ARTICLE

Modulating the Catalytic Activity by the Mechanical Bond: Organocatalysis with Polyamide [2]Rotaxanes bearing a Secondary Amino Function at the Thread

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The modulation of the catalytic activity of degenerate succinamide-based [2]rotaxanes by changes at their macrocyclic component is disclosed herein. These systems, bearing an acyclic secondary amine function at the thread as the active site and incorporating different polyamide macrocycles, were evaluated as organocatalysts in an iminium- and enamine-type processes. The results of kinetic studies clearly show a drastic variation of their catalytic efficiency, which apparently correlated with the electronics and dynamics of the entwined macrocycle.

Introduction

The integration of mechanically interlocked molecules (MIMs)[1] into the catalyst's toolbox for homogeneous catalysis is attracting significant attention during the last years. Different research groups have disclosed different mechanized systems as either organocatalysts[2] or ligands in metal-catalysed transformations,[3] including their use in asymmetric processes.[4,5] In rotaxane-based catalysts, the possibility of controlling the ring position along the thread by the application of an input enables the design of switchable rotaxane-based catalysts. The bulky macrocycle conceals or exposes the active sites placed at the thread, altering their catalytic capability in terms of activity (ON/OFF),[6] enantio- or diastereoselectivity switching[7] or election between activation modes.[8] Thus, as a general trend, the free threads are usually more reactive than the dampened interlocked systems, although less selective.

Notwithstanding, we have recently found that a series of rotaxane-based organocatalysts bearing a polyamide macrocyclic counterpart showed improved catalytic activities when compared with their non-interlocked threads (Figure 1a).[9] Such interlocked systems, having succinamides as stations and a secondary amine function as the active site, catalyse an iminium-type reaction in high conversion with low catalyst loading, thus showing that the effects of the mechanical bond on the catalyst efficiency are remarkable. The polyamide macrocycle activates the catalysis, probably by the establishment of hydrogen bonds between the amide-NHs of the ring with the substrates[10] as well by the intervention of a zwitterionic iminium intermediate boosted by the mechanical bond.[11]

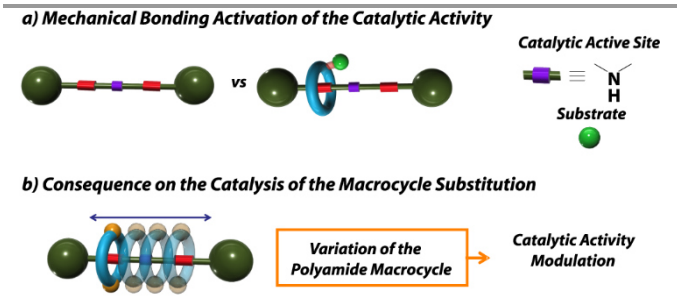

Fig. 1 Effects of the mechanical bond on mechanized aminocatalysts: a) Cooperative activation of the catalysis;[9] b) Modulation of the catalytic activity of rotaxanes by the action of different macrocycles.

For the optimization of an organocatalyst, a fine tuning of the backbone is frequently required. Thus, the activity and/or selectivity can be improved by changing the electronics (by placing electron-withdrawing or donating groups nearby the active center),[12] or the interaction surface (e. g. increasing of π-π interactions),[13] among others. By following a similar strategy, we herein evaluate the capacity of the mechanical bond for regulating the catalytic performance of a range of rotaxane-based organocatalysts by tuning the macrocyclic component (Figure 1b). It is known that the variation of the substitution pattern at polyamide macrocycles alters their electronics and thus the acidity of their amide-NHs.[14] Having this in mind as well the foreseeable influence of the mechanical bond on the efficiency of this type of catalysts, we envisaged that the reaction rates exhibited by these rotaxanes when used as catalysts would be tamed when macrocycles with different electronics are entwined.[15] Here we disclose the results of our studies guided by the lines above and the kinetic experiments we carried out with the aim of correlating the electronics of the ring with the catalytic outcomes.

