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Equilibrium swelling behavior of thermally responsive metal affinity hydrogels, Part I: Compositional effects

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ABSTRACT

Copolymer hydrogels were synthesized from *N*-isopropylacrylamide (NIPAAm) and vinyl iminodiacetic acid (VIDA) monomers, incorporating thermally responsive swelling and metal affinity properties. Compared to pure NIPAAm hydrogels, the copolymer hydrogels showed significantly increased swelling due to the hydrophilic VIDA groups while still retaining their sharp phase transition behavior. However, excessive amounts of VIDA caused the gels to lose this behavior and not fully collapse even at temperatures as high as 80 °C. When chelated with copper the VIDA groups became less hydrophilic, partially reversing the increased swelling due to VIDA, enabling the gels to regain their phase transition behavior. Increasing the crosslinking density in the gels generally had the effect of decreasing their swelling. However, for gels with higher VIDA amounts, increasing the crosslinking density unexpectedly caused the hydrophilic groups with bound waters to resist the hydrophobic group-induced collapse at high temperatures. The results suggest that the NIPAAm, VIDA and crosslinker amounts and copper chelation are essential elements in the molecular design of the gel to retain a sharp phase transition. These variables were used to develop a phase transition phase diagram.

1. Introduction

The clearly defined and sharp phase transition behavior of *N*-isopropylacrylamide (NIPAAm) based hydrogels has prompted numerous efforts to find applications for this property [1–5]. These applications usually involve modifying the gel in some manner, most commonly by copolymerizing the NIPAAm with other monomers. The goal of these modifications is to impart additional properties to the hydrogel while retaining their phase transition behavior. However, such modifications often significantly alter the environmentally responsive phase transition of the resulting hydrogel.

We have been attempting to develop environmentally responsive affinity hydrogels, i.e. hydrogels with affinity ligands to bind targeted molecules for small scale separations. In particular, we have sought to develop thermally responsive NIPAAm copolymer hydrogels with metal affinity ligands which retain the excellent phase transition behavior of poly(NIPAAm) hydrogels. Initially we sought to copolymerize NIPAAm with acrylamide, followed by the functionalization of the resulting gel with metal affinity groups [6]. While these gels did display both affinity and phase transition properties, these were far from being satisfactory. Attempts by other investigators produced similar results as well [2,7].

The principal difficulties encountered in such transformations are two-fold. The first is that by adding co-monomers and crosslinkers to NIPAAm hydrogels we alter their phase transition. The addition of buffers, salts and target molecules to the solution also strongly affects this process [8]. As will be briefly discussed below, the reason for this change is that the primarily hydrophobic nature of NIPAAm hydrogels and the structure of the associated aqueous phase are fundamentally altered by these additions, both of which are central to the swelling mechanism of hydrogels. Second, functionalization after polymerization results in an uneven distribution of functional groups in the gel adversely effecting the phase transition and binding properties.

The swelling of the mostly hydrophobic NIPAAm hydrogels is due to the formation of pentagonal shaped clathrate water structures around the hydrophobic regions which are separated from each other by high entropic, hexagonal, and hydrogen bonded free water networks [9–15]. Increasing temperatures cause gradual collapse of the hydrogen bonded free water networks and increased vibration of the molecules which results in the hydrophobic regions joining together and decreasing the amount of clathrate structures. Beyond a certain temperature these changes increase dramatically and combine to cause the hydrogel phase transition in the hydrogel [16,17].

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While the above mechanism is well known; it is sometimes not recognized how sensitive it is to changes in the structure and aqueous environment of the hydrogel. Addition of more hydrophilic co-monomers increases the swelling of the gel by better separating the hydrophobic groups, but larger amounts of co-monomer suppresses the phase transition by reducing the amount of hydrophobic groups available for pentagonal clathrate structures to form around [6,19]. Hydrophobic co-monomers also affect the phase transition, but through a different mechanism. Functionalization with ionic groups can change the osmotic balance of the gel causing greater swelling. These effects were responsible for most of the changes in the phase transition behavior observed in the functionalized hydrogel that we developed initially.

Recently, we proposed an alternate approach to NIPAAm-based hydrogel development employing molecular design to achieve a similar hydrophobic/hydrophilic balance as the original gel [20]. In this approach the co-monomer is first molecularly designed and synthesized to have the correct hydrophilic/hydrophobic balance *and* to include the affinity ligand, followed by copolymerization with NIPAAm. The affinity ligand was included in the co-monomer to avoid the non-uniform distribution problem mentioned earlier. Preliminary studies indicated that the resulting hydrogel had a phase transition behavior close to that of pure NIPAAm hydrogels and had a uniform distribution of metal affinity ligands.

While our earlier study focused on the synthesis of the molecularly designed hydrogel, in this study we examine its phase transition behavior in detail. The sensitivity of the phase transition to the gels' internal structure and external environment means that its molecular design must be optimized to produce the desired behavior, requiring the synthesis of gels of various compositions. The gels also have to be tested in the presence of the target molecules, along with associated buffers and salts, as their presence in solution and their binding to the gel will also affect the phase transition. These behaviors must also be understood in terms of the water structures inside and outside the gels as this is central to further improvements through molecular design. In this study, the effect of varying the gel composition on the swelling behavior will be examined. In the second part of this study the effect of the solution conditions on the swelling behavior of this gel will be examined [21].

