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Swelling Equilibria for Temperature-Sensitive Ampholytic Hydrogels

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Swelling Equilibria for Temperature-Sensitive Ampholytic Hydrogels

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Abstract

Temperature-sensitive N-isopropylacrylamide (NIPA)-based ampho-lytic hydrogels were synthesized by copolymerizing NIPA with the cationic monomer methacrylamidopropyl trimethylammonium chloride (MAPTAC) and the anionic monomer sodium styrene sulfonate (SSS). The total nominal charge density of the hydrogels was held constant at 8 mol % (dry basis), while the molar ratio of anionic to cationic moieties within the hydrogels was varied. Swelling equilibria were measured in water at 6°C, and in aqueous sodium chloride solutions ranging in concentration from 10^{-5} to 5 M and temperature ranging from 6 to 56°C. Consistent with expectations, the swelling behavior of the hydrogels was found to be controlled by temperature at low salt concentrations; as the sodium chloride concentration increased, temperature control of hydrogel swelling decreased. Slight antipolyelectrolyte behavior was observed for the hydrogel prepared with equal molar amounts of MAPTAC and SSS.

Introduction

Temperature-induced collapse of N-isopropylacrylamide (NIPA)-based hydrogels is related to lower-critical-solution phase separation in aqueous polymer solutions, and to the coil-globule transition of a single poly(NIPA) chain. For example, aqueous poly(NIPA) solutions exhibit a lower critical solution temperature (LCST) at approximately 31°C (Heskins and Guillet, 1968); the end-to-end distance of an infinitely dilute poly(NIPA) chain in water decreases dramatically as the temperature rises above 31°C (Fujishige et al., 1989); and NIPA-based hydrogels exhibit volume collapse as the solution temperature exceeds approximately 33°C. LCST behavior in aqueous polymer solutions is due

to hydrogen bonding, i.e., specific, orientation-dependent interactions between solution constituents (Hirschfelder et al., 1937). Temperature-sensitive hydrogels have been suggested for use in separation processes (Feil et al, 1991; Freitas and Cussler, 1987), as a support for biocatalysts (Park and Hoffman, 1992), and in drug-delivery systems (Okano et al., 1990).

Beltran et al. (1990) measured temperature-dependent swelling equilibria in aqueous sodium chloride solutions for cationic NIPA-based hydrogels. Beltran et al. considered simultaneously the effects of temperature and ionic strength on the swelling of cationic NIPA-based electrolytic hydrogels; at low ionic strength and fixed temperature, they found that the swelling of ionized NIPA-based hydrogels in water and in salt solutions is highly dependent on the degree of hydrogel ionization: as salt concentration approached 1 M, all hydrogels studied were found to have approximately the same water content. At a fixed NaCl concentration, hydrogel swelling could be reduced by increasing the solution temperature above the LCST.

Polymeric ampholytes, materials containing cationic and anionic functional groups, have received much recent attention (Bekturov et al., 1990; Higgs and Joanny, 1991; McCormick and Johnson, 1990). The properties of polymeric ampholyte materials include a high degree of hydrophilicity, good biocompatibility, moderately high mechanical strength in the the water-swollen state, and adjustable permeability to liquids depending on the type of fixed-charge groups present and the conditions of polymer preparation. The foremost practical use of ampholytic polymers is in the preparation of membranes with high water flux for (predominantly) biomedical applications (Philipp et al. 1991).

The first systematic research in this area was performed by Michaels and coworkers (1965) who, for the first time, prepared stoichiometric polyanion-polycation complexes from anionic and cationic vinyl monomers.

Some results for covalently cross-linked ampholytic polymers have been reported (Salamone et al., 1974; Salamone et al., 1977; Itoh et al., 1986; Huglin and Rego, 1991a,b; Rego and Huglin, 1991; Huglin and Rego, 1992; Katayama et al., 1992a,b). As part of a study on the synthesis of inner-salt polymers from vinylimidazolium sulphobetaines, Salamone et al. (1977) added a cross-linking agent to some of their syntheses to form materials with hydrogel characteristics. The effect of cross-link density on equilibrium water content of the ampholytic hydrogels was studied. Contrary to expectations, water content was found to *increase* with cross-link density; this increase was attributed to the introduction of cationic groups through the cross-linking agent.

Linear ampholytic polymers are known to be water-soluble only in the presence of low-molecular-weight salt; chain expansion increases in salt solutions of high concentration. This behavior has been attributed to intra- and/or inter-macromolecular attractions between ionic groups and the screening of these attractions by the added salt (Peiffer and Lundberg, 1985). Since linear polyelectrolytes may be characterized by a marked decrease in end-to-end distance in salt solutions, the behavior of ampholytic polymers in aqueous salt solutions has been referred to as antipolyelectrolyte behavior in the literature (Huglin and Rego, 1991a).

