Hydrophobic Association and Temperature and pH Sensitivity of Hydrophobically Modified Poly(*N*-isopropylacrylamide/acrylic acid) Gels

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ABSTRACT: Hydrophobically modified poly(acrylic acid/*N*-isopropylacrylamide) gels were synthesized by the radical copolymerization of acrylic acid/*N*-isopropylacrylamide with a small amount of the hydrophobic comonomer 2-(*N*-ethylperfluorooctanesulfoamido)ethyl acrylate, stearyl acrylate, or lauryl acrylate in *tert*-butanol with ethylene glycol dimethacrylate as a crosslinker. Swelling kinetics and fluorescence measurements showed that the hydrophobic association ability of fluorocarbon groups was stronger than that of hydrocarbon analogues in modified hydrogels that contained both physical and chemical crosslinking networks. The effects of the fractions and the species of the hydrophobe on the gel swelling and pH and temperature sensitivity were studied. The results indicated that the swelling behavior and pH and temperature sensitivity of the gels were affected by the degree of hydrophobic modification. A hydrogel with a suitable 2-(*N*-ethylperfluorooctanesulfoamido)ethyl acrylate content (0.349 mol %) showed good pH and temperature sensitivity. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 87: 2406–2413, 2003

INTRODUCTION

Since the 1980s, when Hoffman and coworkers[1–3] suggested that responsive hydrogels could be used in a variety of novel applications, including controlled drug delivery,[1] immobilized-enzyme reactors,[2] and separation processes,[3] hydrogels sensitive to external conditions have become an important area of research.[4,5]

The swelling response ability of a polymeric gel network can generally be attributed to the effects of the repulsion and attraction of functional groups attached to the gel network. The repulsion and attraction can arise from a combination of four noncovalent interactions: electrostatic, hydrophobic, van der Waals, and hydrogen-bonding.[6] Of these, hydrophobic interactions can induce physical crosslinking that affects the gel swelling behavior. Compared with chemical crosslinking, physical crosslinking arising from hydrophobic association is sensitive to the external environment, and gel mesh sizes are reversibly capable of accommodating a solute and inhibiting its diffusion. Therefore, these polymer gels can be expected to act as intelligent materials in controlled or targeted drug release.[7] Obviously, it is necessary to understand the relationship between the hydrophobic microstructure and the macroscopic properties of hydrogels. Fluorospectroscopy is no doubt the most extensive and informative characterization technique because of its high sensitivity and the strong dependence of the fluorescent behavior of probe molecules on the microenvironment.[8,9]

N-Isopropylacrylamide (NIPAM) gel[4,5] is a well-known thermosensitive gel that shows a discontinuous volume-phase transition in response to temperature changes. However, hydrophobically modified poly(*N*-isopropylacrylamide) (HM-PNIPAM) hydrogels and their responses to pH and temperature pulse stimuli are reported rarely.

To this day, most reported hydrogels are formed only by chemical crosslinking[10] or by physical crosslinking,[11] and hydrogels with hydrophobic association acting as physical crosslinking are mainly modified with hydrocarbon groups.[12] As for fluorocarbon-modified hydrogels containing both physical and chemical crosslinking, few articles can be retrieved.[13] However, compared with their hydrogenated counterparts, fluorinated chains have a stronger hydrophobic association ability. A CF_2 group is equivalent to 1.7 CH_2 units in terms of hydrophobicity.[14] In our previous works about hydrophobically modified water-soluble polymers (HMWSPs),[15–17] the synthesis

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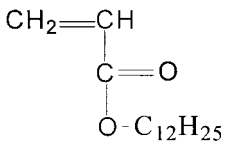
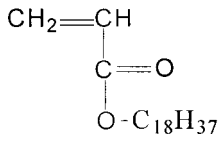
and rheological properties of hydrophobically modified poly(acrylic acid),[15] the interactions of fluorocarbon-modified polyelectrolytes with various surfactants,[8,16] and the fluorescence of HM-PNIPAM[17] were studied. The results showed that in these HMWSPs, fluorocarbon hydrophobes exhibited much stronger associations than their hydrogenated counterparts because of their low cohesive energy density and surface energy. Therefore, we decided to explore the hydrophobic association of fluorocarbon groups in hydrogels.

