DOI: 10.1002/masy.200750846

Application of Polyelectrolytic Temperature-Responsive Hydrogels in Chemical Sensors

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Summary: A rapidly expanding field of on-line process monitoring and on-line control in biotechnology, food industry, pharmaceutical industry, process chemistry, environmental measuring technology, water treatment and sewage processing requires the development of new micro fabricated reliable chemical and biosensors that are specific for particular species and can attain the analytic information in a faster, simpler and cheaper manner. Using a functionalised polymer coating in sensors provides the possibility to detect, transmit and record the information regarding the concentration change or the presence of a specific analyte (a chemical or biological substance that needs to be measured) by producing a signal proportional to the concentration of the target analyte. However, the sensor response time and signal reproducibility are limited by the visco-elastical and hysteresis behaviour of the polymer material. We propose some methods improving the properties of the chemical sensors on the basis of thermo-shrinking N-isopropylacrylamide (NIPAAm) copolymer gels.

Keywords: ATR-FTIR spectroscopy; chemical sensor; pH-sensitive; polyelectrolytic hydrogel; swelling behaviour; temperature-sensitive

Introduction

The application of ''stimuli-responsive'' or ''smart'' cross-linked gels in chemical sensors is based on their ability to a phase transition under the influence of external excitations (temperature, pH, concentration of additives in water). The external stimulus lowers an energy barrier between two possible gel states: a stable state (shrunk gel) and a metastable state (swollen gel), and thereby makes possible the gel transition into the swollen state.[1,2] The difference in the energy barrier heights for the forward and the backward transitions causes a hysteresis behaviour of the gel in the dynamic range of its phase transition. The latter affects the signal reproducibility and response time of the hydrogel based chemical sensors and should be taken into account at the sensor improvement.

In the present work we discuss the influence of the dynamic hysteresis on the swelling/deswelling kinetics of the temperature-sensitive PNIPAAm gels exhibiting lower critical solution temperature (LCST) behaviour and propose polymer film preparation conditions and measurement conditions, which are necessary for high signal reproducibility and high long-term stable sensor sensitivity.

Experimental Part

Sensor Operational Principle

The change ΔG in the Gibbs energy of the heterogeneous system (consisting of the

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polymer network, of the fluid inside the polymer network, and of the surrounding fluid) induced by the external stimulus causes a pressure difference π between the gel phase and the surrounding solution (so called osmotic pressure). In our experiments, this pressure was monitored by a corresponding electrical output signal U_{out} of the pressure sensor chip containing the gel layer in its cavity. The sensor chip was bonded to a socket with inlet and outlet flow channels. The aqueous solution to be measured has been pumped through the inlet channels into the chip cavity and has induced the swelling or shrinking processes of the hydrogel.[3]

Hydrogel Material Preparation and Characterization

The thermo-shrinking chemically cross-linked N-isopropylacrylamide (NIPAAm) (with *N,N'*-methylene-bisacrylamide (BIS) as the cross-linking agent) and photo cross-linkable co-polymer of NIPAAm, 2-(dimethyl maleimido)-N-ethylacrylamide (DMIAAm) as the chromophore, and poly(2-vinylpyridine) (P2VP) were prepared and characterized according to.[3]

The molecular weight (M_n) of the copolymers was determined by gel permeation chromatography (GPC) with a PL120 instrument equipped with RI detector using PSS 'GRAM' columns. The samples were measured at 50 °C in dimethylacetamide (DMAc) containing 0.42 g/l lithium bromide as mobile phase with a flow rate of 1 ml/min. The chemical composition of the copolymers was determined by ^{1}H NMR (Table 1). The ^{1}H NMR spectra were recorded on a BRUKER DRX 500 spectrometer (500 MHz). The solvent was used as an internal reference.

The phase transition temperature of the 5 wt% aqueous polymer solution was determined by differential scanning calorimetry (DSC) with a TA Instruments DSC 2920. The P2VP-block-P(NIPAAm-co-DMIAAm) block copolymer has a lower value of the phase transition temperature T_c ($T_c = 25\,°C$) than PNIPAAm ($T_c = 33\,°C$) due to the additional hydrophobic P2VP and DMIAAm components (Table 1).

