Controlling Mechanical Geometrical Isomerism

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Supporting Information Placeholder

ABSTRACT: Mechanical geometric isomerism, which arises when bilaterally dissymmetric components are interlocked such that their internal mirror planes can be made congruent, is under-explored using simple prochiral components. Here we demonstrate that a single intercomponent H-bond appears sufficient to control the formation of rotaxanes and catenanes containing canonical mechanical geometric stereochemistry and identify a new mechanical stereogenic unit of rotaxanes, which yielded to a shuttling auxiliary synthesis.

Mechanical bond formation between two rings, to give a catenane, or a ring and a dumbbell-shaped axle, to give a rotaxane,[1] can result in stereochemistry even when the non-interlocked components are non-stereogenic.[2] If no improper symmetry operation remains in the interlocked structure they are referred to as "mechanically chiral", the potential for which was recognized in 1961 by Wasserman and Frisch.[3] Mechanically chiral catenanes can be subdivided into structures containing a planar (two oriented rings) or axial (two facially dissymmetric rings) stereogenic unit, both of which have now yielded to stereoselective synthesis using chiral auxiliary approaches,[4,5a] as have their cousins, mechanically planar chiral[4c,6,7] and the recently identified mechanically axially[5] chiral rotaxanes.

Interlocking of a facially dissymmetric macrocycle with an oriented ring does not result in a chiral structure because the internal mirror planes of the individual components can be made congruent. However, such catenanes (Figure 1b) display mechanical geometric isomerism because the rings can be interlocked in two ways to give distinguishable diastereomers characterized by the relative orientation of vectors associated with the macrocycles. Similarly, a facially dissymmetric ring encircling an axle whose ends are distinguishable results in mechanical geometric isomeric rotaxanes (Figure 1a). The latter are sometimes referred to as "orientational isomers", which is perhaps unhelpful as all mechanical stereogenic units arise due to distinguishable orientations of the subcomponents.

The majority of reported rotaxane and catenanes geometric isomers where the mechanical bond provides the sole stereogenic unit[8] we could identify are based on calixarenes[9,10] or similar macrocycles[11] whose facial dissymmetry arises due to a fixed cone-shaped conformation of the threaded ring.[12] Thus, facial dissymmetry is expressed over the whole macrocycle, which has been shown to allow stereoselective synthesis of mechanical geometric isomers. However, the minimum requirement for facial dissymmetry is a single covalent prochiral center.[13] To our knowledge, the only examples of such rotaxanes were reported by Bode and Saito,[14] but in this case no stereoselectivity was reported.

Here we report the first stereoselective synthesis of canonical rotaxane (Figure 1a) and catenane (Figure 1b) geometric isomers based on simple prochiral components. Surprisingly a single H-bond between the macrocycle and axle appears to be sufficient to permit good stereocontrol.[15] Furthermore, by considering that these catenane and rotaxane isomers are related by the notional opening and stoppering of the oriented ring of the former (Figure 1b), we identified a new rotaxane mechanical geometric stereogenic unit; if instead the facially dissymmetric ring of the catenane is opened and stoppered, a new, previously unremarked upon form of geometric isomerism is revealed (Figure 1c). This new rotaxane stereogenic unit is not suitable for our simple H-bond-controlled approach. However, our chiral interlocking auxiliary strategy[6e] allows an oriented ring to be stereoselectively threaded onto a prochiral axle and, using this approach, we were able to produce both isomers of a rotaxane displaying this new stereogenic unit.

