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## ARTICLE

# Double Thermo-Responsive Hydrogels from Poly(vinylcaprolactam) Containing Diblock and Triblock Copolymers.

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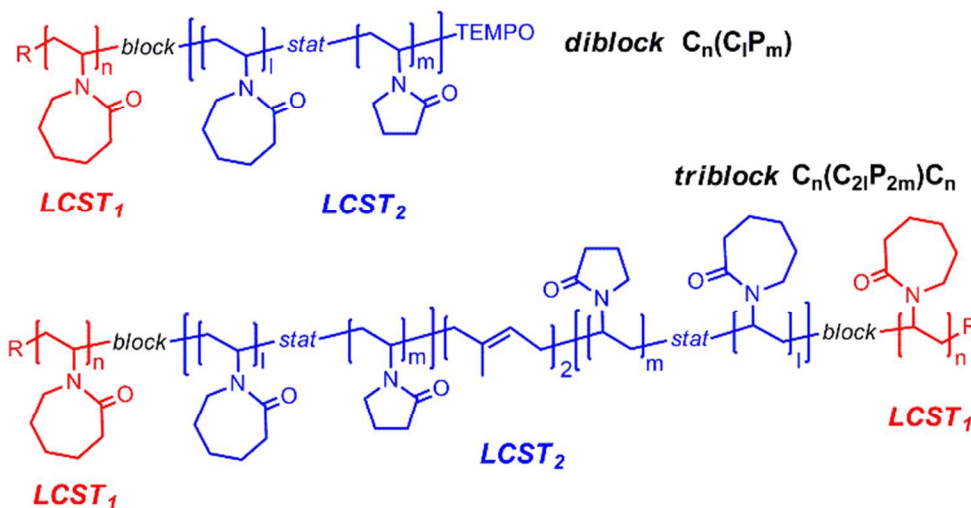
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The thermally-induced gelation and gel properties of concentrated aqueous solutions of double thermoresponsive poly(N-vinylamide)-based di- and triblock copolymers are studied by rheology. The copolymers under investigation, prepared by cobalt-mediated radical polymerization and coupling reaction, are composed of poly(vinylcaprolactam) (PNVCL) blocks and of a statistical poly(vinylcaprolactam-*stat*-vinylpyrrolidone) segment with a cloud point temperature ( $T_{CP}$ ) higher than the one of PNVCL. Heating the di- and triblock solutions beyond the first phase transition temperature favors gel formation while heating above the second  $T_{CP}$  leads to opaque gels without macroscopic demixing. Moduli of the triblock hydrogels are systematically higher than those of the corresponding diblocks, even above the second transition. Rheological data suggest distinct micellar structures for each copolymer architecture: densely packed micelles of diblocks and 3-D networks of bridged micelles for triblocks. Strain sweep experiments also emphasize the positive effect of the micelle bridging on the elasticity and stability of the hydrogels. The formation and properties of the obtained gels are also shown to depend on the copolymer concentration, block length and composition. Addition of salt also permits to tune the phase transition temperatures of these double thermoresponsive hydrogels.

## Introduction

Poly(vinylcaprolactam) (PNVCL) is a water soluble polymer gaining much attention notably in the biomedical area<sup>1, 2</sup> due to its biocompatibility<sup>3, 4</sup> and thermoresponsiveness<sup>5</sup> around the body temperature. The lower critical solution temperature (LCST) behavior of PNVCL in water has been extensively studied<sup>5-8</sup> and a large number of drug delivery systems including micelles, hydrogels and hybrid particles were developed based on this thermal response.<sup>9</sup> As a matter of fact, progress in the controlled radical polymerization of NVCL<sup>10</sup> has played an important role in this renewed focus on this polymer known for decades. Through CRP techniques like atom transfer radical polymerization<sup>11-14</sup>, radical addition fragmentation chain transfer<sup>15-22</sup> and organometallic mediated radical polymerization (OMRP),<sup>23-27</sup> well-defined thermo-responsive PNVCL sequences could be associated with hydrophilic or hydrophobic segments. The reversible temperature triggered assembly of such block copolymers in water was demonstrated, opening new perspectives in the field of stimuli-responsive encapsulation/release applications. Recently, double thermoresponsive diblock and triblock copolymers were made from NVCL and N-vinylpyrrolidone (NVP), a comonomer recognized as a precursor of biocompatible polymers.<sup>28</sup> More precisely, gradual heating of aqueous solutions of PNVCL-*b*-P(NVCL-*stat*-NVP) and PNVCL-*b*-P(NVCL-*stat*-NVP)-*b*-PNVCL promoted a transition from free chains to micelles before full dehydration and collapse of the block copolymers.<sup>28</sup> Hydrogels composed of three-dimensional networks of cross-linked PNVCL swollen by water is another class of materials of interest for biomedical applications, and for drug delivery in particular.<sup>29-36</sup> These hydrogels are mostly obtained by

