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Preparation and Characterization of Photo-Cross-Linked Thermosensitive PNIPAAm Nanogels

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ABSTRACT: Thermosensitive nanogels were prepared from photo-cross-linkable copolymers of *N*-isopropylacrylamide (NIPAAm) and 2-dimethylmaleinimido ethylacrylamide (DMIAAm). The colloidal nanogels were formed by UV-irradiated solutions of thermosensitive polymers in water at 45 °C. The size of nanogels could be controlled by the concentration of photopolymer solutions, the amount of chromophore DMIAAm in the photopolymer chains, and sodium dodecyl sulfate (SDS) concentrations. Analytical ultracentrifugation could reveal the degree of swelling of the different nanogel preparations, confirming the data from dynamic light scattering. In addition, the quantitative determination of un-cross-linked polymer species was possible. Even the determination of the degree of swelling distribution was reported for a nanogel for the first time. Hydrogel particles could be prepared with low SDS concentration or even in the absence of a surfactant. Therefore, the effects on swelling produced by the addition of alcohols to these nanogels could be investigated, excluding the influence of SDS on the swelling behavior of these nanogels.

Introduction

Poly(*N*-isopropylacrylamide) (PNIPAAm) nanogels can exhibit dramatic and reversible changes in volume and hydrophobic−hydrophilic properties upon heating between 30 and 35 °C in aqueous media. These submicrometer-sized particles have recently attracted considerable attention from the scientific community. They have been used in various fields of life science and technology, such as in controlled drug delivery systems, in enzyme and cell immobilization, and in separation technology.[1−5]

Until recently, PNIPAAm nanogels have been traditionally prepared by emulsion or precipitation polymerization. In a typical emulsion polymerization *N*-isopropylacrylamide (NIPAAm) as monomer, potassium persulfate as initiator, sodium dodecyl sulfate (SDS) as surfactant, and *N,N′*-methylenebis(acrylamide) (BIS) as cross-linker have been used to prepare PNIPAAm latices.[6−11] Various colloidal nanogels with different compositions and structures have been tailor-made by similar procedures.[12−16]

However, nanogels obtained by these conventional methods show inhomogeneous cross-linking densities; i.e., each particle has a gradient in its cross-linking density. It has been shown in kinetic studies that BIS was consumed more rapidly than NIPAAm.[9] The values for the ratio of the nanogel radius of gyration to its hydrodynamic radius were in the range 0.3−0.6 as determined by light scattering. This supports the hypothesis about the structure of a nanogel particle having a dense cross-linked core with dangling PNIPAAm chains at the periphery.[17,18] The use of a surfactant is also necessary in traditional methods to stabilize the system during the reaction. However, the presence of surfactants, such as SDS, influences the properties of the resulting nanogels. For example, it increases the phase transition temperature and affects the swellability of the temperature-sensitive microgels. In addition, it is not simple to prepare functional nanogels with complex morphologies by traditional methods.

In previous publications we reported the development of a novel method to synthesize sensitive nanogels via photo-cross-linking reactions.[19−21] This method can overcome the above-mentioned limitations. The principle of this method is based on the phase transition phenomena of temperature-sensitive polymers in combination with photochemistry. At elevated temperatures the phase-separated structure of aqueous PNIPAAm copolymer solutions was fixed by UV irradiation. This new synthesis strategy offers a number of advantages. First, this method uses predefined polymers, the properties of which are already known. These properties include compositions, molecular weight, and thermal behavior of the polymers. Second, this method may produce sensitive nanogels with homogeneous cross-linking densities, since these nanogels are prepared from polymers with randomly distributed chromophores. Third, one can prepare the nanogels with or without the use of surfactant. This is particularly important, as in some cases such as investigations of the influence of additional solvents on the degree of swelling of sensitive nanogels, the presence of surfactant might significantly influence the results because surfactants themselves also interact strongly with nanogel particles via hydrophobic tails. Finally, it has been demonstrated that by the use of the photo-cross-linking method functional nanogels with more complex structures can be achieved.[20,21]

We have recently studied the influence of chromophore content, surfactant concentration, and irradiation time on the size of the nanogels prepared by the photo-cross-linking route.[19] The resultant nanogel particles were rather spherical and showed large changes in hydrodynamic diameters in the vicinity of the phase transition temperature (T_c). However, because of the cross-linking method, a relatively high cross-linker (chromophore) content had to be used resulting in a continuous phase transition. In the current work we describe the influence of polymer concentration on the particle size, the efficiency of the photo-

