

Catalytic “Click” Rotaxanes: A Substoichiometric Metal-Template Pathway to Mechanically Interlocked Architectures

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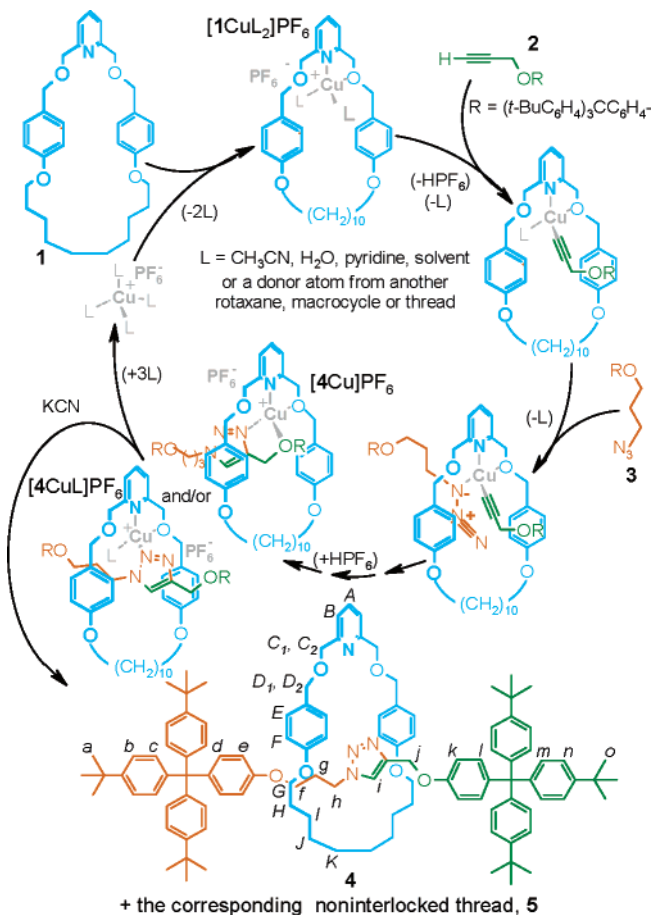
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The introduction of copper(I)-template strategies by Sauvage and colleagues in the mid-1980s marked the first practical synthetic routes to molecular catenanes, rotaxanes, and knots.¹ This seminal idea utilizes the tetrahedral coordination geometry of a Cu(I) atom to hold a pair of bidentate ligands in a mutually orthogonal orientation creating a crossover point that directs subsequent macrocyclization or “stoppering” reactions toward threaded architectures. Other template syntheses followed² (based on aromatic stacking, hydrogen bonding, hydrophobic interactions, etc.), leading to the rich variety of synthetic methods available today. However, all current approaches require a stoichiometric quantity of template and generally call for pre-established, strongly binding, recognition motifs on each of the components of the interlocked molecule. Here we describe a rotaxane-forming protocol in which the Cu(I) atom functions as a catalyst as well as a template and turns over during the reaction, permitting substoichiometric amounts of the metal to be used. A permanent coordination site is only needed on the macrocycle. The rest of the interlocked compound is assembled through functional groups that react together under catalysis of the metal, which also serves to hold the fragments in position such that their catalyzed reaction leads to the desired interlocked product.

The strategy utilizes the Cu(I)-catalyzed³ 1,3-cycloaddition⁴ of organic azides with terminal alkynes, recently popularized as a “click” reaction⁵ by Sharpless and others.^{3,6,7} In organic solvents, tertiary amines or, better, pyridines, considerably enhance the reaction kinetics,^{3b,8} suggesting that a macrocycle bearing an endotopic ligating nitrogen atom could direct such a catalyzed reaction through its cavity.⁹ The 2,6-disubstituted pyridine macrocycle **1**, previously used¹⁰ as both a mono- and bidentate ligand in metal-coordinated rotaxanes and catenanes, appeared to be a suitable candidate to investigate this idea (Scheme 1). Commercially available Cu(CH₃CN)₄PF₆ was chosen as the copper source, avoiding ligands that might compete too strongly for the metal with the macrocycle and other reactants.

