

Thermo-Sensitive Swelling Behavior in Crosslinked *N*-Isopropylacrylamide Networks: Cationic, Anionic, and Ampholytic Hydrogels

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SYNOPSIS

Crosslinked polymer networks of *N*-isopropylacrylamide (NiPAAm) containing small amounts of either anionic or cationic comonomers, or mixtures of both were fabricated and characterized in terms of their aqueous swelling and critical behavior. These gels demonstrate critical transition temperatures in aqueous media between a highly solvated, swollen gel state and a collapsed, dehydrated network over temperature ranges comparable to that of pure NiPAAm, with modifications of gel critical points and respective temperature ranges dependent upon comonomer type and content. Copolymer gel swelling ratios are significantly larger than those reported for pure homopolymer NiPAAm gels, even when only 0.5 mol % of comonomer is incorporated. At temperatures exceeding the collapse transition point, all copolymer gels collapse to a state of nearly complete dehydration, demonstrating short-time collapsed-state swelling ratios far lower than those of pure NiPAAm networks. Collapse kinetics for the ionomeric gels are much more rapid than those of pure NiPAAm, achieving collapse state equilibrium on time scales of seconds. Swelling behavior as a function of pH, buffer type, ionic strength, crosslinking, and temperature is detailed over a range of copolymer compositions. © 1993 John Wiley & Sons, Inc.

INTRODUCTION

A number of water-soluble polymer systems—polymethyl methacrylic acid,¹ poly(vinyl alcohol-*co*-ethylacetate),² poly(ethylene oxide),³ and *N*-isopropylacrylamide (NiPAAm)^{4,5}—demonstrate critical behavior leading to phase separation at elevated temperatures. The temperature characteristic of this event for each system is termed the lower critical solution temperature (LCST) and has been analyzed in terms of a large negative entropy change in the water-swollen polymer network at this critical point. Phase separation is usually manifested as a large, discontinuous volume change.

NiPAAm hydrogels demonstrate a nearly continuous (diffuse first order or second order) volume transition and associated phase transition from a low temperature, highly swollen gel network to a

collapsed, high temperature phase near its critical point between 31–35°C.^{4–6} The phase transition is analogous though fundamentally distinct from the LCST of its linear, soluble form and has been identified with the increase in entropy of the solvent—water—in the polymer network with increasing temperature, compensating for the decrease in entropy of the relatively hydrophobic polymer network as it collapses near the critical point.⁷ The overall contribution to the free energy of the gel system is negative, leading to this spontaneous and reversible behavior at this critical temperature.

Recently, efforts to incorporate hydrophilic,^{8,9} hydrophobic,¹⁰ and amphiphilic comonomers,¹¹ as well as efforts to build interpenetrating networks (IPNs)^{12,13} into NiPAAm systems have been reported for various applications as well as fundamental studies on its critical behavior. This has been followed by recent efforts to characterize the LCST of water-soluble linear NiPAAm solutions in the presence of various co-dissolved solutes, including salts and ionic polymers.^{14,15} However, gel-phase

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transitions are critically dependent on gel composition: all efforts have shown that increasing the amount of comonomer in the system by direct copolymerization, increases the critical point of each system and broadens the temperature range of the transition. At sufficiently high contents of comonomers or other network additives, critical behavior is no longer observed. Moreover, addition of salts to soluble NiPAAm depresses its LCST.

NiPAAm gels containing sodium acrylate (SA) in pure water have been studied previously by Tanaka and coworkers.^{5,16-18} Their results have indicated that incorporation of small amounts of anionic SA (0–2 mM) into NiPAAm networks produces continuous swelling transitions in macroscopic gels at critical temperatures, and higher SA contents elicit a discontinuous swelling transition. Moreover, the gel-transition temperature increases monotonically as a function of SA content. Volume changes associated with gel transitions dramatically increase as a function of increasing SA content, indicating the effect of ionized groups within the hydrogel network. NiPAAm gels containing cationic comonomers have also been reported.^{19,20} Swelling behaviors for these systems generally reflect the influence of the basic comonomer in broadening the NiPAAm swelling transition over all pH ranges, although some large pH-induced increases in swelling ratio are observed with pH-sensitive cationic comonomers.¹⁹ Most recently, acrylamide ampholyte hydrogels containing both sodium styrene sulfonate and methacrylamidopropyl trimethylammonium chloride (MAT) as opposite-charged ionic comonomers have also been reported.²¹ These gels show asymmetric swelling behavior in aqueous salt solutions, demonstrating higher swelling ratios in ampholyte gels of high cationic monomer content than for similarly prepared gels containing anionic monomer. The hydrophobicity of anionic styrene sulfonate was rationalized to inhibit swelling in the net anionic ampholyte gels and produce swelling asymmetry through a number of mechanisms. As comonomer ratios approach unity, ampholyte gels were observed to approach a single swelling ratio at higher ionic strengths, indicating that charge screening becomes a dominant effect governing gel swelling.

Okano and coworkers have published extensively about the behavior and properties of various NiPAAm gels in aqueous media.^{6,10,12,13,22-26} One significant feature reported regards the formation of a collapsed NiPAAm skin layer on the hydrogel surface above the critical temperature for these gels.^{18,22-27} This skin thickens with time above the critical temperature to become rate-limiting to water

permeation or flux out of the gel as it attempts to collapse at temperatures above the critical temperature. A hydrostatic pressure gradient develops in these collapsing gels, resulting in a dynamic surface rupture, or alternatively, a slow outward water permeation through the skin that can last for months until collapsed state equilibrium is reached.²⁸ Surface skin formation in NiPAAm copolymers has shown to be influenced by comonomer content. Hydrophobic comonomers, including *N*-alkyl methacrylates, show a chain length dependence on NiPAAm skin properties.²³⁻²⁷ Novel solute release properties of these copolymer gels, including reversible on-off switching and pulsatile release kinetics^{10,22-27} are relevant to a number of pharmaceutical and materials engineering interests.

