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Dimension Changes in a Chemomechanical Polymer Containing Ethylenediamine and Alkyl Functions as Selective Recognition Units

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Treatment of polymethyl methacrylate with dodecylamine and diethylenetriamine produces a chemomechanical polymer, which undergoes large macroscopic motions as a result of selective recognition of substrates (effectors) in the surrounding aqueous solution. The kinetics of these fully reversible expansions and contractions are compared to those of effector absorption and desorption. The expansion correlates with a polymer particle weight increase, which is in turn found to be largely a function of the uptake of water necessary for solvation of the effector molecules. The selectivity of the motions depends on the nature and placement of the effector ionic sites, and also on the size and nature of the organic residues. Ion pairing between the protonated amine functions and inorganic anions or anionic groups of organic effectors plays a decisive role. The large effects seen with aromatic effectors such as nucleotides, in contrast with saturated analogues, point to cation–π and C–H–π interactions as essential elements for the distinction between different effectors, including isomeric compounds. The material exhibits symmetric expansion/pH profiles, which depend distinctly on the ionic strength of the solution. The strong dependence of the motions not only on the applied pH, but also on the concentrations of two simultaneously active effectors, such as AMP and phosphate, present chemically induced logical gate functions; this is tentatively explained by a two-site binding model. In contrast, the large expansions produced by simultaneous action of, for example, copper or zinc and amino acids or peptides are due to co-complexation between the metal ions and known organic chelators. With such ternary complexes, volume expansions by factors of up to 15 are possible with effector concentrations as low as 0.25 mM. The sensitivity can be further increased by miniaturization of the polymer particles; the velocity of the response can be optimized by increasing the surface-to-volume ratio.

Introduction

Many efforts in supramolecular chemistry are currently being directed towards implementation of functions, resulting in smart or intelligent new materials.[1] Stimuli-responsive polymers, which can be viewed as early steps towards artificial muscles, have seen considerable development after the first related report in 1950 with polymers in solution.[2] Such systems can be activated by voltage (Electrically Activated Polymers, EAPs),[3] particularly in the form of ionic polymer-metal composites (IPMCs),[4] with conducting polymers,[5] by light,[6] by temperature,[7] by pH and salt changes,[8] or by other external signals.[9,10]

Particularly promising has been the use of gels, in which swelling or contraction can again be induced, often as result of phase transitions, by a large range of external stimuli.[11,12] Such gels are of great interest with respect to many applications, in particular for drug release.[13] Although they can assume a multitude of states,[14] a heuristic distinction has been made between a loose swollen state, stable at lower temperatures, and a shrunken, collapsed state resulting from, for example, temperature increase. In the swollen state a target molecule – i.e., a drug – is believed to adsorb preferentially through single contacts with loose receptor sites of the polymer network, whereas in the shrunken state multipoint interactions can lead to higher affinity.[12a] Imprinting techniques, in which a target molecule serves for generation of complementary binding cavities,[15] have also been applied to gels.[16] It has been shown that, through polymerization after imprinting and subsequent release of the substrate molecule in the swollen state, the collapsed state can retain sufficient memory to bind the ligand with increased selectivity, although the effects until now have been rather modest.[12,17] As one example, selective swelling has been reported in a thermosensitive gel that was polymerized in the presence either of adrenaline or of ephedrine, and then showed concentration-dependent swelling induced only by the compound that had been used for imprinting.[18]

The strategy underlying our work is an attempt to bridge the gap between the established pathways for molecular recognition with polymers, supramolecular chemistry in solution, and the recently developed so-called molecular ma-

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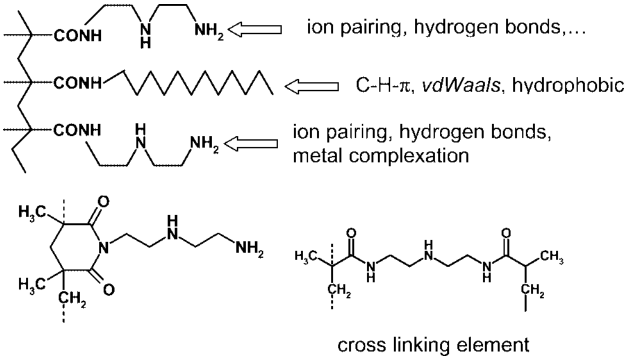
chines,[19] which until now still need, for example, transducers and/or spectroscopic devices for communication with the outside world. The major difference of our approach to the polymer-based techniques described above lies in the implementation of supramolecular binding sites in polymeric networks in such a way that interaction with substrates induces **selective** macroscopic size changes (often, but not necessarily, expansion), not necessarily by phase changes of the gels.[20,21] Host units developed in traditional solution supramolecular chemistry are immobilized in polymer networks that possess sufficient flexibility, absorbance capacity, and uptake or release velocity for selected substrates to ensure a large mechanical response within reasonable time. Furthermore, it has previously been shown that introduction even of simple recognition elements into such networks can result in cooperative effects including macroscopic logical gate functions,[22] which are actually more difficult to produce with supramolecular systems in solution. Related ternary complexes formed between two effectors and the polymeric binding units expand the possible applications considerably.[23] It has also been shown that manipulation of the polymeric particle size allows regulation of sensitivity and speed of the mechanical response.[24] This has been already achieved with miniaturization of sensors,[25] although limitations due to insufficient affinity must be kept in mind. The aim is the development of self-regulating systems capable of exhibiting mechanical motions as selective responses to external effector compounds and able to liberate or take up, for example, drugs without any additional devices. As well as this, actuators for, for example, flow control by chemical gates are feasible, as has already been shown in the case of temperature and pH-dependent gel swelling.[26] In this paper we present evidence of the mechanism of the observed dimension changes, and describe in detail both the preparation and new reactions of a chemomechanical polymer containing ethylenediamine and alkyl functions as selective recognition units.

Preparation, Structural Characterization and Experimental Procedures

The polymer was obtained by treatment of polymethyl methacrylate simultaneously with dodecylamine and diethylenetriamine in excess, in a molar ratio of, say, 1:9. The ethylenediamine units are introduced for ion pairing with anions, for cation–π interactions with aromatic effectors, and for binding of transition metal ions such as copper(II), whilst the alkyl chains are expected to produce lipophilic interactions of, for example, the C–H–π type. Scheme 1 and Scheme S1 (Supporting Information; see also the footnote on the first page of this article) show the expected structures of corresponding polymer units, although these may differ considerably because of the necessarily statistical nature of the network. The chemomechanical and the mechanical properties, such as softness/hardness of the material, vary to a degree with the mode of preparation (such as even stirring speed), so it is difficult to reproduce the same expansion/contractions and ab-/desorption profiles exactly with different preparations (see Exp. Section). However, the observed dimension changes were not only completely reversible, but were also reproducible with a given polymer; in many cases the expansions were corroborated by double experiments, usually showing <5% deviation of, say, the length of a film particle. The results reported here were obtained with two polymers **A** and **B**, which differ slightly in their methods of preparation and their properties; **A** was a softer material and showed larger dimension changes at neutral pH than film **B**, which showed larger changes at elevated pH. The chemomechanical properties of the material remain the same after complete drying at 80 °C in vacuo and subsequent re-swelling in water, even with a polymer that has previously been significantly expanded by, for example, interaction with NaOH (expansions still reproducible within ±5%). After complete desorption the material also shows the same expansion as before with new added effector, although after repeated cycles the mechanical stability starts to show fatigue and the material becomes softer.



Scheme 1. Possible structural units of the polymer; other structures see Scheme S1 (Supporting Information).