We were delighted to find that simple overnight stirring of an equimolar mixture of pyridine macrocycle **1**, alkyne **2**, azide **3**, and the Cu(I) salt in CH₂Cl₂ afforded—after demetalation with KCN—a mixture of [2]rotaxane **4** (57%) and the noninterlocked triazole thread **5** (41%), together with some of the unconsumed starting macrocycle (Table 1, entry 1). The ¹H NMR spectrum of **4** in CDCl₃ (Figure 1b) shows upfield shifts of several signals with respect to its noninterlocked components **1** and **5** (Figure 1a and c, respectively). The shielding, typical of interlocked architectures in which the aromatic rings of one component are positioned face-on to another component,¹⁰ is observed for all the nonstopper resonances of the axle (H_{f-j}) in **4**, indicating that the macrocycle is able to access the full length of the thread. In contrast, the equivalent spectrum (Figure 1d) of the rotaxane re-metalated with Cu(CH₃CN)₄PF₆ (CH₃COCH₃, RT, 1 h, quantitative) shows pronounced shielding of H_j and H_k with respect to **5** (Figure 1c) but

Scheme 1. Proposed Catalytic Cycle for the Cu(I)-Template Synthesis of [2]Rotaxane **4** from **1**, **2**, and **3** (ref 9)



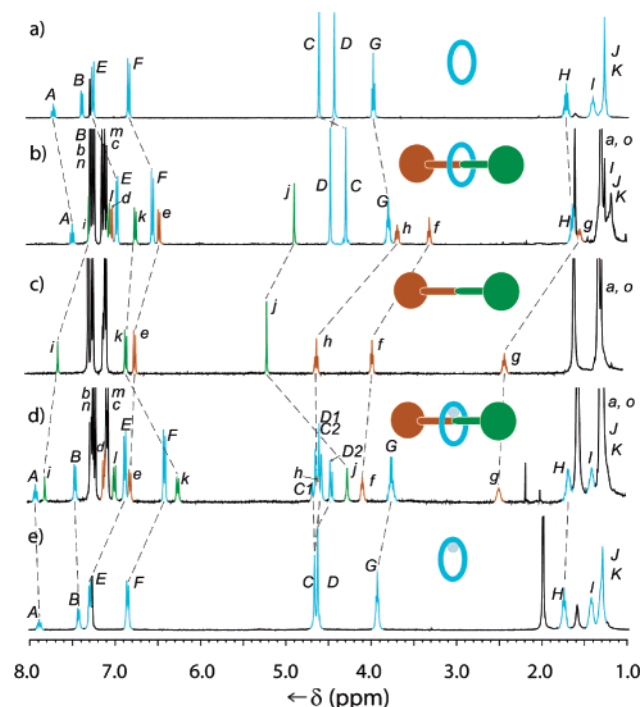
not H_h, H_g, or H_f. This suggests that the Cu binds to the macrocycle and thread in the rotaxane via two sets of bidentate N,O donor interactions (rapidly oscillating involvement between the two oxymethylene groups in the case of the macrocycle), fixing the interlocked components in a position consistent with the observed shielding effects. In other words, in CDCl₃, the structure of the rotaxane–metal complex corresponds to that of [4Cu]PF₆ shown in Scheme 1.

