Mechanically axially chiral catenanes and noncanonical mechanically axially chiral rotaxanes

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Abstract

The term chiral was introduced by Lord Kelvin over a century ago to describe objects that are distinct from their own mirror image. Chirality is relevant in many scientific areas, but particularly chemistry because different mirror image forms of a molecule famously have different biological properties. Chirality typically arises in molecules due to a rigidly chiral arrangement of covalently bonded atoms. Less generally appreciated is that molecular chirality can arise when molecules are threaded through one another to create a mechanical bond. For example, when two molecular rings with chemically distinct faces are joined like links in a chain the resulting structure is chiral even when the rings themselves are not. We re-examined the symmetry properties of such mechanically axially chiral catenanes and in doing so identified a straightforward route to these molecules from simple building blocks. This also led to the discovery of a previously overlooked mechanical stereogenic unit that can arise when such a ring encircles a dumbbell-shaped axle to generate a rotaxane. These insights allowed us to produce the first highly enantioenriched axially chiral catenane and the same approach gave access to a molecule containing the newly identified 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 function¹⁰. Thus, chemists have invested significant effort to develop methods that produce molecules with control over their stereochemistry, the formal term that refers to the factors that determine molecular shape⁶. A major part of this effort, which has led to two Nobel prizes^{11,12}, has focused on methods to selectively make molecules in one mirror image form because these are hard to separate using standard techniques.

Although chirality is a whole-molecule property¹³, 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. 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,¹⁴ molecular knots,¹⁵ and mechanically interlocked molecules⁸.

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” stereochemistry¹⁶; 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 composed of an oriented ring encircling an axle whose ends are distinct are also chiral (Fig. 1a)¹⁷. 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^{18,19,20,21,22}, recent efforts have allowed them to be accessed in good enantiopurity using standard synthetic approaches^{23,24,25,26,27,28}.

In 2002, Puddephat and co-workers reported a chiral catenane composed of two achiral rings with distinct faces (C_{nv}) (Fig. 1b)⁹. A small number of axially chiral catenanes as a racemic mixture have been reported⁹, but no enantiopure examples where the mechanical bond provides the sole source of stereochemistry have been disclosed to date²⁹. Furthermore, unlike the example of topologically chiral catenanes, the notional process of ring opening and stoppering of the minimal representation of such mechanically axially chiral catenanes does not result in a chiral rotaxane (Fig. 1b). To address this challenge, 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 (Supplementary section 12). This led us not only to an efficient approach to enantiopure mechanically axially chiral catenanes but also to recognize and synthesize a noncanonical class of mechanically chiral rotaxanes that had previously been overlooked.

Results And Discussion

Insights from semi-structural schematic representations. The minimal schematic 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 chemically is by including a prochiral unit in both rings (**I**, Fig. 1c)^{9,29}. Strikingly, whereas the minimal schematic 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 noncanonical mechanically axially chiral stereogenic (Supplementary section 12.1) unit that displays similar co-conformational diastereoisomerism (**V**).

Building on the semi-structural analysis above, we returned to the general symmetry properties of mechanically axially chiral molecules (Supplementary section 12.1). Whereas the components of catenane **II** and rotaxane **IV** have C_{1v} point group symmetry, more generally mechanical axial stereochemistry will arise in catenanes whose rings have C_{nv} symmetry and rotaxanes whose axle has C_{1v} symmetry. Such structures will tend to exhibit prochirality³⁰ – any single structural modification that does not lie on a symmetry plane will result in a chiral object (Supplementary section 12.2). As a direct consequence, although mechanically axially chiral molecules can always, in theory, adopt a highly symmetrical co-conformation (e.g. **II** and **IV**) 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 (e.g. **III** and **V**). These lower

symmetry arrangements exist as pairs of co-conformational diastereomers and are an inherent property of mechanically axial chiral molecules (Supplementary section 12.3).

A co-conformational auxiliary approach to axially chiral catenanes and rotaxanes. Having recognized that co-conformational diastereoisomerism is a fundamental property of mechanically axially chiral molecules (Supplementary section 12.3), it became obvious 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 initially 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^{18,31,32,33}.

