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## How small can a catenane be, if we consider quantum tunnelling?†

 Sindy Julieth Rodríguez-Sotelo,<sup>‡</sup> Juan Julian Santoyo-Flores<sup>‡</sup> and Sebastian Kozuch<sup>‡\*</sup>

We explored the kinetic stability of the smallest possible alkane-based catenanes and pseudo-rotaxanes, focusing on their heavy atom quantum tunnelling instability. We found that the “corset effect” exerted by a ten-membered ring renders other rings unstable even under deep cryogenic conditions, where it may be taken as stable if tunnelling is neglected.

The idea of creating mechanically interlocked molecules (MIMs) held together without the intervention of chemical bonds is over a century old.<sup>1–4</sup> Only in the sixties, the first [2]catenane<sup>5</sup> (two connected rings) and rotaxane<sup>6–8</sup> (a macrocycle enclosing a chain molecule) were observed. A closely related class, known as pseudo-rotaxanes (macrocycles threaded by a molecular axle, a key intermediate in the synthesis of rotaxanes) also emerged as a useful model for studying dynamic host-guest interactions (Fig. 1).<sup>9,10</sup> This established the basis for further development for potential applications such as molecular machines, molecular switches, and others.<sup>11–15</sup>

The search for small catenanes and pseudo-rotaxanes is an intense research area in which stability plays a fundamental role. A computational study suggested that two symmetrical alkane-based rings with 14 members (herein termed “ $R_{14}R_{14}$ ”) represent the smallest structures able to resist fragmentation under standard laboratory conditions.<sup>16</sup> However, even [2]cycloundecane-catenane ( $R_{11}R_{11}$ , the smallest ring studied in ref. 16) proved to be viable, as it exhibited a stable local minimum on the potential energy surface. This was therefore considered to be semi-classically (SC) stable at low temperatures. While these computational findings provided insights into small catenane structural stability, the additional factor of quantum tunnelling (QT) must be considered, as it can

dramatically affect the kinetic stability of molecules at low temperatures.<sup>17–20</sup> Under deep cryogenic conditions, the study of SC mechanisms is sometimes insufficient to fully comprehend the decomposition of metastable molecules, as the wave-nature of atoms might permit their tunnelling through the barrier. QT can emerge on systems with relatively low barriers and light reacting atoms, but especially when short atom displacements are involved. Such conditions can appear in bond-breaking reactions of strained systems,<sup>18–20</sup> even when “heavy atoms”<sup>21,22</sup> (*i.e.*, not hydrogen) cause the rearrangement. This phenomenon is particularly important in assessing the stability of organic molecules, where carbon-carbon bond cleavage is common.

In catenanes, the general structural integrity is maintained by mechanical bonds,<sup>23</sup> which provide both flexibility and robustness, with the structural and dynamic size thresholds at the molecular level being directly relevant to the design of their functional architectures.<sup>24</sup> Fully separating the interlocked components requires breaking covalent bonds, which can only be achieved under harsh conditions. This raises theoretical questions: in a fully quantum regime, can tunnelling influence the kinetic stability of catenanes and pseudo-rotaxanes? What is the minimum number of carbons that can keep a [2]catenane or a pseudo-rotaxane stable, when

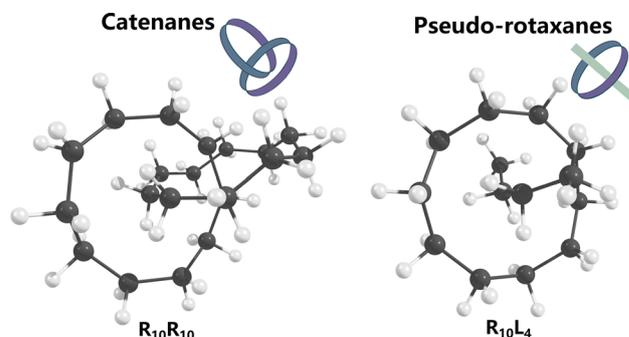


Fig. 1 Geometric arrangement of catenanes and pseudo-rotaxanes.