Itoh et al. (1986) also studied the solution properties of cross-linked poly(sulfobetaine)s and observed antipolyelectrolyte swelling behavior with these materials. Hydrogel membranes containing inner-salt groups

were prepared by copolymerization of a sulfobetaine monomer and acrylamide in the presence of a cross-linker. The membranes were found to be opaque in water and were found to swell slightly and turn transparent when placed in 1M aqueous NaCl. The composition of the hydrogel studied by Itoh et al. was not reported. Similar antipolyelectrolyte swelling behavior in aqueous salt solutions was observed by Huglin and Rego (1991a) for a cross-linked poly(sulfobetaine) hydrogel.

Baker et al. (1992b) measured isothermal swelling equilibria in aqueous NaCl solutions for a series of acrylamide-based ampholytic hydrogels. Baker et al. found that, while all hydrogels studied had similar water contents in 1M NaCl, as the NaCl concentration decreased, the hydrogel containing a ratio of cationic groups to anionic groups of nearly unity maintained the same water content, while hydrogels that had ratios different from unity swelled with decreasing NaCl concentration; the larger the deviation of the ratio of cationic character to anionic character from unity, the greater the swelling. The experimental results were rationalized by Baker et al. using Donnan-equilibria arguments.

Katayama et al. (1992a,b) studied the swelling behavior of acrylamide-based ampholytic hydrogels in water and in acetone-water mixtures. The hydrogels exhibited large, sometimes discontinuous, changes in swelling as a function of solution composition which could be characterized by the number of constituent cationic and anionic groups. The hydrogels also exhibited LCST behavior; in acetone/water solutions, the hydrogels collapsed with increasing temperature. Katayama et al. suggested that the observed thermo-shrinking behavior of the hydrogels was due to specific interactions between polymer and solvent; it did not

originate from the ampholytic properties of the material. Temperature-sensitivity in acetone/water mixtures has been observed previously for polyelectrolyte hydrogels by others (Tanaka, 1981).

In this work, we report results for temperature-sensitive swelling equilibria in aqueous salt solutions of N-isopropylacrylamide (NIPA)-based ampholytic hydrogels. Thus, this work extends the recent work (referred to above) by Baker et al. (1992b) and Beltran et al. (1990).

Experimental Section

Materials. N-isopropylacrylamide (NIPA) and N,N'-methylenebisacrylamide (Bis) were supplied by Eastman Kodak. Methacrylamidopropyl trimethylammonium chloride (MAPTAC) (50% by weight in aqueous solution) and sodium styrene sulfonate (SSS) were obtained from Aldridge; sodium metabisulfite (SMB), ammonium persulfate (APS), and sodium chloride (NaCl) from Fisher. All reagents were used as received. All water used in synthesis and swelling measurements was distilled, and then purified and filtered through a Barnstead Nanopure II system.

Synthesis. Hydrogels were prepared by aqueous free-radical copolymerization of NIPA, MAPTAC, and SSS, using Bis as the cross-linker. Polymerization was initiated by APS using SMB as an accelerator. The hydrogels were formed between silanized glass plates (10x10cm) separated with a 1.0mm Teflon gasket.

The compositions of the various hydrogels were determined by the nominal amounts of reagents present in the hydrogel-feed solution. Four parameters were used to define this composition:

$$\%T = \frac{\text{mass of all monomers (g)}}{\text{volume of water (ml)}} * 100 \quad (1)$$

$$\%C = \frac{\text{moles of Bis in feed solution}}{\text{total moles of monomer in feed solution}} * 100 \quad (2)$$

$$\%MAPTAC = \frac{\text{moles of MAPTAC in feed solution}}{\text{total moles of monomer in feed solution}} * 100 \quad (3)$$

$$\%SSS = \frac{\text{moles of SSS in feed solution}}{\text{total moles of monomer in feed solution}} * 100 \quad (4)$$

Three hydrogels were prepared. %T and %C were held constant (at 15% and 0.5% respectively), while %MAPTAC and %SSS were varied. Holding the total nominal charge density constant at 8%, hydrogels were prepared with 5% MAPTAC and 3%SSS (designated 5M-3S below), with 4% MAPTAC and 4% SSS (4M-4S), and with 3% MAPTAC and 5% SSS (3M-5S).

