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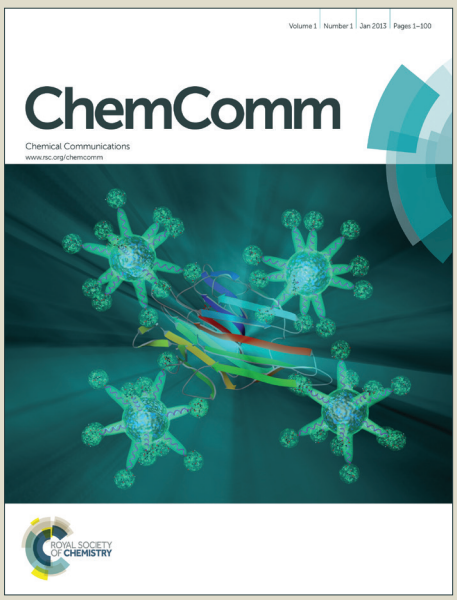

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CuAAC "click" Active Template Synthesis of Functionalized [2]Rotaxanes Using Small *exo*-Substituted Macrocycles: How small is too small?

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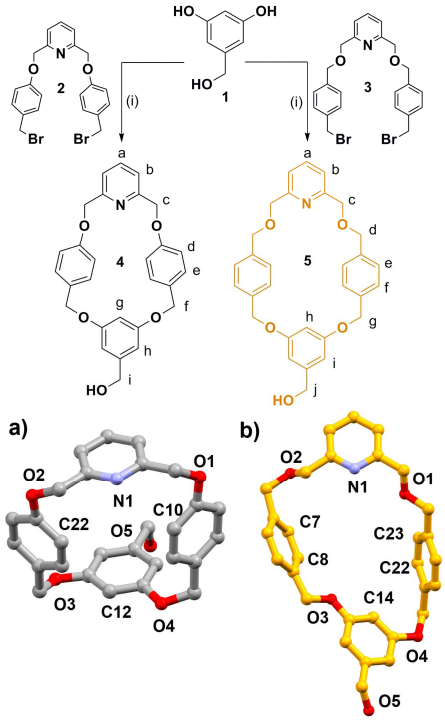
Two "small" 22- and 24-membered *exo*-alcohol functionalised pyridyl macrocycles are exploited in the CuAAC active-template synthesis of [2]rotaxanes. The 24-membered macrocycle forms [2]rotaxanes in good yields while the smaller 22-membered macrocycle does not lead to interlocked products.

The development of reliable template methods for the synthesis of mechanically interlocked architectures (MIAs)[1] has meant that these molecules have become important building blocks for a range of nanotechnologies. MIAs, particularly rotaxanes, generated using supramolecular forces (hydrogen bonding and π-π interactions) have been extensively exploited to generate a wide range of functional nanoscale systems.[2] Conversely, metal (both passive[3] and active[4] templated systems have not received as much attention in this regard. This is, in part, connected to the fact that the macrocycles used to generate these systems are often quite large (>30-membered) and as such there is a need to use large stoppers, such as triphenylmethyl (trityl) units which can be difficult to functionalise.

Recently, Goldup and co-workers[5] have demonstrated, using the highly efficient Cu(I)-catalysed Huisgen 1,3-dipolar cycloaddition of terminal azides and alkynes (CuAAC) "click" 'active' metal template (AMT) reaction[6a-c, 6d] developed by the Leigh group, that the use of smaller bipyridine (bipy) macrocycles leads to very high yields of [2]rotaxanes. Exploiting the functional group tolerance of the CuAAC they generated a family of [2]rotaxanes with a range of different small stoppers. A 26-membered bipy macrocycle[5] proved the most efficient system but due synthetic difficulties Goldup and co-workers were unable to test if smaller macrocycles were also competent in the CuAAC-AMT reaction. However, they have gone on to shown that related 26-membered bipy macrocycles can be used to generated mechanically planar chiral rotaxanes[7] and to trap the Cu(I) triazolide intermediate of the CuAAC reaction.[8] It is a matter of some interest to discover the smallest useful macrocycle that can be exploited in this reaction, in terms of atom efficiency, to get away from traditionally bulky stoppers and to increase the potential functional diversity of the MIAs.

We have been attempting to use the CuAAC-AMT strategy to generate functionalised MIAs for a variety of purposes.[9] Here, as part of work towards novel MIAs, we build on the efforts of Goldup and co-workers[5] and examine the use of two smaller 22- and 24-membered *exo*-alcohol functionalised pyridyl macrocycles in the CuAAC-AMT synthesis of [2]rotaxanes. The 24-membered macrocycle forms alcohol functionalised [2]rotaxanes in good yields while the smaller 22-membered macrocycle does not lead to interlocked products. Furthermore, the presence of the reactive alcohol functionality potentially allows the post-synthetic modification of the [2]rotaxanes and should enable the generation more highly functionalised interlocked systems.



