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Light-Triggered Capture and Release of DNA and Proteins by Host–Guest Binding and Electrostatic Interaction

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Abstract: The development of an effective and general delivery method that can be applied to a large variety of structurally diverse biomolecules remains a bottleneck in modern drug therapy. Herein, we present a supramolecular system for the dynamic trapping and light-stimulated release of both DNA and proteins. Self-assembled ternary complexes act as nanoscale carriers, comprising vesicles of amphiphilic cyclodextrin, the target biomolecules and linker molecules with an azobenzene unit and a charged functionality. The non-covalent linker binds to the cyclodextrin by host–guest complexation with the azobenzene. Proteins or DNA are then bound to the functionalized vesicles through multivalent electrostatic attraction. The photoresponse of the host–guest complex allows a light-induced switch from the multivalent state that can bind the biomolecules to the low-affinity state of the free linker, thereby providing external control over the cargo release. The major advantage of this delivery approach is the wide variety of targets that can be addressed by multivalent electrostatic interaction, which we demonstrate on four types of DNA and six different proteins.

Introduction

Physiological processes in living organisms are regulated by small molecules, as well as large biomacromolecules.[1] Classic drug therapy focuses on relatively simple organic molecules due to the easier synthetic access and higher bioavailability, but over the last 30 years, the importance of biopharmaceuticals has steadily increased.[2] Peptides and proteins already serve as powerful drugs, but their low in vivo stability remains an unsolved problem.[3] To harness the full therapeutic potential of these potent molecules, an effective and universal transporter system is required. Recent advances in this area are primarily based on polymer hydrogels and nanogels.[4] Other examples of stimuli-responsive protein delivery systems include nanocapsules based on a pH-degradable polymeric shell,[5] nanostructured lipid carriers,[6] and polyelectrolyte nanoparticles.[7] Another challenge in modern medicine is gene therapy by transfection of DNA and RNA. In this case, a delivery system is essential to enable cellular uptake of the nucleic acids and protect them from hydrolysis and enzymatic decomposition. Promising artificial vectors include polyionic supramolecular complexes ("polyplexes") of DNA with corresponding polycations.[8] Cargo release was realized in response to pH,[9] reduction potential,[10] or light.[11]

In the past, we have established vesicles of amphiphilic cyclodextrin (CDV) as a versatile platform for the display of functional guests on the membrane surface.[12] For this purpose, cyclodextrins (CDs) are equipped with long, hydrophobic alkyl chains and hydrophilic oligo(ethyleneglycol) head groups. The resulting amphiphiles can be cast into thin films via evaporation from organic solvent, stirred with aqueous buffer and extruded through a polycarbonate membrane. This procedure yields unilamellar bilayer vesicles with about half of the macrocycles present on the outside of the CDV (Scheme 1). The cavities of CD are accessible for guest molecules, for example, azobenzene, which in turn can be modified with other functionalities to build up complex supramolecular structures. Azobenzenes are especially interesting guest molecules, given that they can be isomerized by UV irradiation at 350 nm from the *trans*-isomer, which binds to CD, to *cis*-azobenzene, which does not. This unique feature has been used for the generation of light-responsive vesicles,[13] microcapsules and mesoporous nanoparticles,[14] organogels[15] and hydrogels,[16] surfaces,[17] supramolecular polymers,[18] and for catalyst-activity control.[19] Our group has recently described the supramolecular complexation and release of polyanionic DNA by using CDV and azobenzene-spermine conjugates.[20] We could also show that azobenzene–carbohydrate guest molecules could mediate the self-assembly of ternary complexes with CDV and lectins through specific interactions between carbohydrates and proteins.[21]

Herein, we combine and expand these two strategies into a supramolecular system for the capture and release of DNA and proteins based on a combination of orthogonal host–guest complexation and electrostatic interaction. Heterobifunctional linker molecules **2**–**5**, containing an azobenzene guest

