Supporting Information

Synthesis of well-defined alkyne terminated poly(*N*-vinyl caprolactam) with a stringent control over the LCST by RAFT

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A. Synthesis of azido terminated-poly(ethylene glycol) (mPEG-N₃)



Fig. S1: Synthesis of azido-terminated mPEG (mPEG-N₃) (C). (i) H₂O, reflux; (ii) DMAP, DCM, r.t.; (iii) DMAP, DIC, DCM, r.t..

Synthesis of azido ethoxy ethanol (Figure S.1, (A)) (adapted from¹): 5.00 mL of 2-(2-chloroethoxy)ethanol (44.87 mmol), 11.67 g of sodium azide (179.50 mmol), 164 mg of hexadecyltrimethyl ammonium bromide (0.45 mmol) and 25 mL of water were mixed in reflux for 24h. After that the mixture were cooled down to room temperature and treated with HCl solution. The water solution was saturated with NaCl and the product was extracted with ethyl acetate (3 times). The organic phase was dried over anhydrous sodium sulfate and the solvent evaporated to give 5.85 g of azido ethoxy ethanol (yield 95%). ¹H NMR (CDCl₃, 400 MHz), δ (ppm)): 2.41 (m, 1H, -OH), 3.42 (t, 2H, -CH₂-N₃), 3.62 (t, 2H, -CH₂-O), 3.70 (t, 2H, -CH₂-O). IR spectra (cm⁻¹): 3400 (v_{OH}), 2100 (v_{N3}).

Synthesis of PEG-COOH (Figure S.1, (B)) (adapted from²): 10.00 g of mPEG₅₀₀₀ (2.00 mmol) ($M_{n,GPC} = 5.06 \times 10^3$; D = 1.03) previous dried thought azeotropic distillation, 0.80g of succinic anhydride (8.00 mmol) and 0.50 g of DMAP (4.00 mmol) were dissolved in 40 mL of DCM and the reaction proceeded at room temperature for 12 h. The solvent was removed under reduced pressure and then the residue was dissolved in 50mL of water. The product was extracted 3 times with DCM (30 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated and the mPEG-COOH was obtained as a white solid. ¹H NMR (CDCl₃, 400 MHz, δ (ppm)): 4.22 (t, 2H, -O-CH₂-),), 3.79–3.42 (m, 454H, (-O-CH₂-CH₂-)₁₁₃),), 3.34 (s, 3H, -CH₃), 2.60 (m, 4H, -(CH₂)₂-). IR spectra (cm⁻¹): 1734 (v_{C=0}). GPC: $M_{n,GPC} = 5.69 \times 10^3$; D=1.04.

Synthesis of N₃-PEG (Figure S.1, (C)) (adapted from ²): 70 .0 mg of azido ethoxy ethanol (0.53 mmol), 2.75 g of PEG-COOH (0.53 mmol) and 7.83 mg of DMAP (0.06 mmol) were dissolved in 30 mL of DCM and the solution bubbled with N₂. 99 µL of *N*,*N*'-diisopropylcarbodiimide (DIC) (0.64 mmol) was added to the previous solution and the reaction proceeded at room temperature overnight. The product was filtrate, concentrated in the rotatory evaporator and then precipitated in a cold mixture of THF:ether (100:400 mL). The product was vacuum dried to obtain the product N₃-PEG₅₀₀₀ as a white powder. ¹H NMR (CDCl₃, 400 MHz, δ (ppm): 4.22 (4H, -O-CH₂-), 4.00 (2H, -O-CH₂-), 3.79–3.42 (456H, (-O-CH₂-CH₂-)₁₁₃), -O-CH₂-), 3.38 (2H, -CH₂-N₃), 3.34 (3H, -CH₃), 2.66 (4H, -(CH₂)₂-). IR spectra (cm⁻¹): 2100 (v_{N3}). GPC: *M*_{n,GPC} = 5.06 x10³; *D*=1.04.



Fig. S2: FTIR-ATR spectra of the PEG-COOH and PEG-N₃.

