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# Interactions of drugs and spin probes with hydrophobically modified polyelectrolyte hydrogels based on *N*-isopropylacrylamide

Tao Lu Lowe, Janne Virtanen, Heikki Tenhu*

*Laboratory of Polymer Chemistry, University of Helsinki, PB 55, FIN-00014 HY Helsinki, Finland*

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**Abstract**

Thermally responsive hydrogels of *N*-isopropylacrylamide containing hydrophobic comonomers were synthesized by free radical polymerization in both toluene and water. Various hydrophobic monomers were used, i.e. methyl methacrylate, hexylacrylate, hexafluoroisopropylmethacrylate and hexafluorobutylmethacrylate. Also polymers containing hydrophilic methacrylic acid were synthesized. The swelling properties of the polymers, as well as polymers containing 30 wt% ephedrine or ibuprofen were investigated in pure water at temperatures from 20°C to 46°C. The swelling ratios of pure gels depended on the ratio of hydrophilic and hydrophobic structural units in the polymer, as well as on the network structures of the gels. The hydrophilic drug ephedrine was bound to polyacid gels causing deswelling of the gels due to electrostatic interactions. Ephedrine did not affect the swelling of the neural gels, however. Addition of hydrophobic ibuprofen made all the hydrogels collapse at room temperature no matter whether the gels were neutral or acidic. Interactions between spin probes, 4-benzoxy-2,2,6,6-tetramethylpiperidine-1-oxyl (BZONO) and 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (amino-TEMPO), and the polymer gels were studied using electron paramagnetic resonance spectroscopy. The hydrophobic probe BZONO resided in the gels below the lower critical solution temperature (LCST) due to hydrophobic interactions, but dissolved, at least partially, in the aqueous phase above the critical temperature. The distribution of BZONO between the gel and the aqueous phase depended on the hydrophobicity of the polymer. Also the hydrophilic probe amino-TEMPO was partially bound into the gels. 

*Keywords:* *N*-isopropylacrylamide; Hydrogels; Drugs

## 1. Introduction

Hydrogels are crosslinked polymer networks swollen with water. Because of their relatively high water contents and their soft, rubbery consistency, hydrogel materials resemble living tissue in their physical properties. Therefore, experimental and theoretical study of synthetic hydrogels has an important biological significance [1,2].

Poly(*N*-isopropylacrylamide) (PNIPAAM) hydrogels are attracting more and more interest in biomedical applications because they exhibit a well-defined lower critical solution temperature (LCST) in water around 31°C–34°C which is close to the body temperature. PNIPAAM hydrogels swell when cooled below LCST, and they collapse when heated above the LCST. By finding the right balance of hydrophobic and hydrophilic comonomers, and by adjusting the number of electric charges in the chain as well as the degree of crosslinking, the structure and physical properties of PNIPAAM hydrogels may be changed [3–11]. Mechanical properties, as well as the swelling and shrinking behavior of the gels, change in response to physical or chemical stimuli, such as temperature, pH, ionic strength, solvent composition and electric fields. Hence, these gels can be expected to act as intelligent materials in drug release [12–14], immobilization of enzymes and cells [15,16], and in separation of aqueous proteins [16,17].

In order to design new synthetic macromolecular materials for controlled or targeted drug release systems, the studies on the interactions of various drugs with polymers have a fundamental importance. Recent experiments in our laboratory [18] have revealed that the interactions of ephedrine and iburofen with aqueous polymer latices strongly depend on the hydrophobicity–hydophilicity of the drugs and the polymers. Polymer gels are excellent model systems for studying molecular interactions since a polymer network can be regarded as a single giant molecule. A small change in certain interactions of a local part of the network can trigger a noticeable change of the macroscopic size of the gel [3].

The measurements of the swelling and collapse of gels as a function of temperature can clarify the role of various

* Corresponding author.

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types of interactions for the generation of the biological functions of hydrogels [3]. Another way of studying the interactions between the polymer networks and molecules with a low molar mass, applied in the present investigation, is electron paramagnetic resonance (EPR) spectroscopy. Nitroxide radicals have been mixed with the polymers, and their distribution between the gel and the surrounding water has been estimated from the spectra. The spin probe technique has often been used to study the mobility of the polymers into which the radicals are added. With this method it is also possible to study specific interactions between the radicals and the host polymers in which they are dissolved [19–22].

This report describes the synthesis and properties of a series of hydrogels based on *N*-isopropylacrylamide (NIPAAM). The hydrogels were hydrophobically modified using the following comonomers: methyl methacrylate (MMA), hexylacrylate (HA), hexafluoroisopropylmethacrylate (HFIPMA), and hexafluorobutylmethacrylate (HFBMA). To some of the polymers, methacrylic acid (MAA) was also added to give them polyelectrolytic properties. The polymers were prepared by free radical polymerization in both toluene and water and they were swollen to equilibrium in pure water. By the swelling measurements, the effects of two drugs, ephedrine and ibuprofen, on the swelling and collapse of the gels were investigated. Ephedrine is a water soluble substance whereas ibuprofen is only sparingly soluble. Two spin probes, hydrophobic 4-benzoxy-2,2,6,6-tetramethylpiperidine-1-oxyl (BZONO) and hydrophilic 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (amino-TEMPO), were used in complementary studies conducted using EPR.

