A Co-conformationally "Topologically" Chiral Catenane

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Supporting Information Placeholder

ABSTRACT: Catenanes composed of two achiral rings that are oriented (C_{nh} symmetry) because of the sequence of atoms they contain are referred to as topologically chiral. Here we present the synthesis of a highly enantioenriched catenane containing a related but overlooked "co-conformationally 'topologically' chiral" stereogenic unit, which arises when a bilaterally symmetric C_{nv} ring is desymmetrised by the position of an oriented macrocycle.

Topology is the study of the properties of objects and networks that are preserved under deformations that do not break connections/surfaces or require surfaces/edges to pass through one another. Chemical topology applies these ideas to molecules.[1] At the simplest level, constitutional isomers are topologically distinct as they differ in the network of atoms. More interesting topological isomerism arises when structures contain identical atomic connections,[2] the most famous examples of which are Möbius ladders (isomers of the untwisted macrocycle),[3,4] molecular knots (isomers of the unknotted ring),[5] and [2]catenanes (isomers of two non-interlocked rings).[6] These structures have non-planar graphs in that there is no two-dimensional projection of their structures in which bonds do not cross over one another and this property is topologically invariant in 3 dimensional space – no matter how the structure is distorted, even drastically altering the geometry around atoms, a planar graph cannot be achieved.[1]

Such topologically non-trivial structures can display chirality in the absence of covalent stereogenic units.[2] Depending on their topology, Möbius ladders[7] and molecular knots[8] can be chiral as a result of the pattern of bond crossing points. Although [2]catenanes do not display unconditional topological stereochemistry,[9] as recognized by Wasserman and Frisch,[10] they can be chiral as a result of the constitutional symmetry of the rings; rings that are "oriented" (C_{nh} symmetry) due to the sequence of atoms in the cycle give rise to topologically chiral catenanes (Figure 1a).[11,12] The absolute stereochemistry of topologically chiral objects is invariant under all topologically allowed deformations in 3 dimensional space.[1]

We recently identified[11c] "missing" stereogenic units that arise in interlocked molecules and give rise to classes of chiral rotaxanes and catenanes that had yet to be discussed or synthesized.[13] An example that presents particular linguistic problems are [2]catenanes in which one ring is oriented (C_{nh}) and the other is bilaterally symmetric (C_{2v}) (Figure 1b). The time averaged structure of such catenanes is achiral but any co-conformation in which the oriented ring does not lie on the internal mirror plane of the C_{2v} ring is chiral. If the structure is designed such that the oriented ring is permanently prevented from occupying said mirror plane, the molecule will display kinetically fixed molecular chirality (Figure 1c).

As with related co-conformational-covalent[14] and co-conformational mechanical planar stereochemistry in rotaxanes,[15,16] this stereogenic unit can be considered to appear due to the oriented ring acting as a substituent of the region of C_{2v} ring that it encircles, effectively reducing its symmetry to C_{1h}. Thus, this stereogenic unit arises because one ring is oriented due to its constitution and the other by the molecular co-conformation and so we have previously provisionally termed such molecules "co-conformationally 'topologically' chiral" to clearly make the link with the established stereogenic unit of topologically chiral catenanes while also highlighting that the stereochemistry of the system is clearly not topologically invariant.

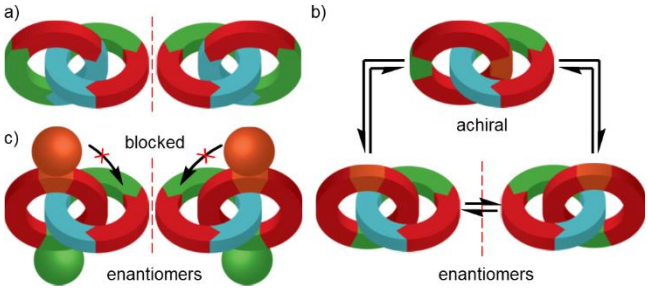


Figure 1. (a) Enantiomeric topologically chiral catenanes (two oriented C_{1h} rings). (b) Achiral and enantiomeric co-conformations of a co-conformationally "topologically" chiral [2]catenane (oriented ring and a C_{2v} ring). (c) Fixed enantiomeric chiral co-conformations of a co-conformationally "topologically" chiral catenane for which co-conformational isomerism is sterically prohibited.

Semantic arguments aside, we set out to synthesise an enantioenriched co-conformationally "topologically" chiral [2]catenane, in part to highlight the potential for interlocked molecules to display hitherto unnoticed stereochemistry. To achieve this, we developed a stereoselective synthesis of topologically chiral [2]catenanes, which was then extended to a co-conformationally chiral target.

The stereoselective synthesis of a co-conformationally chiral catenane requires: i) the oriented ring to be incorporated at a defined position around the C_{2v} macrocycle, and ii) the oriented ring to be installed stereoselectively. The first requirement can be met by forming the mechanical bond such that the oriented ring is trapped between bulky groups. The second is the same problem as encountered in the synthesis of any topologically chiral [2]catenane.[17] Although the majority of enantioenriched topologically chiral catenanes in which the mechanical bond is the sole source of stereochemistry[18] have been accessed by chiral stationary phase HPLC (CSP-HPLC) separation,[12] we recently developed an auxiliary approach in which a

