Polymer Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/polymers

2x0mm (600 x 600 DPI)

Journal Name RSCPublishing

ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Post-polymerization modification of reactive polymers derived from vinylcyclopropane: 2. Poly(vinylcyclopropane) derivative with physical gel and UCST behaviour in ethanol/water mixtures

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In this paper we describe a new polymer that combines an upper critical solution temperature (UCST) and reversible physical gelation in ethanol/water mixtures. The polymer, namely poly(1-cyano-*N*-propylcarboxyamidovinylcyclopropane) (poly(CNPCAVCP)), was synthesized by post-polymerization modification of poly(1-cyano-1-pentafluorophenoxycarbonyl-2-vinylcyclopropane) (poly(CPFPCVCP)) with *n*-propylamine. The stimuli responsiveness of the polymer was investigated in ethanol and ethanol/water mixtures by varying the water concentration in the mixture. It was found that, depending on the water concentration, the mixture features an upper critical solution temperature (UCST), physical gelation or both. In addition, it was observed that the hysteresis between the heating and the cooling phase was very large (about 45 °C).

Introduction

Stimuli-responsive polymers are polymers that can undergo strong physical modification when they are subjected to external stimuli such as temperature, pH and light[1–4]. When thermo-responsive polymers in solution are submitted to temperature variation, they can usually respond to the stimulus by featuring a lower critical solution temperature (LCST), upper critical solution temperature (UCST) or physical gelation. Polymers with physical gelation properties have become of great interest because of their potential applications in many fields such as drugs release, tissue engineering, extraction processes, cosmetic, or coating.[5–7] Physical gelation is essentially caused by the reversible formation and growth of clusters in a three dimensional polymeric cross-linked network[8–11] and is often favoured by the presence of hydrogen bonds, crystalline regions, ionic clusters, ionic or dative interactions.

Polymers featuring a upper critical solution temperature behaviour (UCST) can be dissolved in solution when heated and precipitate upon cooling; making them suitable for nano-technological and biomedical applications. Some polymers are known to exhibit a upper critical solution temperature in polar solvents and most of them are based on (meth)acrylamide, oxazoline, ureido or betaine moieties[12–19].

Recently, we reported on the synthesis of new poly(vinylcyclopropane) (PVCP) derivatives that feature a upper critical solution temperature in ethanol and ethanol/water mixtures[20]. In the present study, we present another new poly(1,1-disubstituted-2-vinylcyclopropane) that combines both a upper critical solution temperature in ethanol/water mixtures and reversible physical gelation. Agarwal et al. observed a similar behaviour when studying the UCST of poly(*N*-acryloylglycinamide) and its copolymers with *N*-acetylacrylamide in water. However, no rheological studies were performed and the concentration of the polymer in solution to observe such phenomenon was higher than 2 wt%.[21] Herein, we describe a system that combines UCST and physical gelation at concentrations lower than 1 wt% in ethanol by addition of small amount of water (between 5 and 15 vol%). Polymers that combine those two behaviours, just by varying the solvent concentration, have not yet been reported.

Experimental

Materials

All chemicals and solvents were commercially available and used as received unless stated otherwise. Tetrahydrofuran

(THF), dichloromethane (DCM), methanol, and 1,4-dioxane were dried using a solvent drying station (Puresolv from Innovative Technology). Deionized water was obtained from a Thermo Scientific Smart2Pure water deionizer. 2,2'-Azobis(2-isobutyronitrile) (AIBN) was recrystallized from methanol.

The monomer 1-cyano-1-pentafluorophenoxycarbonyl-2-vinylcyclopropane was synthesized as previously described[20].

