Tuning Hydrogel Mechanics Using the Hofmeister Effect

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The mechanical properties of hydrogels are commonly modified by changing the concentration of the molecular components. This approach, however, does not only change hydrogel mechanics, but also the microstructure, which in turn alters the macroscopic properties of the gel. Here, the Hofmeister effect is used to change the thermoresponsiveness of polyisocyanide hydrogels. In contrast to previous Hofmeister studies, the effect is used to change the phase transition temperatures and to tailor the mechanics of the thermoresponsive (semiflexible) polymer gels. It is demonstrated that the gel stiffness can be manipulated over more than two orders of magnitude by the addition of salts. Surprisingly, the microstructure of the gels does not change upon salt addition, demonstrating that the Hofmeister effect provides an excellent route to change the mechanical properties without distorting other influential parameters of the gel.

1. Introduction

Smart materials that are responsive toward chemical, mechanical, optical, and/or thermal stimuli have been an increasing focus for materials scientists.[1,2] For the further development of these materials for biomedical applications,[3,4] it is desirable to use simple and readily applicable stimuli to control the response of the material. One such stimulus is the addition of salts. It has been known since 1888 that salts have the ability to precipitate proteins from aqueous solutions; an effect known as the Hofmeister effect.[5,6] The Hofmeister effect not only describes protein precipitation or stabilization, it can be applied universally to describe the behavior of thermoresponsive aqueous systems. For instance, the addition of salts changes the lower critical solution temperature (LCST) of aqueous solutions of synthetic thermoresponsive polymers, such as poly(*N*-isopropylacrylamide) (PNIPAM),[7] ethylene glycol-based triblock copolymers,[8] and ethylene glycol functionalized methacrylates.[9] In these examples, the nature of the salt and its concentration are the parameter to tailor the precipitation temperature of the polymer solutions.

Studies focusing on the Hofmeister effect are commonly restricted to the manipulation transition temperatures of (polymer) solutions. So far, limited attention has been paid to the application of this effect to direct the macroscopic mechanical properties. The large morphological and volume change at the LCST of PNIPAM-based gels[10] make mechanical studies meaningless. A series of studies on the Hofmeister effect on supramolecular hydrogels showed a dependence of the mechanical properties, but this was merely induced by the hugely different morphologies found for the different assembly conditions of the gels.[11–13]

Here, we describe for the first time that we can use the Hofmeister effect to controllably manipulate the mechanical properties of polymer hydrogels. As expected, the addition of salts directly affects the gelation temperature and, for our thermoresponsive hydrogel, this changes the stiffness of the gel over two orders of magnitude at a constant temperature, for instance 37 °C. We construct hydrogels that range from very soft to stiff, but all at identical concentration. To achieve such change in mechanical response, one commonly needs to vary parameters such as concentration, morphology and bundle (or fiber) diameter and stiffness.[14] Some of these are difficult to control, while others simultaneously change many important network characteristics; for instance, the concentration changes the biomedically relevant pore size and stiffness of the gel (as well as nonlinear gel properties). The salts, however, are able to shift the mechanics, without changing porosity and network morphology.

The polymers we use are ethylene glycol-functionalized polyisocyanides (PICs, **Figure 1**b), which form a thermoreversible gel upon heating when dissolved in water.[15] At the LCST, the polymers become hydrophobic and form a network of entangled semi-flexible bundles of polymer chains. The mechanical properties of the PIC hydrogels mimic those of biological gels,[15] including the nonlinear mechanics at large stress (or strain), which is markedly different than that of other synthetic hydrogels. The mechanics of PIC hydrogels is readily tuned by changing concentration, temperature, and polymer length.[16] Here, we add two additional parameters to this list: the nature of the salt (more precisely the anion) and its concentration.

For a long time, the molecular basis of the Hofmeister series was related to the effect of ions on the bulk structure of water.[17] More recently, however, it was shown that salts generally do not affect the bulk water structure.[18,19] Instead, more recent theories hypothesize that direct interactions between ions and macromolecules and their first hydration shell can explain the effects first described by Hofmeister.[7,20–23]

The Hofmeister effect is usually more pronounced for anions than for cations and some ions have a stronger effect than others. The general order of the anions, termed the Hofmeister series is shown in Figure 1a.[7,24] The ions on the

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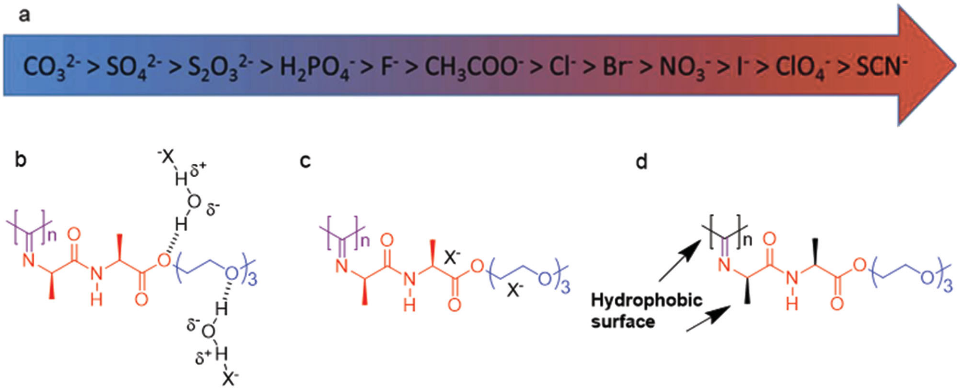