Ben-Gurion University of the Negev, Beer-Sheva 841051, Israel.

E-mail: kozuch@bgu.ac.il

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‡ Equal contributors.

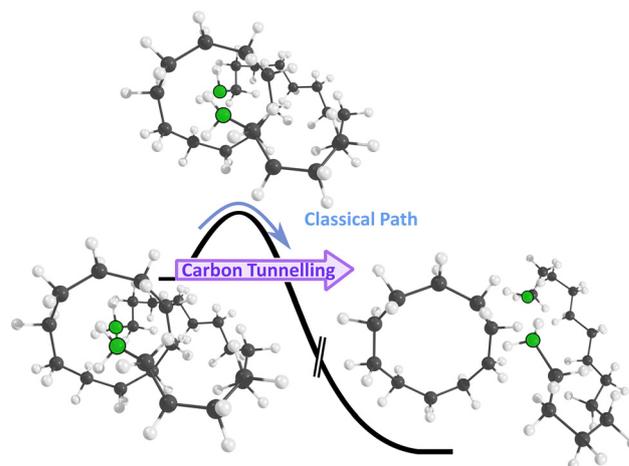
**Table 1** ZPE included threshold energies in  $\text{kJ mol}^{-1}$ , imaginary frequencies at the transition state in  $\text{cm}^{-1}$ , longest C–C bond length in Å, and tunnelling and semi-classical rate constants in  $\text{s}^{-1}$  from ground state QT (10 K) and including thermally activated QT under liquid  $\text{N}_2$  conditions (77 K) for studied [2]catenanes and pseudo-rotaxanes

System	$\Delta E^\ddagger$	$\nu^\ddagger$	C–C	10 K		77 K	
				$k_{\text{QT}}$	$k_{\text{SC}}$	$k_{\text{QT}}$	$k_{\text{SC}}$
<b>R<sub>10</sub>R<sub>10</sub></b>	6.2	239	1.760	$3 \times 10^7$	$10^{-23}$	$4 \times 10^8$	$8 \times 10^7$
<b>R<sub>10</sub>R<sub>11</sub></b>	6.9	232	1.758	$2 \times 10^3$	$10^{-26}$	$8 \times 10^7$	$3 \times 10^7$
<b>R<sub>10</sub>R<sub>12</sub></b>	7.1	234	1.731	$4 \times 10^{-1}$	$10^{-27}$	$6 \times 10^7$	$2 \times 10^7$
<b>R<sub>10</sub>R<sub>13</sub></b>	5.9	221	1.757	$4 \times 10^6$	$10^{-25}$	$2 \times 10^8$	$3 \times 10^7$
<b>R<sub>10</sub>R<sub>14</sub></b>	8.0	241	1.747	$9 \times 10^3$	$10^{-31}$	$2 \times 10^7$	$6 \times 10^6$
<b>R<sub>10</sub>R<sub>15</sub></b>	6.3	216	1.765	$4 \times 10^6$	$10^{-24}$	$3 \times 10^8$	$7 \times 10^7$
<b>R<sub>10</sub>R<sub>20</sub></b>	26.8	178	1.706	$10^{-21}$	$10^{-140}$	$2 \times 10^{-7}$	$6 \times 10^{-8}$
<b>R<sub>11</sub>R<sub>11</sub></b>	23.9	263	1.706	$10^{-12}$	$10^{-155}$	$3 \times 10^{-4}$	$8 \times 10^{-5}$
<b>R<sub>10</sub>L<sub>4</sub></b>	37.9	245	1.671	$10^{-25}$	$10^{-188}$	$10^{-13}$	$10^{-14}$
<b>R<sub>10</sub>L<sub>6</sub></b>	38.7	203	1.675	$10^{-39}$	$10^{-191}$	$10^{-14}$	$10^{-14}$
<b>R<sub>10</sub>L<sub>8</sub></b>	39.6	184	1.676	$10^{-39}$	$10^{-195}$	$10^{-14}$	$10^{-15}$
<b>R<sub>10</sub>L<sub>10</sub></b>	39.5	174	1.677	$10^{-34}$	$10^{-194}$	$10^{-9}$	$10^{-9}$

