Multivalent molecular shuttles. Effect after increasing the number of centers in switchable catalysts.

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Abstract: A family of three molecular shuttles based upon ammoniun/triazolinium salt motifs having one, two and three catalytic centers were prepared along with their corresponding non-interlocked threads. The switching process for all rotaxanes was tested in an *in situ* procedure in solution. Furthermore, their capability of performing organocatalysis was carried out with two Michale-type reactions by iminium activation in order to know whether increasing the number of catalytic centers presented in the same organocatalytic shuttle is a decisive factor to improve their working processes or not if compared with single active site organocatalytic shuttles under the same conditions.

Introduction

Rotaxanes incorporating catalytic centers in their structure have attracted the attention of many authors in this decade [1] demonstrating their suitability as an effective reaction field. On the other hand, several switchable catalysts have been developed [2] inspired by how nature can control the rate and outcome of reactions catalyzed by enzymes due to trigger-induced events. [3] Synthetic catalysts able to achieve similar influence in natural processes would become a breakthrough in science.

Switchable catalysts having in their structure rotaxane-based secondary amines are of particular interest, due mainly to their potential activation modes (iminium,[4] enamine[5] and trienamine[6]) and the ease of switching among all potential stations. They are mechanically interlocked architectures whose internal motion can be exploited to control both the rate and outcome of several reactions by shielding and exposing a catalytic center.[7]

Moreover, it's well known that multivalent catalysts based on polymers or dendrimers are generally better than their monovalent counterparts due to the framework connecting them.[8]

In order to advance in the knowledge on these elegant architectures, we found very interesting to synthesize a new family of molecular shuttles with dibenzyl amine stations able to perform several kinds of reactions. The difference among them will be the number of catalytic centers that present in their structure, with the objective to compare they behavior in two typical Michael-type reactions which are well-known to be good benchmarks for comparison purposes.

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Results and Discussion

Synthesis and switching process

All molecular shuttle-based organocatalysts consist of 1, 2 or 3 axles containing dibenzyl ammonium and methyl triazolinium salts as binding sites along with anthracene stoppers (Figure 1). Additionally, they bear 1, 2 or 3 dibenzo-24-crown-8 macrocycles, which is well known to establish very good associations with ammonium salts. [9] Noninterlocked threads analogues were prepared as well for comparing their spectroscopical and chemical properties (Figure 2).

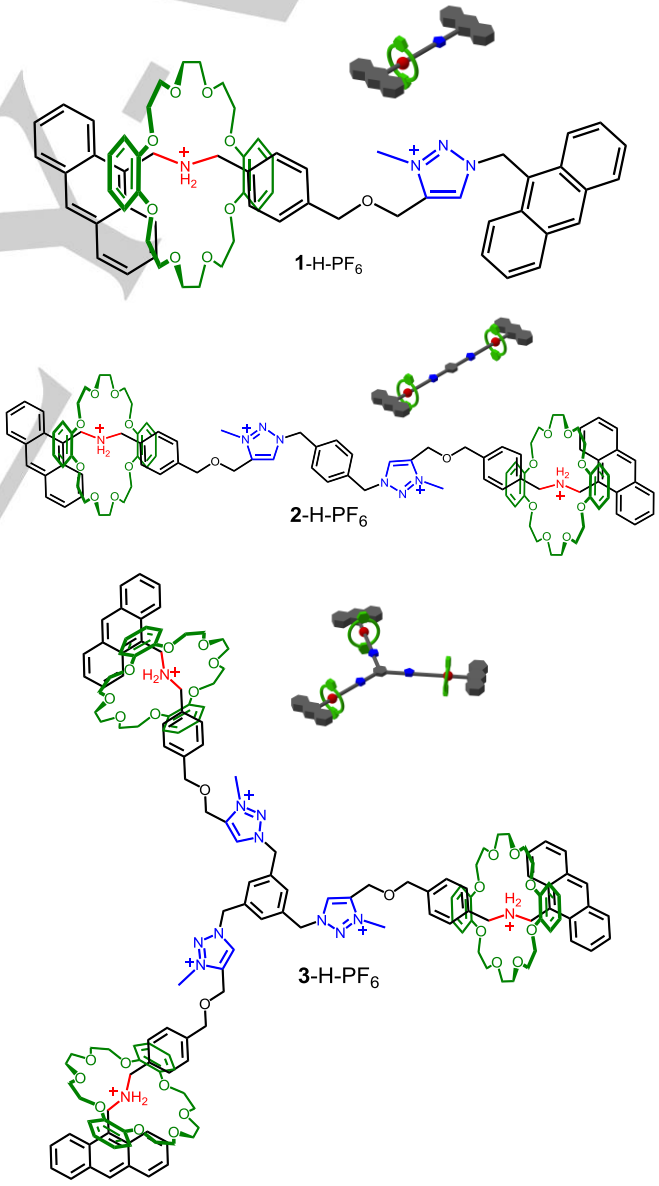


Figure 1. Molecular shuttles with 1, 2 and 3 catalytic sites treated in this study