chemical cross-linking via copolymerization of NVCL with divinyllic comonomers like poly(ethylene glycol) di-acrylate or methacrylate, N,N'-methylenebisacrylamide, etc.<sup>37-41</sup> Nevertheless, gelation by physical cross-linking is becoming more and more popular due to the possibility to easily reshape the materials. For example, pH- and thermo-responsive polymeric hydrogels were prepared from P(NVCL-*co*-methacrylic acid) via acid-amide hydrogen bonds.<sup>42</sup> Another category of physical hydrogels consists in aqueous micellar gels.<sup>43-45</sup> The latter are formed either by discrete spherical micelles of block copolymers packed into an ordered structure in water (around 20 wt%) or by the three dimensional network formed by ABA triblock copolymers where the central block acts as bridge between the micellar cores made by hydrophobic interactions between the outer blocks of the triblock. Thermoresponsive micellar gels based on poly(N-isopropylacrylamide) or polypropylene oxide are also reported. Depending on the structure of the block copolymers, crossing the LCST induces a liquid-gel<sup>45-56</sup> or a gel-demixed system transition<sup>57, 58</sup>. Although the presence of several thermo-sensitive transitions clearly generates more flexibility and enlarges the scope of applications of these hydrogels, reports on such double thermoresponsive gels are particularly rare in the literature.<sup>59-61</sup> Moreover, in spite of the advantages of PNVCL and of the availability of the PNVCL-based block copolymers, no NVCL-based micellar gels have been reported so far. In this work, we evaluate the ability of NVCL- and NVP-containing copolymers to form double thermo-responsive micellar hydrogels. To this end, the above mentioned PNVCL-*b*-P(NVCL-*stat*-NVP) diblocks and PNVCL-*b*-P(NVCL-*stat*-NVP)-*b*-PNVCL triblocks were selected (Figure 1).



**Figure 1.** Structures of the double thermo-responsive NVCL and NVP-based diblock and triblock copolymers used in the hydrogel formation.

While their double thermo-responsiveness and their multistep assembly has been demonstrated in dilute aqueous solutions (0.1 wt%),<sup>28</sup> their behavior at higher concentrations (from 12.5 wt% to 25 wt%) and capacity to form dual responsive gels have never been explored. Therefore, rheological measurements were conducted on these copolymer solutions in order to emphasize the temperature induced transitions and characterize the resulting hydrogels. Importantly, the copolymers were prepared by controlled radical polymerization process in order to ensure a good control of the size, composition, and so of the LCST of each sequence.<sup>28</sup> The effect of the architecture, block length, composition, presence of salt and copolymer concentration on the gelation phenomenon and gel properties are addressed.

## Experimental Section

### Materials

The PNVCL-*b*-P(NVCL-*stat*-NVP) diblocks and PNVCL-*b*-P(NVCL-*stat*-NVP)-*b*-PNVCL triblock copolymers represented in Figure 1 were produced by cobalt-mediated radical polymerization and coupling reaction (CMRP and CMRC, respectively) following a recently reported procedure.<sup>28</sup> The copolymers were considered as pairs since triblock copolymers results from the coupling of the corresponding diblocks. The molecular characteristics and transition temperatures of the copolymers in diluted solutions are mentioned in

Table 1. For the sake of clarity, the PNVCL-*block*-P(NVCL-*stat*-NVP) and PNVCL-*block*-P(NVCL-*stat*-NVP)-*block*-PNVCL copolymers were labeled based on their composition:  $C_n(C_1P_m)$  and  $C_n(C_2I_2P_2m)C_n$  where **C** and **P** correspond to NVCL and NVP, respectively, and **n** and **l** denote the number of NVCL units and **m** the number of NVP units.

### Rheological study

The copolymer solutions with concentration ranging from 12.5 wt% to 25 wt% were prepared by dissolution of the copolymers in double distilled water at room temperature. The same procedure was used for the preparation of the copolymer solution in a 2 M NaCl aqueous solution. Rheological measurements were performed on an ARES G2 rheometer from TA instruments using a cone plate geometry (0.0997 rad, diameter 25 mm) equipped with a peltier plate to control the temperature. Silicone oil drops were used to cover the surface of the samples in order to limit the evaporation during the experiment. Different procedures have been used: Temperature ramp from 30 to 80 °C (3 °C/min, 3% strain at 6.283 rad/s), frequency sweep from 100 rad/s to 0.1 rad/s (3% strain) and strain sweep from 1% to 100 % (6.283 rad/s). It has to be pointed out that a temperature ramp at 1 °C/min has also been performed and gave results similar to those obtained at 3 °C/min. The data were collected with the TRIOS software.

**Table 1.** Cloud point temperatures ( $T_{CP}$ ) of the NVCL/NVP-based di- and triblock copolymers in dilute conditions (0.1 wt%)

Copolymers	$M_n$ (g/mol) <sup>a</sup>	$\bar{D}$ <sup>a</sup>	$T_{CP1}$ (°C)	$T_{CP2}$ (°C)
$C_{68}(C_{74}P_{191})$	41400	1.13	50	70
$C_{68}(C_{148}P_{382})C_{68}$	64500	1.24	52	58
$C_{132}(C_{40}P_{172})$	43100	1.08	45	70
$C_{132}(C_{80}P_{344})C_{132}$	71900	1.24	40	50
$C_{236}(C_{55}P_{154})$	57500	1.06	40	67
$C_{236}(C_{110}P_{308})C_{236}$	110500	1.13	40	43
$C_{282}(C_{54}P_{594})C_{282}$	76200	1.08	40	/ <sup>b</sup>
$C_{282}(C_{54}P_{594})C_{282}$ <sup>c</sup>	128000	1.13	25	68

For details about the TCP measurements, see ref<sup>28</sup>. <sup>a</sup> Exact molar mass and dispersity determined by DMF-SEC using a MALLS detector and an RI detector with PS calibration, respectively. <sup>b</sup> No second  $T_{CP}$  was detected below 95 °C. <sup>c</sup> Determined in 2 M NaCl aqueous solution.

