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Poly(*N*-acryloyl-*N*′-propylpiperazine): A New Stimuli-Responsive Polymer

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ABSTRACT: A new water-soluble stimuli-responsive poly(*N*-acryloyl-*N*′-propylpiperazine) (PAcrNPP) was synthesized and characterized. The polymer exhibited a lower critical solution temperature (LCST) in water at 37 °C. The phase transition temperature was highly sensitive to pH changes. The effects of some simple salts and cationic surfactants were studied. The enthalpy of phase separation determined by microcalorimetry was 21.4 kJ mol^{-1}. This value corresponds to the breaking of one hydrogen bond per monomer unit. Dynamic light scattering studies indicated some aggregations of polymer chains below the LCST. No such aggregations were observed for the lower analogues, poly(*N*-acryloyl-*N*′-methylpiperazine) (PAcrNMP) and poly(*N*-acryloyl-*N*′-ethylpiperazine) (PAcrNEP) which exhibited no LCST. The cross-linked polymer gels were sensitive to both pH and temperature. Their response time to swelling and deswelling was 150 min. The water sorption of the gels was non-Fickian under both acidic and neutral conditions.

Introduction

In recent years, water-soluble stimuli-responsive polymers, which exhibit a lower critical solution temperature (LCST), have attracted a great deal of interest owing to their potential applications in controlled drug delivery,[1] immobilized enzyme reactors,[2] and separation processes.[3] These polymers are soluble in aqueous solutions but undergo phase transition in response to various stimuli such as pH, temperature, electric field, magnetic field, etc.[4−6] A large number of water-soluble polymers exhibiting LCST have been reviewed.[2,7] Polymer systems, which respond to more than one stimulus, in particular to pH and temperature, have recently attracted much attention because of their relevance to physiological and biological systems.[4,8−10] Most of the systems described use either (*N*,*N*-dimethylamino)ethyl methacrylate (DMAEMA) or acrylic acid (AA) derivatives as the pH-sensitive component and *N*-isopropylacrylamide (NIPAM) as the temperature-sensitive component.

This report describes the synthesis and characterization of a new type of thermal- and pH-responsive polymer, PAcrNPP.

Experimental Section

Materials. Acryloyl chloride (Fluka) and ethylene glycol dimethacrylate (EGDMA) (Fluka) were distilled under reduced pressure and stored in a refrigerator. *N*-Propylpiperazine dihydrobromide (Acros), *N*,*N*-methylenebisacrylamide (BMA) (Baker), and 2,2-dimethoxy-2-phenylacetophenone (DMPA) (Aldrich) were used as received. 1,4-Dioxane (Merck) was distilled under nitrogen over metallic sodium and was used fresh. Tetrahydrofuran (Baker) was refluxed with metallic sodium for 5 h followed by distillation and was stored over molecular sieves. All other materials were used as received.

