Effects of pH on dynamics and rheology during association and gelation via the Ugi reaction of aqueous alginate

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Abstract

Effects of solution pH on the physical properties of a semidilute aqueous alginate solution without cross-linker agent and during gelation via the Ugi multicomponent condensation reaction at a fixed cross-linker concentration have been investigated. Both rheology and turbidity results on the alginate solution without cross-linker revealed enhanced associations at low pH. In the course of the cross-linker reaction, the time of gelation is shortest at pH = 3.5 and at pH values above 3.8 no gel is formed but only a viscosification of the solution is observed. The turbidity during the cross-linking reaction rises as the pH increases from 3.5 to 5. Furthermore, the initial change of the turbidity in the course of the cross-linking process is more pronounced at higher pH. The dynamic light scattering (DLS) results of the reaction mixture at pH = 4.0 (ergodic features at this condition) show that the chain relaxation is slowed down as the reaction proceeds. The effect of pH on the kinetics of the Ugi reaction is discussed.

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1. Introduction

Hydrogels belong to a class of polymers that can swell largely in water by maintaining their three-dimensional network structure in the swollen state. The mechanical, solvent permeability, swelling and hydrophilic/hydrophobic properties of a hydrogel are tuned by choice of polymer/monomer and hydrogel synthesis. Among the polymers that can form hydrogels are biopolymers such as alginate, collagen, and chitosan. These polymers are attractive for pharmaceutical applications because they are biocompatible. This property makes them to potential materials for drug release system and tissue engineering [1].

Sodium alginate is regarded as biocompatible, non-toxic, non-immunogenic and biodegradable polymer, which makes it an attractive candidate for biomedical applications. It is a naturally derived linear polysaccharide comprised of β-D-mannuronic acid (M-block) and α-L-guluronic acid (G-block) units arranged in blocks rich in G units or M units, separated by blocks of alternating G and M units [2,3]. The chemical structure of alginate is shown in Scheme 1. The physical properties of alginates depend not only upon the uronic acid composition but also on the relative proportion of the three types of block [4].

A simple way to form a hydrogel of a semidilute solution of alginate is by introducing a divalent cation, such
as calcium (Ca\(^{2+}\)), to form an ionic cross-linked gel [5]. Alginate gels that are ionically cross-linked possess a range of mechanical properties, which depend on the nature of alginate (M/G ratio), especially the length of the G block [6,7]. However, these ions can be exchanged with other ionic molecules in aqueous environments, giving rise to a deterioration of the original properties of the hydrogels [8]. In addition to ionic hydrogels, alginate can form acid gels at pH below the pK\(_a\) value of the uronic acid residues [9]. By adding the slowly hydrolyzing glucono-δ-lactone (GDL), alginate is acidified and forms alginic acid gel [10,11]. These gels have been proposed to be stabilized by intermolecular hydrogen bonds [12]. The mechanical properties of both ionic hydrogels as well as acid gels are sensitive to the nature of the alginate. Another approach that is powerful in forming hydrogels of polysaccharides is chemical cross-linking reactions of the Ugi or Passerini type [13].

The Ugi reaction [13,14] is a four-component condensation as shown in Scheme 2. The reaction mixture contains an amine which condenses with the carbonyl to yield an imine. The protonated imine and the carboxylate react with the isocyanide to give an α-(acylamino) amide. This type of reaction has been utilized for the synthesis of an alginate-based network for the immobilization of an enzyme [15]. By using a bi-functional cross-linker, a hydrogel with diamide linkages between chains can be produced. Crescenzi et al. [16] have used lysine ethyl ester as diamine cross-linker, which reacts with hyaluronic acid to obtain a hydrogel. De Nooy et al. [17,18] have employed Ugi and Passerini reactions to form hydrogels from polysaccharide solutions. Compared with the ester linkages formed from Passerini reaction, which is apt to hydrolysis, the amide linkage formed in Ugi reaction is much more stable.