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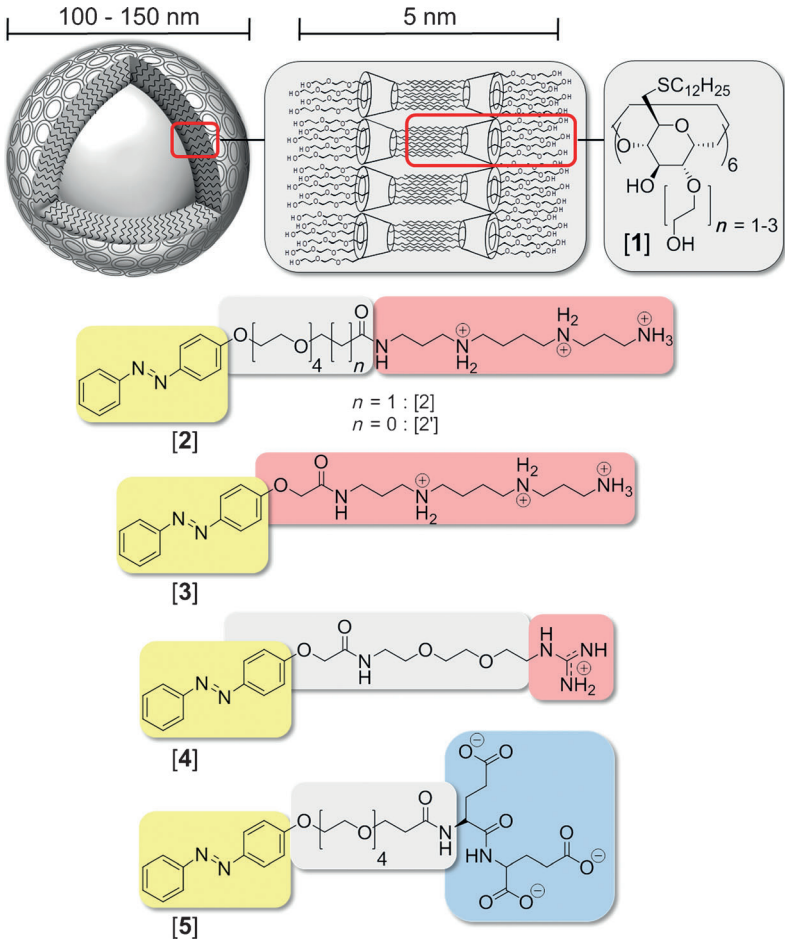


Scheme 1. Schematic illustration of cyclodextrin vesicles and structures of host and guest molecules used in this study. **1**: Amphiphilic α-cyclodextrin; **2**: azobenzene spermine conjugate with tetra(ethyleneglycol) spacer; **3**: azobenzene spermine conjugate; **4**: azobenzene guadinium conjugate; and **5**: azobenzene tricarboxylate with tetra(ethyleneglycol) spacer.

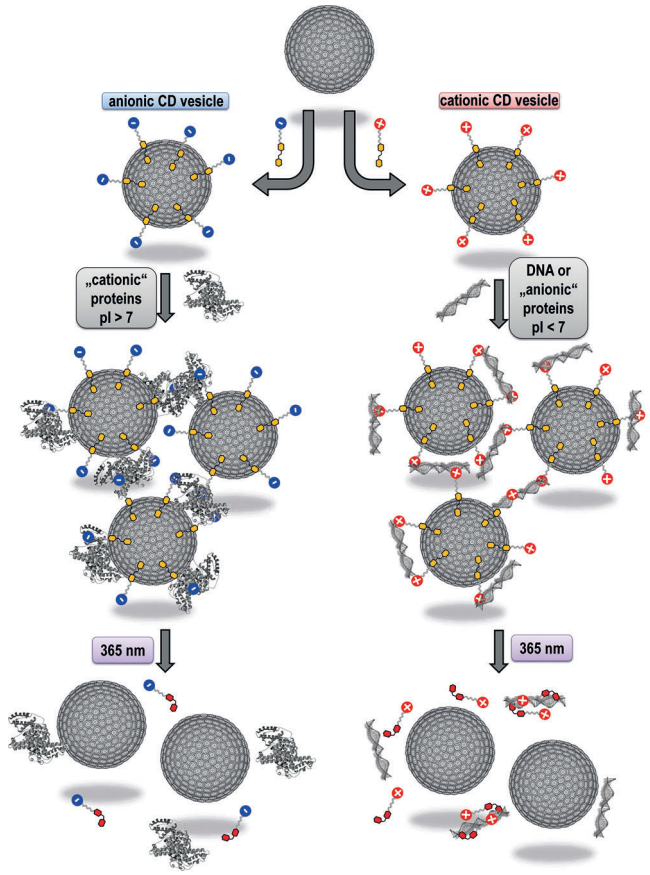
unit and a charged functionality, selectively bind both CDV and charged biomolecules. The conformation of the azobenzene and thus the formation of host–guest inclusion complexes can be controlled by UV irradiation. Ultimately, this leads to light-responsive aggregation or displacement of proteins and DNA. We optimized complexation and investigated the impact of multivalency by probing the influence of the spacer and the charged moiety in the linker molecule. We also explored the effect of the biomolecule target and its charge distribution by testing DNA strands of different length, as well as multiple proteins with different pI values. To this end, we employed optical-density measurements at $\lambda = 600$ nm (OD_{600}), dynamic light scattering (DLS), and ζ-potential measurements. The interaction between CD and linker molecules was confirmed by isothermal titration calorimetry (ITC).

