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Active Metal Template Synthesis of [2]Catenanes

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Abstract: The synthesis of [2]catenanes by single macrocyclization and double macrocyclization strategies using Cu(I) ions to catalyze covalent bond formation while simultaneously acting as the template for the mechanically interlocked structure is reported. These "active metal template" strategies employ appropriately functionalized pyridine ether or bipyridine ligands and either the CuAAC "click" reaction of azides with terminal alkynes or the Cu(I)-mediated Cadiot−Chodkiewicz heterocoupling of an alkyne halide with a terminal alkyne. Using one macrocyclic and one acyclic building block, heterocircuit (the rings are constitutionally different) [2]catenanes are produced via the single macrocyclization route in up to 53% yield by optimizing the reaction conditions and relative stoichiometry of the starting materials. Alternatively, with the active template CuAAC reaction, a single acyclic unit can be used to form a homocircuit (two identical rings) [2]catenane in 46% yield through a one-pot, double macrocyclization, procedure. Remarkably, <7% of the corresponding noninterlocked macrocycle is isolated from this reaction, indicating the efficacy of Cu(I) as both a template for the catenane and a catalyst for covalent bond formation in the reaction.

Introduction

The synthesis of catenanes and rotaxanes was revolutionized by the application of template-directed syntheses,[1] in which the components are preorganized prior to covalent capture of the interlocked architecture. Although a large number of different types of template-directed reactions have been successfully employed to form rotaxanes in threading-followed-by-stoppering strategies,[1a] "clipping" approaches to rotaxanes and catenanes (involving single or double macrocyclization of ligands, directed by the template)[2] are rather more demanding and have only been demonstrated with a small number of different macrocyclization reaction types. Of these, Williamson ether synthesis,[2] the Huisgen−Meldal−Fokin Cu(I)-catalyzed 1,3-cycloaddition of azides with terminal alkynes (the CuAAC "click" reaction),[3,4] amide or ester bond-forming reactions,[5] ring-closing metathesis,[6] imine bond formation,[1u,6f,7] and metal−ligand coordination[8] are the most commonly used. The effectiveness of these reactions for catenane synthesis lies in their reactive end groups being sufficiently stable in solution to react overwhelmingly in the desired fashion even when accessing the required reaction geometry is a rare event (as it is for the cyclization of large

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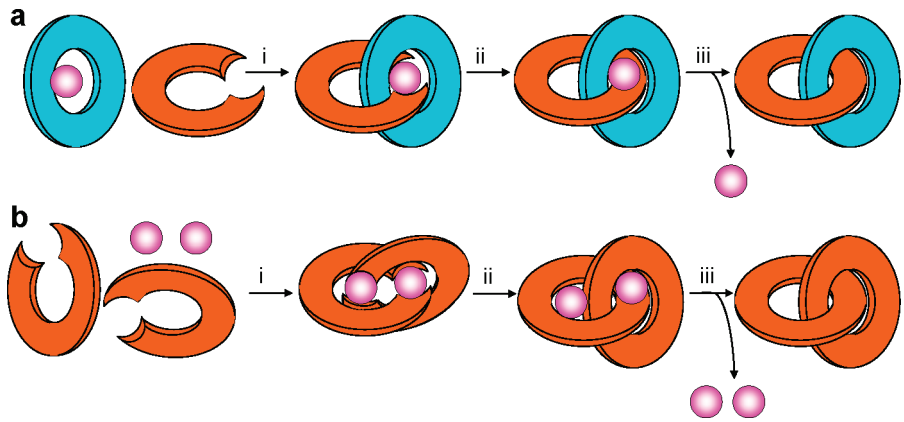

Figure 1. The active metal template approach to catenane synthesis. (a) Single macrocyclization route: (i) Template assembly of a macrocyclic ligand and an acyclic ligand about the metal ion (shown in pink) is followed (ii) by a covalent bond-forming reaction between the end groups of the acyclic ligand, catalyzed by the metal ion, through the cavity of the macrocycle. (iii) Decomplexation affords the metal-free [2]catenane. (b) Double macrocyclization route: (i) Template assembly of the acyclic ligands about one or more metal ions is followed by (ii) successive or simultaneous macrocyclization reactions. (iii) Decomplexation affords the metal-free homocircuit (both macrocycles are the same) [2]catenane. The two routes are analogous to the single and double macrocyclization strategies introduced by Sauvage for the synthesis of catenanes by "passive" metal template methods.[2]

rings), and hence give predominantly macrocyclic products under high dilution. The yield of catenane versus noninterlocked macrocycle then depends on how effectively the template preorganizes the ring-closing reaction to take place while one component is threaded through the cavity of the other.

