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From high molecular weight precursor polyrotaxanes to supramolecular sliding networks. The 'sliding gels'

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Abstract

This paper presents the synthesis and characterization of an original class of supramolecular networks, the 'sliding' gels. In this new class of network materials the crosslink points are not fixed but sliding. The molecular structure is based on intermolecularly crosslinked α-cyclodextrins/poly(ethylene-glycol) precursor polyrotaxanes. A synthetic method was developed to obtain various high molecular weight precursor polyrotaxanes with various amounts of α-cyclodextrins (α-CD) per template chain (the so-called degree of complexation, *N*). The crosslinking reaction of the precursor polyrotaxanes was carried out with the divinyl-sulfone allowing an efficient and good control of the crosslinking density. This control permitted to obtain various network materials with unusual physical/mechanical properties depending on the crosslinker amount and on *N*. The unusual properties originate from the sliding character of the crosslink points, in these new network materials, which induces a variable and eventually controllable mean mass distribution of the entanglement length. The mechanical spectroscopy and rheological experiments showed two viscoelastic regimes evidencing the molecular mechanism of the change of the mean mass distribution between the crosslink points due to the sliding of α-CD rings on the template PEG chain.

Keywords: Polyrotaxanes; Supramolecular sliding network; Hydrogel

1. Introduction

In the last decade, materials for biomedical applications have shown a particular interest for biocompatible and biodegradable polymer hydrogels [1–7]. Biodegradable hydrogels were proposed for many applications ranging from drug delivery [1,2,5] to tissue engineering [2,3,7]. Polymer hydrogels to this day can be distinguished in two classes: the covalent hydrogels, with permanent crosslinks (chemical bonding), and the physical hydrogels with reversible crosslinks (physical bonding). Physical hydrogels are obtained by non-covalent cohesive interactions such as ionic or hydrogen bonding [8]. The physical hydrogels have weaker mechanical properties as opposed to the covalent hydrogels with permanent chemical bonding. A new class of supramolecular networks, where the crosslink points are not fixed but sliding, has been proposed and developed by Okumura et al. [9–11]. Their structure is based on intermolecularly crosslinked α-cyclodextrins/poly(ethylene-glycol) precursor polyrotaxanes [12–14]. The intermolecular crosslinking between the precursor of α-cyclodextrins/PEG polyrotaxanes leads to the formation of a supramolecular sliding network, the 'sliding gels' [15], as shown in Fig. 1.

This new class of supramolecular sliding network materials has unusual physical/mechanical properties, which are not yet studied in depth and/or understood. In this paper, we present a mechanical spectroscopy study of the 'sliding gels' by varying the crosslinker amount and the degree of complexation,[1] *N*, of the precursor polyrotaxanes. For this purpose, a specific synthetic method was developed to obtain various high molecular weight precursor polyrotaxanes [16] and their corresponding supramolecular sliding networks.

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[1] Complexation degree *N* is defined as the number of α-cyclodextrins per template polymer (PEG).

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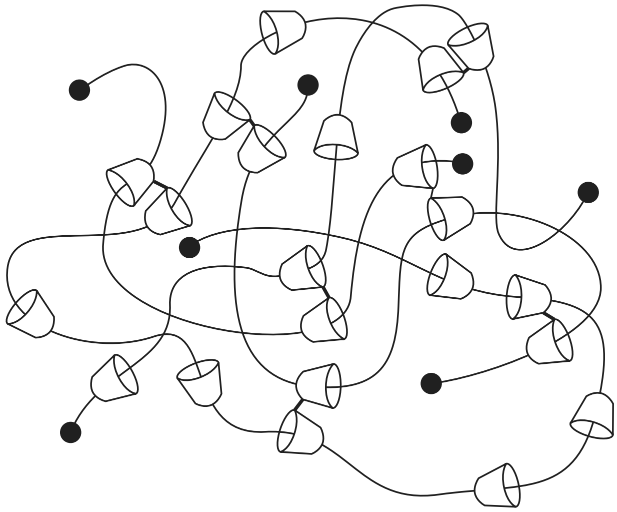


Fig. 1. Schematic representation of the sliding gel.

2. Experimental section

2.1. Materials

Poly(ethylene glycol) (PEG) with a molecular weight of 20 kg mol^{-1} and polydispersity of 1.05 was supplied by Serva Electrophoresis GmbH and dried by an azeotropic distillation from toluene before use. α-Cyclodextrins (α-CD) was purchased from Acros and dried over phosphorus pentoxide (P_2O_5) under reduce pressure before use. Dinitrofluorobenzene (DNFB) was purchased from Lancaster and used as received. Triethylamine (from Lancaster) was distilled over potassium hydroxide before use. Divinyl-sulfone (DVS) was purchased from Aldrich and used as received. Dimethylformamide (DMF) (from Fluka) and dimethylsulfoxyde (DMSO) (from Acros) were distilled over KOH before use. All other chemicals were purchased from Lancaster, Sigma or Aldrich and used as received.

