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Mechanistic Insight into the Spirocyclopropane Isoxazolidine Ring Contraction

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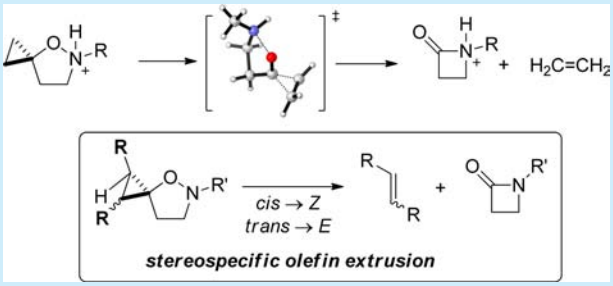
Supporting Information

ABSTRACT: A mechanistic study of the ring contraction of spirocyclopropane isoxazolidines to form β-lactams is reported. Based on experimental and computational investigations, we propose a concerted mechanism that proceeds with retention of configuration during cyclopropane cleavage.

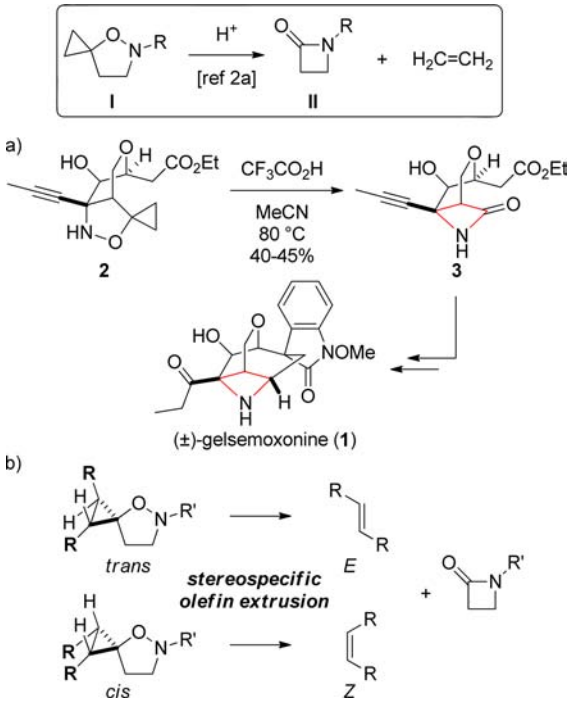


The β-lactam motif holds a prominent position in medicinal and pharmaceutical chemistry largely due to its role as the key functional unit in many antibiotic agents and as a scaffold.[1] Accordingly, chemists have been exploring strategies for the preparation of functionalized β-lactams for many decades. In 2000, Brandi and Cordero reported a novel transformation of 5-spirocyclopropane isoxazolidines (**I**) when treated with protic acids to give β-lactam products (**II**) with extrusion of ethylene (Scheme 1, box).[2] We have recently reported the total synthesis of the *Gelsemium* alkaloid (±)-gelsemoxonine (**1**) taking advantage of the ring contraction to build up the central azetidine of this highly compact natural product (Scheme 1a).[3] Treatment of spirocycle **2** with trifluoroacetic acid at 80 °C delivered the densely functionalized azetidinone **3** in moderate yield. Further manipulation of the amide carbonyl enabled access to the azacyclobutane found in gelsemoxonine. Herein, we report mechanistic computational and experimental studies on the spirocyclopropane isoxazolidine ring contraction, which indicate that the reaction proceeds concertedly with retention of configuration during the cyclopropane cleavage step (Scheme 1b).

Despite the potential utility of the spirocyclopropane isoxazolidine ring contraction for the preparation of highly substituted β-lactams and azetidines, the mechanism of this transformation still remains to be fully understood. Following the synthesis of gelsemoxonine, in anticipation of other applications for the ring contraction process we decided to embark on a closer mechanistic investigation of this intriguing reaction.

Several mechanistic hypotheses have been formulated to account for the conversion of **I** into **II**.[2] In particular, the discussion has focused on the two alternative pathways outlined in Scheme 2. Initial protonation of the nitrogen of the isoxazolidine substrate is expected to weaken the N−O bond in **4**. Concerted rupture of the cyclopropane and the N−O bond could lead, *via* a transition state such as **5**, to the observed product (path a). Alternatively, initial homolytic cleavage of the labile N−O bond has been invoked to explain the reaction outcome through a stepwise mechanism. Biradical **6** is

