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Maximizing the [*c2*]daisy chain to lasso ratio through competitive self-templating clipping reactions

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Self-templating two-component coupling reactions allowed the isolation of two threaded products with different molecular sizes: a lasso-type [1]rotaxane and a [*c2*]daisy chain rotaxane. Their distribution in the final reaction mixture varies as a factor of the concentration of the reactants. Through this methodology we obtained a large 84-membered cyclic multistation [2]rotaxane.

The chemistry of the mechanical bond has been a topic of great interest in recent years.[1,2] Among the wide and heterogeneous breadth of interlocked structures, [2]rotaxanes,[3] consisting of a linear component encircled by a cyclic one, have become advantaged scaffolds due to their inherent properties, such as steric protection[4] or motion switching.[5,6] Accordingly, rotaxanes have found relevant applications, including the assembly of molecular machinery.[7,8] The development of rotaxane-based molecular machines requires the rational design of the corresponding interlocked architecture, incorporating subunits that allow the controlled motion between the components at will, in order to perform a specific function. Nature is a source of inspiration for the preparation of synthetic molecular devices with biomimetic operability,[9] such as [*c2*]daisy chains rotaxanes[10] designed to simulate the contractile mechanism of sarcomeres in muscles. The contraction/extension of these entwined systems can be controlled under external stimuli.[11] In this context, the preparation of complex structures, including lasso-shape rotaxanes,[12] [*c2*]daisy chains rotaxanes[10] or higher order interlocked arrangements[13] is worth to be remarked.

To date, most of the reported examples of dimeric muscle-type [2]rotaxanes are constituted by crown ethers,[14] cyclodextrins[15] or cyclobis(paraquat-*p*-phenylene) rings,[16] among others.[17] Usually, this kind of compounds are obtained by self-recognition of a lariat-type compound followed by a stoppering step. Interestingly, the dynamic covalent self-assembly of lasso and [*c2*]daisy chain rotaxanes wholly made from peptides have been recently described.[18] To our knowledge, the synthesis of multistation [c2]daisy chain rotaxanes via self-templating clipping approach has not been reported to date.

We previously described the synthesis of a series of lasso-like isomers of benzylic amide [1]rotaxanes (**1a-c**), built through a two-component clipping protocol (Fig. 1, left).[19] The entwined **1a-c** were prepared by a (1 + 1) coupling of an acyclic diamine having a templating arm with isophthaloyl dichloride. Intriguingly, other interlocked compounds with higher complexity resulting from competitive coupling reactions could not be detected. We hypothesized that the low solubility and thus, precipitation of the potential supramolecular precursors could prevent the formation of more complex structures. Herein, we report our efforts for preparing a multistation [*c2*]daisy chain rotaxane through a unprecedented double clipping reaction which competes with the [1]rotaxane formation (Fig 1).

We first attempted the clipping reaction of the self-templating diamine **2** with isophthaloyl dichloride by using different $CHCl_3/CH_3CN$ mixtures, aiming to increase the solubility of the potential intermediates (see ESI† for further details). Under these conditions, [1]rotaxane **1a** was obtained in low yields (4-7%) as the unique compound. Although the mass of a dimeric species was detected in the reaction mixture by ESI-MS, no other interlocked product could be isolated from this reaction. Alternatively, we envisioned that the incorporation of a 5-(*tert*-butyl) group at the dichloride benzene ring could increase the solubility of the key self-templating intermediate which could enhance in turn the outcome of the clipping reaction. By employing 5-(*tert*-butyl)isophthaloyl dichloride as a reactant, this (1 + 1) coupling reaction ([**2**] = 1.1 mM) afforded the 42-membered lasso **3** in a yield (22.1%) (Scheme 1, Table 1) more than four times higher than that obtained for the unsubstituted subrogates **1**.