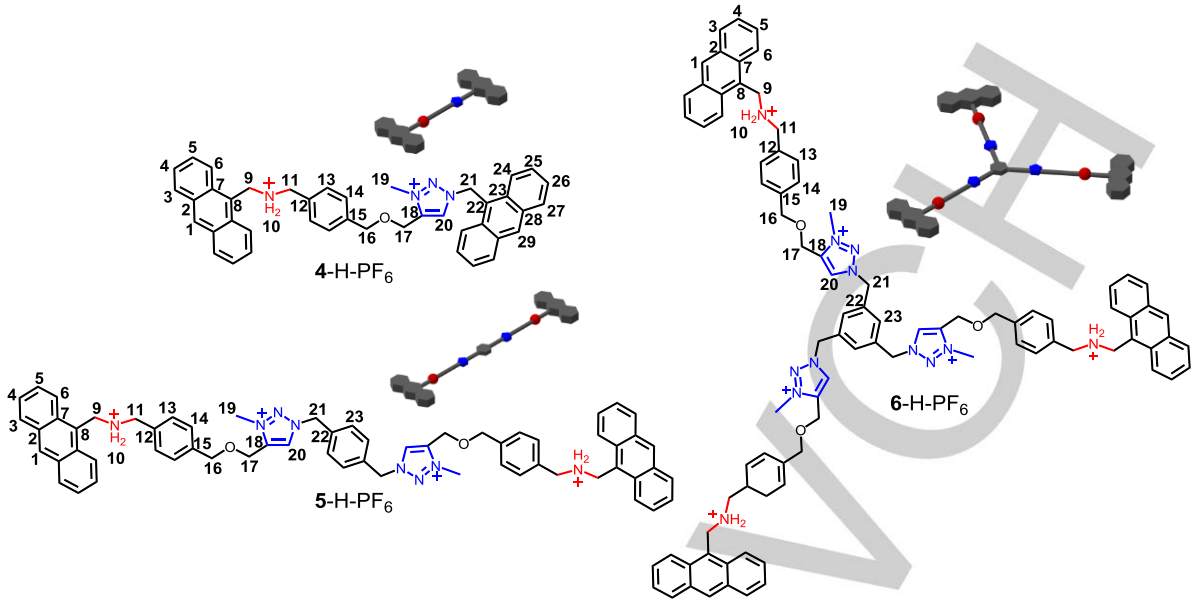
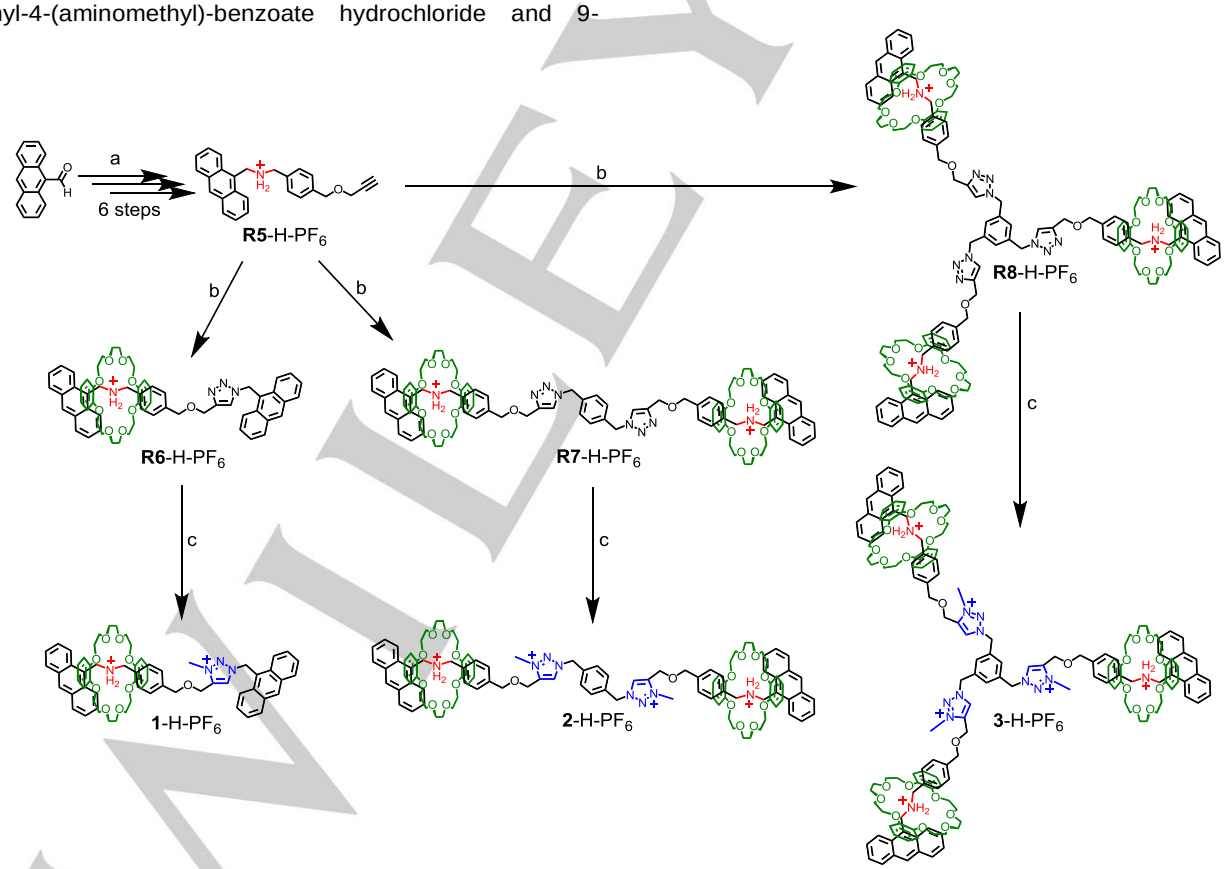


Figure 2. Non-interlocked thread analogues prepared.

