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COMMUNICATION

Multi-responsive copolymers: using thermo-, light- and redox stimuli as three independent inputs towards polymeric information processing†

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We report on triple responsive polymers, exhibiting a distinct and reversible lower critical solution temperature in water that can be altered by light and redox stimuli, and we suggest their evaluation for molecular information processing.

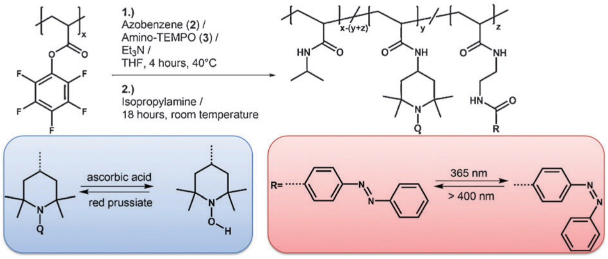
The translation of external stimuli, *e.g.* light, pH or temperature, into a physical response of a polymer has gained tremendous attention recently due to the broad range of applications of these materials ranging from drug delivery and tissue engineering to coatings and microelectromechanical systems.[1] Molecular logic gates have broadened the perspective of responsive polymers. However, so far mostly small molecules were investigated for logical computations.[2,3] Only a small number of examples take advantage of polymers.[2–5] For example when envisioning multi-input logic gates, functional polymer synthesis with an unprecedented precision and versatility is required, which was not available until very recently. Hence, polymeric systems promise a superior role due to their versatility in the type of in- and output signals, which was only demonstrated in just a small number of examples until now.[5–7] Further, their application as molecular memory devices has been discussed.[8–10] Although these systems currently suffer from the accumulation of side products during data storage and a short retention time in the range of minutes, they still have a great potential as a "bottom-up" strategy for designing molecular information processing devices.[10]

In this communication, we report on the synthesis and characterization of triple responsive polymers, exhibiting a distinct lower critical solution temperature (LCST) in water. We focused on thermo-, light- and redox responsive copolymers and their reversible change in LCST after applying an additional external stimulus. These responsive systems were investigated in the context of polymer information processing devices.

Triple responsive statistical copolymers were synthesized using a post-polymerization modification strategy utilizing well-defined poly(pentafluorophenyl acrylate) (PPFPA), prepared by the RAFT polymerization technique.[11] PPFPA was then converted with *N*-(2-aminoethyl)-4-(2-phenyldiazenyl) benzamide (azobenzene) and 4-amino-2,2,6,6-tetramethyl-1-oxyl-piperidine (amino-TEMPO) followed by the reaction with an excess amount of isopropylamine (Scheme 1) yielding statistical copolymers based on thermo responsive poly(*N*-isopropylacrylamide) (PNIPAM), containing light responsive azobenzene moieties and redox sensitive TEMPO side groups. Azobenzene is known for its wavelength dependent photo-induced *cis–trans* isomerization. The reversible conformation change from *trans* to *cis* is accompanied by an increase of local polarity due to a change in the dipole moment of the chromophore.[12] TEMPO is known to undergo reversible electron transfer reactions and used in energy storage applications.[13] Recently, PNIPAM copolymers with TEMPO moieties have been shown to act as double responsive materials.[14]

Following this strategy, two different triple responsive copolymers **PI** and **PII** were synthesized, varying in their amounts of azobenzene and TEMPO. The polymers were purified by dialysis against water and one subsequent precipitation step into diethylether. ESR spectroscopy was used to confirm the existence of the paramagnetic TEMPO functionality. The contents of azobenzene and TEMPO in **PI** and **PII** were evaluated by ^{1}H-NMR. However, due to the paramagnetic character of the TEMPO moiety, this could only be achieved after treatment of a sample with ascorbic acid to reduce the TEMPO radical. **PI** contained 1.6 mol% of azobenzene and 3.5 mol% of amino-TEMPO, while **PII** contained 2.3 mol% of azobenzene and 5.7 mol% of amino-TEMPO.