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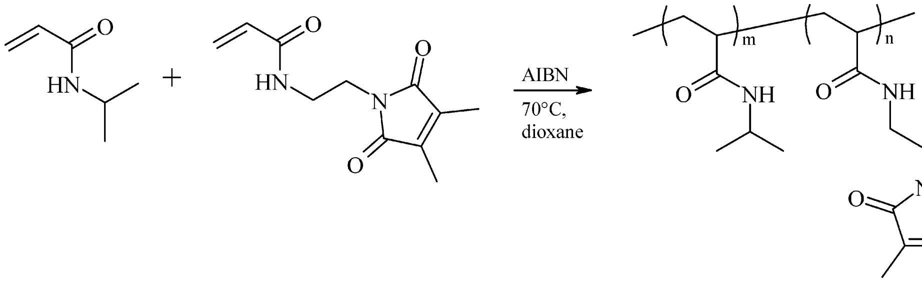
Scheme 1. Schematic Synthesis of Photo-Cross-Linkable Polymers



cross-linking reaction, and the degree of swelling of the nanogels in water and different water/alcohol mixtures using analytical ultracentrifugation and laser light scattering as the main analytical techniques.

Experimental Section

Materials. Diaminoethane (Fluka), dimethylmaleic anhydride (97%, Lancaster), acryloyl chloride (Merck), di-*tert*-butyl dicarbonate (97%, Acros), and sodium dodecyl sulfate (SDS) were used as received. *N*-Isopropylacrylamide (Merck) was recrystallized from distilled hexane, and 2,2′-azobis(isobutyronitrile) (AIBN) was recrystallized from methanol prior to use. All solvents were purified according to standard methods.

Synthesis of the Chromophore. 2-Dimethylmaleinimido ethylacrylamide (DMIAAm) was synthesized in four steps as described recently.[19,21]

Synthesis of Photo-Cross-Linkable Copolymers. The PNIPAAm homopolymer and copolymers were obtained by free radical polymerization of NIPAAm with DMIAAm initiated with AIBN at 70 °C in dioxane under nitrogen with a total monomer concentration of 0.55 mol L^{-1}. After required times the polymer was precipitated in diethyl ether, purified by reprecipitation from dioxane into diethyl ether, and finally dried in a vacuum for 24 h.

Preparation of Nanogels via Photo-Cross-Linking. Solutions of photopolymers with various concentrations and predetermined amounts of SDS in distilled water were prepared at room temperature. The mixtures were stirred to dissolve all solid components and then were filtered and left overnight before performing the next steps.

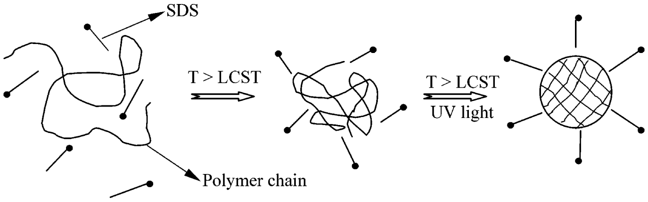
To synthesize the nanogels, the photopolymer solutions were heated to 45 °C while being stirred in a reactor. The concentration was 5 g L^{-1} unless otherwise stated. The solutions turned turbid within a few minutes, indicating the occurrence of a phase transition of the photopolymers. Under these conditions, copolymer chains aggregated to form particles. After 15 min at a temperature of 45 °C, the solutions were irradiated using a UV lamp (100 W, OSRAM GmbH Berlin-Munich). Samples were then drawn off at different irradiation times for characterization.

Photopolymer solutions and corresponding nanogels are abbreviated by their feed mole percentage of chromophore (5 and 10), SDS concentration (0 for 0.000 mmol L^{-1} SDS, 1 for 0.085 mmol L^{-1} SDS, and 2 for 2.680 mmol L^{-1} SDS), and time of UV irradiation (0 to 60). 10−1−30, for instance, is the sample of nanogels from solution of photopolymer with 10 mol % feed chromophore composition, 0.085 mmol L^{-1} SDS, and 30 min UV irradiation.

Characterization. For dynamic laser light scattering (DLS) a 700 DLS spectrometer (Otsuka Electronics Co.) was used to determine the average hydrodynamic particle size at different temperatures. Approximately 2.5 mL of colloidal nanogels was transferred into a sample cell after being passed through a 4.5 μm filter. The data were taken with a He−Ne laser (632 nm wavelength) at an angle of 90° and at various temperatures (10−50 °C).

For static laser light scattering (SLS) a FICA 50 spectrometer with a He−Ne laser (632 nm wavelength) was used to determine the mean average radius of gyration of the nanogels. The data were taken at a temperature of 25 °C with angles varying from 15° to 145°.

Scheme 2. Formation of Colloidal Nanogels by Photo-Cross-Linking



Analytical ultracentrifugation (AUC) was performed on a Beckman Optima XL-I ultracentrifuge (Beckman Coulter, Palo Alto, CA), while simultaneously applying UV−vis absorption and Rayleigh interference optics. Sedimentation velocity experiments were performed at 25 and 40 °C. 380 μL of colloidal nanogels was used for each measurement. Distilled water was used as a reference sample.

