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Double thermoresponsive di- and triblock copolymers based on *N*-vinylcaprolactam and *N*-vinylpyrrolidone: synthesis and comparative study of solution behaviour†

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Poly(*N*-vinylcaprolactam) (PNVCL) and poly(*N*-vinylpyrrolidone) (PNVP) are water soluble polymers of interest especially in the biomedical field. Moreover, PNVCL is characterized by a lower critical solution temperature close to 36 °C in water, which makes it useful for the design of thermoresponsive systems. In this context, we used the cobalt-mediated radical polymerization (CMRP) and reaction coupling (CMRC) for synthesizing a series of well-defined NVCL and NVP-based copolymers, including statistical copolymers as well as double thermoresponsive diblocks and triblocks. Dynamic light scattering and turbidimetry analyses highlighted the crucial impact of the copolymer composition and architecture on the cloud point temperature (T_{CP}) of each segment and also their influence on the multistep assembly behaviour of block copolymers. Addition of NaCl enabled us to adjust the inter- T_{CP} range of the di- and triblock in which selective precipitation of one block and self-assembly of the copolymer were favoured. Overall, data presented here provide a basis for the synthesis of a broad range of NVCL/NVP based copolymer architectures with a tunable thermal response in water.

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Introduction

Development of stimuli-responsive polymers, whose properties and solubility can be triggered by small changes in their environment (temperature, pH, electric or magnetic field, light, *etc.*), has become an important field of research in the last few years.^{1–3} These materials have attracted great interest because they sustain a wide variety of applications notably in the biomedical area as bio-sensors, drug or gene delivery carriers or supports for tissue engineering, to name just a few.^{4–6}

Temperature is very popular to regulate the solubility of polymers^{7–11} because no additive is required, the hydration/dehydration cycle can be repeated endlessly, at least under non-degradative conditions for the polymer chain, and it is

easily controllable. Some thermoresponsive polymers are only soluble in water upon heating above a given temperature called the upper critical solution temperature (UCST) while others precipitate when heated above a given temperature called the lower critical solution temperature (LCST).¹² Several common polymers exhibit a LCST behaviour in water including poly-(oligoethylene glycol(meth)acrylate)s,^{13,14} poly(propylene oxide),^{15,16} poly(vinylether)^{17,18} or poly(2-oxazoline)^{19,20} but the most studied sequence remains poly(*N*-isopropylacrylamide) (PNIPAM), which undergoes a coil-to-globule transition at 32 °C.^{9,21,22} Nevertheless, poly(*N*-vinylcaprolactam) (PNVCL),^{23–27} whose LCST (~36 °C) is close to body temperature, has proven to be a valuable alternative to PNIPAM especially for biomedical applications.^{23,24} In contrast to PNIPAM, PNVCL does not produce toxic low-molecular-weight amines during hydrolysis and offers a higher biocompatibility as proved by cytotoxicity assays.^{23,24} Moreover, PNVCL does not exhibit a hysteresis phenomenon in the coil-to-globule-to-coil transition in contrast to PNIPAM which forms interchain hydrogen bonds in the collapsed state.²¹

The solution behaviour dependence of PNVCL as a function of temperature has been thoroughly studied.^{25–29} The LCST of this polymer is around 36 °C but it varies with the molar mass and the end-groups of the polymer.^{25,30–32} In this respect, con-

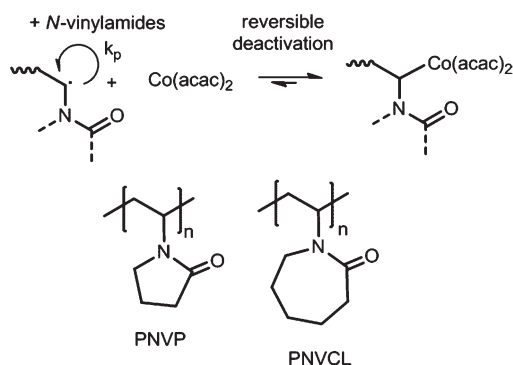
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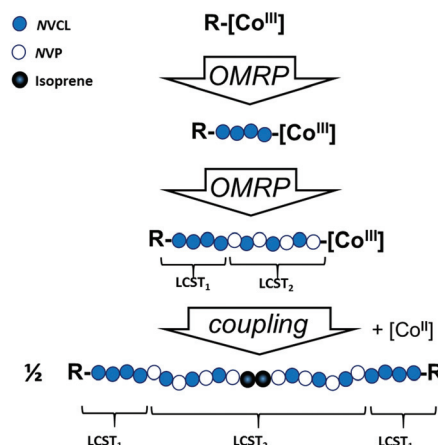
†Electronic supplementary information (ESI) available: Additional structural characterizations and the thermal response studies of the copolymers were carried out by nuclear magnetic resonance, turbidimetry, dynamic light scattering. See DOI: 10.1039/c4py00852a

trolled radical polymerization enables not only tuning of the molar mass of the PNVL but also design of statistical copolymers with precise NVCL content^{33,34} and copolymers containing one or more PNVL segments.^{34–43} Some CRP techniques have distinguished themselves for the controlled polymerization of *N*-vinyl amides and NVCL in particular,⁴⁴ *i.e.* the reversible addition fragmentation chain transfer (RAFT/MADIX),^{30–33,35–38} atom transfer radical polymerization^{42,43,45,46} and the organometallic-mediated radical polymerization (OMRP)^{47,48} based on cobalt complexes.^{34,39–41,49} The latter is based on the reversible deactivation of the growing radical chains by the metal complex. In particular, bis-acetylacetonatocobalt(II) ($\text{Co}(\text{acac})_2$) is a very efficient controlling agent for the polymerization of non-conjugated *N*-vinylamides including NVCL (Scheme 1).⁴⁹ Narrowly distributed PNVL containing block copolymers with thermally induced self-assembly behaviour, like poly(vinyl acetate)-*b*-PNVL and poly(vinyl alcohol)-*b*-PNVL, were also prepared by OMRP.^{39–41} The controlled statistical radical copolymerizations of NVCL with *N*-methyl vinyl acetamide (NMVA) or vinyl acetate (VAc) were also achieved by OMRP and the LCST of these copolymers could be precisely tuned up and down by incorporation of precise amounts of vinyl amide or vinyl ester comonomers, respectively.³⁴ After that, a well-defined NVCL-based diblock having two LCSTs could also be prepared by sequential OMRP of NVCL followed by the controlled copolymerization of NMVA with the residual amount of NVCL.³⁴ Although examples of double thermoresponsive diblocks^{9,20,34,50} and single thermoresponsive triblocks^{15,51–55} are rather common, only a handful of double thermoresponsive triblocks have been reported^{56–59} and none of them based on NVCL.

Herein, we report the first synthesis of NVCL-based symmetrical ABA triblock copolymers having two discrete LCSTs. The latter are composed of PNVL external blocks and a central block made of NVCL and *N*-vinyl pyrrolidone (NVP), *i.e.* PNVL-*b*-P(NVL-co-NVP)-*b*-PNVL (Scheme 2). Briefly, the triblocks were obtained by isoprene-assisted bimolecular radical coupling^{60–62} of the corresponding double thermo-responsive PNVL-*b*-P(NVL-co-NVP) diblocks formed by OMRP. A series



Scheme 1 OMRP mechanism for *N*-vinylamides including NVCL and NVP.



