Conformational Imprinting Effect on Stimuli-Sensitive Gels Made with an "Imprinter" Monomer§

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ABSTRACT: A new type of monomer, called Imprinter, combined with its copolymerization with a stimuli-sensitive monomer, allows gels with receptor sites of reversible affinity to be created. Imprinter-Q is a dimeric monomer that has two cationic groups linked by a 1,2-glycol bond, which is easily cleavable. Weakly cross-linked gels have been prepared using Imprinter-Q, *N*-isopropylacrylamide, and cross-linker *N,N′*-methylenebis(acrylamide). After breaking the 1,2-glycol link, the members of each cationic pair are close together, and they can capture target molecules via a multiple-point electrostatic interaction. The higher affinity of these gels for disodium nitroisophthalate (NPA) or dipotassium naftalenedicarboxylate (NDC) in comparison with control gels, which were prepared with randomly distributed cationic groups, proved that the gels prepared with Imprinter-Q memorized the position of the pairs of cationic groups after swelling and reshrinking. Although the efficient adsorption was expected to depend on the correspondence between the spacing of the two juxtaposed cationic groups of the gel and the spacing of the two anionic groups of the adsorbate, it was found that NPA and NDC (carboxyl spacing 60% longer than in NPA) are adsorbed with similar efficiency. The control gels experienced difficulty in forming pairs, and their affinity for NPA or NDC decreased exponentially as a function of cross-linker concentration. In contrast, the topological constrains were completely absent in the imprinted gels, showing that memorization had been achieved. This "conformational imprinting effect" was tested for several concentrations of Imprinter-Q and permanent cross-linkers.

Introduction

The design of synthetic polymers capable of specific molecular recognition and recovery has received much attention during the past years.[1−4] Wulff, Mosbach, and others developed an imprinting technology where receptor sites are created by polymerization in the presence of target molecules. The materials formed by applying this technology present high affinity and selectivity to the desired target molecules.[5−8] However, since the backbone of the plastic matrix has a rigid structure, changes in conformation are not possible, and its affinity cannot be altered. This is an important limitation for some chemical and biomedical applications and suggests the need of developing flexible macromolecules able to change their affinity for the target depending on external stimuli.

Synthetic polymer gels that experiment a reversible phase transition depending on the environmental conditions serve as a basis to create flexible gels, able to undergo quick changes in conformation and able to respond to external stimuli by reverting to a specific conformation, in which certain functions may be developed.[9,10] To be able of recognize a specific target, these gels have to show a "conformational imprinting effect" as a consequence of the following three steps (Figure 1):

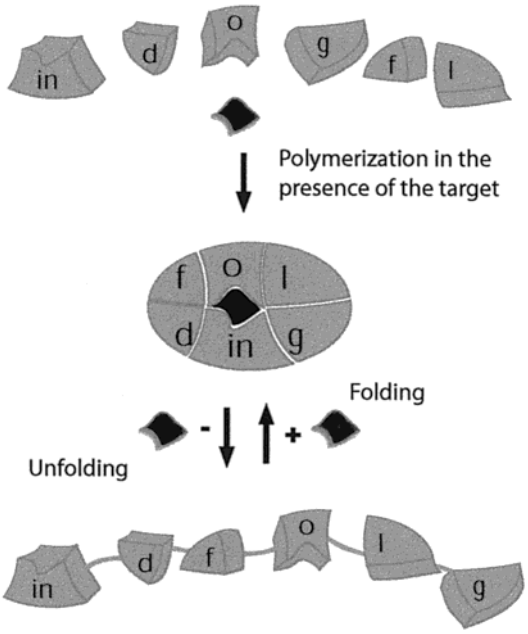

Figure 1. Schematic representation of the conformational imprinting effect.

(a) Polymerization after the monomers are allowed to equilibrate their spatial arrangement. The resulting polymer should be in the lowest energy conformation to create the driving force to memorize the conformation of the network and the location of functional groups, which form the receptor centers. (b) Break of the inter-

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action between the functional groups that form each receptor site to destroy the initial conformation. (c) Addition of specific molecules that can interact with the functional groups; the memory of the conformation is recalled by reconstructing the original conformation of the gel.

On the basis of these ideas, weakly cross-linked gels synthesized in the presence of target molecules have been prepared imitating the usual imprinting technology. Although there was a decrease in selectivity with respect to the imprinted plastics, it was possible to gain in control of affinity through changes in the conformation induced by external stimuli. Recently, Alvarez-Lorenzo et al.[11] have shown for the first time a conformational imprinting effect in *N*-isopropylacrylamide (NIPA)−lead dimethacrylate gels that can reversibly swell and shrink in response to temperature. After washing lead out and swelling, the affinity for divalent ions disappeared. When the gels were shrunken again, the affinity was recovered, and the original relative position of the carboxylic groups was recalled. Control gels made using randomly distributed methacrylic acid monomers showed a much lower affinity. The success of the imprinting can be attributed to the fact that the degree of dissociation between lead and two methacrylate molecules during polymerization is negligible, and therefore lead is responsible for fixing the juxtaposition of pairs of methacrylates.[12]

