VIP Rotaxane Synthesis

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One Template, Multiple Rings: Controlled Iterative Addition of Macrocycles onto a Single Binding Site Rotaxane Thread**

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Dedicated to Sir J. Fraser Stoddart on the occasion of his 65th birthday

The introduction[1] and subsequent spectacular growth[2–8] of template strategies[2] to molecules with multiple mechanically interlocked components (rotaxanes,[3,4,8] catenanes,[5,6,8] and Borromean rings[7]) has revolutionized approaches to their synthesis. However, despite the many different template systems and innovative assembly processes developed thus far, a feature common to all current methods is that they each employ at least one binding site per macrocycle, that is, a minimum of $n-1$ templates per n interlocked components. Here we describe a strategy (Figure 1) for assembling multi-ring rotaxanes in which just a single ligation site is used to clip on as many macrocycles as required (and the length of the thread will permit), through the repetition of three simple steps. The method (Scheme 1) involves the repetitive coordination and macrocyclization of a tridentate ligand for palladium about a stoppered molecular thread (**L1**), sequentially forming rings of type H_2**L2** to iteratively[8b] generate [2]-, [3]-, and [4]rotaxanes. Overcoming the restriction of only one ring per template unit—especially the ability to re-utilize the template despite the proximity of a previously cyclized component—should aid the synthesis of increasingly complex higher order interlocked assemblies (for example, defined sequences of different rings on a molecular strand).

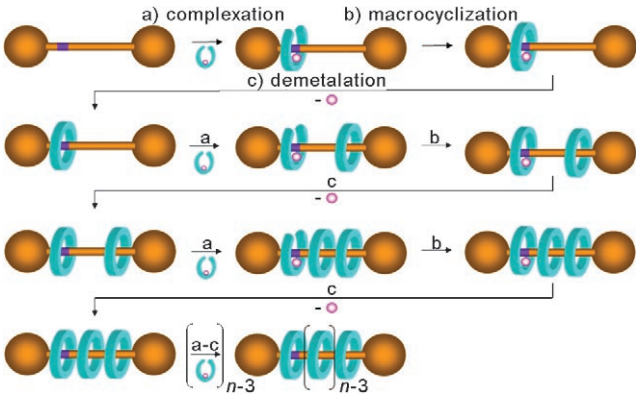

Figure 1. An iterative [*n*]rotaxane synthesis utilizing a single template unit (shown in purple) and the repetition of three simple steps: a) complexation of an acyclic ligand (shown in light blue) to the template site; b) macrocyclization; c) demetalation.

The single template site iterative assembly of multiple ring rotaxanes utilizes a square-planar geometry Pd^{II}-based "clipping" methodology previously developed[9] as a "classical" (that is, one macrocycle per binding site) template synthesis of rotaxanes and catenanes. The metal atom is first bound to a tridentate 2,6-pyridinedicarboxamide ligand (significantly, this involves deprotonation of the ligand amide groups[9]). The resulting complex [**L3**Pd(CH_3CN)][9] is coordinated to a monodentate pyridine unit on a thread such that subsequent macrocyclization by ring-closing metathesis (RCM) occurs around the thread to generate an interlocked architecture.[10] The key to extending this protocol so that further ligands can be cyclized around the template after the first is decomplexed, is the observation that whilst [**L3**Pd(CH_3CN)] will readily exchange its labile coordinated acetonitrile molecule for a pyridine unit (see Scheme 1, step a), it does not undergo tridentate ligand exchange with protonated (that is, metal-free) versions of the 2,6-pyridinedicarboxamide system (for example, H_2**L4** and H_2**L5**; Scheme 1, steps d and g). Thus, a pyridine group on a thread can repetitively be used to replace acetonitrile ligands of [**L3**Pd(CH_3CN)], with the resulting complexes then being macrocyclized one at a time.

To demonstrate the effectiveness of this strategy in a multi-ring rotaxane synthesis, a suitable thread **L1** was prepared (see the Supporting Information) with a single pyridine unit as the only potential template site and sufficient space—provided by a C_{11} alkyl chain—between the stoppers to accommodate several macrocycles. As anticipated, stirring **L1** with [**L3**Pd(CH_3CN)] in dichloromethane resulted in rapid formation of [**L3**Pd**L1**] (92%, Scheme 1, step a). Macrocyclization with the Grubbs first-generation RCM catalyst and subsequent hydrogenation[11] gave the saturated palladium [2]rotaxane [**L4**Pd] (72%, Scheme 1, step b). Treatment with potassium cyanide (Scheme 1, step c) then afforded the metal-free [2]rotaxane H_2**L4** in 62% overall yield for the first iterative cycle.

