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Stereocontrolled Synthesis of β-Lactams within [2]Rotaxanes: Showcasing the Chemical Consequences of the Mechanical Bond

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Supporting Information

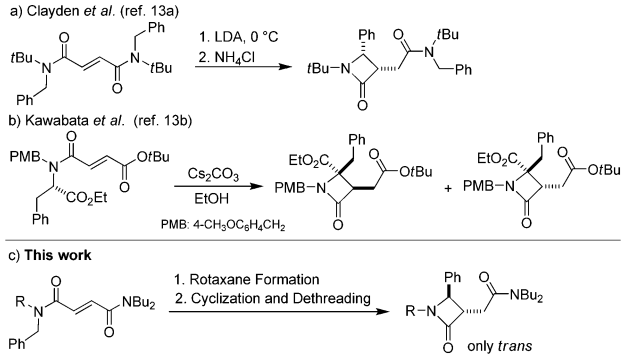
ABSTRACT: The intramolecular cyclization of *N*-benzylfumaramide [2]rotaxanes is described. The mechanical bond of these substrates activates this transformation to proceed in high yields and in a regio- and diastereoselective manner, giving interlocked 3,4-disubstituted *trans*-azetidin-2-ones. This activation effect markedly differs from the more common shielding protection of threaded functions by the macrocycle, in this case promoting an unusual and disfavored 4-*exo*-*trig* ring closure. Kinetic and synthetic studies allowed us to delineate an advantageous approach toward β-lactams based on a two-step, one-pot protocol: an intramolecular ring closure followed by a thermally induced dethreading step. The advantages of carrying out this cyclization in the confined space of a benzylic amide macrocycle are attributed to its anchimeric assistance.

The remarkable catalytic performance of Nature's enzymes represents a stimulating source of inspiration.[1] In fact, the use of artificial hosts for transiently trapping compounds and controlling their reactivity has been an important challenge for 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 recent years, the chemical behavior of the entwined components of mechanically interlocked compounds[6,7] has been explored for 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]

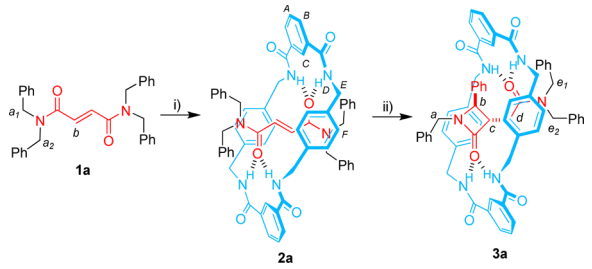
During the course of our investigations with amide-based [2]rotaxanes,[11] we serendipitously found that the thermal treatment of an interlocked *N*-benzylfumaramide in the presence of a base cleanly produces an interlocked β-lactam, resulting from a formal intramolecular Michael addition of a benzyl 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] Clayden et al. published an example of 4-*exo*-*trig* cyclization of a benzyllithium fumaramide to exclusively afford the *cis*-β-lactam in low yield (Scheme 1a).[13a] Almost a decade later, Kawabata et al. described the conjugated addition of axially chiral enolates generated from α-amino acids to provide a *cis*–*trans* mixture of β-lactams (Scheme 1b).[13b] With these precedents in mind, we found it of interest to study the cyclization of *N*-benzylfumaramides 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).

First, 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 in DMF by using Cs_2CO_3 as base (Scheme 2).

Scheme 1. Intramolecular 4-*Exo*-*trig* Ring Closures of Fumaramide Derivatives



Scheme 2. Cyclization within Rotaxane 2a[a]



[a]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%.