The present work has been motivated by our interest in effecting rapid discontinuous transitions in hydrogels with increased volume changes over those observed for pure NiPAAm. We have directed our efforts at modulating the NiPAAm skin layer that forms on the gel surface as the network starts to collapse with increasing temperature. Incorporation of comonomers into NiPAAm networks influences the structure of the collapsed network and its permeability and barrier properties. Additionally, we were interested in comparing effects for different charged species in NiPAAm networks—anionic, cationic, and ampholytic gel networks—on gel swelling and collapse. We report here the aqueous swelling behavior of crosslinked NiPAAm copolymer networks containing small amounts of either anionic SA, cationic MAT, or both species as comonomers. We have observed the effects of charged comonomers on thermal, ionic strength, pH, and compositional dependent NiPAAm gel properties. Addition of minute amounts of ionic comonomers to NiPAAm networks produces hydrogel systems with greatly enhanced swelling ratios while retaining critical behavior. Incorporation of only 0.5–5 mol % of the anionic SA or cationic MAT produces marked influences on both swelling and collapse equilibrium states and kinetics of these processes over homopolymer NiPAAm gel systems. Ampholyte NiPAAm gels containing ratios of each comonomer produce gels with charge compensated swelling behavior.

EXPERIMENTAL

Materials

All solvents used were reagent grade. NiPAAm monomer (Eastman Kodak) was recrystallized twice from hexane/benzene (4 : 6 ratio). Sodium acrylate

(SA, Pfaltz & Bauer) was used as received. Methylene-bis-acrylamide (MBAAm, Aldrich) was recrystallized from ethanol. Tetramethylethylenediamine (TEMED) and ammonium persulfate were both obtained from Aldrich and used as received. MAT was purchased from Polysciences as a 50 wt % aqueous solution and used as received. All buffer salts and solutes were reagent grade compounds. Water for buffers and gel swelling was first reverse-osmosis filtered (deionized) and then Millipore filtered to yield purified water having 18 M Ω /cm resistivity.

Copolymer Gel Fabrication

NiPAAM-*co*-SA, NiPAAM-*co*-MAT, and NiPAAM-*co*-SA-*co*-MAT hydrogels were synthesized using MBAAm as a crosslinking agent. For aqueous redox polymerizations, ammonium persulfate and TEMED were used as initiators in a procedure adapted from that used by Cole et al.²⁹ Aqueous solutions of mixed monomers of NiPAAM and SA, MAT, or SA/MAT were made in nitrogen-bubbled Millipore water in a series of compositions (NiPAAM/SA, NiPAAM/MAT, and NiPAAM/SA/MAT mole ratios: 100 : 0, 99.5 : 0.5, 99 : 1, 98 : 2, 97 : 3, 96 : 4, 95 : 5, 90 : 10) and concentrations (5.0, 7.5, 10.0, 12.5, 15 mol % total monomer content in water). A range of MBAAm concentrations (0.5, 0.7, 1.0, 1.2, 1.5, and 2 mol %) was used with the monomer solutions. Ammonium persulfate and TEMED were mixed into the aqueous solutions and bubbled with nitrogen for 15 min before mixing with monomer solutions. The complete mixtures were injected between clean glass plates separated by 2-mm thick gaskets (2 mm OD crosslinked silicone rubber O-ring material) with care taken to avoid the introduction of air bubbles into the gel. The plates were clamped securely and suspended in a water bath at 20°C for 1 h. The resulting hydrogel films were then separated from the plates and allowed to swell in deionized water/ethanol (30% alcohol) for 3 days, followed by swelling in pure deionized water for 1 week. Swollen copolymer hydrogel membranes were subsequently cut into disks of 1-cm diameter using a cork borer, dried ambiently for 1 day, and under vacuum for 3 days at room temperature.

Swelling Measurements

For measurements across a range of pH conditions, a series of buffers with maximum buffering capacities at various pH values were made. Potassium phthalate (pH 3), sodium acetate (pH 5), phosphate

(pH 7–9), Tris (pH 8–10), and borate (pH 10) buffers were made in a series of ionic strengths as stocks in stoppered, acid-cleaned flasks. Small amounts of 0.1 N NaOH or HCl were added to adjust final buffer pH. Dried hydrogel disks were initially immersed and equilibrated in buffer solutions in glass vials at 20°C for 2 days. These vials were in turn immersed in a shaking water bath (American Scientific Model YB-521) at a series of temperatures from 20 to 70°C for 2 h. Each sample was then removed from the water bath and from its respective vial, tapped with a dampened Kim-wipe towel to remove excess surface water, and weighed directly using an electrobalance (Ohaus GA200D). The dry weights were measured on the same balance after desiccating the same gels for 3 days under vacuum at room temperature until constant dry weights were maintained. Swelling ratios (SR) were calculated from the following formula:

$$\text{SR} = (\text{wet weight} - \text{dry weight}) / (\text{dry weight})$$

$$\text{or } (W_t - W_d) / W_d \quad (1)$$

Water content in gels as a function of temperature was calculated as:

$$\% \text{ water} = (W_t - W_d) / (W_0 - W_d) \quad (2)$$

where W_t = gel weight at temperature, t ; W_d = gel dry weight; and W_0 = fully hydrated weight of gel.

Swelling measurements were determined as a function of SA, MAT, or SA/MAT content, MBAAm crosslink content, pH, ionic strength, monomer concentration during polymerization, and temperature.

