTP/AIBN : 40/1/0.18 gave the results shown in *Entry 1*, **Table 1**.

Figure 1a shows a linear first order kinetic plot consistent with a constant concentration of propagating radicals. Furthermore, the linear evolution of $M_{n,SEC}$ with monomer conversion was also observed in **Figure 1b**. This result demonstrates that no significant irreversible termination reaction and transfer reaction occurred during the polymerization. The different value between $M_{n,SEC}$ and the theoretical number-average molecular weight ($M_{n,th}$) was attributed to the difference in hydrodynamic volumes between poly(pCF_2MA)s and poly(methyl methacrylate) standards used for calibration. Finally, the dispersities of poly(pCF_2MA) containing 18 monomers units [named poly(pCF_2MA)$_{18}$)] remained low ($Đ_M$ = 1.14) suggesting that all chains grew simultaneously. In conclusion, the RAFT polymerization of pCF_2MA in DMF at 70 °C using CTP as a chain transfer agent was well-controlled. This result was confirmed by RAFT polymerization pCF_2MA performed under the same conditions (DMF at 70 °C) but with the molar ratio of pCF_2MA/CTP/AIBN equal to 31/1/0.18 (*Entry 2*, **Table 1**). Once again, a low dispersity of poly(pCF_2MA)$_{16}$ ($Đ_M$ = 1.13) was obtained. Furthermore, the formation of the resulting poly(pCF_2MA) was confirmed by spectroscopy.

Table 1: RAFT polymerization of pCF_2MA using CTP and AIBN in DMF at 70 °C

Entry	Sample[a]	$[pCF_2MA]_0$:$[CTP]_0$:$[AIBN]_0$	Time (min)	Conv.[b] (%)	$M_{n,th}$[c] (g.mol^{-1})	$M_{n,NMR}$[a] (g.mol^{-1})	$M_{n,SEC}$[d] (g.mol^{-1})	$Đ_M$[d]
1	poly(pCF_2MA)$_{18}$	40: 1: 0.18	480	47	6972	6687	6140	1.14
2	poly($pCF2MA$)$_{16}$	31: 1: 0.18	480	44	5135	5975	4460	1.13

[a] The sample name of poly(pCF_2MA) is followed by a number corresponding to the number of monomer units and $M_{n,NMR}$ determined by comparing the integration area values of the signal at 4.86 ppm [-OC**H**(CH_3)$_2$] and of the signal at 7.47-7.91 ppm (C_6**H**$_5$-) on the ^{1}H NMR spectra. [b] pCF_2MA conversion rate determined by ^{1}H NMR spectroscopy by comparing the integration area value of the signal at 5.49 ppm and 6.03 ppm. [C**H**$_2$=C(CH_3)-] and of the signal at 4.86 ppm [-OC**H**(CH_3)$_2$]. [c] $M_{n,th}$= [($[pCF_2MA]_0$/$[CTP]_0$)xconv./100]x356 + 279. [d] Determined by SEC in DMF using poly(methyl methacrylate) standards.

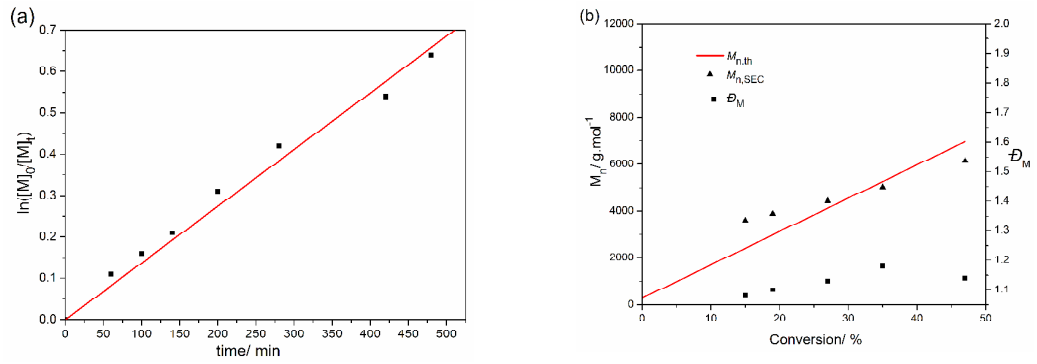


Figure 1: RAFT polymerization of pCF_2MA using CTP as chain transfer agent with (a) $Ln([M]_0/[M]_t)$ versus time and (b) evolution of the number average molecular weights and dispersities versus monomer conversion with $[pCF_2MA]_0:[CTP]_0:[AIBN]_0 = 40 : 1 : 0.18$, at 70 °C in DMF.

