Supramolecular Machines and ARchitectures Team D15

Tightening or Loosening a pH-Sensitive Double-Lasso Molecular Machine Readily Synthesized from an Ends-Activated [c2]Daisy Chain

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Introduction

Interlocked and knotted molecules have been the subject of studies during the past years, essentially because they have fascinating architectures. Thus, several interlocked cyclic structures including strips, links, rings and non-composite molecular knots have been synthesized to date. In most cases, studies reporting knotted molecules have usually focused on the methodological challenge in synthesizing these molecules, and, to the best of our knowledge, with the exception of catenanes, knots have not yet been elaborated into elements of molecular machinery. Since the properties of a molecule rely tremendously on its topology, molecular machines harnessing such cyclic interlocked structures or analogues would have much potential in material or biological applications. We have previously reported the straightforward synthesis of a unique double-lasso molecule from a non-symmetrical [c2]daisy self-assembling, which did not act as a molecular machine as expected.[1] Here, we present the ready access to a completely novel double-lasso molecular machine (Figure 1) from an ends-activated [c2]daisy chain, and the contraction and the stretching of this molecule upon variation of pH.[2] To the best of our knowledge, the topology of this interlocked double-lasso structure is unique among molecules synthesized to date. We propose to call it a rota-macrocycle by analogy with rota-catenane.

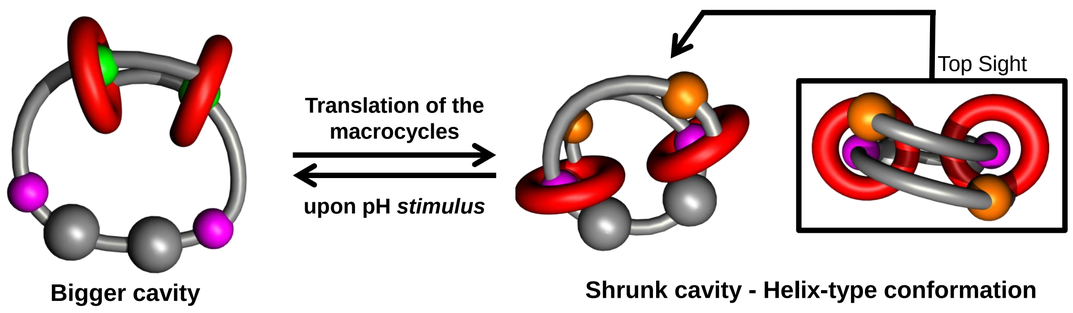
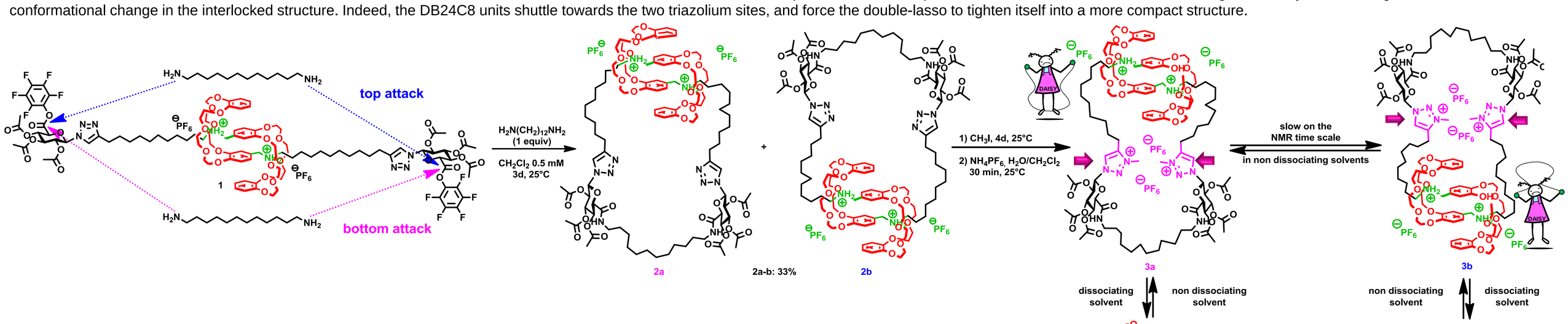


