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Reversible Light Switch for Macrocycle Mobility in a DNA Rotaxane

Finn Lohmann,[†] Damian Ackermann,[†] and Michael Famulok*

LIMES Institute, Chemical Biology & Medicinal Chemistry Unit, c/o Kekulé Institute of Organic Chemistry and Biochemistry, Gerhard-Domagk-Strasse 1, 53121 Bonn, Germany

Supporting Information

ABSTRACT: A recent trend in DNA nanotechnology consists of the assembly of architectures with dynamic properties that can be regulated by employing external stimuli. Reversible processes are important for implementing molecular motion into DNA architectures as they allow for the regeneration of the original state. Here we describe two different approaches for the reversible switching of a double-stranded DNA rotaxane architecture from a stationary pseudorotaxane mode into a state with movable components. Both states only marginally differ in their respective topologies but their mechanical properties are fundamentally different. In the two approaches, the switching operation is based on strand-displacement reactions. One of them employs toehold-extended oligodeoxynucleotides whereas in the other one the switching is achieved by light-irradiation. In both cases, multiple back and forth switching between the stationary and the mobile states was achieved in nearly quantitative fashion. The ability to reversibly operate mechanical motion in an interlocked DNA nanostructure opens exciting new avenues in DNA nanotechnology.

Molecular architectures that exhibit controllable mechanical function are of paramount significance in nanomechanics and nanorobotics. This in turn constitutes a major challenge for their design and construction via self-assembly. Ingenious methods that allow for the assembly of highly complex two- and three-dimensional architectures have been developed in DNA nanotechnology.[1] Structural DNA nanotechnology has created different static topologies of increasing complexity in the second and third dimensions in a "bottom-up" approach.[2] In contrast, dynamic DNA nanotechnology produces devices that can be operated in an autonomous and reconfigurable manner by controlling the kinetics of strand-displacement reactions.[3] In this way, controllable mechanical motion in which individual DNA components in a device move relative to one another is achieved by hybridization of two complementary strands that displace one or more prehybridized strands.[3f] This mechanism allows for the rational engineering of DNA nanoarchitectures with dynamic properties, including switches, sensors,[4] stepped walkers and spiders,[5] robot arms and tweezers,[6] autonomous machines,[3] and the like. Even though strand-displacement and toehold switching mechanisms[7] have been used to reversibly control dynamics of several DNA architectures, repetition cycles remain limited due to unavoidable dilution of the system and accumulation of side products. An alternative is the incorporation of azobenzene tethered DNA into DNA architectures to control the formation and dissociation of DNA-duplexes by light. Upon irradiation with either visible or UV light, the azobenzene residues isomerize to the *trans*- or to the *cis*-configuration and as a consequence base pairing with complementary oligodeoxynucleotides (ODNs) is switched on or off, respectively.[8]

Classes of attractive devices for incorporating dynamic properties into DNA nanoarchitectures are interlocked assemblies like rotaxanes, catenanes, and others. Rotaxanes are mechanically interlocked molecules consisting of at least one macrocycle that is threaded over a dumbbell-shaped structure and is trapped by bulky stoppers.[9] Thereby, rotaxanes possess a unique mechanical bonding motif unavailable in conventional building blocks, allowing the threaded macrocycle to exhibit unhindered rotation around, or directional mobility along, a thread axle. We have recently reported the design, assembly, and characterization of rotaxanes in which both, the dumbbell-shaped molecule and the macrocycle are made of dsDNA.[10]

Here, we demonstrate the multiple switching between an immobile pseudorotaxane state (Figure 1a) and a state in which the thread macrocycle can shuttle unhindered along the axle and rotate around it. To achieve this change in mobility, we employed two distinct external stimuli for strand displacement reactions. One is based on toehold oligonucleotides,[7] the other one uses light.[8] Thereby, the feasibility of the different

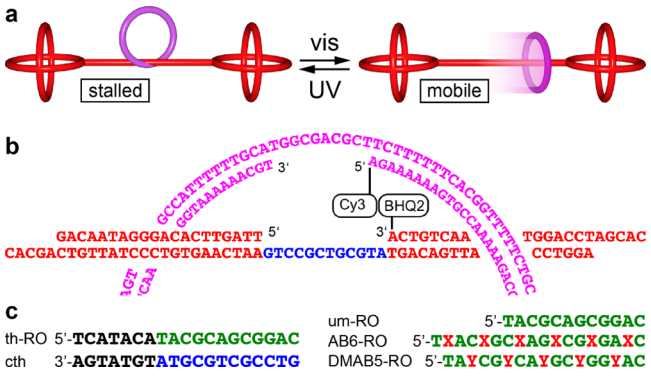

Figure 1. (a) Light triggered reversible switching between an immobile DNA-pseudorotaxane state (left) and a DNA-rotaxane state in which the macrocycle is in free motion along the axle (right). (b) Secondary structure from the relevant part of the macrocycle and the axle. (c) List of the ODNs used to achieve the switching: X, azobenzene residue; Y, 2′,6′-dimethylazobenzene residue.