RESULTS AND DISCUSSION

We note here that experimental techniques used in this work contrast work by others in observing critical behavior in NiPAAM gels. Most other work reported for this gel has examined temperature-dependent behavior by approaching the critical point from higher temperatures; that is, observing the collapsed-to-swollen state transition by cooling. We report temperature-dependent swelling by warming gels from fully swollen states below the critical point and incubating at elevated temperatures for 2 h before measuring swelling changes. These two methods will produce different results for gel swelling/deswelling kinetics.¹⁸ Figure 1 shows the differences between pure NiPAAM gel collapse and that for NiPAAM/SA 97 : 3 after a temperature jump be-

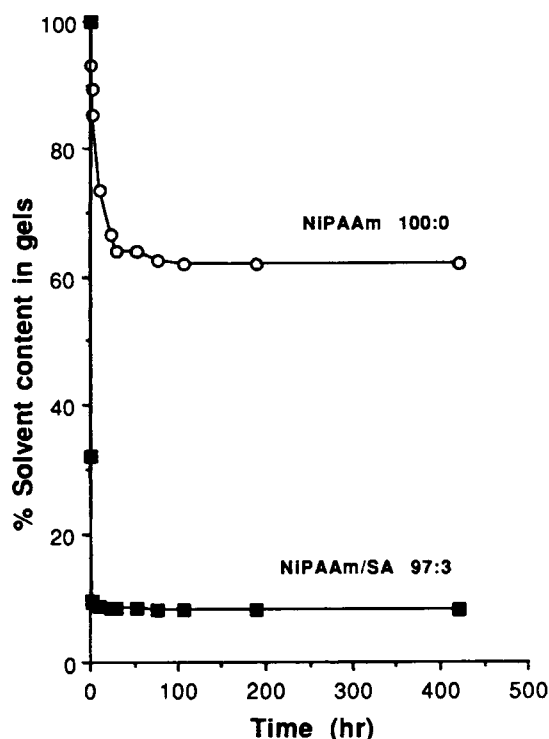


Figure 1 Contrasting collapse kinetics between 100% NiPAAm and NiPAAm/SA 97 : 3 hydrogels at pH 7 (0.1M PBS buffer) undergoing thermal transition from 20 to 40°C.

tween swollen (20°C) and deswollen (40°C) states as a function of time. The anionic NiPAAm gel shows a very rapid collapse directly to equilibrium within a few minutes, while the kinetics for pure NiPAAm are orders of magnitude slower¹⁸ and equilibrium is achieved only after long periods of time. For ionic gels, swelling-collapse equilibria are achieved well within the 2-h incubation times for these measurements. Formation of the collapsed NiPAAm skin on the gel surfaces directly influences these kinetics and will be addressed later in detail.

Changing pH should influence the protonation of only SA groups in the NiPAAm gels. Changes in gel swelling, therefore, should reflect SA ionization and both SA and MAT content in the NiPAAm gel networks. Figures 2–6 display the swelling behaviors of NiPAAm copolymer hydrogels containing various amounts of SA and MAT comonomers at various pH values as a function of temperature. Pure NiPAAm, as a reference, shown in Figure 2 at pH 7, shows very limited collapse behavior upon heating in contrast to that already reported for cooling.⁹ The pure NiPAAm gel shows an initial swelling ratio of nearly 12 at 20°C that decreases to approximately

8.5 above 35°C (350% decrease in swelling). Qualitatively, the gel goes from a transparent disc at low temperature to a smaller, condensed white, opaque disc above the critical point. Both of these swelling results for pure NiPAAm gels are independent of buffer or pH: that is, roughly equivalent NiPAAm swelling behavior is observed in all buffer systems presented herein.

Incorporation of the anionic comonomer SA produces swelling ratios that increase dramatically at all pH values over that seen for pure NiPAAm. At pH 8 (Fig. 2), relatively high levels of SA incorporation (95 : 5 mole ratio) demonstrate maximum swelling capability (SR = 28) at low temperature as well as the maximum transition to a collapsed state above the transition (SR ~ 1). Also notable is the fact that the addition of only minute amounts of SA comonomer (0.5 mol %) radically changes the swelling behavior of the gels over pure NiPAAm without changing the critical point. The hierarchy of swelling at this and all pH values is directly related to SA content, with the gel of lowest SA ratio (99.5 : 0.5) showing lowest swelling ratios at low temperature and lowest degree of collapse at higher tem-

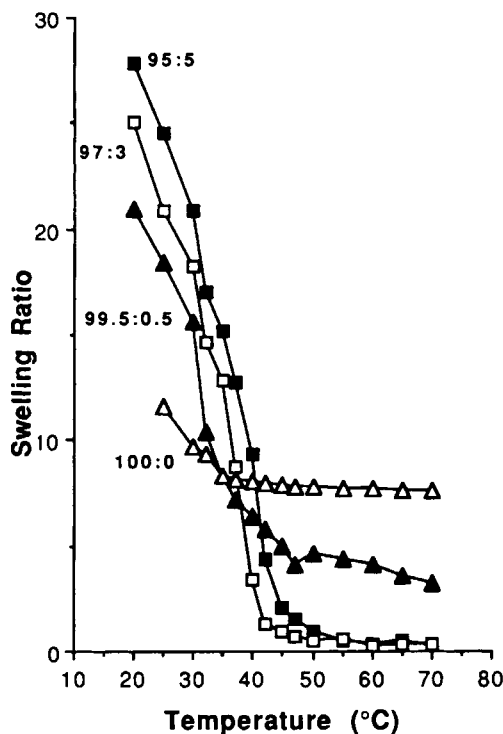


Figure 2 Swelling behavior of anionic NiPAAm copolymer hydrogels containing various amounts of sodium acrylate comonomer at pH 8 as a function of temperature. Buffer: Tris, 50 mM.

peratures. Nevertheless, all anionic gel swelling behaviors are substantially greater than those observed for pure NiPAAm gels over these time courses.