Figure 1. The Hofmeister series and the possible interactions between its anions and ethylene glycol-functionalized polyisocyanide in water. a) The general order of the anions in the Hofmeister series with the kosmotropes on the left side and the chaotropes on the right side. b) Hydrogen bonds between water molecules and the ethylene glycol side chains are destabilized through polarization by the anion X^-. c) Direct binding of the anion to the polymer, leading to ion accumulation at the polymer/water interface. The precise binding mode is not known in detail. d) The anions can interfere with the hydrophobic hydration of the polymer backbone by increasing or decreasing the surface tension at the polymer/water interface.

left-hand side of the series are kosmotropes, or well-hydrated ions; they decrease protein solubility and decrease the LCST of thermoresponsive polymers. The ions on the right-hand side are chaotropes, or poorly hydrated ions, which increase protein solubility and raise the LCST of thermoresponsive polymers.

Based on studies of PNIPAM[7] and ethyleneglycol-based triblock co-polymers,[8] we can expect that three different salt-hydration water-PIC interactions will contribute to the Hofmeister effect (Figure 1b–d). The first effect of the added ions is the destabilization of the hydrogen bonds between the polymer and its hydration water molecules (Figure 1b), which is expected to lead to a decrease in the gelation temperature, T_{gel}, of the PIC hydrogel. The approach of a well-hydrated anion to a hydrophilic site of the polymer reduces the water-polymer interaction and renders the polymer less soluble.[8] For such well-hydrated anions, the ability to polarize the hydrating water molecules correlates to the entropy of hydration, ΔS_{hydr}, of the anion.[25] For poorly hydrated anions, this effect is less pronounced. On the other hand, direct anion binding (Figure 1c) leads to an increase in T_{gel} as the binding of the anion to the polymer adds extra charge and hence, increases the solubility of the polymer. Poorly hydrated anions usually show a stronger binding affinity than well-hydrated anions.[25,26] The binding site of chaotropic anions to the polyisocyanide is not known at the moment. Earlier work has indicated that both the amide groups[27,28] and the ethylene glycol tails[8] may participate in direct binding. Since the amide groups of the polyisocyanide are difficult to access due to steric effects and their participation in intramolecular hydrogen bonding, we prefer not to speculate on the precise binding mode. Finally, interactions of the ions with the hydration shell of the hydrophobic surface of the polymer (Figure 1d) could either increase or decrease T_{gel}, depending on the nature of the particular salt.[29] Salts that also increase the interfacial tension at polymer/water or air/water interfaces reduce the gelation temperatures while salts with molar surface tension increments lower than unity increase T_{gel}.[8]

Our approach is to use rheology to study the effect of ions on the thermal response and on the stress response of the PIC hydrogels. We show that the anions follow the Hofmeister series, whereas cations have no significant effect on gel properties. The first part of the manuscript describes how the classical Hofmeister effect changes phase transition temperatures of PIC hydrogels by tens of degrees Celsius. The second part demonstrates how this effect is used to tailor the linear and nonlinear mechanics of hydrogels and how this is quantitatively described by known ionic parameters.

2. Results and Discussion

2.1. Gelation Temperature with Different Anions

In MilliQ water without any salt added, PIC shows a gelation temperature, $T_{\mathrm{gel}} = 19$ °C.[16] We define T_{gel} as the onset of the increase in the storage modulus G' with temperature. We prefer to use the onset of G' over the G'/G'', since G'' and thus the crossover temperature is frequency dependent. In addition, we determined the gelation temperature by a test-tube-tilting test that yields gelation temperatures on cooling the sample. Values of T_{gel} are given in Tables S1 and S2 (Supporting Information). The storage modulus was measured using macroscopic rheology, by applying a small oscillatory deformation at a frequency of 1.0 Hz while heating the sample at a rate of 1.0 °C min^{-1}. The PIC concentration was kept constant at 1.0 mg mL^{-1} (0.1 wt%) for all measurements. **Figure 2**a shows how the temperature profiles of the storage moduli change with the nature of the (sodium) salts added to the PICs solutions; the salt concentrations were kept constant at 0.5 M. From this figure, it is clear that the type of anion added has a large influence on the T_{gel} of the hydrogel. These changes in T_{gel} were also observed in micro-DSC experiments (Supporting Information, Figure S1). The ten anions studied follow the trend of the Hofmeister series: the chaotropic anions I^-, ClO_4^-, and SCN^- increase T_{gel}, while the other anions lower