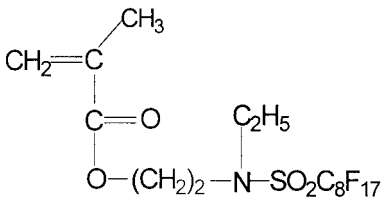
In this work, hydrophobically modified NIPAM/acrylic acid (AA) and poly(*N*-isopropylacrylamide) (PNIPAM) copolymer gels were synthesized. Three kinds of hydrophobes [2-(*N*-ethylperfluorooctanesulfoamido)ethyl acrylate (FMA), stearyl acrylate (SA), and lauryl acrylate (LA)] were incorporated into the gel networks. With fluorescence and swelling measurements, we compared the hydrophobic associations of hydrocarbon groups and fluorocarbon groups for hydrogels that contained both chemical and physical crosslinking. The responses of the hydrophobically modified gels to pH and temperature pulse stimuli were also studied.



Lauryl acrylate (LA)



Stearyl acrylate (SA)



2-(N-ethylperfluorooctane-sulfoamido)ethyl methacrylate (FMA)

Scheme 1 Molecular structures of the hydrophobic comonomers.

EXPERIMENTAL

Materials

NIPAM was recrystallized in benzene/hexane. AA was vacuum-distilled before use. FMA was recrystallized from methanol twice and dried *in vacuo* before use. SA, LA, and ethylene glycol dimethacrylate (EGDMA) were purchased from Aldrich Co., OH. Azobisisobutyronitrile (AIBN) was purified by recrystallization in methanol. The chemical structures of the three hydrophobic comonomers are depicted in Scheme 1.

Gel synthesis

The macroscopic hydrogels were prepared by the radical copolymerization of NIPAM/AA with and without a certain amount of the hydrophobic comonomers (FMA, SA, and LA) in *tert*-butanol. In all cases, the total monomer concentration was kept at 1.5 mol/L. The contents of AIBN as an initiator and EGDMA as a crosslinker were kept at 0.05 and 1 mol % (relative to the total monomer), respectively. The aqueous mixture, before the addition of AIBN, was bubbled with nitrogen gas for 10 min in an ice–water bath, and then the ethanol solution of AIBN was injected. The reaction was performed in a sealed cylindrical glass tube (inner diameter = 10 mm) equipped with a nitrogen inlet tube at 60 ± 0.5°C for 24 h. Polymerizations were carried out to high fractional conversions (>90%), as indicated by the weight ratio of the dry gel to the initial total monomer.

The resulting gels were removed, cut into disks, and then soaked in a large amount of absolute ethanol for 1 week. The solvent was exchanged once every 2 days for the removal of monomers and oligomers that were not actually incorporated into the hydrogels. After at least 1 week, the gels were dried in a vacuum oven at 40°C until a constant weight was obtained. The monomer feed and F conversion in the copolymers gels are listed in Table I.

Characterization

Anion chromatography

Anion chromatography is based on the anion-exchange process occurring between a mobile phase (eluent and anion) and a stationary phase (a crosslinked polystyrene bead modified with quaternary ammonium groups). The separation of anions (fluorocarbon-modified copolymers were burned to produce F anions) is based on the affinity difference between the F anion and quaternary ammonium. The concentration of the F anion is detected by conductivity. With the direct injection of a 50-mL sample, the detection limit was approximately 10 ppb. Therefore, the concentration of F anion could be precisely determined with an error of not more than ±3% in our

TABLE I
Monomer Feed and Fluoro-Conversion in the Syntheses of the Gels[a]

Sample	Yield (wt %)	AIBN	Feed (mol %)				Actual (mol %)[b]	Hydrophobe conversion (%)
			EGDMA	NIPA	AA	FMA	FMA	
AF-N0	95	0.05	1	0	98	2.0	1.822	96
NF-A0	97	0.05	1	98	0	2.0	1.803	93
NAF-A1	95	0.05	1	93	5	2.0	1.767	93
NAF-A2	93	0.05	1	88	10	2.0	1.774	95
NAF-A3	96	0.05	1	68	30	2.0	1.785	93
NA-F0	94	0.05	1	68	30	0	0	—
NA-F1	92	0.05	1	68	30	0.4	0.349	95
NA-F2	97	0.05	1	68	30	0.8	0.722	93
NA-F3	96	0.05	1	68	30	2.0	1.785	93
NA-F4	92	0.05	1	68	30	2.35	1.955	90
NA-F5	94	0.05	1	68	30	2.5	2.162	92
NA-L2	93	0.05	1	68	30	0.8	—	85

[a] In gel samples, the feed amounts of monomer AA, chemical crosslinker EGDMA, and initiator AIBN were 1.5, 0.015, and 0.00075 mol/L, respectively. In the name of the samples, the letters of N, F, A, and L denote NIPAM, FMA, AA, and LA, respectively.
[b] The F conversion was measured by anion chromatography.

experiments. The fluorocarbon content determined by anion chromatography (Dionex 2110 I, Dionex, Sunnyvale, CA) is listed in Table I.