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X-ray analysis of a single crystal of **3a** (see SI, Figure S4, for NMR details) confirmed its interlocked structure and the *trans* configuration of the azetidinone ring (Figure 1). Whereas one of

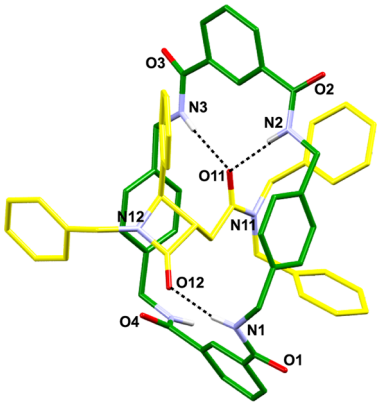
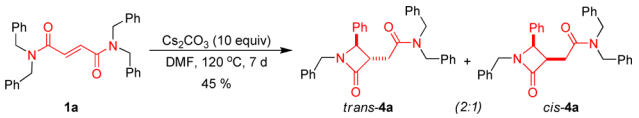


Figure 1. X-ray structure of the [2]rotaxane **3a**. Intramolecular hydrogen bond lengths [Å] (and angles [deg]): O11HN2, 2.42 (161.6); O11HN3, 2.23 (176.0); O12HN1, 1.85 (166.3).

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 bulkier cyclic thread.

Aiming 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 (Scheme 3).[6a] Even with an excess of

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



Cs_2CO_3, **1a** remained unaltered after heating at temperatures under 100 °C for 24 h, probably due to the low basicity of each benzylic proton.[14] Total consumption of **1a** requires an extended thermal treatment at 120 °C for 7 days using 10 equiv of Cs_2CO_3 to obtain the expected β-lactam **4a** in 45% yield as a diastereomeric mixture in a 2:1 ratio in favor of the *trans* isomer, along with a complex mixture of side products.

The shorter reaction time of the intramolecular addition to the interlocked Michael acceptor when compared with that of the non-interlocked reactant contrasts with most of the reported reactions on the axis of hydrogen-bonded rotaxanes, in which the main effect is on the kinetic stabilization of the threaded function.[6,8] Moreover, with the high diastereoselectivity (>99:1), only the *trans* lactam is obtained, without any reaction byproducts (Scheme 2). These are are advantages of carrying out this process in the inner part 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 SI, Tables S1−S5). Whereas DMF or DMSO

Table 1. Intramolecular Cyclization of 2a 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	DMSO	Cs_2CO_3 (1)	60	6	95
3	DMF	CsOH (1)[c]	60	3	100
4	DMF	NaOH (1)	60	3	100
5	DMF	KOH (1)	60	3	100
6	DMSO	CsOH (1)[c]	60	3	100
7	DMF	CsOH (1)[c]	25	6	100
8	DMF	Cs_2CO_3 (1)	25	16	8
9	DMF	CsOH (0.1)[c]	100	24	89
10	DMF	Cs_2CO_3 (0.1)	60	48	92

[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.

as solvent allowed quantitative conversions (Table 1), chloroform, acetonitrile, and ethanol were completely unproductive (see SI, Table S3). The use of organic bases (pyridine, piperidine, DIPEA, or DBU) kept the substrate intact (SI, Table S2). Although different metal carbonates were assayed, only cesium carbonate reached a full conversion, probably due to its good solubility in polar solvents (Table 1, entries 1 and 2). We found that metal hydroxides such as NaOH, KOH, and CsOH also achieved complete cyclization of **3a** (Table 1, entries 3−6) at 60 °C, reducing the reaction time to 3 h. Remarkably, the use of CsOH allows complete reaction at room temperature in 6 h (Table 1, entry 7), which contrasts with the failed cyclization of **3a** using Cs_2CO_3 as base under the same conditions (Table 1, entry 8). Note that using CsOH as base in the cyclization of non-interlocked fumaramide **1a** led to a *cis*−*trans* mixture of **4a** in 51% yield after 3 days (SI, Table S1).

Keeping in mind the interest in developing a synthetic strategy to obtain non-interlocked azetidinones, the result in entry 7 becomes crucial, as it would allow us to carry out this transformation with kinetically stable pseudorotaxanes (*vide infra*) which, after dethreading,[15] would set free the appealing four-membered cyclic guest. Finally, it is also noteworthy that this conjugate addition efficiently occurs with use of catalytic amounts of base (Table 1, entries 9 and 10), although after longer reaction times.

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-donating 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, in turn easily prepared from fumaric acid derivatives (see SI for synthetic details). Intramolecular cyclizations of **2a−g** were carried out in the presence of cesium hydroxide to afford the interlocked *trans*-β-lactams **3a−g** in high yields (85−99%) (Table 2). Fumaramides **2b−d**, having only one benzyl at the amide group, showed lower reaction rates than **2a** and required an excess of base to complete their cyclization.

