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ARTICLE

Mechanical bonding activation in rotaxane-based organocatalysts

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We report here the enhanced efficiency as organocatalysts of a series of succinamide-based hydrogen-bonded [2]rotaxanes functionalized with an acyclic secondary amine as the catalytic active site. We also evaluated their catalytic activity, comparing with that of their non-interlocked threads, in an iminium-type process between crotonaldehyde and acetylacetone. The presence of an interlocked polyamide macrocycle notably increased the catalytic activity of the entwined organocatalysts. The mechanized catalysts rapidly form the reactive iminium intermediate with the aldehyde, increasing its population. The hydrogen-bonding interaction established between the macrocycle and the electrophile has been proposed as one of the reasons for the rapid formation and stabilization of this key intermediate.

Introduction

The synthesis and study of mechanically interlocked molecules (MIMs) has experienced a huge evolution during the last decades.¹ The mechanical bond provides stability and unique internal dynamics to the entwined molecules, making them ideal candidates to be applied in numerous fields, remarking the design of molecular machinery.² Amongst the different uses of the MIMs, different research groups have lately focused on the applicability of these systems as ligands in metal-catalysed processes³ and organocatalysts,⁴ including their use in selective asymmetric transformations.⁵ In catalysts with rotaxane structure,⁶ the mechanical bond offers singular features⁷ that can be advantageous for the control of the reaction outcomes, such as their ability to create dynamic enzyme-like 3D cavities due to the orthogonal disposition of the entwined components, a feature difficult to build in conventional covalent catalysts.⁸ In addition, the well-known protecting effect of the mechanical bond,⁹ kinetically stabilizing the functional groups located inside the macrocyclic cavity, has been successfully exploited for the development of an extensive number of rotaxane-based switchable catalysts.¹⁰ The precise control of the position of the bulky macrocycle along the thread allows to conceal or expose the active site placed on the thread, altering the catalytic capability of the systems in terms of activity (ON/OFF),¹¹ enantio- or diastereoselectivity switching,¹² or selection between diverse activation modes.¹³ As a consequence, the non-interlocked threads are generally more reactive than the hampered interlocked systems.

Herein we evaluate the behaviour as organocatalysts of a series of succinamide-based hydrogen-bonded [2]rotaxanes, bearing a catalytically active acyclic secondary amine at the thread (Figure 1). These interlocked organocatalysts contain either one single or two binding-sites embedded into the axis, which offer different internal dynamics. The comparison of the catalytic activity of the non-interlocked threads versus the rotaxanes will allow us to determine the effect of the mechanical bond on their catalytic performance (Figure 1, inset I). Aimed to explore the consequences of the ring translational motion on the catalysis, the comparison between the one single and the two binding-sites rotaxanes is also examined. The translational ring dynamics at the two-binding-site rotaxane largely contrasts with that of the single succinamide-based surrogate. The ring is located most of the time over the succinamide station in the one binding-site system, leading to a nearly full exposition of the active site (Fig. 1a). In the case of the two identical binding-site rotaxane (a so-called degenerate rotaxane),¹⁴ the ring continuously moves back and forward from one station to the

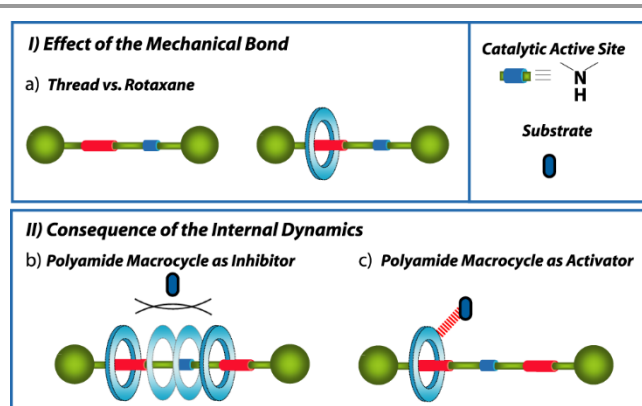


Fig. 1 Different scenarios studied in this work: (I.a) Effect of the mechanical bond in the catalysis: Thread versus rotaxane-based organocatalysts; II.b) Catalytic activity decrease due to the steric hindrance of the polyamide macrocycle; II.c) Catalytic activity enhancement by hydrogen-bonding activation of the substrates triggered by the polyamide macrocycle.

