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Synthesis of a [2]catenane by ring closing metathesis of a [2]rotaxane prepared by crown ether active templation†

Sean R. Barlow and Nicholas H. Evans *

The high yielding synthesis and spectral characterization of a [2]catenane prepared by Grubbs catalyzed ring closing metathesis of a [2]rotaxane prepared by crown ether active template synthesis is described.

Introduction

[2]Catenanes[1] – molecules consisting of two interlocked macrocyclic rings – are typically synthesized by templated self-assembly followed by covalent bond formation. Classic examples of templates/templating interactions used in the self-assembled synthesis of [2]catenanes include metal cations,[2] π–π stacking[3] and hydrogen bonding.[4] Considering the emerging functional applications of [2]catenanes (*e.g.* receptors in host–guest chemistry[5] and as catalysts in chemical reactions[6]) – the ready access to such species is paramount.

As part of investigations aiming to achieve post-synthetic modification of mechanically interlocked molecules[7] – we wished to prepare a [2]catenane possessing amide N–H functionality not sterically blocked by the interlocked architecture. Our attention was caught by the recently disclosed crown ether active templation methodology for the synthesis of rotaxanes.[8] Conversion of a [2]rotaxane into a [2]catenane is possible by cyclizing an appropriately functionalized axle component.[9] We therefore proposed that by attaching terminal vinyl groups to the axle of a [2]rotaxane prepared by crown ether active template synthesis (CEATS), that cyclization to a [2]catenane could be achieved by Grubbs catalyzed ring closing metathesis (RCM) (Fig. 1).[10] This communication details the successful execution of this proposed strategy, hence demonstrating that CEATS may be used to prepare [2]rotaxane precursors to [2]catenanes.[11]

Results and discussion

Our successful route, used the amide-forming CEATS (rather than our original plan to use the nucleophilic aromatic substitution variant), requiring synthesis of amine (**HA-1**) and activated ester (**HA-2**) half-axles (Schemes 1 and 2).[11] Trifluoromethyl and *tert*-butyl groups were included in **HA-1** and **HA-2** respectively to act as steric blocking groups to ensure capture of crown ether macrocycle upon axle formation.[12] Rigid aromatic spacers to the terminal vinyl groups were also included to entropically aid the final RCM cyclization step.

The synthetic route to amine half-axle **HA-1** is presented in Scheme 1. Phenol **2**[13] was alkylated with the mesylate of compound **1**[14] to afford compound **3**. Subsequent hydrolysis of the ester generated carboxylic acid **4**. This was then converted to its acid chloride (using oxalyl chloride and catalytic DMF) and

