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To cite this version:
Elise Guegain, Chen Zhu, Erika Giovanardi, Julien Nicolas. Radical Ring-Opening Copolymerization-Induced Self-Assembly (rROPISA). Macromolecules, 2019, 52 (10), pp.3612-3624. 10.1021/acs.macromol.9b00161. hal-02323831

HAL Id: hal-02323831
https://hal.science/hal-02323831
Submitted on 21 Oct 2019

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Radical Ring-Opening Copolymerization-Induced Self-Assembly (rROPISA)

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Abstract

Radical ring-opening copolymerization-induced self-assembly (rROPISA) was performed by copolymerizing benzyl methacrylate (BzMA) and cyclic ketene acetalts (CKA), such as 2-methylene-4-phenyl-1,3-dioxolane (MPDL) or 5,6-benzo-2-methylene-1,3-dioxepane (BMDO), in heptane at 90 °C by reversible addition-fragmentation chain transfer (RAFT) polymerization from a poly(lauryl methacrylate) (PLMA) macro RAFT agent. The chain lengths of both the solvophilic macro-RAFT agent and the solvophobic block, together with the initial amount of CKA were independently varied to achieve various compositions. The amount of CKA in the copolymers was ranged from 4 to ~40 mol.% by adjusting the monomer stoichiometry, leading to nearly complete degradation for CKA contents above ~15 mol.%. rROPISA led to stable nanoparticles in all cases, ranging from 40 to 500 nm in diameter, depending on the experimental conditions, as assessed by DLS and TEM. Low average diameters and very narrow particle size distributions were obtained for CKA contents below 20 mol.%, except for a targeted solvophobic chain length of 300 that gave narrow particle size distributions up to 50 mol.% in CKA. Morphological investigation revealed the formation of spheres for all copolymer compositions, which was assigned to both the nature of the RAFT agent used and insertion of CKA in the solvophobic block, that prevent formation of other morphologies.
Introduction

Polymerization of vinyl monomers in dispersed media is a widely employed process to produce polymer particles. Besides traditional polymerization processes (e.g., emulsion, dispersion),\(^1\) polymerization-induced self-assembly (PISA) rapidly became a well-established, one-pot process to prepare well-defined block copolymer nano-objects at high concentrations (ca. 10–50 wt.%).\(^2\)-\(^4\) PISA relies on the use of solvophilic living polymer precursors synthesized by reversible deactivation radical polymerization (RDRP) techniques, which are further chain-extended with a solvophilic monomer, which at a certain degree of polymerization becomes solvophobic. The resulting amphiphilic block copolymers then self-assemble in situ into self-stabilized spheres, worms or vesicles; the final morphology being mainly governed by the relative volume fractions of the solvophilic and solvophobic blocks. Also, no additional surfactant is required for the colloidal stabilization of the nano-objects formed, which represents a crucial advantage over traditional polymerization processes in dispersed media. In the past few years, tremendous effort has been paid to unleash the full potential of PISA by variation of the monomer pairs and experimental conditions,\(^5\) leading for instance to stimuli-responsive nano-objects\(^6\) such as those made by polymerization-induced thermal self-assembly (PITSA),\(^7\) more effective Pickering emulsifiers,\(^8\)-\(^10\) potential boundary lubricants for engine oils,\(^11\) or nanoparticles for catalysis\(^12\) and potential biomedical applications.\(^13\)-\(^15\) Photoinitiated PISA (photo-PISA) has also been developed for the preparation of a broad range of different morphologies with ultrafast polymerization kinetics at room temperature under visible light irradiation.\(^16\)-\(^20\) However, polymerizations of traditional vinyl monomers in dispersed media share a common feature, that could also represent a limitation for certain applications: they produce non-degradable polymer particles.

Except for degradable poly(alkyl cyanoacrylate) nanoparticles that are obtained by emulsion polymerization in acidic conditions,\(^21\) degradable polymer nanoparticles are
exclusively obtained by formulation of preformed degradable polymers (e.g., polyesters, polypeptides) using emulsification methods (e.g., nanoprecipitation, emulsion/solvent evaporation). However, it usually leads to low solids content dispersions (ca 1–5 wt.%) which represents a major limitation in terms of use and industrial development. There is indeed an unmet fundamental and industrial need for new synthetic strategies to develop degradable polyester-like particles that could circumvent the limitations of current systems in terms of process and colloidal features, and advantageously replace some specific traditional latexes to yield more eco-friendly materials.

Vinyl polymers are very attractive and present advantageous benefits compared to traditional polyesters (e.g., ease of synthesis in various media, broad diversity in terms of architectures and compositions, numerous functionalization strategies, etc.) that were made possible especially since the advent of RDRP. Developing synthetic strategies to enable complete or partial degradation of vinyl polymers are of great importance because their accumulation in the environment is of increasing concern and it could offer new opportunities for the application of these materials. Also, a broad range of vinyl polymer nanoparticles have been proposed for biomedical applications, but their lack of degradability is a severe drawback for their use. Among the different strategies to confer degradability to vinyl polymers, radical ring-opening polymerization (rROP) from cyclic ketene acetals (CKA) is one of the most efficient ones for the incorporation of ester groups in the polymer backbone. Recent years have seen a resurgence of interest in CKAs, which may be explained, at least in part, by their ability to copolymerize with traditional vinyl monomers (e.g., vinyl acetate, methacrylic esters) by both conventional free-radical polymerization and RDRP techniques.

However, to the best of our knowledge, there is no example of PISA systems or emulsion/dispersion (co)polymerizations based on CKAs. Only two related studies have been
published so far. Paulusse, Armes and co-workers reported on the copolymerization of 3-methylidene-1,9-dioxa-5,12,13-trithiacyclopentadecane-2,8-dione, a cyclic allylic sulfide derivative that polymerizes by rROP, with 2-hydroxypropyl methacrylate by PISA to induce in-chain disulfide group leading to order-order morphological transition under a reducing environment. In addition, free-radical miniemulsion polymerization was used to prepare CKA-containing polymer particles. Miniemulsion polymerization is considered as a simplified model of emulsion polymerization as the nucleation step directly occurs in the already formed droplets. In this work, 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) was used as a CKA and homopolymerized or copolymerized with styrene under conventional free-radical polymerization leading to degradable particles.

In this context, we report for the first time, the radical ring-opening copolymerization-induced self-assembly (rROPISA) from CKAs as a robust and straightforward strategy to obtain degradable vinyl particles directly in dispersed medium (Figure 1). By choosing appropriate experimental conditions, stable diblock copolymer particles with finely controlled macromolecular (e.g., block chain lengths, amount of CKA in the second block) and colloidal characteristics (e.g., average diameters, particle size distribution) were obtained, and exhibited adjustable degradation in agreement with the amount of CKA inserted.
**Figure 1.** Synthesis of core degradable block copolymer nanoparticles by RAFT-mediated radical ring-opening copolymerization-induced self-assembly (rROPISA) from cyclic ketene acetals (CKA).