## 2. Experimental

### 2.1. Materials

*N*-isopropylacrylamide (NIPAAM) purchased from Polysciences Inc. was purified by recrystallization in hexane. The comonomers, hexafluoroisopropylmethacrylate (HFIPMA; Polysciences), hexafluorobutylmethacrylate (HFBMA; Polysciences Inc.), methyl methacrylate (MMA; Fluka), hexylacrylate (HA; Polysciences), and methacrylic acid (MAA; Polysciences) were used without further purification, as were the initiators, potassium persulfate (KPS; Merck) and azobisisobutyronitrile (AIBN; Fluka). *N*,*N*′-methylene bisacrylamide (BA, Serva) and ethyleneglycol dimethacrylate (EGDMA, Polysciences) were used as crosslinkers, and *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TEMED; Aldrich) as an accelerator. Low molar mass drugs ephedrine and ibuprofen were from Sigma. Spin probe 4-benzoxy-2,2,6,6-tetramethylpiperidine-1-oxyl (BZONO) was prepared by esterifying 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl with benzoic acid. 4-Amino-2,2,6,6-tetramethylpiperidine-1-oxyl (amino-TEMPO; Aldrich) was used as obtained. Water used for polymerizations, swelling tests and EPR measurements was deionized in an Elgastat UHQ-PS purification system. The chemical structures of ibuprofen and ephedrine, as well as the nitroxides, are shown in Fig. 1.

### 2.2. Syntheses of polymer gels

The polymers were prepared by radical crosslinking polymerization in both toluene and water. The preparation of the gels in toluene was carried out at 70°C using AIBN as initiator. The polymers were a crosslinked homopolymer of *N*-isopropylacrylamide, TG1, and crosslinked copolymers TG2-TG5 containing either MMA or HA as a hydrophobic comonomer, and MAA as a hydrophilic comonomer. The reaction was conducted in a closed beaker (diameter = 8 cm) equipped with a nitrogen inlet tube. NIPAAM (26.5 mmol), a correct amount of comonomers and 2 mol% of crosslinker EGDMA were dissolved in 18 ml of the solvent. After a 30 min nitrogen purging, 4 mol% AIBN and 1 mol% TEMED dissolved into 2 ml toluene were added into the monomer solutions. The reaction was allowed to proceed for 4 h. The resulting gels were washed first with ethanol, then with various mixtures of ethanol and deionized water, and finally with pure water, for 1 day in each liquid in order to remove all unreacted compounds. The transparent gels were cut into discs (1 cm diameter) and dried first at room temperature for a week and then in vacuum overnight.

The syntheses of the gels in water have already been described in detail elsewhere [11]. The polymers were a

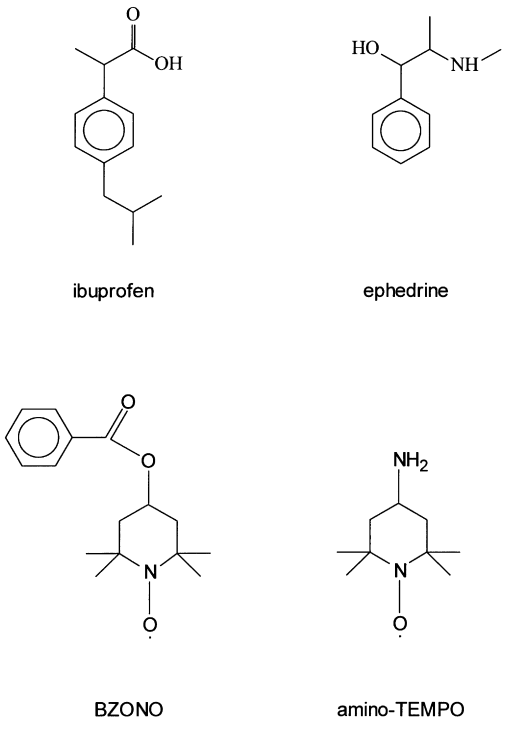


Fig. 1. Structural formulae of ephedrine, ibuprofen, BZONO and amino-TEMPO.

Table 1
Monomer feed in the syntheses of the gels in toluene

| Sample | Component/mol ratio | | | | Component/mol ratio | | |
|---|---|---|---|---|---|---|---|
| | NIPAAM | MMA | MAA | EGDMA | NIPAAM | HA | EDGMA |
| TG1 | 100 | | | 2 | | | |
| TG2 | 90 | 10 | | 2 | | | |
| TG3 | 80 | 15 | 5 | 2 | | | |
| TG4 | 90 | | 10 | 2 | | | |
| TG5 | | | | | 95 | 5 | 2 |

NIPAAM, *N*-isopropylacrylamide; MMA, methyl methacrylate; and HA, hexylacrylate; MAA, methacrylic acid; EGDMA, ethyleneglycol dimethacrylate.

crosslinked homopolymer of *N*-isopropylacrylamide, WG1, and crosslinked copolymers WG2 and WG5 with HFIPMA or HFBMA as hydrophobic monomers, and with MAA as a hydrophilic monomer. Homopolymer WG1 was polymerized in water, but the copolymers were prepared in aqueous solutions containing a few drops of ethanol. Tables 1 and 2 summarize the monomers used in the synthesis of various polymer networks, as well as the abbreviations used for various monomers and polymers.

### *2.3. Gel characterization*

#### *2.3.1. Swelling measurements*

Three dry pieces of each polymer were weighted. One of them was swollen as such in pure water. Polymer samples containing 30 wt% of ephedrine or ibuprofen were prepared by first dissolving the drugs into few drops of ethanol, and adding the ethanol solutions to the polymers. After drying in vacuum, the polymers loaded with drugs were swollen in pure water. The samples were equilibrated at a certain fixed temperature for 1 day, removed from the solvent and weighted quickly after being wiped with filter paper to remove excess water on the gel surface. Temperature was increased stepwise from 20°C to 46°C. The swelling ratio was defined as the mass of swollen gel per mass of dry gel.

#### *2.3.2. Drug concentration in the water phase*

Drug concentration in the water phase was measured by UV spectroscopy. Gel particles loaded with drugs as described earlier were allowed to equilibrate for 24 h in a known volume of water at 20°C. Then, 1 ml samples were taken from the water layer above the gels. Next, the gels were equilibrated for another 24 h at 46°C and a new sample was taken. Before measuring the concentrations, the aqueous samples containing ibuprofen were diluted with ethanol to prevent precipitation. Taking into account the swelling ratio of the gel, the total amount of the drug dissolved in water could be calculated.