Scheme 2 General strategy for the synthesis of double thermo-responsive block copolymers by OMRP and radical coupling reaction.

of di- and triblocks with different block lengths were prepared in order to evaluate the relationship between the macromolecular features of the copolymer on the LCSTs and the self-assembly behaviour in water. A great advantage of the radical coupling approach is the fact that triblocks have exactly the same block compositions as the parent diblocks from which they were generated and also the same length for the PNVL blocks, which allows a direct comparative study of their thermal response.

Experimental section

Materials

N-Vinylpyrrolidone (NVP, >99%, Aldrich) and isoprene (99%, Aldrich) were dried over calcium hydride, degassed by two freeze–thawing cycles before distillation under reduced pressure and stored under argon. High purity *N,N*-dimethylformamide (DMF, >99%, Acros) and dichloromethane (CH_2Cl_2 , 99.98%, Acros) are degassed by bubbling. Bis-(acetylacetonato) cobalt(II) ($\text{Co}(\text{acac})_2$) (>98%, Acros) was stored under argon and used as received. 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO, 98%, Aldrich) and *N*-vinylcaprolactam (NVCL, 98%, Aldrich) were used as received. 2,2'-Azobis(4-methoxy-2,4-dimethyl valeronitrile) (V-70, 96%, Wako) was stored at -20°C and used as received. The alkyl-cobalt(III) adduct initiator ($[\text{Co}(\text{acac})_2-(\text{CH}(\text{OAc})-\text{CH}_2)_n\text{R}_0]$, R_0 being the primary radical generated by 2,2'-azobis(4-methoxy-2,4-dimethyl valeronitrile) (V-70, Wako) was prepared as described previously⁶³ and stored in a CH_2Cl_2 solution at -20°C under argon.

Characterization

The molar masses (M_n) and molar mass dispersity ($\mathcal{D}$) of the P(NVL-*stat*-NVP) random copolymers were determined by size-exclusion chromatography (SEC) in dimethylformamide (DMF) containing LiBr (0.025 M) relative to polystyrene (PS) standards at 55°C (flow rate: 1 mL min^{-1}) with a Waters 600 liquid chromatograph equipped with a 410 refractive index

detector as well as two PSS GRAM analytical columns (1000 Å, 8 × 300 mm, particle size 10 µm) and one PSS GRAM analytical column (30 Å, 8 × 300 mm, particle size 10 µm). The absolute molar masses of the PNVL-*block*-P(NVP-*stat*-NVCL) and PNVL-*block*-P(NVP-*stat*-NVCL)-*block*-PNVL block copolymers and their PNVL precursors were determined by SEC equipped with a multiangle laser light scattering (MALLS) detector in DMF/LiBr (0.025 M). The Wyatt MALLS detector (120 mW solid-state laser, k_4^1 658 nm, Dawn Heleos S/N342-H) measures the excess Rayleigh ratio R_h (related to the scattered intensity) at different angles for each slice of the chromatogram. The specific refractive index increment (dn/dc) of each (co)polymer was measured using a Wyatt Optilab refractive index detector (k_4^1 658 nm). Data were processed with the Astra V software (Wyatt Technology). ^1H NMR spectra of reaction mixtures were recorded in CDCl_3 at 298 K with a 250 MHz Bruker spectrometer and ^1H NMR spectra of final polymers with a 400 MHz Bruker spectrometer.

Statistical cobalt-mediated radical copolymerization of NVCL and NVP. A bent 50 mL flask containing NVCL (9.18 g, 65.9 mmol) was connected to a 100 mL Schlenk flask equipped with a magnetic bar and degassed by three vacuum-argon cycles. The NVCL was melted at 40 °C under vacuum to eliminate oxygen. A solution of alkyl-cobalt(III) initiator ($[\text{Co}(\text{acac})_2-(\text{CH}(\text{OAc})-\text{CH}_2)_{\sim 4}\text{R}_0]$ in CH_2Cl_2) was introduced under argon in the 100 mL Schlenk flask (1.0 mL of a 0.1 M stock solution, 0.1 mmol) and the dichloromethane was evaporated to dryness under reduced pressure at room temperature. The melted NVCL at 40 °C was then transferred onto the CMRP initiator before addition of distilled NVP (0.77 mL, 0.81 g, 7.3 mmol) under argon (NVP/NVCL molar feed ratio = 10/90, $M_{\text{nth } 100\%} = 100\,000\text{ g mol}^{-1}$). The reaction mixture was stirred at 40 °C and the monomer conversion was monitored by ^1H NMR spectroscopy in CDCl_3 . After 5.5 h, the monomer conversion reached 24% for NVCL and 17% for NVP. A volume of 1.5 mL of a degassed solution of TEMPO in DMF (1.5 mL of 0.32 M stock solution, 0.48 mmol) was injected into the medium in order to stop the polymerization and eliminate the cobalt complex from the copolymer chain-end, according to a previous report.⁶⁴ The mixture was dissolved in approximately 20 mL of DMF and the polymer was recovered by precipitation in diethylether (Et_2O , 200 mL). The polymer was then filtered,

dried under reduced pressure and purified by dialysis overnight in deionized water using a Spectra/Por®1 membrane (6–8 kDa, 8 mL cm^{-1}). The final P(NVCL-*stat*-NVP) copolymer was collected as a white powder after lyophilization of the aqueous solution. The molecular parameters of the copolymer were measured by SEC in DMF using PS as a calibration ($M_{\text{n SEC}} = 28\,900\text{ g mol}^{-1}$, $D = 1.05$). The composition of the copolymer previously dissolved in D_2O and dried at 60 °C overnight was determined by ^1H NMR (400 MHz) in CDCl_3 (NVCL/NVP molar ratio in the copolymer = 82/18) (see Fig. S1†).

Similar experiments were carried out with various NVCL/NVP molar ratios (see Table 1). The molecular parameters of the copolymers were measured by SEC in DMF using PS as a calibration: NVCL/NVP molar ratio in the copolymer = 73/27, $M_{\text{n SEC}} = 24\,900\text{ g mol}^{-1}$, $D = 1.06$; NVCL/NVP molar ratio in the copolymer = 58/42, $M_{\text{n SEC}} = 22\,000\text{ g mol}^{-1}$, $D = 1.10$; NVCL/NVP molar ratio in the copolymer = 51/49, $M_{\text{n SEC}} = 33\,600\text{ g mol}^{-1}$, $D = 1.10$; NVCL/NVP molar ratio in the copolymer = 43/57, $M_{\text{n SEC}} = 40\,400\text{ g mol}^{-1}$, $D = 1.12$; NVCL/NVP molar ratio in the copolymer = 28/72, $M_{\text{n SEC}} = 29\,300\text{ g mol}^{-1}$, $D = 1.24$; data are presented in Table 1.