**Experimental part**

**Material**

Lauryl methacrylate (LMA, 96%) and benzyl methacrylate (BzMA, 96%) were purchased from Sigma-Aldrich and passed through basic alumina prior to use. 2-Phenyl-2-propyl benzodithioate (also called cumyl dithiobenzoate, CDB, 99%) was purchased from Sigma-Aldrich and used as received. 2-Methylene-4-phenyl-1,3-dioxolane (MPDL) was prepared as reported elsewhere using the cyclic bromoacetal as an intermediate\(^\text{54}\) and 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) was prepared as reported elsewhere using cyclic bromoacetal as an intermediate.\(^\text{55}\) 2,2'-Azobis(2-methylpropionitrile) (AIBN, 98%) was purchased from Acros (Belgium). *Tert*-butyl peroxy-2-ethylhexanoate (Trigonox 21S or T21s) initiator was supplied by AkzoNobel. 4-Cyano-4-[(dodecylsulfanylthiocarbonyl)sulfanyl]pentanoic acid (CDSPA, 97%), anhydrous heptane,
ruthenium(III) chloride hydrate (RuCl₃) and sodium periodate (99.8%) were obtained from Sigma-Aldrich (UK). All other reactants were purchased from Sigma-Aldrich at the highest available purity and used as received. Deuterated chloroform (CDCl₃) was obtained from Eurisotop. All other solvents were purchased from Carlo-Erba.

**Analytical method**

**Nuclear magnetic resonance (NMR) spectroscopy.** ¹H NMR spectroscopy was performed in 5 mm diameter tubes in CDCl₃ at 25 °C on a Bruker Avance 300 spectrometer at 300 MHz. The chemical shift scale was calibrated based on the internal solvent signals (δ = 7.26 ppm).

**Size exclusion chromatography (SEC).** SEC was performed at 35 °C with two columns from Polymer Laboratories (PL-gel MIXED-D; 300 × 7.5 mm; bead diameter, 5 μm; linear part, 400–400 000 g.mol⁻¹) and a differential refractive index detector (Spectrasystem RI-150 from Thermo Electron Corp.), using chloroform (CHCl₃) as eluent at a flow rate of 1 mL.min⁻¹ and toluene as a flow-rate marker. A conventional calibration curve was based on poly(methyl methacrylate) (PMMA) standards (peak molar masses, \(M_p\) = 625–625 500 g.mol⁻¹) from Polymer Laboratories. This technique allowed \(M_n\) (number-average molar mass), \(M_w\) (weight-average molar mass), and \(M_w/M_n\) (dispersity, \(D\)) to be determined. SEC of degraded copolymers was performed in the presence of 0.1 % (v/v) of trifluoroacetic acid (TFA, 99%) in chloroform (in both the mobile phase and the sample) to avoid the formation of aggregates and/or interaction with the columns because of carboxylic acid chain ends.

**Dynamic light scattering (DLS).** Nanoparticle diameters (\(D_z\)) and particle size distribution (PSD) were measured by dynamic light scattering (DLS) with a Nano ZS from Malvern (173° scattering angle) at a temperature of 25 °C. Copolymer dispersions were diluted in heptane (80 vol.%, viscosity = 0.42 cP, \(n = 1.39\) at 20 °C) prior to light scattering studies.

**Transmission electron microscopy (TEM).** The morphology of the nanoparticles was observed by TEM using a JEOL JEM-1400 operating at 80 kV. Images were acquired using
an Orius camera (Gatan Inc, USA). 5 μL of diluted block copolymer nanoparticle suspensions (0.1%, v/v) were deposited for 30 s on copper grids covered with formvar-carbon film. The excess solution was blotted off using a filter paper. Samples were then stained using ruthenium(IV) oxide for 7 min at 20 °C. This heavy metal compound acted as a positive stain to improve contrast. The ruthenium(IV) oxide was prepared as follows: ruthenium(III) chloride (30 mg) was added to water (5 mL) to form a black slurry; addition of sodium periodate (200 mg) with stirring produced a yellow solution of ruthenium(IV) oxide within 5/10 min. The number-average diameter $D_n$, the weight-average diameter $D_w$, the z-average diameter $D_z$ as well as a polydispersity index were defined using the following equations:

$$D_n = \frac{\sum_i n_i D_i}{\sum_i n_i} \quad \text{Eq. 1}$$

$$D_w = \frac{\sum_i n_i D_i^2}{\sum_i n_i} \quad \text{Eq. 2}$$

$$D_z = \frac{\sum_i n_i D_i^6}{\sum_i n_i D_i^2} \quad \text{Eq. 3}$$

Polydispersity index = $D_w / D_n$ \quad \text{Eq. 4}

**Synthetic procedures**

**Synthesis of poly(lauryl methacrylate) macro-CTA (PLMA).**

A typical solution copolymerization procedure was conducted as follows for PLMA$_{22}$ macro-CTA. In a 40-mL vial, fitted with a rubber septum and a magnetic stirring bar, a mixture of LMA (5.00 g, 1.97 × 10$^{-2}$ mol), AIBN (6.5 mg, 3.94 × 10$^{-2}$ mmol), CDSPA (127.8 mg, 3.16 × 10$^{-1}$ mmol, CSPDA/AIBN molar ratio = 8.0 × 10$^{-3}$) and anhydrous toluene (5 g, 5.8 mL) was degassed under stirring by argon bubbling for 15 min at room temperature. The mixture was then immersed in a preheated oil bath at 70 °C for 4 h. $^1$H NMR spectroscopy was used to determine the monomer conversion (by integrating the two oxymethylene protons of LMA at 4.0-4.2 ppm) and $DP_{n,NMR}$ (by comparing the integrated signals of the two oxymethylene...
protons of PLMA at 4.0 ppm and the two protons in the α-position to the carboxylic acid of CDSPA at 3.3 ppm), whereas $D_P_{n,SEC}$, $M_n$ and $D$ were obtained by SEC. The copolymer was then precipitated twice in methanol (MeOH) and dried under high vacuum until constant weight. The same procedure was followed by adapting the amount of the reactants for PLMA$_{18}$ [LMA (5.00 g, 1.97 × 10$^2$ mol), AIBN (10.5 mg, 6.40 × 10$^{-2}$ mmol), CDSPA (210.0 mg, 5.20 × 10$^{-1}$ mmol) and anhydrous toluene (5 g, 5.8 mL)], for PLMA$_{26}$ [LMA (2.50 g, 9.84 mmol), AIBN (3.2 mg, 1.97 × 10$^{-2}$ mmol), CDSPA (63.9 mg, 1.58 × 10$^{-1}$ mmol) and anhydrous toluene (2.55 g, 3.0 mL)] and for PLMA$_{37}$ [LMA (5.00 g, 1.97 × 10$^{-2}$ mol), AIBN (3.2 mg, 1.97 × 10$^{-2}$ mmol), CDSPA (63.9 mg, 1.58 × 10$^{-1}$ mmol) and anhydrous toluene (5 g, 5.8 mL)].