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approaches with regard to efficient switching can be directly compared.

To apply the toehold approach to a DNA rotaxane that allows for multiple, reversible switching of macrocycle mobility, we assembled a pseudorotaxane that contained spherical stoppers[10,11] (Figure 1a). The switching is designed to occur by incubating the pseudorotaxane with an ODN, called toehold-release-ODN (th-RO) that is fully complementary to the axle's 12-mer single-strand (ss) region, but contains an additional 7 nucleotide toehold at the 5′-end (Figures 1b and 2a). Addition of the th-RO to the pseudorotaxane displaces the

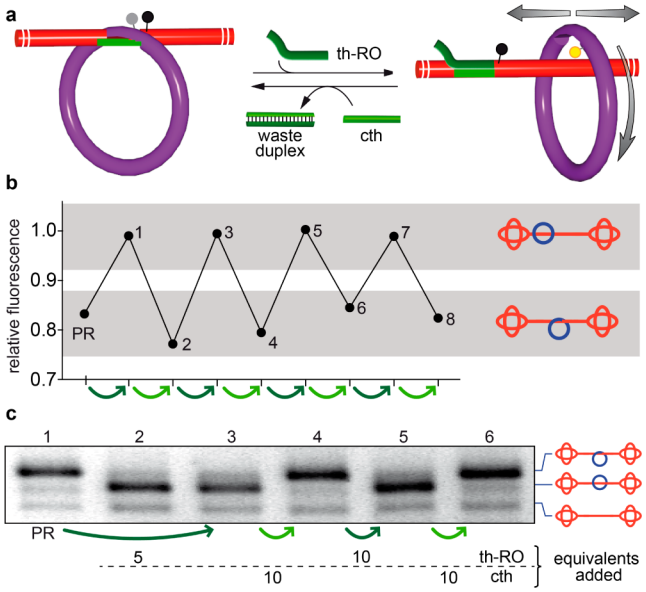

Figure 2. Reversible toehold-RO induced pseudorotaxane-rotaxane switch. (a) Schematic of the macrocycle displacement mechanism of the pseudorotaxane/rotaxane switch. PR, pseudorotaxane at starting point; th-RO, toehold-RO; cth, complementary toehold; waste duplex, hybridization product from th-RO and cth; gray/yellow sphere, Cy3-label; black sphere, BHQ2-label. (b) Fluorescence quenching experiment using the Cy3-BHQ2-labeled pseudorotaxane. Dark green arrows, addition of th-RO; light green arrows, addition of cth. The numbers refer to the respective switching events. (c) Analytical agarose gel of pseudorotaxane-rotaxane switching. Pseudorotaxane before (lane 1) and after consecutive additions of the th-RO, and its complementary cth, respectively (lanes 3–6) (equivalents of th-RO and cth added are listed below). Lane 2 shows the genuine rotaxane. The amount of the free dumbbell (fastest migrating band) is constant in each lane (entire gel 2c is displayed in Figure S6).

stalled macrocycle from its 8-mer hybridization site, rendering it fully mobile; addition of an ODN that is complementary to the complete th-RO, called cth, reverts the process, by generating a 19-mer dsDNA as waste (Figures 1c, 2a; see Table S1 for all ODNs used in this study). A similar concept was recently established for the switching from a pseudocatenane to a catenane state in a single-stranded DNA architecture.[13] To monitor the release of the macrocycle by fluorescence dequenching the macrocycle 5′-gap-end was labeled with the fluorophor Cy3 and the axle 3′-gap-end with the quencher BHQ2 (Figures 1b and 2a).

As evident from Figure 2b, addition of the th-RO to the pseudorotaxane led to a marked increase in fluorescence at 570 nm due to rotaxane formation by th-RO-induced displacement of the macrocycle (Figure 2b, switch 1). To switch the system back to the pseudorotaxane state, cth was added (switch 2). Correspondingly, further addition of th-RO led to regeneration of the rotaxane (switch 3), these consecutive switching events could be repeated again and again (switches 4–8).