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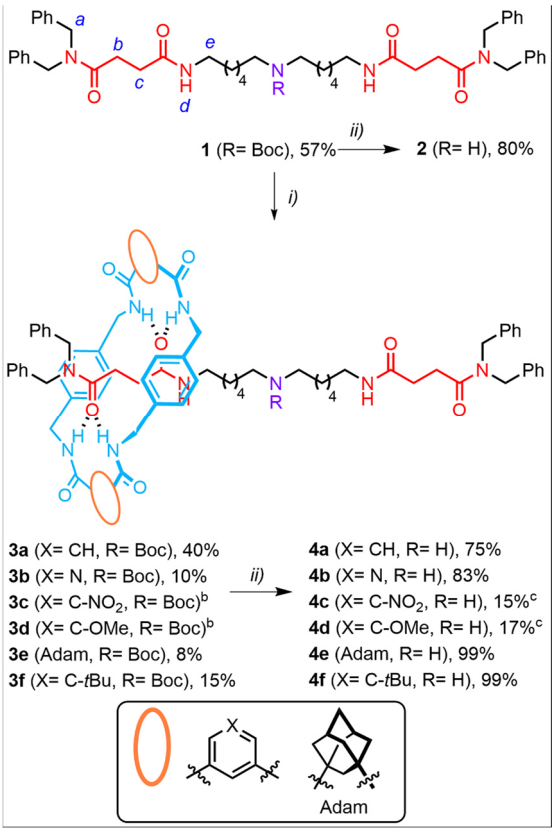
Results and discussion

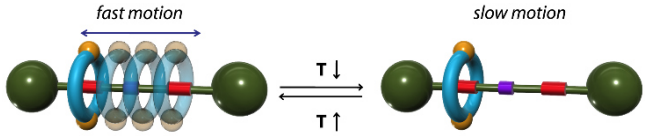
The synthesis of a set of Leigh-type [2]rotaxanes **3a-f** was achieved starting from the *N*-Boc protected thread **1** by following a five-component reaction with *p*-xylylenediamine and the suitable diacyl dichloride (Scheme 1).[9,16] The further high-yielding *N*-Boc deprotection of thread **1** and rotaxanes **3a-f** respectively afforded the active thread **2** and the rotaxanes **4a-f**, ready to be tested as organocatalysts.[17]

With rotaxanes **4a-f** in hand, we first studied the ring-shuttling dynamics between the two identical succinamide stations placed at the threads.[18] The different macrocyclic backbones modify the acidity of the amide-NHs, thus altering the strength of the intercomponent hydrogen bonds between the binding sites of the thread and the ring and, consequently, the internal dynamics of the components.[14] The back and forth motion of the ring along the thread in rotaxanes **4** was analyzed by temperature-dependent ^{1}H-NMR experiments (Table 1, Figures S1-4 and Table S1). At high temperatures, the macrocycle is moving quickly between both succinamide stations and thus an averaged co-conformation is observed by ^{1}H NMR. By decreasing the temperature, the translational motion is gradually reduced. At one point, as a result of a co-conformational freezing, the splitting into two sets of NMR signals occurred in various protons (H_{b+c} and H_e, see Scheme 1 for lettering), corresponding to the two different magnetic



Scheme 1 Synthesis of the interlocked systems **3** and **4**.[a,b,c]. [a]Reaction conditions: i) *p*-xylylenediamine (4 equiv), acyl dichloride (4 equiv), Et_3N (12 equiv), $CHCl_3$, 25 °C, 4h; ii) TFA, $CHCl_3$, 25 °C, 12 h.[b] Not isolated by column chromatography (see SI for further details); [c] Overall yield from thread **1** (2 steps).

