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Resolution of a Molecular Trefoil Knot

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The chirality of a molecular system can generally be analyzed in terms of Euclidian geometry, using metric elements (distances and angles).[1−3] The topological properties of the chemical object represent an upper level of description, leading to the notion of topological chirality.[4,5] For any molecule to be topologically chiral implies (but this is not sufficient) that its molecular graph be nonplanar. Only very few cases of such nonplanar systems are known, an important family of such compounds consisting of interlocking rings (catenanes).[6,7] Topologically chiral [2]catenanes have been described in recent years[8] but their resolution could only be carried out at the analytical level.[9]

Molecular knots are topologically novel systems *par excellence*, the classical trefoil knot being the prototype of a chiral object[10] (Scheme 1).

Knots have been created at the molecular level,[11,12] a recent synthetic improvement allowing their preparation at a truly preparative scale[13] (∼0.3 g per batch). The development of this new procedure led us to attempt the resolution of the molecular trefoil knot **K**, which we now report.

Our strategy for making knots is based on the three-dimensional template effect of transition metals, which are able to gather and interlace coordinating molecular strings prior to the ultimate cyclization step. This implies that the knotted molecules are obtained as cationic dicopper(I) complexes, which should allow the crystallization of diastereomeric salts, provided an enantiomerically pure chiral counterion is used. The principle of the resolution process and the molecular structure of the compounds utilized are represented in Figure 1.

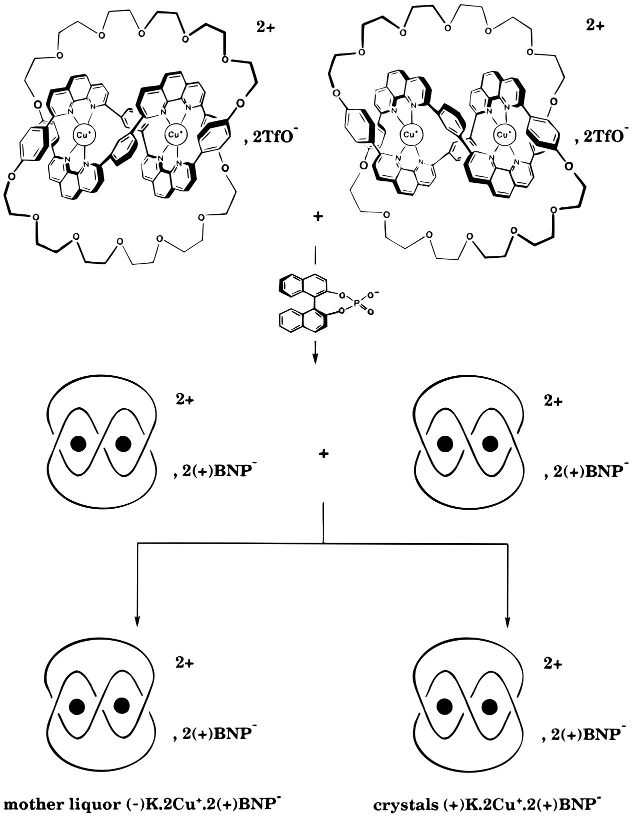
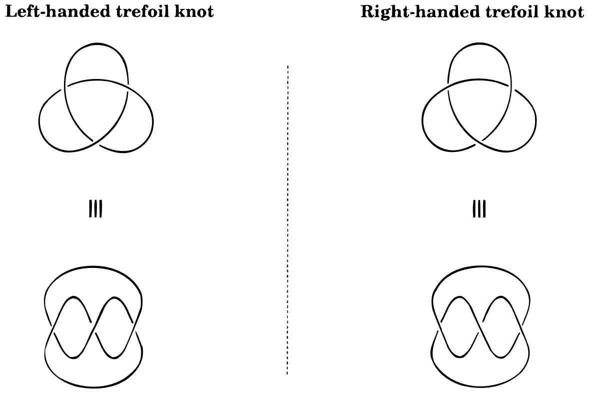


Figure 1. Principle of the resolution of the dicopper(I) molecular trefoil knot.

Scheme 1



Left-handed trefoil knot **Right-handed trefoil knot**

Anion exchange using the racemate (±)-**K**·$2Cu^+$·$2TfO^-$, prepared as described in ref 13, was performed using (*S*)-(+)-BNP^- (BNP^- is 1,1′-binaphthyl-2,2′-diyl phosphate,[14] potassium salt) in a two-phase system (CH_2Cl_2/H_2O). The mixture of diastereomers (−)-**K**·$2Cu^+$·2(+)-BNP^- and (+)-**K**·$2Cu^+$·2(+)-BNP^- was isolated by flash chromatography over alumina. It was subsequently dissolved in CH_3NO_2 (100 mg in 5 mL; deep red solution) in a cylindrical container (vial), and benzene was added on top of the solution, without stirring. After the solution stood overnight, an intense red microcrystalline solid formed. It was filtered off, and the mother liquor was evaporated, leading to 33.5 mg of (−)-**K**·$2Cu^+$·2(+)-BNP^- (ee > 98%). The solid (66.3 mg) contained 70% of (+)-**K**·$2Cu^+$·2(+)-BNP^- and 30% of the other diastereomer. It could be further recrystallized to afford a sample of nearly pure (+)-**K**·$2Cu^+$·2(+)-BNP^- (44.1 mg).