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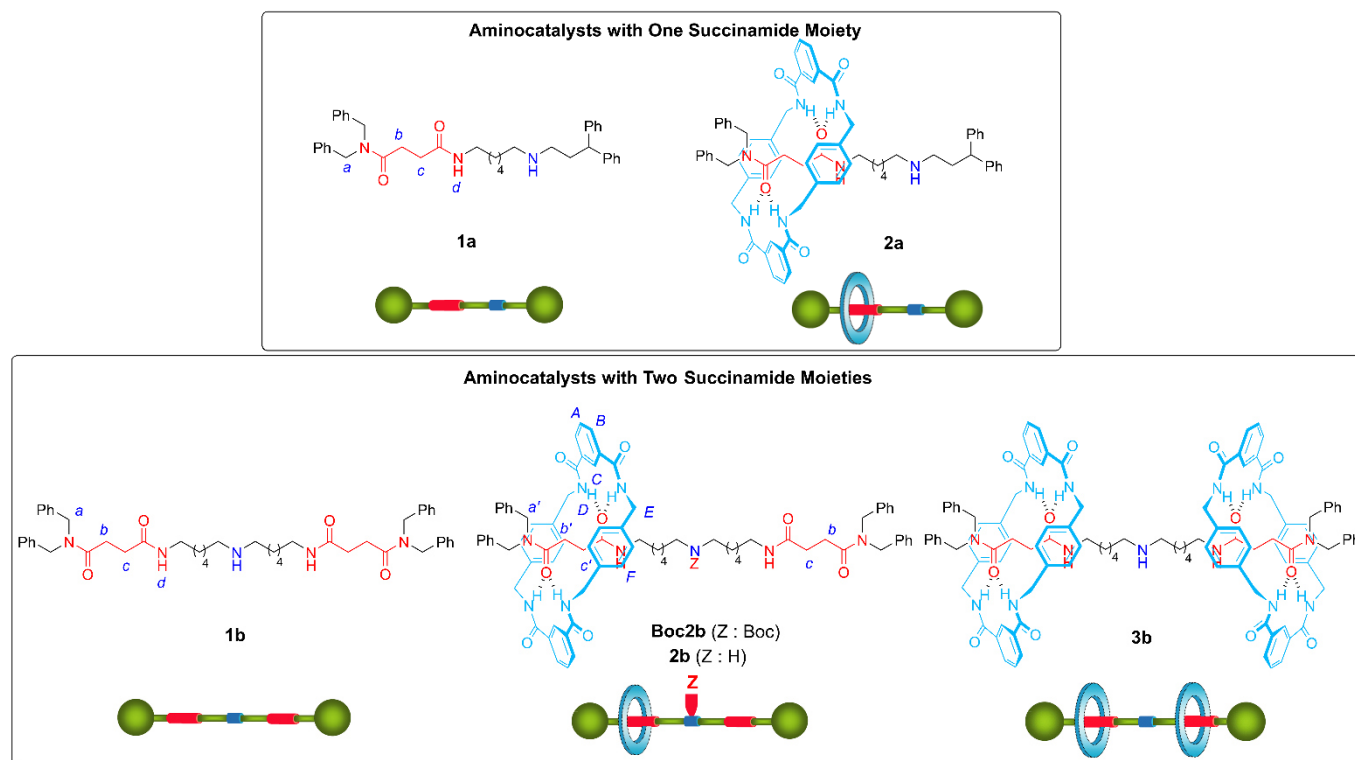


Fig. 2 Synthesized systems evaluated as organocatalysts.

other (Figure 1, inset II). Thus, two possible scenarios may be envisioned when system is used as catalyst: the bulky polyamide macrocycle (blue ring in Figure 1) momentarily conceals the active site, restricting the approaching of the substrates and decreasing the catalytic activity of the catalyst (Figure 1b); or, the polyamide macrocycle¹⁵ activates the process by establishing hydrogen-bonding (HB) interactions with the substrates (Figure 1c). The weakly acidic protons of the $-\text{CONH}-$ groups present on the interlocked macrocycle might be enabled to orient and/or activate the substrates, stabilizing the transition states and cooperatively increasing the overall catalytic rate. The Michael addition between acetylacetone and crotonaldehyde was selected as the model iminium-type catalytic process.