Results and Discussion

The synthesis of amphiphilic α-CD **1** was carried out as described previously.[12b] Unilamellar vesicles with a diameter of 100 nm were prepared by extrusion in aqueous buffer (pH 7.2). The synthesis and characterization of linker molecules **2**–**5** is described in the Supporting Information. The conjugates **2**, **2′**, and **5** consist of an azobenzene unit and a charged moiety, which is either spermine or a dipeptide of glutamic acid, connected through a hydrophilic tetra(ethyleneglycol) spacer. Linker molecule **2′** was used in previous studies and results are shown for comparison. Linker molecule **2** is more straightforward to prepare and was used for all further experiments. Molecule **3** carries a spermine moiety linked to an azobenzene functionality without a spacer. Finally, linker **4** comprises guanidine and azobenzene moieties, connected through a short di(ethyleneglycol) spacer.

The azobenzene unit of the heterobifunctional linker molecules **2**–**5** is known to form light-responsive inclusion complexes with CDV.[22] By irradiation with UV light, CD-binding *trans*-azobenzene can be transformed into the polar, bent *cis*-isomer, which does not bind to CD. However, *cis*-azobenzene displays a local absorption maximum around 350 nm, and therefore, the re-isomerization to the *trans*-isomer is also promoted by UV irradiation. As a consequence, exposure to UV light leads to a so-called photostationary state, in which both isomers exist in dynamic equilibrium. The photoisomerization of **2**–**5** is shown in Figures S1–S4 in the Supporting Information. The binding to CD was confirmed by ITC and results are shown in Figures S14–S16 in the Supporting Information. The binding constants of azobenzene for CDV are slightly reduced compared to unmodified α-CD ($K_a \approx 6 \times 10^3$ M^{-1}) due to steric hindrance of host–guest interaction by the oligo(ethyleneglycol) residues, present on the vesicle surface.[12b]

The trapping of DNA and proteins is realized by electrostatic interaction of the charged moiety incorporated in the linker molecules with anionic or cationic residues on the biomolecules. Despite the low affinity of a single binding unit, complexation proceeds readily due to multivalent interaction of the biomolecule with multiple linker molecules bound to the same vesicle. CDV functionalized with heterobifunctional linkers should therefore act as supramolecular "adhesive", capturing oppositely charged target molecules in a ternary complex. Photoisomerization of the azobenzene moiety in the linker molecules from *trans* to *cis* should then lead to dissociation of the host–guest complex, thereby switching from a multivalent



Scheme 2. Schematic presentation of the electrostatic aggregation of guest decorated cyclodextrin vesicles induced by "cationic" proteins (left) and "anionic" proteins or DNA (right).

display of binding sites on the vesicle surface to a state of low-affinity monovalent interaction of the free linker (Scheme 2). We recently applied this strategy for the supramolecular trapping and photoresponsive release of polyanionic single stranded DNA comprising 50 nucleotides (50-mer ssDNA) with CDV and positively charged linker molecule **2**'.[20] In contrast, under the same conditions double stranded DNA (dsDNA, 2000 bp) could only be captured, but light-controlled dissociation of the ternary complex was not feasible.[20]

