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COMMUNICATION

## Modulating the expression of chirality in a mechanically chiral rotaxane†

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**The expression of mechanical chirality by a hydrogen bond templated rotaxane, as detected by  $^1\text{H}$  NMR spectroscopy, may be modulated by affecting the co-conformational behaviour of the rotaxane through varying solvent or by addition of acid and base.**

The synthesis and functional application of chiral rotaxanes and catenanes is a blossoming area of research within supramolecular chemistry.<sup>1-3</sup> A mechanically interlocked molecule (MIM) may be made chiral by inclusion of a classical chiral element (e.g. a chiral centre, axis or plane).<sup>4-6</sup> Alternatively, a MIM may be chiral by virtue of the mechanical bond, so-called *mechanical chirality*. Commonly encountered occurrences of mechanical chirality in MIMs are [2]catenanes consisting of two directional rings and [2]rotaxanes consisting of directional ring and axle components (Figure 1a).<sup>7-9</sup>

Noteworthy recent achievements with chiral MIMs include the successful preparative scale preparation of enantiopure mechanically chiral rotaxanes without resorting to chiral HPLC for the separation of enantiomers,<sup>10,11</sup> chiral MIMs being used as enantioselective receptors and asymmetric catalysts,<sup>12-19</sup> and induction of single-handed helicity of a polymer by use of a mechanically chiral rotaxane as the source of chirality.<sup>20</sup>

MIMs are perhaps most well-known for the possibilities of controlled large amplitude motion of their interlocked components, through either change of environment, or application of a stimulus.<sup>21,22</sup> Examples of such controlled motion in chiral MIMs are rare. Leigh and co-workers have reported upon rotaxanes where the expression of chirality (as detected by circular dichroism) was modulated by solvent and temperature<sup>23</sup> and light.<sup>24</sup> More recently the same group, disclosed a pH switchable rotaxane catalyst for controlled asymmetric Michael additions.<sup>25</sup> Takata *et al* have also demonstrated control of the handedness of a polyacetylene helix by use of a pendant chiral rotaxane switch.<sup>26</sup> In all these rotaxanes, the chirality arose from inclusion of a classical chiral element.

Here we present the preparation of a novel mechanically chiral [2]rotaxane **1** whose detectable *mechanical* chirality may be modulated by solvent as monitored by  $^1\text{H}$  NMR spectroscopy. Further it also demonstrated that the expression of chirality may also be reversibly modulated by the addition of acid and then base (Figure 1b). By dissolving the rotaxane in a hydrogen bond accepting solvent, or adding trifluoroacetic acid (TFA), the templating hydrogen bond interactions between the macrocycle and the amide of the axle are disrupted. The resulting changes in co-conformational behaviour are reported by variation in the appearance of a proton environment in the  $^1\text{H}$  NMR spectrum of the rotaxane.

Mechanically chiral [2]rotaxane **1** was prepared using our recently reported hydrogen bond templated strategy (Scheme

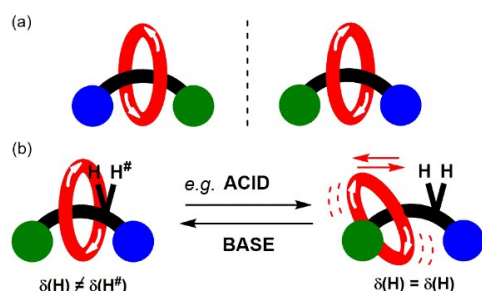


Figure 1: Schematic representations of: (a) the enantiomers of a mechanically chiral [2]rotaxane consisting of directional ring and axle; (b) stimuli controlled variation in co-conformational behaviour of a mechanically chiral [2]rotaxane, that leads to modulation in expression of chirality as detected by  $^1\text{H}$  NMR spectroscopy.