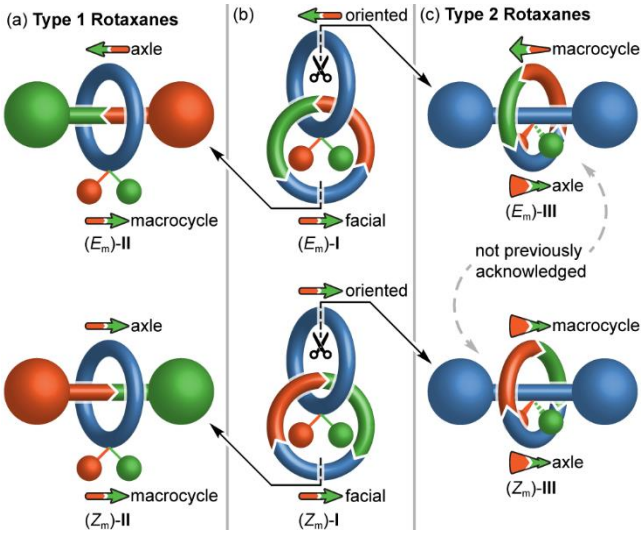
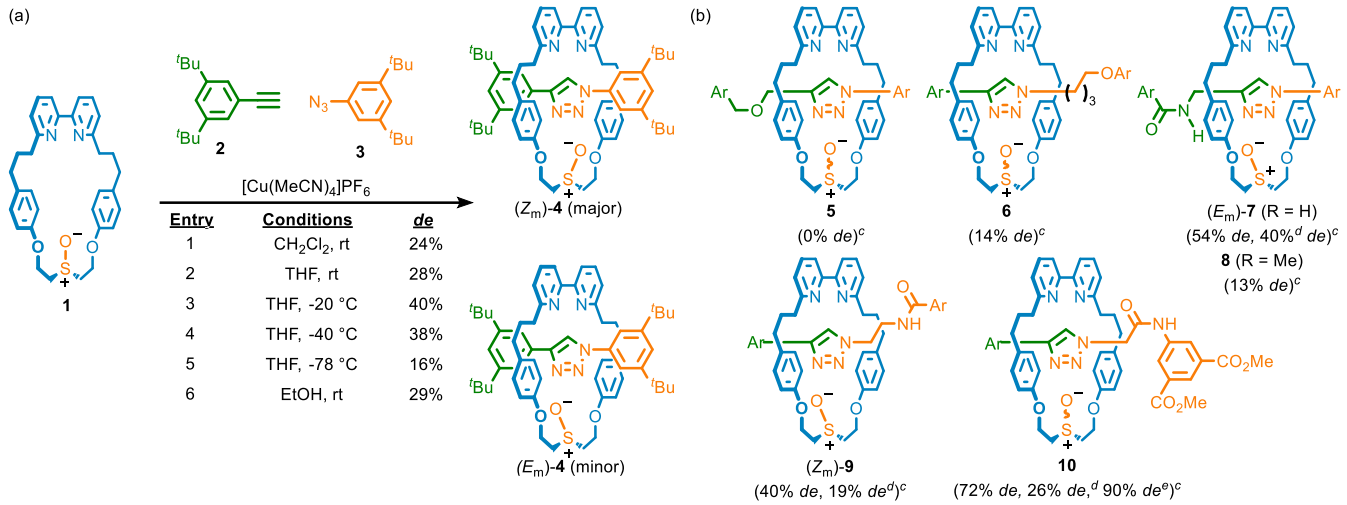


Figure 1. Cartoon representation of the canonical mechanical geometric stereogenic units of (a) rotaxanes and (b) catenanes and (c) the newly identified non-canonical rotaxane stereogenic unit. Their notional interconversion through macrocycle cleavage is illustrated. Vectors associated with the individual components are indicated using arrows to highlight the origin of the observed geometric isomerism.

Scheme 1. AT-CuAAC synthesis of rotaxane geometric isomers of type 1.[a,b]



[a]Reagents and conditions: **1** (1 equiv.), **2** (1.1 equiv.), **3** (1.1equiv.), $[Cu(MeCN)_4]PF_6$ (0.96 equiv.), $^iPr_2EtN$ (2 equiv.) THF, rt, 16 h. [b]Where the stereochemistry of the major isomer was determined this is indicated. [c]Determined by ^1H NMR analysis of the crude reaction product. [d]The reaction was conducted in EtOH. [e]The reaction was conducted at –40 °C.