Synthesis of the PNVL-*block*-P(NVCL-*stat*-NVP) diblock copolymer $\text{C}_{132}(\text{C}_{40}\text{P}_{172})$. A bent 50 mL flask containing NVCL (15.0 g, 107.7 mmol) was connected to a 100 mL Schlenk flask equipped with a magnetic bar and degassed by three vacuum-argon cycles. The NVCL was melted at 40 °C under vacuum to eliminate oxygen. A solution of alkyl-cobalt(III) initiator ($[\text{Co}(\text{acac})_2-(\text{CH}(\text{OAc})-\text{CH}_2)_{\sim 4}\text{R}_0]$ in CH_2Cl_2) was introduced under argon in the 100 mL Schlenk flask (3 mL of a 0.1 M stock solution, 0.3 mmol) and the dichloromethane was evaporated to dryness under reduced pressure at room temperature. The melted NVCL at 40 °C was then transferred onto the CMRP initiator ($M_{\text{nth } 100\%} = 100\,000\text{ g mol}^{-1}$). The reaction mixture was heated at 40 °C under stirring and ^1H NMR analyses of aliquots were carried out to follow the monomer conversion. When the NVCL consumption reached 27%, a sample was picked from the medium, diluted in DMF containing LiBr and added with traces of TEMPO before SEC-MALLS analysis (dn/dc of PNVL = 0.0916 mL g^{-1} , $M_{\text{n MALLS}} = 18\,400\text{ g mol}^{-1}$, $D_{\text{MALLS}} = 1.03$ and $D = 1.05$ with the PS calibration). Then, NVP (13.7 mL, 14.28 g, 128.0 mmol) was added under argon to the reaction mixture with the residual NVCL and the polymeriz-

Table 1 Statistical cobalt-mediated radical copolymerization of NVCL and NVP in bulk at 40 °C

Entry	In the feed (mol%) NVP/NVCL	$[\text{monomers}]/$ $[\text{R-Co}(\text{acac})_2]$	Time (h)	Conv. ^a (%)		M_{n}^b (g mol^{-1})	D^b	In the copolymer ^c (mol%) NVP/NVCL
				NVCL	NVP			
1	10/90	731	5.5	24	17	28 900	1.05	18/82
2	20/80	747	5	22	22	24 900	1.06	27/73
3	30/70	759	4	22	34	22 000	1.10	42/58
4	40/60	780	5.5	30	24	33 600	1.10	49/51
5	50/50	803	5	25	35	40 400	1.12	57/43
6	60/40	803	5.5	34	29	29 300	1.24	72/28

^a Determined by ^1H NMR 250 MHz in CDCl_3 . ^b Determined by SEC in DMF containing LiBr (calibration PS). ^c Determined by ^1H NMR 400 MHz in CDCl_3 .

ation was pursued at 40 °C (comonomer feed NVP/NVCL: 63/37). After 2 h, the mixture became viscous. Based on the ^1H NMR spectrum of the reaction mixture in CDCl_3 , the NVP consumption reached 19% and the cumulative NVCL conversion was 43%. A volume of 25 mL of DMF was added to decrease the viscosity. Half of the solution was further used for the synthesis of the triblock (see the procedure below) while the rest was transferred using a cannula to another 100 mL Schlenk flask containing 100 mg of TEMPO (0.64 mmol, degassed by three vacuum–argon cycles) in order to produce the cobalt-free PNVCL-*block*-P(NVCL-*stat*-NVP) diblock. After treatment with TEMPO, the diblock was precipitated in diethylether (250 mL), filtered, dried and purified by dialysis using a Spectra/Por®1 membrane (6–8 kDa) in deionized water. The PNVCL-*block*-P(NVCL-*stat*-NVP) copolymer was collected as a white powder after lyophilization of the aqueous solution. SEC-MALLS measurements were carried out in DMF in order to determine the molecular parameters of the copolymer (dn/dc of PNVCL-*block*-P(NVCL-*stat*-NVP) = 0.0992 mL g^{-1} , $M_{\text{n MALLS}}$ = $43\,100 \text{ g mol}^{-1}$, D_{MALLS} = 1.05 and D = 1.08 with PS calibration). The composition of the P(NVCL-*stat*-NVP) block was determined by ^1H NMR (81/19: NVCL/NVP) and allowed to attribute the degree of polymerization of each segment of the copolymer (PNVCL₁₃₂-*block*-P(NVCL₄₀-*stat*-NVP₁₇₂)).

Synthesis of PNVCL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVCL block copolymers C₁₃₂(C₈₀P₃₄₄)C₁₃₂. The above mentioned PNVCL-*block*-P(NVCL-*stat*-NVP)-Co(acac)₂ diblock (0.15 mmol) in DMF (12.5 mL) was reacted with 2 mL of isoprene (1.36 g, 20.0 mmol) at room temperature overnight in order to produce the triblock counterpart by radical coupling reaction.^{60–62} The resulting PNVCL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVCL triblock copolymer was precipitated in diethylether (250 mL), filtered, dried and purified by dialysis using a Spectra/Por®1 membrane (6–8 kDa) in deionized water. It was then collected as a white powder after lyophilization of the aqueous solution. SEC-MALLS measurements in DMF containing LiBr (0.025 M) determine the molecular parameters of the copolymer (dn/dc of PNVCL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVCL = 0.0969 mL g^{-1} , $M_{\text{n MALLS}}$ = $71\,900 \text{ g mol}^{-1}$, D_{MALLS} = 1.19 and D = 1.24 (calibration PS)). The composition of the P(NVCL-*stat*-NVP) block is the same as the diblock (entry 2 in Tables 2 and S1†).

A series of PNVCL-*block*-P(NVCL-*stat*-NVP) diblock and PNVCL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVCL copolymers with different block lengths and compositions have been prepared accordingly (see Tables 2 and S1† for molecular characteristics and polymerization conditions). In order to distinguish the PNVCL-*block*-P(NVCL-*stat*-NVP) and PNVCL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVCL copolymers based on their composition, C_n(C_lP_m) and C_n(C_{2l}P_{2m})C_n labels were used where C and P correspond to NVCL and NVP, respectively, and *n* and *l* denoted the number of NVCL units and *m* the number of NVP units.

C₆₈(C₇₄P₁₉₁) & C₆₈(C₁₄₈P₃₈₂)C₆₈ (entry 1 in Tables 2 and S1†). $M_{\text{n MALLS}}$ PNVCL = 9500 g mol^{-1} , D_{MALLS} = 1.04, dn/dc = 0.0916 mL g^{-1} , D = 1.07 (calibration PS), $M_{\text{n MALLS}}$ PNVCL-*block*-P(NVCL-*stat*-NVP) = $41\,400 \text{ g mol}^{-1}$, D_{MALLS} = 1.05, D = 1.13 (calibration PS), dn/dc = 0.0872 mL g^{-1} , NVCL/NVP molar ratio in the statistical copolymer = 72/28, dn/dc = 0.0951 mL g^{-1} , $M_{\text{n MALLS}}$ PNVCL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVCL = $64\,500 \text{ g mol}^{-1}$, D_{MALLS} = 1.16, D = 1.24 (calibration PS).

C₂₃₆(C₅₅P₁₅₄) & C₂₃₆(C₁₁₀P₃₀₈)C₂₃₆ (entry 3 in Tables 2 and S1†). $M_{\text{n MALLS}}$ PNVCL = $32\,800 \text{ g mol}^{-1}$, D_{MALLS} = 1.04, D = 1.06 (calibration PS), dn/dc = 0.0916 mL g^{-1} , $M_{\text{n MALLS}}$ PNVCL-*block*-P(NVCL-*stat*-NVP) = $57\,500 \text{ g mol}^{-1}$, D_{MALLS} = 1.05, D = 1.06 (calibration PS), dn/dc = 0.0906 mL g^{-1} , NVCL/NVP molar ratio in the statistical copolymer = 74/26, dn/dc = 0.0906 mL g^{-1} , $M_{\text{n MALLS}}$ PNVCL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVCL = $110\,500 \text{ g mol}^{-1}$, D_{MALLS} = 1.06, D = 1.13 (calibration PS).

