Supporting Information for

Poly(HPMA)-based Copolymers with Biodegradable Side Chains Able to Self Assemble into Nanoparticles

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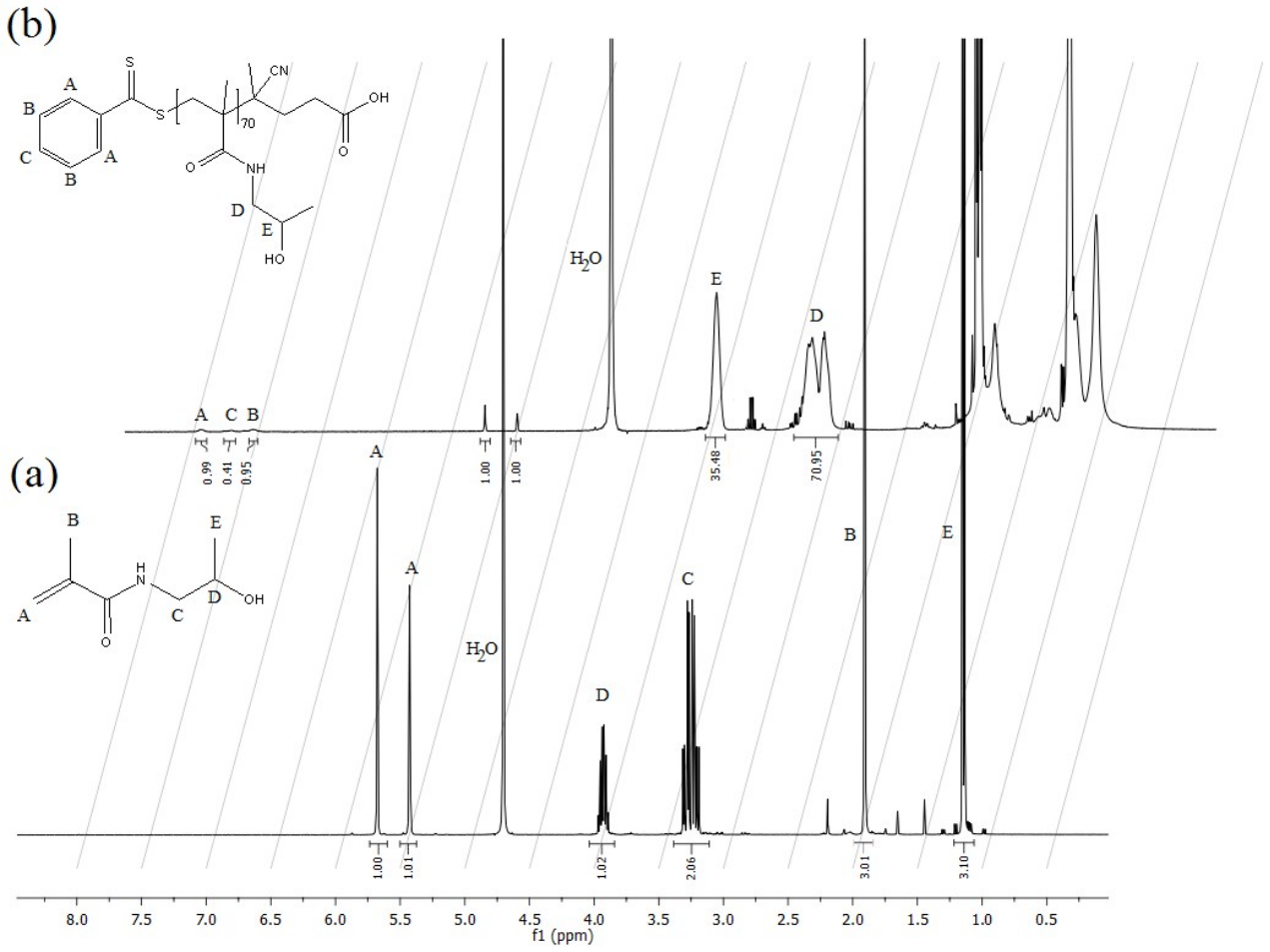

Figure S1. ^{1}H NMR spectra recorded in D_2O for: (a) HPMA monomer and (b) poly(HPMA)-macro RAFT agent.

