Stereocontrolled synthesis of β-lactams within [2]rotaxanes: a showcase of the chemical consequences of the mechanical bonding

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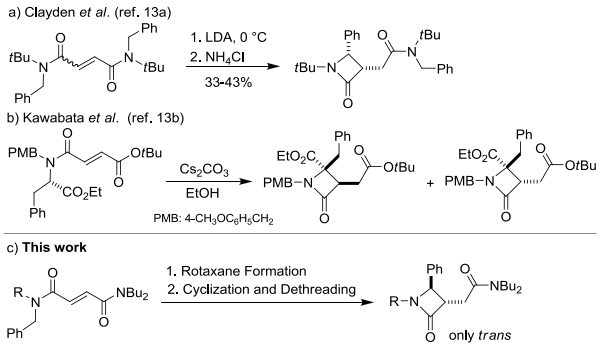
ABSTRACT: The intramolecular cyclization of *N*-benzyl fumaramide [2]rotaxanes is described. The mechanical bond of these substrates activates this transformation to proceed in high yields and in a regio- and diastereoselective manner giving interlocked 3,4-disubstituted *trans* azetidin-2-ones. This activation effect differs from the common shielding stabilization of threaded functions through amide-based macrocycles promoting an unusual and disfavored 4-*exo*-*trig* ring closure. Further kinetic and synthetic studies allowed us to produce an original approach towards β-lactams through a one-pot protocol based on an intramolecular ring closure followed by a thermally-induced dethreading step. The advantages for carrying out this cyclization in the confined space of a benzylic amide macrocycle were attributed to the anchimeric assistance of the surrounding macrocycle.

The remarkable catalytic performance of the Nature's enzymes represents a stimulating source of inspiration.[1] In fact, the use of hosts for transiently trapping compounds and controlling its reactivity has always been an important challenge for the chemists.[2] In this regard, compounds having a void or cavity such as self-assembled capsules,[3] molecular cages[4] and macrocycles[5] are vigorously investigated in this arena. Also, in the last years, the govern of the chemical behavior of the entwined components of mechanically interlocked compounds[6,7] is being explored with purposes such as the kinetic stabilization of the encapsulated functionalities,[8] the development of novel configurable catalysts[9] and the building of processive catalytic interlocked systems.[10] The features of these processes mimic those of the active site of an enzyme resulting in an enhancement of the reaction parameters (rate and selectivity).[2]

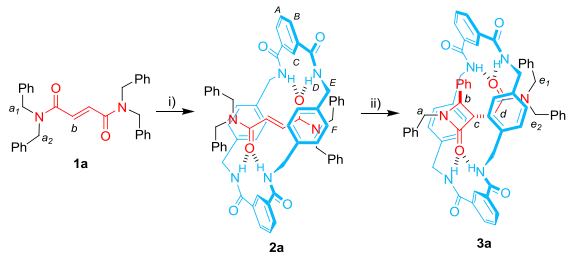
During the course of our investigations with amide-based rotaxanes[11] we serendipitously found that the thermal treatment of an interlocked *N*-benzylfumaramide in the presence of a base cleanly produces an interlocked β-lactam resulting from a formal intramolecular Michael addition of a benzyl group of the axis to the olefin. Interestingly, among the arsenal of methods to get β-lactams,[12] this type of transformation has been barely reported.[13] In this regard, Clayden and coworkers published an example of 4-*exo*-trig cyclisation of a benzyllithium fumaramide to exclusively afford the cis β-lactam in low yield (Scheme 1a).[13a] Almost a decade after, the Japanese research group headed by Kawabata described the conjugated addition of axially chiral enolates generated from α-amino acids to enantioselectively provide a *cis*-*trans* mixture of β-lactams (Scheme 1b).[13b] With these precedents in mind we get on the study of the cyclization of *N*-benzyl fumaramides within hydrogen bonded [2]rotaxanes to yield interlocked β-lactams. Herein we report the chemical consequences for carrying out this process in the confined space of a macrocycle and the stereoselective synthesis of β-lactams through a one-pot protocol based on an intramolecular 4-*exo*-trig ring closure of an interlocked fumaramide followed by a thermally-induced dethreading step (Scheme 1c).

Scheme 1. Intramolecular 4-exo-trig ring closures of fumaramide derivatives.



Firstly, we assayed the intramolecular cyclization of the rotaxane **2a**, obtained from *N,N,N',N'*-tetrabenzylfumaramide (**1a**) acting as template, in DMF to exclusively afford the interlocked β-lactam *trans*-**3a** after a mild heating period of 6 h at 60 °C using just one equiv. of Cs_2CO_3 (Scheme 2).