Results and Discussion

Polymer Concentration. The PNIPAAm photopolymers were prepared as shown in Scheme 1.[19,22] These copolymers possessed a LCST behavior. This property could be used to prepare colloidal nanogels. At elevated temperatures the phase-separated structure of aqueous PNIPAAm copolymer solutions was fixed by UV irradiation (Scheme 2).

PNIPAAm nanogels were prepared from the same photopolymer solution (5 mol % DMIAAm in the feed composition) in distilled water with polymer concentrations of 0.1, 1, 5, and 10 g L^{-1}. After 60 min of UV irradiation the samples were diluted with water to a final concentration of 0.1 g L^{-1} for the DLS measurements.

The formation of PNIPAAm particles in aqueous solution is probably similar to particle formation following a nucleation mechanism in precipitation polymerization. The polymer particles with a diameter in the range of nanometers in water at 45 °C were then irradiated under UV light.

Figure 1 shows the influence of polymer concentration on the particle size of PNIPAAm nanogels. Within each state (swollen or shrunken), the average diameter of nanogel particles increased linearly with the cubed root of the total polymer concentration with an intercept, corresponding to zero-added polymer of 55 nm at 40 °C. According to Pelton et al., PNIPAAm particles smaller than this diameter are colloidally not stable.[23] This linear relationship implies that particle formation can be explained by homogeneous-coagulative nucleation. These observations are in excellent agreement with results reported by Pelton's research group, when they measured the particle sizes of PNIPAAm dispersions produced by heating solutions of linear PNIPAAm.[23] However, particle concentration increased linearly with polymer concentration (data not shown).

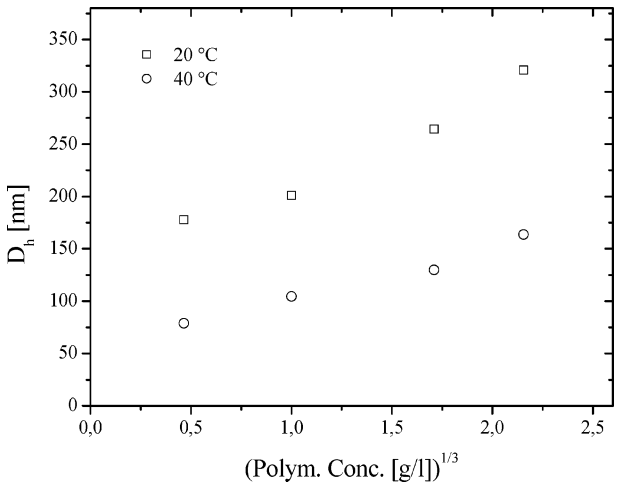


Figure 1. Influence of polymer concentration on average hydrodynamic diameter (D_h) of PNIPAAm nanogels 5−1−60 at 20 °C (□) and 40 °C (○).

By determining this relation at low temperature, the current study has also been able to fill a gap left by Pelton and his associates. While their research used non-cross-linked PNIPAAm particles, which reverted to polymer solutions upon cooling, the PNIPAAm particles used in this study were already cross-linked, enabling them to maintain their UV-irradiated form when cooled.

AUC Measurements. AUC measurements can be used to access the soluble fraction as well as the degree of swelling of nanogels.[24] The soluble fraction can easily be determined as it is washed out of the microgels upon sedimentation. The free polymer chains will sediment slower than the nanogels due to their lower molar mass so that their concentration can be determined. The volume degree of swelling Q can be calculated from the sedimentation coefficients s of the unswollen and swollen spherical particles via[24]

$$Q = \left(\frac{s_{\text{unswollen}}}{s_{\text{swollen}}}\right)^3 \tag{1}$$

under the assumption that no soluble fraction is present. In the presence of a soluble fraction ($1 - f$), which can easily be detected as a slower sedimenting component, the equation has to be extended to

$$Q = \left(\frac{f}{s_{\text{swollen}}} \frac{\rho_{\text{compact}} - \rho_{\text{solvent}}}{18\eta} d_{\text{compact}}{}^2\right)^3 \tag{2}$$

with η = solvent viscosity, ρ = density, and d = diameter, where compact means completely unswollen. The particle diameter of the compact unswollen particles can either be determined in a nonsolvent[24] or for the thermosensitive PNIPAAm microgels in the collapsed state which is reached at 40 °C according to light scattering measurements.[19,21] The particle density is, on the other hand, available via conventional density measurements.