2. Experimental

2.1. Materials

The monomer NIPAAm and crosslinker *N*,*N*-methylenebisacrylamide (MBAAm, ultra pure grade) were purchased from Polysciences, Inc. The NIPAAm was recrystallized from hexane before use. The co-monomer *N*-(6-(acrylamido)hexanoyl)-iminodiacetic acid sodium salt (VIDA) was synthesized according to the procedure discussed in an earlier study [20]. The photoinitiator riboflavin (99% purity) and accelerator *N*,*N*,*N*,*N*-tetramethylethylenediamine (TEMED, 99.5% purity) were obtained from Sigma–Aldrich. Deionized water for equilibrium swelling studies was purified from a US Filters filtration system and used for all experiments.

2.2. Gel synthesis and functionalization

Copolymer hydrogels of NIPAAm and VIDA were synthesized with different weight percentages of co-monomer VIDA and crosslinker MBAAm. A 15% (w/v) monomer (NIPAAm and VIDA) solution was used to synthesize all gels. While both pure NIPAAm and copolymer hydrogels were synthesized using the same techniques, the procedure used to synthesize a copolymer hydrogel will be described here. For this synthesis, 1.3 g of NIPAAm, 0.2 g of VIDA and 0.055 g of MBAAm were dissolved in 10 ml of DI water. The solution was evacuated for 4 min to remove any dissolved oxygen following which 50 μl of 0.1% (w/v) riboflavin solution and 8 μl of TEMED were added. The reaction mixture was transferred between two dimethyldichlorosilane coated glass plates separated by 0.5 mm spacers and irradiated with UV light (365 nm 30 W, UV products-XX15) for 2 h at room temperature. The 0.5 mm thick NIPAAm–VIDA hydrogels so obtained were cut into 1.6 cm discs and immersed in DI water for at least 3 days with frequent water changes to remove any unreacted monomers. The thoroughly washed gels were incubated in 0.05 M $CuSO_4$ solution for 24 h at room temperature to obtain copper chelated gels of Cu–NIPAAm–VIDA. The Cu–NIPAAm–VIDA gels were repeatedly washed with DI water for 3 to 4 days and then swollen and shrunk 2 times in DI water by increasing and decreasing the temperature between 5 °C and 60 °C to ensure that there was no unbound copper entrapped in them.

2.3. Equilibrium swelling studies

The equilibrium swelling of the hydrogels in DI water was determined by recording the relative change in their diameter with temperature. The gel samples were equilibrated in 150–200 ml of the solution of interest for 24 h at 20 °C before the experiment. The change in the diameter of the gel between 20 °C and 80 °C was determined after equilibrating it at each intermediate temperature for 2.5 h. From swelling kinetics measurements it was found that a time of 2.5 h was sufficient to ensure that all samples reached equilibrium. A temperature controlled Neslab GP300 water bath attached to a Neslab FTC 350 chiller was used to vary the temperature and a Gaertner Scientific *X*-axis measuring microscope was used to measure the diameter of the gel. Assuming isotropic behavior, the relative change in volume, V/V_0 can be calculated using Eq. (1),

$$V/V_0 = \left(\frac{D}{D_0}\right)^3 \tag{1}$$

where, V_0 and D_0 are the volume and diameter of the gel, respectively, just after synthesis and V and D are the equilibrium volume and diameter of the gel, respectively, at a particular temperature. The points of intersection of the tangents to the phase transition (PT) curve at the beginning and end of the phase transition, were used to designate the onset and offset temperatures of the phase transition. The onset temperature was defined as the lower critical solution temperature (LCST) and the slope of the line connecting the onset and offset temperatures was defined as the sharpness factor of the phase transition of the gel.

Each volume measurement was done at least 3 times and the average value was used. The errors in these measurements were much less than 1% so they were not considered. For selected samples the swelling measurements at different temperatures were done more than once to verify the data. An example of swelling data obtained from multiple measurements for a NIPAAm–VIDA hydrogel sample is shown in Fig. 1. This shows that the error bars are quite small except near the phase transition.