Scheme 1. Spirocyclopropane Isoxazolidine Ring Contraction



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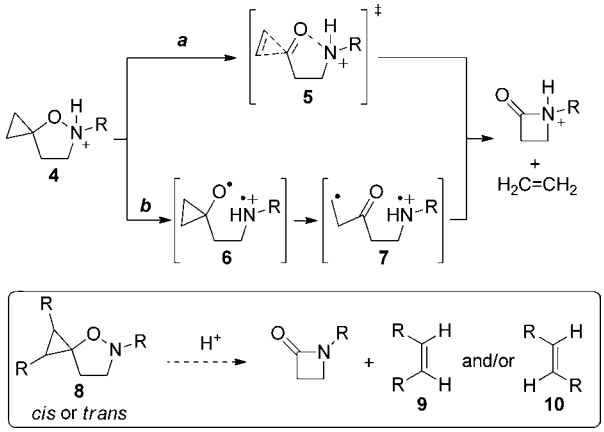
Scheme 2. Mechanistic Hypotheses for the Ring Contraction

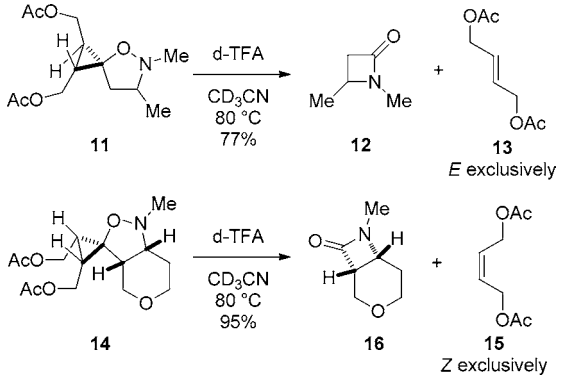


produced first and subsequently undergoes cyclopropane ring opening to give a second intermediate **7** (path b). The latter route parallels the mechanism proposed for the biosynthetic generation of the plant hormone ethylene from aminocyclopropanecarboxylic acid (ACC), whereby two stepwise single electron oxidation events produce radical intermediates similar to the ones proposed for the ring contraction **6** → **7**.[4] In a report focused on the reaction chemistry of spirocyclobutane isoxazolidines, Gandolfi and Brandi have alluded to unpublished computational studies concerning the spirocyclopropane isoxazolidine ring contraction whereby they indicated that *N*-protonation of the substrate is the initiating step of the reaction.[5] However, the authors comment that they could not distinguish between concerted and stepwise radical mechanisms based on the calculations. Furthermore, while ethylene loss from an intermediate radical analogous to **7** might be thermodynamically favorable, competing processes, such as H-atom abstractions or alternative ring-closing pathways, would have been expected a priori to occur more rapidly.[6] This is in line with the thermal rearrangement of spirocyclopropane isoxazolidines in the absence of acid, which affords piperidones, rather than *β*-lactams and ethylene, for which radical intermediates have also been suggested.[7]

We surmised that a combination of experimental and computational investigations would lead to a better understanding of the mechanism of this unusual ring contraction. In particular, we envisioned investigating the stereochemical course of the reaction by substitution of the cyclopropane ring in the isoxazolidine. Interestingly, the reaction had not previously been performed on substituted substrates that would permit evaluation of the loss or preservation of configurational information in the cyclopropane as it undergoes conversion to olefins (*cis*-/*trans*-cyclopropanes → *E*-/*Z*-olefins), as shown in Scheme 2. In the case of a stepwise mechanism proceeding *via* a radical intermediate such as **7** (Scheme 2, path b) the stereochemical information encoded in the substrate would be expected to be lost, resulting in the production of a mixture of olefins **9** and **10**. By contrast, if the reaction proceeded in a concerted fashion (Scheme 2, path a), stereoretentive formation of alkenes would be expected.

We initially prepared a substrate incorporating two *trans*-configured esters (R = CO_2Et) on the three-membered carbocycle. However, treatment of this compound with trifluoroacetic acid (TFA) did not lead to ring contraction and unchanged starting material was recovered (see Supporting Information). We next synthesized *trans*-substituted cyclopropane derivative **11** (Scheme 3).[8] As outlined in Scheme 3, a solution of **11** in CD_3CN was treated with deuterated

Scheme 3. Ring Contraction of Substituted Cyclopropanes 11 and 14



trifluoroacetic acid (d-TFA) (2.0 equiv) and heated to 80 °C. The ensuing ring contraction of isoxazolidine **11** was monitored by NMR spectroscopic analysis. After 30 min the complete disappearance of **11** and formation of *β*-lactam **12** and alkene **13** was observed by ^{1}H NMR spectroscopy. Chromatographic purification of the product mixture gave **12** in a 77% yield. Most interestingly, alkene **13** was isolated as a single stereoisomer with an *E*-configuration.[9] We next prepared *cis*-configured substrate **14**[8] and subjected it to similar ring contraction conditions (Scheme 3). Only *Z*-configured alkene **15**[9] was isolated along with expected azetidinone **16** (95% yield). Taken together, these results suggest that ring contraction proceeds either *via* a concerted mechanism or through a pathway involving intermediates that do not undergo C−C bond rotation over the time domain that collapse to product occurs. As an important aside, the high yield in which these reactions proceed should be noted, as it has consequences for the preparative implementation for these reactions.

