Mechanically axially chiral catenanes and noncanonical chiral rotaxanes

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SUMMARY

Chirality, the property of objects that are distinct from their own mirror image, is important in many scientific areas but particularly chemistry, where the appearance of molecular chirality because of rigid arrangements of atoms in space famously influences a molecule's biological properties. Less generally appreciated is that two molecular rings with chemically distinct faces combined like links in a chain results in a chiral structure even when the rings are achiral. To date, no enantiopure examples of such mechanically axially chiral catenanes has been reported. We re-examined the symmetry properties of the mechanically axially chiral motif and identified a straightforward route to such molecules from simple building blocks. We also identify that common representations of axially chiral catenanes obscure that a previously overlooked stereogenic unit arises when a ring is threaded onto a dumbbell-shaped molecule to generate a rotaxane. These insights allowed us to demonstrate the first stereoselective syntheses of an axially chiral catenane and a noncanonical axially chiral rotaxane motif. With methods to access these structures in hand, the process of exploring their properties and applications can now begin.

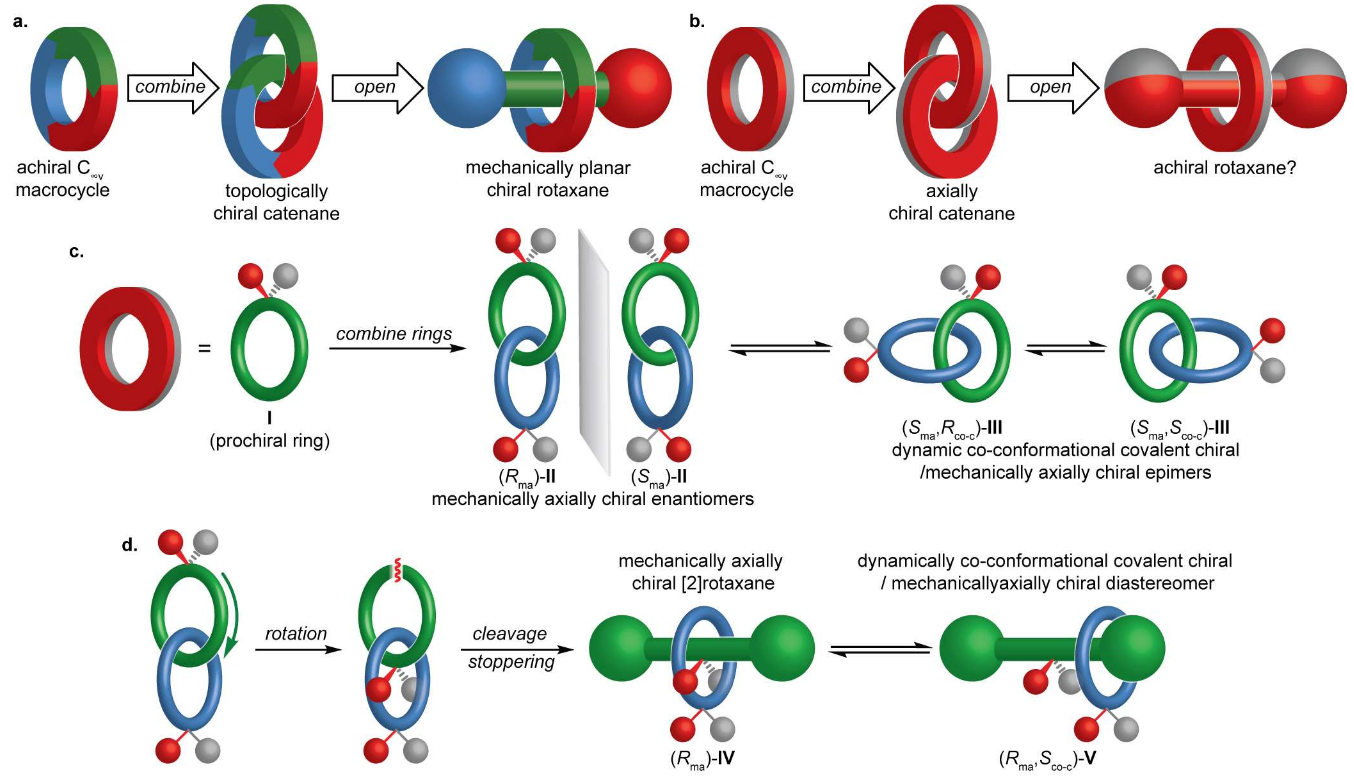
INTRODUCTION

The shape of a molecule is a major determinant of its function[1]. Thus, chemists have invested significant effort in developing methods to produce molecules with control over their stereochemistry, the formal term that refers to the factors that determine molecular shape[2]. A major part of this effort, which has now led to two Nobel prizes[3,4], has focused on being able to selectively make molecules in one mirror image form because the non-superimposable mirror image forms (enantiomers) of chiral molecules are hard to separate using standard techniques. Although chirality is a whole-molecule property[5], chemists often trace the appearance of molecular chirality back to one or more rigidly chiral arrangements of atoms in the structure. The most famous of these is the "stereogenic center" embodied by a tetrahedral carbon atom bonded to four different substituents, although stereogenic planes and axes are also found in important natural and synthetic structures[2]. Chiral molecules containing such classical covalent stereogenic units have been studied extensively. Less explored are chiral molecules whose stereochemistry arises absent any covalent stereogenic unit, such as Möbius ladders,[6] molecular knots,[7] and mechanically interlocked molecules[8].