It was observed that the NIPAAm–VIDA and Cu–NIPAAm–VIDA gels showed different types of conformation changes during these studies. The NIPAAm–VIDA gels with low crosslinking density and high VIDA composition underwent irregular deformations during the phase transition, whereas the Cu–NIPAAm gels did not show such behavior. The sample shown in Fig. 1 is an example of a NIPAAm–VIDA gel prone to such deformations and this is the reason for the large error bars near the phase transition. Hirotsu and coworkers have made similar observations with ionic NIPAAm gels [19]. Under these circumstances, the measured diameter of the

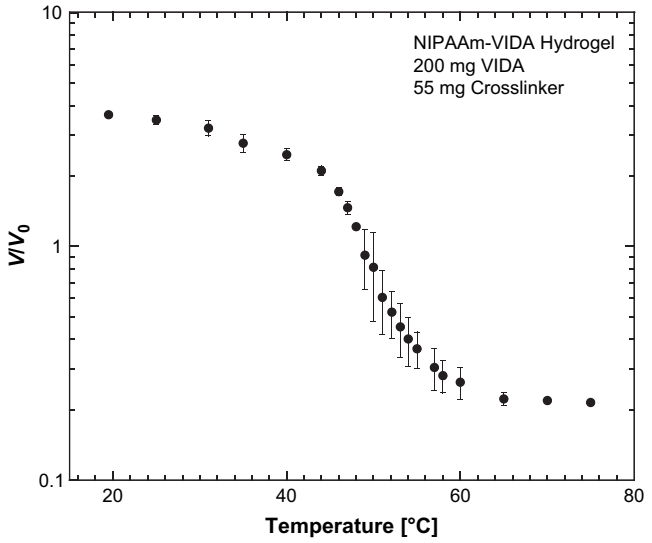

Fig. 1. Equilibrium swelling data for a NIPPAm–VIDA hydrogel sample showing variation of the data near the phase transition.

gel was less than the actual diameter because the circular disc shaped gels took on a wavy conformation. Increasing the equilibration time or slightly tapping the gel with a spatula decreased such irregularities. In cases where the gel did not regain their circular conformation, the longest diameter of the gel was noted. It is not clear from the published literature if this type of phase transition can be interpreted as a discontinuous type. These irregularities in the gel conformation can be attributed to relaxation time of the gel network, skin formation, pore structure of the gel or coexistence of phases [22,23].

The NIPAAm gel was used as the control for the studies of the effect of gel composition on the phase transition behavior of the copolymer gels. The gels used for these studies and their compositions are listed in Table 1. The error bars are omitted in subsequent figures showing swelling data as the errors are small and also because they detract from the clarity of the figures.

3. Results and discussion

The copolymer hydrogels synthesized using the free radical solution polymerization technique with the photochemical initiator system discussed earlier, were found to be very homogenous and had reproducible equilibrium swelling properties. Synthesizing the co-monomer with the affinity ligand prior to polymerization, rather than functionalizing the gel with the ligand after polymerization, clearly contributes to the homogeneity. For the remainder of this work we will focus on the swelling and phase transition of the gels. Gels with two different co-monomer concentrations and four different crosslinker concentrations were synthesized to study the effect of composition on their equilibrium swelling in DI water. The gel compositions and the solution conditions for these studies are listed in Table 1.

Table 1
The compositions, phase transition temperatures, and sharpness factors of NIPAAm, NIPAAm–VIDA and Cu–NIPAAm–VIDA gels studied

Gel type	Composition (mg)	Solution	LCST (°C)	Sharpness factor
NIPA	Cl-55	DI water	33.5	−0.41
	Ci-27	DI water	34.0	−1.1
NIPA–VIDA	VIDA-100, Cl-55	DI water	38.5	−0.15
	VIDA-200, Cl-55	DI water	46.0	−0.26
	VIDA-200, Cl-40	DI water	47.0	−0.43
	VIDA-200, Cl-27	DI water	50.0	−0.69
	VIDA-300, Cl-27	DI water	53.5	−0.89
	VIDA-300, Cl-55	DI water	NTO	–
	VIDA-300, Cl-87	DI water	NTO	–
Cu–NIPA–VIDA	VIDA-100, Cl-55	DI water	37.2	−0.34
	VIDA-200, Cl-55	DI water	39.0	−0.17
	VIDA-200, Cl-40	DI water	42.0	−0.57
	VIDA-200, Cl-27	DI water	42.5	−0.64
	VIDA-300, Cl-55	DI water	42.1	−0.20

The VIDA and crosslinker amounts in these gels are listed while the remainder is NIPAAm for a total weight of 1500 mg. Here NTO means no phase transition was observed and Cl is the crosslinker.

3.1. Effect of VIDA concentration

The design of the vinyl terminated iminodiacetic acid (VIDA) co-monomer was based on balancing the hydrophilic metal affinity ligand end group (Cu^{2+}-iminodiacetic acid) and the polar acrylamide group with a hydrophobic spacer arm, as seen in Fig. 2. Co-monomers that are more hydrophilic than NIPAAm tend to increase, and co-monomers that are more hydrophobic tend to decrease, the phase transition temperature of NIPAAm-based hydrogels [11,24]. The ionic affinity ligand and the polar amide groups in the VIDA co-monomer would significantly change the phase transition behavior of NIPAAm gels and this has to be counteracted by increasing the length or surface area of the alkyl spacer between them. Increasing this surface area would initially increase the swelling of the gel, but beyond a critical value would result in significantly diminished swelling. Our experience with acrylamide and other co-monomers, and the work of other investigators, suggested that a co-monomer with a pentyl spacer group would provide the optimal hydrophobic surface area and was used in the synthesis of VIDA [6,25,26].