Encouraged by these results, we investigated this system in more detail. To explore the effect of the DNA length on the aggregation and release, we subjected single stranded 25-mer and 100-mer oligonucleotides to the same conditions. Addition of DNA to a mixture of CDV and **2** in aqueous buffer caused an immediate increase in OD_{600} (Figure 1 A) and particle size increased from 100 to about 1000 nm (Figure 1 B). The rate and degree of aggregation can be altered by changing the concentration of the linker. At high concentration, rapid and extensive aggregation was observed, whereas aggregation was much slower and gave a lower final OD_{600} at low concentration (data shown for 25-mer and 100-mer DNA in Figure S5 in the Supporting Information). Binary mixtures lacking one of the components did not show any aggregation.[20] These results imply that in the presence of CDV, linker **2** can induce the formation of ternary supramolecular complexes with DNA strands of different lengths. We then investigated the photoresponsiveness of these complexes. For the single-stranded DNAs, irradiation of the ternary mixtures for 40 min at 350 nm lead to a decrease in particle diameter from roughly 1000 to 100 nm (Figure 1 B), and the optical density was reduced to about 0.05, corresponding to the value for free vesicles (Figure 1 C). In contrast, we recently reported that OD_{600} and particle size remained high when double-stranded DNA was irradiated under the same conditions (Figure S6 in the Supporting Information).[20] These findings suggest that within certain size limits, oligonu-

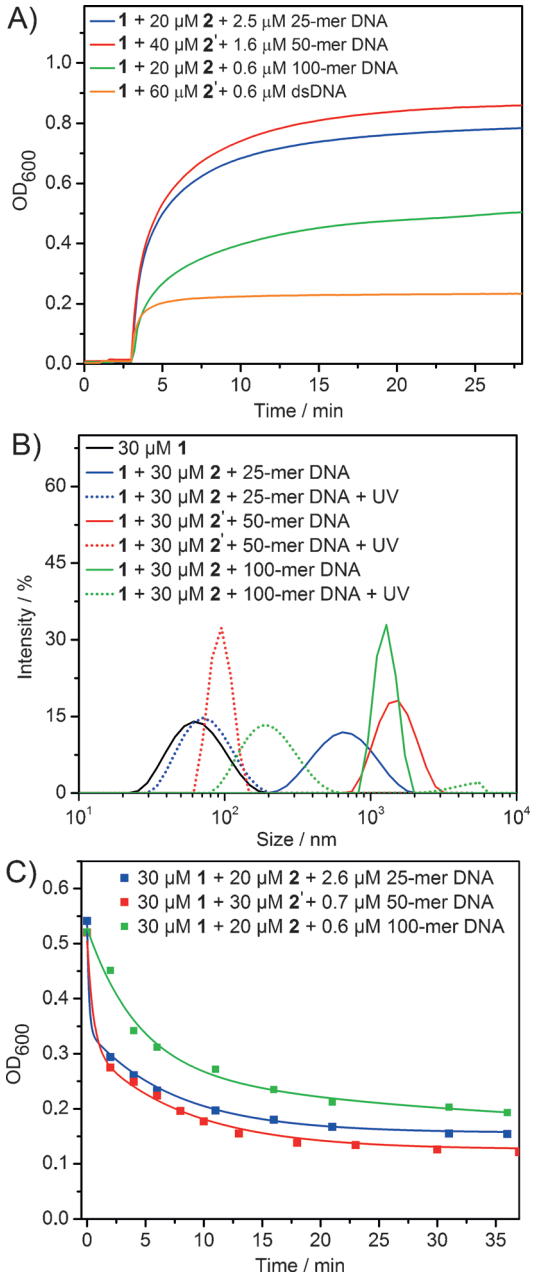


Figure 1. Light-responsive aggregation and dissociation of ternary complexes. A) Time-dependent OD_{600} measurements. B) Size distribution by DLS. C) Light-induced dissociation of the complex. Concentrations: [**1**] = 30 μM; [**2**] = {20, 30, 40, 60} μM, [25-mer DNA] = 2.6 μM, [50-mer DNA] = 0.7 μM, [100-mer DNA] = 0.6 μM, [dsDNA] = 40 nM.

cleotides can be captured and released independent on their length. Exceeding this limit, the double stranded DNA can be trapped in the supramolecular complex, but photoinduced dissociation does not occur.