In 1961 Wasserman and Frisch identified that interlocked molecules called catenanes (two molecular rings joined like links in a chain) can display non-classical "mechanical" stereochemistry[9]; when both rings are oriented (C_{nh} symmetry) a catenane exists in two mirror image forms (Figure 1a). A decade later, Schill proposed that rotaxanes (a molecular ring trapped around a dumbbell-shaped molecule) composed of an oriented ring encircling an axle whose ends are distinct are also chiral (Fig. 1a)[10]. In both cases, the sub-components that make up the interlocked structure are not themselves chiral, which is readily emphasized using commonly employed schematic representations that focus on the symmetry properties of the components (Fig. 1a). These representations also make clear that such topologically chiral catenanes and mechanically planar chiral rotaxanes are related notionally through ring opening. Although such molecules were initially challenging to make as single enantiomers[11,12,13,14,15], recent efforts have allowed them to be accessed in good enantiopurity using standard synthetic approaches[16,17,18,19,20,21].

In 2002 Puddephat and co-workers reported a chiral catenane composed of two achiral rings with distinct faces (C_{nv}) (Fig. 1b). However, unlike the example of topologically chiral catenanes, the notional process of ring opening and stoppering of the minimal representation of such axially chiral catenanes does not result in a chiral rotaxane (Fig. 1b). A small number of racemic axially chiral catenanes have been reported[22,23], but no enantiopure examples where the mechanical bond provides the sole source of stereochemistry have been disclosed to date[24]. We re-examined the mechanical axial stereogenic unit of catenanes with a focus on not just the symmetry of the components but how this arises structurally. This led us not only to an efficient approach to enantiopure axially chiral catenanes but also to recognize and synthesize a noncanonical class of mechanically axially chiral rotaxanes that had previously been overlooked.

Figure 1. Schematic depictions of the mechanical stereogenic units of chiral catenanes and rotaxanes (stereolabels are arbitrary). (a) The mechanical topological and planar chiral stereogenic units of catenanes and rotaxanes are related by a notional ring opening process. (b) The minimal schematic representation of a mechanically axially chiral catenane suggests that there is no analogous axially chiral rotaxane. (c) Semi-structural representations of axially chiral catenanes reveal that such molecules can display co-conformational covalent chirality alongside the fixed mechanical stereogenic unit. (d) The semi-structural representation reveals that rotaxanes display a related but previously unrecognized form of stereochemistry.



