

A topologically chiral catenane that is not topologically chiral

Noel Pairault,[‡] Federica Rizzi,[‡] David Lozano, Ellen M. G. Jamieson, Graham J. Tizzard, Stephen M. Goldup*
Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ (UK), *s.goldup@soton.ac.uk

SUMMARY

To consider the topology of a molecule its structure is reduced to labelled vertices (the atoms) and edges (bonds between them) to generate a molecular graph¹. If only covalent bonding interactions are included^{2,3}, such graphs are like the structural diagrams commonly employed to describe molecules, except that in topological terms, atomic geometry is largely irrelevant; most molecules can be represented as a two-dimensional network and most covalent stereogenic units are topologically irrelevant. In 1960, Wasserman synthesized a molecule in which two rings are held together like in a chain, which is a topological isomer of the separated components, leading to the realization that molecules could be topologically non-trivial. This insight found wider implications in biochemistry and materials science but also led to the assumption that the stereochemistry of chiral catenanes is inherently topological in nature. We show this is incorrect by synthesizing an example whose stereogenic unit is identical to previous reports but whose stereochemistry is Euclidean. Thus, we can unite the stereochemistry of catenanes with that of their topologically trivial cousins, the rotaxanes, paving the way for a unified approach to their discussion.

INTRODUCTION

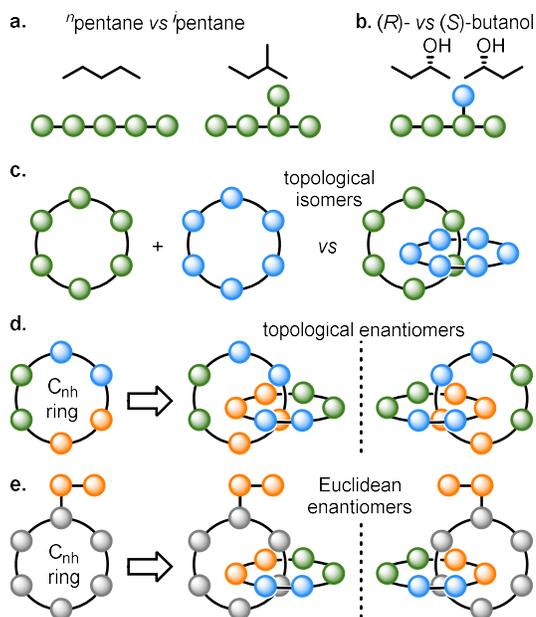
Topology and topological are often misapplied in chemistry to mean “shape”, perhaps through confusion with topography and topographical respectively¹. Formally, chemical topology finds its roots in mathematical topology⁴, the study of the properties of networks, surfaces, and objects under topologically allowed transformations. One of the first applications of topology in chemistry was to enumerate the available isomers of higher order alkanes (C_nH_{2n+2})⁵ and there is continued interest in how molecular topology can be used to analyze chemical structures and their properties⁶. Conversely, the proposal by Lord Kelvin that atoms were the manifestation of knotted vortices motivated Tait to develop the first systematic categorization of knots⁷.

The key difference between a chemical topologist's graph and a chemist's structural diagram is that the former does not consider molecular rigidity or geometry; when considering its topology, a molecular graph can be distorted arbitrarily provided the bonds are not broken or pass through one another – all other transformations are valid including the stretching of bonds and distortion of bonding geometry to an unphysical extent. Using this approach, we can distinguish between the topological properties of different classes of molecular isomers using the terms “homeomorphic” (same atomic connectivity) and “isotopic” (same molecular graph). Constitutional isomers (e.g., of pentane, **Fig. 1a**) are neither homeomorphic (different connectivity) or isotopic (graphs cannot be manipulated to become identical). Stereoisomers that are distinguished by differences in their arrangement of atoms in space due the geometric properties of atoms (**Figure 1b**) are homeomorphic (same connectivity) and isotopic (can be deformed into one another) – they are topologically identical as the difference between the isomers is lost once their Euclidean properties are relaxed.

