

Swelling Equilibria for Weakly Ionizable, Temperature-Sensitive Hydrogels

Sagrario Beltran, John P. Baker, Herbert H. Hooper,[†]
Harvey W. Blanch, and John M. Prausnitz*

Chemical Engineering Department, University of California, Berkeley, California 94720, and
Materials and Chemical Sciences Division, Lawrence Berkeley Laboratory,
1 Cyclotron Road, Berkeley, California 94720

Received May 21, 1990; Revised Manuscript Received July 23, 1990

ABSTRACT: Swelling equilibria in aqueous citrate-phosphate buffer solutions are reported for thermally sensitive poly(*N*-isopropylacrylamide) hydrogels containing weakly ionizable groups. The comonomers containing these groups were sodium acrylate and 2-(dimethylamino)ethyl methacrylate to produce gels with, respectively, acidic and basic character. Gel swelling was measured as a function of pH, ionic strength, and temperature. With increasing ionization, the temperature range over which the gel volume change is greatest becomes larger and shifts to higher temperatures.

Introduction

Much attention has been directed in recent years at hydrogels that undergo large volume changes in response to small variations in solution conditions.¹ Temperature and pH have been the solution variables of greatest interest, primarily because these variables change (or can be changed) in typical physiological, biological, and chemical systems. Temperature- and pH-sensitive gels have been suggested for use in a variety of novel applications including controlled drug delivery,^{2,3} immobilized-enzyme reactors,⁴ and separation processes.⁵

Temperature-sensitive gels can be prepared from *N*-substituted acrylamide derivatives (e.g., *N*-isopropylacrylamide, and *N,N'*-diethylacrylamide) which exhibit lower critical solution phase transitions (LCST behavior) in the un-cross-linked, homopolymer form in aqueous solution.⁶ Gels prepared from these polymers exhibit volume collapse upon warming.^{7,8} Gels that are sensitive to pH are prepared by copolymerizing weakly ionizable electrolytes into a polymer network.² Variations in solution pH induce a change in network ionization and a corresponding change in swelling capacity.

Previous studies of temperature- and pH-sensitive gels have usually considered systems sensitive to only one of the two variables. In previous work, we have investigated the swelling properties of acrylamide gels containing a strong electrolyte⁹ and also those of temperature-sensitive poly(*N*-isopropylacrylamide) gels containing a strong electrolyte.⁷ In this work, we report swelling behavior for two gels that are both temperature- and pH-sensitive. We have studied a *negatively* ionizable gel (poly(*N*-isopropylacrylamide) copolymerized with sodium acrylate) and a *positively* ionizable gel (poly(*N*-isopropylacrylamide) copolymerized with 2-(dimethylamino)ethyl methacrylate); we have also studied *uncharged* poly(*N*-isopropylacrylamide) gel as a reference system. We report swelling behavior in aqueous citrate-phosphate buffer solutions as a function of temperature, pH, and solution ionic strength.

Experimental Section

Gels were synthesized by free-radical solution copolymerization of *N*-isopropylacrylamide (NIPA) with a comonomer and a cross-

linking agent. Three gels were prepared: (1) uncharged poly-NIPA gel (no comonomer); (2) a negatively ionizable, or weakly acidic gel (sodium acrylate (SA) as the comonomer); and (3) a positively ionizable, or weakly basic gel (2-(dimethylamino)ethyl methacrylate (DMA) as the comonomer). *N,N'*-Methylenebisacrylamide (BIS) was used as chemical cross-linker for all gels. The polymerization reaction was similar to that described by Hooper et al.⁷ However, in this work, the reaction was initiated with ammonium persulfate (APS) and accelerated with tetramethylethylenediamine (TEMED). All gels were prepared with the same nominal composition. The diluent (water) concentration at preparation was fixed at 0.92 volume fraction water (0.08 volume fraction of monomers with respect to total solution volume). The relative monomer concentrations, on a water-free basis, were 0.01 mole fraction BIS and 0.1 mole fraction comonomer. For poly-NIPA gel, no comonomer is used. For a 100-mL reaction solution, initiator and accelerator concentrations were 0.05 g of APS and 0.4 cm³ of TEMED. The initial solution was prepared in an ice bath and then poured into chilled molds (pairs of glass plates separated by 0.1-cm Teflon spacers). The molds were held at 10 °C for 48 h, which is sufficient time for completion of reaction. Careful temperature control was necessary to ensure that the negative (exothermic) heat of reaction did not induce phase separation during polymerization; such separation would occur near 32 °C, the lower critical solution temperature for NIPA in water.