tunnelling is considered? These issues go beyond the traditional utility of MIMs and molecular machines, addressing the essential academic theme of stability and synthesizability under extreme circumstances. To investigate such effects, often inaccessible to direct experimental observation, we studied a series of minimal interlocked systems using quantum chemical methods. This allowed us to define which systems may be potentially isolated (even if they provide a daunting synthetic challenge), and which systems are physically impossible to be created.

We termed the studied systems as **R<sub>n</sub>R<sub>m</sub>** and **R<sub>n</sub>L<sub>m</sub>** for [2]catenanes and pseudo-rotaxanes. **R** and **L** denote cycloalkane rings and linear alkanes, respectively, and the subindex indicates the number of methylene links. The studied cases are shown in Table 1, with the optimized geometries provided in the ESI.†

The SC degradation rate constants ( $k_{\text{SC}}$ ) were computed with canonical variational transition state theory (CVT),<sup>25</sup> and QT corrected values ( $k_{\text{QT}}$ ) were obtained with small curvature tunnelling (SCT) correction<sup>26</sup> using Polyrate17<sup>27</sup> (an example of a Polyrate input file is provided in the ESI.†). All electronic energy computations were performed with Gaussian 16,<sup>28</sup> with Gaussrate17B<sup>29</sup> acting as an interface between the two packages. The potential energy surface was computed at the PBE<sup>30</sup>/6-31G(d) level, a fast method for the heavy QT computations, which semi-quantitatively agreed with the barriers obtained with DLPNO-CCSD(T1),<sup>31,32</sup> as carried out with ORCA 6<sup>33</sup> (all presented energies include zero-point energies obtained with PBE/6-31G(d)). The details for the selection process of the electronic structure method are provided in the ESI.† To improve the rate constants, the DFT computed energy surface was improved with a double-layer ISPE correction,<sup>34</sup> using the threshold energies obtained with DLPNO-CCSD(T1)/cc-pvqz. However, the obtained threshold energies of the most reacting systems are especially low, making the errors prominent in relative terms, even if the quantum structure method is of high quality. Since rate errors grow exponentially with energy errors, we acknowledge that the final results will be of

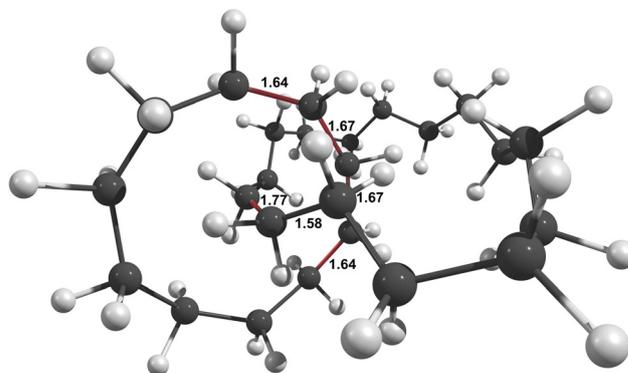


**Fig. 2** Schematic representation of the quantum tunneling-induced ring opening in the **R<sub>10</sub>R<sub>15</sub>** [2]catenane. The intact catenane in the left consists of the **R<sub>10</sub>** and **R<sub>15</sub>** interlocked rings. The larger one undergoes a C–C bond cleavage caused by the pressure exerted by the smaller ring *via* quantum tunnelling, resulting in the ring opening.

semi-quantitative value.<sup>35</sup> Nevertheless, as we shall see, the results are clear-cut.