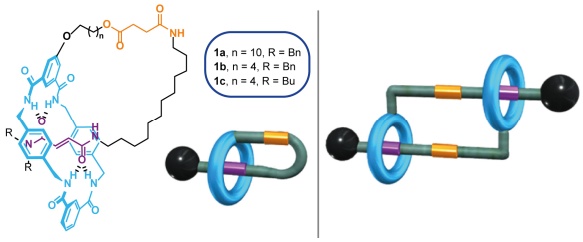

Fig. 1 Lasso [1]rotaxanes **1a-c** (left)[19] and cartoon representation of the target interlocked [*c2*]daisy chain rotaxane (right).

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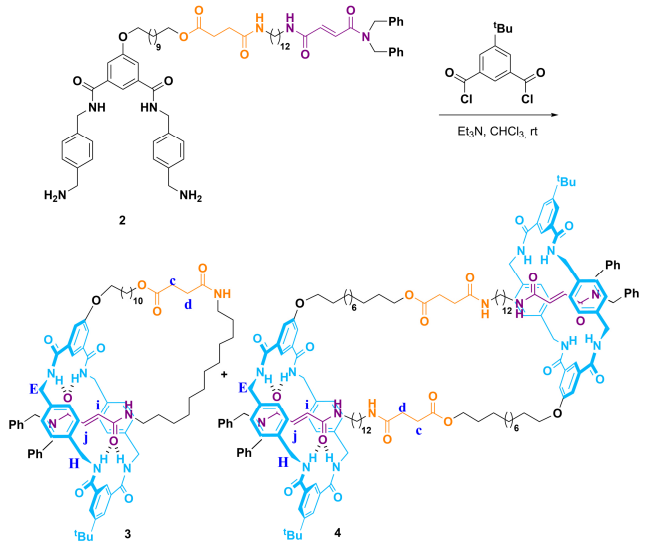

Scheme 1 Synthesis of the benzylic amide macrocycle-based lasso **3** and [*c2*]daisy chain rotaxane **4** *via* competitive clipping reactions.

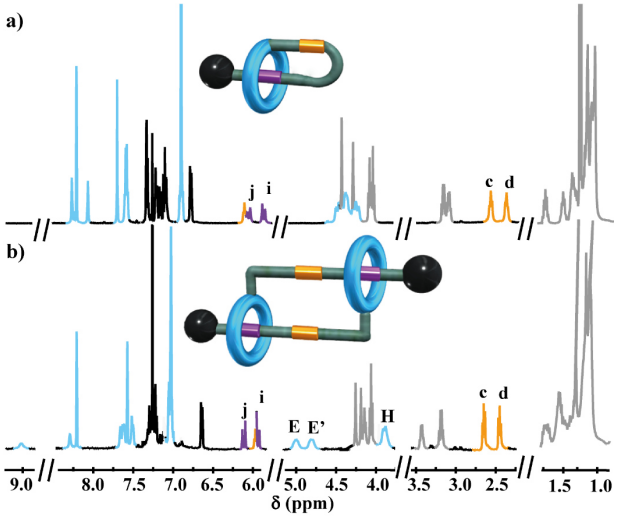

Fig. 2 Partial ^{1}H NMR spectra (401 MHz, $CDCl_3$, 298 K) of (a) lasso **3** and (b) [*c2*]daisy chain rotaxane **4**. Lettering shown in Scheme 1.

In this experiment, traces of a dimeric product, which could not be isolated from the reaction crude, were detected by ESI-MS (Table 1, entry 1).[20] We next hypothesised that the entropically unfavoured formation of higher order species would be assisted by increasing the concentration of reactants in solution. Delightfully, by starting from a 2.2 mM solution of diamine **2** (Table 1, entry 2) a new product could be isolated in 0.4% yield, which turned out to be the 84-membered cyclic [2]rotaxane **4**. Under these experimental conditions, the yield of the lasso **3** was considerably reduced to a value of 16.3%. Encouraged by these results, we sequentially increased the concentration of **2**. Thus, a 4.4 mM solution of acyclic diamine **2** (Table 1, entry 3) led to the [*c2*]daisy chain rotaxane **4** in 1.2% yield. Finally, the ratio of [2]rotaxane:[1]rotaxane (**4:3**) could be increased up to 1:1.4 with a 8.8 mM solution of **2.** Under these conditions the yield of **4** rised up to 3.1% (Table 1, entry 4), more than thirty times higher than that obtained when the most dilute solution of **2** is employed (Table 1, entry 1).[21] Unfortunately, we were not able to obtain any type of interlocked products by using higher concentrations of diamine **2** (Table 1, entry 5).[22] Note that an increase in the concentration of **2** leads to a reduction of the overall yield of both mechanically interlocked compounds through the irreversible formation of multiple amide bonds.

