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## ARTICLE

# Synthesis of Triazolium-Based Mono- and Tris-branched [1]Rotaxanes Using a Molecular Transporter of Dibenzo-24-Crown-8

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P. Waelès,<sup>a</sup> C. Clavel,<sup>a</sup> K. Fournel-Marotte<sup>a</sup> and F. Coutrot<sup>a\*</sup>Received 00th January 2012,  
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We report a diverted route to [1]rotaxane and tris-branched [1]rotaxane which are devoid of any efficient template and which could not be obtained by classical straightforward strategies. The described chemical route relies on the utilization of a “macrocycle transporter”, which is able first to bind a macrocycle, second to link temporarily a triazolium-containing molecular axle, third to deliver the macrocycle around the new docked axle through molecular machinery in a [1]rotaxane structure. The extended encircled thread is eventually cleaved by an amine or a triamine to afford the triazolium-containing [1]rotaxanes, releasing at the same time the transporter of macrocycle as a recyclable specie.

## Introduction

Since the properties of molecules are closely related to their three-dimensional structure, mechanically interlocked molecules,<sup>1</sup> which hold very singular architectures, seem to be very appealing potential targets in a wide range of research fields. It follows that improving their chemical access is of the highest interest, even though it might be a challenging task in some cases. Among the numerous interlocked molecular architectures, the [1]rotaxane<sup>2</sup> molecular architecture holds a particular place as a single molecule. It consists of a macrocycle that surrounds a molecular thread, in which both components are connected together through a covalent bond. Several different chemical routes have been used to synthesize [1]rotaxanes until now (Figure 1). The scarcest strategy relies on a covalent bond formation and was reported by Hiratani *et al.* in 2004 (synthetic pathway (a)):<sup>3</sup> in that case a key bicyclic intermediate is statistically attacked either by the inner of the macrocycle to afford the [1]rotaxane, or by the outside of the macrocycle to provide the non-interlocked analogue. More frequently encountered are the other strategies relying on the use of weak interactions as the driving force to assemble the molecular elements into the self-interlocked architecture. They can be divided in three main synthetic pathways. The first one relies on the preliminary template-directed synthesis of a semi [2]rotaxane, then on the chemical connection between the surrounded axle and the macrocycle (synthetic pathway (b)).<sup>4</sup> The second one uses a “hermaphrodite” molecule, that is to say a macrocycle that is covalently bonded to a molecular axle which contains a site of interaction for the macrocycle (synthetic pathway (c)). In that case, the non-interlocked molecule remains in equilibrium with the pseudo[1]rotaxane, until this latter is capped either by a hindering<sup>5</sup> or a rigid stopper<sup>6</sup> at the extremity of the axle. The third templated path-

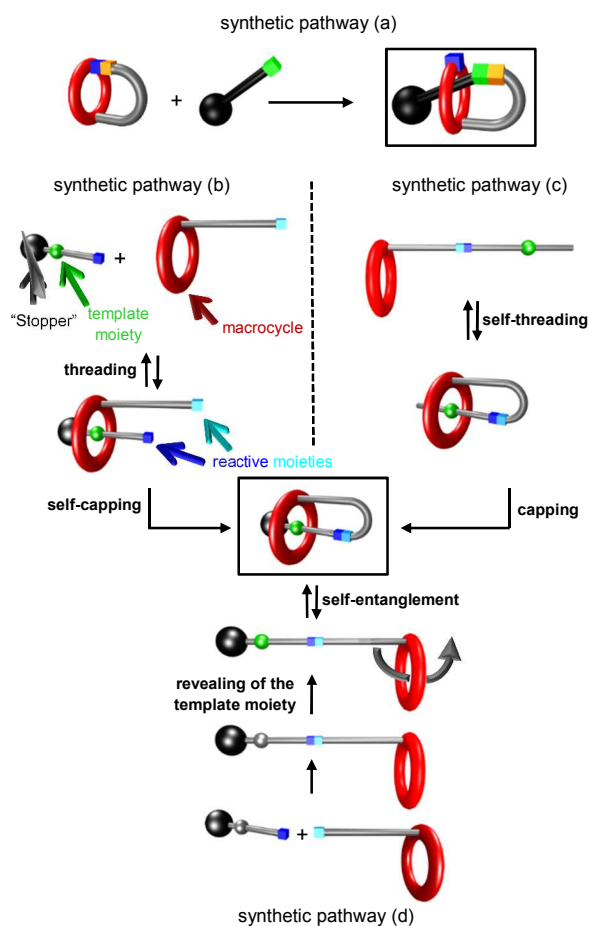


Fig. 1 Chemical templated routes to [1]rotaxanes.

-way consists in a self-entanglement strategy of a “hermaphrodite” molecule that already contains a stopper at the extremity of the axle (synthetic pathway (d)). In that particular case, no threading of the bulky extremity is allowed, so that the only way to interlace the molecule is to perform a pirouette of one part of the macrocycle (*i.e.* the one connected to the axle) with respect to the other.<sup>7</sup> This last templated strategy is probably a tougher chemical pathway to set up since it requires a macrocycle of a bigger cavity to allow the self-entanglement, although enough interactions must be maintained at the same time between the template and the macrocycle to get the [1]rotaxane structure. Herein, we report on the synthesis of triazolium-containing mono- and tris-branched [1]rotaxanes which are devoid of any efficient template for the macrocycle (Figure 2). They only contain a triazolium moiety which serves as a molecular station of poor affinity for the dibenzo-24-crown-8 (DB24C8) derivative in a locked rotaxane.

