A Kinetic Self-Sorting Approach to Heterocircuit [3]Rotaxanes

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Abstract: In this proof of concept study, we use an active-template coupling to demonstrate a novel kinetic self-sorting process that iteratively increases the yield of the target heterocircuit [3]rotaxane product at the expense of other interlocked species.

The synthesis of heterocircuit rotaxanes in which several different rings are threaded onto a single axle is complicated significantly by the potential for sequence isomerism: even with just two distinct macrocycles, a heterocircuit [3]rotaxane with a non-centrosymmetric axle exists as two isomers, and the stereochemical complexity rises as the number of rings increases. However, this raises the synthetic complexity of the thread and only limited, stereochemically trivial examples have been reported. Alternative stepwise approaches to heterocircuit [n]rotaxanes have been developed; Sauvage and co-workers reported the coupling of kinetically inert pseudorotaxane complexes, and in 2010 Leigh and co-workers used an iterative clipping of macrocycles around a single binding site to produce both stereoisomers of a [3]rotaxane in a stepwise manner.

Self-sorting, in which multiple components selectively assemble themselves into complex architectures, is a particularly successful and attractive approach for the synthesis of complex supramolecular systems and materials. In 2008, Schalley and co-workers demonstrated a self-sorting for stereospecific [3]rotaxane synthesis by using the steric requirements of threading – rather than the affinity of the macrocycles for a given binding site – to determine the arrangement of rings on the axle, and this approach has since been extended to more complicated architectures. More recently, Stoddart and co-workers introduced the “cooperative capture” method in which the synergetic binding of guests by cucurbiturils and cyclodextrins, or cucurbiturils and Ogoshi’s pillaren, produces pre-organised heterocircuit pseudorotaxanes, which are then captured using Steinké’s catalytic self-threading reaction in excellent yield with high stereospecificity.

Self-sorting reactions typically operate under thermodynamic control, allowing the system to correct “errors”, although the trajectory to achieve equilibrium can be kinetically complex. In keeping with this, previous reports of self-sorting [n]rotaxane synthesis rely on passive templates to direct the assembly of a thermodynamically preferred pseudo-rotaxane complex before covalent bond formation kinetically traps the interlocked assembly. Leigh’s active template (AT) approach to mechanical bond formation is unusual in that the mechanical bond can, in theory, be formed solely under kinetic control – the covalent bond forming reaction simply takes place faster through the cavity of the macrocycle. As a consequence, an unusual feature of AT-derived products is that they often retain only weak attractive interactions between the covalent subcomponents and thus are typically unstable with respect to dethreading.

This suggests an opportunity to develop self-sorting reactions that are governed only by the kinetic stability of the products. Here we report the realization of this proposal: a stereoselective four-component coupling in which kinetic self-sorting amplifies the yield of a target heterocircuit [3]rotaxane.

![Figure 1. Schematic of our proposed self-sorting approach to [3]rotaxanes.](image-url)

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Our proposed AT self-sorting process (Figure 1) requires two macrocycles, I and II, with different internal diameter and two half-threads, III and IV, of different steric bulk. Focusing on the fate of the larger of the two rings (I, blue), four threaded products are possible: [2]rotaxane V, homocircuit [3]rotaxane VII and stereoisomeric heterocircuit [3]rotaxanes VIII and IX. If only one of the half-threads is bulky enough to retain the larger macrocycle this mixture is simplified as macrocycle I can dethread in all cases except product VIII, in which its path is blocked by smaller macrocycle II, which is in turn held in place by the smaller stopper, an example of Schalley’s “cascade stoppering”. Crucially, the escape of macrocycle I renders it available for further AT coupling, suggesting that this “ratcheted” self-sorting process will amplify the yield of VIII above the natural selectivity of the reaction. Overall, [3]rotaxane VIII is the only stable interlocked product derived from I, alongside the products of dethreading (recovered I non-interlocked thread X and II) and the products of direct AT couplings of macrocycle II.
We previously observed homocircuit [3]rotaxane formation in high yield when certain bipyridine macrocycles were used in Leigh’s AT Cu-mediated alknye-azide cycloaddition (ATCuAAC) reaction. Thus, in order to develop our proof-of-concept self-sorting process, we set out to explore the mixed-macrocycle AT-CuAAC reaction in the presence of macrocycles 1 and 2 (Scheme 1), which have previously been shown to have significantly different propensities for 3[3]rotaxane formation.