Table 1. Kinetic and thermodynamic parameters for macrocycle shuttling obtained from VT-^{1}H NMR spectra of the degenerate [2]rotaxanes **4**.



entry	4	$\Delta\nu$ (Hz)[a]	T_c (K)[b]	k_c (s^{-1})	$\Delta G^{\ddagger}$(kcal·mol^{-1})[c]
1[d]	**4a**	712	278	1581.7	12.2
2	**4b**	578	293	1284.0	13.0
3	**4c**	1120	308	2488.0	12.6
4	**4d**	636	283	1412.8	12.5
5	**4e**	754	248	1674.0	10.8
6	**4f**	706	248	1567.2	10.8

[a] Variation of the frequency of the signals related to the protons of the succinamide functions H_{b+c} (see lettering in Scheme 1). [b] NMR temperature calibration was performed using a pure methanol sample. [c] Calculated value ± 0.2. [d] Data taken from ref 9.

environments of the empty and occupied ones. From the separation of these signals ($\Delta\nu$) at the slow dynamic regime and the coalescence temperature (T_c), the energy barriers ($\Delta G^{\ddagger}$) for the macrocycle shuttling can be calculated (Table 1 and Table S1). We found notorious variation of the calculated energy barriers depending on the structure of the ring. Thus, the model unsubstituted rotaxane **4a**, the adamantane-based **4e** and the ^{t}Bu-substituted system **4f** showed the lower translational energies (Table 1, entries 1 and 5-6), whereas the most electron-deficient macrocycle **4c** showed the highest one (entry 3). The exchange rates of the protons H_e at different temperatures were also calculated by fitting the Lorentzian line of the peak at temperatures higher than T_c, allowing to calculate the exchange constants of each system **4** at 298 K (see ESI, Table S2 and Figures S6-12). The Hammett plot of $\log(k_4/k_{4a})$ (k = exchange rate constant of the protons H_e at 298 K) against the σ_m values of the substituents at the aromatic rings of the macrocyclic moiety indicates a direct correlation between the shuttling dynamics and the electronics (see ESI, Figure S13).

Next, we explored the catalytic activity of the degenerate rotaxanes **4** in an iminium-type transformation,[19] the conjugate addition of acetylacetone **6** to crotonaldehyde **5** (Figure 2). The respective conversion towards the formation of the Michael adduct **7** catalysed by rotaxanes **4** was monitored by ^{1}H NMR spectroscopy (Figures S14-27). In our previous study, we found that the rotaxane **4a** (▲) was a faster catalyst than its thread **2** (●) in this transformation, with a half-life time of $t_{1/2}$ ~ 1.8 h for **4a** and $t_{1/2}$ ~7 h for thread **2** (Figure 2a).[9] Under the same conditions (2 equiv of crotonaldehyde **5**, 1 equiv of acetylacetone **6**, 0.125M, 5 mol% catalyst), the catalytic efficiencies of the rest of rotaxanes **4** were analyzed (Figure 2b). Interestingly, rotaxanes with electron-deficient aromatic groups at the macrocycle, i. e. rotaxane **4b** (pyridine core, ●) and rotaxane **4c** (NO_2 substituted isophthalic moiety, ◆), showed to be the less active catalysts. Rotaxane **4d** (OMe substituted, ■) was also slower than the model catalyst **4a**. In contrast, the adamantane-based rotaxane **4e** (●) and rotaxane **4f** (tBu substituted, ■) exhibited a reactivity similar to that of **4a**.