A comparison of the room-temperature ^{1}H NMR spectrum of H_2**L4** in CD_2Cl_2 (Figure 2c) with that of the free components macrocycle H_2**L2** and thread **L1** (Figure 1a and b, respectively) confirms the interlocked nature of the product. The most significant differences in the spectra are

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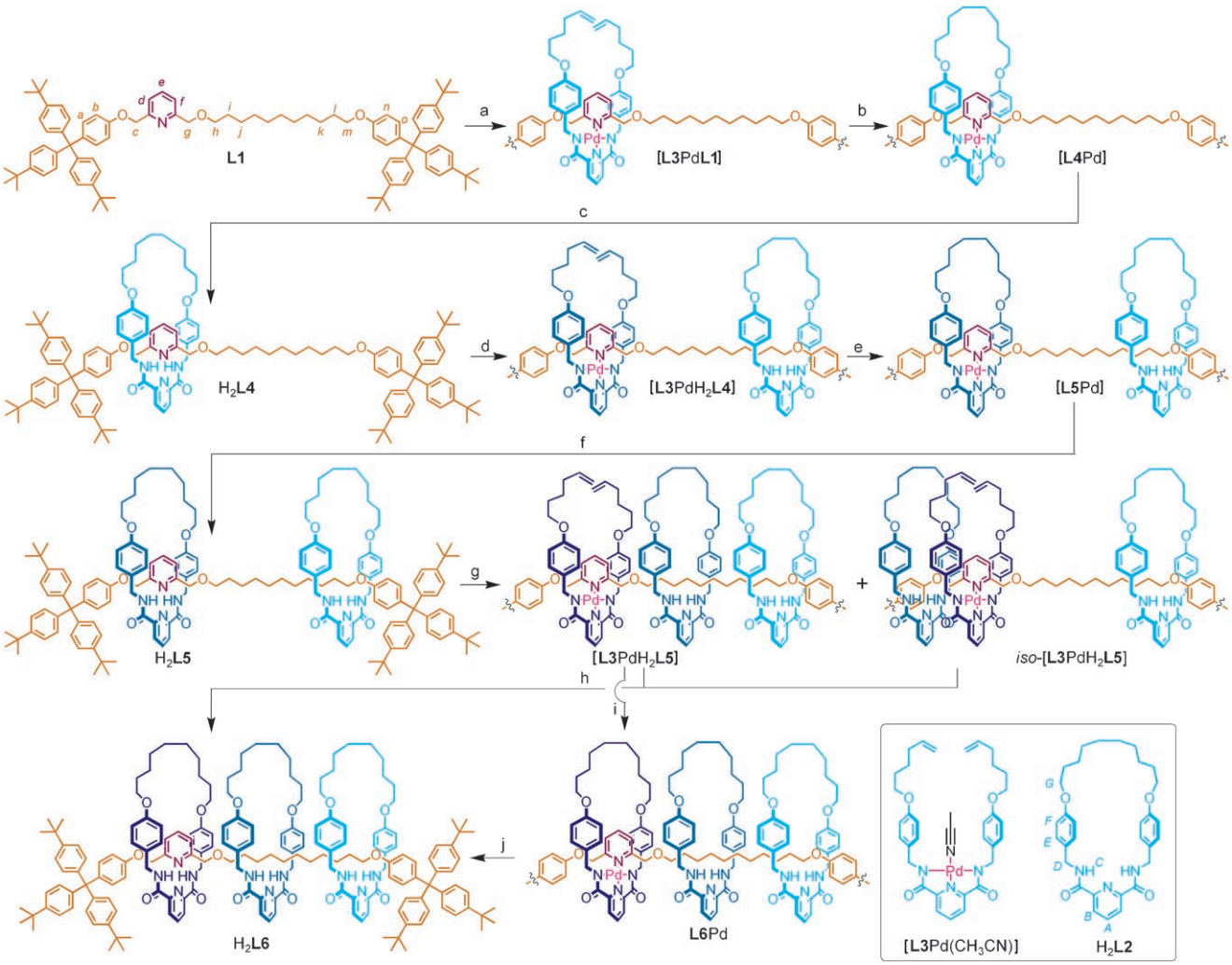

