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Synthesis of catenanes and molecular knots by copper(I)-directed formation of the precursors followed by ruthenium(II)-catalysed ring-closing metathesis

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Contents

Abstract

Catenanes and knots are fascinating molecular systems, but for several decades these compounds have been regarded as exotic species due to synthetic difficulties. We have proposed template strategies based on transition metals (mostly copper(I)), and this approach has allowed us to make a wide family of interlocking rings and knots in the course of the last 15 years. A very recent and practically important improvement now permits relatively easy preparation of some of these systems with, in some cases, almost quantitative yields. The key step is the ring-closing metathesis (RCM) of olefins, using the extremely efficient and mild catalysts developed by Grubbs et al. in the last few years, and consisting of ruthenium carbenes. © 1999 Elsevier Science S.A. All rights reserved.

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Catenanes and knots are fascinating molecular systems, due to their topological properties [1–4], and their analogy with interlocking and knotted rings in biology (DNA [5,6], and proteins [7]). They are also promising compounds in relation to materials science [8,9], coordination chemistry [10,11] and molecular machines and motors [12–14]. This latter aspect of their specific properties makes catenanes and related systems excellent candidates as models of biological molecular motors [15–17] or, in a long term prospect, as components in molecular electronics and information storage devices [8,11–14]. For several decades, catenanes have been regarded as exotic species [1,2] in spite of existing procedures for synthesising macrocyclic compounds in high yields [18]. Since the development of template strategies based on transition metals [10,19], acceptor–donor organic complexes [8,20] and hydrogen bonded precursors [21,22], interlocking rings are much more accessible as testified by the many reports devoted to them since the mid-1980s. However, the cyclisation reaction(s) affording the desired catenanes and knots can still be a limiting step, with most of the time poor to moderate yields. Interestingly, catenanes incorporating transition metals in their backbone (mostly, palladium(II)) have been obtained in remarkably high preparative yields [23]. It is noteworthy that in this latter case, catenane formation takes place under thermodynamic control. As will be discussed below, this also applies to the present work. Among the many cyclisation reactions available, C–N and C–O bond formations have been used preferentially to C–C coupling reactions. An essential requirement is that the conditions of the ring-forming reaction are mild enough to avoid any dissociation of the precursor complex. Recently, the ring-closing metathesis (RCM) reaction has been used with remarkable success for making macrocyclic compounds, in high yield and under mild conditions [24,25]. In particular, Grubb's catalysts are easy to use, tolerant to a large variety of chemical functions and, in addition, they turn out to be operative under extremely mild conditions [26]. We have recently employed this methodology for making catenanes and knots in surprisingly high yields [26,27].

1. Synthesis of [2]-catenanes

The first transition metal-templated syntheses of catenanes were reported long ago [19]. In the present work, copper(I) has once more been used as the gathering and orienting centre, the molecular strings to be intertwined or threaded through a presynthesized ring being end-functionalized by olefinic groups. The principle of the catenane synthesis is described in Fig. 1.

Most of the building blocks used have already been utilized extensively in previous work from our group [10,11,19]. They are based on the 2,9-diphenyl-1,10-phenanthroline (dpp) chelate, incorporated in a ring or in a non-cyclic unit. The organic precursors and the compounds prepared are represented in Fig. 2.