The active template[16] Cu-mediated alkyne-azide cycloaddition (AT-CuAAC)[17] between readily available,[18] prochiral sulfoxide macrocycle **1**,[5a] aryl alkyne **2** and aryl azide **3** at rt in CH_2Cl_2 (**Scheme 1a**, entry 1) gave geometric isomers (E_m)-**4** and (Z_m)-**4** in low stereoselectivity (24% *de*).[19] These could be separated by flash chromatography and subsequent analysis of the separated products by single crystal x-ray diffraction (SCXRD) allowed the major and minor isomers to be identified as (E_m-)-**4** and (Z_m)-**4** respectively. Replacing the solvent with THF marginally improved the selectivity (28% *de*, entry 2), as did lowering the reaction temperature to –20 °C (40% *de*, entry 3), although the selectivity was reduced again at lower temperatures (entries 4 and 5). Using EtOH as a reaction solvent was comparable to THF (entry 6).[20] When a propargylic alkyne was employed with **3** in THF to generate rotaxane **5**, no stereoselectivity was observed (Scheme 1b), whereas the reaction of an alkyl azide and **2** to give rotaxane **6** proceeded in low stereoselectivity (14% *de*).

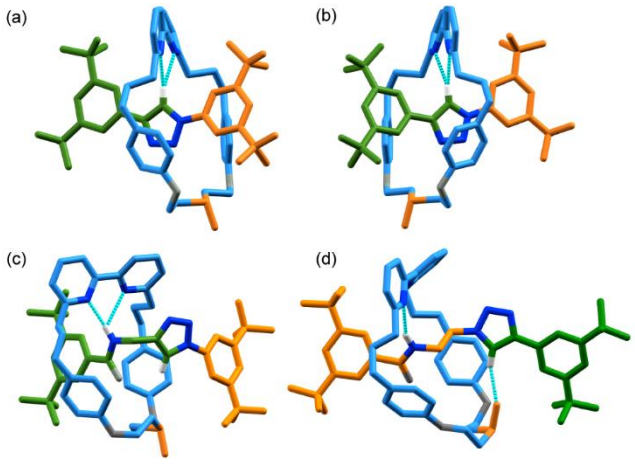


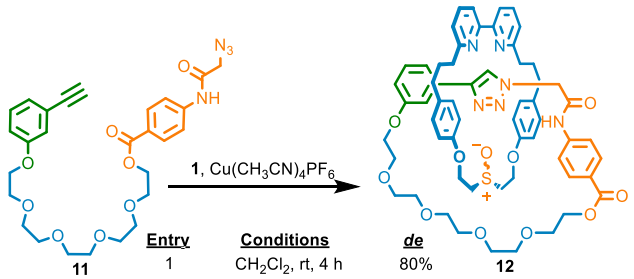
Figure 2. (a) Solid state structures of (a) (Z_m)-**4**, (b) (E_m)-**4**, (c) (Z_m)-**6** and (d) (E_m)-**9** with key intercomponent interactions highlighted. Colors as in **Scheme 1**, including the sulfoxide (SO) moiety to empahsise the macrocycle faces, except O (grey), N (light blue), H (white). Majority of H omitted for clarity.

We recently observed that a single H-bond was sufficient to control the stereoselective synthesis of mechanically axially chiral rotaxanes based on macrocycle **1**.[15] In keeping with this, when a propargylic amide was reacted with **3** to give **7**, a significantly improved stereoselectivity (54% *de*) was obtained, which was reduced in EtOH (40% *de*). The corresponding N-methyl amide gave rise to rotaxane **8** in low selectivity (13% *de*). The AT-CuAAC coupling of **2** and an alkyl azide bearing a simple amide gave rotaxane **9** in moderate stereoselectivity (40% *de*), which was reduced in EtOH (19% *de*), demonstrating that the amide can be placed in either coupling partner. Finally, rotaxane **10**, whose amide unit is more electron deficient than that of **9** was produced in good (70% *de*) at rt, which was improved (90% *de*) when the same reaction was conducted at –40 °C.[21] Replacing the reaction solvent with EtOH once again led to reduced selectivity (26% *de*).