Instrumentation

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz FT-NMR spectrometer in deuterated chloroform. ^{19}F NMR spectra were recorded on a Varian Gemini-2000 spectrometer in deuterated chloroform. Chemical shifts (δ) are given in ppm relative to TMS. FTIR measurements were recorded on a Nicolet iS10 spectrometer from Thermo Scientific. GPC was performed at room temperature with THF as an eluent on a system equipped with: an Intelligent Pump AI12 HPLC pump from Flom, a PLDG 802 degasser from Polymer Laboratories, a RI 101 refractive index detector from Shodex, two 5µm polypore columns from Polymer Laboratories. Chromatograms were analysed with the software NTeQGPC V6.4 (version 1.03) software from hs GmbH. Molar mass and PDI were calculated against Polystyrene standards. Turbidity measurements were performed on a Jasco V-630 UV-Visible spectrophotometer equipped with a Jasco temperature controller and a Jasco MCB-100 mini circulation bath at a wavelength of 500 nm. The samples were first heated under a suitable temperature inorder to fully dissolve the polymer and let cooled down to room temperature. After that, measurements were started using a tightly closed quartz cuvette of 10 mm path length. Transmittance was measured with a heating/cooling rate of 1 °C/min. Microscopy image (SEM) was taken with a LEO Gemini 1525 FE-REM microscope.

Rheology

Small Amplitude Oscillatory Shear (SAOS) measurements were carried out on a stress controlled rheometer (AR-G2, TA Instruments, Newcastle, DE, USA) with a conical concentric cylinder (stator inner radius = 15 mm, rotor outer radius = 14 mm, cylinder immersed height = 42 mm, solvent trap used). All measurements were kept in the linear viscoelastic limits of deformation (γ = 1-2 %). The rubber-elastic plateau G'_P was determined from the frequency independent regime of the storage modulus G' at 1 rad.s^{-1}. The network parameters (molecular weight between net points M^*_e, crosslink density ν_e, crosslink distance ξ) were calculated according to equation 1-3[22,23]:

$$M_e^* = \frac{c \cdot R \cdot T}{G'_p} \qquad (1)$$

$$\nu_e = \frac{G'_p \cdot N_A}{R \cdot T} \qquad (2)$$

$$\xi = \left(\sqrt[3]{\nu_e}\right)^{-1} \qquad (3)$$

Where c is the polymer concentration, R the universal gas constant, N_A the Avogadro constant and T the temperature.

Sample preparation for SEM

Samples of the *n*-propyl and the isopropyl isomer in ethanol/water (90/10) with UCST in ethanol/water were deposited on a well cleaned piece of silicon wafer and dried for few minutes at room temperature. After that, the samples were dried at 40 °C in a vacuum oven for 24 hrs, pasted on a SEM pin mount and coated with carbon before measurement. Another sample of the gel was freeze-dried under reduced pressure and a piece of it was also pasted on a SEM pin mount and coated with carbon for measurement.

Synthesis of Poly(CPFPCVCP)

Poly(CPFPCVCP) was prepared as described in the literature.[20] The corresponding monomer (3 g, 9.9 mmol) and AIBN (0.0325 g, 0.19 mmol) were placed in a Schlenk tube and sealed with a septum. Dry dioxane (1.5 mL) was added through the septum. Four freeze-pump-thaw cycles were conducted; the flask was filled with argon at the end, placed in a preheated oil bath of 60 °C and stirred for 20 hours. The resulting viscous mixture was cooled down to room temperature and 4 mL of chloroform was added and the polymer precipitated in a mixture of methanol/water (9:1) and re-precipitated twice. The polymer was dried under reduced pressure at 40 °C yielding 2.59 g. M_n = 81530 M_w/M_n = 2.13. ^{1}H-NMR ($CDCl_3$): δ/ppm: 5.79 (br, 2H), 2.77 (br, 4H), ^{19}F-NMR ($CDCl_3$): δ/ppm: -152.04 (m, 2F), -155.63 (m, 1F), -161.02 (m, 2F). FT-IR (ATR mode): 1786 cm^{-1} (C=O PFP ester), 1655 cm^{-1} (C=C).