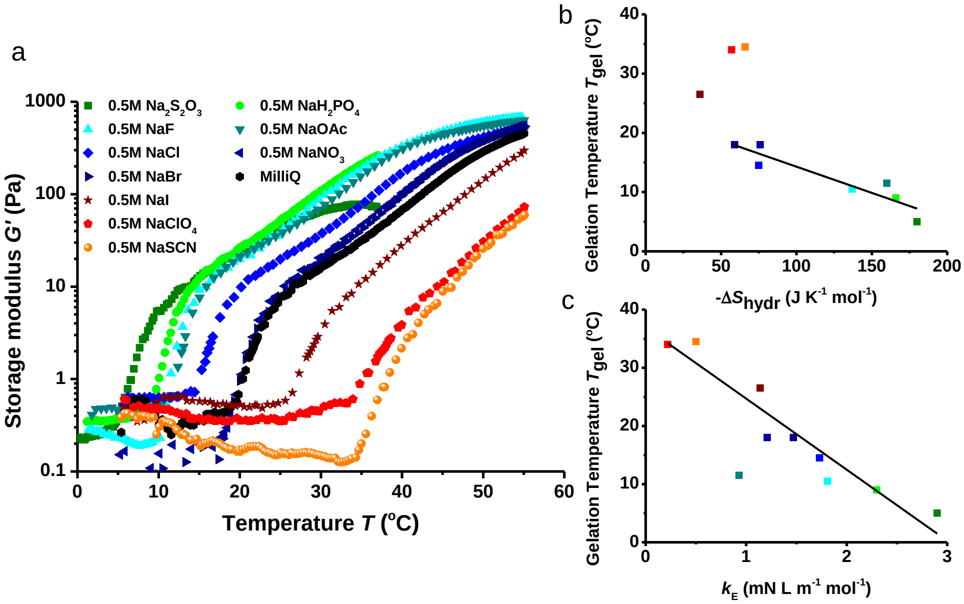

Figure 2. Linear rheology of PIC hydrogels with different sodium salts. a) Temperature ramps of the storage modulus show large variations in the gelation temperature for different anions. b) The gelation temperature T_{gel}, defined as the onset of the increase in G' relative to the baseline, plotted versus the entropy of hydration ΔS_{hydr} of the anions. The colors match the legend of panel (a). The solid line represents a linear fit for the kosmotropic anions, but the chaotropic anions cannot be described by this fit. The hydration entropy values are obtained from ref. [30]. c) T_{gel} plotted versus the surface tension increment k_E of the anions. The colors match the legend of panel (a). The gelation temperature decreases with increasing k_E over the whole range. The solid line represents a linear fit for all ions except for acetate. The k_E values are obtained from ref. [24], except for $H_2PO_4^-$ from ref. [31] and $S_2O_3^-$ from ref. [32]. An overview of the used data is given in Table S1 in the Supporting Information.

T_{gel} compared to MilliQ water (black curve in Figure 2a). The addition of the strongly kosmotropic sulfate or carbonate salts at the same concentration inhibited gel formation, which we attribute to a shift of T_{gel} to below 0 °C.

To gain better insight in the dominating contributions to the Hofmeister effect in the PIC solutions, we tried to correlate the observed gelation temperatures to the entropy of hydration, ΔS_{hydr}, or to the molar surface tension increment, $k_E = (\partial\Delta\gamma/\partial m)_T$,[33] of the anions.[7,8,24,25,34] For the PIC hydrogel, T_{gel} correlates very well to the anions' surface tension increment (Figure 2c), which suggests that the removal of hydration waters from the hydrophobic polymer backbone (the mechanism of Figure 1d) plays an important role in the gelation process. The only exception to this trend is the acetate anion, which is at the kosmotropic side of the Hofmeister series but has a very low k_E. This odd behavior has been associated to the poor bulk solvation of the methyl group of the acetate anion and the favorable contribution of the hydrophobic effect to the thermodynamics of transferring it to the water surface or interface.[24] The removal of hydration water from the polymer backbone is likely to lead to bundling of the individual polymer chains, which is a crucial step in the gelation process of the PIC hydrogel.[15]

We also observe a decrease in the gelation temperature with increasing hydration entropy of the anions (Figure 2b), but exclusively for the kosmotropic anions. This relation for the kosmotropes suggests that the gelation can also be correlated to the dehydration of the more hydrophilic ethylene glycol side chains of the polymers, as we suggested before.[15] Because the kosmotropic ions are most strongly hydrated, they can polarize the water molecules, which weakens the hydrogen bonds with the ethylene glycol side chains (mechanism in Figure 1b). This ability to polarize hydration water is directly correlated to ΔS_{hydr} of the anion.[25] Weakening of the hydrogen bonds leads to desolvation of the ethylene glycol groups at lower temperatures and consequently to a lower gelation temperature, in the presence of kosmotropic anions.

2.2. Gelation Temperature with Different Cations

Besides for anions, a Hofmeister series has also been established for cations. The usual ordering of the cation series for proteins[35,36] is

$$NH_4^+ > K^+ > Na^+ > Li^+ > Ca^{2+} > Mg^{2+}$$

The cations on the left-hand side decrease the solubility of proteins, while those on the right increase their solubility. The effects of cations, however, tend to be much less pronounced than those of anions,[37] because the cations are generally excluded from the polymer/water interface.[38,39] We expected an effect for the ethylene glycol functionalized PICs, since the oxygen atoms of the oligoglycol side chains may interact with cations in a similar way to crown ethers. Such direct cation binding would lead to additional charge and increased solubility of the polymer and thus to an increased T_{gel}.

