

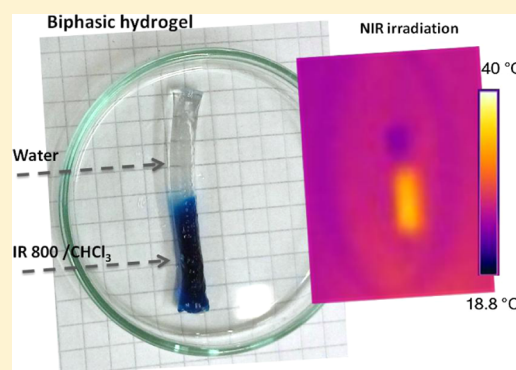
Poly(*N*-isopropylacrylamide) Cross-Linked Gels as Intrinsic Amphiphilic Materials: Swelling Properties Used to Build Novel Interphases

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S Supporting Information

ABSTRACT: The hydrophilic nature of hydrogels allows their swelling in aqueous solutions. In that way, any substance loaded inside the gel is exposed to the aqueous media and could be released if it is soluble in water. However, only substances that are soluble in water can be loaded inside a gel, which can be swelled only in water. In this work, we studied the swelling of poly(*N*-isopropylacrylamide) (PNIPAM) gels in nonaqueous solvents and their solutions with water. PNIPAM gels swell strongly in highly polar solvents, but they do not swell in slightly polar solvents (e.g., toluene). However, it is possible to swell the gel in mixtures containing toluene. The observed properties of PNIPAM gels allow describing them both as solvogels or amphigels. When the loaded substance is soluble in one solvent (e.g., water) and not in another (e.g., chloroform), the substance is not released but exposed to the new media. As a proof of concept, a colorimetric pH sensor active in CHCl_3 and a Cu^{1+} sensor in water were built. Moreover, using a ternary solution containing toluene linear polystyrene can be loaded inside the gel, making a semi-interpenetrated network. Because PNIPAM swells in water and solvents immiscible in water, a liquid/liquid interphase can be set inside a gel. A near-infrared absorbing dye (soluble in CHCl_3) is loaded in only half of a thermoresponsive PNIPAM gel. Upon near-infrared irradiation, only the region where the dye is loaded heats up driving the phase transition of PNIPAM.



1. INTRODUCTION

Three-dimensional cross-linked networks of hydrophilic polymer chains where the free polymer segments are solvated by water constitute a hydrogel. One of the most interesting features is their capability of swelling greatly (100–20 000%)^{1–3} in water, exposing the polymer chains to the aqueous media. However, it is well known that the swelling can decrease (shrinking) upon changes in the surrounding media (temperature, pH, ionic force, presence of surfactants). During the last decades, an extensive study of synthesis and properties of hydrogels has been performed.^{4–6} Due to their outstanding properties, the hydrogels provide a platform for a wide range of applications including microfluidics,⁷ biomimetic,⁸ biosensor/bioactuator,⁹ bioseparation,¹⁰ and tissue engineering.^{11,12} Among others, poly(*N*-isopropylacrylamide) (PNIPAM) is one of the most studied hydrogels. Beside large swelling in water, PNIPAM show thermosensitive properties because they suffer a hydrophilic to hydrophobic phase transition at temperatures (32–34 °C) close to those basal of the human body (36–37 °C). This property allows the release of previously loaded drugs in response to temperature changes and could be used to build different thermally activated devices. Due to their hydrophilic nature, the biggest drawback of these systems is the difficulty on loading hydrophobic drugs

that is crucial in applications like drug delivery in cancer therapy or in the area of visual sensors.^{13–15} In these cases, the reported strategies to overcome this impediment are quite complex including synthesis of specific monomers,¹⁴ several synthetic steps, or typical conditions of synthesis^{16,17} that affect the properties of the final polymeric matrix. On this sense, there is an extensive data reporting the swelling of PNIPAM hydrogels in organic solvent/water mixtures, for example, ethanol/water, methanol/water,¹⁸ acetone/water,¹⁹ and dimethylsulfoxide (DMSO)/water.²⁰ Those systems show a well-known swelling/shrinking behavior where the polymeric chains are soluble in the pure solvent but insoluble in the mixture of both, where the gel shrinks. This is known as co-nonsolvency phenomenon¹⁸ and could be explained as the result of the competitive adsorption,^{21–24} meaning that the good solvent is preferentially retained inside the gel.

However, the study of cross-linked polymers where the free rotation chains are solvated by pure organic solvents, known as solvogels, is quite limited.^{19,25–27} Another approach to load hydrophobic substances inside hydrogels involves synthesizing

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amphiphilic polymer gels,^{28,29} which are made of copolymer networks bearing both hydrophilic and hydrophobic monomer units.^{30–35} Usually, vinylic monomers with pendant long alkyl chains (hydrophobic) are copolymerized with vinylic monomers with short or without pendant alkyl chains (hydrophilic).³⁶ Indeed, in some cases, *N*-isopropylacrylamides have been used as the hydrophilic monomer unit of polymers^{37–39} and gels.⁴⁰ On the other hand, to the best of our knowledge, the only intrinsic amphiphilic polymers that are swellable both in water and a nonaqueous solvent are poly(oxazoline)s.^{41–43} Some poly(oxazoline)s have similar properties to PNIPAM. Indeed, poly(isopropyl-oxazoline) (whose monomer unit is isomeric with *N*-isopropylacrylamide) shows a lower critical solution temperature (LCST) of 36 °C, quite similar to that of PNIPAM (32 °C), and the hydrogels show similar LCST values.⁴⁴

In this work, we study the swelling of PNIPAM hydrogels not only in different solvent mixtures with water but also in pure nonaqueous solvents (alcohols, ketones, amides, chlorocarbons). Some of them (e.g., chloroform) are even immiscible with water. Moreover, PNIPAM can be also swelled in solvent mixtures containing low-polarity solvents (e.g., toluene), which could dissolve nonpolar (or slightly polar) molecules. To the best of our knowledge, this is the first time that the swelling capacity of PNIPAM in ternary mixtures is reported. From the ternary mixtures containing toluene, polystyrene (PS, a substance insoluble in water but soluble in toluene) is loaded inside a PNIPAM gel. After removing the solvent, the gel is swelled in water and the mechanical properties of the material were found to be improved due to the reinforcing effect of the PS semi-interpenetrated inside the PNIPAM cross-linked network.