Table 1 Yields[a] of lasso **3** and [*c2*]daisy chain rotaxane **4** by starting from different concentrations of the self-templating diamine **2**.[b]

Entry	[2] (mM)	Yield of 3 (%)[a]	Yield of 4 (%)[a]	4:3
1	1.1	22.1	-	0:1.0
2	2.2	16.3	0.4	1:40.8
3	4.4	9.9	1.2	1:8.3
4	8.8	4.4	3.1	1:1.4
5	17.6	-	-	-

[a] Average yields of isolated product obtained from two independent reactions. [b] In all cases, equimolar amounts of **2** and diacid dichloride were used.

Spectroscopic data of **3** and **4** reveal the threading of the pendant arm through the assembled benzylic isophthalamide macrocycle. However, their unambiguous identification on the basis of their ^{1}H and ^{13}C spectra turned out to be futile due to their analogous patterns of resonances (Fig. 2). Indeed, as we expected, both products adopt extended conformations in which the macrocycles are sitting over the fumaramide stations. As a consequence, the resonances corresponding to the olefinic protons, H_i and H_j, are downshifted in comparison to that of the *N*-Boc protected precursor of **2**.[19] The methylene protons of the benzylic amide macrocycles in **4**, H_E and H_K, resonate as independent broad singlets (Fig. 1b). This fact indicates restricted rotation of the amide macrocycles in the [*c2*]daisy chain rotaxane, contrary to that observed for the lasso **3**. The signals attributable to the succinamide stations, H_c and H_d, appear at nearly identical chemical shifts compared to those of unthreaded precursors.[19] The symmetrical ^{1}H NMR of **4** suggests that this dimeric species is cyclic, ruling out the possibility of a linear [*a2*]daisy chain.

Diffusion measurements are effective to estimate molecular size and thus, to differentiate between products of different orders. The unambiguous identification of **3** and **4** was possible by determining their diffusion coefficients (*D*).[23] Therefore, we performed NMR diffusion measurements on solutions of **3** and **4** in $CDCl_3$ at 298 K (see ESI† for experimental details). A graphical representation of the intensity changes $ln(I/I_o)$ as a function of G^2 (Fig. 3) shows different slopes for [1]rotaxanes (**1a-c** and **3**) and the dimeric interlocked product **4**, confirming their different dimensions. Moreover, the ratio between the *D* values of **3** (D = 5.04 $m^2 \cdot s^{-1}$) and **4** (*D* = 3.74 $m^2 \cdot s^{-1}$) is 1.35 which correspond to an approximate 2:1 mass ratio (see ESI† for a more detailed discussion).[24] The hydrodynamic radius estimated from the *D*