The LCST behavior by means of cloud points of the triple responsive polymers was investigated using turbidity measurements. A concentrated solution (5 mg mL^{-1}) of **PI** and **PII** in



Scheme 1 Synthesis of triple responsive PNIPAM based copolymers containing azobenzene and TEMPO moieties.

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Table 1 LCST of **PI** and **PII** depending on three stimuli: temperature, light and redox (temperature shift with respect to initial LCST)

Stimuli	$LCST_{PI}$/°C (ΔLCST)	$LCST_{PII}$/°C (ΔLCST)
None	14.9 (±0)	13.9 (±0)
Ascorbic acid	16.1 (+1.2)	17.7 (+3.8)
Irradiation 365 nm	16.4 (+1.5)	18.0 (+4.1)
Irradiation >400 nm	16.1 (+1.2)	17.7 (+3.8)
Red prussiate	15.0 (+0.1)	14.0 (+0.1)

0.1 M $NaSO_4$ was heated in a cuvette and the transmittance was measured as a function of temperature using a UV/Vis spectrometer. Although pure PNIPAM shows a sharp LCST, introduction of further moieties required the addition of sodium sulfate as a cosmotropic salt to obtain sharp LCSTs (see ESI†).[14] Generally, introduction of the TEMPO and azobenzene groups in **PI** and **PII** resulted in more hydrophobic polymer chains and thus decreased the LCST (Table 1). Adding ascorbic acid to the polymer solution reduced the TEMPO moieties,[15] which resulted in an increase of the LCST. The conversion from the oxyl- into the more hydrophilic hydroxylamine group resulted in an improved hydrophilic interaction with the solvent, likely also due to hydrogen bonding. The amount of TEMPO functionalities within the polymer demonstrated the impact of this stimulus: the higher the amount of TEMPO moieties, the higher the change in LCST. For **PI** (3.5 mol% TEMPO) the increase of the LCST was determined as 1.2 °C. In contrast, the LCST of **PII** (5.7 mol% TEMPO) increased by about 3.8 °C. Noteworthily, a stepwise reduction of the TEMPO moiety allowed a successive increase of LCST.[14] When **PII** was stepwise reduced by the addition of ascorbic acid the LCST raised by 1.3 °C in a first reduction step and then by 0.6 °C in a second reduction step. This dependence of the temperature shift on the amount of TEMPO moieties reduced offers the possibility to fine-tune the LCST.

Subsequent irradiation with UV light (365 nm) resulted in an additional increase of the LCST by 0.3 °C, due to the isomerization of the azobenzene moiety. The amount of the chromophore in both polymers **PI** and **PII** was almost identical. Consequently, the impact of the irradiation was identical for both polymers as the LCST increased in both cases by 0.3 °C.

The photoisomerization could be reversed by irradiation with light with $\lambda > 400$ nm.[12] Irradiation resulted in the *trans* isomer of azobenzene, which lowered the local polarity and thus decreased LCST again. The experiment confirmed that the former increase of 0.3 °C (*cis* state) was fully reversible after re-isomerization with visible light. Notably, this also demonstrated the accuracy of the stimuli responses of the polymers (Table 1, Fig. S4, ESI†).

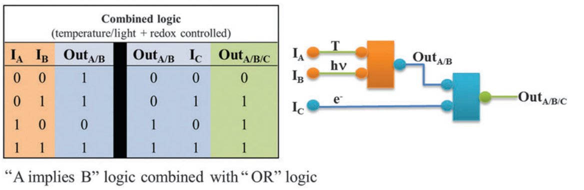
Oxidation of the hydroxylamine moiety back to the radical was achieved by addition of red prussiate (potassium ferricyanide), which led to a significant decrease of the LCST, demonstrating that the redox stimulus could be completely reversed as the initial LCST was reobtained. A second redox cycle with the same polymer proved the full reversibility of the redox stimulus (see ESI†). The successive replication is in accordance with the work of Nishide and Oyaizu and confirms that decomposition of TEMPO groups or irreversible side reactions can be excluded.[13]

However, it is known that the addition of salts might have a significant influence on the LCST.[16] The influence of added salts was investigated on a PNIPAM model system (ESI†). Being aware of this strong influence, the polymer solutions of **PI** and **PII** were purified accordingly after treatment with ascorbic acid or red prussiate. Thus, the results in Table 1 are without the influence of additional salts, *i.e.* after purification.