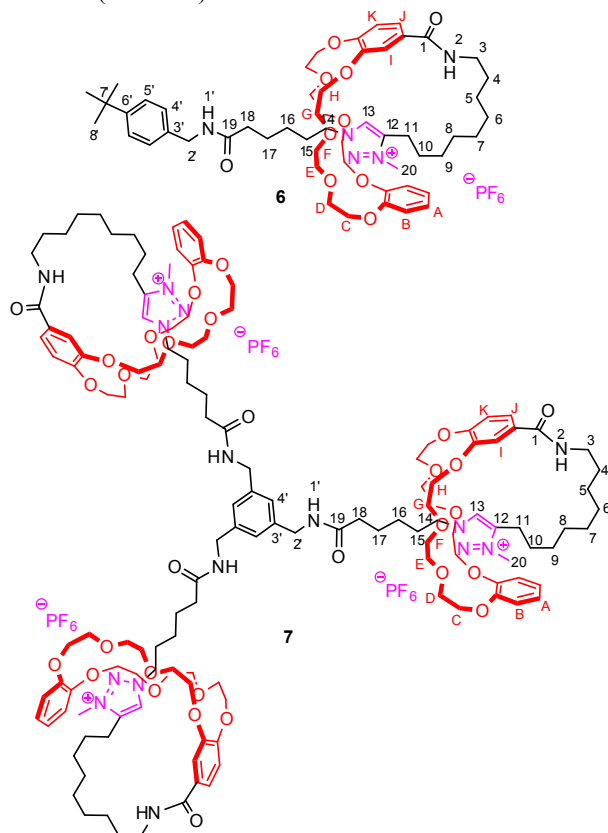


Fig. 2 Synthesized [1]rotaxanes 6 and 7 with atoms assignments.

The newly proposed synthetic strategy relies on the use of a recyclable transporter of macrocycles **A** whose utility is to catch a macrocycle and to deliver it to another axle (Figure 3).<sup>8</sup> As it has been designed to contain an efficient template moiety for the macrocycle, **A** initially captures with efficacy the macrocycle with the first aim of forming the semi[2]rotaxane **B** in a similar fashion than in the illustrated strategy (b) of figure 1. Extension of the encircled axle, then self-capping through the linking between the thread end and the substituted macrocycle provides the locked [1]rotaxane structure **D**. At this step, a second site of interaction of much poorer affinity for the macrocycle is also created in the encircled axle. Molecular machinery is subsequently used to trigger the tightening of the [1]rotaxane lasso **D**, through the shuttling of the macrocycle around the final targeted axle. The final step of the strategy

consists in the cleavage of the axle of the tightened [1]rotaxane **E** using a functionalized stopper, thus providing simultaneously the contracted [1]rotaxane **F** and the initial modified axle **G**. Eventually, the initial transporter **A** can be regenerated through the recycling of **G**. What is here very important to point out is the effectiveness of the strategy. Indeed, the final triazolium-containing [1]rotaxane **F** (*i.e.* 6 and 7) cannot be efficiently generated using the other already reported strategies. Although the second created site of interaction for the macrocycle (*i.e.* triazolium) acts as an effective molecular station for the shuttling of the macrocycle in the locked [1]rotaxane structure, it would not permit to drive the rotaxane formation through intermolecular interactions, this being mainly due to the entropic factor.<sup>9</sup>

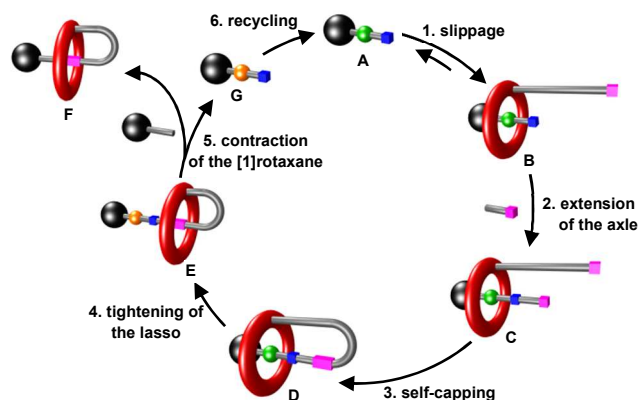


Fig. 3 A novel route to [1]rotaxane **F** based on a recyclable macrocycle transporter **A**.