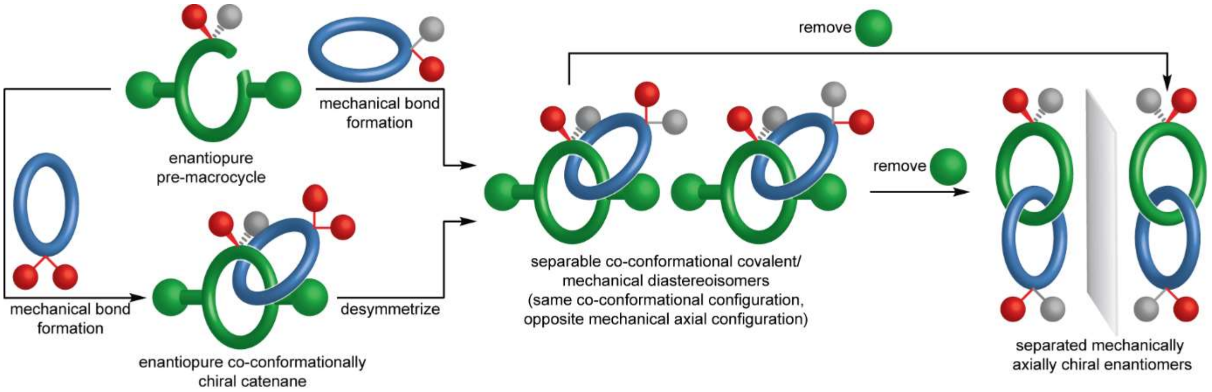
RESULTS AND DISCUSSION

Insights from semi-structural cartoons. The minimal cartoon representation of a mechanically axially chiral catenane (Fig. 1b) does not specify how the facial dissymmetry of the macrocycles arises. The most obvious way this can be achieved is by including a prochiral unit in both rings (**I**, Fig. 1c)[22,23,24,]. Indeed, it is hard to avoid the appearance of prochirality[25], whether that arises due to a center (shown), plane or axis, in the structure of mechanically axially chiral catenanes. Furthermore, although there is always a highly symmetrical arrangement of rings available (**II**) that only expresses mechanical axial stereochemistry, if either ring is displaced from this arrangement the resulting structure contains both a mechanically axially chiral stereogenic unit and a co-conformational covalent stereogenic unit (**III**). These lower symmetry arrangements exist as pairs of co-conformational diastereomers.

Strikingly, whereas the minimal cartoon representation of a mechanically axially chiral catenane suggests there can be no rotaxane equivalent of this stereogenic unit (Fig. 1b), the semi-structural representation reveals that the notional ring opening process gives rise to a chiral rotaxane (Fig. 1d); even when the ring encircles the prochiral unit of the axle (**IV**) there is no representation that is achiral. Thus, we see that rotaxanes can display a previously unremarked upon mechanically axially chiral stereogenic unit that displays similar co-conformational diastereoisomerism (**V**).