To obtain a more quantitative picture of the consecutive toehold-induced switching, we directly visualized the amounts of rotaxane and pseudorotaxane by nondenaturing gel electrophoresis. This is possible because the rotaxane, even though it contains 19 additional bases due to the hybridized th-RO, exhibits a slightly higher electrophoretic mobility than the pseudorotaxane (Figure 2c). Because the assembled pseudorotaxane was employed without any further purification, a small portion of the unthreaded dumbbell architecture is present in the sample, the amount of which remains the same during all switching events. For comparison, lane 1 contains the pseudorotaxane, lane 2 the rotaxane, generated by addition of a complementary unmodified ODN (um-RO). In lane 3, the addition of th-RO to the pseudorotaxane is analyzed. Virtually quantitative switching to the rotaxane has occurred. Addition of the cth quantitatively regenerates the pseudorotaxane (lane 4), and so on (lanes 5, 6). These results demonstrate that reversible switching between the immobile pseudorotaxane and the mobile rotaxane state is achieved by alternating addition of toehold oligonucleotides.

The disadvantages of the th-RO based switching mechanism are that (i) the switch molecules need to be delivered externally, (ii) the fairly high consumption of material, (iii) the generation and accumulation of waste, and (iv) the systematic dilution of the sample in every cycle. To overcome these limitations, we sought to establish a light-triggered switching approach based on azobenzene containing "release ODNs" (ROs). Azobenzene moieties were synthetically incorporated into 12-mer ODNs, thereby obtaining photoactive AB-ROs (Table S1 and Figure S1d–f). In the *cis*-form, the azobenzene residues exist in a nonplanar form that prevents the RO from efficient hybridization to its complementary sequence in the axle. When the azobenzene residues are photoisomerized into the planar *trans*-form, the RO can form a stable 12-mer duplex by displacing the macrocycle from its 8-mer-hybridization site in the pseudorotaxane. Photoisomerization back to the *cis*-form reverts the process.

In a preliminary study, to establish a photoswitchable rotaxane, the optimal RO in terms of reversible strand displacement has been selected from 6 differently functionalized oligonucleotides (Table S1 and Figure S1e). Optimal photoresponse was observed for AB6-RO that contained 6 azobenzene residues (Figures 1c and S2). This optimized AB6-RO and the relevant part of the primary structure of the other components was then employed in the design of the rotaxane. In a pilot study we assembled a rotaxane that contained 168-bp dsDNA nanorings as stoppers. This type of rotaxanes is known to disassemble into the free macrocycle and the dumbbell via a slippage mechanism[14] after release of the hybridized macrocycle by the RO.[10] Fluorescence spectroscopy as well as gel shift analysis of a pseudorotaxane probe, which was first incubated with *cis*-AB6-RO, show that disassembly to the dumbbell and the macrocycle only occurs after light induced isomerization of the AB6-RO to its *trans*-form (Figure S3). Both observations indicate the potential reversible switching process.

We next assembled a pseudorotaxane containing spherical stoppers.[11] These architectures allow for multiple switching of the macrocycle mobility because the corresponding rotaxanes are mechanically stable.[10] Similar to the analysis performed with

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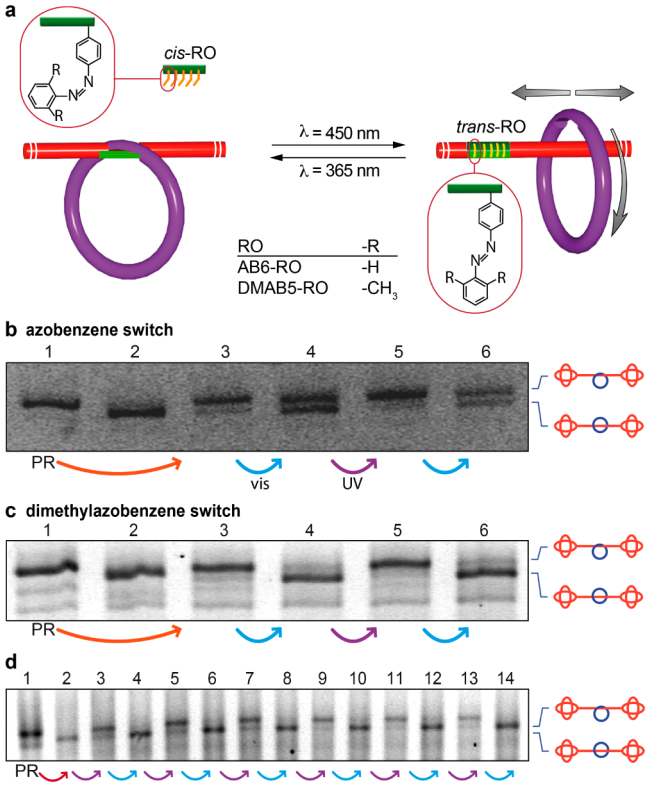