To address the stimuli responsive moieties independently, a second experiment was conducted by stimulation of the light-responsive chromophore moieties first and then reduction of the TEMPO moieties. Interestingly the impact of the light-responsive moiety is increased in comparison to the previous situation, with an increase of LCST by 0.5 °C for **PI** after irradiation with UV light (365 nm). We believe that the effect of the LCST on the azobenzene moieties depends on the composition of the polymer, as shown previously.[12,17] The isomerization of the azobenzene moieties in the presence of the less hydrophilic TEMPO led to a more pronounced impact in comparison with the more hydrophilic hydroxylamine. The subsequent reduction of TEMPO led to a further increase of the LCST by 0.5 °C. Further irradiation with UV light raised the LCST again by 0.3 °C, suggesting that the *cis–trans* relaxation of azobenzene already happened along with the oxidation process (see ESI†). With respect to the initial LCST the temperature was shifted by 1.3 °C, which was similar to the previous situation.

Translating this information into the context of information processing, several combinations are possible with one system. In general a logic gate is the physical expression of the Boolean function and uses one or more inputs to produce a single output.[18] The stimuli responsive functionalities can be addressed independently and therefore, in a triple responsive polymer, three different inputs are available: temperature (input A: I_A), light (input B: I_B) and the redox-sensibility (input C: I_C). In this context $I_A = 0$ is correlated to keeping the polymer solution below LCST, while $I_A = 1$ is equal to heating the solution to a temperature 0.4 °C higher than LCST. Accordingly $I_B = 0$ means the sample has not been irradiated and $I_B = 1$ corresponds to the irradiated polymer solution and thus isomerization into *cis*-azobenzene. $I_C = 0$ indicates a sample that has not been treated with ascorbic acid and $I_C = 1$ is equivalent to the hydroxylamine. The output signal (Out) can either be Out = 0 for insoluble or Out = 1, which means the polymer is soluble. The direct addressing of just two responsive groups like temperature and light or temperature and redox-sensibility corresponds to "A implies B" logic or "A implies C", respectively, which was already described in the literature.[6] The combination of three stimuli leads to a new, more complex logic circuit: if temperature and light stimuli are stimulated first an "A implies B" output is generated. If the resulting output $Out_{A/B}$ is subsequently combined with the redox input as an "OR" logic gate, it results overall in the statement "always true, if not only A". The circuit fulfilled associativity, *i.e.* it does not matter in which sequence the stimuli are applied (see Boolean logic truth tables in Fig. 1).

A logic gate yields a logic output response as a result of an input signal, but it does not allow storing the information. In contrast, a flip-flop element offers the possibility of storing information for sequential logic operations.[9] The bistable



Combined logic (temperature/light + redox controlled)					
I_A	I_B	$Out_{A/B}$	$Out_{A/B}$	I_C	$Out_{A/B/C}$
0	0	1	0	0	0
0	1	1	0	1	1
1	0	0	1	0	1
1	1	1	1	1	1

"A implies B" logic combined with "OR" logic

Fig. 1 Truth table for a logic system with 3 inputs. First, the stimuli temperature (I_A) and light (I_B) give a logical output through an "A implies B" logic, which is combined with the redox sensitive input (I_C).

states of the TEMPO- and the azobenzene moieties suggest the potential use as a Set/Reset (SR) flip-flop device. The paramagnetic state and the reversible conversion into the hydroxylamine as well as the *cis–trans* isomerization of azobenzene offer the possibilities of saving two bits with only one polymer. The saved information is translated into the fully reversible change of the LCST.