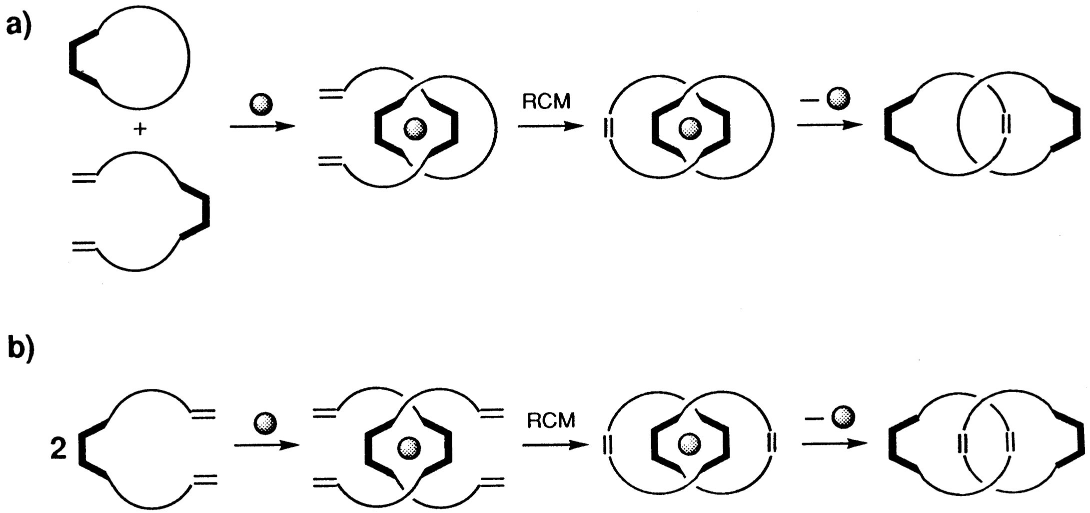


Fig. 1. Principle of catenanes syntheses utilizing a transition metal-based template strategy and RCM. (a) Transition metal-directed threading of an open chain fragment through a coordinating ring followed by RCM and removal of the template. (b) Formation of an intertwined precursor complex followed by 2-fold RCM and demetallation. The black circle represents the template (copper(I) in the present work).

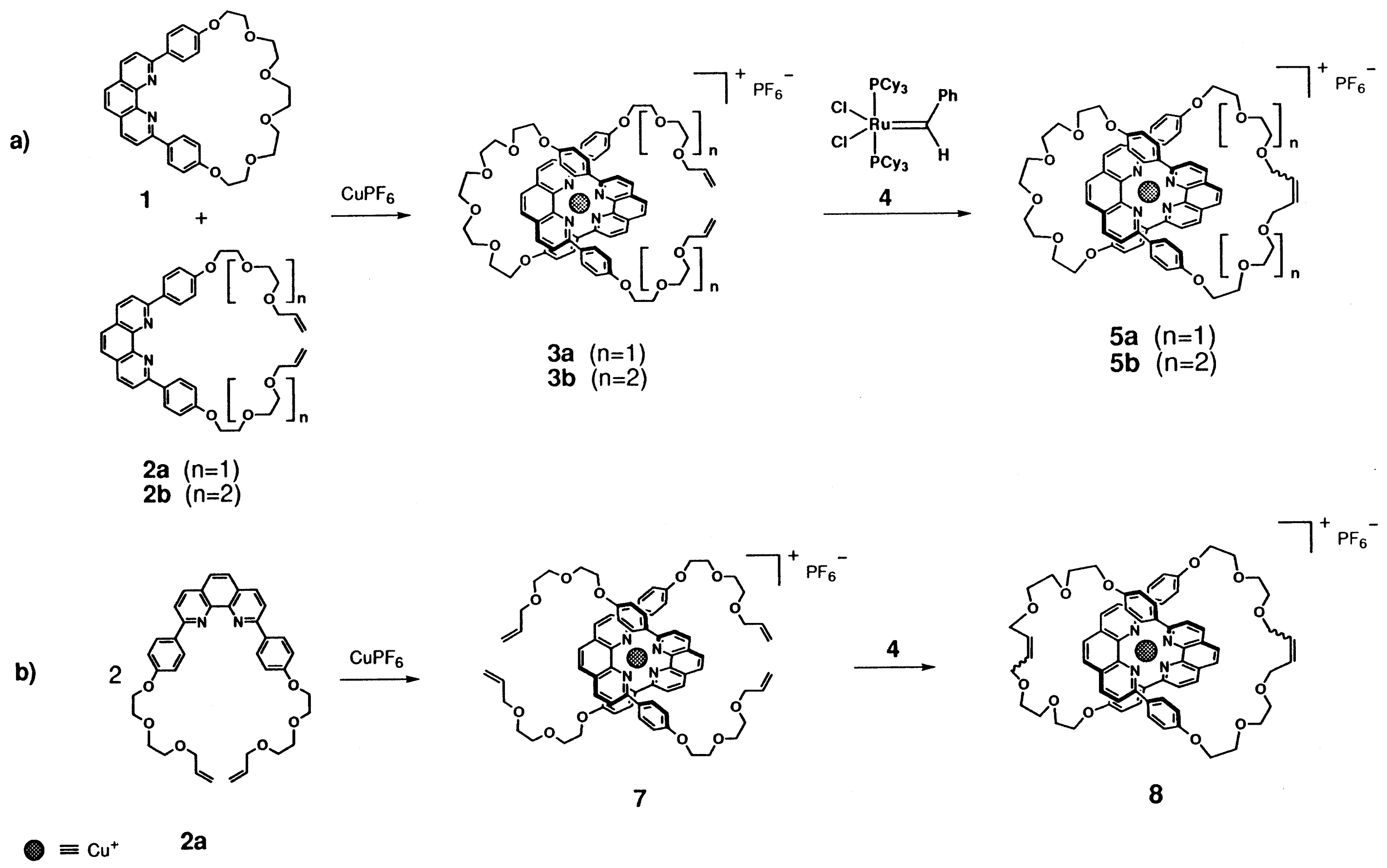


Fig. 2. Synthesis of [2]-catenates following: (a) the threading route; and (b) the entwining strategy.