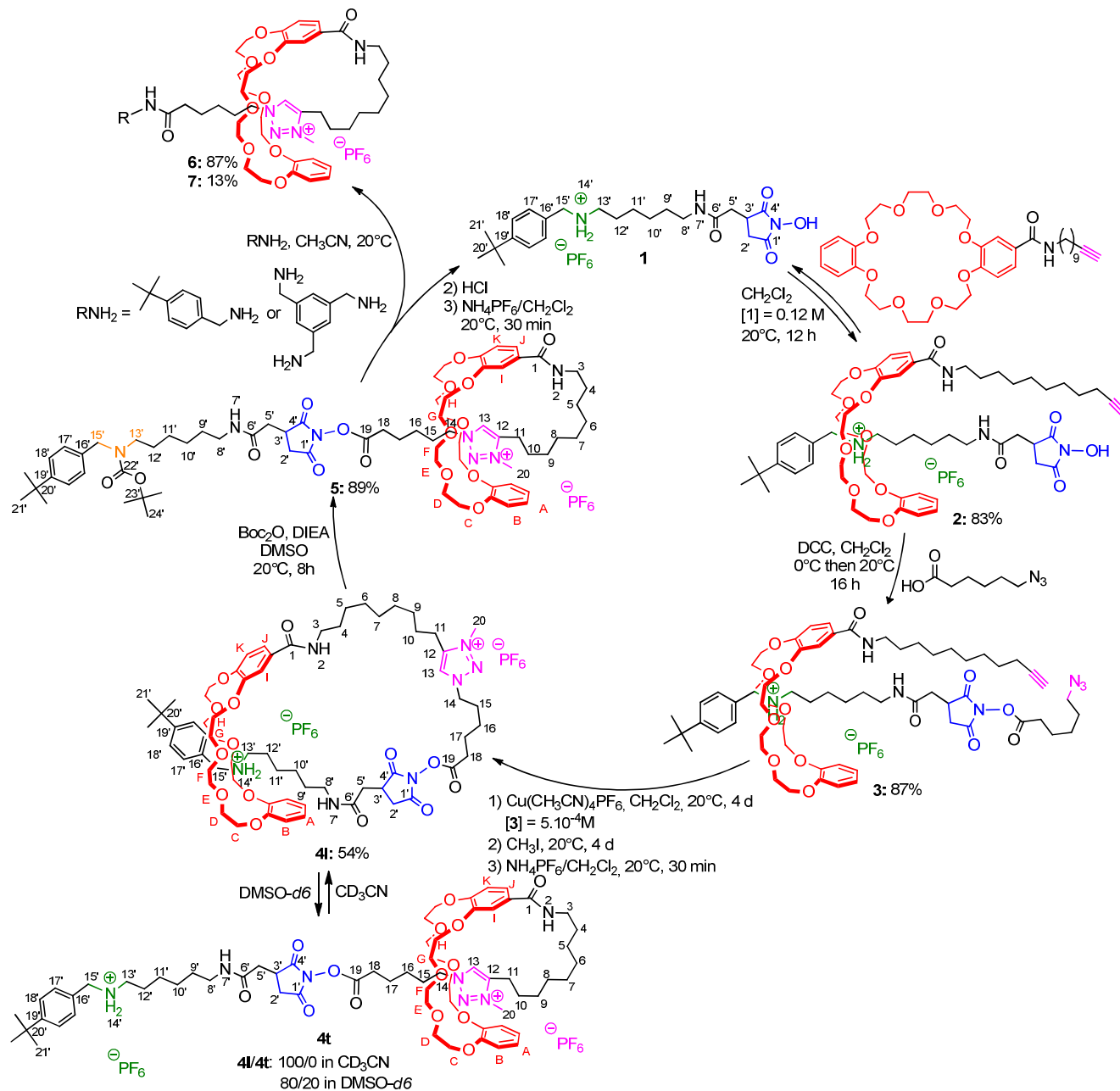
## Results and discussion

### Preparation of the loosened extended [1]rotaxane **D**.

The synthetic sequence begins by the slippage<sup>10</sup> of a transporter of macrocycle **1** (Scheme 1). It contains an ammonium moiety (in green) which initially serves as an efficient template for the DB24C8.<sup>11</sup> It also contains a *tert*-butylbenzyl stopper (in black) at one extremity and a *N*-hydroxysuccinimide (NHS) moiety (in blue) at the other end. The semirotaxane architecture **2** could be obtained in a 83% yield after stirring during 12 h in dichloromethane at room temperature, 3 equivalents of the DB24C8 derivative and 1 equivalent of **1** at a concentration of 0.12 M. The bulkiness of the NHS is responsible for the long slippage process and for the stability of the product. Indeed, it is noteworthy that the rotaxane **2** is stable as a powder and can be kept many days without observing any disassembly. Furthermore, the unthreading is also very slow in hydrogen-bond promoting solvent such as dichloromethane, which is beneficial here since it allows the purification of **2** by sephadex chromatography. The extension of the encircled axle was then carried out by esterification of the free hydroxyl group of the NHS-containing rotaxane **2** with the azido hexanoic acid, using dicyclohexylcarbodiimide as coupling reagent. On one hand, it provides a *N*-hydroxysuccinimide ester moiety which will be of utility for the final cleavage step of the strategy. On the other hand, the incorporated azido moiety (in purple) gives the opportunity to self-cap the [1]rotaxane architecture through cyclization. The azido moiety of the extended [2]rotaxane **3** was therefore connected to the alkyne-containing macrocycle, through the copper(I)-catalyzed Huisgen<sup>12</sup> alkyne-azide 1,3-dipolar cycloaddition.<sup>13</sup> High dilution ( $5.10^{-4}$  M) conditions were employed to provide the [1]rotaxane architecture in a

satisfactory yield of 60%. The so-created triazole moiety was further methylated before being submitted to an anion exchange using ammonium hexafluorophosphate, affording **4l** with an overall yield of 54% from **3**. This alkylation reveals the *N*-methyltriazolium in **4** as the second site of interaction for the DB24C8 derivative.<sup>14</sup> In hydrogen bonds promoting solvents, as long as the ammonium remains protonated, the DB24C8 derivative is mainly localized around the best ammonium station, resulting in a loosened conformation of the lasso. Since

the chemical route to the targeted [1]rotaxanes **6** and **7** requires the large-amplitude shuttling of the macrocycle along the thread toward the triazolium station, the displacement of the equilibrium from the loosened lasso **4l** to the tightened lasso **4t** was envisaged. We first studied the effect of a variation of the polarity of the medium. Through a more efficient subsequent approach, an *N*-carbamoylation of the ammonium station was then considered.



**Scheme 1** Preparation of mono- and tris-branched triazolium-containing [1]rotaxanes using the recyclable macrocycle transporter **1**.

