

Poly(N-vinylcaprolactam)-b-poly(ethylene glycol)-b-poly(N-vinylcaprolactam) Triblock Copolymers

Synthesis by ATRP and thermal gelation properties of the aqueous solutions

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Poly(N-vinylcaprolactam)-poly(ethylene glycol) – poly(N-vinylcaprolactam) triblock copolymers were synthesized for the first time by the ATRP of N-vinylcaprolactam (NVCL) initiated from poly(ethylene glycol) (PEG) macroinitiators with 2-chloropropionate groups at both ends and catalyzed by the CuCl/5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane (Me₆Cyclam) system. Their polydispersity was larger than 1.8, indicative for a lower control degree of the process, which was ascribed to the slow deactivating behaviour of the catalytic system. The triblock copolymers synthesized displayed thermosensitive behaviour in aqueous solution, undergoing sol – gel transition on the interval 30 - 60°C. It was found that the aggregation (cloud point) and gelation temperatures, as well as the rheological properties of the polymer aqueous solutions depended on the chain length of both PEG and PNVCL blocks.

Keywords: N-vinylcaprolactam, poly(ethylene glycol), triblock copolymers, ATRP, thermal gelation

Hydrogels are polymeric networks made up of hydrophilic polymers and able to incorporate large amounts of water [1]. Their crosslinking is either chemical, through covalent bonds, resulting in the so-called permanent hydrogels, or physical, by means of various types of physical interactions, resulting in most cases reversible hydrogels [2-8].

Depending on their structure, hydrogels can suffer a drastic change of their swelled-state volume under the action of some environmental stimuli, like temperature, pH, ionic strength, etc [9,10]. These particular hydrogels are called stimuli sensitive/responsive hydrogels or environmentally sensitive/responsive hydrogels. Among them, the temperature-sensitive ones have been considerably investigated as temperature is a very effective and easy to apply stimulus for many applications.

In this case, the temperature change induces a modification of the swelling behaviour in the permanent hydrogels, i.e. an abrupt decrease or increase of the gel volume in water at the transition temperature [11]. In the case of reversible hydrogels, gel dissolution or gel formation occur at the transition temperature, property based on which these materials found important applications. Depending on the solution (sol) - gel transition, reversible hydrogels can be divided into 3 classes: a) hydrogels with low critical solution temperature (LCST), i. e. when temperature raises over LCST the polymer passes from a soluble state to an insoluble one; b) hydrogels that by warming pass successively, at different temperatures, through a sol-gel transition, followed by a gel - sol one, like for example the poly(ethylene oxide) - poly(propylene oxide) - poly(ethylene oxide) triblock copolymers; c) hydrogels whose sol-gel transition occurs during a chilling process, like for example gelatin.

Among the temperature-sensitive hydrogels, the most studied are the ones belonging to the first category. Examples of polymers of this category are poly(N-isopropylacrylamide) (PNIPAM), poly(N-vinylcaprolactam) (PNVCL), poly(methyl vinyl ether), poly(propylene glycol), hydroxypropylcellulose, etc. and various copolymers where LCST can be adjusted by varying the hydrophilic monomer - hydrophobic monomer ratio. An interesting application of this type of hydrogels is represented by injectable hydrogels [7,12,13]. These are solutions or very soft gels that can be introduced into the human body by means of a syringe, but at the body temperature or a little less (32 - 37°C), they switch to a crosslinked gel state.

A polymer structure that may lead to injectable hydrogels is represented by triblock copolymers having a water – soluble middle block whose solubility in water is not affected by temperature variations, and side polymer blocks that display LCST in water within the temperature range of interest [9,10]. These triblock copolymers are soluble in water at temperatures below LCST, but at temperatures higher than LCST, the thermosensitive side blocks become insoluble in water and associate, leading thus to the hydrogel with a crosslinked shape. The material keeps water due to the middle block which is permanently soluble in water.

The middle block is very often represented by poly(ethylene oxide)/poly(ethylene glycol) (PEO/PEG), due to its remarkable properties like water solubility, biocompatibility, ability to control the bioactivity of surfaces, lack of toxicity, etc.[14], while PNIPAM forms very often the side blocks [15].