To illustrate the synthetic procedure, we give details for the preparation of the 4M-4S hydrogel. Added to 76.0 ml water were 12.79 g NIPA, 0.095 g Bis, 2.07 ml MAPTAC solution, and 1.02 g SSS. The solution was stirred with a magnetic stirrer until well-mixed, then degassed under 27-in Hg vacuum. Concurrently, solutions of both APS and SMB were prepared by separately dissolving 0.25 g in 20 ml water. These two solutions and the monomer solution were degassed at the same time. After 1 hr, all three solutions were transferred to a nitrogen atmosphere. Under nitrogen, the solutions were cooled to near 0°C using an ice bath. After cooling, 4 ml of the accelerator (SMB) was transferred to the monomer solution, followed by 4 ml of the initiator (APS). The resulting mixture was stirred until well-mixed and then injected via syringe between the silanized glass plates for polymerization. The plates

were removed from the nitrogen atmosphere and stored in a refrigerator at 6°C. After 48 hr, hydrogel slabs were removed from the plates and punched into 1 cm disks. The hydrogel disks were soaked in water which was refreshed periodically to leach away the soluble fraction and initiator residues.

Swelling in Water. Hydrogels were swollen to equilibrium in water at 6°C. Equilibrium was reached in one week; approach to equilibrium was monitored by mass measurement of the swollen hydrogels. Once equilibrium was attained, the swelling ratio in water was determined for each hydrogel. Equilibrated disks were weighed, dried at room temperature, and re-weighed. The swelling ratio in water is defined as the mass ratio of swollen hydrogel (at 6°C) to dry hydrogel.

Swelling in Aqueous Sodium Chloride. Swelling ratios were measured in the temperature range 6 to 56°C. The swelling media were aqueous sodium chloride solutions, ranging in ionic strength from 10^{-2} to 5.0 M. Two swelling experiments were performed in parallel at two different temperatures: two sets of water-equilibrated hydrogel disks were transferred to each of the salt solutions and allowed to equilibrate concurrently at 6 and at 20°C. The hydrogels and surrounding solutions were placed in sealed containers to prevent evaporative losses which could appreciably increase solution ionic strength. To compensate for possible solvent exchange between hydrogel and external solution, NaCl solutions bathing the hydrogels were changed every other day. Mass measurements of the hydrogels were taken to monitor for the attainment of equilibrium. After one week, mass measurements did not change. The swelling ratios were determined by:

$$\text{Swelling ratio} = \frac{\text{mass gel in water at 6°C}}{\text{mass dry gel}} \times \frac{\text{mass gel in salt solutions at T°C}}{\text{mass gel in water at 6°C}} \quad (5)$$

After the hydrogels were at equilibrium in the salt solutions, the solution temperatures were increased. The equilibrated gels at 6°C were exposed to 37°C; the gels at 20°C were taken to 56°C. Temperature control was achieved using two air baths. After 24 hours, equilibrium at these higher temperatures was reached, and swelling ratios were determined. All swelling studies were performed in triplicate.

Results and Discussion

Figure 1 shows swelling equilibria in water for three NIPA-based ampholytic hydrogels in water at 6°C. The number of osmotically-active counterions in the hydrogel phase increases as the molar ratio of MAPTAC to SSS diverges from unity. Conversely, the ability of a hydrogel to neutralize itself is enhanced as this ratio approaches unity. The hydrogels with net electrolytic character absorb water because the osmotically-active counterions generate a net osmotic pressure between the hydrogel interior and the exterior water. The 4M-4S hydrogel is apparently self-neutralized, because most diffusible ions have been dialyzed from the hydrogel interior while swelling to equilibrium in water, and thus swells less compared to the other two hydrogels.

In water, the 5M-3S hydrogel (net cationic character) swelled 39% more than the 3M-5S hydrogel (net anionic character). Similar results were obtained by Baker et al. (1992b) and by Katayama et al. (1992) for analogous series of acrylamide-based ampholytic hydrogels. Baker et al.

described three possible mechanisms, possibly working in concert, to explain the observed "asymmetric" swelling behavior. These mechanisms are discussed briefly below:

(1) Compositional drift during polymerization coupled with incomplete conversion of monomer. This may account for the difference in swelling observed for the 3M-5S and the 5M-3S hydrogels. To illustrate, assume that all of the MAPTAC present in the feed solution of each hydrogel was incorporated into the network, while a fraction of the SSS was not. Then the net cationic character in the 5M-3S hydrogel would be greater than 2%, while the net anionic character in the 3M-5S hydrogel would be less than 2%. The net cationic hydrogel, because of its higher net charge, would be expected to swell more than the net anionic hydrogel.

(2) Hydrophobicity imparted to the net anionic hydrogels by styrenic moieties. Hydrophobic styrenic moieties inside the 3M-5S hydrogel may tend to make this hydrogel less solvophilic compared to the 5M-3S hydrogel.

(3) Differences in activities of the counterions to the charged groups. Since a quaternary-amine group is bulkier than a sulfonate group, the electric field near the interface between the amine group and water will be weaker than the corresponding field at the sulfonate-water interface. Because of the difference in electric-field strength surrounding the two functional groups, the attraction between counterion and functional group should be weaker for MAPTAC than for SSS. Thus, the counterions for the quaternary-amine group may be more osmotically active than the counterions for the sulfonate group, resulting in a higher swelling ratio for the net cationic hydrogels.