Swelling measurements

For the swelling measurements in different pH buffer solutions, gels were swollen in Britton–Robinson buffer solutions with the desired pH at 20°C for 1 day.

For the temperature-response studies, the gels first were equilibrated in deionized water at 20°C for at least 1 week so that they could attain an extended chain conformation and then were immersed in deionized water at 20 and 50°C for 30 min alternately. Similarly, for the pH-response studies, gels first were equilibrated in a buffer solution with a pH value of 11.98 for at least 1 week and then were immersed in buffer solutions with pH values of 11.98 and 1.81 for 30 min alternately. Gravimetry was based on short-time temperature and pH changes.

The hydrogels, swollen under different conditions, were quickly taken out and weighed. Before the weighing, the surface water of the samples was carefully wiped off. The swelling capacity was recorded gravimetrically as follows:

$$\text{Swelling ratio} = (M_t - M_0)/M_0$$

where M_t and M_0 denote the weights of the swollen gels and dry gels, respectively. All the reported swelling ratios were averages of at least three trials.

Fluorescence measurements

Fluorescence spectra were recorded on an FZ-1 fluorescence spectrophotometer with 2-nm slits for excitation and emission. Pyrene was used as a probe. The excitation wavelength was 334 nm. The ratio of the intensities of the third vibronic peak (384 nm) to the first (373 nm) of the fluorescence spectrum of the monomer pyrene was used as an estimate of the polarity of the pyrene microenvironment.

For fluorescence measurements, gels were prepared in a special square model for the formation of a suitable size gel that could fill completely the quartz cell of the fluorescence spectrophotometer. The gels were put into the quartz cell filled with a fixed amount of a pyrene–water solution (8×10^{-7} mol/L). Before the fluorescence measurements, the gels were allowed to stay at least 2 days in the dark to absorb the pyrene solution fully. The final concentration of the polymer was equal to 5×10^{-5} g/L.

RESULTS AND DISCUSSION

Effect of the hydrophobe on the swelling properties of the gels

The swelling behaviors of the gels in deionized water are reported for systems consisting of three kinds of hydrophobes (LA, SA, and FMA) with different contents. The effects of the hydrophobe content and type on the equilibrium swelling ratios of the gels are shown in Figure 1. The swelling ratios of the hydrogels sharply decrease with a small increase in the hydrophobe content, indicating that hydrophobic association is formed in the hydrogels. Micellar-like hydrophobic domains, which act as physical crosslinkers to restrain the swelling of the gel networks, arise from hydrophobic side groups dangling on the gel networks. With the FMA content higher than 0.8 mol %, the equilibrium swelling ratios of the gels change lit-

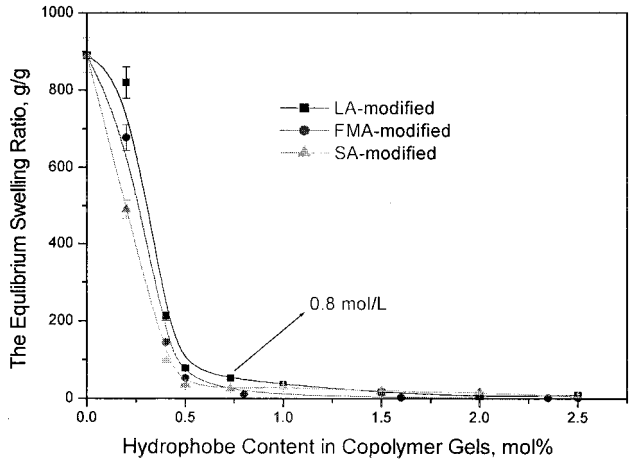


Figure 1 Effect of the hydrophobe content on the swelling properties of the hydrogels.