Solution Characterization

For the pH sensor signal calibration, the buffered solutions of ionic strength $I = 0.2$ M were used which varied between pH values of 2 and 5. For the measurements of the content of metal ions in aqueous solutions, $CaCl_2 \times 2H_2O$, $CaSO_4 \times 0.5H_2O$, $FeSO_4 \times 7H_2O$, $CuSO_4 \times 5H_2O$, $ZnSO_4 \times 7H_2O$, $MnSO_4 \times H_2O$, and $NiSO_4 \times 6H_2O$ salts were used.

Hydrogel Material Conditioning

After the sensor preparation, an initial gel conditioning procedure was performed. An initial gel swelling in de-ionized water at low temperature ($T < T_c$) for 24 h preceded the deswelling/swelling cycling at increasing/decreasing temperature. During the first operation the hydrogel sensor often shows a bad repeat accuracy and a drift of the sensor parameters. It was found that the repeating sensor signal precision can be significantly increased by performing a number of conditioning cycles.

The conditioning process was accomplished after 5–7 swelling cycles (Figure 1). The sensor's output voltage was measured during the swelling/deswelling of the hydrogel layer under variable, tightly controlled ambient conditions (temperature and relative

Table 1.
Chemical composition, molecular weight M_n and phase transition temperature T_c of the used hydrogels.

Gel	Polymer composition, mol%				M_n, g/mol	T_c, °C
	NIPAAm	P2VP	DMIAAm	BIS		
1	73.1	18.9	8.0		44600	25
2	72.9	21.9	5.2		41500	24.5
3	96			4	63200	33

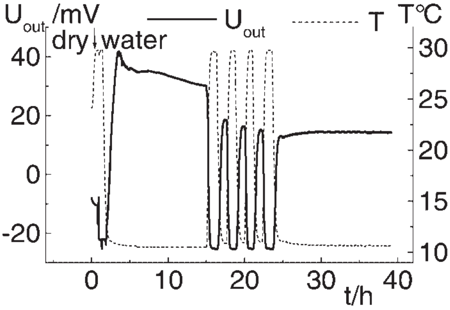

Figure 1.
Initial gel conditioning procedure in de-ionized water (Gel 1).

humidity uncertainties were $\Delta T = \pm 0.5\ K$ and $\Delta\varphi = \pm 2\%\ rh$, respectively).

ATR-IR (Attenuated Total Reflection Infrared) Spectroscopy

The local structure of P2VP-block-P(NIPAAm-co-DMIAAm) gel has been investigated by using (ATR)-IR spectroscopy during the thermally induced shrinkage. The ATR-FTIR measurements were performed on the *in-situ* ATR-FTIR Attachment for Sorption Measurements (OPTISPEC, Zürich), consisting of a special mirror setup and a removable *in-situ* ATR double channel flow cell surrounding a trapezoidal silicon internal reflection element (Si-IRE). The polymer layer was spun directly onto Si-IRE (a half of the IRE surface was coated), dried, and then crosslinked by UV irradiation. The resulting dry layer thickness was 2 μm. A Fourier Transform Spectrometer (IFS 55, BRUKER) was used with a globar source and a liquid nitrogen cooled mercury-cadmium- telluride (MCT) detector. The ATR-FTIR spectra were recorded using the novel SBSR (single beam sample reference) technique for reproducible spectral background compensation at the measurements in aqueous environments. Thereby, the ATR plate is divided into a lower reference and an upper sample half, sealed separately by O-rings forming a sample (S) and a reference (R) compartment on the IRE surface. During the measurement, intensity spectra (I_S, I_R) of the S- and R-compartment are alternatively recorded by the SBSR method and computationally 'ratioed' according to

$$A_{SBSR} = -\log(I_S/I_R). \qquad (1)$$

The resulting absorption spectra A_{SBSR} enable an accurate compensation of background absorptions due to the SiO_x layer, the solvent (water), the water vapour (spectrometer), and ice on the MCT detector window.[4] The solution was injected and cycled through the *in-situ* ATR cell by a peristaltic pump in combination with an addressable valve system operated under computer control.

