DNA Nanostructures Hot Paper

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A Shape-Memory DNA-Based Hydrogel Exhibiting Two Internal Memories

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Abstract: *The synthesis of a shape-memory acrylamide–DNA hydrogel that includes two internal memories is introduced. The hydrogel is stabilized, at pH 7.0, by two different pH-responsive oligonucleotide crosslinking units. At pH 10.0, one of the T-A·T triplex DNA bridging units is dissociated, resulting in the dissociation of the hydrogel into a shapeless quasi-liquid state that includes the other oligonucleotide bridges as internal memory. Similarly, at pH 5.0, the second type of bridges is separated, through the formation of C-G·C$^+$ triplex units to yield the shapeless quasi-liquid state that includes the other oligonucleotide bridges as internal memory. By reversible pH triggering of the hydrogel between the values 10.0⇔7.0⇔5.0, the two internal memories cycle the material across shaped hydrogel and shapeless quasi-liquid states. The two memories enable the pH-dictated formation of two different hydrogel structures.*

The design of stimuli-responsive DNA-based hydrogels attracts substantial recent interest. The crosslinking of nucleic acid-tethered polymer chains through the formation of duplex bridging units provides a general means to generate DNA-based hydrogels.[1] The hydrogel-to-polymer solution transitions of these systems were induced by strand displacement,[2] temperature,[3] enzyme[3,4] or DNAzyme[5] cleavage of the bridging units. Other DNA-based hydrogels undergoing cyclic and reversible hydrogel-to-polymer solution included metal-ion (e.g., Ag^+) -induced bridging of duplex DNA and their separation by ligands eliminating the ions (e.g., cysteamine),[6] the pH-induced formation of i-motif-crosslinked hydrogels (at pH 5.2) and the separation of the i-motif structure at neutral pH,[7] the K^+-ion-stimulated crosslinking of polymer chains by G-quadruplex units and the separation of the hydrogel by means of 18-crown-6-ether that eliminates the K^+ ions,[8] the use of light,[9] and the use of different Hoogsteen-type pH-sensitive triplex DNA as bridging units of the polymer chains.[10] Different applications of stimuli-responsive DNA-based hydrogels were suggested, including controlled drug release,[11] sensors,[12] switchable catalysis,[8] and catalyzed synthesis of conducting wires,[13] separation of substrates,[14] and the triggered activation of enzyme cascades.[5]

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Shape-memory polymers represent an interesting class of smart, stimuli-responsive materials. These polymers are processed into a permanent shaped structure that is programmed into a temporary shape that includes a memory to restore the original shape, in the presence of an appropriate trigger.[2,3,6,8,13a,15] A variety of triggers such as thermal, light or magnetic stimuli were used to activate shape-memory materials.[3,9,15f] Different applications of shape-memory materials were suggested, including their use as sensors, functional materials for inscription,[16] matrices for controlled drug release,[17] and materials for actuating microdevices.[18] The information encoded in oligonucleotide[19] sequences provides versatile means to design shape-memory polymers. By one approach,[20] a shape-memory hydrogel undergoing gel-to-quasi-solid transition was reported. In this system, polymerase-woven DNA strands were swollen by water in shape molds to form shaped hydrogels. Exclusion of the water from the shaped hydrogels yielded collapsed shapeless quasi-solid structures that reformed the hydrogel upon swelling the material with water. A second approach to yield shape-memory DNA-based hydrogels involved the use of polymer chains, for example, acrylamide chains that are modified with oligonucleotide tethers that are capable to crosslink the polymer chains by two different mechanisms. One crosslinking element provides the code (memory) to restore the shaped hydrogel and the second crosslinking element provides the switching stimuli to trigger the transition of the system between shaped hydrogel and shapeless, quasi-liquid states, respectively.[7] Accordingly, the shaped hydrogel is formed in the mold using the two crosslinking mechanisms as elements that stabilize the hydrogel shape. The triggered elimination of the stimuli-switchable crosslinking element transforms the hydrogel into a shapeless quasi-liquid state that includes the second crosslinking element as an internal memory that dictates the reformation of the shaped hydrogel upon the stimuli-triggered restoration of the switchable crosslinking units. Indeed, an oligonucleotide-modified acrylamide-shaped hydrogel was formed in the mold using duplex DNA and pH-sensitive i-motif bridges as stabilizing crosslinkers. The pH-induced separation of the i-motif units weakened the hydrogel, resulting in the quasi-liquid shapeless system. The residual duplex linkers provided, however, an internal memory, by providing the dictated entanglement of the polymer chains to restore the shaped hydrogel upon the pH-induced reformation of the i-motif bridges.[7,21] A similar shape-memory DNA-based hydrogel was constructed using duplex DNA and pH-sensitive triplex DNA units as crosslinking units.[22] Also, hybrid structures consisting of several stimuli-responsive acrylamide–DNA hydrogels could be simultaneously triggered to undergo transitions between the