In 1961⁸, Wasserman and Frisch recognized that some molecular structures cannot be reduced to a planar molecular graph, in that there is no two-dimensional projection of their three-dimensional structure in which no edges cross one another, and that such structures have isomers to which they are homeomorphic (same atomic connectivity) but not isotopic (different topology). This observation was inspired by Wasserman's synthesis of a molecular catenane in which two molecular rings are joined like links in a chain⁹, which are topological isomers of the separated components (**Fig. 1c**). Other classes of molecules that display topological isomerism have since been reported, including Mobius structures^{10,11,12}, knots¹³ and covalent systems in which bond crossings are enforced.

Wasserman and Frisch also highlighted that catenanes could exist as topological enantiomers if both rings are “oriented” due the sequence of distinguishable atoms embedded in their molecular graph (**Fig. 1d**)⁸. Such catenanes have since been referred to simply as “topologically chiral”, alongside Mobius ladders and some knots,^{14,15} which display topological enantiomerism independent of their constitution. Although it is clearly correct to discuss catenanes in terms of their topology, perhaps for this reason, no one has to our knowledge challenged the idea that the stereochemistry of catenanes containing two oriented rings is inherently topological in nature.

Figure 1. Example structures and molecular graphs exemplifying key concepts in chemical topology. Molecular structures and the molecular graphs of **a.** the constitutional isomers of pentane and **b.** the enantiomers of 2-butanol. **c.** Schematic molecular graphs of two non-interlocked rings and the topologically isomeric [2]catenane. **d.** Schematic molecular graph of an oriented ring (C_{nh} symmetry; $n = 1$) and the canonical chiral catenane it gives rise to in which stereochemistry is determined by atom sequence and thus topological in nature. **e.** Schematic molecular graph of a ring that is oriented (C_{nh} symmetry; $n = 1$) by exocyclic bond geometry and the non-canonical chiral catenane it gives rise to whose stereochemistry is analogous to that shown in **d.** but unambiguously Euclidean.



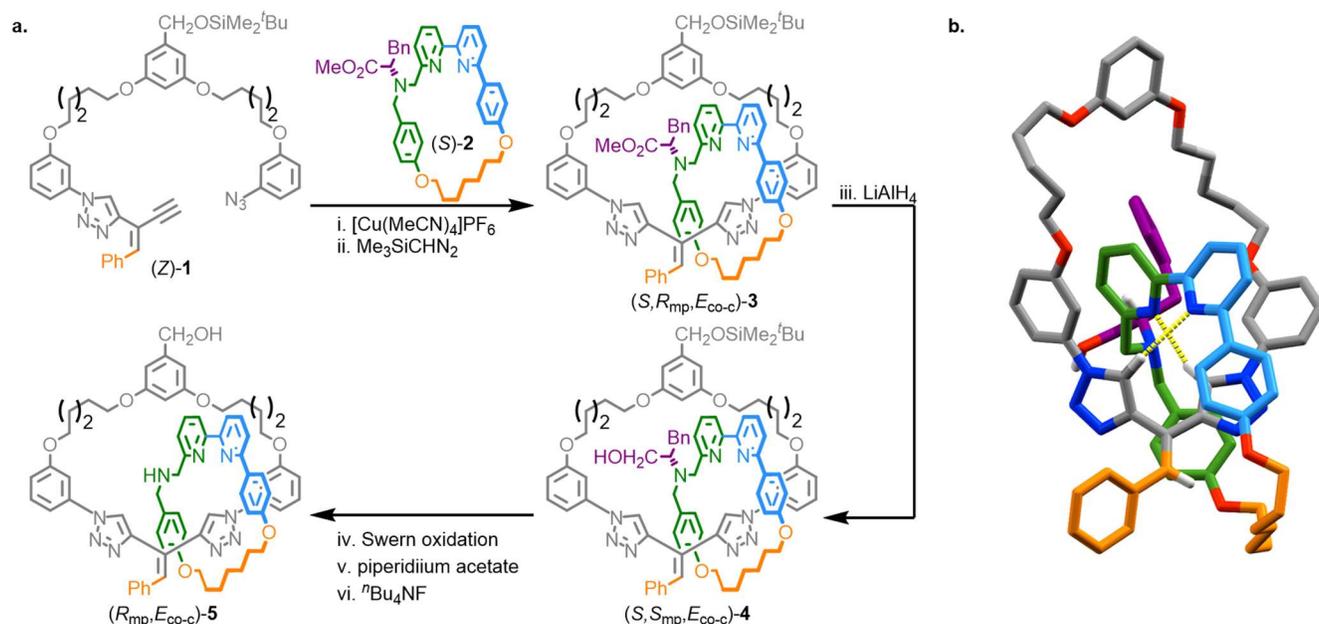
In their discussion⁸, and in all subsequent reported synthetic examples¹⁶, Wasserman and Frisch envisaged the stereogenic unit in a topologically chiral catenane as arising due to a defined sequence of atoms in their rings (**Fig. 1d**). In this case the stereogenic unit is indeed topological in nature; to generate the other enantiomer, one ring must pass through the other or the order of atoms in one ring must be changed. Focusing on the symmetry of the rings, we see that the stereogenic unit arises because the sole improper symmetry element of one ring (the mirror plane parallel to the macrocycle) cannot be made congruent with that of the other and so no improper symmetry elements remain in the catenane structure. Thus, the “topologically chiral” stereogenic unit of catenanes can be defined as arising when two C_{nh} rings (principal axis perpendicular to the ring plane) are interlocked. This analysis suggests that any structural feature that results in a C_{nh} ring will be suitable for the construction of a chiral catenane.