#### *2.3.3. EPR spectra*

EPR spectra were recorded with a Varian E4 spectrometer equipped with a temperature controller. Samples of dry polymer WG1 or WG3 were prepared that contained 10% or 20 wt% of the nitroxides of the mass of the polymer. The polymers were immersed in an excess amount of ethanol for 1 day and dried by evaporating ethanol for 4 days at room temperature. Approximately 1 mg of dried labeled polymers and 40 $\mu$l deionized water were mixed in glass capillaries with o.d. 1 mm. EPR spectra were measured first at 20°C, then at temperatures 5°C, 20°C, 40°C and 60°C. Samples were allowed to equilibrate for 1 day at each temperature. Samples used for EPR measurements are shown in Table 3.

## 3. Results and discussion

### *3.1. The interactions of ibuprofen and ephedrine with the hydrogels*

#### *3.1.1. The gels synthesized in toluene*

Fig. 2 shows the swelling ratios in water of the hydrogels synthesized in toluene, as a function of temperature (see Table 1 for the composition of the polymers). The gel

Table 2
Monomer feed in the syntheses of the gels in water

| Sample | Component/mol ratio | | | | Component/mol ratio | | | |
|---|---|---|---|---|---|---|---|---|
| | NIPAAM | HFIPMA | MAA | BA | NIPAAM | HFBMA | MMA | BA |
| WG1 | 100 | | | 4.9 | | | | |
| WG2 | 90 | 10 | | 5.4 | | | | |
| WG3 | 80 | 15 | 5 | 5.6 | | | | |
| WG4 | | | | | 90 | 10 | | 5.4 |
| WG5 | | | | | 80 | 15 | 5 | 5.6 |

NIPAAM, *N*-isopropylacrylamide; HFIPMA, hexafluoroisopropylmethacrylate; and HFBMA, hexafluorobutylmethacrylate; MAA, methacrylic acid; BA, *N*,*N*′-methylene bisacrylamide.

Table 3
Samples for EPR measurements

| Sample | Probe content (wt%)[a] | |
|---|---|---|
| | BZONO | amino-TEMPO |
| WG1B10 | 10 | |
| WG1B20 | 20 | |
| WG3B10 | 10 | |
| WG3B20 | 20 | |
| WG1AT10 | | 10 |
| WG3AT10 | | 10 |

[a] wt% of the mass of the polymer.

TG1 which is a crosslinked homopolymer of NIPAAM, displays a sharp change in the swelling behavior around 31°C, and so does the gel TG2. Sample TG5, crosslinked PNIPAAM with hexyl acrylate as the only comonomer, shows practically no swelling over the temperature range studied. Gel TG4 deswells gradually with increasing temperature, which is typical for several ionic PNIPAAM derivatives. Below the LCST the swelling ratios decrease with increasing hydrophobicity of the polymers, in the order: TG4 > TG1 > TG2 > TG5. The swelling ratio of TG3 is lower than those of TG1 and TG2. This evidently results from the high amount of methyl methacrylate used in the synthesis, which compensates the effect of the acidic groups on the swelling.

The swelling ratios of the gels are replotted against temperature in Fig. 3 and compared with the swelling ratios of the samples containing ephedrine and ibuprofen. Ephedrine does not affect the swelling behavior of non-ionic gels TG2 and TG5, but decreases the swelling ratios of anionic gels TG3 and TG4. Ephedrine is a water soluble weak base. When added into the acidic gels, it obviously binds to the polymer by interaction with the carboxylic groups. The binding of ephedrine thus reduces the repulsion between the negative charges of the chain, and the swelling ratio decreases.

Polymers containing ibuprofen show very limited swelling in water, if any. Ibuprofen is a weak acid and only sparingly soluble in water. Because of the hydrophobic interaction between ibuprofen and the polymers, the polymer chains are highly aggregated, this preventing the diffusion of water into the gels. The only exception is the PNIPAAM homopolymer, sample TG1, which swells even when loaded with ibuprofen. There is no logical explanation for this observation, however, and it may very well be due to the inhomogeneous distribution of ibuprofen inside the polymer. As was noted already, TG5 does not swell in water at temperatures above 20°C and therefore, the effects of ephedrine and ibuprofen on the gel TG5 are not obvious.

### *3.1.2. The gels synthesized in aqueous solutions*

Fig. 4 shows the swelling ratios against temperature for the gels synthesized in water. Samples of the homopolymer gel WG1 and the partially fluorinated gels WG2–WG5 all collapse when heated above the LCST. At elevated