Scheme 2. Cyclization within rotaxane 2a.[a]



[a]Reaction conditions: (i) isophthaloyl dichloride, *p*-xylylenediamine, Et_3N, $CHCl_3$, **2a**, 36 %; (ii) Cs_2CO_3 (1 equiv), DMF, 60 °C, 6 h, **3a**, 99%.

In contrast with the symmetry of the aliphatic region of the ^1H NMR spectrum of the rotaxane **2a** (Figure 1A), that of **3a** displays

a complex set of signals corresponding to the three different AB systems of the thread (in black) and the three signals belonging to the 4-methylenecarboxamidoazetidin-2-one motif (in red) (Figure 1B). The coupling constant of 1.9 Hz for the hydrogen at the position 4 of the lactam ring, H_b, of **3a** lies in the range (1.5-2.2 Hz) to other reported *β*-lactams[14] having two adjacent substituents with a relative *trans* disposition allowing us to assign the same configuration in this case. ^{1}H NMR spectrum (Figure 1C) of the non-interlocked thread *trans*-**4a** (*vide infra*) was compared with that of **3a** showing an upfield shift of the signals of the protons of the thread [e.g., $\Delta\delta(H_c)$ = 2.4 ppm] due to the electronic currents of the benzylic amide macrocycle.

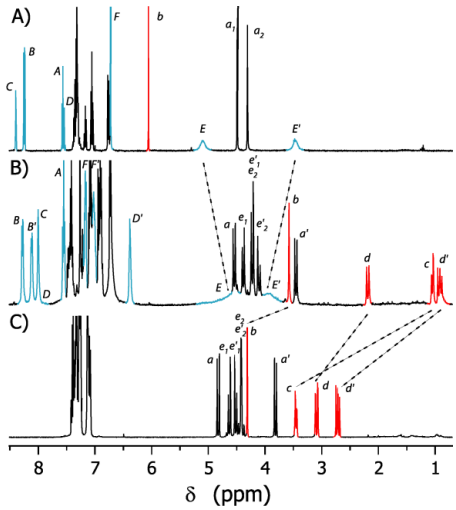


Figure 1. ^{1}H NMR (400 MHz, $CDCl_3$, 298K) spectra of: (A) fumaramide [2]rotaxane **2a**, (B) *β*-lactam [2]rotaxane *trans*-**3a** and (C) *β*-lactam *trans*-**4a**. Letter assignments are in Scheme 2.

An X-ray analysis of a single crystal of **3a** confirmed its interlocked structure and the *trans* configuration of the azetidinone ring (Figure 2). Whereas one of the isophthalamide units establishes a bifurcated hydrogen bond with the $CONBn_2$ carbonyl group of the thread through both NH amide protons the other isophthalamide moiety forms a strong hydrogen bond with the *β*-lactam carbonyl group although by means of only one of the NH amide protons. The fourth amide group of the macrocycle adopts now a *transoid* conformation, probably the ideal one for enlarging the macrocyclic void and easing the accommodation of the bulky cyclic thread.

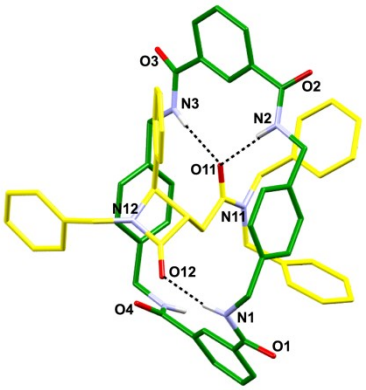
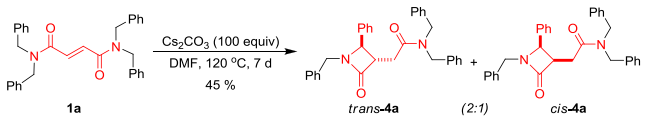


Figure 2. X-Ray structure of the [2]rotaxane **3a**. For clarity, carbon atoms of the macrocycle are shown in green and the carbon atoms of the thread in yellow; oxygen atoms are depicted in red, nitrogen atoms are depicted in blue, and selected hydrogen atoms are white. Intramolecular hydrogen-bond lengths [Å] (and angles [deg]): O11HN2 2.42 (161.6); O11HN3 2.23 (176.0); O12HN1 1.85 (166.3).