Peiffer and Lundberg (1985) studied ampholytic linear copolymers composed of MAPTAC and SSS, and also of MAPTAC and sodium vinyl sulfonate (SVS). They found MAPTAC-SVS copolymers to be much more soluble in aqueous electrolyte solution than MAPTAC-SSS copolymers. Peiffer and Lundberg concluded that the SSS-containing copolymers had sufficient hydrocarbon character to reduce chain expansion in aqueous electrolyte solutions. This suggests that the observed asymmetry occurs independent of the formation of a cross-linked network; therefore, explanation (2) may explain the observed behavior, while explanation (1) does not.

The net cationic and net anionic hydrogels collapse when placed in sodium chloride solution at 6°C (Figure 2): the swelling ratio of the 5M-3S hydrogel dropped from 162 to 38 when transferred from water to 0.01M NaCl, while the swelling ratio for the 3M-5S hydrogel dropped from 116 to 34. As suggested by Baker et al. (1992b), the concentration of osmotically-active (mobile) ions is always greater inside a hydrogel with a net fixed charge than in the external solution because the fixed charges require counterions for the maintenance of electroneutrality. The main driving force for the swelling of the hydrogels studied here is the difference in mobile ion concentration between hydrogel and the external solution. This driving force is reduced as the ionic strength in the swelling medium rises. Swelling for the 4M-4S hydrogel remained the same when transferred from water to 0.01M NaCl.

Temperature-induced collapse of NIPA-based hydrogels may be observed in dramatic fashion by examining Figures 2 through 5; the ordinates of the graphs are scaled the same to facilitate qualitative comparisons. Swelling equilibria in sodium chloride solutions are plotted

for the three hydrogels at 6°C (Figure 2), 20°C (Figure 3), 37°C (Figure 4) and 56°C (Figure 5). Regardless of the ionic content of the hydrogel, water is rejected from the hydrogel interior as the solution temperature is raised to 56°C.

The hydrogels may become highly collapsed (swelling ratio less than 5.0) in one of two ways: (1) All hydrogels studied collapse to a swelling ratio of 5.0 or less in 5M NaCl, independent of the solution temperature. at an NaCl concentration of 5M, the dissolved NaCl apparently ties up all of the water leaving little for hydrating polymer. (2) In 56°C solution, all hydrogels collapse to a swelling ratio of 5.0 or less, independent of the NaCl concentration. NIPA polymer hydration is not favored at 56°C, a temperature significantly above the LCST of the hydrogels.

Figure 6 shows a cross-plot of the data for the 4M-4S hydrogel. Here, swelling is plotted versus ionic strength for all four temperatures studied. A slight increase in swelling as the NaCl concentration is raised from 0.1 to 0.1M is seen for this hydrogel at 6, 20 and 37°C, suggesting slight antipolyelectrolyte behavior; because of scatter in the data, only the increase in 6°C solution is significant. The swelling curves at these temperatures reach maxima and then collapse onto a single point in 5M NaCl solution. Apparently the added NaCl serves to salt-out NIPA polymer as the NaCl concentration approaches 5M. Interestingly, NaCl has been observed to salt-in acrylamide-based *polyelectrolyte* hydrogels at concentrations approaching 5M (Baker, 1992a); work is currently being performed to examine the behavior of acrylamide-based *polyampholyte* hydrogels at such NaCl concentrations.

Conclusion

Polyelectrolyte solution behavior for electrolytic hydrogels, the decrease in swelling of an electrolytic hydrogel as the ionic strength of the swelling medium is raised, has been reported by many authors over the years. A few authors (mentioned above) have observed slight antipolyelectrolyte solution behavior for ampholytic hydrogels; a slight decrease in hydrogel swelling as the salt concentration in the swelling medium is raised. Slight antipolyelectrolyte behavior was observed in this work for the NIPA-based hydrogel prepared with equimolar amounts of cationic and anionic monomer; scatter in the data obscures the significance of the results.

Additional work is needed to explain thoroughly the asymmetric swelling behavior observed in Figure 1. Required is a series of comonomer analogs that vary in hydrophobicity. Also, comonomers that vary in the bulkiness of the charged group would have to be available. Changes in monomer chemistry inevitably lead to changes in network structure through the reactivity ratios of all possible monomer pairs. In any future work, hydrogel synthesis would have to be closely monitored so that differences in network structure and charge density do not affect the results. Network characterization must be performed to achieve increased understanding of the swelling asymmetry.

