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Donor–acceptor molecular figures-of-eight†

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The intermolecular template-directed synthesis, separation and characterisation of two constitutional isomers that are self-complexing donor–acceptor [1]rotaxanes has been achieved by click chemistry, starting from a π -electron deficient tetracationic cyclophane containing two azide functions and a π -electron rich 1,5-dioxynaphthalene-containing polyether chain terminated by propargyl groups.

Self-complexing compounds,¹ as well as pretzelanes,² that exhibit both chirality³ and bistability⁴ have been synthesised using *intramolecular template-directed protocols* starting from precursors of the tetracationic cyclophane, cyclobis(paraquat-*p*-phenylene)⁵ (CBPQT⁴⁺) which ends up being monofunctionalised on one of its *p*-xylylene linkers. Here, we describe how isomeric “Molecular 8” compounds,⁶ which we refer to as Figure-of-Eight (Fo8) molecules, can be synthesised (Scheme 1a) using an *intermolecular template-directed strategy*. Thus, isomeric CBPQT⁴⁺ derivatives **1**⁴⁺, functionalised with azides on both *p*-xylylene linkers, act as the recognition sites for the binding of a 1,5-dioxynaphthalene-containing polyether chain **2** terminated by propargyl ethers, which react subsequently under Cu-mediated azide-alkyne cycloaddition (CuAAC) conditions⁷ to give a mixture of *cis* and *trans* isomers of the molecular Fo8 **3**⁴⁺. This architecture has been realised previously by Vögtle *et al.*⁶ who preformed a [2]rotaxane and then inserted a couple of covalent linkers into the mechanically interlocked molecule (MIM) to produce a self-threaded “Molecular 8” which is topologically trivial,⁸ unlike the Figure-Eight knot or the Figure-Eight catenane.⁹ The “Molecular 8”, however, resembles the rose Figure-Eight in appearance and leads logically to our naming the [1]rotaxanes reported here as molecular Fo8s. Furthermore, the topology is similar to that found in macrobicyclic compounds¹⁰ with protonated bridgehead nitrogen atoms when their relative

orientations resemble the transition state which is passed through between the *out-out* and *in-in* forms.

Access to the molecular Fo8s, employing donor–acceptor interactions as the source of their templation, necessitates that we identify bisfunctional CBPQT⁴⁺ derivatives which would not have their binding affinities impaired—either sterically or electronically—by the substituents, yet also be highly reactive. With these requirements in mind, we chose the electronically benign¹¹ and sterically small azide function¹² to achieve bisfunctionality of the CBPQT⁴⁺ ring. Starting from commercially available 2-bromo-1,4-dimethylbenzene, the template-directed synthesis¹³ (see ESI) of **1**⁴⁺ was achieved in four steps. The bisfunctionalisation of the CBPQT⁴⁺ ring results in the formation, in an approximately 1 : 1 ratio, of two regioisomers, namely *cis*-**1**⁴⁺ and *trans*-**1**⁴⁺ in which the azide functions are, respectively, (i) pointing towards the same bipyridinium (BIPY²⁺) unit and (ii) pointing towards the two different BIPY²⁺ units. Although the *cis* and *trans* isomers of **1**⁴⁺ could not be separated and identified unambiguously by ¹H NMR spectroscopy, a doubling up of peaks (Fig. S4 in ESI), shifted from each other by 0.5 ppm in the ¹³C NMR spectrum, provided evidence for a *ca.* 1 : 1 mixture of isomers. X-Ray crystallography, performed on a single crystal grown by slow evaporation of EtOH into a solution of **1**·4PF₆ in DMF, revealed (Fig. S5 in SI) the presence of disorder associated with the constitutional locations—*cis* and *trans*—of the two azide functions on the CBPQT⁴⁺ ring. All attempts to separate *cis*-**1**·4PF₆ from *trans*-**1**·4PF₆ have so far been in vain. The mixture of isomers was employed in the template-directed synthesis of molecular Fo8 compounds which, in the event, we have been able to separate by high performance liquid chromatography (HPLC) as their *cis* and *trans* isomers.