## Results and Discussion

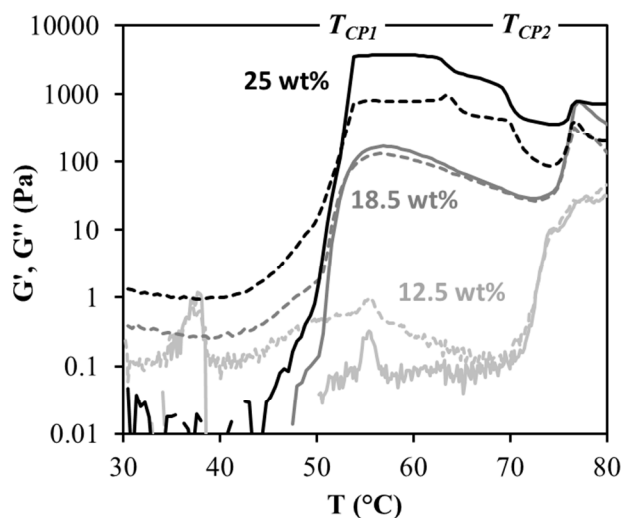
The degree of polymerization and composition of a series PNVC-*b*-P(NVCL-*stat*-NVP) diblocks and PNVC-*b*-P(NVCL-*stat*-NVP)-*b*-PNVCL triblocks investigated here are reported in Table 1. The latter also summarizes the cloud point temperatures ( $T_{CP}$ ) of diluted aqueous solutions (0.1 wt%) of these copolymers measured previously by dynamic light scattering and turbidimetry.<sup>28</sup> Below are listed some relevant conclusions to bear in mind before starting the study in more concentrated regimes. As a rule, the incorporation of a more hydrophilic monomer (NVP) in a PNVC segment increases its  $T_{CP}$ .<sup>28</sup> Additionally, the  $T_{CP}$  of PNVC is increased when a more hydrophilic block is attached to it whereas the  $T_{CP}$  of the statistical copolymer decreases when the overall length of the PVCL block(s) increases. The selective precipitation of the PNVC blocks upon heating led to the formation of well-defined micellar objects in the “inter-LCST” temperature range but, in contrast to the diblocks, only a slight difference was observed between the two  $T_{CPs}$  for the triblocks. A more detailed discussion about these results can be found in our previous report.<sup>28</sup> Since the transition temperature of a PNVC solution is known to be concentration dependent,<sup>5</sup> differences in  $T_{CP}$  values can be expected for the concentrated copolymer solutions (from 12.5 to 25 wt%) investigated here and those reported under dilute conditions (Table 1, 0.1 wt%). Moreover, provided that the copolymer concentration is high enough, gelation of the copolymer solutions should occur upon increasing the temperature above the  $T_{CP}$  of the PNVC segments ( $T_{CP1}$ ) followed by the dehydration of these gels at temperatures higher than the  $T_{CP}$  of the statistical NVCL/NVP segment ( $T_{CP2}$ ).

### Concentrated diblock copolymer solutions

Figure 2 shows the evolution of the storage and loss modulus of a diblock copolymer with intermediate PNVC block length, i.e.  $C_{132}(C_{40}P_{172})$ , as a function of temperature at three different concentrations (12.5 wt%, 18.5 wt% and 25 wt%). The concentration has a significant impact on the gel properties as discussed below. No increase in storage modulus is observed when a 12.5 wt% aqueous solution of  $C_{132}(C_{40}P_{172})$  is heated above the transition temperature of its PNVC block ( $T_{CP1} \sim 45$  °C). At this concentration, the average distance between the micelles is too large to form a packed structure and then a gel. An increase of the modulus is only observed above 70 °C, so above the second cloud point temperature of copolymer ( $T_{CP2}$ ), i.e. when a total desolvation of the polymer has occurred. This modulus increase at temperatures superior to  $T_{CP2}$  is due to the absence of macrophase separation and for the formation of particles leading to a colloidal gel. An increase in modulus is also observed when concentrated solutions of homo-PNVC or P(NVCL-*stat*-NVP) copolymers reached their unique  $T_{CP}$

(Figure S1), which proves that these types of polymers preserve an affinity towards water even above their LCST preventing macroscopic phase separation.<sup>6</sup> Moreover, the increase in modulus when crossing the  $T_{CP2}$  of the  $C_{132}(C_{40}P_{172})$  diblock (Figure 2) is much more pronounced than in the case of PNVC or P(NVCL-*stat*-NVP) copolymers (Figure S1). In the former case, the self-assembly of the copolymer into micelles before the total desolvation certainly helps the formation of well-defined particles and ultimately of a colloidal gel with higher modulus.

