ACCOUNTS
of chemical research

Supramolecular Interactions in Chemomechanical Polymers

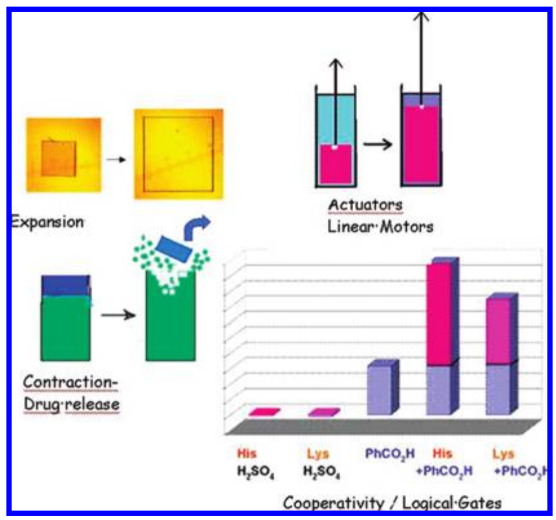
HANS-JÖRG SCHNEIDER*,† AND ROBERT M. STRONGIN‡

†FR Organische Chemie, Universität des Saarlandes, D 66041 Saarbrücken, Germany, ‡Department of Chemistry, Portland State University, Portland, Oregon 97207

RECEIVED ON DECEMBER 20, 2008

CONSPECTUS

Molecular recognition is the basis for the operation of most biological functions; outside of nature, it has also been developed to a high degree of sophistication within the framework of supramolecular chemistry. More recently, selective noncovalent interactions, which constitute molecular recognition, are being used in intelligent new materials that transform chemical signals into actions, such as the release of drugs. The presence of supramolecular binding sites allows chemomechanical polymers to operate as sensors and actuators within a single unit without the need for any additional devices such as transducers or power supplies.



A polymer can be designed so that a particular chemical substance, most often in aqueous surroundings, will trigger either a large expansion or a large contraction, depending on the mechanism. The translation of binding energy into mechanical motion can, with a suitable arrangement of the materials in tubes or on flexible films, be harnessed for unidirectional drives, flow control, the liberation of drugs, or the uptake of toxic compounds, among other applications. Miniaturization of the polymer particles allows one to enhance both the sensitivity and speed of the response, which is of particular importance in sensing.

The basis for the selective response to external effector compounds, such as metal ions, amino acids, peptides, or nucleotides, is their noncovalent interaction with complementary functions covalently bound to the polymer network. With suitable polymers, selectivity between structural isomers, and even between enantiomers, as triggers can be achieved. As with supramolecular complexes in solution, the underlying interactions in polymers comprise a variety of noncovalent binding mechanisms, which are not easy to distinguish and quantify, and more so with polymers that are not monodisperse. In this Account, we present systematic comparisons of different polymers and effector classes that allow, for the first time, the characterization of these contributions in chemomechanical polymers: they comprise ion pairing, metal coordination, stacking, cation$-\pi$, dispersive, and hydrophobic forces. In contrast, hydrogen bonding has a major role primarily in the hydrogel network structure itself.

The fully reversible polymer volume changes are essentially determined by water uptake or release. In gels derived from boronic acid, glucose can serve as a cross-linking effector in promoting contractions via strong, reversible covalent bond formation in a highly distinctive manner. Cooperativity between two different effector compounds is more frequently seen with such polymers than in solution: it leads to logical AND gates by different motions of the particles, with a direct communication link to the outside world. For example, with a polymer that bears several recognition sites, triggering peptides induce motion only if Zn^{2+} or Cu^{2+} ions are simultaneously present.

The molecular recognition mechanisms that cause volume changes in polymers share similarities with extensively studied supramolecular systems in solution, but there are also remarkable differences. In this Account, we bring the knowledge learned from solution studies to bear on our systematic analysis of polymeric systems in an effort to promote the effective harnessing of the forces involved in chemomechanical polymers and the smart materials that can be created with them.

Published on the Web 07/02/2009 www.pubs.acs.org/acr
10.1021/ar800274u CCC: $71.50

1. Introduction

Chemists, including the present authors, have studied supramolecular complexes and the underlying mechanisms of molecular recognition in much detail, relying on sophisticated instrumentation and data analyses. Nature achieves highly efficient control of biological systems without a battery of electronic devices. It is thus not surprising that scientists seek to systematically produce similar control systems that do not need electronics for their operation. Chemomechanical polymers are evolving as simple devices that can perform simultaneously as self-contained sensors and actuators within tiny particles.

Intelligent materials have a built-in capacity to respond to external stimuli with specific responses.[1] They are of interest for a manifold of possible applications, particularly as actuators and sensors.[2] Nanoparticles may be used as carriers for drugs or also gene delivery.[3] The release can be triggered by a temperature change, by magnetic fields, or by light.[4] Nanopores of mesostructured silica nanoparticles can perform as nanovalves;[5] they can be triggered by pH changes, light, redox reactions, competitive binding of another compound, or even enzymes.[6]

Polymers exhibiting shape changes triggered electrochemically mainly via applied voltage can perform as artificial muscles[7] or, for example, be used in microfluidics.[8] They rely, however, on a suitable power supply. Molecular imprinting is used to implement cavities in hydrogels, which selectively recognize compounds of the same or similar structures to those used in the imprinting process by shape and by noncovalent interactions.[9] Temperature or pH changes, as well as light or redox input, can control, for example, the helix transitions of peptides.[10]

Side-chain functionalization of polymers[11] leads to materials with promising applications ranging from liquid crystals to drug-releasing or electro-optical systems.[12] Noncovalent interactions between the side groups play a major role in controlling the structure of the resulting self-assembling materials but also allow the selective binding of external compounds, often by hydrogen bonding[13] but also by metal coordination. Gelation processes and corresponding sol−gel transitions can also be used, for example, for drug release, for instance, by dissolution of the drug-containing gel after adding an effector.[14] Hydrogels that undergo physicochemical changes upon external stimulation are increasingly used for many applications.[15]

Chemomechanical polymers, which exhibit reversible volume changes triggered by external compounds, were until now usually stimulated by pH gradients.[2b,16,17] They may function in drug release,[18] microfluidic devices, blood circulation control, etc. Only recently was it elucidated how suitable binding sites in such polymers, mostly hydrogels, may lead to selective molecular recognition of, for example, specific metal ions, amino acids, peptides, nucleotides, and carbohydrates. Interactions with antibodies[19] or with DNA[20] can also trigger macroscopic signals in such smart materials. Accordingly, one can design drug release devices that are triggered by the levels of such effector compounds in the body.[2b,21] The selective uptake of toxic compounds could also operate in this manner. The binding energy translated into mechanical motion can be used in actuators with linear movements.

This Account focuses on the recognition mechanisms of chemically triggered size changes of polymers, in particular on the similarities and remarkable differences in comparison to molecular recognition in solution. However, even the interactions in solution of host−guest complexes typically involve several binding mechanisms, which are not easy to distinguish and quantify.[22] The interactions within polymers are even more complex, and due to their mostly statistical nature, structural characterizations pose many more challenges. Although for these reasons conclusions regarding binding mechanisms in chemomechanical polymers are particularly daunting, it will be seen that, in principle, all noncovalent interactions studied to date involving supramolecular complexes in solution can exist and can be used in these smart materials, with sometimes surprising differences.

2. Principles: Expansion and Contraction; Water Uptake and Release; Phase Transitions?

Figure 1 illustrates the fundamental events stimulated by the reaction of guest molecules with the acceptor groups A within a chemomechanical polymer, such as **P1**−**P5** (Scheme 1). Contraction is the result of either noncovalent or covalent cross-linking between receptor groups and the guest or effector molecules, with concomitant release of water. Expansion results from uptake of the guest molecules, which require simultaneous uptake of solvation water. That water uptake or release is the major contributor to the observed volume changes has been shown by the comparison of water content before and after exposure of the polymers to external effector molecules. The water-swollen hydrogels already contain up to 98% water before the addition of an effector: all reported effector-induced changes refer to this starting value.

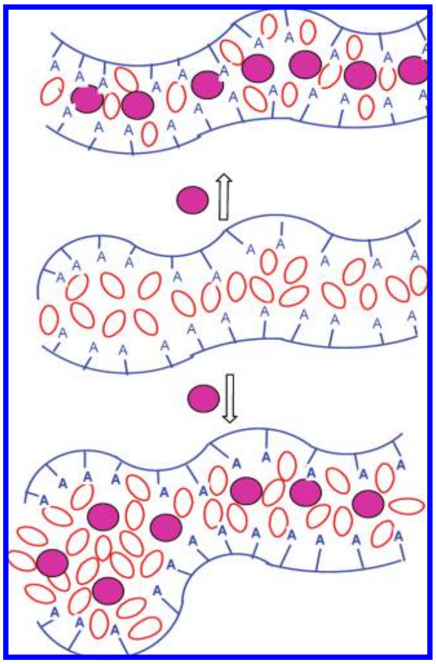


FIGURE 1. Contraction by guest molecule uptake, cross-linking, and water release (upper part) and expansion by guest molecule and solvation water uptake (lower part).