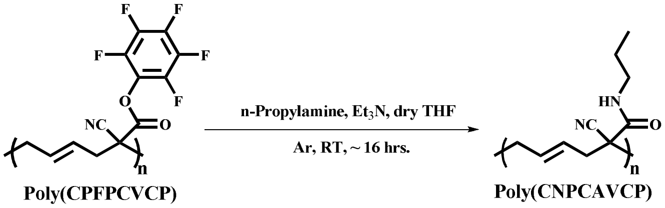
Post-polymerization modification of Poly(CPFPCVCP) with *n*-propylamine

Poly(CPFPCVCP) (300 mg, 1 mmol) was added to a Schlenk tube, was degased and then filled with argon. 2 mL of THF was added and, after dissolution of the polymer, *n*-propylamine (2 mmol) and triethylamine (2 mmol) were successively added; and the mixture was stirred at room temperature for 16 hrs. After dialysis against methanol and acetone, the obtained polymer was dried in a vacuum oven. M_n = 43500 g/mol, M_w/M_n = 2.20. ^{1}H-NMR ($CDCl_3$): δ/ppm: 6.52 (br, 1H amide proton), 5.63 (br, 2H double bond protons), 3.21 (br, 2H), 2.68 and 2.40 (br, 4H), 1.53 (br, 2H), 0.92 (br, 3H). FT-IR (ATR mode): 3318 cm^{-1} (NH secondary amide) 2237 cm^{-1} (C≡N) 1651 cm^{-1} (C=O amide).

Results and discussion

Synthesis of polymers

Poly(CPFPCVCP) was prepared according to the literature starting from 1-cyano-1-pentafluorophenoxycarbonyl-2-vinylcyclo propane.[20] Post-polymerization modification with *n*-propylamine (scheme 1) yielded the desired polymer: poly(1-cyano-*N*-propylcarboxyamidovinylcyclopropane) poly(CNPCAVCP). The disappearance of the fluorine signal in the ^{19}F-NMR spectrum and the shift of the carbonyl signal from about 1786 cm^{-1} to 1651 cm^{-1} and the appearance of the amide signal at 3318 cm^{-1} in the FT-IR spectrum (figure 1), confirmed that the modification was successful and quantitative. The chemical structures of the polymers were assigned using ^{1}H-NMR (figure 2).



Scheme 1: Post-polymerization modification of poly(CPFPCVCP) with *n*-propylamine.

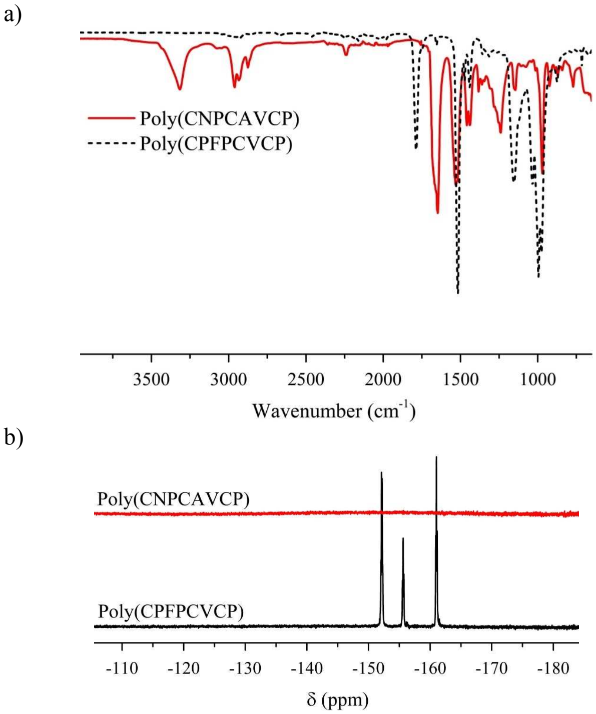


Figure 1: (a) FT-IR and (b) ^{19}F-NMR spectra of poly(CPFPCVCP) and poly(CNPCAVCP).