cyclic shape and shapeless states.[21] In all of the systems, the hydrogels included a simple memory for triggering the shape-to-shapeless transitions. In the present study, we demonstrate the preparation of a hydrogel that includes two shape-memory elements that each stimulate reversible stimuli-triggered transitions between the shaped hydrogel and the shapeless quasi-liquid states. We further demonstrate that we can encode two memories into the shaped hydrogel, allowing the generation of two programmed stimuli-triggered hydrogel structures.

The "two-memory" DNA-based hydrogel is based on the crosslinking of the acrylamide hydrogel matrix by two pH-responsive DNA bridging motifs that form Hoongsteen-type triplex DNA structures (Figure 1 A). One of the triplex structures is based on protonated cytosine–guanosine–cytosine bridges, C-G·C$^+$, formed at pH 5.0 and dissociated at pH 7. The second triplex structure consists of thymine–adenine–thymine bridges, T-A·T, that are formed at pH 7.0 and are being dissociated at pH 10.0. Accordingly, acrylamide copolymer chains were generated by the radical polymerization of the 5′-acrydite nucleic acids (**1**), (**2**), (**3**), and acrylamide at a ratio corresponding to 6:6:5:527. The resulting polymer chains exhibited an average molecular weight of 250 000 (determined by NMR spectroscopy,[10,22] see Figure S1 in the Supporting Information), and the ratio of DNA subunits to unsubstituted acrylamide units was determined spectroscopically to be 1:31 (for the determination of the loading, see Figure S2). The single strand (**4**) was added to an aqueous polymer solution at 95°C and pH 7.0 and the solution was allowed to cool down to room temperature. A hydrogel matrix was formed. This hydrogel was crosslinked by the different bridges: One involved the duplex between the free tether of (**1**), existing at pH 7.0 as free tether, with the single strand (**2**) associated with the polymer. The second bridging unit consisted of the triplex T-A·T formed, at pH 7.0, between the tethers (**3**) linked to the polymer and (**4**) solubilized in the polymer solution, (**3**)/(**4**)/(**3**). That is, the hydrogel was cooperatively stabilized, at pH 7.0, by the (**1**)/(**2**) duplexes and the (**3**)/(**4**)/(**3**) triplex units (state I). Subjecting the hydrogel to pH 10.0 leads to the separation of the T-A·T triplex structure, (**3**)/(**4**)/(**3**), to the duplex (**3**)/(**4**)- and (**3**)-modified polymer chains. The dissociation of the T-A·T bridges weakens the hydrogel, resulting in the transformation of the hydrogel into a quasi-liquid state (state II). Restoring the pH of the system to pH 7.0 regenerates the triplex structure of (**3**)/(**4**)/(**3**), resulting in the re-formation of the (**1**)/(**2**)- and (**3**)/(**4**)/(**3**)-crosslinked hydrogel state (state I). Similarly, subjecting the hydrogel to pH 5.0 results in the intramolecular stabilization of the C-G·C$^+$ triplex structure of (**1**), and the concomitant separation of the (**1**)/(**2**) duplex bridges. The separation of the duplex (**1**)/(**2**) weakens the hydrogel, and it is transformed to a quasi-liquid state (state III). Restoring the pH of the system to pH 7.0 separates the triplex structure of (**1**), resulting in the regeneration of the duplexes (**1**)/(**2**) and the re-formation of the (**1**)/(**2**)- and (**3**)/(**4**)/(**3**)-crosslinked hydrogel state (state I). That is, the polymer chains crosslinked by the (**1**)/(**2**) and (**3**)/(**4**)/(**3**) bridges exists at pH 7.0 as a hydrogel, yet it is transformed to a quasi-liquid state at either pH 5.0 or pH 10.0.