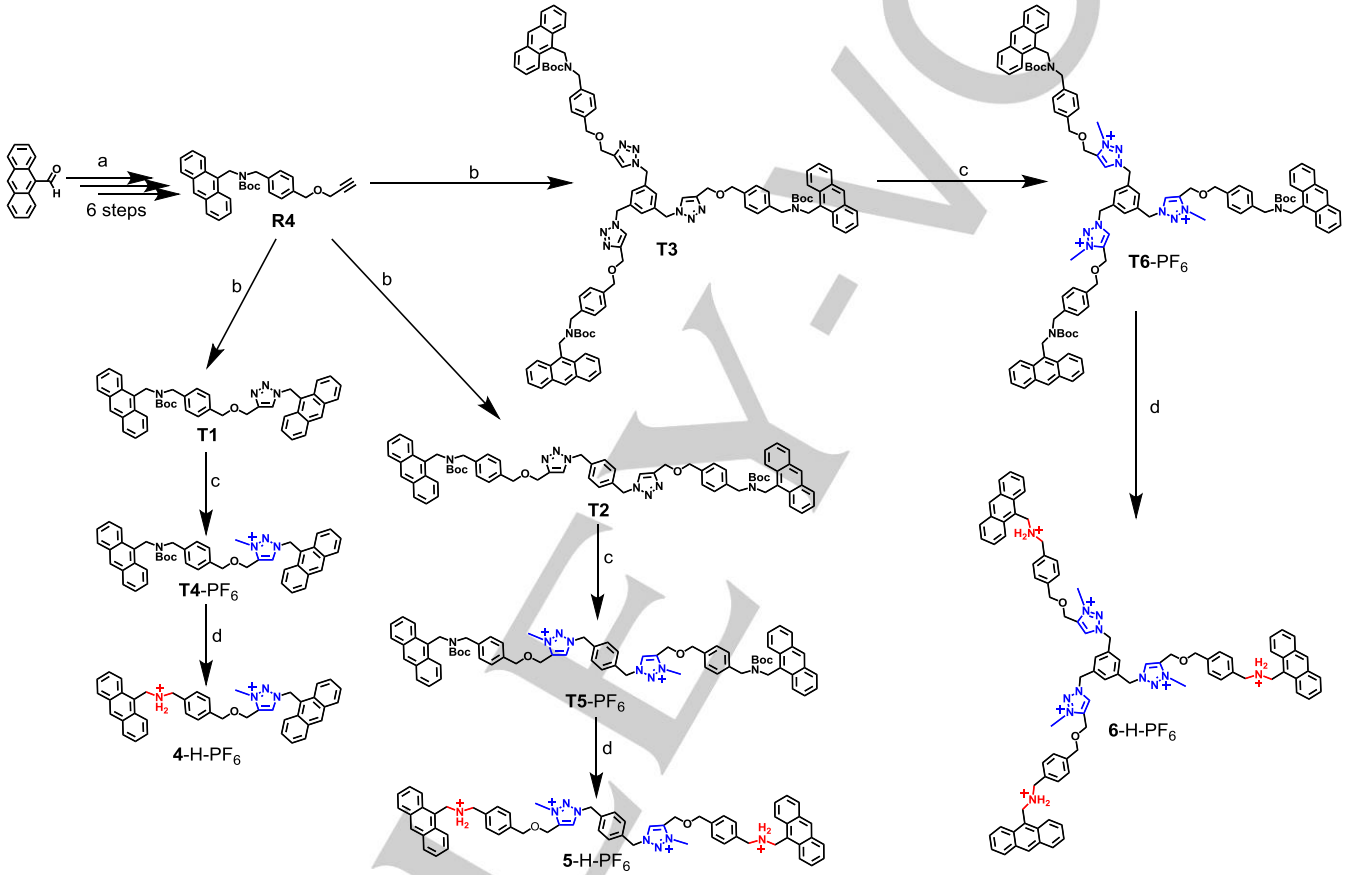
The synthetic procedure for the compounds presented begins with the preparation of ammonium salt **R5**-H-PF_6 (Scheme 1). This product was obtained in 6 steps from methyl-4-(aminomethyl)-benzoate hydrochloride and 9-anthracenecarboxaldehyde with an overall yield of 52%. This molecule is a common building block for all rotaxanes.



Scheme1. Synthesis of shuttles **1**-H-PF_6, **2**-H-PF_6 and **3**-H-PF_6. Reagents and conditions: a) 1. Methyl-4-(aminomethyl)-benzoate hydrochloride, MW; 2. $NaBH_4$, MeOH; 3. $LiAlH_4$, THF, -78ºC; 4. Boc_2O, I_2, MeOH; 5. NaH, propargyl bromide, THF; 6. CF_3CO_2H, NH_4PF_6, H_2O/DCM. b) DB24C8, 9-(azidomethyl)anthracene, 1,4-bis(azidomethyl)benzene or 1,3,5-tris(azidomethyl)benzene, $[Cu(NCMe)_4]PF_6$, 2,6-lutidine, DCM. c) 1. Me_3OBF_4; 2. NH_4PF_6, H_2O/DCM.