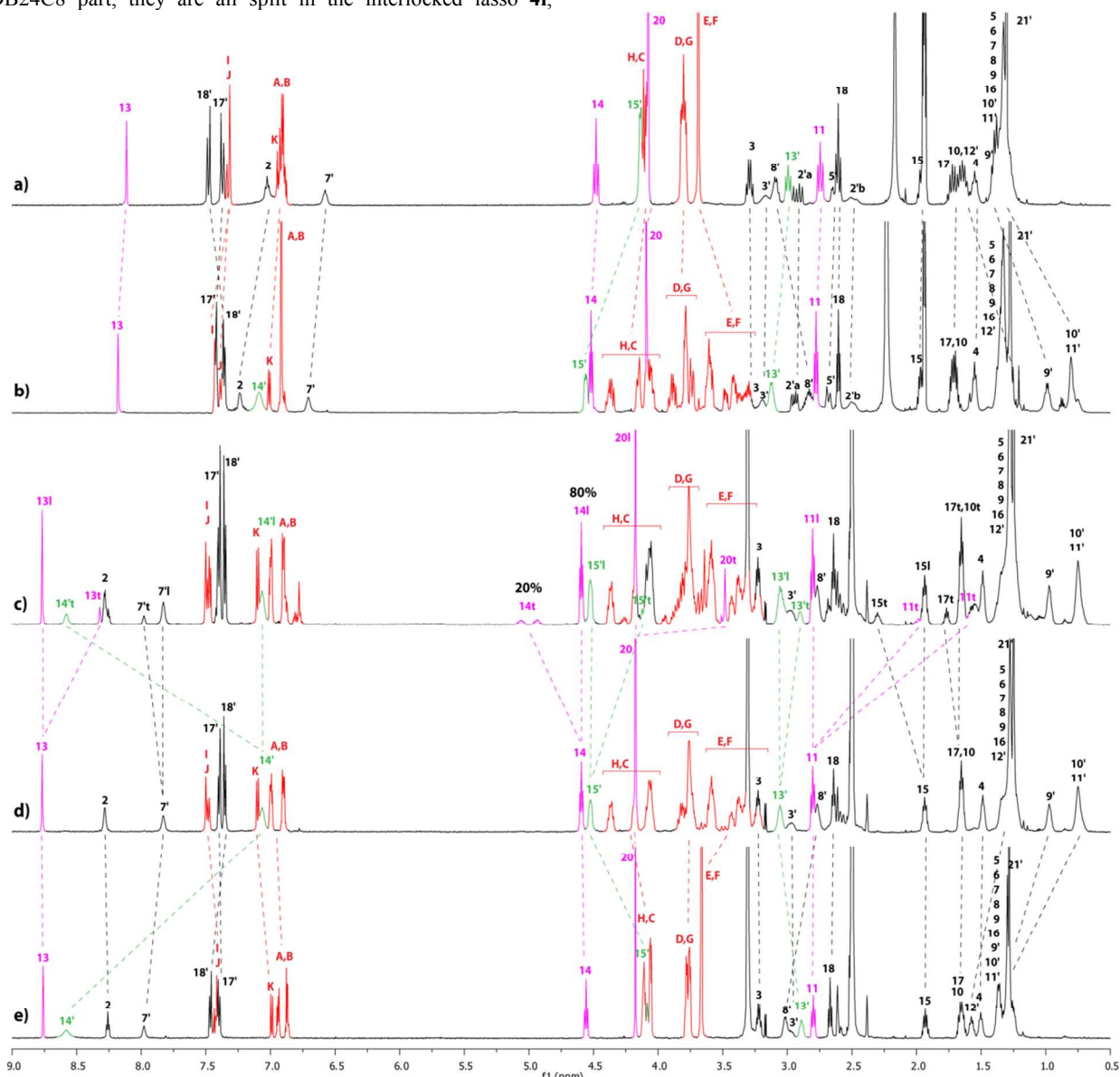
### Tightening of the Lasso through Solvent-Dependent Molecular Machinery.

The partial tightening of the loosened lasso **4l** was found to be possible through molecular machinery, upon variation in solvent polarity (Scheme 1). In acetonitrile, the DB24C8 derivative resides exclusively around the ammonium station, affording the loosened

conformation for the lasso **4l**. This was demonstrated by the direct comparison between the <sup>1</sup>H NMR spectra of the [1]rotaxane **4l** and its non-interlocked analogue **4u** (Figure 4, a-b). First of all, only one set of <sup>1</sup>H NMR signals can be observed in **4l**, which indicates the presence of the DB24C8 only around one of the two stations.<sup>15</sup> Moreover, no significant variation of the chemical shifts is observed for the hydrogen atoms (H<sub>11</sub>, 13, 14, 20) of the triazolium moiety of

lasso **4l** and the non-interlocked analogue **4u**. On contrary, the hydrogen atoms belonging to the ammonium station, *i.e.* H<sub>15'</sub> and in a lesser extent H<sub>13'</sub>, are both shifted downfield in **4l** (respectively  $\Delta\delta = 0.42$  and  $0.13$  ppm), due to their hydrogen bonding interactions with the oxygen atoms of the DB24C8. At the same time, hydrogens H<sub>8'-12'</sub> are all more or less shielded in **4l** (from  $-0.54$  to  $-0.25$  ppm) because of their localization in the shielding cavity of the aromatic rings of the DB24C8. Concerning the methylene hydrogens H<sub>C-H</sub> of the DB24C8 part, they are all split in the interlocked lasso **4l**,

because they are facing the two non-symmetrical ends of the threaded axle. Besides, it is to note the upfield shift underwent by hydrogens H<sub>E-F</sub> in **4l**, due to their localization in the shielding cavity of the benzyl ammonium aromatic ring of the encircled axle, therefore corroborating the localization of the DB24C8 around the ammonium station in acetonitrile. In DMSO, the behaviour of the lasso **4** appeared slightly different (Figure 4, c-e).



