Macromol. Symp. **2004**, *207,* 193-215

The Use of Hydrophobic Spacers in the Development of New Temperature- and pH-Sensitive Polymers

*A. Licea-Claveríe,**[1] *E. Rogel-Hernández,*[1,2] *R. Salgado-Rodríguez,*[1]
J. A. López-Sánchez,[1] *L. A. Castillo,*[1,2] *J. M. Cornejo-Bravo,*[2] *K.-F. Arndt*[3]

[1] Instituto Tecnológico de Tijuana, Centro de Graduados e Investigación, A.P. 1166, 22000 Tijuana, B.C., México
[2] Universidad Autónoma de Baja California, Facultad de Ciencias Químicas e Ingeniería, Calzada Universidad S/N, Mesa de Otay, 22300 Tijuana, B.C., México
[3] Technische Universität Dresden, Institut für Physikalische Chemie und Elektrochemie, D-01062 Dresden, Germany

Summary: The preparation and characterization of two series of methacrylic acid derivative polymers is described. One series contains aliphatic spacers with one to ten methylene units, while the other series includes an aromatic ring with changes in the position of the acid, as spacer. Both series of polymers were obtained as methoxy-ester protected acid polymers and as polymers containing free acid groups in different amounts. pH-sensitive gels and temperature-sensitive *N*-isopropylacrylamide (NIPAAm) copolymers were prepared by using some of the monomeric structures described. The pH of the swelling transition of the gels changed from 3.5 up to 9.0 as a function of the spacer length and type. The lower critical solution temperature (LCST) of NIPAAm copolymers in water was lowered from 33.6 °C to 6 °C as a function of the co-monomer content and type. The observed changes in the pH of the swelling transition of gels and in the LCST of NIPAAm copolymers can only be explained if hydrophobic-hydrophobic and hydrogen-bonding interactions are considered in connection with the specific chemical structure of the monomers used.

Introduction

Sensitive polymers and gels change their volume in dependence on the properties of the environment in them they are, mostly through a liquid. This volume change is reversible and can be continuous or discontinuous, depending on the chemical structure of the sensitive polymer or gel. Toyoichi Tanaka brought these materials to the attention of the public worldwide through his pioneering work on temperature sensitive *N*-Isopropylacrylamide (NIPAAm) polymers and copolymers, and on solvent sensitive acrylamide polymers.[1,2] The thermodynamics of the behavior of sensitive gels is qualitatively described by the Gibbs free energy of the system resulting from three main contributions: an elastic contribution, a mixing contribution, and an ionic contribution in the case of gels with ionizable groups.[3]

DOI: 10.1002/masy.200450318

As pointed out by Tanaka, there are other fundamental interactions that influence greatly the phase transition behavior of these materials, such as hydrophobic and hydrogen-bonding interactions.[4] These specific interactions are not included explicitly in most theories of phase-transitions or the swelling behavior of gels. Exceptions are the work by Saito *et al.*[5] which includes a term dealing with the hydrophobic contribution of isopropyl groups of NIPAAm to the temperature driven phase transition of that polymer gel, and the work by Prausnitz *et al.*[6] dealing with hydrogen-bonding as the main factor to explain the behavior of temperature driven phase-transitions.

For pH-sensitive polymers a similar case is found: no explicit terms are provided for hydrophobic interactions or for hydrogen-bonding interactions affecting the pH-driven phase transition of gels. However, hydrophobic interactions could be implicitly considered through changes in the Flory-Huggins χ-parameter. For example, in the model published by Peppas *et al.*[7] for pH-sensitive gels, it is predicted that through changes in χ from 0.1 to 0.9 the equilibrium swelling degree of the gel is changed in the non-ionized state, while the pH for the swelling transition remains the same. The same model predicts that changes in the pK_a of the acid groups of the gel at constant χ results in changes in the pH of the swelling transition. According to experimental results the former is not correct. For example, Siegel *et al.*[8,9] reported a shift to lower values of the pH of the swelling transition for polybasic gels of *N,N'* dimethylaminoethylmethacrylate (DMAEM) when hydrophobic co-monomers of n-alkylmethacrylates are introduced. Khokhlov *et al*[10] later reported a shift to higher values in the pH of swelling transition in the case of hydrophobically modified polyacrylic acid gels. Although a change of the pK_a as a result of the more hydrophobic environment was considered, from both works it can be concluded that the main factor is additional hydrophobic attractive forces opposing the electrostatic repulsion forces.

The role of hydrogen-bonding interactions is most likely to be observed in amphoteric hydrogels, since they usually combine acid groups with basic groups in their structure. In fact, Tanaka *et al.*[11] reported in their study of amphoteric hydrogels that multiple equilibrium states for the same system in the same pH-value were observed, and they suggested that additional hydrogen-bonding forces can play an important role in that behavior. Since the chemical structure of NIPAAm includes a secondary amine group capable of hydrogen bonding interactions, there is also a possibility that such interactions play an important role in the behavior of NIPAAm-copolymeric gels in addition to the well documented mixing, elastic and ionic contributions. Interestingly, T. Tanaka *et al.*[12] reported hydrogen-bonding as the driving force for phase transition in the case of polyacrylamide-poly(acrylic acid) interpenetrating networks (IPN's) but not in NIPAAm copolymers whose chemical structure is very similar.

The goal of our work is to contribute to the understanding of, and to quantify the role of hydrophobic spacer groups of controlled hydrophobicity to the behavior of both pH-sensitive and temperature sensitive polymers. Furthermore, through protecting-deprotecting synthetic strategies, we study the role of hydrogen-bonding on the behavior of temperature sensitive NIPAAm copolymers.

Experimental

Reagents and Solvents

All chemicals and solvents used in the synthetic procedures were obtained either by Aldrich Chemicals, or by Productos Químicos Monterrey and were used as received. The only exceptions were the following: 2-hydroxybenzoic acid, 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, 4-hydroxyphenylacetic acid and methyl 4-hydroxybenzoate were obtained by Acros Organics and were used as received. 2,2'-Azobisisobutyronitrile (AIBN, Aldrich) was purified by re-crystallization from methanol. *N*-isopropylacrylamide (NIPAAm, Aldrich) was re-crystallized from hexane. Ethyleneglycoldimethacrylate (EGDMA, Aldrich), was purified by passing it through a column of inhibitor-remover for hydroquinones and paramethoxyphenol (Aldrich). Pyridine (Aldrich, anhydrous) and 4-dioxane (Spectrum, HPLC-grade) were further dried by using molecular sieves followed by distillation. THF (Spectrum, HPLC-grade), was dried by using sodium/benzophenone followed by distillation.