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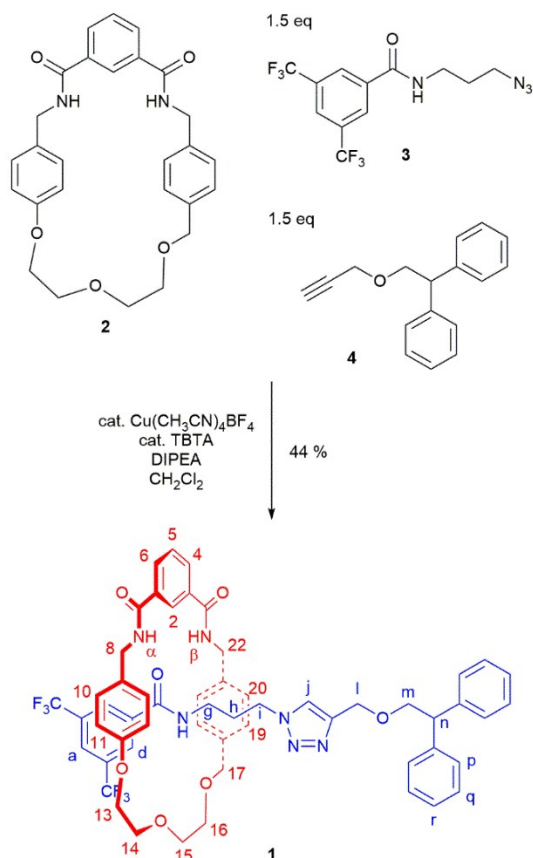
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† Electronic Supplementary Information (ESI) available: Experimental procedures; copies of spectral characterisation data; further data and protocols for titrations and details of computational modelling. See DOI: 10.1039/x0xx00000x



1).<sup>27</sup> A novel rotationally asymmetric macrocycle **2** (for synthesis see page S3 ESI<sup>†</sup>) was dissolved in dichloromethane in the presence of 1.5 equivalents of azide **3**<sup>27</sup> and 1.5 equivalents of alkyne **4**<sup>28</sup>. Catalytic  $\text{Cu}(\text{CH}_3\text{CN})_4\text{BF}_4$  and TBTA and 1.6 equivalents of DIPEA were added and the reaction stirred overnight at room temperature under an inert atmosphere. After aqueous work-up and careful silica gel column chromatography, rotaxane **1** was isolated in 44 % yield.



Rotaxane **1** was characterised by NMR and IR spectroscopy and mass spectrometry (see Figure 2 and pages S18–S26 ESI<sup>†</sup>). Preliminary inspection of the  $^1\text{H}$  NMR spectrum (in  $\text{CDCl}_3$ ) reveals that the macrocyclic aromatic protons **10**, **11**, **19** and **20** are markedly downfield (6.10 – 6.75 ppm) of the typical aromatic region, consistent with interlocked structure formation (Figure 2). A peak attributable to the molecular ion peak at  $m/z = 1037.3949$  is also observed in the positive-ion electrospray mass spectra (see page S26 ESI<sup>†</sup>). An analytical sample of rotaxane **1** was submitted to chiral HPLC, with almost complete resolution of the two enantiomers achieved using a CHIRAL-PAK AD-H column (see Figure 3).

Like for the analogous achiral rotaxane previously reported,<sup>27</sup> the  $^1\text{H}$  NMR spectrum of rotaxane **1** has separate peaks for each of the two protons in environments **8** and **17** (but interestingly not **22**), arising from the two faces of the macrocyclic ring being inequivalent due to the directionality of the threaded axle.

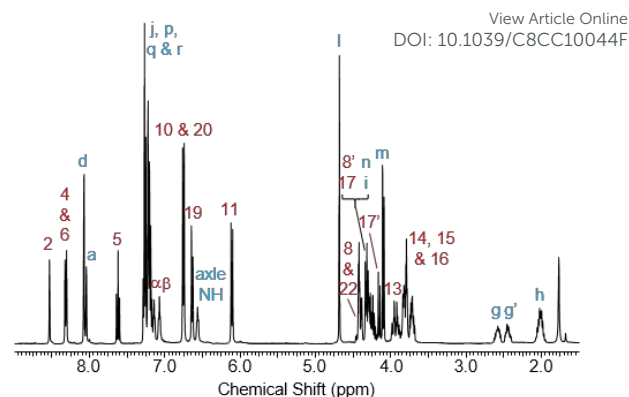


Figure 2 –  $^1\text{H}$  NMR spectrum of rotaxane **1** ( $\text{CDCl}_3$ , 400 MHz, 298 K). Atom labels are defined in Scheme 1.