Although halogenated solvents give the highest yields of rotaxane, the reaction proved to be tolerant to a range of media, including semi-aqueous conditions (entry 2). The use of excess **2** and **3** generates high yields (up to 94%) of [2]rotaxane with respect to the amount of macrocycle used (entries 3 and 4); however, significant quantities of the noninterlocked thread (**5**) are produced in all the noncontrol entries in Table 1. Carrying out the reaction using the conditions of entry 4 but with no macrocycle present and starting with a stoichiometric equivalent of rotaxane (**4**) or thread

Table 1. Variations in the Experimental Conditions and Reactant Stoichiometry for the Synthesis of [2]Rotaxane **4**^a

entry	equiv of 2 and 3	equiv of CuPF ₆	solvent	T (°C)	duration	conversion to triazole 2 + 3 → 4 + 5	yield of [2]rotaxane 1 → 4
1	1	1	CH ₂ Cl ₂	25	12 h	>95%	57%
2	1	1	H ₂ O/ <i>n</i> BuOH	25	10 days	>95%	22%
3	3	1	CH ₂ Cl ₂	25	24 h	>95%	83%
4 ^c	5	1	CH ₂ Cl ₂	25	72 h	92%	94%
5	1	0.2	CH ₂ Cl ₂	25	10 days	30%	20%
6	1	0.2	CH ₂ Cl ₂ ^b	25	10 days	>95%	38%
7	5	0.2	CH ₂ Cl ₂ ^b	25	20 days	44%	59%
8	1	0	ClCH ₂ CH ₂ Cl ^b	25 then 70	12 h then 72 h	trace	0%
9	5	0.2	ClCH ₂ CH ₂ Cl ^b	25 then 70	12 h then 24 h	94%	82%

^a All reactions were carried out at 0.1 mM concentration with respect to **2** and **3**, with 1 equiv of macrocycle **1**, and without the need for an inert atmosphere nor distilled or dried solvents. A general experimental procedure is provided in the Supporting Information. ^b With 3 equiv of pyridine. ^c To assess the efficacy of the rotaxane and thread as ligands for a catalytic copper species, the reaction conditions from entry 4 were repeated with no macrocycle present but starting with 1 equiv of **4** or **5** instead. The resulting conversions of **2** + **3** → **5** were 2 and 9%, respectively.

**Figure 1.** ¹H NMR spectra (400 MHz, CDCl₃, 298 K) of (a) macrocycle **1**, (b) [2]rotaxane **4**, (c) thread **5**, (d) [2]rotaxane–CuPF₆ complex [4Cu]PF₆, (e) macrocycle–CuPF₆ complex [1CuL₂]PF₆. The assignments correspond to the lettering shown in Scheme 1.

(**5**) instead gave low conversions to the triazole (**2** and 9%, respectively; see Table 1 footnote b), showing that both rotaxane and thread are poor ligands for generating a catalytic copper species. Clearly, the noninterlocked thread produced in the rotaxane-forming reactions arises from the macrocycle-promoted Cu catalysis being able to take place around, rather than solely through, the cavity of **1**. We are currently exploring the noninterlocked:interlocked selectivity of other ligand designs.

We next investigated the use of substoichiometric amounts of copper to determine whether the metal would turn over as a template

as well as a cycloaddition catalyst. When using 20 mol % (with respect to **1**) of Cu(CH₃CN)₄PF₆ at room temperature, the reaction appeared to stop after rotaxane equivalent to the amount of copper present had been formed (entry 5). This suggests that the multi-dentate rotaxane sequesters the transition metal during the reaction, inhibiting further catalytic activity. Addition of pyridine as a competing ligand enabled the catalyst to turn over producing a substoichiometric reaction (entries 6 and 7), but the reaction was extremely slow at 25 °C. Elevating the temperature (entry 9) gives an improved yield (82%) of rotaxane **4** in a reasonable period of time (36 h) using only 4 mol % Cu(I) with respect to both **2** and **3**.

The requirement for only a catalytic amount of a template represents a new development in the strategies available to mechanically interlocked architectures. Chelation to catalytic centers could lead to rotaxane- and catenane-forming protocols based on other metal-mediated reactions, including cross-couplings, condensations, and other cycloaddition reactions.

Supporting Information Available: General synthetic experimental procedure and characterization and spectroscopic data for **4**, **5**, and their precursors. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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