Results and discussion

Aimed to study the different scenarios proposed in Figure 1, we assembled the rotaxane **2a**, having one single succinamide as binding-site, and rotaxane **2b**, with two identical succinamide stations (Figure 2). An acyclic secondary amine was placed in the systems as the active site. The five-component reaction

between *p*-xylylenediamine, isophthaloyl chloride, and the corresponding Boc protected threads **Boc1** afforded the Leigh-type [2]rotaxanes **Boc2**,¹⁶ that after acid deprotection, yielded the organocatalysts **2** (see ESI for the complete synthetic protocols). The corresponding [3]rotaxane **3b** was also isolated in a minor amount during the assembly reaction of **2b** (Figure 2).

The comparison of the ^1H NMR spectra of the single succinamide-based thread **1a** and its rotaxane **2a**, indicates that the macrocycle predominantly settles over the succinamide station (the signals related to the succinamide H_b and H_c experienced a significant shifting due to the shielding by the macrocycle, $\Delta\delta = 1.48$ ppm; see Figure S2). Similarly, the comparison of the ^1H NMR spectra of the thread **1b** and the rotaxanes **Boc2b** and **2b**, recorded in CDCl_3 , allowed us to trace in each case the relative position of the macrocycle along the thread (Figure 3). The methylene protons of the succinamide binding site (H_{b+c} , in red) in thread **1b** appeared at 2.78 and 2.58 ppm (Figure 3a). The bulky Boc group in rotaxane **Boc2b**, which acts as a steric barrier, prevents the free translational movement of the macrocycle along the embedded thread, leading to the compartmentalization of the interlocked system (Figure 3b).¹⁷

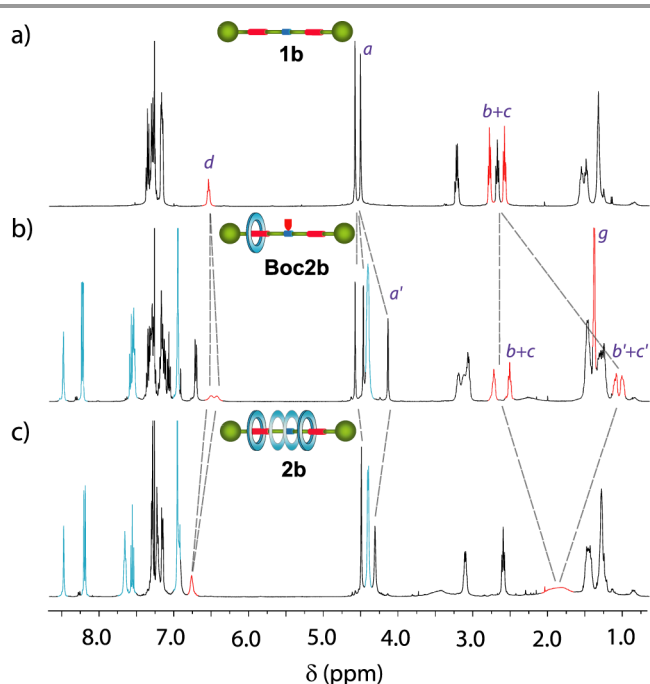


Fig. 3 Stacked ^1H NMR spectra (400 MHz, CDCl_3 , 298 K) of: a) thread **1b**; b) compartmentalised [2]rotaxane **Boc2b**; c) degenerate [2]rotaxane **2b**. See lettering in Scheme 1.

Two succinamide stations with different magnetic environments are then noticeable: one occupied by the macrocycle, whose $\text{H}_{b'+c'}$ nuclei are shielded ($\delta = 1.08$ and 1.00 ppm), and an unoccupied one in which nuclei H_{b+c} appeared at similar chemical shifts to those of the thread **1b** ($\delta = 2.72$ and 2.51 ppm). Moreover, the signals related to the methylene protons of the transoid benzyl groups (H_a) also experienced important changes, upshifting $\Delta\delta = 0.37$ ppm. After the Boc removal, the macrocycle can move back and forward between the two stations of **2b** (Figure 3c). The signals related to the two equivalent succinamides appeared between 2.00–1.60 ppm as a broad multiplet. Note that its chemical shift is approximately the average of the corresponding shifts of the occupied and unoccupied binding sites in **Boc2b**.