After reaction completion, the gels were removed from the molds and cut into 1-cm-diameter disks. The disks were placed in excess deionized water, which was replaced daily, for 1 week. The equilibrated gel disks in water served as starting samples for the remaining experiments. Several sample disks were dried in a vacuum oven to determine the hydration of the water-equilibrated gels. Other disks were placed in various aqueous buffer solutions (described below) to determine pH, ionic strength, and temperature effects on swelling. Water-equilibrated samples were weighed, placed in solution, and then reweighed upon equilibration in solution. The surface wetness was removed by blotting the samples with laboratory tissue prior to weighing. The swelling capacity (g of swollen gel/g of dry gel) was determined by using the known hydration of the gels in deionized water.

Results and Discussion

Figure 1 presents swelling equilibria at 7 °C for poly-NIPA-co-DMA and poly-NIPA-co-SA gels in aqueous citrate-phosphate buffer. Swelling was measured as a function of buffer ionic strength, which varied from 0.005 to 0.5 M. Solution pH was fixed to obtain maximum swelling (ionization) for each gel, thereby allowing ionic strength effects to be observed most clearly. The pH was fixed at 8 for the poly-NIPA-co-SA gel and at 3 for the

* To whom correspondence should be addressed at the University of California.

[†] Present address: Air Products and Chemicals, Allentown, PA 18195.

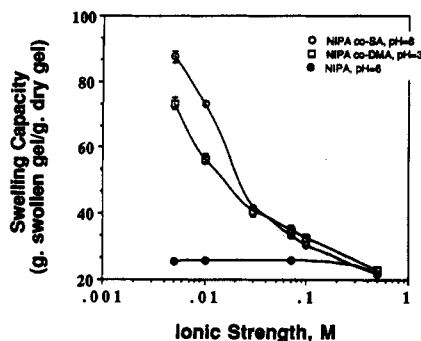


Figure 1. Swelling equilibria at 7 °C for NIPA copolymer gels in aqueous citrate-phosphate buffer solutions. Ionic strength of the buffer varied from 0.005 to 0.5 M.

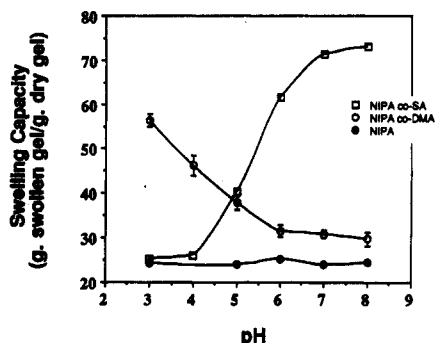


Figure 2. Swelling equilibria at 7 °C and 0.01 M ionic strength for NIPA copolymer gels in aqueous citrate-phosphate buffer solutions. The solution pH varied from 3 to 8.

poly-NIPA-co-DMA gel. As shown in Figure 2, no pH effect was seen for the poly-NIPA gel, which was placed in buffer solutions with pH 6 for five different ionic strengths. As observed in previous work, gel swelling in electrolyte solutions at low ionic strength is strongly dependent on the degree of gel ionization.^{7,9} As ionic strength rises, the ionized gels deswell; at 0.1 M ionic strength, the three gels have nearly identical water contents. The effect of ionic strength on the swelling of ionized gels seen in Figure 1 is similar to that observed elsewhere⁷ and has been explained by using Donnan-equilibria arguments.^{9,10} As ionic strength rises, the difference in concentration of mobile ions between the gel and solution is reduced, thereby decreasing the osmotic swelling pressure of these mobile ions inside the gel.