B. NVCL handling and purification

The NVCL monomer is a hygroscopic solid at room temperature ($T_m \sim 35 - 38^{\circ}C$), and very sensitive to hydrolysis.^{3, 4} The monomer purity was found to vary substantial among suppliers and even among batches from the same supplier (¹H NMR spectrum of the PNVCL in Annex E, Figure E.2 (a)). The presence of monomer inhibitors, namely the N,N'-di-sec-butyl-pphenylenediamine and contaminants, contributes to an yellowish color of the monomer, which requires a careful purification. Several purification procedures reported in the literature were endeavored. In the first attempt, the monomer was distilled under reduced pressure to remove the inhibitors.⁵⁻⁷ This procedure was proved to be ineffective since the monomer could easily degrade due to the high temperatures employed in the distillation (above 90 °C) (¹H NMR spectra of the degraded PNVCL in Annex E, Figure E.2 (b)) Other authors reported the recrystallization from hexane,^{8, 9} but it was found to be ineffective to remove all the monomer impurities. Therefore, in order to remove the inhibitors without the degradation of monomer, the NVCL was dissolved in hexane, the solution was slightly heat above NVCL melting point (35 -38 °C), and then passed through a basic alumina column to remove the inhibitors. After recrystallization, the pure white crystalline monomer was filtered, vacuum dried and then stored at 4 °C. The presence of impurities was checked by ¹H NMR spectroscopy (Fig. S3).



Fig. S3: ¹H NMR spectrum of NVCL in CDCl₃.

The peaks observed at 7.32 ppm (**b**, -*CH*-), 4.37 ppm (**a**, -*CH*₂-), 3.52 ppm (**c**, -*CH*₂-N-), 2.57 ppm (**d**, -*CH*₂-CO-) and 1.64 ppm (**e**, -(*CH*₂)₃-) are in agreement with the expected NVCL chemical structure.

In addition to the purity of monomer, for the RAFT polymerization of NVCL, all of the reagents and solvents should be in an anhydrous form in order to avoid undesired side reactions. It is reported that the presence of water traces in the system could lead to NVCL hydrolysis during the polymerization reaction.¹⁰ As a consequence, the monomer may participate in two distinct and competitive reactions: the monomer addition or the monomer degradation (e.g. hydrolysis). These two distinct mechanisms are responsible for monomer consumption, but only the first generates the NVCL polymer. This issue is particular relevant for the synthesis of well controlled macromolecules, in which the polymer MW should increase linearly with monomer

conversion. If the monomer is consumed in side reactions, rather than in polymerization, the final monomer conversion obtained by ¹H NMR spectroscopy, from the comparison of the polymer and monomer signals, will not be consistent with the evolution of the theoretical molecular weight $(M_{n,th})$. The hydrolysis of the NVCL monomer is a topic of discussion in some literature reports.4, 10 The NVCL acidic hydrolysis leads to the formation of ε -caprolactam and acetaldehyde molecules (Fig. S4).¹⁰ In order to prove the existence of the NVCL degradation products in the polymerization reaction media, due to the possible presence of water traces, a simple experiment was carried out by mixing the monomer with the reaction solvent, 1,4-dioxane (99.8 % purity), at 60 °C. Samples from the initial mixture and the mixture after 1h at 60 °C were analyzed by ¹H NMR spectroscopy. The spectrum shown in Fig. S5 reveals the appearance of the acetaldehyde characteristic peak around 9.7 ppm (from the proton in the -CHO- aldehyde bound), and ε -caprolactam around 3.20 ppm, indicating the above supposition. Another direct evidence of the presence of the acetaldehyde in the mixture was the increase of pressure inside the reactor. The acetaldehyde has a boiling point around 20 °C, meaning that at experimental temperature (60 °C), it is gaseous leading to the increase of pressure inside the reactor.



Fig. S4: Schematic representation of NVCL hydrolysis, giving ε -caprolactam and acetaldehyde.¹⁰



Fig. S5: ¹H NMR spectra of NVCL and 1,4-dioxane before and after 1h at 60 °C, in CDCl₃.