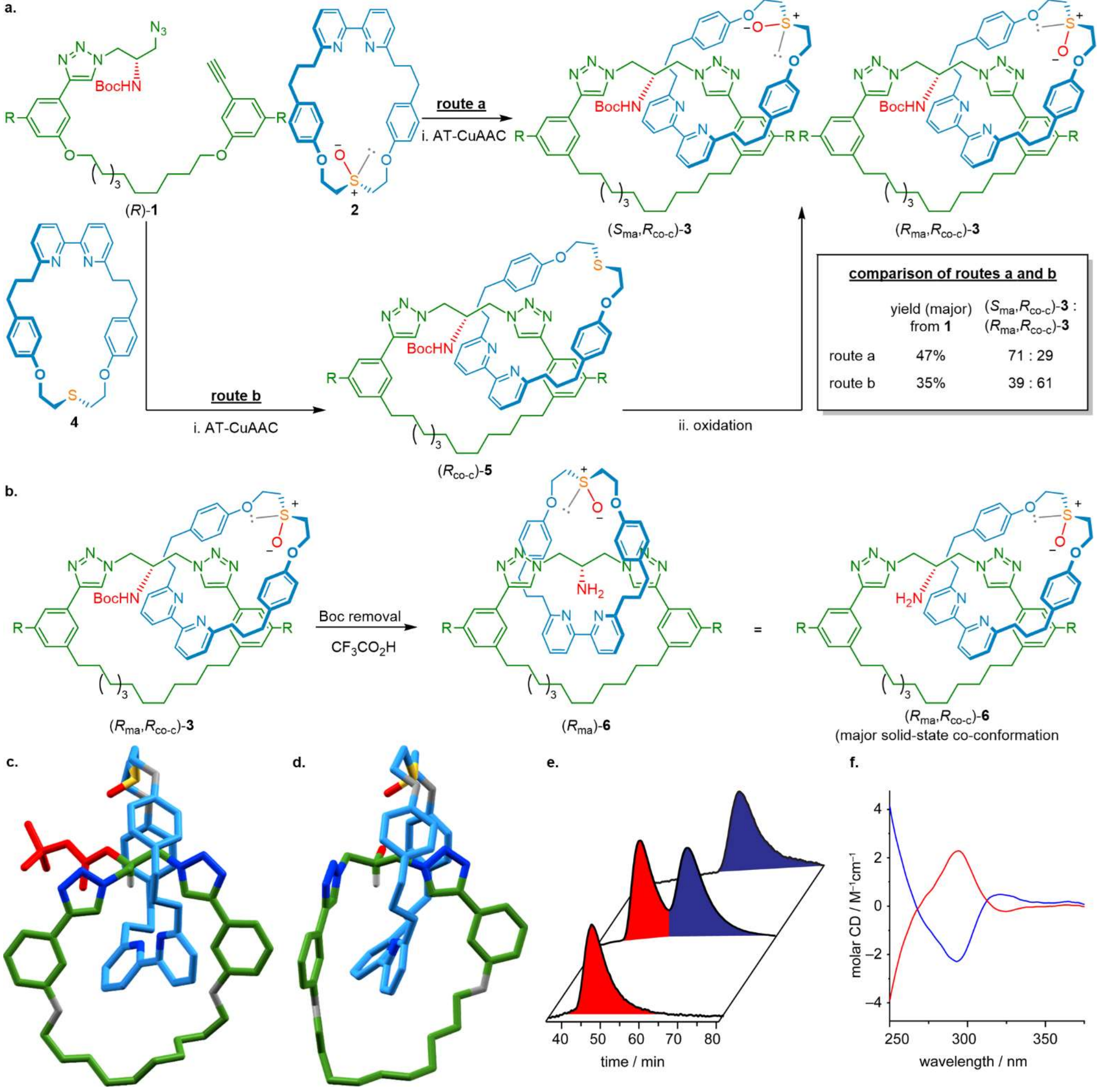
Having recognized that co-conformational diastereoisomerism is a fundamental property of mechanically axially chiral catenanes and rotaxanes, we proposed that a co-conformational stereogenic unit could act as a temporary source of chiral information in their synthesis (Fig. 2). By forming a mechanical bond selectively on one side of a prochiral unit (route a) and designing the structure such that co-conformational exchange is blocked, the mechanically axially chiral catenane product would be formed as a pair of separable diastereomers with identical co-conformational configuration (here $R_{\text{co-c}}$) but opposite mechanical axial configuration (R_{ma} or S_{ma}). Alternatively, installing a facially symmetrical ring on one side of a prochiral center would give rise to a single co-conformational enantiomer (route b). Subsequent desymmetrisation of the faces of the ring would give rise to the same pair of diastereomers. Removal of the groups preventing co-conformational motion would give mechanically axially chiral enantiomers in which the mechanical bond provides the sole fixed source of stereochemistry. An advantage of this co-conformational chiral auxiliary approaches is that co-conformational enantiomers can be made using chiral pool starting materials by choosing where the mechanical bond is formed[11,26,27,28].

Figure 2. Proposed co-conformational auxiliary approach for the synthesis of axially chiral catenanes. If the prochiral substituents and blocking groups are large enough to prevent co-conformational isomerism, the diastereomers can be separated and then converted into enantiomeric axially chiral catenanes.