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Figure Captions

Figure 1 Swelling equilibria in water at 6°C for three NIPA ampholytic hydrogels with 15% T and 0.5% C. The amount of charged comonomer present in the hydrogel-feed solution was fixed at 8% (molar basis). Asymmetry is observed in swelling behavior between the net anionic hydrogels and the net cationic hydrogels.

Figure 2 Swelling equilibria in aqueous NaCl at 6°C for three NIPA/MAPTAC/SSS copolymer ampholytic hydrogels. The data in Figures 2 through 5 are plotted on the same axes to facilitate qualitative comparisons.

Figure 3 Swelling equilibria in at 20°C for three NIPA/MAPTAC/SSS copolymer ampholytic hydrogels.

Figure 4 Swelling equilibria in aqueous NaCl at 37°C for three NIPA/MAPTAC/SSS copolymer hydrogels.

Figure 5 Swelling equilibria in aqueous NaCl at 56°C for three NIPA/MAPTAC/SSS copolymer ampholytic hydrogels. Because the hydrogels are very near to a completely collapsed state, no trends are apparent.

Figure 6 Swelling equilibria in aqueous NaCl for the 4% MAPTAC - 4% SSS hydrogel at all temperatures studied. Data shown for this hydrogel in Figures 2 through 5 are re-plotted in this figure.

Figure 1

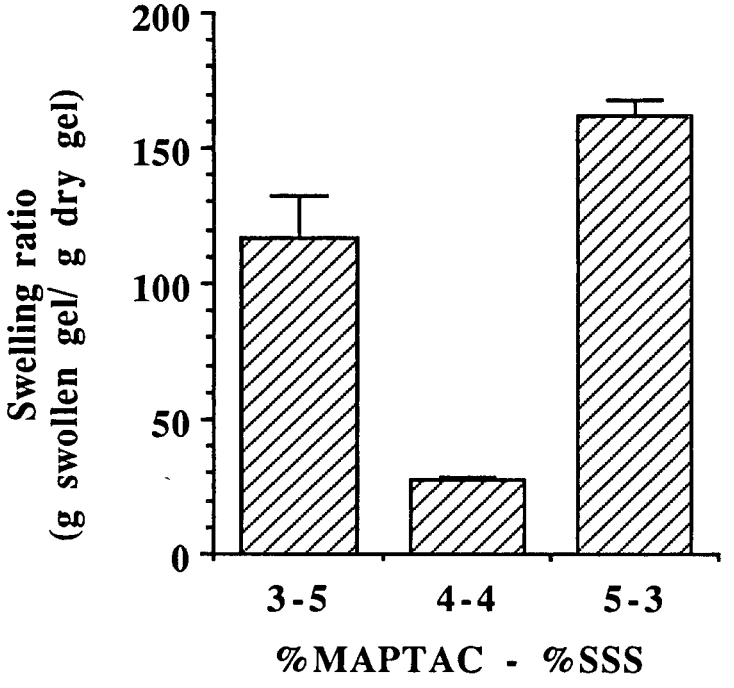

200
150
100
50
0
Swelling ratio
(g swollen gel/ g dry gel)
3-5
4-4
5-3
%MAPTAC - %SSS

