

Supporting Information

MRI-visible nanoparticles from hydrophobic gadolinium poly(ϵ -caprolactone) conjugates

Barbara Porsio, Laurent Lemaire, Sarah El Habnoui, Vincent Darcos, Florence Franconi, Xavier Garric, Jean Coudane, Benjamin Nottelet*

Experimental section

1. Synthesis of clickable Gd(III) chelate (diN_3 -DTPA(Gd(III))) **1**

In a first step, 1-azido-3-aminopropane was prepared according to a previously described procedure.¹ A solution of 3-chloropropylamine hydrochloride (4 g ; 30.8 mmol) and sodium azide (6 g ; 92.3 mmol) in water (1 mL per mmol) was heated at 80°C overnight. After removing most of the water by distillation under vacuum, the reaction mixture was cooled in an ice bath. Diethyl ether (50 mL) and then KOH pellets (4 g) were added keeping the temperature below 10°C in an ice bath. After separation of the organic phase, the aqueous layer was further extracted with diethyl ether (2 X 20 mL). The combined organic layers were dried over MgSO₄ and concentrated to give oil which was purified by distillation. 2.46g of colorless oil was obtained (80% yield). NMR ¹H (300 MHz, CDCl₃), δ (ppm) : 3.33 (t, 2H, CH₂N₃) ; 2.55 (t, 2H, CH₂NH₂) ; 2.34 (s, 2H, NH₂) ; 1.55 (q, 2H, CH₂CH₂CH₂). FT-IR (ATR, cm⁻¹) : 2100 (N₃).

In a second step, diN_3 -DTPA was synthesized according to a modified described procedure.² Typically, 1-azido-3-aminopropane (0.62 g ; 6.2 mmol) was reacted with DTPA dianhydride in anhydrous DMF (20 mL) at room temperature and under nitrogen for 24 hours. DMF was distilled off under vacuum until 2–3 mL in volume and precipitated into diethyl ether. The obtained solid was further dissolved in water and lyophilized to yield a white solid (1.48 g,

95% yield). NMR ^1H (300 MHz, DMSO), δ (ppm) : 3.4 (6H, $\text{CH}_2\text{CO}_2\text{H}$) ; 3.1 (12H, $\text{N}(\text{CH}_2)_2\text{N}$ and $\text{NCH}_2\text{C}(\text{O})$) ; 2.8 (8H, $\text{CH}_2\text{NHC}(\text{O})$ and CH_2N_3) ; 1.7 (4H, $\text{CH}_2\text{CH}_2\text{N}_3$). FT-IR (ATR, cm^{-1}) : 2100 (N_3). LC-MS (ES+, m/z): 558.4 Da [$\text{M}+\text{H}^+$].

Pyridine (1.44 mL ; 17.9 mmol) was added to an aqueous solution of $\text{diN}_3\text{-DTPA}$ (1 g ; 1.79 mmol). After 10 minutes stirring at room temperature a clear solution was obtained and $\text{GdCl}_3\cdot 6\text{H}_2\text{O}$ (1.33 g, 3.58 mmol) was added. Complexation was let to run under stirring at 40°C for 24 hours. Water and pyridine were removed by distillation under vacuum. The resulting solid was dissolved in water before purification on a Chelex® 100 resin. After freeze drying **2** was obtained as a white solid (90% yield).

Absence of free Gd(III) was checked by a Methyl Thymol Blue (MTB) test³ and the content of complexed Gd(III) in **1** was quantitatively determined by ICP-MS. FT-IR (ATR, cm^{-1}) : 2100 (N_3). MALDI-TOF (dithranol, m/z) : 713.16 Da [$\text{M}+\text{H}^+$] ; 1423.33 Da [$2\text{M}+\text{H}^+$] (theoretical 713.17 and 1425.34). Gd(III) content of the chelate (ICP-MS) : 15.4wt%.