Scheme 1 Synthesis of the 22- and 24-membered *exo*-alcohol functionalised macrocycles **4** and **5**: (i) K_2CO_3, acetone, 55 °C, 72 h. Labelled ball-and-stick diagrams of the macrocycles **4** (a) and **5** (b). Selected distances (Å) for **4** N1-C12 6.900(3), C22-C10 4.671(3), C21-C9 4.615(3) and **5** N1-C14 7.607(2), C23-C7 6.457(2), C22-C8 6.021(2).

The small *exo*-alcohol functionalised macrocycles were prepared using Williamson ether reaction conditions (Scheme 1). Under

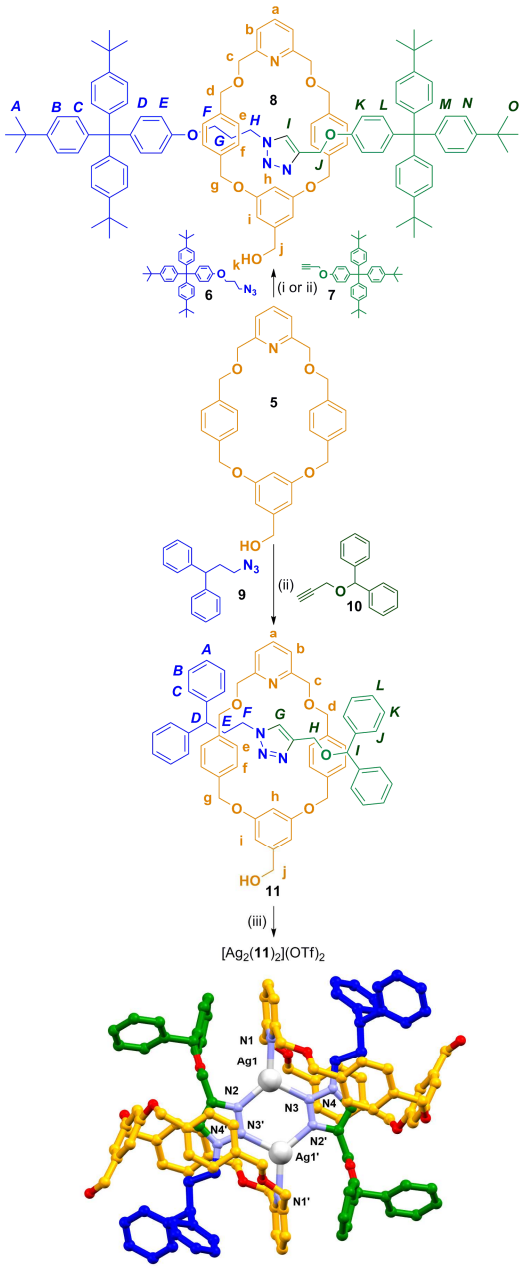
pseudo high dilution conditions, equimolar solutions of 3,5-dihydroxybenzyl alcohol (**1**) and one of the dibromides (either **2** or **3**) were heated at 55 °C with K_2CO_3 in acetone for 72 hours providing the macrocycles **4** (26%) and **5** (31%) in modest isolated yields, respectively. The macrocycles have been characterized using ^1H and ^{13}C NMR spectroscopies, high resolution electrospray ionisation mass spectrometry (HR-ESMS), elemental analyses and the molecular structures of **4** and **5** were confirmed using X-ray crystallography (Scheme 1 and ESI†).

Vapour diffusion of diethyl ether into a chloroform solution of one of the macrocycles produced single crystals suitable for X-ray diffraction. The molecular structures of **4** and **5** (Scheme 1a-b) were as expected with 22-membered system displaying a smaller cavity (N1-C12 6.900(3) Å) than the 24-membered species (N1-C14 7.607(2) Å). In both structures there are hydrogen bonding interactions between the pyridyl nitrogen atom and the OH group of the neighbouring macrocycle. For **4** this interaction generates a one dimensional chain of macrocycles arranged in a head-to-tail fashion supported by hydrogen bonds between the pyridyl nitrogen atom and the OH group of the neighbouring macrocycle (N1---O5′ 2.775(2) Å, O5′-H5′---N1 170.1(1)º, ESI†). In the larger system (**5**) the hydrogen bonding (N1---O5′ 2.841(2) Å, O5′-H5′---N1 170.69(8)º) generates a dimer of macrocycles (ESI†).