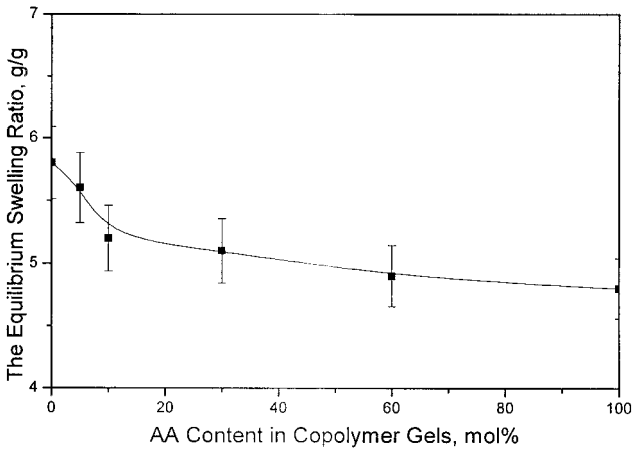


Figure 2 Effect of the AA content on the swelling properties of the hydrogels.

tle. In this case, the physical crosslinking obtains saturation.

It can be seen in Figure 1 that the swelling ratios of the hydrogels decrease in the order LA < FMA < SA. This can be explained by the structural differences of the hydrophobes. It is well known[18] that the stronger hydrophobic interactions can be induced by an increase in the length of the alkyl chain because the transfer energy of the hydrocarbon molecules from an aqueous solution to a pure hydrocarbon environment increases significantly. Among the three types of hydrophobes in this system, the LA group has weaker hydrophobicity than the SA group (containing $C_{18}H_{37}$) because of the shorter length of the hydrophobic chain (containing $C_{12}H_{25}$). For comparison, the fluorocarbon group FMA (containing C_8F_{17}) exhibits a stronger ability of hydrophobic association than the hydrocarbon group LA, although the chain length of the latter is longer. Therefore, the fluorocarbon groups possess stronger hydrophobic character than their hydrocarbon analogues because of their lower values of the cohesive energy density and surface energy.[19] In fact, the cohesive energy of one CF_2 is about 2.12 kT,[20] which can be understood as the energy needed for one CF_2 to enter into hydrophobic microdomains from water; however, the cohesive energy of one CH_2 is about 1.15 kT.[20] The swelling ratio data prove that the hydrophobicity of the hydrophobes increases in the order LA < FMA < SA.

It is a general trend that the swelling ratios of gels increase with the content of an acidic comonomer containing ionizable groups.[21] However, as can be seen in Figure 2, the swelling ratios of the gels are almost unchanged with the increase in the AA content. This proves that the hydrophobic association of the fluorocarbon groups is so strong that the hydrophobic interaction predominates over the electrostatic interaction. The enhanced swelling ability, which arises from the increase in AA, is screened by the high degree of physical crosslinking induced by the hydrophobic association of FMA groups.

Swelling dynamics of the copolymer gels

The swelling kinetic curves for the hydrogels with different component proportions are shown in Figure 3. FMA-modified gels have a slower water-absorbing speed and a lower swelling ratio than the unmodified hydrogel (NA-F0). In addition, the higher the content is of FMA, the slower the swelling speed is and the lower the swelling ratio is. It is proved again that strong hydrophobic association, acting as physical crosslinking, is formed by FMA groups. As a result, the outer water is restrained from entering into gel networks. Noticeably, in comparison with the gel AF-N0, which contains 1.822 mol % FMA but no NIPAM, the gel NA-F1 contains an additional 68 mol % NIPAM but only 0.349 mol % FMA. However, the equilibrium swelling ratio of the former is much lower

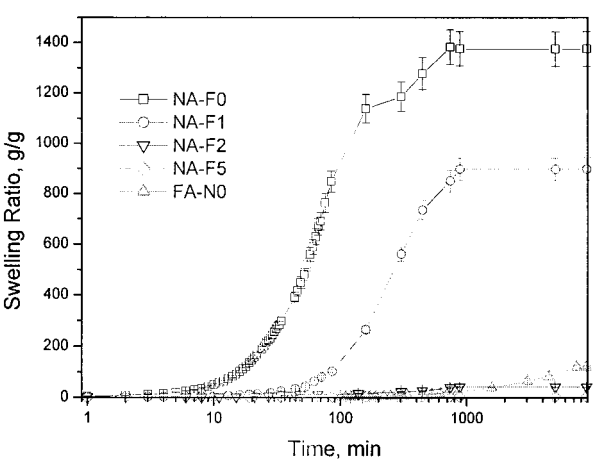


Figure 3 Swelling dynamic curves of the hydrogels with different component proportions.