Synthesis of monomers

Several methoxy-protected methacrylic acid derivatives with hydrophobic spacer groups (Figure 1) were synthesized through esterification reactions by one of the following two different synthetic routes: reaction of methacrylic anhydride with corresponding hydroxy-esters or reaction of potassium methacrylate with corresponding bromo-esters. Details on the synthetic routes used can be found elsewhere,[13] the schematic description of each route is given in Figure 2.

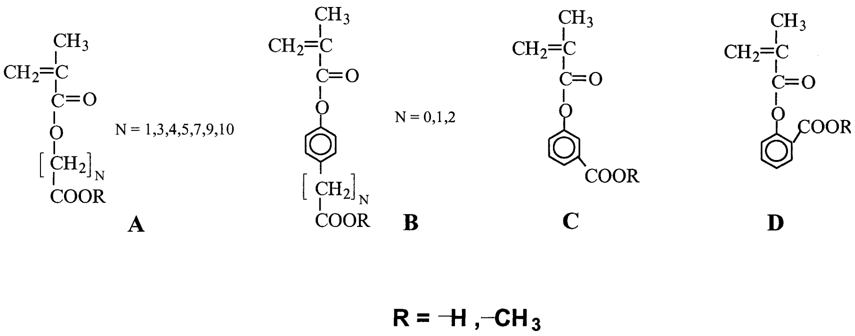


Figure 1. Structures of methacrylic acid derivatives with hydrophobic spacers: A-aliphatic, B-aliphatic-aromatic, C-aromatic and D-aromatic.

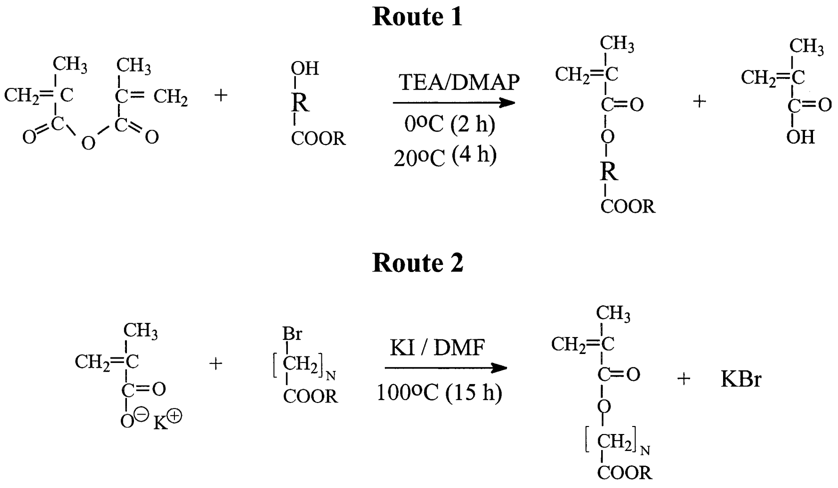


Figure 2. Synthetic routes used for the preparation of methacrylic acid derivatives with hydrophobic spacer groups.

By a slight modification of the synthesis route #1, methacrylic acid derivatives with aromatic spacers and free acid groups were also prepared (monomers B-0, B-1, C and D). As an example we describe the synthesis of the monomer 2-methacryloyloxy benzoic acid (D):

> At 0 °C, 7.5 g (50 mmol) of methacrylic anhydride was added to a solution of 6.91 g (50 mmol) 2-hydroxybenzoic acid and 0.49 g (4 mmol) dimethylaminopyridine in 8.42 mL triethylamine and 20 mL dichloromethane. The solution was stirred for 5h at 0 °C followed by stirring overnight at room temperature. The solution was partitioned between dichloromethane and a HCl solution (3N, 4 x 25 mL), and the organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue after evaporation was chromatographed on silica gel, 200-400 mesh (eluent: petroleum ether/ether 70:30). The product was a white solid.

Methacrylic acid derivatives with aliphatic spacers and free acid groups (monomers A-4, A-7 and A-10) were prepared by deprotection reaction of the prepared methoxy-protected monomers with aliphatic spacers. As an example we describe the synthesis of 11-methacryloyloxyundecanoic acid (A-10):

> To a refluxing solution of 6.16 g (50 mmol) of dry LiI in 50 mL of anhydrous pyridine, 3.31 g (11.65 mmol) of methoxy-11-methacryloyloxyundecanoate (protected A-10) and 0.96 g (11.7 mmol) of sodium acetate were added under nitrogen. Refluxing was continued for 24 h. The solution was then cooled and the solvent removed under vacuum. The residue was dissolved in 20 mL water. Then this solution was acidified to pH=2 by using 6N HCl. The acid solution was extracted with diethylether (3 x 30 mL), and the organic extracts were dried with magnesium sulfate, with the solvent evaporating under reduced pressure. The product was purified by chromatography on silica gel, 70-230 mesh (eluent petroleum ether:diethylether, 70:30).