Synthesis of *N*-Acryloyl-*N*′-propylpiperazine (AcrNPP). *N*-Propylpiperazine was obtained from its dihydrobromide by neutralization with 2 M NaOH followed by extraction with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. It was then filtered and evaporated on a rotary evaporator. The *N*-propylpiperazine was used fresh, as it was prone to oxidation on storage. *N*-propylpiperazine (0.08 mol, 10.0 g) and triethylamine (0.08 mol, 7.97 g) were dissolved in 300 mL of dry THF in a Claisen flask. The flask was cooled in an ice bath and was maintained under an inert atmosphere by passing through dry nitrogen gas. Acryloyl chloride (0.08 mol, 7.10 g) dissolved in THF (30 mL) was added dropwise for 30 min. The contents of the flask were stirred vigorously, and the reaction mixture was allowed to equilibrate to room temperature, after which the reaction was continued for 10 h. Triethylamine hydrochloride was removed by filtration. The filtrate was concentrated on a rotary evaporator, followed by distillation under reduced pressure. Hydroquinone dimethyl ether (1% solution) was added prior to distillation to inhibit any polymerization of the monomer. The fraction that distilled between 110 and 112 °C was collected with 55% yield; n_D^{20}: 1.5020. Elemental analysis: $C_{10}H_{18}N_2O$ (Scheme 1), calculated (%): C, 65.93; H, 9.89; N, 15.38. Found (%): C, 65.95; H, 9.89; N, 15.39. ^{1}H NMR ($CDCl_3$): δ 0.81−0.85 (t, 3H, $-CH_3$), 1.41−1.47 (m, 2H, $-CH_2-$), 2.24 2.28 (m, 2H, $\rangle N-CH_2-$), 2.38−2.40 (m, 4H, $\rangle(CH_2)_2-N-$), 3.51−3.63 (d, 4H, $-CO-N(CH_2)_2\langle$), 6.48−6.75 (q, 1H, $=CH-$), 6.17−6.21 (q, 1H, $CH_2=$, cis), 5.59−5.62 (q, 1H, $CH_2=$, trans) ppm. ^{13}C NMR ($CDCl_3$): δ 127.8 ($\mathbf{C}H_2=$), 128.7 ($=\mathbf{C}H-$), 165.2 ($-\mathbf{C}=O$), 42.1, 45.9 ($-CO-N(\mathbf{C}H_2)_2\langle$), 52.9, 53.5 ($\rangle(\mathbf{C}H_2)_2-N-$), 60.5 ($\rangle N-\mathbf{C}H_2-$), 20.0 ($-CH_2-$), 12.1 ($-\mathbf{C}H_3$) ppm.

Synthesis of Polymers. AcrNPP (5.6 mmol, 1.02 g) and AIBN (0.5 wt %, 0.02 g) were dissolved in 20 mL of freshly distilled dioxane. The mixture was degassed three times by a freeze−thaw cycle. Polymerization was carried out at 70 °C for 24 h. The polymer was precipitated in anhydrous ether (400 mL), purified by reprecipitation and dried in a vacuum at 45 °C (yield 65%, white powder); [η] 0.25 dL/g in DMF at 30 °C and $T_g = 100$ °C.

Synthesis of Cross-Linked Gels. Cross-linked gels of AcrNPP were prepared by photoinitiated polymerizations in bulk and solution using EGDMA and BMA (Scheme 1) as cross-linkers, respectively. For bulk polymerization, AcrNPP (8.2 mmol, 1.5 g), EGDMA (2 wt %), and DMPA (0.5 wt %) were mixed in a glass ampule. The content was purged by bubbling dry nitrogen gas for 15 min. The sealed ampule was then sonicated for 5 min to expel air bubbles, and the polymerization was carried out in a photochemical reactor by UV irradiation ($\lambda > 300$ nm) for 30 min. The clear, transparent polymer was immersed in diethyl ether for 2 weeks to remove

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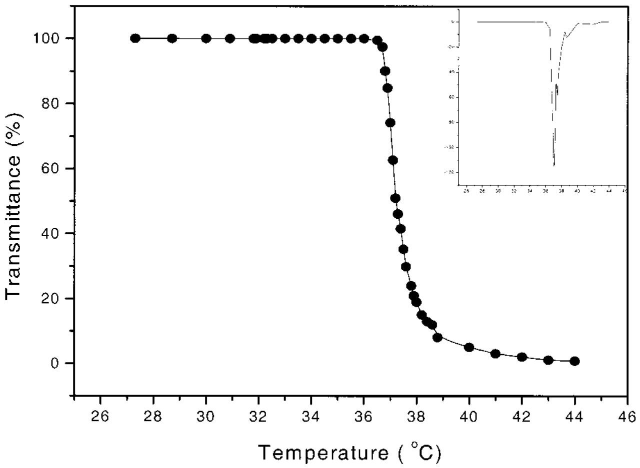
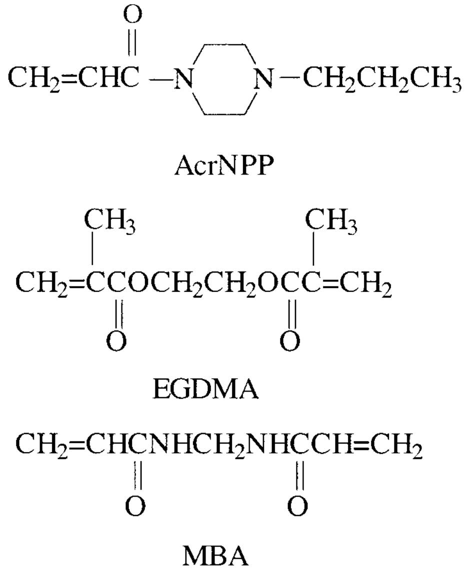


Figure 1. Percent transmittance versus temperature curve for 1 wt % PAcrNPP in water. Inset: *Y*-axis is the derivative of percent transmittance with temperature.