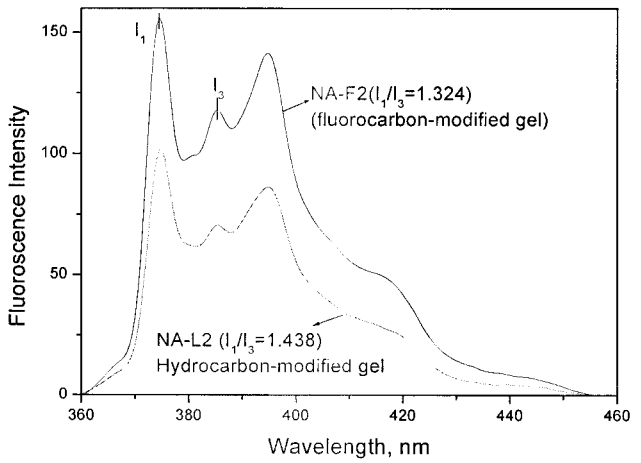


Figure 4 Typical fluorescence spectra for the hydrophobically modified NIPAM/AA hydrogels.

than that of the latter. This shows that the hydrophobic association of FMA is much stronger than that of NIPAM.

Hydrophobicity

Fluorescence measurements with pyrene as a probe are conducted (1) to confirm the presence of hydrophobic microdomains in hydrophobically modified hydrogels and (2) to detect changes in the polarity and rigidity of these hydrophobic microdomains as a function of the hydrophobic side-chain type and content. This ratio increases with the hydrophobicity of the probe environment,[22] changing from approximately 1.8 in water to approximately 0.6 in nonpolar solvents such as hexane.[17] As pyrene is relatively insoluble in water, it will partition primarily into the hydrophobic microdomains, thereby providing a method for measuring hydrophobic association in the gel networks.

Typical fluorescence spectra for FMA-/LA-modified hydrogels (NA-F2 and NA-L2) with 0.8 mol % hydrophobe and 20 g/g of water (i.e., the polymer concentration is 5×10^{-5} g/L) are given in Figure 4. Qualitatively, the fluorescence spectra are shown in Figure 4, where the I_1/I_3 intensity ratios are 1.324 and 1.438 for NA-F2 and NA-L2 hydrogels, respectively. These two ratio values are both lower than that of pyrene in water (1.8),[17] indicating that significant hydrophobic association formation occurs for the two kinds of hydrogels. Surely, the former (with the lower I_1/I_3 value) presents a stronger hydrophobic environment than the latter.

I_1/I_3 as a function of the hydrophobe content for fluorocarbon- and hydrocarbon-modified hydrogels is shown in Figure 5. As the contents of the hydrophobic comonomers increase, I_1/I_3 ratios obviously decrease (i.e., 1.80 for the hydrogel NA-F0 and 1.204 for the hydrogel NA-F5). That the greater hydrophobic modification causes the lower value of I_1/I_3 indicates that the solubilization of the probe in a more hydrophobic environment increases with the aggregating degree of hydrophobic side chains. It is noticeable that the more obviously decreasing trend is induced for fluorocarbon-modified gels rather than for hydrocarbon-modified gels, and this proves again that the hydrophobicity of the fluorocarbon group FMA is stronger than that of the hydrocarbon group LA.

Pulsatile temperature stimuli

The temperature sensitivities of the copolymer gels are shown in Figure 6. As seen in Figure 6(a), the amount of the releasing water of hydrogel NA-F1 at 50°C is larger than that of the absorbing water at 20°C. After a temperature circle (i.e., 20–50–20°C), the swelling ratio of gel NA-F1 decreases. It is ascribed to the change in the balance between the hydrogen-bonding interaction that is disrupted during the process of increasing temperature and the hydrophobic interaction. In the inner portions of the gels, water molecules form the ordered structure by hydrogen bonding. For hydrophobically modified gels, some hydrogen bonds are rearranged, and a kind of iceberg structure is formed around the hydrophobic side chains.[23] If the hydrophobic side chains associate with one another, the iceberg structure will be destroyed. In the whole process, ΔH (enthalpy, the change of heat in system) is negligible. Because the entropy change is positive ($\Delta S > 0$) (ΔS, entropy, the disorder level of particle in system), the process of hydrophobic association is spontaneous ($\Delta G < 0$) (ΔG, the change in Gibbs free energy). The increase in the temperature will promote hydrophobic association, which is disadvantageous for the swelling process of the hydrogels. Therefore, the temperature sensitivity of the gels is related to the hydrophobic association directly.