Synthesis of polymers with aliphatic spacers

Two series of polymers with aliphatic spacers were synthesized, one with methoxy-protected acid groups through solution free radical polymerization of the synthesized A-monomers and the second with free acid groups through selective saponification reactions of the former polymers. Details on the preparation and saponification are reported in our previous paper.[13]

Synthesis of polymers with aromatic and aliphatic-aromatic spacers

Two series of polymers with aromatic spacers were synthesized, one with methoxy-protected acid groups and the second with free acid groups. As an example of the polymerization of monomers with protected acid groups (protected monomers B-0, B-1, B-2, C and D) we describe the synthesis of poly(methyl-methacryloyloxysalicylate) (PolyD):

> 2.86 g (13 mmol) of methylmethacryloyloxysalicylate (protected monomer D) and 21.3 mg (1 mol%) of AIBN were placed in an Schlenk-flask. Dry THF (15 mL) was then added and stirred under cooling until complete dissolution. The Schlenk-flask was degassed at –40 °C and was purged with argon at least five times by conventional freeze-thaw techniques prior to sealing. The polymerization was run at 60 °C for 72 h to allow maximum yield. After polymerization, the polymer was precipitated into a large excess of petroleum ether. The polymer was purified by re-dissolving it in THF and by precipitating it again in petroleum ether. The polymer was then dried in vacuum for 24 h. The polymerization of the monomers with free acid groups (non protected B-0, B-1, C and D) was performed following the same procedure as described above with the following changes: the solvent used was dry 4-dioxane, the polymerization temperature was 70 °C and the polymer products obtained were purified by re-dissolving in 4-dioxane and precipitation in petroleum ether. These polymers were dried in vacuum for only 8 h, but at 50 °C.

Preparation of pH-sensitive Gels

Two series of gels with free acid groups were obtained, one with aliphatic spacers through selective saponification reactions on methoxy-protected acid gels (two steps), and the second series with aromatic spacer groups, directly from the monomers with free acid groups (one step). As an example of the two-step strategy for the preparation of gels with free acid groups of monomers A-1, A-3, A-5, A-9 and A-10, we describe in detail the preparation of the gel from methacryloyloxyacetic acid (A-1):

In a round bottom flask, 2 g (12.66 mmol) of methyl-methacryloyloxyethanoate (protected A-1), 48.72 μL (0.26 mmol) of EGDMA and 21 mg (0.13 mmol, 1 mol%) of AIBN, were dissolved in 3 mL of dry THF. The flask was degassed at –40 °C and was purged with argon at least five times by conventional freeze-thaw techniques prior to sealing with a rubber septum. The solution was transferred using a syringe to a system consisting of two silanized glass plates (10 x 10 cm), separated by a silicone gasket (2 mm in diameter), held together by metal clamps. The assembly was placed in the vertical position in an oven for 24 h at 60 °C, allowing formation of a gel. After cooling at room temperature, the glass plates were separated and the residual solvent was allowed to evaporate. From the gel-sheet obtained, discs were cut (3.75 mm diameter). The gel-discs were washed with THF for 72 h, changing solvent every 4 h. Then the gel-discs were taken out of the solvent, allowed to dry in air for 48 h and finally in vacuum at room temperature for 24 h. For the deprotection reaction 0.6 g of dry gel discs were allowed to swell in dry pyridine, then the gel-discs and 0.3 g (3.8 mmol) of sodium acetate were transferred to a refluxing solution of 2.5 g (18.5 mmol) of LiI in 30 mL of dry pyridine. The mixture was refluxed under argon for 18 h. After cooling, the solution was decanted and the gel discs were washed with THF/water mixtures of the following composition in sequential manner: 100/0, 75/25, 50/50, 25/75, 0/100. Each washing step took 24 h. Afterwards the gel-discs were contracted by THF/water mixtures by using the reverse sequence. The gel discs were finally allowed to dry in air for 48 h and under vacuum for additional 24 h at room temperature.

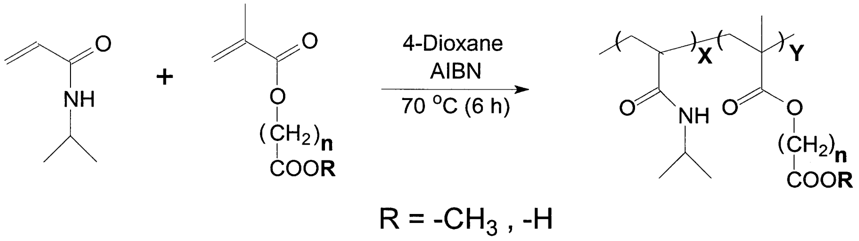
As an example of the preparation of gels with aromatic spacers and free acid groups in one step (from monomers B-0, C and D) we describe in detail the preparation of gel of 2-methacryloyloxybenzoic acid (non protected monomer D):

In a round bottom flask, 2 g of 2-methacryloyloxybenzoic acid (9.7 mmol), 37.5 μL (0.2 mmol)) of EGDMA and 21 mg (0.13 mmol) of AIBN, were dissolved in a mixture of 4 mL of dry THF and 3 mL of dry dichloromethane. The flask was degassed at –40 °C and was purged with argon at least five times by conventional freeze-thaw techniques prior to sealing with a rubber septum. The solution was transferred using a syringe to the system consisting of two silanized glass plates, separated by a silicone gasket described above. The assembly was placed in vertical position in an oven for 24 h at 60 °C, allowing a gel to form. After cooling at room temperature, the glass plates were separated and the residual solvent was allowed to evaporate. From the gel-sheet obtained, discs were cut (4.45 mm diameter). The gel-discs were washed with THF for 72 h changing solvent every 4 h. Then the gel-discs were taken out of the solvent, allowed to dry in air for 48 h and finally in vacuum at room temperature for 24 h. For the preparation of the gel of 3-methacryloyloxybenzoic acid (unprotected monomer C) and the gel of 4-methacryloyloxybenzoic acid (unprotected monomer B-0), the same procedure was used, except that the solvents used were THF (3 mL) and 4-dioxane (6 mL) respectively. In both cases the discs cut from the gel-sheets obtained were larger (8.53 mm diameter).

Synthesis of NIPAAm Copolymers

Two series of NIPAAm copolymers with aliphatic spacer groups were obtained, one with protected acid groups and the other with free acid groups. For these the monomers A-4, A-7 and A-10 were used in several ratios to NIPAAm (Figure 3). As an example of the procedure we describe in detail the preparation of the copolymer of NIPAAm with 5 mol% of 5-methacryloyloxy pentanoic acid (non protected monomer A-4):

3.33 g (29.45 mmol) of NIPAAm, 0.29 g (1.55 mmol) of 5-methacryloyloxy pentanoic acid (non protected monomer A-4) and 15.3 mg (0.3 mol%) of AIBN were placed in an Schlenk-flask. Dry 4-Dioxane (10.5 mL) was then added and stirred under cooling until complete dissolution. The Schlenk-flask was degassed at –40 °C and was purged with nitrogen at least three times by conventional freeze-thaw techniques prior to sealing. The copolymerization was run at 70 °C for 6 h. After copolymerization, the product was precipitated into a large excess of diethylether. The copolymer was purified by re-dissolving it in THF and precipitating it again in diethylether. The copolymer was finally dried in vacuum at 40 °C for 24 h. Both series of copolymers were prepared by using the same procedure, although in some cases (the copolymers with higher content on hydrophobic co-monomers with free acid groups), hot THF was needed in the purification step.