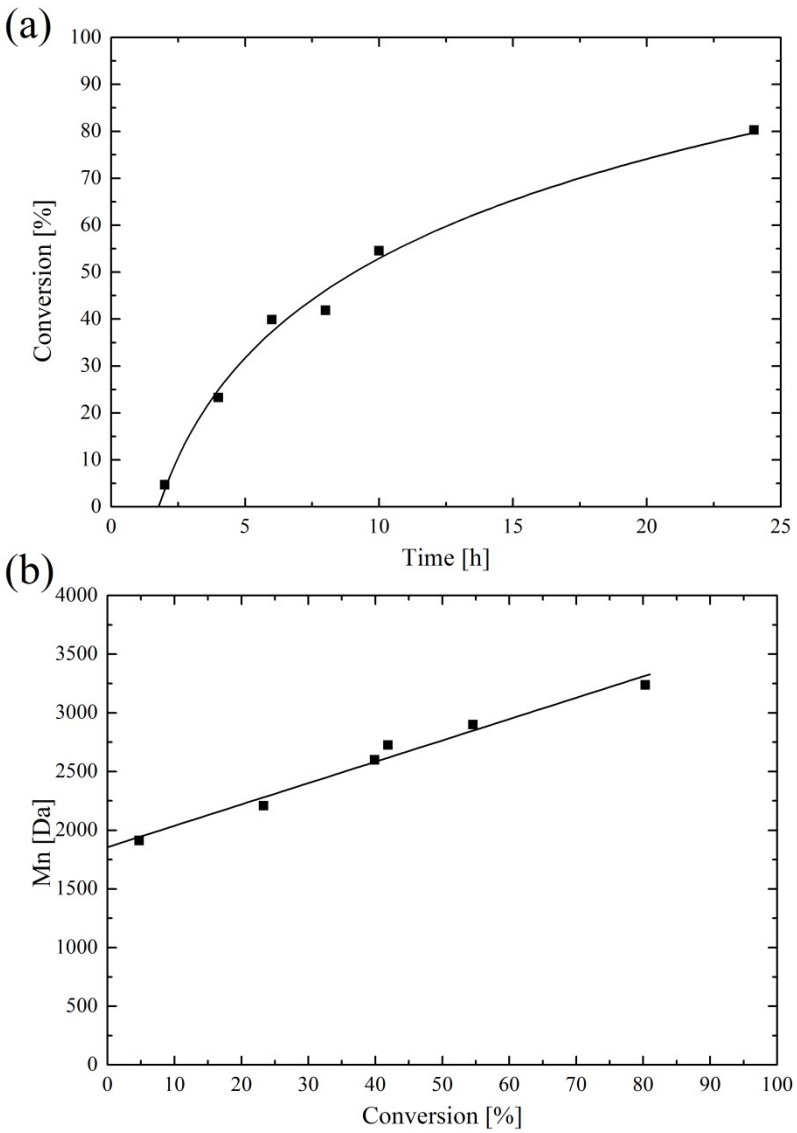

Figure S2. (a) Conversion versus time in the RAFT polymerization of the HPMA, obtained with a CTA/Initiator mole ratio equal to 3. The line represents the best logarithmic fit of the experimental data (R^2 = 0.991). (b) Number average molecular weight obtained from a PEG standard universal calibration versus conversion for the same experimental set. The line represents the best linear fit of the experimental data (R^2 = 0.976).