These results can be explained by the fact that host–guest complexation with CDV is only possible with *trans*-azobenzene. Irradiation with UV-light causes photoisomerization into the *cis*-isomer, which is not a suitable guest for CDV and therefore dissociates from the vesicles. This leads to the above-mentioned loss of multivalency and thus to release of the ssDNA. Nevertheless, a small amount of *trans*-azobenzene is still present in the photostationary state. Although this amount is not sufficient to effectively bind the shorter oligonucleotides, the larger dsDNA can still complex several linker molecules on the same vesicle, forming a stable multivalent complex. Our findings thereby illustrate the crucial role of multivalency in this system.

To get deeper insight into the system and optimize complexation, we then focused our interest on the influence of the linker molecule. Having shown that the aggregation and release of the tested single-stranded DNAs is comparable, we selected 50-mer ssDNA and dsDNA for that purpose. Figure 2

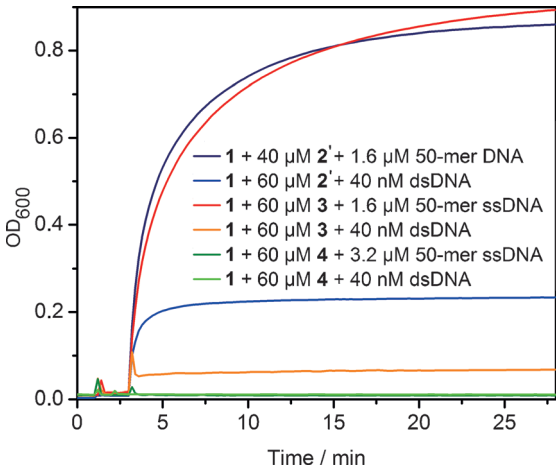


Figure 2. Time-dependent measurement of OD_{600} showing the formation of ternary complexes of DNA and CDV with linker molecules **2′**–**4**; Concentrations: [**1**] = 30 μM; [**2′**] = {40, 60} μM; [**3**] = [**4**] = 60 μM; [50-mer DNA] = {1.6, 3.2} μM, [dsDNA] = 40 nM.

shows the OD_{600} of ternary mixtures of CDV and DNA with different linkers (**2′**–**4**). In the case of linker molecule **3**, only ssDNA showed aggregation and consequently an increase in optical density from 0.01 to about 0.91, which is comparable to the results with linker **2′** discussed above. Under the same conditions, dsDNA did not display substantial aggregation: OD_{600} increased to only 0.07. The aggregation was also followed by DLS (Figure S7 in the Supporting Information). The average particle diameter increased from about 100 nm for the free vesicles to more than 1000 nm after addition of 50-mer DNA. In contrast, the particle diameter was unaffected by addition of dsDNA. Finally, measurements of the zeta potential were carried out (shown for 50-mer DNA in Figure S8 in the Supporting Information). The highly negative surface potential of bare CDV (−26 mV) increased to +3.2 mV when the vesicles were decorated with **3**, which is less positive than the surface potential previously detected for CDV covered with linker **2′** (+11 mV). In contrast to **2′**, linker **3** is lacking the tetra(ethyleneglycol) spacer. It is reasonable to assume that the spacer allows the spermine groups of **2′** to reach away from the CDV so that they are exposed to the aqueous medium and accessible for DNA. Evidently, the spacer causes a higher ζ-potential and enables stronger interaction with the negatively charged binding partner. The lack of a spacer in **3** prevents the effective display of positive charges and the negative surface potential of the CDV prevails, leading to repulsion of the polyanionic DNA. Additionally, it should be considered that without the spacer, the binding sites for DNA are displayed rather rigidly and close to the vesicle surface. It can be assumed that this allows binding of ssDNA only, since this target is shorter and more flexible than the dsDNA.