To determine the degree of swelling and the soluble fraction left after the nanogel preparation, four samples were selected for AUC measurements. As can be seen in Table 1 samples 5−1−30 and 10−1−30, which were irradiated for 30 min, showed no soluble fractions, indicating that all linear chains have been connected to the network. However, there was an opposite observation for samples 5−1−10 and 5−2−30 showing a significant soluble fraction. In the case of sample 5−1−10 this might be expected because the photo-cross-linking reaction could not progress to completion within only 10 min of irradiation.[19] Non-cross-linked polymer chains were trapped in the network particles and could only be separated under the influence of a high centrifugal field. The soluble fraction found in sample 5−2−30 may be explained as follows. The particles of 5−2−30 were rather small due to the small number of photopolymer chains precipitated in each particle compared to samples 5−1−30 and 5−0−30.[19] The small number of polymer chains in each particle led to a small number of chromophore groups. To form networks via photo-cross-linking, these chromophores must have a chance to meet each other. Therefore, the small number of chromophores decreased the efficiency of the cross-linking reactions, and un-cross-linked polymer chains were found even after long irradiation.

Table 1. AUC Data of Different Nanogels in Swollen and Collapsed States[a]

	s [Svedberg]				
sample	25 °C	40 °C	$1 - f$ 25 °C	$d_{\text{collapsed}}$ [nm] 40 °C	*Q* 25 °C
5−1−10	216	1243	0.24	87	30.5
5−1−30	403	1207	0	80	26.9
5−2−30	15	53	0.23	20	7.0
10−1−30	232	322	0	45	2.7

[a] s = sedimentation coefficients, $d_{\text{collapsed}}$ = diameter of the compact particles, and $1 - f$ = soluble fractions. The diameter of the collapsed particles was calculated with the densities of 5−1−10 = 1.187 g cm^{-3}, 5−1−30 = 1.214 g cm^{-3}, 5−2−30 = 1.146 g cm^{-3}, and 10−1−30 = 1.18 g cm^{-3} (data not shown).

The size of initially formed particles depends on the SDS content and the polymer concentration. Particles prepared under identical conditions have had the same size in the collapsed state independent of the cross-linking density. As the soluble fraction could not be released individually, measurements of such particles showed the same diameter as traced in DLS.[19] At 40 °C, in the collapsed state, samples 5−1−10 and 5−1−30 showed almost the same particle diameter and sedimentation coefficient despite the fact that almost 25% soluble component was traced for 5−1−10 at 25 °C. At elevated temperatures free chains were trapped in the collapsed networks.

To calculate Q for samples with a soluble fraction, ρ_{compact} has to be known. For samples with no soluble fraction the diameter of the collapsed particles can be obtained from DLS measurements, and ρ_{compact} can be calculated via a modified Svedberg equation under the assumption that the particles were solid spheres:

$$d_{\text{TK}} = \sqrt{\frac{18\eta s_{\text{compact}}}{\rho_{\text{compact}} - \rho_0}} \tag{3}$$

The density of the collapsed particles was calculated to be 1.158 g cm^{-3} via the density of PNIPAAm[25] and the assumption that the collapsed particles contain 40% water, which has been found for corresponding macrogels in our group as well as in the literature.[25] Although this is just an assumption for hydrogel particles and there are small uncertainties for the real values of PNIPAAm density and water content, the density values can be assumed to be close to correct as independent sedimentation experiments in H_2O and D_2O on separately prepared particles with a variety of chromophore or SDS contents as well as illumination times have revealed compact particle densities in the interval 1.146−1.214 g cm^{-3} (5−1−10: 1.187 g cm^{-3}; 5−1−30: 1.214 g cm^{-3}; and 5−2−30: 1.146 g cm^{-3}) with an average of 1.18 g cm^{-3} in reasonable agreement with our above estimation (data not shown).

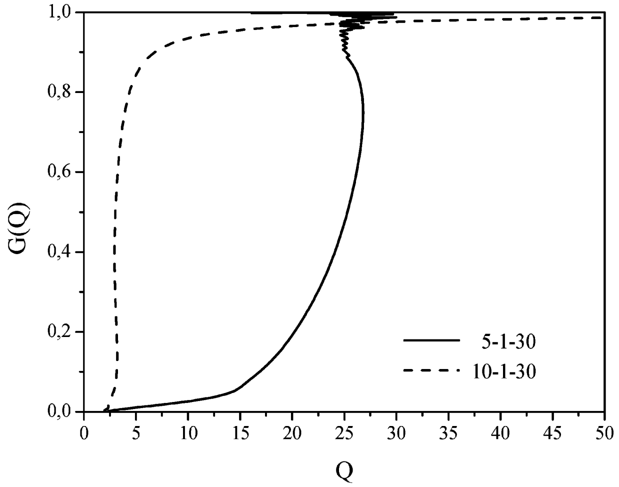


Figure 2. Volume degree of swelling distributions evaluated from sedimentation coefficient distributions in the collapsed and swollen state.

Since there is a linear relationship between the polymer concentration and the particle size, the diameter of the collapsed particles after extracting the soluble fraction can be estimated from the initial diameter and the remaining polymer fraction *f*. It has to be noted that the soluble fractions only occur at 25 °C. At 40 °C, they are built into the already existing polymer particle by aggregation. The degrees of swelling are listed in Table 1.