To extend this behavior to more general technology, a new series of functional monomers have been designed, which we call "Imprinters". An Imprinter is a molecule that has three functional parts, two or more polymerizable double bonds, two or more functional groups, and a link connecting the functional groups that is easily cleaved afterward, such as a disulfide bond or a 1,2-glycol structure. As a new representative of this kind of monomers, we synthesized Imprinter-Q (2,3-dihydroxy-*N,N,N′N′*-tetramethyl-*N,N′*-bis{3-[(2-methylacryloyl)aminopropyl}-1,4-butanediaminium dibromide) which has two quarternary ammonium cationic groups. Imprinter-Q is a novel substance that has not been reported in the literature[13] (Figure 2). We describe its synthesis and how, using Imprinter-Q and NIPA, it is possible to develop hydrogels that are able to adsorb with high efficiency charged molecules, and simultaneously the process can be switched on and off. In a previous paper,[14] an imprinted hydrogel was obtained, without template polymerization, using a monomer with a disulfide bond that, after polymerization, was oxidized and transformed in two sulfonic groups in contact each other. Thus, the hydrogel was suitable for the binding of a divalent cation. In the present case, the linkage between the quaternary ammonium groups of each Imprinter-Q is broken after polymerization to obtain pairs of cationic groups. Since the members of each pair are separated by a well-defined distance, they can capture specifically molecules containing two anionic groups. The NIPA component of the gel is responsible for the swelling at temperatures lower than 33 °C and collapsing when the temperature is raised.[15] We compared this gel with a reference gel with randomly distributed cationic groups (Figure 3).

Experimental Section

Materials. *N*-(3-(Dimethylamino)propyl) methacrylamide, 1,4-dibromo-2,3-butanediol, methanol, 2-propanol, ethyl acetate, dimethyl sulfoxide, 2,2′-azobis(isobutyronitrile) (AIBN), 5-nitroisophthalic acid (NPA), sodium benzoate (BZT), and dipotassium 2,6-naftalenedicarboxylate (NDC) were from Sigma-Aldrich (WI). *N*-Isopropylacrylamide (NIPA) and methacrylamidopropyltrimethylammonium chloride (MAPTAC) were kindly provided by Kohjin Co. Ltd. and Mitsubishi Rayon Co. Ltd. (Japan), respectively. *N,N′*-Methylenebis(acrylamide) (BIS) was obtained from Bio-Rad Laboratories (CA).

Synthesis of Imprinter-Q. A solution of 1,4-dibromo-2,3-butanediol (11.4 g) in methanol (60 mL) was added to a stirred solution of *N*-(3-(dimethylamino)propyl)methacrylamide (16.6 g in 120 mL of methanol). The reaction was carried out at 60 °C for 23 h. Methanol was removed by evaporation. The remaining oily liquid was dissolved in 2-propanol (120 mL). The solution was poured into a large amount of ethyl acetate (1800 mL). The precipitate was taken out by decantation and washed again with ethyl acetate. The solvent was evacuated in a rotary vacuum pump for 24 h. A white hygroscopic powder was obtained. Yield: 23.7 g (88%). ^{1}H and ^{13}C NMR spectra were obtained using a Varian UNITY-300 spectrometer, operating at 300 and 75 MHz, respectively. After recording the ^{1}H and ^{13}C NMR spectra of the product in deuterium oxide (10 wt %, 0.7 mL), an aqueous solution of $NaIO_4$ (0.2 N, 0.12 mL) was added in the NMR sample tube. Later, $NaBH_4$ (18 mg) was added to the same sample tube and mixed for 10 min. The ^{1}H and ^{13}C NMR measurements after the addition of the chemicals were completed within 10 min.

Preparation of the Gels. The gels were prepared by free radical polymerization using *N*-isopropylacrylamide (NIPA, 6 M), Imprinter-Q, and cross-linker BIS in dimethyl sulfoxide. To study the influence of the proportion of functional groups, we fixed the cross-linker proportion (40 mM BIS) and used a Imprinter-Q concentration ranging from 4 to 40 mM. For the cross-linker dependence study, the cross-linker BIS ranged from 10 to 200 mM, while the Imprinter-Q concentration was fixed at 16 mM. After the addition of 2,2′-azobis(isobutyronitrile) (AIBN, 10 mM, initiator), the solutions were immediately transferred to test tubes in which glass capillaries (∼0.5 mm i.d.) were placed. The solutions filled the capillaries and were then degassed under vacuum for a few seconds. The polymerization was carried out at 60 °C for 24 h. After gelation was completed, the gels were taken out the capillaries and consecutively washed with deionized water, 10 mM NaOH and 10 mM HCl, and again with deionized water (3 days in each medium). To break the 1,2-glycol bond in the Imprinter-Q mers, the gels were introduced into 0.1 N $NaIO_4$ for 30 min, rinsed with deionized water, and transferred into 0.1 N $NaBH_4$ for 30 min.[16] Finally, the gels were washed with deionized water and 10 mM HCl, immersed in deionized water, and collapsed at 60 °C to reduce the amount of water bonded. The gels were removed from the solution and dried under vacuum for 1 week.