In order to gain detailed mechanistic insight, we embarked on a computational study of the reaction (Figure 1). For this purpose, the ring contraction of *N*-protonated spirocyclopropane isoxazolidine **17** was examined applying the (U)-B3LYP/6-31+G(d) level of theory for geometry optimizations, followed by energy calculations at the (U)CCSD(T)/6-31+G(d) level of theory together with a CPCM solvation model to account for the solvent (MeCN) employed in the reaction.[10] Although the computational treatment of singlet biradicals is challenging, unrestricted DFT has successfully been employed.[11] Application of the T1 diagnostic by Lee and Taylor[12] at the coupled cluster CCSD(T) level showed that, with the exception of the initial ring-opening transition state (i.e., $\mathbf{TS}_{17,18}$), all structures gave a T1 value less than 0.02. CASSCF and RO-DFT methods were therefore additionally applied for $\mathbf{TS}_{17,18}$ and the closely surrounding potential energy surface (see Supporting Information for further information). In accordance with a previous report by Brandi and Gandolfi,[5] we found that nitrogen protonation significantly lowers the barrier for N−O bond scission to $\Delta G^{\ddagger}$ = 24.8 kcal/mol[13] ($\Delta G^{\ddagger}$ = 42.2 kcal/mol for unprotonated N−O[14]), whereas protonation of the oxygen does not lead to a barrier-lowering effect. As outlined in Figure 1, protonated substrate **17** was found to undergo concerted opening of the cyclopropane ring with concurrent release of ethylene and formation of intermediate

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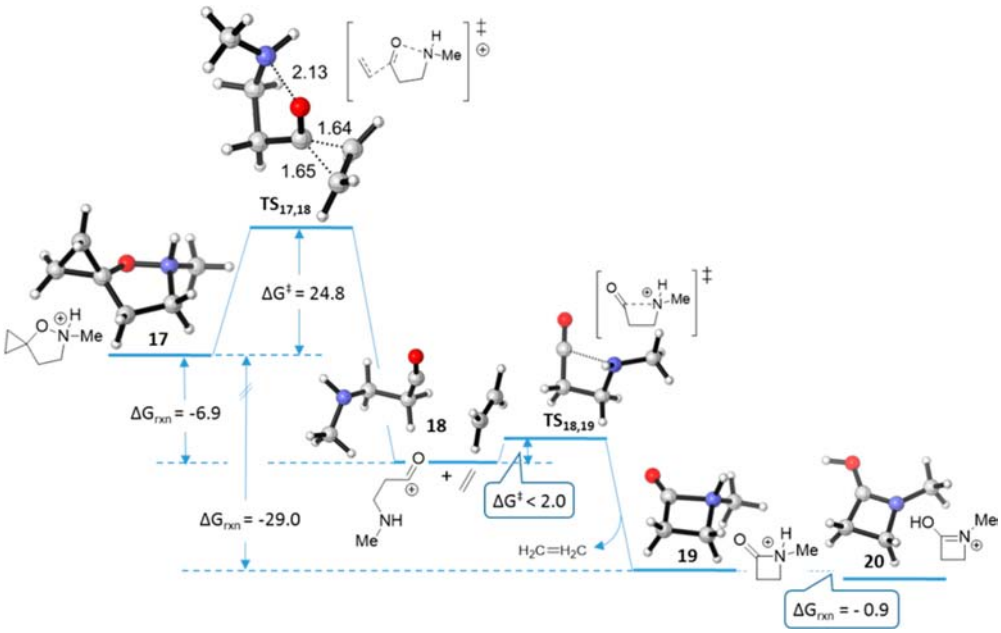

Figure 1. Favored ring contraction pathway calculated at the CPCM (MeCN) UCCSD(T)/6-31+G(d)//UB3LYP/6-31+G(d) level of theory. Concerted N−O bond scission/cyclopropane ring opening takes place under spontaneous loss of ethylene.[10,13,15]

complex **18**. Notably, no stable intermediate is formed en route to **18**.[15] This finding is in agreement with the experimental results presented above. Moreover, the reaction paths for substituted cyclopropanes, such as **11** and **14**, were calculated and found to result in the stereoretentive formation of the corresponding alkene coproduct (see Supporting Information).