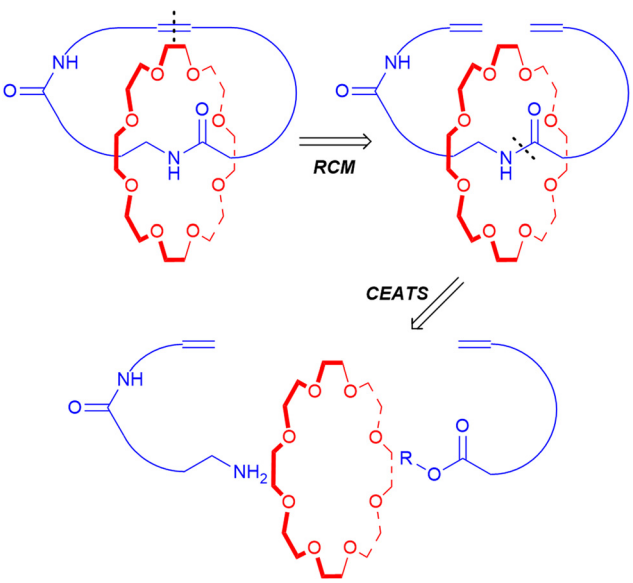
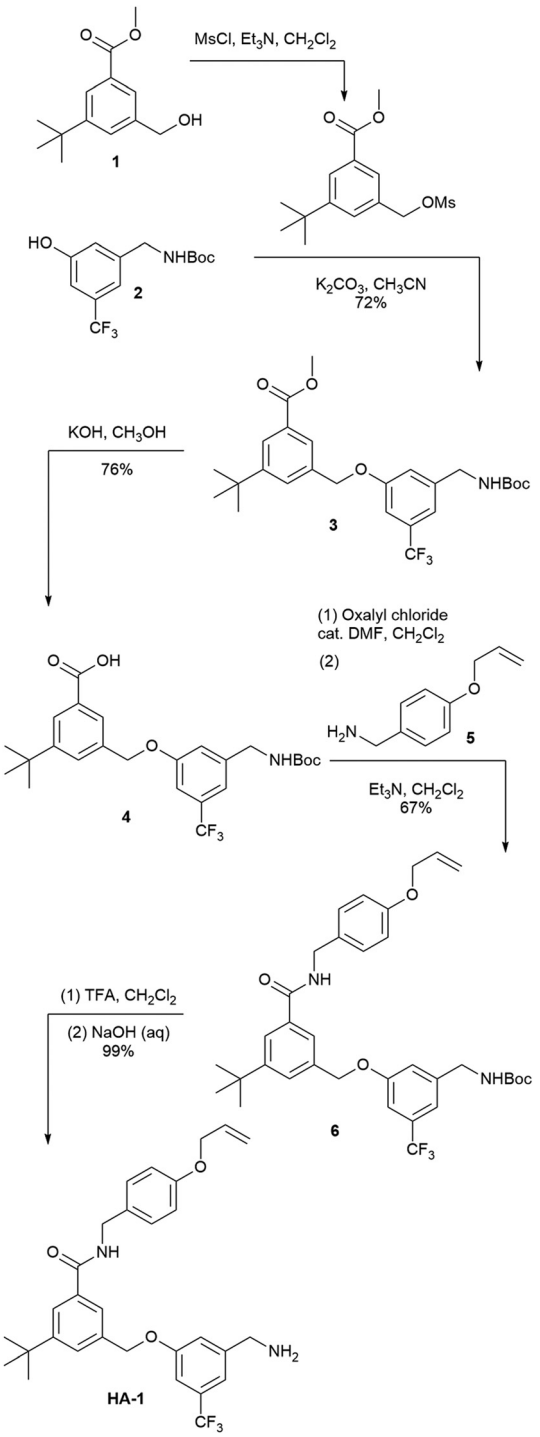


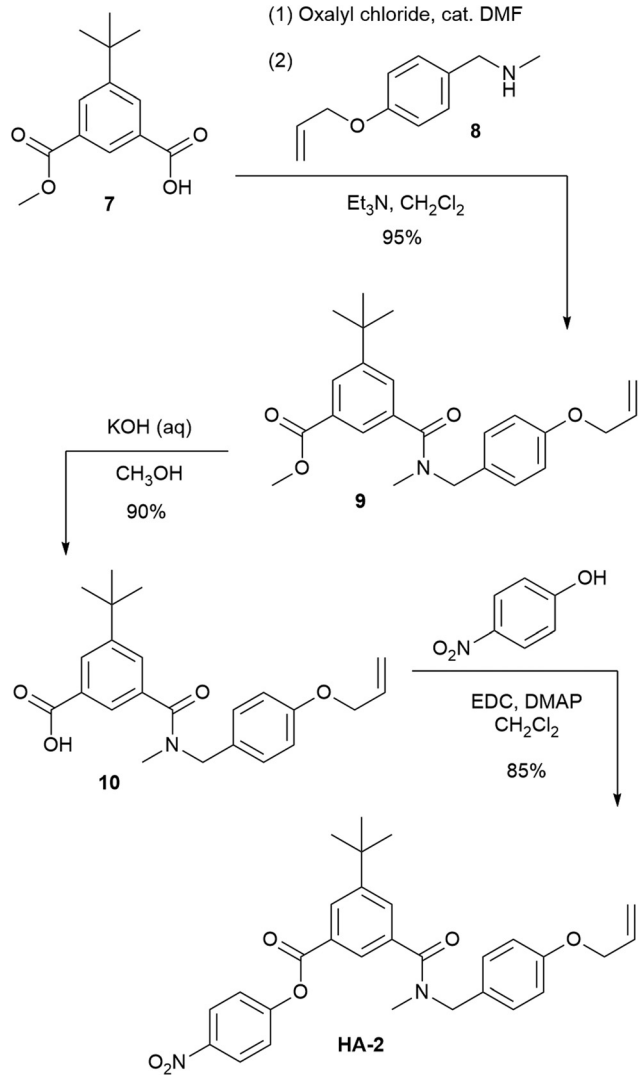
Fig. 1 Schematic retrosynthetic analysis of target [2]catenane.