Scheme 1. Structural Formulas of AcrNPP, EGDMA and MBA



any unreacted monomers, with the ether being replaced daily. The polymer was then swelled in water and cut into small disks (ca. 1.5 mm) and dried to constant weight in a vacuum. The photoinitiated solution polymerization was carried out in a similar way except 2 wt % BMA was used as the cross-linker in 5 mL of methanol.

LCST Measurements. The LCST of the polymer solution was determined spectrophotometrically using a Perkin-Elmer (Lambda 2) UV/vis spectrophotometer connected to a temperature controller (e.g., Figure 1). The polymer concentration was always maintained at 1 wt %, and the absorbance at 486 nm was measured. Microcalorimetric measurements were carried out using a high-sensitivity Microcal MC-2 differential scanning calorimeter (MDSC) (Microcal, Northampton, USA). The Origin software was used for data collection and analysis. Sample was run against distilled water as the reference solution. The solutions were maintained under nitrogen atmosphere to suppress the formation of any bubbles. The enthalpy change for the transition ΔH was calculated from the area of the transition peak.

Titrations. Potentiometric titration of the polymer was carried out in order to study the effect of charge on the phase separation of the polymer. It was performed using an ABU93 Triburette titration system (Radiometer, Copenhagen, Denmark) for the determination of the percent charge in the polymer near LCST. The instrument was integrated with a standard RS232C interface, and the titration was automated by the ALIQUOT titration program.

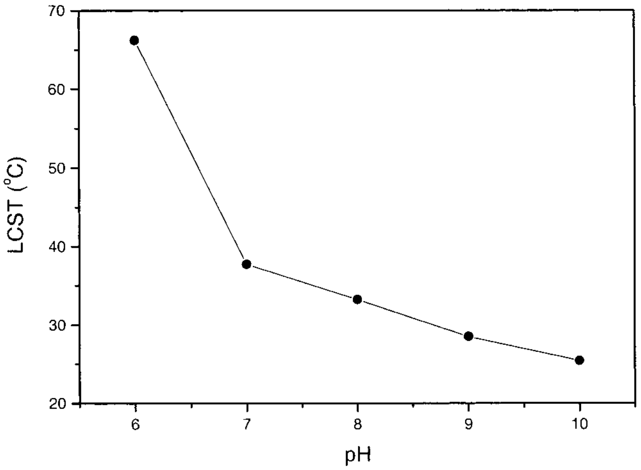


Figure 2. Effect of pH on LCST of 1 wt % PAcrNPP solution.

Laser Light Scattering (LLS) Measurements. A commercial laser light spectrometer (Brookhaven BI 200SM goniometer) system equipped with a 532-channel BI9000AT digital multiple-τ correlator was used. The light source was a power adjustable vertically polarized argon ion laser with a wavelength of 488 nm. The measured temperature was controlled using a Science/Electronic water bath. In dynamic LLS, a precise intensity–intensity–time correlation function in the self-beating mode was measured. The REPES inverse Laplace transform routine[11] supplied with the GENDIST software package was used to analyze the time correlation functions. The probability of reject was always set to 0.5. All the test samples were filtered through a 0.2 μm filter (Whatman) in order to remove any dust, and the solutions were allowed to equilibrate at room temperature for 24 h.