In [2]catenanes and pseudo-rotaxanes, the degree of stress caused by the close packing can be evidenced by the elongation of C–C bonds, mostly in the interacting regions between catenanes, see Fig. 2 and 3. In the most strained catenanes, the C–C length in the ring intersection exhibits significant elongation, reaching up to 1.77 Å in **R<sub>10</sub>R<sub>15</sub>** (for comparison, the observed shortest bond was 1.54 Å, essentially a standard alkane single bond). Noteworthy, the greater strain always appears in the larger ring, while for the ten-membered ring no bond is longer than 1.70 Å (except, of course, for the symmetrical **R<sub>10</sub>R<sub>10</sub>**, see bond lengths in Fig. 2, 3, Fig. S1, Table S2 and ESI.†).

Our results indicate that the smaller ring (**R<sub>10</sub>**) exerts a localised compression to the C–C bond in the intersection zone of the larger ring, a phenomenon that we called the “corset effect”. This constricting effect of the small ring on a single bond of the large ring must necessarily be of the same magnitude compared to the opposed expanding force of the bond of



**Fig. 3** [2]Catenane **R<sub>10</sub>R<sub>15</sub>**, with selected bond lengths.

the larger ring exerted over the smaller one (a kind of “action and reaction”). However, the former is a collective effect over a single bond, while the latter involves a single bond expanding the ring structure equally over many bonds, diluting the force. The corset effect can therefore explain why larger rings are the most labile, despite being the ones with smaller intrinsic ring strain.

This is evident when comparing the threshold energies of breaking the large and the small rings in  $\mathbf{R}_{10}$  (see Table 1 and Table S5, ESI†). For instance, in the case of  $\mathbf{R}_{11}\mathbf{R}_{11}$ , breaking a C–C bond essentially is as difficult as breaking the small ring of  $\mathbf{R}_{10}\mathbf{R}_{11}$ , with lifetimes ( $\tau = 1/k_{QT}$ ) of centuries. This makes  $\mathbf{R}_{11}\mathbf{R}_{11}$  the smallest catenane in this series that, when considering QT, remains kinetically stable at any temperature. This longer lifetime highlights the key role of internal stress distribution and inter-ring packing in determining kinetic stability. However, for  $\mathbf{R}_{11}\mathbf{R}_{11}$  around 40 K, the reaction does proceed with a significant acceleration through thermally activated tunnelling, enhancing the reaction rate by nine orders of magnitude (see Table S6, ESI†).  $\mathbf{R}_{10}\mathbf{R}_{12}$  also has a surprising weight of thermally activated tunnelling (shown in pink in Fig. 4), due to some low-energy geometry reorganization in the reaction.<sup>36–38</sup> Interestingly, the barrier height does not always predict which reaction would be faster, as the barrier width is also a tunnelling factor. For instance,  $\mathbf{R}_{10}\mathbf{R}_{10}$  has a slightly higher barrier than  $\mathbf{R}_{10}\mathbf{R}_{13}$ , but the latter is one order of magnitude slower. This can be understood from the larger imaginary frequency of the reaction with the smaller ring, corresponding to a sharper potential energy profile, usually indicating a narrower barrier.

Of note, any attempt to stabilise a C–C bond inside an  $\mathbf{R}_n$  was unsuccessful, since the ring promptly “guillotines” the bond in a barrierless process.

In contrast to catenanes, for pseudo-rotaxanes the longest C–C bond inside the  $\mathbf{R}_{10}$  ring does not exceed 1.68 Å (see Fig. S3, Table 1, Table S4 and ESI†). The bond-breaking threshold energies are still low, but much larger than those for catenanes. This indicates that although the corset effect is

the main culprit for the instability of the compounds, the residual strain of the large rings slightly adds to the lability of the bonds. In pseudo-rotaxanes, without any ring strain, the reaction requires relatively much higher energies, making these systems stable even under liquid  $N_2$  conditions, with a negligible QT influence. The same was observed for  $\mathbf{R}_{10}\mathbf{R}_{20}$ , where the size and floppiness of the large ring mimic the free nature of the linear alkane in pseudo-rotaxanes, producing a much higher decomposition threshold energy compared to smaller rings.