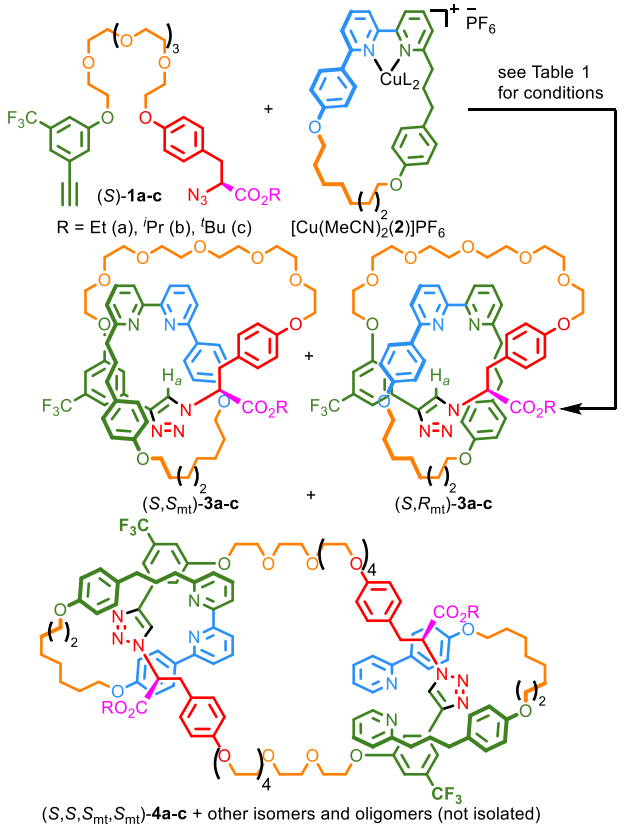
chiral covalent auxiliary directs the stereoselective formation of the mechanical bond.[19] However, in this proof-of-concept synthesis, the stereoselectivity of the mechanical bond formation was low (*dr* ~ 2 : 1), which required the mechanical epimers to be separated prior to removal of the auxiliary, limiting the utility of this methodology for more complicated targets. To overcome this challenge, we set out to extend a phenylalanine-based auxiliary, developed for the synthesis of mechanical planar chiral rotaxanes,[20,21] to the synthesis of topologically chiral [2]catenanes.

Table 1. Effect of reaction conditions and structure of **1** on the AT-CuAAC synthesis of topologically chiral catenanes **3**[a]

entry	R	T (°C)	t (h)	2 : 3 : oligos[a]	*de*[a]	yield
1	Et	60	4	34 : 44 : 22	70 %	n.d.
2	Et	60	8	47 : 37: 16	62 %	n.d.
3	Et	25	4	15 : 44 : 41	74 %	39%
4	^{i}Pr	25	4	14 : 30 : 56	82 %	26%
5	^{t}Bu	25	4	77 : 11 : 12	68 %	n.d.[b]

[a]Determined by ^{1}H NMR analysis of the crude reaction product (ESI section S10). [b]Not isolated due to low conversion of **2**.

Scheme 1. Synthesis of topologically chiral catenanes 3[a]



[a]Reagents and conditions: (*S*)-**1** in $CHCl_3$-EtOH (1 : 1, 10 mM) was added to $[Cu(CH_3CN)_2(\mathbf{2})]PF_6$ (1 equiv., 24 mM), ^{i}Pr$_2$NEt (2 equiv.) in $CHCl_3$-EtOH (1 : 1). For full conditions see Table 1.

Tyrosine-derived pre-macrocycle (*S*)-**1a** was synthesized (96% *ee*, Figure S40) and reacted under pseudo high-dilution active template[22] Cu-mediated alkyne-azide cycloaddition[23] (AT-CuAAC) conditions[24] with bipyridine macrocycle **2**.[25] Catenane **3a** was produced with reasonable stereoselectivity (Table 1, entry 1), based on ^{1}H NMR analysis of the crude reaction product; proton H_a of the diastereomers of **3a** resonate at 8.98 (major) and 9.07 (minor) ppm, respectively (Figure S111).[26] ^{1}H NMR analysis also suggested the presence of several other interlocked species, characterized by higher ppm (9.51 – 9.61; Figure S286) triazole resonances. LCMS analysis indicated that these signals were due to [3]catenane **4**, which can be formed as 3 diastereomers, and the corresponding [2]catenane (not shown, 2 diastereomers) containing a single bipyridine ring (ESI section S10). We were unable to obtain pure samples of these structures.[27]

Longer addition times (entry 2) resulted in diminished diastereoselectivity, perhaps due to epimerization of the covalent stereogenic center, and lower conversion of macrocycle **2**. Lowering the reaction temperature resulted in enhanced diastereoselectivity (74% *de*) and reduced quantities of oligomeric species, allowing catenane **3b** to be isolated in 39% yield and 74% *de* (entry 3). Although increasing the equivalents of **1a** resulted in higher conversion of **2**, lower yields of **3a** were obtained as the non-interlocked triazole-containing macrocycle was challenging to remove. Varying the solvent did not improve diastereoselectivity or conversion of **2** (ESI section S8). Applying the same conditions to (*S*)-**1b**, which features a bulkier ^{i}Pr ester, gave catenane **3b** in 82% *de*, albeit the conversion of macrocycle **2** was diminished and the formation of oligomeric biproducts was increased, resulting in a low isolated yield (26%, 82% *de*, entry 4). Surprisingly, (*S*)-**1c** gave poor stereoselectivity (68% *de*, entry 5) and low conversion of **2** (~25%). Pleasingly, single crystal x-ray diffraction (SCXRD) analysis of a racemic sample of catenane **3b** produced using *rac*-**1b** allowed the relative stereochemistry of the major diastereomer to be tentatively assigned as (S^*,S_{mt}^*). Thus, the major product of (*S*)-**1b** and macrocycle **2** is assigned as (S,S_{mt})-**3b** (Figure 2a).[28]