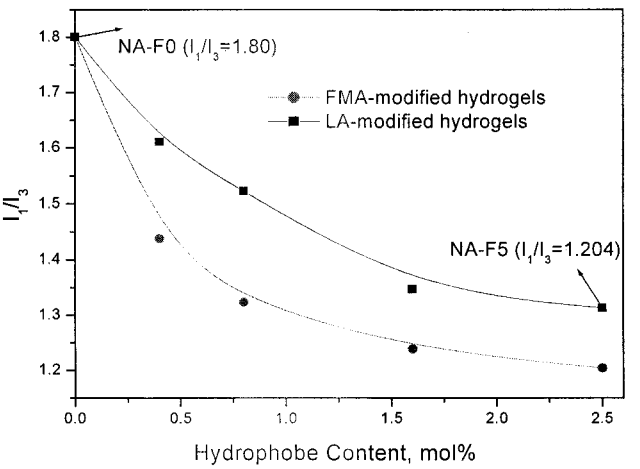


Figure 5 I_1/I_3 for pyrene in the hydrogels as a function of the hydrophobe content.

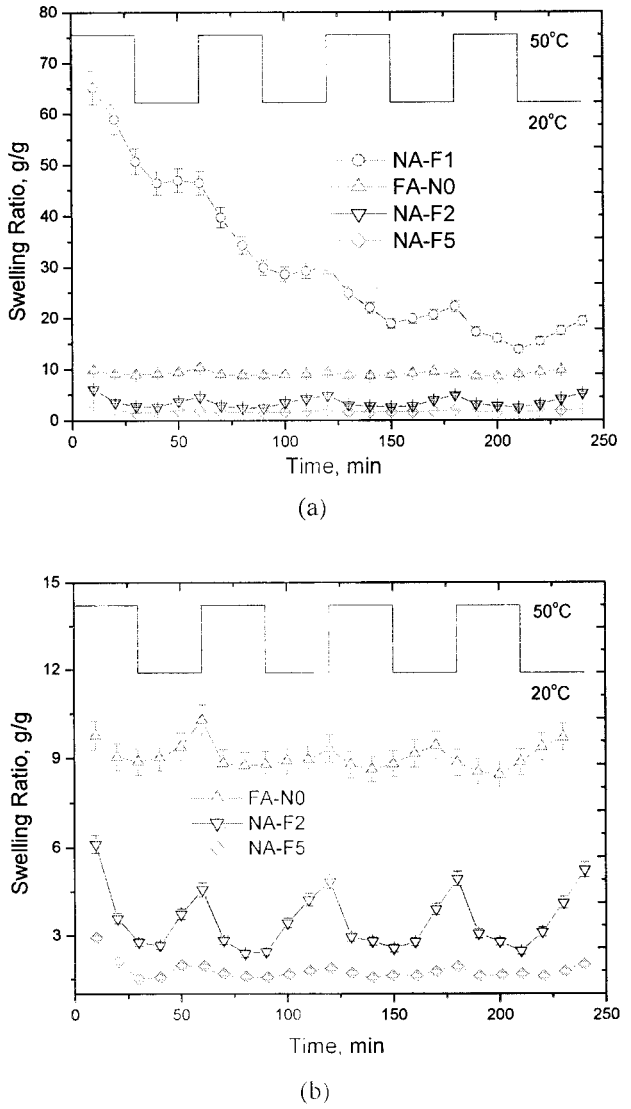


Figure 6 Effect of the alternate temperature stimulus on the swelling properties of the hydrogels with different component proportions: (a) comparison of four kinds of gels (NA-F1, FA-N0, NA-F2, and NA-F3) and (b) comparison of three kinds of gels (FA-N0, NA-F2, and NA-F3).

As mentioned previously, the hydrophobic association of FMA is much stronger than that of NIPAM; this has been proven by the smaller equilibrium swelling ratio for AF-N0 than for NA-F1 (Fig. 3). From Figure 6(a), during the whole process of temperature pulse, the gel AF-N0 (without NIPAM) shows all along a lower water-absorbing ability than the gel NA-F1. This proves that under temperature stimulation, the fluorocarbon group FMA all the time has a stronger ability for hydrophobic association than the hydrocarbon group NIPAM.