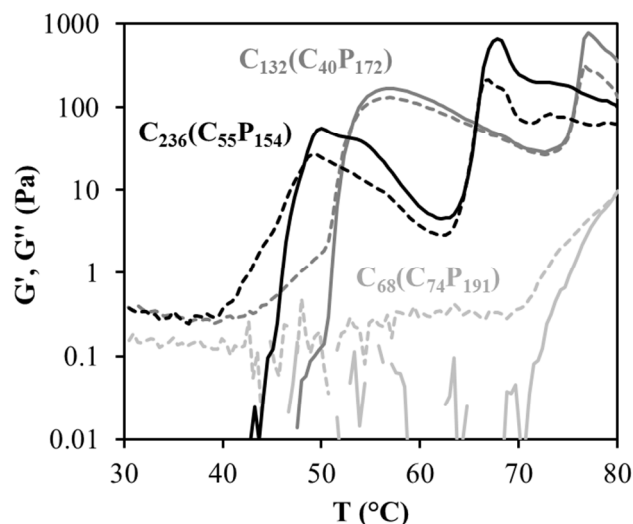
At higher concentration of  $C_{132}(C_{40}P_{172})$  (18.5 wt% and 25 wt%), the increase in modulus already occurs around 50°C, i.e. at the  $T_{CP}$  of the PNVC block meaning that the micelles are now packed enough to form a gel. The difference between  $G'$  and  $G''$  increases with concentration as expected for micellar gels of this type<sup>62</sup>; a soft gel ( $G' \approx G''$ ) is obtained at 18.5 wt% while a harder gel ( $G' > G''$ ) is obtained at 25 wt%. The decrease of the moduli observed when increasing the temperature beyond the first transition detected by rheology (from 50 to 70 °C) probably results from a change in the level of dehydration of the NVCL-based objects. This hypothesis is consistent with the quite broad thermal transitions reported in the literature.<sup>8</sup> A further increase of the solution temperature from 50 °C to 70 °C causes a slight loss in modulus. Above  $T_{CP2}$  (~70 °C), the modulus increases again, possibly because of the collapse of the micellar corona leading to the aforementioned colloidal gel.



**Figure 2.** Storage ( $G'$ , full line) and loss ( $G''$ , dotted line) modulus as a function of temperature for the  $C_{132}(C_{40}P_{172})$  diblock copolymer at different concentrations : 25 wt% (black), 18.5 wt% (grey dark),

and 12.5 wt% (grey light).  $T_{CP1}$  and  $T_{CP2}$  were added to the graph as an indication of the cloud point temperature region of PNVL and P(NVL-*stat*-NVP), respectively.

In addition to the copolymer concentration, the molecular features of the PNVL-*b*-P(NVL-*stat*-NVP) diblock also influence the gel formation, as illustrated by Figure 3 that compares the moduli of the three diblock copolymers ( $C_{68}(C_{74}P_{191})$ ,  $C_{132}(C_{40}P_{172})$ ,  $C_{236}(C_{55}P_{154})$ ) at a given concentration (18.5 wt%). For the shortest PNVL block length ( $C_{68}(C_{74}P_{191})$ ), no increase of the modulus is observed at the first LCST, so upon dehydration of the PNVL segment and formation of the micelles. It is worth noting that increasing the concentration of this diblock to 25 wt% does not induce gelation. In contrast, copolymers with longer PNVL block length ( $C_{132}(C_{40}P_{172})$ ,  $C_{236}(C_{55}P_{154})$ ) form already stable hydrogels at the first LCST. This difference emphasizes the crucial impact of the molecular parameters of the copolymers, and so of the resulting micelles, on the properties and behavior of the gels. Again the phase transition temperatures of concentrated solutions (12.5-25 wt%), that can reasonably be associated to the increase in modulus, are slightly different from those of dilute solutions (0.1 wt%) but followed the same trend. Importantly, phase transition temperatures at higher concentrations appear broad compared to the ones of diluted solutions but we should bear in mind that rheological measurements accounts for the whole material whereas turbidimetry and DLS only emphasize the onset of the phase transition.

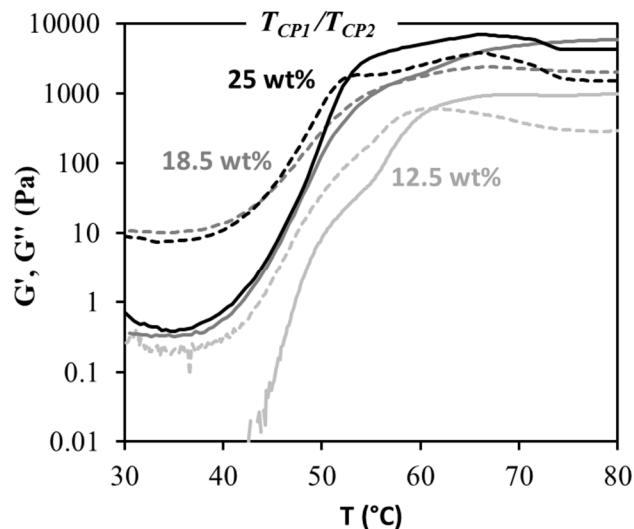


**Figure 3.** Storage ( $G'$ , full line) and loss ( $G''$ , dotted line) modulus as a function of temperature for  $C_{68}(C_{74}P_{191})$  (grey light),  $C_{132}(C_{40}P_{172})$  (grey dark) and  $C_{236}(C_{55}P_{154})$  (black) at 18.5 wt%.