Furthermore, slow crystallization by vapor diffusion of benzene through a solution of the mixture of both diastereomers in CH_3NO_2 afforded beautiful needle-shaped crystals of (+)-**K**·$2Cu^+$·2(+)-BNP^-.

^1H NMR spectroscopy clearly indicated that both isolated solids each contain a single diastereomer (ee > 98%). The three ^1H NMR spectra obtained respectively for (±)-**K**·$2Cu^+$·2(+)-BNP^-, the crystals of (+)-**K**·$2Cu^+$·2(+)-BNP^-, and the mother liquor (containing (−)-**K**·$2Cu^+$·2(+)-BNP^- after evaporation) are shown in Figure 2.

Necessarily, the chiral counterion (*S*)-(+)-BNP^- makes the medium asymmetrical, inducing clear diastereotopic splitting

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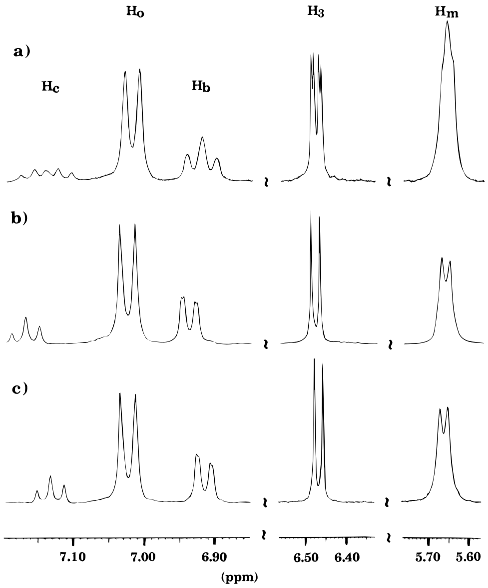

Figure 2. ^{1}H NMR at 400 MHz in CD_2Cl_2 (aromatic region, selected peaks) of the racemate (a), the diastereomers (−)-**K**·2Cu$^+$·2(+)-BNP$^-$ (b), and (+)-**K**·2Cu$^+$·2(+)-BNP$^-$ (c).

of the ^{1}H NMR signals. It is also likely that $\pi-\pi$ interactions between the aromatic double-stranded helical core of **K**·2Cu$^+$ and the naphthyl nuclei of BNP$^-$ play an important role. The chemical shift difference for the signals of (+)-**K**·2Cu$^+$·2(+)-BNP$^-$ and (−)-**K**·2Cu$^+$·2(+)-BNP$^-$ ($\Delta\delta$) may give some indication regarding the interaction between **K**·2Cu$^+$ and BNP$^-$. It is noteworthy that $\Delta\delta$ is much larger for the protons of the 1,3-phenylene spacer ($\Delta\delta = 0.035$ and 0.048 for H_b and H_c, respectively) than for the less central H atoms ($\Delta\delta = 0.014$ and 0.000 for H_o and H_m, respectively), which indicates that (+)-BNP$^-$ interacts preferentially with the central part of **K**·2Cu$^+$. Furthermore, since the signals for the protons of (+)-**K**·2Cu$^+$ are shifted upfield compared to those of (−)-**K**·2Cu$^+$, it is reasonable to assume a better interaction (and thus larger ring current effects) between (+)-**K**·2Cu$^+$ and (+)-BNP$^-$ than between (−)-**K**·2Cu$^+$ and (+)-BNP$^-$.

The optical rotation values were measured on the two diastereomerically pure samples in CH_2Cl_2 and were corrected for (+)-BNP$^-$ according to the following equation

$$\alpha_{\mathrm{obs}} = \mathrm{l}(C_{\mathbf{K}\cdot 2\mathrm{Cu}^+})([\alpha]_{\mathrm{D}\mathbf{K}\cdot 2\mathrm{Cu}^+}) + \mathrm{l}(C_{(+)-\mathrm{BNP}^-})([\alpha]_{\mathrm{D}(+)-\mathrm{BNP}^-})$$

that is

$$[\alpha]_{\mathrm{D}\mathbf{K}\cdot 2\mathrm{Cu}^+} = \frac{\alpha_{\mathrm{obs}} - \mathrm{l}(C_{(+)-\mathrm{BNP}^-})([\alpha]_{\mathrm{D}(+)-\mathrm{BNP}^-})}{\mathrm{l}(C_{\mathbf{K}\cdot 2\mathrm{Cu}^+})}$$