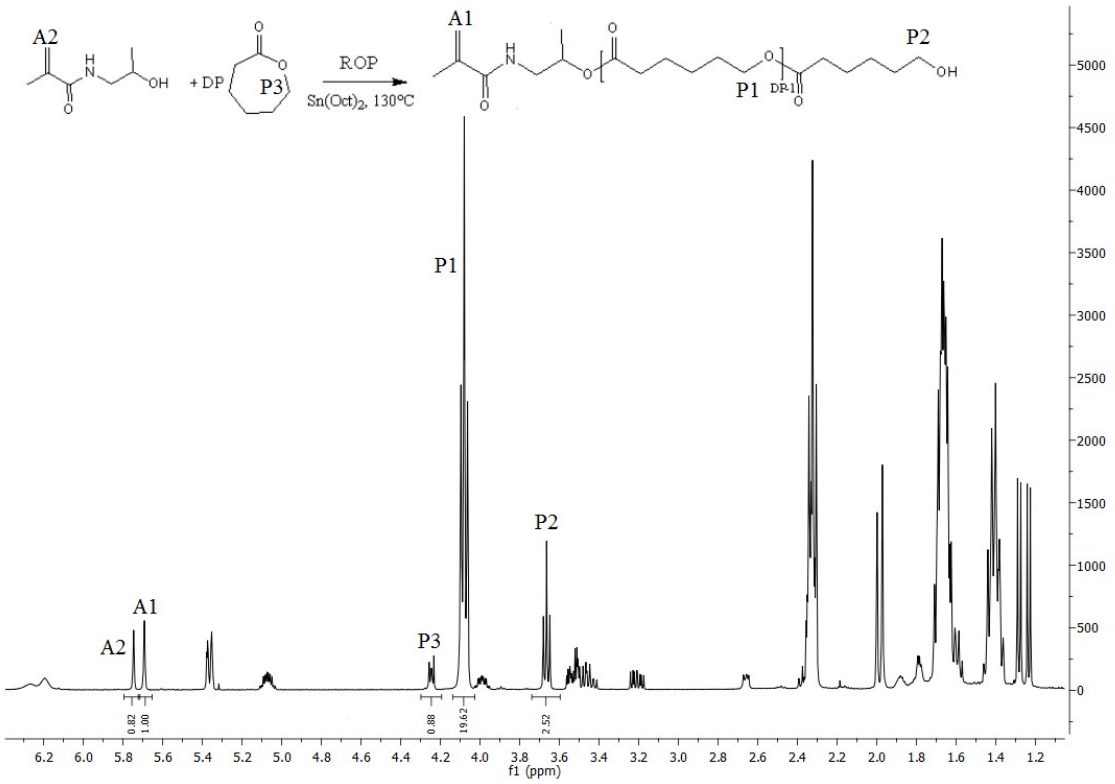

Figure S3. ^{1}H NMR spectrum (in $CDCl_3$, Bruker 400 MHz) of the oligo(caprolactone) obtained via direct Ring Opening Polymerization (ROP) using HPMA as the co-catalyst and $Sn(Oct)_2$ as the catalyst, with a HPMA/$Sn(Oct)_2$ mole ratio of 100.

From **Figure S3** it is possible to observe that a very poor HPMA conversion is obtained when using it as the co-catalyst in the ROP of the ε-caprolactone. In particular, the HPMA conversion and the ε-caprolactone conversion can be calculated according to Equation S1 and S2, respectively.

$$\chi_{HPMA} = \frac{A1}{A1 + A2} \tag{S1}$$

$$\chi_{\varepsilon-CL} = 1 - \frac{P3}{P1 + P2 + P3} \tag{S2}$$

While the conversion of the ε-caprolactone is very high (i.e. 95%), the HPMA conversion reaches only the 55% after 4 hours. This poor reactivity is due to the HPMA being a secondary alcohol, and then less active in the ROP. As a consequence, a direct ROP using the HPMA as the co-catalyst leads to a very poor control over the final macromonomer molecular weight (Mw). The mean DP obtained by this process can be evaluated according to the following Equation S3.

$$DP = \frac{P1}{P2} + 1 \tag{S3}$$

In this case, an average DP of 9 is achieved instead of the targeted DP=5. This is why a three-step process is necessary to assure high conversions and the desired macromonomer structure.

Figure S4 reports the ^{1}H NMR spectrum for the HPMA-CL5 macromonomer obtained with the three step process.

