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ARTICLE

Synthesis and gelation properties of poly(2-alkyl-2-oxazoline) based thermo-gels

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A series of new thermo-gelling polymers based on thermo-responsive poly(2-alkyl-2-oxazoline)s has been prepared by grafting different poly(2-alkyl-2-oxazolines) onto a polar carboxymethylcellulose backbone. Thermo-reversible gelation is observed at low concentrations (less than 5% by weight of thermo-gelling polymer). Rheology reveals that these polymers show tuneable gelation temperatures, which vary with concentration and poly(2-oxazoline) composition. This allows the gelation point to be adjusted to biologically relevant temperatures, offering a novel material with potential applications in areas such as drug delivery and tissue engineering.

Introduction

Polymer gels form an important class of systems in soft condensed matter. Many natural proteins and polysaccharides form physical gels, typically upon *decreasing* the temperature, examples of which include gelatin, pectin, agarose, agar and carrageenan¹. In contrast, synthetic thermo-gelling polymers may undergo a liquid-to-gel transition with *increasing* temperature and therefore have potential applications ranging, for example, from drug delivery² to tissue engineering³.

One of the features of a thermo-gelling polymer is the inclusion of thermo-responsive segments, which reversibly collapse as a result of a thermal stimulus⁴. These segments collapse into hydrophobic micro-domains at a cloud point temperature T_{cp} , which corresponds to a transition from a mono- to a bi-phasic system characterized by a lower critical solution temperature (LCST)⁵. The suspension becomes cross-linked and the hydrophilic component traps the solvent, usually water, within the gelled network as illustrated in Figure 1.

Several thermo-gelling materials have been reported including poly(esters)⁶, Pluronic® derivatives⁴, poly(amides)⁷ and poly(acrylamides)^{8–10}. In particular, poly(acrylamide) thermo-gels have acquired significant attention. These utilize poly(*N*-isopropyl-acrylamide) (PNiPAAM), a commonly used thermo-gelling polymer which displays an LCST of 32 °C, within the range required for biological applications². There are however two significant drawbacks with PNiPAAM. Firstly, strong hysteresis arises from intramolecular hydrogen bonds that are formed within the polymer above its LCST as a result of the hydrogen donor/acceptor properties of PNiPAAM¹¹. Secondly,

the corresponding monomer is suspected to be a carcinogen, hindering the polymer's acceptance for biological applications¹². This has stimulated research into potentially safer alternatives.

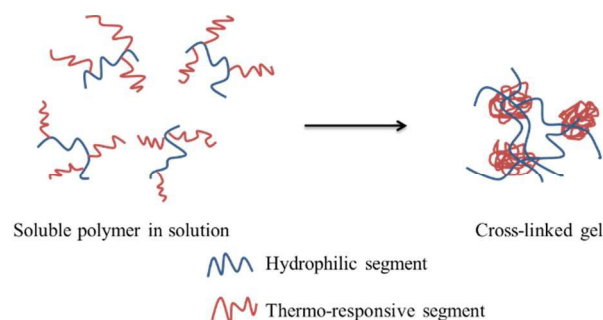


Figure 1. Illustration of the thermo-gelling mechanism for brush polymers

In our study we focus on poly(2-oxazolines). These are synthesized via a cationic ring opening polymerization which allows polymers with a narrow polydispersity index (PDI) to be prepared. In addition, it provides a convenient route for controlling end-group functionality through careful design of the initiator and terminator¹³, see Figure 2. One poly(2-oxazoline) of considerable interest is poly(2-isopropyl-2-oxazoline) (PiPrOx), which has an LCST of 36°C¹⁴, similar to that of PNiPAAM. Other poly(2-oxazolines) displaying thermo-responsive behaviour include poly(2-ethyl-2-oxazoline) (PEtOx) and poly(2-*n*-propyl-2-oxazoline) (PnPrOx), which have an LCST of 65°C and 24°C, respectively^{15,16}. The LCST can further be tuned *via* co-polymerization with more

hydrophilic or hydrophobic monomers which affects the T_{cp} . For example, co-polymerization of *i*PrOx with the more hydrophilic EtOx will increase the T_{cp} , whereas this can be reduced through the use of the more hydrophobic 2-butyl-2-oxazoline (*n*BuOx)¹⁷. The tunable nature of a poly(2-oxazoline)'s cloud point temperature, coupled with the inherent control of the side-chain length and of its end groups makes poly(2-oxazoline)s potentially useful biocompatible polymers¹⁸.