Copolymer synthesis

From now on, PLMA-$b$-P(BzMA-c0-MPDL) copolymers will be abbreviated as $L_xB_zM$, with $x = D_P_{n,PLMA}$, $y = D_P_{n,PBzMA}$ and $M = MPDL$, whereas PLMA-$b$-P(BzMA-c0-BMDO) copolymers will be abbreviated as $L_xB_zB$, with $x = D_P_{n,PLMA}$, $y = D_P_{n,PBzMA}$ and $B = BMDO$.

Synthesis of poly(lauryl methacrylate)-$b$-poly[(benzyl methacrylate)-co-(2-methylene-4-phenyl-1,3-dioxolane)] (PLMA-$b$-P(BzMA-c0-MPDL)). A typical synthesis of PLMA$_{18}$-$b$-P(BzMA$_{150}$-c0-MPDL) ($L_{18}B_{150}M$) by RAFT dispersion polymerization at 15 wt.% solids and with $f_{MPDL,0} = 0.2$ was as follows: In a 40-mL vial, fitted with a rubber septum and a magnetic stirring bar, a mixture of BzMA (0.628 g, 3.57 mmol), MPDL (0.144 g, 8.92 × 10$^{-1}$ mmol), T21s initiator (1 mg, 4.63 × 10$^{-3}$ mmol) and PLMA$_{18}$ macro-CTA (0.117 g, 2.38 × 10$^{-2}$ mmol; macro-CTA/initiator molar ratio = 5.0) were dissolved in heptane (5 g, 7.3 mL). The mixture was degassed under stirring by argon bubbling for 15 min while immersed in an ice
bath (to avoid solvent evaporation). The mixture was then immersed in a preheated oil bath at 90 °C for 24 h. Samples were periodically withdrawn to determine the BzMA conversion by $^1$H NMR spectroscopy (by integrating the two oxymethylene protons of BzMA at 4.9 and 5.2 ppm) and the macromolecular characteristics, $M_n$ and $D$, by SEC. The nanoparticle colloidal characteristics, $D_z$ and PSD, were obtained by DLS whereas their morphology was assessed by TEM. The nanoparticles were dried under reduced pressure and solubilized in a minimal amount of THF before precipitation (twice) in a mixture of cyclohexane/diethyl ether (1/1; v/v) and dried under high vacuum until constant weight. $F_{\text{MPDL}}$ was determined by using integrated proton signals $e$, $g$ and $h$ in Figure 6 as follows: $I_g / [I_e + (I_e - (1 - I_h / I_g))]$. The same procedure was repeated with a polymerization time of 20 h for $f_{\text{MPDL,0}} = 0.4$ [BzMA (0.491 g, 2.79 mmol), MPDL (0.301 g, 1.86 mmol), T21s initiator (0.8 mg, 3.60 $\times$ 10$^{-3}$ mmol), PLMA$_{18}$ macro-CTA (0.091 g, 1.86 $\times$ 10$^{-2}$ mmol) and heptane (5.0 g, 7.3 mL)], for $f_{\text{MPDL,0}} = 0.6$ [BzMA (0.343 g, 1.95 mmol), MPDL (0.474 g, 2.93 mmol), T21s initiator (0.5 mg, 2.49 $\times$ 10$^{-3}$ mmol) and PLMA$_{18}$ macro-CTA (0.064 g, 1.30 $\times$ 10$^{-2}$ mmol) and heptane (5.0 g, 7.3 mL)] and for $f_{\text{MPDL,0}} = 0.7$ [BzMA (0.265 g, 1.50 mmol), MPDL (0.569 g, 3.51 mmol), T21s initiator (0.4 mg, 1.99 $\times$ 10$^{-3}$ mmol) and PLMA$_{18}$ macro-CTA (0.049 g, 1.00 $\times$ 10$^{-2}$ mmol) and heptane (5.0 g, 7.3 mL)]. Similar syntheses were also achieved from PLMA$_{22}$ and PLMA$_{37}$ macro-CTAs.

The $D_P$ of the P(BzMA-$co$-MPDL) block was also varied ($D_{P,P\text{BzMA}} = 75$ and 300) together with $f_{\text{MPDL,0}}$, by adjusting the initial amount of PLMA macro-CTA and/or the initial amounts of BzMA and MPDL as follows for $L_{18}$Bz$_{75}$M with $f_{\text{MPDL,0}} = 0.2$ [BzMA (0.575 g, 3.26 mmol), MPDL (0.130 g, 0.80 mmol), T21s initiator (1.8 mg, 8.43 $\times$ 10$^{-3}$ mmol), PLMA$_{18}$ macro-CTA (0.209 g, 4.26 $\times$ 10$^{-2}$ mmol) and heptane (5.0 g, 7.3 mL)], for $L_{18}$Bz$_{75}$M with $f_{\text{MPDL,0}} = 0.4$ [BzMA (0.454 g, 2.58 mmol), MPDL (0.289 g, 1.78 mmol), T21s initiator (1.4 mg, 6.56 $\times$ 10$^{-3}$ mmol), PLMA$_{18}$ macro-CTA (0.165 g, 3.35 $\times$ 10$^{-2}$ mmol) and heptane (5.0 g,
7.3 mL), for L$_{18}$Bz$_{75}$M with $f_{\text{MPDL},0} = 0.6$ [BzMA (0.330 g, 1.88 mmol), MPDL (0.455 g, 2.81 mmol), T21s initiator (1.0 mg, 4.45 × 10$^{-3}$ mmol), PLMA$_{18}$ macro-CTA (0.119 g, 2.41 × 10$^{-2}$ mmol) and heptane (5.0 g, 7.3 mL)], for L$_{18}$Bz$_{75}$M with $f_{\text{MPDL},0} = 0.7$ [BzMA (0.265 g, 1.88 mmol), MPDL (0.465 g, 2.81 mmol), T21s initiator (0.8 mg, 3.55 × 10$^{-3}$ mmol), PLMA$_{18}$ macro-CTA (0.093 g, 1.88 × 10$^{-2}$ mmol) and heptane (5.0 g, 7.3 mL)], for L$_{18}$Bz$_{300}$M with $f_{\text{MPDL},0} = 0.6$ [BzMA (0.265 g, 1.88 mmol), MPDL (0.465 g, 2.81 mmol), T21s initiator (0.8 mg, 3.55 × 10$^{-3}$ mmol), PLMA$_{18}$ macro-CTA (0.093 g, 1.88 × 10$^{-2}$ mmol) and heptane (5.0 g, 7.3 mL)] and for L$_{18}$Bz$_{300}$M with $f_{\text{MPDL},0} = 0.7$ [BzMA (0.265 g, 1.88 mmol), MPDL (0.465 g, 2.81 mmol), T21s initiator (0.8 mg, 3.55 × 10$^{-3}$ mmol), PLMA$_{18}$ macro-CTA (0.093 g, 1.88 × 10$^{-2}$ mmol) and heptane (5.0 g, 7.3 mL)]. Similar syntheses were also achieved to yield L$_{22}$Bz$_{75}$M, L$_{22}$Bz$_{300}$M, L$_{37}$Bz$_{75}$M and L$_{37}$Bz$_{300}$M, with $f_{\text{MPDL},0} = 0$–0.7.