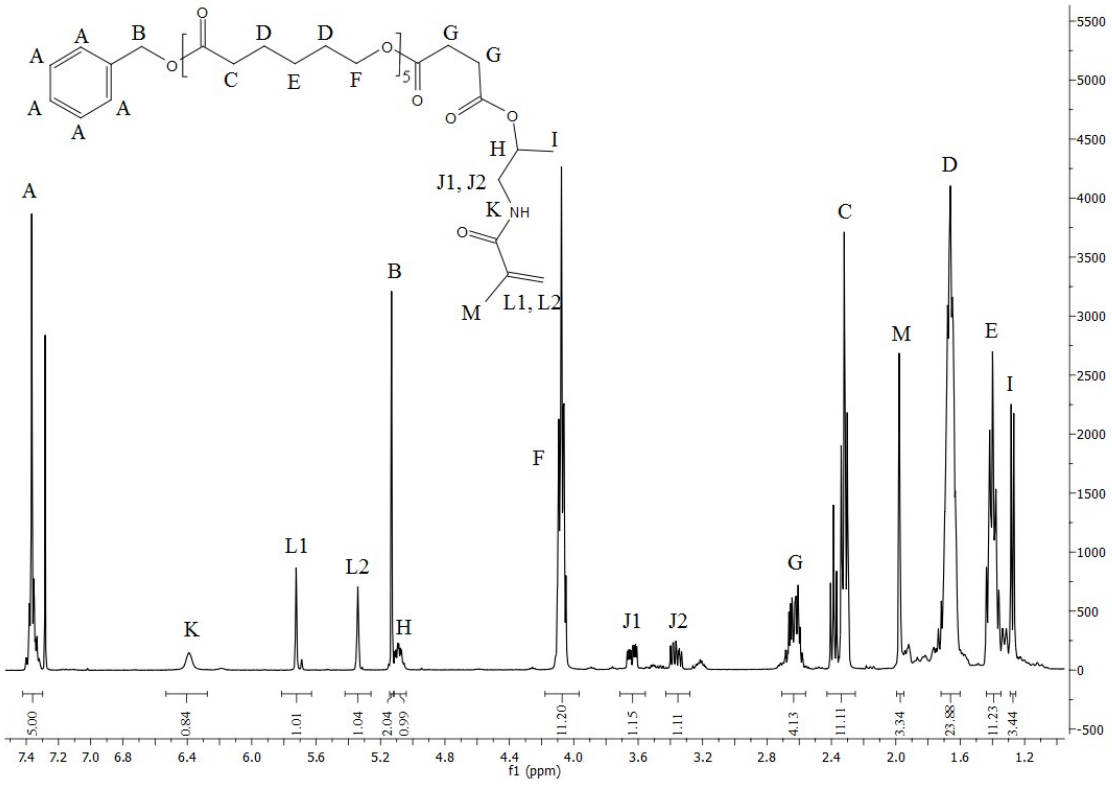

Figure S4. ^{1}H NMR spectrum (in CDCl3, Bruker 400 MHz) for the HPMA-CL5 macromonomer synthesized with a three step process including: (i) ROP of the ε-caprolactone using the benzyl alcohol as the co-catalyst; (ii) acylation with succinic anhydride and (iii) DCC-mediated esterification of the product with HPMA.

In this case the oligo(ε-caprolactone) DP can be calculated according to Equation S4.

$$DP_{3step} = \frac{F}{B} \tag{S4}$$

In this case the obtained average DP is equal to 5.4, which is very close to the targeted value of 5.

In **Figure S5**, the MALDI-TOF spectrum for the same batch of the HPMA-CL5 macromonomer is reported.

