

Trefoil Knot

Combining Coordination Chemistry and Catalysis To Tie a Knot by an Active-Metal Template Strategy**

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 chemical topology · click chemistry ·
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Knotted molecules have been targeted in the past decades, essentially because they consist of very curious and fascinating molecular architectures and because their synthesis remains a real challenge for chemists. However, molecular knots^[1] have been discovered in natural biological macromolecules, and thus knotted molecules can now also be envisaged as being interesting molecular targets with potential biological activities. Indeed, different kinds of knots have been found in DNA^[2] and proteins, and it has been suggested that their pronounced rigidity and chirality could result in unusual biochemical activities compared to their linear analogues. Two examples of natural macromolecules that contain knots are the lactoferrin protein and the ascorbic acid oxidase enzyme, which possess a remarkable ability to transport iron(III) ions and for enzymatic oxidation, respectively.^[3] Other knotted molecules such as circulin A and B^[4] (knotted proteins) and cyclotides^[5] (knotted peptides) exhibit antiviral activity against HIV. The natural lasso peptides, which consist of 16–21 amino acid residues, contain a lasso structure which is responsible for their biological activity as receptor antagonists and enzymatic inhibitors.^[6] The reasons why chiral knotted organic molecules are of interest to study are: 1) because they can mimic natural knotted macromolecules by incorporating some fragments of natural biologically active molecules in their structure, 2) because their chiral supramolecular conformation could yield a new generation of catalysts for stereoselective synthesis, and 3) because some knots could contain a cavity, which could be used as a carrier for a drug. Whereas molecular biology uses enzymes such as topoisomerases to build knots in peptides, proteins, RNA, and DNA, the main chemical route to these structures utilizes a template effect based on noncovalent interactions between precursors. Dietrich-Buchecker and Sauvage synthesized the first molecular knot (namely a trefoil knot, Figure 1) in 1989 through preorganizing two copper(I) ions and two bischelate-

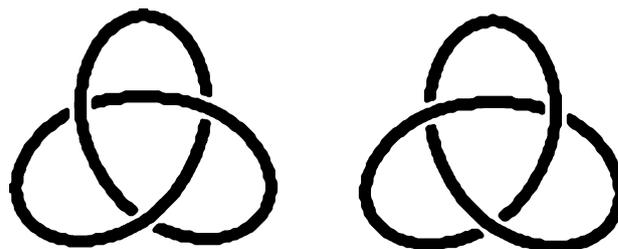


Figure 1. Schematic representation of trefoil knot enantiomers.