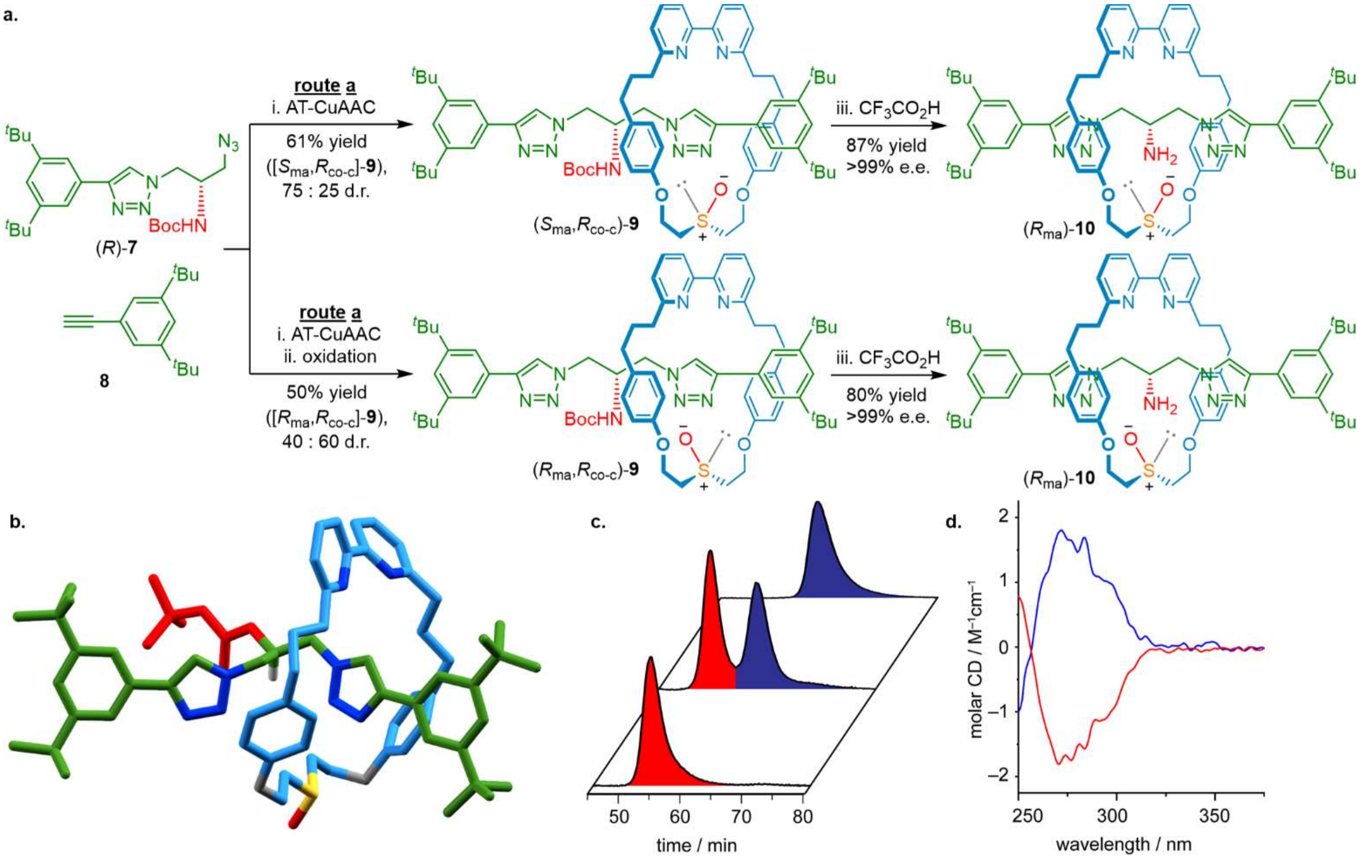
Proof-of-concept synthesis of an axially chiral catenane and rotaxane. (*R*)-Serine was elaborated to pre-macrocycle (*R*)-**1** (Supplementary section 2) (Fig. 3a). Macrocycle **2**, which contains a prochiral sulfoxide, was readily synthesized (Supplementary section 3) using a Ni-mediated macrocyclization protocol[29]. Catenane formation was achieved by reacting (*R*)-**1** with macrocycle **2** under active template[30] Cu-mediated alkyne-azide cycloaddition (AT-CuAAC)[31] conditions[32] to give separable diastereomers **3** in which co-conformational motion is prevented by bulky ester and *N*-Boc groups (route a). Catenanes **3** could also be accessed by reaction of (*R*)-**1** with macrocycle **4** to give ($R_{\text{co-c}}$)-**5** followed oxidation to give catenanes **3** (route b). Both routes proceeded with appreciable but opposite stereoselectivity. Single crystal x-ray diffraction (SCXRD) analysis of the major product of of *rac*-**1** and **2** allowed the major stereoisomer produced in routes a and b to be assigned. Conversion of diastereomers **3** to structures in which the mechanically axially chiral stereogenic unit is the only fixed source of stereochemistry can be achieved by removing the Boc group (Fig. 2b) or reducing the esters (Supplementary sections 5 and 6 respectively). Accordingly, removal of the Boc group from (R_{ma},$R_{\text{co-c}}$)-**3** or (S_{ma},$R_{\text{co-c}}$)-**3** gave (R_{ma})-**6** (>99% e.e.) and (S_{ma})-**6** (>99% e.e.) respectively (Fig. 3e). The enantiomeric nature of these structures is supported by circular dichroism (CD) analysis (Fig. 3f). The solid-state structure of *rac*-**6** (Fig. 3d) contains both co-conformational diastereomers with the (R^{*}_{ma}-$R^{*}_{\text{co-c}}$) co-conformation observed to dominate (~80 : 20).