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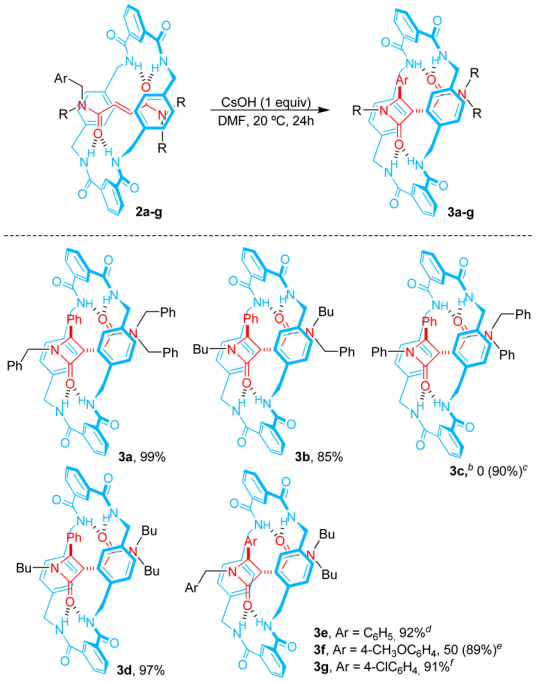
Table 2. 4-*Exo-trig* Ring Closure of *N*-Benzylfumaramides within [2]Rotaxanes 2a–g[a]

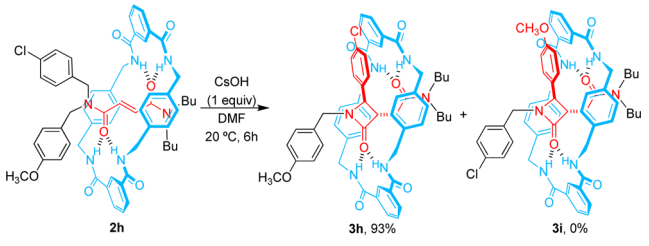


[a]Complete conversions were observed by ^{1}H NMR. Yields refer to isolated pure compounds. For convenience, **2a** and **3a** are also included herein. [b]The lactam ring quantitatively hydrolyzed, giving the interlocked 3-(phenylamino)propanoic acid derivative (see SI). [c]Based on the isolated hydrolysis compound. [d]Cyclization finished in 12 h. [e]A conversion of 90% required 5 equiv of CsOH and 48 h. [f]Cyclization finished in 40 min.

Intramolecular cyclization of the interlocked fumaramides **2e–g** also produced 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 (SI, Figure S1). Thus, the presence of donor substituents, e.g., a methoxy group, on the benzyl groups of the thread of **2f** notably slowed down the transformation, needing up to 48 h to reach conversions similar to those of the unsubstituted cases. In this vein, an electron-withdrawing substituent such as *p*-Cl at the ring of the benzyl units of **2g** notably accelerated the cyclization, which ended in less than 1 h. Note that this behavior predetermines the regiochemical outcome of the cyclization of **2h** to exclusively yield the lactam **3h** derived from the addition of the *p*-chlorobenzyl anion (Scheme 4).

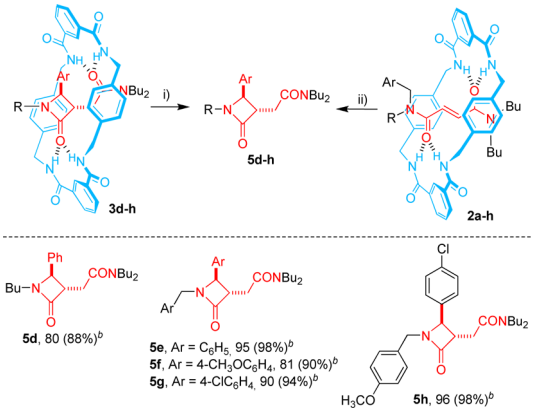
Rotaxanes **2d–g**, having one NBu_2 terminus, can be considered as kinetically stable pseudorotaxanes since under appropriate thermal conditions these complexes dissociate into

Scheme 4. Regiocontrolled Ring Closure within Rotaxane 2h



their non-interlocked components.[16] In fact, the half-life of **2e** in DMSO-d_6 at 373 K is only 6 min (SI, Figure S2). 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**. For instance, the half-life of **3e** in DMSO-d_6 at 373 K is 39 min (see SI, Figure S3). Heating solutions of the pseudorotaxanes **3d–h** in DMF extrudes the corresponding *β*-lactams **5d–h** in a quantitative manner (Table 3, conditions (i)).