Feed-Composition of Methoxy-protected Copolymers					Feed-Composition of Copolymers with free acid-groups				
X [mol%]	Y [mol%]	n=4	n=7	n=10	X [mol%]	Y [mol%]	n=4	n=7	n=10
95	5	✓	✓	✓	95	5	✓	✓	✓
90	10	✓	✓	✓	90	10	✓	✓	✓
85	15	✓	✓	✓	85	15	✓	✓	✓
80	20	✓	-	-	80	20	✓	-	-

Figure 3. Copolymerization of NIPAAm with methacrylic acid derivatives having aliphatic spacer groups.

Characterization of polymers and copolymers

The methacrylic acid derivative monomers with hydrophobic spacers were characterized by ^{1}H-NMR (200 MHz) spectra recorded in deuterated chloroform ($CDCl_3$) solution on a Varian Gemini 200 spectrometer at room temperature. ^{1}H-NMR-spectra of the protected polymers were obtained on a Varian Gemini 200 spectrometer (200 MHz) (acetone d_6, room temperature) or on a Bruker RDV500 spectrometer (500 MHz) ($CDCl_3$, room temperature). The deprotected polymers (with free acid groups) were characterized by the same NMR-techniques, using either deuterated methanol (methyl-d_3-alcohol-d) or deuterated dimethylsulfoxide (di-methyld_3 sulfoxide) as solvent. The ^{1}H-NMR-spectra of NIPAAm-copolymers with protected acid groups were obtained by the same NMR-techniques using $CDCl_3$ at room temperature and those of NIPAAm-copolymers with free acid groups were obtained using deuterated methanol (methyl-d_3-alcohol-d) at room temperature.

The glass transition temperatures (T_g's) of the polymers and NIPAAm-copolymers were determined using a Mettler DSC-30 calorimeter, at a heating rate of 10 K/min, the only exception being the polymers with aromatic spacers and free acid groups whose T_g's were determined by using a MDSC from TA-Instruments (2920) at a heating rate of 5 K/min using a modulation of 1 K every 60 s. The weight-average molecular weights (Mw) and molecular dimensions ($<r^2>$) were measured by static light scattering (SLS) using an SLS 2-goniometer (SLS-Systemtechnik, Germany). The measurements were performed with a He-Ne laser (λ_o = 632.6 nm) in the angular range 30° - 145° (in 5° steps). The refractive index increment (dn/dc) in the given solvent needed for the evaluation of the light scattering results were measured using a DR-1 differential refractometer (SLS-Systemtechnik, Germany). Measurements were made at 25 °C in acetone (protected polymers with aliphatic spacers), THF (protected polymers with aromatic spacers and NIPAAm-copolymers) and methanol (deprotected polymers with aliphatic spacers and some NIPAAm-copolymers). The deprotected polymers with aromatic spacers were evaluated by solution viscosity in THF at 25 °C by using Ubbelohde-Viscometers. The molecular weights reported were calculated by using the Kuhn-Mark-Houwink constant values reported for polymethylmethacrylate.[14]

Solution behavior of polymers and copolymers

Potentiometric Titrations

Potentiometric titrations were performed on aqueous polymer solutions to study the polyelectrolytic behavior of the methacrylic acid derivative polymers with free acid groups. In order to diminish ionic strength variations during the titration experiments, polymer solutions (0.01 N) were prepared using an aqueous 0.1 N NaCl-solution as solvent. The pH of the polymer solution was adjusted to pH = 11 by adding appropriate amounts of a 0.1 N NaOH-solution. The titration experiments were performed starting with 25 mL of a given polymer solution and adding 0.1 N HCl in 0.1 mL steps under stirring. The measurements were performed at 25°C under argon atmosphere and pH was monitored using a Corning pH meter 430. The pH-value was recorded only after it remains constant (about 10 min after each acid addition). Every polymer solution becomes turbid at different pH-values; nevertheless, the titration was continued until the pH of the solutions reached a fairly acid value (pH≈2.2).

Determination of the lower critical solution temperature (LCST)

Aqueous solutions (pure water and buffer of pH=8) of PolyNIPAAm and NIPAAm-copolymers were prepared at a concentration of 5 mg/mL. For some of the copolymers prepared, cooling at 5 °C was needed to allow dissolution. The solutions were prepared and were stored in a refrigerator at 4 °C until measurement. The LCST was evaluated by modulated differential scanning calorimetry (MDSC) using the endothermic peak observed by heating according to [15]. The equipment used was a MDSC from TA-Instruments (2920) at a heating rate of 2 K/min using a modulation of 1 K every 60 s.

pH-dependent swelling experiments

Eleven phosphate-buffered solutions with adjusted ionic strength (0.15 M) having nominal pH values from 2 to 12 were prepared. The exact pH value was measured using a Corning pH meter 430. Preweighed dry gel-discs were placed in 11 vials, to each of which 15 mL of a particular buffer solution was added, and the gel-discs were allowed to swell for 24 h. Afterwards the buffer-solutions were replaced and the gel-discs allowed to stand in the fresh solutions for an additional 24 h. Finally the swelled gel-discs were taken out from the buffer-solutions, the excess liquid tapped out by using filter paper, and were weighed. The gel swelling, as water sorption capacity was evaluated according to following equation:

$$\%H = (W_s - W_d)/W_d \qquad (1)$$

where W_s is the weight of the swollen gel and W_d is the weight of the dry gel. All swelling experiments were performed in triplicate and the average values (e.g. %H) were taken.