The reduced TEMPO moiety will be considered as the memory state output yielding logic $Q_1 = 1$, while the paramagnetic state will be defined as logic state $Q_1 = 0$. The Set input $S_1 = 1$ represents the addition of ascorbic acid and the Reset input $R_1 = 1$ means the addition of red prussiate. The operation of the logic element is shown in Fig. 2. When the system is in logic state $Q_1 = 0$ or in logic state $Q_1 = 1$ and the inputs $S_1 = 1$ and $R_1 = 0$ are applied to the system, the system is set to state 1, which is achieved by addition of ascorbic acid. But when the system exists in the logic state 0 or in the logic state 1 and is subjected to the $S_1 = 0$ and $R_1 = 1$, the system is reset to the logic state 0, *i.e.* red prussiate is added.

The azobenzene moiety offers an additional SR flip-flop. Similar to the previous situation the *trans*-isomer corresponds to the logic state $Q_2 = 0$, while the *cis*-state is considered as logic $Q_2 = 1$. If UV light with 365 nm is applied to the system, existing in the state $Q_2 = 0$, the memory element is set to logic $Q_2 = 1$, this corresponds to the $S_2 = 1$, $R_2 = 0$ setting and results in the *cis*-configuration of the system. The $Q_2 = 1$ state can be deleted by the input configuration $S_2 = 0$, $R_2 = 1$ and is realized by irradiation with light > 400 nm. The exact state of the flip-flop is read by temperature and determined by the reversible change of the LCST. Because of the orthogonal responses of the TEMPO- and azobenzene moieties, two bits can be stored successively. If both memory elements exist in the logic state 1 then this is taken into account and can be observed through the additional LCST at 16.4 °C. The truth table of the flip-flop system is shown in the ESI.† Noteworthily, the two states of the TEMPO moiety are stable over months, while the relaxation of the *cis* isomer of the azobenzene to the *trans*-conformation occurs with a half-life of 11 days in the dark,[12] *i.e.* the stored data are lost after this period. The volatile character of molecular memories is a common problem, however, the present polymer has a 1000 fold increased half-life compared to previous molecular memories.[8]

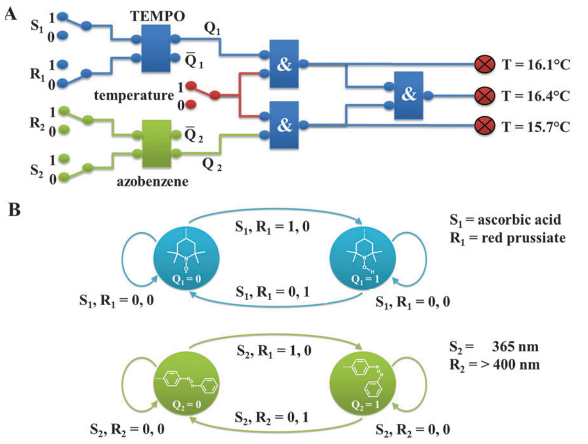


Fig. 2 (A) Circuit of the flip-flop device of **PI**: two flip-flops combined with the temperature query *via* AND gates. (B) Representation of two Set/Reset flip-flop devices (blue: TEMPO, green: azobenzene).

In summary, post-polymerization modification provides an easy access to multi-responsive polymers, which respond independently to temperature-, light- and redox-sensitive stimulations. These systems exhibited a distinct and an adjustable LCST switching window. It was shown that this property could be tailored during the synthesis by adjusting the corresponding moiety, and additionally fine-tuned directly in the application by the degree of conversion of the TEMPO into the hydroxylamine functionality. The stability of every state facilitates the implementation of different polymer information processing systems. The realization of several information processing techniques within only one system is exceptionally fascinating. The unique application as a polymer memory device, in the sense of Set/Reset flip-flop, for two bits in one polymer is remarkable. It gives reason to except more complex computing processes in the near future based on polymeric materials, which exhibit multifaceted properties.

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