C. RAFT polymerization of NVCL



Fig. S6: RAFT polymerization of NVCL mediated by X_1 , in 1,4-dioxane at 60 °C. (a) First-order kinetic plot, (b) evolution of MW and D with conversion (the dashed line represents theoretical MW at a given conversion). Reaction conditions: $[NVCL]_0/[X_1]_0/[AIBN]_0 = 140/1/0.2 \text{ (molar)}, [NVCL]_0/[1,4-dioxane]_0 = 1/2 \text{ (w/w)}.$

D. Characterization of PNVCL



Fig. S7: Determination of dn/dc values of PNVCL samples in DMF at 60°C. (PNVCL samples prepared by RAFT polymerization using AT-CTA or PAT-CTA in 1,4-dioxane at 60 °C. PAT-PNVCL: $M_{n,th}$ =48.0 x 10³; $M_{n,GPC}$ =59.46 x 10³, D=1.20; AT-PNVCL: $M_{n,th}$ =32.0 x 10³; $M_{n,GPC}$ =29.05 x 10³, D=1.28).



Fig. S8: GPC traces of PMMA standard (grey line) and PNVCL samples synthesized through FRP (black straight line) and MADIX/RAFT polymerization (black dash line).



Fig. S9: FTIR spectra of protected alkyne terminated PNVCL (PAT-PNVC) and alkyne terminated PNVCL obtained after the deprotection reaction (AT-PNVCL) ($M_{n,GPC}$ = 38.40 x 10³; D = 1.28).

Entry	Sample	M _{n,GPC} x10 ³	Ð	%N (w/w)	% C (w/w)	%H (w/w)	%S (w/w)
1	PAT-PNVCL ^a	28 10	1 20	9.158	63.809	9.678	0.244
2	AT-PNVCL ^b	36.40	1.20	8.715	62.933	9.058	0.301
3	PAT-PNVCL ^a	22.02	1.20	9.168	63.981	9.476	0.621
4	AT-PNVCL ^b	32.82	1.26	9.275	65.205	9.508	0.622
5	PAT-PNVCL ^a	41.25	1 27	9.056	63.344	9.167	0.405
6	AT-PNVCL ^b	41.33	1.2/	9.339	65.947	9.788	0.583

Table S1: Elemental analysis of the PNVCL samples synthesized by RAFT polymerization mediated by PAT- X_1 .

^{*a*} sample of pure PNVCL synthesized by RAFT polymerization mediated by PAT-CTA; ^{*b*} sample of pure PNVCL after the deprotection reaction of the alkyne chain-end functionality.



Fig. S10: Schematic representation of the dithranol (DT) and some DT impurities (found in the MALDI-TOF-MS spectrum of PNVCL) and the correspondent MW.



Fig. S11: Schematic representation of the mechanisms of thermolysis of PNVCL.



Fig. S12: MALDI-TOF-MS (a) in the linear mode (using DT as a matrix) from m/z 5000 to 18000 and (b) enlargement of the spectrum from m/z 6200 to 7200 of alkyne-terminate PNVCL after the deprotection reaction ($M_{n,GPC}$ = 18.9 2x 10³, and D = 1.33).



Fig. S13: MALDI-TOF-MS in the linear mode (using DT as a matrix) from m/z 6400 to 7100 of alkyne-terminate PNVCL after the deprotection reaction ($M_{n,GPC}$ = 18.92 x10³, and D = 1.33).

