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Synthesis of Poly(*N*-isopropylacrylamide) Hydrogels by Radiation Polymerization and Cross-Linking

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Poly(*N*-isopropylacrylamide) [poly(NIPAAm)] shows a typical thermal reversibility of phase transition in aqueous solutions. That is, it precipitates from solution above a critical temperature called the lower critical solution temperature (LCST) and dissolves below this temperature. When it is cross-linked, the obtained hydrogel collapses above LCST, while it swells and expands below LCST.[1,2] This hydrogel has received much attention recently and has been used as a model system to demonstrate the validity of theories describing the coil–globule transition,[3] swelling of networks,[4] and folding and unfolding of biopolymers. It has also been proposed for various applications ranging from controlled drug delivery[5] to solute separation.[6]

Poly(NIPAAm) hydrogel is usually synthesized at room temperature from an aqueous solution of the monomer by using a redox initiator composed of ammonium persulfate and *N,N,N′,N′*-tetramethylethylenediamine in the presence of *N,N′*-methylenebisacrylamide as a cross-linker.[1–9] Since the LCST of poly(NIPAAm) is around 32 °C, the polymerization at room temperature proceeds in a homogeneous solution. Recently, poly(NIPAAm) hydrogels were synthesized by starting the polymerization below the LCST and then elevating the temperature above it, by which method macroporous gels with fast temperature response were obtained.[8,9]

Our idea is to apply a radiation-induced polymerization method for the synthesis of poly(NIPAAm) hydrogels. This method offers unique advantages for synthesis:[10] it is a simple and additive-free process at all temperatures, and the degree of cross-linking can be easily controlled by irradiation conditions. Therefore, radiation methods are especially attractive for the synthesis of hydrogels with potential biomedical application where the residual chemical initiators (usually highly toxic materials) may contaminate the product. By this method, it is possible to combine into one step the synthesis and sterilization of the product, and it is economically competitive when compared to conventional methods.[11] Although certain monomers and polymers require for cross-linking either relatively high radiation doses[12] or the presence of a small amount of multifunctional monomer (to act as cross-linker), in the case of poly(NIPAAm) no additive is necessary to get hydrogel with good mechanical properties at relatively low doses. To our knowledge, this work is the first report about the synthesis of poly(NIPAAm) gels without any additives.

In the present work, 10% w/w aqueous solutions of NIPAAm (Eastman Kodak) were prepared in glass tubes with 3-mm inner diameters. All irradiations were carried out under a nitrogen atmosphere at 25 °C with a ^{60}Co γ source with doses up to 200 kGy at a dose rate of 1 kGy/h. After the polymerization the gels were removed from the tubes and washed in distilled–deionized water for 3 weeks. The swelling of the gels was determined gravimetrically after 24 h of equilibration in water at each predetermined temperature. The swelling was defined as a weight ratio of the swollen sample to the dried one. All measurements were carried out in triplicate. The reproducibility was better than 10% in all cases. The gel fraction was measured after Soxhlet-type extraction in ethanol for 24 h and drying the extracted gel in vacuum to constant weight. The gel percentage was calculated from the weight ratio of the ethanol-insoluble fraction and the feed monomer. The sol fraction was calculated by subtracting the gel percentage from 100.

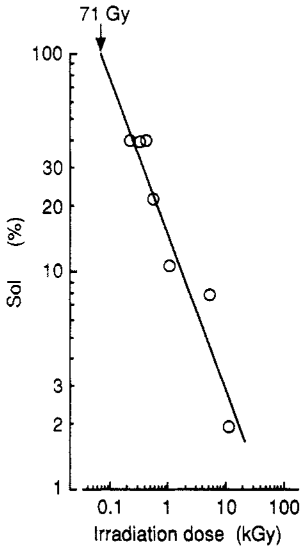

Figure 1. Logarithmic relationship of soluble fractions as a function of the dose for 10% w/w aqueous solutions of NIPAAm.