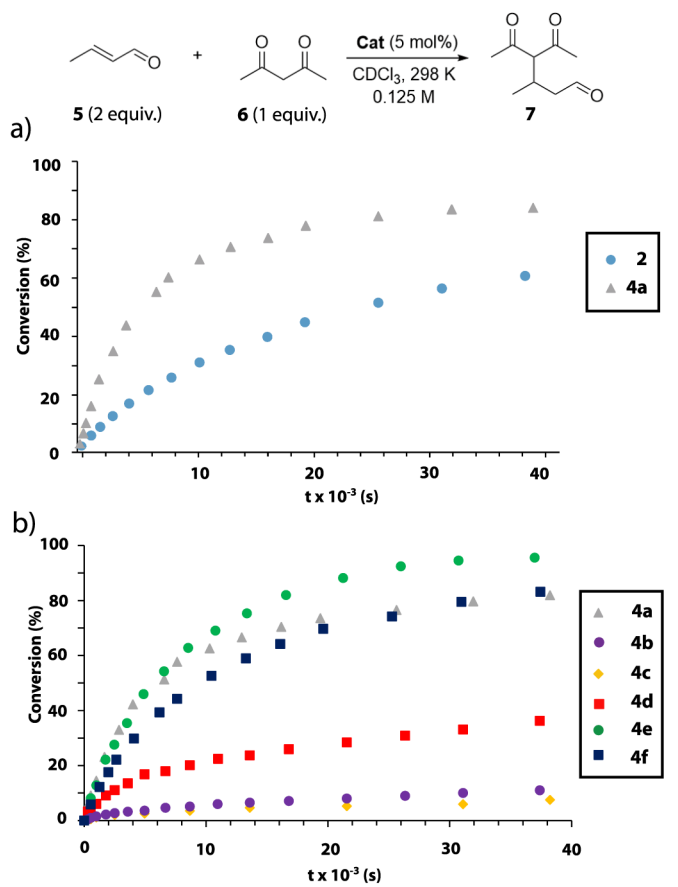


Fig. 2 Plot of conversion (%) *versus* time of the Michael addition of acetylacetone **6** (1 equiv) to crotonaldehyde **5** (2 equiv) catalysed by: a) thread **2** (●) and rotaxane **4a** (▲) (data taken from ref 9); b) rotaxanes **4a** (▲), **4b** (Py, ●), **4c** (-NO_2, ◆), **4d** (-OMe, ■), **4e** (Adam core, ●) and **4f** (-tBu, ■). The conversions were measured during time by ^{1}H NMR (400MHz, 298 K, $CDCl_3$), using CH_2Br_2 as internal standard.

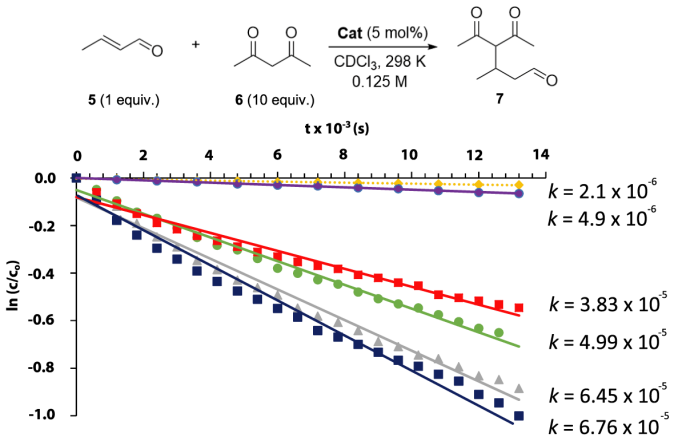


Fig. 3 Plot of $\ln(c/c_0)$ *versus* time for the determination of the rate constants of the Michael addition of acetylacetone **6** (10 equiv) to crotonaldehyde **5** (1 equiv, 0.125M) under pseudo-first-order conditions catalysed by: rotaxane **4a** (▲), **4b** (Py, ●), **4c** (-NO_2, ◆), **4d** (-OMe, ■), **4e** (Adam core, ●) and **4f** (-tBu, ■). The rate constant values (k, s^{-1}) are the average of two independent measurements, with an error of less than 10%.