It is noteworthy that if PNIPAM swell in both solvents (e.g., *N*-methyl pyrrolidone (NMP) and water), any substance loaded in one solvent (e.g., NMP) is retained when the former is removed and becomes exposed to the other solvent (e.g., water) upon swelling in the later. If the loaded substance is soluble in only one solvent of the pair, the loading and swelling procedure allows exposing a substance to a solvent in which it is insoluble (or slightly soluble). In that way, it could interact with ions in the solution. We used the effect to fabricate a pH sensor and a copper sensor. A pH sensor was developed by swelling the PNIPAM in methyl orange (MO)/water solution and then the loaded gel is used to sense pH changes in an organic solvent (chloroform) in which the dye is insoluble. In a second study, the bathocuproine (BC) ligand was loaded inside the gel using ethanol as solvent and allowed to sense Cu¹⁺ ions in water by change in color.

Of special interest is the fact that PNIPAM also swells strongly in solvents immiscible with water (e.g., chloroform). In that way, a gel containing two immiscible liquid phases can be obtained. Using this effect, a biphasic PNIPAM hydrogel was developed by swelling the hydrogel in a chloroform/water interphase. As an application, a near-infrared (NIR) absorbing dye (IR800) soluble in chloroform is loaded in only half of a thermoresponsive gel creating an asymmetric gel where only the modified part (by loading IR800) collapses when NIR light is absorbed by the dye.

2. EXPERIMENTAL SECTION

2.1. Materials. *N*-Isopropylacrylamide (NIPAM) used as monomer was obtained from Scientific Polymer Products (purity > 99%). *N,N*-Methylenebisacrylamide (BIS),

N,N,N',N'-tetramethylenediamine (TEMED), and ammonium peroxydisulfate (APS) were purchased from Aldrich. *N*-Methyl pyrrolidone (NMP) (Sigma Aldrich, 99%), ethanol (Cicarelli, 99.5%), tetrahydrofuran (THF) (Aldrich, 99.9%), chloroform (CHCl₃) (Cicarelli, 99%), acetone (Cicarelli, 99.5%), formic acid (Biopack, 85%), cyclohexane (Cicarelli, 99%), acetonitrile (ACN) (Aldrich, 99.5%), toluene (Biopack, 99.5%), carbon tetrachloride (Aldrich, 99.5%), dimethylsulfoxide (DMSO) (Sintorgan, 99.9%), isopropanol (Cicarelli, 98%), and poly(ethylene glycol) (PEG 200) (Aldrich) were used as received. Water used in this work was bidistilled. All other reagents are of analytical quality.

2.2. Synthesis of the Hydrogel. PNIPAM hydrogels were synthesized via free-radical polymerization of NIPAM using BIS as a cross-linking agent. APS and TEMED were used as the initiator system of polymerization. The synthesis was done following the procedure describe elsewhere.⁴⁵ Briefly, BIS (2% mol based on NIPAM) was dissolved in an aqueous solution of NIPAM monomer (0.5 M) and the solution was purged by bubbling N₂ gas to eliminate O₂. Next, polymerization initiator system (APS (0.001 g/mL) and TEMED (10 μL/mL)) was added. The polymerization was carried out in a sealed glass tube at room temperature (20 °C) for 3 h, time enough to achieve gelation. The formation of the hydrogels is easily followed by naked eye by simply putting the closed vial upside down and checking when the solution is not a fluid any more due to network formation. To finish the polymerization process and remove unreacted chemicals, the hydrogels were immersed in distilled water at room temperature for 48 h and the water was renewed several times. A cylindrical gel (Ø 0.7 cm) was obtained and then cut into small disks of ~2 mm thickness unless otherwise specified. Finally, the disks were dried in an oven at 50 °C for approximately 24 h until constant weight was achieved.

Given the purity (>99%), NIPAM was used without further purification, as we reported previously.⁴⁶ The physicochemical properties (swelling degree, phase transition temperature) and the structural characterization (Fourier transform infrared, FTIR) suggest that the gels are typical for PNIPAM.

2.3. Swelling Kinetics for PNIPAM Hydrogels in Pure Solvents. Swelling kinetic measurements were carried out for PNIPAM hydrogels in different pure solvents (aqueous and nonaqueous). Dried hydrogel disks, previously washed and weighed, were placed in the solvent at room temperature (20 °C). The sample was removed from the solution, at certain time intervals, and superficially dried with a tissue paper, weighed in an analytic balance, and placed back in the bath. The measurements were repeated until constant weight. The swelling percentage (% Sw) is calculated as a function of time according to eq 1

$$\% \text{ Sw} = \frac{(W(t) - W_0)}{W_0} \times 100 \quad (1)$$

where $W(t)$ represents the weight of hydrogel in swollen state at time t and W_0 is the weight of dried hydrogel (xerogel). The graphics of % Sw vs time were made to analyze the swelling kinetic.

When the gel reaches the equilibrium condition, the weight of gel (W_{eq}) does not change with time. Experimentally, the kinetics were carried out until at least three successive measures of weight showed a minimum difference of less

than 5% in % Sw. The percentage of equilibrium swelling (% Sw_{eq}) is calculated by eq 2.

$$\% \text{ Sw}_{\text{eq}} = \frac{(W_{\text{eq}} - W_{\text{d}})}{W_{\text{d}}} \times 100 \quad (2)$$

The studied solvents were water, *N*-methyl pyrrolidone (NMP), ethanol, tetrahydrofuran (THF), and chloroform (CHCl₃). Other solvents (acetone, formic acid, cyclohexane, acetonitrile, toluene, carbon tetrachloride, dimethylsulfoxide, isopropanol, and poly(ethylene glycol) (PEG 200)) were just characterized according to their equilibrium swelling capacity (% Sw_{eq}).

2.4. Swelling Capacity in Binary and Ternary Solvent Mixtures. The degree of swelling (Sw), defined as the relation between the wet hydrogel weight in the equilibrium state (W_{eq}) and the dried hydrogel weight (W_o), is a normal way of studying the swelling capacity in hydrogels.

$$\text{Sw} = \frac{W_{\text{eq}}}{W_{\text{o}}} \quad (3)$$

The Sw of PNIPAM hydrogels was studied in different binary and ternary mixtures. To perform this study, a dried hydrogel piece, previously weighed (W_o), was immersed in the desired solvents mixture. After 48 h, necessary time to reach the equilibrium, W_{eq} was recorded.

The studied binary mixtures were ethanol/water, NMP/water, ethanol/NMP, NMP/CHCl₃, CHCl₃/toluene, and water/ACN. The mixtures were prepared by varying the % v/v of one component between 0 and 100%, with an increment of 10%.

The swelling behavior of a hydrogel in ternary solvent mixtures was also studied. Particularly, we worked with ternary mixtures containing water, ethanol, and toluene. The composition of each mixture was chosen according to the component of the three-phase diagram.⁴⁷ To obtain miscible mixtures, the six chosen compositions (Table 1) were located above the saturation curve.