At 25 °C in the swollen state the particles 5−1−10 despite the loss of 24% soluble fraction showed a smaller sedimentation coefficient than the particles 5−1−30, indicating a higher friction of the 5−1−10 particles at 25 °C. These particles were less cross-linked and possessed a lower density and a larger diameter. The higher friction led to a decrease of the sedimentation coefficient despite the larger diameter. The smaller size and lower sedimentation coefficient of sample 10−1−30 under the same preparation conditions in the swollen state at 25 °C are attributable to its higher chromophore content, leading to a higher cross-linking density.

These findings are comparable with DLS and PFG-NMR results reported in previous sections/studies.[19] Since the nanogels with low SDS content were fully cross-linked after 30 min of UV irradiation, they could be used for further characterization.

Increasing the irradiation time from 10 to 30 min caused two effects: first, more chains were incorporated into the network (decrease in the soluble fraction), and second, more junction points between already connected chains were formed (decrease of degree of swelling). A more pronounced influence on the degree of swelling could be observed by increasing the amount of surfactant or the chromophore content.[19]

For samples without a soluble fraction, the degree of swelling can be calculated according to eq 1. Thus, normalization of the integral sedimentation coefficient distributions and relation of the sedimentation coefficients of swollen and unswollen particles at the same mass fraction allows the calculation of a degree of swelling distribution. The results for samples 5−1−30 and 10−1−30 are given in Figure 2.

Although small errors in the sedimentation coefficients amplify as they are weighed to the third power in the degree of swelling distribution calculation and become obvious in the nonmonotonically increasing distributions and the large oscillations at high mass fractions of sample 5−1−30, the overall distribution is realistic. The results in Figure 2 show that the degree of swelling distribution and thus the degree of cross-linking distribution of both samples are quite narrow. For sample 5−1−30, 20% particles have a *Q* between 2.3 and 20.3 and 60% a *Q* between 20.3 and 26.7, indicating a rather narrow degree of cross-linking distribution. The distribution for sample 10−1−30 is even narrower for the majority of the particles, where 20% particles have a *Q* between 4.3 and 110 and 60% a *Q* between 2.9 and 4.3. However, fundamental differences between the particles also become obvious from the above degree of swelling distributions. Whereas the highly cross-linked sample 10−1−30 shows a very broad tailing toward degree of swelling of up to 110 indicating that a minor amount (<20%) is only weakly cross-linked with a broad degree of cross-linking distribution, sample 5−1−30 shows the opposite behavior where a minor part < 20% is stronger cross-linked than the majority of the particles. This investigation might reveal some cross-linking reactions not deriving from chromophore reactions. However, in control experiments with PNIPAAm homopolymer no cross-linking could be observed. Since cross-linking density for sample 10−1−30 is already high the same trend could not be detected. The occurrence of particles with lower cross-linking density for sample 10−1−30 can be attributed to the lower molecular weight of the prepolymer,[22] resulting in less effective cross-linking. These results show that the degree of swelling distribution reveals a much more detailed view into the nature of a cross-linking reaction. The sedimentation coefficient distributions show the pronounced polydispersity of all samples. With the exception of sample 10−1−30, which shows a slight indication of bimodality, all sedimentation coefficient distributions show a pronounced tailing toward lower sedimentation coefficients, which are equivalent to smaller or less cross-linked particles.

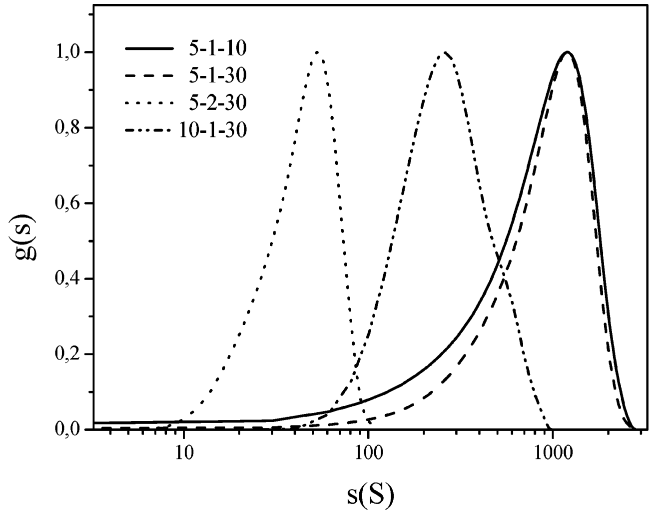


Figure 3. Sedimentation coefficient distribution of the deswollen particles at 40 °C on a logarithmic scale (not corrected for diffusion broadening).

