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# Programmed Synthesis by Stimuli-Responsive DNAzyme-Modified Mesoporous $SiO_2$ Nanoparticles**

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***Abstract:*** *DNAzyme-capped mesoporous $SiO_2$ nanoparticles (MP $SiO_2$ NPs) are applied as stimuli-responsive containers for programmed synthesis. Three types of MP $SiO_2$ NPs are prepared by loading the NPs with Cy3-DBCO (DBCO = dibenzocyclooctyl), Cy5-$N_3$, and Cy7-$N_3$, and capping the NP containers with the $Mg^{2+}$, $Zn^{2+}$, and histidine-dependent DNAzyme sequences, respectively. In the presence of $Mg^{2+}$ and $Zn^{2+}$ ions as triggers, the respective DNAzyme-capped NPs are unlocked, leading to the "click" reaction product Cy3-Cy5. In turn, in the presence of $Mg^{2+}$ ions and histidine as triggers the second set of DNAzyme-capped NPs is unlocked leading to the Cy3-Cy7 conjugated product. The unloading of the respective NPs and the time-dependent formation of the products are followed by fluorescence spectroscopy (FRET). A detailed kinetic model for the formation of the different products is formulated and it correlates nicely with the experimental results.*

The entrapment of substrates in the pores of mesoporous $SiO_2$ nanoparticles (MP $SiO_2$ NPs) and their controlled release by means of stimuli-responsive caps attracts substantial research interest.[1,2] Different applications of these NPs were suggested including controlled drug delivery,[3–5] sensing,[6] imaging,[7,8] and switchable catalysis.[9–11] Various stimuli were applied to unlock the pore caps and release the loaded substrates. These included pH,[12–15] redox reagents,[16–18] photonic signals,[19,20] and enzymes[21–24] as triggers. Also, the cooperative operation of gated nanoparticles was recently reported.[25] One class of stimuli-responsive MP $SiO_2$ NPs includes nucleic-acid-capped NPs. Bulky duplex nucleic acids, hairpin systems, pH-sensitive nucleic acids, and G-quadruplexes were used to cap the pores. Unlocking the nucleic acid gates through the formation of aptamer–ligand complexes,[26] pH-induced reconfiguration of i-motif structures to random coils,[27] crown-ether-stimulated separation of $K^+$-ion-stabilized G-quadruplexes,[28] or enzymatic digestion of DNA caps were reported.[29] The present study introduces the novel application of stimuli-responsive MP $SiO_2$ NPs for programmed synthesis. We introduce metal-ion-dependent catalytic nucleic acids (DNAzymes) as functional caps of MP $SiO_2$ NPs loaded with different reagents. Specific triggers lead to the dictated release of the loads and their programmed reactions. The study provides a general innovative paradigm for programmed synthesis in the presence of functional nanoparticle assemblies.

