A Co-conformationally "Topologically" Chiral Catenane

Arnau Rodríguez-Rubio, Andrea Savoini, Florian Modicom, Patrick Butler and Stephen M. Goldup*

Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ (UK), *s.goldup@soton.ac.uk

ABSTRACT

As recognized in the early 1960s, catenanes composed of two achiral rings that are oriented (C_{nh} symmetry) as a result of the sequence of atoms they contain are topologically chiral. Here we present the first synthesis of a highly enantioenriched catenane containing a related but overlooked "co-conformationally 'topologically' chiral" stereogenic unit, which arises when a bi-laterally symmetric C_{nv} ring is desymmetrised by the position of an oriented macrocycle.

INTRODUCTION

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 same 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 the same atomic connections,[2] the most famous examples of which are Möbius ladders (topological isomers of the untwisted macrocycle),[3,4] molecular knots (topological isomers of the unknotted ring),[5] and [2]catenanes (topological 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 at least once and this property is topologically invariant in 3 dimensional space – no matter how the structure is distorted, even drastically altering the geometry around atoms, it is impossible to achieve a planar graph without breaking bonds.[1]

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

We recently identified[11c] several "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. 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). If co-conformational motion is unhindered, their time averaged structure 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 fixed molecular chirality (Figure 1c). This stereogenic unit can be considered to rely on the oriented ring acting as a substituent of the region of C_{2v} ring that it encircles, as in the case of co-conformational-covalent[12] and -mechanical stereochemistry in rotaxanes,[13] effectively lowering the symmetry of the unoriented ring to C_{1h}. We have provisionally termed such molecules as "co-conformationally 'topologically' chiral" to clearly make the link with the conditional topological stereogenic unit of catenanes and emphasize their potentially stereodynamic nature. However, this label is oxymoronic as the stereochemistry of the system is not topologically invariant, hence the quotation marks.

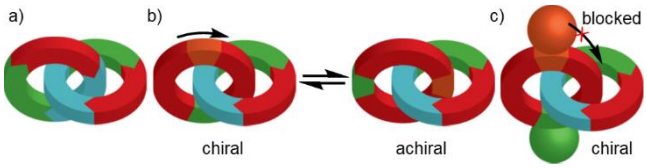


Figure 1. (a) A topologically chiral catenane composed of two oriented (C_{1h}) rings. (b) Chiral and achiral co-conformations of a co-conformationally "topologically" chiral [2]catenane composed of an oriented ring and a C_{2v} ring. (c) A fixed chiral co-conformation of a co-conformationally "topologically" 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.