These hydrogen bonding interactions could potentially interfere with the metal ion coordination required for the AMT "click" reaction. As such we examined the coordination chemistry of the new macrocyclic ligands with both Cu(I) and the larger isoelectronic Ag(I) ions. ^1H NMR and HR-ESMS experiments on 1:1 mixtures of either $[Cu(CH_3CN)_4](PF_6)$ (1 eq.) or AgOTf (1 eq.) and one of the macrocycles **4** or **5** (1 eq.) confirmed metal ion complexation. The mass spectra all displayed prominent peaks due to [macrocycle (**4** or **5**) + M (Cu or Ag)]$^+$ ions while the ^1H NMR spectra of the 1:1 mixtures were also indicative of metal ion complexation with large downfield shifts observed for the pyridyl protons H_a and H_b in each case (ESI†). The solid state structures of the silver(I)-macrocycle complexes for both **4** and **5** confirmed that coordination to the macrocycle is through the pyridyl nitrogen atoms and that the alcohol oxygen does not interact with the metal ions (ESI†).

Having confirmed that **4** and **5** will coordinate to metal ions, CuAAC-AMT reactions were attempted with both systems. Initially, one of the macrocycles **4** or **5** (1 eq.), and the azide **6** (5 eq.), and alkyne **7** (5 eq.) stoppers were added to a CH_2Cl_2 solution containing $[Cu(CH_3CN)_4](PF_6)$ (1 eq.) and the resulting reaction mixture was stirred at 40 °C (Scheme 2). The reactions were monitored using thin-layer chromatography (TLC) and HR-ESMS and were found to proceed to completion over 48 hours. TLC analysis of the reaction mixture containing the smallest macrocycle **4** only showed the presence of the "free" macrocycle and the non-interlocked thread, no additional spots due to the [2]rotaxane were observed. This was further supported by the mass spectrum of the reaction mixture which only displayed ions due to the macrocycle, and the non-interlocked thread, no interlocked product could be detected. In contrast, TLC analysis of the reaction mixture containing the "larger" 24-membered macrocycle **5** showed three species, macrocycle, thread and the [2]rotaxane **8**. The formulation of **8** was confirmed using HR-ESMS. The spectrum displayed a major peak at *m/z* = 1635 whose isotope pattern was consistent with [**8**+Na]$^+$ ions (ESI†). After workup **8** was isolated in 17% yield. The yield of the AMT reaction could be further improved by exploiting the conditions used by Goldup and co-workers,[5] heating the reaction in a sealed tube at 80 °C for 72 hours generated **8** in 70% isolated yield.[10]

It is postulated the difference in reactivity, of the macrocycles **4** and **5**, in the CuAAC-AMT is connected to the size and conformation of the smaller macrocycle **4**. If the conformation of **4** observed in the solid state is maintained in solution then the CuAAC-AMT reaction would occur around rather than through the macrocycle's cavity. Additionally, the cavity size of **4** may be too small to accommodate the required bond formation process.



Scheme 2 The CuAAC active metal template [2]rotaxane synthesis using the *exo*-alcohol functionalised 2,6-bis[(alkyloxy)methyl]pyridine macrocycle **5**: (i) $[Cu(CH_3CN)_4](PF_6)$ (1 eq.), azide stopper (5 eq.) alkyne stopper (5 eq.), CH_2Cl_2, 40 °C, 48 h; (ii) $[Cu(CH_3CN)_4](PF_6)$ (1 eq.), azide stopper (5 eq.) alkyne stopper (5 eq.), CH_2Cl_2, 80 °C, 72 h; (iii) AgOTf, methanol, RT, 1h. Bottom, the molecular structure of the bis-([2]rotaxane) dimer $[Ag_2(\mathbf{11})_2](OTf)_2$. Selected distances (Å) and angles (°) for $[Ag_2(\mathbf{11})_2](OTf)_2$: Ag1-N1 2.216(3), Ag1-N2 2.191(3), Ag1-N3 2.278(2), N3-Ag1-N1 114.39(9), N2-Ag1-N1 132.1(1), N3-Ag1-N2 113.30(9). Symmetry codes x,y,z and –x,-y,-z.

Consistent with the HR-ESMS data the ^1H and DOSY NMR spectra of the isolated material were indicative of [2]rotaxane formation. All the proton signals due to the macrocyclic and thread components of **8** displayed the same diffusion co-efficient (D = 3.39 × 10^{-10} m^2 s^{-1}) indicating that they are part of the same species. ^1H

NMR spectrum of **8** in $CDCl_3$ (Figure 1b) was very similar to that of previously reported "click" AMT [2]rotaxanes.[5, 6c, 6d, 7-8] Large upfield shifts, with respect to its non-interlocked components (Figure 1a and c, respectively) are observed for several signals. This type of shielding is commonly observed in interlocked architectures which feature aromatic units positioned face-on to the thread component of the rotaxane. The triazole protons (H_I) on the thread was shifted downfield presumably due to a hydrogen bonding interaction (C-H---N) between the nitrogen atom of the pyridine and the hydrogen atom on the 1,2,3-triazole.[5, 7-8] Additionally, the resonances corresponding to the macrocycle's methylene groups protons (H_d and H_g) split into diastereotopic pairs due to the reduced symmetry within the [2]rotaxane.