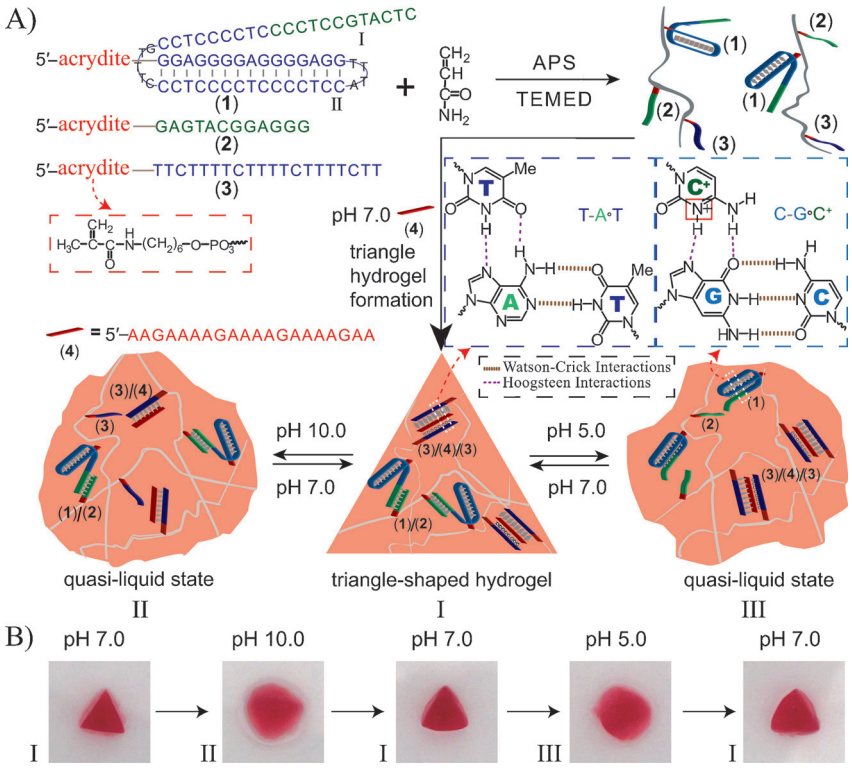

Figure 1. A) Synthesis of a shape-memory DNA-based acrylamide hydrogel that includes two pH-responsive crosslinking motifs. At pH 7.0 the two crosslinking elements stabilize the shaped hydrogel structure. At pH 5.0 or at pH 10.0 the shaped structure is transformed into a quasi-liquid shapeless configuration because of the removal of one of the crosslinking motifs. B) Images of the cyclic pH-stimulated transitions of the shape-memory hydrogel across a triangle-shaped stiff hydrogel structure and a shapeless soft, quasi-liquid, state. The quasi-liquid states include one of the crosslinking motifs as an internal memory. State I is generated at pH 7.0 and transformed to state II at pH 10.0. Subjecting state II to pH 7.0 regenerates state I that, upon subsequent treatment at pH 5.0, forms state III. The shapeless state III regenerates state I upon treatment at pH 7.0.

The fact that the hydrogel state at pH 7.0 is stabilized by two different bridging units (**1**)/(**2**) and (**3**)/(**4**)/(**3**) suggests that a shaped hydrogel at pH 7.0 undergoes at pH 5.0 a transition to a quasi-liquid phase, where the bridges (**3**)/(**4**)/(**3**) provide a memory to regenerate the shaped structure at pH 7.0. Similarly, the transformation of the shaped hydrogel to the quasi-liquid state at pH 10.0 retains the bridging units (**1**)/(**2**) intact, and these provide an encoded memory to regenerate the shaped structure at pH 7.0. Figure 1 B confirms that these shape-memory features of the hydrogel are, indeed, preserved. In this experiment, a triangle-