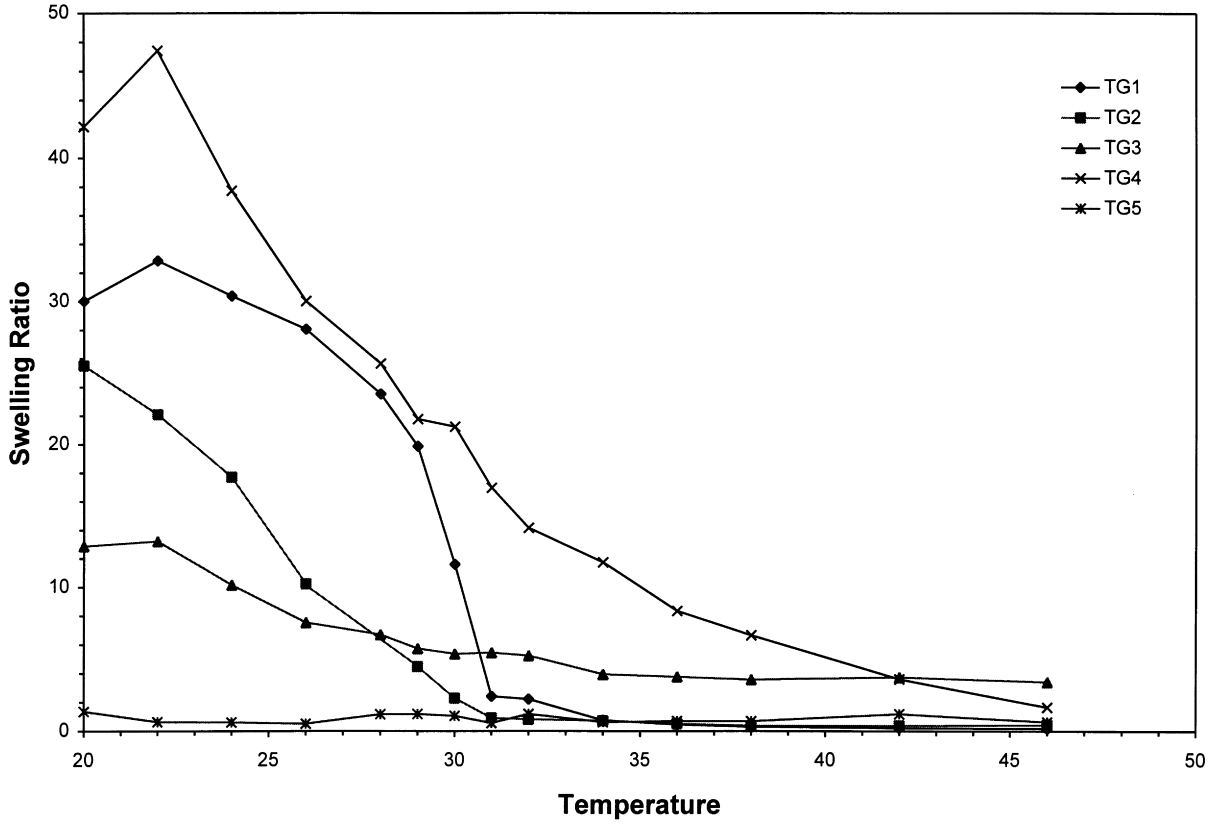


Fig. 2. Swelling ratios of the hydrogels synthesized in toluene as a function of temperature (°C) in pure water.

temperatures, after the volume transition, all gels reach a stable state and the swelling ratios have a constant value.

In our previous study [11], it has been observed that the network structure of the hydrogels WG2 and WG3 is homogeneous, but that of the gels WG4 and WG5 is heterogeneous. A heterogeneous gel is an opaque one with a clustered network, whereas the polymer and the crosslinks are more evenly distributed in a homogeneous gel. The homogeneous acidic gel WG3 behaves as is typical to a polyelectrolyte gel; swelling more than the corresponding neutral one (WG2). This, however, is not the case with the heterogeneous acidic gel WG5 which at 20°C swells slightly less than the corresponding neutral gel WG4. Below the LCST, ephedrine does not affect the swelling of the non-ionic gels WG1, WG2 and WG4. However, for the ionic gels WG3 and WG5, the swelling ratios of the gels containing ephedrine are smaller than those of the pure gels regardless of the differences in the homogeneity of the networks. It is worth noting that ephedrine decreases the swelling ratio of the gel TG1, but does not affect that of the gel WG1, even though TG1 and WG1 are both crosslinked homopolymers of *N*-isopropylacrylamide. This means that the binding of ephedrine into the gels WG1 and TG1 depends on the method used to prepare the gels. Ibuprofen affects the swelling in a way very similar to that shown already in Fig. 3. However, the gels WG1–WG4 swell to a certain extent even when loaded with ibuprofen.

The concentrations of ibuprofen and ephedrin in water around the gels were measured by UV spectroscopy after equilibrating the samples for 24 h first at 20°C and then, another 24 h at 46°C, respectively. It turned out that the gels bind most of the drugs at both temperatures. Ibuprofen naturally does not easily diffuse into water, and in 24 h at 20°C, only 1–3 wt% of the initial amount was released from the gel. At 46°C, 2–6 wt% of ibuprofen left in the gel was released. Also ephedrine was released slowly. In 24 h,