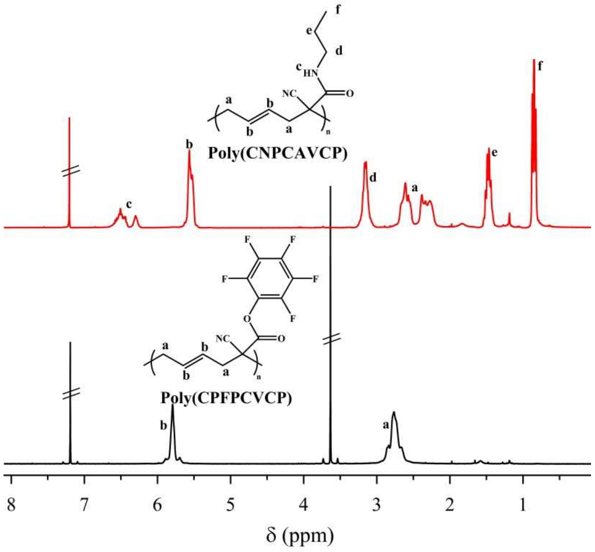


Figure 2: ^{1}H-NMR spectra of poly(CPFPCVCP) and poly(CNPCAVCP).

UCST in ethanol and ethanol/water mixture

The UCST behaviour of poly(CNPCAVCP) was measured in ethanol and ethanol/water mixtures. In ethanol, UCST was measured for polymers concentrations 1, 2.5, 5 and 10 mg/mL. Noteworthy, for all investigated concentrations a large hysteresis of about 45°C was observed and was found to slightly decrease by lowering the heating/cooling rate (see ESI). The UCST in ethanol was slightly decreased with decreasing polymer concentration. The UCST behaviour in ethanol/water mixture was measured for polymer concentrations of 10 mg/mL and 5 mg/mL with the water content being 5, 10, 15 and 20 vol%, respectively (figure 4). The addition of 5 and 10 vol% water led to a significant decrease (about 15°C) of the cloud points and a slight increase of the hysteresis by 5°C to 50°C between the heating and the cooling cycle (figure 5). At 15 and 20 vol% of water, the cloud point was increased again and the hysteresis decreased by about 5°C and 10°C respectively. Interestingly, the samples with 5, 10 and 15 vol% water showed a gelation of the solution upon cooling and this will be discussed in the next section in more detail.

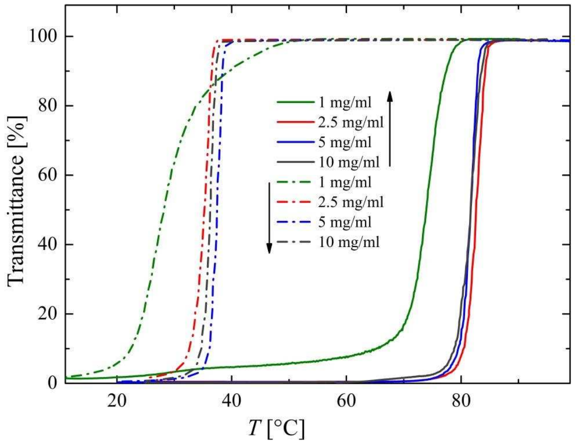


Figure 3: UCST of poly(CNPCAVCP) in ethanol: cooling (dash-dotted lines) and heating (solid lines).

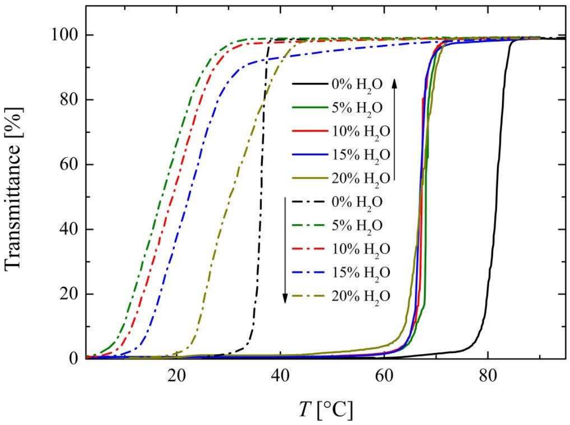


Figure 4: UCST of poly(CNPCAVCP) in different ethanol/water mixtures at 10 mg/mL: cooling (dash-dotted lines) and heating (solid lines).