C₂₈₂(C₂₇P₂₉₇) & C₂₈₂(C₅₄P₅₉₄)C₂₈₂ (entry 4 in Tables 2 and S1†). $M_{\text{n MALLS}}$ PNVCL = $39\,200 \text{ g mol}^{-1}$, D_{MALLS} = 1.05, D = 1.06 (calibration PS), dn/dc = 0.0916 mL g^{-1} , $M_{\text{n MALLS}}$ PNVCL-*block*-P(NVCL-*stat*-NVP) = $76\,200 \text{ g mol}^{-1}$, D_{MALLS} = 1.09, D = 1.08 (calibration PS), dn/dc = 0.0867 mL g^{-1} , NVCL/NVP molar ratio in the statistical copolymer = 8/92, dn/dc = 0.0849 mL g^{-1} , $M_{\text{n MALLS}}$ PNVCL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVCL = $127\,700 \text{ g mol}^{-1}$, D_{MALLS} = 1.14, D = 1.13 (calibration PS).

Aqueous solution behaviour. The transmittance of the aqueous solutions of polymers (1 g L^{-1} and 10 g L^{-1}) was recorded on a Jasco V630 UV-vis spectrophotometer at 700 nm equipped with a temperature controller system (ETCS-761). The heating/cooling rate was 1 °C min^{-1} between 25 °C and 85 °C. The cloud point temperature (T_{CP}) was defined at the half drop transmittance from the initial transmittance. DLS experiments were performed on a Malvern CGS-3 apparatus

Table 2 Characteristics of the NVCL and NVP containing di- and triblock copolymers prepared by CMRP and CMRC

Entry	PNVCL		PNVCL- <i>b</i> -P(NVCL- <i>stat</i> -NVP)				PNVCL- <i>b</i> -P(NVCL- <i>stat</i> -NVP)- <i>b</i> -PNVCL		
	M_{n}^a (g mol^{-1})	D^a	$M_{\text{n P(NVCL-} \text{stat-NVP})}^a$ (g mol^{-1})	D^a	NVCL (mol%) in the <i>stat</i> segment ^b	Label ^c	M_{n}^a (g mol^{-1})	D^a	Label ^c
1	9500	1.07	31 900	1.13	28	C ₆₈ (C ₇₄ P ₁₉₁)	64 500	1.24	C ₆₈ (C ₁₄₈ P ₃₈₂)C ₆₈
2	18 400	1.05	24 700	1.08	19	C ₁₃₂ (C ₄₀ P ₁₇₂)	71 900	1.24	C ₁₃₂ (C ₈₀ P ₃₄₄)C ₁₃₂
3	32 800	1.06	24 700	1.06	26	C ₂₃₆ (C ₅₅ P ₁₅₄)	110 500	1.13	C ₂₃₆ (C ₁₁₀ P ₃₀₈)C ₂₃₆
4	39 200	1.06	37 000	1.08	8	C ₂₈₂ (C ₂₇ P ₂₉₇)	128 000	1.13	C ₂₈₂ (C ₅₄ P ₅₉₄)C ₂₈₂

^a Exact molar mass and dispersity determined by DMF-SEC using a MALLS detector and an RI detector with PS calibration, respectively.

^b Determined by ^1H NMR taking into account the exact molar mass of the PNVCL segment. ^c C and P designate NVCL and NVP, respectively. The numbers associated with these letters correspond to the degree of polymerization of each monomer. Detailed polymerization conditions are provided in Table S1.

equipped with a He–Ne laser with a wavelength of 633 nm. The measurements were performed in water at 90° angle at a concentration of 1 g L^{−1}. Data were analysed using the CONTIN method, which is based on an inverse-Laplace transformation of the data and gives access to a size distribution histogram.

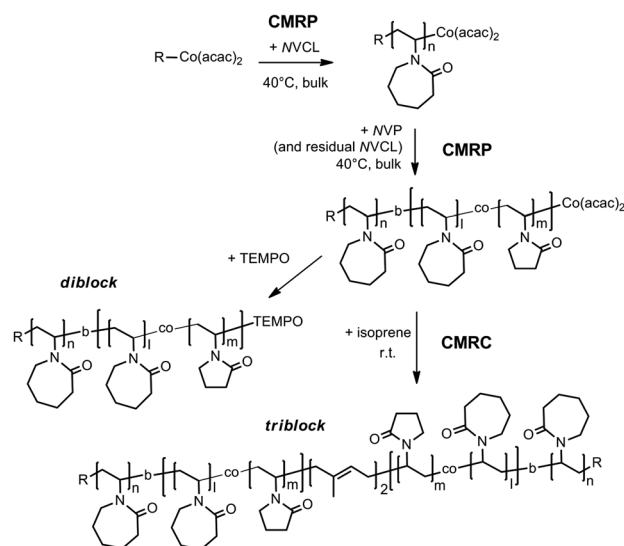
Results and discussion

Copolymer synthesis by CMRP

This section is exclusively dedicated to the synthesis of the NVCL and NVP containing statistical, diblock and symmetrical triblock copolymers. The control of the radical copolymerization of this pair of *N*-vinylamides using Co(acac)₂ as mediating species will be presented as well as the macromolecular features of each copolymer like composition, block length, dispersity, *etc.* The solution behaviour and the thermal response of these copolymers will be addressed and compared in the next section. Nevertheless, when reading through the synthesis section, it is interesting to keep in mind that increasing the NVP content in a PNVL backbone is expected to increase the LCST of the polymer segment because PNVP is more hydrophilic than PNVL and does not exhibit LCST in pure water.⁶⁵

First, the controlled statistical radical copolymerization of NVCL and NVP was performed in bulk at 40 °C by CMRP using a low molecular weight alkyl-cobalt(III) adduct (R–Co(acac)₂) as the initiator. The latter consists of oligoPVAc (average number of 4 VAc units) capped by Co(acac)₂ whose synthesis and ability to initiate the CMRP of *N*-vinylamides has been previously reported.⁴⁹ Upon heating, homolytic cleavage of the R–Co(acac)₂ bond occurs releasing the initiating fragment (R•) and the metallic controlling agent which reversibly traps the growing radical chains. Table 1 summarizes the NVP/NVCL statistical copolymers prepared in this study. Several comonomer feed ratios were tested and the monomer/initiator molar ratio was adjusted to target the P(NVCL-*stat*-NVP) copolymer of 100 000 g mol^{−1} at full monomer conversion. Although CMRP of NVCL remains efficient above 60%,⁴⁹ the above mentioned NVP/NVCL copolymerizations were stopped between 20% and 35% in order to ensure an optimal control of the polymerization and well-defined NVP/NVCL statistical copolymers with molar masses ranging between 20 000 and 40 000 g mol^{−1} were produced accordingly. In this case, the dispersity of the copolymers slightly increases with the NVP content in the feed. This observation is consistent with the better control reported for the NVCL homopolymerization compared with the NVP under the same experimental conditions.⁴⁹ The compositions of the resulting copolymers were determined by ¹H NMR (see Fig. S1†). The NVP content was systematically a bit higher in the copolymer than in the feed, which is in good agreement with the reactivity ratio reported in the literature (*r*_{NVCL} = 1.7, *r*_{NVP} = 2.8).⁶⁶