In addition to its structure, the co-monomer composition will have an effect on phase transition behavior of the gels and this is shown in Fig. 3. Addition of the VIDA co-monomer significantly increases the extent of swelling and the LCST. There are several reasons for this effect. The primary one is that the ionization of the twin carboxylic acids in VIDA will introduce an osmotic pressure gradient causing significantly increased swelling of the gel. Additionally, the greater hydrophilicity of the co-monomer compared to NIPAAm means that the hydrophobic groups are now more separated allowing more clathrate structures to be formed around them, leading to greater swelling. The alkyl spacer of VIDA will also contribute clathrate structures. The greater separation also means that higher temperatures are needed to bring the hydrophobic groups together resulting in higher LCST temperatures. The ionic groups in the gel will have bound water molecules surrounding them contributing to gel swelling and this is relatively unaffected by temperature. This counteracts the temperature induced collapse of the gel prompted by the collapse of clathrate structures around hydrophobic groups. While the extent of the swelling and the LCST are affected due to the reasons discussed here, Fig. 3 and Table 1 clearly show that the addition of VIDA did not change the nature of the phase transition which remains almost as sharp as in the pure NIPAAm gel, except when the VIDA amount in the gel reaches 300 mg.

When VIDA concentration is increased relative to NIPAAm, Fig. 3 shows that there are changes in the swelling behavior of the gel. Initially increasing the VIDA concentration up to 100 mg contributes to greatly increased swelling at lower temperatures, due to

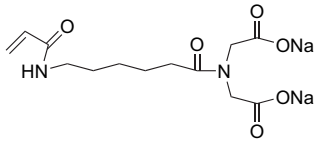

Fig. 2. *N*-(6-(Acrylamido)hexanoyl)-iminodiacetic acid disodium salt (VIDA).

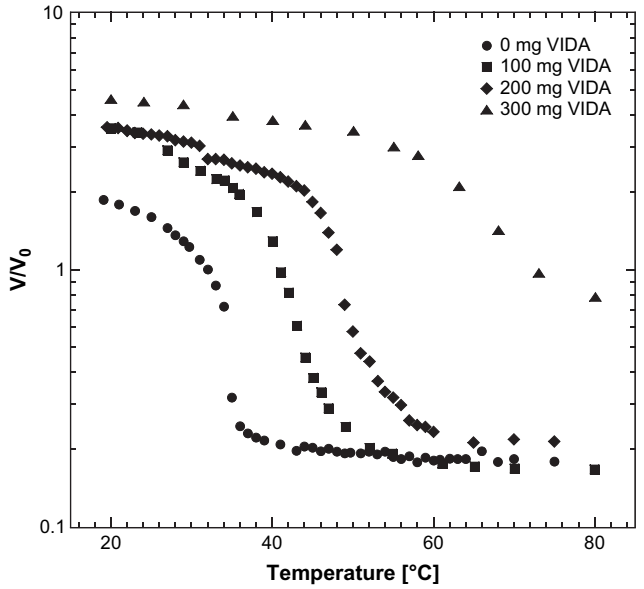

Fig. 3. Equilibrium swelling with temperature of pure NIPAAm and NIPAAm–VIDA gels with 100, 200 and 300 mg VIDA, all with 55 mg crosslinker.

increased osmotic pressure, bound water in hydrophilic groups and the better separation of hydrophobic NIPAAm groups. However, there is very little change in the swelling of the gels at lower temperatures when the VIDA concentration is increased from 100 to 300 mg.

While the overall phase transition behavior of the gels from 0 to 200 mg of VIDA are quite similar, Fig. 3 does show an increase in the LCST temperature of the gel with more VIDA. As discussed above, this increase is due to the greater difficulty of bringing hydrophobic groups together for gel collapse. Gels with increased VIDA of 200 mg require temperatures above 60 °C to bring about their complete collapse, making it difficult to measure the complete phase transition.

Finally, it is clear that when VIDA is increased to 300 mg the gel no longer has a sharp phase transition behavior. The swelling of the gel is more linear with temperature and it is not completely collapsed even at 80 °C. This represents a point at which the hydrophilic groups in the gel are so numerous that the phase transition mechanism is now quite different. At lower VIDA concentrations, the collapse is induced by hydrophobic groups which squeeze the bound water from hydrophilic groups. The hydrophobic induced collapse still occurs in the gel with 300 mg of VIDA, but it cannot completely squeeze all the hydrophilic group bound water anymore. As mentioned above, even in the gel with 200 mg of VIDA, the complete collapse is achieved with some difficulty at temperatures above 60 °C. There is a "tail" in the swelling curve for this gel beginning at ~50 °C where the collapse with temperature is slower. This most likely corresponds to the last bound waters being squeezed out of the hydrophilic groups.

The above observations suggest that at a critical VIDA concentration between 200 and 300 mg the hydrophilic/osmotic effects become more dominant than the hydrophobic effects in the gel, preventing its total collapse. Hence high VIDA concentrations should be avoided to retain the nature of the phase transition of the NIPAAm-based gels. As a result VIDA/NIPAAm weight ratios above 1:6 are not recommended for these gels.

