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Use of Cleavable Coordinating Rings as Protective Groups in the Synthesis of a Rotaxane with an Axis that Incorporates More Chelating Groups Than Threaded Macrocycles

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Abstract: A new methodology allowing preparation of a linear "unsaturated" [3]rotaxane consisting of an axis incorporating more coordination sites than threaded rings was developed. It was based on the preliminary synthesis of a "saturated" [5]rotaxane consisting of a four-chelating site axis threaded through four macrocyclic components, two of them being cleavable rings incorporating a lactone function and the two others being "secure" non-cleavable rings. The stoppering reaction was based on click chemistry. Subsequently, cleavage and removal of the two lactone-containing macrocycles from the [5]rotaxane in basic medium afforded the desired "unsaturated" [3]rotaxane in quantitative yield.

Keywords: click chemistry · copper · molecular machine · protecting groups · rotaxanes

Introduction

Catenanes and rotaxanes have fascinated chemists for decades,[1] although these species were more laboratory curiosities or discussion objects than chemical species prepared at a macroscopic scale until strategies based on templates were introduced.[2] In the course of the last three decades, the complexity of the molecules prepared has gradually increased either in terms of topology or in relation to their function. One of the most spectacular examples is certainly the Borromean rings,[3] prepared at the molecular level by Stoddart and co-workers in 2004. As far as rotaxanes are concerned, although they are, strictly speaking, topologically planar, these compounds have always been associated to catenanes and are thus, most of the time, considered as topologically interesting compounds. From the simple [2]rotaxane, consisting of a ring threaded by an axis (i.e., a dumbbell, that is, when voluminous groups have been attached at the axis extremities), several groups have focused their effort on the synthesis of multi-rotaxanes consisting of more than two organic components.[4] Multi-rotaxanes can thus be divided into two families: 1) several threads pass through the same ring or 2) several rings are threaded by a single string-like molecular component. The combination of points (1) and (2), namely several rings threaded by several filaments, has only been reported once by Leigh, Winpenny, and co-workers with hybrid organic/inorganic rotaxanes.[5] Cyclodextrins have been used to generate linear multi-rotaxanes of the second type, most of the time as polymers or oligomers.[6] Recently, the record for a single rotaxane of the second category was reported by Belowich and co-workers who could isolate a [20]rotaxane.[7] This mechanically interlocked molecule consists of a long thread passing through 19 rings. It was obtained in an amazingly good yield following the "clipping" approach. Threading of several filaments through the same ring is less common and mostly restricted to rotaxanes or pseudo-rotaxanes with a large cyclodextrin[8] as cyclic components or to transition metal-based species.[9]

Molecular machine prototypes based on [*n*]rotaxanes containing only one axis and $n-1$ rings are particularly promising.[10] In fact, one of the very first molecular machines based on interlocking ring compounds was a [2]rotaxane, prepared and studied long ago.[11] It was named the "molecular shuttle", a term coined by Stoddart, Kaifer, and co-workers. In this remarkable dynamic system, a single ring (electron acceptor) could either interact with an aromatic amine (donor) or an aromatic ether. Another early molecular machine prototype based on copper(I) and copper(II), named a "swinging catenane",[12] could be set in motion using an electrochemical signal. For both systems, the "molecular shuttle" and the "swinging catenane", the existence of two dramatically different geometries was due to the fact that a ring could interact in a bimodal fashion with the rest of the molecule. The essential feature of a molecular shuttle is simply that there are more functional groups or stations in the rotaxane axis than threaded rings. In a sense, the system is thus "unsaturated" since with the same filament of the shuttle, two rings instead of one could be threaded. Therefore, motion is tightly connected to unsaturation: the system can rearrange provided it can occupy two or more states, implying that in the case of transition-metal-based compounds, the number of chelating groups introduced in the axis is

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Supporting information for this article (including labeling and ^{1}H NMR spectra of compounds **5**, **9**, **11**$^+$, **12**$^+$, **13**, **10**, **2**, **1** and HR-MS of compounds **1** and **2**) is available on the WWW under http://dx.doi.org/10.1002/chem.201301717.

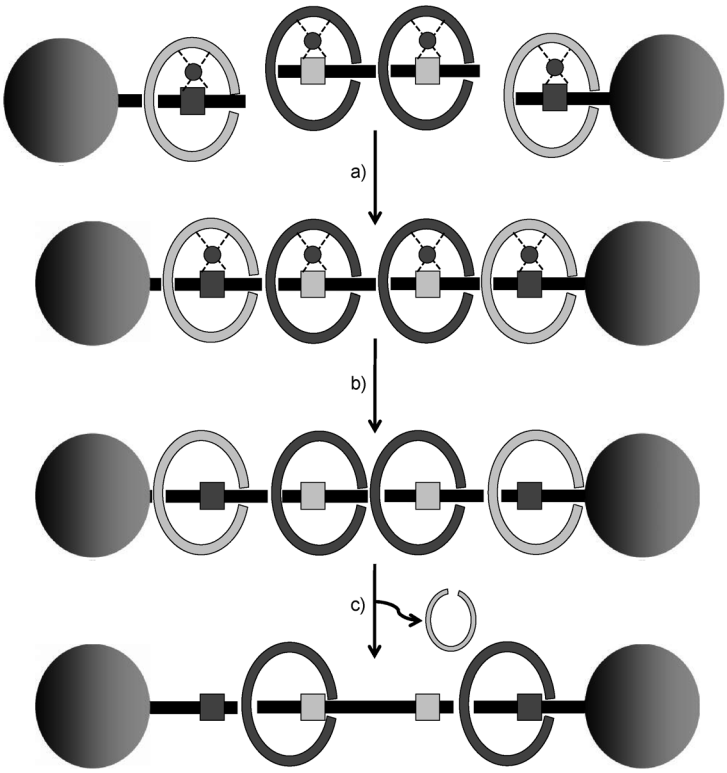
larger than the number of threaded macrocycles. Such rotaxanes open the way to more complex shuttling motions than simple [2]rotaxanes. For example, a [3]rotaxane consisting of two rings threaded by a rod incorporating four chelating groups should enable a double shuttling motion to operate.[13]

Results and Discussion

Design of the system and synthetic strategy: Many catenanes and rotaxanes have been prepared in our group following the traditional copper(I)-directed gathering-and-threading strategy.[14] After formation of the threaded copper(I)-complexed species, attachment of bulky groups at the ends of the filament-like component affords the desired rotaxane or, alternatively, interconnection of these two ends leads to a catenane. To prepare "unsaturated" species, that is, rotaxanes containing both free coordinating sites in the axis and copper-complexed chelating groups, a promising strategy could be to use certain macrocyclic units as "protective groups" vis-à-vis the free coordination sites. An important requirement would be that these protective groups can be cleaved when liberation of the coordinating site is needed to create the unsaturation. This approach presents the obvious advantage that the final stoppering reaction would be performed on a pseudo-rotaxane that has no free coordination sites. The reaction of choice for stoppering pseudo-rotaxanes is certainly the copper-catalyzed azide–alkyne cycloaddition (CuAAC), also known as the click-chemistry reaction.[15] This methodology turned out to be extremely efficient for making rotaxanes in our group[16] as well as in others.[17] The only weak point of this strategy seems to be the sensitivity of the system to the presence of free chelating groups in the medium and in particular in the pseudo-rotaxane to be stoppered. Indeed, bad stoppering yields have often been obtained in our team when free chelating groups were present, a particularly disappointing case being that of an attempted synthesis of a double molecular shuttle.[13] A promising approach would thus to build a "saturated" rotaxane with as many complexed metal centers as threaded rings, the stoppering reaction being a priori highly favorable due to the absence of free coordination sites. Subsequently, if some of the rings can be cleaved and thus released, the desired unsaturated rotaxane should be obtained. Following this principle, we would now like to report the high-yield synthesis of a [3]rotaxane whose axis incorporates four chelating groups, this axis being threaded through two macrocycles only. The general strategy is depicted in Scheme 1.