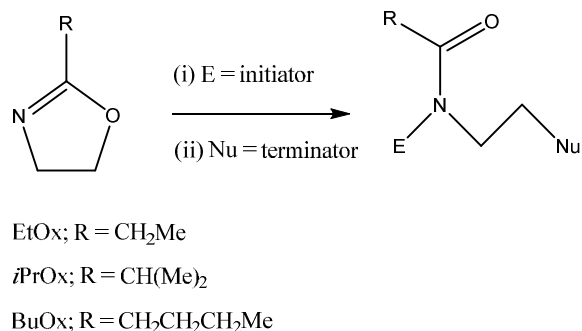


Figure 2. Monomers and their corresponding polymeric oxazolines prepared in this work

In the present investigation we have used PiPrOx as the basis for our thermo-responsive component. It has previously been grafted onto polysaccharides in order to investigate their self-assembly and crystallization, but no thermo-gelling behaviour was reported²⁰. Given the control over the cloud point temperature of PiPrOx we anticipated that this would allow tuning of the gelation temperature of a PiPrOx-based thermo-gelling polymer.

For the hydrophilic component of the thermo-gelling polymers we have used the cellulose derivative carboxymethylcellulose (CMC), which has been shown previously to create thermo-gelling polymers in conjunction with PNiPAAM^{9,19}. Cellulose and its derivatives are commercially available, cheap, and biocompatible, making them ideal candidates for inclusion in biologically useful materials. CMC in particular is biocompatible and is commonly used as a food additive and in eye drops, which makes it a convenient candidate for the

hydrophilic component.

In this paper we first discuss the synthetic approach used to prepare a thermo-gelling polymer based on PiPrOx coupled to CMC, report its characterization, and demonstrate that it displays a tunable gelation at biologically relevant temperatures over the range of 20–37 °C. We then investigate the gelation behaviour of this class of thermo-gels by means of rheology, in order to assess their potential use as biological materials.

Results and Discussion

Synthesis

Carboxymethylcellulose is a commercially available derivative of cellulose in which the backbone has been functionalized with carboxylic acid groups. This provides a convenient route for attachment of the poly(2-alkyl-2-oxazoline) arms while keeping the backbone highly hydrophilic, an important prerequisite for creating a gelling polymer.

It has been shown previously that using an excess of dicarboxylic acid results in the polymer chain being terminated, whilst also providing a residual carboxylic acid unit at the terminal end of the polymer²¹. In a similar manner we have found that use of excess 1,3-diaminopropane resulted in an amine-terminated polymer chain (Figure 3). This has the potential to link polymer chains together, however, we did not observe any evidence for this in the gel permeation chromatography (GPC) traces. Whilst the presence of terminal amine was undetectable by NMR or IR, its presence was inferred by the Kaiser test. This showed a positive blue color when used with these polymers, which indicates the presence of a primary amine.

Table 1. Thermo-responsive amine-terminated poly(2-alkyl-2-oxazoline)s

Polymer	Butyl ^a (% Mol)	Mw ^b (g/mol)	Mn ^b (g/mol)	PDI	T_{cp} ^c (°C)
PiPrOx	0	44.42.2	39.85	1.11	38.5
PiPrOx- <i>n</i> BuOx	33	42.24	35.21	1.19	14.17

^a NMR, ^b GPC (Chloroform:Methanol, 3:1, 2 mM LiBr), ^c Determined using fluorescent spectroscopy (4mg ml⁻¹ in phosphate buffer saline).