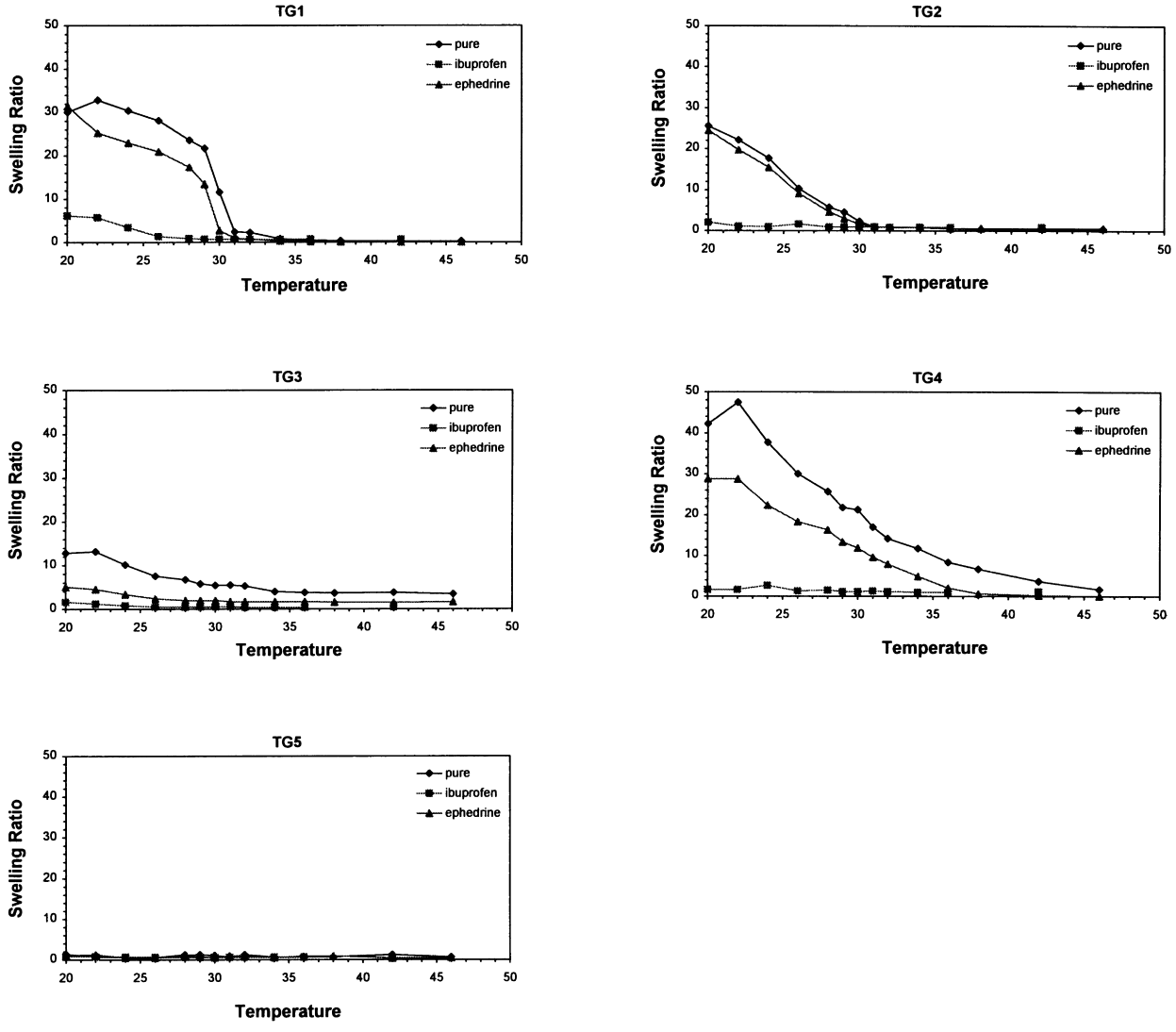


Fig. 3. The effect of ephedrine and ibuprofen on the swelling of the gels synthesized in toluene. The top curves represent the pure polymers, the curves below these, the polymers loaded with ephedrine. The lowest curves show the swelling ratios of the polymers containing ibuprofen. (Temperature in °C).

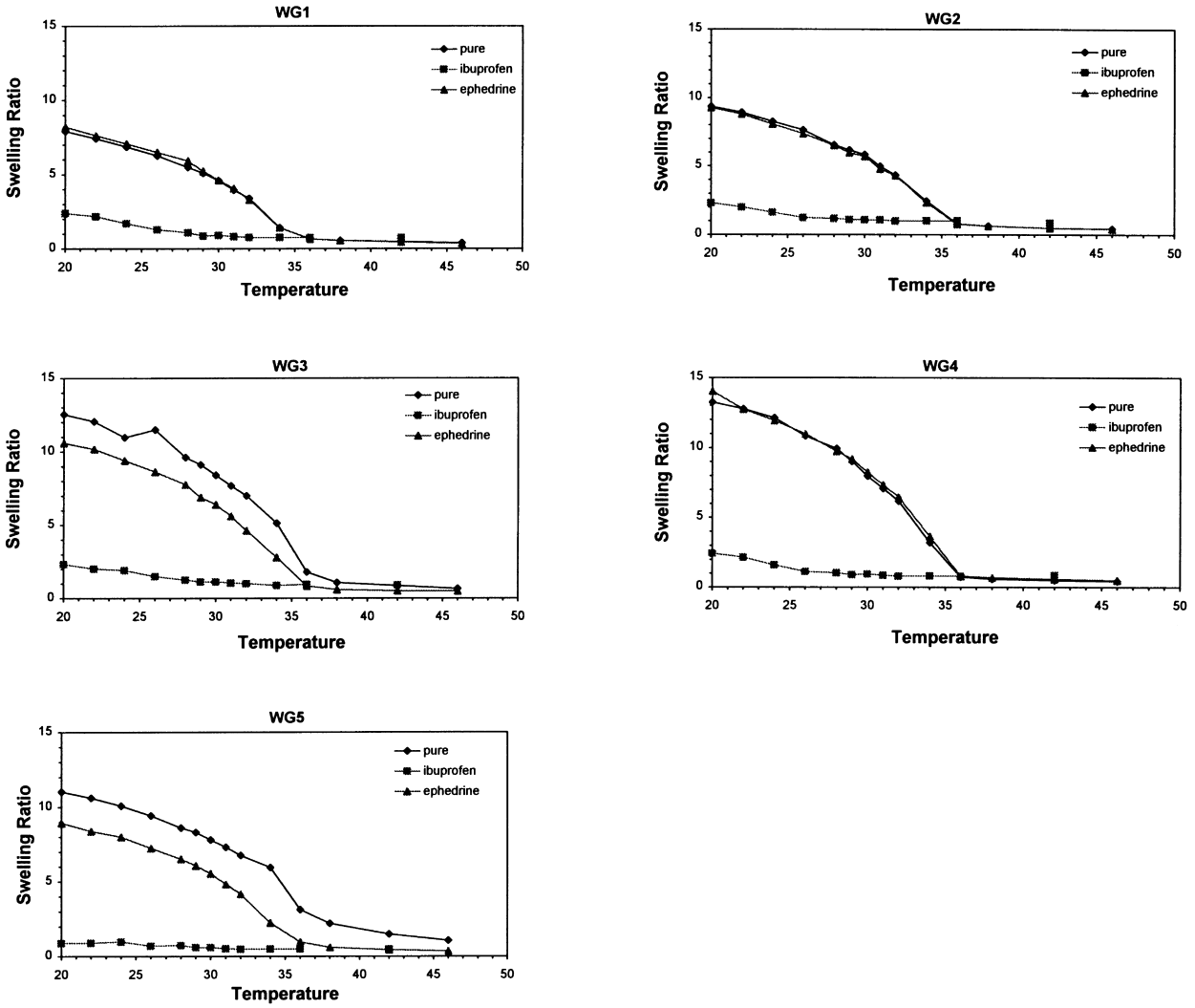


Fig. 4. The effect of ephedrine and ibuprofen on the swelling of the gels synthesized in water. Top curves, pure polymers; mid curves, the polymers containing ephedrine; and the lowest curves, polymers containing ibuprofen. (Temperature in °C).