We recently developed[9] an approach to rotaxane synthesis in which a metal ion ligated endotopically within a macrocycle mediates bond formation between two suitably functionalized building blocks through the macrocycle cavity to assemble the thread. This "active metal template" strategy[9] takes inspiration from ligand couplings employed in transition metal catalysis and opens up a broad range of metal-mediated bond formations for possible use in the synthesis of rotaxanes, the requirement being that the key bond-forming reaction can be directed by the catalyst to proceed through the macrocyclic cavity rather than external to it. Such active metal template processes, where a single species acts as both the template and the catalyst for covalent bond formation, clearly also offer potential for the synthesis of catenanes (Figure 1). Using a metal ion to simultaneously bind to and activate the tethered ends of an acyclic building block to react through the cavity of a macrocycle could lead to reactions with unstable intermediates that would otherwise not lead to interlocked products being used for possible catenane-forming reactions. Active template processes also offer the possibility of traceless assembly[9i] (as the coordinating functional groups are often chemically changed during the reaction into noncoordinating elements) and could be used to prepare catenanes containing multiple rings or having only very weak residual intercomponent interactions, molecules

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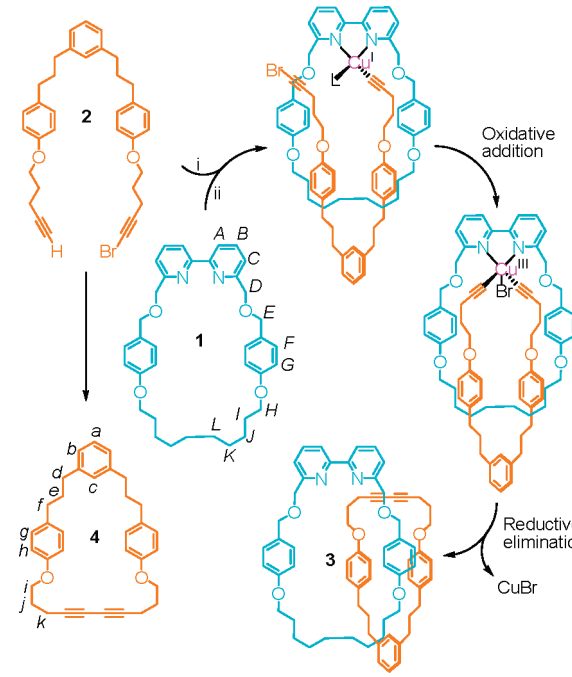
that are often difficult or impossible to achieve with standard template-directed approaches. Here, we report on the application of the active metal template concept to catenane synthesis using both single macrocyclization and double macrocyclization strategies. Heterocircuit (the rings are different) and homocircuit (the rings are the same) [2]catenanes are assembled using appropriately functionalized bidentate pyridine ether or bipyridine ligands and either the Cu(I)-catalyzed CuAAC reaction or the Cu(I)-mediated Cadiot−Chodkiewicz[10] heterocoupling of an alkynyl halide and a terminal alkyne.

Active Metal Template [2]Catenane Synthesis Using the Cadiot−Chodkiewicz Reaction

We initially investigated a modified Cadiot−Chodkiewicz coupling[11] of a bromoalkyne with a terminal alkyne mediated by a Cu^{I} complex of bidentate bipyridyl macrocycle **1**,[9d] due to its efficacy in active template rotaxane-forming reactions.[9g]

Scheme 1. Active Metal Template Cadiot−Chodkiewicz Synthesis of [2]Catenane **3** from Bipyridyl Macrocycle **1** and Alkyne-Bromoalkyne **2**[a]



[a] Reagents and conditions: (i) LiHMDS, THF, −78 °C; (ii) CuI (1 equiv), 5 equiv of **2**, 80 °C, 72 h, 21% (over two steps). L = I, Br, or THF.