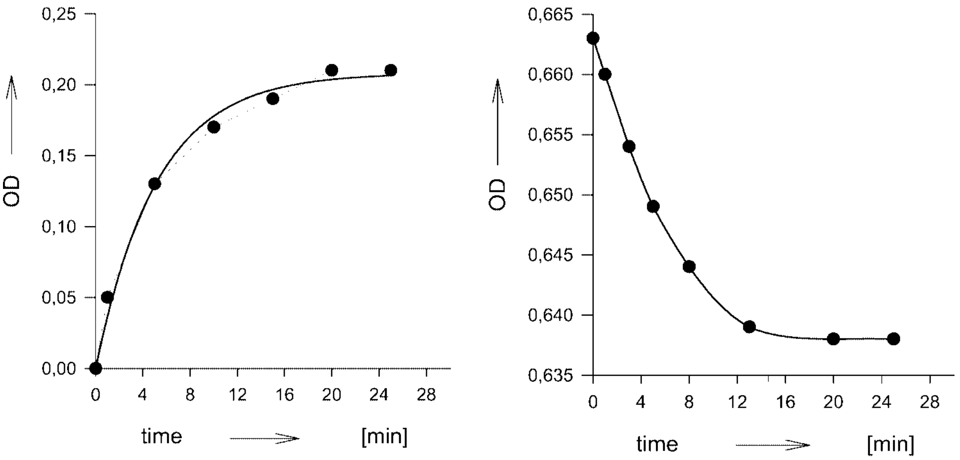
Detailed information on the properties and structures of the polymers is difficult to obtain, due to the very large water content (see below), and in particular the necessarily inhomogeneous composition, which is a prerequisite for the required flexible nature of the materials. The molecular weight distribution of the polymer is given by the starting material (average MW about 500000); the degree of cross-polymerization by the diethylenetriamine used in the preparation must be kept so low that it cannot be determined by classical methods. However, an upper limit of a few percent cross-linking can be inferred by the binding capacity, or loading factors (see section below), which, for strong binders such as copper ions, for example, are close to the maximum capacity expected for the presence of diethylenetriamine units on at least 7/8 of all carboxylic functions of the starting polyacrylate, assuming that the remaining 1/8 positions are occupied by the dodecylamine residue (for roughly equally fast reactions of diethylenetriamine and dodecylamine added at a molar ratio of 9:1). The observed loading factors indicate that at least half of the carboxylic ester groups in the starting material have reacted. The presence only of covalently linked binding functions in the polymer is corroborated not only by the reaction conditions, but also by the long water washing and drying procedures necessary and by the matching expansions obtained after desorption, washing and subsequent re-loading of the effector. Elemental analysis of dried samples gave only tentative information, pointing to the presence of additional structures beyond the ones shown in Scheme 1 (see also Scheme S1, Supporting Information). A H-CP MAS NMR spectrum, taken with material swollen in DMSO, shows all signals expected from the substructures (see Scheme 1 and Scheme S1 in the Supporting Information), due to the statistical nature of the polymer, with broad, mostly featureless lines (see Supporting Information). Accurate signal integration was therefore not possible, but the signal areas are in general agreement with the substructure distribution proposed on the basis of elemental analysis (Scheme S1, Supporting Information).

The soft, transparent hydrogels were obtained from DMSO solutions poured onto flat glass surfaces, after the material had been heated in vacuo in the form of films of about 0.5 mm thickness, containing about 75 ± 3% water after swelling for some hours (determined by weight loss after drying). Expansions and contractions were determined with the already water-swollen material, which was cut into small pieces, after immersion in effector solution or in solutions of different pH, with use of a measuring microscope and a digital camera coupled to a PC with measuring software. In most cases average changes in one dimension (Δl) were taken as average of both length and width changes. Volume changes Δv were calculated with the assumption of the same expansion factors for the film thickness; the thickness also showed significant swelling, but could not measured as accurately. Where appropriate, corrections were made in order to give the net effect $\Delta\Delta l$ or $\Delta\Delta v$ of an effector above the effect of a simultaneous change of, say, pH, buffer, or metal ion.

Absorption of the effectors was measured by UV or Vis absorbance changes, the polymer film pieces being immersed in effector solution and the decrease being followed; desorption was measured with the aid of excess blank water or water containing decomplexation agents, such as acid for metal ion desorption, with subsequent observation either through the absorbance increase, or by complexometric titration of metal ions. Desorption measurements usually showed a higher apparent loading due to excess effector adherence to the polymer surface, which is difficult to counter in a fully reproducible way (see discussion below).

Results

The spectroscopically determined **loadings** of the organic effectors were, for example, 3.5×10^{-5} mol per mg dry weight of the polymer **B** with the nucleotide GMP (Figure 1) and about 1.58×10^{-5} mol mg^{-1} with 2-naphthoic acid and polymer **A** (see Figure S1). With the metal acetates of Cu^{2+} and Mn^{2+}, complexometric titrations after desorption (Table S1) yielded higher total loadings, based on molecular weight and polymer composition calculated by assuming complete reaction of all carboxylic groups with ethylenediamine and dodecylamine in the starting ratio of 9:1, and based on complexation of one metal. Lower limits of loading factors were estimated on the assumption of complexation of one metal ion with a single ethylenediamine unit. The high loading factors obtained for Cu^{2+} and Mn^{2+} (minimum 60%) reflect the particularly strong affinities of these ions towards ethylenediamine units, whereas the smaller affinities for Ni^{2+} and Zn^{2+} gave about 45% minimum loadings in each case. The binding capacities of organic effectors, overestimated in our earlier publication due to the unspecific binding mentioned above, are lower, although **larger** dimension changes are often seen with such organic effectors (see below).



(a) (b)

Figure 1. Absorption and desorption kinetics with GMP. Absorption (a) and desorption (b) with 5.0 mM GMP [ε = 13700 with polymer **B**, ca 2 × 5 × 4 mm (about 1.7 mg in wet stage); in 2.5 mM phosphate buffer at pH 11.0],; (a) k = 0.16 min^{-1}, $t½$ = 4.2 min; b) k = 0.19 min^{-1}, $t½$ = 3.6 min, first-order nonlinear least square fit. Measured stepwise after: a) 1:100 dilution, b) 1:10 dilution. Loading calculated from: a) 1.75×10^{-4} mol (3.7×10^{-5} mol mg^{-1}); from (b) 1.5×10^{-4} mol (3.1×10^{-5} mol mg^{-1}).

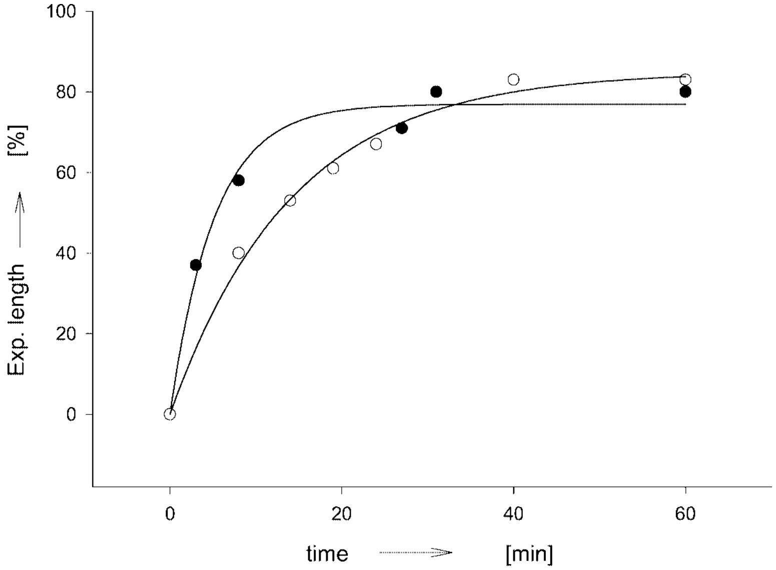


Figure 2. Film thickness effects on expansion kinetics, elongation induced by 0.5 M sodium benzoate, measured with polymer film **A** (size about 5 × 3 mm), in water at pH 7.0. First-order kinetics, nonlinear least squares fitting; with thinner film (full circles,about 0.5 mm) $k = (0.188 \pm 0.02)\mathrm{min}^{-1}$, $t½ = 3.7$ min; with thicker film (open circles, about 1 mm) $k = (0.068 \pm 0.007)\ \mathrm{min}^{-1}$, $t½ = 10.2$ min.

The **kinetics** of size changes and absorptions or desorptions both followed first order equations (Figure 1 and Figure S1). Expansions with the frequently used film size of about 5 × 2 × 0.4 mm usually showed a half-life time of $t½ = (3.5 \pm 2)$ min, fairly independently of the effector nature. As would be expected, the rates went up a with a thinner film or with a smaller volume of the polymer particles (Figure 2), due to the increased surface/volume ratio. This is also the reason for the faster expansion seen at the corners of the particles, which therefore often assume a cushion-like, or more disordered form before they become completely flat at the reaction end. Absorption and desorption were typically about twice as fast as expansion or contraction.

The **pH-induced** elongations were similar with both polymers **A** and **B**, with a single minimum at physiological pH as long as a salt concentration of at least 0.05 M was maintained (Figure 3).

Lowering the salt (NaCl) concentration resulted in distinctly different profiles (Figure 4, Table S2), explained below in the context of cooperativity effects. The pH-induced size changes also followed first-order kinetics (Figure 5, Figure S2, Table S3); with relatively large polymer **A** pieces of about 5 × 3 × 0.4 mm the half-life times were typically $t½ = 5$ min, and showed no regular dependence on the pH, with up to ± 1 min deviations due to film size differences.