2.2. SEC and ^{1}H NMR measurements

SEC measurements were performed in DMSO (HPLC grade) on two PL-gel 5 μm mixed-C, a 5 μm 100 Å and a 5 μm Guard columns in a Shimadzu LC-10AD liquid chromatograph equipped with a Shimadzu RID-10A refractive index detector and a Shimadzu SPP-M10A diode array UV detector. ^{1}H NMR spectra were recorded in water, DMSO-d_6 or $CDCl_3$ on a Bruker 300 UltrashieldTM 300 MHz with an internal lock on the 2H-signal of the solvent.

2.3. Rheological measurements

The experimental set-up that was used is a Rheometrics-RSA II strain controlled rheometer. This RSA II rheometer is equipped with one normal force transducer (1kFRT) that can detect normal forces within the range 0.001–10 N. An air oven with N_2 cooling allows a temperature range from −150 to 600 °C. The instrument is equipped with a STD motor having a strain resolution of 0.05 μm and a frequency range between 10^{-3} and 100 rad s^{-1}.

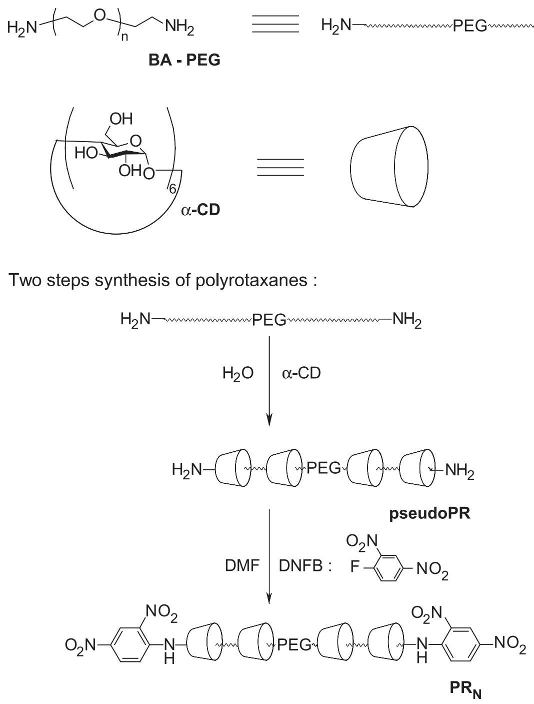
The configuration chosen for mechanical spectrometry and step strain experiments was the parallel plates configuration. The samples (typically, diameter of 12.75 mm and thickness of 3 mm) were immersed in distilled water during all the experiments in order to maintain the same state of water content in the material avoiding the drying and the deswelling of the samples during the time of the experiments. Relaxation experiments have been done by a step strain compression of 10%. Mechanical spectrometry was carried out at frequencies from 0.01 up to 100 rad s^{-1} with strain amplitude of 2.5%. A pre-strain of 5% was applied to the sample before the start of the test and ensured that the sample was always in compression during the experiments.

2.4. Preparation of α,ω-bis-amine-terminated poly(ethylene-glycol) (BA-PEG)

The synthesis of BA-PEG was carried out according to an adaptation of the procedure of Mutter [17] and was previously reported in Ref. [16].

2.5. Synthesis of polyrotaxanes

Solutions of α-CD (typically 1 g for 7 ml H_2O) and BA-PEG (1 g for 5 ml H_2O) were mixed in the right ratio and stirred at 70 °C between 30 min and 48 h. After this step, the temperature of the solution was decreased to 5 °C and the reaction mixture was stirred during 48 h or until precipitation. The solid was collected by centrifugation (9000 rpm) of the dispersion, washed two times with distilled water to eliminate free cyclodextrins and not complexed polymers, and dried over P_2O_5 under vacuum. The pseudo-polyrotaxanes were obtained with the yield ranging between 30 and 60% depending on the initial ratio R_0 corresponding to the ratio of the mole number of α-CD over the mole number of BA-PEG. The dried pseudo-polyrotaxanes were then dissolved under nitrogen atmosphere at 25 °C in distilled DMF (1 g for 4 ml DMF). Dinitrofluorobenzene was added in large excess and the solution was stirred at 25 °C during 24 h. The resulting polyrotaxanes were precipitated in ether, washed three times with 100 ml ether and dried under reduced pressure at 30 °C. To eliminate further the free α-CD and the non-complexed polymers, the polyrotaxanes were washed with a saturated sodium chloride solution. Polyrotaxanes were insoluble in this solution and were recovered by centrifugation (5000 rpm). The product was dried, re-dissolved in DMSO, precipitated in ether, washed again three times with 100 ml ether and dried under reduced pressure at 30 °C during 48 h. Polyrotaxanes were obtained with a yield ranging between 40 and 70% (Scheme 1 for