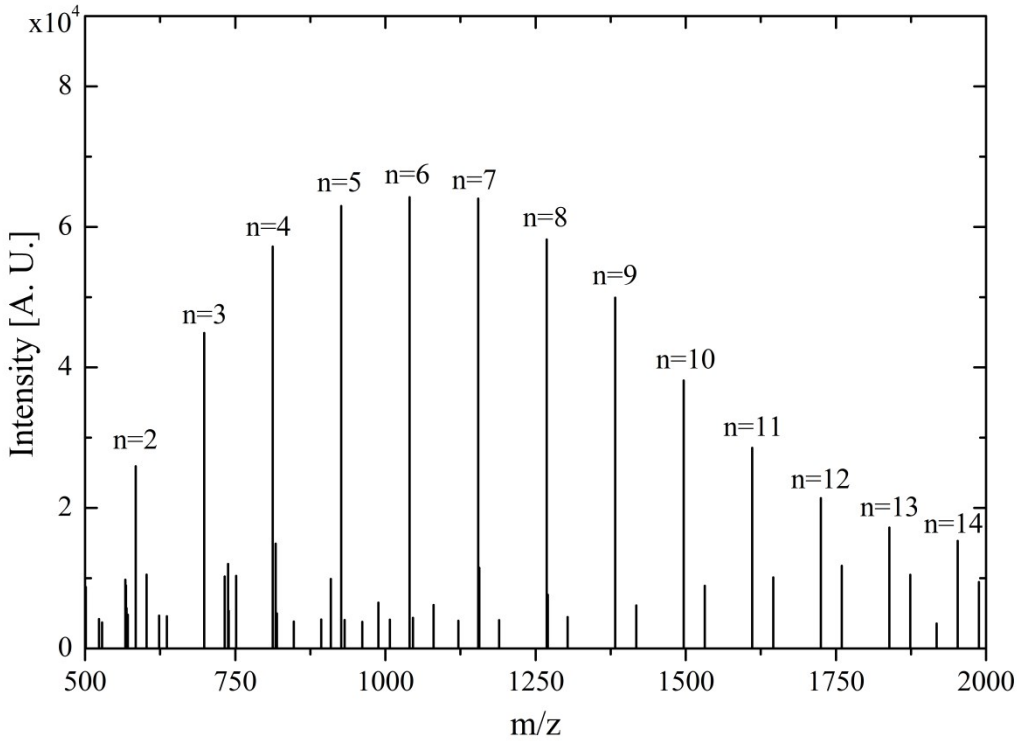

Figure S5. MALDI-TOF spectrum for the HPMA-CL5 macromonomer recorded on an Ultraflex II TOF Bruker spectrometer (Bremen, Germany) using 2-[(2E)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]-malononitrile (DCTB) as the matrix material.

From a close inspection, it is possible to observe that the material is obtained quite pure after the process. Further, the Mw distribution is centred on a DP equal to 6, in agreement with the findings from the ^{1}H NMR analysis. The number-averaged molecular weight (Mn) found from the MALDI-TOF is equal to 1179 g/mol, with a PD of 1.14, as expected from a living polymerization like the ROP. These values for the Mn and polydispersity are further confirmed by the GPC analysis. The chromatogram obtained using THF as the eluent at a 0.5 mL/min flow rate is reported in **Figure S6**.

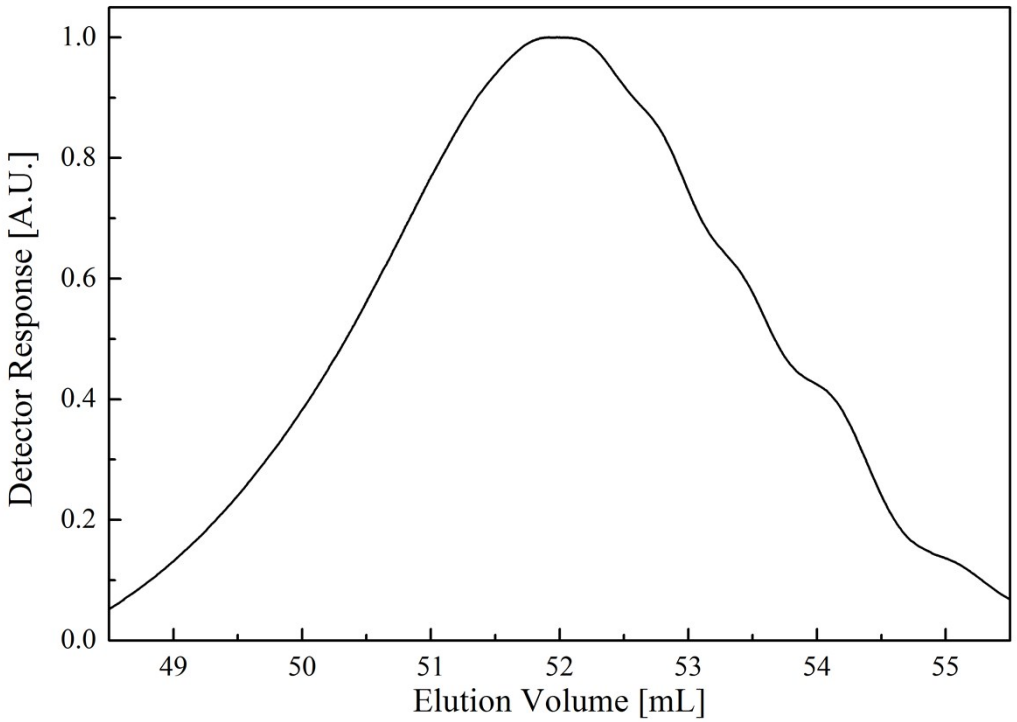

Figure S6. GPC trace of the lipophilic macromonomer obtained using THF as the eluent and a flow rate of 0.5 mL/min.

