Organic & Biomolecular Chemistry

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View Article Online
DOI: 10.1039/C8OB02234H

Journal Name

ARTICLE

Light-driven Exchange between Extended and Contracted Lasso-like Isomers of a Bistable [1]Rotaxane

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The synthesis of a set of benzylic amide [1]rotaxanes via a self-templating clipping approach is described. This methodology supposes the 1+1 coupling of isophthaloyl dichloride with an acyclic diamine precursor incorporating a templating arm. The structure of the threaded compounds was determined in both solution and solid state. The conversion into the corresponding unthreaded isomers, also obtained by deslipping of [2]rotaxane models, was evaluated in competitive and non-competitive hydrogen-bonding solvents. The switch of the extended and contracted lasso-like isomers of a bistable [1]rotaxane by an olefin isomerization promoted by UV light irradiation was also accomplished and their ring positional integrity examined.

Introduction

For more than a half century, the mechanical bond has been a source of inspiration for a respectable sum of scientists of different disciplines.[1] Several significant aspects have clearly contributed to boost the research on these molecular systems: (i) their identification as synthetic challenges,[2] (ii) the mastering of the non-covalent interactions[3] needed for guiding their preparation and controlling the relative position of their intertwined components, (iii) the discovery of examples in Nature[4,5] and (iv) the design of artificial molecular motors[6,7] and machines.[8,9]

Among the entwined structures, [2]rotaxanes,[10] consisting of a ring threaded by a rod having two bulky groups at the ends, have become privileged scaffolds. Thus, they have been employed in the fabrication of molecular switches,[11] catalysts,[12] sensors,[13] electronic devices,[14] synthesizers,[15] pumps[7e] and others.[9d] However, the formal previous members of this family, [1]rotaxanes, consisting of a ring threaded by a covalently linked arm having a bulky group at the end, have underwent a limited development. The self-inclusion properties of less kinetically stable pseudo[1]rotaxanes have been studied mainly in systems having macrocycles such as cyclodextrins,[16] crown ethers,[17] pillarenes[18] and cyclobis(paraquat-*p*-phenylene) motifs.[19] Usually, the exchange between unthreaded and threaded forms of these species can be controlled mainly by hydrophobic interactions,[16,18] hydrogen bonding,[17] and donor-acceptor interactions.[19,20]

Since the Vögtle pioneering work to obtain [1]rotaxanes by intramolecular covalent bridging of the components of a [2]rotaxane,[21] most of the implemented methodologies to [1]rotaxanes involves the use of a cyclic precursor via different template-driven approaches.[17i] By contrast, few examples of [1]rotaxanes have been obtained from an acyclic component through a self-templating clipping protocol.[19b,c]

Switchable [1]rotaxanes incorporating more than one binding site embedded into its arm have been scarcely reported.[17c,f,g,h,l,19b] These entwined systems are able to respond to external stimuli such as pH[17c,d,f,g,h] or redox processes[19b] allowing a controlled gliding ring to exchange between translational isomers.

Herein we report the synthesis and operation of bistable amide-based [1]rotaxanes obtained via a self-templating clipping approach. These entwined compounds were designed to allow a photoexchange between its extended and contracted lasso[5,22] conformations. NMR studies and X-ray diffraction analyses were decisive to unambiguously determine the structure of these unprecedented entangled polyamides against other possible interlocked structures such as dimers or trimers. Competitive experiments yielding [1] and [2]rotaxanes were also carried out in order to disclose the features of this unprecedented [1+1] condensation. An optimization of the linker length between the ring and the nearby binding station was also achieved to guarantee the stability of the two lasso conformations. The positional integrity of the cyclic moiety over the two binding stations of the [1]rotaxane was evaluated in a series of solvents with different H-bonding ability.

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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic and mass spectrometry data for all new compounds, and full crystallographic details of **1b** (CCDC 1846028).