Reference gels (i.e., nonimprinted) were synthesized in the same way, using MAPTAC instead of Imprinter-Q.

Characterization of the Gels. *Degree of Swelling.* Equilibrium diameters d of the cylindrical gels in water were measured using a microscope equipped with a color video camera. The degree of swelling was expressed as

$$\text{degree of swelling:} \quad V/V_0 = (d/d_0)^3 \tag{1}$$

where d_0 was the gel diameter upon polymerization.

Adsorption Studies. Pieces of cylindrical gel (10−20 mg dry weight) were placed in 4 mL aqueous solutions (8 μM−0.5 mM) of disodium 5-nitroisophthalate (NPA), dipotassium 2,6-naftalenedicarboxylate (NDC), or sodium benzoate (BZT). The solutions also contained 1 mM NaCl to provide monovalent sodium ions to replace the target molecules (NPA, NDC, or BZT). The samples were kept swollen (20 °C) or shrunken (60 °C) for 48 h while being stirred. Equilibrium concentration of NPA, NDC, or BZT in the medium was measured spectrophotometrically at 266, 240, or 224.5 nm, respectively. The amount of target adsorbed by the samples was then evaluated as the difference between the initial and the final quantities in the medium.

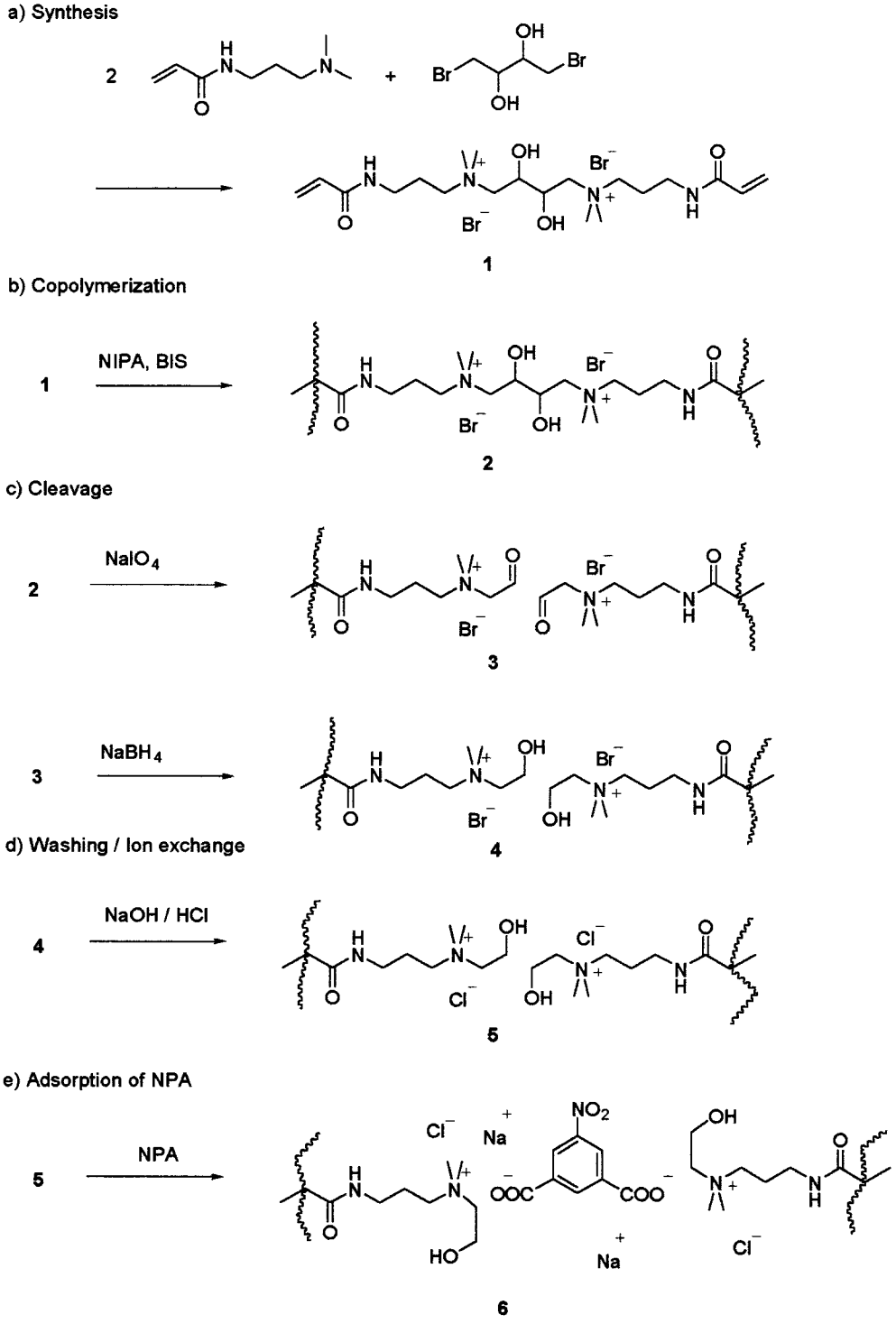

Figure 2. Synthesis of Imprinter-Q and preparation of Imprinter-Q/NIPA gels.