Next, CMRP and CMRC methods were used to produce novel double thermoresponsive NVCL and NVP-based diblocks and triblocks (Scheme 3). Inspired by a recent one-pot pro-



Scheme 3 Synthesis of NVCL and NVP containing diblocks and triblocks by CMRP and CMRC.

cedure for the copolymerization of NVCL and NMVA,³⁴ our general strategy consists of the controlled radical homopolymerization of NVCL from R–Co(acac)₂ in bulk at 40 °C up to 27% of conversion followed by injection of a precise amount of NVP which copolymerizes with the residual NVCL leading to the targeted PNVL-*block*-P(NVCL-*stat*-NVP)-Co(acac)₂. After dilution with dimethylformamide, the resulting PNVL-*block*-P(NVCL-*stat*-NVP)-Co(acac)₂ copolymer solution was divided into two equal parts. One of them was treated with TEMPO in order to eliminate the metal at the chain-end of the PNVL-*block*-P(NVCL-*stat*-NVP) diblock. The other portion was reacted at room temperature with an excess of isoprene compared with the cobalt promoting the radical coupling of the diblock by CMRC and the formation of the corresponding PNVL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVL triblock. Briefly, the allyl radical resulting from the addition of one isoprene unit at the copolymer chain-end is neither prone to propagate at room temperature nor to react with the Co(acac)₂. Consequently, massive dimerization of these allyl radicals terminated chains occurs.^{60–62,67} Importantly, the degree of polymerization of the PNVL block and composition of the P(NVCL-*stat*-NVP) segment are identical in the triblocks and the parent diblocks, which is serious advantage for comparing the thermal properties of both architectures, as will be discussed later.

Table 2 summarizes the molecular parameters (*M*_n, DP, *D*) of the PNVL precursors, the PNVL-*block*-P(NVCL-*stat*-NVP) diblocks and the final PNVL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVL triblocks. Detailed polymerization conditions are provided in the experimental section and in Table S1.† The exact molar mass of the polymers was obtained using a DMF-SEC chromatograph equipped with a multi-angle laser light scattering (MALLS) detector and the *D* using a PS calibration. The composition of the P(NVCL-*stat*-NVP) statistical segment in the

diblock and the triblock was determined by ^1H NMR by taking into account the degree of polymerization of the PNVL block that it is linked to.

The low dispersity of the polymers, the composition of the statistical segment and the increase of molar mass at each step of the process provide a reliable basis to conclude on the efficacy of this synthetic approach. The overlay of the chromatograms in Fig. 1 confirms the efficiency of the PNVL-*block*-P(NVL-*stat*-NVP) by chain extension carried out from the PNVL-Co(acac)₂. Although not quantitative, the radical coupling reaction is efficient because the molar mass of a large majority of the chains double when treating the PNVL-*block*-P(NVL-*stat*-NVP)-Co(acac)₂ with isoprene. Indeed, a limited amount of unreacted diblocks (15% by deconvolution of the SEC chromatograms) contaminates the final PNVL-*block*-P(NVL-*stat*-NVP)-*b*-PNVL triblock (Fig. 1). The latter results from partial deactivation of the diblock chain-end before coupling.

In this way, we designed a series of NVL and NVP di- and triblocks with various block lengths and compositions. Because copolymers with two discrete LCSTs are targeted, we ensured that the statistical P(NVL-*stat*-NVP) segments of copolymers are NVP-rich (see Table 2) to make sure that their transition temperature sufficiently differs from the LCST of the PNVL block.

Thermoresponsive behaviour of the copolymers

In this section, the solution behaviour and the thermal response of the copolymers prepared above will be addressed starting with the statistical P(NVL-*stat*-NVP) copolymers. As indicated in Table 1, the latter differ by their NVP/NVL composition but their molar mass remains in the same range. The cloud point temperature (T_{CP}) of the aqueous solution of each copolymer (0.1 wt%) was measured by turbidimetry. The trans-

mittance *versus* temperature plots, also called cloud point curves are shown in Fig. S2.† A heating rate of $1\text{ }^\circ\text{C min}^{-1}$ was used and we considered that the cloud point was reached when half of the transmittance of the solution was lost. The T_{CP} of each P(NVL-*stat*-NVP) copolymer was then plotted as a function of their NVP molar fraction (Fig. 2). For the sake of the comparison, the T_{CP} of a homoPNVL ($37\text{ }^\circ\text{C}$) was added on the graph. Because NVP is more hydrophilic than NVL that contains two additional aliphatic carbons in the lactam ring, the higher is the NVP content in the copolymer, the higher is the phase transition temperature (Fig. 2). For example, a T_{CP} of $72\text{ }^\circ\text{C}$ was obtained when the NVP molar fraction in the copolymer was 0.57 (entry 5, Table 1). Note that no phase transition was detected below $100\text{ }^\circ\text{C}$ for the copolymer containing 72 mol% of NVP (entry 6, Table 1). Although the dependence of the transition temperature with the NVP content does not appear to be linear, it is now possible to precisely tune the T_{CP} of a P(NVL-*stat*-NVP) copolymer by adjusting its composition.

With these data in hand, we investigated the solution behaviour of the PNVL-*block*-P(NVL-*stat*-NVP) diblocks and PNVL-*block*-P(NVL-*stat*-NVP)-*block*-PNVL triblocks. Theoretically, both types of copolymers should be double thermoresponsive, the T_{CP} of the PNVL block(s) being inferior to the one of the NVP/NVL statistical segments. Moreover, the transition temperature of one block could be influenced by the adjacent segment(s). Therefore, the impact of the copolymer architecture and composition on the T_{CP} of each segment are key issues addressed in the present work as well as the organization of the di- and triblock copolymers in solution at different temperatures. Overall, an increase of the temperature is expected to change the solubility of the blocks in a stepwise fashion, inducing a multistep self-assembly behaviour described in Scheme 4. Below (region I) and above (region III), both T_{CP} s, the copolymer chains should be fully soluble and aggregated in water. At intermediate temperatures (region II,

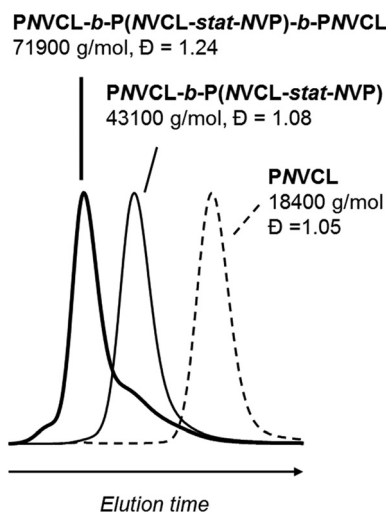


Fig. 1 Overlay of the SEC chromatograms of the homoPNVL precursor (C_{132}), the PNVL-*block*-P(NVL-*stat*-NVP) diblock ($C_{132}(C_{40}P_{172})$) and the PNVL-*block*-P(NVL-*stat*-NVP)-*b*-PNVL triblock ($C_{132}(C_{80}P_{344})C_{132}$) by sequential CMRP chain extension and CMRC (see Table 2, entry 2).

