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# 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, i.e. if it can not be converted to its mirror image by continuous deformation in 3D-space.[1] This property implies that the graph of the molecule is non-planar. Molecular systems with an *intrinsically* non-planar graph are scare. Their graphs can be contracted to Kuratowski's graphs $K_5$ (the complete graph on five vertices) or $K_{3,3}$ (the complete bi-partite graph on two sets of three vertices each).[2-4] Many examples of such systems are known, the 3-rung Möbius strip prepared by Walba et al. more than 20 years ago being a particularly representative example.[5]

Interlocking rings (catenanes) and knots have *extrinsically* non-planar graphs. As discussed by Schill long ago,[6] an achiral [2]catenane can be desymmetrized by a suitable substitution of its constitutive rings leading to a topologically chiral species. Such catenanes, containing two oriented rings, have been made 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 object is topologically chiral without having to colour edges or orient rings. These prototypical non-planar systems are represented in Figure 1.

Figure 1

Molecular knots have been prepared some time ago using a copper(I)-templated strategy.[9] They have been resolved and crystallized, and thereby their absolute configuration was determined.[10] More recently, another family of molecular knots has been elaborated by

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Vögtle and coworkers, 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 centre used as template.[14]

As far as we know, topologically chiral compounds have never been prepared in a stereoselective way. We would now like to report that a trefoil knot can be prepared stereoselectively from two molecular threads, these fragments being chiral in the Euclidian sense. The present report is thus concerned with the conversion of classical (or Euclidian) chirality into topological chirality. The principle of the synthesis is depicted in Figure 2.

Figure 2

The trefoil knot is constructed around two copper(I) centers, by the use of the chiral ligand bis[5,6] pinene-bipyridine[*m*-phenyl] [17], which contains stereogenic carbon centers in the pinene moiety. In principle, two diastereomeric forms are possible upon formation of the trefoil knot. Our synthesis proceeds in a completely stereoselective way. Only one of the two different topological enantiomers is obtained.

The strategy for making the knot in a stereoselective way takes advantage of the template effect of copper(I) and of the properties of the bis-pinene bipyridine type ligand which induces chirality at the metal centers (Figure 3).

The molecular frame for the present trefoil knot is based on a class of ligands, the CHIRAGEN family, developed in recent years by some of us. [18]

Figure 3

**1** represents a ligand where two 2,2'-bipyridine units are connected through a *m*-phenylene bridge. Its synthesis was reported recently [17]. The $CH_2$ groups near the pyridine ring contain two diastereotopic protons. Alkylation at this position proceeds in a diastereoselective manner yielding the doubly alkylated molecule **2**.

The latter **2** forms a double-stranded helix with Cu(I) **3** in a complexation reaction. As observed visually (formation of a deep red complex) and by UV/VIS spectroscopy, this dinuclear complex is formed rapidly and quantitatively. The ESI-MS shows only one peak at *m/z* 1070.53. The $^1$H-NMR spectrum indicates a $C_2$-symmetric arrangement at the ligands. In addition a strong de-shielding (8.90 ppm to 10.19 ppm) of the proton (a) in the bridge occurs. No doubling of this signal is observed, indicating a very high (> 95%)of the formation of the double helix **3** (Figure 4).

Figure 4

The CD-spectrum with a positive exciton-couplet gives the absolute configuration at the individual copper centers, which is Λ, thus inducing a configuration *M* in the double stranded helix **3**, as expected from the CPK models.
Ring closing metathesis (RCM) [19] is applied for the formation of the knotted system (Figure 5).

Figure 5

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

Figure 6

Treatment with a large excess of potassium cyanide in acetonitrile / dichloromethane (1:1) yielded after 12 hours an almost colorless oil in quantitative yield, which is the final product **5.** It can be remetallated in a rapid reaction (seconds), yielding a product which is identical to **4**. The $^1$H-NMR spectrum of **5** shows broad signals at room temperature. We believe that this is due to reptation within the molecule, as observed previously for another molecular trefoil knot[16]. The ESI-MS gives the *m/z* 1964.22 molecular mass and a number of fragmentation products can be observed too. As opposed to the dialkylated ligand **2**, **5** shows a pronounced CD signal in the range 280-340 nm. This is due to a relatively compact arrangement of the bipyridine units, leading to a through space coupling of the $\pi-\pi^*$ transitions, in a similar way as in the metallated species.