At pH 3, swelling trends remain generally the same as at pH 8 (Fig. 3). However, magnitudes for low-temperature swelling ratios for the 95 : 5 NiPAAm/SA gel system are significantly reduced over that seen at pH 8. Moreover, swelling ratios of the collapsed states decrease for all compositions. The contrast with hydrogel behavior at pH 8 is a direct effect of protonation of the comonomer carboxylate groups at this lower pH (bulk carboxylate $pK_a \approx 5.6$). Hydrophilic, ionized SA at high pH produces electrostatic repulsion, yielding highly expanded gel networks (greater SR) at lower temperatures. Additionally, the ionized groups disrupt NiPAAm skin formation at high temperatures, allowing both water to rapidly escape outward with gel collapse and gels to collapse further without hydrostatic pressure opposition.

Data taken from higher pH buffers (pH 9) continue the swelling/deswelling trends seen at pH 8; that is, swelling ratios for all compositions increase dramatically over those at low pH and over pure

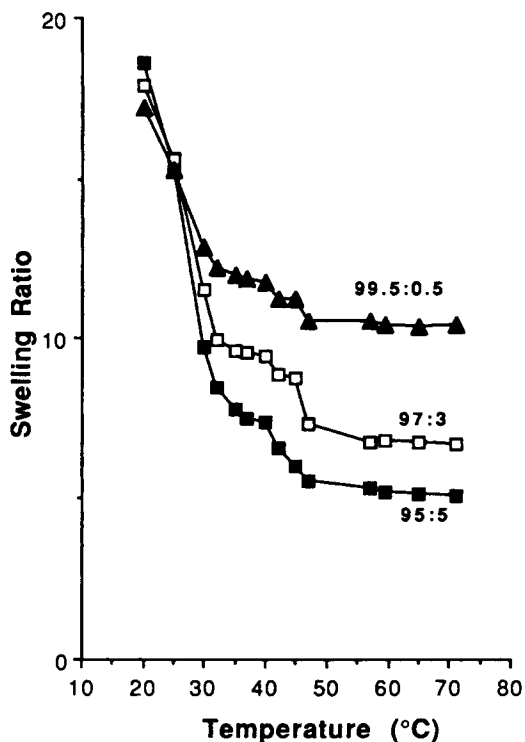


Figure 3 Swelling behavior of anionic NiPAAm copolymer hydrogels containing various amounts of sodium acrylate comonomer at pH 3 as a function of temperature. Buffer: potassium phthalate, 50 mM.

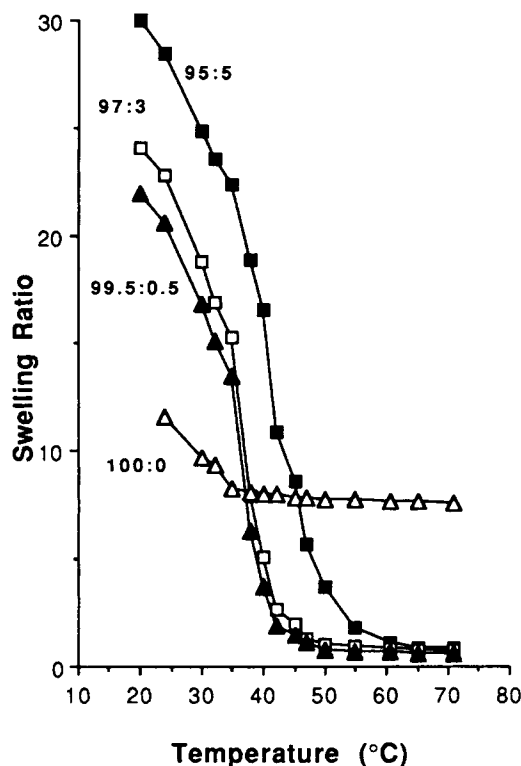


Figure 4 Swelling behavior of anionic NiPAAm copolymer hydrogels containing various amounts of sodium acrylate comonomer at pH 9 as a function of temperature. Buffer: Tris, 50 mM.

NiPAAm. Figure 4 shows data for copolymer gel swelling at pH 9. Maximum swelling ratios for 95 : 5 gels are over double ($SR > 30$) the swelling observed for pure NiPAAm. Only swelling ratios for gels of higher SA content are significantly increased over those at pH 8, indicating that SA-containing gels further ionize between pH 8 and pH 9. This reflects the differing activity of counterions and charged SA groups within the gel compared to free solution ionized states. Moreover, copolymer gel collapsed states above the transition temperature show swelling ratios that approach a value of 1. Recalling that the pure NiPAAm gel collapses to a shrunken state above the critical transition region, yielding a swelling ratio of 8.5 under these conditions, a swelling ratio near unity is a remarkable condition reflecting the dramatic phase transition these systems undergo that is completely dependent upon SA addition to the gel. Qualitatively, this is observed as a shrunken gel state that is many times smaller and condensed than the starting gel. In these cases, where the swelling ratio approaches unity, the collapsed copolymer gel is nearly completely dehy-

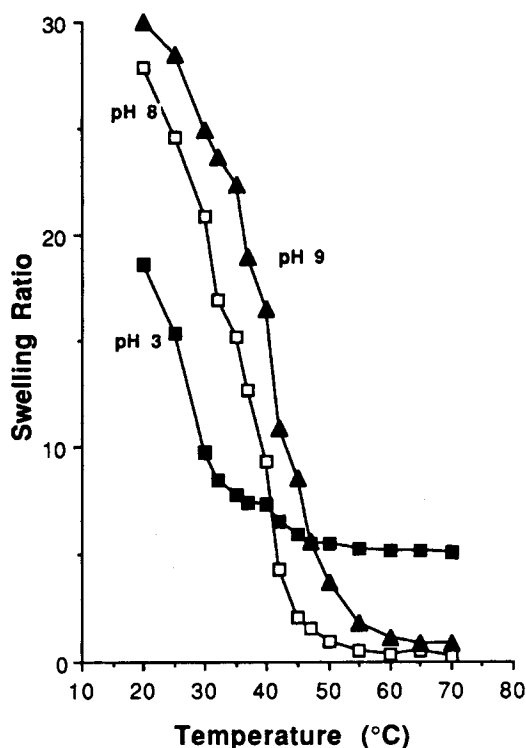


Figure 5 Influence of pH on the swelling behavior of anionic NiPAAm/SA copolymer 95 : 5 hydrogels as a function of temperature. Buffer concentration: 50 mM.

