Design and synthesis of the first triply twisted Möbius annulene

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As long as 50 years ago theoretical calculations predicted that Möbius annulenes with only one π surface and one edge would exhibit peculiar electronic properties and violate the Hückel rules. Numerous synthetic attempts notwithstanding, the first singly twisted Möbius annulene was not prepared until 2003. Here we present a general, rational strategy to synthesize triply or even more highly twisted cyclic π systems. We apply this strategy to the preparation of a triply twisted [24]dehydroannulene, the structure of which was confirmed by X-ray analysis. Our strategy is based on the topological transformation of 'twist' into 'writhe'. The advantage is twofold: the product exhibits a lower degree of strain and precursors can be designed that inherently include the writhe, which, after cyclization, ends up in the Möbius product. With our strategy, triply twisted systems are easier to prepare than their singly twisted counterparts.

ost objects in our everyday lives exhibit two sides: in and out, or front and back. Möbius bands are exceptions. Any band with an odd number of twists has one side and one edge. Ribbons with an even number of twists (including zero) exhibit two sides. Unfortunately, sidedness is not an intrinsic topological parameter because its definition requires the object to be embedded in a surrounding space. Orientability is an intrinsic property, and therefore is used frequently to describe the topology of objects¹⁻³. An object is said to be non-orientable if a chiral shape drawn onto the surface can be transformed into its mirror image simply by moving it over the surface. This seems trivial, but, for instance, the Fisher formula of D-lactic acid drawn onto a Möbius band is transformed into the structure of L-lactic acid by shifting it once around the ribbon. If our universe were non-orientable it would be possible to convert D-lactic into L-lactic acid by simply moving a sample around in space (see Supplementary Fig. 1). Other examples of non-orientable objects are the Klein bottle, Boy's surface, the Roman surface and the Crosscap (see Supplementary Fig. 2). The peculiar properties of non-orientable surfaces have attracted and inspired mathematicians, as well as artists, musicians and authors. Interest in chemistry started in 1964 when Edgar Heilbronner predicted that Möbius annulenes, being aromatic with 4n electrons, would violate the Hückel rules⁴. The 180° twist induces strain in the π system and reduces π overlap. Heilbronner concluded that therefore only [n]annulenes with a ring size larger than n = 20 would be stable. This forethought was confirmed recently by theoretical calculations⁵⁻¹⁰. Using a systematic generation procedure, and by subsequent energy calculations of several hundred thousand [n]annulene isomers of ring sizes n = 8-24, we can prove that there are numerous Möbius annulenes (about 50% of all structures); however, there is no Möbius global minimum among the uncharged [n] annulenes^{11–14}. Obviously, the energy gain through Möbius aromaticity is overcompensated by the strain imposed by the twist. Unfortunately, the numerous higher-energy local-minimum structures are kinetically unstable. They would immediately 'untwist' and release strain energy, even at low temperatures, to form the more stable Hückel structures. The first Möbius annulene synthesis, therefore, used a strategy to stabilize the strained part of the Möbius ring by a suitable

molecular framework $^{15-17}$. Meanwhile, a number of Möbius-extended porphyrins have been synthesized that have a stability similarly enhanced by steric constraints $^{18-21}$.

Results and discussion

Topological design. Given the tremendous problems in synthesizing singly twisted Möbius systems, triply twisted annulenes seem to be rather out of reach. On realistic inspection, strain and reduced π overlap loom. Moreover, a simple synthetic analysis adds further implications to the heap of obstacles. From a naive point of view one could propose a cyclotrimerization of three singly twisted precursors or, alternatively, the cyclization of a triply twisted starting structure (Fig. 1a). However, as soon as one leaves this rather low level of abstraction, and dares to translate the rather simple-minded picture into real chemistry, one gradually realizes that the situation is fairly hopeless. How to stabilize a 180°, or even a 540°, twist in a linear π system—by substitution or a molecular rack? Even if one could do so, a simple cardboard model reveals that a twisted band would never bend. Hence, the ends of the bands would not find each other for cyclization. Anyhow, putting aside all the above concerns, if the target structure (against all odds) could form, it would be tremendously strained.

In this quandary, hope comes from topology. It is an everydaylife experience (telephone cord, garden hose) that twisted bands wind around themselves to release strain. Topologists call this phenomenon the projection of 'twist' into 'writhe' (Fig. 1b).