The kinetics of the shuttling movement of the macrocyclic tetralactam along the thread in **2b** was analysed by ^1H VT-NMR spectroscopy (see ESI for further details, Figure S1 and Table S1).¹⁸ Above room temperature the macrocycle is uninterruptedly moving between both succinamide stations, and an averaged co-conformation is observed by ^1H NMR. When the temperature is gradually decreased, the shuttling motion slowed down until the splitting of the resonances for the succinamide moieties is observed below 278 K (T_c). At this temperature, a co-conformational “freezing” occurred, observing one succinamide shielded by the macrocycle and the second one naked. From the separation of the signals corresponding to the two succinamides at the slow dynamic regime, an energy barrier of $12.17 \text{ kcal mol}^{-1}$ for the macrocycle shuttling was calculated, which is in the range of other amide-based degenerate rotaxanes,¹⁹ with a shuttling rate of 1571 s^{-1} . Next, we explored the catalytic activity of the synthesized systems **1** and **2**. Dibutylamine was also tested as a simplified catalytic model. The secondary amine as the active site allows

these systems to participate as aminocatalysts in iminium-type transformations.^{20,21} We chose the conjugate addition of acetylacetone **5a** to crotonaldehyde **4a** as the model iminium-type catalysed process, monitoring the formation of the Michael adduct **6aa** over time by ^1H NMR spectroscopy (Figure 4, see ESI for further experimental details, Figures S3–21). The reactions were conducted with freshly distilled crotonaldehyde (**4a**, 2 equiv.), acetylacetone (**5a**, 1 equiv., 0.125 M) and 5 mol% of the corresponding catalyst in CDCl_3 ²² at 298 K without the need of additives²³ (see Tables S2–3 for the optimization of the reaction conditions). CDCl_3 is a non-competitive solvent in which the intercomponent hydrogen-bonding network between the thread and the macrocycle in the interlocked systems survives.²⁴ Thread **1b** (with 2 succinamides, ●) was more active than thread **1a** (one succinamide, ◆) in catalysing the Michael addition.²⁵ Note that the plot with dibutylamine (●) is almost overlapped with that catalysed by the thread **1a**. Rotaxanes **2** are more effective catalysts than threads **1**, pointing to an active role of the threaded polyamide macrocycle. Rotaxane **2a** ($t_{1/2} \sim 2 \text{ h}$, ✕) showed a faster reaction rate than that of the non-interlocked thread **1a** (reaction too slow to measure the $t_{1/2}$, ◆). The same trend was found when comparing the activities of the rotaxane **2b** ($t_{1/2} \sim 1.8 \text{ h}$, ▲) and that of the thread **1b** ($t_{1/2} \sim 7 \text{ h}$, ●). Rotaxane **2b** (▲) (Figure S15 displayed the monitoring of the reaction over time followed by ^1H NMR) was the most active catalytic species, obtaining almost 90% conversion of the adduct **6aa** after 12h, versus the 70% conversion achieved with rotaxane **1a**. Having in mind that the macrocycle in the two-station rotaxane **2b** is continuously translocating between the two succinamide moieties, and thus temporally encapsulating the amine active site, this activity enhancement is an intriguing fact. As we envisioned, the reaction catalysed by the highly hindered [3]rotaxane **3b** was slower than that catalysed by the [2]rotaxane **2b** (less than 50% conversion after 12h, not shown in Figure 4; see Figure S22). The presence of two macrocycles mechanically linked to the thread hampers the access of the substrates to the active site, drastically reducing the catalytic performance of the system.

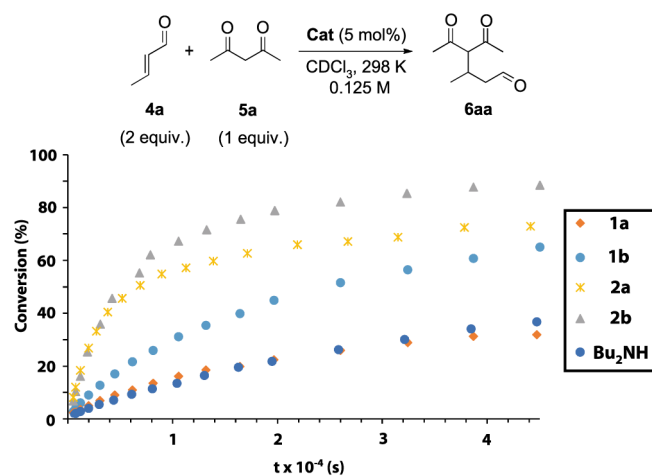


Fig. 4 Plot of the conversion (%) versus time of the Michael addition between crotonaldehyde and acetylacetone catalyzed by: thread **1a** (◆), thread **1b** (●), rotaxane **2a** (✕), rotaxane **2b** (▲) and dibutylamine (●). The conversion was determined by ^1H NMR using CH_2Br_2 as internal standard.