3.2. Effect of crosslinker density

For the pure NIPAAm hydrogels, the moderate crosslinker amounts used in this study had very little effect on the swelling as shown in Fig. 4(a). From this we can conclude that the crosslinker effects observed in the copolymer hydrogels, as shown in Fig. 4(a), are due to the presence of VIDA [27]. Increasing the crosslinker density diminishes the swelling and the LCST of gels, and in these effects it resembles the effect of decrease in VIDA concentration in the copolymer gels, as discussed above. However, there is one difference in how the crosslinker affects the gel and this is seen in Table 1 and Fig. 4. In every instance increasing the crosslinker density results in the gradual reduction of the sharpness of the phase transition.

An important observation of what occurs to the hydrogel with 300 mg of VIDA is shown in Fig. 4b. In gels with 27 mg of crosslinker the sharp phase transition behavior is retained. However, the hydrophilic group-induced "tail" described earlier is quite visible beginning at ~60 °C and the temperature has to be raised to ~80 °C to bring about its complete collapse. When the crosslinker density is raised to 55 mg the sharp phase transition behavior is lost and it is more linear with only a partial collapse by 80 °C. With 87 mg of crosslinker the behavior is similarly linear but the swelling is reduced significantly at all temperatures. These results suggest that the amount of crosslinker in the gel affects the phase transition behavior in a manner similar to that of the amount of VIDA, although the reasons for each are different as discussed below. This

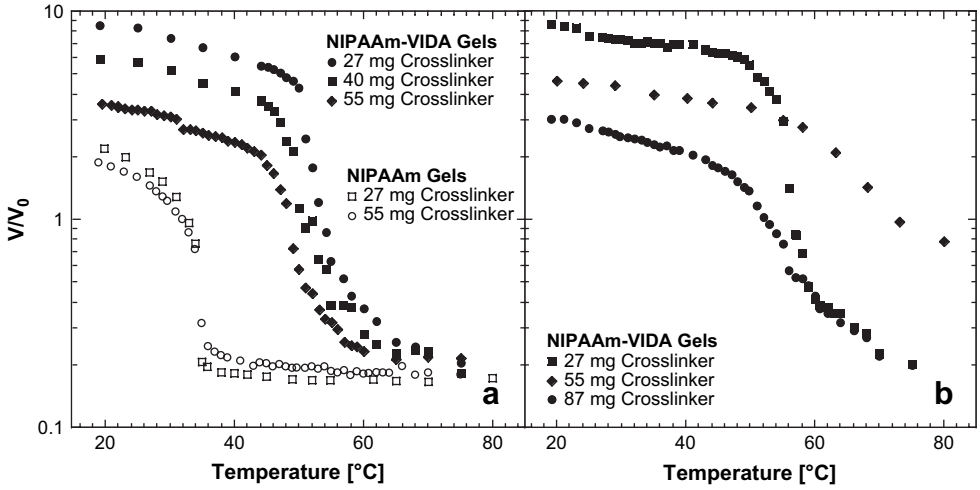

Fig. 4. The effect of crosslinker concentration on the temperature dependent equilibrium swelling of the hydrogels: (a) pure NIPAAm gels and NIPAAm–VIDA gels with 200 mg of VIDA; (b) NIPAAm–VIDA gels with 300 mg of VIDA.

means that for each gel of a particular VIDA concentration there is a critical crosslinker concentration below which the gel retains its sharp transition behavior. As the amounts of both VIDA and crosslinker are increased the gel becomes more prone to losing its sharp phase transition behavior.

The crosslinker does increase the hydrophobicity of the gels, but this effect is likely to be small given its limited concentration compared to other groups. Its principal effect is to make the gels more rigid, restricting both their swelling and collapse. The swelling of the gels is diminished as the crosslinker chains restrict the expansion of the gel where they are present, while other regions will swell unrestrictedly. Similarly, when the temperature is increased some regions of the gel will collapse without restrictions while others will require increasingly higher temperatures to overcome the effect of crosslinker chains, resulting in a gradual rather than a sudden collapse. In pure NIPAAm gels with mostly hydrophobic groups present the crosslinker has minimal effect at such low concentrations. At higher temperatures when the swelling due to the clathrate structures are broken everywhere, the amounts of crosslinker used in this study cannot affect the phase transition behavior of the pure NIPAAm gels. However, in the copolymer hydrogels there is always the balance between the hydrophobic groups and hydrophilic groups with bound waters less likely to breakdown at higher temperatures. The amount of crosslinker in such gels can easily tip the balance causing a gel with a sharp phase transition behavior to lose this property.