where α_{obs} is the observed value in degrees, C is the concentration in mol L^{-1}, $[\alpha]_D$ is the optical rotation in degree mol^{-1} L dm^{-1}, and l is the length of the cell in decimeters. For (+)-**K**·2Cu$^+$·2(+)-BNP$^-$, $C = 4.57 \times 10^{-5}$, $\alpha_{\mathrm{obs}} = +0.333$, $\mathrm{l} = 1$, $[\alpha]_{\mathrm{D}(+)-\mathrm{BNP}^-} = +197.3$, and $[\alpha]_{\mathrm{D}(+)-\mathbf{K}\cdot 2\mathrm{Cu}^+\cdot 2(+)-\mathrm{BNP}^-} = +7300 \pm 100$. For (−)-**K**·2Cu$^+$·2(+)-BNP$^-$, $C = 5.25 \times 10^{-5}$, $\alpha_{\mathrm{obs}} = -0.345$, $\mathrm{l} = 1$, $[\alpha]_{\mathrm{D}(+)-\mathrm{BNP}^-} = +197.3$, and $[\alpha]_{\mathrm{D}(-)-\mathbf{K}\cdot 2\mathrm{Cu}^+\cdot 2(+)-\mathrm{BNP}^-} = -6600 \pm 100$.

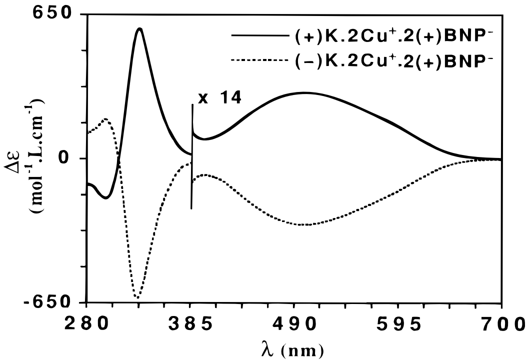

Figure 3. Circular dichroism spectra of both diastereomers; these are perfect mirror images since the auxiliary chiral anion does not absorb in the represented region ($\lambda > 280$ nm).

The optical rotation corrected for (+)BNP$^-$ values are therefore $[\alpha]_{\mathrm{D}(-)-\mathbf{K}\cdot 2\mathrm{Cu}^+} = -7000 \pm 100$ (mother liquor) and $[\alpha]_{\mathrm{D}(+)-\mathbf{K}\cdot 2\mathrm{Cu}^+} = +6900 \pm 100$ (crystals).

The circular dichroism (CD) spectra of both diastereomers are shown in Figure 3. As expected in this region (280−700 nm), the two spectra are mirror images, since (+)-BNP$^-$ does not absorb light above 280 nm. In the visible region, $\Delta\epsilon$ values reach a maximum near the absorption maximum (510 nm) of the metal-to-ligand charge transfer (MLCT) band ($\Delta\epsilon = +20.7 \pm 0.6$ mol^{-1} L cm^{-1} for (+)-**K**·2Cu$^+$·2(+)-BNP$^-$ and $\Delta\epsilon = -21.3 \pm 0.6$ mol^{-1} L cm^{-1} for (−)-**K**·2Cu$^+$·2(+)-BNP$^-$).

In order to prepare a compound whose chirality is of pure topological origin, (+)-BNP$^-$ was exchanged for PF_6^-. The $[\alpha]_D$ values measured on these complexes were identical to those obtained for the (+)-BNP$^-$ salts within experimental errors ($[\alpha]_D = +7000° \pm 100$ mol^{-1} L dm^{-1} for (+)-**K**·2Cu$^+$·2PF_6^- and $[\alpha]_D = -7100° \pm 100$ mol^{-1} L dm^{-1} for (−)-**K**·2Cu$^+$·2PF_6^-).

Since the resolution technique was truly preparative, demetalation and metal exchange could be carried out. Removal of copper(I), using KCN in CH_3CN under reflux followed by workup, gave a pale yellow species corresponding to the partially protonated ligand ($[\alpha]_D = +2000° \pm 100$ mol^{-1} L dm^{-1} for (+)-**K** and $[\alpha]_D = -1900° \pm 100$ mol^{-1} L dm^{-1} for (−)-**K**. These values are high and comparable to those measured for heterohelicenes.[15]

Remetalation with copper(I) led back to the original dicopper(I) molecular knot with the same $[\alpha]_D$ value.

In conclusion, crystallization of the diastereomeric salts of a dicopper(I) trefoil knot allows separation of its enantiomers. Not too surprisingly, the optical rotation properties of the compounds are comparable to those of heterohelicenes. Optically pure knots, complexed to copper(I) or to other metal centers, should be of great interest in relation to enantioselective electron transfer and interaction with biological molecules (DNA).

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