Table 1. Molar Composition of the Ternary Mixtures

mixture	X _{water}	X _{ethanol}	X _{toluene}
T1	0.63	0.36	0.01
T2	0.45	0.50	0.05
T3	0.34	0.56	0.10
T4	0.26	0.54	0.20
T5	0.10	0.39	0.50
T6	0.04	0.27	0.70

As a proof of concept, the incorporation of polystyrene (PS) inside PNIPAM hydrogel was made by sorption from a ternary mixture containing toluene. PS is a linear polymer insoluble in water, ethanol, and binary mixtures of water/ethanol. At 0.75 mg/mL, PS was dispersed in T5 mixture and a disk of dried hydrogel was swollen in dispersion under constant stirring to keep the PS/T5 dispersion stable at room temperature (20 °C) during 24 h, time enough to reach suitable swelling. The employed vials were properly closed to avoid the evaporation of the mixture and the stirring set at minimum so as not to damage the gel during the swelling stage. Alternatively, PNIPAM was swollen in T5 without PS, in the same experimental conditions, and the differences were recorded by optical photographs and attenuated total reflection (ATR)

spectroscopy. For the ATR measurements, the swelled gels were dried in an oven at 50 °C until constant weight. Fourier transform infrared spectroscopy measurements were recorded in ATR mode with a resolution of 4 cm⁻¹ on a FTIR PerkinElmer (Model Spectrum Two). The device was equipped with a DynaScan interferometer. The software used as interface was Spectrum 10.

Besides, uniaxial compression measurements were performed on individual cylindrical hydrogels in their water-swollen states to study the elastic moduli (E') of the hydrogel before and after interpenetration with PS. E' was measured as described before⁴⁸ for the bare hydrogels and for the hydrogel-PS. Therefore, to compare the samples, the bare hydrogel was subjected to the same treatment as the hydrogel loaded with PS, i.e., swelling in T5 mixture, drying, and reswelling in water. The temperature of all the measurements was 25 ± 0.5 °C. The experiments were performed three times and the results averaged.

2.5. Loading of Water-Soluble and -Insoluble Molecules Inside Hydrogels. Bathocuproine (BC) (Aldrich), which is a water-insoluble (log P_{ow} = 7.51) chelating agent and (4-[4-(dimethylamino)phenylazo]benzenesulfonic acid sodium salt) (methyl orange (MO), Aldrich), which is an azoic water-soluble indicator dye.

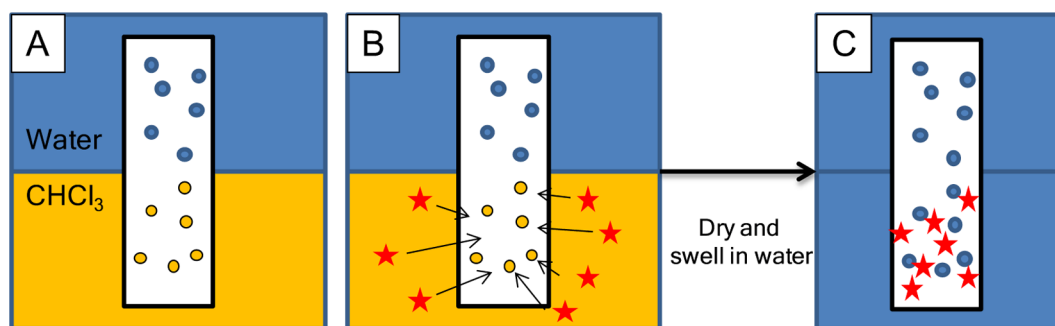
BC was dissolved in absolute ethanol at 1 mM concentration. PNIPAM gel was placed in this solution and swelled until reaching an equilibrium (24 h). Then, the gel was dried in an oven (at 40 °C) to remove alcohol and swollen in copper(I) aqueous solution. In the same way, MO was loaded into PNIPAM by swelling from a 1 mM aqueous solution for 24 h. Then, the gel was dried at 40 °C and swollen in CHCl₃ until equilibrium (during 24 h). The acids or bases to be sensed are dissolved in chloroform.

2.6. Phototriggered Thermal Collapse in a Biphasic Hydrogel. To study an application of the swelling ability in organic and aqueous solvents, the phototriggered thermal collapse of a PNIPAM hydrogel was studied in a biphasic hydrogel. With this aim, IR 800 (97%, Sigma-Aldrich), a NIR absorbing dye that allows light to heat conversion, was loaded from chloroform in half of hydrogel swollen in a water/chloroform interphase (Scheme 1). Briefly, dry PNIPAM hydrogel synthesized with a cylindrical shape without cutting was placed in a water/chloroform interphase with IR 800 (0.07 mg/L) dissolved in organic phase for 48 h. Then, the hydrogel was dried in stove (at 40 °C) to remove both solvents and reswell in water. To study the photothermally triggered collapse, the whole hydrogel was irradiated with a NIR lamp (Hydrosun 750, 750 W) for 50 s until the collapse of one section was observed. The temperature was recorded at different time points with an infrared camera (FLIR E30, 25° optic, 60 Hz).

3. RESULTS AND DISCUSSION

During the last decades, several studies on the swelling capacity of PNIPAM hydrogels in aqueous solutions have been conducted, but there is a lack on the characterization of these systems in organic solvents. The aim of this study was to examine the solvency properties of PNIPAM hydrogels both in water and organic solvents and to develop different applications of PNIPAM as solvogen.

3.1. PNIPAM Swelling in Pure Solvents. 3.1.1. Swelling Capacity in Equilibrium. To study the solvency properties of PNIPAM hydrogels, the swelling in equilibrium was measured

Scheme 1. Schematic Representation of Building a Nonaqueous/Aqueous Interphase into Hydrogel^a

^aBlue circle (blue concentric circles, water molecules), yellow circle (yellow circle solid, chloroform molecules), and red stars (red star solid, dye molecules). (A) Cylindrical hydrogel swollen in water/chloroform interphase. (B) Cylindrical hydrogel swollen in water/dye (dissolved in CHCl_3) interphase. (C) Cylindrical hydrogel obtained in (B) was dried and swollen in water.

in several organic solvents and compared with water. The results are shown in Figure 1. As expected, water is the best