RESULTS AND DISCUSSION

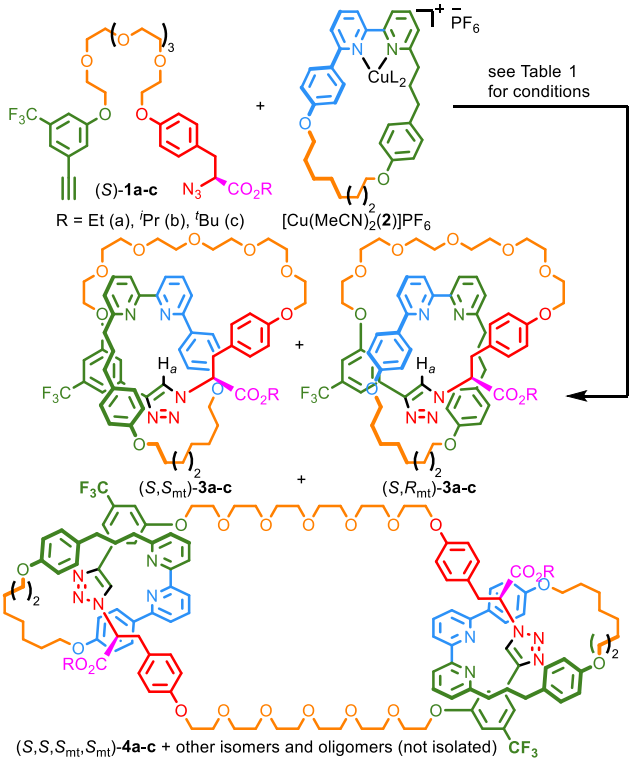
To stereoselectively synthesise a co-conformationally chiral catenane we must: i) incorporate the oriented ring at a defined position around the bilaterally symmetric macrocycle, and ii) ensure that the oriented ring is installed stereoselectively. The first requirement can be met by forming the mechanical bond such that the oriented ring is trapped between bulky groups that prevent co-conformational exchange. The second is more challenging and is essentially the same problem as encountered in the synthesis of any topologically chiral [2]catenane.[14] Although the majority of topologically chiral catenanes in which the mechanical bond is the sole source of stereochemistry[15] have been synthesized as racemates and then separated by chiral stationary phase HPLC (CSP-HPLC),[16] recently we developed an auxiliary approach in which a covalent stereogenic unit directs the stereoselective formation of the mechanical bond.[17] Separation of the mechanical epimers before removal of the auxiliary gave the enantiopure product. However, in this proof-of-concept synthesis the stereoselectivity of the mechanical bond formation was low (*dr* ~ 2 : 1); unless the mechanical epimers can be separated, which is far from assured, this auxiliary has limited utility for synthesis of structurally more complicated chiral 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.
4	Et	25	4	15 : 44 : 41	76 %	39%
5	^{i}Pr	25	4	14 : 30 : 56	82 %	26%
6	^{t}Bu	25	4	77 : 11 : 12	58 %	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), $^{i}Pr_2NEt$ (2 equiv.) in $CHCl_3$-EtOH (1 : 1). For full conditions see Table 1.

Thus, we investigated whether a phenylalanine-based auxiliary developed for the stereoselective synthesis of mechanical planar chiral rotaxanes[18,19] could be applied in the synthesis of topologically chiral [2]catenanes. Tyrosine-derived pre-macrocycle (*S*)-**1a** was synthesized (96% *ee*, Figure S37) and reacted under previously reported pseudo high-dilution active template[20] Cu-mediated alkyne-azide cycloaddition[21] (AT-CuAAC) conditions[22] with oriented

bipyridine macrocycle **2**.[23] Catenane **3a** was produced with reasonable stereoselectivity (Table 1, entry 1), based on ^{1}H NMR analysis of the crude reaction product (Figure S99); proton H_a of the diastereomers of **3a** resonate at 8.98 (major) and 9.07 (minor) ppm, respectively.[24] ^{1}H NMR analysis of the crude reaction product also suggested the presence of several other interlocked species, characterized by higher ppm (9.51 – 9.61) 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). Unfortunately, we were unable to obtain pure samples of these intriguing chiral structures.[25]

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 (76% *de*) and reduced quantities of oligomeric species, allowing catenane **3b** to be isolated in 39% yield (entry 4). Unfortunately, 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 either 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 somewhat diminished and the formation of oligomeric biproducts was increased, resulting in a low isolated yield (26%, entry 6). Surprisingly, (*S*)-**1c** gave poor stereoselectivity (58% *de*, entry 6) 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}^*) and thus the major product of (*S*)-**1b** and macrocycle **2** is assigned as (S,S_{mt})-**3b** (Figure 2bi). Although the solid-state structure of **3b** supports the

assumption, based on the high ppm chemical shift of H_a,[24] that the bipyridine ring encircles the triazole moiety in the isolated samples of catenanes **3**, over time changes were observed in their ^{1}H NMR spectra that suggest this is a metastable co-conformation; isolated samples of catenanes **3** reversibly isomerize to new species in which H_a resonates at lower chemical shift (ESI section S11). This co-conformational isomerization also helps explain the challenges encountered in purifying the observed oligomeric species.