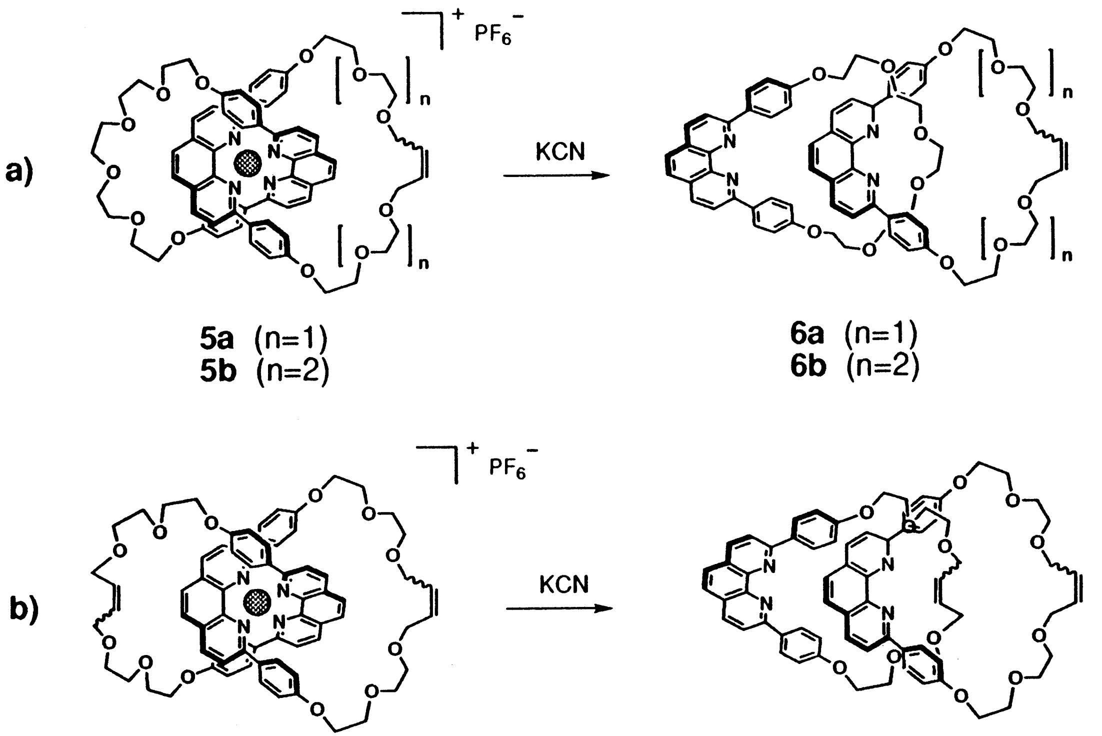
The ligand **1** was obtained as previously published [19]. **2a** and **2b** were prepared by alkylation of 2,9-di(*p*-hydroxyphenyl)-1,10-phenanthroline with 2-(2-chloroethoxy) ethanol/Na_2CO_3 and 2-[2-(2-chloroethoxy)ethoxy] ethanol/Na_2CO_3 respectively, followed by alkylation of the aliphatic alcohols with allylbromide/NaH. By reacting the 30-membered ring **1** with stoichiometric amounts of $Cu(CH_3CN)_4^+ \cdot PF_6^-$ and coordinating open-chain unit **2a** or **2b**, the threaded system **3a** or **3b** was formed quantitatively. Complexes **3a** or **3b** were submitted to intramolecular RCM with catalyst **4** (**4** = $Cl_2(PCy_3)_2$,Ru=CHPh, Cy = Cyclohexyl, Ph = Phenyl) to afford the corresponding catenates **5a** or **5b** in extremely good yields (90%). Compounds **5a** and **5b** contain, besides the 30-membered ring, a 32- or 38-membered olefinic ring, respectively. As for the other compounds discussed in this review article, they were unambiguously characterized by ^1H-NMR, FAB-MS (FAB, fast atom bombardment). Demetallation of the copper catenates **5a** and **5b** with KCN afforded the catenands **6a** and **6b**, respectively, in almost quantitative yield (Fig. 3a). The newly formed double bond in **5a** or **5b** is mostly *trans* ($>95\%$).