Results and Discussion

Investigation of the Local Structure of the Gel

Two series of ATR-FTIR measurements for a water-swollen P2VP-block-P(NIPAAm-co-DMIAAm) layer (Gel 2) were performed at temperatures increasing from 10 °C to 50 °C (Figure 2a). The change rate of temperature was 2 K/min. The ATR-spectra show increasing intensities of amide I (ν(C=O) at 1630 cm^{-1}) and amide II (ν(NH) at 1550 cm^{-1}) bands accompanied by a decrease of the ν(OH) band intensity (negative band at 3400 cm^{-1}) due to a thermally induced removal of water from the gel layer (Figure 2b). However, no shifts in the wave number positions of the amide I and II bands were obtained, which were observed for aqueous solutions[5–7] of pure PNIPAAM or PNIPAAM copolymer gels.[8] In these pure PNIPAAM systems, shifts could be assigned to changes in the degree and type of hydrogen bonding between the amide groups and water (upon coil/globul transitions): amide I (mainly ν(C=O)) shifts downward and amide II (mainly ν(N-H)) upward. The lack of such shifts in our systems can be explained by their high degree of crosslinking, restricting the mobility of the polymer chains and thus preventing hydrophobic association. Interestingly, although a significant removal of water could be obtained from the ν(OH) band, obviously the amide groups of our

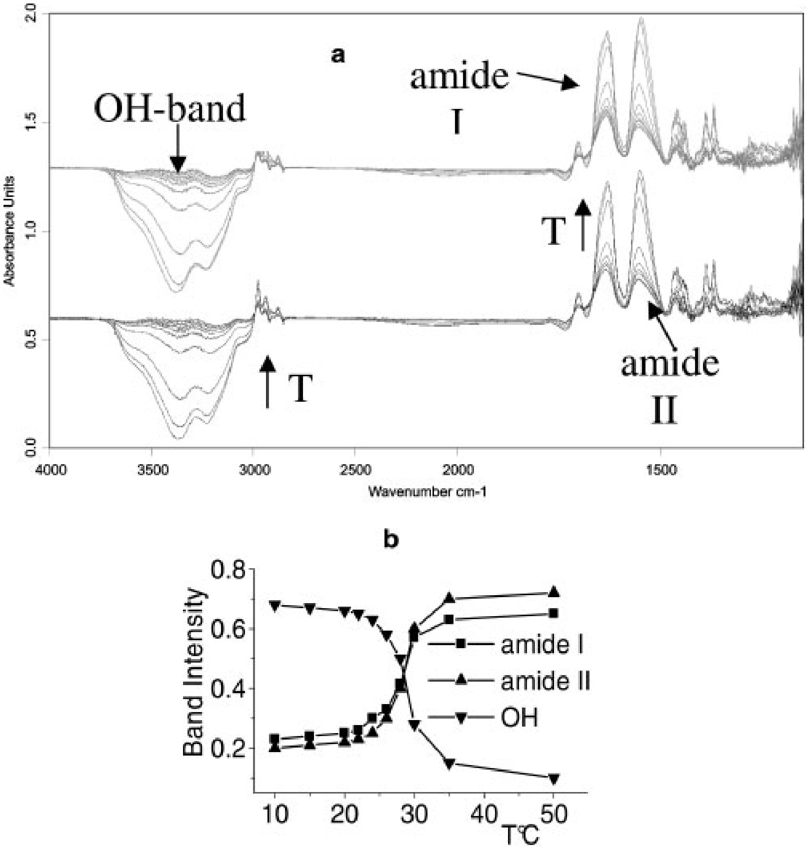

Figure 2.

In-situ ATR-FTIR spectra (A_{SBSR}) of the water-swollen P2VP-block-P(NIPAAm-co-DMIAAm) layer recorded during the thermally induced shrinkage (a) and corresponding changes of the IR-absorbance band intensities (b).

copolymer system kept their hydration state, since their amide bands did not shift.

Monitoring of the Swelling/Deswelling Kinetics

Our chemical sensor offers a perfect possibility for on-line monitoring of the gel behaviour kinetics (Figure 3). Two sets of experiments have been performed. In the first set, the sensor's output voltage U_{out} has been measured during the hydrogel swelling/deswelling at temperatures changing with a rate of ca. 0.8 K/min (Figure 3a, 3b). A temperature-sensitive PNIPAAm gel demonstrates a broad loop of the dynamic hysteresis under the sinusoidal temperature change (Figure 3b). The loop broadness depends on the change rate of temperature. In the second set, a step-mode temperature change has been used (Figure 3c, 3d). In this case, the equilibrium in the swelling degree was reached at every temperature step (Figure 3c). Figure 3d depicts a narrow hysteresis loop between the swelling and the deswelling curves, which have a same shape in this case. Figure 4 compares the shapes of the hysteresis loops obtained at different temperature change regimes.