DOI: 10.1039/C8OB02234H

Results and discussion

Synthesis and characterization of amide-based (pseudo)[1]rotaxanes

Molecular shuttles, [2]rotaxane-based systems[23] in which the ring translocates between two or more binding sites or stations by means of a biased Brownian motion, are among the early interlocked molecular constructions. The tactical incorporation of one switchable station to obtain non-degenerate shuttles allows the exchange of co-conformational states in response to an external stimulus.[8d] Inspired by the light-driven molecular shuttles developed by Leigh *et al.*,[24] based on a hydrogen-bonded [2]rotaxane structure, we aimed to synthetize [1]rotaxanes shown in Figure 1. The proposed entwined compounds have a benzylic amide macrocycle incorporating an arm with succinamide-ester and fumaramide stations[24a,b] connected by a C_{12} alkyl chain. The deliberated incorporation of these binding sites in this entwined design could guarantee a reasonable positional ring discrimination of the extended and contracted isomers by means of a photoisomerization of the olefinic binding site. Nevertheless, other structural factors might probably need to be optimized as, for instance, the length of the alkyloxy linker between the ring and the adjacent binding site.

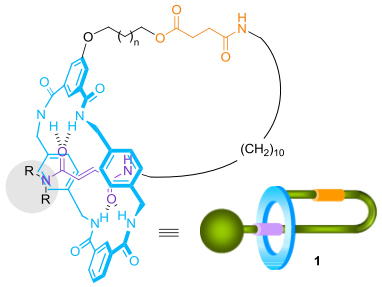
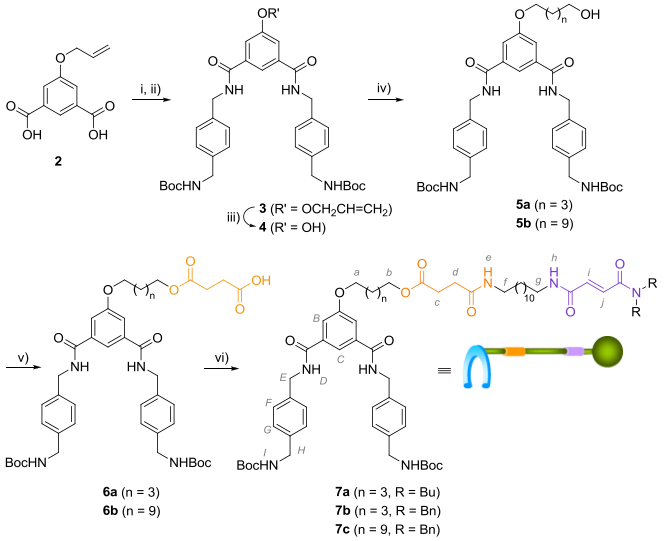


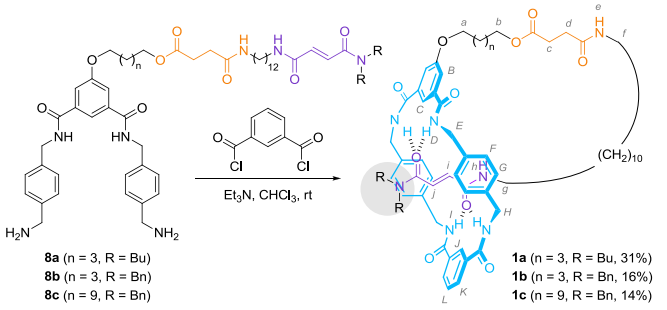
Fig. 1 Bistable [1]rotaxanes **1** and its schematic representation.