Scheme 1. General scheme of polyrotaxanes synthesis.

details). ^{1}H NMR in DMSO-d_6: $\delta = 5.65$ (m, 6H, OH-2 of α-CD), 5.48 (m, 6H, OH-3 of α-CD), 4.80 (m, 6H, CH-1 of α-CD), 4.45 (m, 6H, OH-6 of α-CD), 3.85–3.60 (m, 24H, CH-3, CH-6, CH-5 of α-CD), 3.53 (s, 4H×454, CH_2's of PEG), 3.38–3.20 (m, 12H, CH-2, CH-4 of α-CD). The average number of α-CD per chain (N) was calculated with the ratio of the integrated signal in the region between 3.4 and 3.9 ppm, which includes the signals of the CH-3, CH-6, CH-5 of α-CD and the CH_2 of the BA-PEG, over the integrated signal in the narrow region around 4.8 ppm, a peak which corresponds to the CH-1 signal of α-CD.

2.6. Synthesis of the 'sliding gel'

All the gels were formed following the same procedure. Various gels have been obtained by varying the amount of crosslinking agent (i.e. divinyl-sulfone) and the type of polyrotaxane. The polyrotaxanes (typically 150 mg) were dissolved in 0.75 mL of a molar solution of sodium hydroxide at 5 °C. The crosslinking agent (DVS, typically between 30 and 150 μL) was dissolved in 0.2 mL of distilled water at 5 °C. After the complete dissolution of the polyrotaxanes, the crosslinker solution was added to the polyrotaxane solution, which was vigorously mixed during a few seconds. The pregel solution was poured in a cylindrical shaped mould in order to obtain a piece of gel in a cylinder form with a diameter of 12.75 mm and a thickness of 3 mm. After this step, the gel was removed from the mould and washed by changing the water several times during a few days in order to eliminate the non-reacted crosslinker and precursor polyrotaxanes.

2.7. Swelling of the 'sliding gel'

The swelling degree (S) was determined by a gravimetric technique and calculated based on the weight of gel according to the equation:

$$S(\%) = \frac{W_S - W_D}{W_D} \times 100 \tag{1}$$

Where W_S and W_D are, respectively, the weights of the swollen and dried gel. These experiments were realized in distilled water and the swelling capacity of the gels was measured at room temperature (22 °C ± 1 °C). For the weight measurements of completely swollen gel, the excess of water on the surface of the gel was wiped off with filter papers. The measurements of the dried gels were obtained after 48 h in an oven at 50 °C.

3. Results and discussion

3.1. Synthesis and molecular characterization of the polyrotaxanes

Polyrotaxanes were synthesized using a general procedure described by Harada [14] (Scheme 1). This route leads to polyrotaxanes with a moderate number of α-CD per chain. It consists of two separate reaction steps (complexation and end-capping). The product from the first step in water, called pseudo-polyrotaxane is isolated by precipitation. At the second step, the pseudopolyrotaxane is end-capped with 2,4-dinitrobenzene blocking groups in DMF in order to obtain the final polyrotaxane. This procedure needs some modifications in order to obtain polyrotaxanes with a different number of α-CD per chain N. For this purpose, we adjusted the initial ratio of α-CD to PEG and the thermal cycle during the complexation step [17]. Indeed the complexation degree N is strongly dependent on the initial ratio R_0 and the time of the complexation process (t_c) at 70 °C just before the quenching at 5 °C. The characteristics and the results of the synthesis for the precursor polyrotaxanes are summarized in Table 1. The purification of the product, by carefully separating high molecular weight polyrotaxanes from free α-CD and non-complexed template PEG, was done by washing with a sodium chloride solution.

Table 1
Parameters for the synthesis and characterization of polyrotaxanes

Sample	PR_{70}	PR_{90}	PR_{120}
$[PEG]_0$ (mmol/L)	2.3	2	2
$[CD]_0$ (mmol/L)	113.5	117.9	117.9
R_0	50	60	60
t_c^a (h)	0.5	24	48
N^b	70±7	90±9	120±12
M_n^b (kg/mol)	88.1	107.6	136.8

[a] Complexation time at 70 °C.
[b] Experimental value determined by ^{1}H NMR.