In our previous work [19], alginate hydrogels were formed with the aid of the Ugi reaction, using 1,5-diaminopentane (DAP) as the bi-functional cross-linker agent. The effects of alginate concentration, as well as the cross-linking density and reaction temperature on the mechanical properties of the formed hydrogels were examined. It is worth noting that the solution pH has a strong impact on the reaction. The Ugi reaction proceeds only at acid conditions and in the above-cited paper the Ugi reaction was carried out at a fixed pH of 3.6 and the resulting samples were characterized by means of different experimental techniques. To gain insight into the effects of small pH changes on the association and gelation characteristics of alginate solutions, we have investigated the thermodynamic, rheological, and dynamical features of the system during the cross-linking process at various pH values. The objective of this work is to understand how the effect of pH can be utilized in the preparation of Ugi gels with tailor-made properties. By changing pH, the reaction kinetics of the Ugi condensation reaction can be affected, with a fundamental alteration of the mechanical characteristics of gelling alginate systems. A basic understanding of Ugi reactions in polysaccharide solutions is desirable in seeking for biocompatible hydrogels that can be used for special pharmaceutical applications.

2. Experimental section

2.1. Materials

An alginate sample, designated LF 10/60 LS, was supplied by FMC Biopolymers, Drammen, Norway. According to the specifications from the manufacturer, this sample has a weight-average molecular weight of 152000 and the guluronic acid to mannuronic acid (G/M) ratio is 0.75.
Dilute alginate solutions were dialyzed against pure water for several days to remove salt and other low-molecular weight impurities, and were thereafter freeze-dried. Regenerated cellulose with a molecular weight cutoff of 8000 was used as dialyzing membrane.

Hydrochloric acid, sodium hydroxide, formaldehyde, 1,5-diaminopentane (DAP), and cyclohexylisocyanide were purchased from Merck or Fluka and were all of analytical grade. These chemicals were used without any further purification. The water was double distilled. All measurements were carried out at 25 °C.

2.2. General procedure for the formation of gel

The freeze-dried polymer was dissolved in double distilled water at room temperature by weighing the components, followed by stirring for several hours. The solution was slightly acidified with dilute HCl solution to obtain the desired pH value, and additional water was added to reach the prescribed polymer concentration. The final pH value of the solutions was determined by PHM210 standard pH meter (Radiometer analytical S.A., France).

Formaldehyde, 1,5-diaminopentane, and cyclohexylisocyanide were added to the solution successively. After the addition of each component, the solution was stirred vigorously to disperse the component homogeneously in the solution. The molar amount of bi-functional cross-linker DAP was calculated with respect to the molar amount of carbohydrate monomers thus determining the theoretical cross-linking density. The other components were added in an excess of about 40%. After the last component cyclohexylisocyanide was added, the solution was stirred vigorously to ensure a homogeneous dispersed solution for the rheology and light scattering measurements.

2.3. Rheological experiments

Shear viscosity and oscillatory sweep measurements were conducted in a Paar-Physica MCR 300 rheometer using a cone-and-plate geometry, with a cone angle of 1° and a diameter of 75 mm. The samples were applied on the plate, and a thin layer of low-viscosity silicone oil was used to cover the free surface of solution to prevent evaporation of solvent. The measuring device is equipped with a temperature unit (Peltier element) that gives a good temperature control over an extended time. The values of strain amplitude were checked to ensure that all measurements were performed in the linear-viscoelastic regime, where the dynamic storage modulus \(G'(\omega)\) and loss modulus \(G''(\omega)\) are independent of strain amplitude. The oscillating sweep experiments were carried over an extended angular frequency \(\omega\) domain.

The rheological behavior of an incipient gel can be described by a simple power law where the dynamic moduli are related as [20]

\[
G' = G''/\tan \delta = S\omega^n \Gamma(1 - n) \cos \delta
\]

where \(\Gamma(1 - n)\) is the gamma function, \(n\) is the relaxation exponent, and \(S\) is the gel strength parameter, which depends on the cross-linking density and the molecular chain flexibility [20]. The phase angle \(\delta\) between stress and strain is independent of frequency \((\omega)\) but proportional to the relaxation exponent:

\[
\tan \delta = G''/G' = \tan(n\pi/2)
\]

These results suggest that the incipient gel can be described by the following scaling relation:

\[
G'(\omega) \propto G'' \propto \omega^n
\]

The gel point (GP) can then be determined [21–23] by the observation of a frequency-independent value of \(\tan \delta\) obtained from a multifrequency plot of \(\tan \delta\) versus reaction time. An alternative method [24] is to plot the “apparent” viscoelastic exponents \(n'\) and \(n''(G' \propto \omega^{n'}\), \(G'' \propto \omega^{n''}\) obtained from the frequency dependence of \(G'\) and \(G''\) against the reaction time, and observing a crossover where \(n = n' = n''\). These two methods should yield the same value of GP.