Department of Chemistry, Lancaster University, Lancaster, LA1 4YB, UK.
E-mail: n.h.evans@lancaster.ac.uk

†Electronic supplementary information (ESI) available: Details of experimental procedures (including further synthetic investigations); copies of characterization spectra. See DOI: https://doi.org/10.1039/d4ob01028k



Scheme 1 Synthesis of amine half axle **HA-1**.



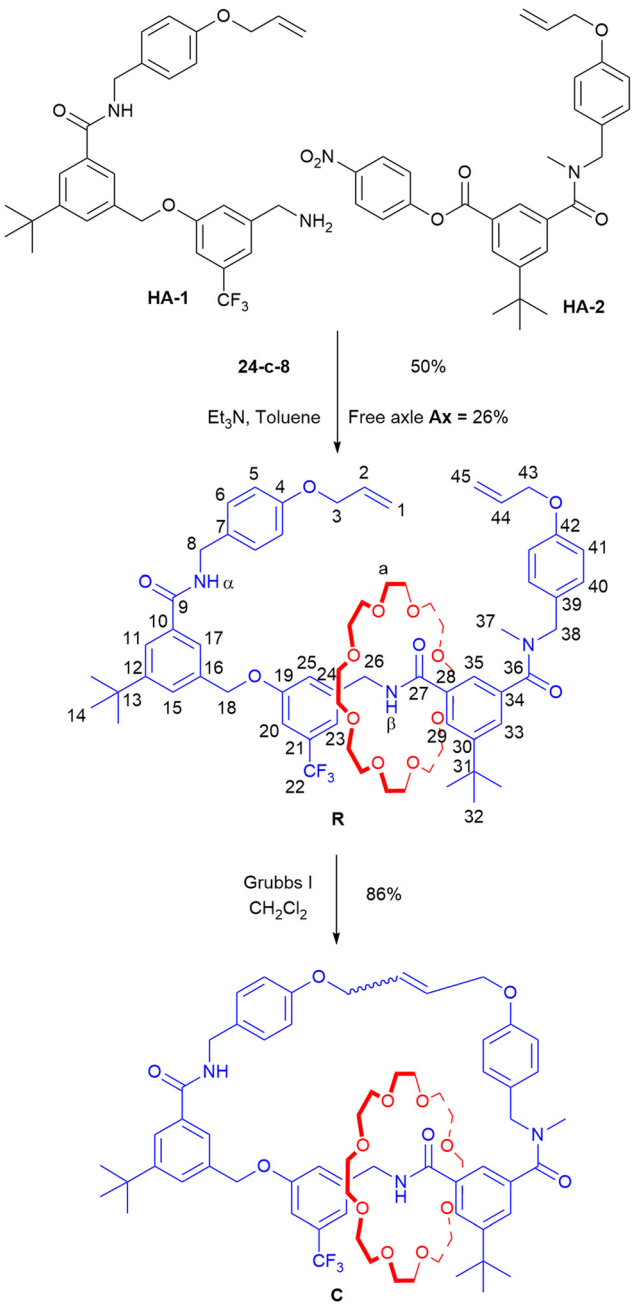
Scheme 2 Synthesis of activated ester half axle **HA-2**.

reacted with amine **5**.[15] The isolated amide **6** was subjected to Boc-deprotection using TFA to afford the amine half axle **HA-1**.

The synthesis of the activated ester half axle **HA-2** is shown in Scheme 2. Installation of the tertiary amide was accomplished *via* an acid chloride mediated amide formation of mono-methyl ester **7**[16] with secondary amine **8**.[17] Hydrolysis of the ester in **9** was then carried out to afford carboxylic acid **10**. Finally, to generate the target activated ester **HA-2**, carboxylic acid **10** was reacted with *p*-nitrophenol *via* EDC-mediated ester formation.