The strategy to obtain the threaded compounds relies on a well-known self-assembly method: the macrocyclic polyether is captured by the ammonium salt in solution followed by CuAAC (Copper(I)-catalyzed Azide-Alkyne Cycloaddition) "click" reaction[10] between the terminal alkyne and an azide functionalized compound. Finally, the triazole just formed was methylated in order to create the second binding site (Scheme 1).[11]

The preparation of non-interlocked thread analogues was very similar, but in these cases the amine was maintained protected until the final step (Scheme 2).[12] This synthesis starts with the cyclization in **R4** instead of **R5**-H-PF_6 with the suitable azide, followed by triazole methylation and a final deprotection step. It must be noted that these compounds are less soluble in common organic solvents and generally less stable than their rotaxane counterparts, providing the first evidences of the importance of ammonium salts encapsulation.



Scheme 2. Synthesis of noninterlocked threads **4**-H-PF_6, **5**-H-PF_6 and **6**-H-PF_6. Reagents and conditions: a) 1. Methyl-4-(aminomethyl)-benzoate hydrochloride, MW; 2. $NaBH_4$, MeOH; 3. $LiAlH_4$, THF, -78ºC; 4. Boc_2O, I_2, MeOH; 5. NaH, propargyl bromide, THF. b) 9-(azidomethyl)anthracene, 1,4-bis(azidomethyl)benzene or 1,3,5-tris(azidomethyl)benzene, $[Cu(NCMe)_4]PF_6$, 2,6-lutidine, DCM. c) 1. Me_3OBF_4; 2. NH_4PF_6, H_2O/DCM. d) CF_3CO_2H, NH_4PF_6, H_2O/DCM.

Up to date, the switching process in this kind of compounds has been attempted in many ways, being the best choice washing briefly the organic solution containing the molecular shuttle with an aqueous solution of NaOH (1M),[7] followed by typical work-up. Nevertheless, this method cannot be considered as a true on/off process because it's never made *in situ*, involving a separation procedure. Our method is a real on/off switching process, carried out entirely *in situ* without any purification step. Thus, this method was applied as follows: 1.1 eq. per binding site of NaOH dissolved in D_2O (1M) was added to a solution of the rotaxane in acetone-d6 under vigorous stirring and a ^1H NMR spectrum was recorded after a few minutes. This media is basic enough to deprotonate the ammonium salt yielding the amine, which is a worse binding site than the triazolinium salt forcing the macrocycle to move along the axis to interact with the second station. The addition of 1.1 eq. per binding site of CF_3CO_2H reprotonates the amine, making it again preferable to establish strong intermolecular interactions for the crown ether recovering the initial position. The role of anthracene moieties is to prevent the undesired dethreading because they are bulky enough.[13]

Although this method described above seems to be more valuable, is not definitive, since the concentration of dissolved salts (sodium trifluoroacetate in this case) is increased as the successive switching cycles are carried out, as well as the amount of HDO, severely complicating proton spectra.

In the case of **1**-H-PF_6, the set of signals corresponding to the benzylic protons (H_9 and H_{11}, red signals in Figure 3) next to the ammonium salt are broadened and downfield shifted if compared to those in the non-interlocked compound **4**-H-PF_6 (see Supporting Information). This confirms strong hydrogen bonding between macrocycle and the ammonium salt in the axle.

