

Efficient Multi-Component Active Template Synthesis of Catenanes

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Supporting Information Placeholder

ABSTRACT: We describe a simple and high yielding active template synthesis of [2]catenanes. In addition to mechanical bond formation using a single pre-macrocycle bearing an azide and alkyne moiety, our method is also suitable for the co-macrocyclisation of readily available bis-alkyne and bis-azide co-monomers and even short alkyne/azide components which oligomerise prior to mechanical bond formation.

Although many of the seminal contributions¹ to the synthesis of mechanically interlocked molecules² focus on catenanes,³ reports of rotaxanes have grown to dominate the field,²ⁱ in part due to the potential for shuttling motions in rotaxanes that makes them attractive for the development of molecular machines.^{4,5} However, the higher synthetic challenge involved in catenane synthesis probably plays a role; whereas rotaxanes can be synthesized readily using threading-then-stoppering methodologies, catenane synthesis requires a macrocyclisation event to capture the interlocked architecture with the attendant competition between cyclisation and oligomerization. To overcome this, catenanes are typically formed under high-dilution conditions, leading to long reaction times and, where the association between the preformed ring and the macrocycle precursor is weak, diminished yields.

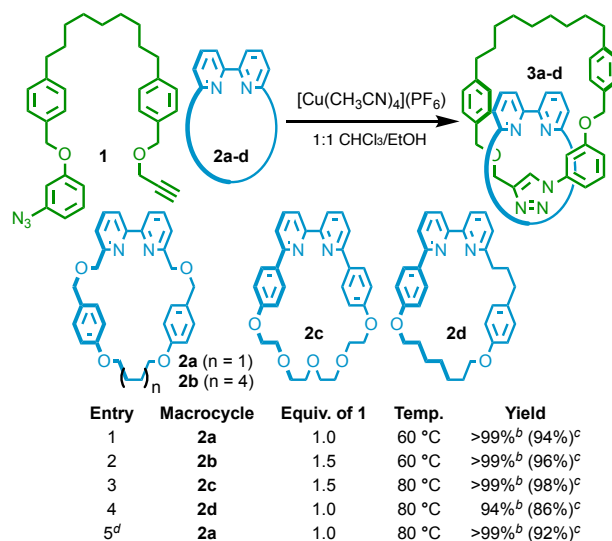
Despite these challenges a variety of catenane syntheses have been disclosed, each with their own advantages and disadvantages.² Reactions that allow the assembly of the new macrocycle from small building blocks such as Stoddart's donor-acceptor⁶ and pimer⁷ systems, and the amide-templated examples developed by Vögtle, Hunter and Leigh are particularly attractive due to their synthetic efficiency.⁸ Similarly, metal-directed passive template (PT) approaches, exemplified by Sauvage's Cu^I-phenanthroline methodology, are widely used thanks to the strong metal-ligand interactions that favor association of the components.⁹ However, these strategies also exemplify the drawbacks of many current methodologies. The former rely on preorganization of the incipient macrocycle through interactions that simultaneously favor cyclisation and catenane formation. This leads to high yields in ideal cases, but minimal structural changes can disrupt these interactions, significantly lowering the yield.^{8c} Conversely, metal-directed PT approaches require high-dilution conditions to prevent oligomerization and, although the stability of the precursor complex ensures efficient threading, cyclisation is typically slow. PT approaches are also ill-suited to the synthesis of sterically hindered products as repulsive interactions disfavor threaded complex formation.

The active template (AT) approach to rotaxanes,¹⁰ has the potential to overcome many of the outstanding challenges in catenane synthesis as AT-reactions typically proceed in high yield and are extremely general with respect to the substrates employed, including sterically hindered examples.¹¹ However, although Leigh and Saito have disclosed AT catenane syntheses,¹² they proceed at low concentration over long reaction times and require a large excess

of macrocycle precursor to achieve reasonable yields.

We recently optimized our small macrocycle¹³ modification of Leigh's AT Cu-mediated azide-alkyne cycloaddition (AT-CuAAC)¹⁴ reaction for the rapid and efficient iterative synthesis of oligorotaxanes.¹⁵ This suggested an opportunity as, were these advantages to be maintained in the formation of catenanes, these conditions might allow efficient pseudo-high dilution reactions. Here we report that this approach is extremely successful, producing catenanes in good to excellent yield with short reaction times. The reaction is general with respect to both macrocycle and pre-macrocycle structure, allowing the synthesis of small, crowded catenanes and the use of simple building blocks *via* a controlled oligomerization pathway.