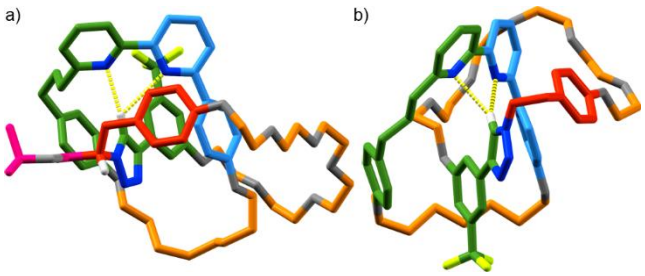
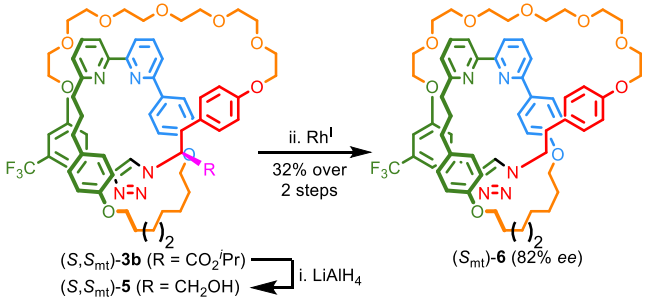


Figure 2. Solid state structures of (a) *rac*-(S,S_{mt})-**3b** and (b) *rac*-**6**. Colors as in Scheme 1 except F (yellow), O (grey), N (dark blue), H (white). Majority of H omitted for clarity. Selected intercomponent interactions highlighted (yellow).

Scheme 2. Decarbonylation of catenane 3b.[a]

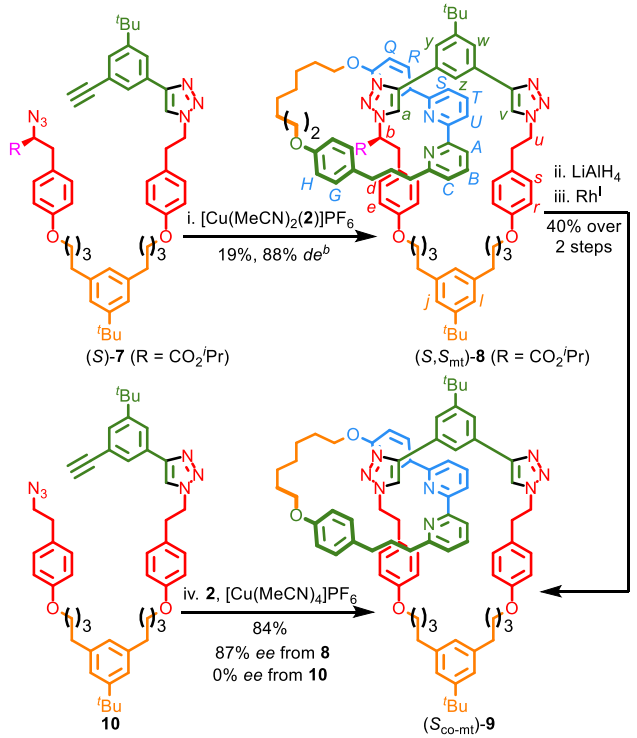


[a]Reagents and conditions: i. $LiAlH_4$, THF, –30 °C, 1 h; ii. $[Rh(cod)Cl]_2$, $[IrCp^*Cl_2]_2$, benzophenone, *rac*-BINAP, K_2CO_3, mesitylene, 170 °C, 5 h.

We then turned to methods to remove the covalent stereogenic unit from the mixture of catenane **3b** diastereomers (Scheme 2). Attempts to ablate the covalent stereocenter of a model compound by radical decarboxylation met with failure due to scission of the triazole N1-C substituent bond (ESI section S9). Ultimately, we found that reduction of ester **3b** to give alcohol catenane **5** followed by tandem Oppenauer-type oxidation / Rh^{I}-mediated decarbonylation[29] gave rise to catenane **6** in reasonable isolated yield (32% over two steps). CSP-HPLC analysis confirmed that the diastereoenriched starting material (82% *de*) was converted with good fidelity to enantioenriched (82% *ee*) catenane **6**. The major stereoisomer of **6** was assigned as (S_{mt}) based on the assigned stereochemistry of the major diastereomer of **3b**. Crystals of a *rac*-**6** suitable for SCXRD analysis were obtained, allowing the structure of the product to be confirmed (Figure 2b).

Finally, we turned to the synthesis of a co-conformationally topologically chiral target (Scheme 3). Pre-macrocycle (*S*)-**7** was subjected to the AT-CuAAC reaction with macrocycle **2**. The product, topologically chiral [2]catenane **8**, was isolated as a mixture of diastereomers (88% *de*), as judged by ^{1}H NMR (Figure 3ai). By analogy with catenane **3b**, which seems reasonable given the similarities of the functional groups reacting and the similar stereoselectivity obtained, the major isomer is tentatively assigned as (*S*,S_{mt})-**8**.