The chelating groups of the axis are 2,2′-bipyridine (bipy) analogues and 1,10-phenanthrolines (phen). The target [3]rotaxane **1** is depicted in Figure 1 as well as its precursor, [5]rotaxane **2**.

Preliminary study: *Choice and synthesis of the macrocycle*: To achieve the synthesis of the desired [3]rotaxane **1** using



Scheme 1. a) Synthesis of a saturated copper-complexed [5]rotaxane from a [3]pseudo-rotaxane that will become the central part of the [5]rotaxane and two singly stoppered [2]pseudo-rotaxanes used as peripheral groups; b) Demetalation of the [5]rotaxane; c) Selective cleavage of the two peripheral rings leading to the desired [3]rotaxane with liberation of the coordinating fragments colored in light gray. Note that the light-gray rings can be cleaved in conditions under which the dark-gray rings stay intact. The copper(I) centers are represented by small dark-gray disks. The light-gray and dark-gray squares are the coordinating groups incorporated in the axis. The coordinating functions included in the rings are not represented here.

the strategy depicted in Scheme 1, the first goal was to design and study a new macrocycle, bearing a function that could allow the opening of the macrocycle, after the formation of the rotaxane. We thought that a lactone would be the simplest function that could survive the classical conditions of copper(I)-templated rotaxane formation, that is, 1) "gathering and threading", 2) CuAAC stoppering of the corresponding pseudo-rotaxane and 3) demetalation of the copper-complexed rotaxane using KCN.[18] The desired macrocyclic lactone **5** was obtained by slow addition, in high dilution conditions, of a stoichiometric mixture of dibromide **4**[19] and diphenol **3** in a DMF suspension of cesium carbonate in 96% yield (Figure 2). This surprisingly high yield could be partly explained by the geometrical complementarity between the two organic fragments to be combined for making the ring.

The ability of lactone **5** to resist the relatively harsh demetalation conditions required for making metal-free [3]rotaxane **1** was tested by dissolving **5** in a concentrated solution (0.1 M) of KCN in a mixture of dichloromethane, acetonitrile and water (3:1:1 respectively). After 24 h of vigorous

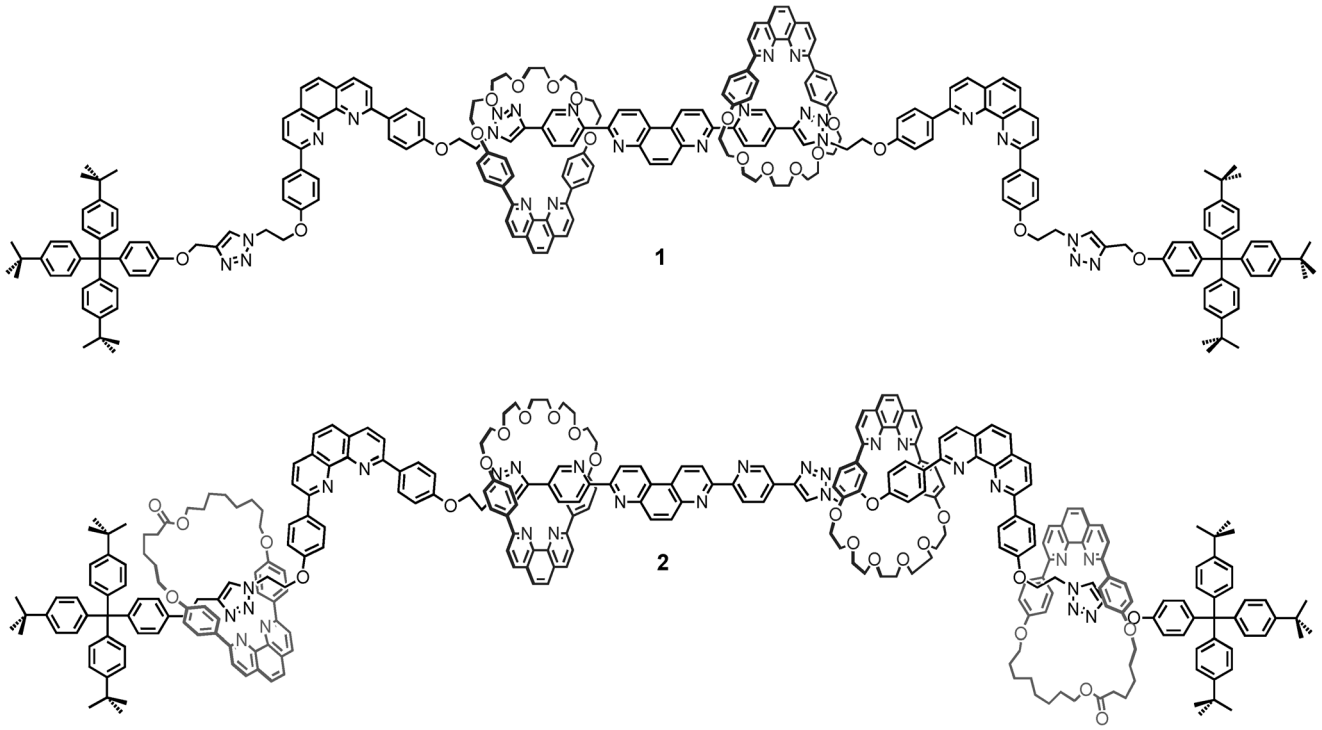


Figure 1. Chemical structure of the target [3]rotaxane **1** and the [5]rotaxane precursor **2**.

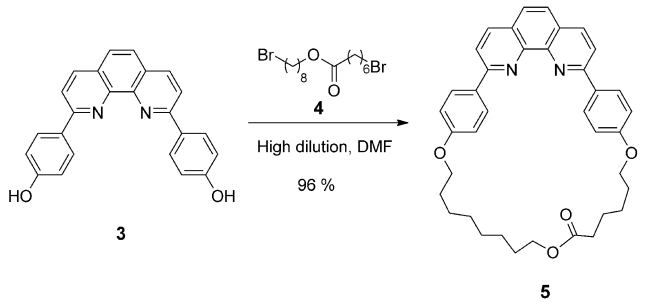


Figure 2. Synthesis of macrocycle **5**.

stirring, the ^{1}H NMR spectrum of the crude compound showed no alteration of the lactone macrocycle **5**.

*A simple model: Metal-free [2]rotaxane **13***: To ascertain the synthesis strategy of Scheme 1, a simple [2]rotaxane **13**, depicted in Figure 4, was prepared by using the key precursor $\mathbf{11}^+$ prepared from **9** (Figure 3). This precursor is common to the synthesis of [2]rotaxane **13** and to the reaction sequence leading to the target [3]rotaxane **1**. Precursor $\mathbf{11}^+$, which contains the lactonic ring **5**, is a threaded species used as a stopper for the preparation of **2**.