drated, even though it is immersed in water. This situation is very different from that observed for pure NiPAAm gels, where equilibrium collapse produces a swelling ratio nearly an order of magnitude higher. Small bubbles of gel, similar to those reported by others,^{18,22} are observed to emerge from the edges of the copolymer discs under these completely collapsed conditions, because of the formation of a NiPAAm skin on the disc surface.^{18,22-27} In addition, the gel physically completely deforms to a small, clear polymer bead with a bubbled surface, qualitatively much different than the white, opaque appearance of the collapsed, pure NiPAAm gel. This condition indicates nearly complete expulsion of water from the copolymer network caused by the incorporation of the ionic comonomer. The pH-dependent data for 95 : 5 gels at different pH values analyzed are collected in Figure 5 for comparison. Swollen gel weights at various temperatures were compared to completely desiccated gel weights to yield data on water contents within gels at various states. The data (not shown) indicate that only 30% of the water in pure NiPAAm gels is expelled by the collapse transition at pH 7 before the overlying collapsed NiPAAm skin layer blocks efflux. Addition

of 1 mol % SA to these gels allows 80% water content reduction and 3–5 mol % SA incorporation produces collapsed gels above the critical transition having only 5% water content or less. These data demonstrate the remarkable result of this collapse transition to mechanically expel hydrogel water and produce networks of varying hydration after collapse.

Swelling curves for NiPAAm gels containing either MAT alone (97 : 3) or both SA and MAT are shown in Figure 6 at pH 3. Under these conditions, the SA group is fully protonated and swelling of the gel sample containing NiPAAm/SA 97 : 3 (no MAT) is reduced because of the lack of charge at this pH. MAT is cationically charged at all pH values studied and its incorporation into NiPAAm gels produces similar pH-independent swelling effects as observed for ionized SA at basic pH (data not shown). In amphoteric NiPAAm gels containing both SA and MAT in various stoichiometries at pH 3, all swelling ratios are significantly increased at lower temperatures and decreased at temperatures above the transition, resulting in greatly enhanced collapse volumes over that shown for NiPAAm/SA gels con-

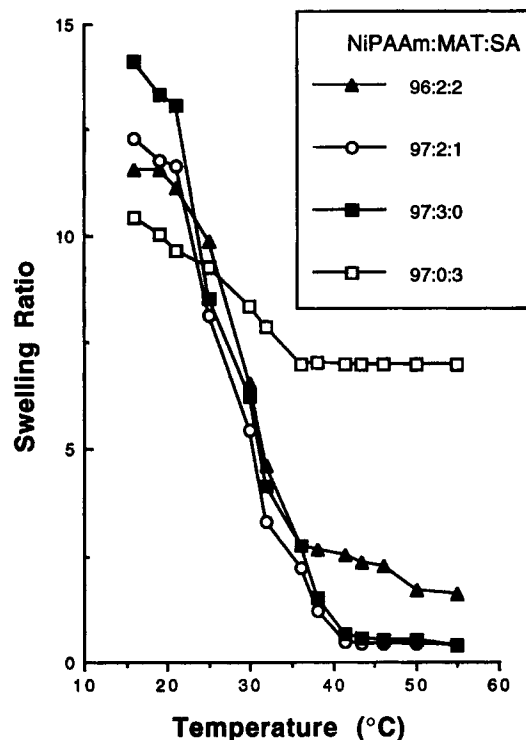


Figure 6 Swelling behavior of amphoteric NiPAAm copolymer hydrogels containing various amounts of cationic MAT and anionic SA comonomers at pH 3 as a function of temperature. Buffer: potassium phthalate, 50 mM.

taining no MAT (NiPAAm : MAT : SA 97 : 0 : 3). Increasing the MAT ratio over SA in these gels results in systematic increases in swollen phase (low temperature) swelling ratios. Collapsed swelling ratios increase with MAT content only up to 2 : 1 MAT : SA ratios then remain constant with increasing cationic content.

Combination of MAT and SA in NiPAAm gels enhances swelling and collapse even at 1 : 1 molar ratios. Figure 7 shows the influence of pH on NiPAAm gels containing 1 : 1 molar ratios of MAT/SA. The presence of MAT's cationic residue enhances swelling at low pH. At basic pH (pH 7 and 9), SA becomes ionized. The net competitive effects of MAT-SA electrostatic attraction and SA-SA and MAT-MAT charge-charge repulsive interactions are demonstrated as enhanced swelling at low temperatures and very low collapse ratios approaching unity at elevated temperatures.

Swelling Effects Derived From Ionic Comonomer Incorporation

Incorporation of negatively charged SA components into the gel networks provides a number of impor-

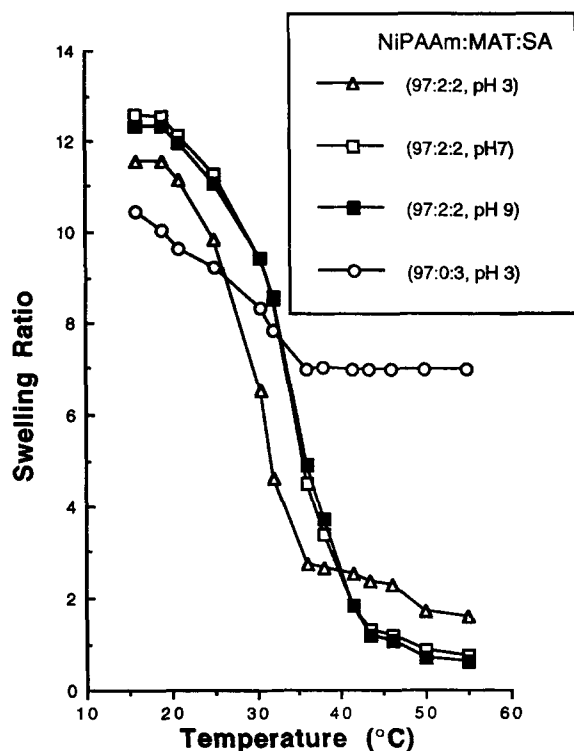


Figure 7 Influence of pH on the swelling behavior of ampholytic NiPAAm copolymer gels as a function of temperature at constant ionic strength (200 mM buffers).