**Synthesis of poly(lauryl methacrylate)-b-poly[(benzyl methacrylate)-co-(5,6-benzo-2-methylene-1,3-dioxepane)] (PLMA-b-P(BzMA-co-BMDO)).** A typical synthesis of PLMA$_{26}$-b-P(BzMA$_{100}$-co-BMDO) (L$_{26}$Bz$_{100}$B) by RAFT dispersion polymerization at 15 wt.% solids and with $f_{\text{BMDO},0} = 0.2$ was as follows: In a 40-mL vial, fitted with a rubber septum and a magnetic stirring bar, a mixture of BzMA (0.273 g, 1.55 mmol), BMDO (0.060 g, 3.67 × 10$^{-1}$ mmol), T21s initiator (0.6 mg, 2.78 × 10$^{-3}$ mmol) and PLMA$_{26}$ macro-CTA (0.104 g, 1.42 × 10$^{-2}$ mmol; macro-CTA/initiator molar ratio = 5.0) were dissolved in heptane (2.3 g, 3.4 mL). The mixture was degassed under stirring by argon bubbling for 15 min while
immersed in an ice bath (to avoid solvent evaporation). The mixture was then immersed in a preheated oil bath at 90 °C for 24 h. Samples were periodically withdrawn to determine the BzMA conversion by \(^1\)H NMR spectroscopy (by integrating the two oxymethylene protons of BzMA at 4.9 and 5.2 ppm) and the macromolecular characteristics, \(M_n\) and \(D\), by SEC. The nanoparticle colloidal characteristics, \(D_z\) and PSD, were obtained by DLS whereas their morphology was assessed by TEM. The nanoparticles were dried under reduced pressure and solubilized in a minimal amount of THF before precipitation (twice) in a mixture of cyclohexane/diethyl ether (1/1; v/v) and dried under high vacuum until constant weight. 

\(F_{BMDO}\) was determined by using integrated proton signals \(e\) and \(g\) in Figure S6 as follows: \(I_g / (I_e + I_g)\). The same procedure was repeated for \(f_{BMDO,0} = 0.4\) [BzMA (0.253 g, 1.43 mmol), BMDO (0.154 g, 9.47 \(\times\) 10\(^{-1}\) mmol), T21s initiator (0.6 mg, 2.78 \(\times\) 10\(^{-3}\) mmol), PLMA\(_{26}\) macro-CTA (0.102 g, 1.46 \(\times\) 10\(^{-2}\) mmol) and heptane (2.9 g, 4.2 mL)], for \(f_{BMDO,0} = 0.6\) [BzMA (0.265 g, 1.50 mmol), BMDO (0.346 g, 2.12 mmol), T21s initiator (0.6 mg, 2.78 \(\times\) 10\(^{-3}\) mmol) and PLMA\(_{26}\) macro-CTA (0.102 g, 1.46 \(\times\) 10\(^{-2}\) mmol) and heptane (4.0 g, 5.8 mL)] and for \(f_{BMDO,0} = 0.7\) [BzMA (0.114 g, 6.46 \(\times\) 10\(^{-1}\) mmol), BMDO (0.222 g, 1.36 mmol), T21s initiator (0.2 mg, 9.26 \(\times\) 10\(^{-4}\) mmol) and PLMA\(_{26}\) macro-CTA (0.040 g, 5.73 \(\times\) 10\(^{-3}\) mmol) and heptane (3.0 g, 4.4 mL)].

**Degradation of PLMA-\(b\)-P(BzMA-co-MPDL) and PLMA-\(b\)-P(BzMA-co-BMDO).** In a 5-mL vial, 50 mg of purified copolymer was dissolved in 2.5 mL of THF/MeOH (50/50; vol/vol). After solubilization, 2.5 mL of potassium hydroxide solution (KOH, 5 wt.\%) in MeOH was added. The cloudy mixture was stirred at room temperature. Samples (1 mL) were periodically taken, immediately dried under vacuum and mixed with 2 mL of chloroform, allowing salts filtration. Finally, the solvent was removed under reduced pressure and degradation products were analyzed by SEC.
**Film degradation.** Films of ~1 mm thickness and 1 cm² surface area were prepared by solvent casting. 0,2 mL of nanoparticles (L₂₇Bz₃₀₀M with F_{MPDL} = 0.19 or 0) were poured into a plastic mold of 1 cm². The mold was covered with aluminum foil and put inside fume hood, and the solvent was evaporated in air at room temperature for at least 24 h to prevent bubble formation. Then the film was further dried under oven at 50 °C overnight to remove the remaining solvent. After weighing, films were placed in individual vials containing 20 mL of 5 wt.% KOH aqueous solution and heated up to 90 °C under 700 rpm stirring (films were placed on top of a small silicone septum placed in the middle of the vial to avoid collision with the magnetic stirrer). Films were withdrawn after 3 days. Water uptake and mass loss were calculated by using the following equations:

\[
\text{Water uptake} = \frac{m_w - m_d}{m_d}
\]

Eq. 5

Where \( m_w \) and \( m_d \) are the mass of the wet film after degradation and of the dried film after degradation (quickly wiped with paper), respectively.

\[
\text{Mass loss} = \frac{m_d - m_0}{m_0}
\]

Eq. 6

Where \( m_0 \) is the initial mass of the film.