The ^1H NMR spectroscopy in deutero acetone (**Figure 2**) shows a signals at 1.40 ppm corresponding to -OCH($C\mathbf{H}_3$)$_2$ (labeled a) and a signal at 4.86 ppm corresponding to -O$\mathbf{C}$H(CH_3)$_2$ (labeled b) showing the presence of phosphonated ester groups of the polymer. The signals characteristics of the ester group of poly(pCF_2MA)$_{16}$ were observed at 4.04 ppm (-COOC$\mathbf{H}_2$-, labeled c) and those of the aromatic protons of CTP at 7.47-7.91 ppm ($C_6\mathbf{H}_5$-, labeled e). Moreover, the presence of the dithioester group at the poly(pCF_2MA)$_{16}$ chain-end was confirmed by the SEC trace of poly(pCF_2MA) using UV detection (absorbance at 309 nm characteristic of dithioester function) (**Figure 3**). In addition, the formation of polymer containing difluoromethylene phosphonate group was also checked by ^{31}P NMR spectroscopy with the signal of the phosphonate at 5.14 ppm, as well as ^{19}F NMR spectroscopy with the signal at -113.08 ppm (Figures S9 and S10 in ESI).

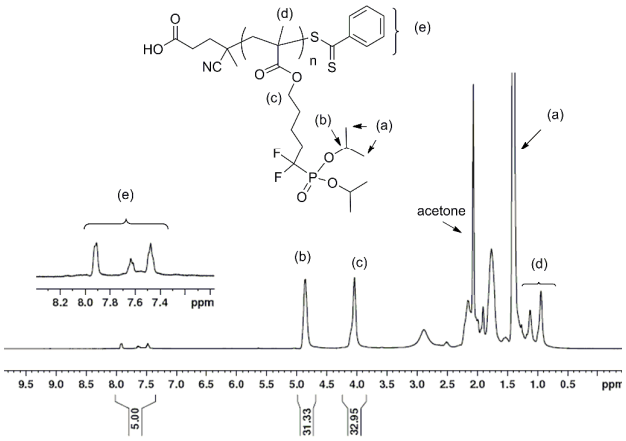


Figure 2: ^1H NMR spectrum of poly(pCF_2MA)$_{16}$ in acetone D_6.

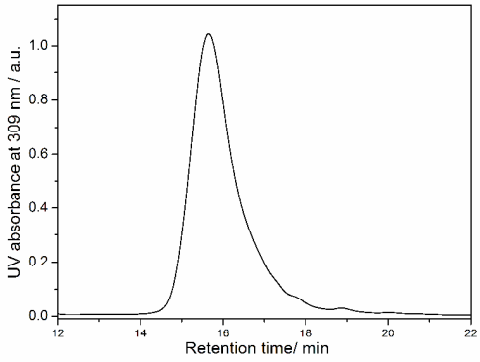
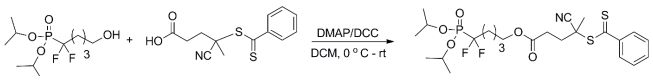


Figure 3: Extracted UV trace of poly(pCF_2MA)$_{16}$ at 309 nm.

Synthesis of pCF_2-terminated poly(methyl methacrylate)

In order to introduce a pCF_2 group at the chain-end polymer, a novel pCF_2-derivated dithioester (pCF_2-CTA) was first synthesized and subsequently used as chain transfer agent to mediate the RAFT polymerization of methyl methacrylate (MMA).

pCF_2-CTA was prepared by the reaction of CTP with the hydroxyl difluorophosphonate precursor pCF_2OH in the presence of DCC/DMAP in DCM (**Scheme 2**).



Scheme 2: Synthesis of pCF_2-CTA.

pCF_2-CTA was formed in 89% yield and its structure was checked by ^1H NMR spectroscopy (**Figure 4**). The signals at 4.12 ppm (labeled f) and those at 7.38-7.92 ppm (labeled j) assigned to the protons of the -COOC$\mathbf{H}_2$- and phenyl groups respectively confirmed the formation of pCF_2-CTA.