**Fig. 4** <sup>1</sup>H NMR Spectra (600 MHz, 298 K) of (a) the non-interlocked analogue **4u** in CD<sub>3</sub>CN, (b) the loosened [1]rotaxane **4l** in CD<sub>3</sub>CN, (c) the loosened and tightened [1]rotaxanes **4l** and **4t** in DMSO-*d*<sub>6</sub> at  $t=20$  h, (d) the [1]rotaxane **4l** in DMSO-*d*<sub>6</sub> at  $t=0$  h, (e) the non-interlocked analogue **4u** in DMSO-*d*<sub>6</sub>. The numbering and colorings correspond to the hydrogen assignments indicated in Scheme 1.

Indeed, although the exclusive loosened conformation **4l** was noticed in DMSO at  $t=0$  (Figure 4, d-e),<sup>16</sup> the appearance of a second set of <sup>1</sup>H signals was noticed upon time. It corresponds to the tightened conformation of the lasso (**4t**). After 22h, the equilibrium between the two translational conformers was reached and a *ratio* **4l**:**4t** of about 80:20 was noticed (figure 4 c). This *ratio* remained unchanged either upon longer time or by heating the sample. Without any doubt, the new set of signals matches with the tightened conformation **4t**, in which the DB24C8 is localized around the triazolium station. This is

quite a surprising result, taking into account the much better affinity of the DB24C8 for the ammonium station than for the triazolium. One may suggest that the solvation effect of the DMSO is stronger on the ammonium than on the triazolium, therefore decreasing the difference of affinity between the two respective stations for the DB24C8, hence triggering the slight displacement of the equilibrium toward the tightened lasso **4t**. The tightening of the lasso **4** in DMSO was evidenced by the direct comparison between the <sup>1</sup>H NMR spectra of the lasso **4t** and the non-interlocked analogue **4u** (Figure 4