Evaluation of Nanogel Structure from Light Scattering Data. To verify the assumption that the photo-cross-linked nanogels had a more homogeneous cross-linked structure than conventional colloidal systems, a combination of static and dynamic light scattering analysis was performed. From this analysis one can determine the dimensionless ratio of the radius of gyration to the hydrodynamic radius:

$$\sigma = \frac{R_g}{R_h} \tag{4}$$

which relates to polymer architectures in solutions. For random coils, the σ values vary in the range of 1.5−1.78, depending on

Table 2. Dynamic and Static Light Scattering Analysis of Nanogels at 25 °C

sample	R_h [nm]	R_g [nm]	$\sigma = R_g/R_h$
5−1−10	128		
5−1−30	141	108	0.76
5−2−30	31	27	0.87
10−1−30	64	56	0.87

the solvent quality, and for hard spheres, σ is equal to 0.778.[17,18] The σ values for the nanogels are listed in Table 2. It was found that the σ values of PNIPAAm nanogels at 25 °C vary within the range of 0.74−0.87. These results differ from those reported by Senff and Richtering,[17,18] where their PNIPAAm nanogels prepared via emulsion polymerization have σ values of 0.55−0.6 at temperatures less than or equal to 30 °C. According to these authors, the values of around 0.6 are caused by the gradient architecture of their nanogels. The particles are strongly swollen, and the network density decreases at the particle surface due to a higher polymerization rate for BIS than for NIPAAm. The nanogel particles had a cross-linked core covered with dangling chains. In the case of the photo-cross-linked nanogels R_h is still higher than R_g, though not much, indicating that the friction which determines R_h (via the Stokes−Einstein law) is less than that found by Senff and Richtering for the nanogels with dangling chains. This suggests a more homogeneous cross-linked structure of PNIPAAm nanogels made by photo-cross-linking. This is also in agreement with the results of the degree of swelling distributions in Figure 2, which show that the majority of the particles are homogeneously cross-linked as evident in a similar degree of swelling. However, absolute values of the hydrodynamic radius are larger measured by DLS because here values are intensity-averaged and AUC values are weight-averaged.

The more homogeneous structure of the hydrogels can be attributed to the two-step synthesis of the particles. In the first step corresponding prepolymers were prepared by free radical polymerization. Within the PNIPAAm prepolymers the cross-linker DMIAAm was randomly distributed in the polymer chains.[22] In the second step, the nanogel particles result from aggregation of hydrophobic globules. By statistical considerations there should not be a difference in the chromophore content and thus in the cross-linking density in the particle core or at the particle shell. Therefore, a gradient in the cross-linking density of the nanogel particles can be avoided. The σ values of the investigated nanogels approach the range for hard spheres. It is supposed that the nanogels have a cross-linked and compact surface, instead of dangling chains, as in the case of nanogels prepared by emulsion polymerization.

Influence of Alcohols on Swelling Behavior of Nanogels. In water-swollen gels of PNIPAAm the LCST and accompanying changes in the polymer conformation result from a disturbance in the balance between hydrogen-bonding and hydrophobic effects. Hydrogen bonding between water molecules and the amide groups of PNIPAAm leads to high orientation of water molecules around the polymer. Such water−polymer interactions contribute favorably to the enthalpy changes associated with the formation of hydrogen bonds but unfavorably to the entropy of mixing. As the solution temperature is raised, the entropy of mixing becomes dominant, leading to a positive free energy of mixing; i.e., a two-phase system is favored.

Cosolvents, which affect such highly oriented structure of water and hydrophobic interactions, are expected to change the LCST of linear PNIPAAm and the swellability of PNIPAAm nanogels. The mixing of two solvents can result in mixtures with very different properties. In the case of cosolvency, which is a very rare phenomenon, a mixture of two nonsolvents for a polymer forms a good solvent. Poly(methyl methacrylate) (PMMA) is an example of a polymer exhibiting cosolvency. Both water and methanol are nonsolvents for this polymer. However, mixtures with different ratios of methanol to water can dissolve PMMA.[26] On the other hand, some polymers are well soluble in two pure solvents, but they cannot dissolve in their mixtures. The latter phenomenon is named co-nonsolvency.[27,28]

PNIPAAm can dissolve in water and in various polar organic solvents. In water, the polymer exhibits a LCST around 32 °C, but this LCST can be changed if methanol or other organic solvents are added to an aqueous solution of PNIPAAm. A phase diagram of PNIPAAm as a function of methanol, THF, and dioxane composition in solvent mixtures shows an initial depression of the cloud point and a sudden increase in solubility. Above the volume fraction of methanol (0.66), the LCST vanishes, suggesting a critical point in the phase diagram. The phenomena were systematically investigated by different research groups.[27−30]

Mielke and Zimehl investigated the influence of four different alcohols on the swelling behavior of cationic and anionic charged PNIPAAm nanogels.[31] The surface charge of latex particles originates from initiator groups. Four alcohols were utilized in the study, including methanol, ethanol, 1-propanol, and 2-propanol. Reverse swelling and deswelling behavior between positive and negative latex systems were described. However, all the nanogels contained surfactants. The presence of SDS may have influenced the swelling behavior of these nanogels because SDS also possesses strong interactions with nanogel particles, where its hydrophobic tail can interact with the hydrophobic parts of PNIPAAm. The influence of alcohols on the LCST and swelling behavior of neutral nanogels has not yet been reported.

