A catenane that is topologically achiral despite being composed of oriented rings

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A catenane whose stereochemistry is Euclidean but equivalent to that of reported topologically chiral catenanes

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ABSTRACT

In 1960, Wasserman synthesized a molecule in which two rings are held together like links in a chain. This molecule, which is called a catenane, is a topological isomer of the separated rings, which highlighted that molecules could be topologically non-trivial. This insight has found wider implications in biochemistry, where the topology of knotted and catenated proteins and oligonucleotides is thought to play a significant role in their properties, but it also led to the assumption that the stereochemistry of catenanes that are chiral due to the orientation of their rings is inherently topological in nature. Here we show that this assumption is incorrect by synthesizing an example that contains the same fundamental stereogenic unit 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 more unified approach to their discussion.

Topology and topological are often misapplied in chemistry to mean “shape”, perhaps through confusion with topography and topographical respectively[1]. Formally, chemical topology finds its roots in mathematical topology[2], the study of the properties of networks, surfaces, and objects under topologically allowed transformations. 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 graph[1]. One of the first applications of topology in chemistry was to enumerate the available isomers of higher order alkanes (C_nH_{2n+2})[3] and there is continued interest in how molecular topology can be used to digitize and analyze chemical structures and their properties[4]. Conversely, the ultimately incorrect proposal by Lord Kelvin that atoms were knotted vortices in the aether motivated Tait to develop a systematic categorization of knots[5].

If only covalent bonding interactions are included[6,7], 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

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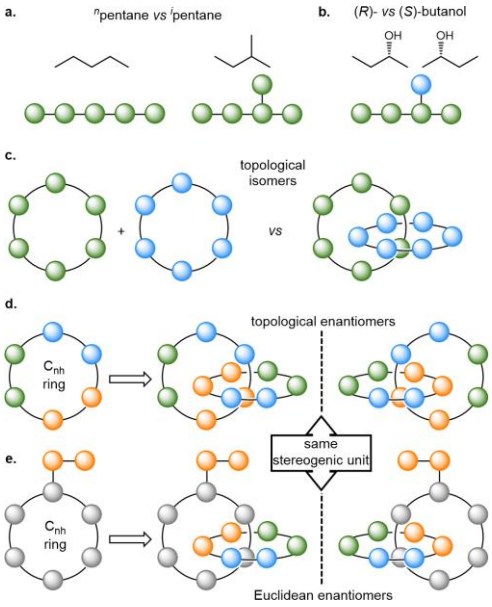
distortion of bonding geometry to an unphysical extent. Using this approach, we can distinguish between the topological properties of different classes of molecular isomers using the terms “homeomorphic” (same atomic connectivity) and “isotopic” (same molecular graph). Constitutional isomers (*e.g.*, of pentane, **Fig. 1a**) are neither homeomorphic (different connectivity) or isotopic (graphs cannot be manipulated to become identical). At the other extreme, stereoisomers that are distinguished by differences in their arrangement of atoms in space due the geometric properties of atoms (**Fig. 1b**) are both 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.

Fig. 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 1961[8], 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 edges (bonds) do not cross one another. Such structures have isomers to which they are

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homeomorphic (same atomic connectivity) but not isotopic (different topology). This observation was inspired by Wasserman's synthesis of a molecular catenane[9] in which two molecular rings are joined like links in a chain, which is the topological isomer of the separated components (**Fig. 1c**). Other classes of molecules that display topological isomerism have since been reported, including Mobius structures[10,11,12], knots[13] and covalent systems in which bond crossings are enforced[14,15]. Topological isomerism also appears in proteins[16] and nucleotides[17] where it is proposed to have a significant impact on their biological function.

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Wasserman and Frisch also highlighted that catenanes could exist as topological enantiomers if both rings are "oriented" due to a sequence of distinguishable atoms embedded in their molecular graph (**Fig. 1d**)[8]. Such catenanes have since been referred to simply as "topologically chiral"[18,19], alongside Mobius ladders[20] and some knots,[21,22] and interlocked molecules containing multiple crossing points[23,24], 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 questioned whether the stereochemistry of catenanes containing two oriented rings is inherently topological in nature.