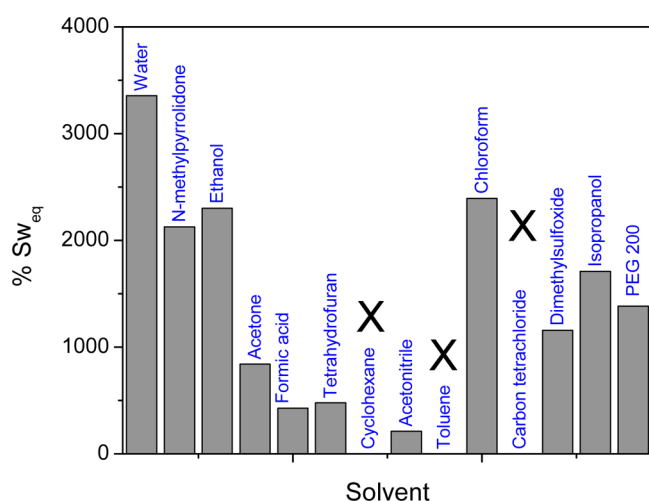


Figure 1. Percentage of equilibrium swelling ($\% \text{Sw}_{\text{eq}}$) of PNIPAM in different solvents at 20 °C during 48 h. *Every reported data were the average of three measurements. X marks the solvents in which the gel swelling is negligible ($\% \text{Sw}_{\text{eq}} = 0$).

solvent for PNIPAM; interestingly, the second best one is chloroform, a nonaqueous solvent immiscible in water. The swelling in a given solvent involves the solvation of functional groups in the polymer chain that overcome the polymer–polymer interactions. The linear segments, between cross-linking points, dissolve in the solvent, making the gel expand until the elastic force of the cross-linked matrix is balanced. The main interaction with the polymer chain involves hydrogen bonding with the amide group. In the case of water, it is possible to build a donor hydrogen bond with $>\text{C}=\text{O}$ and an acceptor hydrogen bond with $>\text{N}-\text{H}$. The alcohols could build hydrogen bonds similar to water. On the other hand, secondary amides (e.g., dimethylformamide or NMP) and ketones only have acceptor bonds with $>\text{N}-\text{H}$. A special case is chloroform, in which a significant contribution of hydrogen bond could also exist.^{49–52}

Moreover, PNIPAM does not swell in nonpolar organic solvents such as cyclohexane, toluene, and carbon tetrachloride ($\% \text{Sw}_{\text{eq}} = 0$), which could not form hydrogen bonding. A plot of the measured swelling as a function of the Hansen parameter for hydrogen bonding (δ_{h}) gives a reasonable

correlation (Figure 2), suggesting that hydrogen bond plays an important role. On the other hand, the gel swelling capacity in

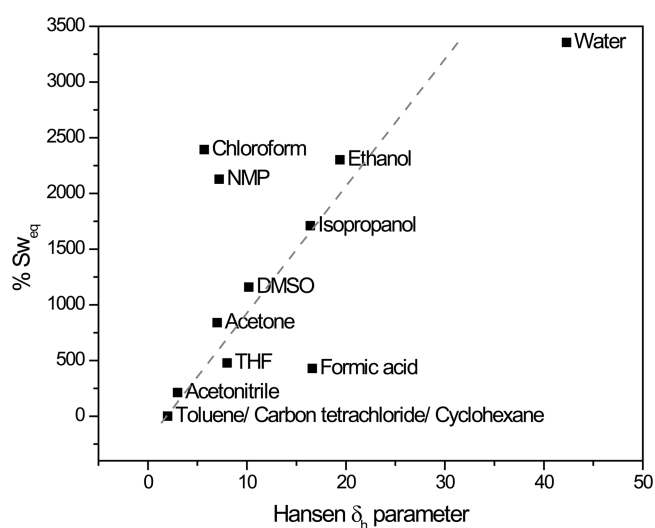


Figure 2. Plot of the percentual swelling capacity as a function of Hansen hydrogen bonding parameter.

some solvents (e.g., CHCl_3 and NMP) exceed the value predicted by the correlation, whereas others (e.g., formic acid and water) show too low values. Those results suggest that other factors (dispersion forces, polar effects) could also play some role.⁵³ It should be remembered that PNIPAM has a defined hydrophobic nature due to the vinylic backbone and the presence of the isopropyl group on the amide. Indeed, it shows a hydrophilic-to-hydrophobic transition at ca. 32 °C due to entropic effects.

One example of the application of this organic solvency property was previously shown by our group.⁵⁴ A cross-linked hydrogel based in PNIPAM is able to swell in NMP. This paved the way to compose materials in which a linear polymer (polyaniline, PANI) was loaded inside a hydrogel by swelling in a true solution of PANI using NMP as solvent.²¹

3.1.2. Swelling Kinetics. Analyzing the obtained results, we chose five solvents that can swell the hydrogel, and they are chemically different between each other. Besides, the immiscibility of chloroform in water is interesting to obtain separate phases inside the same gel. Figure 3 shows the swelling kinetics ($\% \text{Sw}$ vs time) when the hydrogel is placed in

water, NMP, ethanol, THF, and CHCl_3 . It can be seen that the kinetics are strongly solvent dependent.

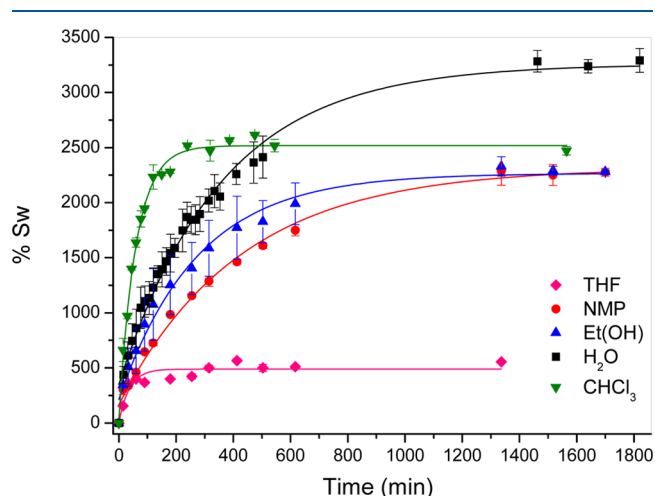


Figure 3. PNIPAM swelling kinetics in water, ethanol, *N*-methyl pyrrolidone, tetrahydrofuran, and chloroform at 20 °C. Fitting (full line) according to eq 4.

The swelling kinetics were fitted using a first-order kinetic,⁵⁵ in accordance with the next equation

$$\% \text{ Sw}(t) = \% \text{ Sw}_{\text{eq}}(1 - e^{-k_s t}) \quad (4)$$

where k_s is the rate constant of the pseudo-first-order swelling model. The obtained values of k_s , $\% \text{ Sw}_{\text{eq}}$ and R^2 are reported in Table 2.

Table 2. Characteristic Parameters for First-Order Swelling Model of a Hydrogel in Different Solvents

solvent	viscosity (cP) at 20 °C	$k_s \times 10^2$ (min ⁻¹)	$\% \text{ Sw}_{\text{eq}}$ (exp)	$\% \text{ Sw}_{\text{eq}}$ (theoric)	R^{2aa}
THF	0.55	2.710	556	489	0.866
CHCl_3	0.56	1.685	2471	2518	0.993
water	1.00	0.301	3290	3258	0.985
ethanol	1.20	0.366	2280	2265	0.983
NMP	1.65	0.235	2276	2317	0.991

^aCorrelation coefficient.