In comparison with NA-F1, the water amounts for the hydrogels NA-F2, NA-F5, and AF-N0 seem to change little under the temperature stimuli [Fig. 6(a)]. Even at a low temperature (20°C), these three kinds of gel networks still collapse tightly. As a result, the differences in the swelling ratios between 20 and 50°C are not obvious. However, from Figure 6(b), the obvious responses to temperature pulse are exhibited for these hydrogels (NA-F2, NA-F5, and AF-N0). Therefore, by an adjustment of the proportions of NIPAM and FMA, the temperature response of hydrophobically modified hydrogels can be designed according to requirements.

Pulsatile pH stimuli

The swelling behaviors of copolymer gels with different FMA contents undergoing pH pulses are shown in Figure 7. The gels exhibit pH sensitivity, swelling in basic solutions, and collapsing in acidic solutions. This is ascribed to the increase in the electrostatic repulsing forces between the ions in the buffered solution and the carboxylic acids at the higher pH value.[24]

The swelling speeds of gels at pH 11.98 are quicker than their collapsing speeds at pH 1.81, which induces a decrease in the swelling ratios after a circle of pH pulses. In addition, hydrogels with different FMA contents show different decreasing trends after a circle of pH pulses. For gels without FMA (the gel NA-F0) or with a low content of FMA (the gel NA-F1), although their swelling ratios cannot revert fully to the first value, the changing amount of water in the gels is great during pH pulse stimuli. For gels with a high content of FMA (the gels NA-F2 and NA-F5), the situation is reversed. The swelling ratios of gels are almost reversible, but the changing amount of water in the gels is small because of the increase in the hydrophobic interactions and the decrease in the AA proportions in the gels. All these results demonstrate that hydrophobic modification with FMA can adjust the pH sensitivity of PNIPAM-AA gels effectively.

Swelling properties of the gels at different pHs

Typical dependencies of the swelling ratios on the pH value of the solution are shown in Figure 8. The swell-

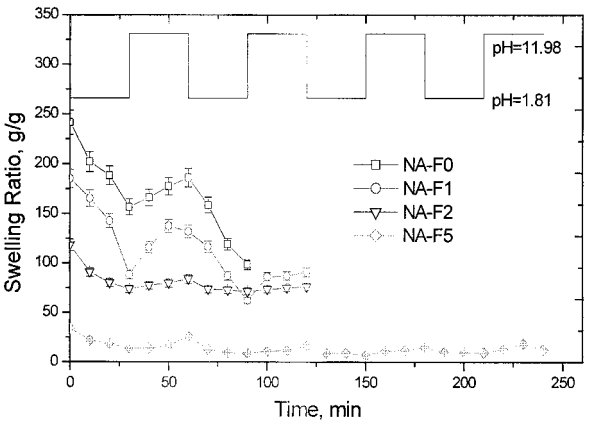


Figure 7 Effect of the alternate pH stimulus on the swelling properties of the hydrogels with different FMA contents.

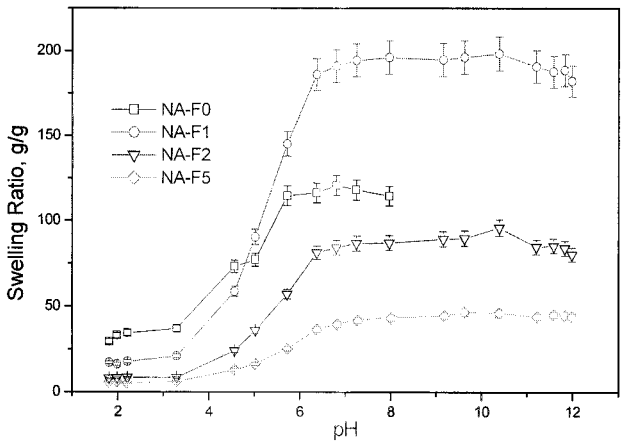


Figure 8 Changes in the swelling ratios with pH for the hydrogels with different FMA contents.

ing ratios are almost constant at pH values higher than 6.8 and increase most quickly at pH values between 4.56 and 6.8 for all the gels. The swelling of the gels upon ionization in polar media is mainly induced by the osmotic pressure exerted by mobile counterions.[25] With the increase in pH, the osmotic pressure from mobile counterions increases, and this induces an increase in the swelling ratios of gels.