As synthetic strategy to tackle the synthesis of [1]rotaxanes **1** we devised a two-component clipping procedure by reacting an acyclic diamine precursor with isophthaloyl dichloride for providing the desired compounds in only one step. These diamine precursors, in its *tert*-butoxycarbonyl diprotected form (**7**, Scheme 1), have an arm with a fumaramide binding site to self-drive the assembly of the [1]rotaxane **1**. In the present study, three different surrogates of **7** were prepared differing in the length of the linker between the succinamide-ester station and the ring, as well as in the bulkiness of the stopper at the fumaramide station (NR_2). The syntheses of **7** were accomplished following the reaction sequence showed in Scheme 1 by using 5-allyloxyisophthalic acid[25] **2** as starting material. The first step required the double amidation of the corresponding acid dichloride with monoBoc protected *p*-xylylenediamine to afford **3**. After the allyl deprotection, a Williamson etherification of the resulting phenol with 5-bromopentanol or 11-bromoundecanol provided the respective alcohols **5** which were used for the nucleophilic opening of succinic anhydride. The amidation of the resulting carboxylic acids **6** with the C_{12} alkyl amines **S1a,b** having a dibenzyl or dibutyl fumaramide moiety was afforded by means of using the Castro's coupling reagent. The wanted acyclic U-shape precursors **7** were obtained in good yields.



Scheme 1 Synthesis of the U-shaped precursors **7**. *Reagent and conditions:* i) $(COCl)_2$, DMF (dimethylformamide) cat., CH_2Cl_2, reflux; ii) $H_2NCH_2C_6H_4CH_2NHBoc$, Et_3N, CH_2Cl_2, 0-25 °C, 93% (two steps); iii) $Pd(PPh_3)_4$, $NaBH_4$, THF (tetrahydrofuran), rt, 96%; iv) $Br(CH_2)_{n+2}OH$ (n= 3 or 9), NaI, K_2CO_3, $(CH_3)_2CO$, reflux, **5a** (n=3), 70%; **5b** (n=9), 93%; v) succinic anhydride, DMAP (dimethylaminopyridine), THF, reflux, **6a** (n=3), 80%; **6b** (n=9), 97%; vi) (*E*)-$R_2NCOCH{=}CHCONH(CH_2)_{12}NH_2$ (**S1a**, R = Bu or **S1b**, R = Bn), Castro's reagent: BOP (benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate), Et_3N, CH_2Cl_2, rt, **7a** (n=3, R = Bu), 82%; **7b** (n = 3, R = Bn), 67%; **7c** (n = 9, R = Bn), 78%. Full experimental procedures can be found in the ESI†.

The (pseudo)[1]rotaxanes[26] **1** (Scheme 2) were obtained by the assembly of the diamines **8**, freshly obtained by the Boc deprotection of **7** with TFA, with isophthaloyl dichloride in the presence of Et_3N. Note that the yield of **1a** (31%) is two-fold that of **1b** (16%) and **1c** (14%) most probably due to the less steric hindrance of the dibutylamino stoppered fumaramide of **1a** versus that of the dibenzylamino **1b** and **1c**.



Scheme 2 Synthesis of benzylic isophthalamide macrocycle-based (pseudo)[1]rotaxanes **1.**

The analytical and spectroscopic data of compounds **1a-c** are in full agreement with a [1]rotaxane structure. Thus, a comparison of the ^{1}H NMR spectra of the precursor **7c** and **1c** (Figure 2) reveals the threading of the side arm through the benzylic isophthalamide ring (in light blue in Figure 2b). As we expected, the entwined structure **1c** adopts an extended lasso conformation in which the ring is sitting over the olefinic binding site. Consequently, the signals corresponding to the fumaramide protons, H_i and H_j, are downshifted by 1.21 ppm

DOI: 10.1039/C8OB02374H

with respect to the unthreaded **7c** due to the shielding effect of the xylylene aromatic rings.