Our results suggest that a single H-bond is sufficient to control the stereoselective synthesis of type I rotaxanes. However, we have previously observed such an H-bonding interaction in the solid-state structure of both diastereomers of epimeric mechanically axially chiral catenanes due to the flexible nature of macrocycle **1**.[5a] The solid-state structures of the major isomers of rotaxanes **7** and **9** reiterate this phenomenon; although both were formed selectively and the expected NH•••O H-bond is observed, counterintuitively the macrocycle is oriented in opposite directions with respect to the amide. Thus, although it appears that a single, relatively weak interaction can control the synthesis of type I geometric isomers, the major product depends on the detailed structure of the half-axle components.[22]

Having established that a polarised NH unit appears sufficient to control the synthesis of type I rotaxanes, we extended our approach to the related catenanes. Pre-macrocycle **11**, which contains an activated amide unit analogous to that of **10**, reacted with **1** under our AT-CuAAC catenane-forming conditions (Scheme 2)[23] to give **12** with good stereocontrol (80% *de*, entry 1). Conducting the reaction in $CHCl_3$-EtOH reduced the stereoselectivity (60% *de*, entry 2) whereas reducing the temperature to 0 °C increased the stereoselectivity (92% *de*, entry 3). Lowering the temperature further (–40 °C) had no significant effect (90% *de*, entry 4). Thus, unsurprisingly given the similarity of the stereogenic units, type I rotaxane geometric isomers and catenane geometric isomers are accessible with good stereocontrol using equivalent strategies.

Scheme 2. Stereoselective synthesis of catenane **12**.[a]



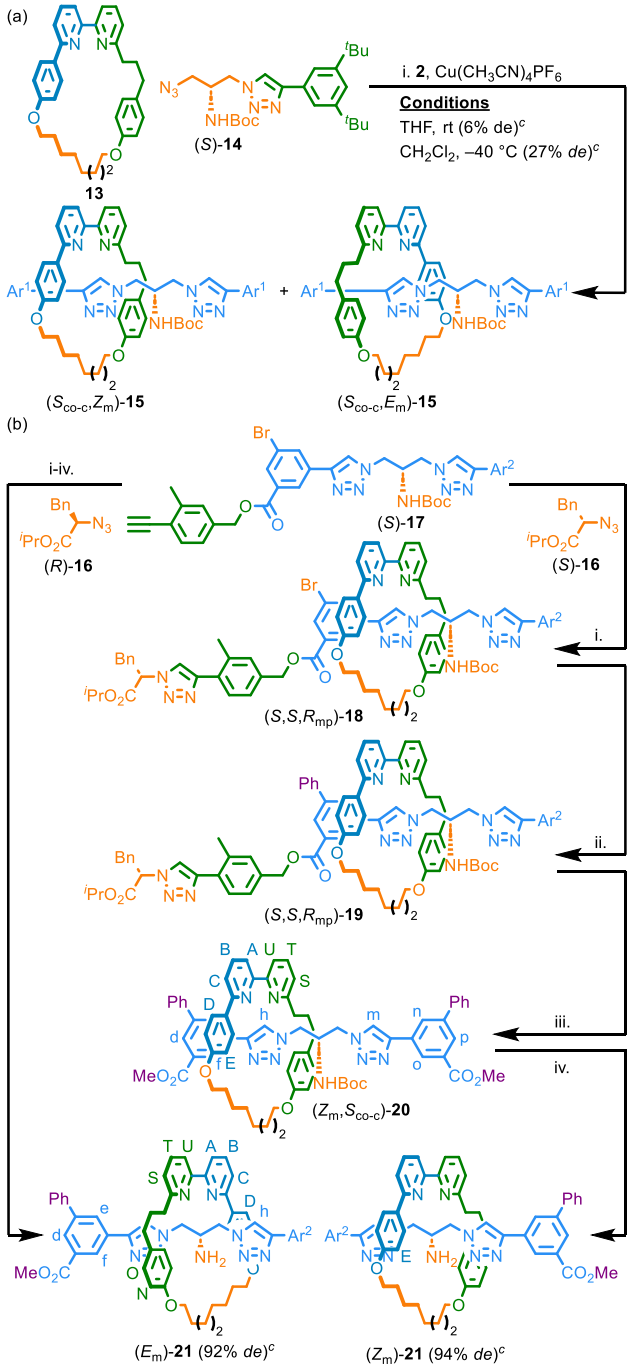
Entry	Conditions	*de*
1	CH_2Cl_2, rt, 4 h	80%
2	$CHCl_3$-EtOH (1 : 1), rt, 4 h	60%
3	CH_2Cl_2, 0 °C, 16 h	92%
4	CH_2Cl_2, -40 °C, 16 h	90%