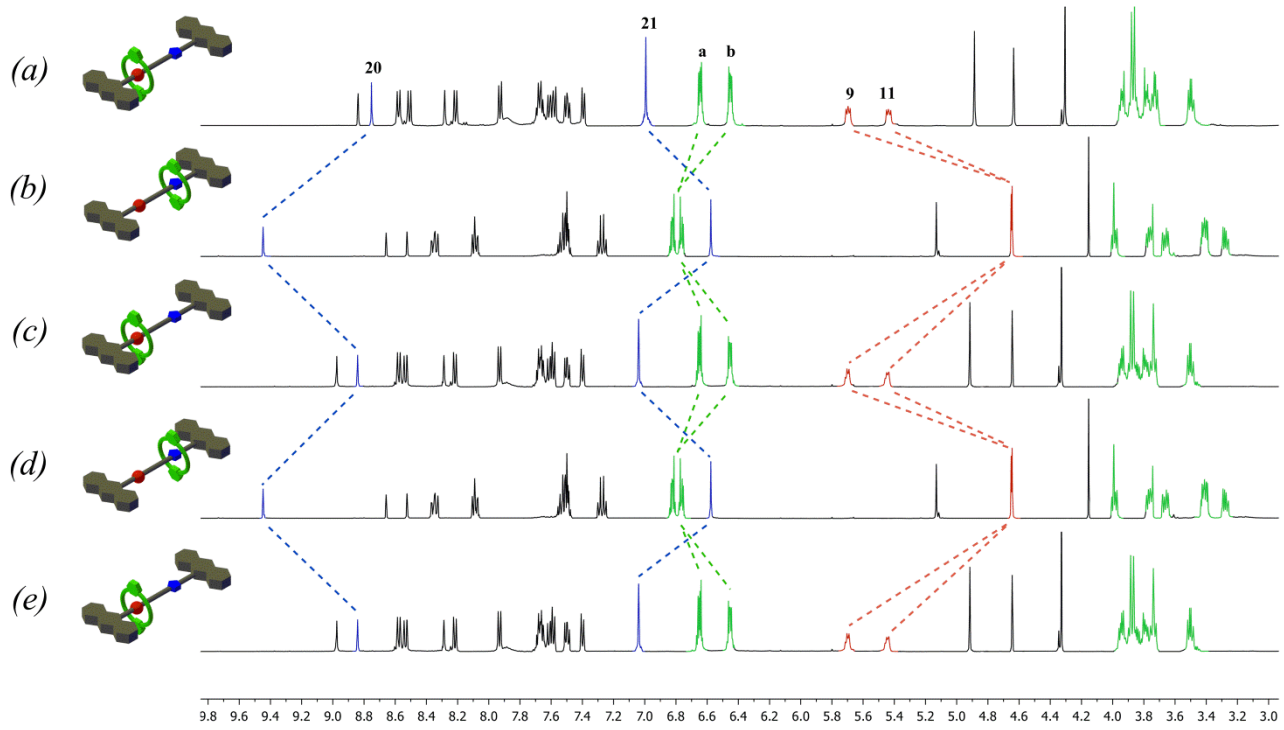


Figure 3. ^{1}H-NMR spectra (500MHz, acetone-d6) of [2] - rotaxane switched 2 times. (a) **1**-H-PF_6; (b) **1**-PF_6; (c) **1**-H-PF_6-CF_3CO_2; (d) **1**-PF_6; (e) **1**-H-PF_6-CF_3CO_2.

Moreover, their relative position is observed in NOESY spectrum as well (Figure 4, left), where correlation cross peaks can be observed between CH_2 macrocycle signals and all nuclei next to the ammonium station in the axle showing the spatial proximity of both fragments.

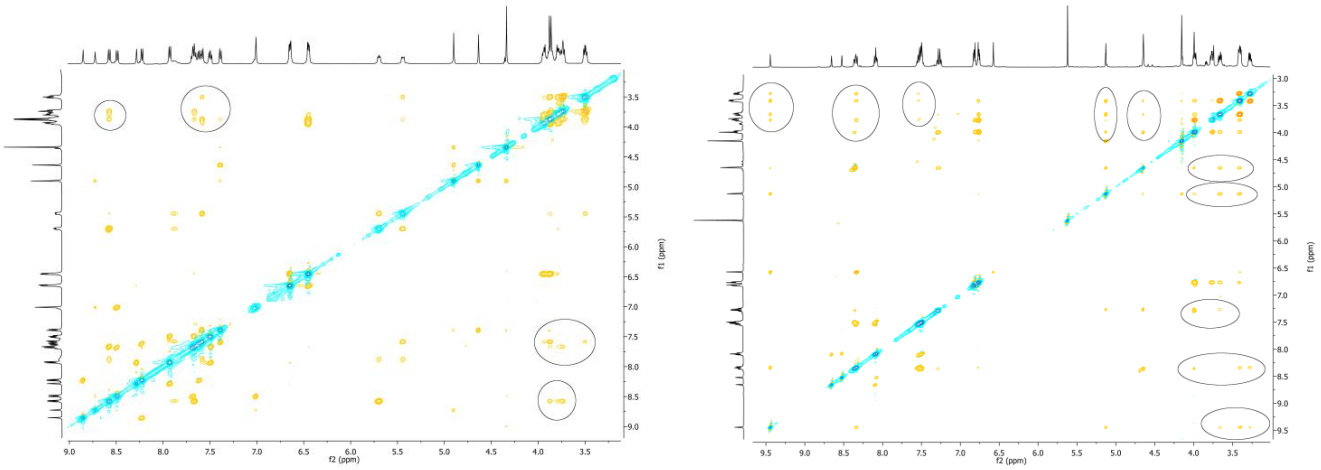


Figure 4. NOESY spectrum (500MHz, acetone-d6) of **1**-H-PF_6 and **1**-PF_6. depicting in circles NOE correlations between the axle and macrocycle mechanically bonded.

When switched (*b* in Figure 3), a set of signals are modified substantially along with other minor changes. The biggest changes are observed, and expected, for the protons closer to shuttle stations. Thus, the most remarkable are the benzylic CH_2 groups next to ammonium salt. They suffer an upfield shift of $\Delta\delta H_9$=-1.05 and $\Delta\delta H_{11}$=-0.79. Furthermore, all protons near the triazolinium are shifted being H_{20} and H_{21} the most significant (blue in Figure 3, $\Delta\delta H_{20}$=0.69 downfield and $\Delta\delta H_{21}$=-0.41 upfield, respectively). Every signal corresponding to the macrocycle have changed as well (green signals in Figure 3). Additionally, NOESY spectrum yields correlation cross peaks between CH_2 macrocycle signals and all nuclei next to the triazolinium station confirming their relative situation.