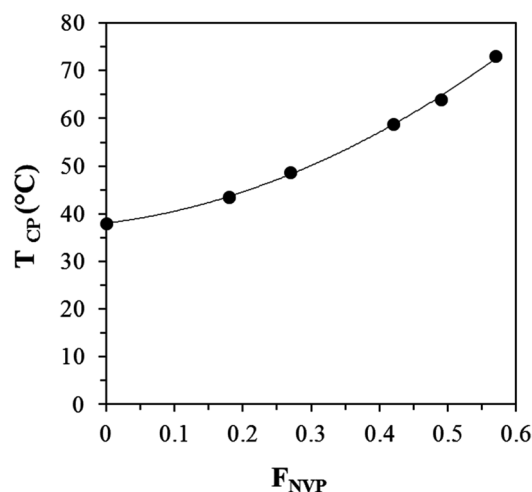


Fig. 2 Evolution of the cloud point temperature (T_{CP}) of the statistical P(NVL-*stat*-NVP) copolymer aqueous solutions (1 mg mL^{-1}) with the NVP molar fraction (F_{NVP}).

$T_{CP1} < T < T_{CP2}$), only the PNVL block precipitates leading to the self-organization of the copolymers in water. For most copolymers (see Table 2), the statistical P(NVCL-*stat*-NVP) segment is longer than the PNVL block. Therefore, it is reasonable to expect the formation of spherical micelles composed of dehydrated PNVL core stabilized by a P(NVCL-*stat*-NVP) corona, the latter consisting of loops in the case of the triblocks.

The thermal response of the block copolymers presented in Table 2 was systematically analysed by combination of turbidimetry and DLS. The study of the $C_{132}(C_{40}P_{172})$ and $C_{132}(C_{80}P_{344})C_{132}$ copolymer pair is presented in detail hereafter (Fig. 3 and 4) while the transition temperatures of all the copolymers determined by a similar approach are collected and compared in Table 3.

Fig. 3 shows the evolution of the transmittance (dotted line) and of the relative scattered light intensity (I/I_0) measured by DLS upon heating the aqueous solutions of $C_{132}(C_{40}P_{172})$ and $C_{132}(C_{80}P_{344})C_{132}$. For the diblock, two marked transitions are observed. The first one, indicated by the increase of the scattered intensity (full line in the upper graph of Fig. 3), appears around 45 °C. This transition corresponds to the selective precipitation of the PNVL block (T_{CP1}). The latter occurs at higher temperature compared to a homoPNVL ($T_{CP} \sim 37$ °C) because in the diblock the PNVL is linked to a more hydrophilic sequence of P(NVCL-*stat*-NVP).⁸ The second phase transition was clearly identified by a sharp loss of transmittance at 70 °C, which is due to the dehydration and precipitation of the NVP containing segment. Importantly, the T_{CP} of the statistical P(NVCL-*stat*-NVP) sequence of the copolymer (70 °C) is drastically lowered by the more hydrophobic, and already collapsed, PNVL block. Indeed, as mentioned above, an isolated NVCL/NVP statistical copolymer with the same composition ($F_{NVP} = 0.81$) should not exhibit a T_{CP} since we did not detect any for the P(NVCL-*stat*-NVP) with a NVP molar fraction of 0.72. The DLS size distribution histograms recorded at different temperatures are presented in Fig. 4. At 35 °C (region I), the sample

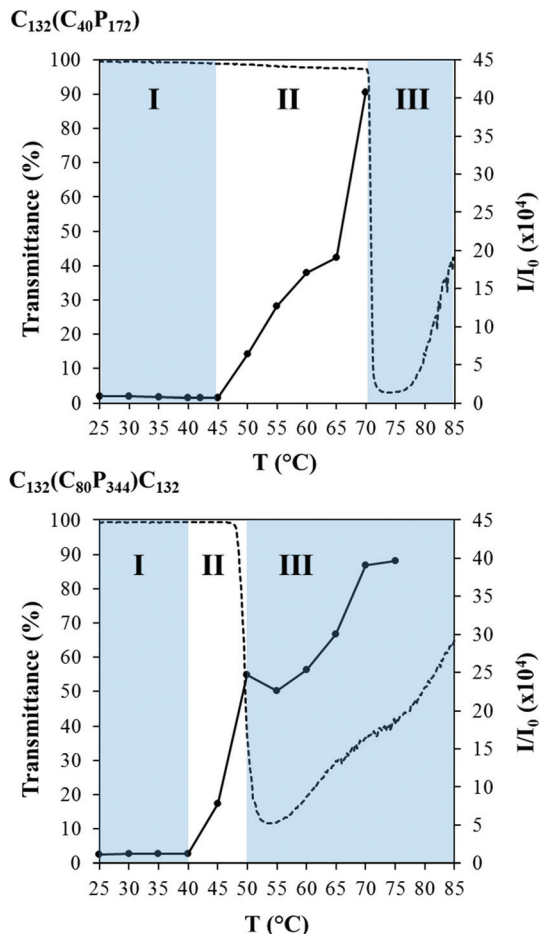
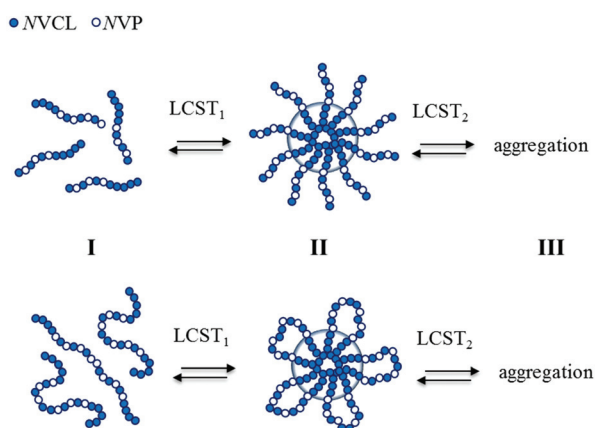


Fig. 3 Transmittance (1 °C min^{-1}) (dotted line) and scattered intensity measured by DLS (full line) for the $C_{132}(C_{40}P_{172})$ diblock and the parent $C_{132}(C_{80}P_{344})C_{132}$ triblock aqueous solutions (1 g L^{-1}) as a function of temperature. See entry 2 in Table 2 for the detailed copolymer characteristics.



Scheme 4 Illustration of the thermally induced phase transitions of the PNVL-*block*-P(NVCL-*stat*-NVP) diblock and the corresponding PNVL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVL triblock.

mainly consists of free chains, corresponding to the main peak being observed around a few nm. The second population, around 100 nm, is probably due to a small fraction of loose aggregates but is negligible being absent from the number-weighted size distribution graph (not shown). At 70 °C (region III), rather large objects are formed (~ 300 nm) suggesting complete aggregation of the copolymer chains. At 50 °C, so in region II corresponding to temperatures between the two T_{CP} s, micelles with an average hydrodynamic radius of 20 nm and a low polydispersity index (0.02) were observed. The morphology of the object has been tentatively studied by transmission electron microscopy (TEM) but aggregation occurred during the deposition on the TEM grid and evaporation of the thermostated solution (55 °C). Considering the copolymer composition, those are probably core-shell spherical micelles. Micelles with a very similar size were observed at several temperatures within region II (see Fig. S3,† for additional DLS curves). Interestingly, in the previously studied PNVL-*block*-P(NVCL-*stat*-NMVA) copolymers, a transition region corresponding to the formation of large and ill-defined objects was