The adsorption isotherms were analyzed in terms of the Langmuir equation:

$$A = SKC_{eq}/(1+KC_{eq}) \quad \text{or} \quad C_{eq}/A = 1/SK + C_{eq}/S \quad (2)$$

where A is the amount of target adsorbed per unit volume of gel in the shrunken state, C_{eq} is the final equilibrium concentration in the solvent, S is the number of adsorbing sites per unit volume of gel or the amount of target necessary to saturate the adsorbing sites, and K is the affinity of one adsorption site for a target molecule. From the slope and the intercept at zero C_{eq} we can deduce both S and K and the overall affinity SK.

Release Experiments. Gels loaded in the shrunken state with NPA were dried in a vacuum for 3 days and then placed in thermostatically controlled vials containing 5 mL of 1 mM NaCl solution under stirring. The amount of NPA released at different times was determined by UV spectrophotometry (266 nm). The influence of temperature changes was analyzed between 20 and 60 °C.

Results and Discussion

Imprinter-Q: Synthesis and Characterization. Imprinter-Q was synthesized by the reaction of *N*-(3-(dimethylamino)propyl)methacrylamide and 1,4-dibromo-2,3-butanediol and purified (Figure 2). ^{1}H NMR (Figure 4A) and ^{13}C NMR (Figure 5A) spectra of Imprinter-Q in deuterium oxide corroborate the chemical structure

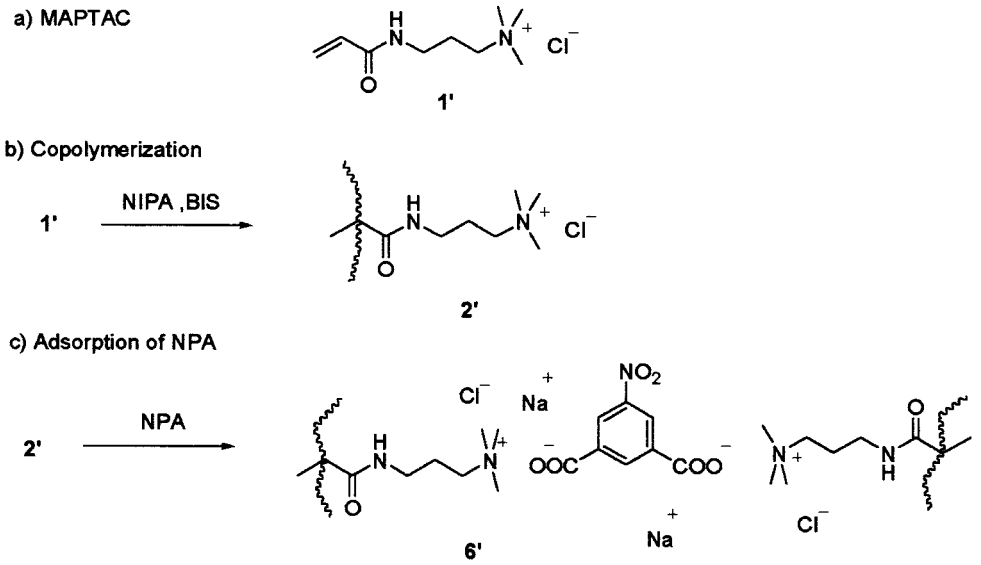

Figure 3. Preparation of gels made with randomly distributed cationic groups.

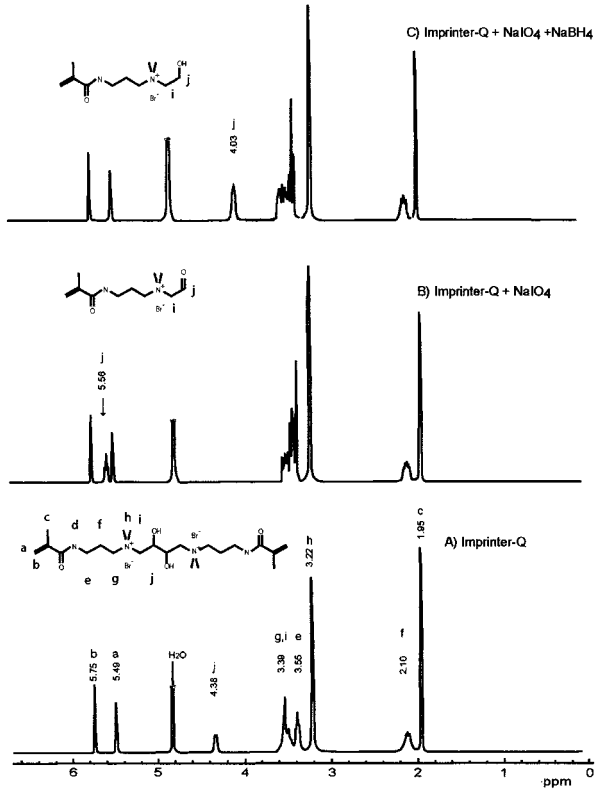

Figure 4. ^{1}H NMR spectra of Imprinter-Q in deuterium oxide before and after treatment to break the 1,2-glycol bond.