After reprotonation, the ring recovers its initial position as expected, but the spectrum is not exactly the first one recorded (*c* in Figure 3). Several signals have been slightly changed when compared to the original one.[14] This effect is not surprising, it's well known that the change of counter ion affects the chemical environment of nearby nuclei,[15] in fact, the triazolinium salt/macrocyclic ether couple is used to bind anions in solution.[16] The switching process can be performed several times without appreciable signs of decomposition (*d* and *e* in Figure 3).

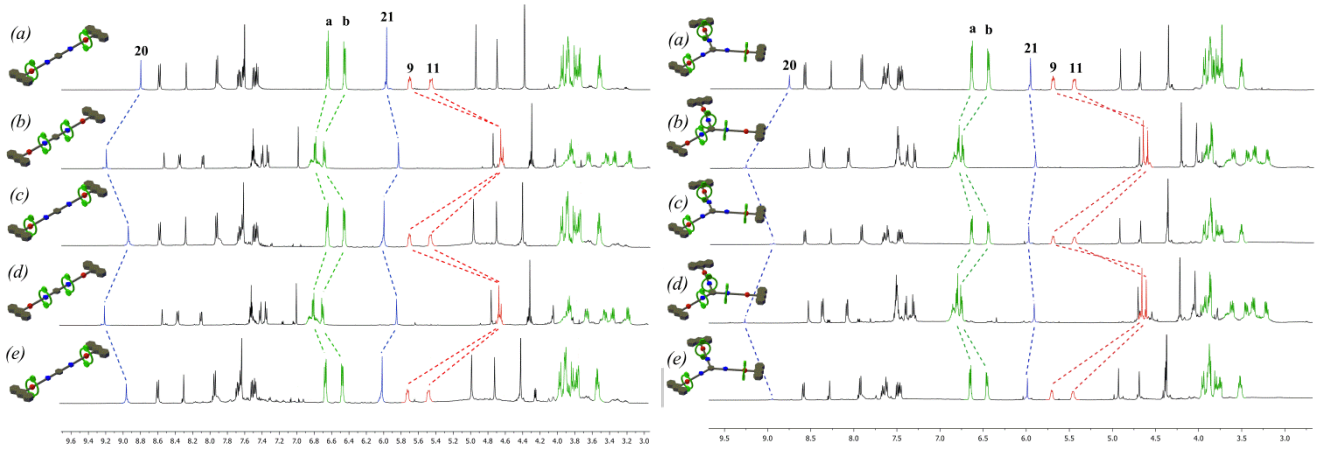
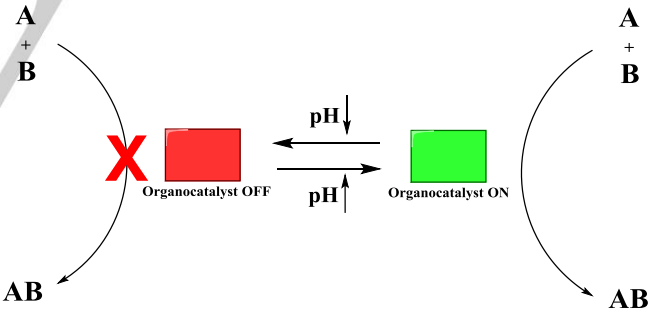


Figure 5. ^{1}H-NMR spectra (500MHz, acetone-d6) of [3] - rotaxane switched 2 times (left). (a) **2**-H-PF_6; (b) **2**-PF_6; (c) **2**-H-PF_6-CF_3CO_2; (d) **2**-PF_6; (e) **2**-H-PF_6-CF_3CO_2; and ^{1}H-NMR spectra (500MHz, acetone-d6) of [4] - rotaxane switched 2 times (right) (a) **3**-H-PF_6; (b) **3**-PF_6; (c) **3**-H-PF_6-CF_3CO_2; (d) **3**-PF_6; (e) **3**H-PF_6-CF_3CO_2.

This new switching procedure for **1**-H-PF_6 was applied for the other shuttles. ^{1}H-NMR spectra of **2**-H-PF_6 (Figure 5, left) and **3**-H-PF_6 (Figure 5, right) are very similar to **1**-H-PF_6, but they show lower number of signals due to their high symmetry. When switched, the variation in chemical shifts was found to be analogous to that observed for the previous shuttle, but some signals corresponding to the macrocycle got broadened showing an expected lack of freedom in Brownian motion due, possibly, to the mutual proximity of the macrocycle ethers. Additionally, in **3**-H-PF_6, the hydrogen of the triazolinium salt (H_{20}) was observed to undergo exchange with deuterium just after the addition of the first aliquot of NaOH 1M in D_2O, showing the acidity of this proton. This effect was then observed for the other molecular shuttles if stored in solution for a long time.

Catalytic behavior

Once observed the control over the position of the macrocycles in all molecular shuttles, two sets of catalytic tests were carried out. Both are Michael-type reactions which can be catalyzed by secondary amines *via* iminium activation yielding an adduct after C-S or C-C bond formation.



Scheme 3. Typical pH-based switchable organocatalyst operation.

According to the regular performance of ammonium-triazolinium switchable organocatalysts, their procedure works as follows: when the catalytic centre is covered by the macrocycle, no reaction should be observed at all because that centre is blocked and reactants are not allowed to access the site (Scheme 3, left), but, if exposed, catalysis takes place (Scheme 3, right).