Acyclic unit **2** has no potential metal-coordinating sites other than the terminal alkyne and bromoalkyne reactive functional groups and should cyclize to form a ring of similar size and shape to others previously demonstrated to accommodate thread-forming reactions in active template rotaxane syntheses.[9] Building block **2** was treated with LiHMDS ($LiN(SiMe_3)_2$) at −78 °C and then added to a solution of macrocycle **1** and CuI in THF, and the resulting mixture was stirred for 4 days at room temperature (Scheme 1), a procedure similar to that used successfully[9g] for rotaxane formation. However, little of the desired catenane product (**3**) was observed, and only a small amount of **2** was consumed under these conditions. Increasing the reaction concentration, raising the reaction temperature to 80 °C, and employing a 5-fold excess of **2** ultimately gave [2]catenane **3** in 21% yield. The proposed mechanism for the active metal template Cadiot−Chodkiewicz catenane synthesis is shown in Scheme 1.[12] The modest yield illustrates how the catenane-forming reaction, in which the reactive end groups must be tethered together, is much more demanding in terms of conformational requirements of the ligands, and probably steric effects, than the equivalent rotaxane-forming reaction (for which nontethered functional groups are reacted through the macrocycle cavity to form the interlocked thread). The yield of

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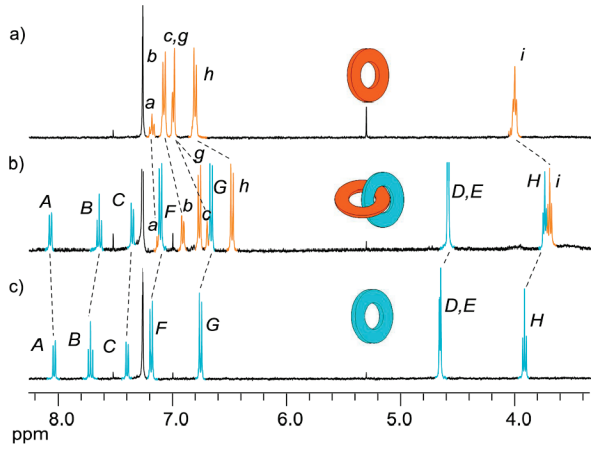


Figure 2. Partial ^{1}H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) bisacetylene macrocycle **4**, (b) [2]catenane **3**, and (c) bipyridine macrocycle **1**. The assignments correspond to the lettering shown in Scheme 1.

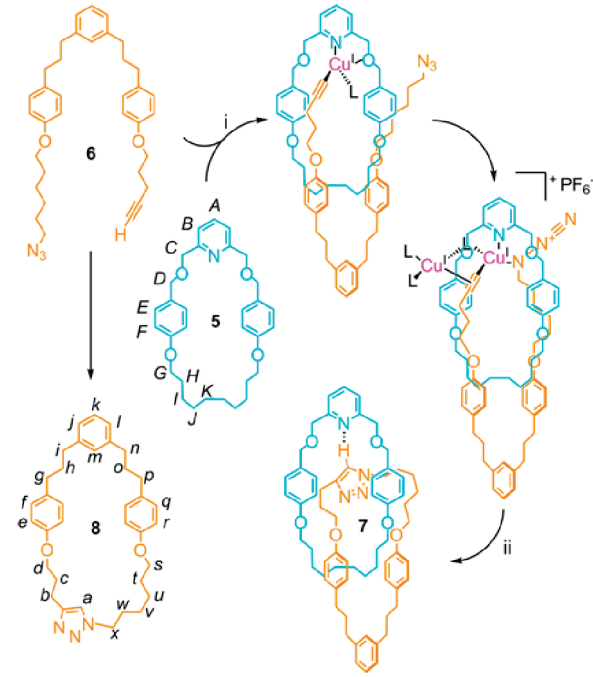
catenane also suffers because the bromoalkyne moiety is present during treatment of the terminal alkyne of **2** with LiHMDS, prior to transmetalation with copper. This leads to some decomposition of the alkyne halide, whereas in the corresponding rotaxane-forming reactions, the terminal alkyne could be treated with LiHMDS and transmetalated with copper before the alkyne halide was added to the reaction mixture.

