Lithium templated synthesis of catenanes: efficient synthesis of doubly interlocked [2]-catenanes

Christiane Dietrich-Buchecker and Jean-Pierre Sauvage*

Laboratoire de Chimie Organo-Minérale, CNRS UMR 7513, Université Louis Pasteur, Institut Le Bel, 4 rue Blaise Pascal, F-67070 Strasbourg, France. E-mail: sauvage@chimie.u-strasbg.fr

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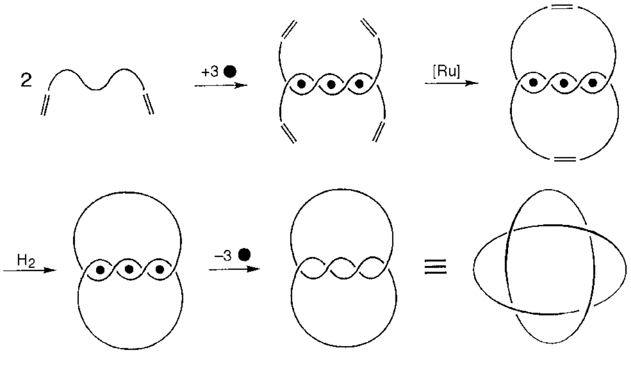
Li^+ (3 equiv.) is used as an assembling centre to generate a double-stranded helical complex from two linear coordinating fragments, each containing three 1,10-phenanthroline units and bearing terminal olefins at their ends; ruthenium-catalyzed ring-closing metathesis on the helical precursor leads to a 4-crossing [2]-catenane in 30% yield, making the procedure reasonably preparative.

The synthesis of interlocking rings[1,2] and molecular knots has undergone spectacular progress in the course of the last 15 years due to the development of templated strategies.[3–5] Copper(I) has been used extensively as an assembling and templating centre,[3] but a few examples based on other transition metals [Ru(II) or Co(II)] have also been reported.[6,7]

To the best of our knowledge, alkali or alkaline-earth cations have never been utilized. We now report that Li^+ is also well adapted to the formation of a double-stranded helical complex used as a precursor, and, in a subsequent reaction, to the synthesis of a doubly interlocked catenane.

Helical transition metal complexes ('helicates') constitute an important field of research in relation with so-called 'self-assembly' processes. Although known for more than two decades,[8] it is only recently that transition metal incorporating helices have been made deliberately and the properties of these multinuclear species studied.[9–11] A double stranded helical complex containing two Na^+ ions has been characterized by ^{1}H NMR spectroscopy.[12] Li^+ is known to display relatively strong affinity for ligands of the aromatic polyimines family.[13] In the present work, Li^+ turned out to be very well adapted to the formation of a trinuclear double helix, which surprisingly appeared sufficiently robust to resist the cyclization conditions.

The general strategy for preparing a 4-crossing [2]-catenane is shown in Scheme 1. It is based on two key reactions: (i) formation of a double-stranded helical precursor from 2 equivalents of a molecular string which incorporates three chelating units, and 3 equivalents of the templating metal; the string-like fragment bears olefinic functions attached at the ends of flexible fragments; (ii) the ring closing metathesis (RCM) reaction leading to the catenate.

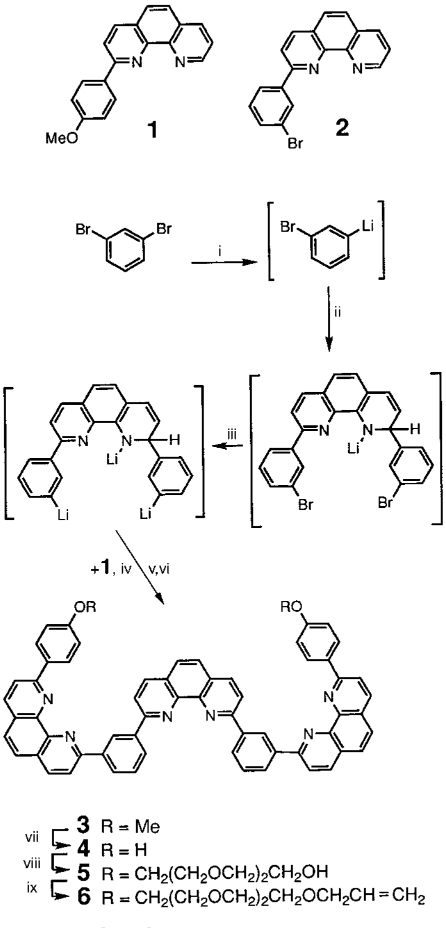


Scheme 1 General strategy for the preparation of 4-crossing [2]-catenanes.

In previous work, we could prepare small amounts of a 4-crossing [2]-catenane. Unfortunately, the yield was so poor (1.8%) that we could only characterize the compound by ^{1}H NMR and mass spectrometry (ES-MS and FAB-MS).[14] The modified strategy we describe now leads to dramatic improvement, affording the new doubly interlocked catenane in 30% yield. The main factors which are responsible for the much more preparative procedure of the present approach are (i) the quantitative formation of the three-lithium ion double-stranded helical precursor and (ii) the very mild and efficient RCM reaction,[15] as already used in previous work for making [2]-catenanes[16] or molecular trefoil knots.[17]

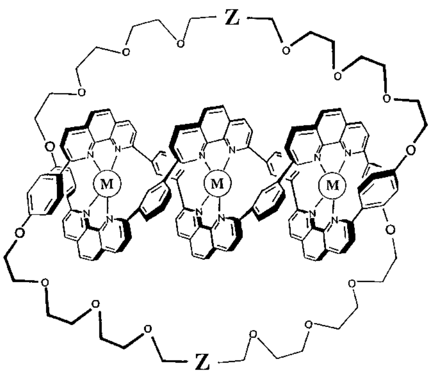
The various compounds prepared as well as the reactions leading to the target molecule are shown in Scheme 2.