2.4. Turbidity measurements

The transmittances of gelling and non-gelling alginate solutions of different pH were measured with a temperature controlled Helios Gamma (Thermo Spectronic, Cambridge, UK) spectrophotometer at a wavelength of 500 nm. The apparatus is equipped with a temperature unit (Peltier plate) that gives a good temperature control over an extended time. The turbidities \(\tau\) of the samples were calculated from:

\[
\tau = (-1/L) \ln(I_i/I_0)
\]

where \(L\) is the light path length in the cell (1 cm), \(I_i\) is the transmitted light intensity, and \(I_0\) is the incident light intensity.

2.5. Dynamic light scattering

In light scattering experiments we probe on a length scale of \(q^{-1}\) where \(q\) is the wave vector defined as \(q = 4\pi n \sin(\theta/2)/\lambda\). Here \(\lambda\) is the wavelength of the incident light in a vacuum, \(\theta\) is the scattering angle, and \(n\) is the refractive index of the medium. The value of \(n\) was determined at \(\lambda = 514.5\) nm for each sample with an Abbé refractometer.

The beam from an argon ion laser (Lexel laser, model 95), operating at a wavelength of 514.5 nm with vertically
polarized light, was focused on the sample cell through a temperature-controlled chamber (temperature controlled to within \( \pm 0.05 \, ^\circ \text{C} \)) filled with refractive index matching silicone oil. The sample solutions were filtered in an atmosphere of filtered air through 5.0 \( \mu \text{m} \) filters (Millipore) directly into precleaned 10 mm NMR tubes (Wilmad Glass Co.) of highest quality.

The full homodyne intensity autocorrelation function was measured at a scattering angle of 90\(^\circ\) with an ALV-5000 multiple-\( \tau \) digital correlator. The correlation functions were recorded in the real time “multiple-\( \tau \)” mode of the correlator, in which 256 time channels are logarithmically spaced over an interval ranging from 0.2 \( \mu \)s to almost 1 h.

When the scattered light obeys Gaussian statistics, the measured homodyne intensity autocorrelation \( g^{(2)}(q,t) \) is related to the theoretically amenable first-order electric field correlation function \( g^{(1)}(q,t) \) through the Siegert relation

\[
g^{(2)}(q,t) = 1 + B|g^{(1)}(q,t)|^2
\]

where \( B \leq 1 \) is the coherence factor that depends on the experimental geometry.

Several experimental DLS studies on complex polymer systems [25–29] have revealed that the decay of the correlation function can initially be described by a single exponential, followed at longer times by a stretched exponential of the Kohlrausch–Williams–Watts type

\[
g^{(1)}(t) = A_f \exp(-t/\tau_f) + A_s \exp[-(t/\tau_{se})^\beta]
\]

with \( A_f + A_s = 1 \). The parameters \( A_f \) and \( A_s \) are the amplitudes for the fast and the slow relaxation mode, respectively. The first term (short-time behavior) on the right-hand side of Eq. (6) is related to a cooperative diffusion coefficient \( D_c \). The second term is expected to be associated with disengagement relaxation of individual chains or cluster relaxation [30–32]. The variable \( \tau_{se} \) is some effective relaxation times, and \( \beta (0 < \beta \leq 1) \) is a measure of the width of the distribution of slow relaxation times. The mean relaxation time is given by

\[
\tau_r = \int_0^\infty \exp[-(t/\tau_{se})^\beta] \, dt = (\tau_{se}/\beta)\Gamma(1/\beta)
\]

where \( \Gamma \) is the gamma function.

In the analysis of correlation function data, a nonlinear fitting algorithm (a modified Levenberg–Marquardt method) was employed to obtain best-fit values of the parameters \( A_f, \tau_f, \tau_{se}, \) and \( \beta \) appearing on the right-hand side of Eq. (6). To avoid complications arising due to nonergodic behavior of the sample, only correlation functions representing non-gelling conditions have been collected.