The phen unit **7**, bearing azide functions at each end, was synthesized according to a procedure previously described by our group,[20] as shown in Figure 3. Since the presence of free coordination sites in the various fragments used in CuAAC reactions is detrimental, leading most of the time to very poor yields, it was decided to mask the coordination site of **7** before performing the click chemistry. Click chemistry between the copper complex of **7**, namely $[Cu(\mathbf{7})_2^+][PF_6^-]$, generated in situ, and the stopper precursor **8**,[21] afforded asymmetrical phen **9**, bearing one azide and one bulky group, in 67% yield with respect to **8**. As expected, this reaction also afforded small amounts of dumbbell **10** and of the non-reacted phen **7**, which could be recovered (Figure 3). The CuAAC reaction was carried out in the presence of an excess of $[Cu(CH_3CN)_4][PF_6]$, since a significant proportion of copper(I) was consumed for complexing **7** (formation of complex $[Cu(\mathbf{7})_2^+]$). A large excess of KCN was subsequently used to remove the excess of copper(I) and to demetalate the various Cu^I complexes. The metal-free phenanthrolines, that is, the asymmetrical phen **9** and the dumbbell **10**, were thus obtained.

The ability of the macrocyclic lactone **5** to act as a protective group for coordinating fragments incorporated in a rotaxane axis was tested on a simple [2]rotaxane, as shown in Figure 4. The "gathering and threading" reaction between the copper complex of the 31-membered ring **5** and the asymmetrical phen unit **9** led quantitatively to the expected [2]semirotaxane $\mathbf{11}^+$ as confirmed by ^{1}H NMR spectroscopy (1D, COSY, NOESY) as well as by electrospray mass spectrometry (ES-MS). The simplest model, namely [2]rotaxane **13** containing the cleavable ring **5** was then synthesized. The singly stoppered copper(I)-[2]semirotaxane $\mathbf{11}^+$ was subjected to CuAAC stoppering in the presence of the bulky propargyl stopper **8** to give the corresponding copper(I)-[2]rotaxane $\mathbf{12}^+$ in 83% yield. It was then subjected to demetalation to quantitatively yield the free [2]rotaxane **13**. Both rotaxanes $\mathbf{12}^+$ and **13** were fully characterized by ^{1}H NMR

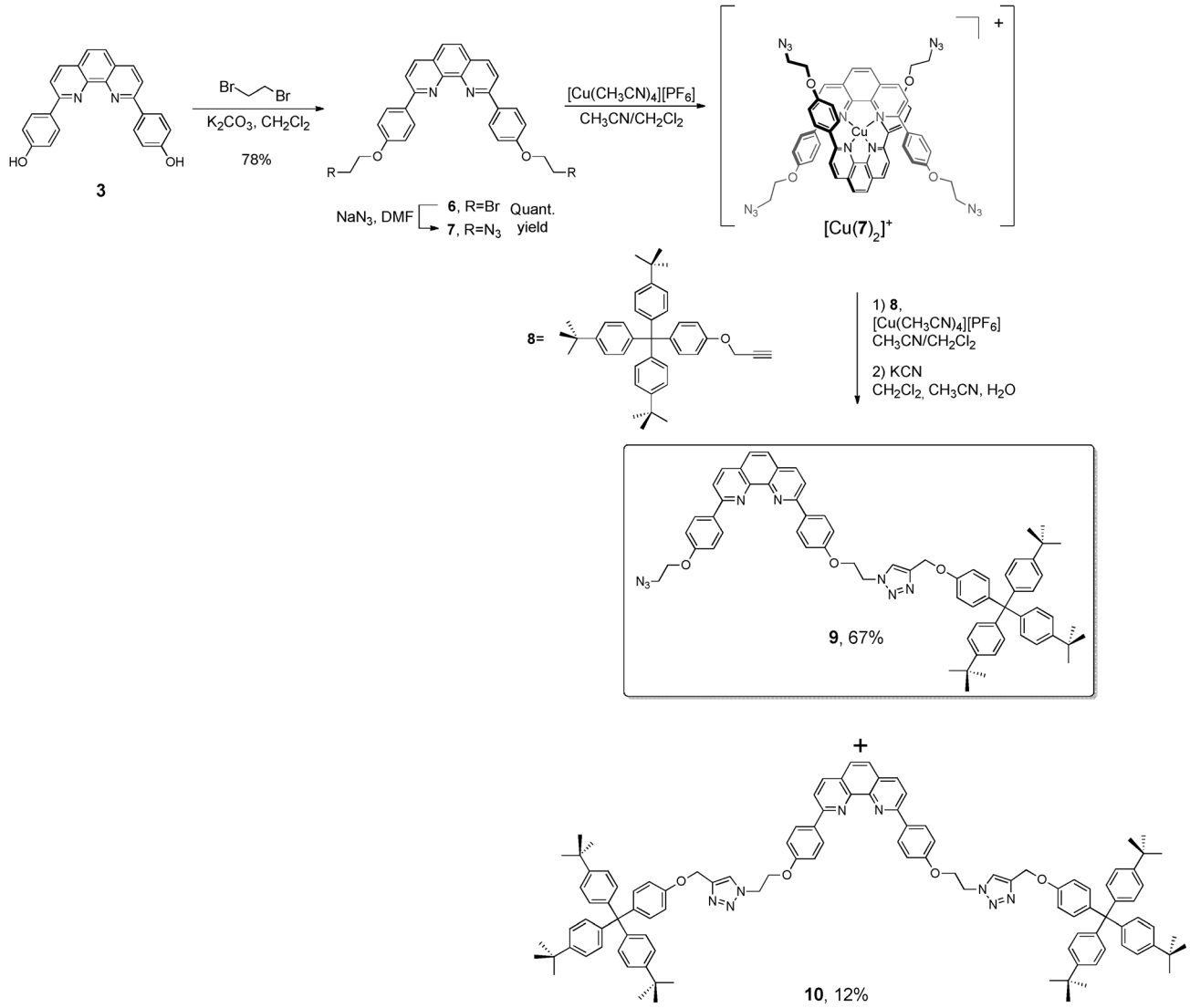


Figure 3. Synthesis of asymmetrical phen **9**. In the click reaction leading to **9** and **10**, the phenanthroline groups are protected by copper(I). Using an excess of copper(I) leads first to an "entwined" complex with two molecules of **7** complexed to the metal center. After formation of the triazole(s), it is necessary to demetalate. As usual, due to its propensity to bind copper(I) generating insoluble cyanide complexes, KCN turned out to be a particularly efficient and convenient reagent, liberating the free ligands **9** and **10**.

spectroscopy (1D, COSY, NOESY) as well as by mass spectrometry (ES-MS). It is particularly noteworthy that the demetalation process did not give rise to any decomposition of the rotaxane by ring opening of the lactone, for instance.

Finally the key step of our strategy, namely opening of the macrocyclic lactone, was tested on this rotaxane (Figure 4). For this purpose, 5 equivalents of KOH in MeOH were added to a solution of [2]rotaxane **13** and stirred for 4 h at room temperature. After separation of the saponification product obtained as an insoluble solid, the filtrate was pumped off to afford quantitatively free dumbbell **10** (Figure 4). Compound **10** was characterized by ^{1}H NMR spectroscopy (1D, COSY, NOESY) as well as by mass spectrometry (ES-MS). The ^{1}H NMR spectrum of this compound exactly matches the one of the byproduct obtained in the synthesis of the asymmetrical phen **9** (Figure 3).