Scheme 1. Efficient AT-CuAAC Syntheses of [2]catenanes **3**.^a



^aReagents and conditions: **1** in 1 : 1 CHCl₃-EtOH (25 mM) added to **2** (25 mM), ^tPr₂NEt (2 equiv) and [Cu(CH₃CN)₄](PF₆) (0.99 equiv) in 1 : 1 CHCl₃-EtOH over 4 h. ^bDetermined by ¹H NMR analysis. ^cIsolated yield. ^dConcentration of **1/2a** = 100 mM.

Precursor **1** was readily prepared and its reaction with macrocycle **2a**¹⁶ investigated with respect to solvent, temperature, concentration and rate of addition of **1** to **2a**, to identify the variables that control reaction selectivity. Unsurprisingly, catenane formation was favored when the addition time, temperature and concentration of **1** and **2a** were balanced to maintain a low instantaneous concentration of **2a** (see ESI). Using this information, we designed general conditions for the synthesis of catenanes **3** from macrocycles **2** (Scheme 1). When one equivalent of **1** was added to macrocycle **2a** in the presence of [Cu(MeCN)₄]PF₆ and ^tPr₂NEt over 4 h, **2a** was completely consumed and catenane **3a** was isolated in 94% yield.

Larger macrocycle **2b** was 88% converted to catenane **3b** on addition of 1 equivalent of **1**. Variation of the addition rate or reaction temperature did not alter the reaction selectivity, indicating that macrocycle **3a** has an inherently lower selectivity for mechanical bond formation. When 1.5 equivalents of **1** (entry 2) were used, **2b** was completely consumed and **3b** was isolated in 96% yield. Macrocycle **2c** also required modification of the conditions to overcome a slower reaction and diminished selectivity for the catenane compared with **2a**; addition of 1.5 equivalents of **1** to **2c** at 80 °C allowed quantitative consumption of **2c** and isolation of [2]catenane **3c** in 98% yield (entry 3). Macrocycle **2d** required elevated temperatures to achieve ~94% conversion to catenane **3d**. Co-elution of the **3d** with the macrocycle derived from **1** precluded addition of excess **1** to increase the conversion and resulted in a diminished isolated yield of 86% (entry 4). Although the reactions of macrocycles **2** with **1** are all extremely efficient,¹⁷ the reaction of **2a** with **1** is particularly robust; **3a** was produced in excellent yield (92%) even when the concentration of **2a** was increased to 100 mM (entry 5).

The high selectivity of the reactions to produce catenanes **3** suggested that the AT-CuAAC reaction would be suitable for a multi-component cyclisation approach to catenanes from small, simple starting materials by a controlled oligomerization pathway, a significant benefit for the production of interlocked molecules on larger scales. To this end, bis-alkyne and bis-azide containing precursors were prepared and reacted with macrocycle **2a** under our standard conditions and the reactions briefly optimized with respect to equivalents of precursors and addition time. Using this approach, catenanes **4** and **5** were produced in good isolated yield through the co-cyclisation of a di-azide and di-propargyl ether or 2,6-diethynylpyridine respectively (Figure 1). Analysis of the crude reaction mixtures indicated that the smallest possible [2]catenanes were produced with complete selectivity (Figures S139-40). Our multi-component synthesis is also suitable for the reaction of α,α' -diazido-*p*-xylene with either di-propargyl ether or 2,6-diethynylpyridine to produce catenanes **6** and **7** in isolated yields of 78% and 72% respectively. In these reactions, the smallest triazole-containing macrocycle that can lead a [2]catenane requires the formation of a hetero-tetramer as the corresponding hetero-dimeric macrocycle is too small to encircle **2a**. Once again, the hetero-tetrameric species was the only observed interlocked product (Figures S141-2).

Having successfully demonstrated a hetero-oligomerisation-then-cyclisation approach to [2]catenanes we turned our attention to the equivalent homo-cyclisation process. Using an azide-alkyne in which the reactive functional groups are 11 atoms apart led to catenane **8** in which the triazole-containing 28 membered ring is homodimeric in 84% yield. In this case, ~10% of the corresponding homo-trimeric catenane was also observed (Figure S*). Decreasing the distance between the alkyne and azide functional groups to 7 atoms resulted in a 50% yield of catenane **9**¹⁸ in which the 30 membered triazole-containing ring is homo-trimeric. Both the corresponding homo-tetramer- and homo-pentamer-derived catenanes were also observed in a combined ratio of ~1 : 2 with **9** (Figure S*). Finally, using a precursor in which the reactive functionality are 5 atoms apart resulted in a 32% isolated yield of tetramer-derived catenane **10**. In this case, a range of impurities were observed up to and including the homo-heptamer-derived product in a combined ~1 : 2 ratio with **10** (Figure S*). Thus, although effective, the homo-oligomerisation-then-cyclisation approach appears to be less selective for a single interlocked product than the hetero-cyclization pathway.