The PNIPAAm particles prepared by photo-cross-linking of PNIPAAm copolymers were neutral, as an AIBN initiator was used in the free radical copolymerization of NIPAAm. In addition, hydrogel particles can be prepared even in the absence of a surfactant.[19] Thus, there is a significant difference between the PNIPAAm nanogels used in this study and those in other systems, in that these nanogels can lack the presence of surfactants (such as SDS). Therefore, when investigating the effects produced by the addition of alcohols to these nanogels, the influence of SDS on the swelling behavior of these nanogels can be excluded. Four alcohols were used, and the sample preparation conditions were almost identical to those used in the preparation of the charged nanogels.[31] PNIPAAm nanogels with 5 mol % DMIAAm were employed for the current investigation. Before measurement, the PNIPAAm nanogels were diluted with alcohols to a final weight fraction of 1 g of polymer L^{-1}. The dispersions in alcohol−water mixtures were left at 20 and 40 °C for 24 h to establish the swelling and deswelling equilibrium. Figure 4 shows the swelling behavior of the PNIPAAm nanogels 5−0−30 in different alcohol−water mixtures at 20 °C.

The neutral nanogel particles first shrunk after alcohols were added. However, they then swell with increasing alcohol fractions, which is similar to the alcohol-induced swelling behavior of cationic and anionic microgels reported in the literature.[31] The degree of swelling and deswelling of the particles varies in different alcohol systems. Alcohols with longer chain lengths have more pronounced effects on the degree of swelling of the nanogels. In fact, the nanogels swell most

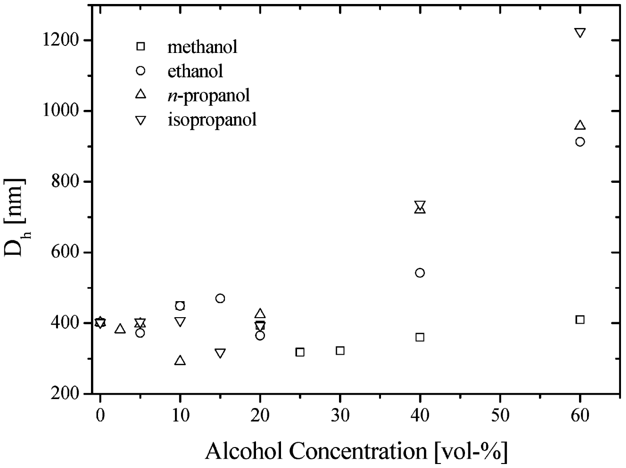


Figure 4. Influence of alcohols on average hydrodynamic diameter (D_h) of PNIPAAm nanogels 5−0−30 in water mixtures at 20 °C (□, methanol; ○, ethanol; △, 1-propanol; ▽, 2-propanol).

considerably in 2-propanol, as compared to 1-propanol and ethanol. The average diameter of nanogel particles increases ∼3 times in the presence of 60 vol % of 2-propanol. However, at the same volume fraction of methanol, the size of the nanogel particles only approaches their original size in pure water. As the methanol concentration increases from zero, the size of the nanogels decreases, achieving a minimum radius at around 30 vol % methanol. These phenomena are in good agreement with results reported by Hirotsu[30] for neutral PNIPAAm macrogels in methanol−water mixtures.

The phenomena described above can be explained in terms of co-nonsolvency[27−30] and hydrophobic interactions between polymer and solvents.[31] At low alcohol concentrations, alcohol molecules are kept apart from the nanogels by the formation of hydration cages around each molecule.[32] Under these conditions, the polymer−water interactions are essentially undisturbed by the presence of the alcohol molecules. As the alcohol volume fraction increases, there are no longer sufficient water molecules to provide clathrate cavities for all the alcohol molecules.[27] The free alcohol molecules can then interact with polymer segments.

The size of swollen nanogel particles decrease in the presence of 10−30 vol % of methanol, 15−30 vol % of ethanol, and 5−15 vol % of 2-propanol or 1-propanol, indicating changes in the relative roles of alcohol−polymer, water−polymer, and alcohol−water interactions. There should be a competition among these interactions within the concentration ranges. It was found that water−methanol interactions are stronger than PNIPAAm−water interactions.[27] The authors suggested that the co-nonsolvency of the methanol−water mixture results from the water−methanol interaction. The different ranges of alcohol volumes in which the nanogels deswell could be attributed to the carbon chain lengths in the alcohols.