2. Synthesis of poly(α -propargyl- ϵ -caprolactone-co- ϵ -caprolactone)s P(Pg-CL) **2**

α -propargyl- ϵ -caprolactone ($\alpha\text{Pg}\epsilon\text{CL}$) was synthesized as previously described.⁴ Polymerization was carried out in bulk using standard Schlenk technique under an inert atmosphere of argon. Amounts of ϵCL and $\alpha\text{Pg}\epsilon\text{CL}$ were added in the reaction flask according to the targeted composition. In a typical experiment, ϵCL (2.66 g, 26.3 mmol), $\alpha\text{Pg}\epsilon\text{CL}$ (0.21 g, 1.4 mmol), $\text{Sn}(\text{Oct})_2$ (37.3 mg, 0.092 mmol) and benzyl alcohol (4.75 μL , 0.046 mmol) were placed in an oven dried Schlenk tube. The tube was fitted with a rubber septum. The solution was further degassed by three freeze-pump-thaw cycles. The resulting mixture was stirred at 140°C for 3.5 hours. To stop the reaction, polymerization was quenched by addition of an excess of 1N HCl. The reaction mixture was poured into cold methanol. The polymer was collected by filtration and dried in vacuum.

The molar ratio of α Pg ϵ CL in the copolyester was calculated by ^1H NMR integration using the ratio of the propargyl signal ($\text{C}\equiv\text{CH}$) at $\delta = 1.96$ ppm versus the backbone signal at $\delta = 4.00$ ppm (CH_2O of the polymer backbone).

^1H NMR (300 MHz, CDCl_3) δ (ppm) = 4.96 (m, $(\text{CH}_3)_2\text{CH}$), 4.02 (t, CH_2O), 3.60 (m, CH_2OH), 2.50 (m, COCHCH_2), 2.26 (t, COCH_2), 1.96 (m, $\text{C}\equiv\text{CH}$), 1.49-1.70 (m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-O-}$), 1.29-1.42 (m, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-O-}$), 1.18 (d, $(\text{CH}_3)_2\text{CH}$). IR (ATR, cm^{-1}) : 3280 ($\text{C}\equiv\text{CH}$), 1720 ($\text{C}=\text{O}$). $F_{\alpha\text{Pr}\epsilon\text{CL}} = 5\%$, $M_{\text{NSEC}} = 25\ 000\ \text{g}\cdot\text{mol}^{-1}$. $M_w/M_n = 1.9$.

3. Synthesis of poly(ϵ -caprolactone-co-5-amino- δ -valerolactone) **4**

Poly(ϵ -caprolactone-co-5-amino- δ -valerolactone) P(CL-co-NH₂VL) was synthesized as previously described.⁵ Polymerization was carried out in bulk using standard Schlenk technique under an inert atmosphere of argon. Amounts of ϵ CL and 5-Z-amino- δ -valerolactone (NH₂-VL) were added in the reaction flask according to the targeted composition. Deprotection of the amino group was carried out under acidic conditions prior to dialysis and freeze-drying. The molar ratio of NH₂-VL in the copolyester was determined by ^1H NMR analysis using the intensities of the signal at $\delta = 3.50$ ppm corresponding to the methine proton of the NH₂-VL units and of the signal at $\delta = 4.00$ ppm corresponding to the methylene protons of ϵ CL NH₂-VL and units. $F_{\text{NH}_2\text{-VL}} = 33\%$, $M_{\text{NSEC}} = 6000\ \text{g}\cdot\text{mol}^{-1}$. $D = 1.2$.