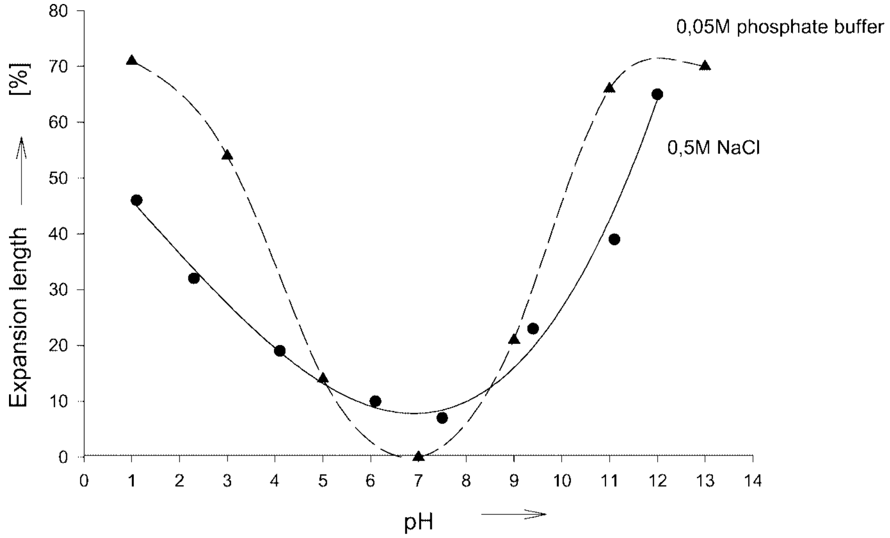


Figure 3. Expansion vs. pH; with polymer **A** in 0.05 M phosphate buffer (circles); with Polymer **B** in 0.5 M sodium chloride (triangles).

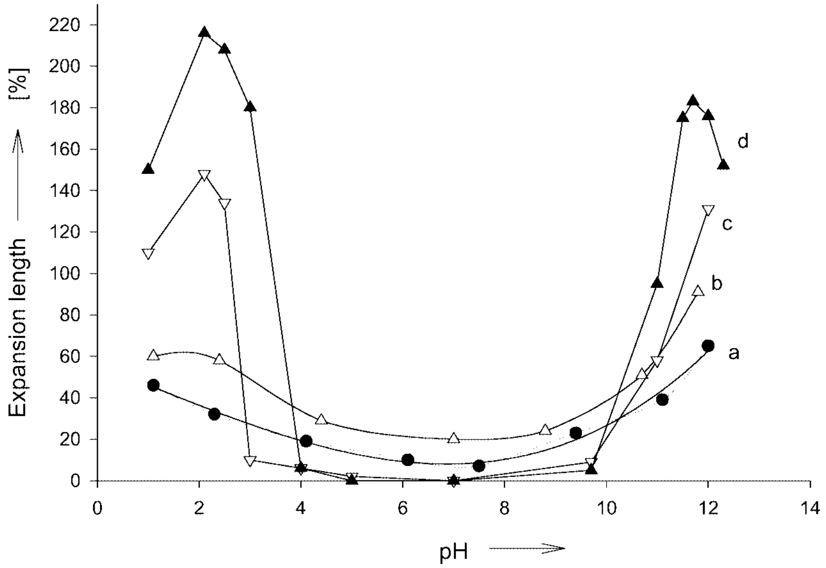


Figure 4. pH expansion profiles at different salt concentrations (with polymer **B**): in 0.5 M (● – a), 0.05 M (Δ – b), and 0.025 M (∇ – c), sodium chloride, and in water in the presence of very dilute HCl or NaOH (▼– d).

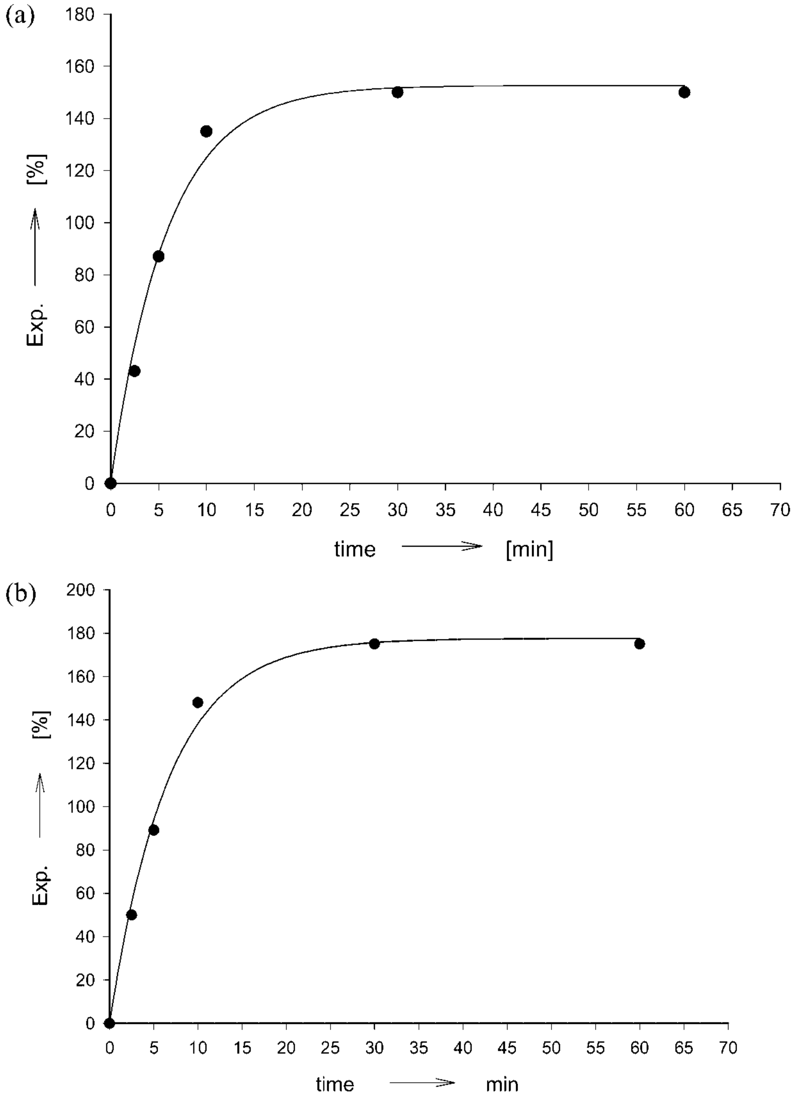
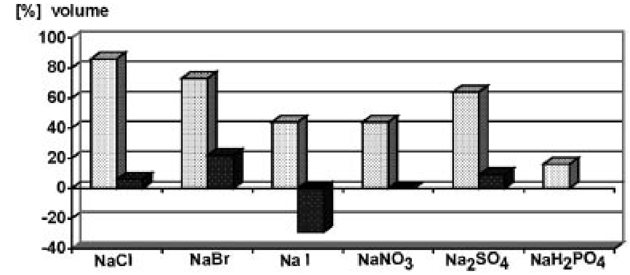


Figure 5. Expansion kinetics at pH 1.0 (a) and pH 11.5 (b) with polymer **B**, polymer piece ca. 1.5×1×0.4 mm: in pure water a) $k = 0.17\ \text{min}^{-1}$, t½ = 4.1 min; (b) $k = 0.15\ \text{min}^{-1}$, t½ = 4.6 min, first-order non-linear least-square fit.

Dimension Changes Induced by Inorganic Ions

In polymer **A**, sodium halides at 0.1 M concentration induced expansions decreasing from NaCl (Δl = 23%, Δl always given in one dimension) to NaBr (20%) to NaI (13%); similar expansions were also observed with $NaNO_3$ (13%), Na_2SO_4 (18%), and NaH_2PO_4 (5%) (Scheme 2, Table S4). The pH in these samples in water remained constant at pH 7.4, and changed in the presence of phosphate only between 6.95 and 7.4, corresponding to negligible pH-dependent dimension variations. The expansions, however, depended critically on the concentrations of the salts in relation to the polymer piece sizes, and also on the concentration of a second effector (Scheme 2, Table S4, Figure S3; see cooperativity effects below). With sodium phosphate a maximum length increase of up to 30% was observed at a distinct concentration, which varied from, for example, 0.01 M to 0.015 M if the polymer film size was increased. Similar maxima of expansion were induced by sodium sulfate and nitrate (Figure S4, Figure 6, measured with polymer **A**), as well as by phosphate (Figure S5, measured with polymer **B**). Sodium chloride deviated from the other salts: the maximum was reached at higher concentrations (Figure S5, see also Table S5), and after a longer time (60 h) a second expansion was observed (Figure S6).



Scheme 2. Volume changes ([%]) induced by different anions; [NaX] = 0.10 M. Left bars (always expansion): in pure water, pH 7.3. Right bars (partially contraction): in presence of 0.02 M phosphate buffer, pH 7.0.

Generally, measurements around pH 7 and in dilute effector solutions (e.g., 1 mM or less with polymer piece sizes around 1.5 × 1 × 0.4 mm) produced pronounced expansion maxima, which could be missed if not enough points were assembled before and after the critical effector concentration. As soon as other salts such as buffers were present in molarities again close to 1 mM for a typical polymer piece size of 1.5 × 1 × 0.4 mm, regular expansions were usually observed with increasing effector concentration. Since pH values differing by more than two units from neutral require the presence of about 1 mM or more of electrolyte, discontinuous expansion profiles were also not observed at pH values below 3 or above 10. As consequence of the interfering effects of pH and salt concentration changes (see above, Figure 4, Table S2) the dimension changes induced by, for example, sodium salts were also strongly affected by the pH; the values in Table S2 thus indicate that 0.05 M sodium chloride produced a strong reduction of the pH effect (at pH 1.0 from 150% to only 60%). Similar results were obtained at pH 11.3 (Table S5).