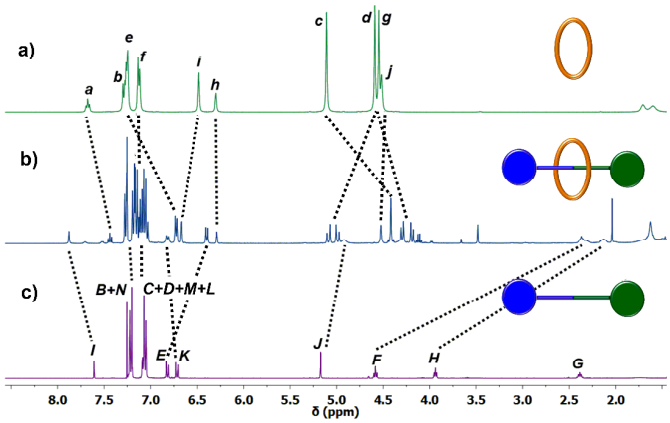


Fig. 1 Partial stacked ^{1}H NMR spectra ($CDCl_3$, 298K) of a) macrocycle **5**, b) [2]rotaxane **8**, c) 1,2,3-triazole thread.

Next we examined if the large trityl stoppers **6** and **7** could be replaced by smaller more readily accessible units in the same way that Goldup and co-workers have already demonstrated with their larger 26-membered bipy macrocycle.[5] Reaction of **5** (1 eq.) with the smaller azide **9** (5 eq.) and alkyne **10** (5 eq.) stoppers in the presence of $[Cu(CH_3CN)_4](PF_6)$ (1 eq.) in CH_2Cl_2 solution at 80 °C (Scheme 2), resulted in the formation of the small [2]rotaxane **11** (52%). The ^{1}H and DOSY NMR spectra and HR-ESMS data (*m/z* = 965 [**11**+Na]$^+$) of **11** were consistent with the formation of the interlocked product (ESI†) and the molecular structure was confirmed using X-ray crystallography (*vide infra*).

There has been considerable recent interest in the development of rotaxane ligands.[2e, 2i] The [2]rotaxane **11** contains both pyridyl and 1,2,3-triazoyl[11] ligating units as such we examined the silver(I) coordination chemistry of the MIA. Vapour diffusion of petroleum ether into a 1:1 mixture of the [2]rotaxane ligand **11** and Ag(OTf) in methanol led to the formation of colourless X-ray quality crystals. The molecular structure of the silver(I) complex was determined using X-ray crystallography and revealed that a 2:2 silver(I)-[2]rotaxane dimer is generated under these conditions (Scheme 2).

The silver(I) ions are coordinated to three nitrogen atoms in a trigonal planar geometry. The pyridyl nitrogen of the macrocycle and the less electron-rich nitrogen atom of the 1,2,3-triazoyl unit of the same rotaxane act as a bidentate chelate ligand for the silver(I) ions. The more electron-rich nitrogen of the 1,2,3-triazoyl unit on a second rotaxane ligand completes the coordination sphere of the silver ions generating the dimeric structure. The 1,2,3-triazole units act as bridging ligands consistent with literature reports on similar complexes.[12] The ^{1}H and DOSY NMR and HR-ESMS spectra of the isolated $[Ag_2(\mathbf{11})_2](OTf)_2$ complex suggest that the interesting bis-([2]rotaxane) structure is maintained in solution (ESI†).

In conclusion we have demonstrated that a "small" readily synthesised 24-membered *exo*-alcohol functionalised 2,6-bis[(alkyloxy)methyl]pyridine macrocycle can be exploited in the CuAAC "click" active-template synthesis of [2]rotaxanes. The related 22-membered macrocycle does not lead to interlocked products under the same condition, and thus it appears that a 24-membered macrocycle represents the lower limit of required macrocycle size for a successful CuAAC-AMT outcome. The small macrocycle size enables the incorporation of much smaller and more readily functionalised stopper units into the MIAs.[5] Furthermore, the presence of the reactive alcohol functionality with the macrocyclic component opens up the possibility for the post-synthetic modification of these [2]rotaxanes, which could be exploited to generate additional molecular complexity. The ready synthesis of multifunctional rotaxanes has potential in a range of areas and efforts to exploit this methodology to synthesise rotaxane ligands, poly-rotaxanes, and molecular machines are currently underway.

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Notes and references

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†Electronic Supplementary Information (ESI) available: the supplementary information contains the experimental procedures, ^{1}H, ^{13}C and DOSY NMR, HR-ESMS and crystallographic data. CCDC reference numbers 997798-997802. See DOI: 10.1039/b000000x/

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