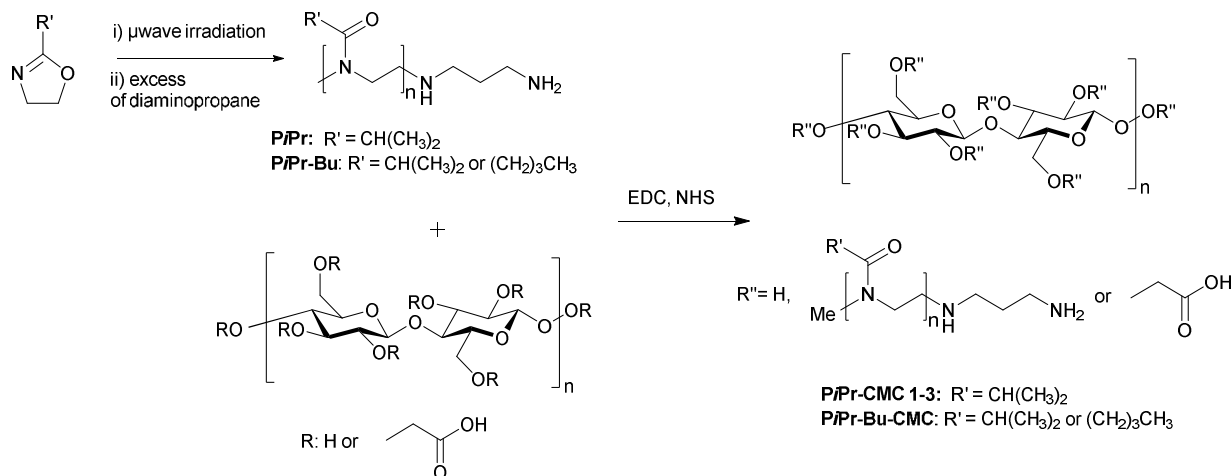


Figure 3. Synthetic approach used to synthesize thermo-gelling polymers.

We chose two poly(2-alkyl-2-oxazoline) arms, poly(2-isopropyl-2-oxazoline) PiPrOx and poly(2-isopropyl-2-oxazoline)-co-(2-*n*-butyl-2-oxazoline) PiPrOx-*n*BuOx (Table 1). We anticipated that the T_{cp} of PiPrOx would be increased by coupling it to the more polar CMC. We therefore explored the behaviour of the co-polymer PiPrOx-*n*BuOx, since it has previously been shown that the inclusion of 2-butyl-2-oxazoline dramatically reduces the T_{cp} . This brings the behaviour of the thermo-gelling polymer into a range suitable for biological applications. However, 2-isopropyl-2-oxazoline and 2-*n*-butyl-2-oxazoline have different reactivity and so a gradient polymer would be expected, in which the butyl oxazoline is the more reactive component¹⁷.

A cross-coupling reaction then allowed the poly(2-alkyl-2-oxazoline)s to be grafted onto the CMC backbone under mild conditions in water as depicted in Figure 3, using a modified procedure based on previous work in the literature^{9,19}. This allowed the reaction to proceed under cold, aqueous conditions (*i.e.* below the T_{cp}), an important consideration as carboxymethylcellulose is insoluble in other less polar solvents. As previously reported for similar reactions^{9,19} the efficiency of the coupling reaction proved to be poor, as indicated by the small percentage of nitrogen in the elemental analysis. This arises from: slowing of the reaction at low temperatures; the poor stability of the coupling agent, which is only stable for a short period of time in water; and the effect of pH limiting the efficiency of the coupling activation of the carboxylic acids which proceeds best at *ca.* pH 5.5.

We have explored the grafting of four polymer compositions onto CMC (Table 2). In addition to PiPrOx-*n*BuOx-CMC, three simpler polymers were synthesized: PiPrOx-CMC-1, PiPrOx-CMC-2 and PiPrOx-CMC-3 (with the proportion of PiPrOx decreasing from 1 to 3); see the Experimental section at the end for details. The gelation properties of each of these were investigated.

Table 2: Thermo-gelling polymers synthesized (full details in the Experimental section)

Thermo-gel	Gelation temperature (°C) ^a
PiPrOx-CMC-1	49
PiPrOx-CMC-2	58
PiPrOx-CMC-3	No gelation
PiPrOx- <i>n</i> BuOx-CMC	29

^a Determined using 4% w/w in phosphate buffer saline.

Gelation behaviour

The gelation of the materials was initially confirmed by visual inspection. The solution containing the thermo-gel became opaque and no longer flowed above the polymer's gelation temperature (Figure 4).

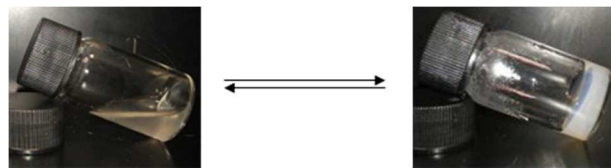


Figure 4. Visual confirmation of thermo-gelling behaviour of PiPrOx-*n*BuOx-CMC (4% by weight in phosphate buffer saline), below the gelation temperature 29 °C (left) and above 37 °C (right).