The synthesis leads to high molecular weight polyrotaxanes which are qualitatively visible in SEC (Fig. 2). The polyrotaxanes were then systematically characterized by ^{1}H NMR. The complexation degree N was determined by using integrations of typical protons of α-CD and PEG (Fig. 3 and Section 2 for details). The estimated values of N by ^{1}H NMR also allowed the calculation of the molecular weight of the polyrotaxanes ($M_n = M_{nPEG} + NM_{\alpha\text{-CD}}$) which were reported in Table 1.

3.2. Synthesis of the‘ sliding gel’

The sliding gel was obtained by intermolecular crosslinking of polyrotaxane precursors. More precisely, the hydroxyl groups of the α-CD are connected via a crosslinker. Divinyl-sulfone was selected as crosslinker for its reactivity in water and its ability to selectively crosslink hydroxyl groups [18], as shown in Scheme 2. The synthesis of the sliding gel has been carried out by varying two main parameters. First, for a given polyrotaxane, the mole number n_{PR} and the molar concentration c_{PR} of polyrotaxanes in the pregel solutions were kept constant while the molar number of crosslinker n_C swept a large range. Secondly, the effect of the complexation degree N has been tested. These gels were prepared with different polyrotaxanes, the c_{PR} was kept constant in the pregel solutions while the mole number of crosslinker n_C was determined to obtain a constant mole number (K) of α-CD per crosslinker:

$$K = \frac{n_C}{n_{CD}} \tag{2}$$

Where n_C and n_{CD} are, respectively, the mole numbers of crosslinker and of α-CD.

From a chemical point of view, the reaction is complete, but from a physical point of view, one cannot ensure that each DVS molecule forms an intermolecular crosslinking between two distinct precursor polyrotaxanes. Whereas parameter K is not exactly the crosslinking density, it is, however, directly related to the level of crosslink in the sliding gel. The experimental parameters of the gel syntheses are reported on Table 2. The aspect of the gels and more particularly the optical properties looked different with the amount of crosslinker. Fig. 4 shows the sliding gels in the swollen and dried states with two different values of K. It appears that a decrease of K leads to an increase of the gel swelling. Thus, it confirms that parameter K is directly related to the crosslinking density. Furthermore, increasing the amount of crosslinker induces a decrease of its transparency and at the highest K it becomes completely opaque. It is also worth noticing that the mechanical properties of the gel change drastically with the crosslinking density. For very low densities, just above the gel point, the gel is very weak and soft while the gel is stronger but less ductile for higher crosslinking densities. These first observations will be further developed in Section 3.3 and will be correlated with the swelling degree and the rheological properties of the sliding gels.

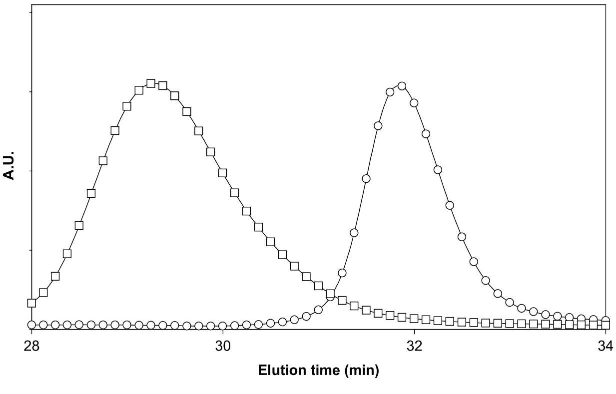


Fig. 2. SEC chromatograms of PR_{70} (-□-), and BA-PEG (-○-).

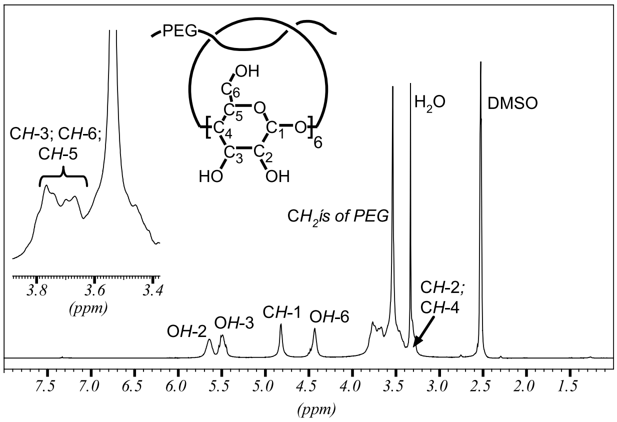
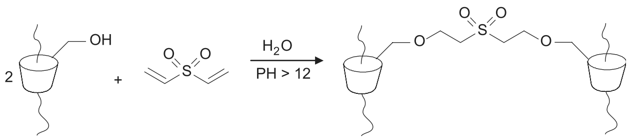


Fig. 3. ^{1}H NMR spectra of PR70 in DMSO-d_6.