Figure 3. Synthesis and analysis of enantiopure axially chiral catenane **6**. (a) Synthesis and separation of catenane diastereomers **3** from (*R*)-**1** by route a or route b (Fig. 2) with opposite diastereoselectivity. Reagents and conditions: i. [Cu(MeCN)$_4$]PF$_6$, N^{i}Pr$_2$Et, CH$_2$Cl$_2$, rt, 16 h; ii. IBX, NEt$_4$Br, CHCl$_3$-H$_2$O (99 : 1), rt, 16 h. (b) Conversion of catenane **3** to enantiomeric catenanes **6**. Reagents and conditions: CF$_3$CO$_2$H, CH$_2$Cl$_2$, 0 °C, 1 h. (c) The solid-state structure of *rac*-(S_{ma},$R_{\text{co-c}}$)-**4** allowed the major products of routes a and b to be assigned. (d) The solid-state structure of (*rac*)-**6** contains (S_{ma},$R_{\text{co-c}}$)-**6** as the major co-conformational diastereomer. Analysis of the enantiomers of catenane **6** by (e) CD and (f) HPLC confirmed their enantiopurity and chiral nature. IBX = 2-iodoxybenzoic acid.



The same strategy was used to synthesize mechanically axially chiral rotaxane **11** (Fig. 3). Serine-derived azide (*R*)-**7** (Supplementary section 7), alkyne **8** and macrocycle **2** were reacted under AT-CuAAC conditions[33] to give rotaxane diastereomers **9** (route a). Rotaxanes **9** could also be accessed by reaction of (*R*)-**7**, **8** and macrocycle **4** followed by oxidation (route b). SCXRD analysis of the major isomer obtained using route b with (*R*)-**7** (Fig. 3b) allowed the major products of routes a and b to be assigned. Removal of the Boc group from separated samples of (R_{ma},$R_{\text{co-c}}$)-**9** and (S_{ma},$R_{\text{co-c}}$)-**9** gave (R_{ma})-**10** and (S_{ma})-**10** respectively in excellent enantiopurity (>99% e.e., Fig. 4c). (R_{ma})-**10** and (S_{ma})-**10** produce mirror-image CD spectra (Fig. 3d) emphasizing the chiral nature of the mechanical axial stereogenic unit.

