# Mutual Influence of pH and Temperature on the Swelling of Ionizable and Thermosensitive Hydrogels

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*Received March 16, 1992*
*Revised Manuscript Received June 1, 1992*

## Introduction

During the past several years, hydrogels which show a significant swelling change in response to external stimuli such as temperature,[1-4] pH,[5,6] ionic strength,[7] and electric potential[8,9] have been investigated for applications ranging from solute separation[10,11] to controlled delivery of solutes.[2-4,12] Recently, hydrogels which demonstrate swelling dependence to more than one variable, in particular temperature and pH,[13-16] have been investigated. These studies suggest that there is an independent, as well as a mutual influence of pH and temperature on gel swelling. The data show both a change in pH-dependent swelling by temperature and vice versa.

pH/temperature-sensitive hydrogels are hydrophilic polymer networks which contain both pH- and temperature-sensitive components. The thermosensitive components are usually monomers which, when polymerized, exhibit a lower critical solution temperature (LCST) in water.[1] The pH-sensitive components are ionizable monomers which, when incorporated in a gel, lead to pH-dependent swelling due to the strong influence of ionization on gel swelling.

The objective of this study is to determine the extent and to clarify the mechanism of the mutual influence of pH and temperature on the swelling of pH/temperature-sensitive hydrogels.

The hydrogels used in this study were synthesized with *N*-isopropylacrylamide (NIPAAm) as the temperature-sensitive component, (diethylamino)ethyl methacrylate (DEAEMA) as the pH-sensitive component, and butyl methacrylate (BMA) as a hydrophobic component to increase the mechanical stability of the gels. The influence of temperature on the pH-dependent swelling was explained by examining the $pK_b$ of DEAEMA as a function of temperature in poly(NIPAAm-*co*-BMA-*co*-DEAEMA) as well as in a nonthermosensitive polymer, poly(acrylamide-*co*-DEAEMA). The influence of ionization on the LCST of un-cross-linked analogs of the gels was examined to explain the influence of the ionizable component on the temperature-dependent swelling.

## Experimental Section

**Materials.** *N*-Isopropylacrylamide (NIPAAm; Eastman Kodak) was recrystallized in hexane. Butyl methacrylate (BMA), ethylene glycol dimethacrylate (EGDMA), and (diethylamino)-ethyl methacrylate (DEAEMA), all from Polysciences Inc., were purified by distillation at 58 °C (18 mmHg), 60 °C (115 μmHg), and 40 °C (190 μmHg), respectively. Acrylamide (AAm; Eastman Kodak) and all other materials were used as received.

**Hydrogel Synthesis.** Hydrogels composed of NIPAAm, DEAEMA, and BMA were synthesized with a NIPAAm/BMA molar ratio of 95/5 and DEAEMA contents of 0, 2, 5, 10, and 20 mol %. Copolymerization in dioxane (50 w/v %) with EGDMA as a cross-linker (0.01 mol of EGDMA/mol of monomer) and BPO as an initiator ($1.3 \times 10^{-3}$ mol of BPO/mol monomer) was performed as previously described.[10]

**Synthesis of Linear Polymers.** Linear polymers, having the same monomer compositions as the hydrogels, were synthesized under conditions identical with those of the gels but without cross-linker. Poly(AAm-*co*-DEAEMA) (10 mol % DEAEMA) was synthesized under the same conditions.

**Swelling.** Hydrogel swelling (the ratio of swollen to dry weight) was determined gravimetrically as a function of temperature in PBS, pH = 7.4.

Swelling as a function of pH was determined in buffer solutions at different ionic strengths and temperatures. $Na_2HPO_4/KH_2PO_4$ solutions (pH = 7) were used for the range between pH 6 and 8, and $NaHCO_3/Na_2CO_3$ solutions (pH = 9), for the range between pH 9 and 11. Aqueous HCl and NaOH solutions (ionic strengths equal to the particular buffers) were added to the buffers to reach the desired pH. The pH of the buffers was measured concurrently with weighing of the gels.

**Titrations.** For the titrations of poly(NIPAAm-*co*-BMA-*co*-DEAEMA) in 0.1 M salt solutions, 100 mg of each polymer was dissolved in approximately 25 mL of 0.1 M NaCl. First, 1-3 mL of 0.1 N HCl was added to charge all amino groups of the polymers. Back-titration with 0.1 N NaOH was performed using an autoburet ABU 80 and pH meter PHM 84 (Radiometer, Copenhagen, Denmark). The temperature was kept constant (±0.2 °C) for 30 min before and during each titration using a water bath.