Molecular modelling was used to identify the bispropargyl ether **2** of the 1,5-dioxynaphthalene (DNP) unit, carrying two hexaethyleneglycol chains, as a suitable guest for the **1**⁴⁺ isomers while also making it possible for two successive CuAAC reactions to take place (Scheme 1a) in DMF and so produce the molecular Fo8s **3**⁴⁺ as a mixture of regioisomers, *cis*-**3**⁴⁺ and *trans*-**3**⁴⁺, in 12% yield. Iterative HPLC with recycling through an XBridge Prep C-18 OBC 19 × 100 mm column, using a gradient of aqueous acetonitrile as the eluent, was used in order to separate the regioisomers as their 4TFA[−] salts. The ¹H NMR spectra of the faster and slower moving isomers, after conversion to their 4PF₆[−] salts, are shown in Fig. 1a and b, respectively. Careful scrutiny of the

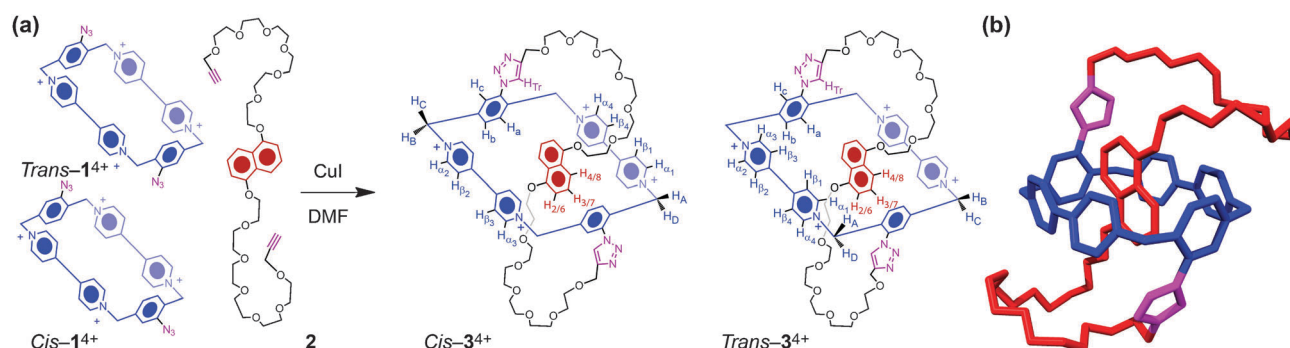
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Scheme 1 Synthesis (a) of the Molecular $\text{Fo8s } 3^{4+}$ from the bisfunctionalised 1^{4+} . Electron-deficient CBPQT $^{4+}$ bisfunctionalised with azides 1^{4+} is “clicked” to the electron-rich bisalkyne **2** to form two regioisomers (*cis* and *trans*) of the molecular $\text{Fo8s } 3^{4+}$. Note that the azides can be oriented such that they are pointing towards opposite BIPY $^{2+}$ units (*trans*) or towards the same BIPY $^{2+}$ unit (*cis*). Furthermore, these orientations are implicated in the regioisomers of the Fo8 . The *trans* isomer (b) of 3^{4+} shows the molecule is reminiscent of a fused ring system with an element of self-complexation. The molecular mechanics minimisation (MMFF94) was accomplished using Spartan 2010.

through-bond (COSY, Fig. 2) and through-space (NOESY, Fig. 3) correlations found in the 2D spectra of each isomer allowed the full ^1H NMR spectroscopic characterisation and assignment of *trans*- 3^{4+} and *cis*- 3^{4+} , respectively. Although the ^1H NMR spectra of the two regioisomers reveal significant differences, they display the same number of resonances. (The labelling of the protons on the structural formulae of *trans*- 3^{4+} and *cis*- 3^{4+} in Scheme 1a corresponds to the assignment of the resonances in Fig. 1a and b, respectively.) These observations are not unexpected based on an analysis of the molecular symmetries and topic relationships¹⁴ of *trans*- 3^{4+} and *cis*- 3^{4+} . The *trans* isomer has C_i symmetry which means that the eight heterotopic protons on one BIPY $^{2+}$ unit are related enantiotopically in pairs to the eight heterotopic protons on the other BIPY $^{2+}$ unit. The outcome is that we expect to observe four resonances for protons α to the nitrogens and also four resonances for the protons β to the nitrogens. This expectation is realised in the ^1H NMR spectrum (Fig. 1a) of the *trans* isomer. By contrast, the *cis* isomer has C_2 symmetry which means that the eight protons in each BIPY $^{2+}$ unit are related homotopically in pairs while the two sets of BIPY $^{2+}$ units are

heterotopic with respect to each other. The outcome is that we expect to observe four resonances for protons α to the nitrogens and also four resonances for the protons β to the nitrogens. This expectation is realised in the ^1H NMR spectrum (Fig. 1b) of the *cis* isomer.

Not only did an analysis of the 2D NMR spectra allow us to assign the 1D ^1H NMR spectra in Fig. 1a and b to the *trans* and *cis* isomers, respectively, but it also assisted us in identifying the conformation shown in Scheme 1b as the major one \ddagger for *trans*- 3^{4+} — and the analogous one in relation to the relative orientation of the DNP unit inside the CBPQT $^{4+}$ ring of the *cis*- 3^{4+} as well. Finally, the minor peaks observed in the ^1H NMR spectra (Fig. 1) are *not* impurities: they are lower symmetry minor conformations which are in slow equilibrium on the ^1H NMR time-scale with their corresponding major conformations as evidenced by the exchange peaks present in the NOESY spectra (Fig. 3 and ESI). These dynamic processes are currently under investigation.