PNVCL is another temperature-sensitive polymer, with a LCST ranging between 30 and 45°C, depending on its molecular weight [16], which, unlike PNIPAM, does not

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produce small, potentially toxic, amide derivatives upon hydrolysis [17]. These features, in addition to its overall low toxicity, makes PNVL a very good candidate to be employed as a component of the biohydrogels.

The present work deals with the synthesis and thermal gelation properties of some PNVL-PEG-PNVL triblock copolymers in aqueous solution. To the best of our knowledge, such block copolymers have not been described in literature yet, although the properties of the aqueous solution of some PNVL-g-PEO graft copolymers have been already reported [16,18,19]. The synthesis of the PNVL-PEG-PNVL triblock copolymers was carried out by atom transfer radical polymerization (ATRP), which is one of the most versatile controlled/living radical polymerization technique [20-22]. ATRP, which uses complexes of transition metals in conjunction with alkyl halides to generate the active radical species, is based on an activation–deactivation equilibrium between the active (the free radicals) and dormant species (the alkyl halide species), the fast deactivation of the radicals being one of the key conditions to obtain a well controlled process.

Experimental part

Materials

α,ω -Dihydroxy PEG with an approximate molecular weight of 2000 mole/g (DHPEG₂₀₀₀, Fluka), 4000 mole/g (DHPEG₄₀₀₀, Fluka) and 6000 mole/g (PEG₆₀₀₀, Scharlau) were used as received. Their hydroxyl numbers, determined by the acetylation method, were 54.55, 27.99 and 19.23 mg KOH/g, respectively, corresponding to number average molecular weights ($M_{n,PEG}$) of 2060, 4010 and 5850 Da, respectively, calculated assuming the presence of two hydroxy groups within each PEG macromolecule. N-Vinylcaprolactam (NVCL, Aldrich, 98%), N,N-dimethylformamide (DMF, Fluka, >99%) and CuCl₂ (Aldrich, 99,999%) were used without further purification. Copper (I) chloride (CuCl, S.C. Silal Trading SRL) was purified by stirring with glacial acetic acid overnight, filtered, washed with anhydrous ethanol and dried under vacuum. Dioxane (Loba Chemie, 99%) was distilled from sodium and stored in a refrigerator in the dark. Diethyl ether (Chimopar S.A.) was distilled at atmospheric pressure and stored in a refrigerator. Distilled water was employed in all experiments involving water. The macroinitiators α,ω -bis(2-chloropropionate) PEG_x (BCPEG_x) were obtained from the corresponding DHPEG_x and 2-chloropropionyl chloride, in toluene, at 105°C, as described in [23]. The cyclic ligand 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane (Me₆Cyclam) was synthesized [24], but the two isomers (tet a and tet b) were collected together. Tris(2-dimethylaminoethyl)amine (Me₆TREN) was prepared from tris(2-aminoethyl)amine (TREN, Acros Organics, 96%) by a procedure similar to that of Ciampolini and Nardi [25] and stored under nitrogen.

Synthesis of the polyNVCL-PEG_x-polyNVCL triblock copolymers

A one neck 15-mL round bottom flask was filled with around 2.4 g NVCL, the calculated amount of BCPEG_x macroinitiator and 8 mL solvent (DMF-water or dioxane-water), and the flask was sealed with a rubber septum. After all components dissolved, the resulting homogeneous solution was bubbled with oxygen-free nitrogen for 80 min to remove oxygen, and the flask was placed in a bath at 20°C. The catalyst solution was prepared separately in a one neck conical bottom 5-mL flask fitted with a side arm, by adding the calculated amounts of CuCl, CuCl₂, and Me₆Cyclam (or Me₆TREN). The flask was sealed with a