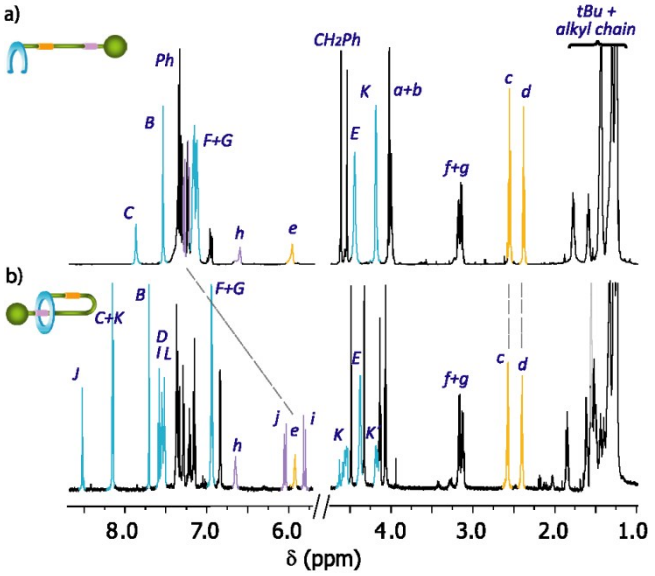


Fig. 2 Partial ^{1}H NMR spectra (600 MHz, CD_2Cl_2, 298 K) of (a) precursor **7c** and (b) [1]rotaxane **1c**. The assignments correspond to the lettering shown in Schemes 1 and 2.

Although interlocked compounds[27] resulting from 2+2 or 3+3 couplings would render similar ^{1}H NMR spectra to that resulting of 1+1 coupling such as **1**, their diffusion coefficients (D) obtained by NMR experiments could serve to distinguish among the potential entwined candidates. Therefore, we carried out ^{1}H PGSE (Pulsed Gradient Spin Echo) diffusion measurements on solutions of **1a-c** in $CDCl_3$ at 298 K affording the D values of 5.67, 5.31 and 5.10 x 10^{-10} $m^2 \cdot s^{-1}$ respectively (see ESI† for experimental details). The hydrodynamic radii calculated from these D values by using the Stokes–Einstein equation (6.9, 7.4, 7.7 Å) are in excellent agreement with the size estimated from computational molecular models (see Table S4 and Fig. S6-8, ESI†). The experimental isotopic distribution of the peaks corresponding to the molecular ion of **1** obtained in the HR-ESI MS measurements also are in agreement with the calculated ones (see Fig. S9, ESI†).

Single crystals suitable for X-ray structure analysis were grown by slow diffusion of diethyl ether into a dichloromethane solution of **1b**. The molecular structure of **1b** (Figure 3) shows the threading of the arm across the benzylic amide ring confirming the [1]rotaxane scaffold (Figures 3A,B). The fumaramide binding site interacts with the macrocycle through the formation of hydrogen bonds involving three NH groups of the ring and two CO groups of the fumaramide (see Figure 3A). The solid-state structure of **1b** also displays an extended lasso conformation of at least 25 members (see Figure 3C). Interestingly, the empty void of the lasso is squeezed due to the establishment of intermolecular hydrogen bonds between the NH amide protons of the arm with hydrogen bond acceptors of neighboring [1]rotaxane molecules (Figures S11 and S12) stabilizing the crystalline net.