Metal ions such as Cu^{2+}, Mn^{2+}, Ni^{2+}, Zn^2 and Co^{2+} also produced expansions, decreasing in that order, once more at optimal concentrations of around 0.01 M with film pieces of about 4 × 2 × 0.4 mm size. At higher concentrations, smaller expansions and even **contractions** occurred, reaching 5% to 20% with Ni^{2+}, Mn^{2+}, Zn^{2+}, Mn^{2+}, and Co^{2+}.[21] The largest expansion (at 80%) was found with Pb^{2+}; the previously reported absence of a distinct maximum with Pb^{2+} may be due to formation of small amounts of insolu-

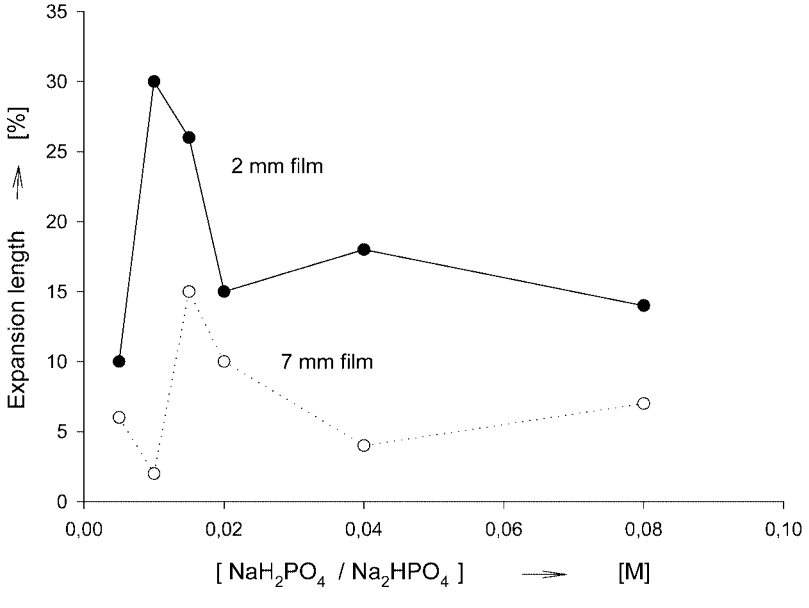


Figure 6. Expansion (length) induced by sodium phosphate, as function of film size (polymer A, pH 7.0; film size about 2 × 2 or 7 × 2 mm, thickness about 0.4 mm).

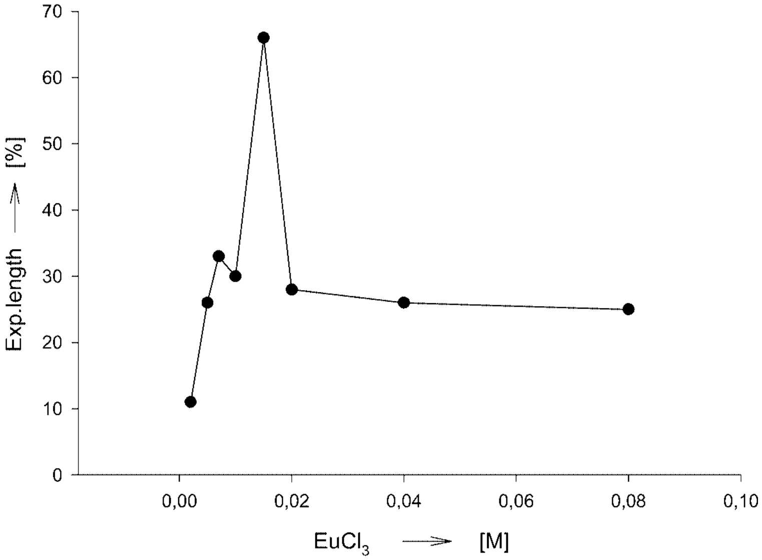


Figure 7. Expansions with $EuCl_3$. Measurements with polymer film **A** (size about 5×3 mm), pH = 6.4±0.15, pH change by presence of polymer max. 0.8 units; see Supporting Information.

ble material. The metal acetates were used without added buffer, but the pH changes accompanying the concentrations were small enough to allow pH-induced dimension changes to be neglected (Figure S7, Figure S8). Noticeably, the Cu- or Pb-induced expansions were larger with polymer **B** than with **A** (which with organic effectors were less active), reaching, for example, Δl = 100% instead of 45%with 5 mM $Cu(OAc)_2$, and Δl = 150% (or 2350% in volume) instead of Δl = 65% with 5 mM Pb^{2+}.

Addition of salts such as sodium chloride, acetate, or tartrate to the Cu^{2+}-containing solutions resulted in strong attenuation of the expansion, with this attenuation increasing in the order of affinity of these anions towards copper ions (Table S6).[23] Remarkably, the copper ions stayed within the polymeric network as far as this can be judged from the blue colour of the pieces (the colour in fact deepens, due to the higher concentrations in pieces of decreasing size).

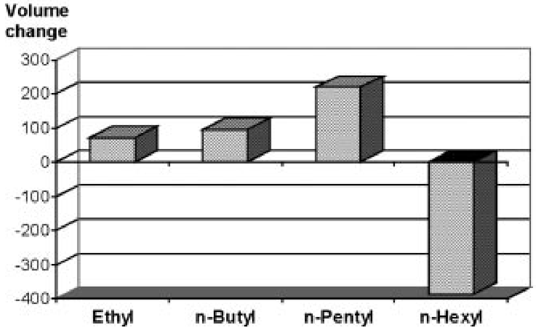
As a cation with a high charge density, and also in view of possible applications for phosphate ester and nucleic acid hydrolysis, the effect of a Eu^{3+} salt was measured.[27] With polymer **A** and neutral pH the expansion in length reached close to 70%, corresponding to a volume increase of 490%. A distinct maximum was observed at a concentration similar to those seen with the transition metal ions (Figure 7).

As mentioned in the Introduction, the response sensitivity of a chemomechanical material or of a sensor is limited not only be the size (volume) of the system,[25] but in dilute effector solutions also by the necessary affinity. This becomes apparent in the maximum volume increase factor of 6.5 (550%) observed with $Cu(OAc)_2$ at 1.0×10^{-5} M and with a polymer piece of 1.1×1.2×0.6 mm (0.8 mm^3); at a lower $Cu(OAc)_2$ concentration such as 5×10^{-6} M no increase is observed. With $Zn(OAc)_2$ the maximum increase with a film piece of similar size (1.0 mm^3) requires a **ten times** higher concentration of 1.0×10^{-4} M, due to the smaller affinity of zinc ions.

Organic Effectors

Cationic Effectors

Because of the positive charges of the amine polymer under acidic or neutral conditions, association of organic substrates also usually required the presence of negative charge in the effector. However, at high pH, at which the polymeric amines are deprotonated, cationic effectors can also produce expansion, as seen with a series of peralkylammonium hydroxides NR_4OH (Scheme 3, Table S7). Here R = ethyl, butyl and pentyl induced 20±6% expansion on top of the pH-induced change of 70%, whereas R = hexyl produced a sharp reversal, with 55±6% contraction. Electroneutral substrates such as phenols or aromatic anilines, which are sufficiently hydrophilic to ensure water solubility, produced no detectable dimension changes (Δl < 5%), unless they were able to form ternary complexes with transition metal ions (see below). The difference from the alkylammonium hydroxides can be tentatively ascribed to the uptake of more solvation water and of counterions, which is needed for all



Scheme 3. Dimension changes (volume, in %) with peralkylammonium hydroxides R_4NOH (after correction for pH-induced change, pH 12.4 to 12.7).

charged effectors. The longer hexyl chains may conversely give rise to partial collapse of the network by association with the dodecyl chains of the polymer.