Scheme 3. Synthesis of co-conformationally "topologically" chiral catenane 9.[a]



[a]Reagents and conditions: i. (*S*)-**7** in $CHCl_3$-EtOH (1 : 1) added to $[Cu(CH_3CN)_2(\mathbf{2})]PF_6$ (1 equiv.), $^iPr_2NEt$ (2 equiv) in $CHCl_3$-EtOH (1 : 1) over 4 h at 60 °C; ii. $LiAlH_4$, THF, –30 °C, 1 h; iii. $[Rh(cod)Cl]_2$, $[IrCp^*Cl_2]_2$, benzophenone, *rac*-BINAP, K_2CO_3, mesitylene, 170 °C, 5 h; iv) **10** in $CHCl_3$-EtOH (1 : 1) added to **2** (1 equiv.), $[Cu(CH_3CN)_4]PF_6$ (0.96 equiv.), $^iPr_2NEt$ (2 equiv.) in $CHCl_3$-EtOH (1 : 1) over 4 h at 60 °C. [b]Determined by ^{1}H NMR.

Auxiliary removal from (*S*,S_{mt})-**8** (88% *de*) yielded [2]catenane **9**, which contains no previously described stereogenic units – it lacks covalent stereogenic units, and the triazole containing ring is not oriented and so the system does not conform to the definition of a topologically chiral catenane. Nevertheless, whereas the compounds produced from **10** and (*S*,S_{mt})-**8** produce identical ^{1}H NMR spectra (Figures 3aii and 3aiii respectively), the latter is clearly highly enantioenriched, whereas the former is racemic as judged by CSP-HPLC analysis (Figure 3b), which indicates that catenane **9** was formed from (*S*,S_{mt})-**8** in 87% *ee*,[30] and circular dichroism spectroscopy (Figure 3c). SCXRD of a sample of *rac*-**9** confirmed the structure of the product.[31] As expected, both enantiomeric co-conformations were observed in the unit cell (Figure 3d). We tentatively assign the product of (*S*,S_{mt})-**8** to be ($S_{co\text{-}mt}$)-**9** as the relative arrangements of the rings cannot change during auxiliary removal.

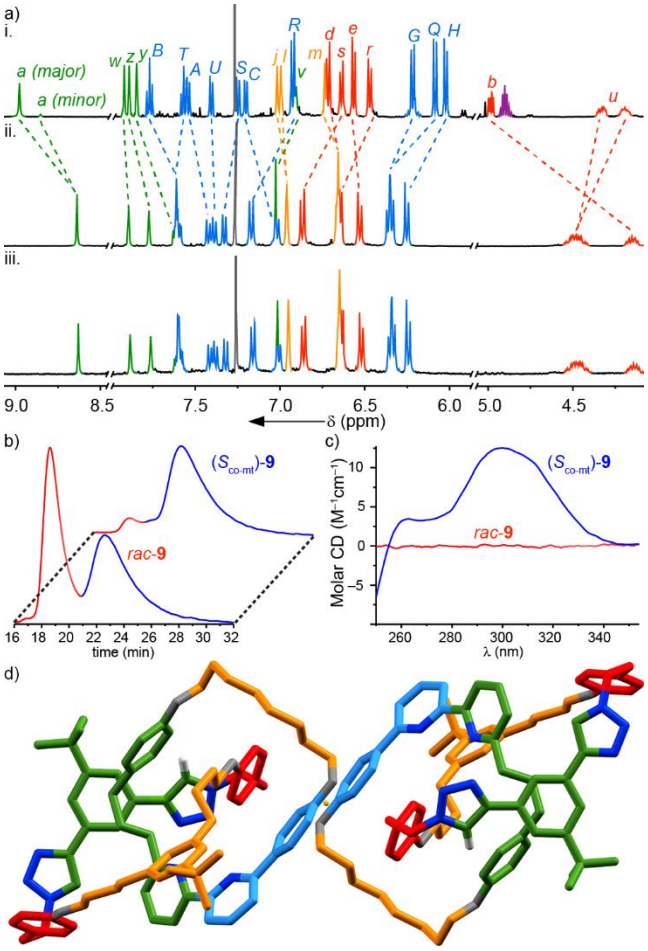


Figure 3. (a) Partial ^{1}H NMR ($CDCl_3$, 298 K) of i. catenane **8**, ii. catenane *rac*-**9** and iii. enantioenriched catenane ($S_{co\text{-}mt}$)-**9**. Atom labels and colors as in Scheme 3, except macrocycle signals (blue). (b) HPLC analysis of catenane *rac*-**9** and ($S_{co\text{-}mt}$)-**9**. (c) Circular dichroism spectra of catenane *rac*-**9** and ($S_{co\text{-}mt}$)-**9**. (d) Solid state structure of *rac*-**9** showing a pair of enantiomeric structures related by a point of inversion (orange). Colors as in Scheme 3 except O (grey), N (dark blue), H (white). Majority Hs omitted for clarity.

In conclusion, we have developed an auxiliary for the synthesis of topologically chiral catenanes in high enantiopurity and applied it to the synthesis of catenane ($S_{co\text{-}mt}$)-**9**, a molecule containing a previously unreported "co-conformationally 'topologically' chiral" stereogenic unit, unambiguously

demonstrating the chiral nature of this overlooked form of mechanical stereochemistry. However, it poses a problem of nomenclature – how can the topological stereochemistry of a molecule depend on its co-conformation? In short, it cannot[1] but, once the fixed co-conformation is considered, the covalent subcomponents of catenane **9** display the same symmetry properties as those that comprise the established stereogenic unit of topologically chiral catenanes, which leads to our linguistic conundrum. One solution to this would be to rename "topologically chiral" catenanes as "mechanically planar chiral", to bring them in line with the analogous rotaxanes to which they are strongly related, but this would require further discussion in the field. Linguistic issues aside, chiral interlocked molecules are attracting increasing attention for applications in catalysis,[32,33] sensing[34] and as chiroptical[35] or stereodynamic switches.[15b,16e] By highlighting their potential to display molecular chirality due to unexplored stereogenic units, we hope to inspire further investigation of their rich stereochemistry.[36]

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SUPPORTING INFORMATION

Procedures and full characterization data (NMR, MS, CD, SCXRD, HPLC as appropriate) for all novel compounds and supplementary discussion.