Our interest for uncovering the role of the mechanical bond, keeping linked both components (macrocycle and thread), on the improved catalytic performance, led us to carry out an additional experiment by employing a mixture composed by thread **1b** and an acyclic tetraamide surrogate, *N*¹,*N*³-bis(4-(benzamidomethyl)benzyl)isophthalamide,^{15a} as catalytic system (see Figure S23-24). The activation effect when this surrogate is present is negligible, observing a behaviour similar to that obtained for the thread **1b** itself. Note that the same experiment using the free macrocycle resulted unfeasible due to the high insolubility of the polyamide ring in CDCl₃.²⁶

Aimed to get insight of the enhanced catalytic activity showed by the interlocked systems, we designed further experiments. The addition of acetylacetone **5a** to crotonaldehyde **4a** catalysed by secondary amines proceeds via the formation of the corresponding iminium intermediates.²¹ Thus, we mixed the corresponding catalyst (dibutylamine, thread **1b** or rotaxane **2b**) in the presence of variable amounts of crotonaldehyde **4a** in CDCl₃ (0.01 M) at room temperature. After this time, the ¹H NMR spectra were registered. In the case of dibutylamine, no change on the spectra was observed after 48 h when added 4 equiv. of crotonaldehyde **4a**. It is known that the presence of catalytic amounts of a Brønsted acid helps the stabilization of the iminium derivatives.²⁷ Thus, the addition of TFA allowed us to observe a considerable amount of corresponding iminium salt intermediate (verified by 1D and 2D NMR experiments, Figures S25-27). In contrast, tiny signals appeared in the spectra of the equimolecular mixture of thread **1b** and crotonaldehyde **4a** after 48 hours, which can be attributable to an iminium intermediate (Figure S28). Remarkably, in the case of the rotaxane **2b** (for clarity, Figure 5 also shows the spectra of the rotaxanes **Boc2b** and **2b**), the appearance of new signals, which increased upon addition of more equivalents of aldehyde and time, rapidly arose (4 hours) (Figure 5c-d). The desymmetrization of the signals related to the rotaxane, increasing the complexity of the spectra, points out to the compartmentalization of the system, as occurred in rotaxane **Boc2b** (Figure 5a). Thus, the formation of the corresponding iminium salt **7b** by reaction of crotonaldehyde with the secondary amine in **2b** precludes the free motion of the macrocycle.²⁸ Accordingly, a signal emerged at 4.14 ppm, attributable to a shielded benzyl group of the stopper (H_{3'}), at similar chemical shift as that of the rotaxane **Boc2b**. Other signals also raised at the macrocycle region (8.5-8.00 ppm) and the aliphatic one (two succinamides are clearly observable, highlighted in red in Figure 5c-d), indicative of the formation of a desymmetrized rotaxane derivative. Moreover, several peaks emerged between 5.50 and 6.00 ppm (H₂₊₃, see numbering in Figure 7), attributable to the olefinic protons of the iminium salt **7b**, at 9.44 ppm (iminium hydrogen, H₁) and 1.00 ppm (CH₃, H₄). The complex ¹³C NMR spectra of this mixture also points to the compartmentalization of the rotaxane **2b** upon reaction with the aldehyde (see ESI, Figure S29). Additionally, when acetylacetone **5a** was added to this mixture, signals attributable