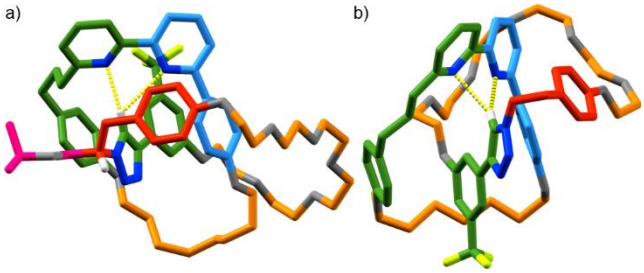
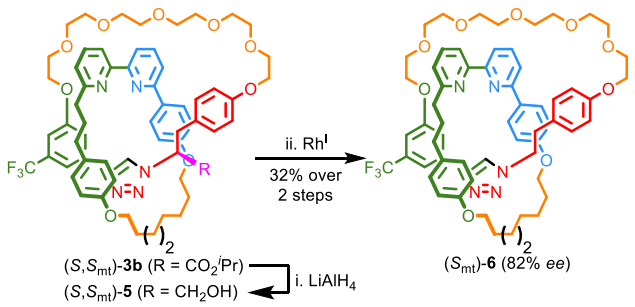


Figure 2. Solid state structures of (a) *rac*-(*S*,*S*$_{mt}$)**-3b** and (b) *rac*-**6**. Colors as in Scheme 1 except F (yellow), O (grey), N (dark blue), H (white). Majority of H omitted for clarity. Selected intercomponent interactions highlighted (yellow).

Having demonstrated that a tyrosine-derived auxiliary can direct the stereoselective formation of a topologically chiral catenane, we turned to methods to remove the covalent stereogenic unit from catenane **3b**. Attempts to ablate the covalent stereocenter in a model compound by radical decarboxylation met with failure due to scission of the triazole N^1-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[26] gave rise to catenane **6** in reasonable isolated yield (32% over two steps). The major stereoisomer of **6** was assigned as (*S*$_{mt}$) based on the assigned stereochemistry of the major diastereomer of **3b**. CSP-HPLC analysis confirmed that the 82% *de* starting material was converted with good fidelity to enantioenriched (82% *ee*) catenane **6**. Crystals of a *rac*-**6** suitable for SCXRD analysis were also obtained, allowing the structure of the product to be confirmed unambiguously (Figure 2b).

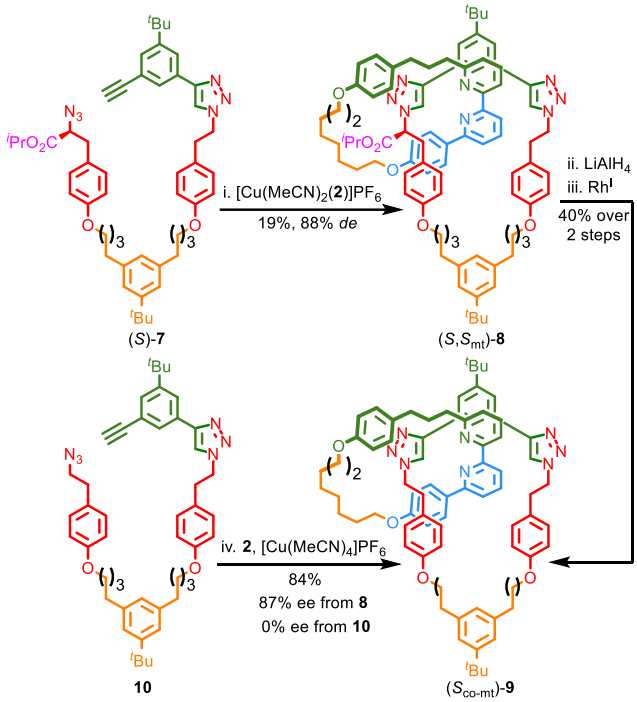
Scheme 2. Decarbonylation of catenane 3b.[a]



[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.