Another conclusion from Figure 8 is that, under acidic conditions, the swelling ratios of the gels decrease with the FMA content. Two reasons for this can be discerned. First, FMA groups form the hydrophobic domains by themselves or by isopropyl groups of NIPAM. These domains act as physical crosslinking points, so a higher degree of ionization is required to destroy them for gels with higher FMA contents. Second, according to Philippova et al.'s result,[12] hydrophobic groups can decrease the local dielectric constant near the network chains. This needs to be proven further.

For gels with higher FMA contents, such as NA-F2 and NA-F5, the hydrophobic absorbing force overcomes the electrostatic repulsive force over the entire pH range. Therefore, they swell less than NA-F0 over the entire pH range investigated. However, the gel NA-F1, at a high pH value, absorbs even more water than NA-F0. This abnormal phenomenon can be explained as follows. In comparison with NA-F0 (without FMA), at a low pH value, in NA-F1 hydrophobic interactions dominate and favor the formation of nonpolar FMA hydrophobic clusters. These FMA hydrophobic microdomains, acting as physical crosslinking points, restrain gel network swelling. On the contrary, at a high pH value, in NA-F1, the electrostatic repulsive force overcomes the hydrophobic absorbing force, and the hydrophobic microdomains from FMA act as reservoirs, promoting the swelling of NA-F1. As a result, the swelling ratio of NA-F1 is less than that of NA-F0 at a low pH value, and the situation is reversed at a high pH value.

The swelling ratios of the copolymer gels with different NIPAM/AA ratios as a function of the pH value of the surrounding solutions are shown in Figure 9. For the gel NF-A0 (without AA), the swelling ratio is independent of the pH value because there is no ionizable group in this kind of gel. The swelling ratios of the other gels with different NIPAM/AA ratios decrease with the ratio of NIPAM/AA because of the increase in the carboxyl number and show distinct swelling transitions at a pH value of approximately 6.8.

CONCLUSIONS

The results of swelling and fluorescence measurements prove that hydrophobic association exists in gel networks, and the fluorocarbon group FMA shows much stronger hydrophobic association ability than the hydrocarbon group NIPAM or LA. The hydrophobicity of the hydrogels increases in the following order: LA < FMA < SA.

The swelling behavior and pH and temperature sensitivity of the hydrogels can obviously be affected by the degree of hydrophobic modification. Hydrogels with appropriate FMA proportions (e.g., NA-F1 gel containing 0.349 mol % FMA) show a good response ability to pulsatile pH and temperature stimuli. Although the NIPAM gels with excessively high FMA contents show temperature and pH responses, their swelling ratios are little changed under pH or temperature stimuli.

The hydrophilic AA units are indispensable for the pH sensitivity of the gels. Otherwise, the swelling ratio remains constant with the increase in the pH value. In comparison with the gel NA-F0 without FMA, at a low pH value (the electrostatic repulsive force is slight), the gel NA-F1 accommodates less water because the hydrophobic domains acting as phys-

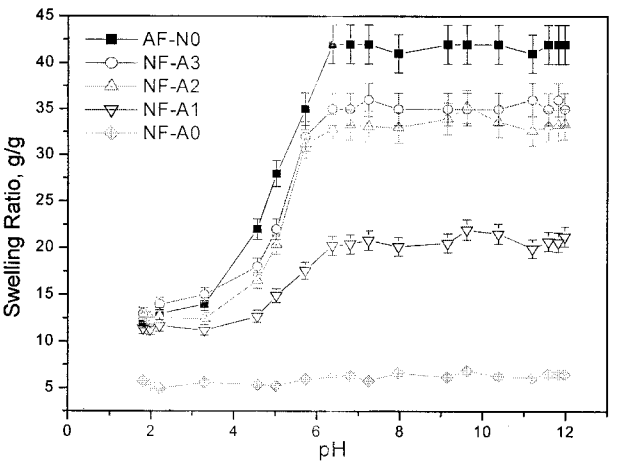


Figure 9 Changes in the swelling ratios with pH for the hydrogels with different AA contents.

ical crosslinkers dominate. At a high pH value (the electrostatic repulsive force is large), the result is the reverse because the hydrophobic domains acting as reservoirs dominate.

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