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REFERENCES

(1) Flapan, E., *When Topology Meets Chemistry*. Cambridge University Press: 2012.

(2) Walba, D. M., Topological stereochemistry. *Tetrahedron* **1985**, *41,* 3161-3212.

(3) Selected examples and reviews: (a) Walba, D. M.; Richards, R. M.; Haltiwanger, R. C., Total synthesis of the first molecular Moebius strip. *J. Am. Chem. Soc.* **2002**, *104,* 3219-3221. (b) Herges, R., Topology in chemistry: designing Mobius molecules. *Chem. Rev.* **2006**, *106,* 4820-42. (c) Nishigaki, S.; Shibata, Y.; Nakajima, A.; Okajima, H.; Masumoto, Y.; Osawa, T.; Muranaka, A.; Sugiyama, H.; Horikawa, A.; Uekusa, H.; Koshino, H.; Uchiyama, M.; Sakamoto, A.; Tanaka, K., Synthesis of Belt- and Mobius-Shaped Cycloparaphenylenes by Rhodium-Catalyzed Alkyne Cyclotrimerization. *J. Am. Chem. Soc.* **2019**, *141,* 14955-14960. (d) Yuan, J.; Song, Y.; Li, X.; Xie, J.; Dong, S.; Zhu, K., A Tubular Belt and a Mobius Strip with Dynamic Joints: Synthesis, Structure, and Host-Guest Chemistry. *Org. Lett.* **2021**, *23,* 9554-9558.

(4) Molecules can also adopt conformations with a Mobius conjugated electronic structure. Selected reviews (and ref 3b): (a) Rzepa, H. S., Mobius aromaticity and delocalization. *Chem. Rev.* **2005**, *105,* 3697-3715. (b) Yoon, Z. S.; Osuka, A.; Kim, D., Möbius aromaticity and antiaromaticity in expanded porphyrins. *Nature Chemistry* **2009**, *1,* 113-122. (c) Stepien, M.; Sprutta, N.; Latos-Grazynski, L., Figure eights, Mobius bands, and more: conformation and aromaticity of porphyrinoids. *Angew. Chem. Int. Ed.* **2011**, *50,* 4288-340.

(5) Selected reviews: (a) Forgan, R. S.; Sauvage, J. P.; Stoddart, J. F., Chemical topology: complex molecular knots, links, and entanglements. *Chem. Rev.* **2011**, *111,* 5434-64. (b) Fielden, S. D. P.; Leigh, D. A.; Woltering, S. L., Molecular Knots. *Angew. Chem. Int. Ed.* **2017**, *56,* 11166-11194. (c) Evans, N. H., Lanthanide-Containing Rotaxanes, Catenanes, and Knots. *Chempluschem* **2020**, *85,* 783-792. (d) Gao, W. X.; Feng, H. J.; Guo, B. B.; Lu, Y.; Jin, G. X., Coordination-Directed Construction of Molecular Links. *Chem. Rev.* **2020**, *120,* 6288-6325.

(6) Bruns, C. J.; Stoddart, J. F., *The Nature of the Mechanical Bond: From Molecules to Machines*. Wiley: 2016.

(7) Nishigaki, S.; Shibata, Y.; Nakajima, A.; Okajima, H.; Masumoto, Y.; Osawa, T.; Muranaka, A.; Sugiyama, H.; Horikawa, A.; Uekusa, H.; Koshino, H.; Uchiyama, M.; Sakamoto, A.; Tanaka, K., Synthesis of Belt- and Mobius-Shaped Cycloparaphenylenes by Rhodium-Catalyzed Alkyne Cyclotrimerization. *J. Am. Chem. Soc.* **2019**, *141,* 14955-14960.

(8) Selected examples: (a) Gil-Ramirez, G.; Hoekman, S.; Kitching, M. O.; Leigh, D. A.; Vitorica-Yrezabal, I. J.; Zhang, G., Tying a Molecular Overhand Knot of Single Handedness and Asymmetric Catalysis with the Corresponding Pseudo-D3-Symmetric Trefoil Knot. *J. Am. Chem. Soc.* **2016**, *138,* 13159-13162. (b) Leigh, D. A.; Pirvu, L.; Schaufelberger, F., Stereoselective Synthesis of Molecular Square and Granny Knots. *J. Am. Chem. Soc.* **2019**, *141,* 6054-6059. (c) Zhong, J.; Zhang, L.; August, D. P.; Whitehead, G. F. S.; Leigh, D. A., Self-Sorting Assembly of Molecular Trefoil Knots of Single Handedness. *J. Am. Chem. Soc.* **2019**, *141,* 14249-14256. (d) Leigh, D. A.; Schaufelberger, F.; Pirvu, L.; Stenlid, J. H.; August, D. P.; Segard, J., Tying different knots in a molecular strand. *Nature* **2020**, *584,* 562-568. (e) Carpenter, J. P.; McTernan, C. T.; Greenfield, J. L.; Lavendomme, R.; Ronson, T. K.; Nitschke, J. R., Controlling the shape and chirality of an eight-crossing molecular knot. *Chem* **2021**, *7,* 1534-1543.