The tris-chelating ligand **3** could be prepared in 11% yield from the monosubstituted phenanthrolines **1**[18] and **2**[19] in a multistep reaction shown in Scheme 2. Ligand **4** obtained



Scheme 2 *Reagents and conditions*: i, Bu^{n}Li, Et$_2$O, 2 °C; ii, **2** in THF, 0 °C; iii, Bu^{t}Li (4 equiv.), −78 °C; iv, **1** (2.5 equiv.) in THF, 10 °C; v, H$_2$O, 0 °C; vi MnO$_2$, excess; vii, HCl, pyridine, 210 °C; viii, Cs$_2$CO$_3$, DMF, 75 °C, ClCH$_2$(CH$_2$OCH$_2$)$_2$CH$_2$OH (excess); ix, NaH, THF reflux, BrCH$_2$CH=CH$_2$ (excess).

$2\ \mathbf{6} + 3\ LiPF_6 \longrightarrow 3\ Li{\bullet}(\mathbf{6})_2^{3+}$



$3Li{\bullet}(\mathbf{6})_2^{3+}$: Z = CH=CH$_2$ CH$_2$=CH (M = Li$^+$)
$3Li{\bullet}\mathbf{7}^{3+}$: Z = CH=CH (M = Li$^+$)
$3Cu{\bullet}\mathbf{7}^{3+}$: Z = CH=CH (M = Cu$^+$)
$3Cu{\bullet}\mathbf{8}^{3+}$: Z = CH$_2CH_2$ (M = Cu$^+$)

Fig. 1 Double stranded helix formation and cyclisation.

quantitatively after demethylation of **3** by HCl–pyridine,[20] was converted to diol **5** in 87% yield by reaction with 2-[2-(2-chloroethoxy)ethoxy]ethanol in DMF at 75 °C in the presence of Cs_2CO_3. **5** led to **6** in 88% yield after formation of the dialcoholate with NaH and subsequent reaction with an excess of allyl bromide in refluxing THF.

The tris-lithium helical precursor $3Li{\cdot}(\mathbf{6})_2^{3+}$ was formed quantitatively by addition of $LiPF_6$ in MeOH to a solution of **6** in CH_2Cl_2 at room temperature (Fig. 1). To avoid competitive protonation solid Li_2CO_3 was subsequently added to the solution until it was weakly basic. The double helix $3Li{\cdot}(\mathbf{6})_2^{3+}$, fully characterized by ^{1}H NMR and ESI-MS, was stable enough to survive the mild RCM conditions (0.05 mol equiv. of Grubbs catalyst $[RuCl_2\{P(C_6H_{11})_3\}_2(=CHPh)]$). The double cyclization could be monitored by ^{1}H NMR spectroscopy in the alkenic region. The unsuccessful attempt to separate the pure tris-lithium doubly interlocked [2]-catenate $3Li{\cdot}\mathbf{7}^{3+}$ from the oligomers arising from the intermolecular metathesis reaction led us to exchange Li^+ with Cu^+. This exchange was slow and required heating at 60 °C of a $3Li{\cdot}\mathbf{7}^{3+}$ acetonitrile solution in the presence of a large excess of $[Cu(MeCN)_4]PF_6$ for several days. Subsequent chromatography afforded the catenate $3Cu{\cdot}\mathbf{7}^{3+}$ in 30% yield. The cyclic alkenes remaining in $3Cu{\cdot}\mathbf{7}^{3+}$, originally present as a mixture of *cis* and *trans* isomers were later reduced by catalytic hydrogenation in EtOH–CH_2Cl_2 (1 : 1) with Pd/C affording $3Cu{\cdot}\mathbf{8}^{3+}$ quantitatively.

The unexpected stability of $3Li{\cdot}(\mathbf{6})_2^{3+}$ as well as the difficulty encountered to exchange the three lithium cations by copper(I) in $3Li{\cdot}\mathbf{7}^{3+}$, both reflect tight, highly entwined molecular structures.

Further evidence for the doubly interlocked topology of $3Cu{\cdot}\mathbf{8}^{3+}$ was obtained after its demetallation (excess KCN in refluxing MeCN) which led quantitatively to the free ligand **9** characterized by very broad and poorly resolved signals of its ^{1}H NMR spectrum : slow restricted molecular motions are clearly related to a topology which implies large mutual crowding between the rings. The FAB-MS of **9** confirms fully our assumption relative to a catenated structure characterized by peaks at *m/z* 2406, corresponding to the ion (**9** + Na^+) and *m/z* 1213.7, 1191.7 corresponding to the ions (**9**/2 + Na^+) and (**9**/2 + H^+), respectively. The two latter signals appear as monocharged species and thus can only originate from the cleavage of one ring followed by fast unthreading of the linear fragment produced.

In conclusion, RCM turned out to be again a surprisingly efficient reaction for preparing interlocking rings such as the present 4-crossing [2]-catenane, converting an exceedingly low yield synthesis, as reported a few years ago,[14] into a preparative procedure. The properties of the new ligand **9** and of its complexes are now under investigation.

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