Equation 4 was used to fit the swelling kinetics of PNIPAM gels in different solvents. The fitting was proposed by Zhao et al.⁵⁵ to fit the swelling kinetics of PNIPAM hydrogels of different porosities. We have used the approach successfully⁵⁶ to fit the swelling kinetics of different hydrogels in water on the basis of PNIPAM. The swelling constant (k_s) correlates well with the viscosity of the hydrogel determined by electrochemical methods. Here, the polymer matrix is maintained constant, but the swelling solvent is changed and a good correlation of the relaxation time with the solvent viscosity is found. Equation 4 allows to compare different systems with common parameters, unlike other approaches where a defined diffusion/relaxation model is fitted to the data and only qualitative comparison between different systems can be made.⁵⁷

As R^2 values indicate, eq 4 gives an excellent fit in all cases and allows to compare different systems with common parameters, unlike other approaches where a defined diffusion/relaxation model is fitted to the data and only

qualitative comparison between different systems can be made.⁵⁷

Although the polymeric chains swell and the hydrogel increase its volume, an opposite elastic force of the polymer resists this change. The rate of swelling is related to the relaxation of the polymer chains and the mass transport of the solvent inside the gel. In this case, the polymeric network is always the same, but the solvent it is not, thus showing different behavior.

The relaxation could be assessed by the half-life time ($t_{1/2}$) of the swelling process. As can be seen (Figure 4), $t_{1/2}$ is directly related to the viscosity of the intaken solvent.

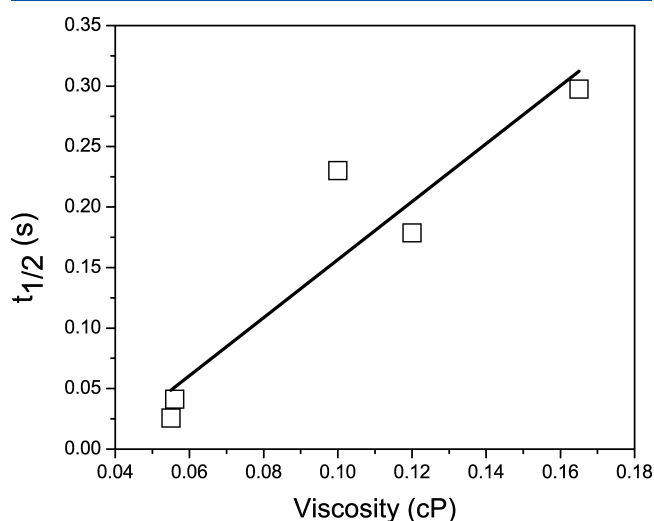


Figure 4. Effect of solvent viscosity on the half-life time of the swelling process.

It could be envisaged that the solvent also affects the polymer relaxation by a plasticizing effect, but it seems that viscosity of the solvent dominates the swelling rate.

3.2. Swelling in Miscible Solvents. **3.2.1. Binary Mixtures.** Six binary mixtures of miscible solvents were studied: ethanol/water, NMP/water, ethanol/NMP, CHCl_3 /NMP, toluene/ CHCl_3 , and ACN/water. Figure 5 shows the degree of swelling in equilibrium state (Sw_{eq}) relative to the v/v fraction of one solvent in the binary mixture.

It can be noted that PNIPAM swell in almost the same degree in pure ethanol or water (Figure 5, top left) but the gel does not swell when the mixture has a concentration of ca. 46% v/v of ethanol in water. The swelling degree does not monotonically change with the amount of ethanol present in the solution (Figure 5). This is likely due to the specific interactions of ethanol and water with functional groups in the mobile polymer chains. In an ideal solution, no specific interactions exist and the molecules of ethanol and water solvate the chains, whereas in this case, the best solvent is enriched inside the gel, swelling the material in a way not directly proportional to the relative concentration in the solution. This is known as “co-nonsolvency effect” and considered to be the result of competitive adsorption.^{18,21,23}

The swelling of PNIPAM in NMP/water mixtures shows the same co-nonsolvency effect and the gel remains in a shrunken state at 64% v/v of NMP. Several studies have shown the same behavior, for example, methanol/water,²³ acetone/water,¹⁹ DMSO/water,²⁰ acetic acid/water, and pyridine/water.²⁵