Results and Discussion

pH-sensitive polymers and gels

The preparation of methoxy protected polymers with hydrophobic spacers, aliphatic and aromatic, was straightforward although polymerization times of 72 h were used as needed to obtain reasonable polymerization yields for the monomers with long aliphatic spacer chains (A-5, A-7, A-9 and A-10). Table 1 shows the main characterization parameters for these polymers.

Table 1. Main characterization parameters of methoxy-protected polymers

NAME	Yield [%]	M_w [g mol^{-1}]	$<r^2>$ [nm]	T_g [°C]
Polymers with aliphatic spacers				
PolyA-1	~100	119 000	18	50
PolyA-3	91	68 500	17	-06
PolyA-4	76	74 700	6.5	-24.7
PolyA-5	65	96 000	19	-41
PolyA-7	36	78 100	15	-
PolyA-9	50	99 000	20	-49
PolyA-10	65	84 200	20	-46
Polymers with aromatic and aliphatic spacers				
PolyB-0	88	54 200	7.5	96
PolyB-1	~100	189 000	21	81
PolyB-2	76	90 100	20	68
PolyC	69	67 600	18	72
PolyD	40	70 500	16	64

Most of the polymerization yields and the molecular weights obtained were acceptable. The glass transition temperatures show that with higher number of methylene units in the spacer chain the T_g value is lower. This is not surprising since the methylene chains are flexible and bring increased flexibility to the whole polymer structure. This effect was also observed for the polymers with aromatic spacers when methylene units were included (PolyB-1 and PolyB-2 as compared with PolyB-0). As a consequence these methoxy protected polymers at room temperature range from viscous liquids (PolyA-5 to PolyA-10) to hard powders (PolyA-1 and all polymers including aromatic spacers).

Table 2 summarizes the results obtained in the preparation of polymers with free acid groups. The results depend on the different synthetic strategies used. Polymers with aliphatic spacers and free acid groups were obtained through selective saponification on the preformed methoxy protected polymers, while the polymers including aromatic spacer units were obtained through polymerization of monomers having already free acid groups. By the first described strategy free acid groups in moderate to high yields were obtained (50 to 80%) but complete conversion was not achieved. The so obtained polymers are hydrophobic polyelectrolytes soluble in weak basic aqueous solutions.[13] For the polymers obtained from monomers having already free acid groups, the polymerization route was not very effective as can be seen by the generally lower molecular weights obtained as compared with the polymers with aliphatic spacers (Table 2, lower rows).

Table 2. Main characterization parameters of polymers with free acid groups

NAME	Content on free acid groups [% of units]	M_w [g mol^{-1}]	T_g [°C]
Polymers with aliphatic spacers			
PolyDA-1	81	72 600	116
PolyDA-3	80	43 000	78
PolyDA-5	51	79 300	-18
PolyDA-9	51	90 000	-26
PolyDA-10	54	45 800	-26
Polymers with aromatic and aliphatic spacers			
PolyDB-0	100	19 000*	107
PolyDB-1	100	34 000*	-
PolyDC	100	20 000*	116
PolyDD	100	23 000*	130

* By Solution Viscosity measurements

Nevertheless, the advantage of these polymers is that they have only units with free acid groups and are polyelectrolytes in nature. We are working currently to develop new synthetic strategies that allow the preparation of A-1 to A-10 monomers with free acid groups and high yields. The T_g values obtained for the polymers with aliphatic spacers and free acid groups show the expected tendency: the longer the methylene spacer groups the lower the T_g is. However, in comparison with the starting methoxy protected polymers, the T_g is always higher indicating polymer-polymer hydrogen-bonding in the solid state through the presence of free acid groups, which are absent in the methoxy-protected polymers. The T_g values for the polymers with aromatic spacers and free acid groups are also higher than the values for methoxy protected similar polymers. Interestingly, the position of the acid group (or methoxy ester group) in the aromatic spacer ring results in considerable changes in the T_g values (compare the lower parts of Tables 1 and 2, last row). We will discuss this issue further when we compare gel behaviors.

The swelling behavior of gels, prepared from methacrylic acid derivatives and aliphatic spacers that include free acid groups by using the deprotection strategy, is shown in Figure 4. Error-bars are drawn and are in most cases smaller than the symbols used in the figure. All those gels show a swelling transition at different pH values of the surrounding solution. This transition depends clearly on the spacer groups of the gel: the longer the aliphatic spacer, the higher the pH needed for the swelling transition. The maximum swelling attained is lower for the gels with longer aliphatic spacer chains, with the exception of GelDA-5. Although all these gels have free carboxylic acid groups, the hydrophobic aliphatic spacers influence their behavior so far that the gels with deprotected A-1, A-3 and A-5 units swell in weak acid solutions while the gels with deprotected A-9 and A-10 units swell in weak basic solutions.

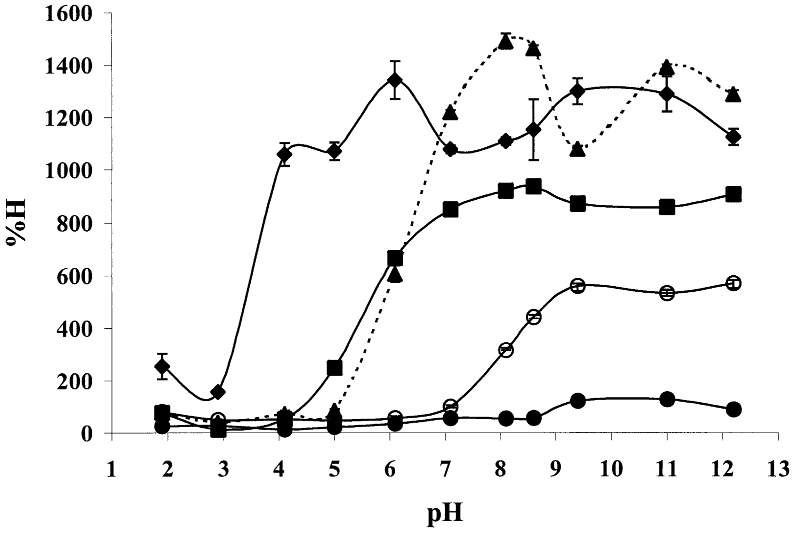


Figure 4. pH-dependent swelling behavior of Gels with aliphatic spacers: ◆ is GelDA-1, ■ is GelDA-3 , ▲ is GelDA-5, O is GelDA-9 and ● is GelDA-10.