We performed rheology on each of these samples. A typical temperature-ramp for PiPrOx-*n*BuOx-CMC is shown in Figure 5. Both G' and G'' were monitored over a temperature range between 10 and 40 °C. We defined the gelation temperature as the crossover point of G' and G'' upon heating (Figure 5), *i.e.* the point at which the material begins to behave more like a solid than a liquid.

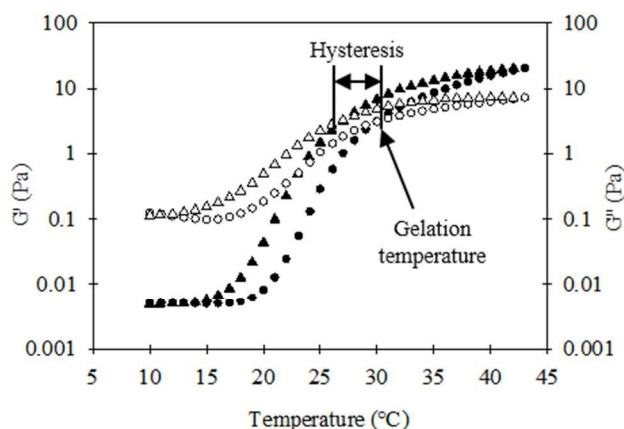


Figure 5. Thermo-reversible gelation of PiPrOx-*n*BOxu-CMC (4% w/w, PBS) at pH = 3, Heating ● (open G'' , closed G'), Cooling ▲ (open G'' , closed G').

Initially both G' and G'' were observed to decrease slightly as the viscosity of the solvent decreased with increasing temperature. Both parameters then increased and subsequently crossed over as the material gelled. Upon cooling a slight hysteresis was observed at the crossover point. This hysteresis is the result of a kinetic phenomenon in which the polymers resist disentanglement, usually resulting from the formation of hydrogen bonds upon gelation. This stabilizes the gel at lower temperatures and is also observed in analogous PNIPAAm thermo-gelling polymers²².

We measured the gelation temperature of the three PiPrOx-CMC samples. For PiPrOx-CMC-1 and PiPrOx-CMC-2 this was found to increase as the amount of poly(2-oxazoline) present decreased. As anticipated, the gelation temperature in these samples was too high to be suitable for biological applications. Polymer PiPrOx-CMC-3, which contained the

lowest proportion of *PiPrOx*, did not gel within the temperature range or concentration tested. Different concentrations were not considered for *PiPrOx*-CMC-1 to 3. However, by replacing *PiPrOx* with *PiPrOx-nBuOx*, the gelation temperature of the resulting thermo-gelling polymer was successfully lowered to 29 °C, a value within the range required for biological applications. In view of this, we investigated its gelation properties further.

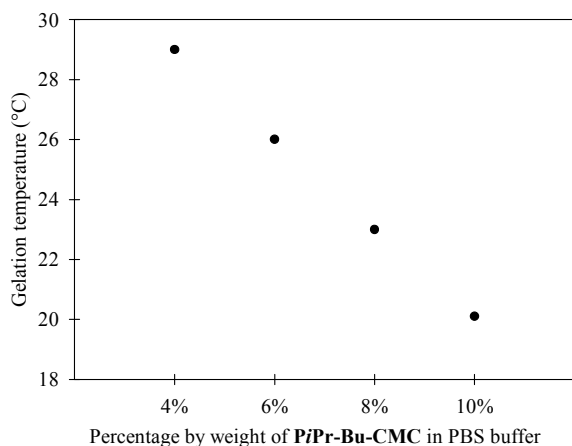


Figure 6. Gelation temperature (●) of *PiPrOx-nBuOx*-CMC in PBS at different concentrations at pH = 3.

We first studied the effect of concentration on the gelation temperature. Above 10% by weight in phosphate buffer saline (PBS), high viscosities were observed as a result of the high molecular weight of *PiPrOx-nBuOx*-CMC. Using elemental analysis and the predetermined molecular weight of the precursor polymers, the molecular weight was estimated to be *ca.* 240 g/mol. We deemed solutions containing greater than 10% polymer to be unsuitable for biological applications, because of their high viscosity and poor economic use of

material.