In their discussion[8], and in all subsequent reported synthetic examples[18,19,,25,26,27,28,29], 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, neither of which is a topologically allowed transformation. 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 template[30] Cu-mediated alkyne-azide cycloaddition reaction between azide/alkyne pre-macrocycle alkene (*Z*)-**1** and chiral bipyridine macrocycle (*S*)-**2** (98% *ee*)[31]. ^{1}H 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 macrocycles[31]. Catenane **3** also contains a co-conformational geometric stereogenic unit[32], the configuration, $E_{co\text{-}c}$, 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 → 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 catenanes **3**, **4** and **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},$E_{co\text{-}c}$)-**4** stereoisomer and thus the absolute stereochemistry of catenanes **3** and **4** derived from (*S*)-**2** can be assigned as (S,R_{mp},$E_{co\text{-}c}$)-**3** and (S,S_{mp},$E_{co\text{-}c}$)-**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})-**5** and (S_{mp})-**5** respectively (see Methods for a detailed discussion on stereochemical assignment in such systems).

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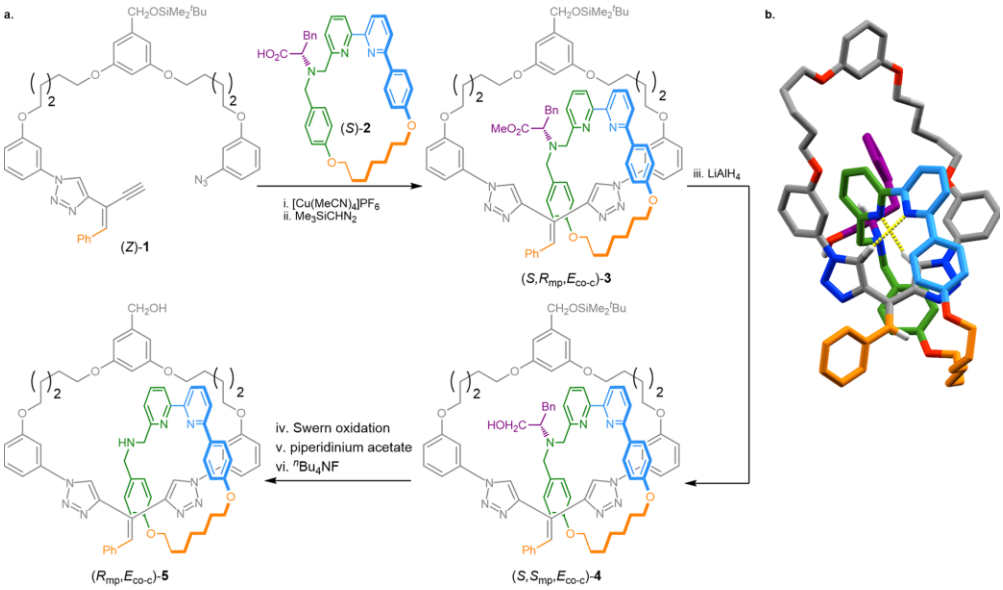
Fig. 2. Synthesis of catenane 5 and the solid-state structure of intermediate catenane 4. a. Synthetic steps used to produce catenane **5**. Reagents and conditions: i. $[Cu(MeCN)_4]PF_6$, N^iPr_2Et, CH_2Cl_2, 35 °C; ii. Me_3SiCHN_2, THF-MeOH (1 : 1), rt; iii. $LiAlH_4$, THF, 0 °C; iv. $(COCl)_2$, Me_2SO, NEt_3, CH_2Cl_2, – 78 °C to rt; v. piperidinium acetate, THF-H_2O (9 : 1), 70 °C; vi. $^nBu_4NF$, THF, 0 °C (yields over six steps from macrocycle **2**: R_{mp}-**5** = 6%, S_{mp}-**5** = 5%, *rac*-**5** = 7%). **b.** Solid-state structure of *rac*-(S,S_{mp},$E_{co\text{-}c}$)-**4** in sticks representation with 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 $CH_2OSiMe_2{}^tBu$ 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 rich 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**). ^{1}H 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 $E_{co\text{-}c}$ isomer was isolated and characterized, this slowly evolved in solution (CD_2Cl_2, 303 K) to an equilibrium mixture containing both co-conformations (~80 : 20 $E_{co\text{-}c}$: $Z_{co\text{-}c}$, Supplementary section 7 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