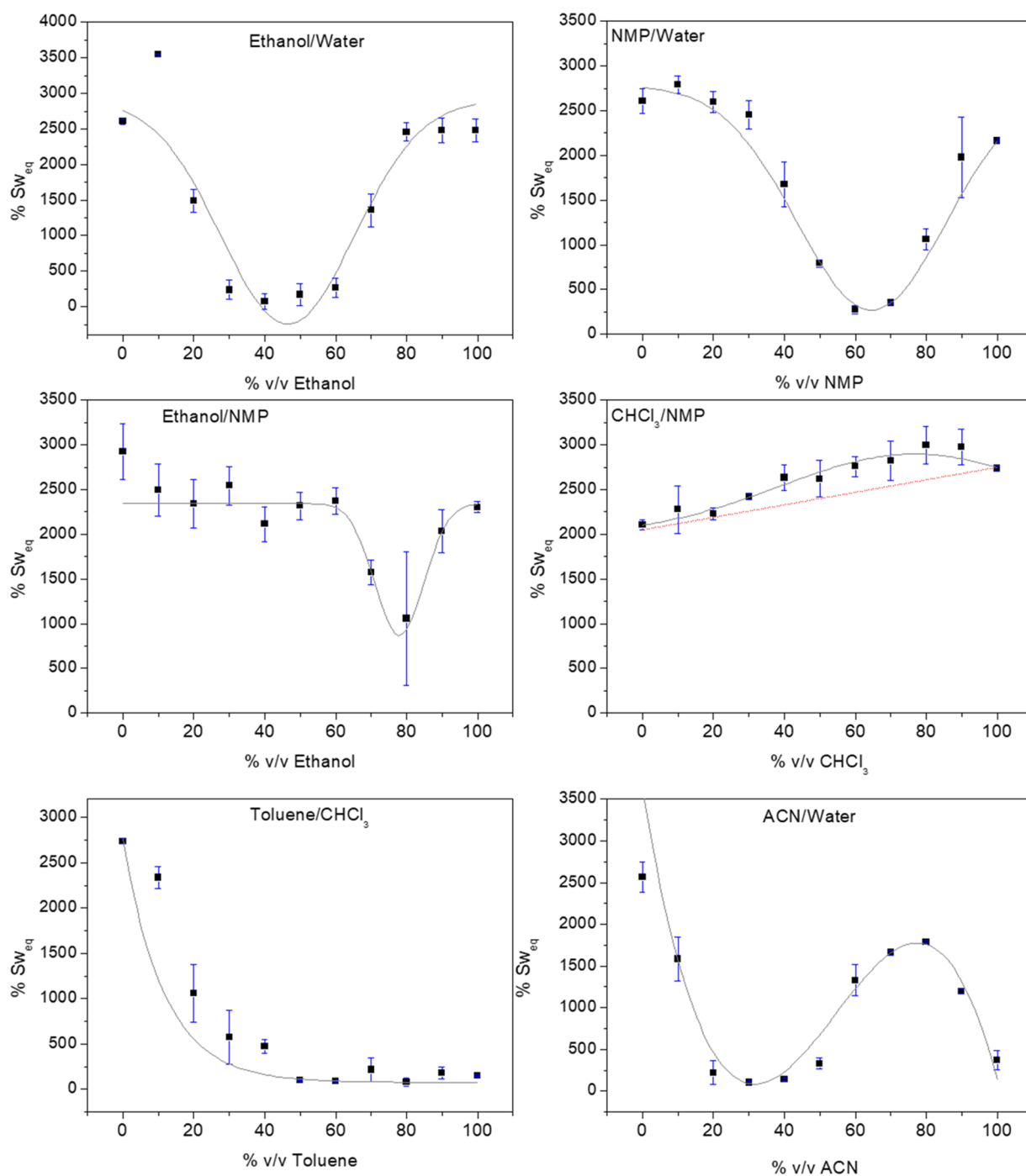


Figure 5. Percentual degree of swelling in equilibrium state for PNIPAM hydrogels at 20 °C in binary mixtures: ethanol/water, NMP/water, ethanol/NMP, CHCl₃/NMP, toluene/CHCl₃, and ACN/water. Square (■, experimental data) and full line (—, fitting).

Interestingly, the ethanol/NMP mixture shows a zone in which the hydrogel does not show significant changes in swelling (between 0 and 60% v/v). This result suggests that the preferential solvation does not exist in that system. However, at larger ethanol/NMP ratio, the swelling shows a minimum that resembles that of the ethanol/water mixtures.

A noteworthy result was observed for PNIPAM in ACN/water mixture, which shows two points of minimal swelling degree or multiple phase transitions, namely, the hydrogel shrinks at two different compositions: 34.6 and 100% v/v ACN/water. This result suggests two kinds of preferential

adsorption on the polymer chains, one acted by ACN and another by water.

For the CHCl₃/NMP system, it could be thought that the polymeric network does not show a co-nonsolvency effect; thus, the behavior of the mixture is almost as that of an ideal solvent (dash red line) and the swelling of the hydrogel increases with the proportion of the best solvent ($\% Sw_{PNIPAM/CHCl_3} > \% Sw_{PNIPAM/NMP}$). It is noteworthy that NMP is a hydrogen-bond acceptor (due to the presence of a $>C=O$ group), whereas CHCl₃ is a hydrogen-bond donor (due to the C–H bond polarized by the electron-withdrawing effect of the three chlorine atoms). Therefore, the solution of

CHCl_3/NMP likely contains associated hydrogen-bond pairs. It seems that PNIPAM could act as a hydrogen-bond acceptor (due to the $>\text{C}=\text{O}$ and $-\text{N}-\text{R}$ groups) and a hydrogen-bond donor (due to the presence of the $-\text{N}-\text{H}$ group), being able to interact in a similar way with both kinds of groups.

Regarding the toluene/ CHCl_3 mixture, the observed behavior was expected because the gel is swellable in chloroform ($\% \text{Sw}_{\text{eq}} = 2392$) but not in toluene ($\% \text{Sw}_{\text{eq}} = 0$). Therefore, $\% \text{Sw}_{\text{eq}}$ decreases when increasing the toluene fraction between 0% up to 60% v/v toluene/ CHCl_3 .

3.2.2. Ternary Mixtures. Six mixtures based on water, ethanol, and toluene were studied. Each mixture was chosen from the phase diagram to obtain miscible mixtures. It is noteworthy that the incorporation of ethanol allows miscible mixtures, whereas two phases are obtained in binary toluene/water solutions. The composition used in each one can be seen in Table 1.

Table 3 summarizes the degree of swelling in equilibrium (Sw_{eq}) for PNIPAM in each ternary mixture. It is possible to observe a maximum swelling when X_{water} is around 0.19.

Table 3. Swelling in Equilibrium (Sw_{eq}) for PNIPAM in Each Ternary Mixture

solvent mixture	Sw_{eq}^a
T1	8.87
T2	20.71
T3	23.30
T4	23.55
T5	24.74
T6	22.14

^aEach data is an average from three measured samples.

The possibility of swelling a hydrogel in water–ethanol–toluene mixtures makes it attractive to load molecules that are not soluble in more polar solvent (water) but soluble in the least polar component of the ternary mixture (toluene). The role of the ethanol is to interact both with water and ethanol, in a way similar to a surfactant. For small molecules, this is likely due to entropic effects, and we have been able to load small molecules. However, we were able to extend the capability to polymers. As a proof of concept, we have employed PS, which is not soluble in water or ethanol⁵⁸ (or ethanol–water binary mixture) but soluble in toluene. Because toluene cannot swell PNIPAM (see Figure 1), it could not be loaded into PNIPAM from pure solvents. Thus, we propose using the T5 mixture to load PS into the hydrogel. Figure 6A shows the optical photographs of PNIPAM after 24 h of swelling in T5 mixture (Figure 6A, left) and a PS/T5 dispersion at 0.75 mg/mL (Figure 6A, right). The photographs were taken after 120 s in contact with air. The presence of PS inside the polymeric network by the change in opacity of the hydrogel (transparent vs white) can be clearly seen when the matrix is taken out of the solution. When in contact with the air, the less interacting solvents evaporate and the PS is precipitated due to its low solubility in water and ethanol.