Sequence-specific cofactor-dependent DNAzymes were used as stimuli-responsive capping units of MP $SiO_2$ NPs for the controlled release of drugs.[30] The present study introduces the use of cofactor-dependent DNAzyme-capped mesoporous $SiO_2$ NPs for a stimuli-dictated copper-free synthesis of "click-chemistry" products[31] (Figure 1a). This is demonstrated using a mixture of MP $SiO_2$ NPs loaded with different reactants, that is, Cy3-DBCO (**1**) (DBCO = dibenzocyclooctyl), Cy5-$N_3$ (**2**), and Cy7-$N_3$ (**3**), and capped with the $Mg^{2+}$, $Zn^{2+}$, or histidine-dependent DNAzyme sequences hybridized with their substrates, (**7**)/(**6**), group I, (**8**)/(**6**), group II, and (**9**)/(**6**) group III, respectively. In the presence of $Mg^{2+}$ and $Zn^{2+}$ ions, Cy3-DBCO (**1**) and Cy5-$N_3$ (**2**) are selectively released from the respective containers, and the click-product Cy3-Cy5 (**4**) is formed. In turn, treatment of the mixture of loaded NPs with $Mg^{2+}$ ions and histidine only unlocks NPs I and III, which leads to the selective release of Cy3-DBCO (**1**) and Cy7-azide (**3**), and the subsequent formation of the click-product Cy3-Cy7 (**5**). The loaded components were designed so that both reaction products, that is, Cy3-Cy5 (**4**) and Cy3-Cy7 (**5**), exhibit intramolecular fluorescence resonance energy transfer, FRET, signals allowing the kinetics probing of their formation. The bimolecular rate constants with which Cy3-DBCO (**1**) reacts with Cy5-$N_3$ (**2**) or Cy7-$N_3$ (**3**) under the current conditions were determined to be $k_{Cy3\text{-}Cy5} = (12 \pm 1)\cdot 10^{-3}\ \mu M^{-1} s^{-1}$ and $k_{Cy3\text{-}Cy7} = (21 \pm 2)\cdot 10^{-3}\ \mu M^{-1} s^{-1}$, respectively (Supporting Information (SI), Figures S1 and S2). We note that upon treatment of the mixture of loaded MP $SiO_2$ NPs with $Zn^{2+}$, $Mg^{2+}$, and histidine, unlocking of all pores proceeds and results in a mixture of Cy3-Cy5 (**4**) and Cy3-Cy7 (**5**).

Time-dependent fluorescence changes were observed upon unlocking the different capped MP $SiO_2$ containers, and the release of the loads, Cy3-DBCO (**1**), Cy5-azide (**2**), and Cy7-azide (**3**), by activating the different DNAzymes using $Zn^{2+}$, $Mg^{2+}$, or histidine as triggers, respectively, (Figure 2a–c, black circles). For comparison, the background-release of the fluorophores from the capped MP $SiO_2$ NPs in the absence of the trigger is depicted in the respective panels (Figure 2a–c, red circles); small fluorescence changes are observed that saturate to a constant value after a short time-interval. These fluorescence changes are attributed to the

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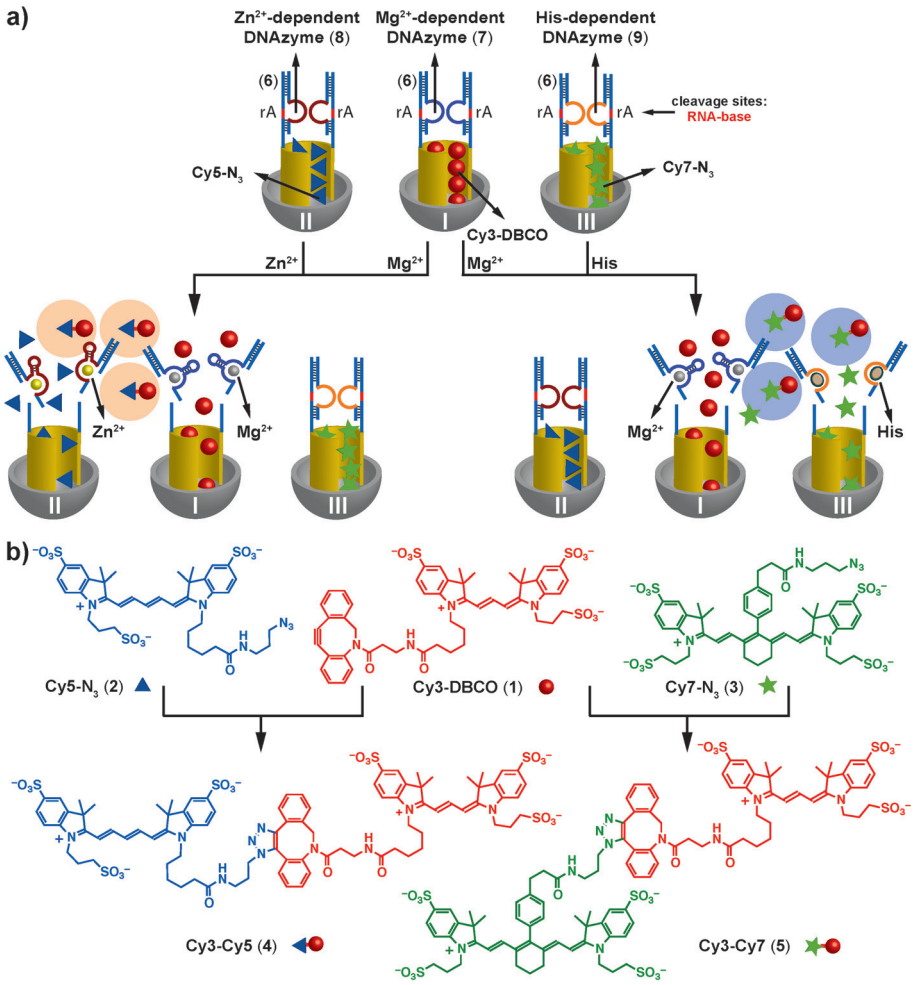