The proposed mechanism for the effect of crosslinker concentration on the gel phase transition is further illustrated in Fig. 5. The gels can be imagined as chains of hydrophobic and hydrophilic groups interconnected by crosslinks to form regions of open and restricted free volumes, as shown in Fig. 5. At low crosslinker densities, the gel contains few restricted free volumes or the number of hydrophilic groups within the restricted free volumes is low. This causes the copolymer gels to show sharp phase transition behavior as the water is easily expelled during gel collapse. At high crosslinker densities when the number of restricted free volumes is high or the number of hydrophilic groups in the restricted free volumes is high, they contribute to increased polymer chain rigidity and increased bound water retention resulting in loss of sharp phase transition behavior.

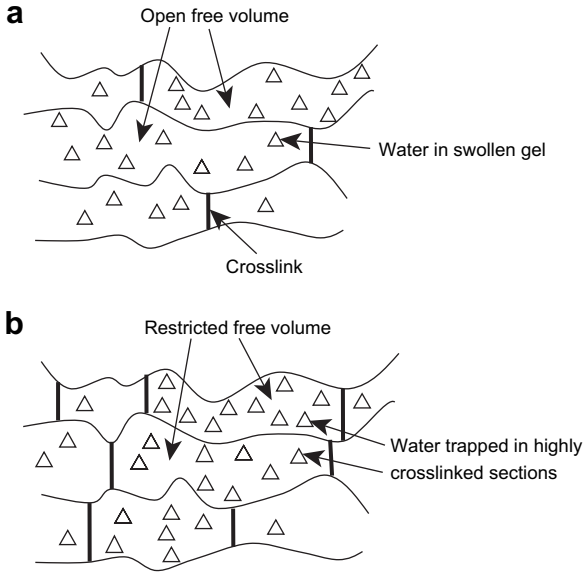

Fig. 5. Illustration of effect of crosslinking on the structure of the hydrogel network: (a) low crosslinked gel with water that can be easily expelled when the gel collapses, and (b) highly crosslinked gel with trapped pockets of water.

3.3. Effect of copper chelation

The gels with different VIDA and crosslinker concentrations studied above were further investigated to determine the effect of Cu^{2+} chelation on their phase transition behavior. Chelation of copper ions by the VIDA co-monomer transforms it from an ionic to a non-ionic and less hydrophilic group. The effect of this transformation is seen in Fig. 6(a). For the copolymer hydrogel with 200 mg of VIDA, the increased swelling caused by the addition of the VIDA co-monomer is substantially reversed, with the swelling approaching that of the pure NIPAAm gel. Additionally, the hydrophilic group-induced tail is no longer present. However, the increase in LCST is only partially reversed with the new temperature near the mid-point between the unchelated copolymer gel and the pure NIPAAm gel. Despite these changes the nature of the phase transition remained unchanged with almost the same degree of sharpness as before. The most dramatic change is observed in the copolymer hydrogel with 300 mg of VIDA, in which the copper chelation transforms the phase transition behavior to a sharp one with complete collapse occurring at ~50 °C. Finally, Fig. 6(b) shows that the effect of the crosslinker on the copper chelated gels is similar to its effect on unchelated ones: increased crosslinker concentrations decrease the sharpness of the phase transition.

These changes are clearly due to the loss of charged groups caused by copper chelation. This significantly reduces the osmotic swelling effect which is the primary cause of the increased swelling and the increased LCST. This means the copper chelated VIDA groups in copolymer hydrogels are only a little less hydrophobic than NIPAAm groups and this accounts for the similarity in the swelling behavior with pure NIPAAm gels. For the hydrogel with 300 mg of VIDA this change is a dramatic one. It is enough to convert its behavior from that dominated by hydrophilic groups to the one dominated by hydrophobic ones with complete collapse of the gel at high temperatures. This effect is a reflection of the careful design of the VIDA co-monomer to achieve a balance between the hydrophilic and the hydrophobic groups in the metal affinity gels, to retain the phase transition behavior of the pure NIPAAm gels.

The higher LCST of the chelated copolymer gels as compared to the pure NIPAAm can be explained in terms of the extent of Cu^{2+} chelation. For the hydrogel with 200 mg VIDA we had estimated in an earlier study that the copper chelation is a partial one, with ~73% of VIDA groups chelated [20]. The unchelated VIDA can still contribute hydrophilic effects and continue to cause a greater separation between the hydrophobic groups in the gel. These effects account for the higher LCST in these gels than for pure NIPAAm gels. For these reasons copper chelation results in only a partial rather than a complete reversal of the swelling behavior of the VIDA copolymer upon copper chelation, but it is still an essential element of its design. For example, the effect of copper chelation may allow the use of higher VIDA/NIPAAm ratios than 1:6, the maximum, suggested earlier.