Synthesis and study of the [5]rotaxane: The sequence of reactions leading first to a [5]rotaxane incorporating complexed coordination sites only and, subsequently, to the desired [3]rotaxane with an unsaturated set of coordination sites in its axis (complexed and free coordination sites) are depicted in Figure 5. As already pointed out, the use of unprotected coordination fragments in the synthesis of multi-rotaxanes turned out to be inefficient. In particular, treatment of $\mathbf{16}^{2+}$ and **9** under usual click-chemistry conditions did not afford the desired compound **1** after demetalation, but an inseparable mixture of multi-rotaxane. This observation tends to justify the use of cleavable rings in the construction of multi-rotaxane **1** as detailed below.

The synthesis of a linear [5]rotaxane has recently been described by our group.[22] This compound is one of the few examples of linear [5]rotaxanes. In addition, there are only

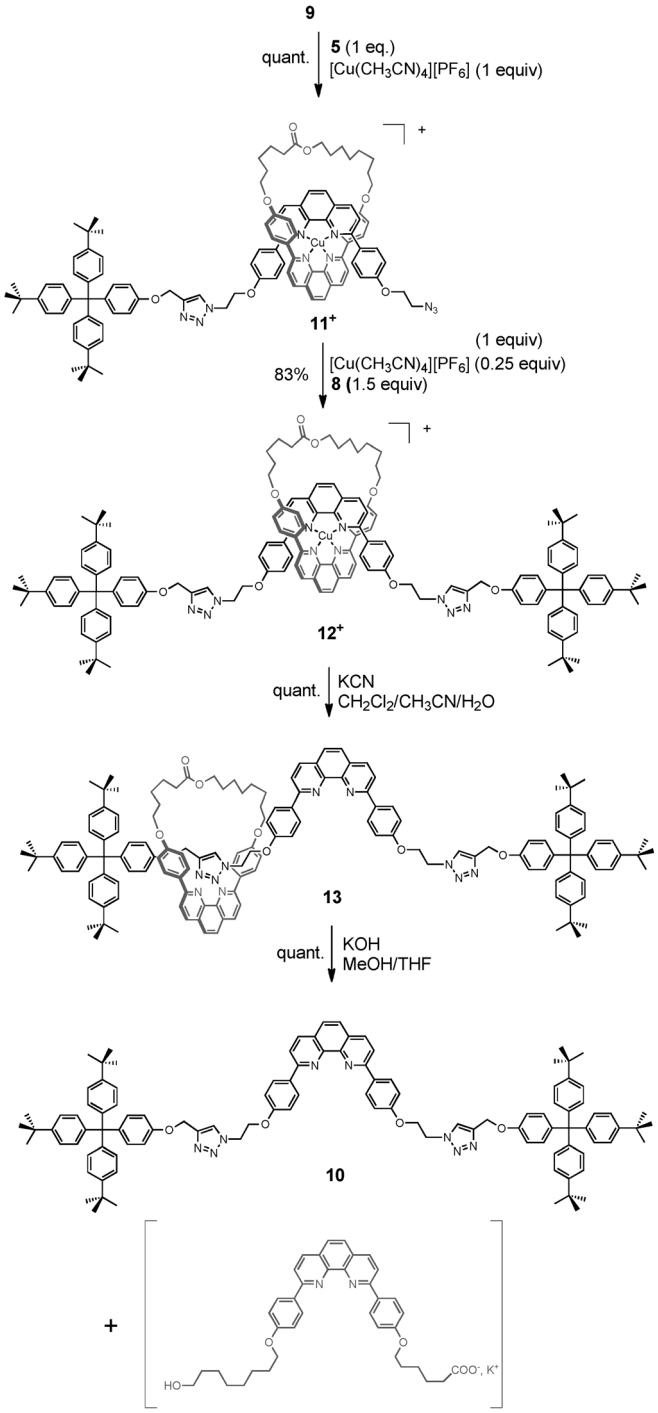


Figure 4. Synthesis of rotaxanes $\mathbf{12}^{+}$ and **13**; opening of the lactone to release free dumbbell **10**. The saponification product (bottom line) was obtained as a highly insoluble K^{+} salt.

few examples of rotaxanes with different rings threaded by the axis[23] and, among them, no example of [5]rotaxane has been reported. The synthesis of **2**, containing two types of threaded macrocycles, was carried out following the strategy implemented in our group for the synthesis of rotaxanes incorporating identical rings. The classical CuAAC reaction was performed in the presence of the above described singly-stoppered pseudo-rotaxane $\mathbf{11}^{+}$ used as a stopper.

The symmetrical copper(I)-[3]pseudo-rotaxane $\mathbf{16}^{2+}$, represented in Figure 5, was synthesized quantitatively from the bis(bidentate) chelate **14**, two equivalents of macrocycle **15**,[2a] and two copper(I) ions according to a previously published procedure.[24] The dinuclear complex $\mathbf{16}^{2+}$ and the singly-stoppered pseudo-rotaxane $\mathbf{11}^{+}$ were then mixed in a 1:2 ratio with catalyst [Cu(tren′)]Br,[25,26] whose structure is indicated in Figure 6, in a mixture of dichloromethane and acetonitrile. After demetalation by KCN, [5]rotaxane **2** was obtained in 61% yield.

[5]rotaxane **2** was characterized by using ^{1}H NMR spectroscopy (1D, COSY, NOESY) as well as mass spectrometry (ES-MS). The number of signals obtained in the ^{1}H NMR spectrum and their easy assignments attested to the high symmetry of the molecule and clearly indicates that the macrocycles are not randomly positioned along the axis but well-ordered, with two identical macrocycles at the external positions and the two others at the internal position, as shown in Figure 5. Although rotaxanes with different rings threaded by the axis have already been synthesized in the past by other groups,[23] [5]rotaxanes consisting of one axis and two pairs of threaded rings were so far unknown.

Rotaxane **2** was then subjected to a saponification-based ring-opening reaction leading to the target [3]rotaxane **1** in quantitative yield. This rotaxane was characterized by ES-MS (see the Supporting Information) and ^{1}H NMR spectroscopy (1D, COSY, NOESY). After removal of the two lactone macrocycles from [5]rotaxane **2**, [3]rotaxane **1** was obtained in quantitative yield as a symmetrical species according to ^{1}H NMR spectroscopic measurements. Slight downfield shifts were observed for some of the protons belonging to the 30-membered rings, as shown in Figure 7. In particular, going from **2** to **1** led to a downfield shift of $\delta = 0.12$ to 0.24 ppm for H-4, H-3, H-5 and H-m. This observation is in line with the number of aromatic fragments in the vicinity of the protons in question. Whereas a slight ring current effect of the lactonic rings onto the chemical shifts of these protons can be expected in **2**, after removal of these rings, the same protons in **1** are less exposed to ring current effects and thus resonate at lower field.

Conclusion

A [3]rotaxane incorporating two macrocycles and one axis incorporating four chelating units was synthesized in good yield according to a new methodology based on cleavable rings as protecting groups. A [5]rotaxane containing two cleavable and two inert rings threaded by the axis was used as precursor. As far as we are aware, the use of cleavable rings as protective groups had never been explored for making linear multi-rotaxanes. The behavior of the [3]rotaxane upon complexation of transition metals is currently under investigation. This methodology paves the way to the synthesis of new molecular machines based on linear rotaxanes such as multimodal molecular shuttles.