***Figure 1.*** a) Schematic depiction of DNAzyme-capped MP $SiO_2$ NPs loaded with different molecules. The triggers that activate the respective DNAzymes are indicated: the MP $SiO_2$ NPs are opened by the respective cofactors $Mg^{2+}$, $Zn^{2+}$, or histidine that cleave the capping units that consist of an oligonucleotide substrate (**6**), and one of the three bound inactive DNAzymes (**7**), (**8**), and (**9**). Release of the entrapped molecules leads to a click-conjugation reaction under formation of a FRET pair, occurrence of the FRET signal is indicated by the orange or purple halo around the products Cy3-Cy5 (**4**) or Cy3-Cy7 (**5**), respectively. b) Structures of the dye reactants loaded in the different MP $SiO_2$ NPs, and the conjugated products formed upon unlocking of the pores by the respective cofactor-dependent DNAzymes.

leakage of fluorophores from partially capped pores, or from large pores that cannot be effectively capped by the DNAzyme–substrate units. From the time-dependent fluorescence changes of the released fluorophores upon unlocking the different caps we evaluated the release rate constants to be: $k_{Zn^{II}} = 0.52 \pm 0.05\ min^{-1}$, $k_{Mg^{II}} = 0.42 \pm 0.04\ min^{-1}$, and $k_{His} = 0.53 \pm 0.05\ min^{-1}$. Selective release of one of the three fluorophores from the three groups of MP $SiO_2$ NPs is apparent from the fluorescence spectra recorded after a time-interval of 60 min (Figure 2d–f). Treatment of group I of MP $SiO_2$ NPs with $Mg^{2+}$ ions results in the release of Cy3-DBCO (**1**), whereas subjecting the group I of NPs to $Zn^{2+}$ ions or His leads only to the fluorescence of the background leakage of Cy3-DBCO (Figure 2d). Similarly, treatment of the NPs of groups II or III with $Zn^{2+}$ ions or histidine, respectively, leads to the release of Cy5-$N_3$ (**2**; Figure 2e) and Cy7-$N_3$ (**3**; Figure 2f), respectively. In the presence of the foreign triggers only the fluorescence of the background leakage of the respective fluorophores is observed. The effective blockage of the pores of mesoporous $SiO_2$ NPs by bulky DNA nanostructures has been reported previously.[26,28,29,32] Furthermore, we may realize that with no unlocking triggers, an inefficient leakage of the load substrates from the MP $SiO_2$ NPs is observed and this leakage process leads to a saturation value after ca. 15 min. Those leakage processes are attributed to the existence of larger pores that are ineffectively locked by the DNA gates.