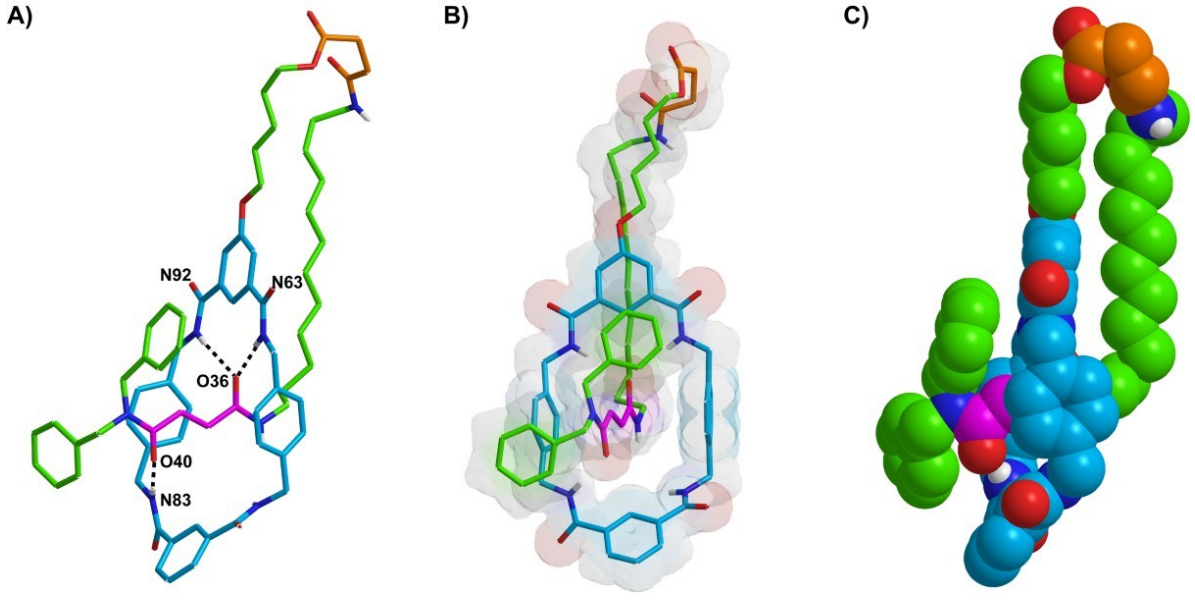


Fig. 3 X-Ray structure of the benzylic isophthalamide [1]rotaxane **1b**. A) Side-on view of a capped-sticks model of **1b** displaying the interaction between the ring and the fumaramide binding site. B) Front view of stick and CPK model of **1b** showing the threading of the arm. C) Peripheral view of a space-filling model of **1b** enlightening its extended lasso conformation. For clarity, non-polar hydrogen atoms, solvent molecules and disorder have been omitted ($C_{macrocycle}$, light blue; C_{arm}, green; $C_{fumaramide}$, purple; $C_{succinamide}$, orange; O, red; N, blue; H, white). Intramolecular hydrogen-bond lengths [Å] (and angles [deg]): O36HN63 2.400 (177.9); O36HN92 2.220 (171.3); O40HN83 2.054 (179.4).

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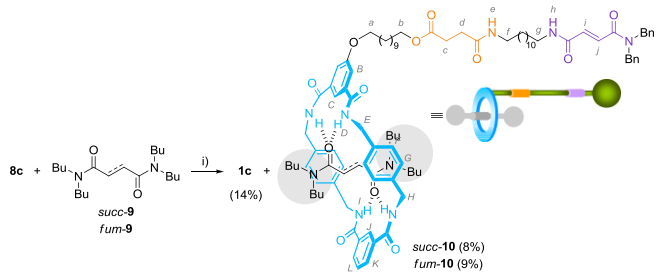
As one may expect, this synthetic approach leading to [1]rotaxane is entropically favored due to the reduced number of components involved in the assembly. Indeed, the entwined **1c** is the major compound even if its formation reaction is carried out in the presence of competitive single binding-site threads such as tetrabutylsuccinamide (*succ*-**9**) or tetrabutylfumaramide (*fum*-**9**) which additionally afford the corresponding interlocked pseudo[2]rotaxanes **10** in lower yields (8% and 9%, respectively) via [1+1+1] couplings (Scheme 3).



Scheme 3 Competitive coupling of the diamine **8c** with isophthaloyl chloride in the presence of single binding-site threads: formation of the [1]rotaxane **1c** using an intramolecular template *versus* the formation of [2]rotaxanes **10** using the intermolecular dicarboxamide-based templates **9**. *Reagent and conditions:* i) isophthaloyl chloride, Et_3N, $CHCl_3$, 25 °C.

Evaluation of the stability of the hydrogen-bonded [1]rotaxanes

An appropriate size of the stoppers of a rotaxane can kinetically stabilize its entangled structure avoiding the thread deslipping through the ring in a broad range of experimental conditions. However, if the size of a stopper is not enough to prevent such dethreading process, a pseudo[1]rotaxane can be converted into its unthreaded isomer (Fig. 4, via A). Formally, it supposes the shifting of the stopper through the ring in the direction of the grey A arrow. In other manner, [1]rotaxanes could also yield the same unthreaded isomer through a tumbling of the ring[16h,17c,19d,28] in which a set of energetically favored bond rotations disentangles its structure (Fig. 4, via B).