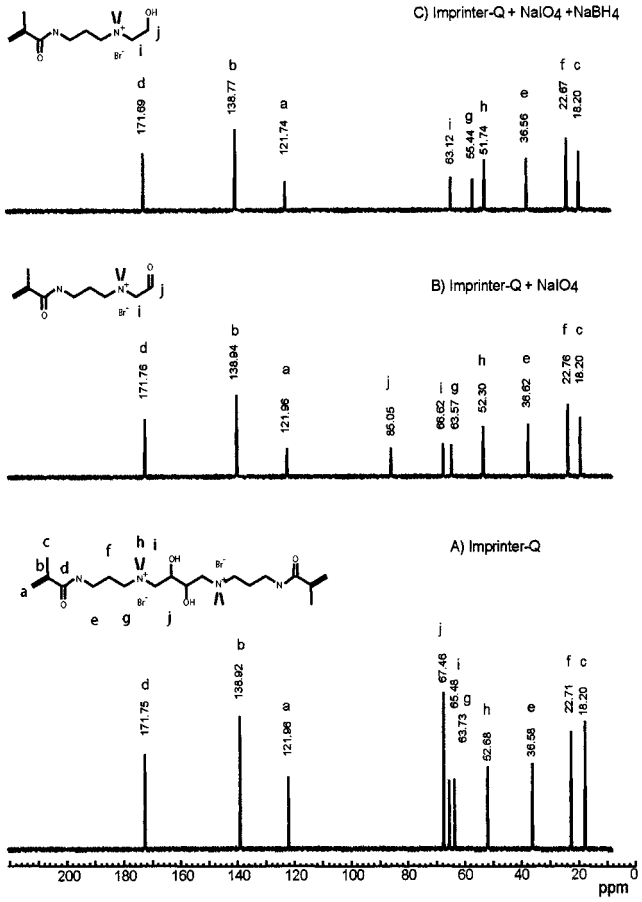

Figure 5. ^{13}C NMR spectra of Imprinter-Q in deuterium oxide before and after treatment to break the 1,2-glycol bond.

of Imprinter-Q and the absence of impurities. To cleave the 1,2-glycol bond in Imprinter-Q, we selected the breaking procedure commonly used in the preparation of poly(vinyl alcohol).[16] After adding $NaIO_4$, aldehyde groups were obtained (spectra in Figures 4B and 5B) that, in the presence of $NaBH_4$, were converted to stable alcohol groups (spectra in Figures 4C and 5C). The main changes in the spectra were observed for the lines assigned to methylene (i) and methine (j) protons and carbons involved in 1,2-glycol linkage between two quaternary ammonium groups. In both figures, the line j may be assigned to the aldehyde proton and carbon in ^{1}H and ^{13}C NMR, respectively, although the chemical shifts observed, 5.6 and 85.05 ppm, are abnormal: the usual values for an aldehyde are about 10 and 200 ppm, respectively. These anomalous chemical shifts may be explained by the effects of the coexistent ionic species. In Figure 4C, the line at 4.03 ppm has an intensity double than that of the ones observed for the corresponding line of j in Figure 4A,B. This line can be assigned in Figure 4C to the methylene j proton generated by the reduction of aldehyde. The line of j is missing in Figure 5C, owing to the effects of iodine and boron compounds. From these results, it can be concluded that

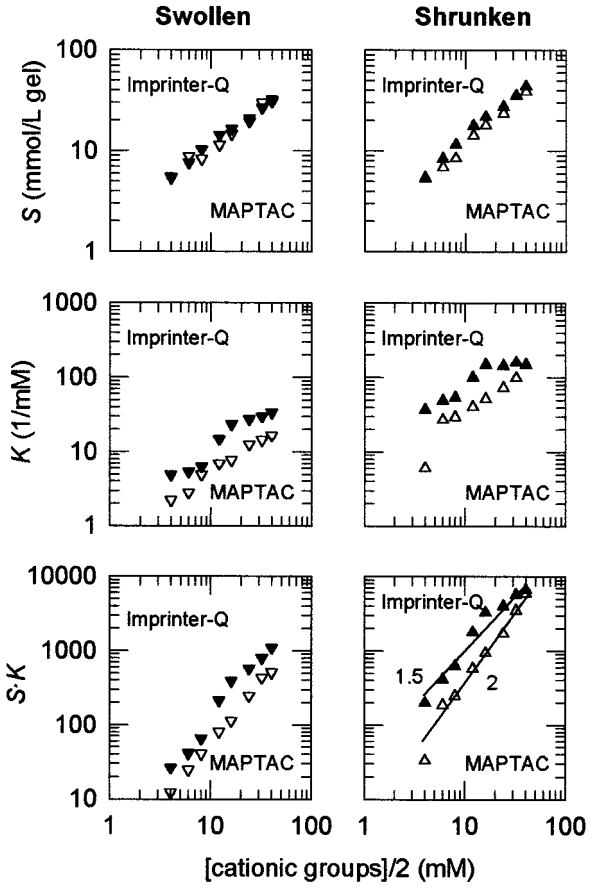

Figure 6. Dependence of the saturation value, *S*, the affinity per adsorption site, *K*, and the overall affinity, *SK*, on the concentration of cationic groups, for Imprinter-Q gels and MAPTAC gels.

the reactions of cleavage of 1,2-glycol and reduction of aldehyde proceed quickly.