3.4. A phase transition phase diagram for NIPAAm-based hydrogels

The results of this study suggest that VIDA and crosslinker compositions and Cu^{2+} chelation affect the phase transition of the copolymer gels and all effects must be understood and controlled to ensure that the gel retains its sharp phase transition behavior. The consistency with which the crosslinker affects the gels, as shown in Fig. 4, suggests that the crosslinker density can also be used as a variable in the molecular design of the hydrogel. Additionally, the different mechanism that crosslinkers employ to affect the swelling behavior makes it easier to implement such adjustments without significantly altering the effects of other components. In order to successfully transform NIPAAm hydrogels into affinity ones it is necessary maximize the amount of VIDA in the copolymer

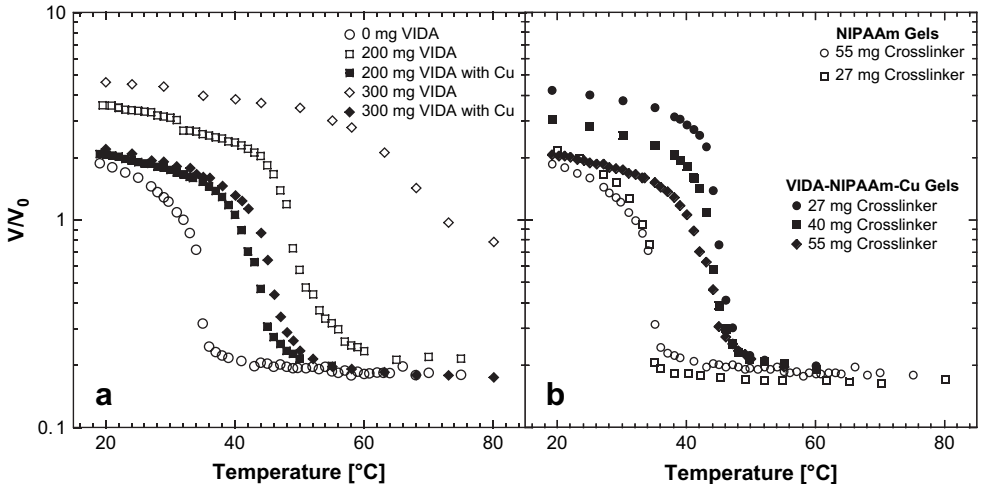

Fig. 6. Change in equilibrium swelling with temperature of pure NIPAAm hydrogel and unchelated and Cu^{2+} chelated NIPAAm–VIDA gels with (a) 200 and 300 mg VIDA, all with 55 mg of crosslinker; (b) 200 mg VIDA and different amounts of crosslinker.

hydrogels. However, as discussed above, increasing the VIDA concentration significantly increases the swelling of the hydrogel and can cause it to lose the sharp phase transition behavior. Similarly, to ensure that the gel has adequate mechanical strength for physical handling the crosslinker density has to be maximized, but this is also limited by its effect on the phase transition behavior.

The above co-monomer, crosslinker and Cu^{2+} effects are summarized in Fig. 7, in the form of a *phase transition phase diagram*. For all the gels considered here the amounts of VIDA and crosslinker are shown, with the remainder being NIPAAm for a total gel weight of 1500 mg. The gels with 27 mg crosslinker/300 mg VIDA and 55 mg crosslinker/200 mg VIDA serve to demarcate the dividing line for phase transition behavior. They have sharp phase transitions, but the presence of hydrophilic group-induced tails in them suggests that a small increase in either VIDA or the crosslinker will cause these gels to lose this phase transition behavior. This is the first time that such a compositional effects phase diagram has been presented for the phase transitions of a hydrogel.

As shown in Fig. 7 copper chelation strongly affects the dividing line between these phase transition behaviors, with loss of sharp phase transition now occurring only at high VIDA *and* crosslinker concentrations. Thus, when chelated with copper, the 55 mg crosslinker/200 mg VIDA hydrogel is transformed from lying near the border of different phase transition behaviors to one well within the sharp phase transition behavior region. This hydrogel may also provide the right balance of mechanical strength and metal affinity for applications such as small scale separations. Depending on the applications, the amount of crosslinker and VIDA can be adjusted while still retaining a sharp phase transition as shown by Figs. 3–5. Thus, the diagram greatly facilitates the molecular design of hydrogels with sharp phase transition behavior for specific applications.

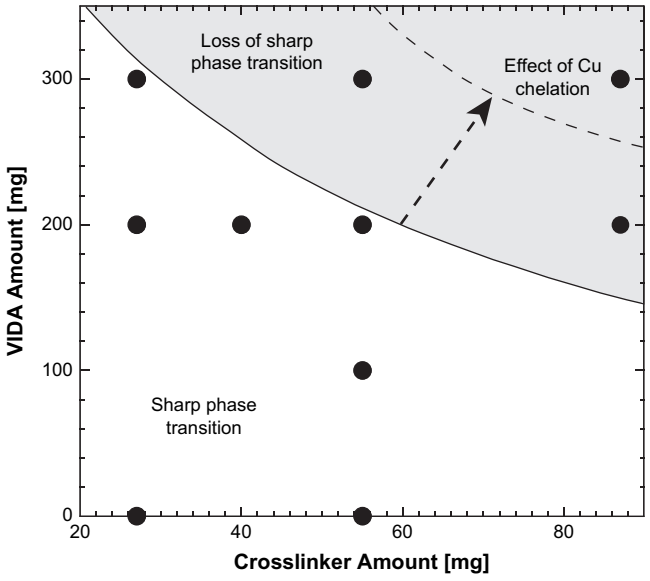

Fig. 7. Phase diagram with crosslinker and VIDA amounts for the phase transition of unchelated and Cu chelated NIPAAm–VIDA gels.