(9) The Solomon link, a topological isomer of a [2]catenane displays unconditional topological chirality: (a) Ponnuswamy, N.; Cougnon, F. B.; Pantos, G. D.; Sanders, J. K., Homochiral and meso figure eight knots and a Solomon link. *J. Am. Chem. Soc.* **2014**, *136,* 8243-51. (b) Cui, Z.; Lu, Y.; Gao, X.; Feng, H. J.; Jin, G. X., Stereoselective Synthesis of a Topologically Chiral Solomon Link. *J. Am. Chem. Soc.* **2020**, *142,* 13667-13671.

(10) Frisch, H. L.; Wasserman, E., Chemical Topology. *J. Am. Chem. Soc.* **1961**, *83,* 3789-3795.

(11) Selected reviews: (a) Evans, N. H., Chiral Catenanes and Rotaxanes: Fundamentals and Emerging Applications. *Chemistry* **2018**, *24,* 3101-3112. (b) Pairault, N.; Niemeyer, J., Chiral Mechanically Interlocked Molecules - Applications of Rotaxanes, Catenanes and Molecular Knots in Stereoselective Chemosensing and Catalysis. *Synlett* **2018**, *29,* 689-698. (c) Jamieson, E. M. G.; Modicom, F.; Goldup, S. M., Chirality in rotaxanes and catenanes. *Chem. Soc. Rev.* **2018**, *47,* 5266-5311. (d) David, A. H. G.; Stoddart, J. F., Chiroptical Properties of Mechanically Interlocked Molecules. *Isr. J. Chem.* **2021**, *61,* 608-621.

(12) Selected examples: (a) Mitchell, D. K.; Sauvage, J.-P., A Topologically Chiral [2]Catenand. *Angew. Chem. Int. Ed.* **1988**, *27,* 930-931. (b) Kaida, Y.; Okamoto, Y.; Chambron, J. C.; Mitchell, D. K.; Sauvage, J. P., The Separation of Optically-Active Copper (I) Catenates. *Tetrahedron Lett* **1993**, *34,* 1019-1022. (c) Yamamoto, C.; Okamoto, Y.; Schmidt, T.; Jäger, R.; Vögtle, F., Enantiomeric Resolution of Cycloenantiomeric Rotaxane, Topologically Chiral Catenane, and Pretzel-Shaped Molecules: Observation of Pronounced Circular Dichroism. *J. Am. Chem. Soc.* **1997**, *119,* 10547-10548. (d) Tai, T. Y.; Liu, Y. H.; Lai, C. C.; Peng, S. M.; Chiu, S. H., Absolute Configurations of Topologically Chiral [2]Catenanes and the Acid/Base-Flippable Directions of Their Optical Rotations. *Org. Lett.* **2019**, *21,* 5708-5712. (e) Ishizu, Y.; Takeyoshi, A.; Hasegawa, E.; Iwamoto, H., Synthesis and Resolution of Optically Active Topologically Chiral Catenane. *Chem. Lett.* **2020**, *49,* 1435-1438.

(13) Recent examples of unusual stereoisomeric behavior in covalent structures: (a) Canfield, P. J.; Blake, I. M.; Cai, Z. L.; Luck, I. J.; Krausz, E.; Kobayashi, R.; Reimers, J. R.; Crossley, M. J., A new fundamental type of conformational isomerism. *Nat. Chem.* **2018**, *10,* 615-624. (b) Reisberg, S. H.; Gao, Y.; Walker, A. S.; Helfrich, E. J. N.; Clardy, J.; Baran, P. S., Total synthesis reveals atypical atropisomerism in a small-molecule natural product, tryptorubin A. *Science* **2020**, *367,* 458-463.

(14) (a) Alvarez-Perez, M.; Goldup, S. M.; Leigh, D. A.; Slawin, A. M., A chemically-driven molecular information ratchet. *J. Am. Chem. Soc.* **2008**, *130,* 1836-1838. (b) Carlone, A.; Goldup, S. M.; Lebrasseur, N.;

Leigh, D. A.; Wilson, A., A three-compartment chemically-driven molecular information ratchet. *J. Am. Chem. Soc.* **2012**, *134,* 8321-8323.

(15) Selected examples: (a) Mochizuki, Y.; Ikeyatsu, K.; Mutoh, Y.; Hosoya, S.; Saito, S., Synthesis of Mechanically Planar Chiral rac-[2]Rotaxanes by Partitioning of an Achiral [2]Rotaxane: Stereoinversion Induced by Shuttling. *Org. Lett.* **2017**, *19,* 4347-4350. (b) Corra, S.; de Vet, C.; Groppi, J.; La Rosa, M.; Silvi, S.; Baroncini, M.; Credi, A., Chemical On/Off Switching of Mechanically Planar Chirality and Chiral Anion Recognition in a [2]Rotaxane Molecular Shuttle. *J. Am. Chem. Soc.* **2019**, *141,* 9129-9133.