3. Results and discussion

3.1. Effect of pH on the solution viscosity

The initial pH value of the neutral alginate solution of 2.2 wt.% concentration is 5.1, which means that the carboxylic acid groups are slightly dissociated. Two types of interactions play an important role in aqueous alginate solution, namely the charge repulsion between ionized carboxylate –COO– groups and the hydrogen bonding formed between carboxylic acid and ionized carboxylate groups. At pH values above the \( pK_a \) value (3.7) of the uronic acid residues, loosening of the network structure occurs as a result from mutual repulsion of ionized carboxyl groups, whereas at low pH the weakening of the electrostatic interactions promotes the development of intermolecular hydrogen bonds and possible entanglements. In aqueous solution, the considered polymer concentration of 2.2 wt.% is well above the overlap concentration, where we expect intermolecular interactions to be dominant. Effect of pH on the shear viscosity for alginate (2.2 wt.%) dissolved in water without the Ugi reactants is depicted in Fig. 1. The general trend is that the viscosity increases with lowering pH, and pronounced rises of the viscosity at low shear rates are observed at pH = 3.4 and 3.6, where also strong shear-thinning features are detected at high shear rates due to the breakup of the intermolecular associations. At pH values below 3.4, this system forms a physical gel. These results show that the rheological response is very sensitive to small pH change in the low pH range, which probably reflects enhanced intermolecular interactions.

Influences of pH on the zero-shear viscosity and the turbidity (measured at 500 nm) for 2.2 wt.% alginate solutions (without Ugi reactants) are shown in Fig. 2. Both the turbidity and viscosity exhibit a similar profile.
over the considered pH range with a strong upturn at low values of pH, suggesting that the electrostatic interactions are suppressed, enhanced intermolecular hydrogen bonds and possible entanglements emerge and association structures are formed. These findings clearly demonstrate that both the thermodynamic features and the rheological response are sensitive to a change of pH in the pH domain around 4. These results demonstrate that the viscoelastic properties of an aqueous semidilute alginate solution can be tuned significantly by changing the pH in this domain.

3.2. Effect of pH on the rheological properties of cross-linked alginate via the Ugi reaction

In this section, results from solutions of different pH cross-linked via the Ugi reaction will be presented and discussed. The time evolution of the absolute value of the complex viscosity (at a constant angular frequency of 10 rad/s) during the gelation process of 2.2 wt.% alginate solutions of different pH at a fixed cross-linking density (12 mol%) is displayed in Fig. 3a. The absolute value of $\eta^*$ increases at early times for the systems with acidified alginate solutions, and it levels off at longer times. The rise of the complex viscosity during the initial stage is more marked as pH decreases, with the highest values at pH = 3.5. At pH = 5.1, $\eta^*$ is virtually independent of the reaction time, indicating that the process of forming cross-links is inhibited at this pH. The dynamic moduli as a function of reaction time are shown in Fig. 3b and c for 2.2 wt.% solutions of alginate at different pH values. The storage modulus $G'$ increases with the reaction time and a maximum plateau value which is nearly three orders of magnitude larger than the initial value appears for the system with pH = 3.5, whereas a modest rise of the loss modulus $G''$ is found at the corresponding conditions. These features reveal that at low pH, the elastic response becomes a dominating factor fairly early in the course of the gelation process.

The gelation times of the above systems are determined by observation of a frequency-independent value of tan$\delta$ obtained from a multi-frequency plot of tan$\delta$ versus time. A typical example is presented in Fig. 4 for a system with 2.2 wt.% alginate at pH = 3.5 and with 12 mol% cross-linker. An alternative method to establish the gel points is to plot the apparent viscoelastic exponents $n'$ and $n''$ versus time and observing a crossover where $n' = n'' = n$ (see the inset of Fig. 4a). Both methods yield the same gelation times, and the effect of pH on the time of gelation is illustrated in Fig. 4b. The shortest gelation time is observed at pH = 3.5 and at pH values of 4.0 and above, no gel is formed during the Ugi cross-linker condensation reaction. The value of $n$ is approximately 0.8 at pH = 3.5 and this value is practically the same for the other pH values where gels are formed. This value is not far from that ($n = 0.72$) predicted for a percolation network [33].

According to the mechanism of the Ugi reaction shown in Scheme 2, the formation of protonated imine is the critical stage for the reaction that can only be realized in acid solution. At acid conditions, the protonated imine and the carboxylate react with the isocyanide to
give an α-(acylamino) amide. In the reaction mixture without added acid (pH = 5.1), or a slightly acidified (pH = 4.0) alginate solution, the proton concentration is too low to protonate the imine sufficiently. Only a few active sites for cross-linking are formed and the Ugi reaction conducted at these conditions will only yield a low extent of reaction, resulting in a weak enhancement of the viscosity. A decrease of the solution pH induces a more favorable condition for the imine protonation process, and thereby promotes a faster gelation and the emergence of a stronger network. The prolongation of the gelation time for the system with the lowest pH is probably due to the small amount of carboxylate rests in the initial alginate solution. Since several carboxylate groups have been protonated into carboxylic acid by adding HCl to the solution to reach a pH of 3.4, the reaction mixture does not initially contain enough carboxylate groups to react with protonated imine and isocyanide. The chemical cross-linking reaction can only proceed when more carboxylate species have been produced by the protonation of the imine.

