Supramolecular Chemistry

Stereoselective Synthesis of a Topologically Chiral Molecule: The Trefoil Knot[**]

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Topological chirality of a molecule is realized when any representation of its graph is topologically distinct from its mirror image, that is, if it cannot be converted into its mirror image by continuous deformation in 3D space.[1] This property implies that the graph of the molecule is nonplanar. Molecular systems with an *intrinsically* nonplanar graph are scarce. Their graphs can be contracted to Kuratowski's graphs K_5 (the complete graph on five vertices) or $K_{3,3}$ (the complete bipartite graph on two sets of three vertices each).[2–4] Many examples of such systems are known, with the 3-rung Möbius strip prepared more than 20 years ago by Walba et al. being a particularly representative example.[5]

Interlocking rings (catenanes) and knots have *extrinsically* nonplanar graphs. As discussed by Schill,[6] an achiral [2]catenane can be desymmetrized by a suitable substitution of its constitutive rings to give a topologically chiral species. Such catenanes, which contain two oriented rings, have been prepared in the past.[7] It has even been possible to resolve them analytically by chiral chromatography.[8] Contrary to a [2]catenane, a trefoil knot is *unconditionally* chiral; the latter object is topologically chiral without having to orient rings. These prototypical nonplanar systems are represented in Figure 1.

Molecular knots were prepared some time ago using a copper(I)-templated strategy.[9] They were resolved and crystallized and their absolute configuration was thereby determined.[10] More recently, another family of molecular knots has been elaborated by Vögtle and co-workers with their synthesis relying on original sets of hydrogen bonds.[11] The enantiomers of some of these knots and their derivatives were also resolved by chiral chromatography in a collaborative project between Vögtle's and Okamoto's groups.[12] Two other examples of synthetic knots have been described,[13–16] including an "open" knotted species constructed around an octahedral metal center as a template.[14]

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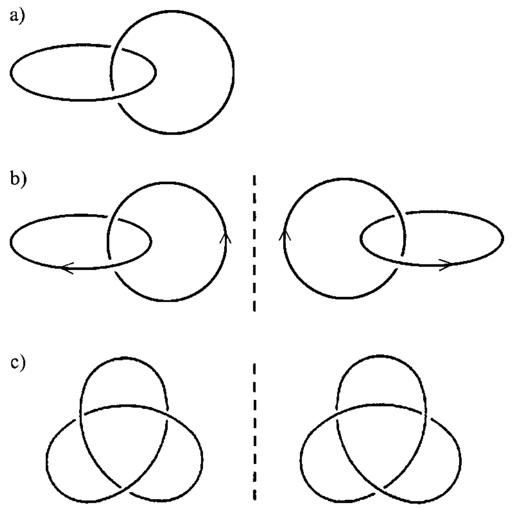

Figure 1. a) A [2]catenane is topologically achiral; b) through orientation of both rings, a chiral object is obtained; c) the trefoil knot is the prototype of topologically chiral objects.

Herein, we report the stereoselective preparation of a topologically chiral compound, a trefoil knot, from two molecular threads that are chiral in the Euclidian sense. The present report is concerned with the conversion of classical (or Euclidian) chirality into topological chirality. The principle of the synthesis is depicted in Figure 2. The trefoil knot is constructed around two copper(I) centers with the chiral ligand 1,3-bis([5′,6′]-pinene-2,2′-bipyridin-2-yl)benzene (**I**),[17] which contains stereogenic carbon centers in the pinene moieties. In principle, two diastereomeric forms are possible upon formation of the trefoil knot. However, our synthesis proceeds completely stereoselectively with only one of the two different topological enantiomers being obtained.

The strategy for the stereoselective preparation of the knot takes advantage of the template effect of copper(I) and of the properties of the bis(pinene-bipyridine) ligand, which induces chirality at the metal centers (Figure 3). The molecular frame for the present trefoil knot is based on the CHIRAGEN family, which is a class of ligands developed by some of us in recent years.[18] The molecule **1**, whose synthesis was reported recently,[17] consists of two 2,2′-bipyridine units connected through a *m*-phenylene bridge. The CH_2 groups in the pinene moieties adjacent to the pyridine rings (indicated by arrows in Figure 3) contain two diastereotopic protons. Alkylation at these position proceeds diastereoselectively to yield the dialkylated ligand **2**.

Ligand **2** forms a double-stranded helix **3** around Cu^I ions in a complexation reaction. As observed by UV/Vis spectroscopy and visually from the formation of a deep red complex, the dinuclear complex **3** is formed rapidly and quantitatively. The ESI mass spectrum shows only one peak at $m/z = 1070.53$. The ^1H NMR spectrum indicates a C_2-symmetric arrangement of the ligands (Figure 4a). Furthermore, there is strong deshielding ($\delta = 8.90$–10.19 ppm) of the aromatic proton (a) in the bridge. The presence of only one well-defined peak for this proton indicates a very high percentage (> 95 %) of formation of the double helix **3** (Figure 4).