rubber septum and cycled four times between vacuum and nitrogen to remove oxygen. Then, 2 mL of degassed solvent were added through a degassed syringe, and the mixture was stirred at room temperature for about 5 min until the catalytic complex formed. The catalyst solution was transferred via a degassed syringe to the polymerization flask, and the reaction mixture was allowed to polymerize with stirring at 20°C for the first 6 h and then at room temperature (reaction time 6-22 h). At the end of the polymerization period, the flask was opened and air was injected into the viscous reaction mixture by means of a syringe, under stirring, to oxidize the catalyst complex and stop the reaction. The solvent was then completely removed in a rotary evaporator under vacuum. The solid residue was dissolved in methylene chloride/chloroform mixture and the resulting blue solution was stirred with a small amount of strongly acidic cation exchange resin in order to remove the catalyst, until a colorless solution was obtained. The resulting solution was dried over anhydrous Na₂SO₄ for several hours, filtered, concentrated under vacuum and poured into a large excess of cold diethyl ether. The precipitate was collected, dried under vacuum over anhydrous CaCl₂, powdered and dried again under vacuum at room temperature until no diethyl ether smell was detected.

Characterization

¹H NMR spectra were recorded on a 300 MHz Varian Gemini 300 BB spectrometer, using deuterated chloroform as the solvent.

The molecular weight distributions were measured on an Agilent Technologies 1200 series gel permeation chromatograph with a PLgel Mixed-C column (300x7.5 mm) and an Agilent 1200 differential refractometer, in DMF, at 23°C and a flow rate of 1 mL/min. Calibration was made with polystyrene standards.

The rheological measurements were carried out on 20 wt.-% aqueous copolymer solutions by using a Bohlin Gemini 150 (Malvern Instruments) rheometer and a 20 mm parallel-plate geometry with a 500 μ m gap. The data were collected in the “controlled stress” mode, at a frequency of 1 rad/s and 0.5°C/min heating rate.

The aggregation temperature (T_{agg}), called also cloud point temperature, was visually determined (the cloud point) by gradually heating (1°C intervals, 15 min at each temperature) a 0.5 wt.-% aqueous copolymer solution (1 mL solution placed in a 10 mm diameter glass tube) in a thermostated bath.

The gelation temperature (T_{gel}) was determined by a tube inversion method [26]. Aqueous polymer solutions (1 mL) of various concentrations, placed in 10 mm diameter glass tubes, were kept for 15 min at constant temperature in a thermostated bath prior to inverting the tube. The experiment was carried out at 1°C intervals. Before switching to the next temperature, the sample was cooled in an ice-water bath and made homogeneous. T_{gel} was considered the temperature at which the polymer solution did not flow by inverting the tube.

Results and discussion

Triblock copolymer synthesis

NVCL is a non-conjugated vinyl monomer that polymerizes only radically. Because of its unconjugated character leading to very reactive radical species, its controlled/living radical polymerization it is very difficult to achieve [27]. That is why the controlled radical polymerization of NVCL was described only recently and only by reversible addition-fragmentation chain transfer

polymerization (RAFT) [28]. To the best of our knowledge, the polymerization of NVCL by ATRP has not been reported in literature yet. However, there are reports in literature dealing with the ATRP of N-vinylpyrrolidone (NVP) [29,30], which is a monomer similar to NVCL from the radical polymerizability point of view. In the case of NVP, the polymerization was carried out in 9/1 vol/vol dioxane/izopropanol [29] or 9/1 vol/vol dioxane-water [30] solvent mixtures by employing a chlorinated initiator/CuCl/Me₆Cyclam as the polymerization initiating system.

We initially attempted to synthesize the PVCL-PEO-PVCL triblock copolymers (fig. 1) by using the powerful ATRP catalyst CuCl/Me₆TREN [31], under experimental conditions similar to those employed to polymerize N-isopropylacrylamide in a living/controlled fashion [32], i.e. BCPEG₄₀₀₀ as the macroinitiator, chloropropionate groups/CuCl/Me₆TREN mole ratio = 1/2/2, 1/1 vol/vol water/DMF mixture as the solvent, reaction time: 2 h at room temperature plus 8 h at 80°C. The material isolated at the end of the reaction was only the addition product between the BCPEG₄₀₀₀ macroinitiator and two NVCL molecules, one at each macroinitiator end, as determined by comparing the areas of the methylene peak of the NVCL units at $\delta = 1.7$ ppm and ethylene oxide units peak at $\delta = 3.6$ ppm in the ¹H NMR spectrum of the addition product (fig. 2). This indicated that the CuCl/Me₆TREN catalytic system was not able to break the NVCL - chlorine bond to promote the ATRP of NVCL, but only the carbon - chlorine bond of the macroinitiator. As a consequence, the addition of NVCL stopped after the first deactivation step.