Upon applying linker **4** instead of linker **2** or **3**, no agglutination was observed for either ssDNA or dsDNA. The OD_{600} of the ternary mixtures remained as low as 0.01 (Figure 2). The particle size of 100 nm, measured by DLS, corresponds to the free CDV (Figure S7 in the Supporting Information). These results illustrate the effect of the protein-binding moiety. In a ternary mixture comprising CDV and **2′**, both DNA samples form supramolecular complexes leading to an increase in OD_{600}. Compared to **2′**, linker **4** comprises a guanidine unit instead of a spermine. Under the tested conditions (pH 7.2), the guanidine is mostly unprotonated and thus not charged. This was confirmed by the negative surface potential of −14.8 mV recorded for CDV after addition of **4** (Figure S8 in the Supporting Information). As a result, this linker should bind to the phosphate backbone of DNA by hydrogen bonding with guanidine rather than by electrostatic interaction. Interestingly, no aggregation was observed, indicating that the DNA cannot bend into the confined geometry that would be needed for multivalent hydrogen bonding. These results indicate that the lack of directionality in the electrostatic interaction between DNA and linker molecules **2′** and **3** is crucial for the formation of a supramolecular complex.

In the second part of this study, we expand the scope of target biomolecules from DNA to proteins. As positively charged linker molecule we selected **2**, which gave the best results in the experiments with DNA. Linker **5** was synthesized for these studies with the same azobenzene and spacer unit, bearing a dipeptide of glutamic acid instead of the spermine. In a first set of experiments, we tested bovine serum albumin (BSA, pI = 4.7), bearing a net negative charge of −15 in combination with cationic linker **2** and polycationic protamine sulfate (PS, pI = 13.3) with a total charge of +20 in combination with anionic linker **5** (Figure 3).

An increase in OD_{600} from 0.05 to about 1.0 was detected for ternary mixtures when protein and linker were oppositely charged, whereas other combinations resulted in no aggregation. The rate and extent of aggregation are controlled by the concentration of the linker: instant and complete agglutination occurred at high concentrations, whereas at low concentration,

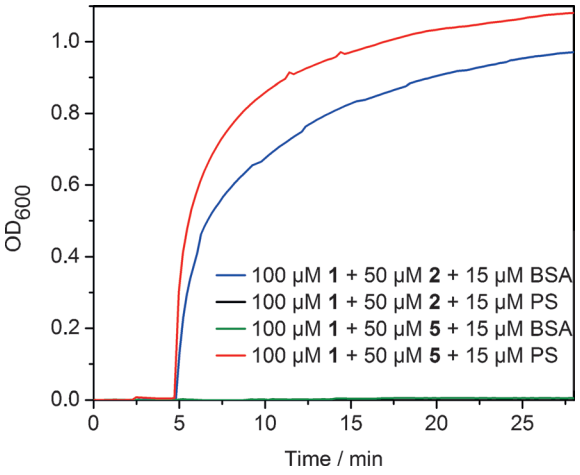


Figure 3. Formation of ternary complexes with proteins: Time-dependent OD_{600} measurements. Concentrations: [**1**] = 100 μM; [linker] = 50 μM; [protein] = 15 μM.

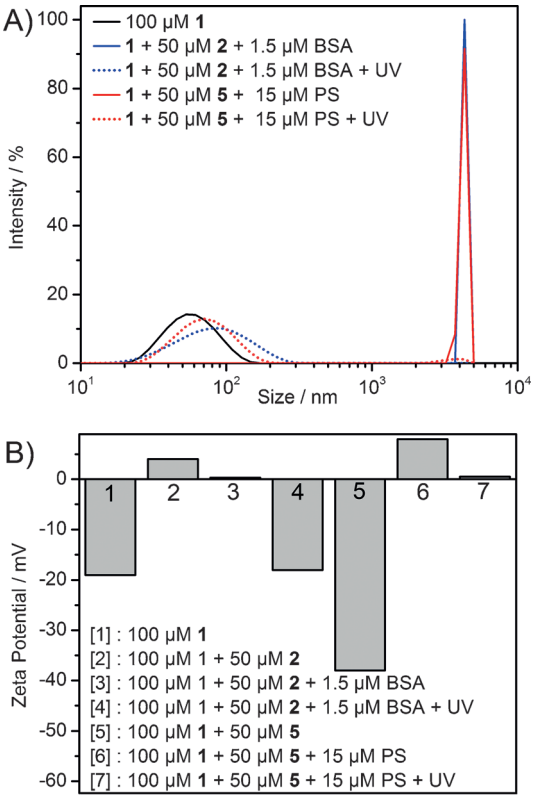


Figure 4. Light-responsive formation and dissociation of ternary complexes with proteins; A) Size distribution by DLS. B) Zeta-potential measurements at 25 °C. Concentrations: [**1**] = 100 μM; [linker] = 50 μM; [BSA] = 1.5 μM; [protamine sulfate] = 15 μM.