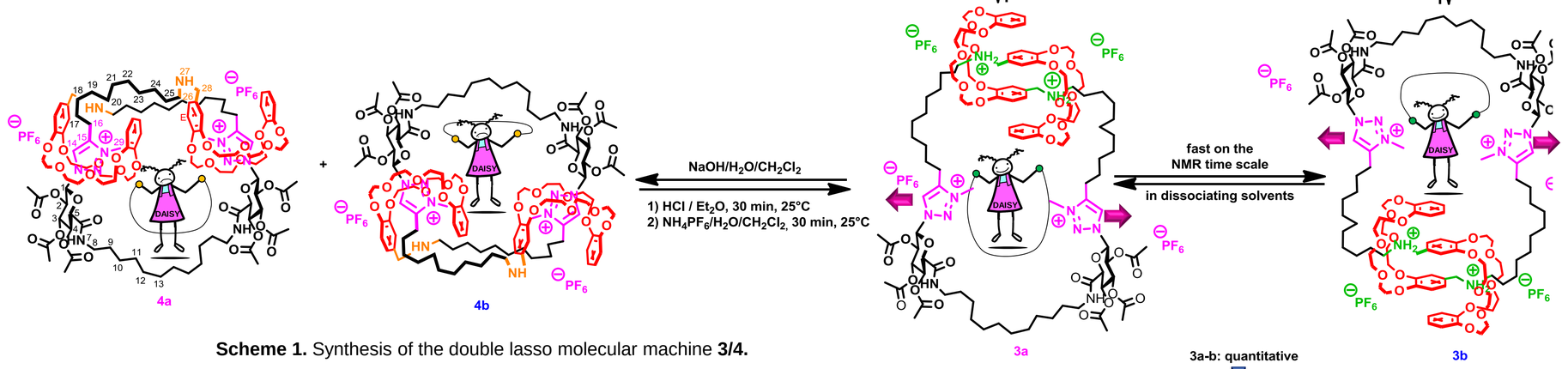
Figure 1. Cartoon representation of the targeted double-lasso molecular machine.

Preparation of the double-lasso macrocycle 3a-b

The previously synthesized activated [c2]daisy chain building-block **1** was cyclised, at a dilution of 5.10^{-4} M in dichloromethane at room temperature, by adding one equivalent of diaminododecane (Scheme 1). This led to the isolated compound **2a-b** with a yield of 33% after purification on a silica gel chromatographic column. No other compound was isolated from the silica gel chromatography, suggesting the side-formation of polymers. It is interesting to note the two possibilities of cyclization of **1** with the diaminododecane: the two amine moieties of the diamine can either react *via* the bottom of molecule **1** to yield **2a** or via the top to yield **2b**. This results in the formation of two rotamers **2a** and **2b**, which can exist as either left- or right-handed helix-type structures with helix inversion occurring through the rotation of the pseudo-macrocyclic loop around the daisy unit. They are not distinguishable by ^{1}H NMR in the stretched conformation of the rota-macrocycle, as long as the pseudo-macrocyclic U-shape chain, which is covalently linked to both extremities of the interwoven [c2]daisy motif, can rotate quickly on the NMR chemical shift time-scale. The movement generated during the conversion between **2a** and **2b** can be likened to a jump rope.

In order to trigger the conformational change of the molecule by molecular machinery, another molecular station was created by methylation of the triazole moieties using iodomethane as both reactant and solvent. After exchanging the iodide counter-anion by a hexafluorophosphate, the double-lasso compound **3a-b** was obtained quantitatively. As expected, in the protonated state, the DB24C8 units surround the best ammonium stations. Since triazolium is a much weaker molecular station than ammonium for the crown ether, a stretched conformation of the double-lasso takes place. However, deprotonation of the ammonium moieties using sodium hydroxide brings about a tremendous conformational change in the interlocked structure. Indeed, the DB24C8 units shuttle towards the two triazolium sites, and force the double-lasso to tighten itself into a more compact structure.





Scheme 1. Synthesis of the double lasso molecular machine **3/4.**

^{1}H NMR evidences for molecular machinery with the double-lasso rota-macrocycles 3/4