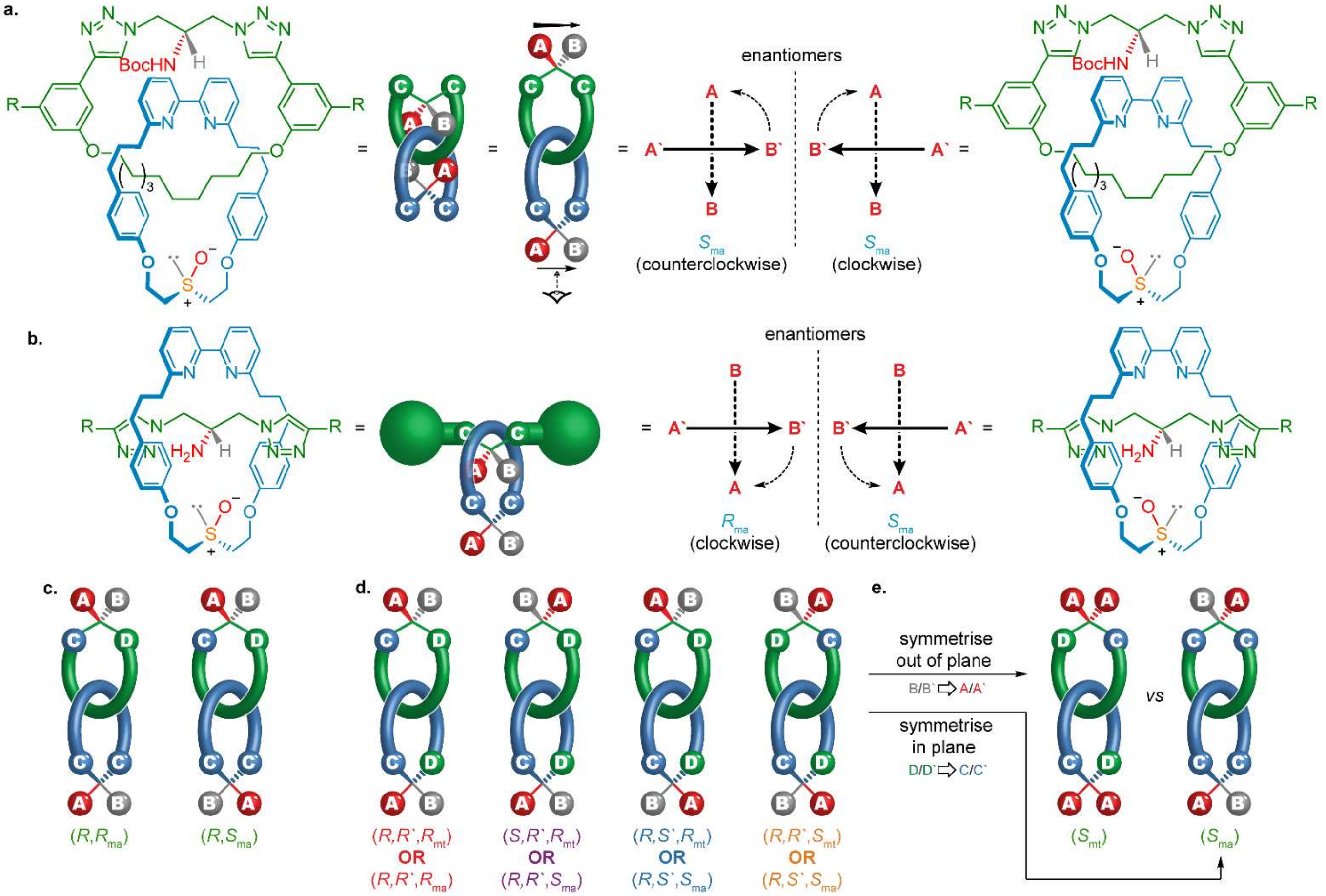
Figure 4. Synthesis of mechanically axially chiral rotaxane **10**. (a) Synthesis of diastereomeric mechanically axially chiral rotaxanes **9** by route a or b gives separable rotaxanes **9** that are converted to **10** by removal of the Boc group. Reagents and conditions: i. macrocycle **2** (route a) or macrocycle **4** (route b), $[\text{Cu(MeCN)}_4]\text{PF}_6$, $\text{N}^i\text{Pr}_2\text{Et}$, CH_2Cl_2, rt, 16 h; ii. IBX, NEt_4Br, $\text{CHCl}_3\text{-H}_2\text{O}$ (99 : 1), rt, 16 h; iii. $\text{CF}_3\text{CO}_2\text{H}$, CH_2Cl_2, rt, 16 h. (d) SCXRD analysis of (S_{ma},$R_{\text{co-c}}$)-**9** allowed the major products of routes a and b to assigned. Analysis of the enantiomers of rotaxane **9** by (c) CD and (d) HPLC confirmed their enantiopurity and chiral nature. IBX = 2-iodoxybenzoic acid.



Stereochemical assignment and properties of the mechanically axially chiral stereogenic unit. The assignment of the mechanically axially chiral stereogenic unit relies on identifying the highest priority faces of each ring, which is only possible if the relative orientation of the prochiral units is specified. Building on a proposal by Stoddart and Bruns, we suggest that in the case of catenanes the in-plane substituents of the prochiral moieties be oriented so they "point" towards one another (Fig. 5a). Conversely, in the equivalent rotaxane, we suggest they be oriented to point in the same direction (Fig. 5b). This counterintuitive proposal, which is subject to approval by the community, is designed to ensure that a mechanically axially chiral rotaxane generated from an axially chiral catenane by ring opening would retain the same stereolabel.