Realizing the selective release of the fluorophore loads from the respective NPs, the programmed synthesis of the "click" reaction products using the mixture of differently loaded MP $SiO_2$ NPs was examined (Figure 3a). Subjecting the mixture of three kinds of NPs to the $Mg^{2+}$ and $Zn^{2+}$ triggers results in the selective unlocking of the MP $SiO_2$ NPs of groups I and II, and the parallel release of Cy3-DBCO (**1**) and Cy5-$N_3$ (**2**). This leads to the "click" reaction yielding Cy3-Cy5 (**4**), as product; the formation of this conjugate is probed by the intense FRET fluorescence signal of Cy5 at $\lambda = 670$ nm (Figure 3b, circles). Furthermore, Figure S3 depicts the rate of formation of the product Cy3-Cy5 upon unlocking NPs of structures I and II with the $Mg^{2+}$ and $Zn^{2+}$ triggers in the absence of the NPs of structure III, and the results are compared to the rate of formation of Cy3-Cy5 in the three NPs system in the presence of the $Mg^{2+}$ and $Zn^{2+}$ triggers (Figure S3). The rates of formation of Cy3-Cy5 in the two different systems overlap. The results imply that the synthesis of Cy3-Cy5 in the NPs mixture is, indeed, selective and originates from the selective unlocking of the NPs I and II. Similarly, triggering the mixture of three kinds of MP $SiO_2$ NPs with $Mg^{2+}$ ions and histidine results in the selective uncapping of NPs that contain Cy3-DBCO (**1**) and Cy7-$N_3$ (**3**), that is, group I and III, resulting in the release of these dyes and their subsequent click-conjugation to form the Cy3-Cy7 conjugate (**5**). The formation of Cy3-Cy7 is followed by the time-dependent changes in the FRET signal of Cy7 at 785 nm (Figure 3c). The rate of formation of Cy3-Cy5 in the

  