Whereas a twist (T_w) is straightforward to define (it is just the sum of the dihedral angles of the vectors normal to the π plane)^{22,23}, the topological parameter 'writhe' (W_r) is less obvious, at least in its precise mathematical definition. Writhe is defined as the double Gaussian integral over a closed curve *C* in three-dimensional (3D) Euclidean space \mathbb{R}^3 (ref. 24):

$$W_{\rm r} = \frac{1}{4\pi} \iint_{C} \frac{\left(\mathrm{d}\mathbf{r}_2 \times \mathrm{d}\mathbf{r}_1\right) \cdot \mathbf{r}_{12}}{\left|\mathbf{r}_{12}\right|^3}$$

 \mathbf{r}_1 , \mathbf{r}_2 : points passing along *C*. $\mathbf{r}_{12} = \mathbf{r}_2 - \mathbf{r}_1$.

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Figure 1 | Strategies to introduce multiple twists in a cycle. a, Naive strategies may include the cyclotrimerization of three components each containing a single twist, or cyclization of a band with three twists. Both strategies are hampered because linear π systems cannot be twisted easily, and if constrained to do so would probably not cyclize easily. b, The transformation of twist (T_w) into writhe (W_r) in a closed band by winding around itself can release strain and suggests an alternative strategy. $T_{\rm w}$ is a measure of how often the upper edge of the band crosses the lower edge in 2D projections (local crossings, top), and W_r is a measure of the number of crossings of the ribbon axis with itself. The middle illustration shows three local self-crossings in the 2D projection of the view along the z axis (orthogonal to the paper plane). To calculate the writhe either the average of self-crossings in all projections from all vantage points has to be calculated or the double Gaussian integral has to be solved. Local crossings and selfcrossings can be either positive or negative. To assign a sign to a crossing the band has to be given a direction and the crossings are analysed as shown in the bottom illustration (right handed, +; left handed, -). T_w and W_r can take any positive or negative real number, L_k is always an integer.

In the case of a polygon (for example, annulenes) the double integral can be replaced by a double sum. Fortunately, there is also a descriptive interpretation: W_r is the average number of self-crossings

observed in 2D projections if the object is viewed from all vantage points (over the sphere of all projection directions)^{22,23,25–27}. $T_{\rm w}$ and $W_{\rm r}$ are real numbers that can be either positive or negative. Both topological parameters are connected by the Călugăreanu theorem²⁸:

$$L_{\rm k} = T_{\rm w} + W_{\rm r}$$

The linking number L_k is always an integer. If the linking number L_k is even $(0, \pm 2, \pm 4, \ldots)$ the band is orientable and two-sided, if L_k is odd ($\pm 1, \pm 3, \pm 5, \ldots$) the ribbon is non-orientable and one-sided. Whereas T_w and W_r of a band are interconvertible by topological transformation (just by stretching, compressing or bending), the linking number L_k can only be changed by cutting the band, twisting and rejoining both ends. Probably the most important implication of twist and writhe interconversion in chemistry or biology is 'DNA supercoiling'. There are enzymes (topoisomerases) that cut the double strand and give it a twist, which results in winding of the DNA around itself (increasing writhe at the expense of twist) to form a more compact superstructure²⁹. Using the definition of the linking number, a topological extension of the Hückel rules can be derived³⁰⁻³³. Annulenes with $L_{\rm k}$ = 0, ±2, ±4 (even) exhibit a two-sided (orientable) π system. They are aromatic with 4n + 2 π electrons. Annulenes with $L_k = \pm 1, \pm 3, \pm 5$ (odd) exhibit a one-sided (non-orientable) π system. They are aromatic with 4nelectrons delocalized in the cyclic π system^{34–36}.

We and others proposed that, similar to 'DNA supercoiling', the strain induced by the twist in annulenes can also be reduced by projection into writhe^{37,38}. In fact, doubly twisted annulenes and porphyrins have been known for a long time³⁷. However, they have not been identified as such, probably because they form figure-eight structures in which the twist is almost completely projected into writhe. Based on quantum chemical calculations, Rzepa and co-workers proposed a number of writhe structures with linking numbers $L_k > 1$ that are aromatic with 4n electrons delocalized in Möbius topological π systems^{39–41}.