#### Concentrated triblock copolymer solutions.

The dependence of the modulus of the triblock copolymer with intermediate PNVL block length ( $C_{132}(C_{80}P_{344})C_{132}$ ) on temperature is represented in Figure 4 for three concentrations (12.5, 18.5 and 25 wt%). In all cases, only one increase in modulus was observed. This observation is consistent with the fact that the two  $T_{CPs}$  of this copolymer in dilute solution (0.01 wt%) measured by DLS and turbidimetry only differ by few degrees (Table 1). As a consequence, the phase transitions corresponding to the cloud point temperatures ( $T_{CPs}$ ) cannot be distinguished by rheology. However, the increase in modulus is much higher than the one observed with the statistical copolymers (Figure S1). Therefore, the dehydrated

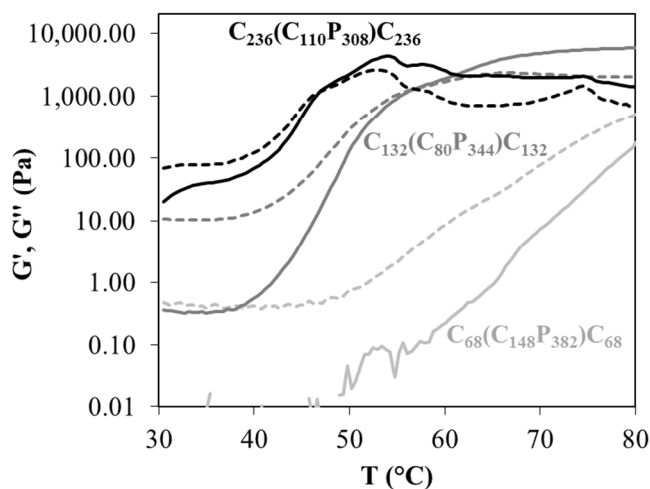
structure of  $C_{132}(C_{80}P_{344})C_{132}$  must strongly differ from the polymer particles generated by the statistical copolymers above both  $T_{CPs}$ . A transient micellar state with the formation of intermicellar bridges between the cores could explain the high modulus observed. In other words, the onset of the modulus increase corresponds to the preferential dehydration of the PNVL outer blocks of the copolymer, promoting the self-assembly of the latter, while the second  $T_{CP}$  corresponding to the desolvation of the inner P(NVL-*stat*-NVP) block cannot be distinguished and takes place during the increase in modulus. Note that the rate of the temperature ramp was decreased from 3 °C/min to 1 °C/min in order to discriminate the  $T_{CPs}$  but similar evolution of the moduli as a function of temperature is obtained in the latter case. In sharp contrast with the corresponding  $C_{132}(C_{40}P_{172})$  diblock,  $C_{132}(C_{80}P_{344})C_{132}$  leads to a gel with significant modulus at 12.5 wt% probably due to the formation of these P(NVL-*stat*-NVP) intermicellar bridges. For the triblocks, a hydrogel can thus be obtained at lower concentration. The moduli still continue to increase after the second LCST. This situation is comparable to the one observed for the diblock copolymers where an increase was observed at  $T_{CP2}$  due to the desolvation of the coronal chains. In the case of triblocks, the intermicellar bridges formed between the two  $T_{CPs}$  tend to link some particles together forming a stronger colloidal gels with much higher modulus above  $T_{CP2}$ . Even though the inter- $T_{CP}$  temperature window is narrow for this triblock, excellent hydrogels can be prepared thanks to the sequential precipitation of the blocks.



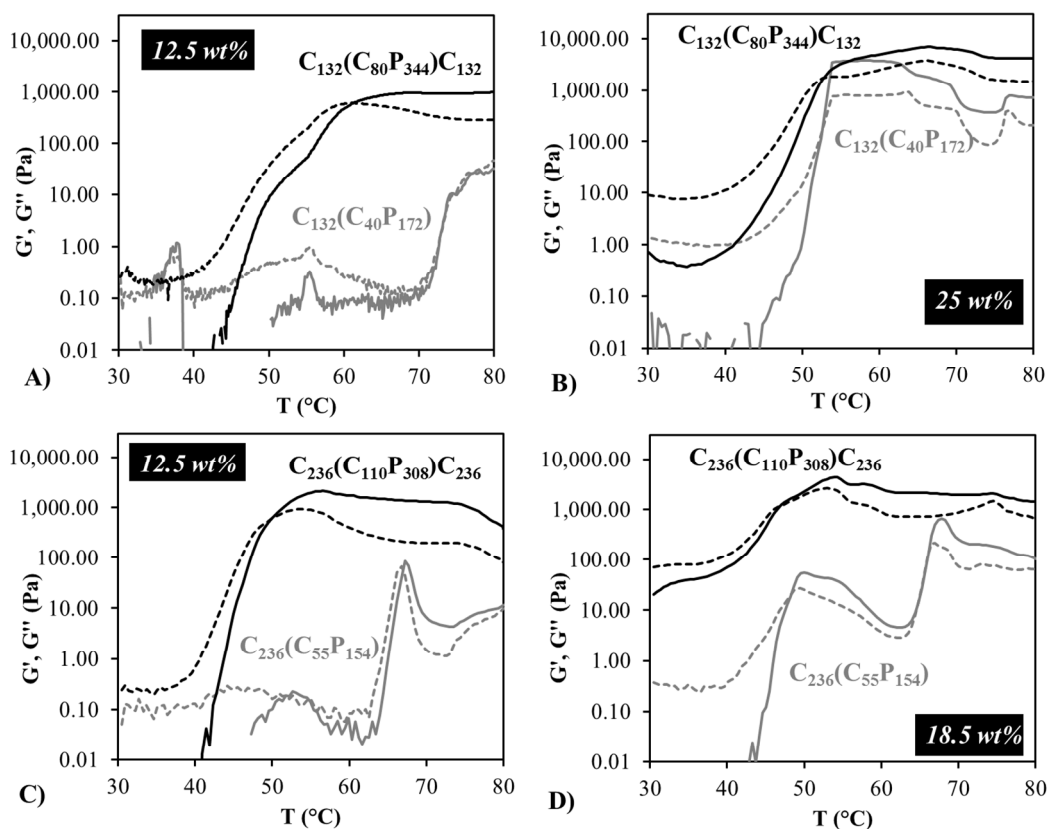
**Figure 4.** Storage ( $G'$ , full line) and loss ( $G''$ , dotted line) modulus as a function of temperature for the  $C_{132}(C_{80}P_{344})C_{132}$  triblock copolymer at different concentration 12.5 wt% (grey light), 18.5 wt% (grey dark), and 25 wt% (black).  $T_{CP1}/T_{CP2}$  were added to the graph as an indication of the cloud point temperature region of both PNVL and P(NVL-*stat*-NVP), according to Table 1.