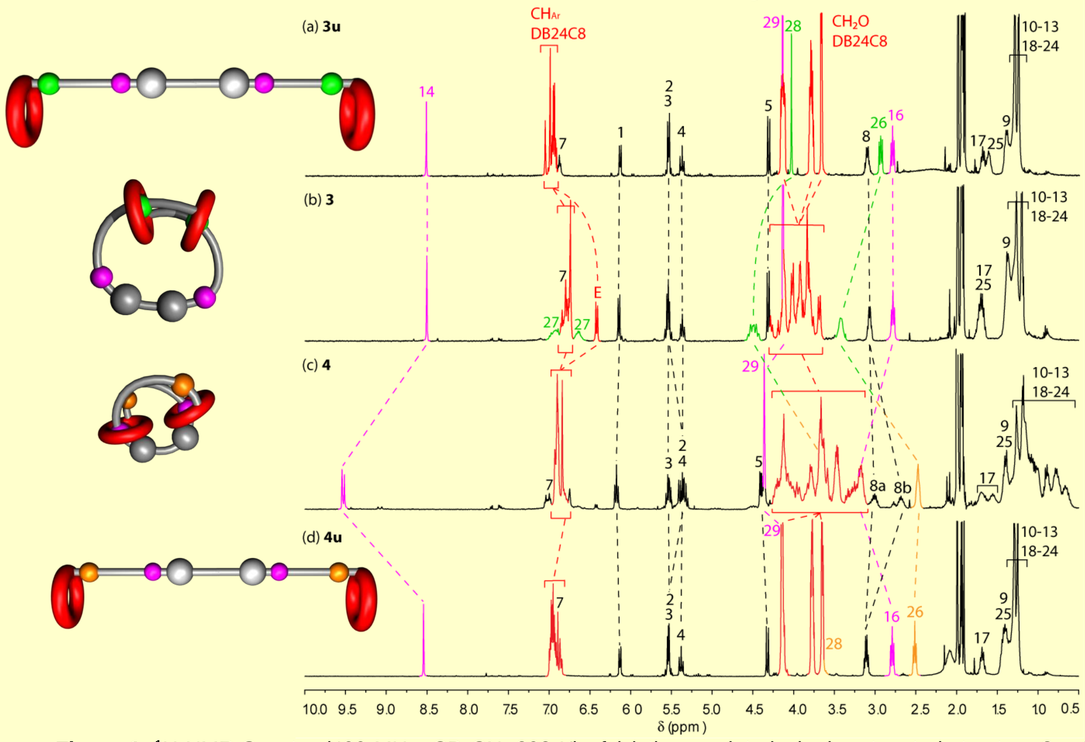


Figure 1. ^{1}H NMR Spectra (400 MHz, CD_3CN, 298 K) of (a) the non-interlocked protonated structure **3u**, (b) the protonated double-lasso macrocycle **3**, (c) the deprotonated double-lasso macrocycle **4a-b**, (d) the non-interlocked deprotonated compound **4u**. The coloring, lettering, and numbering correspond to the proton assignments indicated in scheme 1.

➢The comparison between the ^{1}H NMR spectra of the double lasso compound **3** and the non-interlocked compound **3u** reveals the interlocked architecture and the exclusive localization of the DB24C8 around the ammonium station (Figure 1a-b).

➢The tightening of the double-lasso structure when passing from protonated **3** to deprotonated **4** was highlighted by direct comparison of the ^{1}H NMR spectra of both double-lasso-containing compounds (Figure 1b-c). The first interesting observation was the appearance of a second set of ^{1}H NMR signals in **4**. This can be attributed to the existence of two species, which are atropisomers in the chemical shift NMR time-scale. The existing atropisomerism is related to the existence of D-sugar units associated with either right- or left-handed pseudo-helixes, which are not exchangeable due to the tightened architecture. At basic pH, the signals of the hydrogens at the methylene groups flanking the ammonia moieties H_{26} and H_{28} of **4** are shifted upfield ($\Delta\delta$ = 0.94 and 0.83 ppm, respectively) with respect to **3**. Deprotonation of the ammonium moieties and subsequent shuttling of the DB24C8 groups should account for this observation. More interestingly, H_{14} ($\Delta\delta$ = *ca.* +1.04 ppm), and to a lesser extent H_{16} and H_{29} ($\Delta\delta$ above 0.20 ppm), which are part of triazolium stations, are all significantly shifted downfield. This variation indicates the new location of the DB24C8 crown ether around the triazolium station.

➢ Comparison of the spectral features of the deprotonated double-lasso **4** with its non-interlocked analogue **4u** further supports the conformational changes discussed above (Figure 1c-d).

Molecular jump ropes dependent on solvent polarity and pH

In the stretched *co*-conformation of the double-lasso **2**, the rope is long enough and its U-shape is stretched enough to jump freely and quickly around the [c2]daisy moiety. This is not always the case in compound **3**. Although no splitting of the NMR signals were noticed for **3** in CD_3CN (Figure 2), a new set of NMR signals appeared in the lesser dissociating solvent CD_2Cl_2, corresponding to the rotamers **3a** and **3b**, whose exchange is slow on the NMR time-scale. Thus, they potentially become diastereoisomers, since they combine both a homochiral component (the D-sugar units) and a daisy link which can exist as either a right- or a left-handed helix (Scheme 1).