**Results and Discussion**

Given the very high water-sensitivity of CKA monomers,⁵⁶ PISA was performed in organic medium to avoid their premature hydrolysis and maximize their insertion in the final copolymer. The strategy we chose, adapted from the work of Armes and co-workers,¹¹ relied on the RAFT-mediated copolymerization of benzyl methacrylate (BzMA) with CKA monomers in heptane at 90 °C from a poly(lauryl methacrylate) (PLMA) macro-RAFT agent (Figure 2). We first used 2-methylene-4-phenyl-1,3-dioxolane (MPDL) as a CKA due to its
structural similarity with BzMA. Also, MPDL has recently been revisited and appears to be easy to synthesize and copolymerizes reasonably well with methacrylic esters, presumably due to its styrene-like propagating radical.42-44, 46, 54, 57

Figure 2. RAFT-mediated synthesis of poly(lauryl methacrylate) (PLMA) followed by radical ring-opening copolymerization-induced self-assembly (rROPISA) of benzyl methacrylate (BzMA) and 2-methylene-4-phenyl-1,3-dioxolane (MPDL) to synthesize degradable PLMA-\(b\)-P(BzMA-\(co\)-MPDL) (\(L_xBz_M\)) diblock copolymer nanoparticles.

A PLMA macro-CTA was first synthesized by RAFT-mediated polymerization of LMA in anhydrous toluene at 70 °C for 4 h using CDSPA as a CTA and AIBN as a radical initiator. A 4.9 kg.mol\(^{-1}\) PLMA with a low dispersity (\(D = 1.18\)) was recovered after purification (PLMA\(_{18}\), Table S1).

The PLMA\(_{18}\) macro-CTA was then used to control the polymerization of BzMA (targeted \(DP_{n,BzMA} = 150\), \(M_n \approx 30\) kg.mol\(^{-1}\), \(L_{18}Bz_{150}M\)) in heptane at 90 °C and 15 wt.% solids in the presence of T21s as a radical initiator and variable initial amounts of MPDL (\(f_{MPDL,0} = 0–0.7\)). The copolymerizations proceeded over a period of 24 h and reached
relatively high monomer conversions (~75–90%) (Figure 3a). Adding MPDL in the comonomer feed slightly decreased the polymerization rate compared to BzMA homopolymerization as the higher $f_{MPDL,0}$, the lower the final BzMA conversion (note that MPDL conversion ranged from 80 to 60% with an increase of $f_{MPDL,0}$). For all initial molar fractions of MPDL, $M_n$ values increased linearly with conversion and were in relatively good agreement with the theoretical values, which gives a good indication on the quality of the control (Figure 3b). Note that the observed discrepancy between theoretical and experimental $M_n$ was likely because PMMA standards used to build the conventional calibration do not strictly reflect the structure of the resulting copolymer. Dispersities were low at 20–40% conversion ($D = 1.14–1.26, M_n \sim 9–10 \text{ kg.mol}^{-1}$) and tended to reasonably increase at high conversion ($D = 1.46–1.62, M_n \sim 20–30 \text{ kg.mol}^{-1}$). The control experiment consisting in a chain extension of the PLMA$_{18}$ macro-CTA with BzMA ($L_{18}Bz_{150}$) yielded a diblock copolymer of $M_n = 29 \text{ kg.mol}^{-1}$ and $D \sim 1.4$.

![Figure 3](image.png)

**Figure 3.** RAFT-mediated dispersion copolymerization of benzyl methacrylate (BzMA) and 2-methylene-4-phenyl-1,3-dioxolane (MPDL) initiated by a poly(lauryl methacrylate)$_{18}$ macro-chain transfer agent ($L_{18}Bz_{150}$) at 15 wt.% solids in heptane at 90 °C as a function of the initial fraction of MPDL ($f_{MPDL,0} = 0–0.7$). (a) BzMA conversion vs. time. Dashed lines connecting data points are guides for the eye only. (b) Number-average molar mass, $M_n$ and
dispersity, $M_n/M_w$, vs. BzMA conversion determined by SEC. The dashed black line represents the theoretical $M_n$.

The initially homogeneous polymerizing solutions all became translucent after ~ 0.5–1 h, which proved the beginning of micellar nucleation and thus the formation of particles via partitioning of the monomer into the growing micelles from the continuous phase. After polymerization, the nanoparticles were analyzed by DLS and TEM. Average intensity-diameters ($D_z$) measured by DLS nicely superimposed with both average volume-diameters and number-diameters (Figure S1), and were in the 80–211 nm range (Figure 4), depending on the initial amount of MPDL; the higher $f_{\text{MPDL},0}$, the higher $D_z$. For $f_{\text{MPDL},0} = 0.2–0.6$, nanoparticles were narrowly dispersed as particle size distribution (PSD) values given by the DLS apparatus were in the 0.02–0.12 range. However, for $f_{\text{MPDL},0} = 0.7$, PSD = 0.33 indicating a broad particle size distribution (which may explain why the average diameter for this experiment was not strictly following the $f_{\text{MPDL},0}$ vs. $D_z$ trend mentioned previously). The different nanoparticle suspensions exhibited excellent, long-term colloidal stability as intensity-average diameters and PSD values measured by DLS were nearly constant for more than a month (Figure 4).
Figure 4. Evolution with time of the intensity-average diameter ($D_z$) and particle size distribution (PSD) measured by DLS of L$_{18}$Bz$_{150}$M nanoparticles as function of the molar fraction of MPDL ($F_{MPDL}$) in the copolymer.

TEM analyses of the four nanoparticle suspensions were in excellent agreement with DLS data in terms of evolution of both average diameters and PSD (Figure 5). Indeed, very small and narrowly dispersed nanoparticles were obtained for $F_{MPDL} = 0.06$ and 0.14 which then tended to increase in size and PSD for higher $F_{MPDL}$ values. Note that average diameters given by TEM were constantly smaller than those from DLS because TEM observation is performed in dry state.
Figure 5. Representative TEM images and particle size distributions ($n = 400–1000$) of $L_{18}Bz_{150}M$ nanoparticles as function of the molar fraction of MPDL ($F_{\text{MPDL}}$) in the copolymer: (a) and (b) $F_{\text{MPDL}} = 0.06$; (c) and (d) $F_{\text{MPDL}} = 0.14$; (e) and (f) $F_{\text{MPDL}} = 0.25$ and (g) and (h) $F_{\text{MPDL}} = 0.37$. Scale bars = 200 nm.