1.5–10 wt% of the initial ephedrine was dissolved in the aqueous phase at 20°C. At 46°C, the corresponding values varied between 2.5 and 16 wt%. It was not possible to find a clear correlation between the chemical structure of the polymers and the amount of the drug released. From this test one may conclude firstly, that the swelling tests described earlier represent the situation where the drugs are mainly held inside the gels and secondly, the release tests need to be done as a function of temperature and time in order to find out the differences between the gels, preferably in mixed solvents. Studies in this direction are in progress and will be reported later.

## 4. Binding of nitroxides into the gels

4-Benzoxy-2,2,6,6-tetramethylpiperidine-1-oxyl (BZONO) radical is only sparingly soluble in water. When 1 mg BZONO was added into 40 $\mu$l deionized water and the mixture was equilibrated for 1 day at room temperature, a part of the solid probe dissolved. The radical dissolved in the aqueous phase shows a well-resolved triplet EPR spectrum, as is shown in Fig. 5. The spectrum is typical for a rapidly tumbling nitroxide. Next, fairly large amounts of BZONO (10 and 20 wt%) were mixed with polymers WG1 and WG3, and the polymers were allowed to swell in water. The purpose was to

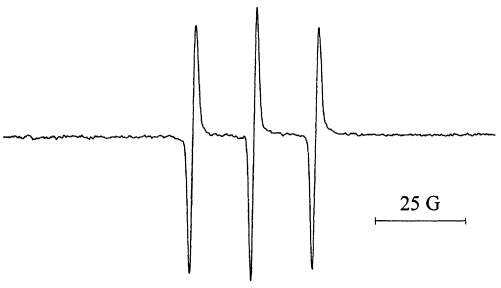


Fig. 5. EPR spectrum of a saturated aqueous solution of BZONO at room temperature.

study the release of BZONO into the aqueous phase from two gels with different chemical structures.

The EPR spectra of the WG1 sample containing 20 wt% BZONO (of the mass of the polymer) are shown in Fig. 6(a). The spectra were measured first at 20°C, then at 5°C, 20°C, 40°C and 60°C. The spectra are composite spectra with quite an exceptional shape owing to the high radical concentration. In a traditional spin labeling experiment, the radical concentration is kept as low as possible to prevent the interaction between the paramagnetic centers of the probe molecules. In the present case, however, most of the nitroxide was bound to the polymer at room temperature. The local spin concentration in the gel particle was very high; radicals in the gel produced a strong singlet spectrum owing to the concentration broadening of the spectral lines. Visual inspection of the samples proved that the nitroxide indeed diffuses into the polymer; the gel samples were evenly red coloured at low temperatures.

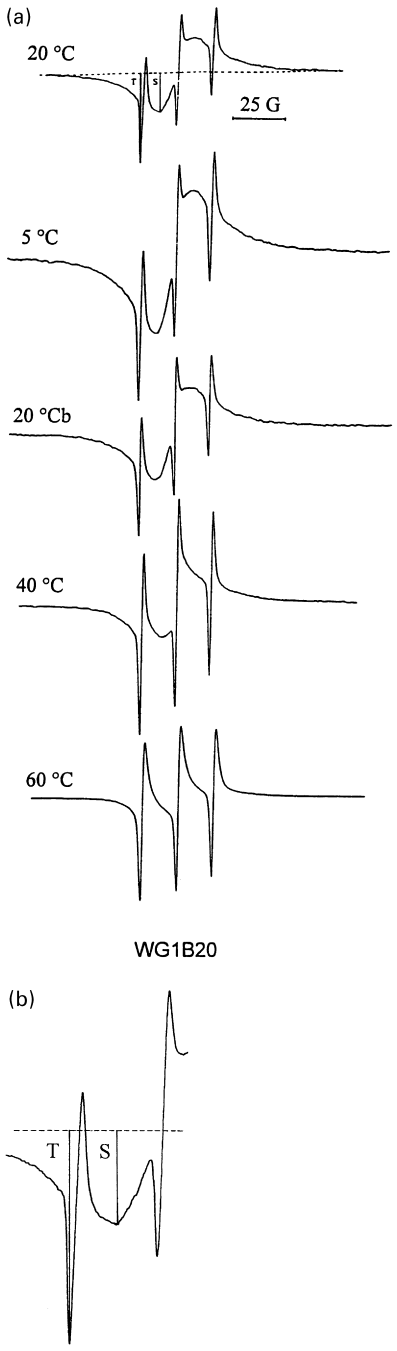


Fig. 6. (a) EPR spectra of the gel WG1 containing 20 wt% of BZONO at various temperatures. (b) Low field line of the EPR spectrum measured at (a), showing the definition of parameters *t* and *s*.

As may be seen from Fig. 6(a), the spectra measured at or below 40°C are composed of a singlet and a triplet. The three line spectrum obviously arises from BZONO dissolved in water and the singlet line from BZONO trapped inside the gel. When the temperature is decreased from 20 to 5°C, the intensity of the singlet line increases but decreases again with increasing temperature. At 60°C, no separate singlet line is observable. Its presence, however, is seen as the unsymmetric shape of the three line spectrum.