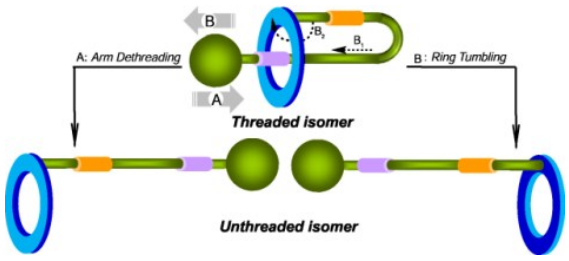
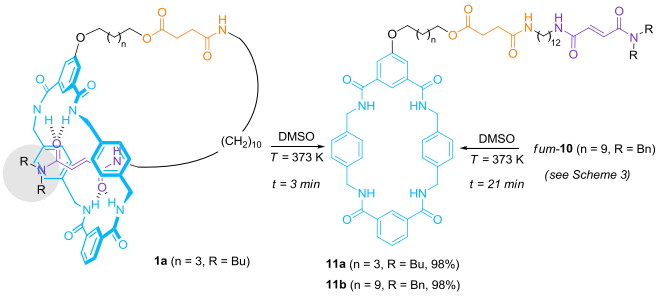


Fig. 4 Unthreading mechanisms of a (pseudo)[1]rotaxane with a ring having two different faces (in dark and light blue). Note that a ring tumbling of the threaded isomer inverts the face of macrocycle during the exchange to the unthreaded isomer. Also for clarity, sequential motions B1 and B2 of the ring tumbling process B are also indicated (dashed arrows).

Formally, it requires a more complex motion involving a ring gliding followed by internal rearrangement of the ring which, finally, ejects the arm from the void of the macrocycle.

Based on our previous studies on the dethreading of hydrogen-bonded [2]rotaxanes,[29] we envisioned that the kinetically stabilized pseudo[1]rotaxane **1a** having a Bu_2N group as stopper could undergo a similar process leading to its unthreaded isomer. We found that entwined **1a** was completely stable in $C_2D_2Cl_4$ solution even at 120 °C after 24 hours. However, in the presence of a strongly competitive hydrogen-bond solvent such as dimethylsulfoxide, **1a** is quantitatively transformed into **11a** (Scheme 4) even at room temperature. The process can be accelerated at 100 °C to be completed in 3 minutes. It should be noted that the dethreading of the analogous [2]rotaxane *fum*-**10** led to the macrocycle **11b** but, in this case, it required heating for 21 min under the same reaction conditions (Scheme 4). In contrast with other reported self-complexing systems,[16-19] we proved that these dethreading processes are irreversible preventing the synthesis of the [1]rotaxane **1a** by using the unthreaded **11a** as starting material.

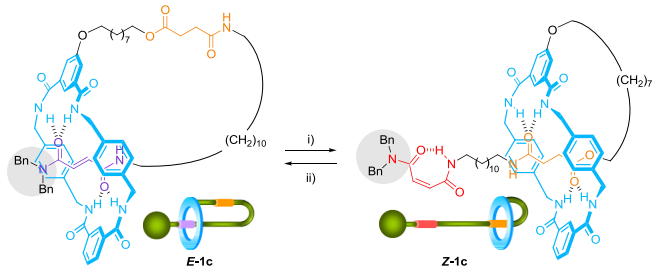


Scheme 4 Dethreading of the [1]rotaxane **1a** and the [2]rotaxane *fum*-**10**.

We have also explored the feasibility for accessing to the unthreaded isomer of one of the [1]rotaxanes by a tumbling process of the benzylic amide macrocycle. To test this possibility, we choose **1c** in which a dethreading process is forbidden as the macrocycle would have to overcome a huge kinetic barrier due to the bulkiness of the Bn_2N-based stopper. However, by monitoring the ^1H NMR spectrum of a solution of the [1]rotaxane **1c** in $C_2D_2Cl_4$ at 130 °C or in DMSO-d_6 at 150 °C for 12 h (Figure S5) we observed that the structure of **1c** kept unaffected recovering its primitive spectrum, at 25 °C, without any other additional signals. These results reveals the large stability of this entangled structure and clearly proves that the benzylic amide macrocycle of **1c** cannot tumble differing from other macrocycles also incorporating 1,3,5-trisubstituted benzene rings.[28]