This mechanism can probably also be resorted to in explaining the induction period that was detected in the rheological data before the commencement of the cross-linking process of the alginate solution with pH = 3.4.

Fig. 5 shows the complex viscosity as a function of solution pH for both the initial and final stage of the cross-linker reaction. It is obvious that the effect of pH on the complex viscosity is very pronounced at low pH, reflecting that the cross-linking ability of the Ugi reaction is sensitive to a pH change at acid conditions. The low values of $|\eta^*|$ and the minor impact of pH on the rheological features at pH values below 4 can be ascribed to the low efficiency of the Ugi reaction at these conditions. At this stage, no cross-linked network is formed and the elastic response of the network is low.

3.3. Turbidity change during the Ugi reaction

Time evolution of the turbidity of mixtures of 2.2 wt.% alginate in the presence of 12 mol% cross-linker agent at different pH values is displayed in Fig. 6a. The values of the turbidity increases with increasing pH, and the initial time dependence of $\tau$ can be described by a power law $\tau \sim p^r$, where $p$ rises as pH increases (see the inset of Fig. 6b). These results suggest that at conditions where the Ugi cross-linker reaction is inefficient (higher pH values) the unreacted components give rise to large-scale heterogeneities, which are reflected in the high turbidity values. The initial growth of the heterogeneities is strongest (largest value of $p$) at the highest pH (the inset of Fig. 6b), which may indicate that the incomplete reaction of the components at this condition generates macroscopic heterogeneities in the reaction mixture. The slight increase of the turbidity at pH = 3.5
announces that the cross-linking zones formed during the chemical gelation do not induce macroscopic inhomogeneities in the connected network, not even far into the post-gel region.

In Fig. 6b, the effects of pH on the turbidity for a 2.2 wt.% alginate solution, without the Ugi components, and for a reaction mixture at the initial (5 min) and final (500 min) reaction stage are displayed. The value of the turbidity of the alginate solution decreases moderately with increasing pH, whereas for the reaction mixtures a strong rise of the turbidity is found in the pH range from 3.8 to 4.5. This reflects the formation of large-scale heterogeneities in this pH domain because of incomplete reaction of the components that are only little soluble in water. The conjecture is that the unreacted components in the mixture contribute to the augmented turbidity of the sample. The results reveal that most of the changes of the turbidity occur after a short time, and only a moderate enhancement of the turbidity takes place in the course of time.

To elucidate changes of the dynamics during the Ugi cross-linking reaction in a 2.2 wt.% alginate mixture (pH = 4.0) under ergodic conditions, DLS measurements were conducted for the non-gelling reaction system at different reaction times. As revealed form the above rheology and turbidity data, reaction mixtures at high pH are turbid and in these systems multiple scattering constitutes a problem, whereas at low pH strong gels are formed and they exhibit non-ergodic features. In the light of this, a 2.2 wt.% alginate solution with pH = 4.0 was chosen for the Ugi cross-linker reaction.

In Fig. 7, the normalized time correlation function data of a mixture of 2.2 wt.% alginate in the presence of 12 mol% cross-linker agent and an initial pH of the solution of 4.0 are depicted during the cross-linking process in the form of semilogarithmic plots. The correlation function is shifted toward longer times as the reaction proceeds. By using Eq. (6), a number of characteristic parameters can be extracted. A quantitative illustration of the development of the fast relaxation time $\tau_f$, slow relaxation time $\tau_s$, and the stretched exponent $\beta$ in the course of the reaction process is displayed in Fig. 8.