Even more surprising is the efficiency of the one-pot synthesis (Fig. 2b)). The intertwined complex **7** was formed quantitatively by reacting $Cu(CH_3CN)_4^+ \cdot PF_6^-$ with two equivalents of **2a**. A 2-fold RCM in **7** led exclusively to the interlocking ring system **8** (90% yield). This catenate consists of two 32-membered rings, the two olefins being again preferentially trans (*trans*/*cis* = 98/2). The corresponding free catenand **9** was obtained almost quantitatively by demetallation of **8** with KCN (Fig. 3b).

The cyclisation yields to prepare the [2]-catenanes of Fig. 2 exceed those for most other large rings, where hydrogen bonds, conformational constraints or other template effects are present [24,28]. At the present stage, it is difficult to explain why the synthetic procedure based on RCM to make **5a**, **5b** and **8** is so efficient. Obviously, this methodology provides an attractive and versatile approach for the synthesis of more complex catenanes and knots. The latter point will be discussed in the next paragraph.

2. Preparation of molecular knots

The synthesis of chemical knots was first reported a few years ago [29], 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 [30]. A more preparative procedure (30% yield) was recently described [31], but we still looked for a more efficient and chemically milder method. The RCM [24,25,28] approach 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: room temperature (r.t.) and neutral medium. In particular the absence of base which strongly affects the stability of the copper(I) precursor complexes, which means partial loss of the template effect. Noticeably, olefin metathesis is also a thermodynamically controlled reaction.



5a (n=1)
5b (n=2)

6a (n=1)
6b (n=2)

8

9

Fig. 3. Demetalation of the copper(I) catenates: (a) the catenates containing two different rings; and (b) the symmetrical catenate.

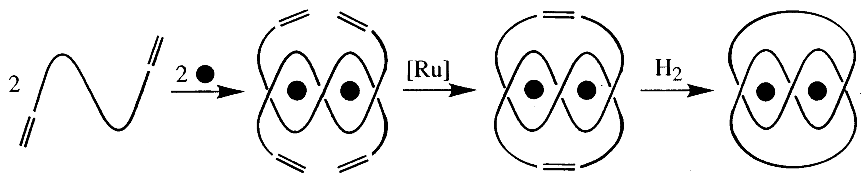
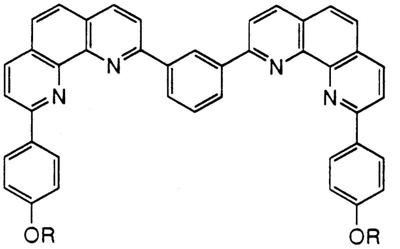
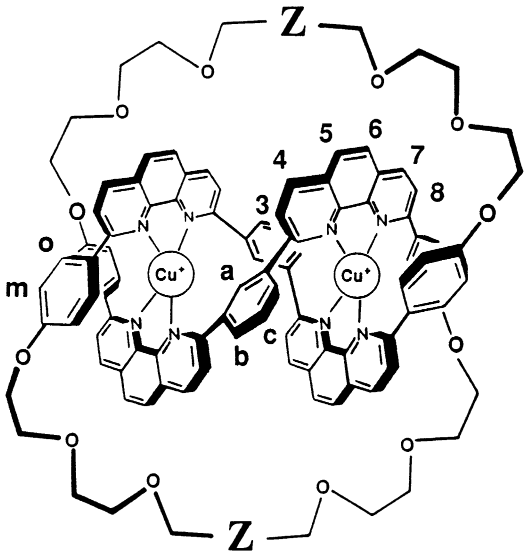


Fig. 4. Synthetic strategy. Two bis-chelate coordinating fragments bearing terminal olefins are gathered and interlaced around two copper(I) centres. RCM with ruthenium catalyst affords the knot.

The strategy (Fig. 4) relies on (i) quantitative formation and high stability of the helical precursor composed of Cu(I) bisphenanthroline units with 1,3-phenylene



10: R = H
11: R = $CH_2CH_2OCH_2CH_2OH$
12: R = $(CH_2CH_2O)_2CH_2CH{=}CH_2$



13: –Z– = $-CH{=}CH_2 \quad CH_2{=}CH-$
14: –Z– = $-CH{=}CH-$
15: –Z– = $-CH_2-CH_2-$
16: Demetalated Trefoil Knot

Fig. 5. Chemical structure of the organic precursors and of the knots.