Figure 2

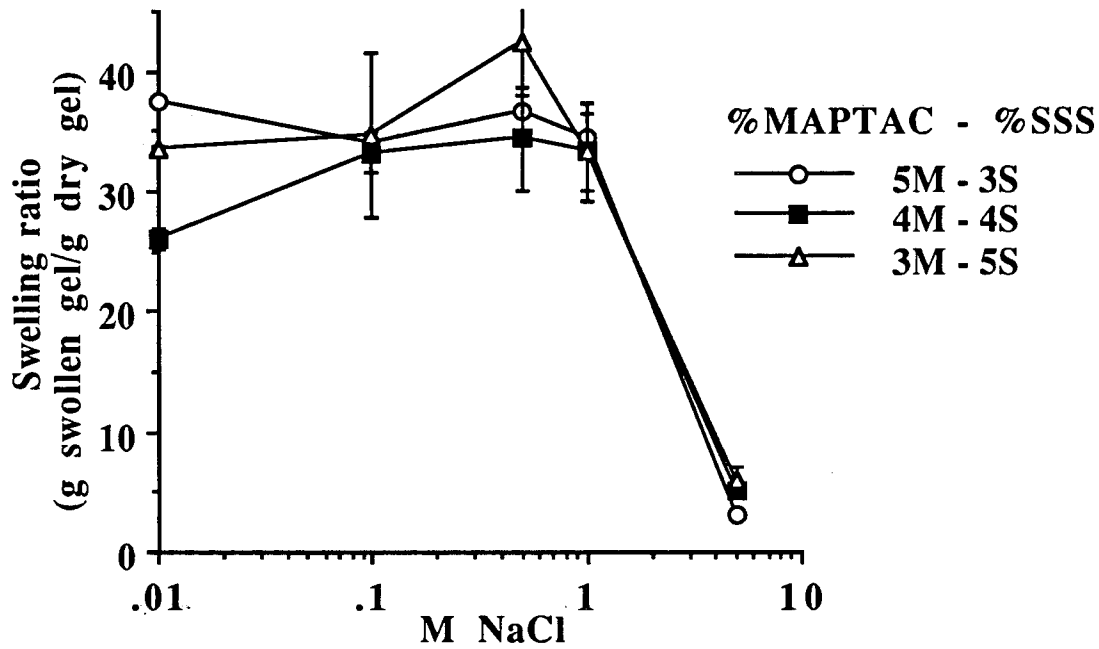

Swelling ratio
(g swollen gel/g dry gel)
40
30
20
10
0
.01
.1
1
10
M NaCl
%MAPTAC - %SSS
5M - 3S
4M - 4S
3M - 5S

Figure 3

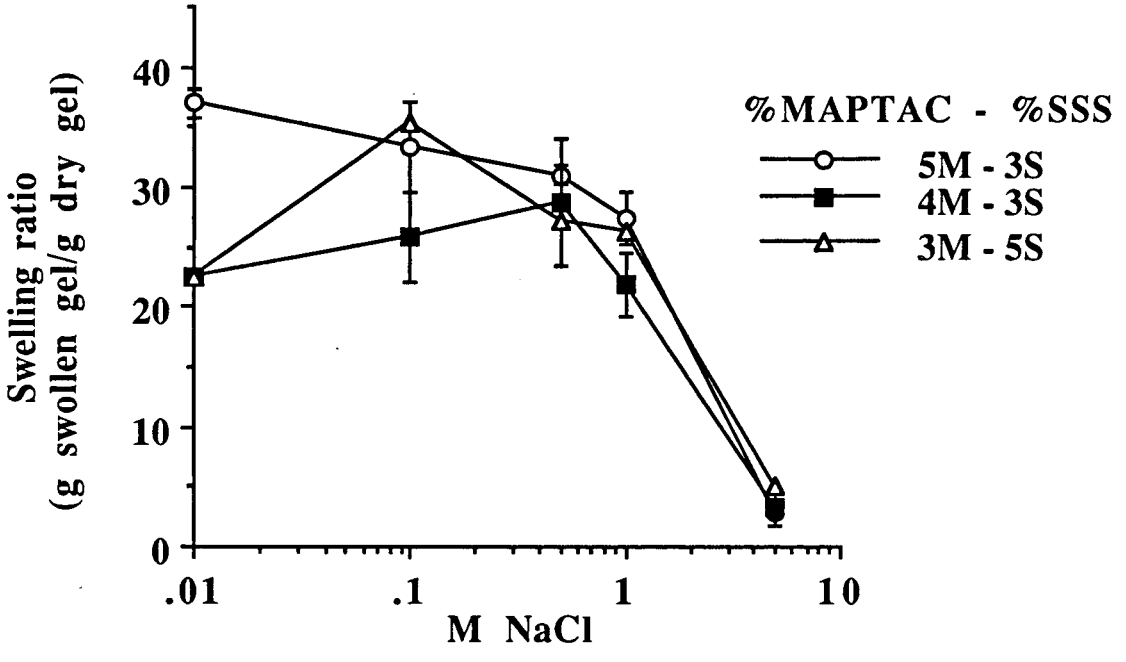

Swelling ratio
(g swollen gel/g dry gel)
40
30
20
10
0
.01
.1
1
10
M NaCl
%MAPTAC - %SSS
5M - 3S
4M - 3S
3M - 5S