Scheme 1. The controlled iterative synthesis of [2]-, [3]-, and [4]rotaxanes H_2**L4**, H_2**L5**, and H_2**L6**. CPK models confirm that the threaded rings cannot pass through the cavities of each other and so the color of each fragment of a structure reflects its origin in the synthetic sequence. a) [**L3**Pd(CH_3CN)], CH_2Cl_2, 5 h, RT, 92%; b) 1. Grubbs catalyst (0.12 equiv), CH_2Cl_2; 2. *ortho*-nitrobenzenesulfonylhydrazide (NBSH), Et_3N, CH_2Cl_2, 72% (over 2 steps); c) KCN, CH_2Cl_2, MeOH, 94%; d) [**L3**Pd(CH_3CN)], CH_2Cl_2, 5 h, RT, 96%; e) 1. Grubbs catalyst (0.12 equiv), CH_2Cl_2; 2. NBSH, Et_3N, CH_2Cl_2, 84% (over 2 steps); f) KCN, CH_2Cl_2, MeOH, 98%; g) method A: [**L3**Pd(CH_3CN)], CH_2Cl_2, 3 days, RT, [**L3**PdH_2**L5**] 51%, *iso*-[**L3**PdH_2**L5**] 37%. Method B: [**L3**Pd(CH_3CN)] (3 equiv), CH_2Cl_2, Δ, 7 days, [**L3**PdH_2**L5**] 81%, *iso*-[**L3**PdH_2**L5**] 5%; h) 1. Grubbs catalyst (0.12 equiv), CH_2Cl_2; 2. NBSH, Et_3N, CH_2Cl_2; 3. KCN, CH_2Cl_2, MeOH, 70% (over 3 steps) i) 1. Grubbs catalyst (0.12 equiv), CH_2Cl_2; 2. NBSH, Et_3N, CH_2Cl_2, 87% (over 2 steps); j) KCN, CH_2Cl_2, MeOH, 97%.

for the signals of the methylene protons adjacent to the pyridine group of the thread (H_c and H_g), which are shifted, particularly that of H_c, upfield in the spectrum of the [2]rotaxane. The macrocycle phenyl resonances (H_{El} and H_{Fl}) are also shielded in the [2]rotaxane while the amide protons (H_{Cl}) move 1.3 ppm downfield, which is indicative of intercomponent hydrogen bonding with the pyridine unit.[12] However, small upfield shifts in nearly all the axle signals in the rotaxane, including the alkyl region, show that this interaction is rather weak and the macrocycle is able to access the full length of the thread in CD_2Cl_2.

For the second iterative cycle, repetition of the three steps (complexation, macrocyclization, and demetalation, Scheme 1, steps d–f) starting from [2]rotaxane H_2**L4** smoothly afforded [3]rotaxane H_2**L5** in 79% overall yield. The crucial complexation of [**L3**Pd(CH_3CN)] to the free pyridine group of H_2**L4** to give [**L3**PdH_2**L4**] (Scheme 1, step d) proceeds in 96% yield in 5 h with no trace of transmetalation to the rotaxane macrocycle. Comparison of the ^{1}H NMR spectrum of [**L3**PdH_2**L4**] in CD_2Cl_2 (Figure 3b) with that of [**L3**Pd**L1**] (Figure 3a) indicates that the displaced macrocycle in the [2]rotaxane spends a significant amount of time over the ether unit furthest from the Pd coordination sphere (1.2 ppm upfield shift of the methyleneoxy resonance of the thread H_m), presumably at least in part as a result of hydrogen bonding between the amide and oxygen atom of the ether.[13] The ^{1}H NMR spectrum of the demetalated [3]rotaxane H_2**L5** in CD_2Cl_2 is shown in Figure 2d. The occurrence of the amide signals at $\delta = 9.4$ and 8.6 ppm (H_{C2} and H_{Cl}) suggest that the hydrogen-bonding interaction between the amide group and the pyridine ring is appreciably stronger than that between the amide and ether groups.[12,13]