As a heterocircuit catenane (the two rings are different), the interlocked nature of **3** was apparent from both mass spectrometry (*m*/*z* of the molecular ion) and ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of [2]catenane **3** in $CDCl_3$ (Figure 2b) displays upfield shifts of nearly all of the signals with respect to those of the noninterlocked components (Figure 2a and c). Such shielding is typical of interlocked architectures in which the aromatic rings of one component are face-on to another component and is most conspicuous for H_F, H_G, and H_H of macrocycle **1** and H_c, H_h, and H_i of macrocycle **4**. The ubiquity of the upfield shifts implies that the two rings are largely free to rotate with respect to one another, as might be expected in a system where there are no strong intercomponent interactions to stabilize a particular coconformation.

Active Metal Template [2]Catenane Synthesis Using the CuAAC "Click" Reaction: Single Macrocyclization Strategy

The qualified success of the catenane-forming active template Cadiot−Chodkiewicz reaction prompted us to try using the CuAAC "click" reaction to form [2]catenanes (Scheme 2, Table 1), a reaction that had also been previously successfully applied to the active template synthesis of rotaxanes[9a,d] and passive template syntheses of both rotaxanes[1t,13] and catenanes.[4] When

Scheme 2. Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **7** from Pyridyl Macrocycle **5** and Azide−Alkyne **6**[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, CH_2Cl_2, or $C_2H_4Cl_2$; (ii) EDTA, $NH_{3(aq)}$. L = CH_3CN, alkyne, azide, or donor atom from another molecule. For the effect of conditions and reagent stoichiometry on the reaction yield, see Table 1.

Table 1. Influence of Reaction Conditions and Reagent Stoichiometry on the Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenanes **7** and **9** (Schemes 2 and 3)[a]

entry	macrocycle (concentration)	equiv of **6**	*T*/°C	time/h	conversion to triazole products (%)	yield (%) of [2]catenane **5**→**7** **1**→**9**
1[a]	**5** (6.5 mM)	1	RT	24	15[b]	<5[b]
2	**5** (6.5 mM)	1	80	96	90	16
3	**5** (6.5 mM)	5	80	240	>98	25
4	**5** (1.25 mM)	5	80	288	>98	53
5	**1** (1 mM)	5	80	500	50	50
6	**1** (5 mM)	5	80	170	>98	49

[a] One equivalent of $[Cu(CH_3CN)_4](PF_6)$ was used relative to the macrocycle (**1** or **5**). All reactions were carried out in $C_2H_4Cl_2$, except entry 1 (CH_2Cl_2). [b] Yield estimated by ^{1}H NMR.

an equimolar mixture of macrocycle **5**,[14] $[Cu(CH_3CN)_4](PF_6)$, and the acyclic azide−alkyne unit **6** in dichloromethane was stirred for 24 h at room temperature, a low conversion to triazole products was observed with only trace amounts of catenane apparent in the ^{1}H NMR analysis of the crude reaction mixture (Table 1, entry 1). Changing the solvent to 1,2-dichloroethane and raising the temperature to 80 °C afforded [2]catenane **7** in 16% yield with near complete conversion of **6** to triazole products (Table 1, entry 2). Finally, by increasing the number of equivalents of **6** relative to **5** and running the reaction at greater dilution (which required extended reaction times), the yield of catenane **7** was increased to a pleasing 53% (Table 1, entry 4). Isolation of the metal-free catenane was facilitated by washing the crude product mixture with a basic EDTA solution.

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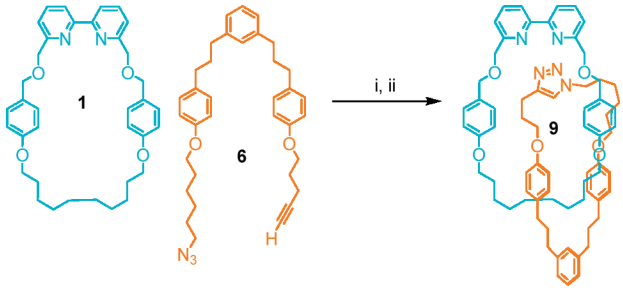
Scheme 3. Single Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **9** from Bipyridyl Macrocycle **1** and Azide−Alkyne **6**[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, $C_2H_4Cl_2$, 80 °C, 7−21 d. (ii) EDTA, $NH_{3(aq)}$, 49−50% (over two steps). For the effect of concentration on the time of reaction, see Table 1.