As can be seen in Table 1 and in the Arrhenius plot of Fig. 4, the smallest [2]catenane considered in this study,  $\mathbf{R}_{10}\mathbf{R}_{10}$ , is severely unstable solely due to heavy atom tunnelling, with a maximum lifetime of nanoseconds. Hence, it would be impossible to isolate and synthesise this molecule even under deep cryogenic conditions.

Essentially, the most significant aspect of this study is that all the  $\mathbf{R}_{10}\mathbf{R}_m$  systems with  $m$  from 10 to 15 exhibit QT instability of different lifetimes (from seconds to nanoseconds), while larger cases, like the  $\mathbf{R}_{10}\mathbf{R}_{20}$  studied here, do not. Interestingly, large rings with an odd number of methylene units are usually less stable than shorter cycles with an even number of links (compare  $\mathbf{R}_{10}\mathbf{R}_{13}$  and  $\mathbf{R}_{10}\mathbf{R}_{15}$  with  $\mathbf{R}_{10}\mathbf{R}_{12}$  and  $\mathbf{R}_{10}\mathbf{R}_{14}$ ). This points to a minor extra geometric instability of the odd-membered rings surrounding the  $\mathbf{R}_{10}$  unit, probably caused by a slightly worse adaptation of these conformers encircling the other chain under strain. This small energetic-geometrical effect is amplified by the highly susceptible QT effect.

In summary, we predict that the smaller alkane-based [2]catenane with a chance of being stable is made of a pair of cycloundecanes. Cycloundecane will cut by a “corset effect” an interlocked cycloalkane. However, if the larger ring is larger than  $\sim 20$  methylene units, or in the case of pseudo-rotaxanes, the flexibility of the large ring or the free open chain is enough to avoid the degradation.

We emphasise again that to computationally obtain the real stability of hypothetical strained molecules at low temperatures, heavy atom quantum tunnelling must always be taken into account. Ignoring these effects may lead to a stability overestimation, as a purely classical analysis would fail to capture the rapid degradation of strained systems; in this case, of small catenanes.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The supplementary information is provided in a pdf file, with the geometries and Gaussian output files available on the ioChem-BD platform for computational chemistry and materials science teams, at the following link: <https://iochem-bd.bsc.es/browse/review-collection/100/446103/f7f3084765a90cd35352cc49>.

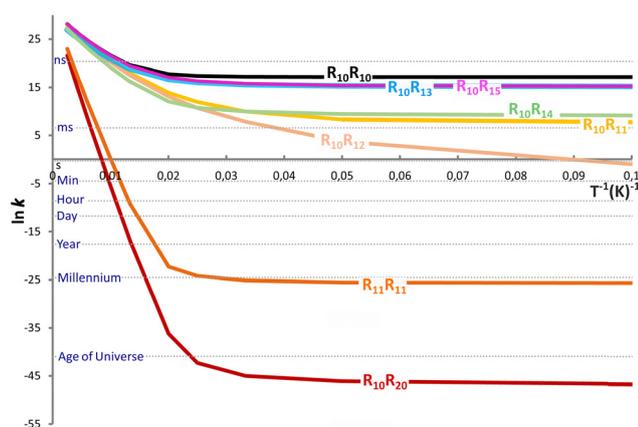


Fig. 4 Arrhenius plot for the degradation by C–C bond breaking of  $\mathbf{R}_{10}\mathbf{R}_m$  and  $\mathbf{R}_{11}\mathbf{R}_{11}$  catenanes. Horizontal dotted lines show, for reference, selected lifetimes.

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