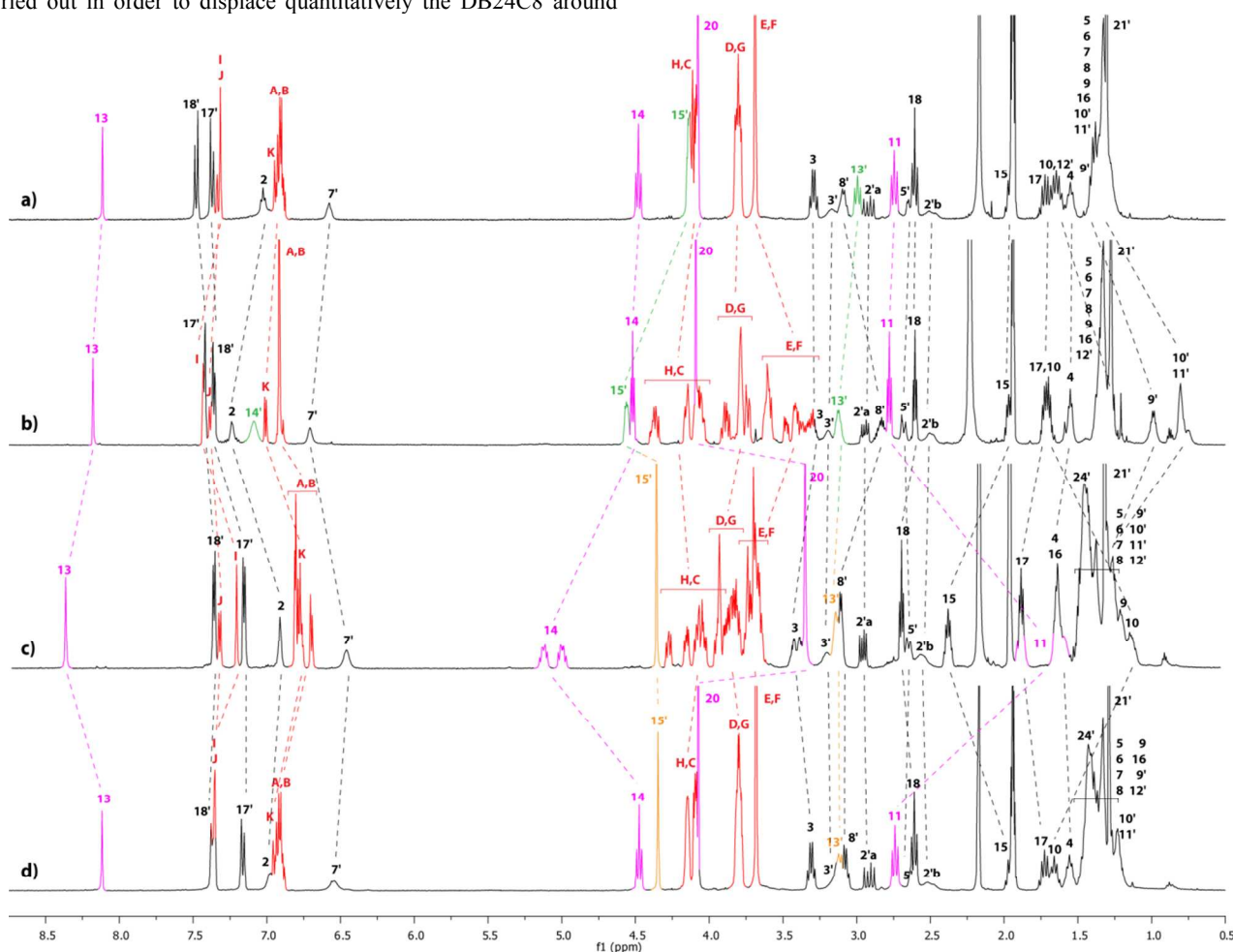


c,e). In DMSO-*d*<sub>6</sub>, and to resume, the new set of signals matches with **4t**: indeed, the chemical shifts of the hydrogen atoms belonging to the triazolium site (*i.e.* H<sub>11,13,14,15,20</sub>) are all affected by the new localization of the DB24C8. In **4t**, it is noteworthy to point out both the deshielding and the splitting of H<sub>14</sub> ( $\Delta\delta = 0.37$  and 0.5 ppm), the downfield shift of H<sub>15</sub> ( $\Delta\delta = 0.37$  ppm), and the shielding of H<sub>11</sub>, H<sub>13</sub> and H<sub>20</sub> ( $\Delta\delta$  from -0.44 to -1.16 ppm).<sup>17</sup> Meanwhile, no variations at all of chemical shifts are noticed between **4t** and **4u** for the hydrogen atoms H<sub>13',14',15'</sub> that belong to the ammonium station, which is in accordance with the tightened conformation. Although a partial tightening of the lasso **4** was possible in the more polar solvent DMSO, the obtained *ratio* (20%) was not found sufficient to efficiently pursue the synthesis of the triazolium-based [1]rotaxanes **6** and **7**. We thus decided to use a chemical *stimulus* to generate the tightened lasso in high yield through the actuation of the molecular machinery.

#### Tightening of the Lasso by Molecular Machinery through the *N*-Carbamoylation of the Ammonium.

In a second approach, the *N*-carbamoylation of the ammonium was carried out in order to displace quantitatively the DB24C8 around

the triazolium station. Similarly to the *N*-acetylation<sup>18</sup>, the *N*-carbamoylation<sup>19</sup> of a complex ammonium/DB24C8 was reported as a tough task in acetonitrile because of the strong hydrogen-bonding interactions between the components. This results in the decrease of the acidity of the ammonium, therefore dramatically diminishing the kinetic of the overall reaction. In a previous paper, we improved the *N*-carbamoylation by using a strong base such as phosphazene, although some side-products resulted from the harsher conditions.<sup>8</sup> Here, the *N*-carbamoylation was successfully achieved without any side-reaction with the help of the weak base diisopropylethylamine and Boc<sub>2</sub>O, however in the more polar solvent DMSO. The DMSO was effectively chosen because its high polarity decreases the binding affinity of the ammonium for the crown ether, hence increasing its acidity and facilitating its deprotonation in very mild conditions. The tightened carbamoylated lasso **5** could be obtained and isolated this way in a 89% yield.<sup>20</sup> The localization of the crown ether around the triazolium was established by comparing the <sup>1</sup>H NMR spectra of the respective loosened and tightened lassos **4l** and **5** with their respective non-interlocked analogue **4u** and **5u** (Figure 5).



**Fig. 5** <sup>1</sup>H NMR Spectra (600 MHz, CD<sub>3</sub>CN, 298 K) of (a) the non-interlocked analogue **4u**, (b) the loosened [1]rotaxane **4l**, (c) the *N*-carbamoylated tightened [1]rotaxane **5**, (d) the non-interlocked analogue **5u**. The numbering and colorings correspond to the hydrogen assignments indicated in Scheme 1.

As already discussed in the precedent section, the comparison between the <sup>1</sup>H-NMR spectra of **4u** and **4l** demonstrated the localization of the crown ether around the ammonium station in **4l** (Figure 5, a-b). After carbamoylation, the crown ether glides

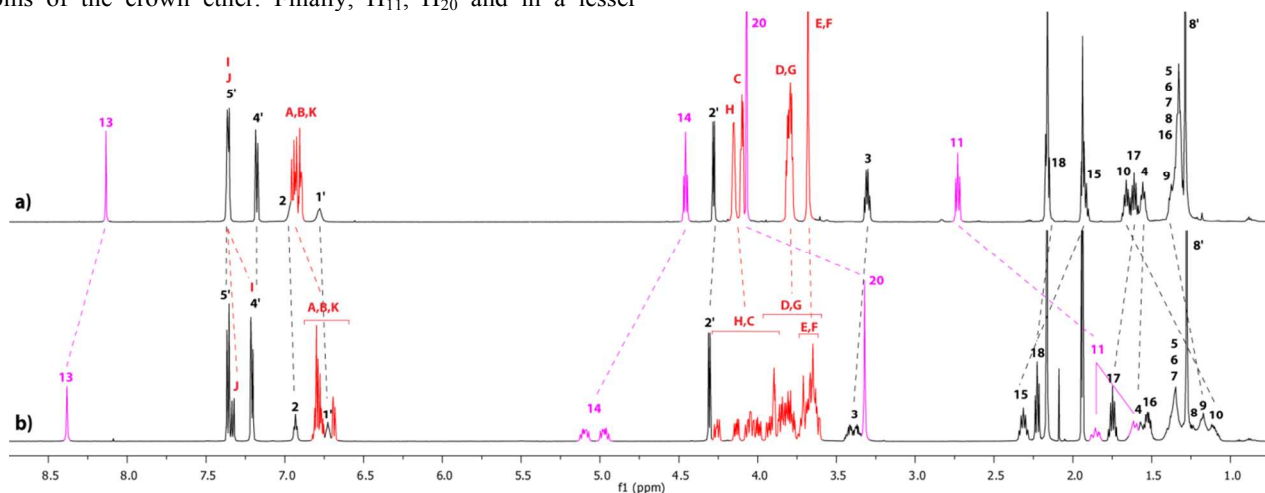
around the triazolium station, resulting in the tightening of the lasso. The conformation of the lasso **5** was evidenced by comparing NMR spectra of **5** with **4l** (Figure 5, b-c). In **5**, the chemical shifts of the hydrogen atoms H<sub>13'</sub> and H<sub>15'</sub>, which