The most important question is now: was MPDL successfully copolymerized with BzMA by rROP and did it lead to tunable amounts of ester groups in the copolymer backbone to yield degradable block copolymer nanoparticles by PISA? To address this crucial point, the different block copolymer nanoparticles were characterized in terms of copolymer composition and degradation (Figure 6). The four different nanoparticle suspensions were dried under high vacuum and the resulting block copolymers were analyzed by $^1$H NMR.
spectroscopy to assess the presence of MPDL units (Figure 6a). Interestingly, $^1$H NMR spectra showed all expected peaks accounting for a PLMA-b-P(BzMA-co-MPDL) structure; in particular protons $g$, $h$ and $i$ of inserted MPDL, methylene protons $e$ in $\alpha$-position to the ester group of BzMA, methyl protons $a$ from BzMA and LMA, and aromatic protons $f$ from phenyl groups of BzMA and MPDL. Importantly, intensities of protons $g$, $h$ and $i$ from MPDL increased with $f_{\text{MPDL,0}}$ which suggested its increasing incorporation with the increase of its initial content in the monomer feed. By $^1$H NMR, the amounts of MPDL in the copolymer ($F_{\text{MPDL}}$) were equal to 0.06, 0.14, 0.25 and 0.37 for $f_{\text{MPDL,0}} = 0.2$, 0.4, 0.6 and 0.7, respectively.
Figure 6. (a) $^1$H NMR spectra in CDCl$_3$ in the 0–8 ppm region. (b) Evolution with time of the number-average molar mass ($M_n$) during degradation under accelerated conditions (THF/MeOH, 2.5% KOH) of L$_{18}$Bz$_{150}$M copolymers as function of the molar fraction of MPDL ($F_{MPDL}$) in the copolymer. Plain lines for $F_{MPDL} = 0.06$, 0.14 and 0.25 represent the exponential decay fit, equation plot: $M_n(t) = M_{n,\infty} + a \times \exp(-t/\tau)$. (c) Picture of films obtained by solvent casting from L$_{37}$Bz$_{300}$M nanoparticles ($F_{MPDL} = 0.19$ and $F_{MPDL} = 0$) and subjected to degradation under accelerated conditions (water, KOH 5%, 90°C, 3 days).
Degradation of the different copolymers was then performed under accelerated conditions (THF/MeOH, 2.5% KOH) to assess the presence of ester groups in the copolymer backbone (Figure 6b). As expected, the MPDL-free PLMA-\(b\)-PBzMA copolymer (\(L_{18}Bz_{150}, F_{\text{MPDL}} = 0\)) gave no degradation as shown by its nearly constant \(M_n\) over time. On the contrary, PLMA-\(b\)-P(BzMA-\(c/o\)-MPDL) copolymers (\(L_{18}Bz_{150}M\)) led to significant and rapid degradation (\(M_n\) decrease ranging from -87 to -96%) in relationship with their respective MPDL content, as shown by the shifts of the SEC chromatograms towards lower \(M_n\) values (Figure S2). Indeed, the higher the MPDL content in the copolymer, the greater the degradation. The \(M_n\) after degradation reached 3100 g.mol\(^{-1}\) for \(F_{\text{MPDL}} = 0.06\), 1300 g.mol\(^{-1}\) for \(F_{\text{MPDL}} = 0.14\) and 700 g.mol\(^{-1}\) for \(F_{\text{MPDL}} = 0.25\). These results are in excellent agreement with the theoretical \(M_n\) after degradation, \(M_{n,\text{th}}\), calculated according to Eq. 7, giving 2920, 1240 and 690 g.mol\(^{-1}\), respectively (Table S2).

\[
M_{n,\text{th}} = MW_{\text{BzMA}} \times (1 / F_{\text{MPDL}} - 1) + MW_{\text{MPDL}} \tag{Eq. 7}
\]

Interestingly, when films of ~1 mm thickness and 1 cm\(^2\) surface area were obtained by solvent casting from \(L_{37}Bz_{300}M\) nanoparticles (\(F_{\text{MPDL}} = 0.19\) and \(F_{\text{MPDL}} = 0\)) and subjected to degradation in water under accelerated conditions (KOH 5%, 90°C) for 3 days, the MPDL-containing film (\(F_{\text{MPDL}} = 0.19\)) led to a 14% weight loss and a 31% water uptake compared to a mass loss of 1.6% and a water uptake of 11% for the MPDL-free film (\(F_{\text{MPDL}} = 0\)). The latter also kept its white color whereas the former became yellowish and very brittle.

Overall, it confirmed the significant insertion of open MPDL units in the main chain of the copolymers and the possibility to fine-tune their degradation by adjusting the initial comonomer stoichiometry. Also, even though the film degradation experiment has been done
under accelerated conditions, the result is already promising because it shows that a material obtained by rROPISA can be degraded conversely to its counterpart obtained by traditional PISA.

Variation of the solvophilic and solvophobic block chain lengths

The chain lengths of the solvophilic and solvophobic blocks were then independently varied by tuning $DP_{n,PLMA}$ and $DP_{n,PBzMA}$, respectively, to access different relative volume fractions. By adjusting the $[\text{CDSPA}]_0/[\text{LMA}]_0$ ratio, two other well-defined PLMA with $M_n = 6100$ and 9800 g.mol$^{-1}$ and low dispersity ($D = 1.17–1.21$) were obtained, denoted as PLMA$_{22}$ and PLMA$_{37}$, respectively (Table S1). Chain-extension of the three macro-CTAs was then performed under otherwise identical experimental conditions as previously described, to cover $DP_{n,BzMA} = 75, 150$ and 300, and variable initial amounts of MPDL ($f_{\text{MPDL},0} = 0.2–0.7$) in each case in order to have a global picture of the system (Table S3).

Overall, the higher $f_{\text{MPDL},0}$, the slower the copolymerizations, with final BzMA conversions ranging, in average, from $\sim 81\%$ for $f_{\text{MPDL},0} = 0.2$ to $\sim 63\%$ for $f_{\text{MPDL},0} = 0.7$. Consequently, for each type of macro-CTA, the final $M_n$ of the copolymer tended to decrease with an increase of $f_{\text{MPDL},0}$ (although inaccuracy from SEC deriving from a change in the nature of the copolymer composition may also play a role). For fixed values of $DP_{n,PLMA}$ and $f_{\text{MPDL},0}$, dispersities tended to increase with the increase of $DP_{n,BzMA}$, likely because of the occurrence of irreversible termination reactions that were more significant for longer copolymer chain-lengths. Interestingly, with PLMA$_{18}$ and PLMA$_{22}$, varying the value of $DP_{n,BzMA}$ from 75 to 300 had no noticeable influence on the amount of MPDL in the copolymer for a fixed value of $f_{\text{MPDL},0}$ as $F_{\text{MPDL}}$ values were $0.06 \pm 0.01$, $0.12 \pm 0.02$, $0.23 \pm 0.03$ and $0.30 \pm 0.04$ for $f_{\text{MPDL},0} = 0.2, 0.4, 0.6$ and 0.7, respectively. However, $F_{\text{MPDL}}$ values were substantially higher when using PLMA$_{37}$ as a macro-CTA. Degradation under
accelerated conditions was also successfully demonstrated for $\text{L}_{37}\text{Bz}_{300}\text{M}$ copolymers (Figure S3-S4), leading to good agreements between experimental $M_n$ after degradation and theoretical values (Table S4), although degradation was slower for $F_{\text{MPDL}} = 0.06$, as $M_n = 16700 \text{ g.mol}^{-1}$ after 1 h but further decreased down to 6200 g.mol$^{-1}$ after 24 h.