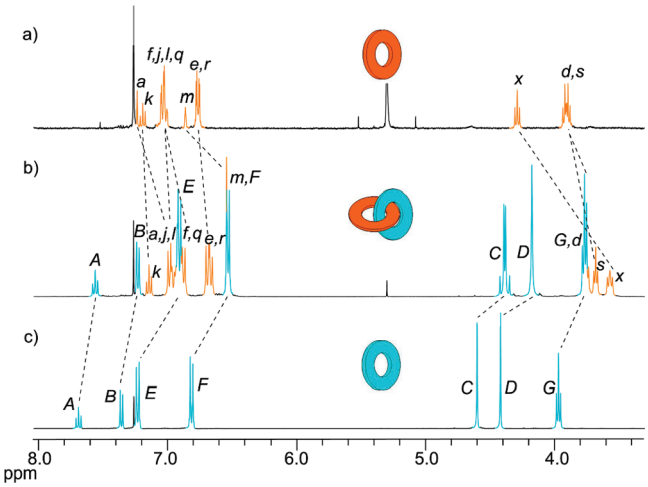


Figure 3. Partial ^1H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) triazole macrocycle **8**, (b) [2]catenane **7**, and (c) pyridine macrocycle **5**. The assignments correspond to the lettering shown in Scheme 2.

The ^1H NMR spectrum of catenane **7** (Figure 3b) shows significant upfield shifts of various signals (H_x ~0.6 ppm, H_m ~0.4 ppm, H_E ~0.3 ppm, and H_F ~0.3 ppm) with respect to the components (Figure 3a and c), consistent with its interlocked architecture. Interestingly, signals corresponding to H_C appear as an AB system, indicating that the two faces of the pyridyl macrocycle are inequivalent. This is a result of the triazole group making the ring threaded through the pyridyl macrocycle inherently unsymmetrical. The chemical shift of H_a of the triazole group suggests it may form a C−H···N hydrogen bond[15] with the pyridine nitrogen atom of the other macrocycle.

Both pyridyl and bipyridyl macrocycles have been found to undergo efficient active template rotaxane assembly with the CuAAC reaction,[9d] although the kinetics of the reactions are very different (the bipyridyl macrocycle reaction is considerably slower) as a result of the reactions proceeding through different types of intermediates. The same trend was seen with the active template catenane-forming reaction (Scheme 3 and Table 1, entries 5 and 6). Although good yields (49−50%) of [2]catenane **9** could be obtained, they required long reaction times (7−21 days) at 80 °C and/or higher reaction concentrations. It is testimony to the very specific reaction preferences of the azide and alkyne functional groups under Cu(I) catalysis that they survive for so long without undergoing side reactions until the apparently very rare event of the groups being in just the right position to react to form catenane occurs.

(15) Li, Y.; Flood, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12111–12122.

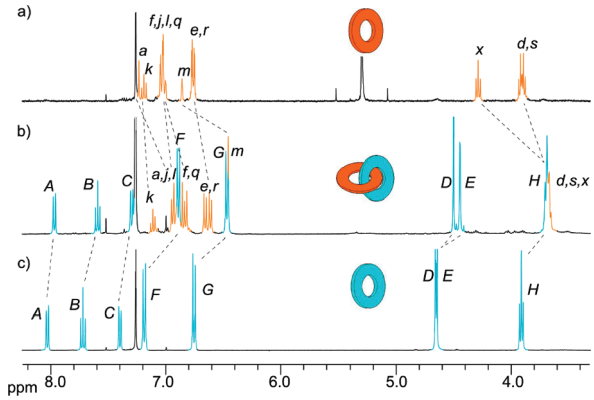


Figure 4. Partial ^1H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) triazole macrocycle **8**, (b) [2]catenane **9**, and (c) bipyridine macrocycle **1**. The assignments correspond to the lettering indicated for macrocycles **1** and **8** in Schemes 1 and 2, respectively.