We tested the influence of cations on the PIC hydrogel by adding different salts with chloride counter ions in a concentration of 0.5 M. The storage modulus of these samples measured as a function of temperature (**Figure 3**a) shows that gel formation is hardly affected by the cations. All samples, ranging from

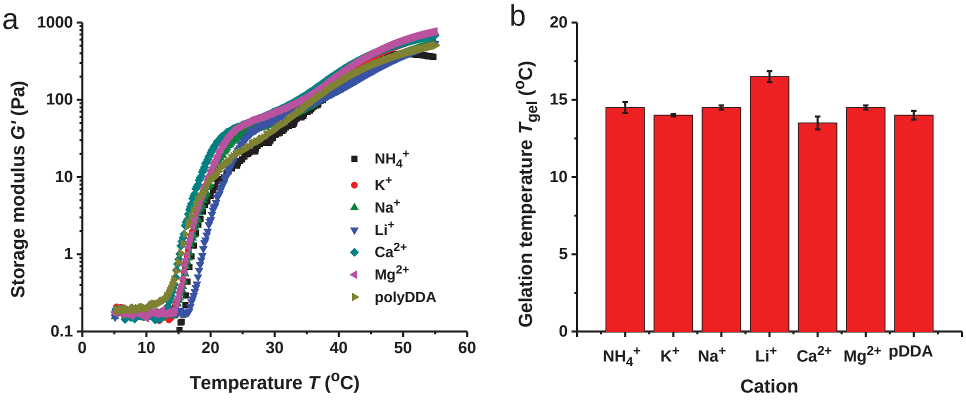

Figure 3. Variation of the cation does not significantly change the gelation temperature. a) Temperature ramps of the storage modulus for PIC gels with different cations, using chloride as counter ion with a concentration of 0.5 M. b) The gelation temperature, defined as the onset of the increase in G′, for gels with different cations. The error bars represent the standard deviation over two samples.

strong ammonium kosmotropes to the chaotropes Mg^{2+} and Ca^{2+}, show a T_{gel} of 14 ± 0.5 °C (Figure 3b); N.B. the lower T_{gel} compared to MilliQ water is the result of the chloride anions rather than the cations. The only exception is lithium, which shows a slightly higher T_{gel} than the other cations. This indicates that in the case of lithium, there may be some cation binding to the polymer, which is probably a result of its smaller size compared to the other cations used. We also tested the influence of a polymer poly-cation (poly(diallyldimethylammonium chloride), pDDA) on the PIC gel to amplify potential cation-polymer binding through an increased effective molarity mechanism (Figure 3a). Even in this case, only the chloride anions display their influence on the gelation behavior and, consequently, any direct interactions of the polymer backbone with the cations may be ruled out.

2.3. Gelation Temperature as a Function of Salt Concentration

In addition to varying the ion type, we also chose to vary the ion concentration. **Figure 4**a shows how the temperature profiles of G′ change with increasing concentrations of NaCl in the PIC gel. T_{gel} shows a clear decrease with increasing chloride concentration. As expected for kosmotropic anions,[7] we find a linear relation with the salt concentration (Figure 4c, blue line): $T_{gel} = T_0 + c_X [X^-]$, where T_0 is the gelation temperature in MilliQ, c_X is a polymer-dependent constant of anion X^- and $[X^-]$ is the anion concentration. For chloride, we find $c = -10.2$ °C L mol^{-1}, which is in line with other ethyleneglycol-based polymers.[8,9]

Increasing the concentration of the chaotropic salt sodium iodide leads to an increase in T_{gel} (Figure 4b). Now, the relationship between T_{gel} and the salt concentration is highly nonlinear