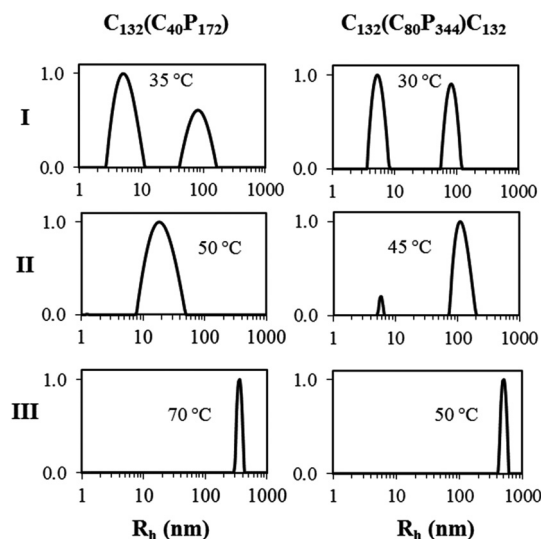


Fig. 4 Intensity normalized CONTIN size distribution of the PNVL-*b*-P(NVL-*stat*-NVP) diblock and the corresponding PNVL-*b*-P(NVL-*stat*-NVP)-*b*-PNVL triblock aqueous solutions (1 g L⁻¹) at various temperatures (I below T_{CP1} , II between T_{CP1} & T_{CP2} , III above T_{CP2}). Additional DLS curves of the copolymers at other temperatures are provided in Fig. S3.†

Table 3 T_{CP} s of the NVCL/NVP-based di- and triblocks

Copolymers	T_{CP1}^a (°C)	T_{CP2}^b (°C)
$C_{68}(C_{74}P_{191})$	50	70
$C_{68}(C_{148}P_{382})C_{68}$	52	58
$C_{132}(C_{40}P_{172})$	45	70
$C_{132}(C_{80}P_{344})C_{132}$	40	50
$C_{236}(C_{55}P_{154})$	40	67
$C_{236}(C_{110}P_{308})C_{236}$	40	43
$C_{282}(C_{27}P_{297})$	35	— ^c
$C_{282}(C_{54}P_{594})C_{282}$	40	— ^c
$C_{282}(C_{27}P_{297})$	25 ^d	63 ^d
$C_{282}(C_{54}P_{594})C_{282}$	25 ^d	68 ^d

Copolymer aqueous solutions (1 g L⁻¹). ^a T_{CP1} values correspond to the onset temperature of the increase of the scattered light intensity measured by DLS (as shown in Fig. 3). ^b T_{CP2} is measured at 50% of transmittance loss on the turbidimetry curves. ^c No second T_{CP} was detected below 95 °C. ^d Determined in 2 M NaCl aqueous solution.

observed prior to micellization upon heating the copolymer solution.³⁴ In contrast, the present PNVL-*block*-P(NVL-*stat*-NVP) diblock exhibits a sharp unimers/micelles transition.

Next, we examined the corresponding $C_{132}(C_{80}P_{344})C_{132}$ triblock under the same dilution condition (1 mg mL⁻¹). Again, two phase transitions were observed. The first one corresponds to the T_{CP} of the PNVL external blocks of the copolymer and occurs around 40 °C as emphasized by the increase of the scattered light intensity measured by DLS (full line in the lower graph of Fig. 3). The second transition corresponds to the precipitation of the central P(NVL-*stat*-NVP) segment of the triblock and was identified at 50 °C on the turbidimetry curve (dotted line in the lower graph of Fig. 3). The DLS size histograms presented in Fig. 4 and S3 show that the triblock copoly-

mer mainly exists as free chains below the first T_{CP} and is fully aggregated above the second T_{CP} , as for the diblock. In the inter- T_{CP} region, a major population around a hydrodynamic radius of about 100 nm is observed. This size seems too large to correspond to simple flower-like micelles, and the associated objects are probably small aggregates of micelles. The ABA triblock copolymer is indeed more prone to aggregation than the diblock because the A blocks can precipitate into two different micellar cores, inducing the formation of bridges between micelles. Moreover, the self-assembly of the triblock in water is more difficult to control because the inter- T_{CP} window (region II) is much narrower compared with the diblock. Although the composition of the blocks of $C_{132}(C_{40}P_{172})$ and $C_{132}(C_{80}P_{344})C_{132}$ are strictly identical, their respective T_{CP} s vary from one architecture to another and are lower in the triblock than in the diblock (see Table 3). Doubling of the molar mass of the copolymer and of the statistical P(NVL-*stat*-NVP) sequence by radical coupling might contribute to this effect. Nevertheless, considering previous reports²⁵ and the present range of molar mass variation, this factor should only be responsible for a decrease of a few degrees of the T_{CP} . By contrast, the presence of a more hydrophobic PNVL block at both extremities of the P(NVL-*stat*-NVP) segment of the triblock should strongly decrease its transition temperature (from 70 °C in the diblock to 50 °C in the triblock). On the other hand, the hydrophobicity of the polymer chain linked to the PNVL block, *i.e.* P(NVL-*stat*-NVP) in the diblock and P(NVL-*stat*-NVP)-*block*-PNVL in the triblock, is globally higher in the triblock than in the diblock. This might account for the lower T_{CP} of the PNVL segment in the triblock (40 °C) compared to the one in the diblock (45 °C) (see Table 3).

Following the same approach, we studied the thermal response of the aqueous solution of the other diblocks and triblocks mentioned in Table 2, which differ by their block length and compositions. All turbidimetry and DLS curves are provided in the ESI (Fig. S3–S10†). The key transition temperatures of each copolymer are reported in Table 3 and discussed hereafter. Except for $C_{282}(C_{27}P_{297})$ and $C_{282}(C_{54}P_{594})C_{282}$, all copolymers exhibited a double thermoresponsive behaviour in water. Again, the T_{CP} s of both the PNVL block and of the NVP containing sequence were lower in the triblock than in the parent diblock. Moreover, the transition temperature of the longer PNVL block is less impacted by the hydrophilic P(NVL-*stat*-NVP) segment. For example, considering the series of diblocks, the T_{CP} of the PNVL was recorded at 50 °C, 45 °C and 40 °C for degrees of polymerization (DP) of PNVL equal to 68, 132 and 236, respectively (Table 3). As a reminder the T_{CP} of homoPNVL is around 37 °C. Interestingly, between T_{CP1} and T_{CP2} , $C_{68}(C_{74}P_{191})$, $C_{132}(C_{40}P_{172})$ and $C_{236}(C_{55}P_{154})$ formed well-defined micelles whose size increases with the length of the PNVL segment. The R_h of the micelles is equal to 15 nm, 20 nm and 30 nm for DP of 68, 132 and 236, respectively (Fig. S5, S3 and S7†). On the other hand, the study of the $C_{68}(C_{148}P_{382})C_{68}$ and $C_{236}(C_{110}P_{308})C_{236}$ triblocks confirmed the difficulty to form well defined objects and to avoid aggregation.