Figure 2 shows that indeed most of the observed volume change is due to additional water uptake, with only minor contributions from the effector molecules themselves.[23] The importance of solvation changes in host−guest complexation has been stressed for many years; in chemomechanical polymers such changes can be quantified by gravimetry[23] and also by FT-IR measurements.[24] In cross-linked chitosan hydrogels, the amount of bound water is related to pH.[25]

Scheme 1 lists the structural elements in the chemomechanical polymers discussed in the context of this Account, together with the most relevant binding contributions. The structures are simplified, and cross-linking bridges are not shown. Observed expansions typically increase with larger effector molecules (Scheme 2)[23] not only because of the space demand but also because of the need for more solvation water.

Size changes in chemomechanical polymers are usually attributed to phase transitions,[15,26] possibly including a multitude of states.[27] Phase transitions are characterized by abrupt changes in the physical properties of the gels as function of temperature, pH, solvent composition, etc. However, in cases where the volume changes of polymers such as **P1**−**P5** triggered by specific effector compounds were measured as a function of their concentration, no such discontinuity was observed. Rather, the profile shown for instance in Figure 3 indicates a steady expansion as function of the effector concentration, resembling a normal saturation isotherm. Although the influence of particle size and discontinuous cooperativity effects (see below) preclude an exact fitting of the isotherms,[23] approximate binding constants K can be inferred, which, for example, for AMP (Figure 3) amounts to $K = 20\ M^{-1}$. This latter value is not far in magnitude from the K values reported in homogeneous solutions for the interaction of AMP and ethylendiamine-type hosts.[28] Similar saturation-like profiles were observed for the contraction of the allylamine polymer **P5**[29] or for reactions of the chitosan hydrogel **P2**.[30]

The profiles in Figure 3 indicate that expansion starts only after some concentration of the effector builds up. In contrast, the spectroscopically measured absorption starts, as expected, immediately after the polymer particles are immersed into the effector solution. The explanation is that the surface of the particles first need to be loaded to some extent before the effector starts to move inside the network.

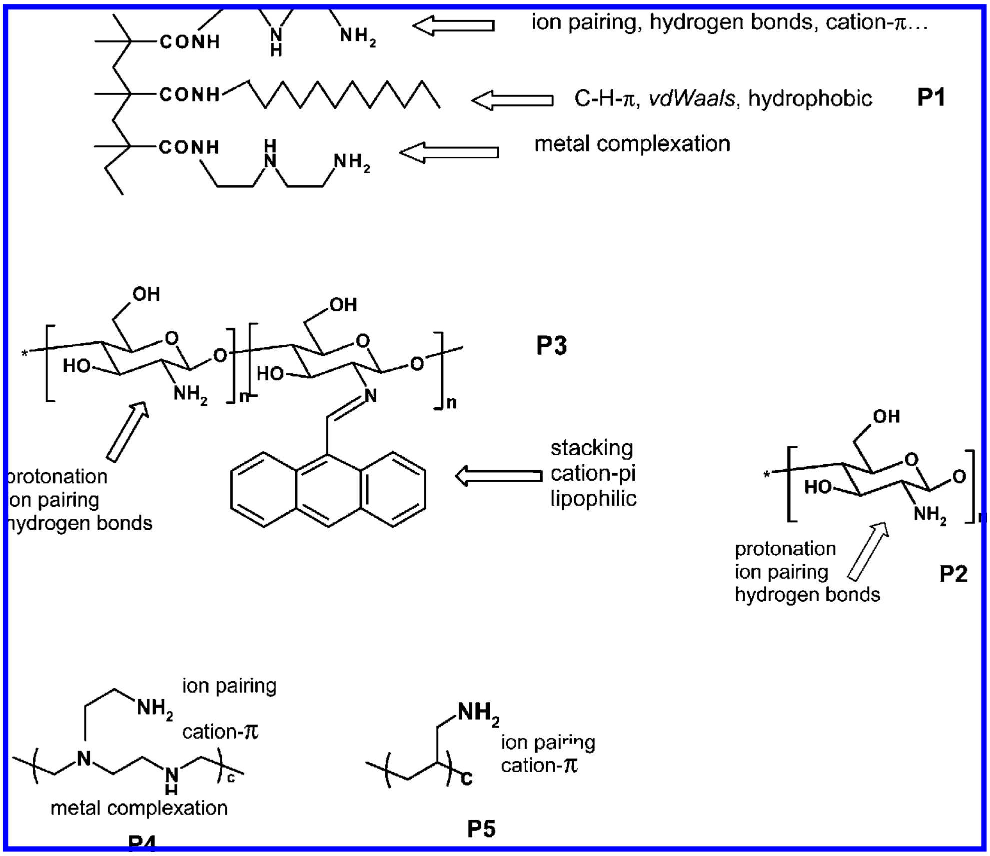
3. Interactions

3.1. Electrostatic and pH Effects, Ion Pairing, and Cross-Linking. Gel size changes induced by pH control are the oldest applications of chemomechanical polymers and have been discussed in detail.[15,17] The basis of the expansions is the electrostatic repulsion between cationic or anionic groups of the polymer as consequence of either lowering or raising the pH value. In most cases, the polymers bear either pH-sensitive amino or carboxylate groups; if both are present, one observes a symmetric pH profile. The break points obviously reflect the pK values of the participating ionogenic groups. It is, however, not primarily the electrostatic repulsion that leads to expansions, but essentially the uptake of water that is needed to solvate not only the charged polymer backbone but also the simultaneously imported counterions, which neutralize the backbone charge. The change of ionic strength concomitant with the pH change is the reason why the pH profiles are smooth as in Figure 4a only in presence of excess salts such as buffers and become quite different if neutral salt concentrations are lowered (Figure 4b).

Counterions exert another important effect by the formation of ion pairs with the charged backbone. The ensuing noncovalent cross-linking counteracts the expansion described above and leads, in the case of ionic chemomechanical polymers, to a strong dependence of the gel volume not only on the concentration of the counterion (visible also in Figure 4) but also on the nature of added salts.

Polyallylamine **P5** shows characteristic pH and ion effects[31] and distinct contraction in the presence of small anions[32] and some organic anions.[33] If chloride inside the polyallylamine

SCHEME 1. Structural Elements in the Chemomechanical Polymers[a]



[a] **P1**, polymethyl(methyl)acrylic derivative (contains to minor degree also other units, see ref 23); **P2**, chitosan; **P3**, chitosan−anthryl derivative; **P4**, polyethylenimin; **P5**, polyallylamin.

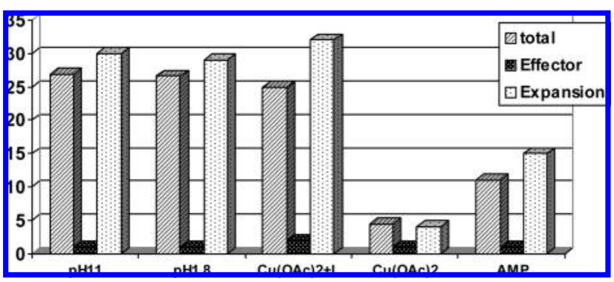
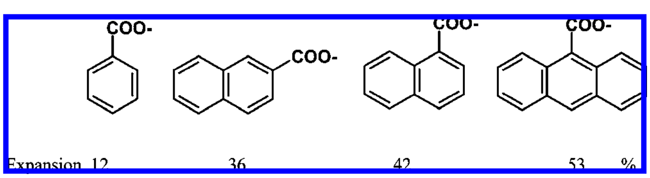


FIGURE 2. Weight increase (scaled per mg) compared with expansion, *V* (in % volume). From ref 23, reproduced with permission of Wiley/VCH, Copyright 2006.

