Rheological Study of Poly(ethylene glycol)/poly(*N*-isopropylacrylamide-*co*-2-acrylamido-2-methylpropanesulphonic acid) Semiinterpenetrating Network Formation

Chi Zhang, Allan J. Easteal

Department of Chemistry, The University of Auckland, Auckland, New Zealand

ABSTRACT: The formation of a series of semiinterpenetrating network (SIPN) hydrogels made by free-radical copolymerization of *N*-isopropylacrylamide (NIPA) and 2-acrylamido-2-methylpropanesulphonic acid (AMPS) with varying comonomer mole ratios, crosslinked with *N,N'*-methylene-bisacrylamide (MBAA) in the presence of poly-(ethylene glycol) (PEG) with average molecular weight 6,000 g mol^{-1} was studied via determination of complex viscosity, η^*, using plate–plate rheometry. The isothermal time dependence of η^* at various temperatures or the variation of η^* with temperature of pregel solutions was utilized to detect the onset of gelation. The SIPN systems were compared with the corresponding gels made under the same conditions in the absence of PEG. The copolymer mainchain composition has a major effect on the time or temperature for onset of gelation and in particular gelation appears to be inhibited to some extent by MBAA when the AMPS/NIPA mole ratio in the pregel solution exceeds 0.5. The presence or absence of PEG in pregel solutions has a lesser effect on gelation. © 2004 Wiley Periodicals, Inc. J Appl Polym Sci 94: 2083–2087, 2004

Key words: rheology; kinetics; viscosity; copolymerization; gelation

INTRODUCTION

A novel pH- and temperature-sensitive semiinterpenetrating hydrogel system, based on crosslinked poly(2-acrylamido-2-methylpropane sulfonic acid-*co*-*N*-isopropylacrylamide) has been developed for peptide or protein drug delivery. The hydrogel, comprising poly(ethylene glycol) (PEG) chains embedded in the copolymer network, was designed as a multifunctional peptide or protein drug linker and hydrogel carrier, for controlled *in vivo* administration of drugs. Incorporation of PEG in the gel increases the potential for hydrogen bond formation, since the lone pairs of electrons on the oxygen atoms of the oxyethylene repeat units in PEG serve as hydrogen bond acceptors.[1] Since they are not covalently bonded to the copolymer network, the PEG chains can be readily separated from the crosslinked network and, as a stable polymer with OH end groups, PEG is very effective as a linker molecule for peptide or protein drugs.[2,3]

In the copolymerization system using free-radical initiation of 2-acrylamido-2-methylpropane sulfonic acid (AMPS), *N*-isopropylacrylamide (NIPA), and *N,N'*-methylenebisacrylamide (MBAA) in the presence of PEG with average molar mass about 6,000 g mol^{-1} (PEG6000), the PEG molecules do not participate in the crosslinking and polymerization reactions, and crosslinking of copolymer chains takes place predominantly in the early stages of copolymer chain growth.[4] In the absence of PEG, the polymerization and crosslinking of AMPS, NIPA, and MBAA gives typical poly(AMPS-*co*-NIPA) copolymer gels. The transition from pregel solution to gel is associated with changes that can be characterized rheologically. At the onset of copolymerization in the presence of a crosslinker, the reaction system is liquid, and the frequency dependence of the real (G') and imaginary (G'') parts of the complex shear modulus are those of an ordinary liquid at low frequency. G' is proportional to the square of the angular frequency (ω) and G'' is proportional to angular frequency.[5] The complex viscosity is given by the expression[6]

$$\eta^* = \eta' - i\eta'' = G''/\omega - iG'/\omega$$

Since the real part (η', commonly referred to as the dynamic viscosity) of the complex viscosity is proportional to G'' and inversely proportional to ω, the viscosity and tanδ (G''/G') are both sensitive to gelation. When the polymer network has formed, the viscoelastic behavior of the gel approximates that of an elastic

Correspondence to: A. J. Easteal (aj.easteal@auckland.ac.nz).

solid. Tanδ is often the most sensitive indicator of molecular motions, transitions, relaxation processes, structural heterogeneities, and morphology of materials.[6,7]

In the present article, the effects of copolymerization variables on gel formation are investigated using parallel plate rheometry, through comparison of the gelation of AMPS/NIPA/MBAA pregel solutions with that of PEG/AMPS/NIPA/MBAA pregels, to reveal the differences between the two systems due to the presence of PEG.