Gel Behavior. Adsorption/Release Studies. The incorporation of Imprinter-Q during polymerization and the suitability of the procedure used to break the 1,2-glycol bonds in the gels were initially tested as follows. First, a gel prepared only with NIPA and Imprinter-Q, without cross-linker BIS, swelled in deionized water without dissolving, showing than Imprinter-Q was acting itself as cross-linker. Second, when this gel was transferred to 0.1 N $NaIO_4$ solution, it dissolved after 10 min, because of the breaking of the 1,2-glycol bonds. Third, we tested using a cross-linked NIPA/MAPTAC gel (no Imprinter-Q) that 0.1 N $NaIO_4$ does not damage other bonds of the polymeric skeleton. This is proved because no changes in the swelling degree of the gel were observed after 12 h in 0.1 N $NaIO_4$ solution. From these observations, we decided to treat all NIPA/Imprinter-Q gels that will be used in the subsequent experiments to ensure complete breakage of the 1,2-glycol bonds in 0.1 N $NaIO_4$ for 30 min.

Influence of Cationic Groups Content. The adsorption of disodium 5-nitroisophthalate (NPA) by both Imprinter-Q and MAPTAC gels was well described by Langmuir's isotherm as formulated in eq 2. The analysis of the dependence of the parameters *S*, *K*, and *SK* on the concentration of cationic groups in the gels (Figure 6), for a fixed low concentration of cross-linker BIS (40 mM), showed that:

(a) Both Imprinter-Q and MAPTAC gels exhibit a linear relationship between the amount of ions needed to saturate the adsorption sites, *S*, and the concentration of the cationic groups in the polymer. Both in the swollen and in the shrunken state, the number of adsorption sites is approximately half the number of cationic groups that were incorporated during the synthetic procedure: S = [cationic groups]/2. This indicates that all cationic groups participate in forming adsorption sites for NPA molecules when the concentration of NPA is high enough.

(b) The affinity per site, *K*, was greater for the Imprinter-Q gels than for the MAPTAC gels in both the swollen and shrunken states. This indicates that in the gels prepared with Imprinter-Q the arrangement of the pairs of cationic groups can create receptor sites of high affinity for a dicarboxylic molecule like NPA. The affinity per site, *K*, was proportional to the concentration of cationic groups and significantly lower in the swollen state than in the shrunken state. When the gel was swollen ($V_{20\ °C}/V_0$ = 6.0−6.5, for 40 mM cross-linker BIS), the distance between the nearest cationic groups increased and the probability of pair formation decreased. The gel lost the imprinting conformation. In the shrunken state ($V_{60\ °C}/V_0$ = 0.9), the cationic groups may come close to each other again, and the affinity for NPA increased by almost 1 order of magnitude. This shows the destruction and re-formation of NPA adsorption sites made of a pair of cationic groups.

(c) The overall affinity of the gels to NPA ions, *SK*, was found to be higher in the Imprinter-Q gels than in the MAPTAC gels, except for the highest concentration of cationic groups. The difference in the affinity between Imprinter-Q and MAPTAC gels is a maximum when the concentration of adsorbing monomers (cationic groups) is lower than that of the cross-linker (40 mM). This can be understood by considering that if the concentration of adsorbing monomers is greater than that of the cross-linker, there will be no topological constrains for the formation of pairs, and thus the imprinting effect will not be perceptible.[11]

In the shrunken state, the slope of *SK* vs the concentration of cationic groups was lower for the Imprinter-Q gels than for the MAPTAC gels (Figure 6). This reflects the fact that the probability that randomly distributed monomers come into the vicinity is proportional to the square of the adsorbing monomer concentration. In contrast, if the gel is synthesized nonrandomly, the probability of a monomer finding a partner nearby becomes higher than in the random case.