In addition, it can clearly be seen that the two axle protons *g* result in separate resonances, which was not observed in the previously reported achiral example.<sup>27</sup> This is attributed to the two protons being diastereomeric, arising from the mechanical chirality of rotaxane **1**. Considering that the neighbouring protons *h* are not split (to any significant extent), the close proximity of the macrocyclic ring, appears to be essential to observe diastereomeric behaviour. Evidence that the macrocycle is residing on the amide of the axle in chloroform (and hence is in closer proximity to protons *g* rather than *h*) is provided by the ROESY spectrum of rotaxane **1** in  $\text{CDCl}_3$  (see page S25 ESI<sup>†</sup>). This reveals through-space inter-component correlations between macrocycle protons and axle protons *d*, *g* and *h*, entirely consistent with the co-conformation depicted in Scheme 1. In addition, DFT calculations (see Figure 4 and pages S44–S45 ESI<sup>†</sup>) indicate that it is energetically favourable for the macrocycle to reside on the axle amide, rather than the triazole, which is the only other possible hydrogen bond donor/acceptor on the axle.<sup>29</sup>

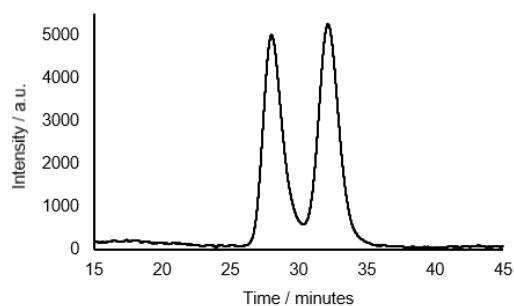


Figure 3 – Chiral HPLC trace of rotaxane **1** (CHIRAL-PAK AD-H 4.6 × 250 mm, 4:1 hexane:IPA. 1.5 mL/min,  $\lambda_{\text{abs}} = 240$  nm).

To test whether the co-conformational behaviour of **1** could be affected by varying the solvent (which may induce motion of the macrocycle by disruption of hydrogen bonding),<sup>30</sup> a solvent screen was carried out (Figure 5). It can be seen clearly that only in  $\text{CDCl}_3$  are the two resonances for *g* and *g'* fully resolved, while in  $\text{D}_6$ -DMSO they have (almost) completely coalesced. For the range of solvents tested here, there is at least a qualitative correlation between decreasing separation of resonances for *g*



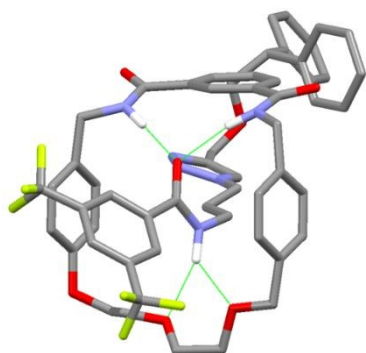


Figure 4 – Minimum energy DFT calculated structure of rotaxane **1**. Hydrogen bonds are represented by green dashed lines. For details of calculations, see ESI†.

and  $g'$  and ability of the solvent to compete as a hydrogen bond acceptor, as reflected by increasing Gutmann donor number of the solvent (chloroform (0) > acetonitrile (14) > acetone (17) > methanol (19) > DMSO (30)).<sup>31, 32</sup>

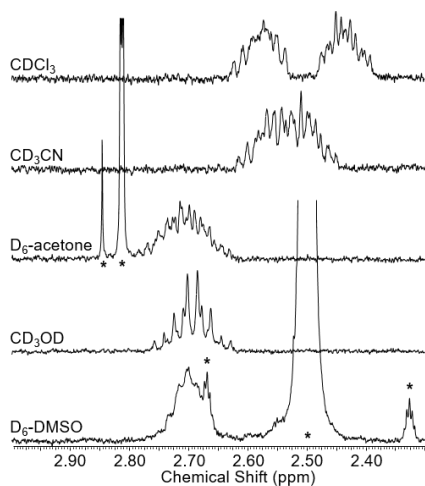


Figure 5 – Partial  $^1\text{H}$  NMR spectra of rotaxane **1** in various solvents (2.5 mM, 400 MHz, 298 K). Solvent peaks marked with asterisks.

Our attention then turned to whether the co-conformational behaviour of the rotaxane could be varied by the addition of acid and base.<sup>33</sup> The addition of excess TFA to a sample of rotaxane **1** dissolved in  $\text{CDCl}_3$  leads to a downfield shift and merging of  $g$  and  $g'$  in the  $^1\text{H}$  NMR spectrum (see Figure 6 and page S36 ESI†). This is consistent with the macrocycle translating away from the axle amide: the alkyl protons  $g$  and  $g'$  will be less shielded and no longer close enough to experience the rotational asymmetry of the macrocycle. Addition of  $\text{D}_5$ -pyridine to neutralise the TFA reverses the shift and restores the separate peaks for  $g$  and  $g'$ .