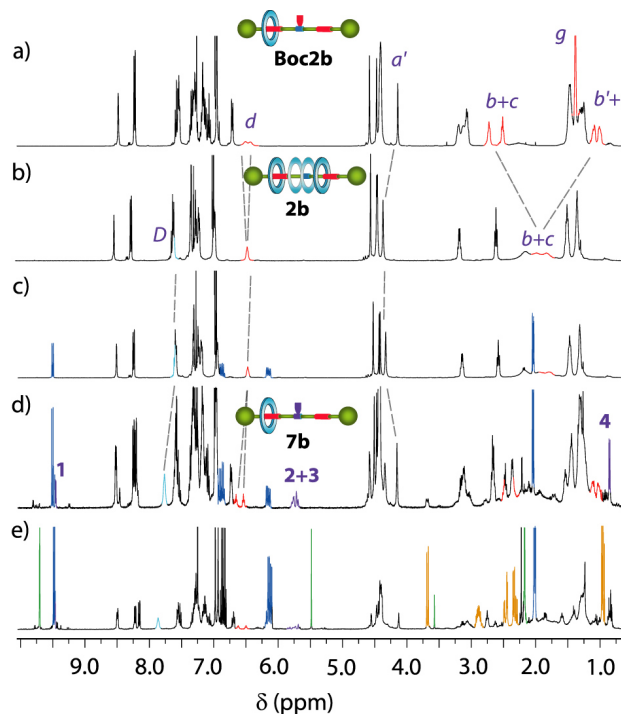


Fig. 5 Stacked ¹H NMR spectra (400 MHz, CDCl₃, 298 K) of: a) Boc-protected rotaxane **Boc2b**; b) rotaxane **2b**; c) mixture of rotaxane **2b** and 1 equivalent of crotonaldehyde **4a** (dark blue) after 3 min; d) mixture of rotaxane **2b** and 2 equivalents of crotonaldehyde **4a** (dark blue) after 24 h; e) addition to (d) of acetylacetone **5a** (green) after 6 hours. Signals corresponding to the Michael adduct **6aa** are highlighted in orange. Signals assigned to the new species **7b** are highlighted in purple and marked with numbers. The assignments correspond to the lettering shown in Scheme 1 and numbering in Figure 7.

to the Michael adduct **6aa** raised after a short time (in yellow, Figure 5e), indicating that the formed intermediate is an active species in the process.

Aimed to gain further evidence of the formation of the iminium salt intermediate **7b**, we performed ¹H PGSE (Pulsed Gradient Spin Echo) diffusion measurements with the mixture of the rotaxane **2b** and crotonaldehyde **4a** (600 MHz, CDCl₃, 298 K). The obtained diffusion coefficients (D) could help to distinguish among the species present in solution, having in mind the large difference of these values expected for crotonaldehyde **4a**, the rotaxane **2b** and the putative intermediate **7b**. Thus, we determined a D value of $2.20 \times 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$ for crotonaldehyde **4a**, and a value of $4.7 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$ for rotaxane **2b**. The intensity decays were followed on the resonances marked with asterisks in Figure 6 (see the ESI† for experimental details, Figures S31-34). The new signals that emerged in the mixture rotaxane **2b** and crotonaldehyde (mixture **2b:4a**, 1:10), tentatively attributable to the hydrogens of the iminium intermediate **7b**, showed a D value of $4.2 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$, slightly smaller than that obtained for the rotaxane **2b**. This data strongly supports the formation of the iminium salt **7b**. After analysis of the data, we propose that the higher catalytic performance showed by rotaxanes **2** when compared with their non-interlocked threads **1** (and with dibutylamine) is predominantly a consequence of the amide functions present at the macrocycle. As initial point, the establishment of hydrogen-bonding (HB) interactions between the amide

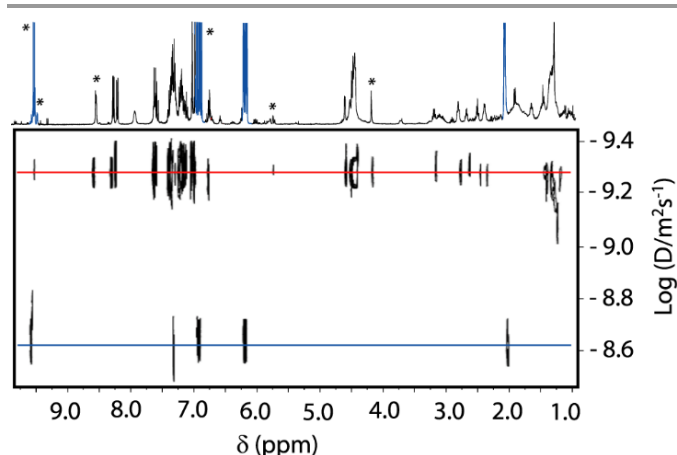


Fig. 6 DOSY NMR spectra (600 MHz, CDCl_3 , 298 K) of a mixture of rotaxane **2b** (2 mM) and crotonaldehyde **4a** (10 equivalents) after 24 hours.