Here we present a chiral catenane whose rings are both oriented, conforming to the definition of the “topologically chiral” catenane stereogenic unit, but whose stereochemistry is Euclidean because the C_{nh} symmetry of one ring arises due to the geometric properties of an exocyclic double bond (**Fig. 1e**).

RESULTS

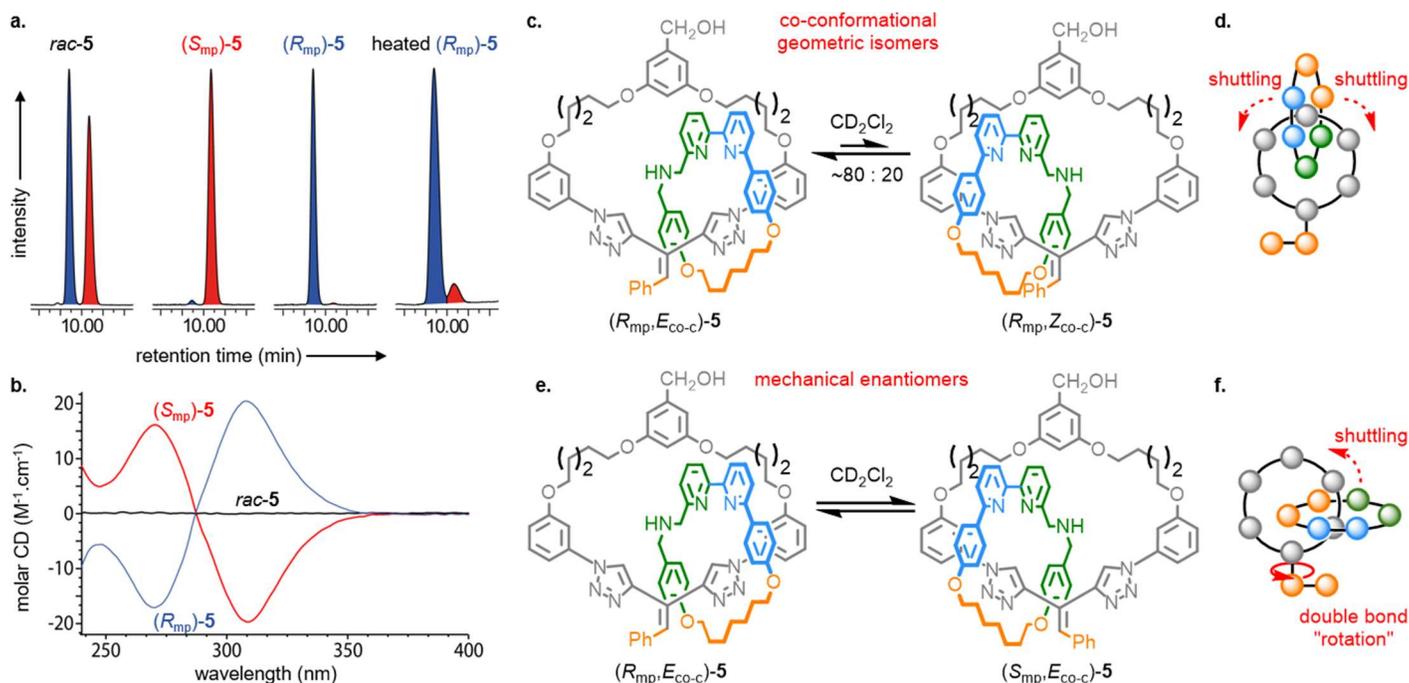
Stereoselective synthesis of chiral catenane 5. Catenane **3** was synthesized (**Fig. 2a**) using an active template¹⁷ Cu-mediated alkyne-azide cycloaddition reaction between azide/alkyne pre-macrocycle alkene (*Z*)-**1** and chiral bipyridine macrocycle (*S*)-**2** (98% ee)¹⁸. ¹H NMR analysis confirmed that catenane **3** was isolated as a single diastereomer (>96% *de*), consistent with the covalent stereochemistry of (*S*)-**2** efficiently controlling the relative orientation of the bipyridine and alkene containing macrocycles¹⁸. Catenane **3** also contains a co-conformational geometric stereogenic unit¹⁹, the configuration, E_{co-c} , of which is controlled by the geometry of the starting pre-macrocycle, (*Z*)-**1**, and fixed in the interlocked product due to the steric bulk of the styrene and silyl ether units which prevent shuttling of the bipyridine macrocycle between the two triazole-containing compartments. The pendant covalent chiral auxiliary unit of catenane **3** was removed following a simple chemical sequence (steps iii \rightarrow v) followed by cleavage of the silyl ether unit (step vi) to give catenane **5** which contains no covalent stereogenic unit. Catenanes **3**, **4** and **5** were characterized in full (see ESI for details). Samples of catenane **5** were also synthesized starting from (*R*)-**2** (98% ee) and *rac*-**2**. The solid-state structure obtained by single crystal x-ray diffraction analysis of intermediate catenane **4** derived from *rac*-**2** (**Fig. 2b**) contains the *rac*-(*S*, S_{mp} , E_{co-c})-**4** stereoisomer and thus the absolute stereochemistry of catenanes **3**, **4** and **5** derived from (*S*)-**2** can be assigned as (*S*, R_{mp} , E_{co-c})-**3** and (*S*, S_{mp} , E_{co-c})-**4**. The absolute stereochemistry of the expected major enantiomers of catenane **5** derived from (*S*)-**2** as and (*R*)-**2** can thus be assigned as R_{mp} and S_{mp} respectively (see Supplementary Information section 7 for a detailed discussion on stereochemical assignment in such systems).