tant interactions. Initially, the acrylate salt dissociates easily, presenting mutually repulsive negative carboxylate residues that prompt network expansion and swelling. These polar groups also add a significant hydrophilic component to a largely hydrophobic (or at least critically balanced amphipathic) NiPAAm network. These two effects support the significant enhancement in aqueous swelling behavior below the critical point seen in these systems over NiPAAm. At and above the critical point, the ionized acrylate groups still attract water. However, being such a small minority component, the acrylate's contribution to swelling above the thermally induced transition is overwhelmed by the entropic drive for NiPAAm dehydration and collapse. This influence can also be analogously attributed to cationic MAT with the notable exception of its pH independence.

The magnitude of gel collapse above the critical point is observed to increase with increasing pH in all gels, demonstrating modest levels of collapse at acid pH, although still significantly greater than those seen for pure NiPAAm. Swelling ratios below the critical temperature regime continue to increase with increasing pH (as pH moves above the pK_a for SA and more ionized groups are created in the network). Final collapse states appear to be independent of gel composition at neutral and basic pH, indicating the dominant collapse effect of NiPAAm in the networks at all contents tested. Nevertheless, despite minute levels of incorporation, anionic SA and cationic MAT remain essential to augmenting collapse, allowing the copolymer gel to expel water through hydrophilic charged domains as it collapses during thermal transition. This is the critical difference between partial collapse states observed in a pure NiPAAm gel and complete collapse seen in those that incorporate just a small amount of ionic comonomers.

Incorporation of small amounts of charged species are proposed to provide the NiPAAm gel matrix with hydrophilic channels that facilitate water movement during thermally induced transitions. Pure NiPAAm and NiPAAm copolymer gels with hydrophobic comonomers are reported to shrink above the transition point only to a degree limited by how much water is allowed to escape from the gel before a collapsed "polymeric skin" of NiPAAm covers the gel surface to block water (and solute) release. Because such polymer skin formation is reversible with temperature, this has been called the "on-off switching effect" for various controlled release strategies.²²⁻²⁷ In the NiPAAm copolymer gels, collapse can therefore be more complete (approach a swelling ratio

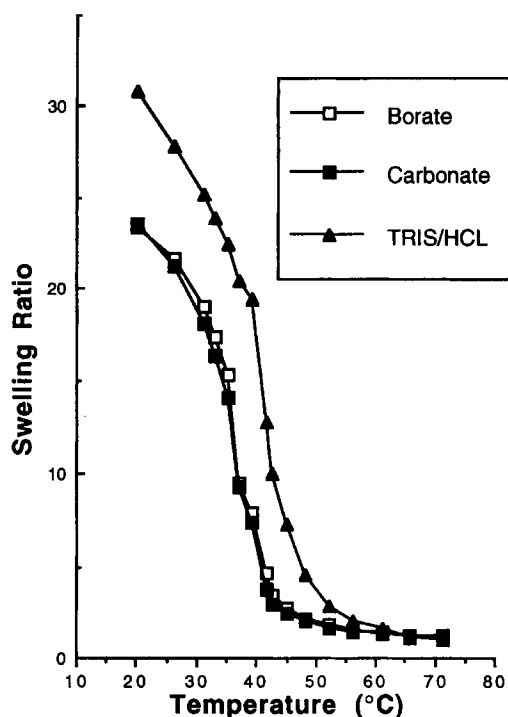


Figure 8 Effect of buffer chemistry on swelling ratios of a NiPAAm/SA copolymer hydrogel (96 : 4) as a function of temperature at pH 9, constant ionic strength (buffer concentration = 50 mM).

close to 1) because the NiPAAm polymeric skin layer that controls and limits water release is, in the charged copolymer gels, perforated with hydrophilic channels that allow water movement out of the gel even above the collapse transition. More importantly, this effect can be created with small amounts of charged constituents that do not significantly alter the position of the critical point. Additionally, the phenomenon is completely reversible; after such a radical collapse above the collapse point, the gel is able to fully recover both its original dimensions and swelling ratio upon cooling.

Physically, the critical behavior exhibited by pure NiPAAm networks during the volumetric change represents a two-phase, nonequilibrium phenomenon, at least over the kinetic regime typically studied (hours to days). The transition itself is diffusion-controlled,³⁰ mediated via thermal convection as the aqueous medium surrounding the gel is heated. Water of higher temperature is transported from bulk media through the boundary layer to the gel surface, causing the surface-exposed polymer chains to react first to the increased temperature and to collapse as their hydration shells are broken. The resulting collapsed polymeric skin formed upon contact with

water heated above the critical point slows further convection and diffusion of higher temperature water into the network. At least in pure NiPAAm systems, the network collapse from the outside eventually produces a situation where diffusion and transport in both directions is inhibited and, over shorter experimental time scales, likely prevented. Gel collapse from its exterior inward traps a pool of hydration water associated with collapsing polymer in the gel interior. Because thermal transport is much more rapid than mass transport in these systems,³⁰ the gel's dehydrated interior then coexists with the collapsed polymer shell around it, and a gradient of hydrostatic pressure of entrapped water exists across these regions.²³⁻²⁶ This pressure gradient resulting from entrapped water distinguishes experimentally those pure NiPAAm networks that cannot collapse completely because of water trapped in their swollen interiors from NiPAAm copolymer gels that preserve their critical behavior, yet permit complete collapse of the polymer network at the transition point. Differences are caused solely by the introduction of small amounts of hydrophilic components that act to channel water through a collapsed polymer network during the critical phenomena. Water channeling is bidirectional, that is, both