[a]Reagents and conditions: a solution of **11** (2 equiv.) was added over the time stated using a syringe pump to **1** (1 equiv.), $[Cu(MeCN)_4]PF_6$ (0.97 equiv.), $^iPr_2EtN$ (4 equiv.).

Finally, we explored the stereoselective synthesis of a rotaxane containing the non-canonical type II mechanical geometric stereogenic unit. In the first instance, oriented macrocycle **13**, serine-based azide (*S*)-**14** and alkyne **2** and were subjected to the AT-CuAAC reaction to yield rotaxane ($S_{co\text{-}c}$,E_m/Z_m)-**15** as an inseparable mixture of co-conformationally chiral, mechanical geometric diastereoisomers (6% *de*, **Scheme 3a**). The same reaction in CH_2Cl_2 at –40 °C also proceeded in low selectivity (27% *de*). The poor stereoselectivity in the formation of **15** is unsurprising; unlike in the synthesis of type I isomers, where the products differ in the face of the macrocycle presented to the alkyne/azide coupling partners, the stereoselective formation of non-canonical type II stereoisomers relies on differentiating which side of the macrocycle is projected towards which substituent of stereocenter of the chiral coupling partner. This challenge is similar to that encountered in the synthesis of mechanically planar chiral rotaxanes, which we have previously identified only proceeds efficiently when an α-chiral azide is used.[6b,f] This is hard to realize practically here as, nominally, it would require iterative CuAAC couplings of a 1,1-bis-azide synthon. However, this analysis also suggests that strategies for the synthesis of mechanically planar chiral rotaxanes can be applied to type II rotaxanes.

To demonstrate this, we applied our chiral interlocking auxiliary approach, which reliably loads macrocycle **13** onto the axle of a rotaxane in a specific orientation,[6f] to synthesize both isomers of rotaxane **21** (**Scheme 3b**). Coupling of azide (*S*)-**16** with half-axle (*S*)-**17** in the presence of macrocycle **14** gave rotaxane (S,S,R_{mp})-**18** in which the co-conformation indicated dominates. Subsequent conversion of the Br substituent to a Ph unit gave rotaxane (S,S,R_{mp})-**19** in which the macrocycle is no longer able to explore the axle. Transesterification with MeOH cleaved the auxiliary to give (Z_m,$S_{co\text{-}c}$)-**20**. Removal of the Boc group provided rotaxane (Z_m)-**21**. The same synthesis was also carried out starting from (*R*)-**16** and (*S*)-**17** to give (E_m)-**21**.

Scheme 2. (a) Direct AT-CuAAC approach to rotaxane geometric isomers **15**.[a] (b) A chiral interlocking auxiliary approach for the synthesis of both geometric isomers of rotaxane **21**.[b]



[a]Reagents and conditions: i. **13** (1 equiv.), **2** (1.1 equiv.), (*S*)-**14** (1.1 equiv.) $[Cu(MeCN)_4]PF_6$ (0.97 equiv.), $^iPr_2EtN$ (2 equiv.), CH_2Cl_2, rt, 16 h. ii. TFA, CH_2Cl_2, rt, 1 h. [b]Reagents and conditions: i. (*S*)-**17** (1.1 equiv.), **13** (1 equiv.), **16** (1.1 equiv.), $[Cu(MeCN)_4]PF_6$ (0.99 equiv.), $^iPr_2EtN$ (2 equiv.), CH_2Cl_2, rt, 16 h. ii. $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, acetone-^{i}PrOH-H_2O (2 : 1 : 1), 60 °C, 3 h iii. K_2CO_3, CH_2Cl_2 : MeOH, rt, 3 h. (iv) TFA, CH_2Cl_2, rt, 1 h. [c]Determined by ^1H NMR analysis of the unpurified reaction product of step i. Ar^1 = 3,5-di-*t*Bu-C_6H_3. Ar^2 = 3-CO_2Me)-5-Ph-C_6H_3.