(16) Catenanes have been shown to display a co-conformational helical stereogenic unit. Selected examples: (a) Hori, A.; Akasaka, A.; Biradha, K.; Sakamoto, S.; Yamaguchi, K.; Fujita, M., Chirality Induction through the Reversible Catenation of Coordination Rings. *Angew. Chem. Int. Ed.* **2002**, *41,* 3269-3272. (b) Vignon, S. A.; Wong, J.; Tseng, H. R.; Stoddart, J. F., Helical chirality in donor-acceptor catenanes. *Org. Lett.* **2004**, *6,* 1095-1098. (c) Hutin, M.; Schalley, C. A.; Bernardinelli, G.; Nitschke, J. R., Helicate, macrocycle, or catenate: Dynamic topological control over subcomponent self-assembly. *Chemistry* **2006**, *12,* 4069-4076. (d) Nakatani, Y.; Furusho, Y.; Yashima, E., Amidinium carboxylate salt bridges as a recognition motif for mechanically interlocked molecules: synthesis of an optically active [2]catenane and control of its structure. *Angew. Chem. Int. Ed.* **2010**, *49,* 5463-5467. (e) Caprice, K.; Pal, D.; Besnard, C.; Galmes, B.; Frontera, A.; Cougnon, F. B. L., Diastereoselective Amplification of a Mechanically Chiral [2]Catenane. *J Am Chem Soc* **2021**, *143,* 11957-11962.

(17) Maynard, J. R. J.; Goldup, S. M., Strategies for the Synthesis of Enantiopure Mechanically Chiral Molecules. *Chem* **2020**, *6,* 1914-1932.

(18) Selected examples that contain both covalent and topological stereogenic units: (a) Armspach, D.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Godi, A.; Moore, C. P.; Prodi, L.; Spencer, N.; Stoddart, J. F.; Tolley, M. S.; Wear, T. J.; Williams, D. J.; Stoddart, J. F., Catenated Cyclodextrins. *Chem. Eur. J.* **1995**, *1,* 33-55. (b) Lam, R. T.; Belenguer, A.; Roberts, S. L.; Naumann, C.; Jarrosson, T.; Otto, S.; Sanders, J. K., Amplification of acetylcholine-binding catenanes from dynamic combinatorial libraries. *Science* **2005**, *308,* 667-669. (c) Prakasam, T.; Lusi, M.; Nauha, E.; Olsen, J. C.; Sy, M.; Platas-Iglesias, C.; Charbonniere, L. J.; Trabolsi, A., Dynamic stereoisomerization in inherently chiral bimetallic [2]catenanes. *Chem. Commun.* **2015**, *51,* 5840-5843. (d) Sawada, T.; Yamagami, M.; Ohara, K.; Yamaguchi, K.; Fujita, M., Peptide [4]Catenane by Folding and Assembly. *Angew. Chem. Int. Ed.* **2016**, *55,* 4519-4522. (e) Inomata, Y.; Sawada, T.; Fujita, M., Metal-Peptide Torus Knots from Flexible Short Peptides. *Chem* **2020**, *6,* 294-303.

(19) Denis, M.; Lewis, J. E. M.; Modicom, F.; Goldup, S. M., An Auxiliary Approach for the Stereoselective Synthesis of Topologically Chiral Catenanes. *Chem* **2019**, *5,* 1512-1520.

(20) (a) Jinks, M. A.; de Juan, A.; Denis, M.; Fletcher, C. J.; Galli, M.; Jamieson, E. M. G.; Modicom, F.; Zhang, Z.; Goldup, S. M., Stereoselective Synthesis of Mechanically Planar Chiral Rotaxanes. *Angew. Chem. Int. Ed.* **2018**, *57,* 14806-14810. (b) de Juan, A.; Lozano, D.; Heard, A. W.; Jinks, M. A.; Suarez, J. M.; Tizzard, G. J.; Goldup, S. M., A chiral interlocking auxiliary strategy for the synthesis of mechanically planar chiral rotaxanes. *Nat. Chem.* **2022**, *14,* 179-187.

(21) Selected examples of stereoselective rotaxane synthesis: (a) Tian, C.; Fielden, S. D. P.; Perez-Saavedra, B.; Vitorica-Yrezabal, I. J.; Leigh, D. A., Single-Step Enantioselective Synthesis of Mechanically Planar Chiral [2]Rotaxanes Using a Chiral Leaving Group Strategy. *J. Am. Chem. Soc.* **2020**, *142,* 9803-9808. (b) Imayoshi, A.; Lakshmi, B. V.; Ueda, Y.; Yoshimura, T.; Matayoshi, A.; Furuta, T.; Kawabata, T., Enantioselective preparation of mechanically planar chiral rotaxanes by kinetic resolution strategy. *Nat. Commun.* **2021**, *12,* 404. (c) Pairault, N.; Bessaguet, A.; Barat, R.; Frederic, L.; Pieters, G.; Crassous, J.; Opalinski, I.; Papot, S., Diastereoselective synthesis of [1]rotaxanes via an active metal template strategy. *Chem. Sci.* **2020**, *12,* 2521-2526.

(22) (a) Crowley, J. D.; Goldup, S. M.; Lee, A. L.; Leigh, D. A.; McBurney, R. T., Active metal template synthesis of rotaxanes, catenanes and molecular shuttles. *Chem. Soc. Rev.* **2009**, *38,* 1530-1541. (b) Denis, M.; Goldup, S. M., The active template approach to interlocked molecules. *Nat. Rev. Chem.* **2017**, *1,* 0061.

(23) Aucagne, V.; Hanni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B., Catalytic "click" rotaxanes: a substoichiometric metal-template pathway to mechanically interlocked architectures. *J. Am. Chem. Soc.* **2006**, *128,* 2186-2187.

(24) Lewis, J. E. M.; Modicom, F.; Goldup, S. M., Efficient Multicomponent Active Template Synthesis of Catenanes. *J. Am. Chem. Soc.* **2018**, *140,* 4787-4791.