The results shown in Figure 1 were used to determine the ionic strength to be used in further experiments. Charge effects are damped at high ionic strength, making that limit undesirable if ionization effects are to be distinguished. An adequate, buffer capacity (≥ 0.01 M) is needed for studying weakly ionizable gels. We therefore used an ionic strength of 0.01 M for all further experiments.

Figure 2 shows pH-dependent swelling behavior at 7 °C for the three gels (poly-NIPA, poly-NIPA-co-DMA, and poly-NIPA-co-SA) in citrate-phosphate buffer; swelling capacity was measured from pH 3 to pH 8. Consistent with expectations, swelling of the polybasic NIPA-co-DMA gel was found to decrease with pH, while the swelling of the polyacidic NIPA-co-SA gel was found to increase with pH. The percentage of DMA groups (nominal $pK_a = 7.7$) ionized in the poly-NIPA-co-DMA gel should be close to 100 at pH 3; similarly, the percentage of SA groups (nominal $pK_a = 4.3$) ionized in the poly-NIPA-co-SA gel at pH 8 should also be close to 100. However, the poly-NIPA-co-SA gel swells 35% more at pH 8 compared to the poly-NIPA-co-DMA gel at pH 3. A plausible explanation for this difference in swelling may be found by considering

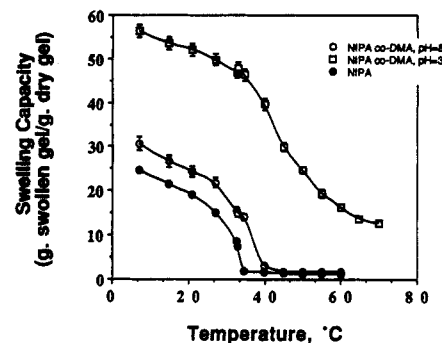


Figure 3. Temperature-dependent swelling equilibria in citrate-phosphate buffer solutions for poly-NIPA gel (pH 6) and poly-NIPA-co-DMA gel (pH 3 and 8).

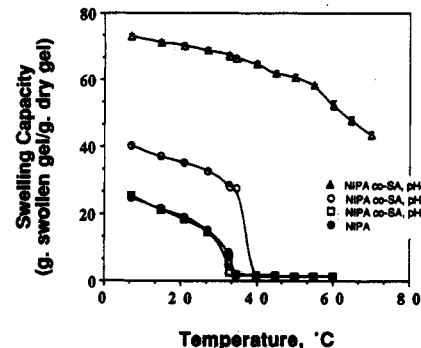


Figure 4. Temperature-dependent swelling equilibria in citrate-phosphate buffer solutions for poly-NIPA gel (pH 6) and poly-NIPA-co-SA gel (pH 3, 5, and 8).

the chemical nature of the two weakly ionizable comonomers used in this work. Whereas the ionizable group in the poly-NIPA-co-SA gel is the carboxylate group, in the poly-NIPA-co-DMA gel it is the bulky, relatively hydrophobic (dimethylamino)ethyl group. The increased hydrophobicity imparted to the poly-NIPA-co-DMA gel by the (dimethylamino)ethyl groups may contribute to the decreased swelling of this gel. Computer simulations of isolated, hydrophobic polyelectrolytes¹¹ provide qualitative support for this explanation; Hooper et al.¹¹ found a decrease in the end-to-end distance of model, isolated polyelectrolytes upon increasing chain hydrophobicity while holding ionization constant.

Figure 3 presents temperature-dependent swelling equilibria in citrate-phosphate buffer solutions of pH 3 and 8 for the poly-NIPA-co-DMA gel. Temperature varied from 7 to 70 °C. Swelling equilibria for uncharged poly-NIPA gel in pH 6 buffer is included in Figure 3 for comparison. The gel exhibits large, continuous changes in water content as a function of temperature. The temperature range where the volume change is greatest (the transition region) is shifted to higher temperatures and is broadened (becomes more continuous) as the gel ionization increases; gel ionization is a function of solution pH. Qualitatively similar results were obtained in previous work with a series of poly-NIPA gels containing varying amounts of a strongly dissociating quaternized-amine comonomer.⁷ In this previous work, gel ionization was fixed at preparation and could not be altered thereafter. An interesting feature of the present work is the ability to alter the gel ionization, and thus shift the transition region of the gel, by changing solution pH.