As pointed out by Khokhlov *et al.*[10] the shift of the pH of the swelling transition to higher values for gels including weak acid groups and some hydrophobic units may have two origins:

1) the decrease of the dissociation constant in the vicinity of hydrophobic units (pK_a shift), or 2) the formation of hydrophobic micro-domains in the collapsed state acting as

additional crosslinks and opposing the gel swelling. Table 3 compares the values of the pH of the swelling transition and the apparent acidity constant at 50% ionization for the parent linear polymers as evaluated by potentiometric titration experiments and calculated using the Henderson-Hasselbach equation [16] at $\alpha = 0.5$.

$$pKa = pH + \log\frac{1-\alpha}{\alpha} \tag{2}$$

Table 3. Swelling characteristics of partially hydrophobic pH-sensitive gels

NAME	Maximum swelling (%H)	pH of swelling transition	Apparent pK_a (α=0.5) of linear polymers
Gels with aliphatic spacers			
GelDA-1	1325	3.5	3.8*
GelDA-3	939	5.5	5.8*
GelDA-5	1490	6.4	6.3*
GelDA-9	565	8.1	7.1*
GelDA-10	125	9.0	7.3*
Gels with aromatic spacers			
GelDB-0	203.5	6.5	5.3
GelDC	221	7.5	5.5
GelDD	4432	8.3	5.8

* From Reference [13]

For gels with 1, 3 and 5 methylene units as spacers, the pK_a of the linear polymers corresponds very well with the observed pH of the gel-swelling transition. This suggests that indeed the acidity constant of the acid groups is lowered (pK_a is increased) due to the hydrophobicity of the environment provided by the spacers. For gels with 9 and 10 methylene units as spacers the pK_a's of the linear polymers do not correspond exactly to the observed pH's of the swelling transitions, suggesting that the long aliphatic chains not only induce a pK_a shift, but they also create micro-domains with strong hydrophobic-hydrophobic interactions. These interactions would act as additional forces opposing to the gel swelling. The result is that an ionization degree greater than 50% of the carboxylic acid units is required to overcome the additional hydrophobic-hydrophobic interactions.

The behavior of the gels with aromatic spacers, differing only in the position of the free carboxylic acid group (ortho, meta or para) was somewhat surprising. Considering the

pK_a values reported for low molecular weight analogs such as methyl benzoic acid, which show pK_a values of 3.91, 4.27 and 4.38 for ortho, meta and para, respectively,[17] we would expect only slight differences in the pH dependent swelling behavior of this gels. Furthermore, the apparent pK_a values from the potentiometric titration experiments of the linear polymers showed differences in the pK_a of only 0.5 pH-units between them, however in a reverse sequence than the low molecular weight compounds (see Table 3, last row).

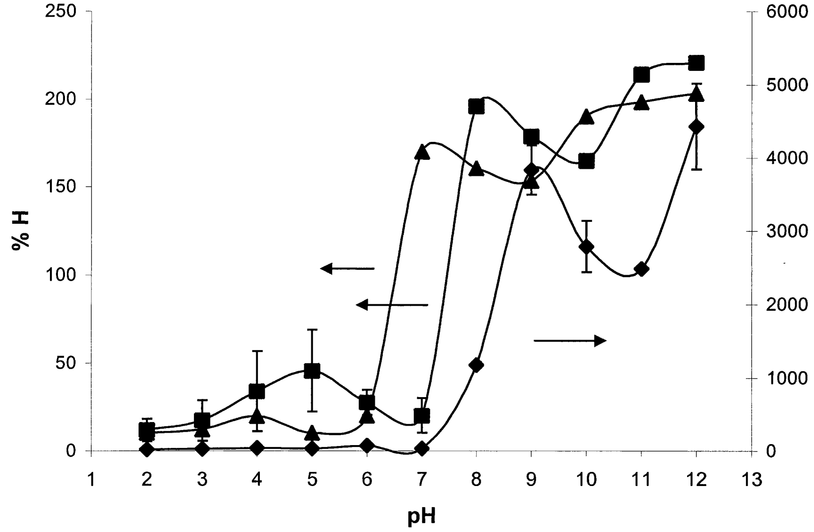


Figure 5. pH-dependent swelling behavior of Gels with aromatic spacers: ▲ is GelDB-0 (para), ■ is GelDC (meta) and ◆ is GelDD (ortho).

Nevertheless, the gel swelling behavior seen in Figure 5 shows that the pH of the swelling transitions varied by almost 2 pH units (error-bars are drawn and are in many cases smaller than the symbols used in the figure). In accordance with our discussion above on gels with aliphatic spacers, and comparing with the values in Table 3, we must conclude that the observed pH values of the swelling transition did not arise from differences in the acidity constant of the carboxylic acid units. Moreover, explaining differences in terms of a more or less "hydrophobic" environment does not seem appropriate. We suggest that the differences observed may arise from the magnitude of hydrogen-bonding interactions resulting from the different positions of the carboxylic acid group in the aromatic ring used as spacer.

Returning to Table 2 and comparing the T_g values for the parent linear polymers, we find the tendency ortho>meta>para. This suggests that polymer-polymer interactions in these otherwise similar polymers, all having free acid groups in 100% of units and molecular weights also similar, are mediated by hydrogen bonds, which strongest when the aromatic sidechains are ortho, followed by meta and para. In the literature we have found one example showing this same trend: the work by J. San Roman *et al.*[18] on methacrylamide polymers with salicylic acids moieties. Those authors reported a T_g value 30 °C higher for the meta (carboxylic acid) substituted polymer compared to the para substituted polymer and discussed their results in terms of stronger hydrogen-bonding interactions in the former polymer. If there are stronger hydrogen-bonding interactions in the ortho structure (deprotected monomer D) than in the meta structure (deprotected monomer C) and these two interactions are stronger than for the para structure (deprotected monomer B-0), then the behavior of the gels prepared from them can be explained as follows: In the collapsed, non-ionized, state the polymer chains have strong hydrogen-bonding interactions in addition to the constraints imposed by the crosslink sites. As soon as the pH of the solution is raised, some ionization of the carboxylic acid groups is achieved and the gels swell accordingly. When 50% of the carboxylic groups are ionized, there is still not enough free energy in the system to overcome the strong hydrogen bonding from the non-ionized groups. The gels do swell but not to a high extent. The pH of the swelling transition therefore does not depend alone on the acidity constant of the polymeric acid groups (apparent pK_a) but also depends on the strong hydrogen-bonding interactions in this kind of polymer chain. Further ionization is needed to overcome these hydrogen-bonding interactions to allow a high swelling degree of these gels.