The gel dose (D_g, dose for incipient gel formation) can be determined by plotting the sol fraction (s) as a function of the irradiation dose (D) on a log–log scale[13] and then extrapolating the resulting straight line to $s = 100\%$. In Figure 1 we show this relationship for the 10% w/w NIPAAm solution, where the gel dose is obtained as 71 Gy. Comparing this gel dose with the doses for other polymers, it is quite low. The reason for this low value might be due to the role played by the radicals formed in the radiolysis of water. It has been reported that, in the case of *N*-vinylpyrrolidone, the introduction of water to the binary mixture of the monomer and cross-linker significantly reduces the gelation dose.[12] When an aqueous solution of a monomer is irradiated, monomeric radicals are generated by both the direct effect of radiation and the indirect effect based on the reaction of the products of water radiolysis with the monomer.[14] The total yield of the reactive intermediates formed in the radiolysis of water (e^-_{aq}, $H^\bullet$, and $OH^\bullet$) is about 6.[15] Some of those intermediates will form radicals on the monomer, while others will undergo recombination or other reactions. If we denote the intermediates by $R^\bullet$ and the monomer by M, the radical formation by the indirect effect may be expressed as:

$$M + R^\bullet = M^\bullet + RH \qquad (1)$$

$$M + R^\bullet = RM^\bullet \qquad (2)$$

According to the literature,[16,17] the monomeric radical which is most probably responsible for the initiation of

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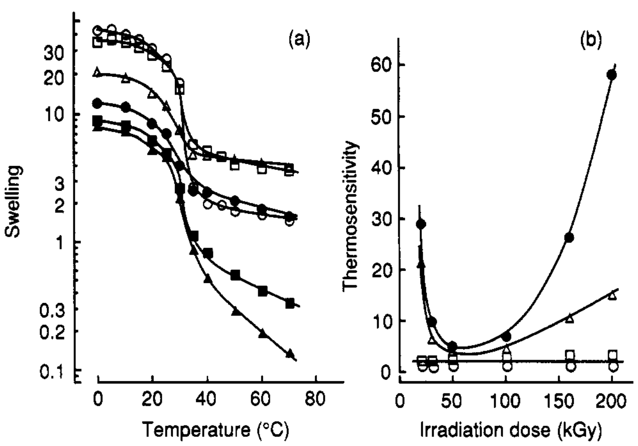
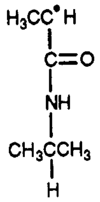


Figure 2. Swelling characteristics of poly(NIPAAm) gels cross-linked during the radiation-induced polymerization of a 10% w/w aqueous solution of NIPAAm. The points represent the average from the measurements of three different samples, and the maximum errors are ± 5% below and ±2% above the LCST. (a) Temperature dependence of the swelling for gels obtained by irradiating up to 20 (○), 30 (□), 50 (△), 100 (●), 160 (■), and 200 kGy (▲). (b) Thermosensitivity (W_0/W_t) of gels as a function of irradiation dose, where "thermosensitivity" is defined as the ratio of swelling of the gel at 0 °C (W_0) and at temperatures (W_t) 20 (○), 30 (□), 40 (△), and 70 °C (●).

the polymerization and cross-linking is the α-carboxyl alkyl radical:



$$\begin{array}{c} H_3CC^{\bullet}H \\ | \\ C{=}O \\ | \\ NH \\ | \\ CH_3CCH_3 \\ | \\ H \end{array}$$

This radical could be formed both by the direct radiation effect and by reaction with OH$^{\bullet}$ radicals. Besides this carboxyl alkyl radical, an isopropyl radical is also produced, based on the indirect effect of radiation, by a hydrogen abstraction on the side chain. But we found that this radical is stable[18] and less likely to participate in the polymerization and cross-linking reactions.

After these processes, monomer radicals combine to form a linear or slightly branched, but soluble, polymer (sol fraction) until the dose reaches the gel point. Once the gel point is reached (at dose = D_g), the amount of gel grows rapidly due to propagation of gel radicals with monomers and recombination of sol–gel radicals.[19]

The details of radical formation and the mechanism of polymerization and cross-linking will be reported later.

In Figure 2 the swelling of the poly(NIPAAm) gels is plotted as a function of temperature for radiation doses ranging between 20 and 200 kGy. With the doses less than 20 kGy, the gels had insufficient mechanical strength required for the swelling experiment.