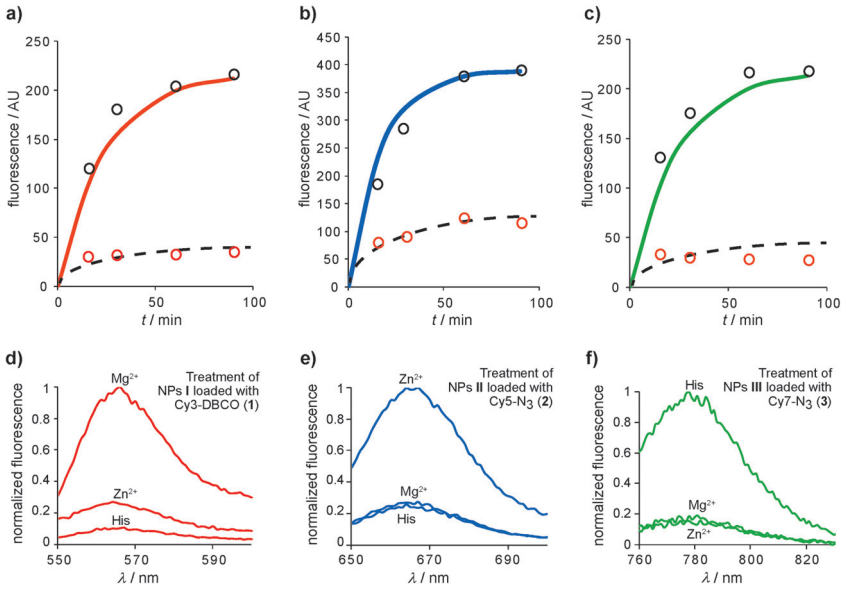


***Figure 2.*** Time-dependent release of: a) Cy3-DBCO (**1**); b) Cy5-$N_3$ (**2**); c) Cy7-$N_3$ (**3**) upon unlocking the MP $SiO_2$ NPs by the respective cofactor-dependent DNAzymes: NPs I: treatment with $Mg^{2+}$ ions, NPs II: treatment with $Zn^{2+}$ ions, and NPs III: treatment with L-histidine. DNAzyme-stimulated release of the respective dye loads (black circles), and background leakage of the loads from incompletely blocked pores (red circles). d–f) Selective cofactor-induced release from the respective capped MP $SiO_2$ NPs. The figures show the fluorescence spectra of the different fluorophores released after a fixed time-interval of 60 min from the loaded NPs using the respective cofactor triggers. d) Release of Cy3-DBCO (**1**) from NP I upon its unlocking with $Mg^{2+}$ ions, neither $Zn^{2+}$ nor histidine do unlock NPs I. e) Selective release of Cy5-$N_3$ (**2**) from NPs II upon treatment with $Zn^{2+}$, both $Mg^{2+}$ and histidine do not unlock these NPs. f) Cy7-$N_3$ (**3**) is only released from NPs III when they are treated with L-His, adding $Zn^{2+}$ or $Mg^{2+}$ ions does not unlock the NPs of type III.

system through the nonselective leakage of the fluorophores from NPs of the configuration I and II is depicted in Figure 3c (orange crosses). Also, Figure S4 shows the rate of formation of Cy3-Cy7 (**5**) upon unlocking the two NPs mixtures I and III by $Mg^{2+}$ ions and histidine (green circles) in comparison to the rate of formation of Cy3-Cy7 in the mixture of three NPs (I, II, and III) upon subjecting the systems to $Mg^{2+}$ ions and histidine (purple circles). The rates of Cy3-Cy7 formation in the two systems overlap, confirming that formation of Cy3-Cy7 in the three NPs mixture originates from the selective unlocking of NPs I and III by the $Mg^{2+}$ ions and histidine triggers. The formation of the click products Cy3-Cy5 (**4**) and Cy3-Cy7 (**5**), was supported by mass spectrometry analyses and complementary FRET characterization of the products. Knowing the amount of the released loads (**1**), (**2**), and (**3**) and the resulting saturated FRET spectra of the resulting product we estimate that the yields of Cy3-Cy5 is $\geq 96\,\%$ and of Cy3-Cy7 is $\geq 94\,\%$, upon unlocking of the containers I/II or I/III, respectively. Finally, the time-dependent fluorescence changes of the FRET fluorescence signals of Cy3-Cy5 (**4**) and Cy3-Cy7 (**5**), upon treatment of the mixture of the three kinds of MP $SiO_2$ NPs with all three triggers, $Mg^{2+}$, $Zn^{2+}$, and histidine, leads to the formation of both products (Figure 3d). Evidently, the two conjugates are formed in parallel, the ratios of which are determined by a combination of their relative release rates and the coupling reaction rates corresponding to the formation of each of the products. This result is consistent with the fact that unlocking of all three NPs together leads to branching of the reaction pathway and the consumption of the released reactant Cy3-DBCO (**1**) by two parallel conjugation pathways.

The results demonstrated that the targeted unlocking of two of the three loaded NPs (I + II or I + III) led to the selective synthesis of two different conjugates. Also, upon triggered unlocking of all three kinds of NPs (I, II, and III) the formation of the two conjugates (Cy3-Cy5 and Cy3-Cy7) was observed. To quantitatively analyze the rates of formation of the different conjugates we formulated a kinetic model of the system (see SI and Figure S5). The concentrations of the different reactants released from the NPs and the concentration of the "click" conjugated products is given by a set of eight differential equations (see the SI, equations (S1)–(S8)). Using the experimental unimolecular rate constants, which correspond to the release of the different loads, and the bimolecular rate constants for the formation of Cy3-Cy5 and Cy3-Cy7, we modeled the progress of the formation of the different products (for example, Figure S6 provides the calculated time-dependent concentrations of all species shown in Figure 3d). Using this method, the theoretically predicted rates of the formation of the different conjugated products in the presence of the respective triggers, and even the background rates of formation of the side-products as result of nonselective leakage, were calculated. These calculated rates of the formation of the different conjugates are overlayed, as solid or dotted curves, on the experimental data shown in Figure 3b–d. Clearly, the theoretical calculated results correlate very well with the experimental results, suggesting that our kinetic model describes well the system.

