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Ternary complex formation inducing large expansions of chemomechanical polymers by metal chelators, aminoacids and peptides as effectors

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Abstract—Formation of supramolecular ternary complexes within a functionalized hydrogel are shown for the first time to lead to large macroscopic motions with biologically important effectors such as aminoacids and peptides. The mechanical motions can be made reversible by the addition of external metal ion complexing agents, and represent also chemical logical gate functions, operating without external devices or power supply.

Selective recognition by intermolecular interactions is a promising basis of intriguing new molecular machines,[1] which, however, still need external devices or transducers, usually including power supply, for communication to the outside world. In contrast, natural systems such as muscles or blood vessels rely on non-covalent interactions with stoichiometrically available chemical stimulators such as ATP. Chemomechanical polymers can provide a first synthetic entry towards such biomimetic actuators,[2] but until now could be triggered mostly by either pH changes, or by unspecific salt or medium effects. Besides thermally or light-switched materials electrically activated polymers are particularly advanced, but again need external power supply for their function.[2,3]

Implementation of supramolecular binding sites in flexible polymers allows for the first time to translate selective molecular recognition events directly into large macroscopic motions.[4] Uptake of effector compounds from the aqueous surrounding can lead to fully reversible size expansions of such polymer films by up to 2000% in volume. It was shown recently how motions in such hydrogels equipped with recognition sites can be triggered selectively by several ionic effectors, including nucleotides[4] and transition metal ions.[5] We now have found that the **combined** action of copper or zinc ions and ligands with suitably functionalized polymers can lead to volume expansions of up to 2700%, exceeding the effect of the metal ions alone by 1500%, and allows detection of otherwise silent effector compounds (see e.g., Fig. 1). This way aminoacids and peptides can be used for the first time to induce directly large volume changes in a responsive polymer. In addition, the sensitivity of the responses is significantly increased, to already less than millimolar concentrations; further sensitivity increase can be reached by minimizing the polymer particle size.[4b]

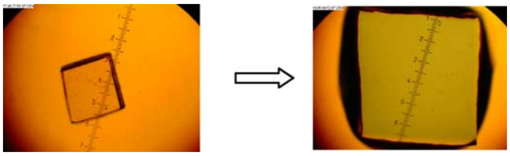

Figure 1. Expansion of a polymer film piece triggered by a complexation with $Cu(OAc)_2$ and Gly-Gly, 0.25 mM; at pH 4.5.

Diethylenetriamine units were introduced in a polyacrylic acid-based hydrogel as binding elements for copper and zinc ions (Scheme 1). In solution and in the solid state metal ions are well-known parts of ternary second sphere coordination complexes, and have been used, for example, for sensing of co-complexed guest molecules.[6] These metals are also known to bind aminoacids,

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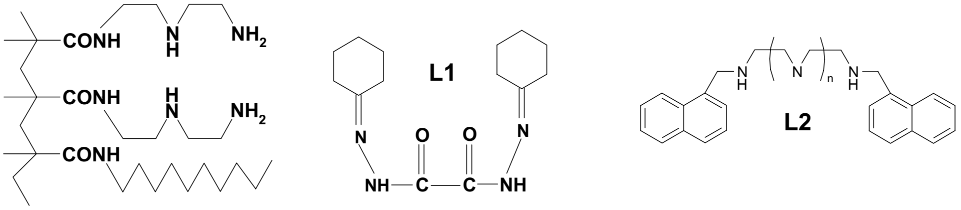

Scheme 1.

peptides and nucleic acid derivatives.[7] Surprisingly, in spite of the large excess of nitrogen atoms available in the polymer for coordination of copper or zinc ions the added ligands lead to sizeable expansions above those observed with the metal ion alone (Table 1). Figure 2 illustrates the mode of action of such ternary complexes; the simultaneous import of metal ions and effectors into the polymer gel leads to the volume increase, much enhanced by uptake of water needed for solvation of both effector molecules. It should be noted, that other than in earlier systems (see e.g., Ref. 2f) a continuous volume increase is observed, without indication of a phase transition.