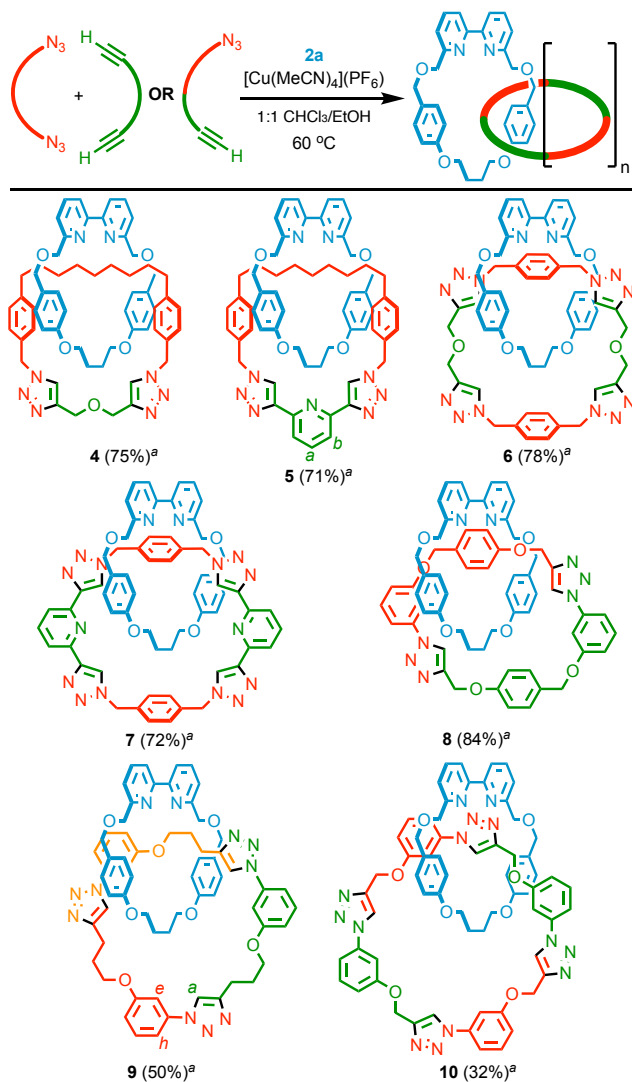


Figure 1. Multicomponent AT-CuAAC [2]catenanes **4-10**. ^aIsolated yield.¹⁸

Catenanes **3-10** were fully characterized by NMR and MS (see ESI). In addition, catenanes **3b**, **3d**, **5**, **7**, and **9** were characterized by single crystal x-ray diffraction (Figures S146-S150). Their solid-state structures suggest that, absent the significant stabilizing intercomponent interactions typically found in interlocked molecules produced using PT approaches, the rings adopt co-conformations that maximize weak, stabilizing contacts such as C-H H-bonding, C-H- π and π - π interactions due to the enforced proximity of the covalent subcomponents (e.g. Figure 2a). In keeping with this, longer contacts were observed in catenane **3b** which contains larger, more flexible bipyridine macrocycle **2b**.

The solid-state structures of **3b**, **3d**, **5**, **7** and **9** all contain a racemic mixture of enantiomers that are related by points of inversion (**3b**, **3d**, **5** and **7**) or glide planes (**9**). This is expected in the case of **3d** which is composed of two C_s -symmetric macrocycles and is thus topologically chiral.¹⁹ However, although **3b**, **5**, **7** and **9** are expected to be, on average, achiral as they contain at least one C_{2v} -symmetric macrocycle, the relative arrangements of the two ring

components in the solid-state produces enantiomeric co-conformations in which each macrocycle desymmetrizes the other, leading to structures with similar stereochemical properties to catenane **3d**. This co-conformational stereochemistry is similar to [2]rotaxanes in which the relative arrangement of the macrocycle and a C_{2v} or C_3 axle leads to mechanical planar²⁰ or covalent point²¹ stereogenic elements respectively. However, to our knowledge the co-conformational chiral stereogenic element of catenanes **3b**, **5**, **7** and **9** has not been highlighted previously. However, despite their crowded nature and the interactions and stereochemistry observed in the solid state, the ¹H NMR spectra of catenanes **3-10** are highly symmetrical with only one triazole resonance observed, suggesting they remain mobile on the ¹H NMR timescale in solution.²²

