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Cyclic tris-[5]helicenes with single and triple twisted Möbius topologies and Möbius aromaticity

Cyclic tris-[5]helicenes have been synthesized using an efficient synthetic strategy based on the Perkin reaction for the assembly of building blocks into large conjugated macrocycles, and on photocyclisation for the rigidification of these flexible precursors. Depending on the relative helicity of their three helicene units, these rigid conjugated macrocycles present persistent shapes of Möbius strips with either single or triple twists. Their Möbius aromaticity has been investigated, in collaboration with Prof. Rainer Herges, by calculation of the anisotropy of the induced current density.

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See Rainer Herges, Fabien Durola et al., Chem. Sci., 2018, 9, 8930.
Cyclic tris-[5]helicenes with single and triple twisted Möbius topologies and Möbius aromaticity†

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Introduction

According to the Hückel rule, annulenes are aromatic with 4\(n\) + 2 electrons and antiaromatic with 4\(n\) electrons delocalized in a cyclic topology.\(^1\)\(^,\)\(^2\) Heilbronner in 1964 predicted that the Hückel rule should be reversed in Möbius annulenes.\(^7\) The latter structures can be envisioned by formally cutting a band in a “normal” annulene, giving one end a 180° twist, and rejoining both ends. Möbius annulenes were predicted to be aromatic with 4\(n\) electrons and antiaromatic with 4\(n\) + 2 electrons. Heilbronner further pointed out that the severe strain induced by the twist should decrease at ring sizes >20. It took 40 years until the first Möbius annulene was synthesized, and Heilbronner’s electron count rules were experimentally confirmed.\(^4\)\(^,\)\(^5\) Within the last 15 years a number of 4\(n\) electron aromatic Möbius annulenes with a 180° twist were prepared. The majority of these systems are extended porphyrins.\(^7\) Heilbronner’s electron count rules should also formally hold for higher twisted systems, or more precisely, for any annulene with an odd number of twists \((n-180°, n = 1, 3, 5...).\) However, the severe strain induced by multiple twists is expected to prevent synthesis or at least should drastically reduce overlap between neighbouring p orbitals. We recently pointed out that there are strategies to overcome these problems.\(^6\)\(^,\)\(^9\) The decisive topological parameter determining aromaticity is not the number of twists \(T_w\), but the linking number \(L_k\).\(^10\) Hückel systems have an even linking number \((L_k = 0, 2, 4...)\) and Möbius objects exhibit an odd linking number \((L_k = 1, 3, 5...)\). \(T_w\) and \(L_k\) are connected by Calugareanu’s theorem: \(L_k = T_w + W_r\) (\(W_r\) = writhe).\(^11\) Besides the precise mathematical definition, Calugareanu’s theorem can be demonstrated by an everyday life experiment. If a band e.g. a two-core power cord is twisted and both ends are joined, the band would wind around itself. Thus, the strain induced by the twists \(T_w\) is released, and projected into writhe \(W_r\) without changing the linking number \(L_k\). Similar arguments hold for molecules. The topological transformation can be used as a strategy to reduce strain, while keeping the topological parameter \(L_k\) constant. We recently used this strategy to synthesize the first triply twisted Möbius annulene.\(^8\) Unfortunately, the building block diethyl-binaaphthalene is too flexible to provide a smooth distribution of dihedral angles along the periphery of the annulene and the conjugation was interrupted by torsional angles close to 90°. We now present the
synthesis of a triple twisted annulene (540°) with small dihedral angles, and thus retaining full conjugation, and a diatropic ring current within the twisted π system in the periphery.

In the last five years, we have developed an efficient and versatile synthetic approach for the formation of large carboxy-substituted polycyclic arenes. It relies on Perkin reactions that yield flexible diaryl maleate-type precursors, followed by catalyst- or light-induced cyclization reactions. This synthetic method has shown considerable potential for the construction of double helicenes as well as for the formation of large conjugated macrocycles. Recently, we have combined these two structural elements in a Perkin-assembled propeller-shaped macrocycle that incorporates two identical [5]helicene fragments. This dimeric cyclo-bis-[5]helicene 1 has been obtained as a racemic mixture of two enantiomers whose helicene fragments have identical helicity: PP or MM. The PM (meso) compound has not been observed, which is in line with the extreme distortion of its simulated structure.