The ^1H NMR spectrum of catenane **9** (Figure 4b) again shows upfield shifts of most of its signals with respect to its noninterlocked components (Figure 4a and c). Signals H_F and H_G of bipyridine macrocycle **1** are each shifted by ~0.2 ppm, consistent with $\pi-\pi$ stacking between the aromatic rings to which H_F and H_G are attached and the aromatic rings of macrocycle **8**. As in catenane **7**, the signals corresponding to H_E appear as an AB system, although this is less pronounced than in the pyridine macrocycle-derived catenane.

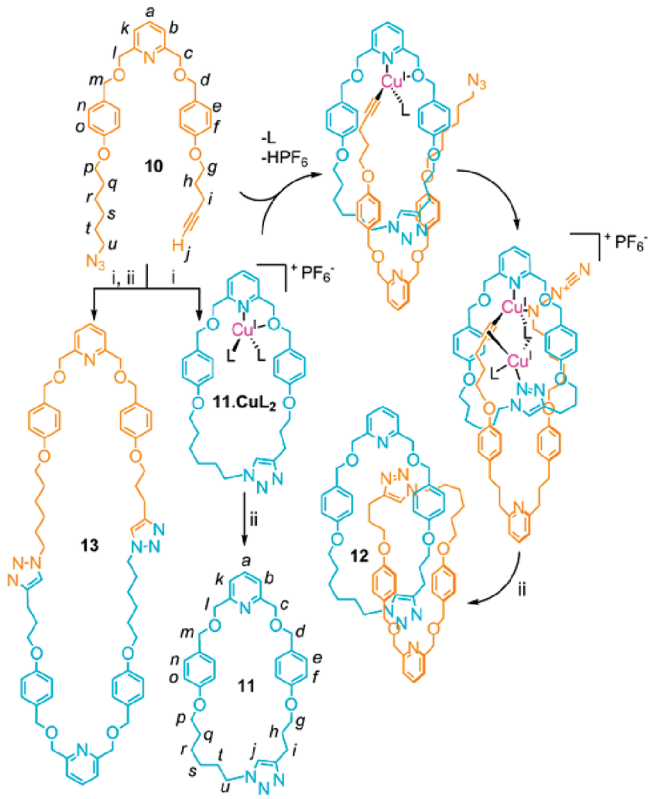
Active Metal Template [2]Catenane Synthesis Using the CuAAC "Click" Reaction: Double Macrocyclization of Two Identical Acyclic Building Blocks

The active template reactions investigated so far (Schemes 1−3) featured a preformed macrocycle as one of the components and involved a single macrocyclization step (Figure 1a) leading to heterocircuit catenanes. We were interested to see whether it would be possible to extend this concept to an active template double macrocyclization strategy (Figure 1b) in which a homocircuit (both interlocked rings constitutionally identical) [2]catenane was assembled in one pot by two successive macrocyclization reactions (the final one, at least, having to be templated by the catalyst) of a single type of building block (Scheme 4).

Ligand **10** incorporates the terminal alkyne and azide groups necessary for the CuAAC reaction, together with a pyridine group for coordination to a Cu ion catalyzing the ring closure of another molecule of **10**. The covalent framework of the ligand was chosen to mimic macrocycle **5** and acyclic unit **6**, which combine effectively to give catenane in the single macrocyclization active template CuAAC reaction (Scheme 2).

Building block **10** was dissolved in $C_2H_4Cl_2$ with one-half of an equivalent of $[Cu(CH_3CN)_4](PF_6)$, and the solution was heated at 80 °C for 5 days (Scheme 4). The yield of [2]catenane proved to be highly dependent on the reaction concentration (Table 2), presumably a reflection of the delicate balance between various types of coordination complexes that can give rise to oligomers, noninterlocked macrocycles, or catenane. Carrying out the reaction at an initial 0.3 mM concentration of **10** gave a remarkable 46% yield of metal-free [2]catenane **12**, isolated after workup with a basic EDTA solution and purification by column chromatography. Very little (<7% as compared

Scheme 4. Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** from Azide−Alkyne **10**[a]



[a] Reagents and conditions: (i) $[Cu(CH_3CN)_4](PF_6)$, $C_2H_4Cl_2$, 80 °C, 5 d. (ii) EDTA, $NH_{3(aq)}$. L = CH_3CN, alkyne, azide, or donor atom from another molecule. For the effect of concentration on catenane yield, see Table 2.