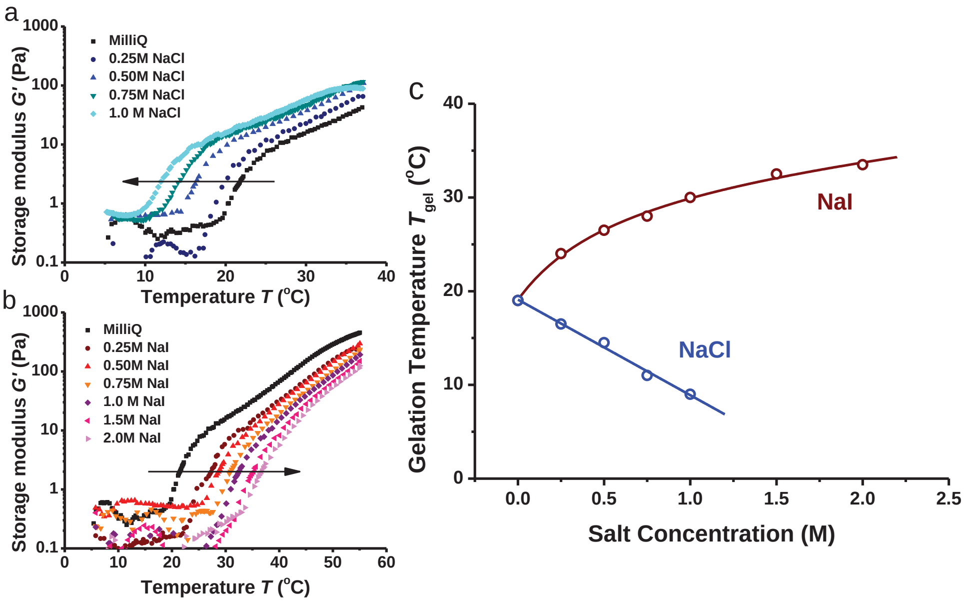

Figure 4. a) Temperature ramps of the storage modulus for PIC gels with increasing concentration of NaCl. b) Temperature ramps of the storage modulus for PIC gels with increasing concentration of NaI. c) The gelation temperature as a function of the salt concentration for gels with NaCl and NaI. The solid lines represent a linear fit for NaCl and a fit with Equation (1) for NaI.

(Figure 4c, red circles), which is an indication of binding of the iodide anion to the polymer, an effect that saturates at higher anion concentrations. The data for NaI in Figure 4c can be fitted to Equation (1), which is the same linear fit as described for the chloride anions, but now extended with a binding isotherm[7]

$$T_{\text{gel}} = T_0 + c_X[X^-] + \frac{B_{\max}K_A[X^-]}{1+K_A[X^-]} \tag{1}$$

Here, K_A is the binding constant of the anion to the polymer and $B_{\max}$ is the maximum increase in T_{gel} due to direct ion binding. From fitting the experimental T_{gel} values of the NaI gel series, we obtain K_A = 1.6 M^{-1} and $B_{\max}$ = 14.8 °C. This relatively high value for $B_{\max}$ highlights that, indeed, direct ion binding has a large effect on T_{gel}. The c_X value we find for NaI is +1.7 °C L mol^{-1}, so in contrast to NaCl where c_X is negative, there is a positive linear contribution of iodide to T_{gel}. Such a positive c_X value has also been observed before for ethylene glycol-based polymers in the presence of poorly hydrated anions.[8] It suggests that increasing the iodide concentration lowers the interfacial tension at the PIC-water interface, which leads to an increase in T_{gel}. This lower interfacial tension is consistent with the effects of poorly hydrated anions on the interfacial tension at oil/water interfaces, where Cl^- increases interfacial tension, while I^- and SCN^- decrease it.[40,41]

From the variations observed in T_{gel} in the presence of different anions, we conclude that the three interactions described in Figure 1 are all contributing to the overall Hofmeister effect of anions on the PICs. The chaotropic ions bind directly to the polymers and lower the surface tension at the polymer-water interface, both leading to a higher T_{gel}. The kosmotropic anions show a correlation with both ΔS_{hydr} and k_E, indicating that they destabilize hydrogen bonds to water and raise the surface tension at the polymer-water interface, both leading to a lower T_{gel}.

2.4. Mechanical Properties as a Function of Salt Concentration

The PIC hydrogels are not only thermoresponsive, but they are also highly responsive to relatively small mechanical stresses.[16] When a stress or deformation is applied to the PIC gel, the material rapidly stiffens, up to a factor of 100 compared to the original stiffness. This nonlinear mechanical response is known as strain stiffening and is common among gels made from biopolymers, such as actin, fibrin, and collagen,[42–45] but rarely found in man-made gels. The mechanical properties of a strain stiffening material such as the PIC gel are best described by three mechanical parameters. The first mechanical parameter is the stiffness of the material in the linear regime at low stress, known as the plateau modulus G_0. The second parameter is the stress onset for the stiffening response, the critical stress σ_c at which the material starts to stiffen. This critical stress represents the sensitivity of the material toward applied stresses. The third parameter is the stiffening index m, which represents the intensity of the stress response (or the responsiveness).[16]

We measured the entire stiffening response (all three parameters) of the PIC hydrogel using a pre-stress protocol [46], where the sample was subjected to a steady pre-stress σ with a small oscillatory stress $\delta\sigma$ superposed, leading to an oscillatory deformation $\delta\gamma$. The stiffness of the gel is represented by the differential modulus $K' = \delta\sigma/\delta\gamma$. **Figure 5**a shows K' as a function of the applied pre-stress for PIC gels with NaCl or NaI added at different concentrations. Each sample shows two well-defined mechanical regimes: a low stress regime where K' is constant with σ where K' equals the plateau modulus G_0, and a high stress regime where K' increases as a function of stress.