Concentration Effects

In the presence of salts or buffers such as 0.02 M to 0.05 M Na_2HPO_4/NaH_2PO_4, organic substrates such as AMP,[20] in contrast with most metal ions, often showed a regular increase with effector concentration, while the magnitude of the increase depended on the film particle size and also on the presence of a buffer (see cooperativity effects) (Figure 8, Figure S9). With no buffer or lower concentrations of buffer (Figure 9), one again often obtained a maximum around the same effector concentrations as with most metal ions (e.g., with benzoic acid). UV/Vis measurements show absorption already beginning at low concentrations, too low for expansion. A 3 × 2 × 04 mm polymer piece immersed in a 10^{-4} M ADP solution thus produced an absorption drop (ΔA) of 0.01, indicating that around 0.5 mg per mg dry polymer were absorbed. Similarly, 10^{-4} M ATP showed a decrease of about 0.02, corresponding to 1.2 mg per mg dry polymer. In line with this, expansion started at a sharp point, later than absorption (see Figure 8), at a concentration at which the effector presumably started to move from the fully occupied surface into the inside of the polymer. The corresponding circle, also involving water uptake and release, is illustrated in Scheme S2. Binding affinities can be only approximately inferred from the expansion/concentration profiles, as the curves not only depend critically on the volume of the polymer piece,[24] but in particular become irregular under most conditions due to cooperativity effects[22] (see below). If saturation-like profiles are observed, as in Figure 8, one can estimate only an apparent binding constant K, which for AMP under the conditions in Figure 8, for example, amounts to $K = 20\ \text{M}^{-1}$; this can only tentatively be compared to K values reported in homogeneous solution for the interaction of AMP and ethylenediamine-type host compounds.[28] From the first part of the particularly discontinuous concentration profiles with transition metal ions and the maximum sensitivities one can estimate affinities which are, as expected, much higher, such as an apparent K value of around $10^5\ \text{M}^{-1}$for Cu^{II} ions.

Cooperativity Effects

Preliminary investigations[22] have already shown that the dimension changes can depend significantly on the presence of a second effector. Examples of the dependence of the observed expansions on pH can be found in the preliminary communications.[20,22] As a consequence of the cooperativity effect, expansion in the presence of an optimal second effector concentration starts at a lower concentration of the first effector, and remains larger than in the absence of such a second effector (e.g., in Figure 9 the first effector is benzoate, the second is sodium phosphate). Similar effects are visible with benzoic acid or terephthalic acid (Figure S9). Figure 10 demonstrates the cooperativity between terephthalic acid and sodium phosphate, and also that the optimal concentration [$E_{2\text{max}}$] of the second effector E_2 depends critically on the size of the film piece. With films of the same width but of different length l, one observes [$E_{2\text{max}}$] = 0.01 M for l = 1.5 mm and [$E_{2\text{max}}$] = 0.018 M for l = 2.6 mm; other measurements (not shown in the Figure) showed combinations of approximately [$E_{2\text{max}}$] = 0.04 M for l = 6.2 mm and[$E_{2\text{max}}$] = 0.08 M for l = 11 mm.

The spectroscopically determined loading factors, as a measure of binding capacity for a given effector, also show a maximum at a distinct concentration of a second effector (Figure 11). Cooperativity is also observed between the chemomechanical action of different transition metal ions (Figure S10), most pronounced with nickel(II) acetate,

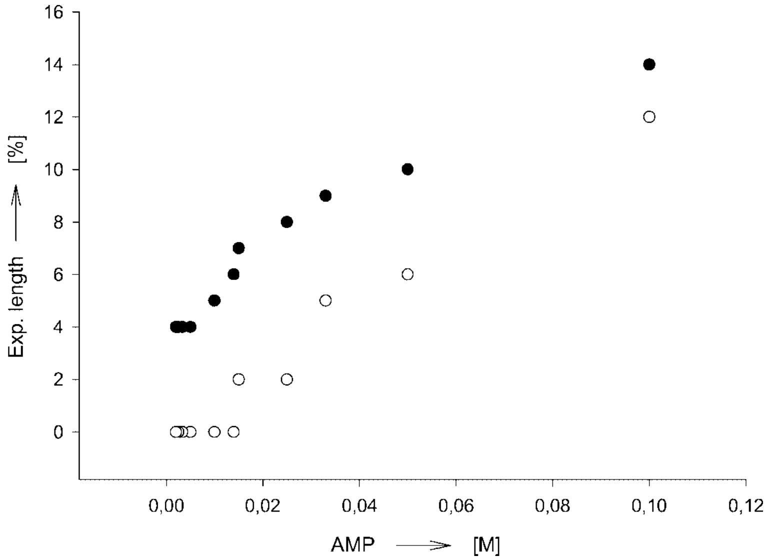


Figure 8. Expansion (length) as function of AMP concentration: polymer **A**, film size 5.0 × 2.0 × 0.4 mm, pH 7.0. Lower trace (open circles): in absence of buffer. Upper trace (filled circles): in presence of 0.02 M NaH_2PO_4 buffer.

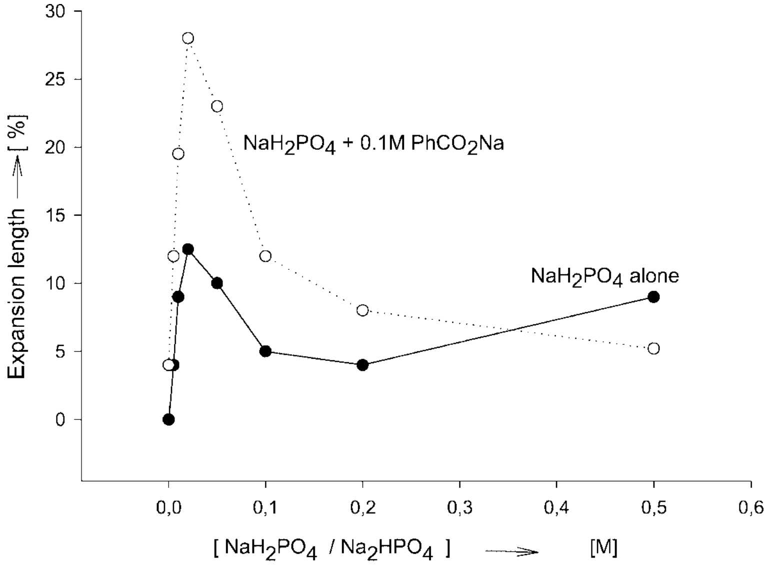


Figure 9. Cooperativity effect: expansion (length) as function of phosphate concentration, in absence and in presence of benzoic acid at pH 7.

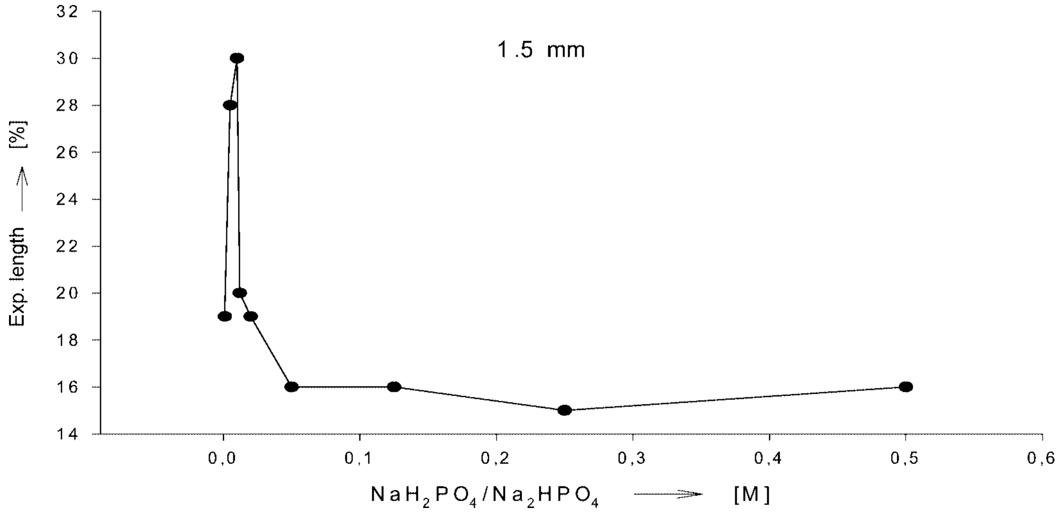


Figure 10. Dependence of expansion on phosphate (NaH_2PO_4/Na_2HPO_4) concentration, induced by 0.1 M terephthalic acid, pH 7.0, with initial polymer size of 1.5 mm: maximum cooperativity at [phosphate] = 0.010 M.

which at a given film size produced a 20% length increase (corresponding to a 73% volume increase) at [$NiOAc_2$] = 0.02 M, whereas in the presence of 0.1 M benzoate about a 30% length decrease (220% volume decrease) occurred. Remarkably, maximum contraction was observed around the same metal ion concentration as needed for maximum expansion (see Figure S10). Similarly, mostly negative cooperativities were found in combinations of Zn, Cu and Pb ions with sodium nitrate, chloride and benzoate: The large Pb^{II} ion is exceptional as the maximum expansion here reached 50% in length (375% in volume), and the negative influence of NaCl as second effector here resulted only in diminished expansion, but not contraction.