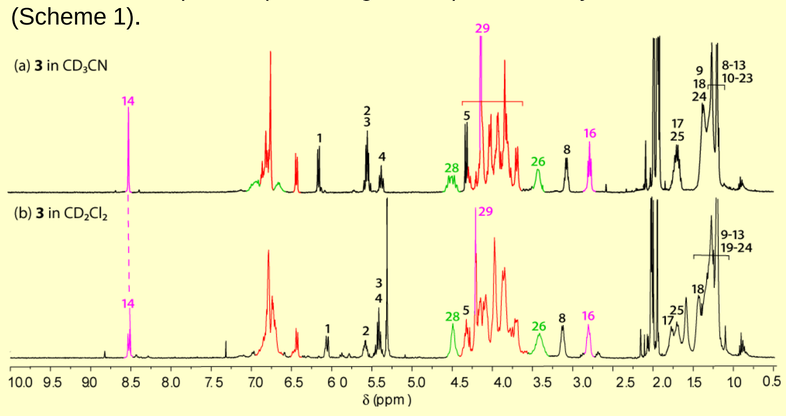


Figure 2. ^{1}H NMR spectra (400 MHz, 298 K) of molecular double-lasso **3** (a) in CD_3CN and (b) in CD_2Cl_2. The coloring, lettering, and numbering correspond to the proton assignments indicated in scheme 1.

This observation can be explained by the smallest repulsion between the triazolium moieties in the lesser dissociating solvent, resulting in a tight U-shape, which induces a slower kinetic rate of the equilibrium between **3a** and **3b**. In more dissociating solvents such as CD_3CN or DMSO-*d6*, the opposite is observed. The most extended U-shape, which is due to the larger repulsion of the triazolium moieties, permits a freer movement around the [c2]daisy chain moiety.

The kinetic parameters of the equilibrium between **3a** and **3b** at 298 K were studied by ^{1}H NMR upon gradual addition of CD_2Cl_2 to a solution of **4** in CD_3CN (Figure 3).

Progressive broadening of the initially unique NMR signal of triazolium H_{14} suggested a decrease of the conversion rate between **3a** and **3b**. Coalescence of the ^{1}H NMR signal of H_{14} was found for a solvent mixture CD_2Cl_2 : CD_3CN 51 : 49. When more CD_2Cl_2 was added, a second set of signals appeared, corresponding to the two isomers **3a** and **3b**. The equation at the coalescence, $k = \pi\delta\nu/\sqrt{2}$(where the line width at half-height of the coalesced H_{14} corresponds to $\delta\nu$ = 6.26 Hz) yielded the rate constant for rotation of the rope k_{rot} = 13.9 ±0.7 s^{-1} for **3** at 298 K in a solvent mixture CD_2Cl_2 : CD_3CN 51 : 49. From this value, we can derive the free enthalpy of activation $\Delta G_{rot}^{\ddagger}{}_{298}$ = 66 kJ.mol^{-1}.

In the deprotonated double-lasso compound **4**, two sets of ^{1}H NMR signals appeared (Figure 1c), in this case independently of solvent polarity, revealing the inability of the U-shape to rotate around the contracted [c2]daisy chain. This is consistent with the existence of a contracted conformational state adopted by **4**, after molecular machinery at basic pH. The preceding experimental evidences reported in figure 1 support this behaviour.

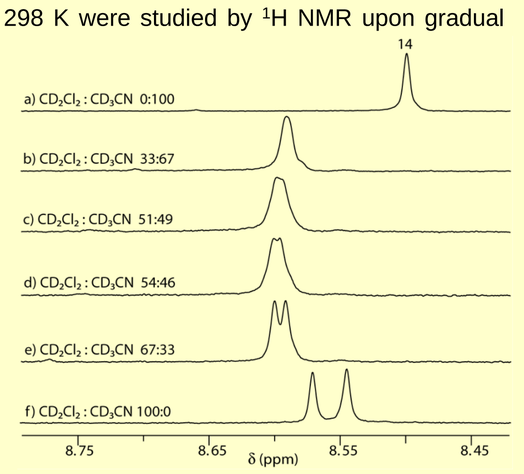


Figure 3. Partial ^{1}H NMR (400 MHz, 298 K) spectra of **3a/3b** showing the solvent effect on the rotation of the jump rope.

Conclusion

We have reported the synthesis of a novel double-lasso molecular machine, in which the control of the translation of the DB24C8 moieties can trigger the rotation of a molecular jump rope. In the protonated state **3**, the loosening double-lasso structure has a large internal cavity, and, in a manner dependent on solvent polarity, the rope defining this cavity is able to clear the [c2]daisy chain. After deprotonation, the rota-macrocycle is tightened, reducing the cavity size, and the rope can no longer move around the [c2] daisy chain. To the best of our knowledge, this is the first example of the synthesis of a rota-macrocycle which can undergo molecular machinery. Such adaptable interlocked double-lasso structures could be of interest as novel molecular drug carriers, able to release their cargo at a selected pH.

[1] C. Romuald, G. Cazals, C. Enjalbal, F. Coutrot, *Org. Lett.* **2013**, *15*, 184-187. [2] C. Romuald, A. Arda, C. Clavel, J. Jimenez-Barbero, F. Coutrot, *Chem. Sci.* **2012**, *3*, 1851-1857.