SCHEME 2. Size Effects with Aromatic Effectors[a]



[a] Expansion in one dimension, polymer **P1**, pH effect (−65%) subtracted.[23]

gel is replaced by added acetate, the improved ion pairing with the carboxylate, which can use both oxygen atoms for contact to the backbone, leads to a 17% contraction (in one dimension), increasing to up to a 69% contraction with phos-

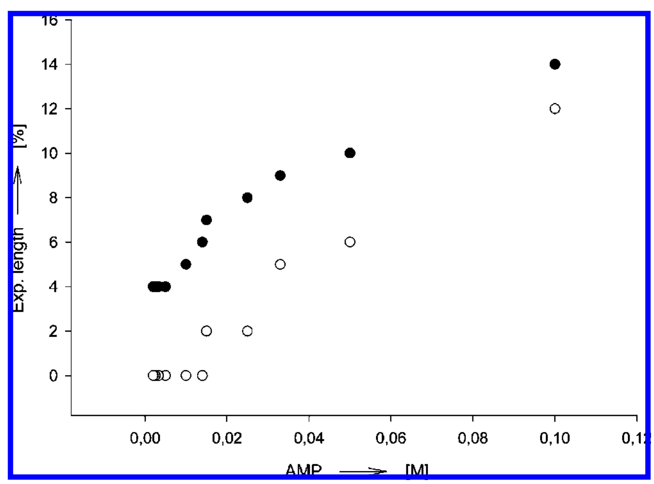


FIGURE 3. Expansion (length) as a function of AMP concentration: polymer **P1** (○) in the absence of buffer and (●) in presence of 0.02 M NaH_2PO_4 buffer. From ref 23, reproduced with permission of Wiley/VCH, Copyright 2006.

phate and with α,ω-dicarboxylates, due to stronger salt bridges.[29] The polyethyleneimine gel **P4** exhibits related pH profiles[34] and again small contractions upon added acetate and larger ones promoted by phosphate and aliphatic dicarboxylates.[35] The expansions observed with the chitosan gel

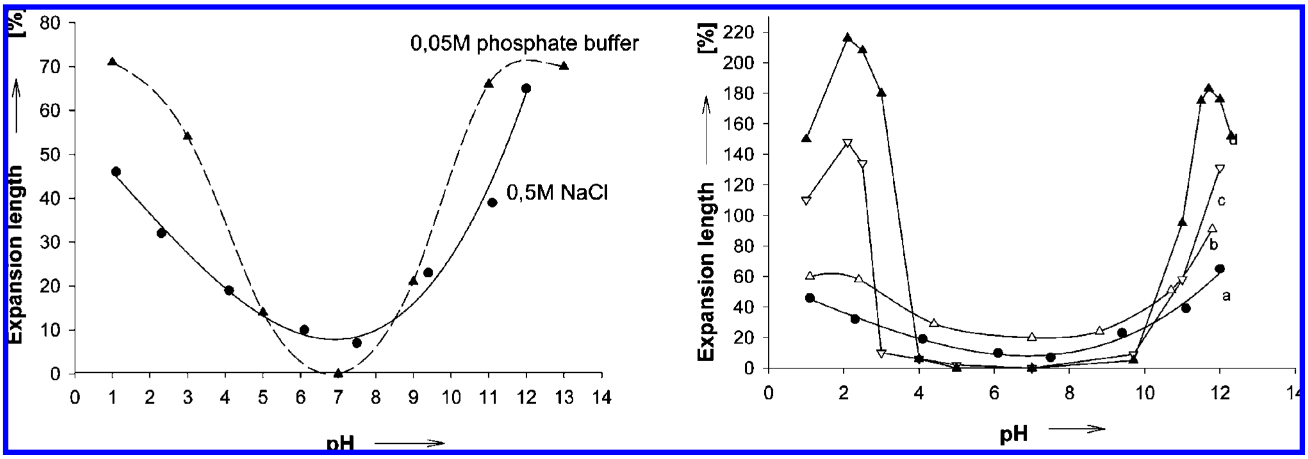


FIGURE 4. Size changes (left) of hydrogel **P1** as function of pH in (●) 0.05 M phosphate buffer and (▲) 0.5 M NaCl and pH profiles (right) at different salt concentrations: (●, a) 0.5 M, (△, b) 0.05 M, and (▽, c) 0.025 M NaCl solution and (▲, d) in water with very dilute HCl or NaOH. From ref 23, reproduced with permission of Wiley/VCH, Copyright 2006.

TABLE 1. Cross-Linking by Ion Pairing[a]

acid, XH	XH	X^-	acid XH	X^-
HCl	135	0	$(COOH)_2$	1 (X^{2-})
H_3PO_4	28 (XH_2^-)	0	$CH_2(COOH)_2$	12
CH_3COOH	131	5	$(CH_2)_2(COOH)_2$	105

[a] Expansion EF [%] of the chitosan gel **P3** by free acid XH and by anion X^- (EF in one direction; with EF = 0% for the gel at pH 7).[43]

P3 are large upon addition of free acids in comparison to the gel at pH 7, because **P3** is essentially unprotonated. The corresponding anions then lead to contraction by cross-linking (Table 1).[35] The exceptions are those expected by the effect of ion pairing: phosphate is monoprotonated at low pH, leading to cross-linking that counteracts the expansion promoted by the acid. Oxalic acid acts as an anion bearing two charges, due to its low p*K* value; the succinate anion leads to particularly small contraction due to the longer chain between the charges, which allows more freedom within the network.

3.2. Metal Ion Chelation. Guidelines for designing metal chelate binding sites in chemomechanical polymers emerge from coordination chemistry. For alkali or alkali earth ions, crown ether-type oxygen ligands are suitable; for heavier metal ions, ethylendiamine-type hosts such as in **P1** are most relevant. A hydrogel containing benzo-18-crown-6-acrylamide exhibits expansion in the presence of Ba^{2+} and does not respond to K^+ or other ions that are known to bind less efficiently. The expansion and a lower critical solution temperature (LCST) of the hydrogel was ascribed to the repulsion among the charged Ba^{2+} complex groups and the osmotic pressure within the hydrogel.[36]

Figure 5 shows that heavy metal ions trigger either large expansion (up to 390 vol % with the largest ion Pb^{2+}) or smaller contractions of gel **P1**.[37] Noticeably, the profiles show, in contrast to other effectors (see, for example, Figure 3), a

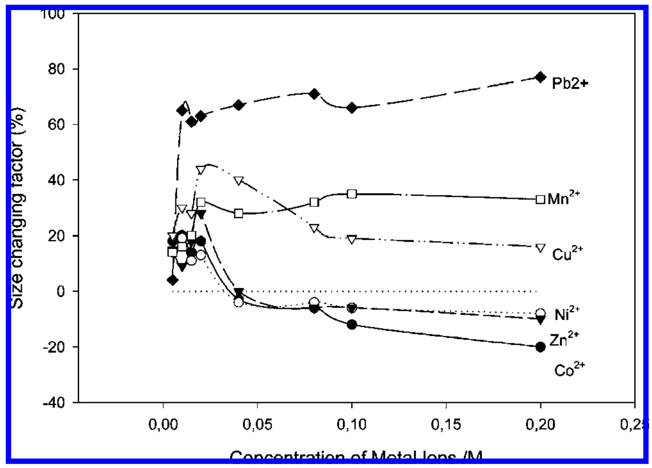
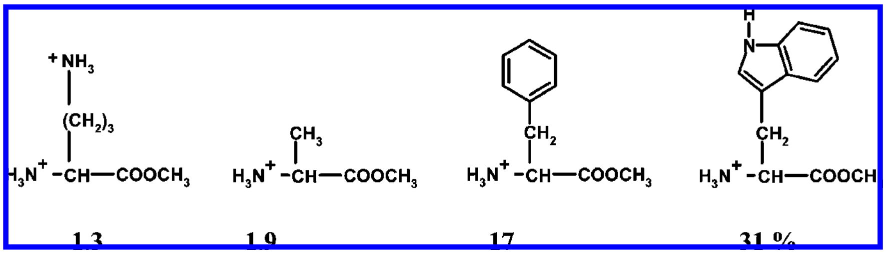


FIGURE 5. Size changes (length increase or decrease) of the polymer film **P1** in the presence of various metal ions.[37]

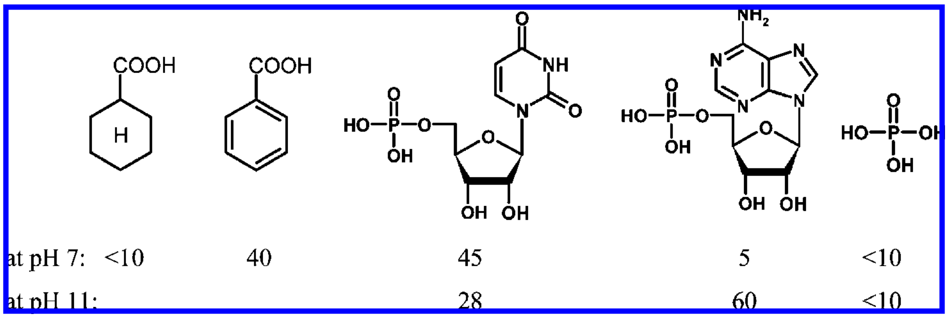
maximum, which for the given gel particle size occurs around 0.02 M. Metal content measurements established that the correspondingly calculated amount of ions were present in the gel particles. The decrease after reaching the maximum expansion, at which approximately one metal ion is occupying one ethylendiamine unit, is obviously due to more weakly bound additional ions, which occupy other centers in the polymer. As expected, the affinity of these metal ions is so strong that all of the ethylendiamine binding sites are occupied. In contrast other effectors such as nucleotides use only part of the available binding sites, as a function of their concentration in the solution. Obviously, the metal ions are not making use of ethylendiamine units in opposing polymer strands after binding to one en unit, because this would lead to contraction and a smaller binding capacity than measured. This and the strong affinity of, for example, Cu or Zn ions to polymers such as **P1** is the basis for the promising cooperativity effects discussed in section 3.6. Again, the uptake of solva-

SCHEME 3. Volume Expansions [%] on Chitosan-Anthrhyl Polymer **P3** with Different Amino Acid Esters[a]



[a] pH and salt effects deducted.[42]

SCHEME 4. Expansion with Polymer **P1** (in % volume) at Different pH Values[a]



[a] Values at pH 11 corrected for the effect of pH alone (about 70%).[23]

tion water is the major contributor to the expansion, as exemplified in Figure 2 with the effect of $Cu(OAc)_2$.