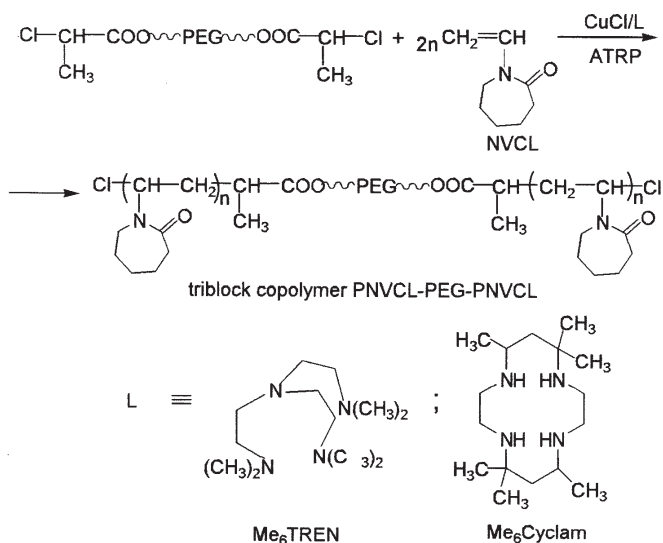


Fig. 1. Synthesis of the PNVCL-PEG-PNVCL triblock copolymers

Further, Me₆Cyclam was tested as the ligand, similarly to NVP polymerization by ATRP [29,30], and under these conditions we succeeded to obtain the block copolymers, in many cases with an almost quantitative yield (table 1). The ¹H NMR spectra of the reaction products contained in all cases the characteristic peaks for both PEG and PNVCL blocks (fig. 3).

The results indicated that the NVCL polymerization was not a controlled process because the polydispersity of the obtained products was similar to that observed in a conventional radical polymerization, i.e. $M_w/M_n \geq 2$. This may be due to the fact that the Me₆Cyclam-containing catalytic system is very likely a system displaying slow deactivation, as already reported for other ATRP catalysts containing Cyclam compounds [33]. A slow deactivation of the growing chains allows for more intense termination

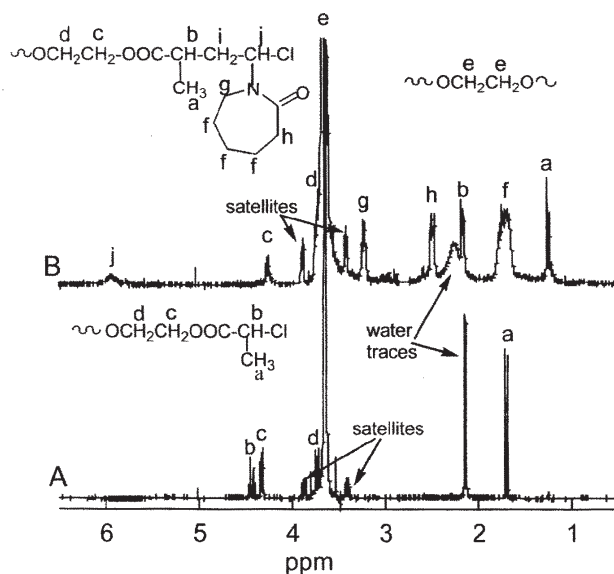


Fig.2. ¹H NMR spectra of the BCPEG₄₀₀₀ macroinitiator (A) and the addition product of BCPEG₄₀₀₀ and NVCL obtained in the presence of the CuCl/Me₆TREN catalytic system