A linear decrease in the gelation temperature was observed as the percentage by weight of thermo-gelling polymer increased (Figure 6). We also observed that G' increased as a function of polymer concentration, illustrating that the higher concentration gels display more solid-like behaviour. Gelation was not observed for the 2% sample of *PiPrOx-nBuOx*-CMC; this could be because this sample's composition is below the critical concentration required for the oxazoline arms to crosslink, an effect similar to that seen for *PiPrOx*-CMC-3.

We observed a change of 1.5°C per percentage by weight of the gelation temperature and, by accurately controlling the concentration, we have demonstrated that it can potentially be tuned within a biologically relevant range.

We then investigated the stability of *PiPrOx-nBuOx*-CMC at two different pH values because of the known pH-sensitivity of carboxymethylcellulose-based thermo-gels. We decided to test this behaviour at an acidic pH around the natural pH of the gel dissolved in solution (*ca.* pH 3), and at that of the biologically relevant PBS (pH 7). We found that the gelation temperature was similar at both pH values (Figure 7).

The long-term stability of the gels is important as applications involving cell culturing or injectable materials require the gelled state to be maintained for extended periods of time. Degradation of similar polymers has been shown in previous work to occur *via* amide-bond hydrolysis between the thermo-responsive arms and the CMC backbone⁹. By holding the gel above its gelation temperature for different durations we can study whether the present polymer degrades. In this study a period of up to two weeks was chosen as being suitable for potential biological applications (Figure 7).

At both pH 3 and 7 we observed a change in both gelation temperature and G' over time. As the samples were held for

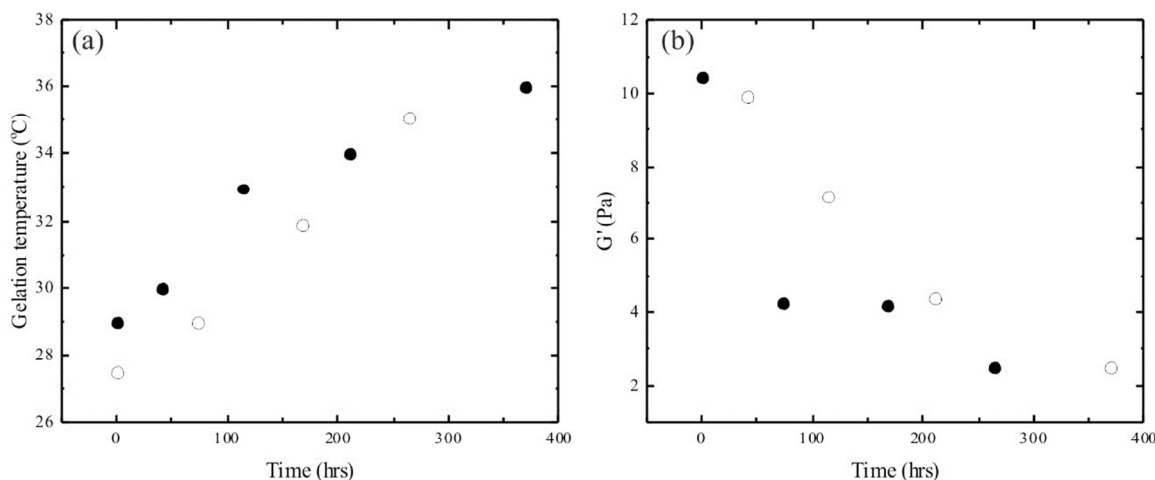


Figure 7. Time dependent degradation of *PiPrOx-nBuOx*-CMC (4% w/w). Change in gelation temperature (a) and G' (b) at 37 °C, for pH 7 (○) and pH 3 (●).

longer periods of time, the gelation temperature increased and G' decreased (Figure 7). This is consistent with the expected breakdown of the polymer. If the thermo-gels are degrading, we expect both the gelation temperature to increase and the gels to lose their mechanical strength, in a manner analogous to the concentration dependence observed previously. Although degradation occurs, it appears to be a slow process. In the time frame investigated here *PiPrOx-nBuOx-CMC* remained gelled and mechanically stable at 37 °C after two weeks. No appreciable difference in the degradation behaviour of *PiPrOx-nBuOx-CMC* was observed at pH 7 or pH 3. It is worth noting that for similar CMC-based PNIPAAm thermo-gelling polymers degradation occurs at a much faster rate⁹.

The behaviour of one sample of *PiPrOx-nBuOx-CMC* at pH 12 (4% w/w) was briefly investigated. At this value we observed an increase in gelation temperature from 29 °C to 47 °C. This was attributable to deprotonation of the carboxylic acid groups at pH 12 which results in repulsion between the cellulose units, thereby inhibiting gelation and entanglement.