3.3. Hydrogen Bonding. Hydrogen bonding can only play a minor role in effector binding to hydrogels, due to the strong competition with excess water. This is borne out by the fact that with all the chemomechanical polymers we have investigated (**P1**−**P5**), electroneutral compounds even possessing strong donor/acceptor functions such as ureas, never induced detectable size changes. However, the polymer network itself and the water inside the gels is strongly stabilized by bridges between H-donor and acceptor groups,[38] particularly in side-chain modified synthetic polymers.[12] Size changes in hydrogels are essentially due to hydrogen bonding with water, which at higher temperature breaks down, with resulting water loss and contraction.[39] Amphililic hydrogelators usually contain amide or hydroxy groups, which allow stabilization of fibers, etc., in the gelation process.[14] Hydrogen bonding plays a major role particularly for organic gelators;[14] and in hydrophobic gels or gel cavities, where water minimally competes, also in sol−gel transitions[40] and in the transition between swollen and collapsed gel phases.[41]

3.4. Stacking and Cation−π Interactions. The well-known attraction between aromatic units can be used in chemomechanical polymers containing suitable binding units, such as with the chitosan derivative **P3** and different amino acids (Scheme 3).[42] The largest expansion is seen with tryptophan and phenylalanine. Smaller but still noticeable effects of aliphatic residues are due to hydrophobic interactions (section 3.5).

The importance of cation−π effects is most clearly seen in the expansions triggered by aromatic effectors with the polymer **P1** (Scheme 4), where saturated rings contribute nothing.[23] A dramatic manifestation of the cation−π effect is evident in the effect of aromatic effectors on chitosan gels **P3**.[30] Tartaric acid or its *O*-*t*-butyl derivative is completely inactive; but aromatic substituents as in the *O*-benzoyl derivative lead to sizable volume changes of the gel, which moreover depend on the chosen enantiomer. MAS 1-H NMR spectra of the complexed gel (Figure 6) exhibit large upfield shifts of the axial glucose protons of the chitosan chain of approximately 2 ppm. This clearly indicates a position of these protons in the shielding cone of the effector phenyl substituent; the corresponding conformation allows strong interactions of the effector aryl unit with the protonated amino group of chitosan. Noticeably, the L-enantiomer leads to much smaller signal changes, in line with its much smaller activity, which allowed for the first direct translation of chiral recognition into mechanical motions.

3.5. Dispersion Forces, Lipophilic Binding. van der Waals and CH−π interactions can also play a role in the interaction of aromatic residues with glucose axial protons in structures such as those shown in Figure 6. However, in view of the

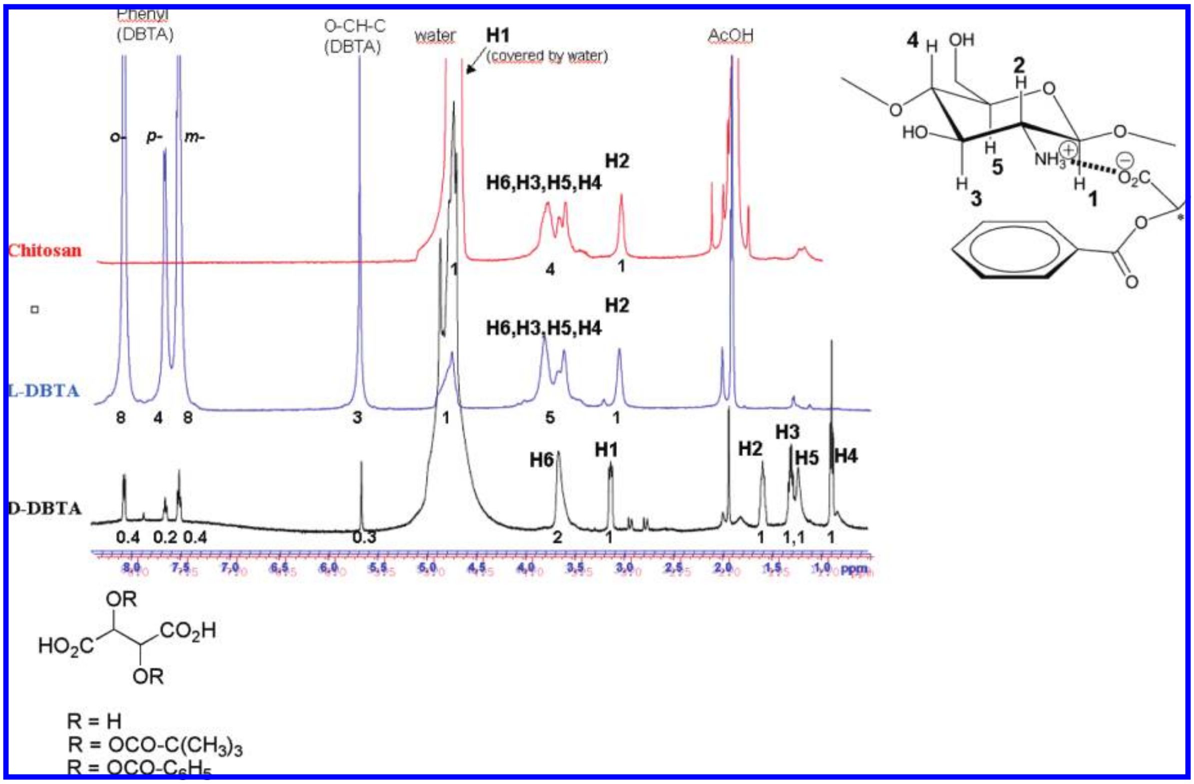
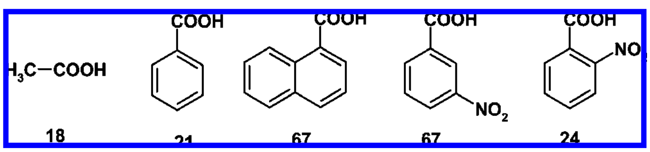


FIGURE 6. MAS 1-H NMR spectrum of the complex between chitosan and *O*-dibenzoyl-tartaric acid (DBTA) enantiomers as effectors and underlying structure.[30]

SCHEME 5. Typical Contractions Triggered by Carboxylates (%, in One Direction) with the Polyallylamine-Derived Hydrogel **P5**[29]



inactivity observed with neutral effectors,[43] such contributions are much weaker than, for example, the cation−π effect. Studies with a polyallylamine-derived hydrogel **P5** show, however, that dispersive interactions between effector molecules can play a major role in chemomechanical activity[29] (Scheme 5). The presence of aromatic units leads to remarkably enhanced contractions even with monoacids, as seen with benzoic and naphthoic acids. With all these effectors, a plateau of the volume change is reached only with a large excess of effector over the available binding sites within a gel piece. These observations are in line with interactions between the effector molecules, which in the case of benzoic and naphthoic acids may be due also to stacking (Figure 7). The large contraction seen with *m*-nitrobenzoate however points strongly to a major contribution from dispersive effects, as found in independent studies with porphyrin complexes.[44] This is corroborated by the strikingly diminished gel size changes with *o*-nitrobenzoate: as in the independent measurements with complexes in solution, steric hindrance of coplanarity with the phenyl residue leads to diminished strength of complexation (Figure 7).

Lipophilic or hydrophobic interactions, which even in solution complexes are difficult to separate from dispersive forces, play a decisive role, for example, in steroid-imprinted polymers[17] and in the distinction of amino acid side chains in metal-mediated complexation with chemomechanical polymers (see section 3.6). The long alkyl substituents introduced in the polymer **P1** provide for a significant lipophilic or hydrophobic interaction. Besides the amino acid selectivity discussed in section 3.6, this is clearly seen in the abrupt change from expansion to contraction of the gel **P1** in the variation of tetraalkylammonium effectors (Figure 8). Here the normal expansion, which increases with the size of the ammonium effector, changes to contraction with the tetrahexyl compound, due to a collapse of network parts by stronger association with the polymer alkyl chains.