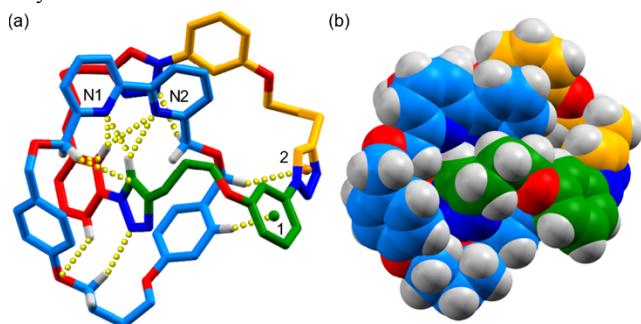


Figure 2. Solid-state structure of catenane **9** in (a) tube and (b) space-filling representations. Selected intercomponent distances in Å: $H_a-N_1 = 2.34$, $H_a-N_2 = 2.76$; $H_b-N_1 = 2.75$, $H_b-N_2 = 2.77$; $H_f-O = 2.86$; $H_D-C_a = 2.94$; $H_D-C_e = 2.96$; $H_D-N = 2.99$; $H_E-\bullet_2 = 2.83$; $H_f-\bullet_1 = 2.81$; $H_f-N = 2.44$. Atom labels as in Figure 1.

The yield of the reactions presented is particularly striking as selectivity for both mechanical bond formation *and* macrocyclization over uncontrolled oligomerization is required for efficient catenane synthesis. Our original hypothesis was that this could be achieved by optimizing the bipyridine-mediated AT-CuAAC reaction, which is highly selective for interlocked products^{10b,13,15,16} as the alkyne and azide reactive functional groups are projected on opposite faces of the ring in the key bond forming step,^{29c} to proceed rapidly under pseudo-high dilution conditions in order to maintain a low instantaneous concentration of the substrates. However, it remained unclear whether secondary interactions between the bipyridine macrocycle and the nascent triazole macrocycle also played a significant role in preorganizing the reaction intermediates to lead to a single major catenane product, although the broad substrate scope observed suggested this was not the case. To investigate this, the reaction of **1** was performed in the absence of a bipyridine ligand. Analysis of the crude reaction mixture by ¹H NMR and LCMS (Figures S133, S138) revealed selective formation of the corresponding monomeric triazole macrocycle, consistent with a simple pseudo-high dilution macrocyclization process. Thus, it seems that the origin of the high yield of our methodology is a combination of the selectivity of the AT-CuAAC reaction and a rapid macrocyclization process, leading to the catenane containing the smallest

possible triazole-containing macrocycle. Importantly, the simplicity of this model allows the rational optimization of conditions for different substrates by balancing the rate of addition and the reaction rate.

In conclusion, we have developed a facile, high-yielding and general AT-CuAAC approach for the synthesis of [2]catenanes that allows a multi-component approach in which readily available precursors, too small to cyclize directly, undergo successive reactions until a final AT-CuAAC reaction gives the interlocked target. Furthermore, the products reported here contain unusually small macrocycles of between 26 and 32 atoms and viewing their structures in space-filling representation (e.g. Figure 2b) serves to underline the crowded nature of the mechanical bond which belies the high yield of their formation. Indeed, catenane **3a** contains rings that are 26 and 28 atoms in circumference and yet it forms in near quantitative yield. In contrast, Sauvage and co-workers found that otherwise identical catenanes were formed in 42%^{1d} or 3.3%²³ yield when the macrocycles to be interlocked were 30 or 27 atoms in circumference respectively, demonstrating the sensitivity of the PT approach to destabilizing steric interactions. Despite the historical significance of catenanes^{1,3} and although existing methodologies have allowed ever more complex targets to be realized,²⁴ the relative challenge of catenane synthesis compared to rotaxanes has contributed to making them less well examined targets. With this new flexible methodology in hand, AT-CuAAC catenanes are as easy if not easier to access than their rotaxane counterparts! Given the wide range of applications for AT-CuAAC-derived rotaxanes, including as catalysts,²⁵ ligands,²⁶ hosts/sensors,²⁷ and molecular machines,²⁸ and the AT-CuAAC reaction's proven ability to access complex threaded systems efficiently,²⁹ we anticipate a similar surge in applications of AT-CuAAC catenanes.

ASSOCIATED CONTENT

Supporting Information

Full synthetic details and characterization data are available free of charge on the ACS Publications website.

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- (18) The isolated yield of **9** was determined from the mass of a purified sample contaminated with ~ 20% dimeric triazole macrocycle **S14** (see ESI). A small quantity of analytically pure of **9** was obtained by crystallization for characterization.
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TOC Graphic