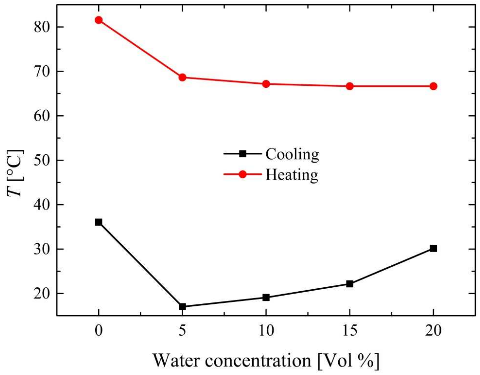


Figure 5: Cloud point (CP) as a function of water content in ethanol for a 10 mg/mL polymer solution at 50% transmittance.

The increase of the clearing point upon heating can be well understood since the addition of water reduces the solubilizing tendency of the solvent for the polymer and hence resulted in an increased solubilisation temperature. The decreasing of the cloud point during the addition of water can be ascribed to the fact that water molecules can easily hydrate the amide moiety of the polymer[12]. The large hysteresis between the heating and the cooling process may be due to the ability of the polymer to form additional intra- and inter-molecular hydrogen bonds during the phase separation state[24,21]. Moreover, the increased hysteresis and the broadness of the transition phase upon cooling at 5, 10 and 15 vol% water can also be related to the gelation that took place before the UCST cloud point is reached (see the rheology part). This can be directly ascribed to the size of the *n*-propyl moiety which is neither small enough to maintain the hydration of the polymer by the solvent mixture after dilution nor bulky enough to accelerate the precipitation of the polymer after dilution. This presence of the propyl moiety is the key factor of the behaviour of this polymer as its replacement leads to a totally different behaviour[19]. Polymers with smaller or larger substituents do not show any sign of gelation in the investigated ethanol/water mixtures. To have a better understanding of the gelation behaviour of this polymer, rheological measurements were performed on the polymer gel at different gelator concentrations.

Physical gelation in ethanol/water mixture

During the UCST measurements, Poly(CNPCAVCP) gelated as the water concentration in ethanol was 5, 10 and 15 vol%, respectively. The gelation was confirmed by rheological studies and the gel strength was found to decrease with increasing water concentration (see ESI). The gel was also analyzed by SEM to get a first understanding of its structure (figure 6). Indications of a fibrillar three dimensional network structure was observed and likely inter- and intramolecular hydrogen bonds are the reason for their formation. This is totally different from the amorphous structure of its homologous polymers with other substituents, which just show a UCST behavior under the same conditions (see ESI for the UCST of the homologous polymer).

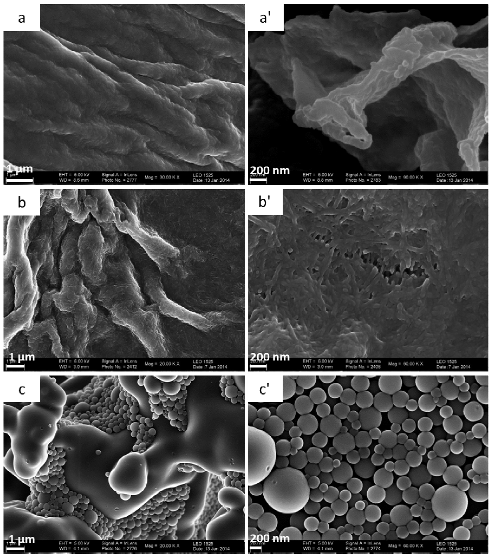


Figure 6: SEM pictures of: freeze-dried gel in ethanol/water (90:10) at 5mg/mL (a and a'); normal dried gel in ethanol/water (90:10) at 5mg/mL (b and b') and normal dried turbid solution of its isopropyl isomer 5mg/mL in ethanol/water (90:10) under cloud point upon cooling (c and c').