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Figures

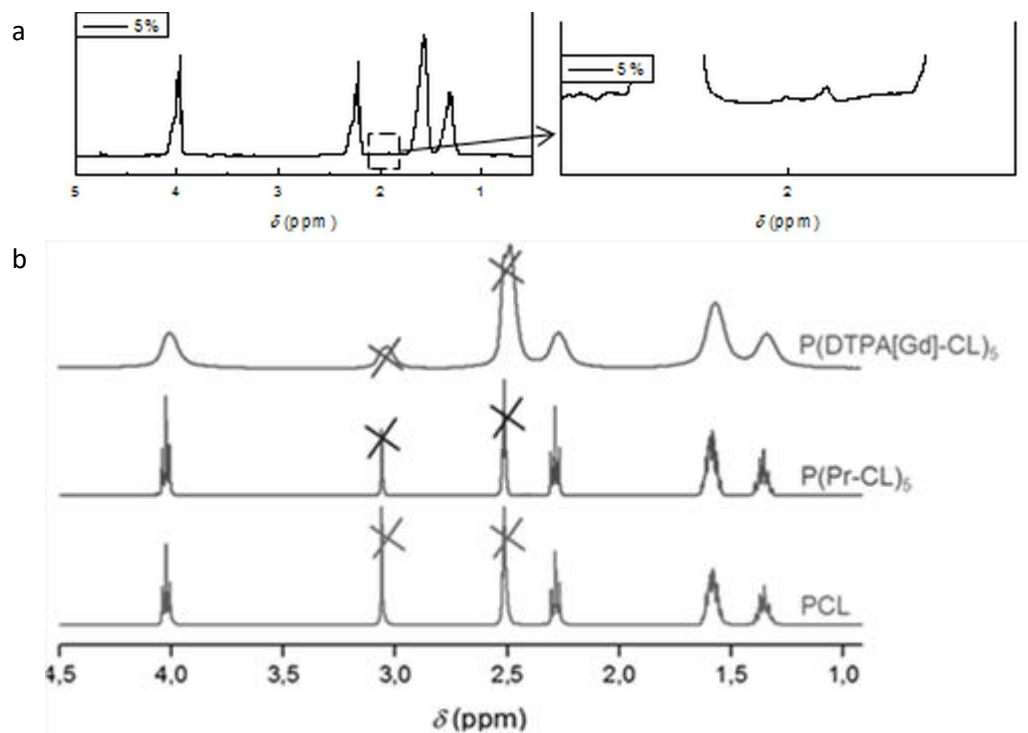


Figure S1. ^1H NMR spectra and inset of (a) P(Pg-CL) (**2**) containing 5 mol% of $\alpha\text{Pg-CL}$ (CDCl_3 , 300MHz) and (b) PCL (pink line), P(Pg-CL) (**2**, green line) and PCL(DTPA(Gd)) containing 2.6 wt% of Gd(III) (**3**, red line) ($d_6\text{DMSO}$, 300 MHz, marks correspond to $d_6\text{DMSO}$ at 2.5 ppm and residual water at 3.3 ppm).