We now set out to develop a general construction principle to design multiply twisted or writhed annulenes. To prove our strategy we synthesized a Möbius dehydroannulene with $L_{\rm k} = 3$. As stated above, a twist is difficult to stabilize in a linear precursor molecule. Therefore, our strategy is based on building blocks that include a 'hidden' writhe (writhe units) instead of a twist. Helicene-type molecules are suitable writhe units. Unlike twisted building blocks, which tend to untwist, helicene-type writhe units are stable because their overlapping ends stabilize the (hidden) writhe. Thus, on the combination of three writhe units, a Möbius annulene with $L_{\rm K} = 3$ could, in principle, be synthesized. Unfortunately, the situation is more complicated. Writhe units are chiral, and they can be combined in an 'additive' and a 'subtractive' manner. Three different situations have to be distinguished (Fig. 2a-c).

The combination of two writhe units with opposite chiralities leads to products with no writhe (the positive and the negative writhe cancel each other). Two writhe units of the same chirality linked together in an additive manner form helical systems in which cyclization is difficult, because the two ends are far from each other. In a subtractive combination the two ends are close. However, ring closure at this stage would be premature as a figure-eight structure with $L_{\rm k} = 2$ and Hückel topology would be formed. Fortunately, π systems in chemistry have a finite thickness, and the ends are thus bent away from each other. Now a third writhe unit of the same chirality exactly fits and can complement the ring (Fig. 2d). The product has $L_{\rm k} = -3$. Nevertheless, it is only weakly strained, because most of the twist is projected into writhe.

Synthesis. To translate our general strategy into the synthetically accessible chemical compound 1, we chose 2,2'-diethynyl-1,1'-

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Figure 2 | Combining building blocks with writhe to produce a triply twisted system and identification of a target structure. **a**-**d**, Different combinations of writhe units (**a**-**c**) and formation of a Möbius ring with $L_k = -3$ (**d**). Structures with $L_k = 3$, $T_w = 0$ and $W_r = 3$ are difficult to draw. **e**,**f**, To derive clearly recognizable chemical structures that can be drawn in 2D, we use the homeomorphic $L_k = 3$, $T_w = -3$ and $W_r = 6$ projection (**e**). The bridging units that connect the loops are not twisted in the 3D structure (**d**). The twists arise from the topological transformation from **d** to **e** and projection into 2D. Target structure **1** is presented in this projection (**f**). However, for the discussion of the topology, and particularly of twist and writhe, or properties that rely on the 3D geometry (such as orbital overlap), please refer to the 3D structure as represented in **d**.

binaphthalene (5, Fig. 3) as the writhe units, and Glaser or Cadiot– Chodkiewicz coupling reactions to connect them to a ring. Structure 1 includes a system of 24 π electrons. Density functional theory (DFT) calculations (B3LYP/6-31G^{*}) predict rather large dihedral angles ($\alpha = 78.8^{\circ}$) and the interruption of conjugation between the naphthyl rings in 1. Nevertheless, the π system of the 24electron periphery exhibits a triply twisted Möbius topology. This is clearly visible in the frontier orbitals (see Supplementary Figs 3 and 4).

The writhe unit 5 was prepared in two steps (Fig. 3). Starting from rac-2,2'-dibromo-1,1'-binaphthyl (2), rac-2,2'-diformyl-1,1'-binaphthyl (3) was prepared in 63% yield using *n*-BuLi and

dimethylformamide (DMF). The Bestmann-Ohira reagent was used to convert 3 into 5 in 74% yield. As a major side-product, 23% of the rac-2-formyl-2'-ethynyl-1,1'-binaphthyl (4) was formed. Even with a fourfold excess of the Bestmann-Ohira reagent a complete conversion could not be obtained. To avoid the excessive formation of polymers a stepwise synthesis of the ring was pursued. At first a linear trimer was prepared from rac-2,2'-bis(bromoethynyl)-1,1'-binaphthyl (7) and the dimethylthexylsilvl (DMTS)-monoprotected writhe unit 8. A final ring-closure reaction should furnish the target Möbius dehydroannulene (Fig. 3). Monoprotection of 5 with dimethylthexylsilyl chloride (DMTS-Cl) is not selective. A mixture of the starting material 5, monoprotected 8 and diprotected 6 in 25%, 65% and 10% yield was obtained. As compared to the expected statistical 25:50:25 ratio, the product ratio is shifted towards monoprotection because of the large size of the DMTS group, which hinders the introduction of a second protecting group. Separation of the three products by column chromatography and deprotection of 6 is no problem. Therefore, an almost complete conversion of 5 into 8 could be achieved after several iterations. A Cadiot-Chodkiewicz coupling reaction of 7 with two equivalents of 8 gave the linear trimer 9 in 32% yield. The main side-products were oligomers. Whereas higher oligomers can be separated easily by chromatography, the dimer and tetramer that result from an incomplete reaction (reactive ethynyl bromide and ethynyl end groups) exhibit similar retention times as those of the trimer target product 9. It is therefore important to drive the reaction to completion at higher temperatures and long reaction times. A separation of the diastereomers 9a/b, 9c/d and 9e/f by analytical HPLC was possible, but not worthwhile on a preparative scale. Notwithstanding that only the enantiomeric pair 9a/b can form the Möbius dehydroannulene, ring closure of either pure 9a/b or the mixture of diastereomers 9a/b, 9c/d and **9e/f** after deprotection with TBAF (tetra-*n*-butylammonium fluoride) would give the same mixture of oligomers as sideproducts. Hence, a final separation of the Möbius compound from oligomeric products is inevitable. The synthesis was therefore continued with a statistical mixture of 25% 9a/b, 50% 9c/d and 25% 9e/f. Deprotection with TBAF gave 10 in quantitative yields. As expected, the mixture of diastereomers of 10 exhibits four signals between $\delta = 2.69$ and 2.74 with equal intensity. The matrix-assisted laser desorption/ionization spectrum finally proved the formation of 10.