3.3. Swelling experiments

The swelling degree S versus K of these sliding gels is shown in Fig. 5. For the gels formed from PR_{70}, two regimes are observed. The first regime, for $K \leq 4.2$, shows a quasi-linear decrease of the swelling degree with the increase of the crosslinking density. In this regime, the swelling degree varied from almost 600% for the less crosslinked sliding gel G_1^{70} to 250% for higher crosslinked sliding gel G_4^{70}. For yet higher crosslinked sliding gels, i.e. for $K \geq 5$, the swelling degree is reaching a plateau close to 230%. Surprisingly, the swelling degree for G_6^{70}, G^{90} and G^{120} is similar and about 230%. For these high levels of crosslinking, the value of N does not play an important role on the swelling. Moreover, when the level of crosslinking density is low the degree of swelling is very high (∼600%). The results reported here



Scheme 2. General scheme of crosslinking reaction with DVS.

Table 2
Parameters for the synthesis and characterization of the ‘sliding’ gels

	N	c_{PR} (mol/L)	n_C (mmol)	K
G_1^{70}	70	1.7×10^{-3}	0.40	3.35
G_2^{70}	70	1.7×10^{-3}	0.45	3.8
G_3^{70}	70	1.7×10^{-3}	0.47	4.0
G_4^{70}	70	1.7×10^{-3}	0.50	4.2
G_5^{70}	70	1.7×10^{-3}	0.60	5.0
G_6^{70}	70	1.7×10^{-3}	0.70	5.9
G_7^{70}	70	1.7×10^{-3}	1.00	8.4
G^{90}	90	1.7×10^{-3}	0.98	5.9
G^{120}	120	1.7×10^{-3}	1.21	5.9

demonstrated to our knowledge for the first time the importance of the level of crosslinking density to the swelling behaviour of the sliding gels. It is worth mentioning also that the swelling degree of the low crosslinking density sliding gels, reported on this manuscript, is comparable to that reported in the literature for similar gel architectures [9,19,20]. The unusual high level of swelling degree of the sliding gels is observed only for the low level of crosslinking densities and not for all sliding gel architectures as the literature let to believe.

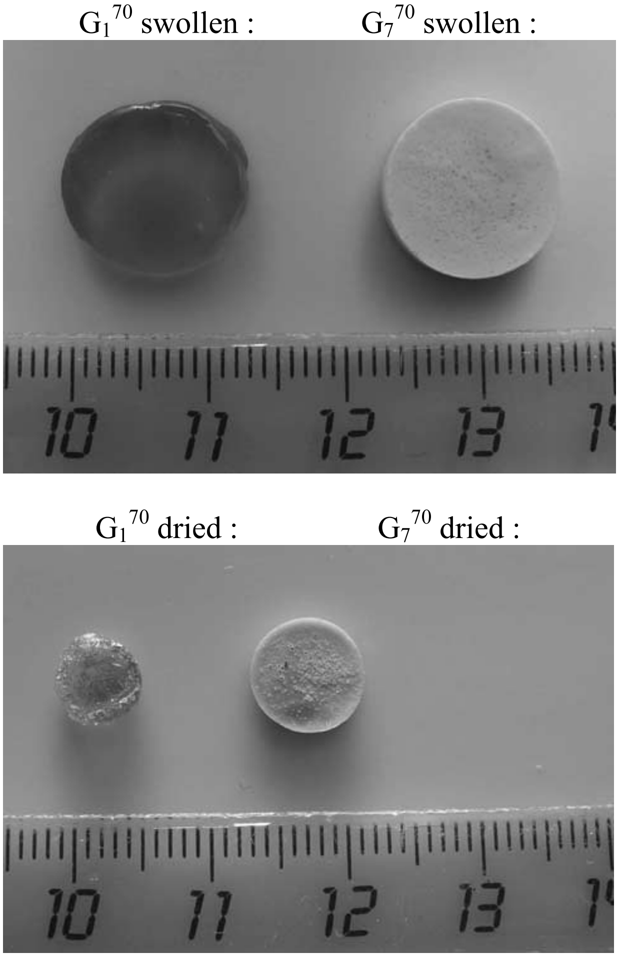


Fig. 4. Pictures of swollen and dried gels at the same scale.