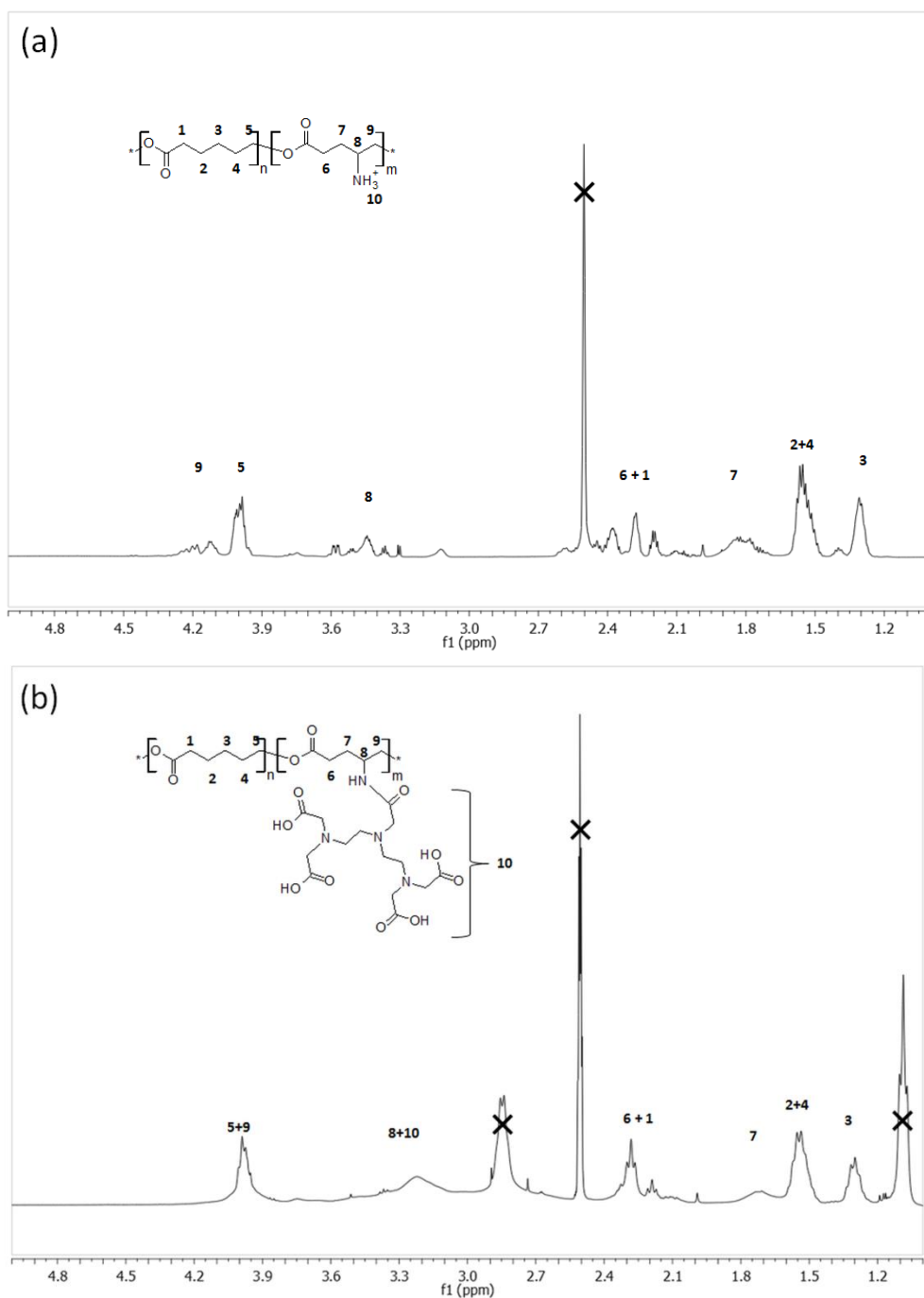


Figure S2. ^1H NMR spectra of (a) P(CL-co-NH₂VL) (**4**) and (b) PCL-co-VL(DTPA(Gd)) (**5**) (d_6DMSO , 300 MHz, marks correspond to d_6DMSO at 2.5 ppm and residual ammonium salts at 1.1 and 2.8 ppm).

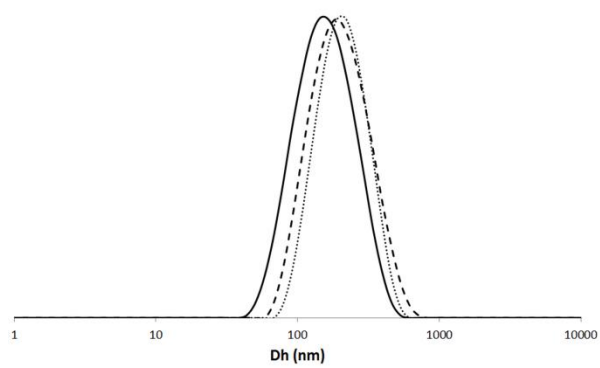


Figure S3. DLS intensity size distribution of PCL nanoparticles (full line) PCLDTPA(Gd) NP3 (dashed line) and PCL-co-VLDTPA(Gd) NP5(dot line).