As a consequence of spin contamination at the broken spin symmetry UB3LYP and UCCSD(T) levels of theory, it is challenging to unambiguously ascribe the nature (radical or polar) of the initial N−O cleavage in $\mathbf{TS}_{17,18}$. However, the observed spontaneous loss of ethylene would not match the generally anticipated reactivity paradigm of radical species. Closer inspection of $\mathbf{TS}_{17,18}$ and the reaction coordinate leading to **18** revealed that while the points in the region immediately following the transition state appear to have certain singlet biradical cation character ($\langle S^2 \rangle$ = 0.9198 at UCCSD(T)), the later points do not, ultimately resulting in **18** that appears to be a closed shell singlet ($\langle S^2 \rangle$ = 0). The NBO charges are as well in accord with this hypothesis, displaying large positive charge at the C═O carbon atom in **18**, as expected for an acyl cation intermediate. Moreover, an increase of negative charge at nitrogen along the reaction coordinate from $\mathbf{TS}_{17,18}$ to **18** was identified. Thus, while the N−O cleavage may display some biradical character, there is a transition to a polar mechanism. The induced partial positive charge at the oxy-cyclopropyl unit triggers spontaneous ethylene loss.[16]

As shown in Figure 1, acyl cation **18** was found to then collapse without any significant activation barrier to protonated lactam **19**. Calculation of the conversion of product **19** to its tautomeric form indicated that iminium **20** is only slightly favored over N-protonated amide **19** (ΔG = −0.9 kcal/mol), which suggests that **19** and **20** are present as an equilibrating mixture of isomers.[17] Consequently, in addition to its barrier-lowering effect, the role of *N*-protonation is to ensure crossover to a polar mechanism that is accompanied by concerted ethylene extrusion.

In summary, based on experimental and computational studies insight has been gained into the acid-mediated ring contraction of spirocyclopropane isoxazolidinones to form *β*-lactam products. We propose a mechanistic scheme that is characterized by a concerted rupture of the cyclopropane ring and the labile N−O bond of the substrate. Finally, one can anticipate wider use of this powerful ring contraction in the service of complex molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization, and details concerning computational studies are given. 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 interest.

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(7) Brandi, A.; Guarna, A.; Goti, A.; Pericciuoli, F.; De Sarlo, F. *Tetrahedron Lett.* **1986**, *27*, 1727.
(8) For the preparation of **11** and **14**, see Supporting Information.
(9) Independently synthesized alkenes **13** and **15** were separately subjected to the reaction conditions (2.0 equiv of TFA, MeCN, 80 °C), but no isomerization of the double bond configuration could be observed.
(10) All calculations were conducted with Gaussian09, Revision A.01; Frisch M. J. et al. See Supporting Information for full reference and further computational details.
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(13) We also calculated this step at CBS-QB3/6-31+G(d) in the gas phase, which gave an activation free energy barrier of $\Delta G^{\ddagger}$ = 21 kcal/mol for the N−O scission/cyclopropane opening. The barrier at the CASSCF(6,6)/6-31G(d)//B3LYP/6-31+G(d) level of theory (in the gas phase) is $\Delta G^{\ddagger}$ = 27.3 kcal/mol.
(14) This is in line with a previous study by Ochoa *et al.* on the thermal rearrangement of spirocyclopropane isoxazolidines in the absence of a proton (Brandi reaction): Ochoa, E.; Mann, M.; Sperling, D.; Fabian, J. *Eur. J. Org. Chem.* **2001**, 4223.
(15) We also undertook optimizations of $\mathbf{TS}_{17,18}$ at CBS-QB3 and in MeCN, which also resulted in concerted ethylene loss upon ring opening, following the IRC. The optimizations with implicit solvation were done with a CPCM model and CBS-QB3/6-31+G(d) or UB3LYP/6-31+G(d) levels of theory. Moreover, single-point energy calculations of crucial points along the coordinate at CASSCF and RO-B3LYP also suggested that the concerted cleavage was energetically favored (see Supporting Information for more details).
(16) In line with this, separate calculations of the acyl radical and amine radical cation units show that the corresponding redox products, acyl cation, and amine are thermodynamically significantly favored (by 27 kcal/mol).
(17) (a) It is generally held that amides undergo preferential protonation at oxygen. However, it has been suggested that amide bond isomerization in the presence of Brønsted acid cataylsts can occur through a kinetically significant intermediate resulting from N-protonation. See: (b) Cox, C.; Lectka, T. *Acc. Chem. Res.* **2000**, *33*, 849. (c) In this respect, it is relevant to the mechanism under study that N-protonation of 2-azetidinones has been proposed to be central to the activity of class A lactamases. See: (d) Atanasov, B. P.; Mustafi, D.; Makinen, M. W. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 3160.