Figure 2. Synthesis of catenane **5 and solid-state structure of intermediate catenane **4**.** **a.** Synthetic steps used to produce catenane **5**. Reagents and conditions: i. $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$, $\text{N}^i\text{Pr}_2\text{Et}$, CH_2Cl_2 , $35\text{ }^\circ\text{C}$; ii. $\text{Me}_3\text{SiCHN}_2$, THF-MeOH (1 : 1), rt (17% over 2 steps, >98% *de*); iii. LiAlH_4 , THF , $0\text{ }^\circ\text{C}$ (72%); iv. $(\text{COCl})_2$, Me_2SO , NEt_3 , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ to rt ; v. piperidinium acetate, $\text{THF-H}_2\text{O}$ (9 : 1), $70\text{ }^\circ\text{C}$ (76% over 2 steps); vi. $^n\text{Bu}_4\text{NF}$, THF , $0\text{ }^\circ\text{C}$ (56%). **b.** Solid-state structure of *rac*-(*S*,*S*_{mp},*E*_{co-c})-**4** in sticks representation with the bipyridine-triazole C-H...N H-bonds indicated (colors as in **a**. with the exception of O [red], H [white] and N [dark blue]; the $\text{CH}_2\text{OSiMe}_2^t\text{Bu}$ has been omitted for clarity).



Stereochemical analysis of catenane **5.** Care had to be taken throughout the synthesis of catenanes **5** to ensure the double bond geometry, which defines the orientation of the triazole-containing macrocycle, was maintained; the electron ring alkene unit is prone to acid-mediated isomerization. Pleasingly, chiral stationary phase HPLC (CSP-HPLC) analysis confirmed that catenanes **5** were formed in excellent stereoselectivity (98% ee, **Fig. 3a**) and that the samples derived from (*R*)-**2** and (*S*)-**2** produce mirror image circular dichroism (CD) spectra, whereas the sample derived from *rac*-**2** did not produce a CD response (**Fig. 3b**). ^1H NMR analysis of the isolated samples of catenane **5** revealed that the bipyridine macrocycle is in slow exchange between the triazole stations (**Fig. 3c**); although the *E*_{co-c} isomer was isolated and characterized, this slowly evolved in solution (CD_2Cl_2 , 303 K) to an equilibrium mixture containing both co-conformations ($\sim 80 : 20$ *E*_{co-c} : *Z*_{co-c}, Supplementary section 4 for a detailed discussion). This process takes place by shuttling of the bipyridine macrocycle around the triazole-containing macrocycle, past the benzylic alcohol unit, and demonstrates that the double bond of catenane **5** has no defined geometry. Thus, the only fixed stereogenic unit of catenane **5** results from the relative orientation of the two rings, as depicted in its highest symmetry representation (**Fig. 3d**).

Figure 3. Analytical data for catenane **5 and the stereoisomerization processes observed.** **a.** Chiral stationary phase HPLC chromatograms of catenanes (S_{mp})-**5**, (R_{mp})-**5**, *rac*-**5**, and the partially racemized sample obtained after heating (R_{mp})-**5**. **b.** Circular dichroism spectra of catenanes (S_{mp})-**5** and (R_{mp})-**5** demonstrating that they are enantiomeric. **c.** The observed co-conformational exchange process between as-synthesized E_{co-c} -**5** and Z_{co-c} -**5**. **d.** A schematic molecular graph of catenane **5** in its highest symmetry representation with the motion that leads to the exchange of co-conformational isomers highlighted. **e.** The enantiomerization process between (R_{mp} - E_{co-c})-**5** and (S_{mp} - E_{co-c})-**5** that takes place over time and confirms the non-topological nature of the stereogenic unit. **f.** A schematic molecular graph of catenane **5** in its E_{co-c} co-conformation with motions that lead to the enantiomerization of this species indicated.