Aimed to compare the effect of the mechanical bonding on the outcome of the studied intramolecular conjugated addition we explored this transformation with the corresponding non-interlocked substrate.[6a] Thus this reaction was carried out with **1a** as substrate in DMF under basic conditions (Scheme 3). However, using an excess of Cs_2CO_3, **1a** remained unaltered after heating at temperatures under 100 °C for 24 hours, probably, due to low basicity of the benzylic protons.[15] Total consumption of **1a** requires an extended thermal treatment at 120 °C for 7 days using 100 equiv of Cs_2CO_3 for obtaining the expected *β*-lactams **4a** in 45% yield as a two diastereomers mixture in 2:1 ratio in favor of the *trans* isomer along with a complex mixture of side products.

Scheme 3. Intramolecular Michael Addition of *N,N,N′,N′*-tetrabenzylfumaramide (1a).[a]



The lower reaction time of the intramolecular addition to the interlocked Michael acceptor when compares with that of the non-interlocked counterpart contrasts with most of the reported reactions on the axis of hydrogen bonded rotaxanes in which the main effect lays on the kinetic stabilization of the threaded function.[6,8] Moreover, the high diastereoselectivity (>99:1), only *trans* lactam is obtained, and the absence of byproducts during the reaction (Scheme 2) are neatly advantages of carrying out this process in the inner of the benzylic amide macrocycle in comparison with the same transformation on the isolated thread (Scheme 3). We next examined further details of the conversion of **2a** in *trans*-**3a** by screening different reaction parameters such as temperature, solvent, base and stoichiometry (Table 1 and Tables S1-5). Therefore, whereas DMSO or DMF allows quantitative conversions (Table 1), chloroform, acetonitrile and ethanol were completely unproductive (see Table S3). The use of organic bases (pyridine, piperidine, DIPEA or DBU) kept intact the substrate (Table S2). Although different metal carbonates were assayed, only cesium carbonate leads the reaction to a quantitative conversion, probably due to its good solubility in polar solvents (Table 1, entry 1). We found that metal hydroxides such as NaOH, KOH and CsOH also achieved the complete cyclization of **3a** (Table 1, entries 5-10), at 60 °C, reducing the reaction time to 3 h. Remarkably, the use of CsOH allows the complete reaction at room temperature in 6 h (Table 1, entry 9) which contrasts with the failure of the cyclization of **3a** using Cs_2CO_3 as base under the same conditions (Table 1, entry 3).

Table 1. Intramolecular cyclization of 3a yielding the *β*-lactam *trans*-3a.

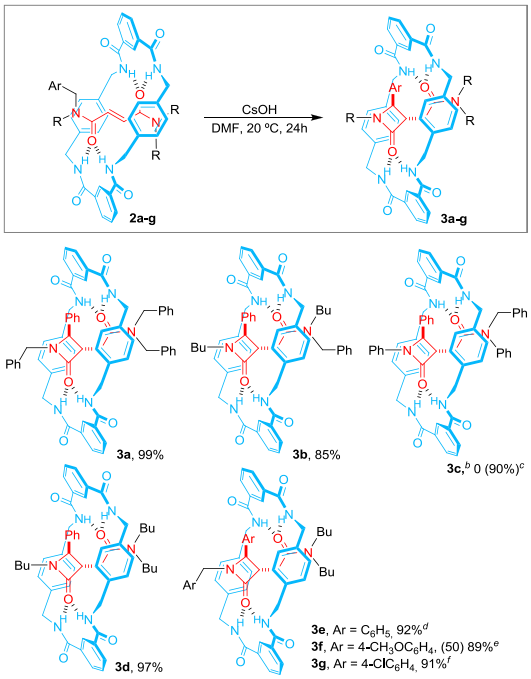
Entry	Solvent[a]	Base (equiv.)	Temp (°C)	t (h)	Conv (%)[b]
1	DMF	Cs_2CO_3 (1)	60	6	100
2	DMF	Cs_2CO_3 (0.1)	60	48	92
3	DMF	Cs_2CO_3 (1)	24	16	8
4	DMSO	Cs_2CO_3 (1)	60	6	95
5	DMF	CsOH (1)[c]	60	3	100
6	DMF	CsOH (0.1)[c]	100	24	89
7	DMF	NaOH (1)	60	3	100
8	DMF	KOH (1)	60	3	100
9	DMF	CsOH (1)[c]	24	6	100
10	DMSO	CsOH (1)[c]	60	3	100

[a]The reaction was carried out at 0.02 M scale. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Cesium hydroxide was dried prior to use by heating at 150 °C under vacuum.

Keeping in mind the interest in developing a synthetic strategy to obtain non-interlocked azetidinones this result become crucial as it would allow to carry out this transformation with kinetically stable pseudorotaxanes (*vide infra*) which, after dethreading,[16] set free the appealing four-membered cyclic guest. Finally, it is also noteworthy that this conjugate addition efficiently occurs by using catalytic amounts of base (Table 1, entries 2 and 6) although it needed extend the reaction time.