In solutions of higher alcohol concentrations, the alcohol−polymer interaction becomes predominant. The hydrophobic interactions of alcohol molecules with hydrophobic groups of PNIPAAm cause the nanogel particles to swell again. It appears that the alcohols with two methyl groups have stronger interactions with the polymer segments than alcohols with only one methyl group.

Figure 5 illustrates the swelling behavior of the 5−0−30 nanogel in alcohol−water mixtures at 40 °C. At this temperature, the nanogels were in their shrunken state in pure water. However, the nanogels exhibited swelling in all alcohol−water mixtures. The degrees of swelling were affected by the nature of the alcohols and their concentrations. In methanol−water mixtures the nanogel diameter increased considerably up to 40 vol % methanol, after which the increases in particle sizes were insignificant. In the mixtures with ethanol, 1-propanol, and 2-propanol, the nanogels swelled significantly with all increasing alcohol fractions until the upper limit for this set of experiments was reached. There appears to be a linear relationship between nanogel diameter and alcohol fraction. At the same alcohol concentration, the nanogels again swell most significantly in 2-propanol and then in 1-propanol, ethanol, or methanol.

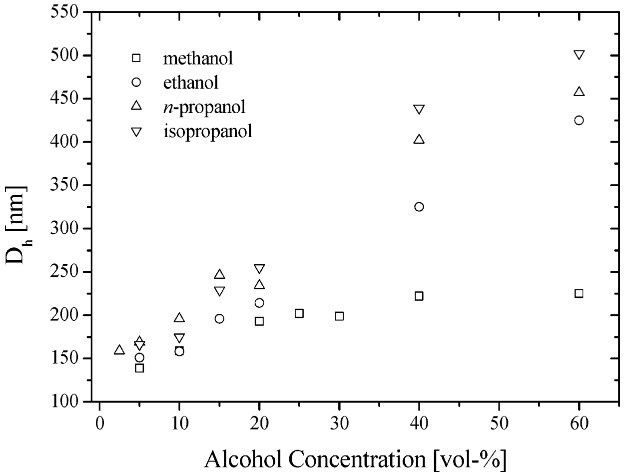


Figure 5. Influence of alcohols on average hydrodynamic diameter (D_h) of PNIPAAm nanogels 5−0−30 at 40 °C (□, methanol; ○, ethanol; △, 1-propanol; ▽, 2-propanol).

The different hydrophobicities of the alcohols, and thus the specific alcohol adsorption to PNIPAAm chains, explain why the nanogel can swell at very low alcohol contents.[31] No co-nonsolvency can take place, as the polymers became hydrophobic and separated from the water at elevated temperatures. The neutral nanogels in alcohol−water mixtures at 40 °C behaved differently to particles in anionic PNIPAAm latex systems. The anionic particles exhibited maximum and minimum average diameters in ethanol and 1-propanol−water mixtures. For cationic particles, the particle diameters increased when the ethanol concentration was raised, but in a 1-propanol−water mixture this trend vanished and maximum−minimum peaks were observed.[31]

In summary, the neutral nanogels studied showed a different behavior in alcohol−water mixtures in comparison to the literature reported charged nanogels. The lack of charges on the particles and the absence of SDS from the systems could have affected this behavior. The deswelling of nanogels in alcohol solutions is due to the co-nonsolvency effect, whereas their swelling at high alcohol concentrations is attributable to hydrophobic interactions between the alcohol molecules and the hydrophobic groups of the polymer chains.

Conclusion

The colloidal PNIPAAm nanogels were formed by UV-irradiated solutions of thermosensitive polymers in water at 45 °C. Within each state of swelling (swollen or shrunken), the average diameter of nanogel particles increased linearly with the cubed root of the total polymer concentration. This linear relationship implies that particle formation can be explained by homogeneous-coagulative nucleation. Particle concentration increased linearly with polymer concentration as well.

Analytical ultracentrifugation could reveal the degree of swelling of the different nanogel preparations, confirming the data from dynamic light scattering. In addition, the quantitative determination of un-cross-linked polymer species was possible.

Even the determination of the continuous degree of swelling distribution was reported for a nanogel for the first time obtained with a single analytical technique and extending the already reported possibility to combine average particle sizes from DLS and centrifugation experiments to yield the swelling degree for various microgels from a distribution.[9] Hydrogel particles could be prepared with low SDS concentration or even in the absence of a surfactant. Therefore, the effects on swelling produced by the addition of alcohols to these nanogels could be investigated, excluding the influence of SDS on the swelling behavior of these nanogels. The deswelling of PNIPAAm nanogels in alcohol solutions is due to the co-nonsolvency effect, whereas their swelling at high alcohol concentrations is attributable to hydrophobic interactions between the alcohol molecules and the hydrophobic groups of the polymer chains.

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