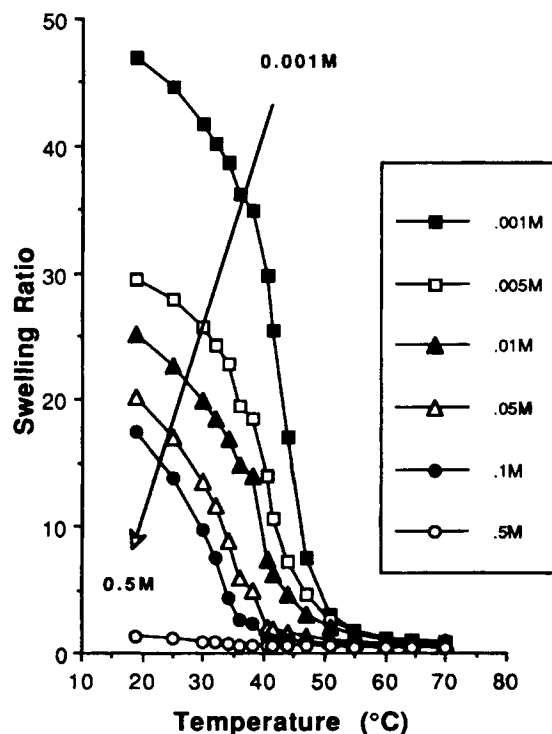


Figure 9 Effect of ionic strength (NaCl addition) on NiPAAm/SA copolymer gel swelling (97 : 3 copolymer) as a function of temperature at pH 7 in phosphate buffer.

into and out of the gel during transition, in order to promote both inward diffusion of higher temperature water producing network collapse, and outward flow of once-bound water necessary in producing the initial swollen state.

Figure 8 shows the effect of buffer chemistry on swelling ratios of a NiPAAm-SA copolymer hydrogel (96 : 4) as a function of temperature at pH 9 at constant ionic strength (50 mM buffer). These data indicate that while inorganic buffers show consistent influences on swelling ratios, the organic Tris buffer enhances swelling at pH 9 by nearly 30%. This effect is proposed to arise from the different activity of tri(hydroxyethyl) ammonium counterions in their association with negatively charged acrylate sites within the gel network compared to bulk ions, leading to unusual osmotic effects that promote more extensive network hydration in the case of the organic buffer, Tris. Coworkers have observed similar effects of buffers (specifically organic buffers) on shifting phase-transition temperatures in lipid dispersions,³¹ but no data are currently available to explain these phenomena.

Increasing ionic strength serves to electrostatically screen the anionic carboxylate residues and

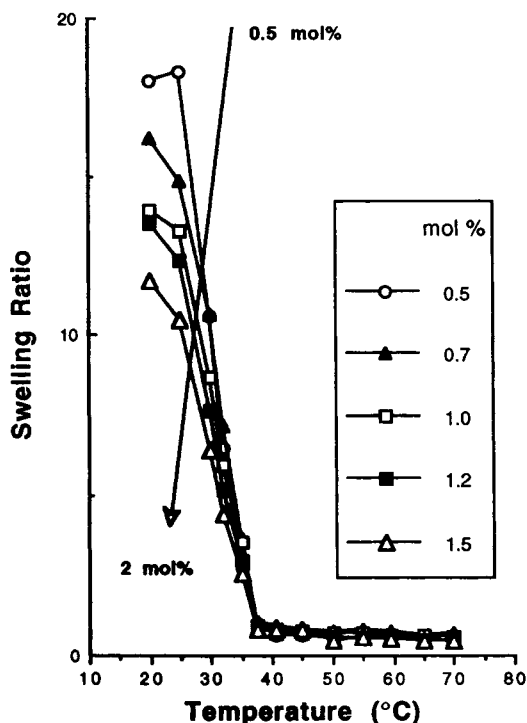


Figure 10 Effect of crosslinker concentration on copolymer gel swelling as a function of temperature in 0.1 M PBS, pH 7, for NiPAAm/SA gels (97 : 3) at 10 mol % monomer feed concentration during polymerization.

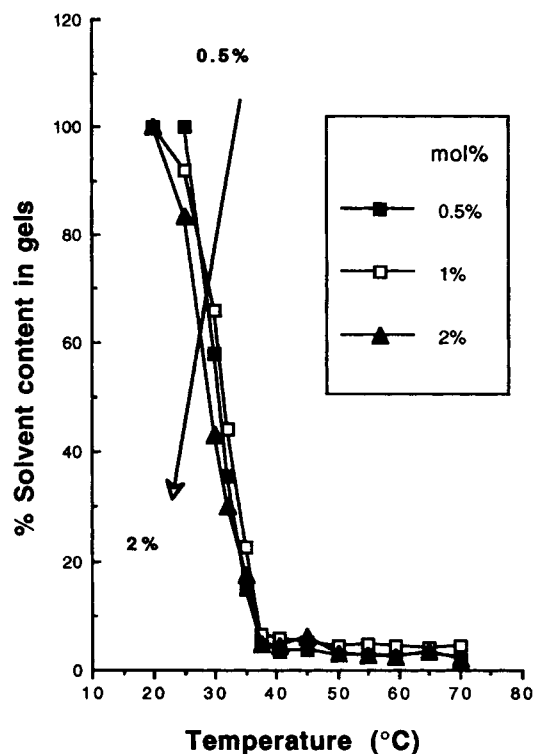


Figure 11 Aqueous solvent content of NiPAAm/SA copolymer gels (97 : 3) as a function of temperature for gel preparations containing increasing MBAAm crosslinker concentrations in the feed. Buffer: 0.1 M PBS, pH 7.