These two sets of experiments show clearly, that the gel swelling occurs slower than the gel deswelling. This means that the energy barrier ΔG_{12} for the transition $1 \rightarrow 2$ from the stable state 1 with an absolute energy minimum (shrunk gel) to the metastable state 2 with a relative energy minimum (swollen gel) is higher than the

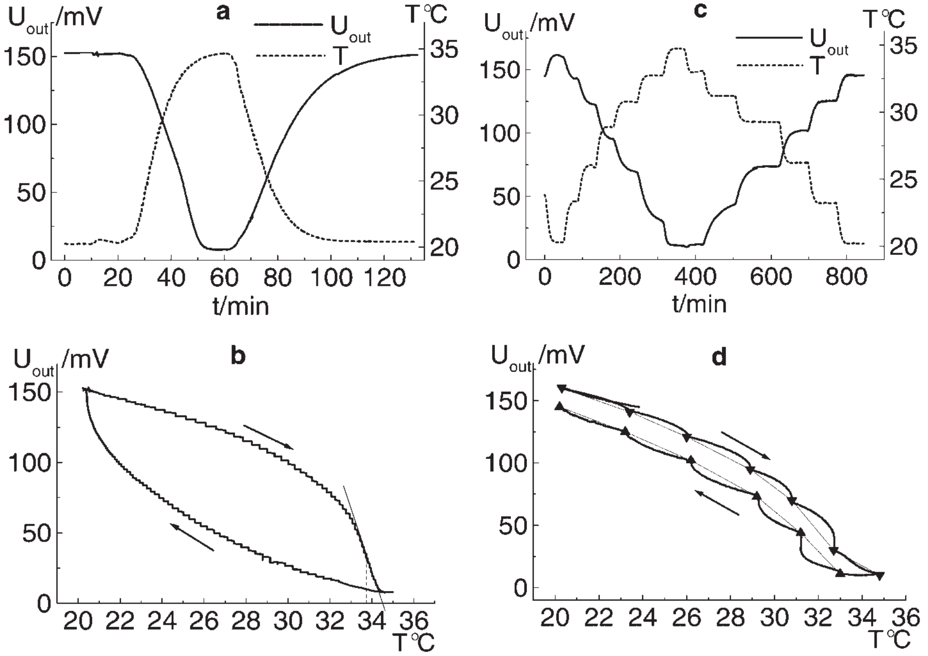

Figure 3.
Sensor output voltage during the swelling/deswelling of PNIPAAm gel (Gel 3) under a quick (a) and a slow step-mode (c) temperature change, and the corresponding hysteresis loops (b, d).

energy barrier ΔG_{21} for the backward transition $2 \rightarrow 1$ (Figure 5). The decreasing temperature as external stimulus X (in this case, this is value $X = 1/(T - T_c)$) lowers the barrier ΔG_{12}, and thereby makes possible the gel transition into the swollen state. This state is characterized by a state variable Y which in our case is the mole number of the absorbed solvent. The expected value of Y depends on the probability $P(Y, t)$ to find the system in a state with the value of Y, which lies in the interval $(Y, Y + dY)$ at time t:

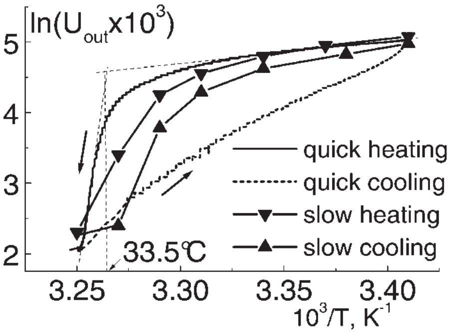

Figure 4.
Comparison of the hysteresis loops obtained at different temperature change regimes.

$$\langle Y(t) \rangle = \int YP(Y, t)dY. \tag{2}$$

Within a discrete description scheme, one obtains (taking in account that $P_1 + P_2 = 1$):

$$\begin{aligned}\langle Y(t) \rangle &= Y_1 P_1 + Y_2 P_2 \\ &= Y_1 + (Y_2 - Y_1)P_2.\end{aligned} \tag{3}$$

The transition rates $w_{12,21}$ depend on the energy barrier $\Delta G_{12,21}$ and on the temperature as

$$w_{12,21} = \tau_0^{-1} \exp(-\Delta G_{12,21}/RT), \tag{4}$$

where T is the absolute temperature, R the universal gas constant, τ_0 the characteristic time constant dependent on the shape of the free energy profile.[9] The probability