belongs to the ammonium station, are slightly affected by both the displacement of the DB24C8 and the introduction of the carbamoyl moiety. More importantly, significant variations are observed for the hydrogens of the triazolium site. Indeed, in **5**, the hydrogens H<sub>13</sub> and H<sub>14</sub> are both shifted downfield (respectively  $\Delta\delta = 0.2$  and  $0.54$  ppm) due to their interaction through hydrogen bonding with the oxygen atoms of the DB24C8. Furthermore, H<sub>14</sub> appears split in the tightened lasso **5**, probably due to the more constrained asymmetric loop of the lasso. Meanwhile, H<sub>11</sub>, H<sub>20</sub> and in a lesser extent H<sub>10</sub> are all shifted upfield in **5** (respectively  $\Delta\delta = -1.05$ ,  $-0.75$  and  $-0.53$  ppm), because they experience the shielding effect of the aromatic ring of the DB24C8. This is consistent with the fact that H<sub>8'-11'</sub> are all deshielded in **5**, because they do not experience any more the shielding effect of the aromatic ring of the DB24C8. Besides, and for the same reason than for H<sub>14</sub>, H<sub>11</sub> appears importantly split in **5**, this being an indicator of the constrained tightened lasso. The localization of the DB24C8 around the triazolium station could also be confirmed by the direct comparison between NMR spectra of **5** and **5u** (Figure 5, c-d). Briefly, the only differences of chemical shifts between **5** and **5u** concern the hydrogens of the DB24C8 and those of the triazolium station. As already mentioned, the hydrogens H<sub>C-H</sub> of the crown ether are split in the interlocked architecture. Moreover, H<sub>13</sub>, H<sub>14</sub> and H<sub>15</sub> are all shifted downfield in **5** (respectively  $\Delta\delta = +0.26$ ,  $+0.59$  and  $+0.41$  ppm) with respect to **5u** due to their hydrogen bonding interactions with the oxygen atoms of the crown ether. Finally, H<sub>11</sub>, H<sub>20</sub> and in a lesser

extent H<sub>10</sub> are all shifted upfield in **5** (respectively  $\Delta\delta = -1.01$ ,  $-0.73$  and  $-0.48$  ppm) because they are localized in the shielding cavity of the aromatic rings of the DB24C8.

#### Contraction of the tightened lasso **5** and characterization of the mono and tris-branched triazolium-based [1]rotaxanes **6** and **7**.

The tightened lasso **5** was designed in such a fashion that the molecular surrounded axle contains a NHS ester that can be cleaved by an amino compound at the end of the multi-step sequence. An amine and a triamine were separately added to **5** in order to synthesize respectively the triazolium-based mono and the tris-branched [1]rotaxanes **6** and **7** (Scheme 1 and figure 2). Adding 2 equivalents of *tert*-butylbenzylamine in acetonitrile afforded quite easily the [1]rotaxane **6** in a 87% yield after purification by sephadex LH 20 chromatography. The synthesis of the tris-branched [1]rotaxane **7** was realized by adding 0.3 equivalent of the 1,3,5-tris(aminomethyl)benzene to 1 equivalent of **5**. The reaction was not as efficient as for the synthesis of **6**, since only 13% of pure tris-branched [1]rotaxane **7** were isolated after successive sephadex and silicagel chromatographies. In this case, the lower yield is not ascribed to a poorer conversion of the contraction reaction but rather to the very tricky purification of the final compound. Characterization of the interlocked molecular architectures **6** and **7** was realized by comparing their <sup>1</sup>H NMR spectra with those of their non-interlocked analogues **6u** and **7u** (respectively Figure 6 and 7).



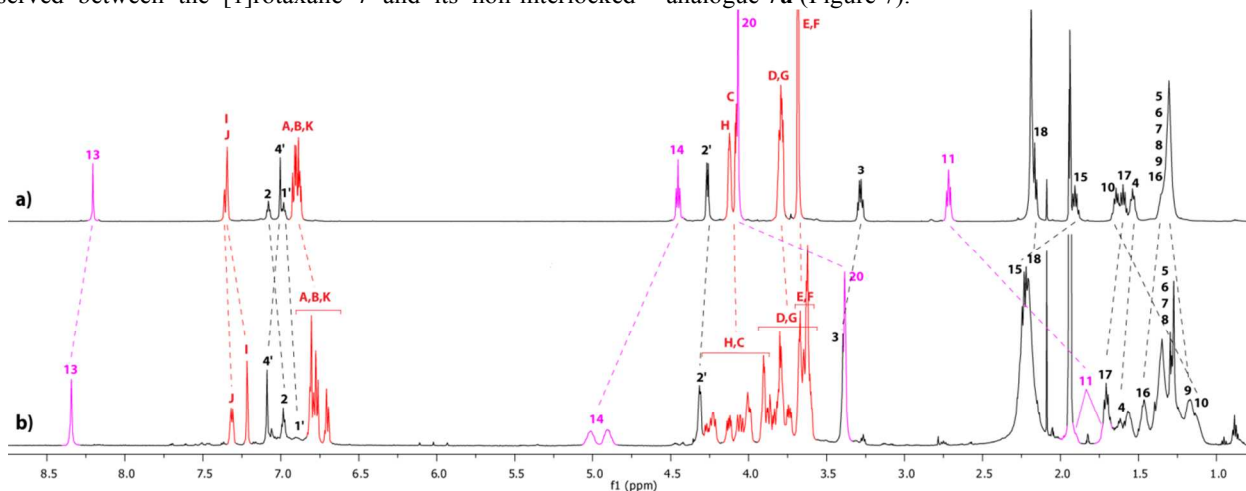
**Fig. 6** <sup>1</sup>H NMR Spectra (600 MHz, CD<sub>3</sub>CN, 298 K) of (a) the non-interlocked analogue **6u**, (b) triazolium-containing [1]rotaxane **6**. The numbering and colorings correspond to the hydrogen assignments indicated in Figure 2.