We also carried out this process under pseudo-first-order conditions (1 equiv. of aldehyde **5** and 10 equiv. of acetylacetone **6**) in order to obtain the respective rates for each rotaxane **4** (Figure 3 and Figures S28-69). The different macrocycles drastically modulate the efficiency of the interlocked systems as catalyst.[21] Under pseudo-first-order conditions, the rotaxane **4f** (^{t}Bu, ■) showed a slightly superior rate (k = 6.76 x 10^{-5} s^{-1}) than the model rotaxane **4a** (▲, k = 6.45 x 10^{-5} s^{-1},) with a $t_{1/2}$ = 2.99 h for **4a** and 2.85 h for **4f**. In contrast, the adamantane-based system **4e** (●) and the MeO-substituted rotaxane **4d** (■) were slightly slower, with a half-life time of $t_{1/2}$ = 4.99 h and 5.32 h, respectively. Finally, the rotaxanes **4b** (pyridine core, ●) and **4c** (nitro substituted, ◆), were almost inactive as catalysts ($t_{1/2}$ = 39.45 h for **4b** and $t_{1/2}$ = 93.27 h for **4c**). Again, the activity of the thread **2** halves that of rotaxane **4a**, almost doubling its half-life time ($t_{1/2}$ = 5.50 h, not showed in Figure 3, see Figure S70).

Interestingly, the same trend was found when the thread **2** and the rotaxanes **4** were tested in the Michael addition of hexanal **8** to *trans*-nitrostyrene **9** towards the formation of the corresponding adduct **10** following an enamine-mediated process[20] (Figure 4, and ESI, Section 6, Figures S72-86). Thread **2** was a slower catalyst than rotaxane **4a**, indicating that the mechanical bond also activates this addition. Moreover, the modulation of the activity is also possible by tuning the entwined macrocycle. Thus, system **4c** (NO_2 substituted) showed to be the slowest catalyst, whereas rotaxanes **4a** (▲), **4e** (●) and **4f** (■) were again the fastest ones.

All these results clearly show that the variation of the macrocyclic counterpart highly influences the catalytic outcomes.[22] Indeed, the Hammett plot of $\log(k_4/k_{4a})$ against the σ_m constants of the substituents at the aromatic rings of the macrocyclic moiety demonstrates a linearity between the catalytic activity and the electronics (ρ = –1.97, R^2 = 0.987) (Figure 5, rotaxane **4e** was excluded in this analysis).[23] This plot

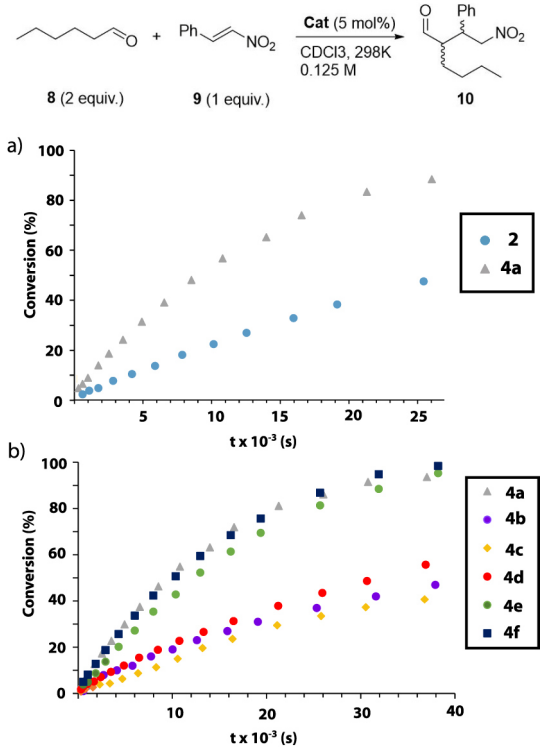


Fig. 4 Plot of conversion (%) *versus* time for the Michael addition of hexanal **8** (2 equiv) to *trans*-nitrostyrene **9** (1 equiv) catalysed by: a) thread **2** (●) and rotaxane **4a** (▲); b) rotaxanes **4a** (-H, ▲), **4b** (Py, ●),**4c** (-NO_2, ◆), **4d** (-OMe, ■), **4e** (Adam core, ●) and **4f** (-tBu, ■). The conversions were measured during time by ^{1}H NMR (400MHz, 298 K, $CDCl_3$), using CH_2Br_2 as internal standard.