Unfortunately, no crystals suitable for x-ray examination have been obtained hitherto, neither of **3** nor of **4**. Nevertheless, a nice crystal structure of a double helix prepared from **1** and two silver(I) atom[20] could recently be obtained. The experimental evidence for the successful synthesis of the trefoil knot **5** and its Cu(I) complex **4** is very strong. The mass and chiroptical behaviour of **3** and **4** indicate very clearly the presence of the two compounds.

In conclusion, the stereoselective synthesis of a topologically chiral molecule has been achieved. The basis of the strategy for the choice of the reaction sequence is the completely stereoselective formation of a doubly-stranded helical precursor from two open-chain bis-chelates, incorporating 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 to topological chirality.

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## FIGURE CAPTIONS

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

Figure 2 : The molecular thread I incorporates two bidentate chelating units, each chelate being chiral ; the black dot is copper(I) atom. In the course of the complexation reaction, only one type of double-stranded helix II is formed (*P* or *M*). The appropriate connections will afford the trefoil knot in an enantioselective fashion from I. Note that although I, $II_M$ and $II_p$ are geometrically chiral, they are *topologically achiral*. By contrast, III is geometrically and topologically chiral.

Figure 3 : The CHIRAGEN family of ligands used for the construction of the molecular knot.

Figure 4 : a) $^1$H NMR spectra of complex 3 and b) of the knotted system 4 before hydrogenation. Small impurity signals (~1% intensity) around 10 ppm are due to unindentified side products.

Figure 5 : Strategy used for the construction of the knot. The knotted system is obtained via a RCM reaction.

Figure 6 : CD spectrum of the left-handed knotted system **4**.

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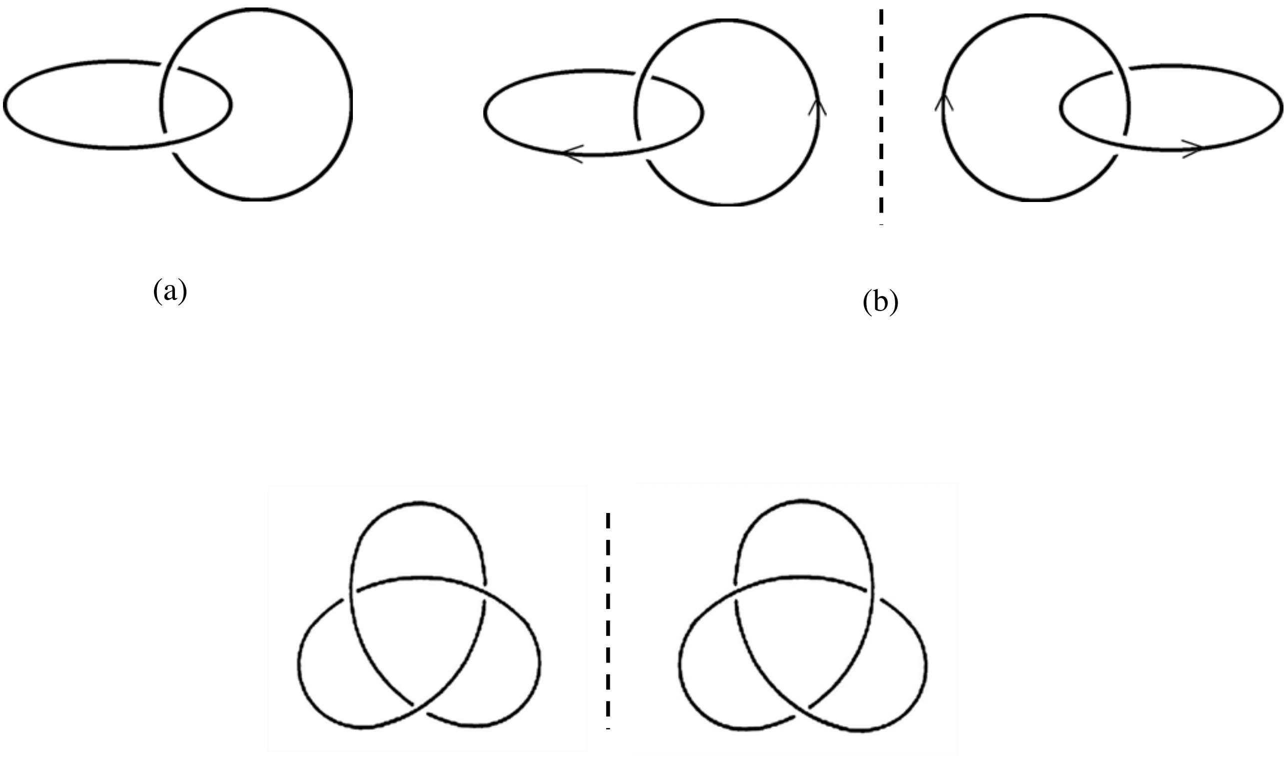
The stereoselective synthesis of a trefoil knot has been achieved. The key reaction to the success of the present procedure is the completely stereoselective formation of a doubly-stranded helical precursor, incorporating appropriate chiral groups.