For the titrations in 0.001 M salt solutions, 10 mg of each polymer was dissolved in 10-15 mL of 0.001 M NaCl solution and 10-25 mL of 0.001 N HCl was added to charge all amino groups. Here, 0.01 N NaOH was used for the titrations in order to complete the titrations using less than 2 mL of NaOH solution, and thus not changing the ionic strength of the solutions significantly.

One hundred milligrams of poly(AAm-*co*-DEAEMA) and poly(NIPAAm-*co*-BMA-*co*-DEAEMA), both containing 10 mol % DEAEMA, in 15 mL of 0.15 M NaCl were titrated at temperatures ranging from 4 to 48 °C (in 0.15 M NaCl) with 0.15 N NaOH after all amino groups were ionized by adding 0.15 N HCl.

**LCST Determination.** Solutions of poly(NIPAAm-*co*-BMA-*co*-DEAEMA), containing 0, 2, 5, 10, and 20 mol % DEAEMA, respectively, were prepared in PBS, pH = 7.4. For each polymer, three solutions (0.01, 0.1, and 1 w/v %, respectively) were prepared. The temperature of the solutions was raised from 15 to 53 °C in 2 °C increments every 10 min, and the absorbance at 450 nm was measured using a Perkin-Elmer Lambda 19 UV/vis/near-IR spectrometer. The LCST was defined as the temperature at the inflection point in the absorbance versus temperature curve.

In the LCST determination of poly(NIPAAm-*co*-BMA-*co*-DEAEMA) (10 mol % DEAEMA), as a function of pH, poly(NIPAAm-*co*-BMA-*co*-DEAEMA) solutions in PBS (0.1 w/v %) were adjusted to different pH by adding 0.15 N HCl or 0.15 N NaOH.

## Results and Discussion

**pH-Dependent Swelling.** The pH-dependent swelling of the poly(NIPAAm-*co*-BMA-*co*-DEAEMA) hydrogels at different temperatures and ionic strengths is shown in Figure 1. Swelling was low at high pH (DEAEMA is uncharged) and high at low pH (DEAEMA is charged). The pH sensitivity, defined as the relative difference between swelling at high and low pH, increases with DEAEMA content and was higher at the lower ionic strength due to increased Donnan effects.[17,18] More importantly, the pH of the swelling transitions (defined as the pH where the swelling curve shows an inflection point) was influenced by temperature.

Titration experiments showed that the pH of the swelling transitions of the gels correlated with the average $pK_b$'s of un-cross-linked analogs of the gels at each temperature and ionic strength (Table I). This implies that

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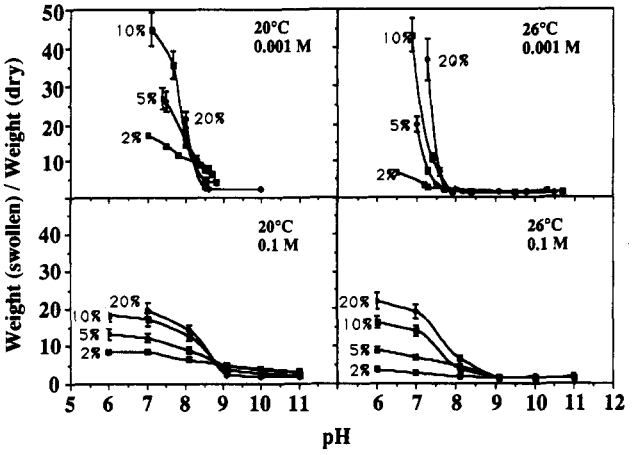


**Figure 1.** pH-dependent swelling of poly(NIPAAm-*co*-BMA-*co*-DEAEMA) hydrogels, containing 2, 5, 10, and 20 mol % of DEAEMA, respectively, at 20 and 26 °C and salt concentrations of 0.1 and 0.001 M ($n$ = 3).