In the [1]rotaxane **6** (with respect to **6u**), and like in all the DB24C8-based interlocked architectures, the methylene hydrogens H<sub>C-H</sub> are all split because they are facing the two non-symmetrical ends of the threaded axle (Figure 6). Besides, the hydrogens of the triazolium station are highly affected by the presence of the DB24C8. The hydrogen atoms H<sub>13</sub> and H<sub>14</sub> and H<sub>15</sub> are shifted downfield in **6** (respectively  $\Delta\delta = 0.24$ ,  $0.58$  and  $0.39$  ppm) because of their interactions through hydrogen bonding with the oxygen atoms of the crown ether. On the contrary, the hydrogens H<sub>10</sub>, H<sub>11</sub> and H<sub>20</sub> are importantly shifted upfield (respectively  $\Delta\delta = -0.45$ ,  $-0.99$  and  $-0.74$  ppm) because they experience the shielding effect of the aromatic rings of the DB24C8. Of particular interest is the shape of the signals of the hydrogens that are in the loop of the lasso. Indeed, in the [1]rotaxane **6**, and as observed in the carbamoylated tightened lasso **5** (Figure 5c) or in the

protonated tightened lasso **4t** (Figure 4c), the hydrogens H<sub>14</sub>, H<sub>11</sub> and in a lesser extent H<sub>3</sub> becomes all split. The chirality of the reported [1]rotaxane architecture (*i.e.* left- or right-handed helix-type lasso) which is due to the non-symmetrical substitution of the crown ether by the threaded axle may account for these results. In fact, the hydrogens that are localized in or close to the chiral loop become diastereotopic in the restrained tightened [1]rotaxane, hence split in the <sup>1</sup>H NMR spectrum. On contrary, no splitting of these hydrogens is observed in the non-interlocked compound **6u**, this being obvious due to the absence of the lasso.

Apart from the fact that the <sup>1</sup>H NMR spectrum of the tris-branched triazolium-containing [1]rotaxane **7** appears a little bit broader<sup>21</sup> than those of **6**, exactly the same trend concerning the chemical shift variations and the splitting of signals was

observed between the [1]rotaxane **7** and its non-interlocked analogue **7u** (Figure 7).



**Fig. 7**  $^1\text{H}$  NMR Spectra (600 MHz,  $\text{CD}_3\text{CN}$ , 298 K) of (a) the non-interlocked analogue **7u**, (b) triazolium-containing [1]rotaxane **7**. The numbering and colorings correspond to the hydrogen assignments indicated in Figure 2.

## Conclusions

Even if interlocked components are considered as very attractive molecular targets, the efficient access to a wide range of them is still restrained, especially because they usually need to contain well-chosen moieties that can interact together in order to drive their assembly. In this paper, we have reported the efficient and straightforward preparation of triazolium-containing mono- or tris-branched [1]rotaxanes that could not be obtained through classical methods. Whereas triazolium consists of a quite effective molecular station for DB24C8 derivatives in a locked structure like rotaxane, it cannot be used as a template to drive the formation of a DB24C8-based interlocked component through intermolecular interactions. This is mainly due to the too weak interactions between the moieties. The possibility to hypothetically synthesize a triazolium-based semirotaxane, from a DB24C8 derivative and a triazolium-containing molecular axle, is highly limited by the loss in entropic factor, which becomes here predominant with respect to the weak gain in enthalpy (*i.e.* the very weak interactions between the two components). Here, the triazolium-containing [1]rotaxane **6** could be obtained using a 5-step sequence from the azido-hexanoic acid in a 36% overall yield. The possibility to add a polyamine at the last step of the synthesis allows the extension of the method to multi-branched<sup>22</sup> triazolium-based [1]rotaxanes. As an example, the tris-branched [1]rotaxane **7** was prepared and isolated. The improvement of the chemical access to a wide range of [1]rotaxanes that does not necessarily contain a template is a substantial advance for the synthesis of new structures of interest.

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## Notes and references

<sup>a</sup> Supramolecular Machines and ARchitectures Team, Institut des Biomolécules Max Mousseron (IBMM) UMR 5247 CNRS, Université Montpellier, ENSCM, case courrier 1706, Bâtiment Chimie (17), 3ème

étage, Faculté des Sciences, Place Eugène Bataillon 34095 Montpellier cedex 5, France.

Tél : (+) 33 4 67 14 38 43 - Fax: (+) 33 4 67 63 10 46

E-mail: frederic.coutrot@univ-montp2.fr

Homepage: www.glycorotaxane.fr

† Electronic Supplementary Information (ESI) available: [Full experimental procedures and characterization data for all compounds]. See DOI: 10.1039/b000000x/

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