

Efficient synthesis of a molecular knot by copper(I)-induced formation of the precursor followed by ruthenium(II)-catalysed ring closing metathesis

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A double-stranded helix constructed around two copper(I) centres used as templates and bearing four terminal alkenes, is converted into a trefoil knot in 74% yield by ruthenium(II)-catalysed ring closing metathesis (RCM); the cyclic alkenes can be quantitatively reduced by catalytic hydrogenation to afford the copper(I)-complexed 82-membered knotted ring.

In molecular biology, knots constructed on double-stranded DNA have been described more than twenty years ago.¹ Recently, the trefoil knot, but also more complex topologies, have been generated from single-stranded DNA.² Some proteins have also been shown to adopt knotted topologies.³ The planned synthesis of chemical knots was first reported a few years ago,⁴ but clearly the yield had to be increased both for the synthetic challenge that this improvement represented and for the interesting properties of this new family of compounds.⁵ A more preparative procedure (30% yield) was recently de-

scribed,⁶ but we still looked for a more efficient and chemically milder method. The ring-closing metathesis approach (RCM)⁷ which we now describe seems to be close to ideal: not only is the yield excellent considering the complexity of the reaction but the procedure takes place under very gentle conditions (without any acid or base, in CH₂Cl₂ at room temp.).

The strategy (Fig. 1) relies on (i) quantitative formation and high stability of the helical precursor composed of copper(I) bisphenanthroline units with 1,3-phenylene linkers between the phenanthroline nuclei,^{5c,6} and (ii) the highly efficient RCM methodology developed by Grubbs and coworkers.⁷

Ligand **2** was obtained in 97% yield by reaction of **1** with 2-(2-chloroethoxy)ethanol in DMF at 80 °C, in the presence of Cs₂CO₃. It could be quantitatively converted to **3** by generating the dialcoholate with NaH and reacting it with an excess of allyl bromide in refluxing THF. The helical precursor **4**²⁺ was

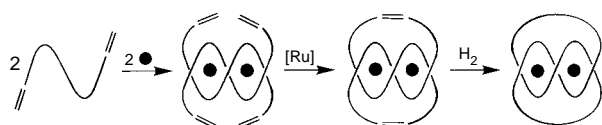


Fig. 1 Synthetic strategy. Two coordinating fragments bearing terminal alkenes are gathered and interlaced around two copper(I) centres. RCM with ruthenium catalyst affords the knot.