The gelation was measured at different gelator concentrations in ethanol/water (95:5) mixtures and it was observed that the lowest gelation concentration in ethanol/water mixture is above 2.5 mg/mL and the gel strength was observed to increase with gelator concentration (see ESI). The frequency dependence of the storage modulus G' for the prepared gels with different polymer concentrations was determined to characterize the solution structure. The results are shown in figure 6.

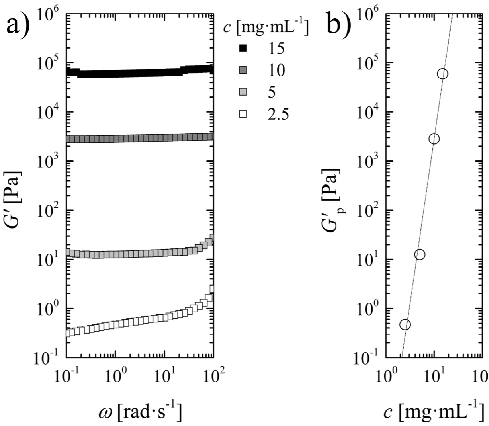


Figure 7: (a) The storage modulus G′ as a function of the angular frequency **(b)** The rubber-elastic plateau G'_p as a function of the polymer concentration *c* in ethanol/water (95:5 vol%).

The angular frequency independence of the rheological material functions indicates the pronounced elasticity of the prepared gels and allows the calculation of the network parameters for an in-depth description of the solution structure (table 1). The rubber-elastic plateau G'_P as a measure for the gel strength is linearly dependent on the polymer concentration as well as the network parameters calculated from it.

Table 1: Network parameters (molecular weight between net points $M^{*}e$, crosslink density ν_e, crosslink distance ξ) with respect to the polymer concentration *c*.

C [mg.mL^{-1}]	G'_P [Pa]	$M^{*}e$ [g.mol^{-1}]	ν_e [m^{-3}]	ξ [nm]
15	5.998 10^4	6.2 10^2	1.4 10^{25}	4.1
10	2.824 10^3	8.7 10^3	6.8 10^{23}	11.3
5	1.255 10^1	9.9 10^5	3.0 10^{21}	69.0
2.5	4.704 10^{-1}	1.3 10^7	1.1 10^{20}	206.1

The crosslink density increased with the gelator concentration, while the crosslink distance decreased. The more the solution is concentrated, the closer is the crosslink-interactions between polymer chains and stronger is the gel. The dilution increased the solvation and reduce polymer – polymer interactions.

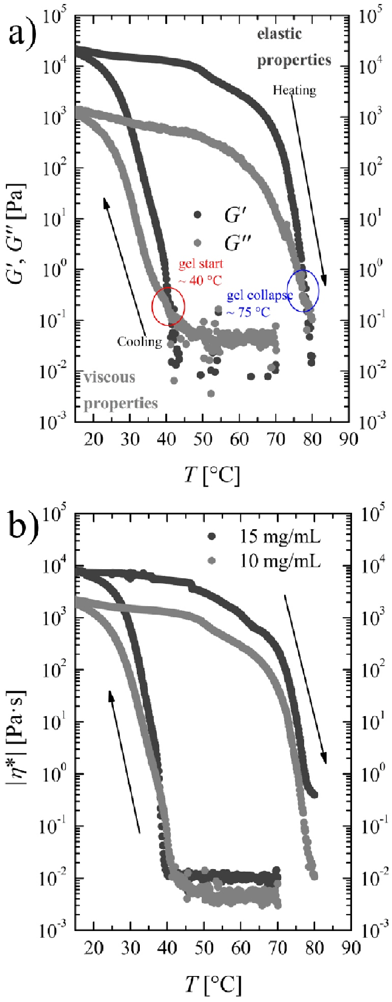


Figure 8: **(a)** The complex dynamic viscosity η^* as a function of the temperature *T* during cooling and heating ramps (0.5°C/min) of the gel at a gelator concentration of 10 and 15 mg/ml in ethanol/water (95:05 vol %); **(b)** The storage modulus G′ and the loss modulus G″ as a function of the temperature *T* during cooling and heating ramps (0.5 °C/min) at a gelator concentration of 10 mg/mL ethanol/water (95:05 vol%)