shaped hydrogel is formed in a mold, where the hydrogel is stabilized by the bridging units (**1**)/(**2**) and (**3**)/(**4**)/(**3**). The triangle-shaped hydrogel (state I) is extracted from the mold. Subjecting the hydrogel to pH 10.0 yields a quasi-liquid, shapeless state II, because of the dissociation of the (**3**)/(**4**)/(**3**) bridges. Acidification of state II to pH 7.0 restores the shaped triangle structure, state I, consistent with the explanation that the bridges (**1**)/(**2**) existing in the shapeless quasi-liquid phase provide an encoded memory of entangled polymer chains that restore the shaped structure upon crosslinking the hydrogel at neutral pH by the two motifs (**1**)/(**2**) and (**3**)/(**4**)/(**3**). Treatment of the triangle-shaped hydrogel at pH 5.0 transforms the hydrogel into the shapeless quasi-liquid state, III, consistent with the dissociation of the bridging units (**1**)/(**2**). The remaining bridges, (**3**)/(**4**)/(**3**), provide, however, the internal memory of polymer chains entanglements. Upon the neutralization of state III to pH 7.0, reshaping of the hydrogel triangle state I is observed because of the crosslinking of the hydrogel by the two bridging motifs, (**1**)/(**2**) and (**3**)/(**4**)/(**3**). It should be noted that the quasi-liquid states II and III are generated upon subjecting the shaped hydrogels to the stated buffer solution for 1 hour. After this time interval no further deformation of the quasi-liquid states was observed. Also, the quasi-liquid states kept for longer time intervals in the respective buffer solution retained their ″memory″ features, allowing the regeneration of the original shapes. Furthermore, the reversible pH-stimulated transitions of the triangle shapes, using the two pH-responsive memories could be cycled for at least six cycles with no visual change in the triangle shape. Nonetheless, we anticipate that the re-shaping efficiency would be hampered upon increasing the number of shape/quasi-liquid cycles, because of the gradual perturbation of the memory elements. Temporary thermal dissociation of some of the crosslinking nucleic acid bridging units, resulting in fluctuations in the polymer chains, are expected to perturb the re-shaping processes. The rigidity of the shaped structures and the fluidity of the quasi-liquid states were probed by microindentation and evaluation of the Young's moduli of the shaped structures. While the shaped hydrogel structure exhibited a Young's modulus corresponding to $Y = 1635 \pm 20$ Pa, the quasi-liquid states revealed a Young's modulus of $Y < 10$ Pa (see the experimental details in the Supporting Information).

To obtain further physical insight to the hydrogel and quasi-liquid state, complementary rheometry and SEM imaging measurements were performed. Figure 2 A depicts the rheometry features of the system. The hydrogel system, at pH 7.0, reveals a storage modulus of $G' \approx 85$ Pa, curve (a), and a loss modulus of $G'' \approx 5$ Pa, curve (b). These values are consistent with the formation of a hydrogel ($G'/G'' = 17$). At pH 10.0, the storage modulus of the system drops to $G' \approx 20$ Pa, curve (c), and the loss modulus exhibits a value of $G' \approx 2.0$ Pa, curve (d), implying that a very soft, quasi-liquid, state is formed. Similarly, Figure 2 A, curves (e) and (f) show that for the acidified system, pH 5.0, the G' and G'' values of the system correspond to 22 Pa and 3.0 Pa, respectively, implying that the system exists in a soft, quasi-liquid state. Figure 2 B depicts the switchable G' and G'' values upon transition of the hydrogel, at pH 7.0, between the quasi-liquid