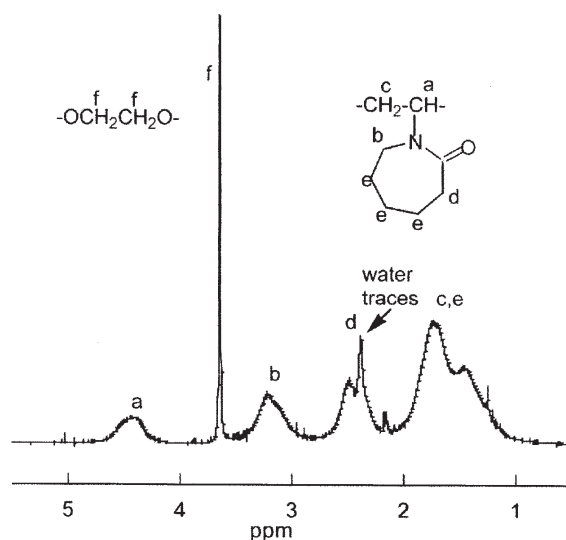


Fig.3. ¹H NMR spectrum of the PNVCL-PEG₄₀₀₀-PNVCL triblock copolymer - DV45 sample

processes by either combination or disproportionation to occur, leading to an increased polydispersity. The different polydispersities of the block copolymers synthesized under various conditions (table 1) may be due to the different amounts of CuCl₂ (the deactivation agent), either formed in situ or purposely added, existing dissolved in the reaction medium.

The employment of the 1/1 vol/vol DMF/water mixture as the solvent led to a high polydispersity of the block copolymers, very likely because of the relatively low solubility of the CuCl₂/Me₆Cyclam complex in the reaction medium. The addition of CuCl₂ up to 40% relative to CuCl improved the control of the polymerization and produced a decrease of the polydispersity, without lowering it to less than 2 (table 1). The GPC traces (fig. 4) shows that by adding CuCl₂ the proportion of the higher MW macromolecules fraction decreased, while that of the lower MW fraction increased, due to the reduction of the coupling of macroradicals, i. e. of the termination by combination.

The increase of the DMF concentration in the solvent mixture (DV45, table 1), determined very likely a higher solubility of the CuCl₂ complex in the reaction medium,

Table 1
EXPERIMENTAL CONDITIONS AND RESULTS FOR THE SYNTHESIS OF PNVC-PEG₄₀₀₀-
PNVCL TRIBLOCK COPOLYMERS BY ATRP IN THE PRESENCE OF Me₆Cyclam AS
THE LIGAND^a

Exp.	Cl:CuCl:CuCl ₂ :Me ₆ Cyclam mole ratio	Solvent vol/vol	Polymer recovery yield %	M _n ^b	M _w /M _n ^c	Reaction time h
DV41	1:1:0:1	DMF/water 1/1	91	22700	3.55	6
DV42	1:1:0.2:1.2	DMF/water 1/1	87	21200	3.15	6
DV44	1:1:0.4:1.4	DMF/water 1/1	90	22300	2.80	6
DV45	1:1:0:1	DMF/water 9/1	51	10800	1.82	20
DV46	1:1:0:1	dioxane/water 9/1	84	18400	2.17	21

^amacroinitiator = BCPEG₄₀₀₀; M_{n,target block PNVC}=20000 Da; ^bM_{n,block PNVC} determined by ¹H NMR by comparing the areas of the -CH-N- peak of the NVCL units at δ = 4.4 ppm and of ethylene oxide units peak at δ = 3.6 ppm in the ¹H NMR spectrum of the PNVC-PEG₄₀₀₀-PNVCL triblock copolymers (fig. 3); ^cpolydispersity index of the triblock copolymer, determined by GPC.

which led to both lower M_n and conversion even after 20 h reaction time, and also to a much lower polydispersity, slightly less than 2.

A better solvent was the mixture dioxane/water 9/1 vol/vol, already reported in literature in connection with the CuCl/Me₆Cyclam catalytic system [30]. The results showed a better control of the polymerization process, as indicated by the polydispersity close to 2 (table 1) and the almost monomodal distribution (fig. 4) of the triblock copolymer.