The addition of anions clearly has a large effect on the low stress regime of these gels. G_0 increases with increasing NaCl concentration, but decreases with increasing NaI concentration. The same trend is observed for the critical stress σ_c (Figure 5b). This means that the kosmotropic Cl^- anion increases the initial stiffness of the gel, but also increases σ_c, which makes the gel less sensitive to applied stress. On the other hand, the chaotropic anion I^- decreases the initial stiffness of the gel and makes the gel more sensitive to stress. At high stresses, however, the gel becomes completely insensitive to the addition of either salt and from $\sigma \approx 20$ Pa onward all curves perfectly overlap (Figure 5a). The curves approach a stiffening index $m = 3/2$ at high stress, which is the theoretical upper limit for m and is associated with enthalpically stretching a polymer

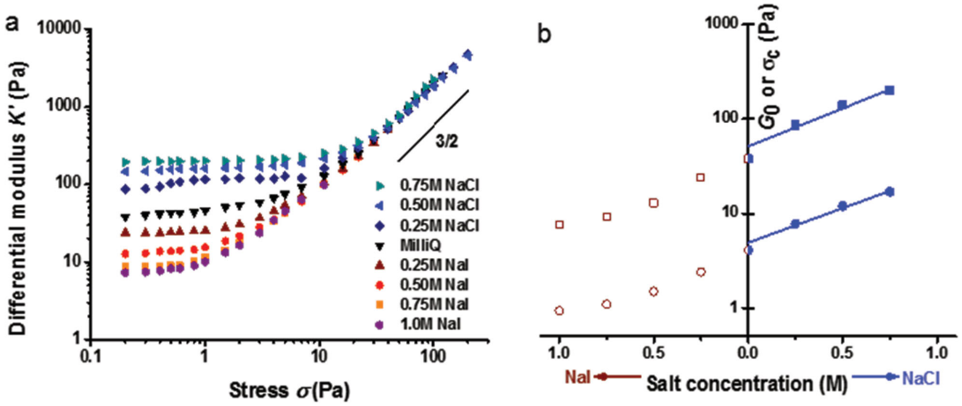

Figure 5. Nonlinear rheology of PIC gels with NaCl or NaI added. a) The differential modulus K' as a function of the applied stress σ for gels with different concentrations of NaCl or NaI at T = 37 °C. b) The plateau modulus G_0 (squares) and the critical stress σ_c (circles) for gels with NaCl (solid blue symbols) and NaI (open red symbols). The data were extracted from the curves in panel (a). The solid blue lines represent fits with Equation (2).

chain along its length.[15] The added salts do not influence the stretching response of these polymers.

The plateau modulus of PIC hydrogels show an exponential increase of G_0 with temperature, $G_0 \propto Te^{2\beta T}$, as a result of the thermal stiffening of the polymer chains and of the network as a whole.[15,16] Since the ions in the Hofmeister series directly affect temperature, we are able to describe G_0 as a function of ion concentration at a specific temperature. For chloride anions, with a linear dependence on the ion concentration (Figure 4c), the modulus becomes a function of the experimental temperature T and the ion concentration $[X^-]$ with the appropriate constant c_X

$$G_0\left(T,[X^-]\right) \propto \left(-c_X[X^-]+T\right)e^{2\beta\left(-c_X[X^-]+T\right)} \qquad (2)$$

For chaotropic anions, one also needs to consider the direct anion binding contribution by means of the binding isotherm term of Equation (1).

Figure 5b shows how both G_0 and σ_c of the hydrogel at T = 37 °C depend on the NaCl salt concentration. The data are fitted to Equation (2), using $c_{Cl} = -10.2$ °C L mol^{-1}, which was obtained from the linear fit of T_{gel} versus the NaCl concentration (Figure 4c). The fit yields an exponential thermal dependence of $\beta = 0.089$ K^{-1}, which is in excellent agreement with earlier T-dependent measurements.[16] For σ_c we find a similar exponential dependence on the NaCl concentration. For NaI we do not find an exponential decrease of G_0 and σ_c with salt concentration, since T_{gel} does not show a linear but a more complex dependence on the ion concentration (Figure 4c).

2.5. Mechanical Properties with Different Anions

Besides shifting the mechanical properties by modifying the salt concentration, one can also consider changing the nature of the salt. So the same pre-stress experiments were performed with gels containing different anions, using sodium as the cation. **Figure 6**a shows K' as a function of stress for these gels with a salt concentration of 0.5 M. At low stress, these curves follow the Hofmeister series for anions similar to the linear rheology. For the cations, we find that the mechanical properties of the gel are identical within the margin of error (Figure S2, Supporting Information).

The chaotropic anions decrease the linear stiffness G_0 but also increase the sensitivity toward stress by lowering σ_c, whereas the kosmotropes increase G_0 and σ_c. At high stress, all curves overlap again, approaching a stiffening index of 3/2, except for the gels with NaSCN and NaClO$_4$ which break at significantly lower stresses due to their low initial stiffness. These strong chaotropes also significantly decrease σ_c, which makes the material extremely sensitive to very small stresses. Earlier, we observed this ultrasensitivity regime for PIC hydrogels at temperatures very close to T_{gel} = 19 °C, where the network is only marginally connected.[16] Salt addition gives access to this highly interesting regime at any desired temperature. Thus, besides lowering T, which experimentally is not always possible, the addition of strong chaotropic ions can also be used as a tool to enter the extremely stress-sensitive marginal regime. In Figure 6a, K' spans almost four orders of magnitude with only one material at one polymer concentration, demonstrating that we can cover a very broad range of stiffness just by adding