Figure 5 compares the rheological behavior of the three triblock copolymers at 18.5 wt%. Again, stronger gels are made by copolymers with longer PNVL outer blocks. Indeed, the core of the micelles that ensure the 3D network, becomes more stable when the length of the PNVL block increases. Moreover, the raise of the modulus occurs at lower temperature for triblocks having longer PNVL outer block, in agreement with the observation made under dilute solution where the  $T_{CP}$  decreased with the increase of the length of the PNVL block (Table 1). A similar behavior has been observed at a concentration of 12.5 wt%. Note that no gelation was

observed for the  $C_{68}(C_{148}P_{382})C_{68}$  solutions whatever the temperature and the concentration used, probably due to the fact that the PNVCCL blocks are too short.



**Figure 5.** Storage ( $G'$ , full line) and loss ( $G''$ , dotted line) modulus as a function of temperature for  $C_{68}(C_{148}P_{382})C_{68}$  (grey light),  $C_{132}(C_{80}P_{344})C_{132}$  (grey dark) and  $C_{236}(C_{110}P_{308})C_{236}$  (black) at 18.5 wt%.



**Figure 6.** Storage ( $G'$ , full line) and loss ( $G''$ , dotted line) modulus as a function of temperature for a)  $C_{132}(C_{40}P_{172})$  and  $C_{132}(C_{80}P_{344})C_{132}$  at 12.5 wt% (A) and 25 wt% (B) and  $C_{236}(C_{55}P_{154})$  and  $C_{236}(C_{110}P_{308})C_{236}$  at 12.5 wt% (C) and 18.5 wt% (D).

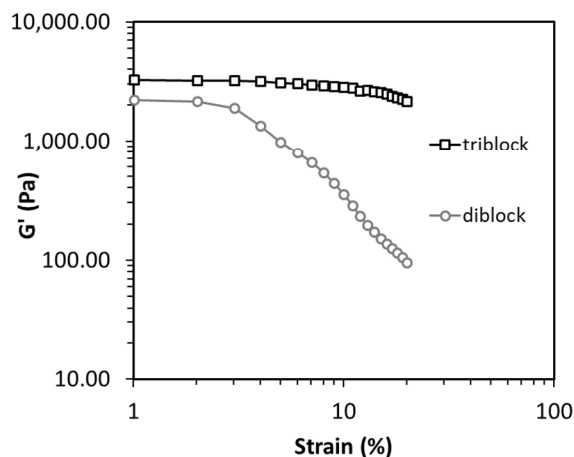
### Comparison of concentrated di- and triblock copolymer solutions.

In order to highlight the difference between the hydrogels formed by the triblocks and by the diblocks, the plots of modulus versus

temperature for some diblock-triblock pairs ( $C_{132}(C_{40}P_{172})$  vs  $C_{132}(C_{80}P_{344})C_{132}$  at 12.5 wt% and 25 wt%,  $C_{236}(C_{55}P_{154})$  and  $C_{236}(C_{110}P_{308})C_{236}$  at 12.5 wt% and 18.5 wt%) have been overlaid in Figure 6. In all cases, the moduli of the triblock hydrogels are superior to the ones of the diblock. Moreover, the moduli are

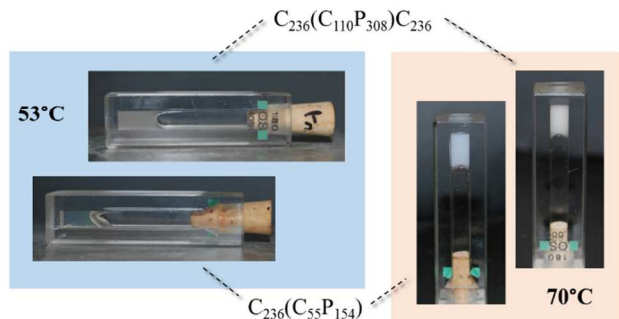
preserved above the second transition, which evidences the beneficial effect of the bridges between micelles of triblocks on the strength and stability of the hydrogels. However, for  $C_{132}(C_{40}P_{172})$  and  $C_{132}(C_{80}P_{344})C_{132}$  at 25 wt%, the differences are much less pronounced because at such a high concentration, micelles form by the diblock are closely packed and the resulting gel is already strong.