Fig. 8a shows the storage modulus G′ and the loss modulus G″ as a function of the temperature *T* during cooling and heating ramps (0.5 °C/min) at a gelator concentration of 10 mg/mL ethanol/water (95:05 vol%) and documents the formation of the gel that was also visually observed in all cases. The storage modulus G' (real part) and the loss modulus G" (imaginary part) represent the elasticity and the viscosity terms respectively. During the heating phase, G' was larger than G" until around 75 °C were the gel start to collapse. In the cooling phase, G' start to be larger than G" around 40 °C were the gel formation start. G' and G" were also found to decrease with increasing water content in the mixture (see ESI), thus showing that the less water the mixture contains, the stronger the gel is.

The complex dynamic viscosity as a function of the temperature for gelator concentration of 10 mg/mL and 15 mg/mL in ethanol/water (95:5 vol%) during the heating and cooling phase was measured in an attempt to correlate the UCST behavior and the gelation process (figure 8b). The starting gelation temperature was found to be around 40 °C during the cooling phase at both gelator concentrations; and the gel collapse was found to start around 75°C. The recorded hysteresis (about 40°C) indicates similarities to the UCST behavior. The interaction between the storage modulus G′ and the loss modulus *G´´* gives a more detailed overview for the gelation process (figure 8a). The crossover point corresponds to the transition from sol to gel (tan δ = *G''/G'* = 1) and is a measure for the gel point.

By comparison of the UCST at 10 mg/mL in ethanol/water (95:05) in figure 4 and the visco-elastic properties in figure 8, we can observe that: (i) during the cooling phase, the gelation takes place at ~40°C, which is before the cloud point is reached at ~15°C. (ii) During the heating phase, the clearance point is reached at ~67°C, which is before the gel collapses at ~75°C. In the cooling process, instead of phase separation as one would expect for a UCST behaviour, the solution started to gelate; likely because of the strong intramolecular hydrogen bonds between amide moieties and dipole-dipole interactions favored solely by the structure and length of the *n*-propyl. The gel formed continuously as the solution was cooled down with time. Later the solvent phase separated inside the gel network because of the hydrophobic interactions with the polymer, resulting in a cloud point.

Conclusions

Using activated ester chemistry on a polyvinylcycloprane derivative, we have synthesized poly(1-cyano-*N*-propylcarboxyamidovinylcyclopropane) (poly(CNPCAVCP)). This polymer combined a UCST and reversible physical gelation behaviour in ethanol/water mixtures, depending on the water concentration. Gelation was observed for a water concentration of 5 to 15 vol% and the gel strength was inversely proportional to the water concentration. SEM analysis of the gel indicated that it had a fibrillar tridimensional structure. Rheology of the gel at different gelator and water concentrations of the solvent mixture was conducted, which allowed calculation of network parameters. We observed a dependence of the gel strength on the concentration and the temperate. The combination of featuring a UCST and physical gelation is unique because the gelation and UCST do not occur at the same temperature.

Acknowledgements

The authors thank F. Scheliga, M. Gröger and S. Bleck at the institute for technical and macromolecular chemistry, University of Hamburg, for the support in GPC measurements, Mrs. Walter of the Zoology institute, University of Hamburg, for SEM measurement and E. Haupt at the inorganic chemistry, University of Hamburg, for the ^{19}F NMR measurements. D. Seuyep gratefully acknowledges the German Academic Exchange Service (DAAD) for awarding a scholarship.

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† Electronic Supplementary Information (ESI) available: [^{1}H NMR of monomer and polymers; rheology graphs; GPC chromatogram.]. See DOI: 10.1039/b000000x/

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