groups²⁹ with crotonaldehyde **4a** might induce an increasing of its electrophilic character towards the ulterior nucleophilic attack of the amine group (Figure 7, Step 1). Indeed, the addition of crotonaldehyde **4a** to rotaxane **2b** instantly triggers a small downfield displacement of the signals related to the NH amide groups of the [2]rotaxane as result of the association between the catalyst and the aldehyde (Figure 5c). In addition, the formation of the intermediate iminium salt **7b⁺·OH⁻** become favoured by an intramolecular assistance of the macrocycle to bind the hydroxyl anion (see Figure 7, Step 2-3). It is known that thioureas and squaramides neutralise the hydroxyl anion formed during iminium type processes, promoting the stabilization of the active iminium salts in the absence of an additional acid as co-catalyst.³⁰ Considering this precedent, we propose that the acidic hydrogens of the aromatic amide groups in rotaxanes **2** can play a similar role than those reported systems, by binding the hydroxyl group of the intermediate **7b⁺·OH⁻** (see Figure 7b-c). The deprotonation of one the amide groups of the ring (or thread) by the hydroxyl group will form the compartmentalised zwitterion **7b** (see Figure 5d and Figure S29).³¹ Indeed, we experimentally proved that an organic base such as tetrabutylammonium hydroxide (TBAH) is able to deprotonate the hydrogens of the NH amides of the ring in rotaxane **2b** (see ESI, Figure S30). The addition of 1 equiv. of lyophilized TBAH to rotaxane **2b** triggers the decreasing of the intensity and shift of the ¹H NMR signals related to the amides. It is worth noting that the mechanical shuttling in the two-station rotaxane **2b** is also important for the enhancement of the catalytic activity of the system,³² enabling the amide groups of the ring easily interact with the crotonaldehyde **4a** in a suitable orientation. In contrast, these amide-aldehyde interactions may be less noticeable in the case of one binding-site rotaxane **2a**, in which the macrocycle is predominantly fixed over the succinamide binding-site by establishing stable bifurcated hydrogen bonds (see Figure S2) and decreasing its ability to form stabilizing HB with the electrophile. This causes a slight decrease of the catalytic activity of **2a** compared with the two-binding site system **2b**.

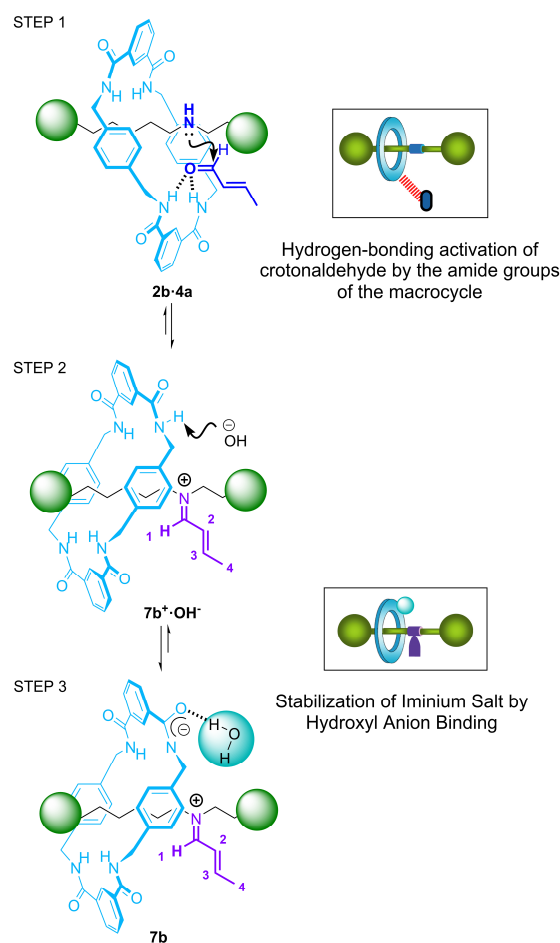
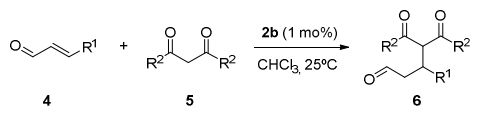


Fig. 7 Proposed pathways to the formation of the iminium intermediate **7b**: Step 1) Hydrogen-bonding activation of crotonaldehyde **4a**; Step 2) Formation of the iminium salt **7b⁺·OH⁻**; Step 3) Macrocycle-assisted hydroxyl anion binding for the stabilization of the zwitterion **7b**.