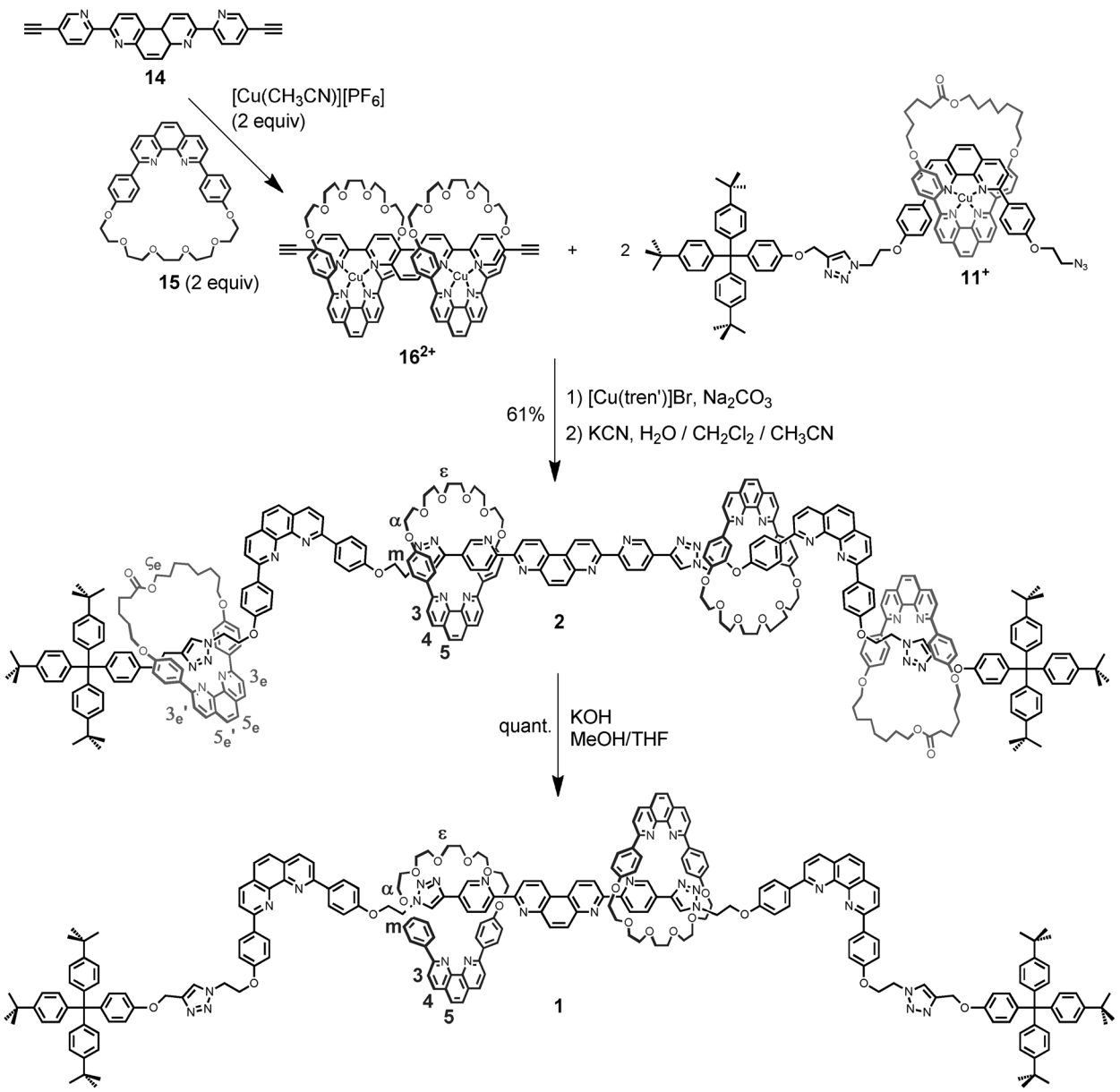


Figure 5. Synthesis of coordinatively saturated [5]rotaxane **2** and its subsequent conversion to the target [3]rotaxane **1** by cleavage of the macrocyclic protective groups.

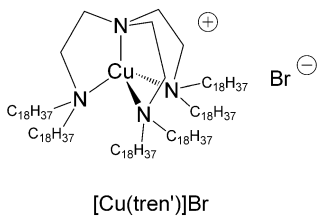


Figure 6. Chemical structure of the catalyst [Cu(tren′)]Br.

Experimental Section

General methods: Dry CH_2Cl_2 was distilled from CaH_2 as the drying agent and dry CH_3CN was purchased from Aldrich. Preparative column chromatography was carried out using silica gel (Merck Kieselgel, silica gel 60, 0.063–0.200 mm).

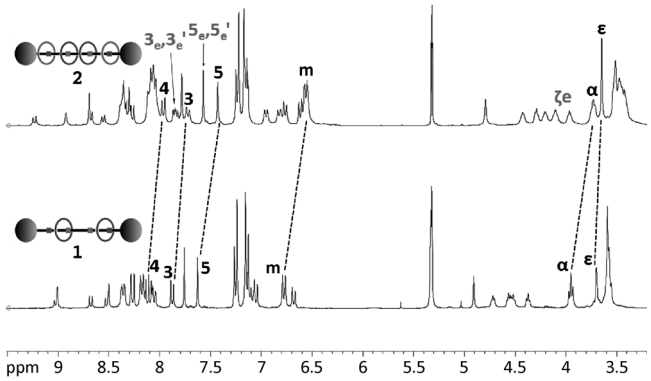


Figure 7. Partial ^{1}H NMR spectra with selected representative protons of rotaxanes **1** and **2** highlighting the preservation of polyether macrocycles **15** and the disappearance of lactone macrocycles **5** between rotaxanes **2** and **1**. The atom numbering is shown in Figure 5.

NMR spectra were acquired on Bruker AVANCE 300 spectrometers. The spectra were referenced to residual proton-solvent references (^{1}H, CD_2Cl_2 at $\delta = 5.32$ ppm, $CDCl_3$ at $\delta = 7.26$ ppm). In the assignments, the chemical shift (in ppm) is given first, followed, in brackets, by the multiplicity of the signal (s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet), the value of the coupling constants in Hz if applicable, the number of protons implied, and finally the assignment. Mass spectra were obtained by using a Bruker MicroTOF spectrometer (ES-MS).