To describe the relative changes in the line intensities, simple parameters are used as defined in Fig. 6(b). The intensities of the low field line of the triplet [*T* in Fig. 6(b)] and of the singlet line [*S* in Fig. 6(b)] were measured. The ratio *T*/*S* gives an approximate estimate of the ratio of the radical concentration in water to the concentration inside the gel particle. The ratios *T*/*S* measured at various temperatures for the gels WG1 and WG3 containing either 10 or 20 wt% BZONO are shown in Fig. 7. Below the LCST, no changes in the ratio *T*/*S* of the gel WG1 are observed. However, the *T*/*S* ratios of the gels WG3 decrease with decreasing temperature from 20°C to 5°C and then start to increase again with increasing temperature back to 20°C, but does not reach the original values. When the temperature is increased to 40°C and 60°C (see Fig. 7), the *T*/*S* ratios of all four samples suddenly start to increase.

From Fig. 7 it is seen that for the same polymer gel at a constant temperature, the ratio *T*/*S* decreases when increasing the content of BZONO from 10 to 20 wt%. This shows that the aqueous phase is saturated with BZONO and increasing the radical concentration increases only the singlet line. It can also be seen that, excluding the first measurement conducted at 20°C, the *T*/*S* ratios of WG3 samples are equal or lower than those of WG1 samples. Comparison of the results obtained in the three consecutive measurements at 20°C, (20°Cb in Fig. 7), 40°C and 60°C shows that the ratios are almost equal for the two polymers at room temperature, but differ noticably at 60°C. The conclusions are as follows. The solubility of BZONO in water increases with temperature. The polymer WG3 is acidic and swells more at room temperature than homopolymer WG1, in spite of its hydrophobic fluorinated substituents. At room temperature the nitroxide is distributed between the polymer and the aqueous phase in a similar way in both polymer samples. Above the LCST, the hydrophobically modified polymer binds more BZONO than the PNIPAAM homopolymer does.

These conclusions are further supported by the experiments conducted using a water soluble nitroxide,

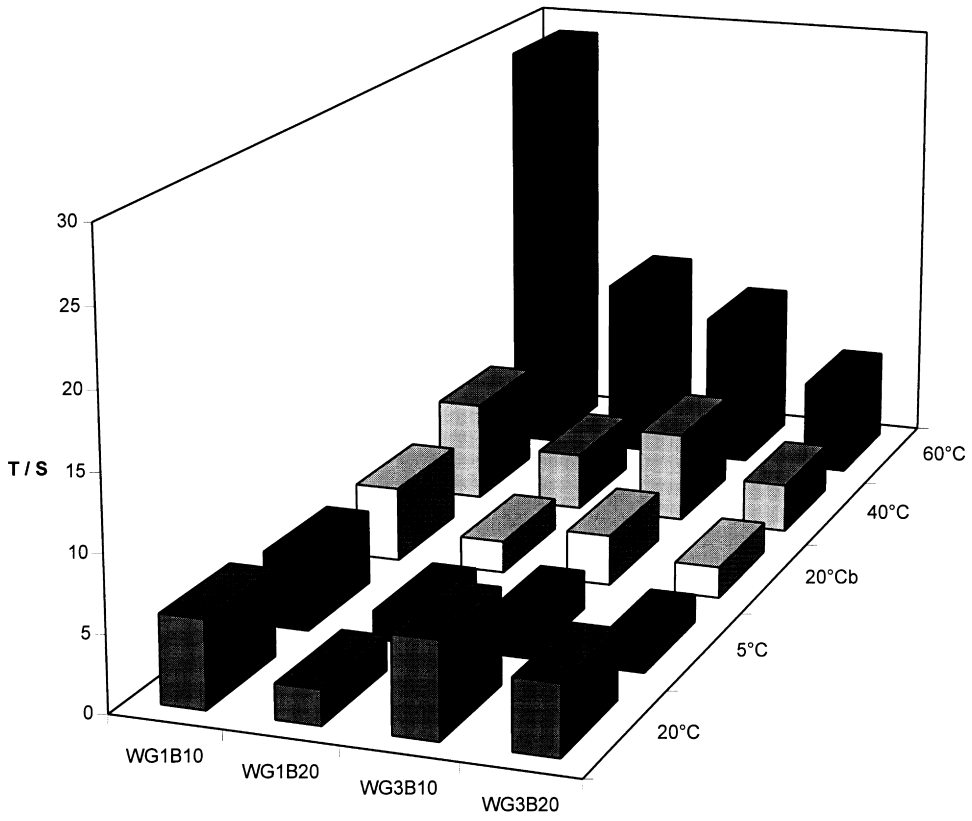


Fig. 7. The ratio *T*/*S* (see text) for gels WG1 and WG3 containing 10 or 20 wt% BZONO at various temperatures.

amino-TEMPO. The nitroxide was mixed with polymers WG1 and WG3, and the EPR spectra were measured below and above the LCST. The spectra of the samples containing 10 wt% amino-TEMPO (of the mass of the polymer) are shown in Fig. 8. All the spectra are triplets, i.e. no separate singlet line is observed. However, in this case the presence of a singlet line may also be deduced from the asymmetric shape of the three line spectra at 40°C, especially in the case of the polymer WG3. Further, it may be seen that the spectral lines broaden with increasing temperature; this would not be the case if the radical was solely dissolved in the aqueous phase outside the gel. It may be concluded that the EPR spectra in this case are also due to radicals located both inside and outside the gel. Increasing the temperature above the LCST makes the polymer shrink, and the local nitroxide concentration inside the spectrometer cavity increases. In the case of amino-TEMPO it is not possible to simply describe the differences in the radical distribution between water and the polymer. However, the strongly unsymmetric spectrum of amino-TEMPO in the gel WG3 probably indicates that the probe binds more strongly to the polymer WG3 than to the PNIPAAM homopolymer.