aggregation was observed to a lesser extent and also much slower (Figure S9 in the Supporting Information). Upon aggregation, the mean particle diameter increased from 100 to 400 nm for PS and to 4000 nm in the case of BSA (Figure 4 A). The resulting complexes were subjected to UV light (λ = 350 nm) for 25 minutes. Photoisomerization of the linker induced rapid recovery of the original particle size for free CDV of 100 nm (Figure 4 A). Dissociation proceeded within two minutes of irradiation, illustrated by the decrease in OD_{600} (Figure S10 in the Supporting Information).

To prove that our concept could be applied to a variety of target proteins, comparative studies with six different proteins were conducted. Out of these, five proteins showed orthogonal aggregation with respect to the total charge of the respective protein and linker (see Figure S11/Table 1 in the Supporting Information). Among the tested proteins, only mono-amine oxidase A (pI = 7.9) was not bound, which can be attributed to its near neutral overall charge. However, horse radish peroxidase (pI = 6.8) showed aggregation, implying that local charge distribution on the protein surface and accessibility of the charged residues for the linkers could affect the extent of electrostatic binding. In conclusion, these results provide clear-cut evidence that proteins can be captured and released from a supramolecular, light-responsive complex. Protein capture is selective with respect to the overall protein charge and can be applied to a variety of target proteins.

The importance of electrostatic interaction for DNA and protein capture was verified by addition of NaCl and competitive binder spermine·4 HCl to a ternary mixture of CDV, **2**, and 50-mer DNA or BSA, respectively. As was described above, DNA was bound in the presence of 150 mM NaCl and OD_{600} consequently increased from 0.01 to about 0.86 (Figure 1 A). However, even in the presence of only 50 mM NaCl, BSA displayed no substantial aggregation and OD_{600} remained as low as 0.03 (Figure S12 in the Supporting Information). This can be attributed to the effective display of negative charges on the DNA, which is an elongated, rod-like molecule. The phosphate groups of the DNA backbone are exposed into the surrounding medium and are easily accessible for electrostatic interaction with the linker. In contrast, in the case of BSA, not all charges are available for complexation due to protein folding. Additionally, local electrostatic repulsion of the positively charged linker by positively charged amino acids in the protein can occur. As a consequence, the monovalent Na^+ can compete with the trivalent spermine linker only in the case of the protein, in which the interaction with the spermine is weaker compared to DNA. However, when the preformed protein complexes were treated with 50 mM NaCl, OD_{600} only decreased to 0.6 implying that the aggregates remained partly intact (Figure S13 in the Supporting Information). To trigger complete release of the DNA, treatment of the ternary complex with competitive tetravalent binder spermine·4 HCl (50 mM) was performed. This molecule is able to displace the linker molecule **2** despite its lower affinity for the DNA, due to the much higher concentration. Consequently, the ternary complex disassembles and the OD_{600} decreases because spermine does not bind to CDV. Taken together, these results consistently support the concept of biomolecule trapping by electrostatic interaction with the heterobifunctional linker molecules.

Conclusion

Capture and release of DNA and proteins was achieved in self-assembled ternary complexes comprising heterobifunctional linker molecules, allowing photoresponsive host–guest complexation with vesicles of amphiphilic α-CD and electrostatic binding of the biomolecules. The crucial role of multivalency for substrate binding was verified in comparative studies with different linkers and target molecules. We utilized a modular strategy for the controlled binding and release of four types of DNA and six different proteins, demonstrating the large scope of possible targets based on the same supramolecular platform. The proof of concept, which we thereby established, can potentially be adapted for the capture and release of RNA or other biomolecules with multiple charges and ultimately to a large number of structurally diverse targets such as charged macromolecules or nanoparticles.