From the Figure it is possible to observe that a monodisperse molecular weight distribution is obtained, as expected from the ROP. The Mn obtained using a calibration based on polystyrene standards is equal to 980 g/mol with a polydispersity of 1.21. These values are in good accordance with those provided by MALDI-TOF spectrum.

In **Figure S7**, the ^{1}H NMR spectrum for the 705 diblock copolymer is shown as an example.

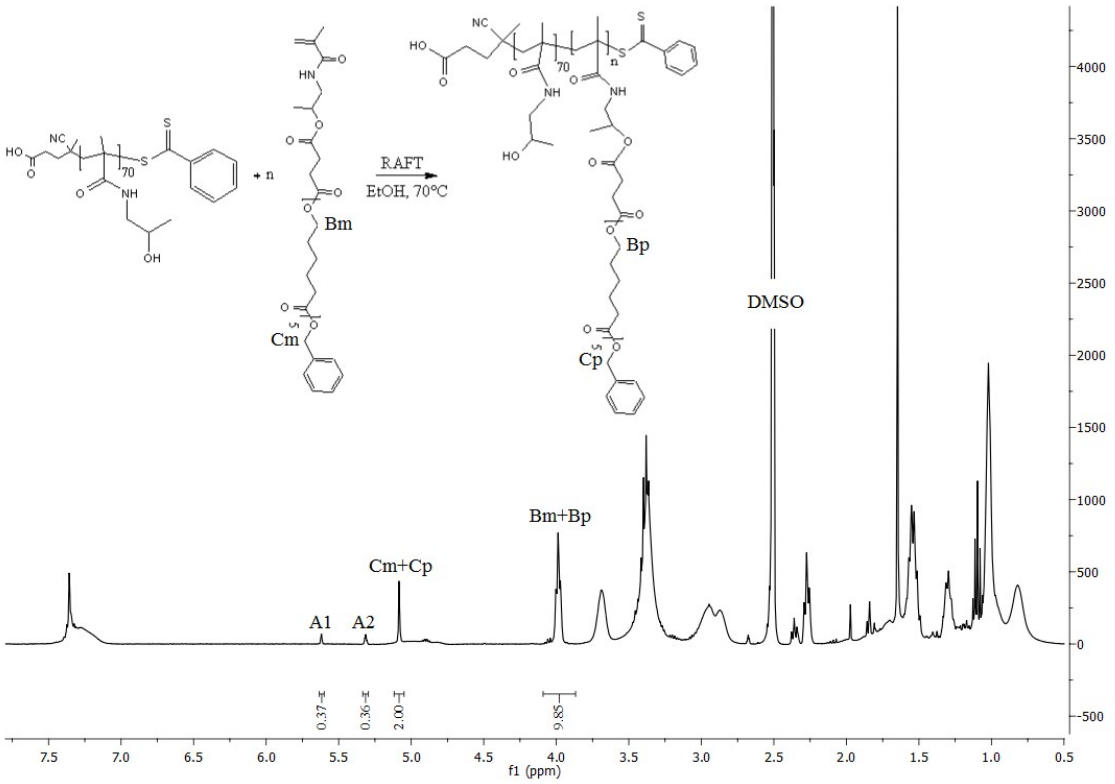

Figure S7. ^{1}H NMR spectrum (in CDCl3, Bruker 400 MHz) of the 705 diblock copolymer, obtained by chain extending the poly(HPMA)70 Macro-CTA with 5 units of the lipophilic HPMA-CL5 macromonomer.

From the ^{1}H NMR spectrum it is possible to evaluate the HPMA-CL5 conversion during the RAFT polymerization. In particular the conversion can be evaluated according to the following Equation S5.

$$\chi_{HPMA-CL5} = 1 - 2\frac{A1}{Cm + Cp} = 1 - 10\frac{A1}{Bm + Bp} \quad \text{(S5)}$$

In this specific case, a 63% monomer conversion is achieved.