Noticeably, in absence of the metal ion all ligands showed no detectable expansion. The kinetics follow clean first order, with 0.1 M effector about $t_{1/2} = 2$ min for 50% expansion (with e.g., 2.5 mM $t_{1/2} = 20$ min); the reactions can be accelerated by using smaller polymer film particles with larger surface to volume ratio.[8] Solubility problems and smaller sensitivities excluded the use of higher pH values, in particular with zinc. As with stimulation by other effectors the observed expansions depend on the pH value as well as on the concentration of additional salts, rendering the system with a chemically induced logical gate function.[9]

The known metal chelators **L1** and **L2** are the first cases where we can observe with our functionalized hydrogel large expansions induced by electroneutral effectors, due to the interacting metal ion. The co-complexation principle allows not only for large effects of otherwise ineffective compounds, but also for—until now only moderate—selectivity beyond the known different affinities[10] with the metal alone. Aminoacids and peptides are effective due to the simultaneous action of both the C- and the N-terminus; ammonium acetate, for example, has negligible effects. The different expansions increasing in the aminoacid order Gly < Phe ≈ Trp < His (Table 1) illustrate that the dodecyl side chain as additional recognition element **L** in the

Table 1. Expansions Δl as % in one dimension l induced by different effector ligands L in combination with copper(II) and zinc(II) acetate (net effect $\Delta\Delta l$ after deduction of metal effect alone[a])

Ligand L	Cu at pH 4.5		Cu at pH 6.3		Zn at pH 4.5	
	Δl	Net $\Delta\Delta l$	Δl	Net $\Delta\Delta l$	Δl	Net $\Delta\Delta l$
L1	215	79				
L2	171	50				
Phe	123	14	45	27	237	37
His	157	22	146[b]	26[b]		
Cys					249	49
Trp	115	15			233	33
Gly	114	9				
Phe-Gly	128	17	39	21	255	55
Trp-Gly	145	28			253	53
Trp-Trp	136	27			[c]	
Asp-Gly	112	<5	29	11	280	80
His-Asp	124	15				
Ala-Ala	120	7				
Gly-Gly	149	32				

[a] Measured at ambient temperature, with concentrations $L = Cu^{2+} = Zn^{2+} = 0.25$ mM; in water with HCl added as far as needed to adjust pH (up to 5×10^{-5} M HCl); Δl as average from length and width of polymer film piece; deviation between duplicates usually ±5%; net effect $\Delta\Delta l$, difference from effect with metal acetates alone (Cu^{2+} effects, for example, vary between 110% and 139%, depending on age and size of the polymer piece; for comparison with and without ligand, however, the same polymer was used); effect of ligand alone: <5%.

[b] Measured at pH 5.7 at CuL = 2.5 mM; measurements with Zn were done with a freshly prepared polymer, which had higher efficiency (e.g., with Gly-Gly and Cu 240% vs 149%).

[c] Precipitation.

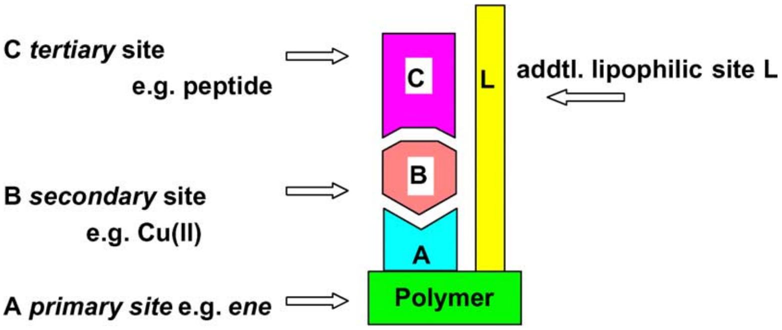

Figure 2. Ternary complex formation.