Table 2: RAFT polymerization of MMA using pCF_2-CTA and AIBN in DMF at 60 °C

Entry	Sample[a]	$[MMA]_0$: $[pCF_2\text{-CTA}]_0$:$[AIBN]_0$	Time (h)	Conv.[b] (%)	$M_{n,th}$[c] ($g.mol^{-1}$)	$M_{n,NMR}$[a] ($g.mol^{-1}$)	$M_{n,SEC}$[d] ($g.mol^{-1}$)	$Đ_M$[d]
1	pCF_2-$PMMA_{72}$	100:1:0.2	16	68	7349	7749	6340	1.08
2	pCF_2-$PMMA_{45}$	98:1:0.1	23	45	4949	5049	4890	1.09

[a] The sample name of pCF_2-PMMA is followed by a number corresponding to the number of monomer units and $M_{n,NMR}$ determined by comparing the integration area values of the signal at 4.86 ppm [-OC**H**$(CH_3)_2$] and of the signal at 3.59 ppm (-COOC**H**$_3$) on the ^{1}H NMR spectra. [b] MMA conversion rate determined by ^{1}H NMR spectroscopy by comparing the integration area value of the signal at 5.47 ppm and 6.01 ppm. [C**H**$_2$=C(CH_3)-] and of the signal at 3.59-3.67 ppm (-COOC**H**$_3$). [c] $M_{n,th}$= [([MMA]$_0$/[pCF_2-CTA]$_0$)xconv/100]x100 + 549. [d] Determined by SEC in DMF using poly(methyl methacrylate) standards.

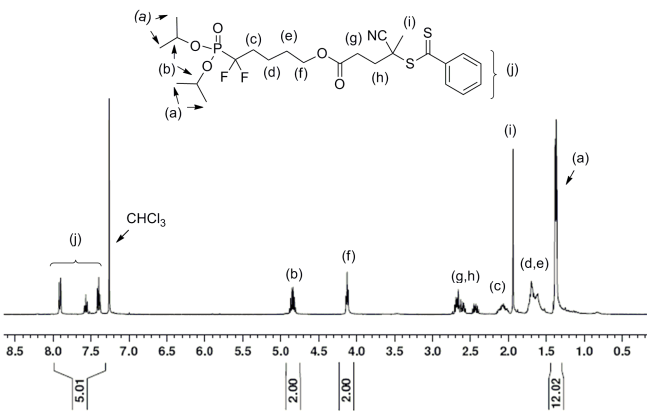


Figure 4: ^{1}H NMR spectrum of pCF_2-CTA in $CDCl_3$.

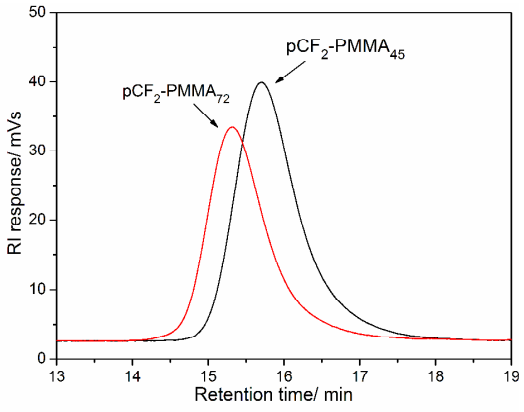
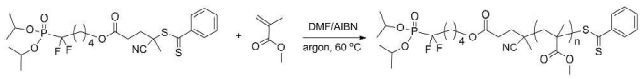


Figure 5: Overlaid SEC traces of pCF_2-terminated PMMA samples containing different monomer units of PMMA chains carrying pCF_2 RAFT end groups.

Following the success of the synthesis of pCF_2-CTA, the RAFT polymerization of MMA was carried out in the presence of pCF_2-CTA used as the chain transfer agent and AIBN used as the initiator in DMF at 60 °C (**Scheme 3**).



Scheme 3: RAFT polymerization of MMA using pCF_2-CTA in DMF at 60 °C.

The results are summarized in **Table 2**. Well-defined poly(methyl methacrylate)s (pCF_2-PMMA) carrying a pCF_2 end group have been obtained with remained low dispersities ($Đ_M$ < 1.10) (**Table 2**). The symmetrical SEC chromatograms of pCF_2-PMMA (**Figure 5**) confirmed the efficiency of pCF_2-CTA to target well-defined polymers.