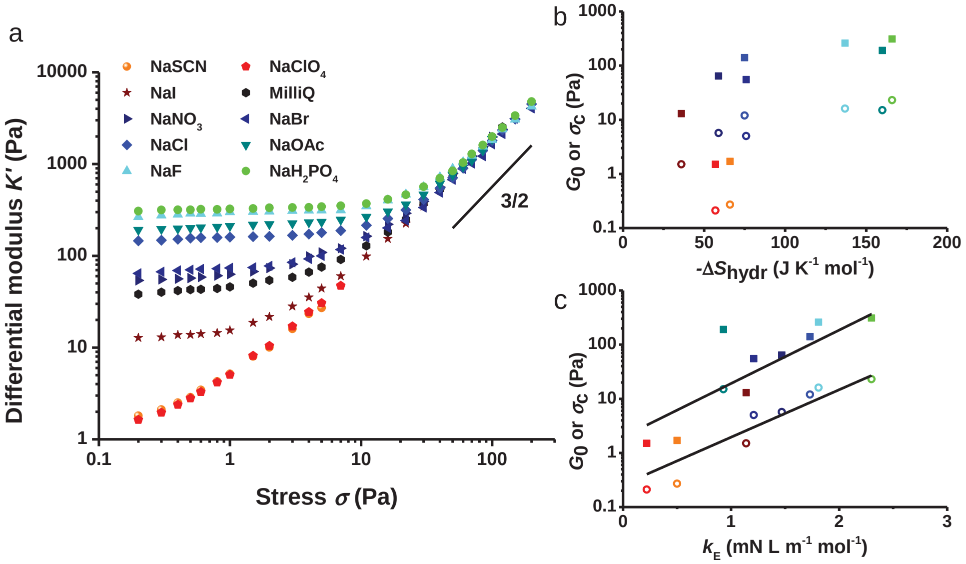

Figure 6. Nonlinear rheology of PIC gels with different sodium salts added. a) The differential modulus K' as a function of the applied stress σ for gels with different sodium salts at a salt concentration of 0.5 M and T = 37 °C. Chaotropic anions decrease the linear modulus of the gel but increase the sensitivity toward applied stress, while kosmotropic anions increase the linear modulus and decrease the sensitivity toward stress. Note that all gels behave similarly at high stress. b) The plateau modulus G_0 (squares) and the critical stress σ_c (open circles) for gels with different anions plotted versus the entropy of hydration of the anions. The colors correspond to the legend of panel (a). The hydration entropy values are obtained from ref. [30]. c) The plateau modulus G_0 (squares) and the critical stress σ_c (open circles) for gels with different anions plotted versus the surface tension increments of the anions. The colors correspond to the legend of panel (a). Both G_0 and σ_c show a remarkably good correlation for both chaotropic and kosmotropic anions. The solid lines represent fits with Equation (3). The surface tension increment values are obtained from ref. [24], except for $H_2PO_4^-$, from ref. [31].

different salts to the PIC gel or, more generally, demonstrating the large impact of the Hofmeister effect on the mechanical properties of hydrogels.

In analogy to the gelation temperature studies, we correlated the mechanical properties of the hydrogels to both ion parameters ΔS_{hydr} and k_{E}. Figure 6b shows an increase of both G_0 and σ_c with ΔS_{hydr} for the kosmotropic anions, while there is no trend observed for the chaotropes. Similar to the results of T_{gel}, we find a remarkably good correlation for G_0 and σ_c with the molar surface tension increment k_{E} (Figure 6c). As expected, the only exception to this trend is the acetate ion. The linear decrease of T_{gel} with k_{E} is expected to result in an exponential increase of G_0 and σ_c with k_{E}. Indeed, the data points in Figure 6c (except for NaOAc) that are recorded at T = 37 °C and anion concentrations of 0.5 M readily fit to Equation (3)

$$G_0(T,k_{\text{E}}) \propto (-bk_{\text{E}}+T)e^{2\beta(-bk_{\text{E}}+T)} \tag{3}$$

where constant $b = 12.2$ °C m mol mN^{-1} L^{-1} is obtained from the linear fit of T_{gel} versus k_{E} (Figure 2c). Fitting the experimental data with Equation (3) yields $\beta = 0.091$ K^{-1}, which is again very close to what we observed before as function of temperature. For σ_c we find a similar exponential increase with a slightly lower exponent $\beta = 0.081$ K^{-1}.

Equation (3) reveals that the surface tension at the polymer-water interface can be used to tune the mechanical properties of the PIC gels over a broad range. At a fixed temperature, increasing the surface tension leads to stiffer gels, while decreasing the surface tension leads to softer gels that are more responsive toward applied stress. The high-stress response of these gels is not affected by changes in the surface tension. The high-stress regime is dominated by enthalpic stretching of the already bundled polymer chains, which is not significantly influenced by the water-polymer and salt–polymer interactions at the polymer interface.