3.4. Step-strain experiments

To correlate the swelling ratio with the mechanical properties, the sliding gels were also characterized with rheological experiments. The relaxation of the sample was monitored by the determination of the Young modulus $E(t)$ of the hydrogel versus time. This test has been used to characterize all the samples but more particularly for the low crosslinked hydrogels where this type of probe is much appropriated to obtain relevant results due to the mechanical weakness of these materials. Fig. 6(a) shows the stress relaxations obtained for the sliding gels synthesized from PR_{70} with crosslinker amount in the range of $3.8 \leq K \leq 8.4$. These stress relaxations show the same trends for all sliding gels, starting from a plateau, corresponding to an immediate elastic response of the material, and followed by a decrease of the Young modulus, which ends to a lower plateau. From Fig. 6(a) and (b) can be observed that the variation of K leads to sliding gels with a large range of mechanical properties. For high level of crosslinking density the Young modulus has a value close to 1 MPa while for lower crosslinking density the value of the Young modulus is 10 to 100 times smaller.

Fig. 6(b) shows the stress relaxations for the sliding gels G^{90} and G^{120} which have the same ratio of K as the G_6^{70}. The relaxation behaviour of the G^{90} and G^{120} is similar to that of the G_6^{70}. The similar values of the Young modulus plateau for the G^{90} and G^{120} were found to be higher than for the

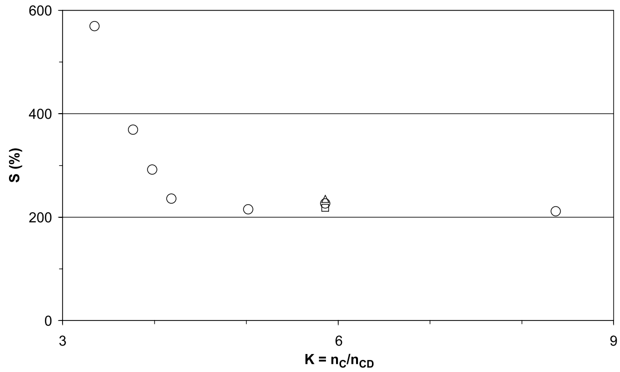


Fig. 5. Swelling degree $S(\%)$ versus K for the gels -○-, G_i^{70}; □, G^{90}; △, G^{120}.

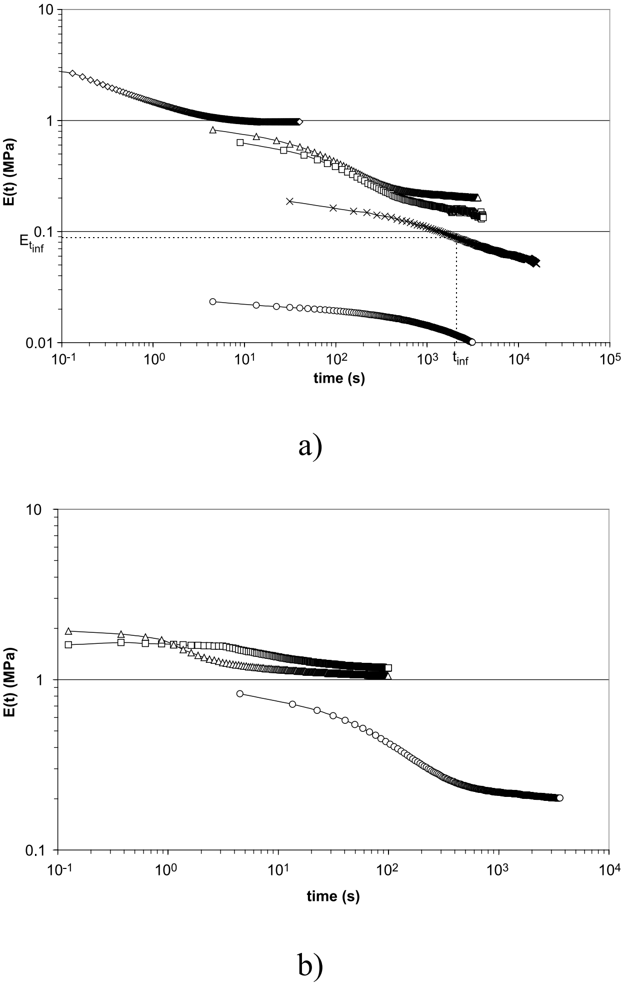


Fig. 6. Time dependence of the Young modulus during relaxation experiments. (a) Gels synthesised from the same PR_{70}. -○-, G_2^{70}; -✕-, G_4^{70}; -□-, G_5^{70}; -△-, G_6^{70}; -◇-, G_7^{70}. The inflexion time t_{inf} and the Young modulus E_{tinf} are shown for G_4^{70}. (b) Gels with the same ratio $K=5.9$. -○-, G_6^{70}; -□-, G^{90}; -△-, G^{120}.