Light-promoted exchange of the extended and contracted isomers of the [1]rotaxanes 1c

For the synthesis of [2]rotaxane-based molecular shuttles, different photoswitchable binding sites have been employed including azobenzenes,[30] stilbenes,[31] olefins,[24,32] spiropirans[33] and, also recently, acylhydrazones.[34] However, in the case of [1]rotaxanes, only azobenzene motifs have been employed as light-driven switches for a couple of cyclodextrin-based systems developed by Tian *et al.*[16d,i,35] The well-known photoisomerization of the fumaramide station embedded into other interlocked compounds[24] prompted us to apply similar irradiation conditions for exchanging the two putative lasso-like isomers of **1c** (Scheme 5). Thus, photoisomerization of *E*-**1c** to *Z*-**1c** using UV light (254 nm) triggers the translation of the ring to the available succinamide-ester binding site due to the decrease of the affinity of the benzylic amide macrocycle for the *Z* olefinic station and thus promoting the formation of the contracted isomer of the [1]rotaxane. This *E* to *Z* isomerization occurs in a moderate 51% isolated yield. The original extended isomer *E*-**1c** was efficiently recovered (95%) by irradiation at 312 nm for 35 min due to the relocation of the ring over the fumaramide station (Scheme 5) or by heating in $C_2D_2Cl_4$ at 120 °C for 5 days (99%). In stark contrast, the photoexchange of the [1]rotaxanes *E*-**1a** and *E*-**1b,** in which a shorter alkyl chain connects the ring and the succinamide ester station, were unsuccessful affording a complex mixture of byproducts.



Scheme 5 Light-driven exchange of the extended and contracted forms, *E*-**1c** and *Z*-**1c**, of the benzylic isophthlamide [1]rotaxane. Conditions: i) 254 nm (62 W·m^{-2}), CH_2Cl_2, 90 min, 51%; ii) 312 nm (56 W·m^{-2}), CH_2Cl_2, 35 min, 95%.

A stacked plot of the ^{1}H NMR spectra of the extended and contracted forms, *E*-**1c** and *Z*-**1c**, of the benzylic isophthlamide [1]rotaxane **1c** is depicted in Figure 5. For comparison, this plot also shows the ^{1}H NMR spectra of *succ-E*-**10** and *succ-Z*-**10** (obtained from *succ-E*-**10** by photoisomerization, see ESI†) as alternative models of the corresponding unthreaded isomers **11b** due to the insolubility of these latter macrocycles in deuterated halogenated solvents. The signals corresponding to the fumaramide station (H_i and H_j) are shifted upfield by 1.2 and 1.3 ppm in *E*-**1c** (Figure 5b) respect to the corresponding signals in *succ-E*-**10** (Figure 5a) due to the location of the ring on this station, whereas the signals of the succinamide station (H_c and H_d) in *E*-**1c** and *succ-E*-**10** appear at nearly identical chemical shifts. Using the method reported by Leigh to determine the positional discrimination of the ring in a hydrogen-bonded molecular shuttle, it has been estimated that the occupancy of the fumaramide station for the [1]rotaxane **1c** in $CDCl_3$ is around 94%, fully comparable to those of analogous bistable [2]rotaxanes.[24a] As one may expected this fidelity value decrease with increasing the hydrogen bond basicity[36] of the deuterated solvent following the sequence $CDCl_3$ (94%), CD_2Cl_2 (93%), THF-d_8 (82%), DMF-d_7 (66%), DMSO-d_6 (20%) (see ESI†). These values are consistent with a reduction of the positional integrity of the ring on the fumaramide site of the extended lasso **1c**, as its stability is progressively decreased by the competing hydrogen bonding to the solvent of the environment.