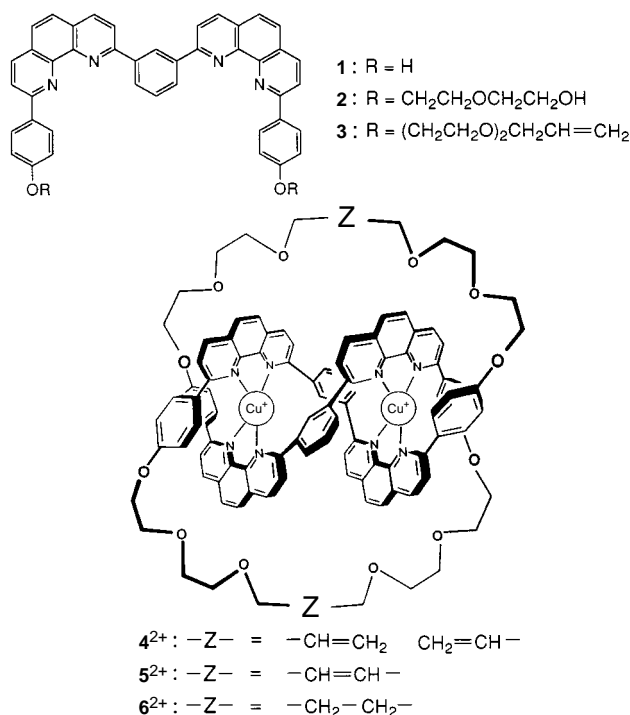


Fig. 2 Chemical structure of the organic precursors and of the knots

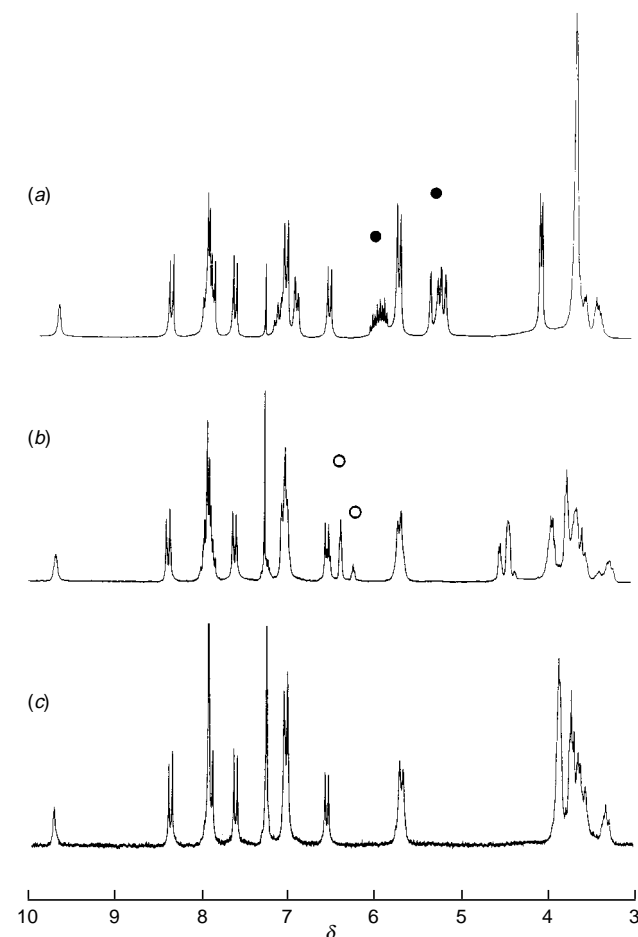


Fig. 3 ¹H NMR spectra of (a) the helical precursor **4**²⁺ with the signals corresponding to the four terminal alkenes (●), (b) the trefoil knot **5**²⁺ with the signals corresponding to the two alkenes incorporated in the molecule (○) and (c) the trefoil knot **6**²⁺ after catalytic reduction of the alkenes

formed quantitatively by the classical way: addition under argon of $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ dissolved in MeCN onto a solution of the bis-chelate **3**. The metathesis was catalysed by $[\text{RuCl}_2\{\text{P}(\text{C}_6\text{H}_{11})_3\}_2(=\text{CHPh})]$ (0.05 mol. equiv.) at a substrate concentration of 0.01 M in CH_2Cl_2 at room temp. The double coupling of the terminal alkenic groups afforded the trefoil knot **5**²⁺ in 74% yield after column chromatography (Fig. 2). The only other products were oligomers arising from intermolecular metathesis reactions.

The dicopper(I) trefoil knot **5**²⁺ is thus obtained in seven steps from commercially available 1,10-phenanthroline, with an overall yield of 35%.

The two cyclic alkenes remaining in **5**²⁺ appeared originally as a mixture of *cis* and *trans* alkenes in a 80 : 20 ratio, according to the ¹H NMR spectrum. We thus obtained the *cis-cis*, *cis-trans* and *trans-trans* products [compare the broad signals in the spectrum in Fig. 3(b) to the narrow and well resolved ones of the spectrum in Fig. 3(c)]. The alkene functionalities could be easily and quantitatively reduced at room temp. by catalytic hydrogenation in EtOH- CH_2Cl_2 (1 : 1) with Pd/C (5 mol% Pd). Cyclisation and reduction could both be monitored by ¹H NMR spectroscopy in the alkenic region, the signals corresponding to the cyclic alkenic groups in knot **5**²⁺ being sharply different from those of the terminal alkenic groups in the precursor **4**²⁺ (see Fig. 3). Moreover, the ¹H NMR spectrum of the knot after reduction is clearly simplified.

The knotted topology of **5**²⁺ could be unambiguously established by ¹H NMR spectroscopy, the signals of the aromatic protons as well as those of the polyoxyethylenic chains in the 3–4 ppm region being highly characteristic.⁸ Further evidence was obtained from FABMS which confirmed the absence of any starting material and displayed the expected mass: a peak at 1965.3 corresponding to $[\text{5}(\text{PF}_6)]^+$ and a peak at 910.1 corresponding to **5**²⁺.

The here-described latest improvements now allow an easy access to trefoil knots and hence render the extensive study of

their specific properties possible. It can also be envisaged that the two alkene functionalities of **5**²⁺, disposed in an antipodal fashion, can be utilized for further functionalization.

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Footnote and References

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