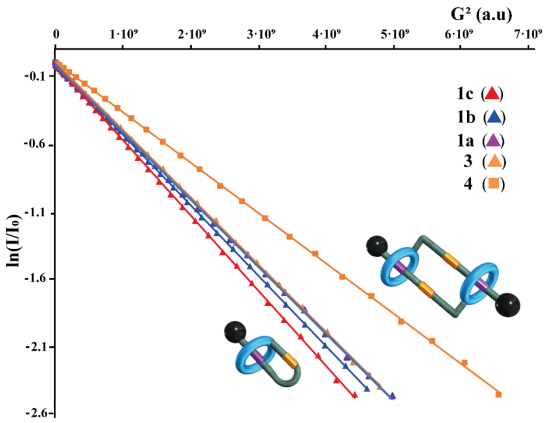

Fig. 3 NMR diffusion experiments (600 MHz, 298 K, $2{\cdot}10^{-3}$ M in $CDCl_3$) of **1c** (▲), **1b** (▲), **1a** (▲), **3** (▲) and **4** (■). Plots of the observed intensity changes $\ln(I/I_o)$ as a function of G^2 (arbitrary units) showing the different decays depending on their translation rates and thus, on their molecular sizes (see ESI).

value of **3** by using the Stokes-Einstein equation[25] (7.8 Å) is in agreement with the size of the molecular lasso and similar to that of the previously reported [1]rotaxanes **1a-c** (7.7-6.9 Å).[19] Accordingly, the value of the hydrodynamic radius of **4** (10.5 Å) supports its larger size.

A energy-minimized model of the interlocked compound **4** computed at the Molecular Mechanics MM2 level reveals the extended form of the side arms.[26] The two olefinic binding sites are surrounded by the macrocycles with distorted chair conformations (Fig. 4, below) similar to the previously reported X-ray structure of the [1]rotaxane **1b** (Fig. 4, above).[19] The radius calculated from the modelized structure (9.1 Å) is in fairly good agreement with the hydrodynamic radius of **4** (10.5 Å), determined from the diffusion coefficient. We attribute the difference between these two values to the elongated and hollow shape of **4** in conjunction with solvation effects.[25]

Finally, we tested the behaviour of the [*c2*]daisy chain rotaxane **4** as a molecular muscle. The photoisomerization of the fumaramide station to a maleamide one would afford a light-driven exchange between the extended (macrocycles placed over the fumaramide stations) and the contracted (macrocycles sited over the succinamide stations) forms of the rotaxanated species, mimicking the sarcomere motion observed in Nature.

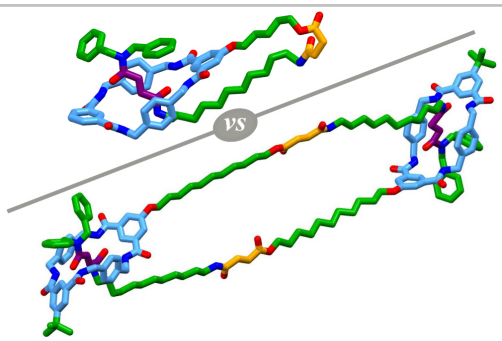

Fig. 4 Side-on view of a capped-stick model of the X-Ray structure of the benzylic isophthalamide lasso **1b** (above),[19] and computed model of [*c2*]daisy chain **4** (below). Hydrogen atoms omitted for clarity.

Despite different irradiation sources, dilution conditions and photosensitizers were used, only complex mixtures of unconsummed (*E,E*) as well as isomeric (*E,Z*) and (*Z,Z*) isomers of **4** resulted probably due to the fact that the common photostationary state of the station fumaramide:maleamide is roundabout 40:60 (in DCM).[27] Even though, this example can be considered as the first approach for the development of rotaxane molecular muscles incorporating two Leigh-type tetralactam macrocycles.

In summary, the assembly of a lasso and a [*c2*]daisy chain rotaxanes have been obtained through a fumaramide-templated clipping competitive reactions in a single step, involving 5-(*tert*-butyl)isophthaloyl dichloride and an isophthalamide-based diamine bearing a templating side arm. The daisy chain:lasso ratio was controlled by adjusting the dilution conditions of the multicomponent clipping reaction and the solubility of the self-templating intermediate diamine. This methodology led to the formation of a large 84-membered [*c2*]daisy chain. Diffusion NMR measurements allowed the unambiguous characterization of the interlocked systems. These results pave the way for the use of this type of scaffold in the development of photoresponsive muscles.

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Conflicts of interest

There are no conflicts to declare.

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