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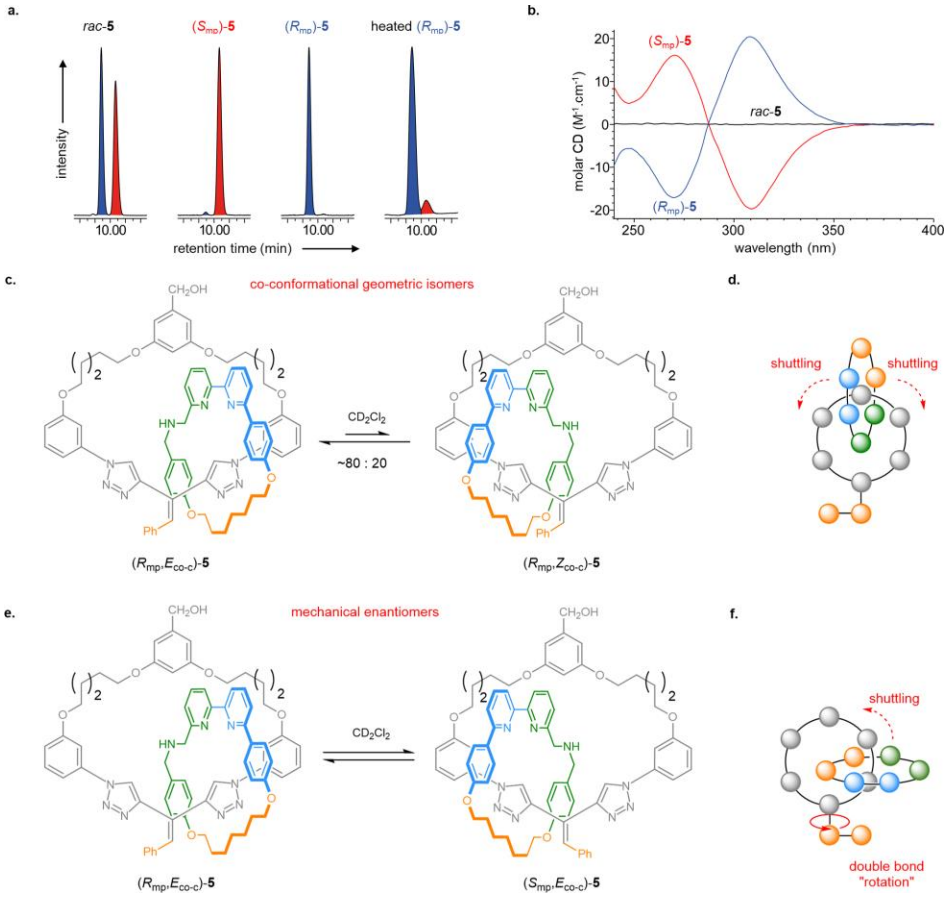
unit of catenane **5** results from the relative orientation of the two rings, as depicted in its highest symmetry representation (**Fig. 3d**).

Fig. 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 $E_{co\text{-}c}$-**5** and $Z_{co\text{-}c}$-**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}-$E_{co\text{-}c}$)-**5** and (S_{mp}-$E_{co\text{-}c}$)-**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 $E_{co\text{-}c}$ 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 $E_{co\text{-}c}$ and $Z_{co\text{-}c}$, a slower racemization process was also observed (**Fig. 3e**). Thus, over time in CD_2Cl_2 solution, the stereopurity of (R_{mp})-**5** decreased from 98% *ee* to 84% *ee* (**Fig. 3a**). Based on the

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apparent protonation of catenane **5** over time, and the behavior of an analogous rotaxane model (Supplementary section 8), we tentatively propose that the enantiomerization of **5** may take place by reversible protonation of the electron rich double bond to give a carbocation intermediate in which there is free rotation between the catenane ring and the benzylidene moiety. 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**).

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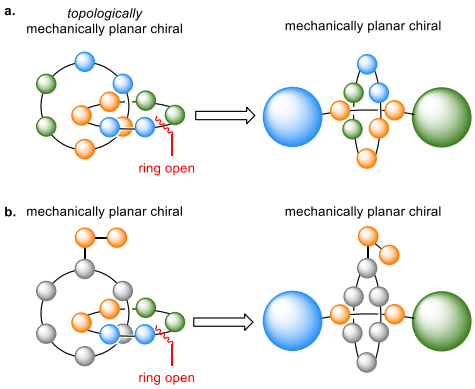
DISCUSSION

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 oriented C_{nh} rings are combined but that, depending on the structure of the rings, the stereochemistry can be either topological or Euclidean (**Fig. 4a** *vs* **Fig. 4b**).