Although PEG is not involved in the copolymerization or crosslinking reactions, the interactions between linear PEG chains and the growing poly(AMPS-*co*-NIPA) copolymer chains and its network were expected to affect the kinetics of gelation and hence mechanical and rheological properties of the gels.

EXPERIMENTAL

Poly(ethylene glycol) with average molecular weight about 6,000 g mol^{-1} was supplied by BDH (Poole, England). *N*-Isopropylacrylamide (from Acros Organics, Geel, Belgium) and 2-acrylamido-2-methylpropanesulfonic acid (Merck-Schuchardt, Hohenbrunn, Germany) were both synthesis grade (> 99%) materials. *N,N′*-methylenebisacrylamide (Sigma–Aldrich, St. Louis, MO) was electrophoresis reagent grade material. Ammonium persulphate (Ajax Chemicals, Auburn, New South Wales, Australia) used as initiator was > 98% pure. All of these chemicals were used without further purification.

A series of pregel solutions with a range of AMPS/NIPA mole ratios were prepared by dissolving the required quantities of AMPS, NIPA, MBAA, APS, and PEG6000 in deionized water to make a constant comonomer concentration of 0.88 mol L^{-1} AMPS + NIPA, 0.035 mol L^{-1} MBAA, and 0.01 mol L^{-1} APS, together with 10% (wt/vol) PEG6000 based on PEG, AMPS, and NIPA. All solutions were kept in capped bottles wrapped with aluminum foil and stored at 0°C before use.

The procedure outlined above was used to prepare a second series of pregel solutions with all of the components except PEG present. The solids content (20% wt/vol) of these solutions was the same as for the corresponding pregel solutions containing PEG.

A Paar Physica model UDS 200 rheometer with a 25-mm-diameter plate–plate measuring system was used in rotation or oscillation mode for pregel solutions. The plate gap was kept at 0.5 mm for pregel solutions, which were dropped onto the center of the lower plate to give a sample area matching the plate area. Experiments were carried out under dynamic conditions either at constant stress (20 Pa) for rotation or at constant shear rate (10 s^{-1}) for oscillation mode. For experiments in which temperature was varied
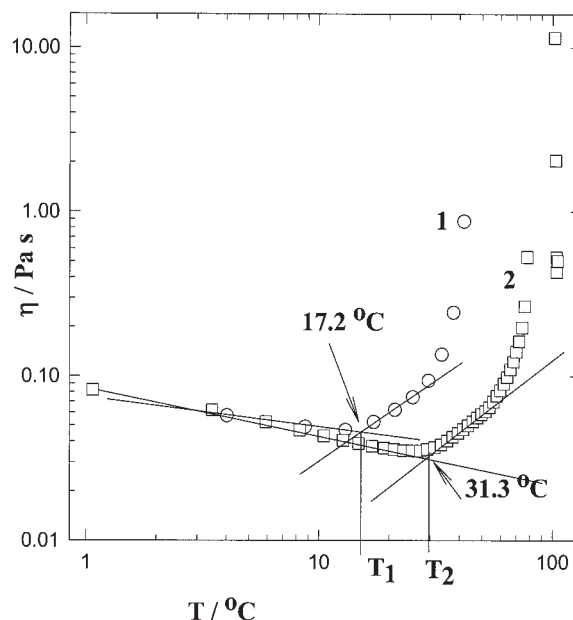

Figure 1 Aging effect on onset temperature for gelation. 1, fresh pregel solution; 2, pregel solution after standing in an ice/water bath for 10 h. Pregel solution composition: 0.195 mol L^{-1} AMPS; 0.531 mol L^{-1} NIPA; 0.01 mol L^{-1} APS, 0.034 mol L^{-1} MBAA, and 50 wt % PEG. The pregel solution was continuously heated at 7°C min^{-1} and the viscosity measured at constant stress (20 Pa) in rotation mode.

continuously, the average heating rate was about 7°C/min.