For $C_{282}(C_{27}P_{297})$ and $C_{282}(C_{54}P_{594})C_{282}$, no precipitation was observed in water below 95 °C because the NVP content in their statistical block was too high ($F_{NVP} = 0.92$), suppressing the second T_{CP} . However, the T_{CP} of the PNVL segment in the diblock (Fig. 5) and in the triblock (Fig. S8†) was detected around 40 °C. These copolymers mainly exist as free chains below 40 °C and self-assembled above the transition temperature. Narrowly dispersed micelles with a R_h of about 30 nm were observed for $C_{282}(C_{27}P_{297})$ between 40 °C and 90 °C (Fig. S9†). In the same range of temperatures, $C_{282}(C_{54}P_{594})C_{282}$ led to assemblies with a hydrodynamic radius between 25 and 35 nm, which probably correspond to flower-like micelles, as well as larger aggregates ($R_h \sim 200$ nm) (Fig. S9†).

The polymer solubility, and LCST of thermoresponsive macromolecules in particular, can be strongly influenced by the presence of salts in the aqueous solution.^{68,69} In particular, hydration and phase behaviour of PNVL and PNVP in water are known to be impacted by the presence of salts which decreases their LCSTs.⁶⁵ This salting out effect was here used to change the T_{CP} of the PNVL segment of $C_{282}(C_{27}P_{297})$ and of $C_{282}(C_{54}P_{594})C_{282}$ and to possibly decrease the solubility of

the statistical $P(NVCL-stat-NVP)$ segment, revealing a second T_{CP} below 100 °C and providing thus double thermoresponsiveness to the copolymer. In a 2 M NaCl aqueous solution, $C_{282}(C_{27}P_{297})$ indeed showed two T_{CP} s (25 °C and 63 °C, Fig. 5) and micelles with a hydrodynamic radius of about 35 nm were observed in the inter- T_{CP} window (Fig. S10†). Addition of salt also shifted downwards the T_{CP} of $C_{282}(C_{54}P_{594})C_{282}$ and for the first time the temperature range of the inter- T_{CP} window was rather large (between 25 °C and 67 °C) (Fig. S8 and S10†). In conclusion, the salting out effect thus appears to be a very useful tool to adjust the transition temperature of NVCL and NVP-based double thermoresponsive block copolymers.

Finally, the reversibility of the temperature induced phase transitions was investigated by turbidimetry for $C_{282}(C_{27}P_{297})$ and $C_{282}(C_{54}P_{594})C_{282}$ in a 2 M NaCl aqueous solution. For the diblock, the T_{CP} s observed upon heating and cooling the solutions were quite similar and hysteresis did not exceed a few degrees (Fig. S11†). Moreover, the objects formed in solution, when increasing and decreasing the temperature, were similar (Fig. S12†) although the micelles detected in the inter- T_{CP} region were larger when cooling the solution. Indeed, the R_h of the micelles observed at 45 °C were around 35 nm and 60 nm in the heating and cooling phases, respectively (Fig. S12†). In such experiments, kinetically frozen micelles are most probably formed considering the abrupt character of the LCST transition. It is therefore not surprising to observe micelles of different sizes during heating and cooling, since it is well-known that the preparation protocol may strongly influence the micellar characteristics in the case of kinetically frozen micelles.⁷⁰ In the case of the triblock $C_{282}(C_{54}P_{594})C_{282}$, as indicated by the turbidimetry curves (Fig. S11†), the re-solubilisation of the copolymer, when cooling the solution was difficult, which prevent us from performing a size analysis by DLS. Nonetheless, its double thermo-responsive character is demonstrated in both the heating and cooling cycles.

Conclusion

A series of novel well-defined thermoresponsive NVCL and NVP-based copolymers, including statistical, diblock and triblock copolymers, were prepared by cobalt-mediated radical polymerization (CMRP) and cobalt-mediated reaction coupling (CMRC). Due to the high level of control on the molecular parameters of the polymers it was possible to compare their thermal properties based on their composition, block length, and architecture. Increasing the NVP content in statistical NVCL/NVP copolymers was shown to increase their lower critical solution temperature in water, 0.7 being approximately the maximum NVP molar fraction for maintaining the T_{CP} of such statistical copolymers below 90 °C. With these data in hand, four pairs of double thermoresponsive di- and triblock composed of PNVL and $P(NVCL-stat-NVP)$ blocks were obtained by sequential CMRP of NVCL and NVCL/NVP polymerizations followed by radical coupling with isoprene. In both types of architectures, the thermal response of PNVL and of the

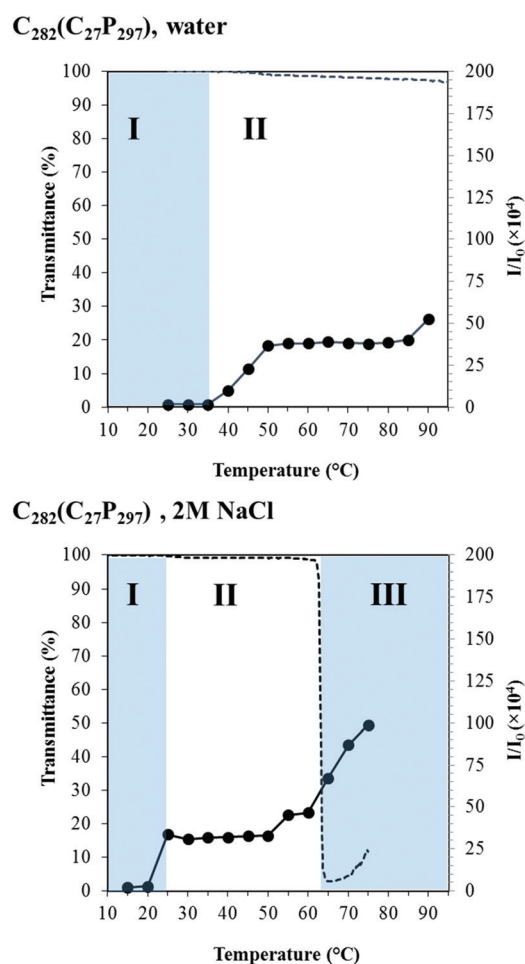


Fig. 5 Transmittance (1 °C min⁻¹) (dotted line) and scattered intensity measured by DLS (full line) for the $C_{282}(C_{27}P_{297})$ diblock (1 g L⁻¹) in water and in 2 M NaCl aqueous solutions as a function of temperature.

P(NVCL-*stat*-NVP) segment influenced each other, the LCST of the PNVC block being increased by the more hydrophilic P(NVCL-*stat*-NVP) block and *vice versa*. As a general trend, the inter- T_{CP} region was narrower and occurred at a lower temperature for the triblock because the central NVCL/NVP block is linked to PNVC at both extremities. In the case of the diblocks, narrowly dispersed micelles were formed from unimers upon heating, and total collapse occurred above the second T_{CP} , confirming the multistep assembly behaviour of the copolymers. For the triblocks, the self-assembly was more difficult to control due to their enhanced tendency to aggregation, linked to their ABA structure, and the narrower inter- T_{CP} window. Moreover, the NaCl salting-out effect was successfully used to adjust the T_{CP} s of these types of copolymers to the extent that the T_{CP} of a NVP rich statistical segment became detectable below 100 °C, making the corresponding di- and triblock copolymers doubly thermoresponsive. Finally, the double thermo-responsive character of the NVCL and NVP-based copolymers was also emphasized in both the heating and cooling cycles. As a result, the data presented here provide a basis to synthesize a broad range of double thermoresponsive NVCL- and NVP-based di- and triblock copolymers with tunable LCSTs and highlight the crucial impact of the architecture of the copolymer on their thermal phase transition.

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