In summary, in the partial hydrophobic gels prepared we have found three cases:

1. The pH of the swelling transition is shifted to higher values than expected due to a shift in the acidity constant resulting from the more hydrophobic environment imposed by the spacer groups (GelDA-1, GelDA-3 and GelDA-5).

2.- The pH of the swelling transition is shifted to higher values than expected, due partially to a shift in the acidity constant resulting from the more hydrophobic environment imposed by the spacer groups, but also due to hydrophobic-hydrophobic interactions opposing the gel swelling predicted by ionization only (GelDA-9 and GelDA-10).

3. The swelling transition is shifted to higher values than expected due to strong hydrogen-bonding interactions opposing the gel swelling predicted by ionization only (GelDB-0, GelDC and GelDD).

Temperature-sensitive copolymers

As seen in Table 4, the composition of the NIPAAm copolymers prepared is in good agreement with the monomer feed composition. The molecular weights are in all cases fairly high and no special trend was observed during the copolymerization procedure. The glass transition temperature (T_g in Table 4 last row) show the expected trend: since the methacrylic acid derivative co-monomers have flexible methylene chains as spacer groups, the higher the co-monomer content, the lower the T_g . This trend is more pronounced in the copolymers with co-monomer A-10, both protected and deprotected. A content of 11.3% of this co-monomer in NIPPAm copolymer resulted in a drop in T_g of 39 ^{o}C. A careful comparison of T_g values for copolymers of similar composition but differing in that one has free acid groups while the other has methoxy protected acid groups, e.g. CoA-10(15) compared with CoDA-10(15), shows that the copolymers with free acid groups always have higher T_g values. This could result from additional hydrogen-bonding interactions in the solid state due to the carboxylic acid groups present in this NIPAAm copolymer series (bottom part of Table 4).

For the copolymer series with methoxy protected acid groups, the solution behavior in pure water corresponds well with the results reported by other researchers[15]: The more hydrophobic the NIPAAm copolymer, e.g. the higher the content of hydrophobic co-monomer, the lower the LCST (Figure 6, solid lines). By deprotecting the acid groups we expected, as generally believed, a less hydrophobic co-monomer structure. Therefore, the hydrophobic effect of the comonomer on the NIPAAm-based coplymer should be weaker. Contrary to the expectation, the LCST of the series of NIPAAm copolymers with comonomers having free acid groups and the same hydrophobic spacers as the protected ones, were found at much lower temperatures (Figure 6, dashed lines). Thinking only in terms of hydrophobicity, this would mean that these copolymers behave more hydrophobically in pure water than do the copolymers with methoxy protected acid groups. As pointed out by H.G. Schild in his review on NIPAAm,[15] there dispute in the literature whether hydrophobic effects or hydrogen-bonding is the main factor responsible for the LCST behavior of polyNIPAAm in particular and of biological polymers in general, in water. In our case, an explanation for this behavior can be found if we consider that carboxylic acid groups could form hydrogen-bonds with the lone nitrogen electronic pairs in the NIPAAm structure (Figure 7).

Table 4. Main characterization parameters of NIPAAm copolymers

NAME	Co-monomer content by NMR [mol%]	M_w [g mol^{-1}]	$<r^2>$ in THF [nm]	T_g [°C]
PNIPAAm	-	237 000	27	138
NIPAAm-Copolymers with methoxy protected acid groups				
CoA-4(05)	6.2	264 000	27	128
CoA-4(10)	9.9	292 000	28	114
CoA-4(15)	16.8	281 000	27	106
CoA-4(20)	20.4	297 000	24	106
CoA-7(05)	7.8	398 000	31	128
CoA-7(10)	11.6	514 000	31	114
CoA-7(15)	15.5	406 000	34	105
CoA-10(05)	4.8	368 000	32	127
CoA-10(10)	8.4	343 000	30	108
CoA-10(15)	11.3	414 000	44	100
NIPAAm-Copolymers with free acid groups				
CoDA-4(05)	7.6	277 000	24	131.6
CoDA-4(10)	12.1	237 000	21	126.0
CoDA-4(15)	18.0	233 000	19	122.2
CoDA-4(20)	21.9	197 000	17	117.2
CoDA-7(05)	7.2	354 000	29	127.9
CoDA-7(10)	12.4	318 000	24	118.6
CoDA-7(15)	17.4	275 000	19*	109.6
CoDA-10(05)	6.6	287 000	24	126.4
CoDA-10(10)	12.8	289 000	22	112.5
CoDA-10(15)	17.3	231 000	23*	99.7

* In Methanol

This would lead to additional polymer-polymer interactions, making phase separation by heating (LCST) a less endothermic process than with pure polyNIPAAm.

If we add a strong base to the solution, the protons of the carboxylic acid groups would be removed and the resulting carboxylates would not be able to bind to the nitrogen electronic pair any more. Moreover, electrostatic charge repulsion would weaken the polymer-polymer interactions, driving the LCST to higher temperatures. This is what we observed indeed by measuring the LCST of the same copolymer in buffer solutions at pH=8 (Figure 8, solid lines). In all cases the LCST is shifted to higher temperatures; moreover, some copolymers that were insoluble in pure water, e.g. copolymers with A-7 and A-10 co-monomers in content higher than 10% or copolymers with A-4 co-monomer in content higher than 15%, are soluble in this buffer-solution. These polymers also show LCST values lower than that of pure polyNIPAAm indicating that the hydrophobicity of the spacer group overcomes the hydrophilicity of the ionized carboxylic acid groups. We believe this is an example of hydrophobicity and hydrogen-bonding working in the same direction: increased polymer-polymer interactions instead of opposing factors for explaining the solubility behavior of partially hydrophobic polymers in water.