Finally, we considered the nature of the stereochemistry in catenanes where one or both prochiral units are replaced with covalent stereocentres as these represent logical precursors to axially chiral targets if these centers were subsequently symmetrized and recently there has been a suggestion that the latter class might contain both mechanical axial and topological stereogenic units[34]. In the former (Fig. 5c), ligand permutation analysis reveals two diastereomers (shown) and their enantiomers (i.e. four stereoisomers), consistent with one covalent centre and one mechanical axial stereogenic unit. In the latter case, ligand permutation reveals four diasteromers (shown) and their enantiomers (eight stereoisomers), consistent with two covalent and one mechanical stereogenic unit. However, the nature of the mechanical stereochemistry is ambiguous as each diastereomer can be assigned using either a mechanical axial or a mechanical topological stereodescriptor, only one of which is required to specify the structure. This suggests that it would be incorrect to describe such catenanes as simultaneously topologically and mechanically axially chiral – one of the stereolabels would be redundant. This analysis may appear philosophical in nature but has implications for the synthesis of chiral catenanes. If a single diastereomer of such a catenane could be isolated, it could be converted to an axially chiral catenane by selective symmetrization of the in-plane substituents, or a topologically chiral catenane by symmetrization of the out of plane substituents (Fig. 5e). This analysis further highlights that how a stereogenic unit is conceptualized can guide the development of new methodologies.

Figure 5. Assignment and further analysis of the mechanical axial stereogenic unit. Methods to assign the stereogenic units of mechanically axially chiral (a) catenanes and (b) rotaxanes by specifying the relative orientation of prochiral moieties. (c) The two diastereomers identified in catenanes containing one prochiral and one fixed covalent stereogenic center. (d) The four diastereomers identified in catenanes containing a covalent stereogenic center in both rings whose structures can be specified using either a mechanical topological or axial stereodescriptor. (e) Selective symmetrization of the in-plane or out of plane substituents of one diastereomers of (d) gives a topologically or axially chiral catenane respectively.



CONCLUSIONS

Semi-structural analysis allowed us to identify an efficient co-conformational auxiliary approach to mechanically axially chiral catenanes and revealed a previously overlooked axially chiral stereogenic unit in rotaxanes. The latter is a rare example of a “new” source of stereoisomerism, as opposed to a new pathway of isomer exchange[35,36] or an overlooked opportunity for atropisomerism[37], as have recently been reported. However, it is so closely related to that of catenanes it is perhaps important consider how it was overlooked for so long which may be at least in part due to the use of schematic cartoons that focus on symmetry without reference to the chemical moieties and can obscure important chemical information. Furthermore, it appears sensible to ask how the stereoisomerism of rotaxanes and catenanes could be systematized and unified rather than treated as separate as they are typically[38]. The same semi-structural approach leads to the surprising conclusion that catenanes based on rings containing a single stereogenic center can be described as either mechanically topologically or axially chiral but that only one such stereodescriptor is required to specify their structure, an observation with implications for future syntheses. Given the increasing interest in applications of chiral interlocked molecules[39,40,41,42,43,28] including examples based on mechanically chiral systems[44,45,46], as well as other exotic or hard to access mechanical stereogenic units[47,48,49,50,51], we anticipate these results will spur progress in the development of functional mechanically chiral systems[52].

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AUTHOR CONTRIBUTIONS

JRJM and SMG developed the co-conformational auxiliary concept. JRJM synthesized **3** and **5** and collected SCXRD diffraction data for a reduced product of catenane **5**. PRG synthesized **10** and **11**. DL optimized the synthesis and purification of **3**, **5**, synthesized **6** and determined the stereochemistry of catenanes **3**. PB collected the X-ray diffraction data of **3**, **6** and **10** and fully refined all SCXRD data. DL and PRG managed the preparation of the Supporting Information. SMG directed the research. All authors contributed to the analysis of the results and the writing of the manuscript.

COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

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