The final intramolecular cyclization of the mixture of diastereomers 10 was performed under Eglinton conditions at high dilution. Besides 11% of the target Möbius ring 1, hexamers, nonamers and dodecamers were formed. A ring with $L_k = 1$ (1c/d), which could be formed from the diastereomers 10c-f, was not observed. DFT calculations predict that this singly twisted Möbius ring is highly strained, and 16.4 kJ mol⁻¹ less stable than the triply twisted Möbius dehydroannulene 1a/b (see Supplementary Fig. 6 and Supplementary Table 1). If one considers that only 25% of 10 (10a/b) can cyclize to give the Möbius product, the yield for ring closure from 10a/b is 44%. To favour the formation of ring systems, the reaction was performed for a period of three weeks at room temperature, and then the temperature was increased by 10 °C per day to 70 °C. Under these reaction conditions the linear trimer 10 was consumed completely (see Supplementary Fig. 7a-c) and thus the number of side-products was reduced. Whereas the Möbius ring 1a/b remained unreacted, the linear oligomeric products with two reactive ends formed longer polymer chains as the reaction proceeded (see Supplementary Fig. 7d,e). The polymers can be separated easily from the Möbius compound 1a/b by chromatography. More difficult was the separation of the hexamers, which was performed by recycling gel permeation chromatography and HPLC (see Supplementary Fig. 8; for experimental details see Supplementary Chapter 3).

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Figure 3 | Synthesis of the Möbius dehydroannulene. a, Reagents: (i) (1) *n*-BuLi, THF, (2) DMF, yield of **3** = 63%; (ii) Bestmann-Ohira reagent, K₂CO₃, MeOH, yields of **5** = 74% and **4** = 23%; (iii) NBS, AgNO₃, acetone, yield of **7** = 96%; (iv) (1) LiN(TMS)₂, THF, (2) DMTS-Cl, yields of **8** = 65%, **5** = 25% and **6** = 10%; (v) TBAF, THF, yield of **8** = 98%; (vi) Pd₂(dba)₃, Lil, Cul, PMP, DMSO, yield of **9** = 32%; (vii) TBAF, THF, yield of **10** = 100%; (viii) Cu(OAc)₂, pyridine, MeOH, yields of **1** = 11%. All references for the synthesis are given in the Supplementary Chapter 3. **b**, Owing to the axial chirality of the writhe units and the three possible ways to combine them, three diastereomers (enantiomeric pairs) are formed on the reaction of **7** with **8**. In principle, the final ring closure of **10a-f** can furnish two cyclic trimers with Möbius topology, besides oligomers and polymers. The Möbius structure **1c/d** with $L_k = 1$ is not formed because ring closure is energetically unfavourable. The red stereo descriptors indicate those stereo isomers that have the correct stereochemistry to form the target (triply twisted) Möbius product (**1a/b**). The compounds that are not highlighted with red stereo descriptors form either oligomers or a Möbius product with $L_k = 1$. TMS, trimethylsilyl; dba, dibenzylideneacetone; DMTS, dimethyl-(1,1,2-trimethylpropyl)silyl; TBAF, tetra-*n*-butylammonium fluoride; NBS, *N*-bromosuccinimide; PMP, 1,2,2,6,6-pentamethylpiperidine; DMSO, dimethyl sulfoxide.