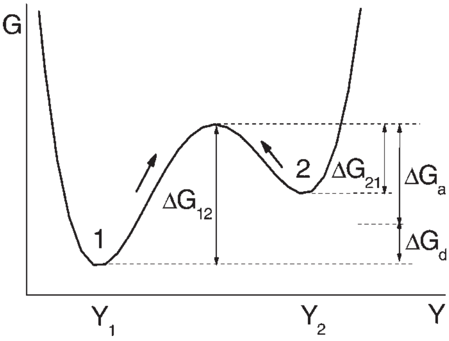

Figure 5.
Energy profile for a bistable system.

distribution $P_2(t)$ obeys the equation:

$$dP_2/dt = w_{12}P_1 - w_{21}P_2 = (P_{2,eq} - P_2)/\tau \qquad (5)$$

Here,

$$\tau^{-1} = w_{12} + w_{21} = 2\tau_0^{-1}\cosh(\Delta G_d/RT)\exp(-\Delta G_a/RT), \qquad (6)$$

$$P_{2,eq} = w_{12}/(w_{12} + w_{21}) = 0.5 - 0.5\tanh(\Delta G_d/RT), \qquad (7)$$

$$\Delta G_a = (\Delta G_{12} + \Delta G_{21})/2, \Delta G_d = (\Delta G_{12} - \Delta G_{21})/2. \qquad (8)$$

The solution of Eq. (5), given the initial probability $P_2(t=0) = P_{20}$, is

$$P_2(t) = P_{2,eq} + (P_{20} - P_{2,eq})\exp(-t/\tau). \qquad (9)$$

Analogous expressions hold for $\langle Y(t)\rangle$ defined by Eq. (3). The probability of the transition 1→2 under the change of external stimulus X is essential if $|\Delta G_d| \leq RT$ (see Eq. (7)). For a certain polymer, the position of the mid point of the hysteresis loop in the $Y_{2,eq} = f(X)$ graph is defined by the value of ΔG_a, whereas the loop broadness is defined by the value of ΔG_d. According to Eq. (9), the system relaxes exponentially to the new state, with a time constant τ given by Eq. (6).

In practice, the values of τ might be large. In case of chemical sensors, one should operate with the value of $\langle Y(t_{ex})\rangle$ (here, t_{ex} is the exposure time at the certain value of X) in order to quickly obtain the information about the value of the control parameter X. In advance, the values of τ should be estimated for certain changes $\partial X$and for those gel layers (taking into account the layer thickness) which are used in the sensors. The equilibrium values $Y_{1,eq}$ and $Y_{2,eq}$ can be calculated using the thermodynamic equilibrium condition for a partition of the solvent and additives between the gel phase and the surrounding solution as described in.[10]

The influence of the gel swelling/deswelling kinetics on the response time and long-term signal stability of the proposed sensors was investigated for the different thicknesses of the polymer layer. A time constant down to 70 s has been found for a 4 μm thick photo-crosslinked hydrogel film.

If one uses a polyelectrolyte gel with ionizable groups, one has a possibility to obtain information about the concentration of the ions in solution. The ionic additives spark off the ionization process in the gel. An induced increase of the backbone charge leads to an increase of the gel hydrophilicity and consequently to a gel swelling. In this case, the control parameter X is the ion concentration c_a.

pH Sensor

The combination of the temperature-sensitive PNIPAAm with a pH-sensitive P2VP component allowed us to realize a pH sensor in the pH range between 2 and 5. Since P2VP-block-P(NIPAAm-co-DMIAAm) is a weak polyelectrolyte (due to the amino groups), its uncompensated backbone charge increases with increasing concentration of H^+ ions in solution. Figure 6 demonstrates the reproducible output characteristic of a pH sensor in a narrow pH range at a constant ionic strength I=0.2 of the buffered solutions. The dynamic hysteresis has been minimized by setting $t_{ex} = const$ for all pH measurements.

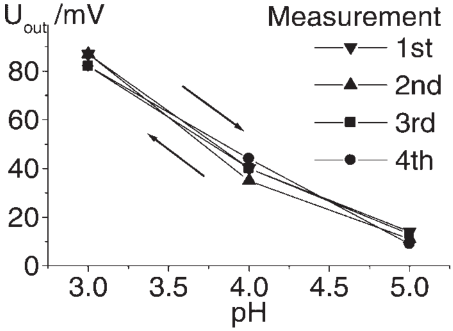

Figure 6.
Output characteristic of pH sensor (with Gel 2) for repetitive forward and backward measurements.