Figure 4

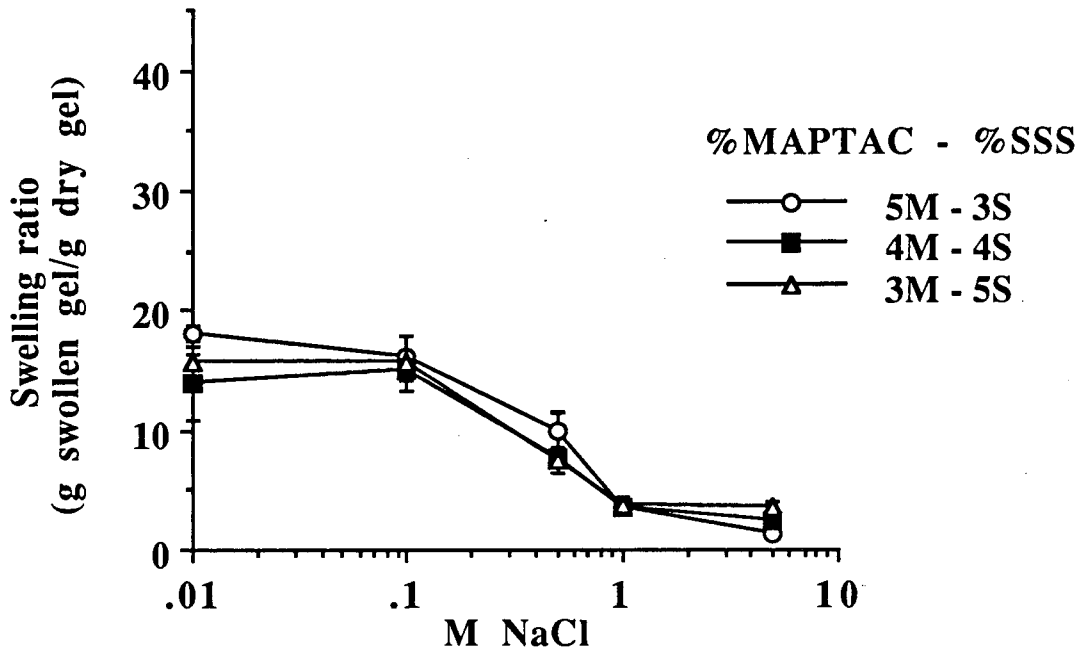

Swelling ratio
(g swollen gel/g dry gel)
40
30
20
10
0
.01
.1
1
10
M NaCl
%MAPTAC - %SSS
5M - 3S
4M - 4S
3M - 5S

Figure 5

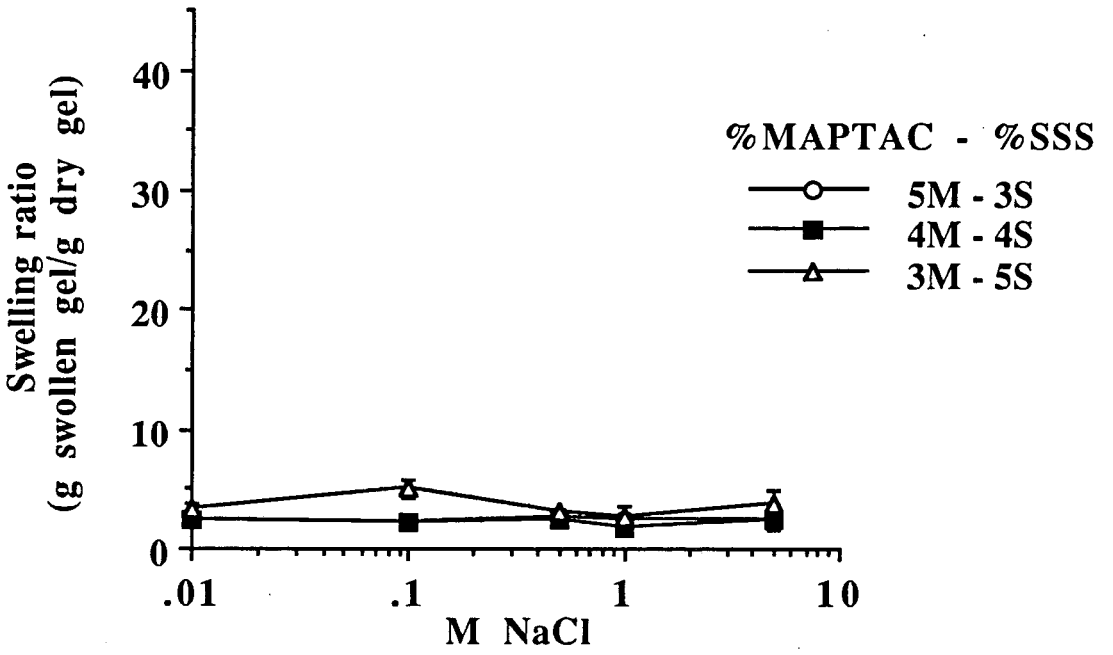
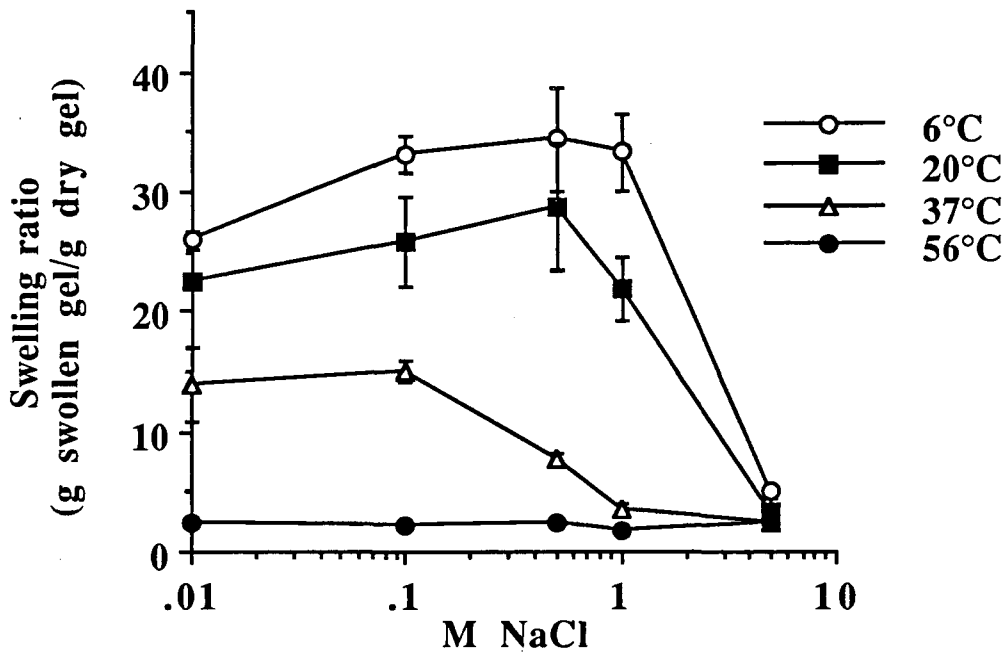