Conclusion

We have synthesized several novel poly(2-alkyl-2-oxazoline) thermo-gelling brush polymers based on a cellulose backbone functionalized with thermo-responsive *PiPrOx-co-nBuOx* arms. We have demonstrated control over the gelation temperature and the visco-elastic properties of these materials by varying the concentration and the composition of the oxazoline arms. We have shown that these polymers are pH sensitive, particularly at pH values higher than 7, but less so at lower pH values. We have investigated the stability of the gel over prolonged periods of time and, although we have observed slight degradation, these materials remain gelled at 37 °C over a period of two weeks. These poly(2-alkyl-2-oxazoline) thermo-gels could potentially provide a useful alternative to more established thermo-gelling polymers, because of the accurate, but simple tuning of their gelation temperature around a range suitable for biological applications.

Experimental section

Materials

Commercially available compounds and solvents were obtained from Sigma-Aldrich or Fisher Scientific and were used as supplied without further purification. 2-Isopropyl-2-oxazoline and 2-*n*-butyl-2-oxazoline were synthesized according to literature procedures²³. The monomers and acetonitrile were freshly distilled over calcium hydride prior to use. Microwave reactions were performed using a CEM discover microwave reactor equipped with an autoloader and polymerization conditions were taken from published literature²⁴. This was connected to a PC running CEM Discover software. The T_{cp} of the thermo-responsive arms was determined by turbidimetry, the T_{cp} was defined as a 10% decrease in transmittance. pH

measurements were undertaken by dissolving the thermo-gelling polymers in the relevant buffer solution. Rheology measurements were performed using a TA Instruments AR-G2 stress-controlled rheometer with a temperature-controlled Peltier lower plate, and a 60mm plate geometry. A solvent trap was fitted to prevent evaporation of water from the samples. All rheological measurements were undertaken in phosphate buffer solution (PBS) at 4% w/v unless specified.

Methods

Synthesis of amine-capped poly(2-isopropyl-2-oxazoline), (*PiPr*)

Two solutions containing respectively 2-isopropyl-2-oxazoline (1 mL, 8.3 mmol) and methyl *p*-toluenesulfonate (3.2 μ L, 0.021 mmol), in acetonitrile (2 mL) were prepared and were added to microwave vials. Each vial was subjected to microwave irradiation for 15 minutes (temperature: 135 °C; pressure: 130 psi). Triethylamine (10 μ L) and 1,3-diaminopropane (100 μ L, 1.2 mmol, 57 times excess) were then added and the solutions were heated to 60 °C for a further 18 hours. The samples were then combined and dialysed (14 kDa cutoff) for 3 days in deionised water. The water was changed twice per day. Finally the samples were lyophilized to yield amine end-capped poly(2-isopropyl-2-oxazoline) (*PiPr*), 91% yield. ¹H NMR (CDCl₃, δ /ppm): 1.05 (br s, 6H), 2.75 (br s, 1H), 3.40 (br s, 4H).

Synthesis of amine-capped poly(2-isopropyl-2-oxazoline)-co-(2-butyl-2-oxazoline), (*PiPr-Bu*)

To prevent batch variation, a stock solution containing 2-isopropyl-2-oxazoline (4.1 mL, 37.11 mmol), 2-*n*-butyl-2-oxazoline (2 mL 15.6 mmol) and methyl *p*-toluenesulfonate (52 μ L, 0.23 mmol), in acetonitrile (12 mL) was prepared and 3 mL of the stock solution was added to each of five microwave vials. Each vial was then subjected to microwave irradiation for 15 minutes (temperature: 135 °C; pressure: 130 psi). Triethylamine (10 μ L) and 1,3-diaminopropane (100 μ L, 1.2 mmol, 26 times excess) were then added to each solution and the solutions were heated to 60 °C for 18 hours. The resulting samples were combined and dialysed (14 kDa cutoff) for 3 days in methanol, the methanol being changed twice per day. The samples were then concentrated under vacuum yielding amine end-capped poly(2-isopropyl-2-oxazoline)-co-(2-*n*-butyl-2-oxazoline) as a powder (*PiPr-Bu*), 86% yield. ¹H NMR (CDCl₃, δ /ppm) 0.85 (br s, 9H), 1.04 (br s, 25H), 1.27 (br s, 5H), 1.52 (br s, 5H), 2.26 (br m, 4H), 2.70 (br s, 5H), 3.40 (br s, 24H).