Further insight into the co-conformational behaviour of rotaxane **1**, upon the addition of TFA in  $\text{CDCl}_3$ , was sought by studying peaks other than  $g$  and  $g'$  in the  $^1\text{H}$  NMR spectrum (see Figure 7 and page S36 ESI†). Protons  $h$  and  $l$  move upfield upon addition of TFA, i.e. these protons are experiencing greater shielding, implying greater residence within the macrocycle cavity. Meanwhile protons  $d$  move downfield suggesting they are further away from the macrocycle cavity. Macrocycle proton 2 moves upfield, consistent with a reduction in hydrogen bonding to the carbonyl O of the axle amide.

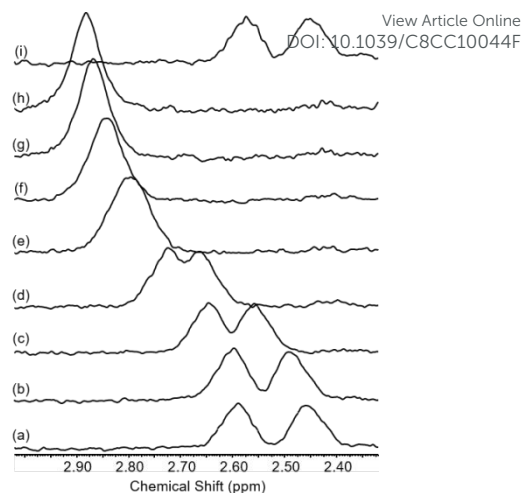


Figure 6 – Partial  $^1\text{H}$  NMR spectra of rotaxane **1** with: (a) 0 eq of TFA, (b) 2 eq of TFA, (c) 5 eq of TFA, (d) 10 eq of TFA, (e) 20 eq of TFA, (f) 30 eq of TFA, (g) 40 eq of TFA, (h) 50 eq of TFA, (i) 50 eq of TFA + 50 eq of  $\text{D}_5$ -pyridine. ( $\text{CDCl}_3$ , 400 MHz, 298 K. Spectra Fourier transformed with a line broadening of 3 Hz.)

Furthermore, a  $^1\text{H}$ - $^1\text{H}$  ROESY NMR spectrum was recorded (see page S43 ESI†). The addition of an excess of TFA resulted in a poor signal/noise ratio, necessitating a large number of scans to identify inter-component correlations, between macrocycle protons and those of axle protons  $d$ ,  $g$ ,  $h$  and  $l$ . Combining this result, with the study of the 1D  $^1\text{H}$  NMR spectra detailed above, and the apparent lack of splitting of any resonance arising from an axle proton environment, we suggest that in the presence of TFA, rotaxane **1** is dynamically occupying multiple co-conformations, rather than the single well-defined co-conformation depicted in Scheme 1. Multiple O atoms (plus the triazole N) may protonate possibly leading to a complicated set of hydrogen bond templated co-conformations.<sup>34</sup> Undoubtedly, there is a significant change in the co-conformational behaviour of rotaxane **1** upon addition of TFA.<sup>35</sup>

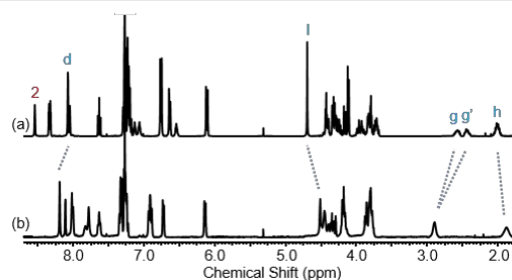


Figure 7 –  $^1\text{H}$  NMR spectra of rotaxane **1** with: (a) 0 eq of TFA and (b) 40 eq of TFA ( $\text{CDCl}_3$ , 400 MHz, 298 K). Selected atom labels are defined in Scheme 1.

In conclusion, it is possible to modulate the detectable chirality in the racemate of a mechanical chiral rotaxane by using two sets of *achiral* parameters – solvent and addition of acid and base – to affect the co-conformational behaviour of the rotaxane. Notably, to observe the influence of mechanical chirality upon the particular proton environment studied here, appears to require strict adherence of the rotaxane to a specific hydrogen bond supported co-conformation. In the future, we envisage that controlled variation between co-conformations of mechanically chiral rotaxanes could be used to create switchable molecular devices for various chiral applications.





Research on chiral rotaxanes and their application is continuing in our laboratories and will be reported in due course.

We express our appreciation to the Faculty of Science and Technology at Lancaster University for a PhD studentship (C. E. G.) and the EPSRC (Institutional Sponsorship Grant: EP/P511183/1) for financial support of an Equality and Diversity internship (T. A. M.-I). N. H. E. also wishes to thank the Royal Society of Chemistry for a Research Grant that funded some preliminary experiments on chiral rotaxanes. At Lancaster University, we thank Dr Geoff Akien for donation of D<sub>5</sub>-pyridine and advice on NMR spectroscopy, Dr David Rochester for the recording of mass spectra and chiral HPLC, as well as Dr Michael Peach for advice on computational modelling.