RESULTS AND DISCUSSION

For pregel solutions heated at a constant rate, the temperature corresponding to a rapid increase in either complex viscosity or shear storage modulus was taken to be the temperature, T_i, corresponding to the onset of gelation. Figure 1 shows typical observations, together with the effect of keeping the pregel solution at 0°C for 10 h prior to heating. The increase of gelation onset temperature ($T_2 > T_1$) after standing at 0°C is most likely due to dissolution of oxygen in the pregel solution, and freshly prepared pregel solutions were used to avoid the aging effect.

Figure 2 shows the marked changes in viscoelastic properties accompanying the transition from pregel solution to gel in a system containing one of the monomers (AMPS), maintained at a constant temperature. The data show clearly that η^*, G' and G'' show very similar time dependence, namely a very rapid increase when the gel starts to form and continuing increase as crosslinking develops further in the material. For the corresponding pregel solution containing 41.8 wt % PEG (Fig. 3), the gelation time, t_{gel}, is increased by about 10%. Figure 3 also indicates that the effect of the relative proportions of comonomers on the gelation
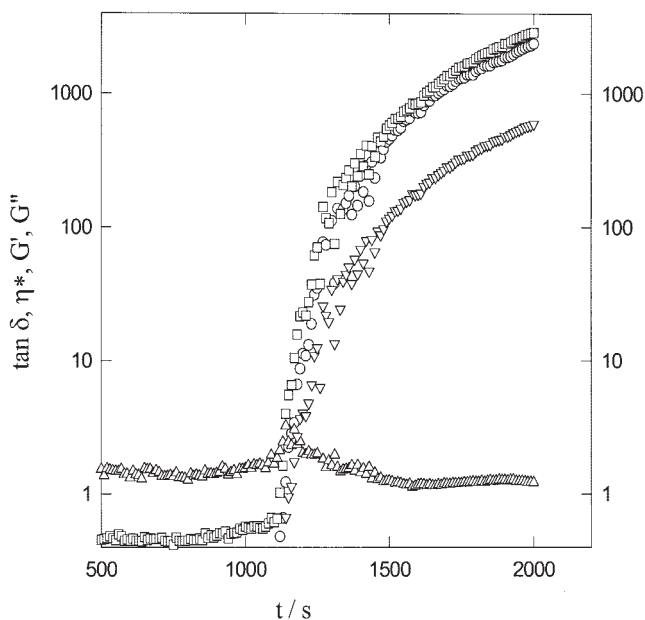
Figure 2 Time dependence of rheological parameters measured in oscillation mode at constant shear rate (10 s^{-1}) and 20% strain, for a 100% AMPS gel maintained at 70°C. ▽, η^*/Pa s; ○, G'/Pa; □, G''/Pa; △, tanδ.

time at 70°C is much more dramatic than the influence of PEG. In the absence of PEG, decreasing the proportion of AMPS from 100 to 40 mol % of the comonomers reduces the gelation onset time to 350 s. Incorporation of PEG in a copolymer gel increases gelation onset
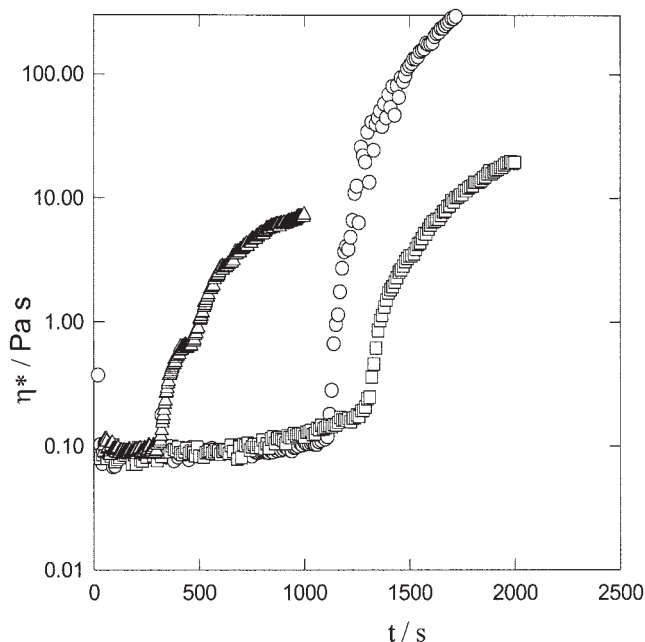

Figure 3 Time dependence of complex viscosity measured in oscillation mode at constant shear rate (10 s^{-1}), for pregel solutions maintained at 70°C. ○, 100 mol % AMPS; □, 100 mol % AMPS + PEG; △, 40 mol % AMPS + PEG.