cationic ammonium groups in the copolymer gel matrix, decreasing the effective distance of their mutually attractive or repulsive interactions and reducing the swelling propensity. Figure 9 shows the effect of ionic strength on gel swelling (96 : 4 copolymer) as a function of temperature in the NiPAAm/SA 97 : 3 copolymer system pH 7 (phosphate buffer). The apparent trend here is that increasing ionic strength of the aqueous media decreases the swelling ratio when below the collapse transition (swollen condition), but does not affect the final collapsed state above the critical region. Moreover, increasing ionic strength leads to decreasing critical temperature values. Extremely high ionic strength values (0.5 M) completely erase the swelling behavior of the copolymer gel as well as any observable transition. These results can be rationalized in terms of chain salting-out properties resulting from removal of hydrating water molecules from the polymer chains to solvate excessive salt present at high ionic strength.

Figure 10 shows the effect of increasing crosslinker concentration on copolymer gel swelling as a

function of temperature in phosphate buffer at pH 7 (0.1M) for NiPAAm-SA gel (97 : 3 mole ratio) at 10 mol % monomer concentration. The trend is that increasing crosslinking leads to predictably decreased swelling ratios in the swollen state when below the critical temperature regime. Collapsed swelling ratios above this point are not affected. However, crosslink density has little apparent effect on critical behavior outside of changing its magnitude. When these data are normalized to reflect the amount of solvent in each gel as a function of temperature compared to their completely desiccated states (Fig. 11), no significant differences in the samples are seen. This indicates that all copolymer gels, regardless of crosslink density, undergo collapse to the fullest extent to nearly complete dehydration. Further data on effect of crosslinker chemistry (data not shown) demonstrates that swelling and collapse in NiPAAm copolymer gels are both independent of crosslinking architecture, although mechanical properties are significantly altered. Crosslinkers based on triallylamine, piperazine bisacrylamide, and cysteine bisacrylamide all show identical swelling ratios and critical transitions.

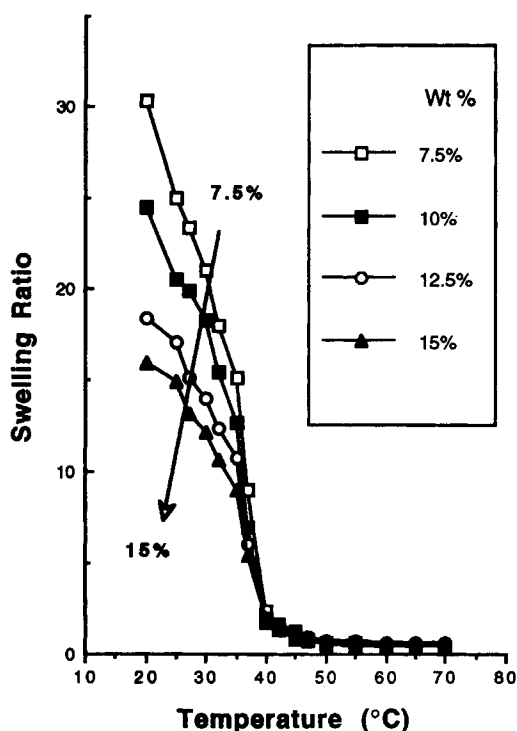


Figure 12 Effect of total monomer feed concentration in the aqueous polymerization medium on the resulting NiPAAm/SA 97 : 3 copolymer gel swelling as a function of temperature: Tris buffer (pH 8, 50 mM).

Figure 12 demonstrates the effect of total monomer concentration in the polymerization medium on the copolymer gel swelling as a function of temperature at pH 8 in Tris buffer (50 mM). The rationale for this experiment was to study whether the copolymer network structure and swelling behavior were affected by the concentration of the monomer solution during polymerization. Again, while swelling ratios in the swollen gel state below the critical temperature regime decrease with changing monomer ratios, the collapsed behavior above this regime remains constant, independent of monomer concentration. In addition, the collapse transition remains unchanged by total monomer concentration in the polymerization medium. This effect is analogous to that produced by changing the crosslinking concentration, resulting in polymer networks with different network architecture induced by monomer feed concentration.

CONCLUSIONS

Introduction of small quantities of ionic, hydrophilic comonomers (sodium acrylate and methacrylamidopropyl trimethylammonium chloride) into crosslinked NiPAAm hydrogel networks substantially alter the thermo-sensitive swelling and collapse behavior of these gel systems during discontinuous volume transitions occurring at their critical points. Swelling ratios in swollen gel states below the critical point are significantly greater than those of pure NiPAAm gels, and collapsed states are much more condensed, approaching swelling ratios near unity for all copolymer gels studied. This behavior is interpreted in terms of a gel structural model that considers the effect of hydrophilic constituents on water transport in transition state networks undergoing critical phenomena. Crosslinked NiPAAm homopolymer gels cannot collapse completely because of a dehydrated, dense polymeric skin overlying the gel exterior above the critical transition produces a nonequilibrium entrapment of water within the gel that supports this model. Complete network collapse after substantially enhanced swelling in the copolymer gel systems provides evidence that water entrapped by gel collapse can diffuse both in and out of the gel, even after polymer skin formation on the gel surface. These phenomena are, to some extent, both composition and pH dependent, although minute amounts of ionic comonomers (0.5 mol %) produce the typical behavior. The ability of ionized comonomers to remain charged and interact electrostatically with aqueous

media and themselves within the copolymer network over a wide range of ionic strengths and pH values is proposed to explain significantly increased swelling and collapse behavior in the crosslinked copolymer gel systems over that for pure NiPAAm.

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