Initial experiments were performed with bulky azide 3 and alknye 4, in order to assess the behavior of the macrocycles in the absence of dethreading. Under these conditions, macrocycle 1 produces a mixture of 2[3]rotaxane 5 and [3]rotaxane 7 (Table 1, entry 1). By contrast, macrocycle 2a produces almost exclusively 2[3]rotaxane 6a with only trace quantities of [3]rotaxane 8a (entry 2), whereas macrocycles 2b (entry 3) and 2c (entry 4) only form the singly interlocked product. To account for the high yield of [3]rotaxane in the case of macrocycle 1, we previously proposed a mechanistic pathway involving dinuclear reactive intermediates A and B, in which one macrocyclic bipyridine coordinates to Cu(s) and the other to Cu(p), with bridging O-Cu interactions stabilising the assembly. The failure of macrocycles 2 to form significant quantities of [3]rotaxane was ascribed to the lack of Cu-O interactions to stabilise doubly threaded intermediates (2a) and the inability of smaller macrocycles to coordinate Cu(s) in a threaded manner (2b and 2c).

![Diagram of proposed intermediates of homocircuit [3]rotaxane formation for 1 and 2](image)

We previously observed homocircuit [3]rotaxane formation in high yield when certain bipyridine macrocycles were used in Leigh’s AT Cu-mediated alknye-azide cycloaddition (AT-CuAAC) reaction. Thus, in order to develop our proof-of-concept self-sorting process, we set out to explore the mixed-macrocycle AT-CuAAC reaction in the presence of macrocycles 1 and 2 (Scheme 1), which have previously been shown to have significantly different propensities for 3[3]rotaxane formation.

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Table 1. Product distribution in the mixed-macrocycle AT-CuAAC reaction

| Entry | Macrocycles | 5 | 6 | 7 | 8 | 9 | 10 |
|-------|-------------|---|---|---|---|---|----|
| 1     | 1 only      | 52 | - | 48 | - | - | -  |
| 2     | 2a only     | -  | 98 | -  | 2.0| - | -  |
| 3     | 2b only     | -  | 100| -  | -  | - | -  |
| 4     | 2c only     | -  | 100| -  | -  | - | -  |
| 5     | 1 + 2a      | 35 | 47 | 13 | 0.53| 3.2 | 1.4 |
| 6     | 1 + 2a      | 22 | 20 | 4.3| <0.25| 2.0 | 1.0 |
| 7     | 1 + 2b      | 34 | 54 | 5.6| -  | 6.7 | -  |
| 8     | 1 + 2c      | 33 | 49 | 8.3| -  | 9.7 | -  |

[a] Reagents and conditions as in Scheme 1. [b] Ratios determined by 1H NMR analysis of crude reaction mixtures. [c] Competition experiment with 0.6 equiv each of 3 and 4, balance of material is recovered 1 and 2a.

When macrocycles 1 and 2a were employed together (entry 5) a complex mixture was produced consisting of all possible interlocked products. Careful 1H NMR analysis of the crude mixture revealed a number of key points. Firstly, under these conditions, simple [2]rotaxanes 5 and 6a were formed in unequal quantities, possibly indicating a difference in reactivity between 1 and 2a. However, when the reaction was run under competition conditions (entry 6), [2]rotaxanes 5 and 6a were formed in near-equall amounts, suggesting that the [2]rotaxane pathway is equally favoured for both macrocycles. Secondly, although macrocycle 2a alone forms only trace quantities of [3]rotaxane 8a, in the presence of 1, 2a is competitively recruited into the [3]rotaxane pathway and the combined yield of heterocircuit rotaxanes 9a and 10a is of the same order of magnitude as homocircuit [3]rotaxane 7. Finally, heterocircuit rotaxanes 9 and 10 were formed in an unequal ratio of isomers, suggesting that there is a significant preference in the position macrocycles 1 and 2a occupy in the mixed-macrocycle equivalents of intermediates A and B. Careful chromatography allowed the major isomer to be isolated and identified by ROESY NMR as [3]rotaxane 9a (Figure S3) suggesting that the intermediate in which macrocycle 1 coordinates to Cu(s) is favoured.

In keeping with the inability of 2b to coordinate Cu(s), the reaction with 1 with 2b (entry 7) led to a simpler product mixture containing [2]rotaxanes 5 and 6b, homocircuit product 7 and single heterocircuit [3]rotaxane isomer 9b. Finally, when 1 and 2c are employed (entry 8), both of which contain the key benzlyc ether unit, the quantity of the sole heterocircuit stereoisomer 9c increases significantly, further suggesting that

![Diagram of experimental setup](image)
the heterocircuit pathway is enhanced when both macrocycles contribute stabilizing Cu-O interactions. Chromatography allowed 9c to be isolated in 20% yield based on 1 and the stereochemistry confirmed by ROESY NMR (Figure S5).

Given the complete stereoselectivity and reasonable yield of doubly interlocked product 9c observed in the reaction of macrocycles 1 and 2c, we selected this combination for investigation under self-sorting conditions. As the sole heterocircuit product formed in the reaction between azide 3 and alkyne 4 is that in which larger macrocycle 1 is situated on the side of the axle derived from the alkyne component, we investigated the reaction of macrocycles 1 and 2c in the presence of alkyne 4 and smaller azides, 11 (Scheme 2).