(*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 protocol³⁴. Catenane formation (Supplementary section 4) was achieved by reacting (*R*)-**1** with macrocycle **2** under active template³⁵ Cu-mediated alkyne-azide cycloaddition (AT-CuAAC)³⁶ conditions³⁷ to give separable diastereomers **3** in which co-conformational motion is prevented by the 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). Routes a and b proceeded with appreciable but opposite stereoselectivity. Single crystal x-ray diffraction (SCXRD) analysis of the major product of *rac*-**1** and **2** allowed the different major stereoisomers produced in routes a and b to be assigned (Fig. 3c, Supplementary section 11.1). 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. 3b and Supplementary section 5) or reducing the esters (Supplementary section 6). Accordingly, removal of the Boc group from ($R_{\text{ma}}, R_{\text{co-c}}$)-**3** or ($S_{\text{ma}}, R_{\text{co-c}}$)-**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 *rac*-($S_{\text{ma}}, R_{\text{co-c}}$) co-conformation observed to dominate (~80 : 20, Supplementary section 11.2).

The same strategy was used to synthesize mechanically axially chiral rotaxane **11** (Fig. 4). Serine-derived azide (*R*)-**7** (Supplementary section 7), alkyne **8** and macrocycle **2** were reacted under AT-CuAAC conditions³⁸ 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 (Supplementary section 11.4) of the major isomer obtained using route b with (*R*)-**7** (Fig. 4b) allowed the major products of routes a and b to be assigned. Removal of the Boc group from separated samples of (*R*_{ma},*R*_{co-c})-**9** and (*S*_{ma},*R*_{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. 4d) emphasizing the chiral nature of the rotaxane mechanical axial stereogenic unit.

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, as proposed by Stoddart and Bruns⁷ (Supplementary section 13.1). However, because this rule had not been applied in a real system, we immediately encountered difficulties; to unambiguously assign the highest priority face of each ring the relative orientations of the prochiral units must be specified. On reflection, 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). The latter, somewhat counterintuitive, proposal is designed to ensure that a mechanically axially chiral rotaxane derived from the notional ring opening of an axially chiral catenane would retain the same stereolabel. The absolute stereochemistry of both mechanically axially chiral catenanes and rotaxanes can then be assigned by viewing the ensemble along the axis connecting the prochiral units and observing the relative orientation of the vectors from the out of plane substituent with the highest priority to the lowest priority as shown; a clockwise direction of rotation from the head of the front vector to the tail of the rear vector is assigned as *R*_{ma} and an anticlockwise path assigned as *S*_{ma}. This approach can be readily extended to molecules where facial dissymmetry arises due to stereogenic axes or planes (Supplementary section 13.2).

Finally, we considered the stereochemical nature of catenanes in which one or both prochiral units are replaced with covalent stereocentres (Supplementary section 14). Such structures represent logical alternative precursors to axially chiral catenanes if they could be prepared diastereoselectively and the in-plane substituents subsequently symmetrized. Furthermore, there has been a suggestion that the latter class might contain both mechanical axial and mechanical topological stereogenic units³⁹. In the case of catenanes containing one stereogenic and one prochiral centre (Fig. 5c), ligand permutation analysis (Supplementary section 14.1) reveals two diastereomers (shown) and their enantiomers (i.e. four stereoisomers total), consistent with one covalent centre and one mechanical axial stereogenic unit.

In the case of catenanes containing a stereogenic centre in each ring, ligand permutation (Supplementary section 14.2) reveals four diastereomers (Fig. 5d) and their enantiomers (eight stereoisomers total), consistent with two covalent and one mechanical stereogenic unit. However, the nature of the mechanical stereochemistry is ambiguous; each structure can be assigned both a mechanical axial or a mechanical topological stereodescriptor, but only one of these is required to fully specify the structure. This analysis suggests that it would be incorrect to describe such catenanes as simultaneously topologically and mechanically axially chiral – one of the stereolabels would be redundant – but that it is unclear which

description should take priority. 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.