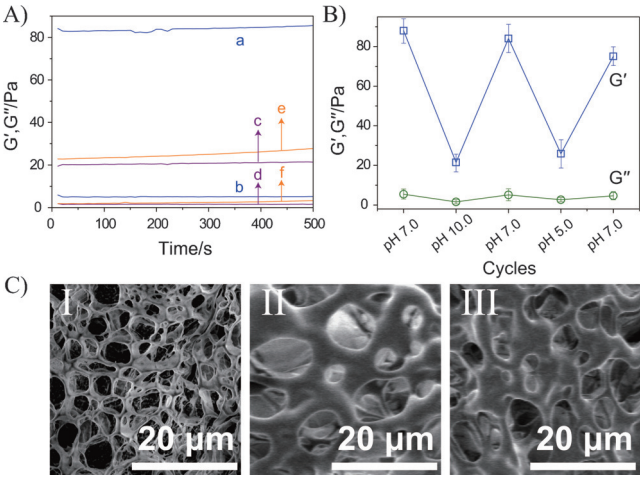

Figure 2. A) Rheometry characterization of the DNA-based acrylamide hydrogel crosslinked by two different pH-responsive crosslinking motifs: a) Storage modulus (G') corresponding to the (**1**)/(**2**)- and (**3**)/(**4**)/(**3**)-crosslinked hydrogel at pH 7.0. b) The loss modulus (G'') of the (**1**)/(**2**)- and (**3**)/(**4**)/(**3**)-crosslinked hydrogel. c) The storage modulus (G') of the (**1**)/(**2**)-crosslinked soft, quasi-liquid state at pH 10.0. d) The loss modulus (G'') of the (**1**)/(**2**)-crosslinked system at pH 10.0. e) The storage modulus (G') corresponding to the (**3**)/(**4**)/(**3**)-crosslinked soft, quasi-liquid system at pH 5.0. f) The loss modulus (G'') corresponding to the (**3**)/(**4**)/(**3**)-crosslinked system at pH 5.0. B) Switchable storage-moduli (G') and loss-moduli (G'') values upon subjecting the (**1**)/(**2**)- and (**3**)/(**4**)/(**3**)-crosslinked hydrogel (pH 7.0) to pH 10.0 and pH 5.0, respectively. C) Au/Pd-coated freeze-dried SEM images corresponding to: (I) the (**1**)/(**2**)- and (**3**)/(**4**)/(**3**)-crosslinked hydrogel at pH 7.0; (II) the soft (**1**)/(**2**)-crosslinked matrix at pH 10.0; (III) the soft (**3**)/(**4**)/(**3**)-crosslinked matrix at pH 5.0.

states at pH 10.0 and pH 5.0, respectively. Figure 2 C panel I depicts the SEM image of the hydrogel at pH 7.0. A porous crosslinked network is observed, consistent with the formation of a hydrogel matrix. Panels II and III in Figure 2 C show the SEM images of the quasi-liquid systems generated at pH 10.0 and pH 5.0, respectively. Fluidic matrices showing large pores, which indicate soft matrices of low crosslinking, are observed.

The successful preparation of a shape-memory hydrogel matrix that can be transformed into two quasi-liquid states that included different codes (crosslinking units) as memories to reshape the original hydrogel structure suggested that one could design a hydrogel that includes two-shape memories that could dictate the programmed formation of two-different shapes by appropriate triggers. This is exemplified in Figure 3 A. The hydrogel is generated in the mold in the form of a "bar" at pH 7.0, step (a), and is extracted from the mold, step (b). This hydrogel is crosslinked by (**1**)/(**2**) and (**3**)/(**4**)/(**3**). The resulting hydrogel is subjected to pH 10.0, resulting in the quasi-liquid state, step (c). This state includes the bridges (**1**)/(**2**) as internal memory code and the appropriate polymer chain entanglement features to reshape the "linear bar" structure. The resulting quasi-liquid state was, then, re-introduced into the mold exhibiting a rectangular structure, and the quasi-liquid matrix was subjected to pH 7.0, to reshape the (**1**)/(**2**), (**3**)/(**4**)/(**3**) hydrogel in a rectangular structure, step (d). (The volumes of the linear and rectangular

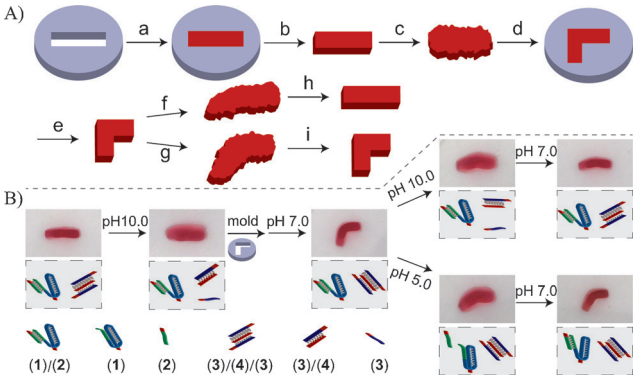

Figure 3. Fabrication and operation of a pH-responsive DNA–acrylamide hydrogel that includes two encoded memories for the triggered assembly of two different structures. A) The stepwise assembly of the two-memory hydrogel in a mold. B) Images corresponding to the pH-triggered, memory-dictated, transitions of the hydrogel between two different structures. The "bar"-shaped (**1**)/(**2**)- and (**3**)/(**4**)/(**3**)-cross-linked hydrogel is prepared in the mold at pH 7.0. The structure is subjected to pH 10.0 to yield the soft, quasi-liquid system that uses (**1**)/(**2**) as memory. The quasi-liquid system is re-introduced into a rectangular mold and subjected to pH 7.0 to yield the "rectangular"-shaped hydrogel. The resulting hydrogel is subjected to pH 10.0 to yield the quasi-liquid system with the internal memory (**1**)/(**2**). Subjecting the system to pH 7.0 restores the "bar" structure. Treatment of the rectangular structure at pH 5.0 yields the soft, quasi-liquid system that includes (**3**)/(**4**)/(**3**) as internal memory. Subjecting the system to pH 7.0 restores the rectangular structure.