The first reaction was already reported by Leigh *et al.*[7a] between trans-cinnamaldehyde and 1H,1H,2H,2H-perfluorodecanethiol (Table 1). It was catalyzed by a molecular shuttle by switching the rotaxane through washing with aqueous NaOH. We performed the same

procedure but switching the rotaxanes with the protocol described above (with near stoichiometric amount of NaOH in D_2O) in order to avoid the possible rate enhancement due to deprotonation of the thiol by the excess of sodium hydroxide (Table 1).

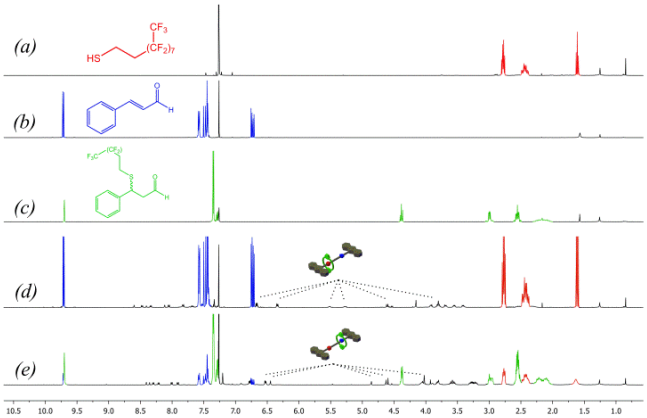


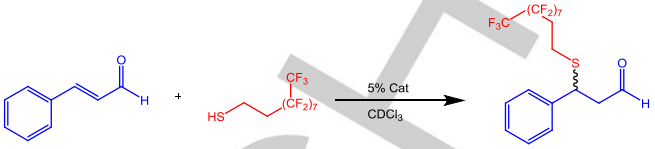
Figure 6. ^{1}H-NMR spectra (500MHz, $CDCl_3$) for the first reaction implying **1**-H-PF_6 as a catalyst, being (a) 1H,1H,2H,2H-perfluorodecanethiol, (b) *trans*-cinnamaldehyde, (c) pure adduct obtained, (d) reaction mixture with **1**-H-PF_6 inactive and (e) reaction mixture with **1**-PF_6 active when maximum conversion achieved.

As expected, when the shuttles are in inactive position (*d* in Figure 6), meaning that the ether is attached to the ammonium station, no reaction is observed at all. On the other hand, when switched to the triazole position, the catalytic site is exposed and the signals corresponding to the adduct appear (*e* in Figure 6). All shuttles follow the behavior described above. This experiment was carried out with non-interlocked threads in both protonated and deprotonated states for comparison.

Thus, entries 1-3 in table 1 show clearly that shuttles in inactive position cannot catalyze the reaction. But, if switched (entries 4-6), the reaction takes place reaching a conversion of 85% for the best rotaxane, **3**-PF_6. Interestingly, the initial rate seems to be very high, although it gets slower until the maximum conversion is achieved. Double rotaxane, **2**-PF_6 (entry 5), is better catalyst than single rotaxane, **1**-PF_6; and triple rotaxane, **3**-PF_6, is the best one (entry 6).

Regarding non-interlocked threads, we found the same trend for **4**-PF_6, **5**-PF_6 and **6**-PF_6 (entries 11 - 13), which are the switched counterpart of active rotaxanes, meaning that they have dibenzyl amines as catalytic sites. Each of them resemble the initial conversion observed, respectively. However, the case of entries 8-10 (**4**-H-PF_6, **5**-H-PF_6 and **6**-H-PF_6) is very different. These compounds are the counterparts of inactive rotaxanes, meaning that they have ammonium salts as catalytic centers. Even in that state, the reaction occurred as well, in contrast to the behavior observed for rotaxanes in inactive position (entries 1-3). This evidence shows the importance of the catalytic center encapsulation because non-interlocked threads are still capable of performing catalysis even in a protonated state, but if this ammonium salt is covered by the macrocycle, the shuttle cannot perform catalysis, the reaction is fully stopped.

Table 1. Results observed in the first reaction.[a]



Entry	Compound	Conversion after 30 minutes[b]	Conversion after 4h[b]
1	**1**-H-PF_6 [c]	0	0
2	**2**-H-PF_6 [c]	0	0
3	**3**-H-PF_6 [c]	0	0
4	**1**-PF_6	50	72
5	**2**-PF_6	68	79
6	**3**-PF_6	80	85
7	Dibenzylamine	10	25
8	**4**-H-PF_6 [c]	8	21
9	**5**-H-PF_6 [c]	12	28
10	**6**-H-PF_6 [c]	20	35
11	**4**-PF_6	45	70
12	**5**-PF_6	65	75
13	**6**-PF_6	74	83

[a] Summarized conditions for all entries: trans-cinnamaldehyde (0.14mmol), 1H,1H,2H,2H-perfluorodecanethiol (0.168mmol). Catalyst load: 5% mol. 1.4mL of $CDCl_3$ and 1.2 eq. for each catalytic site of NaOH.
[b] Determined by integration of CH_2 signals in ^{1}H-NMR spectra. Given in %.
[c] These compounds were not treated with NaOH.

Nevertheless, all these dumbell-shaped molecules are generally better catalysts than dibenzylamine under the same conditions (entry 7), confirming that their structure enhance catalysis behavior in their active sites.