Swelling Measurements. The swelling of cross-linked polymers was determined gravimetrically. Sodium acetate–acetic acid (pH 2.6–5.6) and sodium hydrogen phosphate–disodium hydrogen phosphate (pH 6.3–9.1) buffer solutions were used. The weight-swelling ratio (*W*) was defined as

$$W = (\text{wet weight} - \text{dry weight})/(\text{dry weight}) \qquad (1)$$

Results and Discussion

LCST Measurements. Figure 1 shows the UV–vis light transmittance measurements (λ 486 nm) of 1 wt % PAcrNPP solution in water at temperatures ranging from 27 to 44 °C. The LCST was defined as the temperature at which the differential of the percent transmittance with respect to the temperature is minimum. The LCST thus determined was 37 °C. The value was close to those of several N-substitutes poly(acrylamides) such as poly(*N*-isopropylacrylamide) (32 °C), poly(*N*-isopropylmethacrylamide) (40 °C), poly(*N*-piperidylmethacrylamide) (LCST 42 °C), and poly(*N*,*N*-diethylacrylamide) (LCST 32 °C).[12]

Effect of Various Stimuli. The effect of pH on the LCST of 1 wt % PAcrNPP solution is shown in Figure 2. The LCST was found to decrease progressively with increasing pH of the medium. At pH 6, the LCST was about 65 °C, an increase of 28 °C over that of the polymer solution in distilled water. Protonation of the tertiary amino groups of the piperazine units leads to electrostatic repulsion causing the polymer to be more soluble and leading to an increasing LCST. At high pH, the protonation is weak and the polymer–polymer interactions are strong, leading to phase separation at lower temperatures. From the results of potentiometric titration of aqueous solutions of PAcNPP at 25 °C, the

Table 1. Effect of Various Cationic Surfactants on LCST of PAcrNPP in Water, Determined Spectrophotometrically

[surfactant] (10^{-3} mol dm^{-3})	surfactant[a]/LCST (°C)			
	DTAB	TTAC	HTAB	HTAC
0.25	29.6	32.4	42.2	35.8
1.0	33.8	39.1	49.3	45.6
3.0	45.6	47.7	58.7	56.8
5.0	50.7	57.8	65.8	62.7

[a] DTAB = dodecyltrimethylammonium bromide; TTAC = tetradecyltrimethylammonium bromide; HTAB = hexadecyltrimethylammonium bromide; HTAC = hexadecyltrimethylammonium chloride.

Table 2. Thermodynamic Parameters of PAcrNPP in Water Determined by Microcalorimetry[a]

ΔH (J/g)	$C_{p,\max}$ (J/g/K)	T_m (°C)	$\Delta T_{1/2}$ (°C)	T_0 (°C)
21.14	2.07	41.08	8.83	32.75

[a] ΔH = enthalpy of phase separation; $C_{p,\max}$ = maximum heat capacity; T_m = temperature at maximum heat capacity; $\Delta T_{1/2}$ = temperature at half-width of the endotherm; T_0 = onset temperature.

total amount of charged monomer units near the LCST was estimated to be approximately 5 mol %. The basicity of PAcrNPP decreases slightly with increasing temperature due to the decreased dielectric constant.[8,13]

The addition of NaCl, KCl, NaBr, and KI resulted in a lowering of the LCST. The effects are similar to those reported for PNIPAM.[14] The effects of several cationic surfactants are shown in Table 1. At very low concentration, the surfactant acts as a simple electrolyte and lowers the LCST. Above the critical aggregation concentration (CAC) the LCST increases owing to the formation of polymer−surfactant complexes, causing an increase in hydrophilicity and a delayed collapse to the hydrophobic conformation.[15,16]

Microcalorimetric Study. The thermodynamic parameters for the phase transition of PAcrNPP determined from microcalorimetric study are summarized in Table 2. In all runs, 1 wt % polymer solution and a scan rate of 60 °C/h were employed. The temperature at the maximum of the endotherm was found to correspond closely to the LCST determined spectrophotometrically, while the onset temperature was about 4.3 °C lower. The enthalpy of phase separation ΔH was 21.1 J g^{-1}, which corresponds to 3.8 kJ mol^{-1} of the repeat unit of the polymer. This value agrees reasonably with those reported for PNIPAM[17] and poly(*N*,*N*-diethylacrylamide).[15]