The better performances of the triblock hydrogels have also been emphasized through strain sweep experiments performed at 60 °C on  $C_{132}(C_{80}P_{344})C_{132}$  and  $C_{132}(C_{40}P_{172})$  (Figure 7). Expectedly, the triblock hydrogel preserves a high modulus on a much larger strain range. On the other hand, the dependence of the moduli on the strain amplitude demonstrates that both copolymers are in the linear viscoelastic regime until 3%.



**Figure 7.** Storage modulus as a function of the strain for  $C_{132}(C_{40}P_{172})$  (grey) and  $C_{132}(C_{80}P_{344})C_{132}$  (black) at 18.5 wt%, 6.283 rad/s and 60 °C.

The macroscopic behavior of the copolymer solutions at different temperatures depicted in Figure 8 for the  $C_{236}(C_{55}P_{154})$  and  $C_{236}(C_{110}P_{308})C_{236}$  solutions (18.5 wt%) is in good agreement with the above mentioned measurements and supports our hypotheses. At 53°C, the interface of the diblock solution is not frozen in contrast to the triblock solution which does not flow. This observation is in accordance with the aforementioned rheological results where a large difference in modulus has been noticed between both architectures in favor of the triblock. At 70°C, however, both hydrogels appear frozen as expected from their high modulus. However, when heated at 70°C, around their second cloud point temperature, both solutions become opaque but no macroscopic demixing is observed, which confirms that the affinity between the copolymers and water remains high.



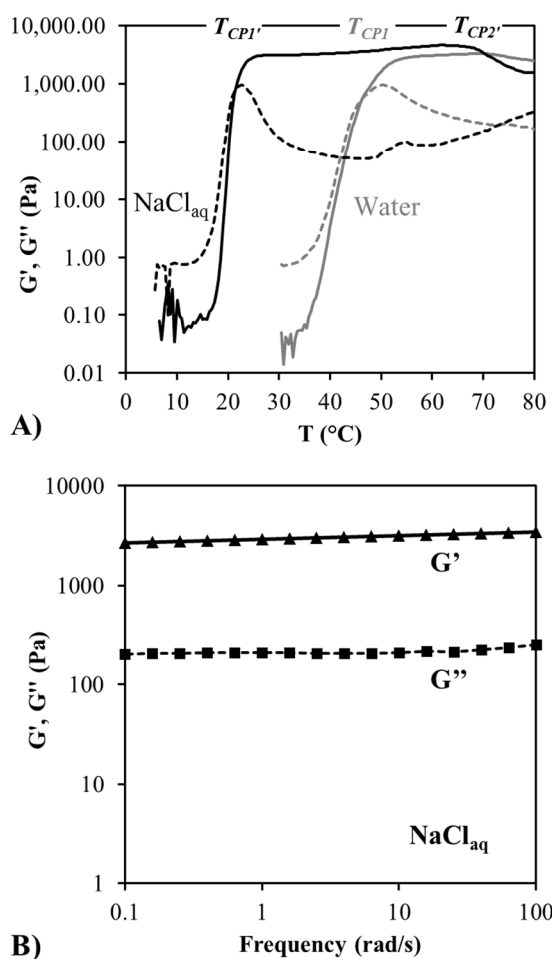
**Figure 8.** Picture of  $C_{236}(C_{55}P_{154})$  and  $C_{236}(C_{110}P_{308})C_{236}$  solutions (18.5 wt%) at 53°C (after 10s in « a 90° position ») and at 70 °C (after 10 min in a « 180° position »).

#### Tuning the thermogelling properties of triblocks by addition of salts.

The LCSTs of thermoresponsive polymers are known to depend on the presence of salts in water, a phenomenon referred to as Hofmeister effect.<sup>63, 64</sup> PNVC and PNVP are no exception and the presence of salts changes their LCSTs.<sup>65</sup> Indeed, both “salting in” and “salting out” effects have been reported for PNVC depending on the nature of the salt, and particularly on the choice of the anions.<sup>65</sup> For example,  $I^-$  and  $Br^-$  raise the cloud point of PNVC, whereas  $Cl^-$  and  $F^-$  lower the transition temperature. On the other hand, changing  $Na^+$  for  $K^+$  have almost no effect on  $T_{CP}$  of PNVC. This effect is of particular importance for thermoresponsive hydrogels since their applications are often associated to complex environments. The salting out effect using NaCl as chaotropic agent was previously used to change the phase transition temperatures of the  $C_{282}(C_{54}P_{594})C_{282}$  triblock in diluted solution (Table 1).<sup>28</sup> At a copolymer concentration of 0.1 wt% in pure water, the  $T_{CP}$  of the PNVC outer blocks was detected at 40 °C but no transition corresponding to the dehydration of the P(NVC-*stat*-NVP) segment was detected below 95 °C due to its high NVP content. In a 2 M NaCl aqueous solution, however, the critical temperatures of both PNVC and P(NVC-*stat*-NVP) blocks were decreased to 20 °C and 68 °C, respectively. In contrast to the above studied triblock copolymers, we expect that the temperature window between both  $T_{CP}$ s of  $C_{282}(C_{54}P_{594})C_{282}$  is large enough in a 2 M NaCl aqueous to emphasize the double thermoresponsive character of the triblock in more concentrated conditions.