With the half axles now in hand, rotaxane synthesis could be attempted (Scheme 3). Half axle **HA-1** and 24-crown-8 (**24-c-8**)[18] were dissolved in dry toluene and stirred for 10 minutes. Then, Et_3N was added followed by slow addition of a solution of 1.3 equivalents of activated ester **HA-2** in dry toluene. The reaction was left to stir at room temperature for four days. The reaction mixture was then concentrated to dryness and purified by column chromatography. Target [2]rotaxane **R** was isolated in a 50% yield.

[2]Rotaxane **R** was characterized by NMR and IR spectroscopies, and high-resolution mass spectrometry. Evidence for rotaxane formation is clearly visible upon comparison of the ^{1}H NMR spectra of [2]rotaxane **R** and free axle **Ax** (Fig. 2). The crown ether protons *a* are split as the two faces of the ring experience different chemical environments. There are also



Scheme 3 Synthesis of [2]rotaxane **R** and [2]catenane **C**.

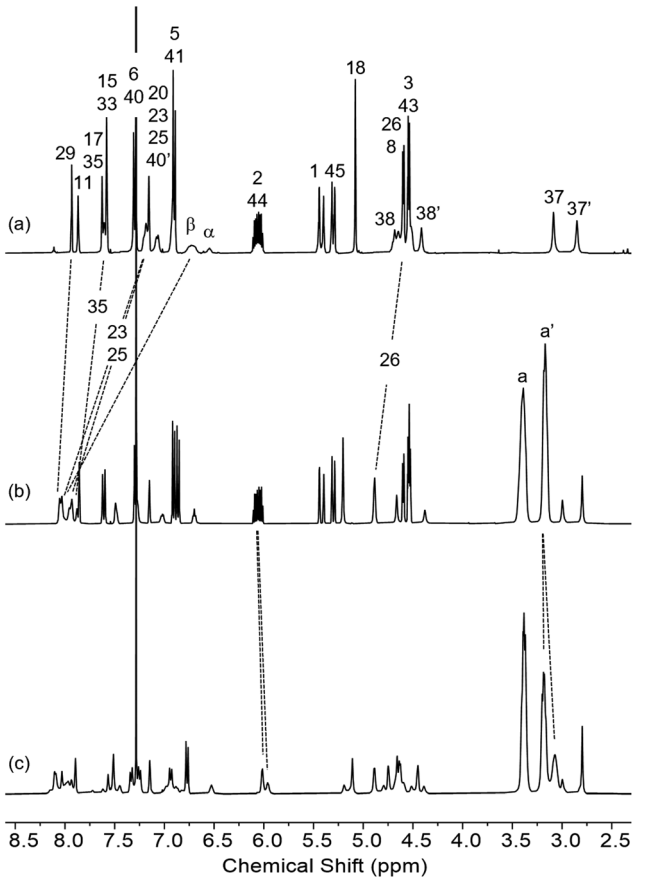


Fig. 2 Partial ^{1}H NMR spectra of (a) the free axle **Ax**, (b) [2]rotaxane **R** and (c) [2]catenane **C** ($CDCl_3$, 400 MHz, 298 K). See Scheme 3 for atom labels.

downfield shifts for the newly formed axle amide N–H *β*, along with axle protons *23*, *25*, *26*, *29* and *35*, arising from hydrogen bonding to oxygen atoms of the crown ether ring. Further evidence to support isolation of [2]rotaxane **R** was provided by detection of the molecular ion peak, $[M + H]^+$, at m/z = 1242.6509 Da, in the high resolution mass spectrum (see ESI†).