Light Scattering Study. The weight-average molecular weight M_w of PAcrNPP determined in THF at 25 °C by LLS was 3.4×10^5 g mol^{-1}. For dynamic LLS study in THF solution, a single decay mode due to the translational diffusion of single polymer chain was observed. A hydrodynamic radius of ~8 nm was obtained. However, for 1 wt % PAcrNPP in aqueous solution under the same conditions, the relaxation time distribution showed two well-separated modes. The fast mode was attributed to the translational diffusion of single polymer chains with the corresponding hydrodynamic radius of ~8.7 nm. The slow mode corresponds to a hydrodynamic radius of 82 nm. These results indicate that PAcrNPP forms aggregates even below the LCST. Interestingly, we have observed similar aggregates below the LCST for 1 wt % poly(*N*,*N*-diethylacrylamide) aqueous solution. For the solutions of two lower analogues of PAcrNPP, PAcrNEP, and PAcrNMP, only one relaxation decay mode corresponding to the translational diffusion of single polymer chain was observed. These two polymers, however, did not show phase transition behavior in the temperature range studied. The hydrophobicity of the polymers increases with an increasing chain length of the N-substituted alkyl group. When the alkyl group contains three carbon atoms, the molecule becomes sufficiently hydrophobic to induce associations even below the LCST.

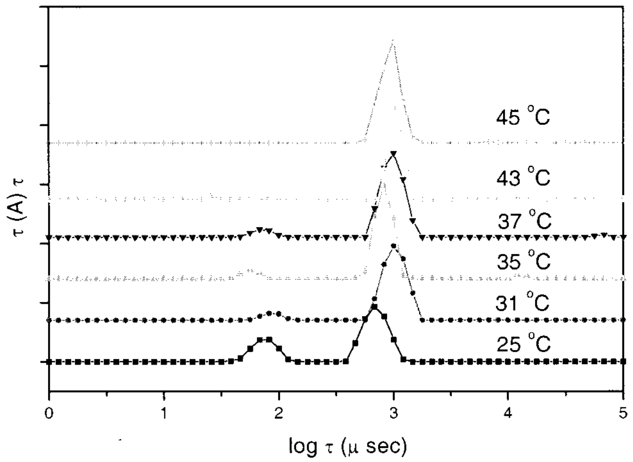


Figure 3. Effect of temperature on the relaxation time distribution of 1.0 g L^{-1} PAcrNPP in water.

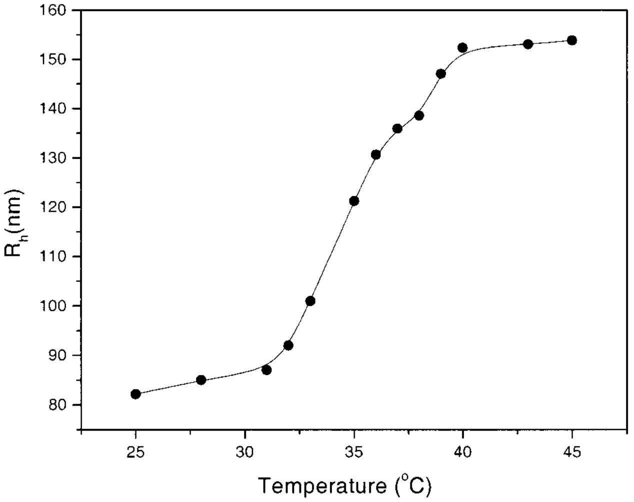


Figure 4. Effect of temperature on the hydrodynamic radius of 1.0 g L^{-1} PAcrNPP in water.

The effect of temperature on the relaxation time distribution of PAcrNPP in water is shown in Figure 3. The corresponding variation in the hydrodynamic radius is shown in Figure 4. The decay modes shifted to the right with increasing temperature. The hydrodynamic radius of the aggregates increased with increasing temperature and reached about 150 nm at temperatures above the LCST. These observations are the consequence of the association of the polymer chains. The critical aggregation temperature was estimated to be 33 °C by plotting the ratio of the area of the fast mode and slow mode versus the temperature. This temperature agreed well with the onset temperature of aggregation, which is 32.8 °C as measured by MDSC.

Swelling Studies of Gels. Figure 5 shows the effect of pH on the equilibrium swelling of PAcrNPP gels. The gels swelled more under acidic conditions due to the protonation of the amine nitrogen of the piperazine unit.