TABLE I
Dependence of Onset Time for Gel Formation on Temperature

T_i (°C)	Gelation onset time/s	
	SIPN pregel	Copolymer pregel
50	360	180
55	300	135
60	210	120
70	100	80

Solution composition (concentrations in mol L^{-1}): AMPS, 0.53; NIPA, 0.35; APS, 0.01; MBAA, 0.035. 50 wt % PEG6000 in SIPN pregel solution. Rheometer used in oscillation mode at constant shear rate (10 s^{-1}) and 20% strain.

time to a much greater extent at low reaction temperatures than at higher temperatures. That trend is illustrated by the data in Table I for pregel solutions with AMPS/NIPA mole ratio of about 1.5. The complex viscosity of the solution containing PEG is 20–90 times smaller than in the absence of PEG [see Figs. 4(a) and (b)], at corresponding temperature and time.

Temperature is clearly a key variable in the kinetics of gel formation, and the isothermal variation of complex viscosity with time, at a range of temperatures, provides an insight into processes taking place at the molecular level in polymerizing systems. Figure 5 shows the isothermal variation of complex viscosity with time, at three reaction temperatures, for a copolymer-based SIPN system with 100 mol % NIPA and 50 wt % PEG. While the viscosity profiles are essentially independent of temperature for reaction times less than about 70 s, they differ markedly at longer times and reflect the expected inverse dependence of gelation onset time (about 120 and 100 s, at 70 and 80°C, respectively) on reaction temperature. A notable feature is the double maxima in η^*, which are particularly sharp at 70°C and whose positions (i.e., the times corresponding to the maximum values) are virtually the same at the two higher temperatures. The results of our NMR study[4] of this system show that, in polymerization of pregel solutions containing NIPA, AMPS and MBAA, the initial rate of polymerization of MBAA is substantially larger than for NIPA and AMPS. Consequently, network fomation through incorporation of MBAA in copolymer chains occurs in the early stages of chain growth, and we can confidently attribute the rapid upturn in η^* at about 50 and 200 s, at 80 and 70°C, respectively, to the onset of crosslinking. The decrease in viscosity after the first maximum may be due to NIPA chain segment contraction, since the temperatures are above the lower critical solution temperature (32°C)[8] for polyNIPA.

The subsequent increase in viscosity at about 500–600 s is thought to be due primarily to main chain
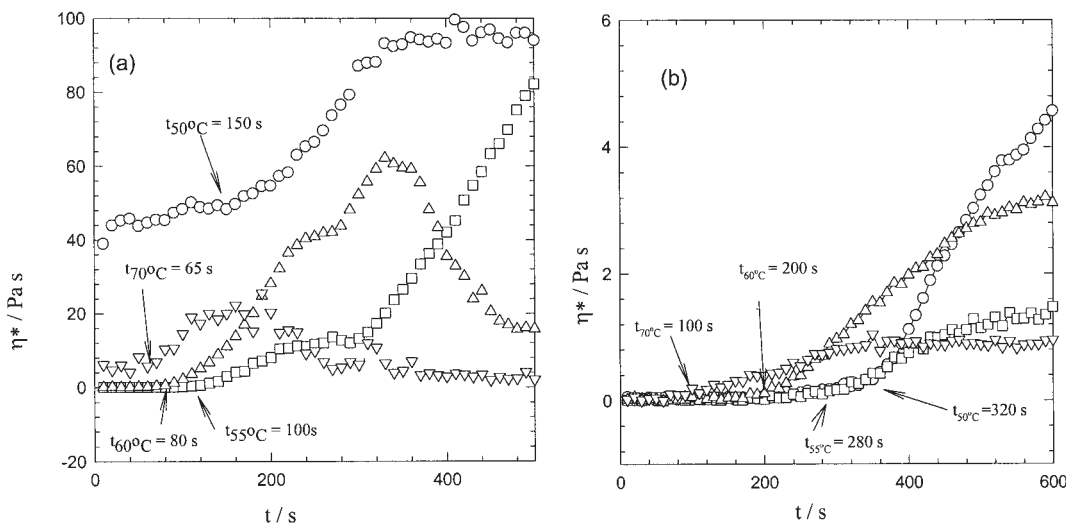
Figure 4 Effect of reaction temperature on time dependence of complex viscosity for (a) copolymer pregel solution, (b) SIPN pregel solution with 50 wt % PEG. Pregel compositions as per Table I. ○, 50°C; □, 55°C; △, 60°C; and ▽, 70°C. Oscillation mode at constant shear rate (10 s^{-1}) and 20% strain.