In order to study the scope of this intramolecular cyclization we prepared a set of fumaramide-based rotaxanes differing in the number of benzylic substituents and their organization at the nitrogen atoms of the dicarboxamide. Electronic variations of the substituents at the amido group were also examined by introducing aryl groups with different electron donor or electron withdrawing groups at the benzylic carbons of the axis. Rotaxanes **2b-g** (Table 2) were obtained in 24-53% yields by five-component clipping reactions using the respective fumaramides, easily prepared from fumaric acid derivatives (see Supp. Info. for synthetic details.). The intramolecular cyclizations of **2a-g** were carried out in the presence of cesium hydroxide to quantitatively afford the interlocked *β*-lactams **3a-g** (Table 2). Fumaramides **2b-2d** having only one benzyl group at the amide group undergo the closure at lower reaction rates than that of **2a** requiring an excess of base to complete their cyclization.

Table 2. 4-Exo-trig ring closure of fumaramides within [2]rotaxanes 2a-g.[a]

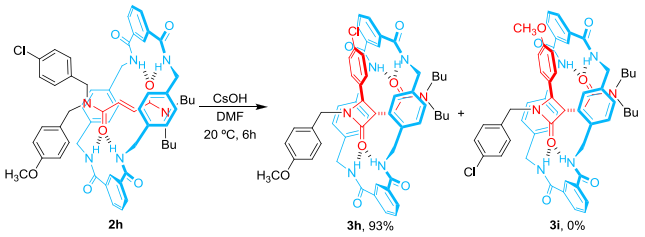


[a]Complete conversions were observed by ^{1}H NMR. Yields refer to isolated pure compounds. For convenience, **2a** and **3a** was also included herein. [b]The lactam ring quantitative hydrolyzed giving the interlocked 3-(phenylamino)propanoic acid derivative (see Supp. Info.). [c]Based on the isolated hydrolysis compound. [d]Cyclization finished in 12 h. [e]Full conversion required 5 equiv of CsOH in 48 h. [f]Cyclization finished in 40 min.

Rotaxanes **2d-2g**, having one NBu_2 terminus, can be considered as kinetically stable pseudorotaxanes since under appropriate thermal conditions these complexes dissociate into their non-interlocked components.[17] In fact, the half-life time of **2e** in DMSO-d_6 at 373 K is only 6 min (see Fig. S2). Also, in the initial attempts of the intramolecular closure of the rotaxane **2d** we noticed the formation of non-cyclizated thread resulting of the dethreading of the starting material but we satisfactorily precluded this unwanted pathway by adding an extra equivalent of base.

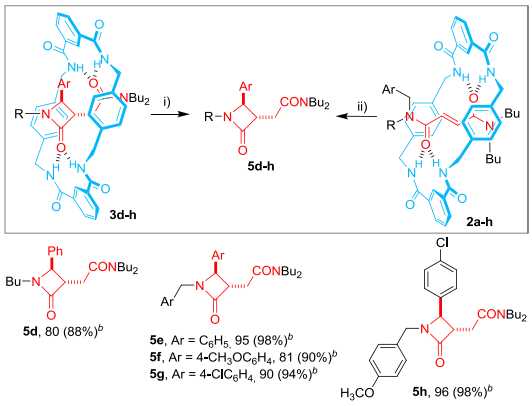
The intramolecular cyclization of the interlocked fumaramides **2e-g** also produces the corresponding 2-azetidinones **3e-g** in excellent yields (89-91%) but these reactions proceeded at different rates depending on the acidity of the methylene protons of the *N*-benzyl group (see Figure S1). Thus the presence of donor substituents, e.g. a methoxy group, on the benzyl groups of the thread of **2f** notably slow down the transformation needing up to 48 h for reaching conversions similar to those of unsubstituted cases. In this vein, electron withdrawing substituent such as a chloro one at the ring of the benzyl unit of **2g** notably accelerate the cyclization which ended in less than one hour. Note that this behavior predetermines the regiochemical outcome of the cyclization of **2h** to exclusively yielding the lactam **3h** derived from the addition of the *p*-chlorobenzyl anion (Scheme 4).

Scheme 4. Regiocontrolled ring closure within rotaxane 2h.