This recognition allows us to unify the stereochemistry of rotaxanes and catenanes composed of oriented components. 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**).

Fig. 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.



The unification of the mechanical planar chiral stereogenic units of rotaxanes and catenanes, as we have recently demonstrated in the context of an analogous mechanical axial stereogenic unit[33], will facilitate future work in the field by highlighting that similar synthetic concepts are likely to be of use for both rotaxanes and catenanes. Furthermore, as the pantheon of mechanical stereogenic units expands,[34] alongside recent developments in covalent stereochemistry[35,36], and applications of stereochemistry in molecular machines[37,38], it is essential that the field remains on a firm theoretical footing. Finally, our results suggest 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.

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AUTHOR CONTRIBUTIONS

S.M.G. secured project funding. S.M.G. and E.M.G.J. 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 **S34** 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.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

METHODS

Commented [SG16]: E8: We have added a methods section, which is complemented by 4 extended data figures. We hope this is ok? Thank you for the suggestion.

Proposed methods for assigning the stereochemistry of the mechanical bond

Methods to assign the absolute stereochemistry of interlocked molecules are still in development. However, we have previously proposed methods[25] for the assignment of absolute stereochemistry in mechanically planar chiral catenanes and chiral rotaxanes by using Cahn-Ingold-Prelog-derived atom priorities[39] to assign the orientation of the covalent subcomponents:

1) Following to the Cahn-Ingold-Prelog (CIP) rules, identify the highest priority atom on one ring and label it as "A"

2) Moving outward from A in spheres, as per the CIP method for assigning covalent stereogenic centres, determine the highest priority atom (CIP) that can be used to define an orientation of the ring (typically a ligand of A) and label it as "B". The orientation of the ring is defined by the vector A → B, which, where relevant, passes through the intervening atoms (*i.e.*, follows the bonds *via* the shortest path).

3) Repeat the process on the second subcomponent to identity its orientation.

4) Orient the assembly with the A → B vector of the axle (rotaxanes) or either ring for (catenanes) passing through the cavity of the other ring away from the observer.

5) The direction of the A → B vector of the ring parallel to the plane of the observer defines the stereolabel: clockwise = R_{mp}, counterclockwise = S_{mp}. The "mp" subscript is included to indicate that the stereodescriptor refers to a mechanically planar stereogenic unit.

Catenane 3

Catenane **3** contains three stereogenic units which are fixed by the method of synthesis as shown (Extended Data Fig. 1a) and whose configuration could be determined by single crystal x-ray diffraction analysis of catenane **4** by making use of the known configuration of the fixed covalent stereogenic centre (see Supplementary Information Section 3).

The most obvious source of stereochemistry is the covalent stereogenic unit of the bipyridine macrocycle. Given that this is fixed in the starting material, (*S*)-**2** gives rise to catenane **3** which contains an *S*-configured covalent stereogenic centre. Less obvious (and more unusual)[32] is the co-conformational covalent geometric stereogenic unit. The double bond in triazole-containing macrocycle has no defined configuration when considered in isolation but in catenane **3** the position of the bipyridine macrocycle can desymmetrize the double bond, giving rise to co-conformational geometric isomerism. Catenane **3** is formed as a single geometric isomer as bipyridine ring is installed on one side of the double bond due to the structure of (*Z*)-**1** and it cannot move between the two triazole-containing compartments. However, a second isomer is technically possible if the bipyridine macrocycle occupies the other compartment (Extended Data Fig. 1b). As with co-conformational point stereochemistry,[40] we assign the geometry of the double bond in catenane **3** by considering the bipyridine macrocycle to be an additional substituent of the atoms in the compartment it encircles. Thus, the $E_{co\text{-}c}$ isomer is produced from (*Z*)-**1**, where the "co-c" subscript highlights that the configuration of this covalent stereogenic unit relies on the co-conformation of the molecule.