		F set			G set			H set			I set			J set	t		Kset	
n		$\mathrm{MW}_{\mathrm{ca}}{}^{a}$	MW _{exp}		$MW_{ca}{}^{b}$	MW _{exp}		MW _{ca} ^c	MW _{exp}		$\mathrm{MW}_{\mathrm{ca}}{}^{d}$	MW _{exp}		MW _{ca} ^e	$\mathrm{MW}_{\mathrm{exp}}$		MW_{ca}^{f}	MW _{exp}
43	F ₁	6430.2	6428.5	G ₁	6442.1 - 6444.2	6442.8	H ₁	6456.1-6458.1	6457.3	I ₁	6472.1	6471.8	J ₁	6486.1	6487.1			
44	F ₂	6569.4	6567.7	G ₂	6581.3 - 6583.3	6582.8	H ₂	6595.3-6597.3	6597.5	I ₂	6611.3	6610.7	J ₂	6625.3	6625.1			
45	F ₃	6708.6	6706.9	G ₃	6720.5 - 6722.5	6720.9	H ₃	6734.5-6736.5	6735.2	I ₃	6750.5	6750.5	J ₃	6764.5	6765.4			
46	F ₄	6847.8	6846.5	G ₄	6859.7 - 6861.7	6861.8	H ₄	6873.7-6875.7	6874.9	I ₄	6889.7	6889.5	J ₄	6903.7	6904.8	K ₁	6541.5	6536.9
47	F ₅	6987.0	6985.9	G ₅	6998.9 - 7000.9	6998.9	H ₅	7012.9-7014.9	7012.9	I ₅	7028.9	7028.1	J ₅	7042.9	7044.0	K ₂	6680.7	6679.3
48																K ₃	6819.9	6817.4
49																K ₄	6959.1	6956.7
50																K ₅	7098.3	7096.7

Table S2: MALDI-TOF-MS peak assignment for alkyne-terminated PNVCL, after the deprotection reaction.

n-the number of repeat units (NVCL), where dep(PAT-X₁) = 260.37 g.mol⁻¹, NVCL = 139.20 g.mol⁻¹, DT=226.23 g.mol⁻¹, SHCSOCH₂CH₃ = 122.21 g.mol⁻¹; $DT_{imp(I)} = 240.21$ g.mol⁻¹; $DT_{imp(I)} = 184.28$ g.mol⁻¹; $DT_{imp(II)} = 198.27$ g.mol⁻¹; $DT_{imp(IV)} = 196.25$ g.mol⁻¹; $DT_{imp(V)} = 210.23$ g.mol⁻¹; $DT_{imp(VI)} = 212.25$ g.mol⁻¹.

^{*a*} MW_{ca}= [dep(PAT- X₁)] +*n*PNVCL + DT_{imp(III};^{*b*} MW_{ca}= [dep(PAT- X₁) +*n*PNVCL] + DT_{imp(IV}) or MW_{ca}= [dep(PAT- X₁) +*n*PNVCL] + DT_{imp(III};^{*c*} MW_{ca}= [dep(PAT- X₁) +*n*PNVCL] + DT_{imp(VI});^{*c*} MW_{ca}= [dep(PAT- CTA) +*n*PNVCL] + DT_{imp(III};^{*c*} MW_{ca}= [dep(PAT- CTA) +*n*PNVCL] + DT_i



Fig. S14: TGA weight loss curves of the synthesized PNVCL and respective monomer, obtained at a heating rate of 10 $^{\circ}C \cdot min^{-1}$.

Table S3: TGA of PNVCL ($T_{x\%}$: temperature at x% mass loss; T_{on} : extrapolated onset temperature).

Entry	T _{5%} / °C	T _{10%} / °C	T _{on} / °C
NVCL	77.55	88.22	107.07
PAT-PNVCL ^a	66.20	353.11	398.85
AT-PNVCL ^b	58.02	363.43	398.98
FRP-PNVCL ^c	78.38	330.74	399.70

^{*a*} obtained from RAFT polymerization of NVCL mediated by PAT-CTA ($M_{n,GPC} = 38.40 \cdot 10^3$ g.mol⁻¹; ^{*b*} obtained after the deprotection reaction of (a); ^{*c*} obtained by FRP of NVCL.

E. Characterization of polymer properties in solution



ig. S15: Percentage transmittance versus temperature plots (right) or number of cycles (left) for the aqueous solutions of the same PNVCL sample (1.0 mg.mL⁻¹) synthesized through RAFT polymerization, for three heating and cooling consecutive cycles.



Fig. S16: Percentage transmittance *vs* temperature plots for the same PNVCL aqueous solution sample (1.0 mg.mL⁻¹) synthesized through FRP, for two heating and cooling consecutive cycles $(1.0 \text{ °C.min}^{-1})$.

F. References

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