Figure 7

## Keywords

Topological Chirality, Double Helix, Stereoselective,

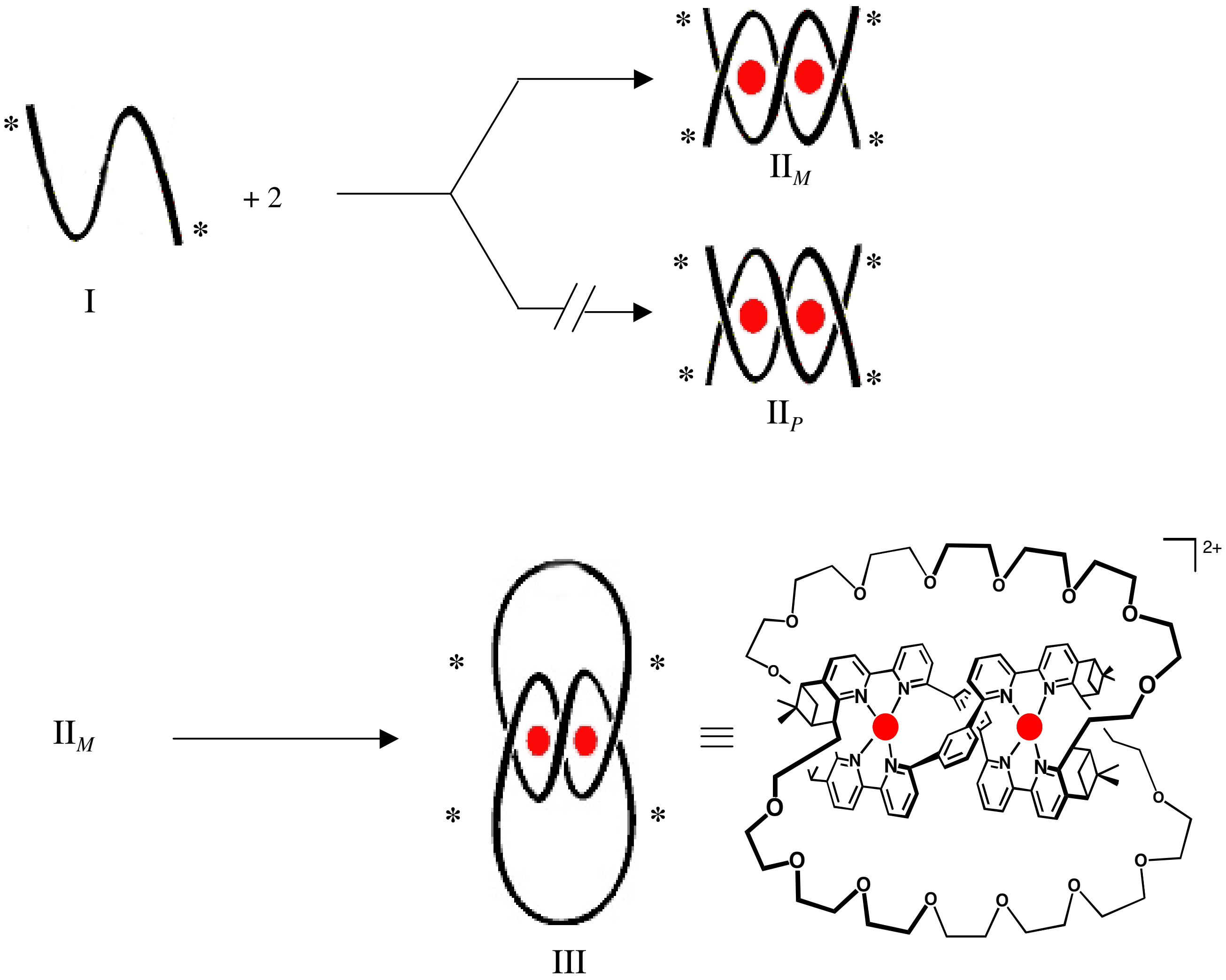


(a)

(b)

(c)