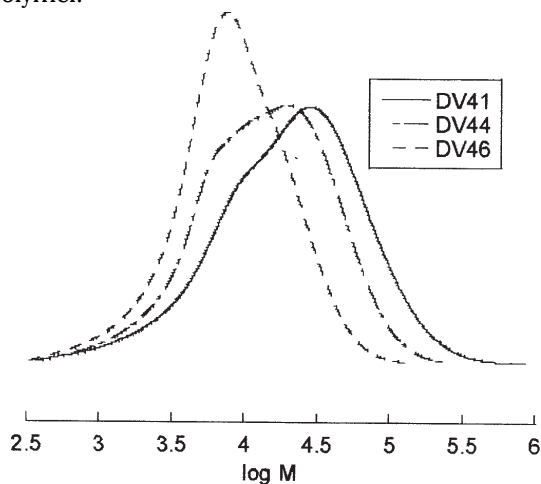


Fig. 4. GPC traces of the triblock copolymers obtained under various conditions

Thermal gelation properties of PNVC-PEG_x-PNVCL triblock copolymers

Based on the results presented above, we decided to study the thermal gelation properties of some PNVC-PEG_x-PNVCL triblock copolymer samples prepared in 9/1 vol/vol dioxane/water solvent mixture. The dependence of T_{agg} and T_{gel} of the triblock copolymer aqueous solutions on the MW of the PNVC and PEG blocks, as well as the variation of the rheological properties of the 20 wt-% triblock copolymer aqueous solutions on temperature were determined.

The results showed that for the same length of the PEG block and the same weight concentration of the polymer aqueous solution, T_{agg} and T_{gel} depended on the molecular weight of the PNVC block, both being lower for higher MW (Table 2, fig. 5), in agreement with previous reports on the phase behavior of PNVC in water [34], and also with the reported dependency of the LCST of PNVC water solutions on the polymer molecular weight [16]. T_{gel} was also dependent on the concentration of the polymer solution (fig. 5), being higher for lower concentrations, in accordance with previous reports [34], as well. In the case of the 5 wt-% solutions, for shorter PNVC blocks the gel did not form up to 80°C, but only a small amount of a disperse precipitate.

The conclusions of the tube inverting experiments were supported by rheological measurements carried out on 20 wt-% triblock copolymer aqueous solutions. Indeed, by increasing the temperature, the viscosity of the solution

Exp.	$M_{n,PNVCL}^b$	T_{agg}^c °C
DV49	3620	36
DV47	8600	36
DV46	18400	35
DV48	22500	34

Table 2
DEPENDENCE OF T_{agg} ON THE MOLECULAR WEIGHT OF THE PNVCL BLOCKS^a

^a macroinitiator = BCPEG₄₀₀₀; Cl:CuCl:Me₆Cyclam=1:1:1; dioxane/water = 9/1 vol/vol;

^b determined by ¹H NMR

^c determined for 0.5 wt-% triblock copolymer aqueous solutions

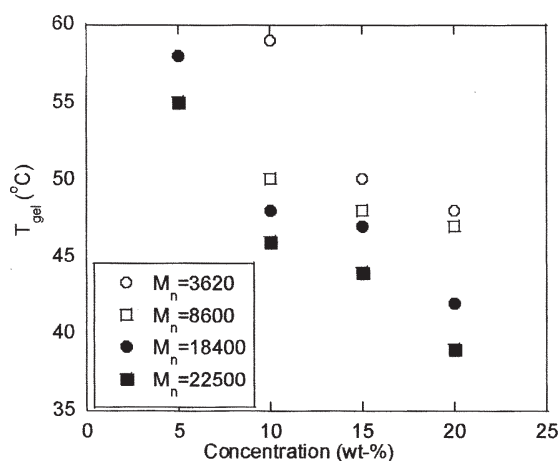


Fig.5. Dependence of T_{gel} on the molecular weight of the PNVCL block and the concentration of the triblock copolymer aqueous solution. Experimental conditions as in table 2