¹H and ¹³C NMR spectra proved the correct stereochemistry of the Möbius ring **1a/b**. The enantiomers **1a** and **1b** exhibit D_3 symmetry. Therefore six signals are observed in the ¹H NMR spectrum, and 12 signals appear in the ¹³C NMR spectrum (see Supplementary Fig. 9). The final proof of the structure and Möbius topology ($L_k = 3$)

was provided by X-ray crystallography (Fig. 4; see Supplementary Chapter 2). The experimentally determined geometry in the solid state is in good agreement with our previous DFT (B3LYP/6-31G^{*}) calculation (see Supplementary Table 2). The racemate **1a/b** crystallized in the centric space group $P2_1/n$ with one Möbius molecule and one

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Figure 4 | Structure of the Möbius dehydroannulene 1a/b with $L_{k} = 3$ **as determined by X-ray crystallography. a,b**, Ball and stick model (**a**) and space-filling model (**b**). α , dihedral angle formed by two adjacent naphthyl units. Chloroform molecules are omitted for clarity. **c**, CD spectra of both enantiomers (**1a/b**, red and blue lines, respectively) of the Möbius dehydroannulene after separation on a chiral column.

chloroform solvate in the asymmetric unit. Separation of the two enantiomers was achieved by chromatography on a chiral column (Chiralcel OD; for details see Supplementary Chapter 1.12). The Cotton effect of the circular dichroism (CD) spectra shows clear mirror images of both enantiomers (Fig. 4c). The CD intensity seems rather strong compared with those of other binaphthyl derivatives⁴², although the Möbius molecule contains three binaphthyl units. This strong CD may partly be associated with the Möbius structure. Topological analysis using the program ANEWWRITHM (F. Köhler, University of Kiel)²⁴ confirms the linking number $L_{\rm k} = \pm 3$ (enantiomers have linking numbers of opposite sign). The values for twist and writhe, $T_w = 1.42$ and $W_r = 1.58$, reveal that more than half of the twist is projected into writhe. This explains the high yield of macrocyclization, and the low strain of the molecule despite its high linking number, $L_{\rm b} = 3$. the rigorous mathematical Besides proof (program ANEWWRITHM), the linking number can be determined by a simple topological procedure (Fig. 5). Consider the π system as a band or construct a band orthogonal to the π system (as in Fig. 5) and cut it down the middle. Depending on the linking number the following objects are obtained: $L_{\rm k} = 0$, two separate



Figure 5 | **Topological procedure to determine the linking number** L_k of the π system of 1. A band orthogonal to the π system is constructed and cut down the middle. The fact that a trefoil knot is obtained confirms the linking number, $L_k = 3$, of the original band (see also Supplementary Fig. 5).

rings; $L_k = 1$, one ring (double the diameter); $L_k = 2$, two rings catenated; and $L_k = 3$, a trefoil knot (see also Supplementary Fig. 5). That a trefoil knot is obtained confirms the linking number $L_k = 3$ of the π system of Möbius annulene 1.

Conclusions

Based on fundamental topological principles, we developed a general strategy to construct multiply twisted Möbius compounds. The key to our strategy is well-defined helical 'writhe precursors'. On cyclization, these writhe units give rise to a high linking number in the final ring product without imposing considerable strain. The successful synthesis of a triply twisted Möbius dehydroannulene ($L_{\rm k} = 3$) presented in this paper proves the practicality of our general design strategy. Möbius compounds are escaping from their cloistered existence. They are no more exotic than catenanes, rotaxanes or other topological structures in chemistry. Triply or more highly twisted Möbius structures are probably easier to synthesize than singly twisted ones. These chiral one-sided compounds exhibit a high potential for a number of applications in molecular and optoelectronics^{43–49}.

Methods

All the synthetic methods are described in the Supplementary Information.

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Author contributions

G.R.S. worked out the topological construction strategy, developed the syntheses, carried out the experiments and characterized the compounds. R.H. developed the topological strategy and directed the study. F.T. prepared the single crystals, collected the data and solved and refined the structure together with K.R. K.R. supervised the X-ray diffraction part of the work. Y.O. and J.S. performed the separation and CD measurement of the enantiomers. G.R.S., R.H., F.T. and K.R. wrote the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to K.R. and R.H.

Competing financial interests

The authors declare no competing financial interests.