Stable nanoparticles were successfully obtained for all diblock copolymer compositions. Similarly to what has been previously seen with $\text{L}_{18}\text{Bz}_{150}\text{M}$ nanoparticles, the increase of $D_z$ vs. $F_{\text{MPDL}}$ was overall observed as shown by DLS (Table S3 and Figure 7). Interestingly, the higher the targeted $D \text{P}_n$, the less marked the increase of the average diameter (Figure 7a,c,e). For instance, for $\text{L}_x\text{Bz}_{300}\text{M}$, $D_z$ values increased by a factor of 1.3–1.9 depending on the macro-CTA used, whereas for $\text{L}_x\text{Bz}_{75}\text{M}$, it ranged from 2.2 to 7.2. Moreover, for $\text{L}_x\text{Bz}_{75}\text{M}$ and $\text{L}_x\text{Bz}_{150}\text{M}$, PSD also increased with the increase of $F_{\text{MPDL}}$ (Figure 7). Conversely, a different behavior was observed for $\text{L}_x\text{Bz}_{300}\text{M}$ as very low PSD values (ca. 0.02) were obtained when for $\text{L}_{18}$ and $\text{L}_{22}$ (Figure 7b,d), whereas for $\text{L}_{37}$, PSD stayed moderately low (~0.15 in average) whatever $F_{\text{MPDL}}$ (Figure 7f). In summary, the best colloidal properties in terms of $D_z$ and PSD were obtained for $\text{L}_{18}\text{Bz}_{300}\text{M}$ and $\text{L}_{22}\text{Bz}_{300}\text{M}$ nanoparticles.
Figure 7. Evolution of the intensity-average diameter ($D_z$) and particle size distribution (PSD) with the molar fraction of MPDL ($F_{MPDL}$) in the copolymer measured by DLS of $L_xBz_yM$ nanoparticles ($x = 18, 22$ and $37$, $y = 75, 150$ and $300$): $L_{18}Bz_{150}M$ (a, b), $L_{22}Bz_{150}M$ (c, d) and $L_{37}Bz_{300}M$ (e, f). Dashed lines are guides for the eye only.

The complete library of $L_{18}Bz_{150}M$ nanoparticles together with $L_{22}Bz_{300}M$ and $L_{37}Bz_{300}M$ nanoparticles were also comprehensively characterized by TEM (Figure 8 and S5, and Table S5) in terms of $D_n$, $D_w$, $D_z$ and polydispersity index (see experimental part). Overall, TEM
analysis gave the same tendencies as those obtained by DLS. In particular, it confirmed the synthesis of very small and narrowly dispersed nanoparticles for the low and intermediate $F_{\text{MDPL}}$ values whatever the composition of the copolymers, and the best colloidal properties across all $F_{\text{MDPL}}$ values for $L_{18}B_{300}M$ nanoparticles.
Figure 8. Representative TEM images and particle size distributions (n = 400–1000) of L_{18}Bz_{y}M nanoparticles as function of DP_{n,PBzMA} and the initial molar fraction of MPDL (f_{MPDL,0}). Scale bars = 200 nm. See Table S5 for TEM data (D_n, D_w, D_z and polydispersity index).

Application to 5,6-benzo-2-methylene-1,3-dioxepane (BMDO)

To illustrate the versatility of the system, rROPISA was performed under similar experimental conditions with 5,6-benzo-2-methylene-1,3-dioxepane (BMDO), which is also a well-known
CKA monomer used in rROP (Figure 9). The copolymerizations were initiated from a short PLMA$_{26}$ macro-CTA (Table S1) and $f_{\text{BMDO,0}}$ was varied from 0.2 to 0.6 for $DP_{n,\text{PBzMA}} = 100$ (Table S6) to target $L_{26}\text{Bz}_{100}\text{B}$ copolymer nanoparticles. In all cases, high conversions were also obtained (85–95 %) with $^1$H NMR spectroscopy showing the expected protons from incorporated BMDO in the copolymer and their increasing intensities with the increase of $f_{\text{BMDO,0}}$ (Figure S6). However, varying $f_{\text{BMDO,0}}$ had less impact on the molar mass and the dispersity than for MPDL-based rROPISA experiments (Table S3), as $M_n$ ranged from 39400 to 30600 g.mol$^{-1}$ and $D$ values stayed rather low and fairly constant (1.30–1.34). Incorporation of BMDO was also slightly higher than for MPDL as $F_{\text{BMDO}}$ ranged from 0.09 ($f_{\text{BMDO,0}} = 0.2$) to 0.37 ($f_{\text{BMDO,0}} = 0.6$).

![Figure 9](image)

**Figure 9.** RAFT-mediated radical ring-opening copolymerization-induced self-assembly (rROPISA) of benzyl methacrylate (BzMA) and 5,6-benzo-2-methylene-1,3-dioxepane (BMDO) to synthesize degradable PLMA-$b$-P(BzMA-$co$-BMDO) diblock copolymer nanoparticles ($L_x\text{Bz}_y\text{B}$).
Stable nanoparticles were successfully obtained for each condition but conversely to rROPISA with MPDL, varying $f_{\text{BMDO},0}$ led to minimal variation of the colloidal properties as $D_z$ slightly increased from 60 to 73 nm (Table S6 and Figure S7), so did PSD values (0.09–0.16). The colloidal properties of the different nanoparticles were confirmed by TEM (Figure 10 and Table S7).

**Figure 10.** Representative TEM images and particle size distributions (n = 500) of $\text{L}_{26}\text{Bz}_{100}\text{B}$ nanoparticles as function of the molar fraction of BMDO ($F_{\text{BMDO}}$) in the copolymer: (a) and (b) $F_{\text{BMDO}} = 0.09$; (c) and (d) $F_{\text{BMDO}} = 0.18$; (e) and (f) $F_{\text{BMDO}} = 0.37$. Scale bars = 200 nm. See Table S7 for TEM data ($D_n$, $D_w$, $D_z$ and polydispersity index).
Degradation of the different PLMA-\(b\)-P(BzMA-\(co\)-BMDO) copolymers under accelerated conditions led to a similar degradation pattern to that obtained from PLMA-\(b\)-P(BzMA-\(co\)-MPDL) copolymers. The higher the BMDO content in the copolymer, the greater the degradation (Figure 11 and S8). The \(M_n\) after degradation reached \(\sim 2900\ \text{g.mol}^{-1}\) for the lowest BMDO content \((F_{\text{BMDO}} = 0.09)\) and complete degradation \((M_n < 1000\ \text{g.mol}^{-1})\) was reached for \(F_{\text{BMDO}} \geq 0.18\), which was in agreement with theoretical \(M_n\) values after degradation and confirmed the significant insertion of open BMDO units in the copolymers (Table S8).