**Table I**
**Comparison of Average p$K_b$'s of DEAEMA in Linear (NIPAAm-*co*-BMA-*co*-DEAEMA) Polymers and pH of Swelling Transitions of (NIPAAm-*co*-BMA-*co*-DEAEMA) Hydrogels**

| salt concn (M) | temp (°C) | pH of swelling transitions[a] | av p$K_b$'s of DEAEMA[b] |
|---|---|---|---|
| 0.1 | 20 | 8.6 | 8.3 (0.1) |
| 0.1 | 26 | 8.0 | 7.8 (0.3) |
| 0.001 | 20 | 7.8 | 7.3 (0.3) |
| 0.001 | 26 | <7.5 | 6.8 (0.3) |

[a] Estimated from swelling data (Figure 1). [b] From titration experiments using polymers containing 2, 5, 10, and 20 mol % DEAEMA, respectively. No significant change of p$K_b$ with polymer ionization and DEAEMA content was found due to the relatively low DEAEMA content. Numbers in parentheses represent standard deviations.

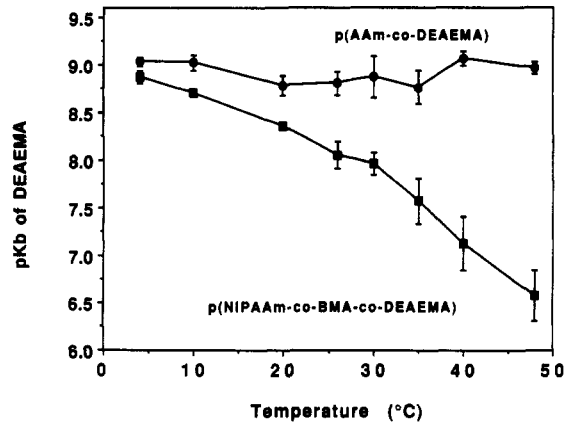


**Figure 2.** p$K_b$ of DEAEMA as a function of temperature in p(AAm-*co*-DEAEMA) and p(NIPAAm-*co*-BMA-*co*-DEAEMA), both containing 10 mol % DEAEMA, in 0.15 M NaCl. (p$K_b$ values are averaged at each temperature from 10% to 90% ionization, with error bars representing standard deviations.)

the influence of temperature on the pH of the swelling transitions is due to its effect on the p$K_b$ of DEAEMA. In order to determine if this is a result of the presence of the thermosensitive component, the p$K_b$ of DEAEMA was determined as a function of temperature in poly(NIPAAm-*co*-BMA-*co*-DEAEMA) and in a nonthermosensitive polymer, poly(AAm-*co*-DEAEMA), both containing 10 mol % DEAEMA (Figure 2). A strong decrease in the basicity of DEAEMA with increasing temperature was observed when DEAEMA was copolymerized with the thermosensitive monomer, while the p$K_b$ of DEAEMA was found to be independent of temperature in the nonthermosensitive polymer. This can be explained by the increasing hydrophobicity of NIPAAm with increasing temperature. Several studies have shown that the incorporation of hydrophobic comonomers into polyelectrolytes leads to a decrease in the acidity or basicity.[17,19-23] This phenomena may be due to the decreased dielectric constant in the polymer environment[17,19] or the structured water around the more hydrophobic polymer.[20] Increased ionic strength caused an increase in the p$K_b$ of DEAEMA, probably due to the shielding of the polymer charges by counterions.

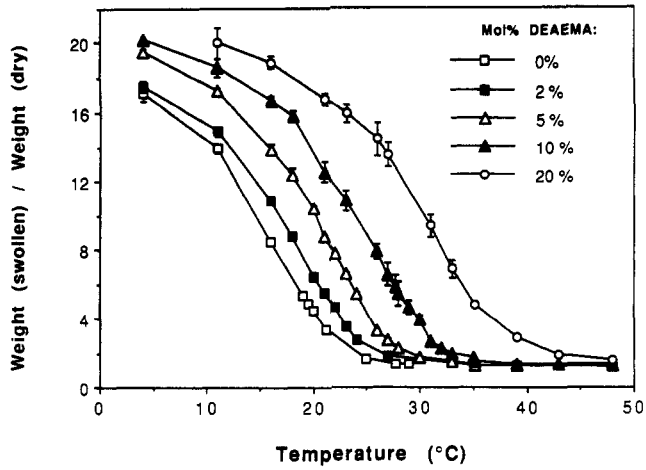


**Figure 3.** Temperature-dependent swelling of poly(NIPAAm-*co*-BMA-*co*-DEAEMA) hydrogels, containing 0, 2, 5, 10, and 20 mol % DEAEMA, respectively, in PBS, pH = 7.4 ($n$ = 3).