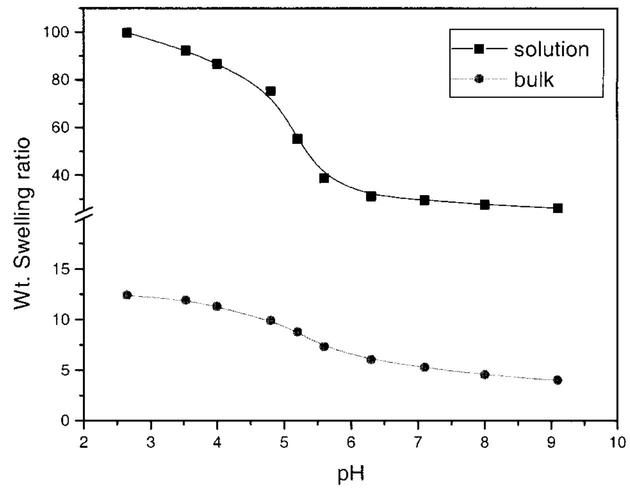


Figure 5. Effect of pH on the equilibrium swelling of PAcrNPP gel at 25 °C.

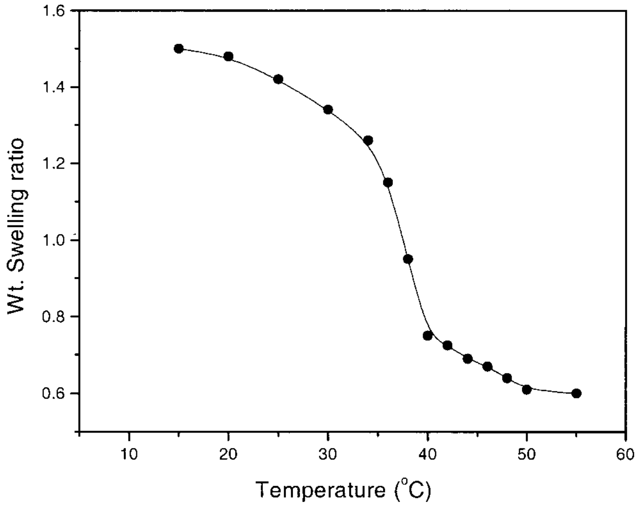


Figure 6. Effect of temperature on the equilibrium swelling of PAcrNPP gel in water.

The gel prepared by solution polymerization showed much higher swelling ratio than that prepared by bulk polymerization.

Figure 6 shows the effect of temperature on the swelling of PAcrNPP gel prepared by bulk polymerization. The gel exhibited reversible thermoshrinking behavior with a continuous transition. The transition occurred between 30 and 40 °C, agreeing well with the LCST at 37 °C of the linear polymer. Above this temperature range, the gel became slightly opaque, indicating the collapse of the polymer chains. Figure 7 shows the swelling–deswelling profile of PAcrNPP at 25 °C by changing the pH from 2.6 to 7.0. The times needed for both the swelling and deswelling processes to reach equilibrium were almost the same, 150 min. The swelling–deswelling cycle could be repeated without any changes in swelling capacity.

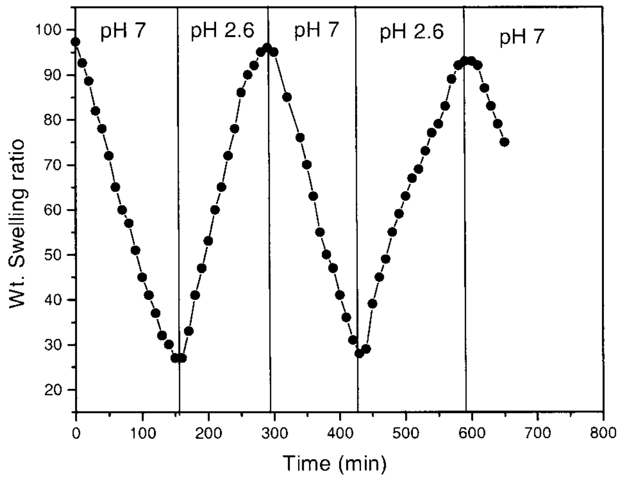


Figure 7. pH-dependent swelling–deswelling profile of PAcrNPP gel at 25 °C.