Moreover, the presence of PS inside the hydrogel was investigated by FTIR-ATR spectroscopy. Figure 6B shows the spectrum of PNIPAM swelled in T5 (gray line) and in the PS/T5 dispersion (black line) after vacuum drying. The apparition of one peak at 1736 cm^{-1} corresponding to the aromatic C–C bonds stretching vibration and two peaks between 1230–1180

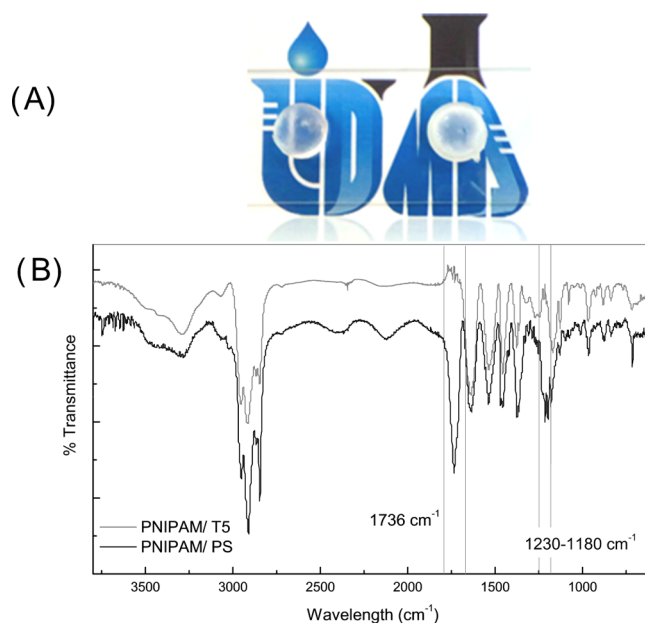


Figure 6. (A) Optical photographs of PNIPAM hydrogel swollen in T5 (left) and a dispersion of PS in T5 at 0.75 mg/mL (right). (B) ATR spectra of PNIPAM/T5 (gray line) and PNIPAM/PS (dispersion in T5) (line black).

cm^{-1} (aromatic C–H deformation) confirms the presence of PS inside the hydrogel.

Besides, the elastic modulus (E') of the PNIPAM hydrogel was compared with the E' of the PS–PNIPAM hydrogel (after the loading of PS inside the network). As it can be seen in Table 4, the E' was considerably increased (ca. 2.5 times) after

Table 4. Elastic Moduli (E') of PNIPAM Hydrogel Previously and after PS Interpenetration

sample	E' (kPa)
PNIPAM	1.135 ± 0.302
PNIPAM–PS	2.830 ± 0.505

the semi-interpenetration with PS, showing that the loading of polymers insoluble in water from nonaqueous solvents or its mixtures can be used as a postmodification technique to improve the mechanical properties of PNIPAM hydrogels.

3.3. Applications of the Amphiphilic Nature of PNIPAM. Hydrogels are materials with different technological applications related to their large swelling capacity in water, which exposes the polymer chains to the surrounding solution. The large swelling of PNIPAM in organic solvents (solvogels) could be used to exchange solvents or other molecules with organic media. However, we think that the ability of PNIPAM to swell both in water and in organic solvents (amphigels) could lead to more interesting applications because a substance can be loaded inside the gel either from water or organic solvent and then exposed to a solvent in which it is insoluble (organic solvent or water respectively) through the swelling of the gel. Therefore, we devise different systems as proof of concept of the different conditions.

3.3.1. pH Sensor in Chloroform. Methyl orange (MO) is an acid/base indicator soluble in water but insoluble in CHCl_3 in its acid form. It was loaded inside a PNIPAM gel from its aqueous solution (1 mM) by swelling until equilibrium a modified gel (PNIPAM–MO) was obtained. Then, the

PNIPAM-MO was dried and swollen in chloroform. The hydrogel swells in the solvent and the dye is not released to the external solution (Figure S1, Supporting Information). Then, the dried hydrogel MO was swollen either in acid (camphorsulfonic acid (CSA, 0.5% w/v)/CHCl₃) or basic (pyridine (1% v/v)/CHCl₃) solutions. In acid media (Figure 7A), it is observed that the dye retained in the HG-MO

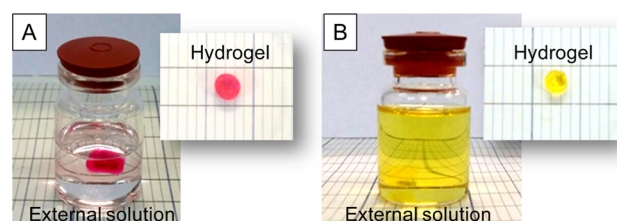
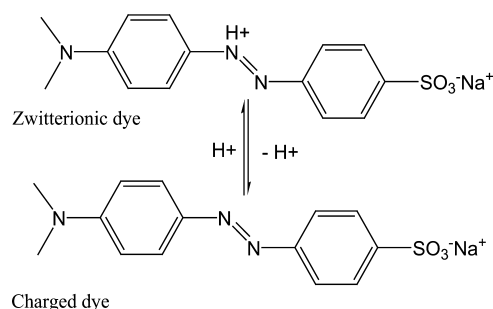


Figure 7. PNIPAM swelling in methyl orange (1 mM in water), drying, and reswelling in (A) camphorsulfonic acid 0.5% w/v in CHCl₃ and (B) pyridine at 1% v/v in CHCl₃.

becomes pink (color of the acid form⁵⁹). On the other hand, in basic solution, the pH indicator turns yellow (color of the basic form⁵⁹) and is released to the external solution (Figure 7B). It is important to note that a drying intermediate stage is necessary to remove the solvent and swell the gel in another solvent immiscible in the first. In a similar way, Bai and co-workers²⁷ have reported the encapsulation of hydrophilic nanoparticles and enzymes into hydrogel nanoparticles from swelling in water and then transfer them into organic media by solvent exchange with water-miscible organic solvents and water-immiscible solvents.

Although MO is insoluble in CHCl₃ in its red zwitterionic state present in acid (CSA) media (Scheme 2), it became soluble in its yellow ionic state (Scheme 2).

Scheme 2. Protonation/Deprotonation of MO



This system could be used as simple device to sense the acidity in organic solvents through changes in color. Swelling of the gel in the testing solution is required, or only the external layer dye will be changed.

3.3.2. Sensor of Copper Ions in Water. Bathocuproine (BC) is an organic ligand that forms a yellow complex with Cu¹⁺ with a stoichiometry of Cu(BC)₂¹⁺ and an absorption peak at 479 nm. PNIPAM was preloaded with BC (PNIPAM-BC) by swelling the dry gel in a BC solution (1 mM) in absolute ethanol. Then, it was dried and placed in Cu¹⁺ solution (1 mM) in water until swelling equilibrium is reached. In the optical photograph (Figure 8), it can be seen that the complex is retained in the polymeric gel structure (yellow) and the outer solution is colorless, suggesting the ligand is not released into the aqueous media. Moreover, this was