On the other hand, the signals corresponding to the maleamide station (H_j and H_i) in *Z*-**1c** (Figure 5d) and *succ-Z*-**10** (Figure 5c) appear at nearly the same chemical shifts, whereas the signals of the succinamide-ester station (H_c and H_d) are now shifted upfield by 1.4 ppm in *Z*-**1c** respect to those in *succ-Z*-**10** due to the ring translocation. This upfield change is also consistent with a contracted lasso configuration of the [1]rotaxane **1c** featured also by a notable positional integrity in a non-disrupting hydrogen-bond solvent such as CD_2Cl_2.

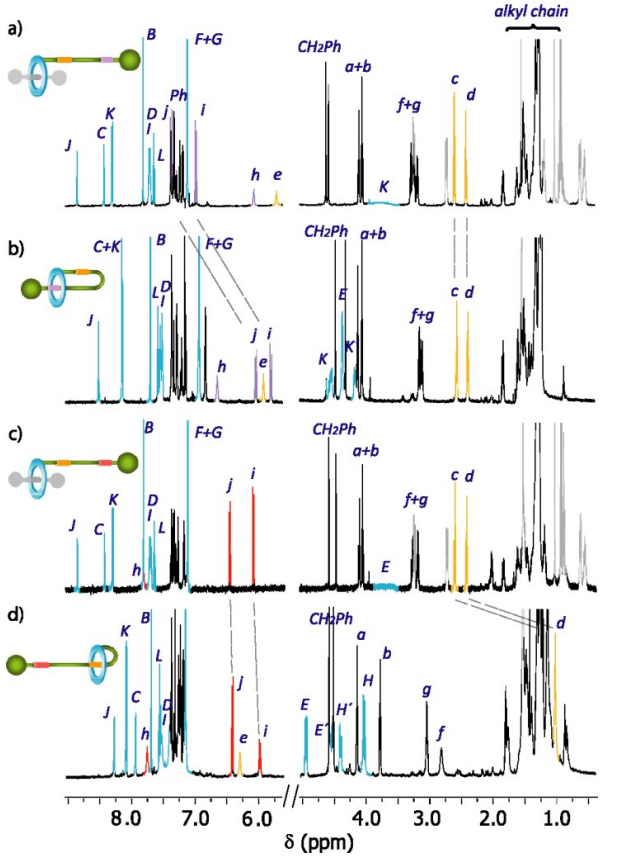


Fig. 5 Partial ^{1}H NMR spectra (600 MHz, CD_2Cl_2, 298 K) of (a) *succ-E*-**10**, (b) [1]rotaxane *E*-**1c,** (c) *succ-Z*-**10** and d) [1]rotaxane *Z*-**1c**. Peaks corresponding to the *N,N,N',N'*-tetrabutylsuccinamide component in *succ-E*-**10** and *succ-Z*-**10** are in grey. Lettering is shown in Schemes 2 and 3.

Conclusions

In summary, we have shown that benzylic amide [1]rotaxanes can be obtained through a self-templating clipping approach in only one step involving the 1+1 coupling of an acyclic U-shaped diamine precursor and isophthaloyl dichloride. The entwined structures were unambiguously characterized and the spatial rearrangement of its loop configuration was exhaustively studied in both solution and solid state. These entwined species can convert into the corresponding unthreaded

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isomers through a thermal treatment in DMSO which induce the deslipping of the terminal stopper of the arm across the macrocycle. The incorporation of two binding sites into the arm of these [1]rotaxanes allows the exchange of theirs extended and contracted slipknotted isomers by an olefin isomerization promoted by UV light irradiation. Both isomers exhibit good lasso integrity thanks to the establishment of hydrogen bonds between the ring and the binding sites in the arm. These results open the doors to the building of a novel generation of molecular machinery having an hydrogen-bonded [1]rotaxane-based scaffold enabled to transform nanoscale mechanical variations into property changes observable in the macroscopic world.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the MINECO (CTQ2017-87231-P), FEDER and Fundacion Seneca-CARM (Project 19240/PI/14) for the financial support. A.S.-S. also thanks to the Fundacion Seneca-CARM for his PhD fellowship.

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