Macrocycle 5: A solution of 2,9-di(*p*-phenol)-1,10-phenanthroline **3** (0.348 g, 0.956 mmol) and 5-bromopentyl-11-bromoundecanoate **4** in DMF (50 mL) was added over 24 h to a suspension of Cs_2CO_3 (1 g, 3.069 mmol) in DMF and the solution was stirred 72 h at 60 °C. The color of the solution turned from yellow to colorless. DMF was removed under vacuum and the residue was taken up in H_2O/CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), the organic phases were combined, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2 to give the desired product **5** as a white powder (540 mg, 0.918 mmol, 96% yield). ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 1.33–1.79 (m, 14H, H-γe, H-ζe), 1.84–1.95 (m, 4H, H-βe, H-ηe), 2.36 (d, J = 7.4 Hz, 2H, H-εe), 4.06–4.18 (m, 6H, H-αe, H-δe, H-θe), 7.13 (d, J = 8.9 Hz, 4H, H-me, H-me′), 7.77 (s, 2H, H-5e, 5e′), 8.08 (d, J = 8.4 Hz, 2H, H-3e, H-3e′), 8.29 (d, J = 8.4 Hz, 2H, H-4e, H-4e′), 8.40 (d, J = 8.9 Hz, 4H, H-oe, H-oe′) ppm; ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 25.1, 26.2, 26.36, 26.40, 29.0, 29.1, 29.2, 29.4, 30.0, 35.0, 64.0, 68.6, 68.8, 115.4, 119.5, 126.0, 127.9, 129.3, 132.5, 132.6, 137.0, 146.4, 156.4, 160.8, 173.9 ppm; MS (ESI): *m/z* (%) calcd for $[(C_{38}H_{40}N_2O_4)Na]^+$: 611.29; found: 611.30 (100) $[M+Na]^+$.

Phenanthroline 9: A solution of compound **7** (960 mg, 1.911 mmol), sodium ascorbate (56 mg, 0.282 mmol), $[Cu(CH_3CN)_4][PF_6]$ (1.065 g, 2.857 mmol) and Na_2CO_3 (94 mg, 0.886 mmol) in a mixture of CH_2Cl_2 and acetonitrile (30 and 20 mL, respectively) was prepared. The solution immediately turned red, showing the formation of complex $[Cu(\mathbf{7})_2]^+$. A solution of compound **8** (522 mg, 0.955 mmol) in CH_2Cl_2 (20 mL) was added to this solution over 1 h and the solution was stirred 72 h at room temperature. Solvents were removed under vacuum. The residue is taking up in a mixture of $CH_2Cl_2/CH_3CN/H_2O$ (2, 1, and 0.25 mL respectively), KCN (1.9 g, 29.177 mmol) was added in one portion and the mixture was stirred for 5 h. Water (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The organic phases were combined and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with a mixture of CH_2Cl_2 and MeOH (99.5:0.5 to 97:3) to give the desired product **9** as a pale-yellow powder (669 mg, 0.640 mmol, 67% yield), the dumbbell **10** (182 mg, 0.115 mmol, 12% yield) and unreacted compound **7** (528 mg, 1.05 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.30 (s, 27H, H-a), 3.66 (t, J = 5.0 Hz, 2H, H-k), 4.28 (t, J = 5.0 Hz, 2H, H-j), 4.51 (t, J = 5.0 Hz, 2H, H-i), 4.83 (t, J = 5.0 Hz, 2H, H-h), 5.17 (s, 2H, H-f), 6.91 (d, J = 8.9 Hz, 2H, H-e), 7.10–7.20 (m, 12H, H-c, H-d, H-m, H-m′), 7.27 (d, J = 8.6 Hz, 6H, H-b), 7.78 (s, 2H, H-5, H-6), 7.89 (s, 1H, H-g), 8.08 (d, J = 8.5 Hz, 1H, H-3), 8.12 (d, J = 8.5 Hz, 1H, H-8), 8.29 (d, J = 8.5 Hz, 1H, H-4), 8.31 (d, J = 8.5 Hz, 1H, H-7), 8.41 (d, J = 6.5 Hz, 2H, H-o), 8.43 (d, J = 6.6 Hz, 2H, H-o′) ppm; MS (ES): *m/z* (%) calcd for $[C_{68}H_{68}N_8O_3H]^+$: 1045.55; found: 1045.55 (100) $[M+H]^+$.

Pseudo-rotaxane 11$^+$: Macrocycle **5** (18.4 mg, 0.0252 mmol) and $[Cu(CH_3CN)_4][PF_6]$ (12.1 mg, 0.0252 mol) were dissolved in degassed CH_2Cl_2 (2 mL) and degassed CH_3CN (1 mL). A solution of **9** (14.3 mg, 0.0252 mmol) in degassed CH_2Cl_2 (2 mL) was subsequently added to this solution through a canula. The resulting solution was stirred 1 h, and the solvents were then evaporated to give, without any further purification, the corresponding [2]pseudo-rotaxane **11$^+$** in quantitative yield (42.7 mg, 0.0252 mmol) according to the ^{1}H NMR spectrum. ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 1.29 (s, 27H, H-a), 1.29–1.82 (m, 14H, H-γe, H-ζe, H-ηe or H-βe), 1.84–1.94 (m, 2H, H-ηe or H-βe), 2.52 (t, J = 7.5 Hz, 2H, H-εe), 3.35–3.50 (m, 6H, H-k, H-αe, H-θe), 3.70 (t, J = 4.5 Hz, 2H, H-j), 3.91 (t, J = 4.2 Hz, 2H, H-i), 4.34 (t, J = 6.5 Hz, 2H, H-δe), 4.70 (t, J = 4.2 Hz, 2H, H-h), 5.27 (s, 2H, H-f), 5.97 (d, J = 8.7 Hz, 2H, H-m″), 5.97–6.05 (m, 4H, H-m), 6.12 (t, J = 8.7 Hz, 2H, H-m′), 6.95 (d, J = 8.7 Hz, 2H, H-e), 7.15 (d, J = 8.6 Hz, 6H, H-c), 7.20 (d, J = 8.7 Hz, 2H, H-d), 7.25 (d, J = 8.6 Hz, 6H, H-b), 7.35 (d, J = 8.7 Hz, 2H, H-o′), 7.41–7.44 (m, 4H, H-o), 7.57 (d, J = 8.7 Hz, 2H, H-o″), 7.79 (d, J = 8.1 Hz, 1H, H-3′), 7.82 (d, J = 8.1 Hz, 1H, H-3e or H-3e′), 7.86 (d, J = 8.3 Hz, 1H, H-3e or H-3e′), 7.92 (d, J = 8.3 Hz, 1H, H-3″), 7.93 (s, 1H, H-g), 7.94 (s, 2H, H-5e, H-5e′), 7.99 (s, 2H, H-5′, H-5″), 8.40 (d, J = 8.1 Hz, 1H, H-4′), 8.41 (d, J = 8.3 Hz, 1H, H-4e or H-4e′), 8.45 (d, J = 8.1 Hz, 1H, H-4e or H-4e′), 8.48 (d, J = 8.3 Hz, 1H, H-4″) ppm; MS (ES): *m/z* (%) calcd for $[C_{106}H_{108}CuN_{10}O_7]^+$: 1695.77; found: 1695.81 (100) $[M-PF_6]^+$