To assign the mechanical planar stereogenic unit we apply the rules outlined above. This approach results in the atom priorities shown (Extended Data Fig. 1c). We note that the assignment of atom B in the triazole-containing ring is non-trivial. Exploring outwards from the Si atom (atom A), the first atoms that could allow us to assign direction in the macrocycle are the carbons *ortho* to the benzylic ether moiety. To differentiate between these two atoms, we explore outwards until we reach the quaternary triazole carbons. At this point we identify that, according to CIP, to differentiate between double bond substituents bonded to the same carbon we consider their relationship to the substituents on the other alkene carbon; the group that is arranged *cis* to the highest priority substituent of the other carbon is assigned a higher priority. Thus, the ortho C that leads to the triazole *cis* to the Ph substituent of the double bond is assigned higher priority, and so labelled as atom B. Finally, we orient catenane **3** so that the A→B vector of the bipyridine

macrocycle passes through the triazole-containing macrocycle away from the observer (Extended Data Fig. 1d) and note that the A→B vector associated with the triazole-containing macrocycle is oriented in a clockwise direction, leading to the assignment of the mechanical planar stereogenic unit as R_{mp} (the subscript identifies the origin of the stereochemistry).

Thus, we can assign the configuration of catenane **3** produced by reaction of (*Z*)-**1** and (*S*)-**2** to be (*S*,R_{mp},$E_{co\text{-}c}$)-**3**.

Catenane 4

Based on the arguments presented above, (*S*,R_{mp},$E_{co\text{-}c}$)-**3** leads to a product (Extended Data Fig. 2a) with *S* covalent configuration and $E_{co\text{-}c}$ co-conformational configuration (neither are affected by the reduction of the ester). The mechanical planar stereogenic unit is assigned as above but reduction of the ester moiety of the bipyridine macrocycle leads to a change in atom priorities (Extended Data Fig. 2b) such that the A→B vector of the bipyridine macrocycle is inverted compared with catenane **3**. Thus, although the relative orientation of the triazole and bipyridine macrocycles is unchanged, when viewed with the A→B vector of the bipyridine ring passing through the triazole macrocycle away from the observer, the A→B vector of the triazole macrocycle is oriented in an anticlockwise direction (Extended Data Fig. 2c), resulting in an S_{mp} stereolabel. Thus, we can assign the configuration of catenane **4** produced from (*S*,R_{mp},$E_{co\text{-}c}$)-**3** to be (*S*,S_{mp},$E_{co\text{-}c}$)-**4**.

Catenane S16 (intermediate between catenanes 4 and 5)

Commented [SG17]: Note: we have included the assignment of S16 here for completeness. We haven't given this a new number as it doesn't appear in the main text. I hope this is ok?

If not, we can put it back in the ESI but it fits better with the flow here.

Catenane **S16** is assigned exactly as for catenane **4** (Extended Data Fig. 3). Thus, we can assign the configuration of catenane **S16** produced from (*S*,S_{mp},$E_{co\text{-}c}$)-**4** to be (S_{mp},$E_{co\text{-}c}$)-**S16**.

Catenane 5

Unlike catenanes **3** and **4**, the bipyridine macrocycle of catenane **5** can move between the two triazole containing compartments, giving rise to a dynamic mixture of $E_{co\text{-}c}$ and $Z_{co\text{-}c}$ co-conformations (Extended Data Fig. 4a; see Supplementary Information section 5 for further

discussion), whose double bond configurations are defined as described above. There is no fixed covalent stereogenic unit. Thus, the only fixed stereogenic unit of catenane **5** arises due to the mechanical planar unit. Removal of the silyl group from the triazole-containing macrocycle results in a change in atom priorities (Extended Data Fig. 4b) compared with catenanes **3**, **4** and S**16**. Using these atom priorities (Extended Data Fig. 4c), we can assign the product of (S,S_{mp},$E_{co\text{-}c}$)-**4** as (R_{mp})-**5** which preferentially adopts the (R_{mp},$E_{co\text{-}c}$)-**5** co-conformation (see Supplementary Information section 5).

REFERENCES FOR METHODS SECTION

39. Cahn, R. S., Ingold, C. & Prelog, V. Specification of Molecular Chirality. *Angew. Chem. Int. Ed.* **5**, 385-415 (1966).
40. Alvarez-Perez, M., Goldup, S. M., Leigh, D. A. & Slawin, A. M. A chemically-driven molecular information ratchet. *J. Am. Chem. Soc.* **130**, 1836-1838 (2008).

SUPPLEMENTAL INFORMATION

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

DATA AVAILABILITY

Raw characterization data will be available upon publication through the University of Southampton data repository. Crystallographic data can be accessed through the Cambridge Crystallographic database (accession numbers: 2207578, 2207579).