Selectivity for Different Structures/Dependence on Loading Factors

As described before,[20,22] the dimension changes vary significantly with the effector structure, and can even reverse at different pH values. The net dimension changes $\Delta\Delta l$ or $\Delta\Delta v$ must thus be obtained by subtracting the effect of different pH or buffer, and in consequence, $\Delta\Delta l$ or $\Delta\Delta v$ then becomes less accurate. In contrast, the total (combined) effects Δl or Δv should fairly accurately reflect the selectivity for different effectors as long as other conditions, such as pH and buffer, are kept constant. In most cases one observes small effects at pH around neutral, and small selec-

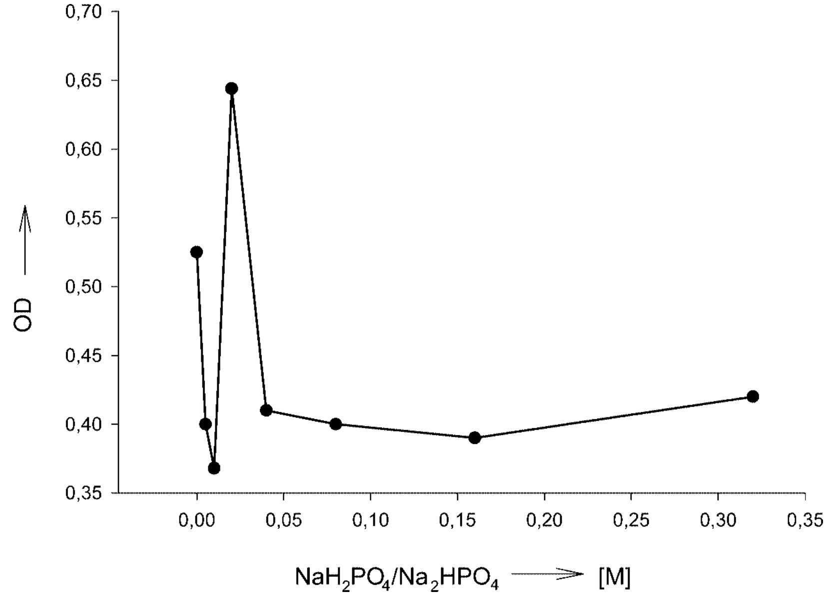
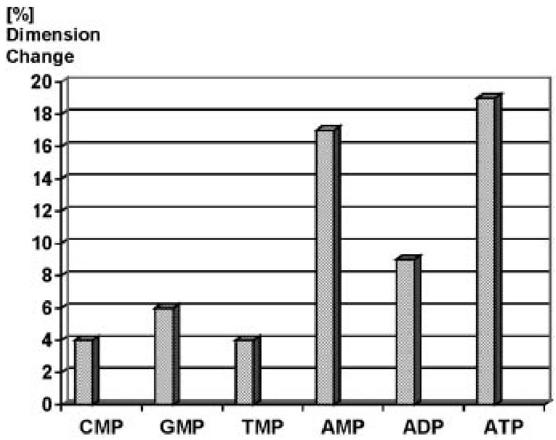


Figure 11. Cooperativity: loading of AMP (optical density OD) as a function of second effector (sodium phosphate); maximum effect also at 0.02 M (polymer **A**, film size ca. 2×1.5×0.5 mm).

tivity at pH above 10, since here, as well as in presence of high buffer concentrations, the dimension changes triggered by pH and/or buffer alone become much larger than the additional changes produced by the particular effector.



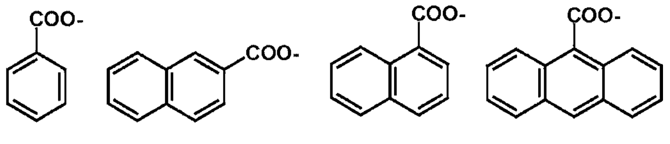
Scheme 4. Nucleotide-induced expansions $\Delta\Delta l$ (in one dimension) after correction for effects induced by pH 9.0 and buffer (0.1 M phosphate) alone; different experiments (see Table S9) showed lower loading for CMP, GMP and TMP (1.4 to 1.8×10^{-5} mol) than for AMP, ADP and ATP (5.1 to 5.5×10^{-5} mol).

Scheme 4, for example, shows that different nucleotides produced distinctly different expansions, and in particular that these expansions correlated with the amount of absorbed effector (the corresponding loading factors were determined as described above by UV measurements; see Table S8). However, the dimension changes are not only a function of the loading factors, but also depend on the nature of the effector. This is seen with metal cations with which high loading factors do not necessarily result in large dimension changes, and is also true for organic effectors, with, for example, the nucleotides AMP and UMP.[20] Scheme 5 shows the regular expansion increase with the larger size of the aromatic effector. Noticeably, saturated frameworks such as cyclohexanecarboxylic acid instead of benzoic acid produce negligible expansions[20] (Table S9 and S10).

Discussion

Expansion with pH Changes

Similar profiles were observed with both polymers **A** and **B** (Figure 3); these, however, turned out also to depend on the concentrations of neutral salts (Figure 4). At low con-



at 1 mM	12	36	42	53
at 10 mM	36	49	51	66

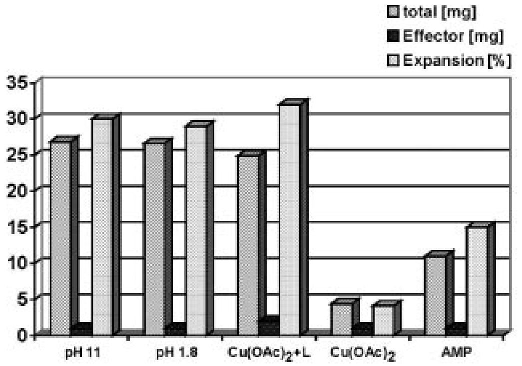
Scheme 5. Size effects with aromatic effectors (% expansion in one dimension, polymer B, pH effect of –65%- subtracted; 5.0 mM Na_2HPO_4 buffer, pH 11.0).

centrations of NaCl and in pure water the profiles show flat bottoms and distinct maxima of expansion at low and high pH values. Since these maxima occur at the same concentrations of either HCl or NaOH as those observed with several effectors we conclude that at low salt concentrations the decisive effect for the expansion is either not, or only to a lesser degree, due to the pH value but to the presence of an optimal electrolyte concentration, in analogy to the maxima discussed above for the effects of phosphate etc.

The expansion under acidic conditions can be understood as in the old case of viscosity change of polyelectrolytes in solution[2] as the consequence of increasing repulsion between the ionic sites, which with amine polymers arise from protonation. The expansion at higher pH is probably due to disruption of hydrogen bonds within the polymer, which under neutral conditions can still exist between partially protonated and free amine sites. In addition importation of hydroxide anions into the polymer network at higher pH requires their solvation, resulting in water uptake, which is critical for all expansions.

Expansion and Water Uptake

The expansion occurring on going from the dry to the swollen state of the polymer through uptake of water is characterized by a weight increase factor of $f = 4 \pm 0.5$. Significantly, the exposure of the already swollen polymer to different effectors in aqueous solution resulted in dramatic weight increase due to additional water uptake. In particular, both at high and at low pH values (at pH 11 and 1.8, respectively) one observes an enormous additional weight increase, by a factor of $f = 26 \pm 1$ (Table 1). Also, expansion induced at close to neutral conditions by an effector such as the copper acetate–cuprizon complex is accompanied by a large weight increase, by a factor of f = 25 with 1 mM copper–cuprizon complex, whereas $Cu(OAc)_2$ alone gives only $f = 4.4$. Comparison with the effector loading [around 5×10^{-4} mol in a film piece of $3 \times 4 \times 04$ mm determined by complexometry for $Cu(OAc)_2$] shows that the weight increase is only marginally due to the effector uptake itself [for $Cu(OAc)_2$ at the given polymer piece size this amounts to about 0.2 mg, whereas the total weight increase is about 13 mg; see Table S11]. Obviously, the large and selective size changes triggered by different effectors are to a large degree the result of different amounts of water accompanying complex formation within the polymer (Scheme 6; Scheme S3).



Scheme 6. Weight increase relative to expansion. Values scaled per mg of wet polymer, in mg of total weight increase due to water and effector and in mg increase due to effector alone (upper limit as estimated from absorption measurements and complexometry); volume expansion Δv (from 1 mm^3 wet), average from length and width increase.

Solvation differences before and after complex formation play a major role in supramolecular complex formation, in particular with ion pairing, also resulting in distinct dynamic differences between the water inside and outside supramolecular cavities.[29] In line with this, ionic effectors produce particularly sizeable dimension changes. Conversion of the observed weight differences into the expected volume changes allows the expansion due to water uptake to be estimated. As mentioned above, the contribution of the effector alone is close to negligible, also in view of the pH effects, which are large and of the same magnitude for both low and high pH. If the density were the same for included water and the polymer before and after effector uptake one would expect a volume increase of the same magnitude as the weight increase (see Table S11). The density of the swollen polymer could not be measured accurately, but from the floating behaviour of the polymer particles in the aqueous solutions it is close to that of water. In line with these assumptions, the volume increase factor $f2$ is, within the error limits, always the same as the weight increase factor $f1$ (e.g., 210% expansion in one dimension corresponds to 2.900% or a factor of 29 in volume increase, whereas the weight increases by a average factor of $f1$ = 27; see Table 1, Scheme 6). The lower expansions observed with copper acetate also roughly obey this rule; the ternary complex with cuprizon (at pH 4.8) again shows the same expected large factors for both weight and volume increase.