3.6. Cooperativity and Logical Gate Functions. Cooperativity between two effector molecules in the sense of a logical AND gate is known from solution chemistry, mostly in the form of a signal dependence not only on the presence of an analyte molecule but also on the pH. With chemomechanical polymers, cooperativity turns out to be a more common

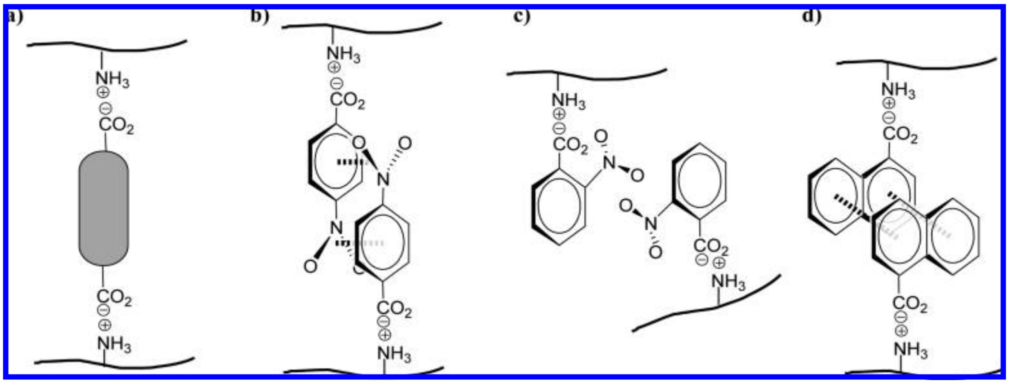


FIGURE 7. Noncovalent cross-linking in the hydrogel **P5** with (a) dicarboxylic acids, (b) *p*-nitrobenzoic acid, (c) *o*-nitrobenzoic acid, and (d) stacking of naphthyl groups.[29]

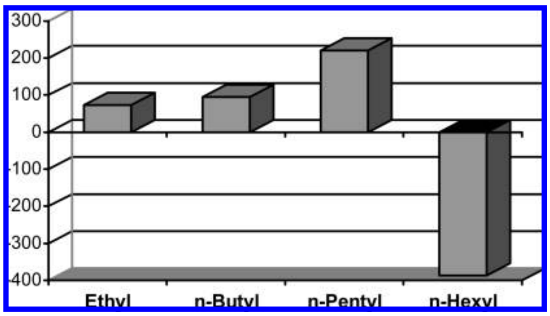
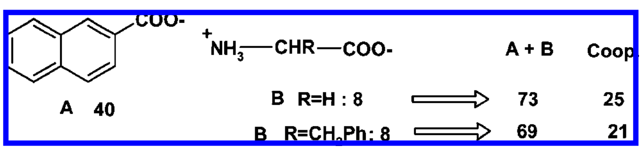


FIGURE 8. Size changes (vol %) of the polymer gel **P1** by tetraalkylammonium hydroxides.[23]

SCHEME 6. Cooperativity between Naphthoic Acid as Component A and Amino Acids as Effector B (% Contraction in One Direction) in Gel **P4**[a]



[a] If A and B react simultaneously contraction is enhanced by 25% or 21%.[35]

phenomenon. Even simple gels such as the polyethyleneimine polymer **P4** show cooperativity (Scheme 6) between, for example, naphthoic acid as component A and amino acids as effector B. If both A and B react, the resulting contraction is enhanced by 20−25%.[35] Figure 9 illustrates how (a) the replacement of chloride by naphthoate can lead to cation−π interactions and COO^- $^+NH_3$ salt bridges and (b) the binding of the second effector amino acid is enhanced by additional COO^- $^+NH_3$ salt bridges, with measurable concomitant water content changes.

A more dramatic, and for many applications very useful, cooperativity in the sense of yes/no responses of the polymer is possible with metal complexes operating in the ethylendiamine-containing polymer **P1**.[45] Here, amino acids or peptides promote volume changes only in presence of, for example, Cu^{2+} or Zn^{2+} ions, depending moreover on the nature of underlying amino acids. Scheme 7 shows how the presence of the metal ions, which themselves lead to only moderate size changes (see section 3.2), allows by occupation of free coordination sites the action of added amino acids or peptides, which otherwise are completely inactive. As mentioned above, the interaction with the lipophilic alkyl chain L implemented in polymer **P1** leads to discrimination among amino acids according to the lipophilicity of their side chains.

3.7. Sugar Recognition in Chemomechanical Gels. To date glucose is the most extensively studied sugar in fully synthetic chemomechanical polymers. This is driven by the need for minimally invasive or noninvasive glucose monitoring and insulin delivery systems.[46] In polyacrylamide hydrogels, relatively unspecific interactions with glucose lead to swelling in response to glucose.[47] Poly(*N*-isopropylacrylamide)-based hydrogels exhibit volume phase transitions upon the addition of sugars arising from changes in structured water and hydrophobic hydration around the isopropyl moieties, rather than via direct interaction between the sugars and the polymer.[48]

Enhanced properties are attained via glucose-imprinted gels.[15,49] Molecularly imprinted polymers (MIPs) function mainly based on shape selectivity and are therefore outside the scope of this Account. However, there are examples of chemomechanical MIPs for glucose that incorporate enhanced supramolecular interactions. One of these, inspired by natural lectins, employs amino acid-mimicking functional monomers. It has affinities for glucose in the range of 1.7 mM, comparable to concanavalin A.[50] In another example of a glucose-selective chemomechanical MIP, ion-pairing interactions were used in imprinting gels with glucose phosphate. This material exhibited binding selective for glucose over fructose.[51]

Configurationally biomimetic imprinted polymers (CBIPs) exhibit enhanced interactions between monomers and the template or analyte. For instance, hydroxyethyl methacrylate

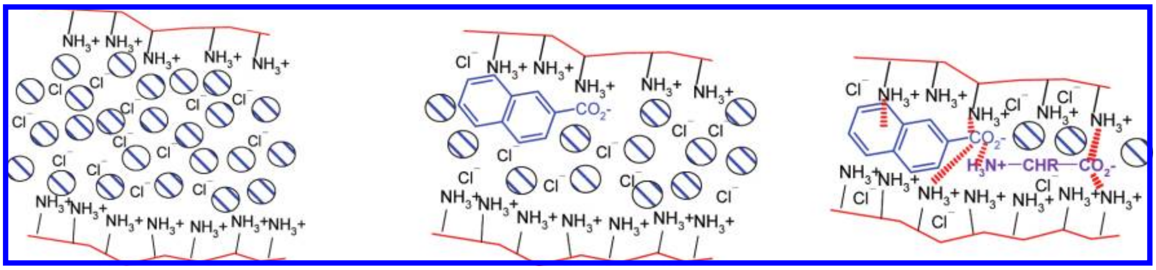
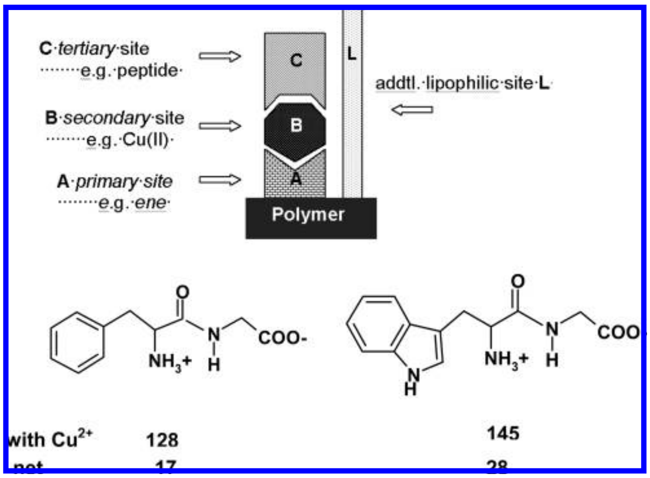


FIGURE 9. Model for cooperative contraction mechanism in gel **P4**, see text; the relevant noncovalent interactions are indicated as dashed lines.[35]

SCHEME 7. Ternary Complexes with Cooperativity between Metal Ions and Amino Acids or Peptides[a]