Figure 4 shows temperature-dependent swelling equilibria in citrate-phosphate buffer solutions of pH 3, 5, and 8 for poly-NIPA-co-SA gel. Temperature varied from 7 to 70 °C. The results shown in Figure 4 are similar to those shown in Figure 3 for the poly-NIPA-co-DMA gel;

the transition region is shifted to higher temperatures and is broadened with increasing gel ionization (increasing solution pH for the poly-NIPA-co-SA gel). Previous workers have reported discontinuous¹² and also continuous¹³ transitions for ionized poly-NIPA gels. The transitions observed here were all continuous, with the possible exception of the poly-NIPA-co-SA gel at pH 5, which appears to be near a discontinuous transition.

To account for the chemical nature of the comonomers, quantitative modeling of these data requires an extension of the model previously developed by the authors.^{7,9} The electrostatic term in our previous model must also be modified to consider weakly ionizable hydrogels in buffer solutions. Efforts toward that end are in progress.

Conclusions

The addition of a weakly ionizable comonomer to a temperature-sensitive gel may affect dramatically the swelling behavior of the gel. The temperature range over which the gel volume change is greatest is shifted to higher temperatures and is continuous with increasing gel ionization. The ionic strength of the buffer solution must be less than 0.1 M for gel ionization to have an effect on gel swelling; the pH of the buffer solution has little effect on gel swelling at ionic strengths higher than 0.1 M.

Incorporation of both temperature- and pH-sensitive monomers in a single network provides flexibility for controlling swelling behavior with solution conditions. In particular, for temperature-sensitive gels containing weakly ionizable monomers, the magnitude and location of temperature-induced gel collapse may be altered significantly by changing solution pH. Through proper selection of the ionizable comonomer, it may be possible to tailor

a temperature-sensitive gel to meet specific process or system needs.

Acknowledgment. This work was supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098. The authors are grateful to David Freed for assistance with the experimental work. S.B. is grateful to the Spanish Ministry of Education and Science (MEC) for a fellowship.

References and Notes

- (1) Tanaka, T. *Gels. Encycl. Polym. Sci. Eng.* **1986**, *6*, 514.
- (2) Siegel, R. A.; Falamarzian, M.; Firestone, B. A.; Moxley, B. C. *J. Controlled Release* **1988**, *8*, 179.
- (3) Hoffman, A. S.; Afrassibi, A.; Dong, L. C. *J. Controlled Release* **1986**, *4*, 213.
- (4) Park, T. G.; Hoffman, A. S. *Appl. Biochem. Biotechnol.* **1988**, *19*, 1.
- (5) Freitas, F. A.; Cussler, E. L. *Chem. Eng. Sci.* **1987**, *42*, 97.
- (6) Taylor, L. D.; Cerankowski, L. D. *J. Polym. Sci.* **1975**, *13*, 2551.
- (7) Beltran, S.; Hooper, H. H.; Blanch, H. W.; Prausnitz, J. M. *J. Chem. Phys.* **1990**, *92*, 2061.
- (8) Ilavsky, M.; Hrutz, J.; Havlicek, I. *Polymer* **1985**, *26*, 1514.
- (9) Hooper, H. H.; Baker, J. P.; Blanch, H. W.; Prausnitz, J. M. *Macromolecules* **1990**, *23*, 1096.
- (10) Ricka, J.; Tanaka, T. *Macromolecules* **1984**, *17*, 2916.
- (11) Hooper, H. H.; Beltran, S.; Sassi, A. P.; Blanch, H. W.; Prausnitz, J. M. *J. Chem. Phys.* **1990**, *93*, 2715.
- (12) Hirotsu, S.; Hirokawa, Y.; Tanaka, T. *J. Chem. Phys.* **1987**, *87*, 1392.
- (13) Hirose, Y.; Amiya, T.; Hirokawa, T.; Tanaka, T. *Macromolecules* **1987**, *20*, 1342.

Registry No. (NIPA)(BIS)(SA) (copolymer), 92694-74-1; (NIPA)(DMA)(SA) (copolymer), 130933-95-8; (NIPA)(BIS) (copolymer), 90398-43-9.