molds were similar). The resulting rectangular-shaped hydrogel structure was extracted from the mold, step (e). The method for the preparation of the hydrogel suggests that, upon transforming the hydrogel into a quasi-liquid soft state, it included the encoded memories to yield two different structures: Treatment of the rectangular shape at pH 10.0 dissociates the hydrogel to the soft matrix that includes the polymer chains entangled with the (**1**)/(**2**) bridging memory, step (f). On the other hand, subjecting the rectangular-shaped hydrogel to pH 5.0 yields a soft, quasi-liquid state, step (g), where the bridging units (**3**)/(**4**)/(**3**) provide the instructive polymer chain entanglement (memory) for reshaping the rectangular structure. That is, subjecting the quasi-liquid matrices generated in steps (f) and (g) will yield two different hydrogel structures, the "linear bar", step (h) or the rectangular structure, step (i), respectively. Figure 3 B depicts the structural images of the hydrogels generated according to Figure 3 A by encoding two different memory codes into the quasi-liquid states. The process for encoding the two shape memories into the hydrogel can be reversed, Figure S3. That is, the hydrogel formed in the mold at pH 7.0, in the form of a bar, is subjected to pH 5.0 to yield the quasi-liquid with the ″linear bar″ memory. The introduction of the quasi-liquid into the rectangular mold, followed by hydrogelation of the system, generated the rectangular shape. Subjecting the resulting structure to pH 5.0 or to pH 10.0 generated the quasi-liquid states that included the two shape-memory elements. Subjecting the quasi-liquid state generated at pH 5.0 to pH 7.0 resulted in the formation of the ″linear bar″, whereas in this system, subjecting the quasi-liquid state generated at pH 10.0 to pH 7.0 yielded the rectangular shape. The results confirm that successful encoding of two different memories into the hydrogel system was accomplished.

In conclusion, the present study has introduced a new type of a DNA-based hydrogel that includes two different stimuli-responsive bridging units that cooperatively stabilize the hydrogel matrix. Specifically, we have implemented two pH-responsive bridging units, where one kind of the bridging units is dissociated at pH 10.0 and the other bridging units are separated at pH 5.0. At pH 7.0 both of the bridging units stabilize the hydrogel structure. These properties of the bridging units stabilize the hydrogel structure. These features of the bridging units allowed us to design two different shape-memory systems undergoing switchable transitions between shapeless, quasi-liquid, states at pH 10.0 and pH 5.0 and a shaped structure at pH 7.0. Furthermore, we have demonstrated that two different memory codes can be imprinted in the hydrogel structure so that, upon the triggered dissolution of the hydrogel to the quasi-liquid state, the programmed, dictated formation of two different hydrogel structures is achieved. A possible application of such two-memory shaped hydrogels could involve the selective activation of DNAzymes and DNAzyme cascades.[23] For example, the incorporation of two different metal-dependent DNAzymes operating at acidic or basic pH values, for example, the UO_2^{2+}- or Mg^{2+}-dependent DNAzyme, would allow the selective pH-stimulated or activation of one of the DNAzymes, upon the dissociation of the hydrogel, and the subsequent activation of DNAzyme cascades. The results suggest that by designing other DNA hydrogels triggered by two stimuli-responsive bridges, for example, photonic/pH, photonic/G-quadruplex, other hydrogels exhibiting two internal shape memories could be designed.

Experimental Section

The DNA sequences used in the present study are: (**1**) 5′-acrydite-GGA GGG GAG GGG AGG TTT ACC TCC CCT CCC CTC CCT TTG CCT CCC CTC CCC TCC GTA CTC-3′; (**2**) 5′-acrydite-GAG TAC GGA GGG-3′; (**3**) 5′-acrydite-TTC TTT TCT TTT CTT TTC TT-3′; (**4**) 5′-AAG AAA AGA AAA GAA AAG AA-3′.

A detailed description of the preparation and characterization of the hygrogel is provided as Supporting Information.

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