This article presents the synthesis and study of trimeric homologs of macrocycle 1: the C2-symmetric cyclo-tris-[5] helicenes 2 (MPP and PMM configurations), and the D3-symmetric cyclo-tris-[5]helicenes 3 (PPP and MMM configurations) which are diastereomers and have been obtained as racemic mixtures (Scheme 1). In contrast to the dimeric case (the non-observed meso isomer of 1), three helicenes of different helicity can be cyclically linked without generating much distortion, thus both possible diastereomers are formed.

Scheme 1  Cyclo-poly-[5]helicenes obtained by photocyclisation of flexible conjugated macrocycles.

Scheme 2  Synthesis of diacetic three-block precursor and its use in the synthesis of four-block macrocycle. (a) High dilution, Ac2O, NEt3, THF, reflux, 48 h, then EtOH, EtBr, DBU, reflux, 24 h, 21%; (b) SOCl2, MeOH, reflux, 4 h, 85%, then KOH, 1,4-dioxane, reflux, 75 min, 47%; (c) Ac2O, NEt3, THF, reflux, 18 h, then EtOH, EtBr, DBU, reflux, 24 h, 65%; (d) KOH, H2O, EtOH, reflux, 18 h, 100%; (e) high dilution, Ac2O, NEt3, THF, reflux, 48 h, then EtOH, EtBr, DBU, reflux, 24 h, 55%.
In both of these two rigid conjugated macrocycles, the adjacent terminal benzene rings at the interhelicene bonds are essentially coplanar, leading to an overall Möbius band geometry of $\pi$ electron systems of both macrocycles. The $C_2$-symmetric isomer has the geometry of a simple (singly twisted) Möbius band, whereas the $D_3$-symmetric isomer has the geometry of a triply twisted Möbius band.

**Results and discussion**

The Perkin condensation of bifunctional arylene–diglyoxylic acids with bifunctional arylene–diacetic acids leads with surprisingly good size-selectivities and yields to the $2 + 2$ macrocyclic products, where four arylene moieties are connected by four maleic bridges. This approach has been used in the reported synthesis$^{18}$ of the four-block flexible macrocycle 4 (Scheme 2, pathway A), with a moderate yield of 21%, precursor of the cyclic dimer of [5]helicene 1 (Scheme 1). Aiming at the formation of the trimeric counterparts 2 and 3 of the latter, the synthetic strategy based on the Perkin reaction involves one common macrocyclic intermediate 5 made of six building blocks: three 1,4-phenylenedicarboxylic acid units 6 and three 4,4'-bis(phenylglyoxylic acid) units 7. The formation of a six-block macrocycle by Perkin reaction from bifunctional simple building blocks has been observed only once, as a minor side product of a four-block macrocycle composed exclusively of biphenyl units.$^{18}$ A stepwise procedure is therefore necessary for the controlled synthesis of large six-block macrocycles by Perkin reaction. We focused on the combination of two complimentary linear bifunctional three-block intermediates ($3 + 3$ approach), which is more convergent than a $5 + 1$ approach and synthetically simpler than a $4 + 2$ approach due to the symmetry of the precursors.