The fast mode is diffusive and in the semidilute concentration regime a cooperative diffusion coefficient $D_c (\tau_f^{-1} = D_c q^2)$ can be determined. In the framework of the “blob” model for semidilute solutions $D_c$, associated with network deformations, can be defined [33] $D_c \approx k_BT/6\pi\eta_0 \xi_h$, where $k_B$ is Boltzmann’s constant, $T$ is the absolute temperature, $\eta_0$ is the solvent viscosity, and the dynamic correlation length $\xi_h$ can be viewed as a characteristic mesh size of the transient network. From the relationships above, we can see that $\tau_f$ is directly proportional to $\xi_h$. The results in Fig. 8a for the fast relaxation time indicate that the average mesh

![Fig. 6. (a) Time evolution of the turbidity at different pH for gelling and non-gelling 2.2 wt.% alginate solutions. (b) Effect of pH on the turbidity at early and late stage of the cross-linking process. The inset plot shows the pH dependence of the exponent $p(\tau \sim t^p)$, describing the early time dependence of the turbidity.](image1)

![Fig. 7. Time evolution of the correlation function in the course of the cross-linking process for a 2.2 wt.% alginate solution with an initial pH of 4.0.](image2)
size decreases as the reaction proceeds. This trend can probably be attributed to the cross-linker reaction, that is, more cross-linking junctions are formed in the course of the reaction and the average mesh size of the network is reduced.

The slow relaxation time $\tau_s$ increases steadily as the reaction proceeds (see Fig. 8b). We may note that the difference in time scale between the fast and the slow relaxation processes spans several orders of magnitude. The raise of $\tau_s$ suggests that the Ugi reaction generates enhanced intermolecular connections, and thereby the disengagement relaxation of individual chains is slowed down. It is interesting to note that the time evolution of the slow relaxation time exhibits a similar pattern of behavior as the corresponding results for the complex viscosity (cf. Fig. 3a), which is also sensitive to chain disengagement. This type of conformity between rheological parameters and the slow relaxation mode in DLS has previously been reported for other complex polymer systems [34–37].

Fig. 8c shows the time dependence of the stretched exponent $\beta$ for the same system. It is evident that $\beta$ in the initial stage of the reaction exhibits a strong drop and this is followed by a moderate decrease at longer times of reaction. The decrease of $\beta$ indicates a broader distribution of relaxation times. The trend of $\beta$ can be rationalized in the framework of the coupling approach elaborated by Ngai [32,38,39]. This model provides a general description of the dynamics in constrained and interacting systems [39]. This approach has been utilized in the analysis of dynamical features in associating and gelling systems of various natures [37,40–43]. In the coupling model, the value of $\beta$ is a direct measure of the coupling strength of the relaxation mode to its complex surroundings. A decreasing value of $\beta$ indicates enhanced coupling effects, as is expected when more chains are cross-linked during the cross-linking process. As a result, the disengagement of chains is slower. The trend of $\beta$ is consistent with the behavior of the slow relaxation time.

4. Conclusions

The effects of pH on the rheology and turbidity of an aqueous semidilute (2.2 wt.%) alginate solution, without and with Ugi cross-linker reactants, have been investigated. In the absence of reactants in the alginate-water solution, the zero-shear viscosity shows a strong upturn at pH values below 4, and a similar trend can also be traced in the turbidity data. At these conditions, the electrostatic interactions are suppressed and the conjecture is that intermolecular association complexes are created through hydrogen bonds. At higher pH, the repulsive forces will counteract the formation of intermolecular associations.

The Ugi multicomponent condensation reaction was conducted under different solution pH with a fixed cross-linker concentration. At pH values of 4 and above, only viscosification of the solutions is observed during the cross-linker reaction, whereas at pH values below 4 chemical gels are formed in the course of time and the most favorable gelation condition is at pH = 3.5. The findings from this work reveal that acid pH values around 3.5 are propitious conditions for the Ugi reaction to proceed in forming effective cross-links for the gel network, whereas at higher pH values the cross-linker process is inefficient and the connectivity of the network is lost. At the latter stage (pH values above 4), the cross-linker ability is low and the unreacted components in the reaction mixture give rise to enhanced turbidity. At low pH, the turbidity is low and it increases only slightly in the post-gel region. This suggests, in contrast to many other chemically gelling systems, that no large-scale heterogeneities are evolved in the post-gel region.

Dynamic light scattering (DLS) measurements have been carried out in a reaction mixture where pH of the
solution is 4.0. The slow relaxation time, characterizing the disengagement relaxation of individual chains, shows that intermolecular associations are formed during the reaction and $\tau_g$ exhibits similar time dependence as the rheological parameters. In light of the coupling model of Ngai, the results of $\beta$ suggest that the relaxation of chains is inhibited by the cross-linking process.

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