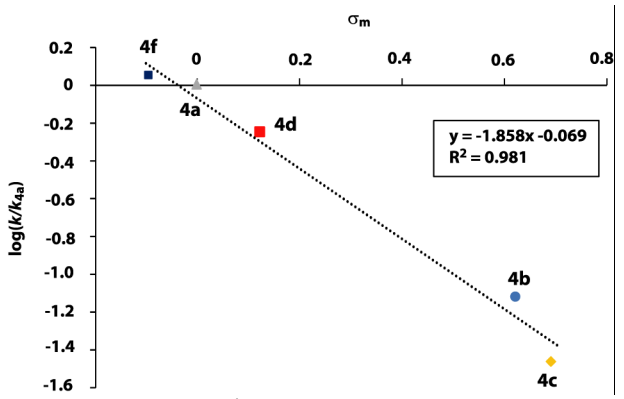


Fig. 5 Hammett plot of $\log(k_a/k_{4a})$ *versus* the substrate electronics (σ_m) in the Michael addition of acetylacetone **6** to crotonaldehyde **5**.

evidences that the presence of electron-poor aromatic groups at the macrocycle slows down the formation of the Michael adduct **7**.

Having into account that the mechanism of this type of organocatalysed processes is complex, the macrocyclic component could take part in any of the key steps of the catalytic cycle (iminium/enamine formation, C-C bond formation or hydrolysis triggering the final compound). The ability of the macrocycle to take part in the catalytic process is directly correlated with the electronics (Figure 5) and, at the same time, the shuttling dynamics. The correlation between the kinetic values of the catalysis and the exchange rates calculated at 298 K for the internal dynamics of each rotaxane corroborates this scenario (see ESI, Figure S71). In the particular case of the adamantane-based rotaxane **4e**, considering the large exchange rate constant for the translational motion at 298K when compared with its aromatic analogues (i. e. **4a** and **4f**), its catalytic rate constant was not as high as expected. Probably the lesser acidity of the NHs of the amide groups precludes a most efficient participation of the mechanical bond on the catalytic process. Thus, the modulation of the catalysis by the mechanical bond described herein can be explained by the availability of the macrocycle. When the macrocycle is not strongly interacting with the succinamide stations, it could cooperatively assist in the catalytic process by interacting with the reactants[24] or stabilizing key intermediates.[25] This scenario is more feasible in the systems with lower translational energy barriers (faster translational motions), i. e. rotaxanes **4a** and **4f**, which in fact resulted to be the most efficient catalysts.

Conclusions

In conclusion, we have synthesized a series of degenerate molecular shuttles with a thread bearing two succinamide binding sites and, in between, an acyclic secondary amine function as the active site. The back-and-forth motion of the macrocycle along the thread was studied, finding a close relationship between the macrocycle dynamics and its electronics. These systems were tested as organocatalysts in iminium- and enamine-type processes for comparison with each other and also with the non-interlocked thread. The results show that the mechanical bond has a deep influence on the catalytic performance of the systems, clearly modulating the corresponding reaction rates, in an extent that jointly depends on the electronics and, at the same time, the internal translational dynamics of the entwined macrocycle. Systems with electron-deficient rings, with higher translational energy barriers, are shown to be the less active catalysts. Thus, the kinetic studies proved the active role that the mechanical bond plays on the catalytic processes, with the entwined macrocycle ring influencing the activity of the active site at the nearby thread. The design of new mechanized systems, including their asymmetric variants, is ongoing in our laboratories with the aim of adding value to the herein disclosed instances of mechanically bonded catalysts.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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