We have recently reported the synthesis of three-block linear intermediates, bearing two acetic acid functions at their extremities for the formation of long phenacenes.$^{17}$ The same synthetic strategy has been applied to the diacetic and diglyoxylic building blocks 6 and 7 in the synthesis of the three-block diacetic precursor 10. 1,4-Phenylene-1,4-diacetic acid 6 was first fully esterified in presence of methanol and $\text{SOCl}_2$ to give dimethyl 1,4-phenylene-1,4-diacetic ester,$^{19}$ which was then partially saponified with one equivalent of potassium hydroxide. The resulting mixture of remaining diester, diacetate and monoacetate monoester compounds was separated by selective pH-

![Scheme 3](https://example.com/scheme3.png)

**Scheme 3** Synthesis of the second three-block precursor 18 and its combination with complimentary three-block precursor 10 to form the six-block macrocycle 5, precursor of cyclo-tris-[5]helicenes 2 and 3. (a) $\text{AlCl}_3$, $\text{CH}_2\text{Cl}_2$, $-10$ °C, 20 min, 71%; (b) $\text{NaHCO}_3$, $\text{H}_2\text{O}$, $\text{EtOH}$, reflux, 16 h, 93%; (c) $\text{Ac}_2\text{O}$, $\text{NET}_3$, THF, reflux, 16 h, then $\text{EtOH}$, EtBr, DBU, reflux, 24 h, 83%; (d) (Bpin)$_2$, $\text{PdCl}_2\text{dpf}$, KOAc, 1,4-dioxane, 90 °C, 2.5 h, 87% with traces of pinacol; (e) Pd(PPh$_3$)$_2$, $\text{K}_2\text{PO}_4$, PhMe, reflux, 20 h, 45%; (f) $\text{NaHCO}_3$, $\text{H}_2\text{O}$, $\text{EtOH}$, reflux, 24 h, 100%; (g) $\text{Ac}_2\text{O}$, $\text{NET}_3$, THF, reflux, 72 h, then $\text{EtOH}$, EtBr, DBU, reflux, 24 h, 29%; (h) I$_2$, AcOEt, UV-irradiation, rt, 48 h, 18% (2) and 18% (3).
dependant solid–liquid extractions to finally give pure mono-
protected phenylene diacetic acid 8. The yield of this mono-
deprotection reaction is satisfying (47%) as it can be carried out on a large scale (10 g) without complicated puriﬁcation and 48% of the starting compound is recovered separately as diacid or
diester. Mono-protected phenylene diacetic acid 8 reacted twice
with diglyoxyl acid 7 by Perkin reaction to afford the three-block
hexaester 9 in good yield (65%), and then full saponiﬁcation by
reaction with potassium hydroxide quantitatively formed the
three-block diacetic acid precursor 10. To verify its reactivity in
the formation of macrocycles, it has been combined with the
diglyoxyl building block 7 (Scheme 2, pathway B) by Perkin
reaction in high dilution conditions to form the four-block
macrocycle 4 with an improved yield of 55%, compared to 21%
when single building blocks 6 and 7 are mixed under the same
reaction conditions (Scheme 2, pathway A).18

The mono-protection of arylene-diglyoxyl acids for the
Perkin reaction not yet having been developed, a different
synthetic approach was pursued for the complimentary three-
block diglyoxyl precursor 18 (Scheme 3). In biphenyl-based
species, the central sigma C–C bond can easily be formed by
usual palladium-catalyzed coupling reactions between
adequately functionalized aryl fragments. Thus bromobenzene
11 was ﬁrst functionalized with one glyoxyl ester function by a
Friedel–Crafts reaction with ethyl oxalyl chloride 12 as an
electrophile in presence of AlCl3 following a recently reported
procedure.20 The glyoxyl ester function of the resulting ester
13 was saponiﬁed efﬁciently by treatment with sodium
hydrogen carbonate and the resulting para-brominated phe-
nylglyoxyl acid 14 reacted then twice with 1,4-phenylenedi-
acetic acid 6 in Perkin conditions to give the dibrominated bis-
maleate precursor 15 with a very good yield (83%). In parallel,
para-brominated phenylglyoxyl ester 13 was transformed into
the corresponding boronic ester 16 by palladium-catalyzed
substitution of the bromo-substituent in presence of bis(pinac-
olato)diboron. In spite of non-removable traces of pinacol in
the latter, it was coupled twice to the dibrominated bis-maleate
precursor 15 by a double Suzuki reaction with Pd(PPh3)4 as a
catalyst. The resulting bis-maleate hexaester 17 was obtained
with a modest yield (45%) for this usually efﬁcient reaction,
because of partial saponiﬁcation of the product in basic
conditions, even in the absence of water. Full saponiﬁcation
of the hexa-ester 17 quantitatively afforded the three-block
diglyoxyl acid precursor 18.