Furthermore, the formation of the pCF_2-PMMA was confirmed by spectroscopic analyzes. The ^{1}H NMR spectrum showed the signals characteristics of PMMA at 3.59 ppm (-COOC**H**$_3$, labeled e) and at 4.86 ppm [-OC**H**$(CH_3)_2$, labeled b)] characteristics of the phosphate esters (**Figure 6**). Moreover, the appearance of the signals at 5.40 ppm in the ^{31}P NMR and -113.08 ppm in the ^{19}F NMR spectra confirms the presence of the functional pCF_2 group at the chain-end polymers (Figures S12 and S13 in ESI). All these results prove that the new pCF_2-CTA is successfully used to control the polymerization of MMA monomer.

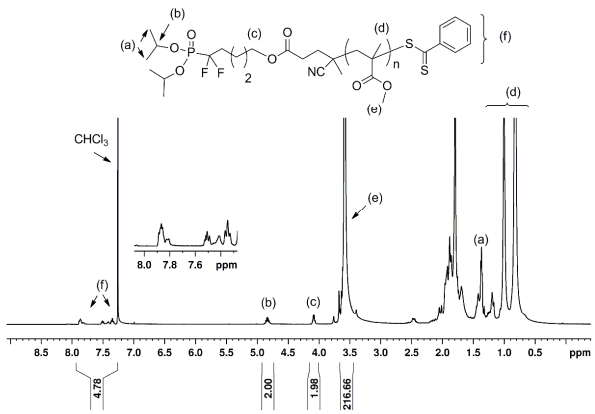
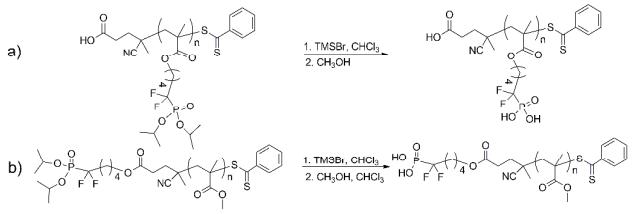


Figure 6: ^{1}H NMR spectrum of pCF_2-$PMMA_{72}$ in $CDCl_3$.

Synthesis of polymethacrylates functionalized with a difluorophosphonic acid group

Polymers carrying difluorophosphonate functions were designed as potential new fire resistant materials. Therefore, the presence of difluorophosphonic acids groups into polymer chain could enhance the chemical and thermal properties of the materials. Well-defined polymethacrylates [poly(pCF_2MA) and pCF_2-PMMA], functionalized with difluorophosphonate groups were dealkylated to afford the corresponding difluorophosphonic acids in order to use them in (bio)materials. Poly(pCF_2MA)$_{16}$ containing 16 monomer units [named poly(pCF_2MA)$_{16}$)] and pCF_2-PMMA$_{72}$ containing 72 monomer units [named (pCF_2-PMMA$_{72}$)] were treated with bromotrimethylsilane (TMSBr) in chloroform at room temperature for 48 h following by methanolysis (**Scheme 4**).



Scheme 4: Synthesis of difluorophosphonic acid polymethacrylates.

The achievement of the dealkylation of poly(pCF_2MA)$_{16}$ was demonstrated by ^{1}H and ^{31}P NMR spectroscopies. These difluorophosphonic acid polymethacrylates are soluble in water, however for a better interpretation, the NMR spectra were carried out in methanol D_4.

Figure 7 compares the ^{1}H NMR spectra of poly(pCF_2MA)$_{16}$ before and after dealkylation. The ^{1}H NMR spectra shows the disappearance of the signals at 1.40 ppm (labeled a) and 4.86 ppm (labeled b) corresponding to the protons of phosphonate ester groups. Moreover, the comparison of ^{31}P NMR spectra before and after dealkylation, shows the complete disappearance of triplet at 5.14 ppm due to the phosphonate ester groups and the presence of a triplet at 5.97 ppm assigned to phosphonic acid groups (**Figure 8**).

Dealkylation of pCF_2-PMMA$_{72}$ was confirmed by ^{1}H NMR spectroscopy analysis. The signal at 4.86 ppm corresponding to -OC**H**$(CH_3)_2$ (labeled c) of the phosphonate ester in pCF_2-PMMA$_{72}$ disappeared in the ^{1}H NMR spectrum of the dealkylated pCF_2-PMMA$_{72}$ (**Figure 9**).