It is half a century since Wasserman and Frisch¹⁵ published their seminal paper on chemical topology in 1961. In the rapidly expanding real estate being claimed by MIMs,¹⁶ topological

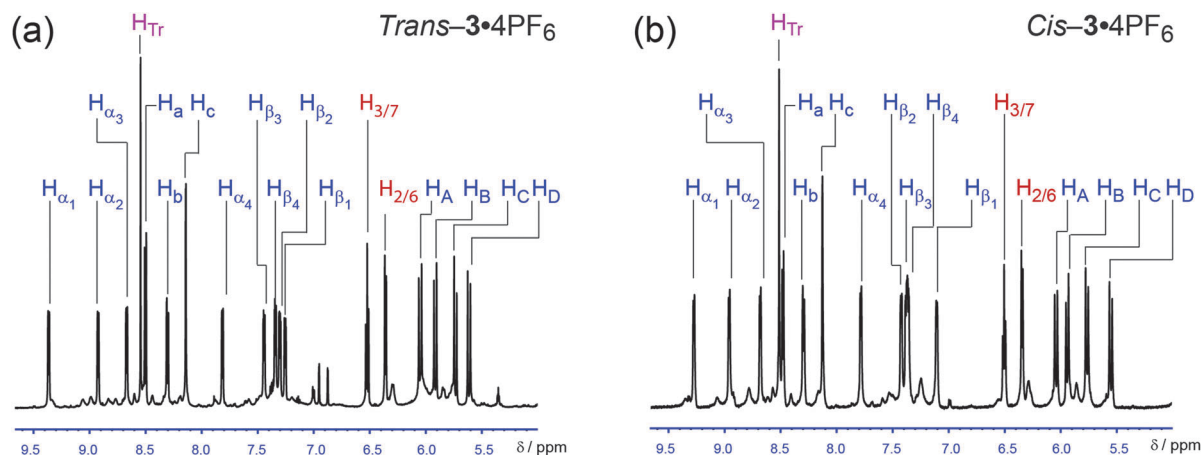


Fig. 1 Partial ^1H NMR spectra (500 MHz, CD_3CN , 298 K) of the constitutional isomers of $3\cdot 4\text{PF}_6$. Both (a) *cis*- $3\cdot 4\text{PF}_6$ and (b) *trans*- $3\cdot 4\text{PF}_6$ contain the same count of heterotopic protons on account of their molecular symmetries and the same number of resonances are observed in their respective ^1H NMR spectra. The small baseline resonances represent as yet unidentified conformations, which are in slow equilibrium on the ^1H NMR time-scale with the major conformations of $3\cdot 4\text{PF}_6$ (ca. 10:1 ratio), as verified by exchange peaks present in the NOESY spectrum illustrated in Fig. 3. See also the ESI.

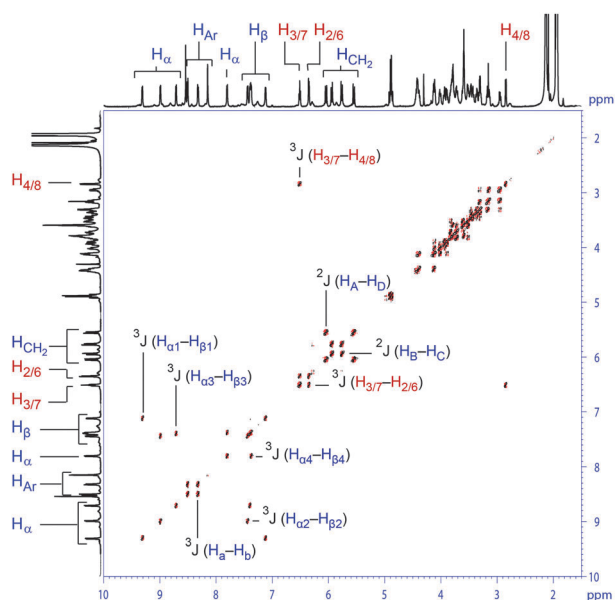


Fig. 2 ^1H - ^1H gDQF COSY (600 MHz, CD_3CN , 298 K) spectrum of *cis*-3-4PF₆ with selected correlations labeled. Through-bond correlations are a key component to assigning each isomer.