Figure 1



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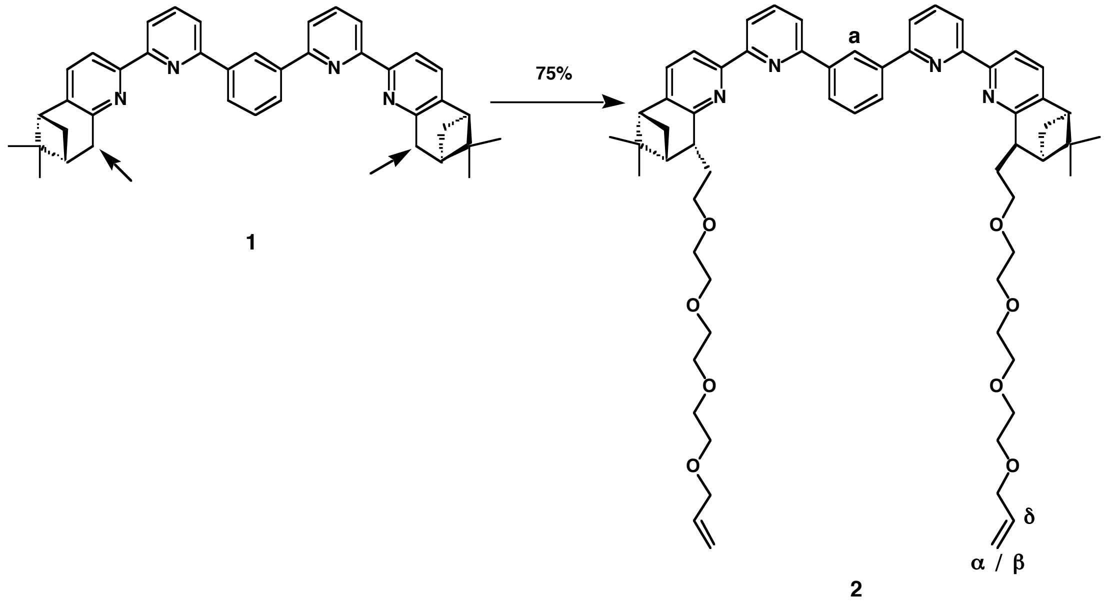