## 5. Conclusions

Hydrophobically modified PNIPAAM hydrogels have been prepared by free radical polymerization in aqueous solutions and in toluene. Various hydrophobic comonomers are used to prepare neutral polymers. Corresponding charged polymers are produced by adding methacrylic acid into the polymerization mixture.

The introduction of the various comonomers affects the local environment of the NIPAAM chains and influence the swelling of the gels. The gels synthesized in toluene behave as expected: hydrophobic monomers decrease the swelling ratios to varying extent and carboxylic monomer increases

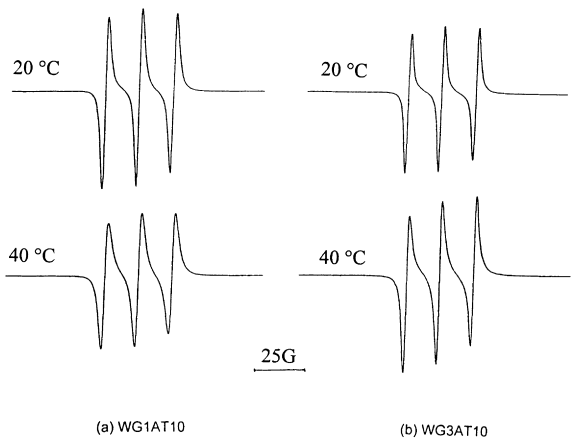


Fig. 8. EPR spectra of the gels WG1 and WG3 containing 10 wt% of amino-TEMPO at 20°C and 40°C.

the swelling. Addition of both hydrophobic and acidic monomers into polyNIPAAM chains leads to a competition between various interactions, and whether the gel swells or shrinks depends on the relative amounts of the comonomers. Some of the gels synthesized in aqueous solutions have heterogeneous structures and the dependence of swelling on the chemical structure is more complicated.

The interactions of ephedrine and ibuprofen with the gels strongly depend on the hydrophobicity of the drugs and the gels, as was clearly seen by measuring the swelling ratios of the gels containing the drugs. Hydrophilic ephedrine decrease the swelling ratios of polyacid gels regardless of the methods used to prepare the gels. However, ephedrine does not affect the swelling ratios of neutral gels. The results suggest that ephedrine is bound to polyacid gels due to electrostatic interactions. Hydrophobic ibuprofen strongly collapses all hydrogels, no matter if the gels are neutral or polyacid gels, and shifts their LCST to lower temperatures as a result of the hydrophobic interactions between ibuprofen and the gels.

The EPR spectra of a spin probe BZONO in gels WG1 and WG3 show that the radical is distributed between the gel particle and the surrounding water. Inside the gels, the radical concentration is very high at room temperature. Increase of temperature increases the water solubility of BZONO, and the radical dissolves into water at elevated temperatures. The gels with different chemical structures have been shown to differ in their capability of keeping BZONO inside the polymer at high temperatures. Also the aqueous soluble amino-TEMPO distributes between polymer and water; however, owing to the high polarity of this radical, the differences in the spectra at various temperatures are less pronounced.

## References


[1] Ratner BD, Hoffman AS. In: Andrade JD, editor. Hydrogels for medical and related applications. Washington, DC: American Chemical Society, 1976.
[2] Hoffman AS. In: DeRossi D, Kajiwara K, Osada Y, Yamauchi A, editors. Polymer gels — fundamentals and biomedical application. New York: Plenum Press, 1991.
[3] Shibayama M, Tanaka T, Han CC. J Chem Phys 1992;97:6842.
[4] Yoshida R, Okuyama Y, Sakai K, Okano T, Sakurai Y. J Membrane Sci 1994;89:267.
[5] Yoshioka H, Mikami M, Mori Y. J Macromol Sci-Pure Appl Chem 1994;A31(1):121.
[6] Brazel CS, Peppas NA. Macromolecules 1995;28:8016.
[7] Sihayama M, Mizutani SY, Nomura S. Macromolecules 1996;29: 2019.
[8] Kawasaki H, Sasaki S, Maeda H. J Phys Chem B 1997;101:4184.
[9] Zhang XM, Hu ZB, Li Y. J Appl Polym Sci 1997;63:1851.
[10] Huglin MB, Liu Y, Velada JL. Polymer 1997;38:5785.
[11] Lowe LT, Benhaddou M, Tenhu H. Macromol Chem Phys, in press.
[12] Wu XS, Hoffman AS, Yager P. J Polym Sci Part A: Polym Chem 1992;30:2121.
[13] Kaneko Y, Yoshida R, Sakai K, Sakurai Y, Okano T. J Membrane Sci 1995;101:13.
[14] Lim YH, Kim D, Lee DS. J Appl Polym Sci 1997;64:2647.
[15] Koopmann J, Hocke J, Gabius H.-J. Biol Chem Hoppe-Seyler 1993;374:1029.
[16] Galaev IY, Mattiasson B. Enzyme Microb Technol 1993;15:354.
[17] Wu JZ, Sassi AP, Blanch HW, Prausnitz JM. Polymer 1996;37:4803.
[18] Lowe LT, Tenhu H. Macromolecules 1998;31:1590.
[19] Rabold GP. J Polym Sci: Part A-1 1969;7:1203.
[20] Cameron GG. In: Allen SG, Bevington JC, editors. Comprehensive polymer science — the synthesis, characterization, reactions and applications of polymers, vol. 1. Oxford: Pergamon Press, 1989.
[21] Marsh D. In: Berliner LJ, Reuben J, editors. Biological magnetic resonance, vol. 8, spin labeling — theory and applications. New York: Plenum Press, 1989.
[22] Pace MD, Snow AW. Macromolecules 1995;28:5300.