With [2]rotaxane **R** afforded in sufficient quantity, synthesis of target [2]catenane **C** was undertaken. To generate the catenane, a ring closing metathesis using Grubbs first-generation catalyst (Grubbs I) under high dilution conditions was selected (Scheme 3). The synthesis began by dissolving [2]rotaxane **R** in dry CH_2Cl_2 to afford a 1.2 μM solution. Grubbs I catalyst (20 mol%) was added portion wise over 30 minutes, then the reaction was stirred in the dark for 16 hours. The reaction mixture was then concentrated to dryness and the crude material chromatographically purified, with [2]catenane **C** isolated in a yield of 86%.[19]

Evidence for the formation of [2]catenane **C** can be observed when comparing its ^{1}H NMR spectrum to that of [2]rotaxane **R** (Fig. 2). Despite broadening of axle peaks, successful cross metathesis is clearly identifiable by loss of terminal alkene protons *1* and *45* and simplification of the multiplet for protons *2* and *44* to two broad singlets (indicating formation of both olefinic geometric isomers).[20,21] Once again, isolation of the target interlocked molecule was provided by detection of the molecular ion peak, $[M + H]^+$, at m/z = 1214.6211 Da, in the high resolution mass spectrum (see ESI†).

Conclusions

The synthesis of a [2]catenane by adaptation of the recently disclosed CEATS of [2]rotaxanes has been demonstrated. The combination of good and excellent yields for, respectively, [2]

rotaxane and [2]catenane formation steps makes the synthetic route described above appealing for the preparation of [2]catenanes.[22] The synthesis of further [2]catenanes, and their subsequent post-synthetic modification to allow for deployment in a range of host–guest applications, is ongoing in our laboratories and will be reported in due course.

Author contributions

NHE proposed the study. SRB conducted the synthesis and characterization of materials. NHE supervised the work, and completed further synthesis and characterization in response to the comments of the reviewers. NHE (with assistance from SRB) wrote the manuscript. SRB (with assistance from NHE) complied the ESI.†

Data availability

Underlying data for this paper are provided in the ESI.† Electronic copies of NMR spectra (including fid files) will be available upon publication from: **https://doi.org/10.17635/lancaster/researchdata/671** and **https://doi.org/10.17635/lancaster/researchdata/685**.

Conflicts of interest

There are no conflicts of interest to declare.

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11 For subsequent investigations, we originally targeted a [2]catenane possessing a single amide N–H, anticipating

RCM of a [2]rotaxane prepared by the nucleophilic aromatic substitution variant of CEATS. However, as detailed in the ESI,† the yields of rotaxane formation were very low. Hence attention turned to preparing a [2]rotaxane by use of the amide formation variant of CEATS. As a consequence, [2]rotaxane **R** and [2]catenane **C** possess two N–H amides – but the amide N–H (β) formed by CEATS is sterically blocked by the **24-c-8** macrocycle.

12 Leigh and co-workers have reported that using the electron withdrawing trifluoromethyl instead of *tert*-butyl group on the amine half-axle leads to higher yields of [2]rotaxane formation in amide- forming CEATS (see ref. 8c).

13 Details of our synthesis of **2** from commercially available materials is to be found in the ESI.†

14 Details of our synthesis of **1** from commercially available materials is to be found in the ESI.†

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19 Chromatographic separation of [2]rotaxane **R** and [2]catenane **C** proved challenging. As reported in the original manuscript submission, using column chromatography, SRB was able to collect two fractions containing predominantly [2]catenane **C**, one >99 : 1 **C** : **R** which was used for spectral characterization. In response to reviewer comments regarding how the yield of the reaction was being reported, NHE repeated the RCM reaction and using preparative TLC isolated pure [2]catenane **C** in the quoted yield of 86%.

20 Rotamers, arising from the presence of the N–Me amide, are observed in the ^{1}H NMR spectra recorded at room temperature in $CDCl_3$ of free axle **Ax**, [2]rotaxane **R** and [2]catenane **C**, as evidenced by splitting of proton *37* resonance in all three spectra. Notably, upon RCM to form [2]catenane **C**, the number of protons exhibiting rotameric behaviour increases, including splitting of the peak for macrocyclic proton *a*′.

21 Hydrogenation of the C=C bond (which may have simplified the ^{1}H NMR spectrum) was not attempted due to the likelihood of cleaving benzylic ether linkages.

22 As suggested by a reviewer, we are planning in future work to investigate the direct CEATS of a [2]catenane by use of a linked amine-activated ester precursor.