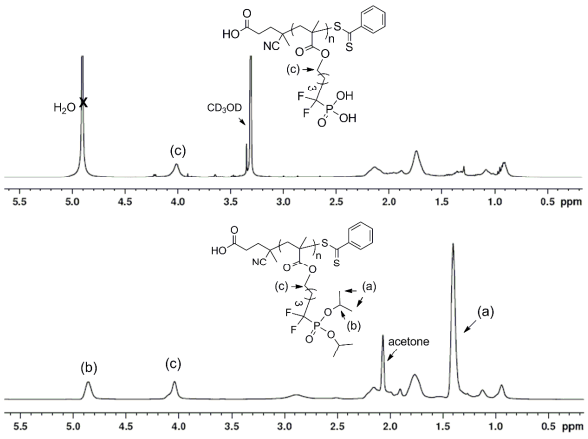


Figure 7: Overlaid ^{1}H NMR spectra of well-defined poly(pCF_2MA)$_{16}$ before dealkylation in acetone D_6 (bottom) and after dealkylation in methanol D_4 (top)

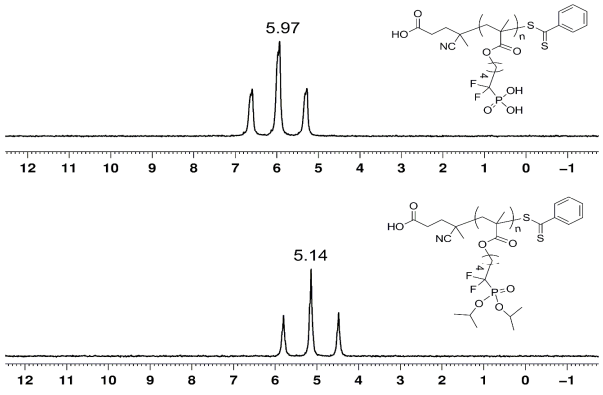


Figure 8: Overlaid ^{31}P NMR spectra of well-defined poly(pCF_2MA)$_{16}$ before dealkylation in acetone D_6 (bottom) and after dealkylation in methanol D_4 (top).

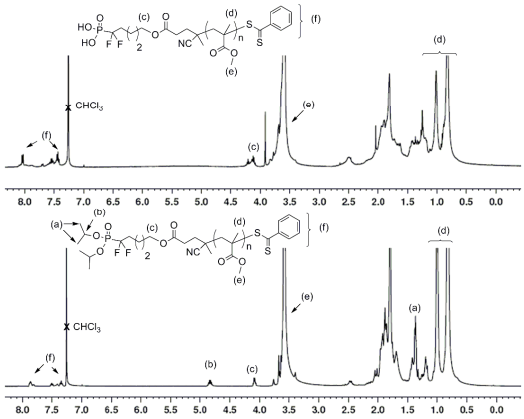


Figure 9: Overlaid ^{1}H NMR spectra of pCF_2-PMMA$_{72}$ chain-ended with a pCF_2 group in $CDCl_3$ before (bottom) and after (top) dealkylation.

Conclusions

In this paper, the introduction of difluorophosphonylated moieties within polymer backbone was achieved by RAFT polymerization of a difluorophosphonylated-based methacrylate. Moreover, a novel chain transfer agent based on a difluorophosphonate moiety (pCF_2-CTA) was synthesized to control the polymerization of MMA and to design pCF_2 functionality at the end of the chain of PMMA by RAFT polymerization. Additionally, the conversion of difluorophosphonate-functionalized poly(methacrylate)s into difluorophosphonic acid analogues was performed successfully using bromotrimethylsilane. Finally, to conclude, it is also important to point out that difluorophosphorus based (co)polymers could contribute to many applications, including flame retardancy, anticorrosion, and in the biomedical field. As these applications are of great interest, we can assume that the development of new RAFT agents (pCF_2-CTA) with other difluorophosphorus monomers and difluorophosphonate, difluorophosphonic acids will continue in the future to study the biocompatibility and thermal stability of the (co)polymers.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Synthetic detail and characterization of pCF_2OH, NMR spectroscopies and SEC characterization. See DOI: 10.1039/b000000x/

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