Rotaxane 12$^+$: A solution of pseudo-rotaxane **11$^+$** (24.7 mg, 0.0134 mmol), compound **8** (11 mg, 0.0207 mmol), $[Cu(CH_3CN)_4][PF_6]$ (1 mg, 2.68 μmol), Na_2CO_3 (0.4 mg, 2.68 μmol), and sodium ascorbate (1.4 mg, 6.7 μmol) in a mixture of degassed CH_2Cl_2 (2 mL) and degassed CH_3CN (1 mL) was stirred overnight. Solvents were removed under vacuum and the residue was purified by flash column chromatography on silica gel eluting with a mixture of CH_2Cl_2 and MeOH (99.5:0.5 to 98:2) to give the desired product rotaxane **12$^+$** as a red solid (26.5 mg, 0.0111 mmol, 83% yield). ^{1}H NMR (300 MHz, CD_2Cl_2) δ = 1.26 (s, 54H, H-a), 1.29–1.76 (m, 14H, H-γe, H-ζe), 1.67–1.76 (m, 2H, H-ηe or H-βe), 1.85–1.92 (m, 2H, H-ηe or H-βe), 2.50 (t, J = 7.6 Hz, 2H, H-εe), 3.34–3.44 (m, 4H, H-αe, H-θe), 3.84 (t, J = 4.6 Hz, 4H, H-i), 4.32 (t, J = 6.4 Hz, 2H, H-δe), 4.64 (t, J = 4.6 Hz, 4H, H-h), 5.23 (s, 4H, H-f), 5.93 (d, J = 8.6 Hz, 2H, H-m or H-m′), 5.97 (d, J = 8.6 Hz, 2H, H-m or H-m′), 6.01 (d, J = 8.6 Hz, 4H, H-m″), 6.93 (d, J = 8.9 Hz, 4H, H-e), 7.13 (d, J = 8.5 Hz, 12H, H-c), 7.18 (d, J = 8.9 Hz, 4H, H-d), 7.23 (d, J = 8.5 Hz, 12H, H-b), 7.30 (d, J = 8.6 Hz, 2H, H-o or H-o′), 7.38 (d, J = 8.6 Hz, 2H, H-o or H-o′), 7.45 (d, J = 8.6 Hz, 4H, H-o″), 7.79 (d, J = 8.1 Hz, 1H, H-3′), 7.72 (d, J = 8.1 Hz, 1H, H-3e or H-3e′), 7.75 (d, J = 8.3 Hz, 1H, H-3e or H-3e′), 7.83–7.88 (m, 6H, H-5e, H-5e′, H-g, H-3″) 7.97 (s, 2H, H-5′), 8.30 (d, J = 8.3 Hz, 1H, H-4e or H-4e′), 8.31 (d, J = 8.3 Hz, 1H, H-4e or H-4e′), 8.44 (d, J = 8.3 Hz, 2H, H-4′) ppm.

Rotaxane 13: KCN was added in one portion (13.1 mg, 0.2 mmol) to a solution of rotaxane **12$^+$** (26 mg, 0.0109 mmol) in a mixture of $CH_2Cl_2/CH_3CN/H_2O$ (1, 0.5 and 0.1 mL respectively) and the solution was stirred for 2 h. Water (5 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic phases were combined and concentrated under vacuum to give, without further purification, the desired rotaxane **13** as a pale-yellow solid (23.7 mg, 0.0109 mmol, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.28 (s, 54H, H-a), 1.30–2.10 (m, 18H, H-γe, H-ζe, H-ηe, H-βe), 2.26 (t, J = 7.5 Hz, 2H, H-εe), 3.70–3.79 (m, 4H, H-αe, H-θe), 4.11 (t, J = 6.3 Hz, 2H, H-δe), 4.16–4.22 (m, 4H, H-i), 4.46 (t, J = 5.1 Hz, 2H, H-h), 4.96 (s, 4H, H-f), 6.74–6.85 (m, 8H, H-me, H-me′, H-m′), 6.95 (d, J = 8.8 Hz, 4H, H-e), 7.12–7.19 (m, 16H, H-c, H-d), 7.25 (d, J = 8.8 Hz, 12H, H-b), 7.66 (s, 2H, H-5e, H-5e′), 7.79 (s, 2H, H-5′), 7.93 (d, J = 8.4 Hz, 1H, H-3e or H-3e′), 7.94 (d, J = 8.4 Hz, 1H, H-3e or H-3e′), 8.07 (d, J = 8.5 Hz, 2H, H-3′), 8.15 (d, J = 8.4 Hz, 1H, H-4e or H-4e′), 8.16 (d, J = 8.4 Hz, 1H, H-4e or H-4e′), 8.19 (s, 2H, H-g), 8.21 (d, J = 8.8 Hz, 2H, H-oe or H-oe′), 8.25 (d, J = 8.8 Hz, 2H, H-oe or H-oe′), 8.30 (d, J = 8.4 Hz, 2H, H-4′), 8.35 (d, J = 8.8 Hz, 4H, H-o′) ppm; MS (ES): *m/z* (%) calcd for $[C_{146}H_{154}N_{10}O_8H]^+$: 2177.201; found: 2177.201 (100) $[M+H]^+$.

Dumbbell 10 obtained from 13: A solution of KOH (11.2 mg, 0.2 mmol) in MeOH (0.4 mL) was added to a solution of the rotaxane **13** (23 mg, 0.0105 mmol) in THF/MeOH (1/1, 4 mL) and the solution was stirred 4 h. The solvents were removed under vacuum, the residue taking up in CH_2Cl_2 and filtrate, leaving an insoluble potassium salt of opened macrocycle **5**. The organic layer was concentrated under vacuum to give the title compound as a colorless paste (15.3 mg, 0.0105 mmol, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.31 (s, 54H, H-a), 4.50 (t, J = 5.0 Hz, 2H, H-i), 4.81 (t, J = 5.0 Hz, 2H, H-h), 5.17 (s, 4H, H-f), 6.89 (d, J = 8.9 Hz, 4H, H-e), 7.11 (d, J = 8.8 Hz, 4H, H-d), 7.16–7.20 (m, 16H, H-c, H-m), 7.28 (d, J = 8.5 Hz, 12H, H-b), 7.77 (s, 2H, H-5′), 7.88 (s, 2H, H-g), 8.06 (d, J = 8.5 Hz, 2H, H-3′), 8.28 (d, J = 8.5 Hz, 2H, H-4′), 8.40 (d, J = 8.8 Hz, 4H, H-o′) ppm; ^{13}C NMR (75 MHz, CD_2Cl_2) δ = 31.5, 34.6, 50.2, 62.3, 63.5, 66.9, 113.9, 115.3, 119.8, 124.4, 124.7, 126.2, 128.2, 129.4, 130.9, 132.4, 133.5, 137.2, 140.7, 144.5, 144.8, 146.5, 148.8, 156.1, 156.7, 159.6 ppm; MS (ES): *m/z* (%) calcd for $[C_{108}H_{114}N_8O_4Na]^+$: 1609.89; found: 1609.92 (100) $[M+Na]^+$.