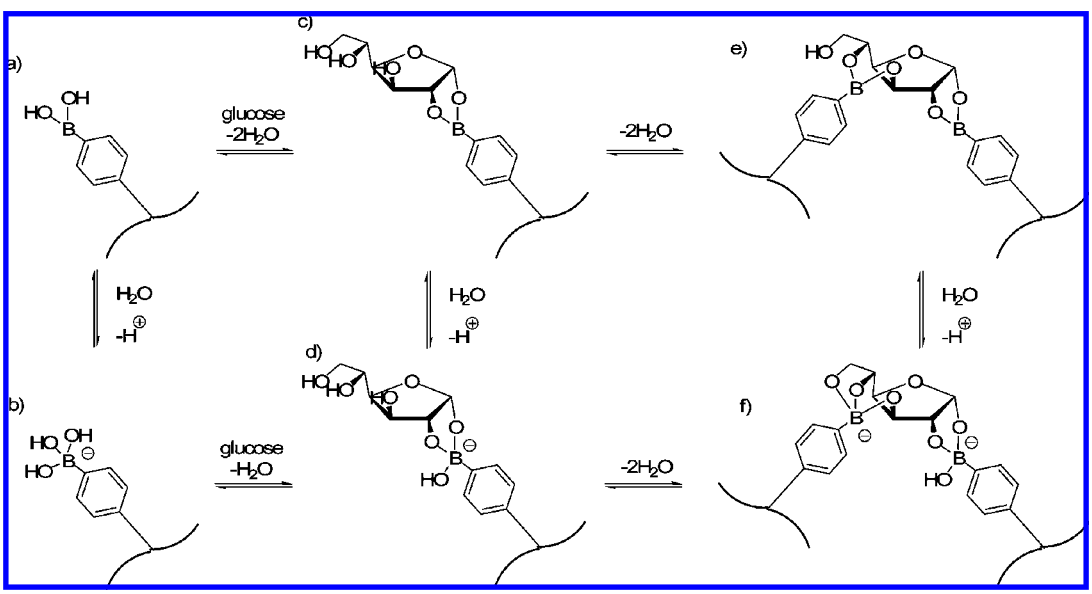
[a] Examples for expansion triggered by peptides (in one dimension); net indicates effect of Cu^{2+} alone deducted.[45]

monomer was used in a recently reported CBIP to enhance hydrogen-bonding interactions with glucose. The binding capacity for glucose in glucose-imprinted copolymers from hydroxyethyl methacrylate and methacrylic acid was found to be 5.5 times higher than that for galactose.[52]

3.8. Fast Covalent Interactions. Reversible covalent binding to *cis*-diols by boronic acids has inspired the design of several chemomechanical gels responding to glucose.[2b] These materials can be subdivided into two main classes: (i) optical signal transduction components and (ii) those for potential use in automated insulin delivery. These potential applications have been reviewed previously.[2b]

To address the challenge[53] of attaining materials functional in biological fluids, we reported the first boronic acid-based chemomechanical polymer composed entirely of synthetic materials that exhibited selective size changes in response to glucose concentration in human plasma.[54] Unlike analogous hydrogels,[2b] flexible supramolecular binding sites (Scheme 1, structure **P1** with arylboronic acid moieties) were appended to a pre-existing polymer (PMMA). The gel exhibited reversibility and insignificant interference from other common blood sugars.

SCHEME 8. Glucose−Boronate Complexes[a]



[a] The preferential binding of the α-glucofuranose was demonstrated in solution (refs 55a and 63) and later observed in hydrogels (ref 58).

Complexes a, c, and e in Scheme 8 predominate under neutral, nonaqueous solution conditions.[55a] However, when cyclic esters such as c and e form upon glucose addition, the boron atom becomes more Lewis acidic. In aqueous media, the equilibrium favors structures such as d and f over c and e, respectively. In a hydrogel, charge formation leads to a Donnan potential and a greater free energy of mixing with water. Thus, monodentate binding as shown in structure d promotes water uptake and swelling.

In biological fluids, however, high ionic strength renders Donnan potential effects insignificant. This was addressed in hydrogels designed to promote cross-linked structures such as f via the formation of a supramolecular complex in which glycol moieties localize sodium cations to stabilize the boronate dianion structures.[56] This promotes gel shrinkage.

In our chemomechanical polymer, glucose-induced shrinkage was tuned by varying the size of the modifiers or cross-linkers.[47] Boronic acid-based gels can exhibit either swelling[57] or shrinkage[58] at high ionic strength conditions by optimization of the concentration of appended boronic acid groups and properties including gel hydrophobicity.[50−59]

Ammonium cations also stabilize boronate dianion structures and promote cross-linking[60] and resistance to pH fluctuations.[61] The incorporation of tertiary amines in a boronic acid hydrogel has also afforded enhanced glucose-induced cross-linking.[62] Interestingly, in related solution studies, boron−nitrogen interactions are most significant in relatively hydrophobic environments.[63] Importantly, selectivity is automatically addressed via the cross-linking mechanism, because it is well-known that glucose is the only major physiologically relevant monosaccharide that forms a bis-boronate structure readily under neutral conditions.

4. Conclusions

Chemomechanical polymers hold a vastly unexplored promise for a large variety of applications. It is hoped that this Account will trigger more investigations, which will address the implementation of more sophisticated molecular recognition sites and the practical use of such smart materials. This will be aided by a better understanding of the fundamental processes involved in chemically induced size changes of these polymers. Systematic analyses with a variety of polymers and effector compounds and advanced methods for the inherently challenging structural characterizations will greatly contribute to this new field of supramolecular chemistry.

HJS thanks the coworkers whose names appear in the references from Saarbrücken, and the Alexander von Humboldt foundation for support. RMS is grateful to the NIH for funding via grant RO1 EB002044.

BIOGRAPHICAL INFORMATION

Professor Hans-Jörg Schneider studied chemistry in Tübingen, München, and Berlin. He obtained his diploma in 1963 and his Ph.D. degree in 1967 at Tübingen (with Prof. M. Hanack). During 1967−1969, he was Postgraduate Research Fellow at the University of California, San Diego (with Prof. R.C. Fahey); during 1969−1971, he worked as Research Assistant of Prof. W. Hückel, Univ. Tübingen. In 1972, he became Professor for Organic Chemistry at the Universität des Saarlandes. The early research interest of Professor Schneider was conformational analysis, strain−reactivity relations, and NMR spectroscopy. Later his group became involved in studies on mechanisms of molecular recognition, new enzyme and receptor analogs, DNA interactions, and artificial esterases or nucleases. More recently his major activity involved molecular recognition in chemomechanical polymers.

Professor Robert Strongin was born in Brooklyn, New York, in 1955. He received a B.A. with Honors in Chemistry from Temple University and a Ph.D. in Organic Chemistry from the University of Pennsylvania under the guidance of Professor Amos B. Smith, III. He was Philip and Foymae Kelso West Distinguished Professor in Chemistry at Louisiana State University before moving to the Department of Chemistry at Portland State University. Professor Strongin's research interests include the design, synthesis, and evaluation of functional chemical sensing agents and new redox and chromophore materials.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: ch12hs@rz.uni-sb.de.

REFERENCES

1 (a) *Intelligent Materials*; Shahinpoor, M., Schneider, H.-J., Eds.; Royal Society of Chemistry: Cambridge, U.K., 2007. (b) Dai, L. *Intelligent Macromolecules for Smart Devices*; Springer: London, 2004.

2 *Polymer Sensors and Actuators*; Osada, O., Rossi, D. E., Eds., Springer: Berlin, 1999. (b) Schneider, H.-J.; Kato, K.; Strongin, R. M. Chemomechanical polymers as sensors and actuators for biological and medicinal applications. *Sensors* **2007**, *7*, 1578–1611.

3 Zhang, Y.; Yu, A.; Wang, Y. J. Polymer nanoparticles for the delivery of drug and gene. *Prog. Chem.* **2008**, *20*, 740–746. See also: Schexnailder, P.; Schmidt, G. Nanocomposite polymer hydrogels. *Colloid Polym. Sci.* **2009**, *287*, 1–11.

4 See, for example: Lu, J.; Choi, E.; Tamanoi, F.; Zink, J. L. Light-activated nanoimpeller-controlled drug release in cancer cells. *Small* **2008**, *4*, 421–426.

5 Overview: Angelos, S.; Johansson, E.; Stoddart, J. F.; Zink, J. I. Mesostructured silica supports for functional materials and molecular machines. *Adv. Funct. Mater.* **2007**, *17*, 2261–2271.

6 Patel, K.; Angelos, S.; Dichtel, W. R.; Coskun, A.; Yang, Y. W.; Zink, J. I.; Stoddart, J. F. Enzyme-responsive snap-top covered silica nanocontainers. *J. Am. Chem. Soc.* **2008**, *130*, 2382–2383.

7 *Electroactive Polymer (EAP) Actuators as Artificial Muscles - Reality, Potential and Challenges*, 2nd ed.; Bar-Cohen, Y., Ed.; SPIE Press: Bellingham, WA, 2004. Shahinpoor, M. Ionic polymer-conductor composites as biomimetic sensors, robotic actuators and artificial muscles - a review. *Electrochim. Acta* **2003**, *48*, 2343–2353. Otero, T. F.; Cortes, M. T. Artificial muscles with tactile sensitivity. *Adv. Mater.* **2003**, *15*, 279–282. Kaneko, D.; Gong, J. P.; Osada, Y. Polymer gels as soft and wet chemomechanical systems - an approach to artificial muscles. *J. Mater. Chem.* **2002**, *12*, 2169–2177. Smela, E. Conjugated polymer actuators for biomedical applications. *Adv. Mater.* **2003**, *15*, 481–494. Mirfakhrai, T.; Madden, J. D. W.; Baughman, R. H. Polymer artificial muscles. *Mater. Today* **2007**, *10*, 30–38. Bar-Cohen, Y. Biomimetics using electroactive polymers (EAP) as artificial muscles - A review. *J. Adv. Materials* **2006**, *38*, 3–9, and references cited therein.