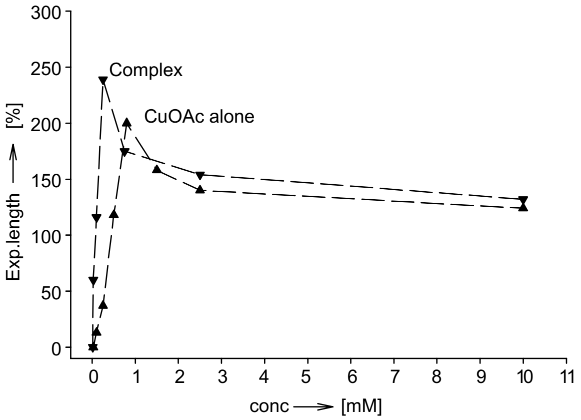

Figure 3. Expansion (in one dimension) as function of the Cu and Gly-Gly complex concentration.

metalated polymer also interacts. In line with known metal complex stabilities,[10] copper ions lead to slightly enhanced expansion with His, as do zinc ions with Cys. Peptides can take advantage of the presence of several polymeric binding sites, and thus show in most cases larger effects than aminoacids, surprisingly as much with Gly-Gly as with other dipeptides, possibly due to smaller conformational distortions. Investigation with larger peptides was until now hampered by solubility problems.

The expansions depend not only on the presence and nature of both metal ions and ligand, but critically also on their concentration. The strong dimension decrease upon addition of metal salt and ligands beyond the binding capacity of the used polymer particle (Fig. 3) has also been observed in other cases, and was attributed to competitive filling of second binding sites by the additional effector.[9] Measurements with some model effectors indicate a maximum expansion with 1:1 stoichiometry of ligand to metal ion, which had to be added simultaneously with the ligands to the polymer film in order to avoid partially irreversible reactions of the polymer particles after further addition of the ligands.

How can the dimension changes be made reversible? One way is to take out the metal ion, which will remove the binding of the effectors to the polymer, and thus lead to contraction of the gel. Figure 4 shows that this is indeed observed upon addition of anions, which can interact with the metal ion. The bidentate tartrate is expected particularly effective for this purpose. The differently complexed copper ions, however, remain essentially within the polymeric network, as far as this can be judged from the persistent color of the polymer film even in the presence of excess tartrate. Stronger complexing agents such as EDTA will be effective in initiating contraction of the materials at even lower concentrations.[11]

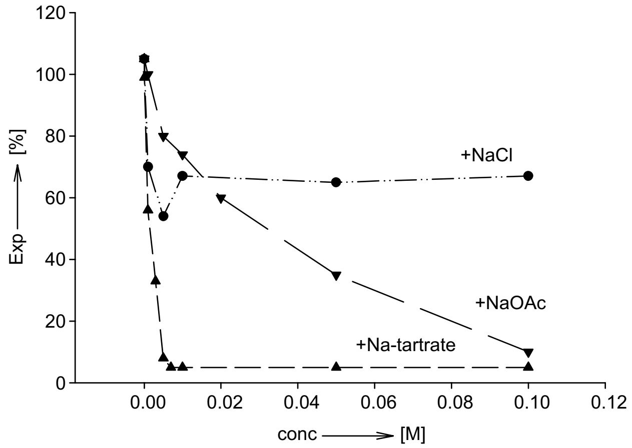

Figure 4. Size changes (in one dimension, in %), as a function of sodium acetate (▼) at pH 5.8 ± 0.3, tartrate at pH 7 ± 0.3, and chloride (●) at 5.8 ± 0.3, with constant Cu(II) concentration ($Cu(OAc)_2$ = 5.0 mM); effect of $Cu(OAc)_2$ alone at 5.0 mM: 105%.

Obviously, the supramolecular chemistry of chemomechanical polymers containing even simple binding sites has a much higher diversity than that expected from structurally related small host compounds in solution. In future such intelligent materials can allow the development of new actuator, drug delivery and sensor systems, which are triggered selectively by different chemical stimuli in quite narrow concentration ranges.

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