growth and network formation. The decease in viscosity that follows is most likely an experimental artifact that arises from reduction of the contact area of the gel sample with the driving plate as a result of evaporation of water from the sample. The second drop of viscosity at 70°C being more pronounced than that at 80°C is most likely due to water loss at 80°C occurring at an earlier time than at 70°C, and water evaporation at a greater rate than at 70°C. It
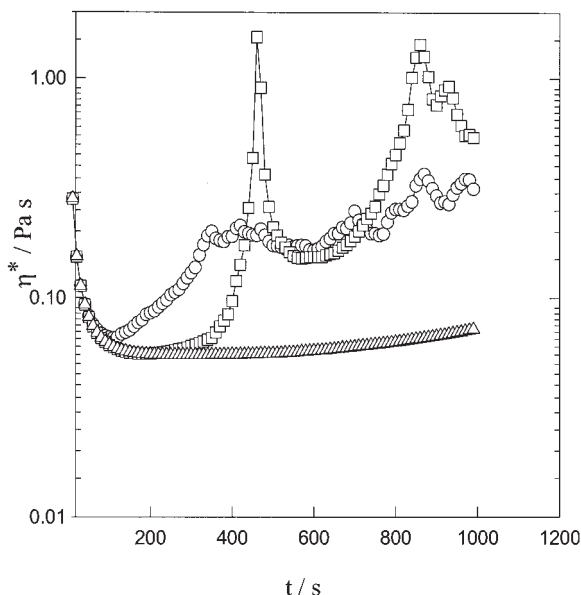
may be, in fact, that the variation of η^* with time at 80°C for times greater than about 300 s was strongly influenced by water loss and consequent reduction of the contact area and those data may not be reliable.

The dependence of gelation onset temperature on the relative proportions of the comonomers, for pregel solutions heated at a constant rate, is illustrated by the data compiled in Table II. The onset temperature was determined from the temperature variation of complex viscosity, as shown in Figure 1. It is interesting to note that gelation occurs at a much lower temperature and is consequently more facile when both NIPA and AMPS are present in the pregel solution, whereas in the absence of MBAA, the rate of conversion of AMPS/NIPA comonomer mixtures to copolymer is strongly dependent on comonomer composition and increases with the proportion of AMPS.[9] It seems, therefore, that reaction of AMPS with MBAA is not favored by the reactivity ratios for that comonomer pair.

Figure 5 Effect of reaction temperature on time dependence of complex viscosity for PEG/NIPA pregel solution with 50 wt % PEG based on NIPA and PEG. △, 60°C; □, 70°C; ○, 80°C. Oscillation mode at constant shear rate (10 s^{-1}) and 20% strain.

TABLE II
Dependence of Gelation Onset Temperature of Pregel Solutions on Comonomer Mixture Composition

AMPS (mol %)	0	12.0	26.7	45.0	68.6	100
$T_i(°C)^a$	83	20	13	21	25	103
$T_i(°C)^b$	83	25	17	50	54	104

[a] Copolymer pregel solutions.
[b] SIPN pregel solutions with 50 wt % PEG6000 based on total solids.
Solution composition (concentrations in mol L^{-1}): (AMPS+NIPA), 0.88; MBAA, 0.035; APS, 0.01. Rheometer used in constant stress (20 Pa) rotation mode; gels continuously heated at 7°C min^{-1}.

CONCLUSION

Rheometry has proved to be a very useful technique to study the kinetics of gel formation through determination of either the isothermal time dependence of complex viscosity or the temperature dependence of η^* when pregel is heated at a constant rate. The onset time or temperature for gel formation for pregel solutions with and without PEG is strongly dependent on comonomer proportions and varies to a lesser extent with the presence or absence of PEG. Copolymerization of AMPS with NIPA is inhibited by MBAA in AMPS rich comonomer mixtures.

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