1

2

Figure 3

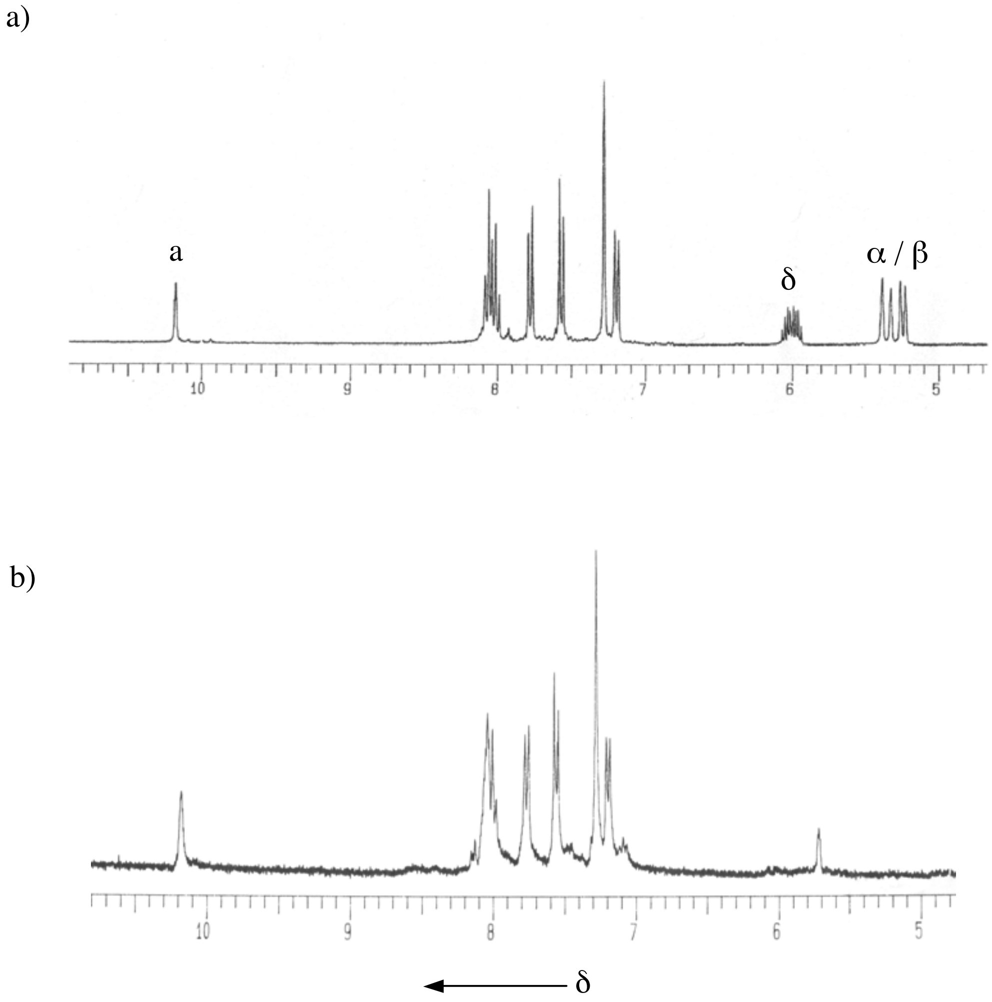
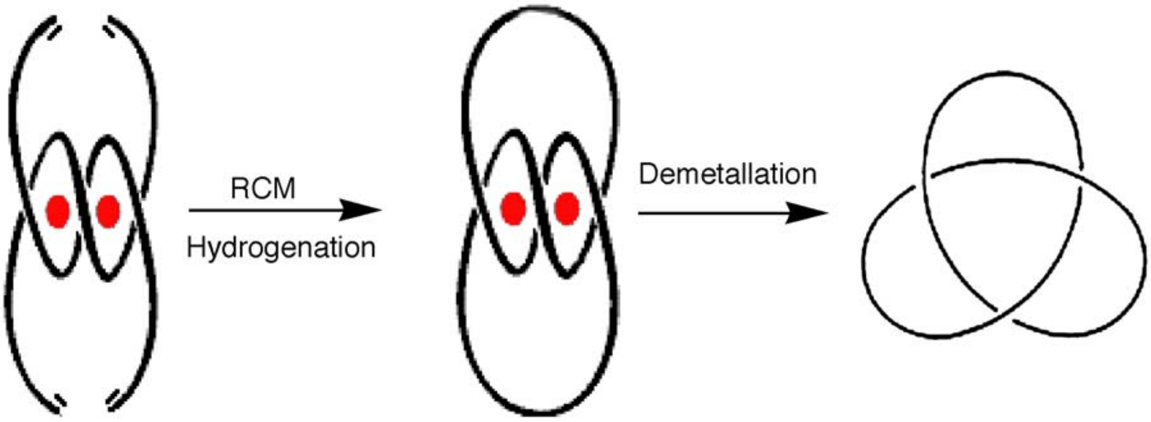
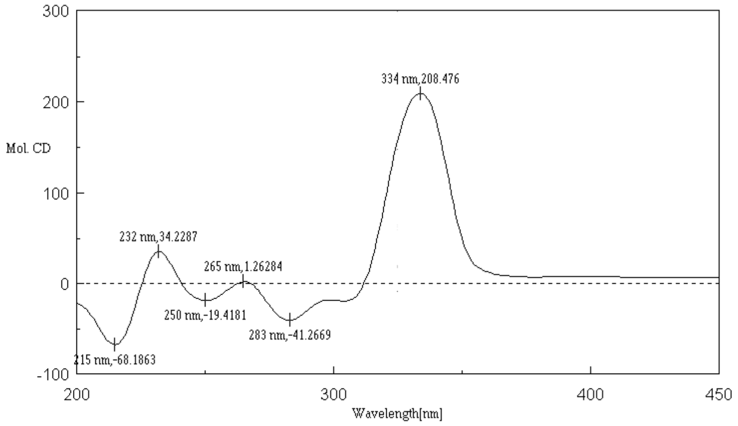


Figure 4



**3** **4** **5**

Figure 5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200
100
0
-100
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232 nm,34.2287
265 nm,1.26284
250 nm,-19.4181
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215 nm,-68.1863
200
300
400
450
Wavelength[nm]

Figure 6

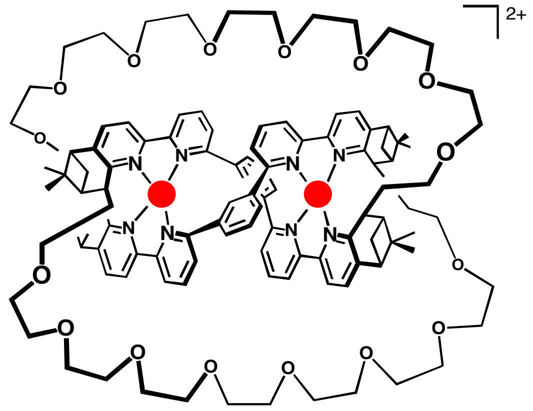

Figure 7