The present study introduces a new paradigm for programmed synthesis using stimuli-responsive substrate-loaded MP $SiO_2$ NPs as carriers. Specifically, we have applied cofactor-dependent DNAzyme sequences and their substrates as capping units of the NPs containers. The selective release of the NPs loads by the DNAzyme–cofactor triggers dictated the composition of the reaction products. We have demonstrated that the targeted unlocking of two loaded MP $SiO_2$ NPs containers within a mixture of three containers led to the selective synthesis of two different coupling products (Cy3-Cy5 (**4**) and Cy3-Cy7 (**5**)). This new synthetic paradigm has important implications beyond the specific coupling of two fluorescent reactants. The availability of many other cofactor-dependent DNAzymes (e.g., $Ni^{2+}$, $Cu^{2+}$, $Pb^{2+}$), and other

  

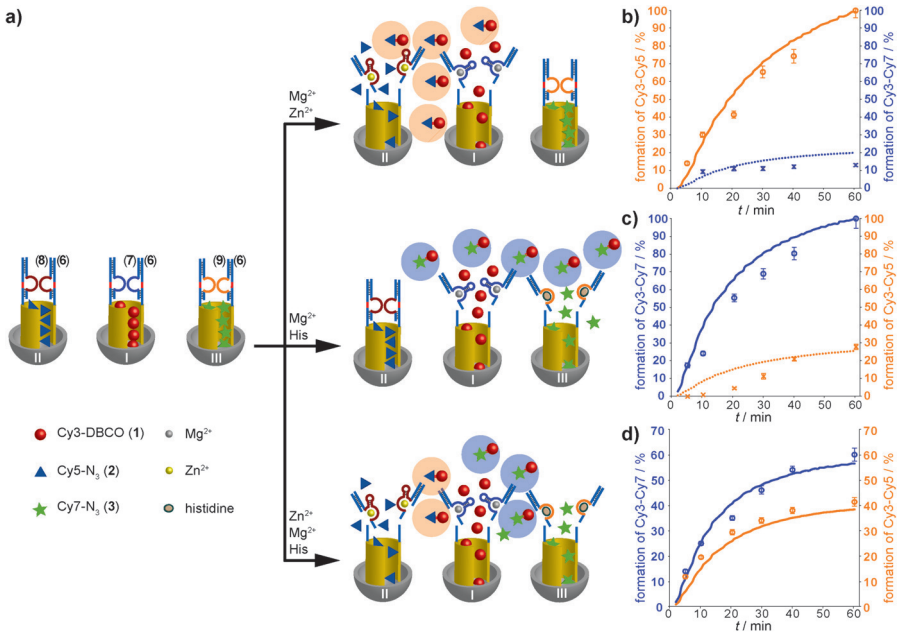


***Figure 3.*** a) Schematic depiction of the programmed synthesis procedure. b–d) Formation of the respective products is followed by the FRET signals in the Cy3-Cy5 (**4**) and/or Cy3-Cy7 (**5**) systems, as indicated by the orange and purple halos around the click products, respectively; the percentages given on *y*-axes are scaled to the highest possible formation of the respective products, which corresponds to ca. 2.5 μM; the axes on the left correspond to the major product, the ones on the right to the minor product. b) Time-dependent normalized FRET signals of Cy5 upon the formation of the Cy3-Cy5 conjugate (**4**) (excitation of Cy3 at $\lambda = 520$ nm, and following fluorescence of Cy5 at $\lambda = 667$ nm), reaction was initiated by the selective unlocking of NPs I and II with $Mg^{2+}$ and $Zn^{2+}$ ions, respectively. For the trigger-activated synthesis: experimental data (orange circles) and theoretically predicted product formation of Cy3-Cy5 (**4**) (orange solid curve); for the background signal: experimental data (purple crosses) and theoretically predicted background formation of Cy3-Cy7 (**5**) (purple dotted curve). c) Time-dependent normalized FRET signals of Cy7 upon the formation of the Cy3-Cy7 conjugate (**5**) (excitation of Cy3 at $\lambda = 520$ nm, and following fluorescence of Cy7 at $\lambda = 780$ nm) through the selective unlocking of NPs I and III with $Mg^{2+}$ ions and histidine, respectively. For the trigger-activated synthesis: experimental data (purple circles) and theoretically predicted product formation of Cy3-Cy7 (**5**) (purple solid curve); for the background signal: experimental data (orange crosses) and theoretically predicted background formation of Cy3-Cy5 (**4**) (orange dotted curve). d) Time-dependent normalized FRET signals of Cy5 and of Cy7 upon the concomitant formation of the Cy3-Cy5 (**4**) and Cy3-Cy7 (**5**) conjugates upon unlocking of all three NPs I, II, and III with the $Mg^{2+}$ and $Zn^{2+}$ ions and with histidine