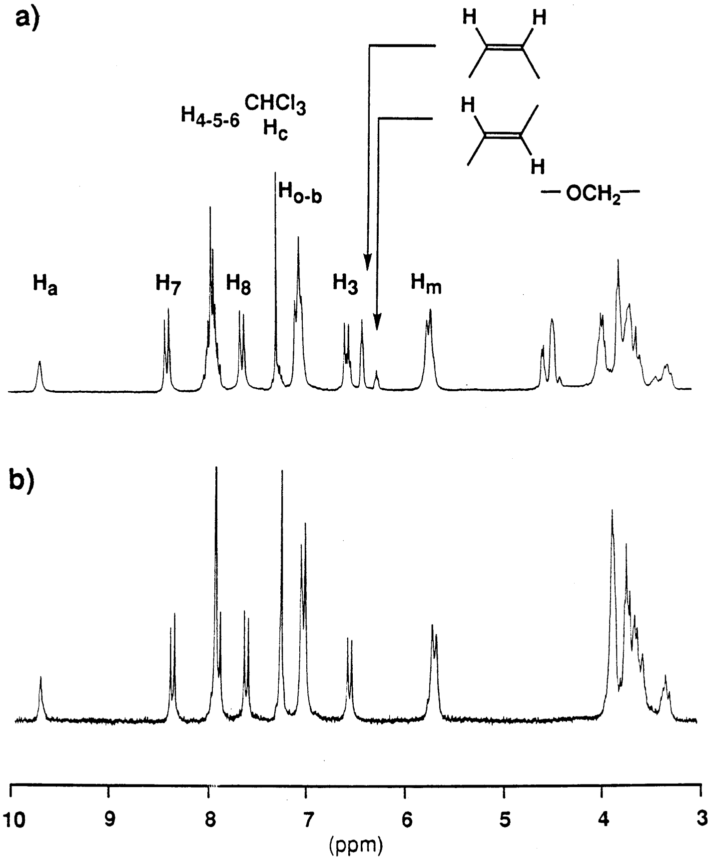


Fig. 6. ^{1}H-NMR (200 MHz) spectra of knots **14** (a) and **15** (b) in $CDCl_3$.

linkers between the phenanthroline nuclei [30c, 31], and (ii) the highly efficient RCM methodology developed by Grubbs et al. [24,25,28].

Ligand **11** was obtained in 97% yield by reaction of **10** with 2-(2-chloroethoxy)ethanol in DMF at 80°C, in the presence of Cs_2CO_3. It could be quantitatively converted to **12** by generating the dialcoholate with NaH and reacting it with an excess of allyl bromide in refluxing THF. The double-helical precursor **13** was formed quantitatively by the classical way: addition under argon of $[Cu(CH_3CN)_4]PF_6$ dissolved in CH_3CN onto a CH_2Cl_2 solution of the bischelate **12**. After isolation of **13**, the metathesis was catalysed by **4** (5% molar) at a substrate concentration of 0.01 M in CH_2Cl_2 at r.t. The double metathesis of the terminal olefins afforded the trefoil knot **14** in 74% yield (Fig. 5) which has to be compared with the 29% yield obtained for the Williamson-type reaction. The only other products were oligomers due to intermolecular metathesis reactions.

The dicopper(I) trefoil knot **14** was thus obtained in seven steps from commercially available 1,10-phenanthroline with an overall yield of 35%.

The two cyclic olefins remaining in **14** appeared originally as a mixture of *cis* and *trans* alkenes in an 80:20 ratio, according to the ^{1}H-NMR spectrum. This ratio can be explained in terms of cyclic strain, which is more pronounced in the case of the knot than in the catenane family. The alkene functionalities could be easily and quantitatively reduced at r.t. by catalytic hydrogenation with Pd/C (5% molar in Pd). Cyclisation and reduction could both be monitored by ^{1}H-NMR in the olefinic region, the signals corresponding to the cyclic alkenic group in knot **14** being markedly different from those of the terminal alkenic groups in precursor **13**. Moreover, the ^{1}H-NMR spectrum of the knot after reduction is simplified as shown in Fig. 6.

The knotted topology of **14** could be unambiguously established by ^{1}H-NMR (1D and 2D-ROESY). Further evidence was brought by FAB-MS spectroscopy which confirmed the absence of any starting material and displayed the expected mass: a peak at 1965.3 corresponding to $[\mathbf{14} \cdot PF_6]^+$and a peak at 910.1 corresponding to $[\mathbf{14}]^{2+}$.

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 envisioned that the two olefins of **14**, disposed in an antipodal fashion, be utilized for further functionalization.

Acknowledgements

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