That the large differences in mechanical properties can be solely attributed to Hofmeister-based temperature effect and not to a change in the morphology is best supported by looking in more detail at Figure 6c. First, the critical stress changes as a function of k_{E}. When a difference in bundle diameters would be the primary origin of the observed difference hydrogel stiffness ($G_0 \propto d_{\text{B}}^3$), σ_c would be expected to remain constant as it is independent of the bundle diameter.[15] Second, the very similar temperature exponent β found for G_0 and σ_c strongly suggests that temperature effects indeed are dominating. Future small angle X-ray scattering (SAXS) experiments are planned to confirm this microscopically.

3. Conclusion

In conclusion, we showed how we can use the Hofmeister series to tune both the thermoresponsive and stress-responsive behavior of PIC hydrogels. Kosmotropic and chaotropic anions have opposite effects: addition of the former yields stiffer and less sensitive hydrogels, while the latter may be employed to gain access to ultrasensitive soft gels. Quantitatively, the (non-linear) mechanical properties can be tailored by the addition of anion X$^-$ considering its concentration and its molar surface tension increment

$$G_0(T,\text{X}^-) \propto \left(-b'k_{\text{E}}\left[\text{X}^-\right]+T\right)e^{2\beta\left(-b'k_{\text{E}}\left[\text{X}^-\right]+T\right)} \tag{4}$$

and

$$\sigma_c(T,\text{X}^-) \propto \left(-b'k_{\text{E}}[\text{X}^-]+T\right)e^{\beta\left(-b'k_{\text{E}}[\text{X}^-]+T\right)} \tag{5}$$

where b' is a polymer-dependent constant. Both Equations (4) and (5) hold as long as direct ion-polymer binding effects (only for chaotropes) are small, otherwise a binding isotherm should be included. The good correlation with the surface tension increment k_{E} of the added anions supports that changes in the surface tension at the polymer-water interface play a key role in the gelation process of these LCST polymers. Increasing this interfacial surface tension triggers the bundling of the polymer chains, which is the key step associated with gel formation at reduced temperature.

The addition of common additives such as salts to tune the mechanical properties of these gels can be exploited in biomedical applications of hydrogels, where varying temperature is not always possible. To improve the mechanics of hydrogels, usually other parameters such as the polymer concentration and cross-linking density are already optimized.[43] Increasing these parameters, however, will also decrease the porosity of the polymer network, which is often an undesired side-effect. The addition of salts to the PIC hydrogels does not affect the structure of the polymer network, but only influences the temperature of gelation and, consequently, the mechanical properties of the gel by changing the interaction between the polymer and the water. In this way, the kosmotropic ions can be used to increase the stiffness of the PIC gels, whereas the chaotropic ions can increase the sensitivity σ_c of the PIC gel toward applied stresses.

4. Experimental Section

Polymer Synthesis and Characterization: The isocyanide monomer[47] was polymerized following a previously described protocol.[16] The molecular weight of the polymer was characterized by viscometry. For these measurements, the polymer was dissolved in acetonitrile (0.1–0.6 mg mL^{-1}) and the intrinsic viscosity of these solutions was measured at 25 °C. The average viscosity molecular weight M_v of the polymer was calculated using the Mark–Houwink equation using previously determined Mark–Houwink parameters of $K = 1.4 \times 10^{-9}$ and $a = 1.75$.[48] This yielded an average viscosity molecular weight of 413 kg mol^{-1}, which corresponds to an average stretched polymer length of 163 nm.

Sample Preparation: All salts used in these experiments were purchased from Sigma Aldrich. The salt and polymer solutions were prepared with 18 MΩ cm purified water. The polyisocyanides were dissolved in cold water at a concentration of 2 mg mL^{-1} by stirring for 24 h in a cold room at 4 °C. Stock solutions of the salts were prepared at double the desired concentration. The polymer and salt solutions were mixed 1:1 on ice to obtain a 1 mg mL^{-1} polymer concentration and the desired salt concentration.

Rheology: Rheological measurements were performed on stress-controlled rheometers (Discovery HR-1 or Discovery HR-2, TA Instruments) in an aluminum parallel plate geometry with a diameter of

40 mm and a gap of 500 µm.[49] Samples were loaded into the rheometer at a temperature of 5 °C, or at 1 °C for samples with a very low gelation temperature, in the liquid state. To determine the gelation temperature, the sample was heated at a rate of 1.0 °C min^{-1} and the complex modulus G^* was measured by applying an oscillatory deformation of amplitude $\gamma = 0.04$ at a frequency of $\omega = 1.0$ Hz. The gelation temperature values given correspond to the onset of the increase in the storage modulus G' relative to the baseline.

To determine the plateau modulus G_0, the sample was heated to 37 °C and equilibrated for 10 min. Before measuring the storage modulus G' by applying an oscillatory deformation of amplitude $\gamma = 0.04$ at a frequency of $\omega = 1.0$ Hz, we confirmed by a frequency ($\omega = 10$–0.1 Hz) and strain sweep ($\gamma = 0.01$–0.1) that indeed, we probe the linear mechanical regime. The nonlinear regime was studied using a pre-stress protocol where the gel at 37 °C was subjected to a constant pre-stress $\sigma_0 = 0.2$–200 Pa with a small oscillatory stress superposed at a frequency of $\omega = 10$–0.1 Hz. The superposed oscillatory stress was at least ten times smaller than the applied pre-stress.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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