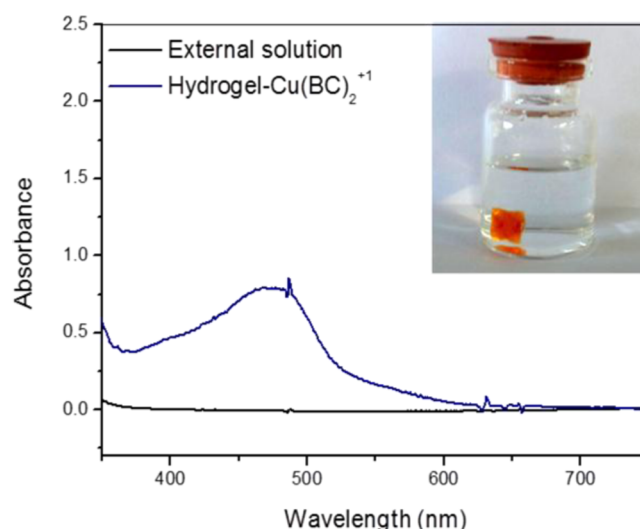


Figure 8. UV-vis spectrum measured inside the gel (PNIPAM-Cu(BC)₂¹⁺, blue line) and the outer solution (black line) at 20 °C.

corroborated by UV-vis spectroscopy (not shown), which shows that the absence of absorbance in the outer solution and inside the gel shows the characteristic absorption peak of Cu(BC)₂¹⁺.

To quantitatively determine the partition of Cu¹⁺ between PNIPAM-BC and water, the partition coefficients (C_p)^{3,45} were carried out. C_p is defined as the molal concentration of metal in the hydrogel ($[M^{n+}]_{\text{hydrogel}}$) relative to molality of metal in the solution ($[M^{n+}]_{\text{solution}}$), once an equilibrium is reached, in accordance with the next equation

$$C_p = \frac{[M^{n+}]_{\text{hydrogel}}}{[M^{n+}]_{\text{solution}}} \quad (5)$$

The partition coefficient of Cu¹⁺ ($C_p\text{Cu}^{1+}$) obtained employing the modified gel (PNIPAM-BC) is 30.2. Other hydrogels bearing anionic monomers, for example, 2-acrylamido-2-methylpropane-sulfonic acid, were studied. In these cases, the coefficients of partition calculated are bigger than PNIPAM (Table S1). In this case, the negative charges seem to interact with the metallic cations through electrostatic interaction.

The modified gel (PNIPAM-BC) acts as a good indicator of copper ions that should be present in the Cu¹⁺ form or converted in such species by reduction.

3.3.3. Asymmetric Photothermal Actuator Using a Biphasic Hydrogel. As can be seen above, PNIPAM gels can be swelled in water (hydrogel) and CHCl₃ (solvogel). Moreover, it is well known that PNIPAM is thermosensitive in water, that is, it suffers a phase transition with deswelling around 32–33 °C. Using differential scanning calorimetry (DSC) (Figure S2) and gravimetry, we observed that PNIPAM does not suffer phase transition in CHCl₃ in the accessible temperature range. However, because water and CHCl₃ are immiscible, they form a liquid/liquid interphase. A dry PNIPAM gel cylinder placed inside the biphasic should swell in each solvent independently, creating an immobilized liquid/liquid biphasic inside the gel. Although there are several possible applications of such a phenomenon, we use it to create an asymmetric actuator based in PNIPAM. A NIR dye (IR800), which is soluble in CHCl₃ and insoluble in water, was loaded only in the half cylinder region swelled by CHCl₃. The NIR dye absorbs light, which is then converted into heat. The

local heat could drive the phase transition of PNIPAM in water. The biphasic gel is dried and swollen in water. Then, the whole cylinder (Figure 9A top) was irradiated with a NIR lamp

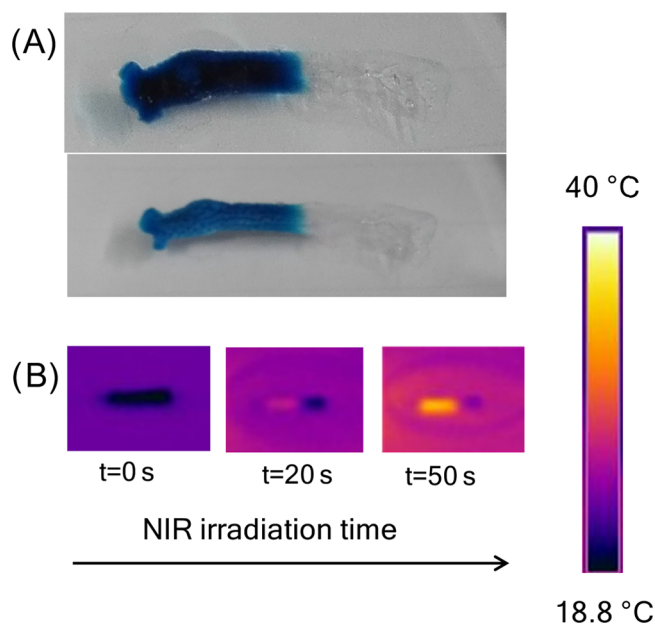


Figure 9. (A) Optical photographs of a biphasic hydrogel before and after 50 s of NIR irradiation. (B) Infrared photographs of a biphasic hydrogel at different time points during NIR irradiation.

until the volume collapse was observed (Figure 9A bottom). As can be seen in Figure 9B, only the region where the NIR dye is loaded showed an increase in temperature and the following collapse after 50 s of irradiation.

This behavior can be used in several applications like IR sensors,⁶⁰ drug-release devices triggered by NIR light,⁶¹ or drive complex movement in engineered hydrogels.⁶²

Although it was proven in macroscopic gel pieces, the principle could be applied in microscopic or even nanometric gel particles as far as they can be set in liquid/liquid interfaces. In that way, small sensors or actuators can be built.

4. CONCLUSIONS

PNIPAM networks are one of the most studied hydrogels for different applications because of drug delivery to sensors. Since they were first developed, several researches on their physicochemical characterization have been conducted. However, considering their hydrophilic nature, they show an important disadvantage at the moment of encapsulating hydrophobic drugs, which minimizes their use in other fields. Although there are some studies about the swelling capacity in solvent mixtures, in this work, we proved, for the first time, their ability to swell in different pure solvents from water to chloroform, allowing the material to be defined as an amphigel. Additionally, PNIPAM can swell in binary or ternary mixtures including solvents of low polarity like toluene. Because the same gel can be swollen in water and in organic solvents, the material can be defined as amphigels.

Using those properties, we devise different applications like acidity sensing in nonaqueous media, metal sensing in water, and an asymmetric photothermal actuator. In the latter, a liquid/liquid biphasic was immobilized inside the gel. The

observed effects could be applied in sensors/actuators devices and also in drug delivery systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpcb.8b07625.

Optical photographs of MO-loaded PNIPAM; Cu^{1+} partition coefficients for different hydrogels at 20 °C; DSC thermograms of PNIPAM in water and chloroform (PDF)

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Author Contributions

The manuscript was written through contributions of all the authors. All the authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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