Figure 7 shows the enormous effect of temperature on switching the adsorption ability of the Imprinter-Q gels on and off. When the dry loaded gels are immersed in the aqueous medium, a fast hydration and swelling take place during which the gels quickly release NPA until equilibrium is reached. Since the adsorption behavior of the gels follows the Langmuir model and the amount of NPA loaded in each gel depends on the proportion in cationic groups, the percentage of NPA released decreases as the proportion of cationic groups increases. However, the total amount of NPA released in the volume selected was higher for the gels containing more cationic groups. It is extremely important to notice that when the temperature increased up to 60 °C, the gels were able to readsorb a significantly high amount of the NPA previously released. This is a new behavior, never before reported to the best of our knowledge, for NIPA gels. Temperature responsiveness of

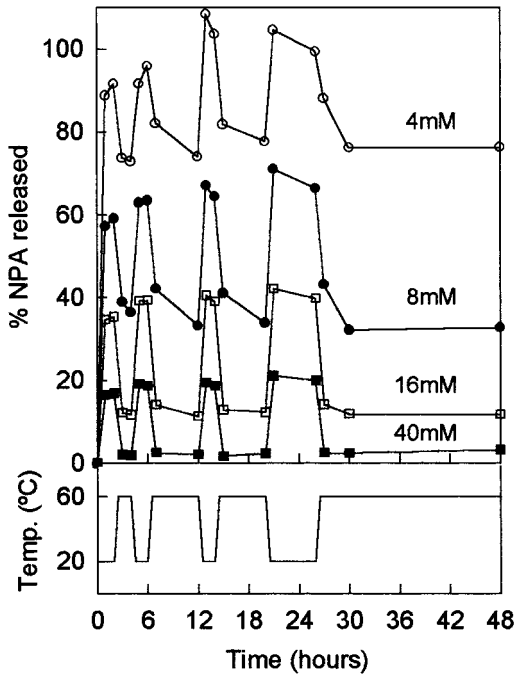

Figure 7. Influence of temperature on the release and readsorption process of NPA by imprinted gels prepared with different concentrations of Imprinter-Q. Cross-linker concentration was 40 mM. Degrees of swelling at 20 and 60 °C were 6.0−6.5 and 0.9, respectively.

NIPA gels has been proposed by several authors as a way to create intelligent materials for controlled release.[17−21] In these previous systems, a substance entrapped in the NIPA network diffused out of the gel in the swollen state, because of the increase in the porosity of the network. In contrast, an increase in temperature induced the network to collapse, which decreased its porosity dramatically, hindering the diffusion of the substance. Therefore, an oscillating release behavior was obtained upon small changes in temperature. In our gels, thanks to the affinity of the receptor groups for NPA, a change from the swollen to the shrunken state induces not only the cessation of the release but also the promotion of a readsorption process. This process occurs quickly and in a way that can be reproduced after several temperature cycles. The MAPTAC gels presented swelling/collapse behavior similar to the Imprinter-Q gels; however, since the affinity for NPA is smaller than in the case of the Imprinter-Q gels, shrunken MAPTAC gels could not readsorb as much as the Imprinter-Q gels.

Influence of Cross-Linking Degree. The effect of the cross-linking degree on the adsorption behavior of the MAPTAC and Imprinter-Q gels is shown in Figures 8 and 9. In the shrunken state, the overall affinity, *SK*, of the MAPTAC gels decreased exponentially as a function of cross-linker (BIS) concentration. The affinity of the Imprinter-Q gels for molecules containing two carboxylic groups (NPA and NDC) was much greater than that of the MAPTAC gels and did not decrease with BIS. A similar phenomenon has already been observed in imprinted gels prepared using lead methacrylate and control gels made with methacrylic acid.[11] These observations are a proof of the random distribution of the cationic groups in the MAPTAC gels as against the juxtaposition of pairs of these groups in the Imprinter-Q gels.[11,22] The exponential decrease of the affinity of the MAPTAC gels can be understood as follows. The cationic

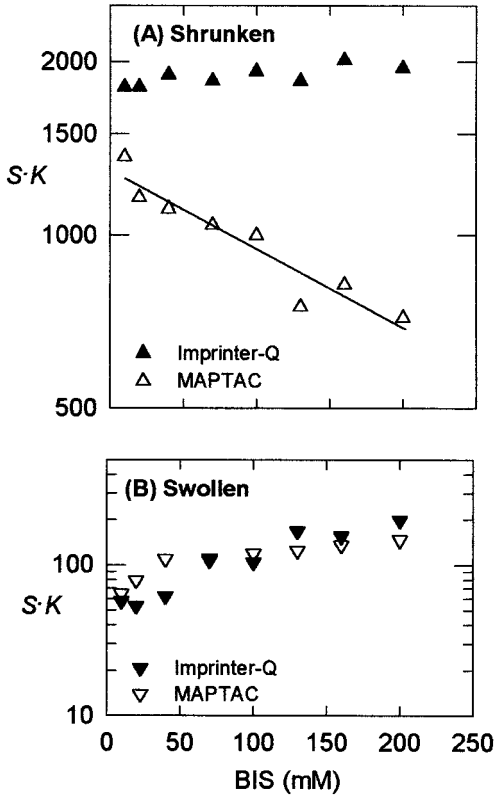

Figure 8. Dependence of the overall affinity, *SK*, of the Imprinter-Q and MAPTAC gels for NPA on the cross-linking density (BIS) in the shrunken (A) and swollen (B) states.