Figure 3. Reversible, light-induced pseudorotaxane-rotaxane switch. (a) Schematic of the switch mechanism mediated by azobenzene or 2′,6′-dimethylazobenzene functionalized ROs, respectively. (b) analytical agarose gel of a pseudorotaxane with spherical stoppers before and after addition of the azobenzene functionalized RO (*cis*-AB6-RO, orange arrow) and alternating irradiation with vis/UV light (blue/purple arrows). Lane 1, pseudorotaxane; lane 2, pseudorotaxane after addition of unmodified um-RO (rotaxane); Lane 3, pseudorotaxane after addition of the *cis*-AB6-RO; lanes 4−6 correspond to lane 3 after repetitive irradiations with vis/UV light as indicated. (c) Reversible and nearly quantitative switching with 2′,6′-dimethylazobenzene functionalized DMAB5-RO (experimental design and conditions for agarose gel electrophoresis are analogous to (b); entire gels 3b and 3c are displayed in Figure S6). (d) An extended gel-shift study of the pseudorotaxane-rotaxane switch, starting with the addition of *trans*-DMAB5-RO (red arrow), demonstrates a decent fatigue resistance over at least 12 switching events.

the toehold triggered rotaxane, we separated the pseudorotaxane from the rotaxane by analytical gel electrophoresis to quantify their respective amounts after each switching event (Figure 3a,b). Lane 3 shows that the ratio of pseudorotaxane: rotaxane is ca. 8:2 in the presence of a 10-fold molar excess of the AB6-RO preisomerized into the *cis*-form. Photoisomerization with visible light into the *trans*-form shifts the ratio to ca. 5:5 (lane 4). Irradiation with UV light regenerates the *cis*-isomer and shifts the ratio back to 8:2 (lane 5), and a second cycle of photoisomerization into the *trans*-AB6-RO again increases the amount of rotaxane to a 5:5 ratio. Clearly, the switching can be detected but unfortunately it does not occur quantitatively.

Because we have maxed out the switching behavior using AB6-RO, no improvement on the basis of azobenzene modified ROs could be expected. Therefore, to realize complete pseudorotaxane-rotaxane conversion by improved response to light stimulation, we synthesized the more bulky 4-carboxamide-2′,6′-dimethylazobenzene phosphoramidite with threoninol as the backbone that recently was introduced by Asanuma and co-workers (Figure S1d,f).[15,16]

We then applied the DMAB5-RO (Figure 1c) to the rotaxane architecture and performed a light-stimulated switching experiment analogous to the one described for the AB6-RO (Figure 3a). Even though the switching of the macrocycle mobility could not be followed by fluorescence spectroscopy due to quenching effects caused by the excess of the DMAB5-RO (Figure S4), the gel-shift experiment in Figure 3c demonstrates that in each switching event the DMAB5-RO achieves nearly quantitative conversion of the structures. To test the robustness of the switching, we performed 12 consecutive switching cycles. As evident from Figure 3d, the DMAB5-RO based system hardly shows fatigue in the switching behavior over at least 12 switching events, and most likely over many more switching cycles. Hence with this 2′,6′-dimethyl-modified azobenzene RO we have developed a switching system for the DNA rotaxane, in which the macrocycle mobility is multiply and nearly quantitatively reconfigured simply by irradiation with light at two different wavelengths without detectable formation of side products. The enhanced thermal stability of the *cis*-form of DMAB5-RO vs AB6-RO contributes to the robustness of the photoresponsive design (Figure S5).

In conclusion, we have described two different methods for the reversible switching of a dsDNA rotaxane between a state with a stationary macrocycle (pseudorotaxane) and one with a mobile one (genuine rotaxane). One approach employs toehold ROs as external stimuli, the other uses light to control the switching. In particular the light triggered method using the 2′,6′-dimethylazobenzene functionalized RO is of immense practical relevance, not only because of its simple implementation but also because, unlike the unsubstituted azobenzene-RO, it leads to nearly quantitative conversion at each switching event.

In contrast to many examples of molecular shuttles in which the macrocycle moves back and forth between two fixed positions, or "stations",[9] the here described DNA-rotaxane switches from a flexible state, in which both the translational and the rotational movements are completely unhindered,[10] into a stalled state. Recently, the force required for the remigration of a fully mobile macrocycle into a state that was stalled by hydrogen-bonding was determined on a single-molecule level using a synthetic small-molecule rotaxane.[17] Molecular systems that can be switched by external stimuli such as pH-change, metal ion complexation, or changes in the electric potential,[9,18] and even light,[19] have been described for small-molecule rotaxanes. A remarkable characteristic of our switchable DNA-rotaxane is the fact that the movement and rotation of the macrocycle that is no less than 75000 Da in size can be fully blocked and restored, respectively, by the minimal structural alteration of five 2′,6′-dimethylazobenzene residues. We expect the light-induced operation of interlocked DNA architectures to open up new possibilities in the field of dynamic DNA nanotechnology.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Materials and Methods, Figures S1−S6, and Table S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author

m.famulok@uni-bonn.de

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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