Experimental Section

Materials and synthesis

α-Cyclodextrin was kindly donated by Wacker Chemie (Burghausen, Germany) and used without further purification. Double-stranded DNA from salmon testes Type III (M $1.3{\cdot}10^6$ g mol^{-1}, ca. 2000 bp) was purchased from Sigma–Aldrich (Taufkirchen, Germany). Single-stranded DNA ($M_{50\text{-mer}}$ 15427 g mol^{-1}) was purchased from Eurofins MWG Operon (Ebersberg, Germany). All other chemicals were purchased from Sigma–Aldrich (Taufkirchen, Germany) or Acros Organics (Schwerte, Germany) and used as received. Aqueous solutions were prepared with milli-Q water and organic solvents were dried according to standard methods before use. The synthesis and characterization of linker molecules **2**--**5** is described in the Supporting Information. Analytical data for these molecules are in agreement with their molecular structure, and NMR spectra are provided as Supporting Information. The synthesis of amphiphilic α-CD **1** was carried out as described previously.[12b]

Preparation of vesicles

A stock solution of **1** in chloroform (2 mg mL^{-1}) was prepared and stored in the freezer. In a round bottom flask, an aliquot of this solution was dried by slow rotary evaporation followed by high vacuum, yielding a thin film of amphiphiles. Aqueous buffer (20 mM HEPES, 10 μM EDTA, pH 7.2) was added and stirred overnight. Unilamellar bilayer vesicles (CDV) were fabricated by pressing the suspension through a polycarbonate membrane (100 nm pore size) with a Liposofast manual extruder.

Isothermal titration calorimetry

Isothermal titration calorimetry (ITC) was conducted on a Nano-Isothermal Titration calorimeter III (model CSC 5300, Calorimetry Sciences Corporation, London, Utah, USA). ITC measurements were carried out in in milli-Q water. 20 Injections of heterobifunctional linker (10 mM) with a volume of 10 μL were titrated into a 1 mM solution of α-CD. The solution was stirred with 250 rpm at 23 °C.

UV/Vis spectroscopy

Absorption spectra and optical density at 600 nm (OD_{600}) were recorded on an Uvikon 923 (Konton Instruments) double-beam spectrometer or V650 Spectrophotometer (JASCO). Samples were prepared in 1.5 mL disposable PMMA cuvettes by using HEPES buffer (20 mM HEPES, 10 μM EDTA, pH 7.2) as a solvent. The optical density of 1 mL solution of amphiphilic α-cyclodextrin **1** was monitored, collecting data points every 12 s. Linker molecules **2**–**5** were added as a 2 mM solution in milli-Q water after 2 min. The corresponding protein or DNA was added at 4 min as a concentrated solution (60 μM–1 mM) in HEPES buffer and the measurement was continued until the OD_{600} was constant.

Dynamic light scattering and zeta-potential measurements

DLS and zeta-potential measurements were performed on a Nano ZS Zetasizer (Malvern Instruments Ltd.) at 298 K. Size determination was conducted in 1.5 mL disposable PMMA cuvettes, zeta potential was measured in disposable capillary cells (DTS 1060, Malvern Instruments Ltd.) at 25 °C by using 1 mL of amphiphilic α-cyclodextrin solution. Data was taken 60 min after the addition of guest to host vesicles and immediately after UV (350 nm) irradiations.

Irradiation experiments

For the photoisomerization of azobenzene from *trans* to *cis*, a Rayonet photochemical reactor (The Southern New England Ultraviolet Company) with 16 RPR-3500 UV lamps emitting at $\lambda = 350$ nm was used. The samples were irradiated in 5 to 10 steps of increasing exposure time up to a total of 25 to 40 min.

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Keywords: cyclodextrins · host–guest systems · molecular recognition · self-assembly · vesicles

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FULL PAPER

Self-Assembly

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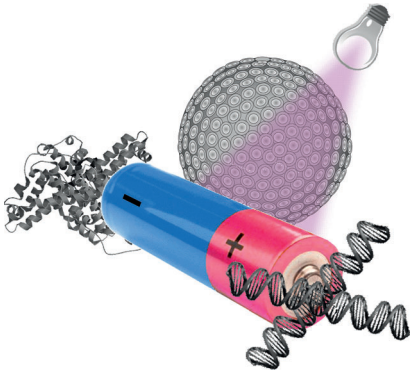
Light-Triggered Capture and Release of DNA and Proteins by Host–Guest Binding and Electrostatic Interaction



Cyclodextrin vesicles bind charged biomolecules, such as DNA or proteins, in the presence of light-responsive charged guest molecules. The complexes can be disassembled under UV-light irradiation based on *trans*/*cis* isomerization of the azobenzene guests (see figure).