8 Bassetti, M. J.; Chatterjee, A. N.; Aluru, N. R.; Beebe, D. J. Development and modeling of electrically triggered hydrogels for microfluidic applications. *J. Microelectromech. Syst.* **2005**, *14*, 1198–1207. See also: Lin, G.; Chang, S.; Kuo, C. H.; Magda, J.; Solzbacher, F. Free swelling and confined smart hydrogels for applications in chemomechanical sensors for physiological monitoring. *Sens. Actuators, B* **2009**, *136*, 186–195.

9 Recent references on imprinted materials: Ye, L.; Mosbach, K. *Chem. Mater.* **2008**, *20*, 859–868. Wang, X. J.; Xu, Z. L.; Yang, Z. G.; Bing, N. C. Molecular recognition in aqueous media with molecular imprinting technique. *Prog. Chem.* **2007**, *19*, 805–812. Wulff, G. Enzyme-like catalysis by molecularly imprinted polymers. *Chem. Rev.* **2002**, *102*, 1–27. Haupt, K. Imprinted polymers - Tailor-made mimics of antibodies and receptors. *Chem Commun.* **2003**, 171–178. Byrne, M. E.; Park, K.; Peppas, N. A. Molecular imprinting within hydrogels. *Adv. Drug Delivery Rev.* **2002**, *54*, 149–161.

10 Lyon, A.; Meng, Y.; Singh, N.; Sorrell, C. D.; St. John, A. Thermoresponsive microgel-based materials. *Chem. Soc. Rev.* **2009**, *38*, 865–874. Mart, R. J.; Osborne, R. D.; Stevens, M. M.; Ulijn, R. V. Peptide-based stimuli-responsive biomaterials. *Soft Matter* **2006**, *2*, 822–835.

11 See, for example: Gauthier, M. A.; Gibson, M. I.; Klok, H. A. Synthesis of functional polymers by post-polymerization modification. *Angew. Chem., Int. Ed.* **2009**, *48*, 48–58.

12 Pollino, J. M.; Weck, M. Non-covalent side-chain polymers. *Chem. Soc. Rev.* **2005**, *34*, 193–207.

13 Xu, H.; Srivastava, S.; Rotello, V. M. Nanocomposites based on hydrogen bonds. *Adv. Polym. Sci.* **2007**, *207*, 179–198. See also: Kopecek, J.; Yang, J. Peptide-directed self-assembly of hydrogels. *Acta Biomater.* **2009**, *5*, 805–816.

14 See: Fages, F.; Vögtle, F.; Zinic, M. Low molecular mass gelators. *Top. Curr. Chem.* **2005**, *256*, 1–55. Estroff, L. A.; Hamilton, A. D. Water gelation by small organic molecules. *Chem. Rev.* **2004**, *104*, 1201–1217. Hwang, I.; Jeon, W. S.; Kim, H. J.; Kim, D.; Kim, H.; Selvapalam, N.; Fujita, N.; Shinkai, S.; Kim, K. Cucurbit[7]uril: A simple macrocyclic, pH-triggered hydrogelator exhibiting guest-induced stimuli-responsive behavior. *Angew. Chem., Int. Ed.* **2007**, *46*, 210–213. Schmidt, J. J.; Rowley, J.; Kong, H. J. Hydrogels used for cell-based drug delivery. *J. Biomed. Mater. Res. A* **2008**, *87A*, 1113–1122. Kumar, A.; Srivastava, A.; Galaev, I. Y.; Mattiasson, B. Smart polymers: Physical forms and bioengineering applications. *Prog. Polym. Sci.* **2007**, *32*, 1205–1237.

15 *Hydrogel Sensors Actuators: Engineering and Technology*; Gerlach, G., Arndt, K. F., Eds; Springer: Berlin, 2008. Richter, A.; Paschew, G.; Klatt, S.; Lienig, J.; Arndt, K. F.; Adler, H. J. P. Review on hydrogel-based pH sensors and microsensors. *Sensors* **2008**, *8*, 561–581. Chaterji, S.; Kwon, I. K.; Park, K. Smart polymeric gels. *Prog. Polym. Sci.* **2007**, *32*, 1083–1122. Calvert, P. Hydrogels for soft machines. *Adv. Mater.* **2009**, *21*, 743–756.

16 Schneider, H.-J.; Kato, K. In *Intelligent Materials*; Shahinpoor, M., Schneider, H.-J., Eds.; Royal Society of Chemistry: Cambridge, U.K., 2007; p 100 ff.

17 Peppas, N. A.; Hilt, J. Z.; Khademhosseini, A.; Langer, R. Hydrogels in biology and medicine. *Adv. Mater.* **2006**, *18*, 1345–1360. Schmaljohann, D. Thermo- and pH-responsive polymers in drug delivery. *Adv. Drug Delivery Rev.* **2006**, *58*, 1655–1670.

18 Alvarez-Lorenzo, C.; Concheiro, A. Intelligent drug delivery systems: Polymeric micelles and hydrogels. *Mini-Rev. Med. Chem.* **2008**, *8*, 1065–1074.

19 Miyata, T.; Jige, M.; Nakaminami, T.; Uragami, T. Tumor marker-responsive behavior of gels prepared by biomolecular imprinting. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 1190–1193.

20 Lin, D. C.; Yurke, B.; Langrana, N. A. Inducing reversible stiffness changes in DNA-crosslinked gels. *J. Mater. Res.* **2005**, *20*, 1456–1464.

21 Huck, W. T. S. Responsive polymers for nanoscale actuation. *Mater. Today* **2008**, *11*, 24–36.

22 Schneider, H.-J. Binding mechanisms in supramolecular complexes. *Angew. Chem., Int. Ed.* **2009**, *48*, 3924–3977.

23 Schneider, H. J.; Liu, T. J.; Lomadze, N. Dimension changes in a chemomechanical polymer containing ethylenediamine and alkyl functions as selective recognition units. *Eur. J. Org. Chem.* **2006**, 677–692. Schneider, H.-J.; Liu, T.; Lomadze, N. Molecular recognition in a supramolecular polymer system translated into mechanical motion. *Angew. Chem., Int. Ed.* **2003**, *42*, 3544–3546.

24 Qu, X.; Wirsen, A.; Albertsson, A. C. Novel pH-sensitive chitosan hydrogels: Swelling behavior and states of water. *Polymer* **2000**, *41*, 4589–4598.

25 Guan, Y. L.; Shao, L.; Liu, J.; DeYao, K. pH-Effect on correlation between water state and swelling kinetics of the crosslinked chitosan/polyether semi-IPN hydrogel. *J. Appl. Polym. Sci.* **1996**, *62*, 1253.

26 Ito, K.; Chuang, J.; Alvarez-Lorenzo, C.; Watanabe, T.; Ando, N.; Grosberg, A. Y. Multiple point adsorption in a heteropolymer gel and the Tanaka approach to imprinting: experiment and theory. *Prog. Polym. Sci.* **2003**, *28*, 1489–1515.

27 Annaka, M.; Tanaka, T. Multiple phases of polymer gels. *Nature* **1992**, *355*, 430–432.

28 *The Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., García-España, E., Eds.; Wiley-VCH: Weinheim, Germany, 1997.

29 Kato, K.; Schneider, H. J. Selectively triggered dimension changes of polyallyamine-based hydrogels. *Eur. J. Org. Chem.* **2008**, 1378–1382.

30 Schneider, H. J.; Kato, K. Direct translation of chiral recognition into mechanical motion. *Angew. Chem., Int. Ed.* **2007**, *46*, 2694–2696.

31 Shin, M. S.; Kim, S. J.; Park, S. J.; Lee, Y. H.; Kim, S. I. Synthesis and characteristics of the interpenetrating polymer network hydrogel composed of chitosan and polyallylamine. *J. Appl. Polym. Sci.* **2002**, *86*, 498–503, and references cited therein.

32 Muta, H.; Miwa, M.; Satoh, M. Ion-specific swelling of hydrophilic polymer gels. *Polymer* **2001**, *42*, 6313–6316.

33 Rama, R. G. V.; Konishi, T.; Ise, N. Ordering in poly(allylamine hydrochloride) gels. *Macromolecules* **1999**, *32*, 7582–7586.