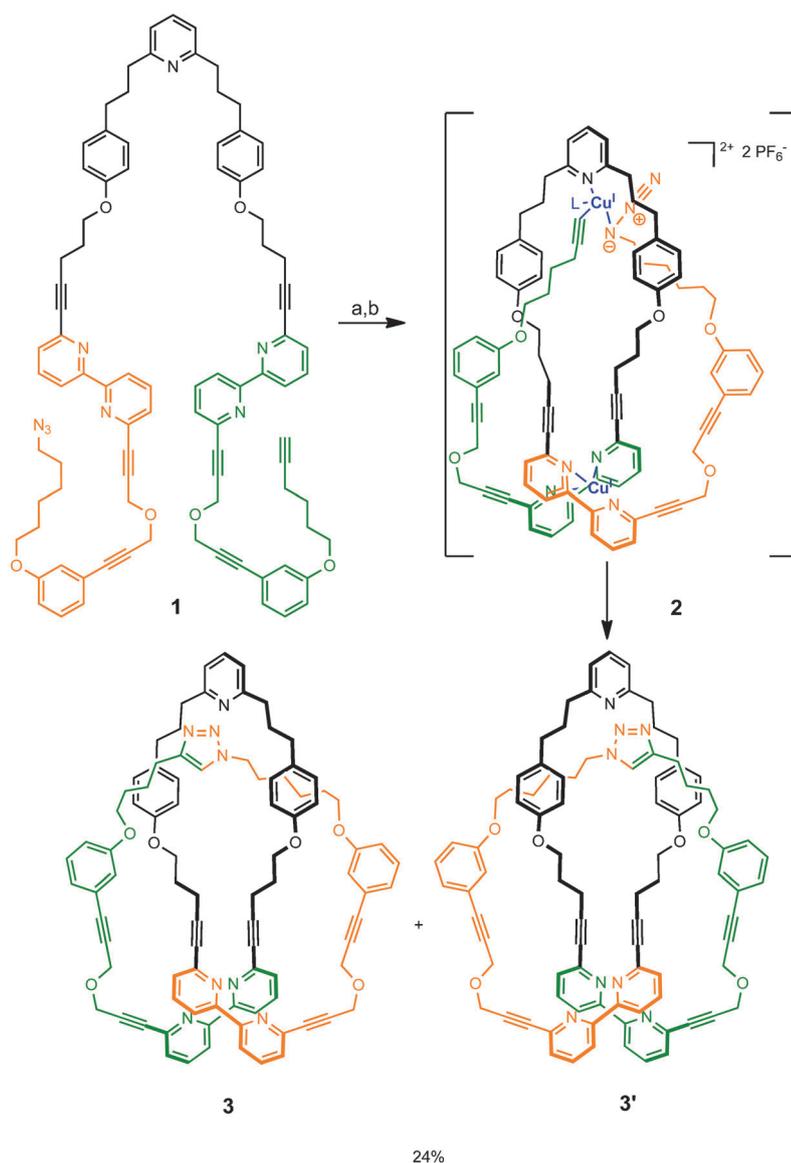
ing threads containing 1,10-phenanthroline units.^[7] Since then, a few research groups have managed to prepare molecular knots by different template-based chemical methods, usually based on the formation of inorganic complexes,^[8] hydrogen bonding,^[9] or donor–acceptor interactions;^[10] however, the efficient synthesis of knots still remains a real “tour de force” because of the necessity to preorganize the interlacing of the molecule in an optimal conformation prior to cyclization.

In a very recent article,^[11] Leigh and co-workers proposed a very elegant synthesis of a trefoil knot by applying their own synthesis method based on an active-metal template.^[12] They succeeded in employing copper(I) ions to both preorganize the knot precursor and as the cyclization catalyst (Scheme 1). With this one-pot strategy, the open flexible precursor **1** could be contorted by coordination chemistry, before being cyclized into the trefoil knot **3**. The design of the molecule was chosen so that a perfect arrangement of the ligands around the metal center forms the necessary entanglement to create the trefoil structure. In this optimal arrangement (compound **2**), two bipyridyl moieties of the lace coordinate to a stoichiometric amount of copper(I) ions to create the loop. At the same time, a catalytic amount of the copper(I) ions complex the two unsymmetrical alkyne and azide extremities of the thread and one pyridine moiety located at the middle of the thread, before catalyzing the closing of the ring by a copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) between the two terminal moieties.^[13] After demetalation, a racemic mixture of left- and right-handed knots **3/3'** was isolated in a very reasonable yield of 24%, considering the very difficult synthetic challenge. With the exception of oligomeric by-products, which were removed by size-exclusion chromatography, the only other isolated product was found to be the unknotted macrocyclic analogue (10%). Evidence for the

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Scheme 1. Synthesis of trefoil knot **3** by the method of Leigh and co-workers. a) $\text{CHCl}_3/\text{CH}_3\text{NO}_2$ (4:1), $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (1.5 equiv), 60°C , 96 h; b) Na_2EDTA , NH_3 . EDTA = ethylenediaminetetraacetate.

three-dimensional trefoil structure was provided by NMR spectroscopy and drift tube ion mobility mass spectrometry. These data revealed the major product was chiral and had a compact, constrained, interlocked structure relative to the very flexible unknotted macrocycle analogue.

The 76-atom trefoil knot synthesized by Leigh and co-workers is the smallest trefoil knot architecture reported to date. Their active-metal template strategy, which combines in a one-pot procedure the coordination of, and the catalysis by,

the copper(I) ions in a CuAAC click reaction, appears to be very versatile and adaptable to the synthesis of a wide range of interlaced structures. Such a straightforward synthetic access to knotted compounds will surely give rise to novel uses and functions of molecular knots in the future.

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