Table 1. Weight increase factor $f1$ after loading by water uptake compared to volume increase factor $f2$, and water content after loading.[a]

	Effector	Water content [%]	$f1$ weight increase	$f2$ volume increase
1	1.0 mM NaOH; pH 11.0	99	26.85	30.0
2	10.0 mM HCl; pH 1.8	99	26.6	29.0
3	10.0 mM AMP; pH11.0	98	11.5	15.0
4	1.0 mM $Cu(OAc)_2$ + cuprizon; pH 4.8	99	25.0	32.0
5	2.0 mM Cu $(OAc)_2$; pH 6.0	95	4.4	4.1
6	(without effector)	77	0.0	0.0)

[a] Measured with polymer B pieces; see Supporting Information; double measurements show deviations of f by ±10% on average; weight increase due to effector alone negligible (calculated from effector content in gel).

Effector Structure and Interaction Mechanisms

Comparison of loading and expansion factors shows that affinity variations are one essential contribution to the different chemomechanical effects. The results are in line with the known and anticipated noncovalent interactions[30] of the effectors with the receptor units incorporated into the polymers. In the strongly aqueous environment, ion pairing between the protonated amines and the anionic effector groups constitutes the major driving force for organic substrates. The alkane chains incorporated into the polymer provide for C–H–π interactions with aromatic units, but the negligible expansions observed with aliphatic carboxylates point to more significant (ammonium–) cation–π interactions. Hydrogen bond between the π-systems and, for example, the amine and amide groups present in the polymers can also contribute at higher pH values. The ethylenediamine (ene) units of the polymers are set up for strong association with transition metal ions, which can by enhanced by chelation with neighbouring ene units. As mentioned above, electroneutral effectors produce no size changes, due to too weak binding, but can do so in ternary complexes with transition metal ions, which give rise to strong binding (see below).

That large dimension changes are also seen with relatively small effectors, such as phosphate and sulfate, more than with chloride, is in line with the increased ability of the former to build up more salt bridges, to bind more water molecules and perhaps even to form hydrogen bonds to the surrounding ethylenediamine units of the polymer (see simulation Figure S11). Organic effectors trigger dimension changes beyond those induced by the corresponding inorganic ion only if they carry an aromatic moiety, which can interact with the docedecyl chains of the chemomechanical polymer by C–H–π interactions, and with protonated amines by cation–π interactions. The sizes of the organic residues also influence the expansion, as seen with the increase from phenyl through naphthyl to anthryl moieties (Scheme 5).

Cooperativity Effects: pH-Dependent Expansions by Different Effectors

As shown above, the observed dimension changes depend in most cases not only on the chosen pH,[22] but also on the concentration of a second effector. Stronger binding and hence expansion at higher or lower pH can be understood in terms of a less tight polymeric network than under neutral conditions, under which hydrogen bonding between the ethylenediamine units prevails. In addition, the cation–π and the N–H–π interactions discussed above can be less pronounced at pH 7, due to the presence also of unprotonated amino functions in the polymer.

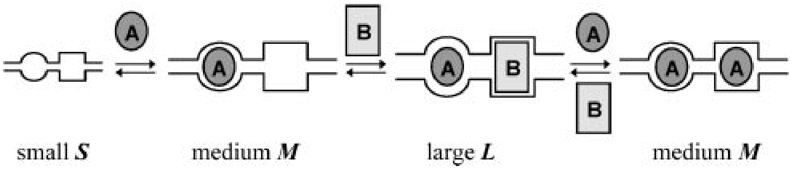
With transition metal ions such as Cu^{II} a sharp decrease in the metal-induced expansions at higher pH values (see Figure in ref.[23]) occurs as protonation of the amine sites takes over from metal complexation at such breakpoints. In line with this, the blue colour of the polymer film disappears at exactly at the same pH at which the Cu^{II} effects become smaller.

Cooperativity Between Different Effector Compounds

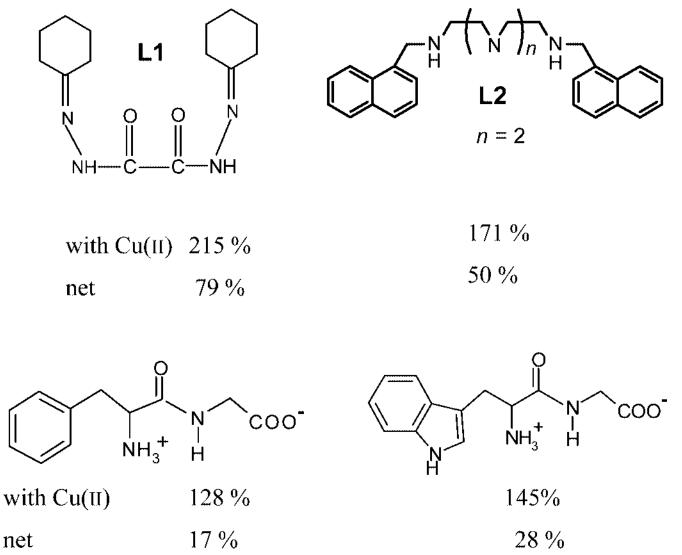
The most remarkable feature of cooperativity between two effectors is the sharp optimum in the concentration necessary to reach not only a maximum of expansion, but also of loading with respect to both effectors, as well as its dependence on the size of the polymer (see Figure 9, Figure 10 and Figure 1 in ref.[24]). The sudden dimension change observed at a certain concentration of one or two effector compounds may suggest a phase transition of the polymer at this point. However, there is no visual optical change to be observed at this point, and it would also be difficult to explain cooperativity between two effectors by a phase transition model. A model, illustrated in Scheme 7, would, with at least two binding sites, be in line with the observed cooperativity, since the results are obviously not just due to simple competing replacements at one binding site. The Scheme would explain the positive cooperativity by the widening, or loosening up, of the second site of a larger effector after the first binding site has been occupied by, say, a phosphate anion. If more of the first effector (e.g., phosphate) is added, this would result in occupation or tightening at the second site (e.g., by phosphate), with expulsion of the larger effector and therefore contraction. Negative cooperativity would imply that occupation of site I by a smaller effector such as chloride would “tighten” the second site, so that a larger effector such as AMP would bind to a lesser degree than in the absence of the other effector.

Ternary Complexes with Copper or Zinc Ions

The formation of ternary complexes not only allows triggering of large chemomechanical motions by otherwise silent effectors, but also gives rise to much higher sensitivities, with up to 15-fold (or 14000%) total volume increases at concentrations as low as 0.25 mM (see Table S12a,b; Figures S12a–S12i).[23] The underlying principle of co-com-



Scheme 7. A model for a positive cooperativity effect (***S***, ***M***, ***L*** refer to the sizes of the cavities).



Scheme 8. Examples of expansion (in one dimension) in ternary complexes; [Cu^{II}] and [effector] 0.25 mM, pH 4.5; net: effect of Cu^{II} alone deducted.

plexation between transition metal ions and metal-binding substrates has been used before only in solution chemistry;[31] it now has been shown to hold particular promise for chemomechanical polymers. Ligands such as **L1** and **L2**, which are very strong complexing agents – Cu^{II} ions, for example – and which carry relatively large organic residues, produce particularly large expansions; the chelating affinity of amino acids and peptides is also strong enough to trigger large motions of the polymer (Scheme 8).

The maximum expansion is always reached with a ligand to metal ion molar ratio of 1:1 (Table S13). The kinetics of expansion are similar to those observed with single effectors, again showing first-order fit and half-life times of around 3 min for 50 % volume change (Figure S13, Table S14). The cooperativity in the ternary complexes has different causes than that between, for example, phosphate and nucleotides discussed above. Whereas direct and favourable interactions between effector A and B, both being anions, cannot play a decisive role in the latter case, the opposite applies with the ternary complexes involving transition metal complexes. That co-complexation with corresponding metal ions is the basis of the observed chemomechanical activity is obvious from the dependence on the chelation strength of the organic partner compound. Ligands with no affinity towards the metal ion, which itself is bound strongly to the polymer, have no effect on the volume of the materials. However, if the organic ligand associates strongly enough to the immobilized metal ion, secondary interactions with other residues incorporated into the chemomechanical polymer, such as alkyl chains, can give rise to selective forces, as seen in the different expansions as a function of the amino acid side chains.

Conclusions

The incorporation of supramolecular binding sites into flexible polymers provides a new route to fully self-regulating actuators without the need for additional measuring systems or power supplies. Such intelligent materials hold promise for the development of molecular machines, artificial muscles, new systems for drug delivery or for isolation of valuable or toxic compounds, and possibly for sensor arrays. The observed dependence of macroscopic motions on the structures of the effector molecules largely follow the rules of solution supramolecular chemistry,[30] but show larger diversity. This is particularly obvious in the cooperative effects between different substrates, which for the first time open the route to chemically triggered logic gates, communicating from interacting molecules directly to the outside world.