Rotaxane 2: Polyether macrocycle **15** (19.9 mg, 0.035 mmol) and $[Cu(CH_3CN)_4][PF_6]$ (13.1 mg, 0.035 mmol) were stirred in a mixture of degassed dichloromethane (5 mL) and degassed acetonitrile (5 mL) for 30 min. This orange solution was slowly added to a suspension of bis(bidentate) chelate **14** (6.7 mg, 0.018 mmol). The solution immediately turned black and was stirred overnight. Solvents were removed under vacuum to give quantitatively the desired pseudo-rotaxane $\mathbf{16^{2+}}$ as a black solid (33.9 mg). A solution of pseudo-rotaxane $\mathbf{11^{+}}$ (71.1 mg, 0.039 mmol) in a solution of degassed dichloromethane (1 mL) and degassed acetonitrile (0.5 mL) was added to a solution of pseudo-rotaxane $\mathbf{16^{2+}}$ (33.9 g, 0.018 mmol), [Cu(tren′)]Br (31.6 mg, 0.018 mmol), sodium ascorbate (7 mg, 0.035), and Na_2CO_3 (1.7 mg, 0.016 mmol) in a solution of degassed dichloromethane (1 mL) and degassed acetonitrile (0.5 mL) and the solution was stirred for 72 h. Solvents were removed under vacuum to give the crude product as a red solid. KCN was added (in one portion (60 mg, 0.921 mmol)) to a solution of this crude product in a mixture of $CH_2Cl_2/CH_3CN/H_2O$ (0.6, 0.3 and 0.05 mL respectively) and the solution was stirred for 4 h at room temperature until the disappearance of the red color. 5 mL of water was added and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic phases were combined and the residue was carefully purified by flash column chromatography on silica gel eluting with a mixture of CH_2Cl_2 and MeOH (99.5:0.5 to 95:5) to give the desired rotaxane **2** as a pale-yellow solid (51.2 mg, 0.011 mmol, 61% yield). ^{1}H NMR (600 MHz, CD_2Cl_2) δ = 1.13–1.34 (m, 70H, H-a, H-γe, H-ιe), 1.40–1.46 (m, 4H, H-δe), 1.51–1.57 (m, 12H, H-βe, H-θe, H-κe), 1.64–1.70 (m, 4H, H-εe), 2.19–2.30 (m, 4H, H-ηe), 3.41–3.46 (m, 8H, H-β), 3.46–3.50 (m, 8H, H-γ), 3.52–3.58 (m, 16H, H-δ, H-αe, H-λe), 3.66 (brs, 8H, H-ε), 3.71–3.78 (m, 8H, H-α), 3.97–4.01 (m, 4H, H-i), 4.06–4.15 (m, 4H, H-ζe), 4.22–4.28 (m, 4H, H-h), 4.31 (t, J = 5.1 Hz, 4H, H-j), 4.42–4.46 (m, 4H, H-k), 4.87 (s, 4H, H-f), 6.51–6.57 (m, 8-H, H-m), 6.58 (d, J = 8.6 Hz, 4H, H-me or H-me′), 6.64 (d, J = 8.6 Hz, 4H, H-me or H-me′), 6.77–6.84 (m, 8H, H-e, H-m′), 6.93–6.99 (m, 4H, H-m″), 7.13–7.16 (m, 16H, H-c, H-d), 7.23 (d, J = 8.5 Hz, 12H, H-b), 7.46 (s, 4H, H-5), 7.59 (s, 4H, H-5e), 7.73 (d, J = 8.1 Hz, 4H, H-3), 7.76–7.81 (m, 4-H, H-5′, H-5″), 7.84 (d, J = 8.4 Hz, 4H, H-3e or H-3e′), 7.86 (d, J = 8.5 Hz, 4H, H-3e or H-3e′), 7.99 (d, J = 8.1 Hz, 4H, H-4), 8.01–8.13 (m, 28H, H-9, H-3′, H-3″, H-4e, H-4e′, H-g, H-o, H-oe, H-oe′), 8.24 (s, 2H, H-11), 8.27 (d, J = 8.5 Hz, 4H, H-4′ or H-4″), 8.30 (d, J = 8.4 Hz, 4H, H-4′ or H-4″), 8.32–8.39 (m, 8H, H-o′, H-o″), 8.58 (d, J = 8.2 Hz, 2H, H-8), 8.70 (d, J = 8.9 Hz, 2H, H-7), 8.72 (s, 2H, H-l), 8.97 (brs, 2H, H-10), 9.23 (d, J = 8.9 Hz, 2H, H-6) ppm; MS (ES): *m/z* (%) calcd for $[C_{306}H_{298}N_{28}O_{26}H_3]^{3+}$: 1595.439; found: 1595.379 (100) $[M+3H]^{3+}$.

Rotaxane 1: A solution of KOH (20.2 mg, 0.36 mmol) in MeOH (1 mL) was added to a solution of rotaxane **2** (43 mg, 9 μmol) in THF (5 mL) and the solution was stirred for 4 h. The solvents were removed under vacuum and the residue taken up in CH_2Cl_2. The organic layer was concentrated under vacuum to give the title compound as a colorless paste (32.5 mg, 9 μmol, 100% yield). ^{1}H NMR (600 MHz, CD_2Cl_2) δ = 1.29 (s, 54H, H-a), 3.55–3.62 (m, 24H, H-γ, H-δ, H-ε), 3.67–3.74 (m, 8H, H-β), 3.95 (t, J = 6.3 Hz, 8H, H-α), 4.37 (t, J = 5.3 Hz, 4H, H-i), 4.52 (t, J = 5.3 Hz, 4H, H-j), 4.56 (t, J = 5.3 Hz, 4H, H-h), 4.72 (t, J = 5.3 Hz, 4H, H-k), 4.91 (s, 4H, H-f), 6.69 (d, J = 8.9 Hz, 4H, H-e), 6.78 (d, J = 8.1 Hz, 8H, H-m), 7.06 (d, J = 8.9 Hz, 4H, H-d), 7.08 (d, J = 8.2 Hz, 4H, H-m″), 7.13–7.16 (m, 16H, H-c, H-m′), 7.25 (d, J = 8.6 Hz, 12H, H-b), 7.63 (s, 4H, H-5), 7.76 (s, 4H, H-5′, H-5″), 7.88 (d, J = 8.3 Hz, 4H, H-3), 8.05 (d, J = 8.4 Hz, 2H, H-3′ or H-3″), 8.06 (d, J = 8.4 Hz, 2H, H-3′ or H-3″), 8.08 (s, 2H, H-g), 8.12 (d, J = 8.3 Hz, 4H, H-4), 8.15–8.21 (m, 10H, H-o, H-9), 8.26 (d, J = 8.4 Hz, 4H, H-4′, H-4″), 8.29 (s, 2H, H-11), 8.33–8.39 (m, 8H, H-o′, H-o″), 8.50 (s, 2H, H-l), 8.52 (d, J = 8.3 Hz, 2H, H-8), 8.68 (d, J = 8.6 Hz, 2H, H-7), 9.01, (s, 2H, H-10), 9.02 (d, J = 9.0 Hz, 2H, H-6) ppm; MS (ES): *m/z* (%) calcd for $[C_{230}H_{218}N_{24}O_{18}H_2]^{2+}$: 1803.85; found: 1803.31 (100) $[M+2H]^{2+}$.

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[26] This catalyst has recently been used in our group for the synthesis of rotaxanes by using click chemistry. For some examples, see ref. [13], [16 f], [20] and [22].

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Rotaxanes

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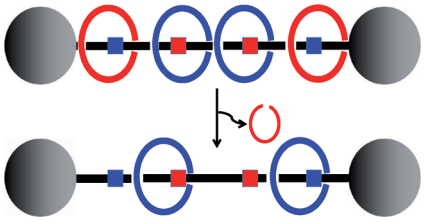
Use of Cleavable Coordinating Rings as Protective Groups in the Synthesis of a Rotaxane with an Axis that Incorporates More Chelating Groups Than Threaded Macrocycles



Securing rotaxanes: A new method of preparing a linear "unsaturated" [3]rotaxane consisting of an axis containing more coordination sites than threaded rings was developed (see figure). It was based on the preliminary synthesis of a "saturated" [5]rotaxane consisting of a four-chelating site axis threaded through four macrocyclic components, with two of them acting as protective groups. Subsequent removal of the protective macrocycles from the [5]rotaxane afforded the desired unsaturated [3]rotaxane in quantitative yield.