Conclusions

Detailed analysis of the symmetry properties of the mechanically axially chiral stereogenic unit of catenanes, and in particular the use of semi-structural representations, allowed us to identify an efficient co-conformational auxiliary approach to mechanically axially chiral catenanes and revealed a previously overlooked noncanonical axially chiral stereogenic unit in rotaxanes. The latter is a rare example of a “new” source of stereoisomerism, as opposed to an overlooked pathway of isomer exchange^{40,41} or an overlooked opportunity for atropisomerism⁴², as have recently been reported. The rotaxane mechanical axial stereogenic is so closely related to that of catenanes it is surprising that it was overlooked for so long, which may in part be due to the use of schematic structures (Fig. 1b) that focus on symmetry without reference to underlying chemical structure; although these are useful they can also obscure important chemical information. Indeed, given that the fixed mechanical stereogenic units of catenanes (topological and axial) now both have an equivalent in rotaxane structures (planar and axial), it appears sensible to suggest that the stereochemistry of rotaxanes and catenanes be unified rather than treated as separate as they are typically⁴³. Our analysis also led to the surprising conclusion that catenanes based on two rings each containing a single stereogenic center can be described as either mechanically topologically or axially chiral but that only one mechanical stereodescriptor is required to specify their structure, an observation with implications for future studies. Given the increasing interest in applications of chiral interlocked molecules^{44,45,46,47,48,33} including examples based on mechanical and co-conformationally chiral systems^{49,50,51}, as well as other exotic or hard to access mechanical stereogenic units^{52,53,54,55,56,57}, we anticipate these results will spur progress in the development of functional chiral interlocked systems⁵⁸. Finally, it should be noted that dynamic stereochemistry related to that of mechanically axially chiral catenanes and rotaxanes can also arise due to conformational and co-conformational processes^{59,60}, both of which have been observed but are poorly understood (Supplementary section 15). These may have potential applications as stereodynamic probes.

Declarations

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AUTHOR CONTRIBUTIONS

JRJM and PRG contributed equally; both have the right to place themselves as first author on their CVs. 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 **9** and **10**, determined the stereochemistry of rotaxanes **9** and managed the preparation of manuscript graphics. 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 **9** 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.

DATA AVAILABILITY STATEMENT

All characterization data for novel compounds (NMR, MS, CD, HPLC) will be made available through the University of Southampton data repository at the point of publication. Crystallographic data has been uploaded to the CCDC and is availability under the accession numbers 2109976 (*rac*-($S_{\text{ma}}, R_{\text{co-c}}$)-**3**), 2115463 (*rac*-**6**), 2109991 (*rac*-**S15**) and 2109992 (($R_{\text{ma}}, R_{\text{co-c}}$)-**9**).

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Figures

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.

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.

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. $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$, $N^i\text{Pr}_2\text{Et}$, CH_2Cl_2 , rt, 16 h; ii. IBX, NEt_4Br , $\text{CHCl}_3\text{-H}_2\text{O}$ (99 : 1), rt, 16 h. (b) Conversion of catenane **3** to enantiomeric catenanes **6**. Reagents and conditions: $\text{CF}_3\text{CO}_2\text{H}$, CH_2Cl_2 , 0 °C, 1 h. (c) The solid-state structure of rac -(S_{ma}, R_{co-c})-**4** allowed the major products of routes a and b to be assigned. (d) The solid-state structure of rac -**6** contains rac -(S_{ma}, R_{co-c})-**6** as the major co-

conformational diastereomer. Analysis of the enantiomers of catenane **6** by (e) CSP-HPLC and (f) CD confirmed their enantiopurity and chiral nature. IBX = 2-iodoxybenzoic acid. R = CO₂Me.

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), [Cu(MeCN)₄]PF₆, NⁱPr₂Et, CH₂Cl₂, rt, 16 h; ii. IBX, NEt₄Br, CHCl₃-H₂O (99 : 1), rt, 16 h; iii. CF₃CO₂H, CH₂Cl₂, rt, 16 h. (b) SCXRD analysis of **(R_{ma},R_{co-c})-9** allowed the major products of routes a and b to assigned. Analysis of the enantiomers of rotaxane **9** by (c) CSP-HPLC and (d) CD confirmed their enantiopurity and chiral nature. IBX = 2-iodoxybenzoic acid.

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. R = CO₂Me.

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