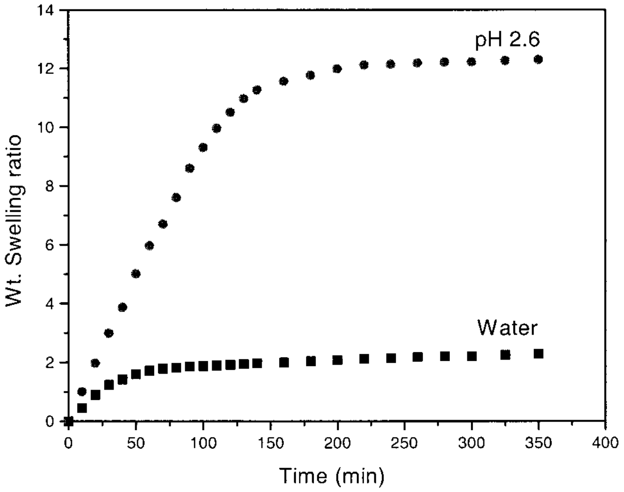


Figure 8. Water sorption kinetics of PAcrNPP gel at pH = 2.6 and in distilled water at 25 °C.

Table 3. Water Sorption Characteristics of PAcrNPP Gels Prepared by Bulk Polymerization with 2 wt % EGDMA at 25 °C

pH	n	k	$D \times 10^7$ (cm^2/s)	W_∞
2.6	0.99	0.008	3.3	12.3
7.0	0.83	0.03	7.2	2.3

Water Sorption Characteristics. Typical water sorption curves of PAcrNPP in solutions of pH 2.6 and water as a function of time are shown in Figure 8. For the sorption kinetics, the initial swelling data were fitted to the approximation of Fick's law (eq 2),[18,19] which can be applied to thin flat sheets in which diffusion through the edges may be neglected,

$$M_t/M_\infty = kt^n \tag{2}$$

where M_t and M_∞ are the mass of water taken up at time t and infinite time, respectively, k is a characteristic constant of the gel, and n is a characteristic exponent of the mode transport of the penetrating molecule. The data were fitted into eq 2 in the range of $M_t/M_\infty \leq 0.6$. The values of n and k were calculated from the slopes and intercepts of the plot of $\log(M_t/M_\infty)$ against log t (t in minutes), respectively. The values are presented in Table 3. For Fickian kinetics in which the rate of diffusion of the penetrant is rate limiting, $n = 0.5$, whereas values of n between 0.5 and 1 indicate the contribution of non-Fickian processes such as polymer relaxation.[20] The values of the swelling exponent n of PAcrNPP were 0.83 and 0.99 in distilled water and in pH 2.6, respectively. This indicates that the swelling transport mechanism is non-Fickian, owing to polymer relaxation. The initial sorption curve is sigmoidal, similar to those observed for certain hydrophilic gels.[21,22] This is attributed to the formation of a swelling front during the period of initial swelling as explained by Siegel.[22] From the gradient of the plot of the initial swelling rate against square root of time, the diffusion coefficient D was calculated by

$$\frac{M_t}{M_\infty} = \left(\frac{4}{l}\right)\left(\frac{Dt}{\pi}\right)^{1/2} = \frac{W_t}{W_\infty} \tag{3}$$

where W_t and W_∞ are weight-swelling ratios at time t and time infinite, respectively, t is the time, and l is the initial thickness of the dried gel. The relatively high value of D for the gel system studied is attributed to the hydrophilic nature of the gel network.

Conclusion

A new type of thermal- and pH-responsive polymer derived from piperazine-based monomers was prepared. The polymer PAcrNPP showed a LCST value of 37 °C in distilled water. The LCST values were greatly affected by the presence of simple salts and cationic surfactants. Increasing the chain length of the N-substituted alkyl group increased the hydrophobicity of the polymer. Hence, the aqueous solution of PAcrNPP exhibited a LCST which PAcrNMP and PAcrNEP did not. The gels derived from these piperazine-based polymers were also responsive to pH and temperature changes.

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