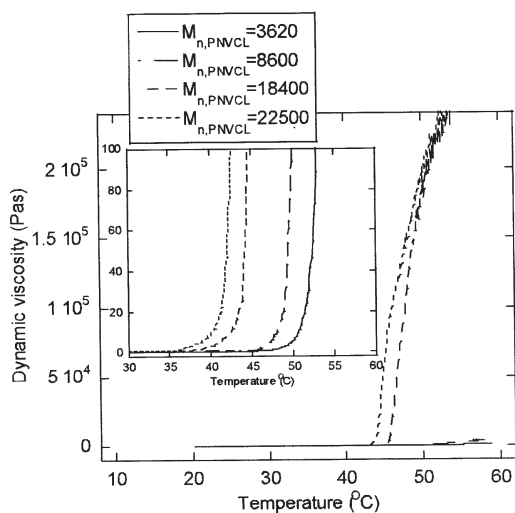


Fig.6. Dependence of the dynamic viscosity of the 20 wt-% triblock copolymer aqueous solutions on the molecular weight of the PNVCL block and temperature. Experimental conditions as in table 2

started increasing at temperatures depending on the molecular weight of the PNVCL blocks (fig. 6). The higher the PNVCL molecular weight, the lower the temperature corresponding to the viscosity increase onset. According to the viscosity measurements correlated with the tube inverting experiments, the gelation of the solution, i.e. no flowing by inverting the tube, occurred at viscosity values in the range 2 – 7 Pas.

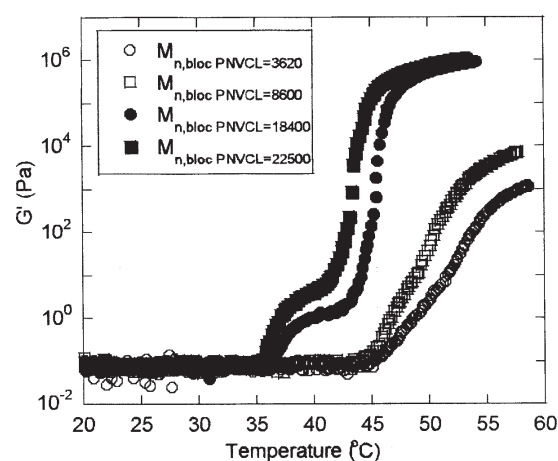


Fig.7. Dependence of G' of the 20 wt-% triblock copolymer aqueous solutions on the molecular weight of the PNVCL block and temperature. Experimental conditions as in table 2

A similar dependency on the MW of the PNVCL block and temperature was noticed in the case of the elastic (storage) modulus G' , recorded for 20 wt-% triblock copolymer aqueous solutions, as well (fig. 7). A higher MW of the PNVCL block shifts the beginning of G' increase to lower temperatures, as in the case of the dynamic viscosity dependence on temperature. Figure 7 also showed that the gels obtained in the case of higher molecular weight PNVCL blocks displayed higher G' values, and therefore better mechanical properties.

One can see also, that for higher MW of the PNVCL block, the G' increase with temperature occurred in two steps. This behavior may be explained by either a larger polydispersity of PNCVL block of higher molecular weight, or based on the already-reported-in- literature two temperature – induced transitions displayed by the PNVCL gels: a lower temperature transition, ascribed to the microsegregation of the hydrophobic domains, and another one at a higher temperature, corresponding to the gel collapse itself [17].

The length of the PEG middle block is another parameter that influenced the thermal gelation properties of the PNVCL – PEG – PNVCL triblock copolymer aqueous solutions. As the MW of the PEG block increased, the hydrophilicity of the triblock copolymer increased as well, leading to increasing T_{agg} and T_{gel} (table 3).

These results were supported by rheological measurements carried out on 20 wt-% triblock copolymer aqueous solutions. The temperature at which the viscosity of the solution started to increase depended on the MW of

Exp.	$M_{n,PEG}$	T_{agg}^b °C	T_{gel}^c °C
DV21	2060	33	38
DV48	4010	34	39
DV61	5850	34	41

^a Cl:CuCl:Me₆Cyclam=1:1:1; dioxane/water = 9/1 vol/vol; $M_{n,PNVCL\ block} = 21500 - 22500$;

^b determined for 0.5 wt-% triblock copolymer aqueous solutions;