triggers, respectively. Excitation of Cy3 at $\lambda = 520$ nm and following the fluorescence of Cy5 and Cy7 at $\lambda = 667$ nm and at $\lambda = 780$ nm, respectively. Purple and orange circles correspond to the experimental data for the formation of Cy3-Cy7 (**5**) and of Cy3-Cy5 (**4**), respectively; purple and orange solid lines correspond to the theoretically predicted formation of Cy3-Cy7 (**5**) and Cy3-Cy5 (**4**), respectively. Error bars were derived from $N = 4$ experiments.

stimuli-responsive mechanisms of DNA-capped MP $SiO_2$ NPs (e.g., separation of G-quadruplexes or dissociation of the caps by the formation of aptamer–ligand complexes) provide means to enrich the library of NPs containers for dictated synthesis. The application of this method for the programmed synthesis of other products, such as peptides, oligosaccharides, and nucleotides may be envisaged.

## *Experimental Section*

The oligonucleic acid sequences used in the present study are as follows (the ribonucleobase cleavage site is indicated in bold, and the respective DNAzyme sequences are underlined):

(**6**) 5'-HS$(CH_2)_6$–CAGTGAAT-T**r**AGG-ACATAGAAGAAGAAG-3'

(**7**) 5'-CTTCTTCTTCTATGT-CAGCGATTCCGGAACGGACAC-CCATGTATTCACTG-3'

(**8**) 5'-CTTCTTCTTCTATGT-CTCCGAGCCGGTCGAAAATTC-ACTG-3'

(**9**) 5'-CTTCTTCTTCTATGT-GATCGGGGCCTGTGCGGGTAG-GAAGTAAATTATTCACTG-3'

The photophysical properties of the dye (**1**), (**2**), and (**3**), the procedure to modify the respective MP $SiO_2$ NPs with the DNAzyme locks, and the method to load the NPs with the respective loads are provided in the Supporting Information. Also the theoretical modeling of the kinetics associated with the formation of the different conjugates, (**4**) and (**5**), are discussed in the Supporting Information.

Release of the dyes from the capsules: The release of the dyes from the MP $SiO_2$ NPs capped with DNAzyme–substrate complexes was analyzed as follows: the respective NPs loaded with Cy3-DBCO (**1**), or with Cy5-$N_3$ (**2**), or with Cy7-$N_3$ (**3**) (10 mg of each) were suspended in HEPES buffer solution (10 mM, pH 7.0; 1 mL), and the mixture was divided into ten samples (100 μL each). Subsequently, a small volume (2 μL) of the aqueous solution of different triggers, i.e., $Mg^{2+}$ or $Zn^{2+}$ ions or histidine, final concentrations 20 mM, 20 mM, and 50 mM, respectively, were added to the samples that were allowed to react (for different time intervals). The resulting mixtures were centrifuged and the NPs were separated, after which the fluorescence spectra of the supernatant solutions were recorded. Formation of the click products Cy3-Cy5 (**4**) and Cy3-Cy7 (**5**) was directly inferred from ESI-MS analysis of the respective reaction mixtures.

**Keywords:** click chemistry · controlled release · DNA nanotechnology · fluorescence · FRET

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