First, the rheological behavior of a 12.5 wt% solution of  $C_{282}(C_{54}P_{594})C_{282}$  in pure water was followed as a function of temperature (Figure 9a). A single modulus increase up to  $10^3$  Pa is observed around 45 °C corresponding to the formation of a network of bridged micelles. These results confirmed that hard gels can be formed in the micellar regime of triblock copolymers. Expectedly,

addition of NaCl in water (2 M) decreases the gelation temperature to 20 °C ( $T_{CP, PNVC}$ ) and shifts the second  $T_{CP}$  into a measurable range (65 °C) (Figure 9b).



**Figure 9.** A) Storage ( $G'$ , full line) and loss ( $G''$ , dotted line) modulus as a function of temperature for  $C_{282}(C_{54}P_{594})C_{282}$  (12.5 wt%) in pure water (grey) and in a 2 M NaCl aqueous solution (black).  $T_{CP}$ s were added to the graph as an indication of each cloud point temperature region. B) Storage ( $G'$ , full line) and loss ( $G''$ , dotted line) modulus as a function of frequency at 40 °C and 3% strain for  $C_{282}(C_{54}P_{594})C_{282}$  (12.5 wt%) in a 2 M NaCl aqueous solution.

Interestingly, the difference between the storage and loss moduli in the temperature range where micelles are formed is more pronounced when NaCl is added. This could be due to the formation of more desolvated micellar cores because of the NaCl (salting out effect as explained above), which would thus decrease possible gel relaxation by chain exchange between micellar cores. This is confirmed by a frequency sweep experiment at 40 °C where no decrease of the moduli has been observed on a wide range of frequencies, showing that no relaxation occurs in this frequency range (Figure 9b). After the second transition, a decrease in storage modulus is observed and its difference with the loss modulus becomes much smaller. This could be due to the progressive desolvation of the P(NVC-*stat*-NVP) chains acting as bridges between the micellar cores. As confirmation, the difference between the moduli for the other triblock copolymers (see Figure 5), where both LCST are crossed at the same time and thus where the middle block acting as bridges is already desolvated, is indeed smaller compared to the  $C_{282}(C_{54}P_{594})C_{282}$  triblock in the micellar (inter-



LCST) region. Overall, a clear double thermo-responsive behavior is evidenced by rheological measurement on 12.5 wt% solution of a NVCL and NVP-based triblock copolymer and the possibility to tune the gelation temperature by addition of salts is demonstrated. As an illustration, we tuned the transition temperatures of the gels by “salting out” effect using a 2M NaCl solution but it should be possible to further vary the  $T_{CPs}$  of the PNVCN-based copolymers by changing the nature or the concentration of the salt, as reported by others for diluted PNVCN solutions.<sup>65</sup>

## Conclusions

In summary, we investigated the thermogelling properties of aqueous solutions of double thermoresponsive AB and ABA copolymers based on PNVCN and P(NVCN-*stat*-NVP) blocks. The PNVCN-*b*-P(NVCN-*stat*-NVP)-*b*-PNVCN triblocks were obtained by radical coupling reaction of the corresponding PNVCN-*b*-P(NVCN-*stat*-NVP) diblocks produced by CMRP. Structural similarities within the diblock/triblock pairs like the PNVCN length and the composition of the statistical segment allowed us to probe the effect of the copolymer architecture on the gel formation and properties. Rheology measurements revealed phase transition temperatures by the changes in modulus upon heating. The gelation temperature and rheological properties of the hydrogels were also found dependent on the polymer concentration, PNVCN block length, composition of the statistical segment and copolymer architecture. In all the cases, triblock hydrogels possessed higher modulus compared to those of the corresponding diblocks, even above the second transition. This difference certainly originates from distinct micellar structures for each copolymer architectures. At appropriate concentration, diblock copolymers developed a modulus increase at both TCPs most probably due to the subsequent formation of a densely packed micellar structure and colloidal gels. On the other hand, the higher moduli and resistance to the strain amplitude increase suggests the formation of a 3-D networks of bridged micelles for the triblocks. The double thermoresponsive character of the gels was confirmed for all diblocks but for triblocks with low NVP content, the slight difference in the cloud point temperatures prevented a clear observation of two distinct temperature induced phase transitions on the rheology curves. Fortunately, after modification of the triblock structure and addition of NaCl, both  $T_{CPs}$  could easily be distinguished. The well-known biocompatibility of PNVCN and NVP and the unique thermogelling behavior of this class of double thermoresponsive NVCL and NVP-based di- and triblock copolymers suggest new prospects in the field of drug delivery for reversible encapsulation and on-demand release of a drug.

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## Notes and references

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