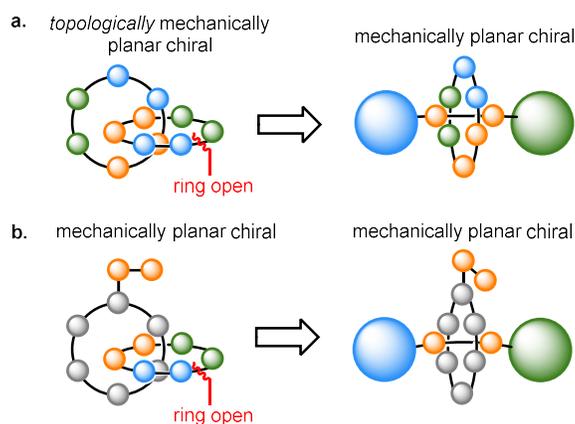
Finally, CSP-HPLC analysis revealed a second stereoisomerization process; alongside the isomerization between E_{co-c} and Z_{co-c} , a slower racemization process was also observed (**Fig. 3e**). Thus, over time (CD_2Cl_2 , 323 K) the stereopurity of (R_{mp})-**5** decreased from 98% ee to 84% ee (**Fig. 3a**). Based on the apparent protonation of catenane **5** over time and the behavior of an analogous rotaxane model (Supplementary section 5), we tentatively propose that the enantiomerization of **5** may take place by reversible protonation of the electron rich double bond. This process is the chemical equivalent of the topologically allowed isomerization of the catenane stereogenic unit by a double bond isomerization process accompanied by shuttling of the bipyridine ring around the triazole-containing ring combined (**Fig. 3f**).

CONCLUSIONS

Our results confirm that catenane **5** exists as a pair of enantiomers whose stereochemistry results from the mechanical bond and whose configuration is defined by the exocyclic double bond. This is consistent with our proposal that this molecule contains a mechanical stereogenic unit analogous to previously reported

catenanes labelled simply as “topologically chiral”, but it should also be clear that in this case the stereochemistry is not topological in nature, as confirmed by the racemization of **5** in solution through double bond isomerization. Given that the highest symmetry representations of both rings of catenane **5** are C_{nh} ($n = 1$), as is the case with all previously reported topologically chiral catenanes, we do not think it is reasonable to consider catenane **5** as a new class of chiral mechanically interlocked molecule. It is much simpler to acknowledge that there is a single catenane stereogenic unit when two C_{nh} rings are combined but that, depending on the structure of the rings, the stereochemistry can be either Euclidean or topological.

Figure 4. Schematic examples of mechanically planar chiral catenanes and rotaxanes. **a.** Catenanes composed of two rings that are oriented as a consequence of a sequence of atoms in the ring are topologically mechanically planar chiral whereas the corresponding rotaxane is simply mechanically planar chiral. **b.** If the ring orientation of one of the macrocycles arises due to bond geometry the corresponding catenane and rotaxane are both simply mechanically planar chiral.



This brings us to a wider point. The stereochemistry of rotaxanes (which are topologically trivial) and catenanes (which are not) is often considered independently but is clearly related; the schematic representation of a topologically chiral catenane can be converted to that of a mechanically planar chiral rotaxane by the notional process of ring opening and stoppering (**Fig. 4a**). Given that we have demonstrated that the “topological” stereogenic unit of catenanes is not inherently topological in nature, we propose that their relationship could be made clearer if both stereogenic units were united under the same name, mechanically planar chiral. In the case of catenanes, some examples will be topologically mechanically planar chiral (all previously reported examples), and others will simply be mechanically planar chiral (catenane **5**).

The unification of the mechanical planar chiral stereogenic units of rotaxanes and catenanes, as we have recently been demonstrated in the context of an analogous mechanical axial stereogenic unit²⁰, will facilitate future work in the field by highlighting that similar synthetic concepts are likely to be of use for both rotaxanes and catenanes. It also suggests that the focus should shift away from the topological properties of the catenanes; although chemical topology is an intriguing topic, we are not aware of any property of catenanes that has been unambiguously linked to their topologically non-trivial nature. Alternatively, perhaps by separating their stereochemistry into topological and Euclidean varieties, as we have done here, it will now be possible to demonstrate a unique property of the former.

SUPPLEMENTAL INFORMATION

Supplemental Information includes experimental procedures and characterization data for all novel compounds.