Comparison of the ^{1}H NMR spectra of rotaxanes **20** obtained starting from (*R*)-**16** and (*S*)-**16** with the inseparable mixture of isomers obtained using the direct AT-CuAAC reaction of the corresponding Boc protected azido-amine (*c.f.*, **15**, see ESI section 5) allowed us to identify the key signals of the two isomers; the products obtained using (*R*)-**16** (**Figure 4b**) and (*S*)-**16** (**Figure 4d**) have distinct ^{1}H NMR spectra and both sets of signals were observed in the sample obtained by the direct AT-CuAAC approach (**Figure 4c**). This allowed us to assign the stereopurity of both (Z_m)-**20** (94% *de*) and (E_m)-**20** (92% *de*) by co-integrating the major and minor signals corresponding to H_h. Similar values (92% and 94% *de* respectively) were obtained by co-integration of signals corresponding to the minor isomer in samples of (Z_m)-**21** and (E_m)-**21**.

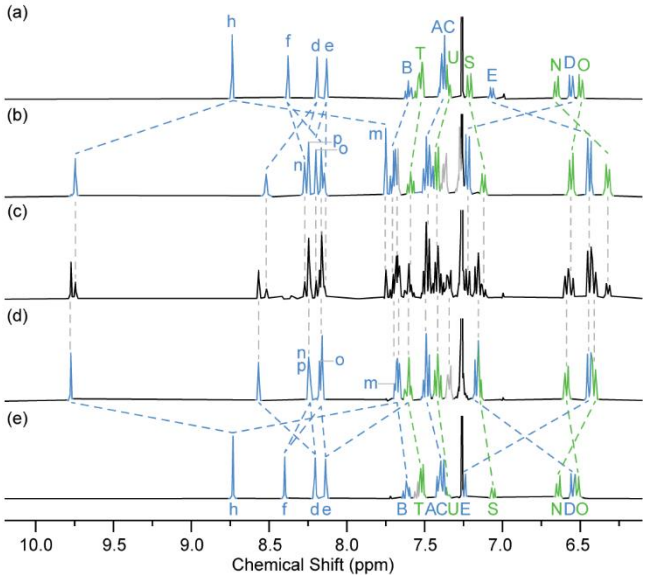


Figure 4. Partial ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) spectra of (a) (E_m)-**21** (94% *de*); (b) (E_m,$S_{co\text{-}c}$)-**20** (92% *de*); (c) **20** (16% *de*, obtained by a direct AT-CuAAC coupling, see ESI section 5), (d) (Z_m,$S_{co\text{-}c}$)-**20** (94% *de*) (e) (Z_m)-**21** (92% *de*). Peak assignment and colors as in **Scheme 3b**.

In conclusion, we have demonstrated that an H-bonding interaction between a prochiral macrocycle and a functional group unsymmetrically disposed in the corresponding half-axle or pre-macrocycle is sufficient to control the formation of the canonical mechanical geometric stereogenic units of rotaxanes and catenanes respectively. Furthermore, having recognized an overlooked rotaxane stereogenic that arises when an oriented macrocycle encircles a prochiral axle, we have demonstrated that although this is challenging to control using a direct AT-CuAAC approach, it yields to a chiral interlocking auxiliary strategy. Given that there are now two forms of rotaxane mechanical geometric isomerism, we suggest that they are renamed as type 1 and type 2, with the numeral based on the order in which they were identified. To date, type I rotaxane isomers based on calixarenes and similar cone-shaped macrocycles, as well as structures expressing combinations of mechanical and covalent stereochemistry have been investigated as components of molecular switches and motors. Here we have demonstrated that such isomerism can be expressed and controlled in much simpler macrocycles, opening up the study of simpler structures. We have also identified a new mechanical geometric stereogenic unit and eagerly anticipate the new uses to which this might be put.

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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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(21) Reducing the temperature further did not improve the observed stereocontrol and led to a slow reaction.

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