While the hydrogel swelling studies were focused on the NIPAAm-based copolymer hydrogels developed here, they have provided considerable insights into the behavior of hydrogels in general, particularly the ones in which phase transition is induced by hydrophobic interactions. If careful attention is paid to the hydrophobic/hydrophilic balance of such hydrogels, it is possible to modify them to include other groups while retaining their overall phase transition behavior. An excess of hydrophilic groups leads to hydrogels that either do not collapse or do so in a linear fashion without a sharp phase transition. Finally, the crosslinker density can play a critical role by modifying the swelling behavior of the gels to allow the hydrophilic groups to resist collapse at high temperatures.

4. Conclusions

Copolymer hydrogels of NIPAAm and VIDA can be synthesized such that they retain the sharp temperature induced phase transition of pure NIPAAm hydrogels. The addition of ionic VIDA groups significantly increased the swelling of the hydrogels. However, copper chelation of these groups eliminates their ionic effects and this partially reversed the effects of VIDA incorporation in the gel. In order to achieve a sharp phase transition it is necessary to achieve a balance between the hydrophobic NIPAAm groups and the more hydrophilic VIDA groups, but with the hydrophobic groups remaining dominant. An excess of hydrophilic groups leads to hydrogels that either do not completely collapse or do so in a linear fashion without a sharp phase transition.

Increasing the crosslinker density in the gels mostly decreased their swelling. However, for gels with higher VIDA amounts, increasing the crosslinker density had the surprising effect of causing the hydrophilic groups with bound waters to resist the hydrophobic group-induced collapse at high temperatures. This

means that the crosslinker density must be considered an essential element of the molecular design process for this hydrogel. This along with other compositional effects allows the development of a phase transition phase diagram for a thermally responsive metal affinity hydrogel for the first time. This diagram in turn allows for the better molecular design of these hydrogels with sharp phase transition behavior for specific applications.

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References

[1] Zhuang Y, Chen L, Zhu Z, Yang H. Polym Adv Technol 2000;11:192.
[2] Dong CL, Hoffman AS. J Controlled Release 1986;4:223.
[3] Hoffman AS. J Controlled Release 1987;6:297.
[4] Kokufuta E, Aman Y. Polym Gels Networks 1997;5:439.
[5] Harmon ME, Tang M, Frank CW. Polymer 2003;44:4547.
[6] Iyer G, Yoon YS, Coleman MR, Nadarajah A. J Appl Polym Sci 2007;105:1210.
[7] Kaneko Y, Yoshida R, Sakai K, Sakurai Y, Okano T. J Membr Sci 1995;101:13–22.
[8] Park TG, Hoffman AS. Macromolecules 1993;26:5045.
[9] Tanford C. The hydrophobic effect – formation of micelles and biological membranes. New York: John Wiley & Sons; 1980. p. 29.
[10] Kesting RE. Synthetic polymeric membranes – a structural perspective. New York: John Wiley & Sons; 1985. p. 172.
[11] Feil H, Bae YH, Feijen J, Kim SW. Macromolecules 1993;26:2496.
[12] Rodríguez-Cabello JC, Alonso M, Pérez T, Herguedas MM. Biopolymers 2000; 54:282.
[13] Annaka M, Motokawa K, Nakahira T. Jpn J Appl Phys 2000;39:6643.
[14] Terekhova IS, Bogatyryov VL, Dyadin YA. J Supramol Chem 2002;2:393.
[15] Taylor CJ, Miller KT, Koh CA, Sloan ED. Chem Eng Sci 2007;62:6524.
[16] Wu C, Zhou S. Macromolecules 1995;28:8381.
[17] Ramon O, Kesselman E, Berkovici R, Cohen Y, Paz Y. J Polym Sci Part B Polym Phys 2001;39:1665.
[19] Hirotsu S, Hirokawa Y, Tanaka T. J Chem Phys 1987;2:1392.
[20] Iyer G, Tillekeratne LMV, Coleman MR, Nadarajah A. Macromolecules 2007;40: 5850.
[21] Iyer G, Tillekeratne LMV, Coleman MR, Nadarajah A. Polymer 2008;49: 3744.
[22] Hirotsu S. In: Dusek K, editor. Responsive gels: volume transition II. Advances in polymer science. New York: Springer Verlag; 1993. p. 16.
[23] Park TG, Choi KH. Macromol Rapid Commun 1998;19:167.
[24] Liu H, Avoce D, Song Z, Zhu XX. Macromol Rapid Commun 2001;22:675.
[25] Badiger MV, Lele AK, Bhalerao VS, Varghese S, Mashelkar RA. J Chem Phys 1998;109:1175.
[26] Inomata H, Goto S, Saito S. Macromolecules 1990;23:4887.
[27] Işik B. J Appl Polym Sci 2004;19:1289.