It has been suggested that LCST behavior is caused by a critical balance of hydrophobic and hydrophilic groups in the polymer side chain.[2,19] At low temperature the strong hydrogen bonding between such hydrophilic groups as NH and C=O and surrounding water[20] will cause the formation of a highly organized water layer[21] around the polymer chains. Thermodynamically, the formation of this structured water contributes to the enthalpy of mixing which outweighs the unfavorable free energy related to the exposure of hydrophobic isopropyl groups of the side chain to water.[2,22-24] The hydrogel will be in a highly swollen state. With increasing temperature the hydrogen bonding weakens, which leads to a reduction in the structuring of water around the hydrophobic groups. As this structured water is released, the interactions between hydrophobic side groups of the polymer increase. At LCST, which is around 32 °C in the present case, these hydrophobic interactions become dominant, which from the thermodynamic point of view means that the entropic term becomes dominant and the free energy of mixing takes a positive value.[23] This will lead to a collapse of the poly(NIPAAm) gel. Recently published DSC investigations support this general observation.[24]

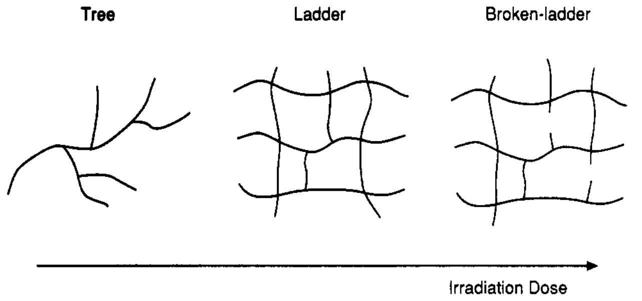


Figure 3. Hypothetical sketch of the poly(NIPAAm) gel structure as it changes with irradiation dose from tree to broken ladder.

Besides the temperature-dependent swelling of poly(NIPPAm) gels, Figure 2 shows an interesting effect of the irradiation dose on the swelling of the gels. Although the swelling of the lightly cross-linked gels is larger than that of the highly cross-linked ones in the case of chemically cross-linked gels, the shrinking is not so different. In our case, on the other hand, the gels synthesized with low doses swell highly but do not collapse to the same degree as the gels synthesized with higher doses. In Figure 2b we plotted the gel "thermosensitivity", defined as a ratio of the swelling at two temperatures, for gels obtained with different irradiation doses. We see that above LCST this thermosensitivity shows a minimum for the gels synthesized with doses around 50 kGy. Our hypothesis is that this effect reflects the microscopial structure of the gel network, which itself changes with dose. We propose the following picture: in the beginning of polymerization with low doses, the network consists of polymer chains united through multifunctional junctions with no or very few closed cycles, thus forming giant molecules with branches and entanglements. This structure would be somewhat similar to Flory's acyclic tree[25] (Figure 3). When the gel swells below LCST, the polymer chains tend to go as far as possible from each other. The swollen coils will exclude one another from the volume defined by their radius of gyration. With increasing dose, the open cycles would close and the fraction of the real network, which we call the ladder structure, would increase. In the ladder the chains are forced together by their cross-link points and will overlap somewhat. The higher the fraction of the ladder over the tree structure, the lower the flexibility of the chains. That means also a lower thermosensitivity. With a higher irradiation dose, the thermosensitivity increases again as shown in Figure 2b. Such a phenomenon has not yet been reported. We can explain it by radiation-induced degradation of the previously formed ladder structure. This degradation will lead to the network structure which we call "broken ladder". This change in the network structure affects only the shrinking of the gel, since the number of real junctions remains unchanged. Above LCST the flexibility of the chains near the breaking point increases and facilitates the hydrophobic interactions between chains.

In conclusion, we have synthesized poly(NIPAAm) hydrogels by a new method of radiation-induced simultaneous polymerization and cross-linking of an aqueous solution of the monomer without any additive. Below LCST, the gels synthesized by lower doses swell to a higher extent than the more cross-linked gels. Above LCST, the swelling percentage increased until about 50 kGy and then decreased with an increase in the dose. We think that the microscopical structure of the gel, which changes from tree to ladder and further on to broken ladder with increasing dose, is responsible for this behavior.

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