Finally, we turned to the synthesis of a co-conformationally topologically chiral target. 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 (90% *de*), as judged by ^{1}H NMR (Figure 3a). 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.), $^{i}Pr_2NEt$ (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.), $^{i}Pr_2NEt$ (2 equiv.) in $CHCl_3$-EtOH (1 : 1) over 4 h at 60 °C. [b]Determined by ^{1}H-NMR.

Reduction and decarbonylation of (*S*,*S*$_{mt}$)-**8** yielded [2]catenane **9**, which contains no previously described stereogenic units – the molecule lacks any covalent stereogenic units, and the triazole containing macrocycle 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, 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 88% *ee*, and circular dichroism spectroscopy (Figure 3c). SCXRD of a sample of *rac*-**9** confirmed the structure of the product and the absence of any covalent stereogenic unit.[27] 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 macrocycles cannot change in the auxiliary removal step.

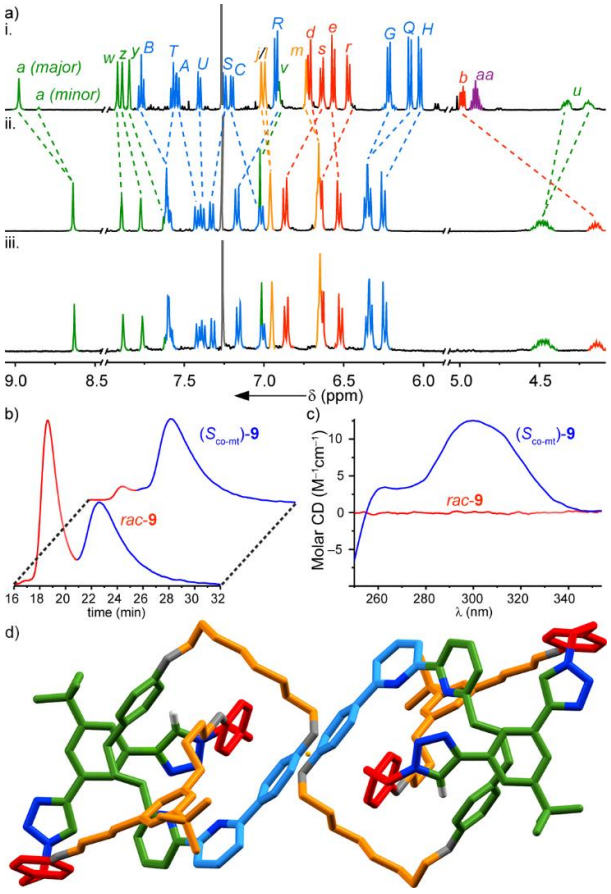


Figure 3. (a) Partial ^{1}H NMR ($CDCl_3$, 298 K) of i. catenane **8**, ii. enantioenriched catenane *rac*-**9** and iii. catenane (*S*$_{co\text{-}mt}$)-**9**. (b) HPLC analysis of catenane (*S*$_{co\text{-}mt}$)-**9** and *rac*-**9**. Atom labels as in Scheme 3. (c) Circular dichroism spectrum of catenane (*S*$_{co\text{-}mt}$)-**9** and *rac*-**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 of H omitted for clarity.

CONCLUSIONS

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 something be simultaneously co-conformationally chiral and topologically chiral? In short, it cannot but, given that the ensemble of covalent subcomponents displays the same symmetry properties as the previously named topologically chiral stereogenic unit of catenanes once the fixed co-conformation is considered, it is hard to see what else to call it. Chiral mechanically interlocked molecules are attracting increasing attention for applications in catalysis,[28] including examples that depend solely on mechanical stereochemistry,[29] sensing[30] and as chiroptical switches.[31] Furthermore, given the similarity between the co-conformational topological stereogenic unit and the co-conformational mechanical planar stereogenic unit in rotaxanes, it seems likely that this new class of chiral catenanes have the potential to act as the basis for stereodynamic switches.[32] Finally, by highlighting the potential for interlocked molecules to display molecular chirality due to unexplored and even unsuspected stereogenic units, we hope to inspire further investigation of their rich stereochemistry.

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