Underlying data for this paper are provided in the experimental section and the ESI. Electronic copies of NMR spectra (including fid files) and computational output files are available from: DOI: 10.17635/lancaster/researchdata/159 & DOI: 10.17635/lancaster/researchdata/255.

### Conflicts of interest

There are no conflicts to declare.

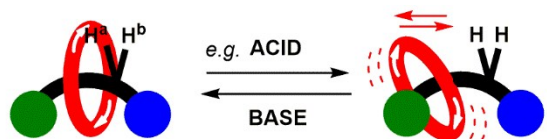
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- Multiple attempts to grow single crystals of rotaxane **1** suitable for X-ray diffraction structural determination have been undertaken, but alas none have been successful.
- For examples of well-defined hydrogen bonded co-conformational behaviour being disrupted in rotaxanes by varying solvent, see: (a) D. A. Leigh, M. A. F. Morales, E. M. Pérez, J. K. Y. Wong, C. G. Saiz, A. M. Z. Slawin, A. J. Carmichael, D. M. Haddleton, A. M. Brouwer, W. J. Buma, G. W. H. Wurpel, S. León and F. Zerbetto, *Angew. Chem. Int. Ed.* 2005, **44**, 3062-3067; (b) T. Da Ros, D. M. Guldi, A. F. Morales, D. A. Leigh, M. Prato and R. Turco, *Org. Lett.*, 2003, **5**, 689-691; (c) J. M. Maloney, R. Shukla, R. A. Marshall, A. M. Beatty, J. Zajicek and B. D. Smith, *J. Org. Chem.*, 2002, **67**, 1436-1440.
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- To provide further insight into the stability of the macrocycle residing on the axle amide, NMR titrations experiments were undertaken where benzanilide was added to macrocycle **2** (see pages S28-S32 ESI<sup>†</sup>). While a pseudorotaxane forms in CDCl<sub>3</sub>, this does not occur in either D<sub>6</sub>-acetone or D<sub>6</sub>-DMSO.
- For examples of hydrogen bonded co-conformational behaviour of rotaxanes and catenanes varied by addition of acid and base, see: (a) M.-V. Martínez-Díaz, N. Spencer and J. F. Stoddart, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 1904-1907; (b) C. M. Keaveney and D. A. Leigh, *Angew. Chem. Int. Ed.*, 2004, **43**, 1222-1224; (c) K.-Y. Ng, V. Félix, S. M. Santos, N. H. Rees and P. D. Beer, *Chem. Commun.*, 2008, 1281-1283; (d) B. Hesseler, M. Zindler, R. Herges and U. Lüning, *Eur. J. Org. Chem.*, 2014, 3885-3901.
- Preliminary DFT calculations have been carried out to identify plausible protonated hydrogen bond templated co-conformations (see page S46 ESI<sup>†</sup>).
- We also investigated whether it was possible to modulate the expression of chirality by the addition of the Li<sup>+</sup> cation. Pirouetting of similar rotaxanes by addition of Li<sup>+</sup> has been reported (W. Zhou, J. Li, X. He, C. Li, J. Lv, Y. Li, S. Wang, H. Liu and D. Zhu, *Chem. Eur. J.*, 2008, **14**, 754-763). It is also possible to imagine shuttling occurring by coordination of Li<sup>+</sup> to the triazole of the axle and polyether of the macrocycle. To test this, LiPF<sub>6</sub> was titrated into a sample of rotaxane **1** in CD<sub>3</sub>CN. A downfield shift and merging of peaks for *g* and *g'* in the <sup>1</sup>H NMR spectrum was observed (see page S38 ESI<sup>†</sup>). However, addition of LiClO<sub>4</sub> (or Zn(ClO<sub>4</sub>)<sub>2</sub>) to rotaxane **1** in CD<sub>3</sub>CN resulted only in modest *upfield* shifts of *g* and *g'* (see pages S40-S41 ESI<sup>†</sup>). We attribute the downfield shifts upon the addition of LiPF<sub>6</sub> to the formation of acidic products from the hydrolysis of the hexafluorophosphate anion.



## Graphical Abstract

5



Expression of mechanical chirality by a rotaxane may be modulated by affecting the co-conformational behaviour through varying solvent or by addition of acid and base.

Expression of mechanical chirality reported by  $^1\text{H}$  NMR