The two three-block diacetic 10 and diglyoxyl 18 precursors
were then coupled together by double Perkin reaction to form
the six-block ﬂexible conjugated macrocycle 5. High dilution
conditions were not used, because of the low solubility of
compound 18, but the cyclic product 5 was obtained with a very
satisfying macrocyclization yield of 28%, after a difﬁcult puriﬁ-
cation process. Irradiation of a 0.07 mM solution of 5 in ethyl
acetate in the presence of iodine and oxygen for two days with
pyrex-ﬁltered light from a medium pressure mercury lamp
afforded a mixture of the two cyclo-tris-[5]helicenes 2 and 3 with
an average yield of 40%. 1H-NMR analysis of this mixture
revealed that these two rigid macrocycles are present in near-
equal proportions. In spite of their structural differences,
helicenes, the crystal structures of the trimers show that the two linked benzene rings of adjacent helicenes are almost coplanar. In these conditions, the conjugated $\pi$ electron systems of these rigid macrocycles have persistent shapes of cyclic twisted ribbons.

A first evidence of the conjugation between the three helicenes composing the cyclo-tris-[5]helicenes 2 and 3 has been obtained from their optical absorption. The cyclo-bis-[5]helicene 1 was expected not to exhibit any conjugation between its two parts due to a lack of coplanarity at the junctions between helicenes. This was confirmed by the absorption spectra, where this cyclic dimer of ester-substituted [5]helicenes behaved approximately like two independent ester-substituted [5]helicenes\(^{21}\) (Fig. 2). In contrast, trimeric cyclo-tris-[5]helicenes 2 and 3 show a significantly modified absorption profile compared to the single [5]helicene.

For a closer inspection of the topology of 2 and 3, we used our program ANEWWRITHM\(^{22}\) and determined the topological parameters $L_k$, $T_w$, and $W_r$. Since both annulenes are not single stranded, there are different conjugation pathways that can be defined within the cyclic $\pi$ system. We distinguish between the inner cyclic pathway with 24 $\pi$ electrons (red line) and the outer pathway with 48 $\pi$ electrons (blue line, Fig. 3). Thus, both conjugation pathways exhibit 4$n$ $\pi$ electrons. In Fig. 3 cyclo-tris-[5]helicenes are represented as topologically stretched 2D projections ($'2'$ and $'3'$), as well as with their native 3D geometry (2 and 3). The stretched representation is easier to conceive, and it reveals that 2 is singly twisted and 3 is triply twisted. Cyclo-helicene 2 is composed of two helicene units of like helicity, and one unit with opposite helicity. In terms of the stretched representation, the opposite twists cancel, and a singly twisted Möbius ribbon results. The helicities of the three helicene units...
in 3 are equal, and the twists add up to a triply twisted Möbius band. Note that the term “twist” has different meanings in the general English language and in topology. In the following we use the topological twist (as defined in the Caluganou theorem: \( L_k = T_w + W_t \)) in combination with the symbol \( T_w \). The topologically stretched geometries would be highly strained, and exhibit reduced overlap between neighbouring p orbitals. In the native geometry large part of the twist \( T_w \) is projected into writhes \( W_t \) by folding into a 3D geometry (Fig. 3). This topological transformation is obviously more efficient in 3 than in 2. Surprisingly, the triply twisted 3 is 5.8 kcal mol\(^{-1}\) more stable than its singly twisted isomer 2. However, if dispersion is included (D3 method, see ESI†) the relative energies are reverse. Obviously, singly twisted 2 is more densely packed which leads to stabilization by an increased intramolecular dispersion interaction. The inner (red) and outer (blue) conjugation pathways in both cyclo-tris-[5]helicenes 2 and 3 exhibit odd linking numbers \( L_k \) (Möbius topology) however, they have different linking numbers \( L_k \) in the same molecule (Fig. 3).