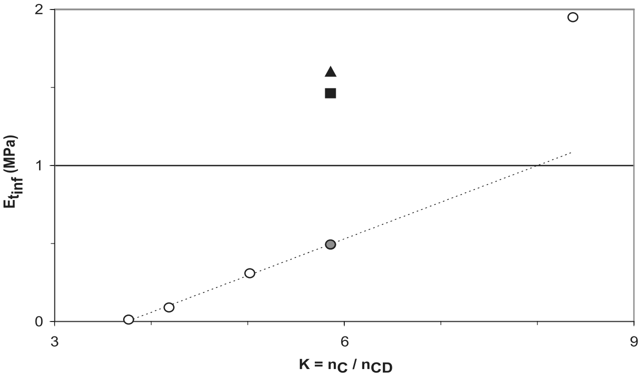


Fig. 7. Young modulus E_{tinf} versus K for different gels. -○-, G_i^{70} and linear fitting for the four first points, ■, G^{90}; ▲, G^{120}.

G_6^{70}. However, the relaxation process is faster for the G^{120} than for the G^{90}. The higher value of the Young modulus for the G^{120} can be rationalised by the higher crosslinking reaction probability due to the high N in the precursor polyrotaxane. The relaxation time t_{inf} is defined to be the inflexion point of the relaxation curve (Fig. 6(a)). This time corresponds to the modulus E_{tinf}. Fig. 7 shows the influence of K on E_{tinf}. For low levels of crosslinking density we can see a linear correlation between K and E_{tinf}. For higher level of the crosslinking density this linear correlation is not valid. In fact, the Young modulus E_{tinf} of the G_7^{70} is two times higher than the modulus that can be calculated by the linear extrapolation of the results reported on Fig. 7. Furthermore, the measured Young moduli E_{tinf} for the sliding gels with the same K increase with N. This increase is very noticeable between G_6^{70} and G^{90} but not very observable between G^{90} and G^{120}. A preliminary explanation for the increase of the Young Modulus at constant K but increasing N can be given on the basis of (a) at the higher N the crosslinking reaction probability is higher leading to higher crosslinking density and (b) at higher N the chance to have intramolecular crosslinking, forming thus local tube segments around the template polymer, is higher leading to rigidification of precursor chains of the network. The influence of K on t_{inf} is shown in Fig. 8 for the sliding gels G_i^{70}, G^{90} and G^{120}. For the G_i^{70}, the increase of K leads to a significant decrease of t_{inf} implying an increase on the elastic behaviour of the material. The first four points of t_{inf} versus K can be fitted with a power law regression. The higher crosslinked sliding gel (G_7^{70}) deviates from this behaviour. The t_{inf} corresponding to the G^{90} and G^{120} were also reported on the Fig. 8. In conclusion the stress relaxation of the sliding gel materials (Fig. 8) is faster with the increase of the N leading to a lower t_{inf}.

3.5. Mechanical spectrometry

Fig. 9 shows the elastic and the loss moduli (respectively, E' and E'') versus the pulsation ω. It is clear that $E' > E''$ over the entire range of frequencies indicating a pronounced

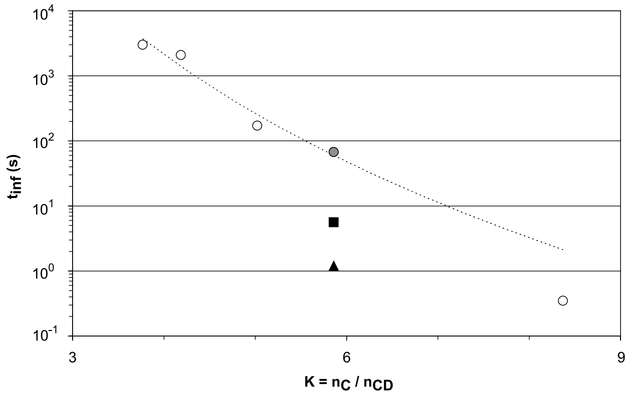


Fig. 8. Inflexion time t_{inf} versus K for different gels. -○-, G_i^{70} and power law fitting for the four first points, ■, G^{90}; ▲, G^{120}.

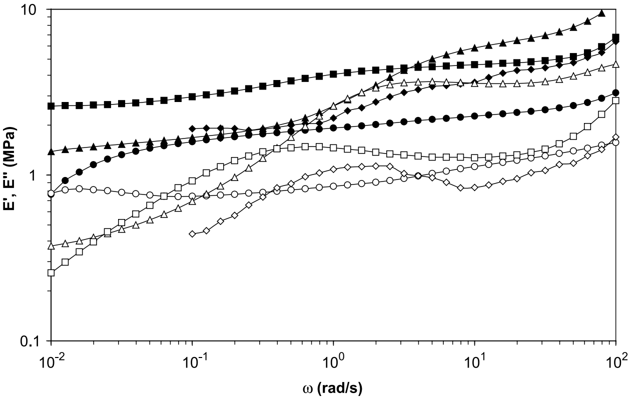


Fig. 9. E' and E'' versus ω at $T=25$ °C. -●-, E' of G_6^{70}; -○-, E'' of G_6^{70}; -◆-, E' of G_7^{70}; -◇-, E'' of G_7^{70}; -■-, E' of G^{90}; -□-, E'' of G^{90}; -▲-, E' of G^{120}; -△-, E'' of G^{120}.