ACKNOWLEDGMENTS

S.M.G thanks the European Research Council (Consolidator Grant Agreement no. 724987) and the Royal Society for a Research Fellowship (RSWF\FT\180010)

AUTHOR CONTRIBUTIONS

S.M.G. secured project funding. S.M.G. and E.M.J.G. conceived the study. F.R. carried out the initial synthesis of catenane **3** and characterized the intermediates leading to this structure. N.P. optimized the synthesis of catenane **3** and its conversion catenane **5**. N.P. and D.L.M. completed the synthesis of the final compounds and their characterization. N.P. performed the isomerization studies on catenane **5**, including the synthesis and analysis of model compounds. N.P. obtained single crystals of catenane **4** and model rotaxane S* for x-ray analysis, which was performed by G.J.T. N.P. led the preparation of the Supplementary Information, including the stereochemical analysis of all interlocked products. S.M.G. wrote the manuscript. All authors contributed to the reviewing and editing of the manuscript and Supplementary Information.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Walba, D. M. Topological Stereochemistry. *Tetrahedron* **41**, 3161-3212 (1985).
2. It has been proposed that a more complete description would include interactions between atoms (eg. H-bonds) by including weighting in the edges linking atoms. See ref. 3.
3. Mislow, K. On the Classification of Pairwise Relations Between Isomeric Structures. *Bulletin des Sociétés Chimiques Belges* **86**, 595-601 (2010).
4. Flapan, E. *When Topology Meets Chemistry*. (Cambridge University Press, 2012).
5. Cayley, E. Ueber die analytischen Figuren, welche in der Mathematik Bäume genannt werden und ihre Anwendung auf die Theorie chemischer Verbindungen. *Berichte der deutschen chemischen Gesellschaft* **8**, 1056-1059 (2006).
6. Devillers, J. & Balaban, A. T. *Topological Indices and Related Descriptors in QSAR and QSPR*. (CRC Press, 2000).
7. Thomson, W. II. On vortex atoms. *Philos. Mag. S. 4*, 15-24 (1867).
8. Frisch, H. L. & Wasserman, E. Chemical Topology. *J. Am. Chem. Soc.* **83**, 3789-3795 (1961).
9. Wasserman, E. The Preparation of Interlocking Rings: a Catenane. *Journal of the American Chemical Society* **82**, 4433-4434 (1960).
10. Herges, R. Topology in chemistry: designing Mobius molecules. *Chem Rev* **106**, 4820-4842 (2006).
11. Ajami, D., Oeckler, O., Simon, A. & Herges, R. Synthesis of a Mobius aromatic hydrocarbon. *Nature* **426**, 819-821 (2003).
12. Segawa, Y. *et al.* Synthesis of a Möbius carbon nanobelt. *Nature Synthesis* **1**, 535-541 (2022).
13. Fielden, S. D. P., Leigh, D. A. & Woltering, S. L. Molecular Knots. *Angew. Chem. Int. Ed.* **56**, 11166-11194 (2017).
14. Zhang, G. *et al.* Lanthanide Template Synthesis of Trefoil Knots of Single Handedness. *J Am Chem Soc* **137**, 10437-10442 (2015).
15. Carpenter, J. P. *et al.* Controlling the shape and chirality of an eight-crossing molecular knot. *Chem* **7**, 1534-1543 (2021).
16. Maynard, J. R. J. & Goldup, S. M. Strategies for the Synthesis of Enantiopure Mechanically Chiral Molecules. *Chem* **6**, 1914-1932 (2020).
17. Denis, M. & Goldup, S. M. The active template approach to interlocked molecules. *Nat Rev Chem* **1**, 0061 (2017).
18. S. Zhang, A. R. Rubio, A. Saady, G. J. Tizzard, S. M. Goldup, manuscript submitted.
19. Corra, S., de Vet, C., Baroncini, M., Credi, A. & Silvi, S. Stereodynamics of E/Z isomerization in rotaxanes through mechanical shuttling and covalent bond rotation. *Chem* **7**, 2137-2150 (2021).
20. Maynard, J. R. J., Gallagher, P., Lozano, D., Butler, P. & Goldup, S. M. Mechanically axially chiral catenanes and noncanonical mechanically axially chiral rotaxanes. *Nat Chem* (2022).