Generic coupling reaction

Carboxymethylcellulose (50 mg, av. mw 90000) was dissolved in distilled water (5 mL). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (50 mg) and *N*-hydroxysuccinimide (25mg) were added to the resulting solution and this was then stirred overnight. The relevant amount of amine-capped poly(2-oxazoline) pre-dissolved in ice cold phosphate buffered saline (PBS) (approx. 5 mL) was added and the solution was stirred at 2 °C overnight. It was then lyophilized and the powder was stirred for one hour in a large excess of methanol (ca. 100 mL). The precipitate was centrifuged, washed twice with methanol, and dried under vacuum to yield a sample of thermo-gelling polymer. The

polymer was characterized using elemental analysis. The following amounts of poly(2-oxazoline) were used; **PiPr-CMC-1** (1 g), **PiPr-CMC-2** (0.5 g), **PiPr-CMC-3** (0.15 g) and **PiPr-Bu-CMC** (1.5 g). Elemental analysis (%): **PiPr-CMC-1** (C, 46.36, H, 7.17, N 4.98), **PiPr-CMC-2** (C, 44.16, H, 6.53, N 4.12), **PiPr-CMC-3** (C, 43.92, H, 6.71, N 3.98) and **PiPr-Bu-CMC** (C, 45.47, H, 7.53, N 5.15).

Rheological characterization

A TA AR-G2 rheometer was used to determine the viscoelastic properties of the samples. Oscillatory tests were performed in order to find the storage (elastic response) and loss (viscous response) moduli, G' and G'' respectively, which together describe the viscoelasticity of the sample. A material is classified as solid-like when $G' > G''$. A material is classified as liquid-like when $G'' > G'$, in which case a thermo-gel is below its gelation point and hence behaves like a liquid. To quantify the thermo-reversible properties of the thermo-gels G' and G'' were measured as a function of temperature, keeping the frequency and amplitude of the oscillation constant. All experiments were performed at a frequency of 5 rad/s and within the linear viscoelastic region (LVR). To this end oscillatory stress sweeps were first performed for each sample at the lowest temperature measured. Stresses were scanned between 0.1 and 100 Pa, and 10 Pa was found to be in the center of the LVR for all samples. Therefore all subsequent measurements were performed at a stress of 10 Pa.

The storage and loss moduli (G' and G'') were measured for a temperature range of 10 - 40 °C (heating cycle), and then from 40 - 10 °C (cooling cycle) in steps of 1 °C min⁻¹. At each temperature, the time dependence of G' and G'' was checked and found to remain unchanged over a period of one minute.

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Notes and references

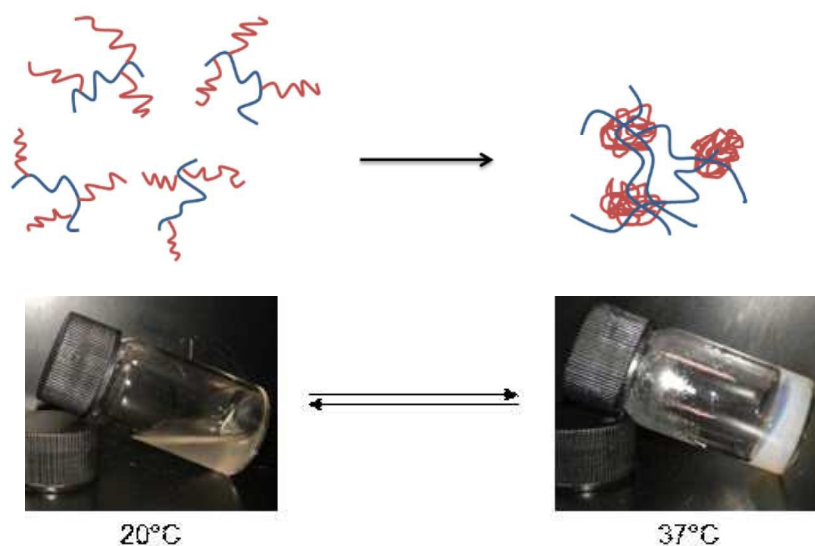
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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [GPC results and T_{cp} for **PiPr** and **PiPr-Bu**]. See DOI: 10.1039/b000000x/

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