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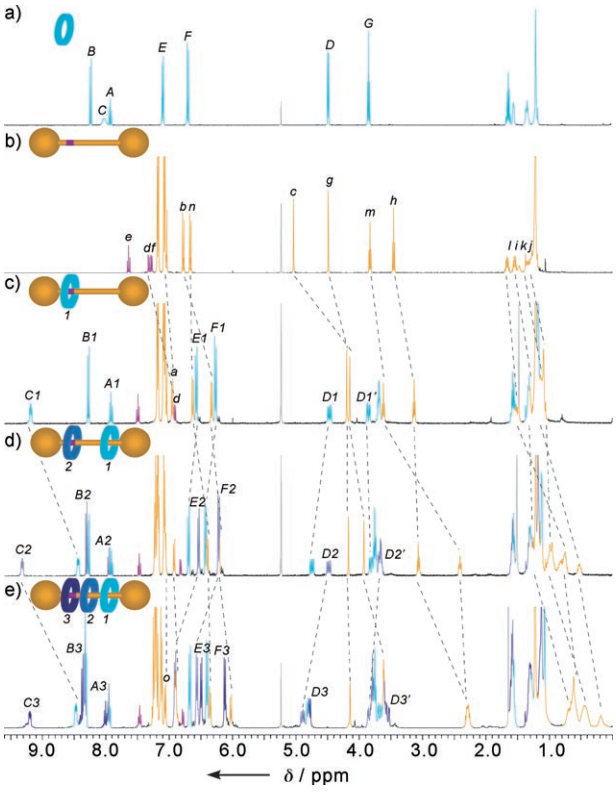

Figure 2. ^{1}H NMR spectra (400 MHz, CD_2Cl_2, 298 K) of the metal-free rotaxanes and their non-interlocked components. a) macrocycle H_2**L2**; b) thread **L1**; c) [2]rotaxane H_2**L4**; d) [3]rotaxane H_2**L5**; e) [4]rotaxane H_2**L6**. The italicized letters and numbers refer to the assignments in Scheme 1 and the component sequences indicated in the schematic representations.

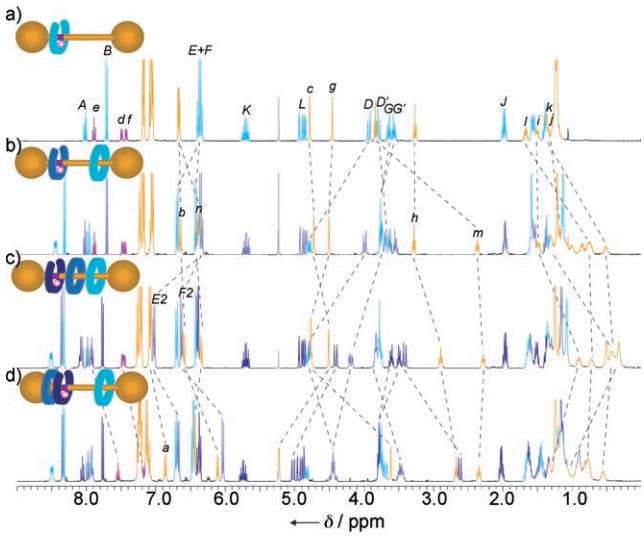

Figure 3. ^{1}H NMR spectra (400 MHz, CD_2Cl_2, 298 K) of the coordination complexes of [**L3**Pd] with the thread, [2]rotaxane, and [3]rotaxane. a) [**L3**Pd**L1**]; b) [**L3**PdH_2**L4**]; c) [**L3**PdH_2**L5**]; d) *iso*-[**L3**PdH_2**L5**]. The italicized letters and numbers refer to the assignments in Scheme 1 and the component sequences indicated in the schematic representations.

The final iterative cycle commenced with the reaction of [3]rotaxane H_2**L5** with [**L3**Pd(CH_3CN)] (Scheme 1, step g, method A). However, the reaction proved extremely sluggish using the conditions previously employed (CH_2Cl_2, 293 K), and after three days the product mixture was separated by column chromatography to give, somewhat unexpectedly, two new kinetically stable products in a ratio of 2:3. Mass spectrometry suggested that the products were isomers of [**L3**PdH_2**L5**] (Scheme 1), in which the two macrocycles are restricted to different regions of the thread by coordination of [**L3**Pd] to the pyridine unit. The major product was assigned by ^{1}H NMR spectroscopy as isomer [**L3**PdH_2**L5**]. Its spectrum (Figure 3c) shows increased shielding of the alkyl region with respect to the similarly derivatized [2]rotaxane [**L3**PdH_2**L4**] (Figure 3b), which suggests that both macrocycles are located over the C_{11} region of the thread. In contrast, the ^{1}H NMR spectrum (Figure 3d) of the minor isomer showed no increase in the shielding of the alkyl region relative to [**L3**PdH_2**L4**]. Rather, significant shifts of the thread methyleneoxy (H_c) and stopper protons H_a and H_e occur, which indicates that this isomer is *iso*-[**L3**PdH_2**L5**], in which the two macrocycles are separated by the coordinated {**L3**Pd} unit.