Swelling ratio
(g swollen gel/g dry gel)
40
30
20
10
0
.01
.1
1
10
M NaCl
%MAPTAC - %SSS
5M - 3S
4M - 4S
3M - 5S

Figure 6


Swelling ratio
(g swollen gel/g dry gel)
40
30
20
10
0
.01
.1
1
10
M NaCl
6°C
20°C
37°C
56°C

Tables

Table 1 Swelling equilibria in water for three NIPA-based ampholytic hydrogels

% MAPTAC - % SSS[a]	Swelling ratio[b]
5 - 3	161.6 (6.0)
4 - 4	27.4 (1.2)
3 - 5	116.4 (16.1)

[a]Mole percent comonomer present in gel-feed solution
[b]Values reported are swelling ratios (g swollen gel/g dry gel). Values in parentheses indicate standard deviations.

Table 2 Temperature-dependent swelling equilibria[a] in salt solutions for the 5% MAPTAC - 3% SSS ampholytic hydrogel

M NaCl	6°C	20°C	37°C	56°C
0.01	37.5 (1.1)	37.0 (1.1)	18.1 (0.6)	2.5 (0.5)
0.1	34.1 (2.1)	33.3 (3.7)	16.1 (0.4)	2.2 (0.5)
0.5	36.6 (3.9)	31.0 (0.7)	9.9 (1.5)	2.6 (0.4)
1.0	34.4 (1.6)	27.4 (2.2)	3.4 (0.4)	2.4 (0.3)
5.0	3.0 (1.0)	2.8 (1.1)	1.4 (0.3)	2.4 (0.8)

[a]Values reported are swelling ratios (g swollen gel/g dry gel). Values in parentheses indicate standard deviations.

Table 3 Temperature-dependent swelling equilibria[a] in salt solutions for the 4% MAPTAC - 4% SSS ampholytic hydrogel

M NaCl	6°C	20°C	37°C	56°C
0.01	26.0 (0.8)	22.5 (0.7)	13.9 (3.1)	2.4 (0.4)
0.1	33.1 (1.6)	25.8 (3.8)	15.0 (0.8)	2.2 (0.4)
0.5	34.3 (4.4	28.6 (5.3)	7.6 (0.5)	2.5 (0.3)
1.0	33.2 (3.2)	21.8 (2.7)	3.5 (0.6)	1.8 (0.2)
5.0	5.1 (0.3)	3.4 (1.0)	2.4 (0.3)	2.5 (0.6)

[a]Values reported are swelling ratios (g swollen gel/g dry gel). Values in parentheses indicate standard deviations.

Table 4 Temperature-dependent swelling equilibria[a] in salt solutions for the 3% MAPTAC - 5% SSS ampholytic hydrogel

M NaCl	6°C	20°C	37°C	56°C
0.01	33.6 (0.2)	22.4 (2.2)	15.7 (0.5)	3.3 (0.4)
0.1	34.7 (6.9)	35.2 (3.2)	15.6 (2.3)	5.0 (0.7)
0.5	42.4 (4.5)	27.2 (3.5)	7.6 (1.1)	3.0 (0.4)
1.0	33.3 (4.1)	26.3 (4.4)	3.7 (0.7)	2.7 (0.8)
5.0	6.0 (1.0)	5.1 (1.5)	3.6 (0.4)	3.7 (1.1)

[a]Values reported are swelling ratios (g swollen gel/g dry gel). Values in parentheses indicate standard deviations.

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