^c determined for 20 wt-% triblock copolymer aqueous solutions

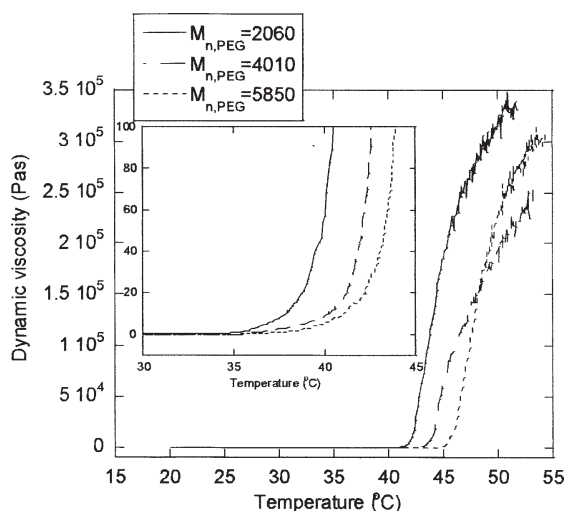


Fig. 8. Dependence of the dynamic viscosity of the 20 wt-% triblock copolymer aqueous solutions on the molecular weight of the PEG block and temperature. Experimental conditions as in table 3

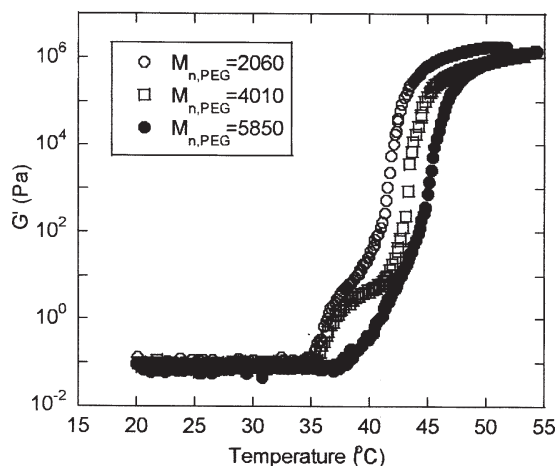


Fig. 9. Dependence of G' of the 20 wt-% triblock copolymer aqueous solutions on the molecular weight of the PEG block and temperature. Experimental conditions as in table 3.

the PEG block (fig. 8). Higher molecular weights of the PEG middle block led to higher temperatures for the viscosity increase onset. From the inverting tube test results correlated to the rheological measurements, it resulted that the gelation of the solutions took place at dynamic viscosities in the range 6 – 11 Pas.

The dependency of the elastic modulus of the 20 wt-% triblock copolymer aqueous solutions on the MW of the PEG block and temperature followed the same trend as in the case of the viscosity (fig. 9). A higher MW of the PEG block shifted the beginning of G' increase at higher temperatures. The maximum values of G' were

approximately the same in all cases due to the similar MW of the PNVCL blocks, confirming that the length of the PNVCL blocks actually determines the value of G' and therefore the mechanical properties of the gels.

Conclusions

Triblock copolymers with PEG middle block and PNVCL side blocks were synthesized by the atom transfer radical polymerization of NVCL initiated from a PEG macroinitiator with 2-chloropropionate groups at both ends and employing the catalytic system CuCl/Me₆Cyclam. The block copolymers synthesized displayed polydispersities larger than 1.8, more characteristic for a conventional radical polymerization process rather than for a controlled one. This was explained by a slow deactivating behaviour of the catalytic system, in agreement with the reported data on other ATRP catalysts containing Cyclam compounds.

The triblock copolymers synthesized displayed thermosensitive behaviour in aqueous solution, which was affected by the chain length of both PEG and PNVCL blocks. The aggregation temperature, determined visually at 0.5 wt-% aqueous solution, and the gelation temperature, determined by the inverting tube method at various concentrations of the aqueous polymer solutions, depended on the MW of the polymer blocks. Increasing the MW of the PNVCL blocks led to decreasing T_{agg} and T_{gel} , while the PEG blocks of higher length determined an increase of both T_{agg} and T_{gel} . For the same triblock copolymer sample, T_{gel} also decreases as the concentration of the solution increases.

The dependence of T_{gel} on the molecular weight of the PEG and PNVCL blocks was supported by rheological measurements (both dynamic viscosity and elastic modulus determinations) performed on 20 wt-% triblock copolymer solutions.

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