The release of the thread through the Bu_2N terminus of interlocked *β*-lactams **3d-h** is slower than that of its corresponding fumaramide predecessors **2d-h** (*vide supra*). For instance, the half-life time of **3e** in DMSO-d_6 at 373 K is 39 min (see Fig. S3). The heating of solutions of the pseudorotaxanes **3d-h** in DMF extrude the corresponding *β*-lactams **5d-h** in a quantitative manner (Table 3, conditions i). Interestingly, both cyclization and dethreading steps are able to consecutively occur in a one-pot protocol by intercalating a neutralization step, thus enabling the direct conversion of the fumaramide [2]rotaxanes into the corresponding *β*-lactams (Table 3, conditions ii).

Table 3. Synthesis of the *β*-lactams 5d-h.[a,b]

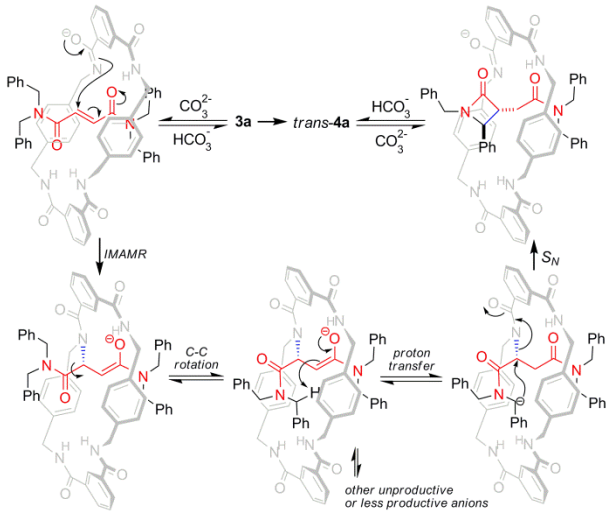


[a] Reaction conditions*:* i) CsOH, DMF, 20 °C, 24 h; ii) CsOH, DMF, 20 °C, 24 h then adjusting pH ≈ 7 and heating at 100 °C, 12 h. Quantitative conversions were observed by ^{1}H NMR. Yields refer to isolated pure compounds. [b]Yields in brackets were obtained by using the one-pot protocol.

In order to explain the role of the macrocycle in facilitating the formation of the interlocked 2-azetidinones of this work we propose these processes might be initiate by the initial deprotonation of one of the four isophthalamide NH protons (Scheme 5), the most acidic ones of the whole supramolecule ($pKa_{calculated}$ = 13). This anion adds to one of the sp^2 carbons of the

fumaramide thread in an intramolecular aza-Michael reaction (IMAMR)[18] generating an enolate capable to internally abstract one of the nearby benzylic protons from the dibenzylamido moieties. Then, the engendered carbanion displaces the anchimeric assistant group[19] by forming the four-membered ring (which after hydrolysis led to final product). The destruction of the π system between both HB acceptors of the starting thread through the herein proposed mechanism forecasts that the cyclization of the *Z* isomer of **2a** also would led to the *trans* β-lactam **3a** as, indeed, it occurs (see Scheme S5). Additionally, the ring closure of **1a** using *N,N'*-bis(4-(benzamidomethyl)benzyl)-isophthalamide as an open-chain surrogate of the benzylic amide macrocycle (see Scheme S6) or the non-interlocked macrocycle itself (see Scheme S7) inhibited the cyclization. Both results further underpin the neighboring group participation of a mechanically linked cyclic polyamide in this transformation.

Scheme 5. Proposed mechanism for the 4-exo-trig ring closure of interlocked fumaramides.



The base-catalyzed intramolecular Michael addition of α-benzyl fumaramides given inside the cavity of a removable benzylic amide macrocycle having two isophtalamide units connected by two *p*-xylylene linkers benefits of the protecting, activating and stereodirecting effects of the mechanical bond. These transformations occurring in a confined space proceeded without the formation of byproducts, at higher reaction rates than those of non-interlocked fumaramides and in a regio- and diastereoselective manner.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, VT-NMR spectra, kinetics measurements, and full crystallographic details of **3a** including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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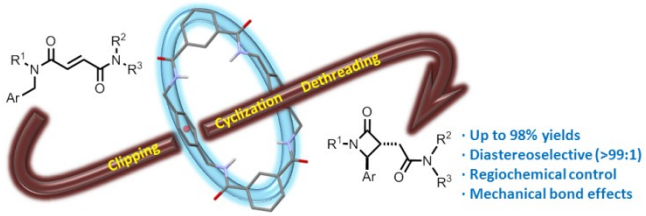
Clipping
Cyclization
Dethreading
· Up to 98% yields
· Diastereoselective (>99:1)
· Regiochemical control
· Mechanical bond effects