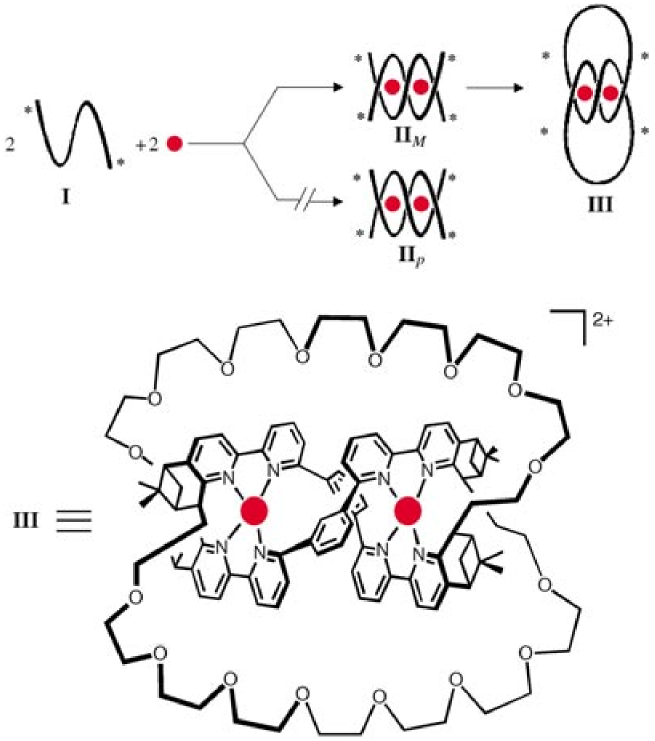

Figure 2. The molecular thread **I** incorporates two bidentate chelating units with each chelate being chiral; the red dot represents the copper(I) atom. In the course of the complexation reaction, only one type of double-stranded helix **II** is formed (with *P* or *M* configuration). The appropriate connections will afford the trefoil knot enantioselectively from **I**. Although **I**, **II**$_M$, and **II**$_P$ are geometrically chiral, they are *topologically achiral*. By contrast, **III** is both geometrically and topologically chiral.

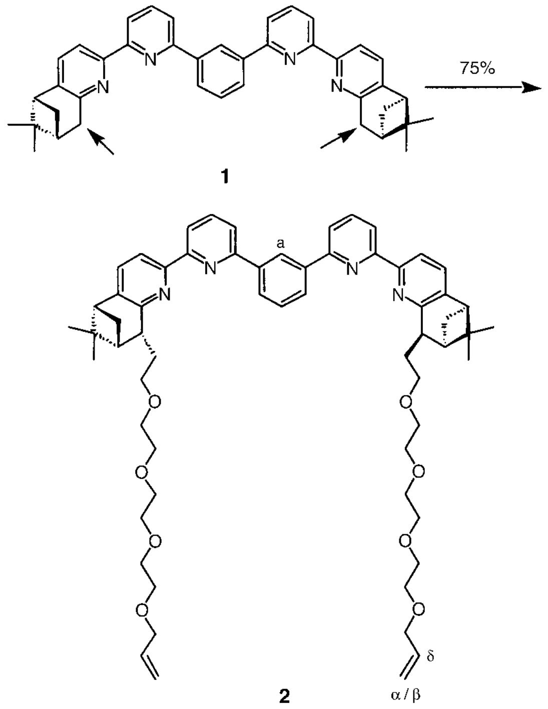

Figure 3. The CHIRAGEN family of ligands used for the construction of the molecular knot (the arrow in **1** indicates the diastereotopic protons).

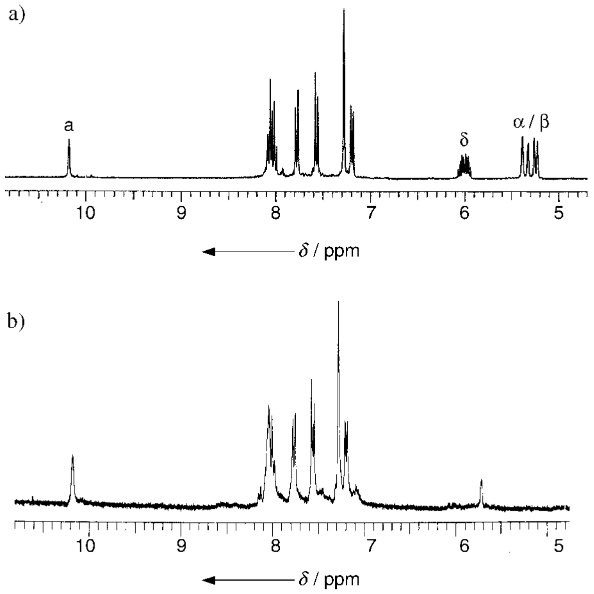

Figure 4. ^{1}H NMR spectra of a) complex **3** and b) the knotted system **4** before hydrogenation. Small impurity signals (intensity ≈ 1 %) around $\delta = 10$ ppm are from unidentified side products.