A similar protocol was applied for the second reaction in which the nucleophile is diethyl malonate (Table 2). The reaction did not proceeded well in chlorinated solvents, so we had to switch to a solvent in which the reaction occurred and the rotaxanes could be soluble at the same time. The best choice was deutered acetonitrile.

Total conversion for **3**-PF_6 could be achieved in this case in the presence of excess of aldehyde, but the reaction times are notably longer at room temperature. Again, when shuttles are protonated, encapsulation takes place preventing catalysis (*d* in Figure 7). If switched, catalysis occur (*e* in Figure 7).

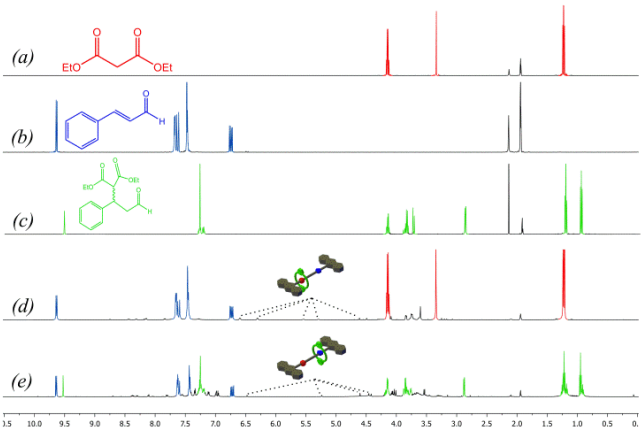
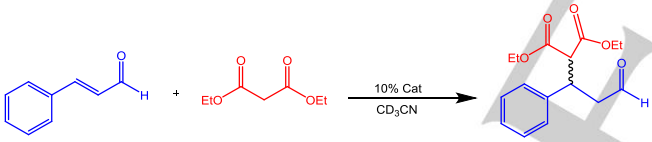


Figure 7. ^{1}H-NMR spectra (500MHz, CD_3CN) of the second reaction, being (a) diethyl malonate, (b) *trans*-cinnamaldehyde, (c) pure adduct obtained, (d) reaction mixture with **1**-H-PF_6 inactive and (e) reaction mixture with **1**-PF_6 active when maximum conversion achieved.

Entries 1-3 in table 2 show no catalysis for shuttles with the ammonium salt covered by macrocycle. The initial conversions of switched shuttles (entries 4-6) resemble the same pattern found for the first reaction, showing the best performance for triple [4]-rotaxane, **3**-PF_6. Their corresponding non-interlocked threads (entries 11-13) behave in a similar way.

Once more, entries 8-9 confirm that these rotaxanes are very good on/off systems because protonated threads are able to perform catalysis, with a similar conversion observed for nonprotonated threads.

Table 2. Results observed in the second reaction.[a]



Entry	Compound	Conversion after 30 minutes[b]	Conversion after 24h[b]
1	**1**-H-PF_6 [c]	0	0
2	**2**-H-PF_6 [c]	0	0
3	**3**-H-PF_6 [c]	0	0
4	**1**-PF_6	5	68
5	**2**-PF_6	13	80
6	**3**-PF_6	20	100
7	Dibenzylamine	12	65
8	**4**-H-PF_6 [c]	5	32
9	**5**-H-PF_6 [c]	14	45
10	**6**-H-PF_6 [c]	19	80
11	**4**-PF_6	6	65
12	**5**-PF_6	15	75
13	**6**-PF_6	22	100

[a] Summarized conditions for all entries: trans-cinnamaldehyde (0.28mmol), diethyl malonate (0.14mmol). Catalyst load: 10% mol. 1.4mL of CD_3CN and 1.2 eq. for each catalytic site of NaOH.
[b] Determined by integration of aldehyde signals in ^{1}H-NMR spectra. Given in %.
[c] These compounds were not treated with NaOH.

Conclusions

In summary, a set of three pH-based molecular shuttles along with their non-interlocked analogues, bearing ammonium and triazolinium groups as stations for threaded macrocycles, have been prepared and their capability of performing switchable organocatalysis have been tested with two different Michael-type reactions.

The results indicate very interesting insights: first of all, the switching process can be done *in situ* avoiding separation procedures. Secondly, a phenylene or a tripled substituted benzene are enough to link axles in big shuttles since all macrocyclic rings can accommodate in a very crowded situation. Regarding their catalytic behavior, the importance of covering catalytic site is evident because they are very effective in preventing catalysis when macrocycle is situated at the ammonium station. Additionally, all rotaxanes behave better than dibenzyl amine itself under the same conditions. Finally, we found that increasing the number of catalytic centers on the rotaxane is a decisive factor improving their performance as the number of catalytic sites is higher.

Nevertheless, the number of sites is not the only factor to be considered, since other factors must be taken into account, being, for instance, the flexibility of the rotaxanes or their solubility the most important.

These results may open a new line involving the synthesis of better designed multivalent molecular shuttles able to enhance even more their performance as on/off catalysts.

Experimental Section

Detailed experimental procedures, as well as NMR spectra for all final compounds are included in the Supporting Information.

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Keywords: molecular shuttles • mechanically interlocked architectures • organocatalysis • rotaxanes

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