Although molecular modelling indicated that the 3,5-di-1,3-butadiene moiety is smaller than the internal cavity of macrocycle 1, the reaction of azides 11a or 11b with alkyne 4 and macrocycles 1 and 2c led to complete consumption of macrocycle 1 to give metastable [2]rotaxanes 12a and 12b respectively, which slowly reverted to macrocycle 1 and the non-interlocked axle. No doubly interlocked products were isolated, suggesting these axes are too hindered to incorporate two macrocycles. Pleasingly, when azide 11c was employed which is both more flexible and less bulky, 1H NMR analysis of the crude reaction mixture (Figure 2b) revealed only the expected products: [3]rotaxane 15c (19%) and recovered 1 (81%), alongside the corresponding non-interlocked thread, and the [2]rotaxane of macrocycle 2c. [3]Rotaxane 14c was not observed. The order of the macrocyclic components on the axle of 15c was again confirmed unambiguously by ROESY NMR analysis (Figure S6).

However, when an additional portion of 2c, 4, 11c and Cu(I) was added and the AT-CuAAC reaction repeated, 1H NMR analysis indicated the conversion of 1 to 15c increased to 31% (Figure 2c; Figure 3), demonstrating that macrocycle 1 is indeed released from products 12c and 13c to be recycled into the reaction network. In this manner, over three further iterations (Figure 2d-f; Figure 3), the conversion of 1 to [3]rotaxane 15c was increased to 55%, demonstrating that self-sorting is indeed in operation, increasing the conversion of 1 to a sole interlocked product. Finally, we compared our iterative self-sorting protocol with the analogous "all in one" reaction. Repeating the AT-CuAAC reaction of 1 in the presence of an excess 2c, 4 and 11 led to 28% yield of 1 to target [3]rotaxane 15c, demonstrating the enhanced efficiency of the iterative kinetic self-sorting process.

Figure 2. Partial 1H NMR stack plot (400 MHz, 298K, CDCl3) with selected signals assigned and integrated of a) macrocycle 1, g) heterocircuit rotaxane 15c and the crude product mixtures after 1-5 rounds of AT-CuAAC coupling (b-f respectively). See Scheme 2 for labelling.

Figure 3. Relative proportions of macrocycle 1 (blue) and [3]rotaxane 15c (red) in the crude reaction mixture as a function of reaction iteration.
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In conclusion, by taking advantage of the bimetallic mechanism of the AT-CuAAC reaction, two different macrocycles can be incorporated into a [3]rotaxane product. Furthermore, by judicious choice of macrocycles, a single stereoisomer of the possible heterocircuit products is formed exclusively, raising the synthetic utility of this reaction and lending significant weight to our previous mechanistic hypothesis.[25] By adapting the reaction to include a self-sorting element based on the kinetic stabilities of the possible products, the yield of this complex interlocked target can be selectively amplified. Challenges still remain; the yield of the heterocircuit target without self-sorting remains low, albeit acceptable. Furthermore, although the self-sorting concept has been demonstrated, the reaction becomes less efficient after the first round of AT-CuAAC possibly due to Cu(I) coordination hindering the escape of macrocycle 1.[30] Studies are on-going to understand and address these remaining hurdles. Having demonstrated the potential for kinetic self-sorting in AT reactions we believe that there is significant potential to develop novel synthetic approaches that harness the detailed mechanisms of AT couplings and/or similar self-sorting processes.[31] These approaches may find wider application in the synthesis of complex, multicomponent interlocked products through the application of reactions in which two, or perhaps more, distinguishable catalytic centers are involved in the key covalent bond forming step.

Experimental Section

General procedure for the synthesis of heterocircuit [3]rotaxanes 10 and 15c: Macrocycle 1 (0.5 eq.), macrocycle 2 (0.5 eq.), azide (1.20 eq.), alkyne (1.20 eq.) and [Cu(MeCN)_4]PF_6 (0.96 eq.) were dissolved in CH_2Cl_2 and the solution was stirred at 100°C (µW) for 2 h. The solution was allowed to return to rt, diluted with CH_2Cl_2 (50 mL) and washed with NH_3-EDTA_aq. The aqueous layer was extracted with CH_2Cl_2. The organic extracts were combined, dried (MgSO_4) and reduced in vacuo.

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If at first you don’t succeed, fall apart. We demonstrate a novel self-sorting approach in which the kinetic stability of the desired [3]rotaxane isomer determines the reaction outcome. All other threaded structures derived from the larger ring are kinetically unstable, allowing the yield of the target to be amplified at the expense of other possible products.
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selected product