Table 3. Synthesis of the *β*-Lactams 5d–h[a]



[a]Conditions: (i) 100 °C, 12 h; (ii) CsOH, DMF, 20 °C, 24 h then adjusting pH ≈ 7 with 2 N aq HCl and heating to 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.

Interestingly, both cyclization and dethreading steps can occur consecutively in a one-pot protocol by intercalating a neutralization step, thus enabling direct conversion of the fumaramide [2]rotaxanes into the corresponding *β*-lactams (Table 3, conditions (ii)).

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 initiated by the initial deprotonation of one of the four isophthalamide NH protons (Scheme 5), reasonably the most acidic ones of the whole supramolecule. This anion could then add to one of the sp^2 carbons of the fumaramide thread in an intramolecular aza-Michael reaction,[17] generating an enolate capable of internally abstracting one of the nearby benzylic protons from the dibenzylamido moieties. The resulting carbanion would then nucleophilically displace the anchimeric assistant group[18] to form the four-membered ring. The polar aprotic solvent, DMSO or DMF, should play a key role in stabilizing the anionic interlocked intermediates.

The vanishing of the double bond of the starting thread through the mechanism proposed herein forecasts that cyclization of the *Z* isomer of **2a** would also lead to the *trans*-*β*-lactam **3a**, as is, indeed, what occurs (see SI, Scheme S5). Additionally, ring closure of **1a** using *N*,*N*′-bis(4-(benzamidomethyl)benzyl)isophthalamide as an open-chain surrogate of the benzylic amide macrocycle (see SI, Scheme S8) or the non-interlocked macrocycle itself (see SI, Scheme S9) inhibited the cyclization. Both results further underpin the neighboring group participation of the mechanically linked cyclic polyamide in this transformation.

The base-catalyzed intramolecular Michael addition of *α*-benzylfumaramides occurring inside the cavity of a removable

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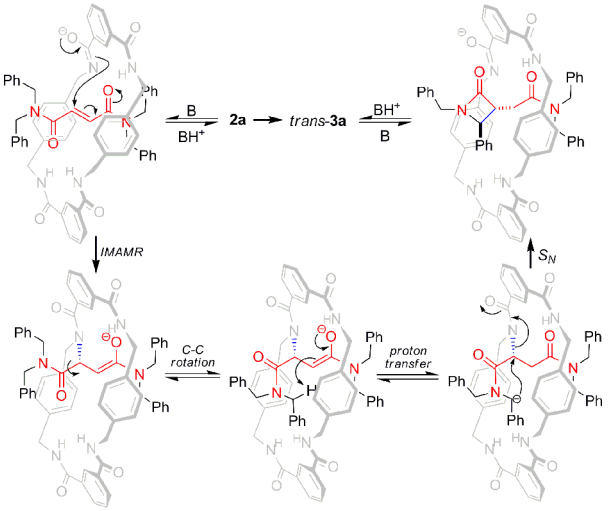
Scheme 5. Proposed Mechanism for the 4-*Exo-trig* Ring Closure of Interlocked Fumaramides[a]



[a]IMAMR = intramolecular aza-Michael reaction.

benzylic amide macrocycle, built from two isophtalamide units connected by two *p*-xylylene linkers, benefits from the activating and stereodirecting effects of the mechanical bond. These transformations, taking place in a confined space, proceeded without the formation of byproducts, at higher reaction rates than those of the non-interlocked fumaramides, and in a regio- and diastereoselective manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05581.

Experimental procedures, spectroscopic data for all new compounds, kinetics measurements, and full crystallographic details of **3a** (PDF)

X-ray crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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