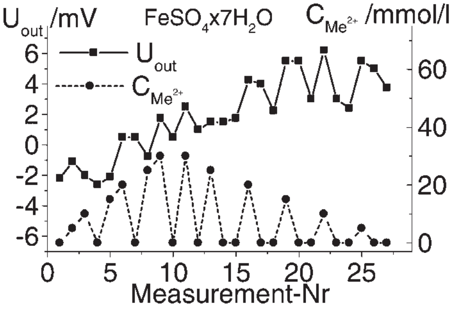

Figure 8.
Signal of sensor (with Gel 1) exposed alternatively to water and to solutions with different concentration of Fe^{2+} ions.

Sensor for the Measurement of the Content of Metal Ions in Aqueous Solutions

The swelling behaviour of the P2VP-block-P(NIPAAm-co-DMIAAm) gel was analyzed as a function of the concentration $c_{Me^{2+}}$ of transition-metal ions in aqueous solutions (Figure 7). The dependence demonstrates a non-monotonic behaviour. At small ion concentrations, an increasing gel swelling has been observed which is accompanied by a T_c-shift to higher values. Figure 8 illustrates the gel hydration increasing from cycle to cycle at alternating immersions in water and in solutions with small concentration of Fe^{2+} ions due to a steadily increasing value of the degree of the amino groups ionization. With further increase of $c_{Me^{2+}}$, more and more metal ions become trapped within the gel which possesses specific coordination binding sites for metal ions. The transition-metal cations form complexes with N atoms which have a pair of unshared electrons and are capable to satisfy the coordination number of the metal.[11] As a result, the electrostatic repulsion between the charged units decreases, and the gel starts to contract. In this case, the metal ions might act as cross-linkers by coordination binding to nitrogen atoms of different chains. It was found that the complexation of the polymer units by bivalent metal ions (due to the formation of chelate rings with metal ions) affects the T_c-shifting toward lower values and increases in accordance with a series: $Ca^{2+} < Fe^{2+} < Cu^{2+} < Zn^{2+} < Mn^{2+} < Ni^{2+}$ (Figure 7). An increasing ionic strength I of the solution at $c_a > 0.03$ mol/l is an additional cause for a decreasing equilibrium swelling. It results from a screening effect of the counter ions, i.e. SO_4^{2-}, which shield the charges on the polymer chains and prevent their efficient repulsion.

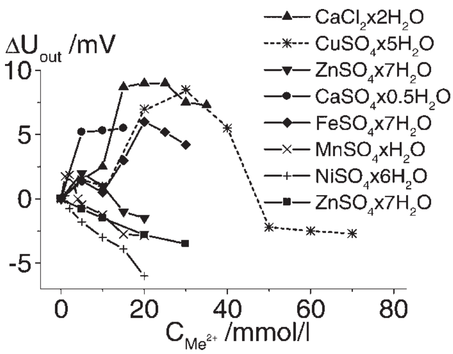

Figure 7.
Sensor output characteristics in solutions with transition-metal ions (Gel 1).

Figure 8 demonstrates that a high signal reproducibility can be ensured only by performing the conditioning procedure before every measurement in order to achieve a certain reference sensor signal. It should be noted that an appropriately chosen rinsing solution should be used for a certain analyte and for a certain polymer. A mixture of the phosphate buffer saline (PBS, 10 mg/ml) yielding pH = 7.3 and 0.01 mol/l EDTA was found as a suitable rinsing solution for theP2VP-block-P(NIPAAm-co-DMIAAm) gel after measurements in solutions with metal ions.

Conclusions

In the present work, temperature-sensitive PNIPAAm gels were applied in chemical sensors. The influence of the gel swelling/deswelling kinetics on the response time and long-term signal stability of the proposed sensors was investigated. The local structure of P2VP-block-P(NIPAAm-co-DMIAAm) gel was studied by using *in-situ* (ATR)-IR spectroscopy. The structural changes were not detected during the thermally induced gel shrinkage. In oder to provide the required high signal reproducibility of the sensors, two procedures were carried out: 1) an initial gel conditioning procedure consisting of a gel swelling in de-ionized water and a subsequent deswelling/swelling cycling, and 2) a regenerating procedure before every measurement in order to achieve a certain reference sensor signal.

Acknowledgements: The authors gratefully acknowledge the support for this work from the Deutsche Forschungsgemeinschaft (Collaborative Research Center (SFB) 287).

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