The circular dichroism (CD) spectrum, with a positive exciton-couplet, gives the absolute configuration Λ at the individual copper centers and thus induces an *M* configuration in the double stranded helix **3**, as expected from Corey–Pauling–Koltun (CPK) molecular models.

A ring-closing metathesis (RCM)[19] reaction is then applied for the formation of the knotted system (Figure 5).

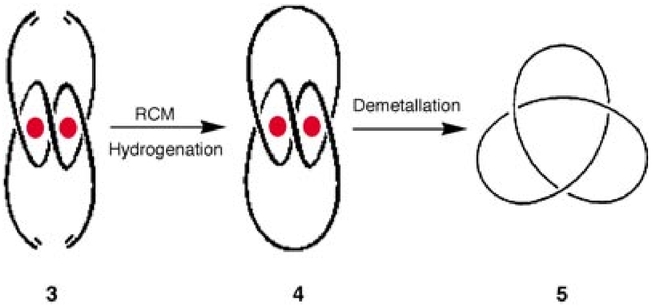

Figure 5. The strategy for the construction of the knot; the knotted system is obtained through a RCM reaction of **3**.

RCM yields three isomers (from *E* and *Z* configurations at the double bonds) in 74 % total yield. Catalytic hydrogenation (Pd/C (20 %), H_2 (3 bar), 16 h) leads to the saturated compound **4** in quantitative yield. The ESI mass spectrum shows one peak at $m/z = 1038.50$. The ^{1}H NMR spectrum again indicates C_2 symmetry and is very similar to that of the open form of the double-helix precursor **3**, except that there are no signals observed for the protons of the double bonds. The CD spectrum of compound **4** is also very similar to that of the open form of the double helix **3** (Figure 6).

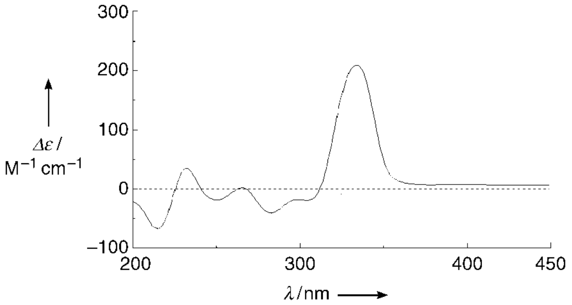

Figure 6. CD spectrum ($\Delta\varepsilon$ = molar circular dichroism) of the left-handed knotted system **4**.

Treatment of **4** with a large excess of potassium cyanide in acetonitrile/dichloromethane (1:1) yielded the final product **5** as an almost colorless oil in quantitative yield after 12 h. The product can be remetallated in a rapid reaction (seconds) to yield a product which is identical to **4**. The ^{1}H NMR spectrum of **5** shows broad signals at room temperature, which we believe is caused by reptation (a snakelike large-scale motion of entangled molecular chains) within the molecule, as observed previously for another molecular trefoil knot.[16] The ESI mass spectrum displays a peak for the molecular ion at $m/z = 1964.22$ as well as a number of fragmentation products. As opposed to the dialkylated ligand **2**, molecule **5** shows a pronounced signal in its CD spectrum in the range 280–340 nm. This arises from a relatively compact arrangement of the bipyridine units which leads to through-space coupling of the π–π* transitions, as with the metallated species.

Unfortunately, we were not able to obtain crystals of either **3** or **4** that were suitable for X-ray crystallographic studies. Nevertheless, the crystal structure of a double helix prepared from **1** and two silver(I) ions[20] was recently obtained. The experimental evidence for the successful synthesis of the trefoil knot **5** and its precursor Cu$^{\mathrm{I}}$ complex **4** is very strong. The mass and chiroptical behavior of **3** and **4** indicate very clearly the presence of the two compounds.

In conclusion, we have demonstrated the stereoselective synthesis of a topologically chiral molecule. The reaction sequence is based on the completely stereoselective formation of a double-stranded helical precursor from two open-chain chelates, which incorporate the appropriate chiral groups.[20] The transformation of the *M* helix **3** to the left-handed knot **5** corresponds to the conversion of Euclidian chirality into topological chirality.

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