**Temperature-Dependent Swelling.** The temperature-dependent swelling in PBS (pH = 7.4) of the poly(NIPAAm-*co*-BMA-*co*-DEAEMA) hydrogels is shown in Figure 3. The swelling ratios of all gels were between 1 and 2 above 50 °C and about 20 below 10 °C. The swelling transitions of all the gels occur within 15 °C but shift to higher temperatures with increasing DEAEMA content.

The negative thermosensitivity observed for the hydrogels in this study is typical of polymer networks based on polymers which show LCST behavior, such as poly(NIPAAm).[3,24] Generally, incorporation of small amounts of ionic comonomers results in a strong increase or disappearance of the gel collapse temperature.[15,16,25] In order to understand why the highly ionizable gels in this study still collapsed, the LCST behavior of the linear polymer analogs of the gels was examined. The LCST's of the linear polymers (Table IIA) corresponded to the collapse temperatures of the gels. In addition, the LCST of poly(NIPAAm-*co*-BMA-*co*-DEAEMA) increased with decreasing pH (increasing charge of DEAEMA; Table IIB), indicating that charge may be the dominant factor influencing the LCST. Moreover, taking the decreasing basicity of DEAEMA with increasing temperature into account, it was found that all polymers separated from the solutions when the amount of charged monomers had decreased to a level of approximately 2.5 mol % (Table II). This means that phase separation and gel collapse with increasing temperature are due to a reduced ionization of DEAEMA. When more DEAEMA is included, a larger fraction of DEAEMA has to be deprotonated in order to reach the critical concentration of charged monomers in the polymer and this will lead to an increased collapse temperature.

## Conclusions

It was shown that poly(NIPAAm-*co*-BMA-*co*-DEAEMA) hydrogels possess unique swelling properties. Gel collapse at high temperatures (at pH = 7.4) was shown to take place even if more than 20 mol % of the ionizable

**Table II**
**LCST of Poly(NIPAAm-*co*-BMA-*co*-DEAEMA) as a Function of DEAEMA Content (at pH = 7.4) and as a Function of pH (for 10 mol % DEAEMA Polymer) in PBS and Percentage of Total Amount of Monomers in Polymers Which Are Charged at LCST**

A. LCST as a Function of DEAEMA Content

| (mol %) DEAEMA | LCST (°C)[a] | $pK_b$ of DEAEMA at LCST[b] | $pK_b$ – pH | total amount of monomers in polymers charged at LCST (%) |
|---|---|---|---|---|
| 0 | 25 | | | 0 |
| 2 | 26 | 8.0 | 0.6 | 1.6 |
| 5 | 33 | 7.6 | 0.2 | 3.1 |
| 10 | 44 | 6.9 | −0.5 | 2.4 |
| 20 | 48 | 6.5 | −0.9 | 2.2 |

B. LCST as a Function of pH

| pH | LCST (°C) | $pK_b$ of DEAEMA at LCST[b] | $pK_b$ – pH | total amount of monomers in polymers charged at LCST (%) |
|---|---|---|---|---|
| 9.3 | 28 | 7.9 | −1.4 | 0.4 |
| 8.5 | 31 | 7.9 | −0.6 | 2.0 |
| 8.0 | 35 | 7.5 | −0.5 | 2.4 |
| 7.4 | 44 | 6.9 | −0.5 | 2.4 |
| 7.0 | 51 | 6.4 | −0.6 | 2.0 |
| 6.1 | *c* | | | |
| 3.7 | *c* | | | |

[a] Independent of polymer concentration (from concentrations of 0.01 to 1 w/v %). [b] From Figure 2. [c] No LCST observed up to 80 °C.

monomer was included due to the increased neutralization of the ionizable monomer with increasing temperature. The temperature range in which the temperature-induced swelling transition occurs is dictated by the amount of ionizable monomer. The pH-induced swelling transition was shown to be controlled by temperature, due to the influence of NIPAAm on the ionization of DEAEMA. These features may be very useful in designing gels with specific temperature- or pH-induced swelling transitions.

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**Registry No.** (NIPAAm)(BMA) (copolymer), 121778-00-5; (NIPAAm)(BMA)(DEAEMA) (copolymer), 142655-98-9.