By using the most active catalyst **2b**, we explore the scope of this process, decreasing the catalyst loading up to 1 mol% (Table 1, see ESI, Figures S35-37). The reaction of the diketones **5a,b** as nucleophiles with crotonaldehyde **4a** smoothly afforded the adducts **6aa** and **6ab** in high conversions in 24 hours (Table 1, entries 1-2), showing that the catalyst **2b** remains active at the low catalyst loading employed. The variation of the aldehyde was also tested. The reaction of cinnamaldehyde **4b** with acetylacetone **5a** provided the corresponding adduct **6ba** in a moderate conversion (Table 1, entry 3). The reaction between crotonaldehyde **4a** and acetylacetone **5a**, without catalyst, was also tested, not observing the formation of the corresponding adduct (Table S2, entry 1). It is noteworthy to mention that this iminium-type transformation has been used for the evaluation of various switchable mechanically interlocked catalysts.^{11b,13a,13b} In these reports, the employment of sodium acetate as an additive was required in order to activate the nucleophile. Moreover, high catalyst loadings (15-20 mol%) and long reaction times (2-5 days) were necessary for obtaining good conversions of the adducts. Remarkably, additives, such as acids, were not required by using our interlocked catalyst, obtaining high conversions in hours at low catalyst loadings (1 mol%).

Table 1. Scope of the Michael addition of activated methylene nucleophiles **5** to α,β -unsaturated aldehydes **4**.^a


entry	4 (R ¹)	5 (R ²)	6 (%) ^b
1	4a (Me)	5a (Me)	6aa (92) ^c
2	4a (Me)	5b (Ph)	6ab (80)
3	4b (Ph)	5a (Me)	6ba (57)

^a Reaction conditions: aldehyde (2 equiv.), nucleophile (1 equiv., 0.5 M), **2b** (1 mol%), CHCl₃, 25 °C, 24 h; ^b Conversion calculated by ¹H NMR after 24 h of reaction; ^c The reaction without catalyst resulted fully unproductive.

Conclusions

In conclusion, we have synthesized a series of mechanically interlocked systems having one or two succinamides as binding-sites. The presence of an acyclic secondary amine at the thread allows these systems to be evaluated as organocatalysts in amino-catalysed transformations. In the case of the two binding-site system, the shuttling dynamics was studied, and the shuttling rate was calculated. We found that the mechanical bond has a deep influence on the catalytic performance of the interlocked systems, importantly increasing the reaction rates when compared with their non-interlocked threads. Moreover, the bis(succinamide)-based [2]rotaxane showed the highest activity when compared with the rest of the systems, probably due to its ring dynamics enabling the activation of the electrophile. Moreover, the generation of the iminium ions without the addition of an external acid highlights the assistance of the mechanical bond (polyamide macrocycle) on the hydroxyl anion binding, contributing to the enhanced catalytic performance. This activation effect strongly contrasts with the well-established hindering consequence of the mechanical bond reported in switchable rotaxane-based catalysts, opening the door to the development of new activation modes in catalysis via mechanical bonding. Research on this line is ongoing in our laboratories, focused on the optimization of the interlocked catalysts for their use in other catalytic processes, including their asymmetric versions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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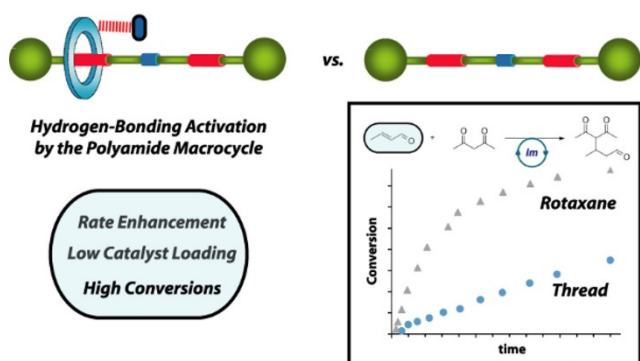
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Mechanical Bond with an Activating Effect in Organocatalysis



Interlocked organocatalysts show an enhanced catalytic performance when compared with their non-interlocked threads. The mechanically-bonded polyamide macrocycle cooperatively activates the substrates, facilitating the formation and stabilization of the catalytically active intermediates.