Whilst the formation of this second isomer appears surprising given the steric demands of the macrocycle and the very limited space available between the pyridine ligation site and the closest bulky stopper, it presumably reflects the fact that an ether oxygen atom is available on that part of the thread to which one of the two amide macrocycles can spend significant time hydrogen bonding. Complexation of [**L3**Pd] to the pyridine unit traps that proportion of macrocycles in that region of the thread and the kinetic stability of the pyridine–palladium bond inhibits equilibration to the less sterically hindered isomer. In agreement with this rationalization, carrying out the reaction at reflux for 7 days (Scheme 1, step g, method B) to induce some reversibility in the formation of the pyridine–palladium bond gave 81% of [**L3**PdH_2**L5**] with only a small amount of the minor isomer.

The final macrocyclization and demetalation steps to give [4]rotaxane H_2**L6** could be carried out on either the single isomer [**L3**PdH_2**L5**] (Scheme 1, steps i and j) or on the mixture of [**L3**PdH_2**L5**]/*iso*-[**L3**PdH_2**L5**] isomers (Scheme 1, step h). The [4]rotaxane obtained from these reactions—in both cases single species—had identical physical properties and indistinguishable ^{1}H NMR spectra (Figure 2e), again supporting the structural assignments of [**L3**PdH_2**L5**] and *iso*-[**L3**PdH_2**L5**]. The ^{1}H NMR spectrum of H_2**L6** in CD_2Cl_2 (Figure 2e) shows three sets of amide signals, and further shielding of both the C_{11} alkyl chain of the thread and in particular the methyleneoxy resonances (H_c, H_g, H_h). The overall yield for the iterative cycle to add the third ring to generate the [4]rotaxane is a pleasing 68% (by way of single isomer [**L3**PdH_2**L5**]).

In conclusion, we have described methodology for preparing multi-ring rotaxanes through the iterative addition of macrocycles to a rotaxane thread bearing a single ligation site. By using this efficient and effective strategy, both the number and the order in which macrocycles are assembled onto a thread can be controlled with unprecedented precision.

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Experimental Section

General procedure for the iterative synthesis of an [*n*]rotaxane from an [*n*−1]rotaxane or thread: a) Complexation: A solution of the metal-free 2,6-disubstituted pyridine ligand (**L1**, H_2**L4**, or H_2**L5**, 0.1–2.0 mmol) and [**L3**Pd(CH_3CN)] (1 equiv for **L1**, H_2**L4**; 3 equiv for H_2**L5**) in anhydrous dichloromethane (30 mL) was stirred for 5 h at room temperature (7 days at reflux for H_2**L5**) under an atmosphere of nitrogen. The mixture was then concentrated under reduced pressure and the crude residue purified by column chromatography to yield the corresponding complex [**L3**Pd**L1**] (92%), [**L3**PdH_2**L4**] (96%), or [**L3**PdH_2**L5**] (81%). b) Macrocyclization: The complex obtained from (a) was dissolved in anhydrous dichloromethane (200 mL for 1 mmol of substrate) and added via a double-ended needle to a solution of the first-generation Grubbs catalyst (0.12 equiv) in anhydrous dichloromethane (850 mL per mmol) under an atmosphere of nitrogen. The solution was stirred at room temperature for 18 h, after which it was concentrated under reduced pressure, and the crude residue subjected to column chromatography to yield the corresponding unsaturated olefin rotaxane–metal complex. This was dissolved in dichloromethane (12 mL for 1 mmol of substrate) and then NBSH (8.0 equiv) and triethylamine (10 equiv) added. The suspension was then stirred overnight. The resultant orange/brown solution was washed with sodium bicarbonate (3 × 75 mL) and the organic layers combined and concentrated to give the saturated rotaxane–metal complex [**L4**Pd] (72% over two steps), [**L5**Pd] (84% over two steps), or **L6**Pd (87% over two steps). c) Demetalation: A solution of the rotaxane–metal complex [**L4**Pd], [**L5**Pd], or [**L6**Pd] (typically 0.1–1.0 mmol) in dichloromethane (50 mL) was added to a solution of potassium cyanide (15 equiv) in methanol (50 mL). The solution was gently heated until it was colorless, and then the overall volume reduced to less than 5 mL. The resultant mixture was dispersed in water (100 mL) and washed with dichloromethane (3 × 50 mL). The combined organic extracts were washed with further water (50 mL) and dried over anhydrous magnesium sulfate. After filtration, the solution was concentrated under reduced pressure to give the demetalated rotaxane (H_2**L4** (94%), H_2**L5** (98%), or H_2**L6** (97%). For full experimental details and compound characterization see the Supporting Information.

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