Experimental Section

Preparation of Chemomechanical Polymer B: Polymethyl methacrylate (*MW* 500000; 1.0 g, 10 mmol), diethylenetriamine (4.12 g, 40 mmol) and dodecylamine (0.90 g, 5 mmol) were added to DMSO (20 mL) and heated to 120 °C with magnetic stirring for 2 h. Heating was continued for another hour at 150–160 °C, and if necessary for about 10 minutes at 180 °C until gel formation had reached a point just before the magnetic stirring bar was no longer moving freely. After cooling, the viscous solution was poured into a flat-bottomed vessel of about 8 cm in diameter, and this was then heated in a dry vacuum oven at 10 mbar, first overnight at 60 °C, and then for 2 h at 80 °C. After the system had cooled, cold water was added, and the resulting transparent film was removed and washed for several hours with water.

The film can be stored in water at about pH 8; after aging of several months it slowly looses some chemomechanical activity in terms of smaller expansions or contraction factors and speed of macroscopic change.

Polymer A: Polymer A was obtained in a similar way, except first with heating at 180 °C whilst stirring in DMSO (20 mL) for 2 h, and then at 190 °C for another 10 min. After the system had cooled, cold water was added and the resulting bulky mass of gel remaining in the flask was washed 2–3 times with water. The gel was placed in a sieve and washed there with running tap water for 24 h. in order to remove excess diethylenetriamine and solvent. The gel polymer was dissolved as far as possible in hot DMSO (about 30 mL), the solution was transferred into a large beaker with a flat bottom, and the DMSO was removed in a vacuum oven at 60 °C overnight, to yield a transparent, sometimes yellowish film.

As pointed out in the Introduction, it is difficult to obtain polymers with the same properties (the authors are prepared to provide samples as long as available to interested parties wishing to engage in new measurements with those).

Heating in vacuo is needed for the removal of remaining excess diethylenetriamine and DMSO, which is not completely removed even after long washing with water.

Attempts to use less diethylenetriamine yielded material of too low flexibility, as too much cross-linking occurred, whilst without or with much less dodecylamine the material is too hydrophilic (water-soluble).

Other solvents such as DMF, THF, dioxane etc. have not yet provided homogenous materials needed to cast films.

If the material is too viscous after the heating steps with DMSO, the film will become harder with reduced flexibility and eventually even inhomogeneous. On the other hand, if the material is not viscous enough, one obtains a mechanically less stable, very soft film. With harder films one observes smaller and slower mechanical motions than with the softer material at pH around 7, whilst at higher pH the opposite applies: the soft material shows larger effects at neutral pH but can be too fragile for handling.

After storage in water the material contains about 75% water, as determined by weight loss after drying in vacuo at 80 °C. The polymers began slowly to decline in magnitude and speed of chemically induced dimension changes only after many months' storage in water.

A NMR CP MAS spectrum was measured with about 20 mg material swollen with 0.2 mL [D$_6$]DMSO, and solvent suppression (PRESAT); spinning rate 8000 rpm, at 298 K. The observed shifts and signal areas are approximately as expected; for numerical data see Figure in the Supporting Information. We thank Dr. J. Zapp and Dr. K. Kato for help with the NMR measurement and evaluation.

Measurements of the Mechanical Motions: The film was cut into pieces of, for example;, 1 × 1 mm; the exact size (in two dimensions, not the thickness) could be determined with a measuring microscope fitted with a digital camera system and suitable evaluation software (*MOTIC)*. The error of measurement in one dimension is usually within 5%; the average deviation in size between duplicate measurements with the same film batch is usually also within 5%.

Expansion and contractions were measured by immersion of the film pieces in appropriate solutions of the effectors, either by direct observation under the measuring microscope system, or after film pieces had been taken out from the solution. For the experiments with ternary complexes, metal acetates and organic effectors were mixed prior to addition to the polymer pieces, in order to avoid otherwise irregular changes of the polymer. The pH was adjusted either with buffer, or in some cases as indicated (e.g., Figure 3, Figure 4) with very dilute HCl and NaOH, and checked before and after expansion or absorption/desorption measurements.

Water Content: Water content was determined by taking the weights of the polymer pieces (size about 3 × 4 × 0.4 mm) before and after drying of film pieces at around 80 °C in 10^{-5} mm vacuum for 24 h.

Absorption and Desorption Measurements: Absorption and desorption were followed by absorbance changes with a Varian Biocary instrument at wavelengths appropriate for the different effectors. For pH control, see above.

Absorptions were measured by stirring or shaking a film piece of about 0.4 mm thickness and 2 × 1.5 mm to 5 × 2 mm with effector solution (e.g., 5×10^{-3} M, 1 mL) and subsequent withdrawal of aliquots and dilution so that the optical density was in the optimal range (Figure 1 and Figure S1).

Measurements by desorption with high effector concentrations yielded somewhat lower apparent effector loading numbers than those observed by optical density decrease during absorption: repeated washing of the films prior to the optical desorption measurements removed the adherent effector material but also started to desorb effector from the polymer inside.

Desorption measurements could be complicated by the presence of DMSO, which could not be completely removed by washing and drying and interfered with the spectra of all aromatic effectors.

In cases of strong effector binding, such as with transition metal ions and the polyamine material, one needs measures such as acidic solutions or strong complexing agents such as EDTA to remove the effector from the film prior to the optical measurement.

Kinetics: The measured dimension changes typically followed clean first-order equations, as shown by nonlinear least square fitting with SIGMAPLOT (e.g., in Figure 1). The same held for kinetics of absorption and desorption (see Figure 1). Desorption could be followed directly and continuously in UV/Vis cuvettes with polymer pieces inside, with simultaneous stirring of the solution.

Loading Measurements with Organic Effectors: A polymer film piece (about 5 × 2 mm) was immersed for 2 days in a solution of 2-naphthoic acid or AMP (about 1 M); after quick washing the effector was liberated from the polymer with occasional stirring in water (2 mL, pH 7), this procedure being repeated several times until the last water portion showed an OD below 0.1 (measurements at 280 nm for 2-naphthoic acid, $\varepsilon = 6.18\times10^3$; at 260 nm for AMP, $\varepsilon = 1.355\times10^4$). From the absorbance of the combined portions, one obtained a total amount of 2.12×10^{-5} mol or 0.73 g/g polymer for 2-naphthoic acid (weight of the used film piece after drying 5.0 mg) and a total of 1.29×10^{-5} mol or 1.17 g/g polymer for AMP (film dry weight 4.0 mg).

On the crude assumption that 90% of the carboxylic groups in the polyacrylate had reacted with diethylenetriamine and 10% with dodecylamine (corresponding to the ratios used), the molecular weight of the monomer unit would be $256\times10\% + 171\times90\% = 179.5$; if this contains 90% amine as binding units the capacity is calculated to reach 75% of the total maximum capacity for 2-naphthoic acid and 60% for AMP.

Metal Salt Binding Capacity: Film pieces typically of 1 × 1 mm were immersed in metal acetate solution (0.1 M) for 8 h, excess metal solution was then removed with filter paper; after quick rinsing with a little water the pieces were placed in HCl (0.5 M, 2 mL) with shaking for 20 min. The desorption was repeated two to three times, each time with about 2 mL of 0.5 M HCl, and finally with water; the combined portions were titrated with buffered solution after addition of about 100 µL of a 1 mg mL^{-1} indicator solution with 0.01 M EDTA. The binding capacity BC was calculated similarly to that for AMP and naphthoic acid, with $BC=C_M/C_T\times100\%$, where C_M and C_T are the amounts of metal salt calculated from EDTA consumption and estimated from the film weight, respectively.

Supporting Information (see also the footnote on the first page of this article): *Experimental details*; *Eleven tables*: Numerical data for binding capacity for metal ions, expansion at various pH values, kinetics of pH-induced expansion, sodium salt effects and cooperativity, effect of NaOAc, tartaric acid and NaCl on expansion induced by $Cu(OAc)_2$, expansions induced by peralkylammonium hydroxides, expansion vs. bound effector with nucleotides, expansions by nucleotides, water content. *Four schemes*: distribution of possible substructures, model for the stepwise absorption and desorption, water content compared to volume increase factor. *Fourteen figures:* absorption and desorption kinetics with 2-naphthoic acid, kinetics of pH-induced expansion, expansion induced by sodium chloride in the presence of sodium salts and cooperativity with benzoate as a function of concentration of the sodium salts, expansion, dimension and pH changes by acetates of Zn^{II}, Cu^{II}, Ni^{II}, Pb^{II}, Co^{II} and Mn^{II} and by $Eu^{III}Cl_3$, expansions induced by terephthalic acid, cooperativity in Ni^{II}-induced expansion, structural model of phosphate binding (force field simulation), visualization examples of expansion with different ligands including amino acids and peptides in the presence of Cu^{II} or Zn^{II} ions, expansion/time profiles for a Cu^{II} complex, NMR CP-MAS spectrum with evaluation.

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