Since the conjugation pathways in 2 and 3 include \( 4n \) electrons, and exhibit odd linking numbers \( L_k \), they should be Möbius aromatic. ACID (anisotropy of the induced current density)\(^{25-27}\) calculations reveal that the situation is more complicated. Similar to the paragon of aromatic compounds benzene, Möbius compound 3 exhibits a diatropic ring current in the outer π system, and a paratropic current in the inner σ system.\(^{26,28}\) In 3 these currents cancel, and almost no net ring current results (Fig. 4).\(^{29}\) In benzene the paratropic current is located within the ring plane, and there are two maximum diatropic ring currents approximately 1 Å above and underneath the ring plane (along the two paths with the highest π electron density).\(^{26,27}\) In the triply twisted Möbius molecule 3, however, the current follows a path mainly restricted to outer part of the molecule, changing the side of the π system three times.\(^{32}\) As a consequence of the inner paratropic ring current in the σ system, the six inner protons (8.88 ppm) are deshielded by 0.58 ppm as compared to the corresponding two protons in the [5]helicene building block 19. The diatropic ring current in the outer periphery (blue) does not induce a strong shift of the remaining 18 protons, because they are not located in the range of the induced magnetic field. Similar arguments hold for the singly twisted Möbius compound 2. There is a diatropic ring current in the periphery and a paratropic current in the σ system in the inner conjugation path (Fig. 3). NICS values\(^{33}\) calculated for Möbius structures 2 and 3 are close to zero (Fig. 3) and corroborate the fact that diatropic and paratropic ring currents almost cancel. Also in agreement with our ACID analysis are the bond length analyses of 2 and 3 using the HOMA method.\(^{34}\) For both Möbius compounds, the HOMA values are considerably larger in the periphery (diatropic, aromatic) than in the inner conjugation path (paratropic, antiaromatic) (see Fig. 3a and b). The C–C bonds connecting the [5]helicene units in 2 and 3 exhibit a bond length of 1.48–1.49 Å which is considerably longer than the bond length in the prototypic aromatic molecule benzene (~1.40 Å). Upon distortion of \( D_{3h} \) benzene towards a \( D_{3h} \) 1,3,5-hexatriene structure with alternating C–C bond lengths of 1.535 Å and 1.337 Å, benzene retains 72% of its diatropic ring current.\(^{35}\) We conclude that a corresponding bond length elongation by 0.01 Å in 2 and 3 does not significantly reduce the ring currents.

**Conclusions**

Highly twisted annulenes have been considered as very challenging targets because of the severe strain and weak π overlap induced by the twist. In contrast to this intuitive conclusion, we prove that even a triple twisted Möbius annulene with a 540° twist in its π system, is easily accessible by standard chemical synthesis. Within the inner and the outer conjugation path of the triply twisted system, no torsional angle between neighbouring p orbitals is larger than 35° and 66°. So, conjugation is still efficient. All conjugation pathways include \( 4n \) electrons and an odd linking number \( L_k \). Hence, they should be Möbius aromatic. A detailed ring current analysis reveals that a paratropic current is induced in the inner σ system, and a diatropic current in the outer π periphery, which almost cancel. The
surprisingly low strain and considerable π overlap is due to a topological transformation of twist into writhe by folding of the Möbius ring into a 3D structure, a process which is similar to the supercoiling of DNA.34 Annulenes with chiral π systems are interesting from another point of view. Theoretical calculations predict that upon irradiation with a strong laser pulse (even in the absence of a magnetic field), ring currents should be induced which are orders of magnitude larger than the currents induced in a superconducting NMR magnet.35,36 Moreover, peculiar nonlinear optical37 and two photon absorption properties38 have been predicted for Möbius annulenes.

Conflicts of interest

There are no conflicts to declare.

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Notes and references