![Figure 11](image)

**Figure 11.** Evolution with time of the number-average molar mass \((M_n)\) during degradation under accelerated conditions (THF/MeOH, 2.5% KOH) of \(L_{26}\)Bz\(_{100}\)B copolymers as function of the molar fraction of BMDO \((F_{\text{BMDO}})\) in the copolymer. Plain lines for \(F_{\text{BMDO}} = 0.09, 0.18\) and 0.37 represent the exponential decay fit, equation plot: \(M_n(t) = M_{n,\infty} + a \times \exp(-t/\tau)\).

Note that, given the non-degradability of the PLMA\(_{26}\) macro-CTA, its SEC trace is still visible for highly degraded copolymers, similarly to PLMA-\(b\)-P(BzMA-\(co\)-MPDL) copolymers (Figure S2, S3 and S8).
**Morphology of the nanoparticles**

PISA is known to give access to block copolymer nanoparticles with different morphologies (i.e., spheres, worms or vesicles) by varying the solvophilic and solvophobic block chain lengths. However, all PLMA-\textit{b}-P(BzMA-\textit{co}-CKA) nanoparticle suspensions obtained in this study were in fact spheres. According to literature, PISA of BzMA in heptane from a short PLMA macro-CTA ($DP_{n,\text{PLMA}} \sim 20$) should conduct to vesicles for $DP_{n,\text{BzMA}} \geq 80$ whereas spheres should be obtained for $DP_{n,\text{PLMA}} \geq 37$ whatever $DP_{n,\text{BzMA}}$. The absence of any other morphologies than spheres for \textbf{L18-22Bz150-300M} and \textbf{L26Bz100B} nanoparticles, where vesicles (or at least mixed phases) would have been expected, could be explained by: (i) the use of a different RAFT agent and/or (ii) the presence of CKA units in the copolymer structure.

CDSPA was selected as a RAFT agent because it could be advantageous to position linear carboxylic acid moieties at the surface of the nanoparticles for further functionalization to access functional materials. However, it has a very different structure than cumyl dithiobenzoate (CDB), the RAFT agent originally used to perform traditional PISA of BzMA in heptane.$^{11}$ This may prevent the formation of other nanoobjects than spheres because of surface-exposed COOH groups. Such a sensitivity to the RAFT agent structure has already been highlighted by Whittaker, Davis and co-workers.$^{58}$ It has also been shown that the morphology transition of diblock copolymer nano-objects was enhanced when the glass transition temperature ($T_g$) of the solvophobic block is lowered, by copolymerization with suitable monomers, leading to increased mobility in the continuous phase. However, since the $T_g$ of PMPDL and that of PBzMA are rather close ($T_g,\text{PMPDL} = 45 \pm 10$ °C$^{54}$ vs. $T_g,\text{PBzMA} = 54$ °C$^{59}$), this hypothesis seemed unlikely.

To decorrelate potential effects of the RAFT agent and MPDL, we performed PISA of:

(i) BzMA ($DP_{n,\text{BzMA}} = 120$) from a PLMA$_{17}$-CDB with $f_{\text{MPDL},0} = 0$ (\textbf{CDB-L17Bz120}) or 0.2
(CDB-L_{17}Bz_{120}M) and (ii) BzMA from PLMA_{17}-CDSPA ($DP_{n,\text{PBzMA}} = 75$) or PLMA_{22}-CDSPA ($DP_{n,\text{PBzMA}} = 75$ or 150) with $f_{\text{MPDL},0} = 0$ (L_{17}Bz_{75}, L_{22}Bz_{75} and L_{22}Bz_{150}, respectively). Whereas CDB-L_{17}Bz_{120} clearly led to vesicles (Figure S9a), incorporation of 11 mol.% of MPDL in the PBzMA block (CDB-L_{17}Bz_{120}M) led to spheres, thus showing the detrimental role of MPDL on the formation of vesicles (Figure S9b). On the other hand, polymerization of BzMA in absence of MPDL from PLMA_{17}-CDSPA and PLMA_{22}-CDSPA (L_{17}Bz_{75}, L_{22}Bz_{75} and L_{22}Bz_{150}) only led to spheres, also demonstrating the negative influence CDSPA compared to CDB on the formation of vesicles (Figure S10). Overall, both the use CDSPA as the RAFT agent and insertion of MPDL in the solvophobic block prevent efficient formation of other morphologies than spheres.

**Conclusion**

For the first time, radical ring-opening polymerization-induced self-assembly was reported by copolymerizing CKA monomers (MPDL and BMDO) with a methacrylic ester derivative in heptane from a macro RAFT agent. It led to stable, narrowly dispersed block copolymer nanoparticles comprising tunable amounts of ester groups in the solvophilic block ranging from 4 to ~40 mol.%. Various structural parameters were varied (e.g.; nature of the CKA, macro-RAFT agent chain length, targeted solvophobic chain length, initial amount of CKA) followed by a comprehensive characterization by DLS and TEM to get insight into the system. Interestingly, stable nanoparticles were obtained in all cases but increasing the amount of CKA led to broader particle size distributions except for a targeted solvophobic chain length of 300. Hydrolytic degradation of the different copolymers was assessed under accelerated conditions and was in good agreement with the amount of CKA inserted. Morphological investigation revealed that spheres were obtained in all cases, which was
assigned to the use CDSPA as the RAFT agent and insertion of CKA in the solvophobic
block, preventing formation of other morphologies.

Not only this work is the first report of rROPISA, but it may also open the door to
further developments regarding degradable vinyl polymer nanoparticles which may find
applications in the biomedical field or for environmental protection.

Supplementary Information

Macromolecular characteristics of the macro-RAFT agents, macromolecular and colloidal
properties of the different copolymer nanoparticles before and after degradation, SEC
chromatograms of the copolymers during degradation, TEM images and particle size
distributions of copolymer nanoparticles, DLS data, $^1$H NMR spectra of BMDO-containing
copolymers, TEM images of control copolymer nanoparticles.

Acknowledgments

We thank the French Ministry of Research for the financial support of the PhD thesis of EG,
the Erasmus internship for the stay of EG and the CSC PhD fellowship (2017-2021) of CZ.
The authors thank Claire Boulogne and Cynthia Gillet for technical assistance in TEM (I2BC,
Gif-sur-Yvette, France). The CNRS is also acknowledged for financial support.

References


17. Tan, J.; Bai, Y.; Zhang, X.; Zhang, L. Room temperature synthesis of poly(poly(ethylene glycol) methyl ether methacrylate)-based diblock copolymer nano-objects via


Table of Contents Graphic

Radical Ring-Opening Copolymerization-Induced Self-Assembly (rROPISA)

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