Table 2. Influence of Concentration on the Double Macrocyclization Strategy Active Metal Template CuAAC Synthesis of [2]Catenane **12** (Scheme 4)[a]

entry	[**10**] (mM)	conversion to triazole products (%)	ratio catenane **12**:macrocycles **11** and **13**	yield of [2]catenane **10**→**12** (%)
1	15	>98	2:3	8
2	6	>98	2:3	16
3	3	>98	5:2	25
4	1	>98	3:1	30
5	0.3	>98	7:1	46
6	0.08	65	1:1	40
7	0.03	25	1:6	6

[a] One-half of an equivalent of $[Cu(CH_3CN)_4](PF_6)$ was used relative to **10**. All reactions were performed in $C_2H_4Cl_2$ at 80 °C over 120 h.

to 46% [2]catenane) of noninterlocked macrocycles **11** and **13** were isolated from the reaction reported in Table 2, entry 5. It is intriguing that even at these relatively low concentrations the double macrocyclization reaction is more selective for the [2]catenane than the corresponding single macrocyclization employing pyridine macrocycle **5** and 1 equiv of the acyclic azide−alkyne building block **6** (Scheme 2 and Table 1, entry 2). A possible explanation could be that the second Cu(I) ion involved in the mechanism of these reactions[3,9d] becomes coordinated to the triazole nitrogen of macrocycle **11**, resulting

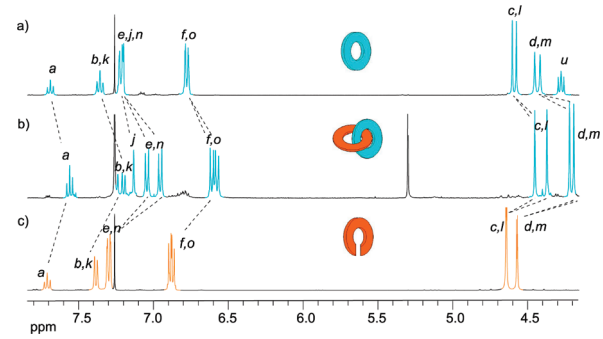


Figure 5. Partial ^1H NMR spectra (400 MHz, $CDCl_3$, 300 K) of (a) macrocycle **11**, (b) [2]catenane **12**, and (c) azide−alkyne building block **10**. The assignments correspond to the lettering shown in Scheme 4.

in a reaction geometry in which interlocking is significantly enhanced, as shown in Scheme 4. As the two Cu(I) centers are linked via both a bridging ligand, L, and coordination to the alkyne, the azide is forced to approach the reactive center through the cavity of macrocycle **11** for the CuAAC reaction to occur, leading predominantly to catenane.

The structure of [2]catenane **12** was confirmed by mass spectrometry (fragmentation and MS−MS studies) and ^1H NMR spectroscopy. The ^1H NMR spectrum of catenane **12** in $CDCl_3$ is shown in Figure 5b. The upfield shifts of the signals as compared to macrocycle **11** (Figure 5a) and building block **10** (Figure 5c) show the same general trends found in the heterocircuit catenane produced by the single macrocyclization active template CuAAC reaction, **7** (Figure 3).

Conclusions

The active template concept developed for rotaxanes can be successfully extended to the more demanding requirements of catenane synthesis. Heterocircuit [2]catenanes were prepared in 21−53% yields through Cu(I)-mediated active template single macrocyclization strategies employing the Cadiot−Chodkiewicz (forming a symmetrical bisacetylene-containing macrocycle) or CuAAC "click" reaction (forming an unsymmetrical triazole-containing macrocycle) and preformed monodentate or bidentate macrocyclic ligands. The CuAAC reaction could also be used to assemble homocircuit [2]catenanes from a single type of acyclic building block in a one-pot procedure in up to 46% yield, a remarkable catalytic assembly reaction notable for its selectivity for the interlocked architecture over noninterlocked macrocyclic products. The application of such strategies to higher order interlocked structures is currently under investigation in our laboratory.

Acknowledgment. We thank Juraj Bella for assistance with the high field ^{13}C NMR studies and Syngenta for a Ph.D. studentship (to P.R.M.). D.A.L. is an EPSRC Senior Research Fellow and holds a Royal Society-Wolfson research merit award.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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