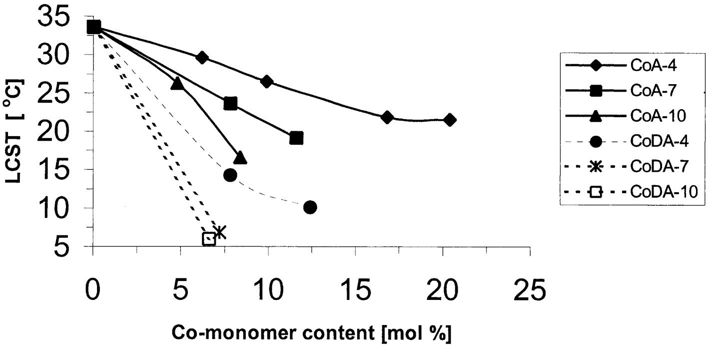


Figure 6. LCST in pure water for NIPAAm copolymers with co-monomers having hydrophobic spacers with protected acid groups (full lines) and free acid groups (dashed lines) as a function of co-monomer content.

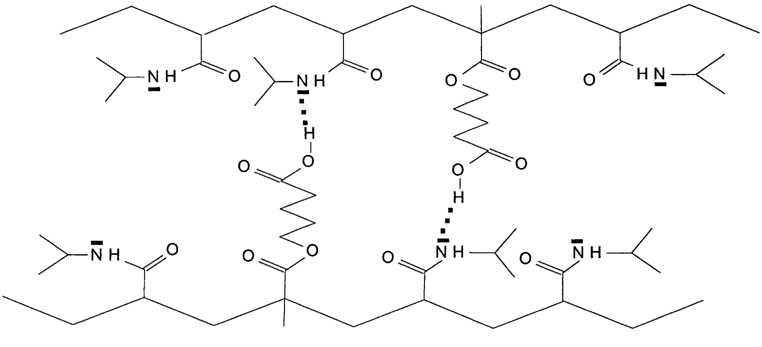


Figure 7. Possible hydrogen-bonding interactions between polymer chains affecting the LCST of NIPAAm-copolymers.

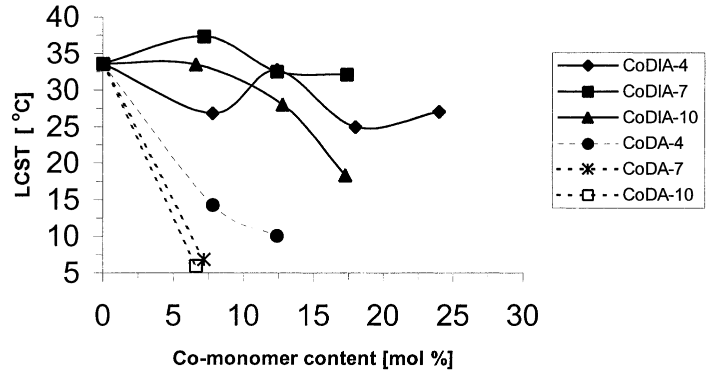


Figure 8. LCST of NIPAAm copolymers with co-monomers having hydrophobic spacers and free acid groups as a function of co-monomer content: In pure water (dashed lines) and in buffer solution of pH=8 (full lines).

Although more experiments are needed to confirm this in similar systems, our results show that both hydrophobic interactions and hydrogen-bonding are very important for the behavior of NIPAAm copolymers depending strongly on the fine chemical structure of the copolymeric units.

Conclusions

The synthesis of methoxy-protected methacrylic acid derivative polymers with aliphatic and with aromatic spacers, was straightforward and yielded polymers of varied physical properties depending on the structure of the spacer used. Either by a deprotection reaction with preformed polymers or by direct polymerization of monomers containing free acid groups, the preparation of polyelectrolytes was achieved. The first route resulted in moderate to high yields (50 – 80%) but with higher molecular weights, and the second one resulted in 100% of free acid units but with lower molecular weights, in comparison.

The pH of the swelling transition of gels prepared varied from 3.5 up to 9.0. This large shift in the pH of the swelling transition results from a combination of three effects:

1) the hydrophobic local environment imposed by the spacer groups altering the acidity constant of the carboxylic acids (pK_a shift).

2) the hydrophobic-hydrophobic interactions in micro-domains acting as a force opposed to the ionization driven swelling.

3) the strong polymer-polymer hydrogen-bonding interactions acting as a force opposed to the ionization driven swelling.

Which effect prevails depends on the fine chemical structure of the monomeric unit.

The LCST of NIPAAm copolymers in water was lowered from 33.6 °C for polyNIPAAm down to 6 °C as a function of the content on hydrophobic co-monomer and also depending on the spacer used. Comonomers with protected acid groups act only in terms of increasing the hydrophobicity of the copolymer chain, which in turns depends on the spacer length used. Comonomers with free acid groups lowered the LCST of NIPAAm copolymers even further through their capability of hydrogen-bonding interactions with the NIPAAm units. This is an example where the water solubility of polymers is decreased by hydrophobic and hydrogen-bonding interactions acting in the same direction.

In general we have demonstrated, with the polymers prepared with hydrophobic spacers, that their solution and swelling behavior cannot be explained only in terms of mixing, elastic and ionic contributions to the free energy of the system. Hydrophobic-hydrophobic and hydrogen-bonding interactions need to be considered in careful connection with their fine chemical structure to understand their behavior.

Acknowledgments

The financial support of the following agencies is gratefully acknowledged: CONACYT-México (Project Nr. 28022-U), COSNET-México (Project Nr. 834.98-P), DFG-Germany (SFB 287), Volkswagen Foundation-Germany (Project Nr. I/76 065). R.S.-R. thanks DAAD-Germany for financing his PHD-Sandwich Program. We thank specially I. Rivero (NMR), D. Scheller (NMR), I. Poitz (DSC) and C. Meissner (SLS) for valuable technical support.

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