34 Kokufuta, E. Polyelectrolyte gel transitions. *Langmuir* **2005**, *21*, 10004–10015, and references cited therein.

35 Kato, K.; Schneider, H. J. Cooperativity and selectivity in chemomechanical polyethylenimine gels. *Langmuir* **2007**, *23*, 10741–10745.

36 Ju, X. J.; Chu, L. Y.; Liu, L.; Mi, P.; Lee, Y. M. A novel thermoresponsive hydrogel with ion-recognition property through supramolecular host-guest complexation. *J. Phys. Chem. B* **2008**, *112*, 1112–1118.

37 Schneider, H. J.; Liu, T. J. Large macroscopic size changes in chemomechanical polymers with binding sites for metal ions. *Chem. Commun.* **2004**, 100–101.

38 Sato, H.; Hirashima, Y.; Suzuki, A.; Goto, M.; Tokita, M. Effects of repeated water exchange on the swelling behavior of poly(sodium acrylate) gels crosslinked by aluminum ions. *J. Polym. Sci. B: Polym. Phys.* **2005**, *43*, 753–763, and references cited therein.

39 Keerl, M.; Smirnovas, V.; Winter, R.; Richtering, W. Interplay between hydrogen bonding and macromolecular architecture leading to unusual phase behavioir in thermosensitive micirogels. *Angew. Chem., Int. Ed.* **2008**, *47*, 338–341.

40 Wang, H.-J.; Hong, X. Z.; Ba, X.-W. Sol—gel transition in nonlinear hydrogen bonding solutions. *Macromolecules* **2007**, *40*, 5593–5598.

41 Yilmaz, Y. Transition between collapsed state phases and the critical swelling of a hydrogen bonding gel. *J. Chem. Phys.* **2007**, *126*, 224501 and references cited therein.

42 Lomadze, N.; Schneider, H. J. A chitosan-based chemomechanical polymer triggered by stacking effects with aromatic effectors including aminoacid derivatives. *Tetrahedron* **2005**, *61*, 8694–8698.

43 Kato, K.; Schneider, H. J. Chitosan-based chemomechanical hydrogels. *Eur. J. Org. Chem.* **2009**, in press.

44 Schneider, H. J.; Lui, T. Additivity and quantification of dispersive interactions. *Angew. Chem., Int. Ed.* **2002**, *41*, 1368–1370.

45 Lomadze, N.; Schneider, H. J. Ternary complexes for large motions of a chemomechanical polymer induced by metal chelators, aminoacids and peptides. *Tetrahedron Lett.* **2005**, *46*, 751–754.

46 (a) Kost, J.; Langer, R. Responsive polymeric delivery systems. *Adv. Drug Delivery Rev.* **2001**, *46*, 125–148. (b) Miyata, T.; Uragami, T.; Nakamae, K. Biomolecule-sensitive hydrogels. *Adv. Drug Delivery Rev.* **2002**, *54*, 79–98. (c) Qiu, Y.; Park, K. Environment-sensitive hydrogels for drug delivery. *Adv. Drug Delivery Rev.* **2001**, *53*, 321–339. (d) Chu, L. Y. Controlled release systems for insulin delivery. *Expert Opin. Ther. Pat.* **2005**, *15*, 1147–1155. (e) Peppas, N. A. Is there a future in glucose-sensitive, responsive insulin delivery systems? *J. Drug Delivery Sci. Technol.* **2004**, *14*, 247–256.

47 Livney, Y. D.; Portnaya, I.; Faupin, B.; Fahoum, L.; Ramon, O.; Cohen, Y.; Mizrahi, S.; Cogan, U. Interactions of glucose and polyacrylamide in solutions and gels. *J. Polym. Sci. B: Polym. Phys.* **2003**, *41*, 3053–3063.

48 Kawasaki, H.; Sasaki, S.; Maeda, H.; Mihara, S.; Tokita, M.; Komai, T. Saccharide-induced volume phase transition of poly(*N*-isopropylacrylamide) gels. *J. Phys. Chem.* **1996**, *100*, 16282–16284. See also: Lapeyre, V.; Ancla, C.; Catargi, B.; Ravaine, V. Glucose-responsive microgels with a core-shell structure. *J. Colloid Interface Sci.* **2008**, *327*, 316–323.

49 For example: (a) Yang, D. H.; Takahara, N.; Lee, S. W.; Kunitake, T. Fabrication of glucose-sensitive TiO2 ultrathin films by molecular imprinting and selective detection of monosaccharides. *Sens. Actuators, B* **2008**, *130*, 379–385. (b) Hilt, J. Z.; Byrne, M. E.; Peppas, N. A. Microfabrication of intelligent biomimetic networks for recognition of D-glucose. *Chem. Mater.* **2006**, *18*, 5869–5875.

50 Seong, H.; Lee, H. B.; Park, K. Glucose binding to molecularly imprinted polymers. *J. Biomater. Sci., Polym. Ed.* **2002**, *13*, 637–649.

51 Wizeman, W. J.; Kofinas, P. Molecularly imprinted polymer hydrogels displaying isomerically resolved glucose binding. *Biomaterials* **2001**, *22*, 1485–1491.

52 Bodugoz, H.; Guven, O.; Peppas, N. A. Glucose recognition capabilities of hydroxyethyl methacrylate-based hydrogels containing poly(ethylene glycol) chains. *J. Appl. Polym. Sci.* **2007**, *103*, 432–441.

53 Arnold, M. A.; Small, G. W. Noninvasive glucose sensing. *Anal. Chem.* **2005**, *77*, 5429–5439.

54 Samoei, G. K.; Wang, W.; Escobedo, J. O.; Xu, X. Y.; Schneider, H.-J.; Cook, R. L.; Strongin, R. M. A chemomechanical polymer that functions in blood plasma with high glucose selectivity. *Angew Chem., Int. Ed.* **2006**, *45*, 5319–5322.

55 (a) Norrild, J. C.; Eggert, H. Evidence for monodentate and bisdentate boronate complexes of glucose in the furanose form - application of $^{1}J_{C-C}$-coupling-constants as a structural probe. *J. Am. Chem. Soc.* **1995**, *117*, 1479–1484. See also: (b) Sponer, J. E.; Sumpter, B. G.; Leszczynski, J.; Sponer, J.; Fuentes-Cabrera, M. Theoretical study on the factors controlling the stability of the borate complexes of ribose, arabinose, lyxose, and xylose. *Chem.—Eur. J.* **2008**, *14*, 9990–9998.

56 Alexeev, V. L.; Sharma, A. C.; Goponenko, A. V.; Das, S.; Lednev, I. K.; Wilcox, C. S.; Finegold, D. N.; Asher, S. A. High ionic strength glucose-sensing photonic crystal. *Anal. Chem.* **2003**, *75*, 2316–2323.

57 Hoare, T.; Pelton, R. Charge-switching, amphoteric glucose-responsive microgels with physiological swelling activity. *Biomacromolecules* **2008**, *9*, 733–740.

58 Ben-Moshe, M.; Alexeev, V. L.; Asher, S. A. Fast responsive crystalline colloidal array photonic crystal glucose sensors. *Anal. Chem.* **2006**, *78*, 5149–5157.

59 Kabilan, S.; Marshall, A. J.; Sartain, F. K.; Lee, M. C.; Hussain, A.; Yang, X. P.; Blyth, J.; Karangu, N.; James, K.; Zeng, J.; Smith, D.; Domschke, A.; Lowe, C. R. Crosslinking of phenylboronic acid receptors as a means of glucose selective holographic detection. *Biosens. Bioelectron.* **2005**, *20*, 1602–1610.

60 Horgan, A. M.; Marshall, A. J.; Kew, S. J.; Dean, K. E. S.; Creasey, C. D.; Kabilan, S. Crosslinking of phenylboronic acid receptors as a means of glucose selective holographic detection. *Biosens. Bioelectron.* **2006**, *21*, 1838–1845.

61 Yang, X. P.; Pan, X. H.; Blyth, J.; Lowe, C. R. Towards the real-time monitoring of glucose in tear fluid: Holographic glucose sensors with reduced interference from lactate and pH. *Biosens. Bioelectron.* **2008**, *23*, 899–905.

62 Dean, K. E. S.; Horgan, A. M.; Marshall, A. J.; Kabilan, S.; Pritchard, J. Selective holographic detection of glucose using tertiary amines. *Chem. Commun.* **2006**, 3507–3509.

63 (a) Franzen, S.; Ni, W. J.; Wang, B. H. Study of the mechanism of electron-transfer quenching by boron-nitrogen adducts in fluorescent sensors. *J. Phys. Chem. B* **2003**, *107*, 12942–12948. (b) Zhu, L.; Shabbir, S. H.; Gray, M.; Lynch, V. M.; Sorey, S.; Anslyn, E. V. A structural investigation of the N—B interaction in an *o*-(*N*,*N*-dialkylaminomethyl)arylboronate system. *J. Am. Chem. Soc.* **2006**, *128*, 1222–1232.