elastic solid behaviour with E' in the order of 1 Mpa. It is noticeable also that E' and E'' do not show a unique plateau, in the probed frequencies range, as it is the case for classical gels or hydrogels [21–23]. Two regimes are present for the higher crosslinked sliding gels (G_7^{70}, G^{90} and G^{120}) identifiable by the two distinct plateaus in the explored frequencies range. The first regime with a lower value of E' is observed at low frequencies, while the second regime is observed at higher frequencies with a higher value of E'. The difference between the two plateau values of E' can be correlated to the fluctuation of the mean mass distribution between crosslink points due to the sliding of α-CD rings on the template PEG chain. Indeed, the viscoelastic response of this new class of supramolecular networks is essentially related to the mean mass between the 'sliding' crosslink points since in the swollen state the entanglement density is very low [24]. The molecular mechanism responsible for the two plateau regimes is related to sliding of the α-CD ring on the template chain. This sliding is easier at the low rather than at the higher frequencies. Consequently, the mean mass distribution between the 'sliding' crosslink points is larger at the low frequencies inducing a lower Modulus. Due to the good reproducibility of the experiments it can be safely concluded that the two regimes, commented above, are not related to the destruction of the network during the measurements. For the G_6^{70} and G_7^{70}, where K is increasing and N constant, the peak of tan(δ) shifts to higher frequencies (Fig. 10). For the G_6^{70}, G^{90} and G^{120}, where K is constant and N is increasing, the peak of tan(δ) is shifting to higher frequencies as well (Fig. 10). Following these observations it can be concluded that the increase of K and/or N induces an increase of the elastic behaviour as was already observed on the relaxation experiments commented here above. The position of the tan(δ) peak confirms, as well, the transition between the two regimes regarding the viscoelastic response of this new class of supramolecular networks.

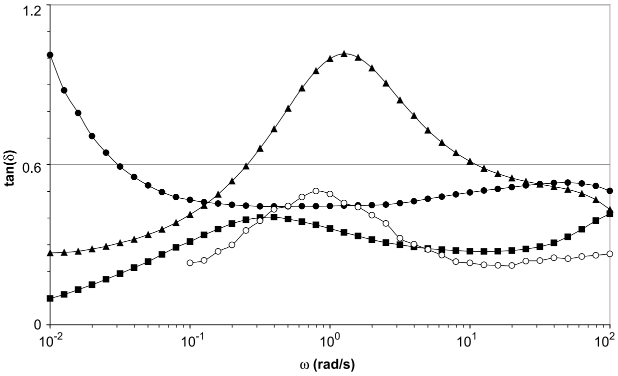


Fig. 10. tan(δ) versus ω at $T=25$ °C. -●-, G_6^{70}; -○-, G_7^{70}; -■-, G^{90}; -▲-, G^{120}.

4. Conclusion

In this study, polyrotaxanes with various complexation degrees, N, were synthesized in order to obtain high molecular weight precursors for the synthesis of 'sliding' gels. The determination of N was performed with different characterisation methods such as ^{1}H NMR and SEC. These precursor polyrotaxanes have been intermolecular crosslinked with divinyl-sulfone (DVS) to form 'sliding' gels with several crosslinking densities. The use of DVS as crosslinker permits a better control of the crosslinking reaction and the formation of gels with large range of mechanical properties (from very soft to elastomeric materials). It is remarkable to notice that these sliding gels are characterized by a very high degree of swelling (about 600%) when the crosslinking density is low. This swelling is reaching very rapidly an upper plateau (230%) when the crosslinking density is increasing. For the high crosslinking densities the swelling was independent on the degree of complexation N. It is expected that the variation of N will have an influence on the swelling at the lower crosslinking densities. The mechanical behaviour of the gels has been tested by mechanical spectroscopy. The relaxation experiments clearly showed an increase of the elastic behaviour of the gel with the increase of the crosslinking densities and the complexation degree N. The most noteworthy fact in these experiments was the presence of two distinct viscoelastic regimes. The molecular mechanism underpinning the macroscopic viscoelastic behaviour of this new class of supramolecular networks is based on the change of the mean mass distribution between the crosslink points where the α-CD rings are sliding on the template PEG chain.

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