(25) Lewis, J. E. M.; Bordoli, R. J.; Denis, M.; Fletcher, C. J.; Galli, M.; Neal, E. A.; Rochette, E. M.; Goldup, S. M., High yielding synthesis of 2,2′-bipyridine macrocycles, versatile intermediates in the synthesis of rotaxanes. *Chem. Sci.* **2016**, *7,* 3154-3161.

(26) The high chemical shift of the triazole protons is attributed to a C-H•••N H-bonding interaction with the bipyridine lone pairs as typically observed in such structures Lahlali, H.; Jobe, K.; Watkinson, M.; Goldup, S. M., Macrocycle size matters: "small" functionalized rotaxanes in excellent yield using the CuAAC active template approach. *Angew. Chem. Int. Ed.* **2011**, *50,* 4151-4155.

(27) Catenanes of the form of **4** contain two covalent stereogenic units and 2 topological stereogenic units as both the central and peripheral rings are oriented. See ESI section S6 for a more detailed discussion.

(28) Although the solid-state structure of **3b** and the high ppm chemical shift of H_a are consistent with the bipyridine macrocycle encircling the triazole unit,[26] over time changes were observed in the ^{1}H NMR spectra of isolated samples of catenanes **3** that suggest this is a metastable co-conformation (ESI section S11).

(29) Kreis, M.; Palmelund, A.; Bunch, L.; Madsen, R., A General and Convenient Method for the Rhodium-Catalyzed Decarbonylation of Aldehydes. *Adv. Synth. Cat.* **2006**, *348,* 2148-2154.

(30) That catenane **9** is formed from **8** at high temperature but the stereopurity of the starting material matches closely with the product is consistent with co-conformational motion being completely blocked. In keeping with this, heating a purified sample of **9** in mesitylene at 170 °C for 24 h did not result in any loss of stereopurity (Figure S260).

(31) We note that that SCXRD data for rac-**9** is poor due to it crystallising as very thin needles (See ESI section S7). However, it is sufficient to confirm the connectivity of the product and the lack of any covalent stereogenic unit in the structure.

(32) (a) Kwamen, C.; Niemeyer, J., Functional Rotaxanes in Catalysis. *Chem. Eur. J.* **2021**, *27,* 175-186. (b) Martinez-Cuezva, A.; Saura-Sanmartin, A.; Alajarin, M.; Berna, J., Mechanically Interlocked Catalysts for Asymmetric Synthesis. *ACS Catal.* **2020**, *10,* 7719-7733. (c) Heard, R. W.; Suarez, J. M.; Goldup, S. M., Controlling catalyst activity, chemoselectivity and stereoselectivity with the mechanical bond. *Nature Reviews Chemistry* **2022**, *6,* 182-196.

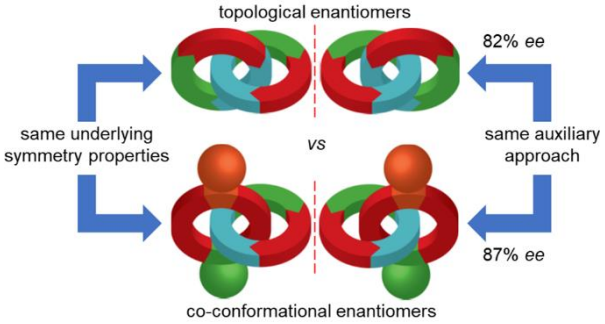
(33) (a) Cakmak, Y.; Erbas-Cakmak, S.; Leigh, D. A., Asymmetric Catalysis with a Mechanically Point-Chiral Rotaxane. *J. Am. Chem. Soc.* **2016**, *138,* 1749-51. (b) Heard, A. W.; Goldup, S. M., Synthesis of a Mechanically Planar Chiral Rotaxane Ligand for Enantioselective Catalysis. *Chem* **2020**, *6,* 994-1006.

(34) Selected examples: (a) Lim, J. Y. C.; Marques, I.; Felix, V.; Beer, P. D., Enantioselective Anion Recognition by Chiral Halogen-Bonding [2]Rotaxanes. *J. Am. Chem. Soc.* **2017**, *139,* 12228-12239. (b) Hirose, K.; Ukimi, M.; Ueda, S.; Onoda, C.; Kano, R.; Tsuda, K.; Hinohara, Y.; Tobe, Y., The Asymmetry is Derived from Mechanical Interlocking of Achiral Axle and Achiral Ring Components -Syntheses and Properties of Optically Pure [2]Rotaxanes-. *Symmetry-Basel* **2018**, *10,* 20. (c) Lim, J. Y. C.; Marques, I.; Felix, V.; Beer, P. D., A Chiral Halogen-Bonding [3]Rotaxane for the Recognition and Sensing of Biologically Relevant Dicarboxylate Anions. *Angew. Chem. Int. Ed.* **2018**, *57,* 584-588.

(35) Gaedke, M.; Witte, F.; Anhauser, J.; Hupatz, H.; Schroder, H. V.; Valkonen, A.; Rissanen, K.; Lutzen, A.; Paulus, B.; Schalley, C. A., Chiroptical inversion of a planar chiral redox-switchable rotaxane. *Chem. Sci.* **2019**, *10,* 10003-10009.

(36) Maynard, J.; Gallagher, P.; Lozano, D.; Butler, P.; Goldup, S., Mechanically axially chiral catenanes and noncanonical chiral rotaxanes. ChemRxiv, 13/12/2021, https://doi.org/10.26434/chemrxiv-2021-rlm8t-v3.

TOC graphic


topological enantiomers
82% ee
same underlying
symmetry properties
vs
same auxiliary
approach
87% ee
co-conformational enantiomers