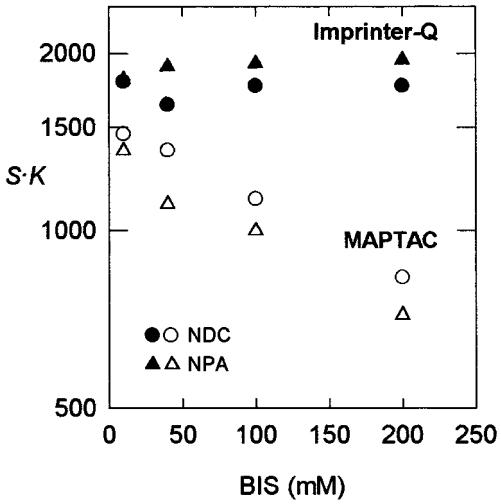

Figure 9. Comparison between the overall affinity, *SK*, of the Imprinter-Q and MAPTAC gels in the shrunken state for NDC and NPA.

groups in the gel can move rather freely within a certain volume determined by the cross-linking density. Indeed, it has been established that, below a certain length scale associated with the cross-link density, the gel behaves like a liquid, allowing the cationic groups to diffuse virtually freely.[23] Beyond that length scale, the gel behaves as an elastic solid body, and in particular, the cationic groups cannot diffuse beyond a given distance. To make a simple estimate of this distance, *l*, we may assume that each cationic group is at one end of a fictitious Gaussian chain with a length half that of the average polymer length between the nearest BIS cross-links[11,22]

$$l = nb = [\text{NIPA}]/[\text{BIS}]/2 \quad (3)$$

Here n is the number of monomer segments of persistent length b. This fictitious Gaussian chain represents the restricted ability of the cationic groups to diffuse within a certain volume in the gel. It has previously been established that the affinity should be proportional to the probability for two adsorbing groups to meet, which is proportional to the Boltzmann factor of the entropy loss associated with the formation of one pair of adsorbing groups[11,22]

$$P = P_0 \exp(-R^2/nb^2) = P_0 \exp(-c[\text{BIS}]/[\text{cationic groups}]^{2/3}) \quad (4)$$

In contrast, for the imprinted gels there was no dependence of the affinity on BIS concentration (Figure 8A). This is because the gel was synthesized using Imprinter-Q as precursors of pairs of cationic groups. The Imprinter-Q gels have much greater adsorption than MAPTAC gels because of the minimization of the topological constrains caused by cross-links and polymer connections. If the Imprinter-Q gel did not memorize the position of the pairs of cationic groups after swelling and reshrinking, a cationic group would have to find a new partner to form a pair, and the probability of forming such a pair would be the same as that in a randomly made gel. There would be no difference, then, between the NPA adsorption by the imprinted and the nonimprinted gels. We can therefore conclude that the excess NPA adsorption by the Imprinter-Q gel comes from the successfully memorized pairs.

Specificity. The overall affinity of Imprinter-Q and MAPTAC gels for NDC (Figure 9) was very similar to that shown for NPA. The distance between two adjacent ammonium groups in the gel after polymerization and the distance between the two carboxylic groups of NPA and NDC were estimated, using CS ChemDraw 5.0 software, as 6.15, 5.02, and 8.09 Å, respectively. As a consequence of the repercussions of gel flexibility on the distance between two ammonium groups, the different spacing of the anionic groups in NPA and NDC does not seem big enough to affect significantly the affinity of the gel for these molecules; i.e., the entropic component does not provide selectivity for a specific dicarboxylic target in the range of small- to medium-size molecules. In addition, the similar behavior between NPA and NDC may be due to a superposition of effects due to ion interactions and hydrophobic bonding, which should be stronger in the larger NDC. Nevertheless, since the enthalpy of the binding process may be different for each target, a modification of the properties of the medium, such as its ionic strength, could allow getting the desirable specificity. This approximation has been already successfully assayed with MAPTAC gels and other anionic targets.[24]

In the case of BZT, a very small adsorption was observed (*SK* values around 30−40). This molecule can only establish a single-point ionic interaction with the gel. In this situation, the adsorption becomes independent of the swelling degree of the gel (the amount adsorbed was similar in both the swollen and the shrunken states) and its cross-linking density since no entropic constraints prevent the adsorption. However, the process is enthalpically much more unfavorable than in the case of a multiple-point ionic interaction. In consequence, these gels have a low affinity for molecules with one carboxylic group and present a clear specificity for molecules with two carboxylic groups.

Conclusions

Imprinter-Q has been found to give weakly cross-linked gels that show higher affinity for molecules with two carboxylic groups than gels made with randomly distributed cationic groups. This observation can be attributed to the imprinting or the memorizing of the conformation during polymerization. This conformation is relatively flexible, allowing the adsorption of target molecules with different spacing between two carboxylic groups. The behavior of Imprinter-Q gels and gels made using monomers with disulfide bonds, previously reported by D'Oleo et al.,[14] demonstrates that dimeric monomers with two functional groups strongly held together by cleavable links such as a disulfide or a 1,2-glycol bond are suitable for making imprinted stimuli-sensitive gels. The concept of Imprinters is expected to enhance the technology for producing more sophisticated gels with multiple imprinted positions, which can exhibit molecular recognition, avoiding the use of template polymerization.

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