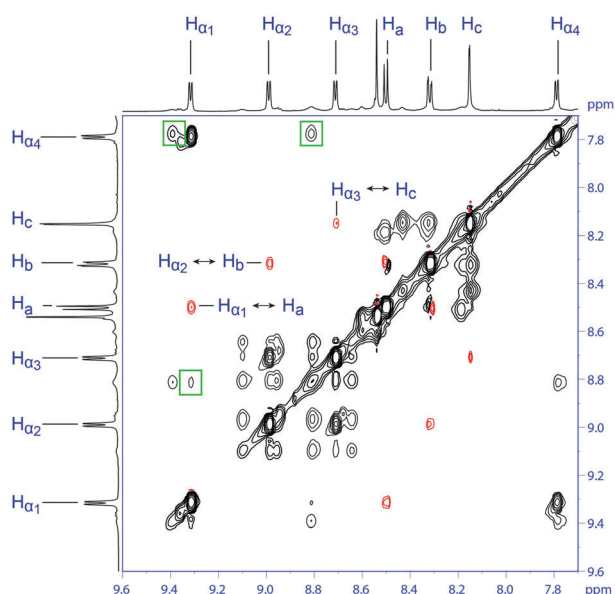


Fig. 3 A region of the NOESY (600 MHz, CD_3CN , 298 K) spectrum of *cis*-3-4PF₆. Note that the black peaks are phased positive which correspond to chemical exchange peaks with the uncomplexed species and the red peaks are phased negative which correspond to positive $n\text{Oe}$'s of the Fo8. This region of the spectrum shows the through-space correlations of the featured BIPY²⁺ protons α to the nitrogen and the *p*-xylene protons. These key correlations allow for the assignment of the protons in this region. Furthermore, the chemical exchange peaks that are boxed in green are a selection of the peaks which indicate that the major species is in exchange with a minor one.

chemistry^{9,17} is going to assume more and more importance in the design and synthesis of compounds, such as Fo8s, which are beyond just simple catenanes, rotaxanes, and knots.¹⁸

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Notes and references

‡ The local C_{2h} symmetry of a 1,5-dioxynaphthalene unit can commute as two different conformations¹⁹ with both the *cis* and *trans* isomers of 3^{4+} . In the case of the latter, the conformation shown in Scheme 1b is predicted by quantum mechanical calculations to be the most stable.

- (a) Y. Liu, A. H. Flood, R. M. Moskowitz and J. F. Stoddart, *Chem. Eur. J.*, 2005, **11**, 369–385; (b) Y. Liu, S. Saha, S. A. Vignon, A. H. Flood and J. F. Stoddart, *Synthesis*, 2005, 3437–3445.
- Y. Liu, P. A. Bonvallet, S. A. Vignon, S. I. Khan and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2005, **44**, 3050–3055.
- (a) Y. Liu, S. A. Vignon, X. Zhang, K. N. Houk and J. F. Stoddart, *Chem. Commun.*, 2005, 3927–3929; (b) Y. Liu, S. A. Vignon, X. Zhang, P. A. Bonvallet, S. I. Khan, K. N. Houk and J. F. Stoddart, *J. Org. Chem.*, 2005, **70**, 9334–9344.
- Y.-L. Zhao, A. Trabolsi and J. F. Stoddart, *Chem. Commun.*, 2009, 4844–4846.
- (a) B. Odell, M. V. Reddington, A. M. Z. Slawin, N. Spencer and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1547–1550; (b) M. Asakawa, W. Dehaen, G. L'abbé, S. Menzer, J. Nouwen, F. M. Raymo, J. F. Stoddart and D. J. Williams, *J. Org. Chem.*, 1996, **61**, 9591–9595; (c) C.-H. Sue, S. Basu, A. C. Fahrenbach, A. K. Shveyd, S. K. Dey, Y. Y. Botros and J. F. Stoddart, *Chem. Sci.*, 2010, **1**, 119–125.
- C. Reuter, W. Wienand, C. Schmuck and F. Vögtle, *Chem. Eur. J.*, 2001, **7**, 1728–1733.
- (a) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021; (b) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064.
- O. Lukin, A. Godt and F. Vögtle, *Chem. Eur. J.*, 2004, **10**, 1878–1883.
- R. S. Forgan, J.-P. Sauvage and J. F. Stoddart, *Chem. Rev.*, 2011, **111**, 5434–5464.
- (a) C. H. Park and H. E. Simmons, *J. Am. Chem. Soc.*, 1968, **90**, 2431–2432; (b) B. Dietrich, J.-M. Lehn and J.-P. Sauvage, *Tetrahedron Lett.*, 1969, **10**, 2885–2888; (c) B. Dietrich, J.-M. Lehn and J.-P. Sauvage, *Tetrahedron Lett.*, 1969, **10**, 2889–2892; (d) For a discussion of macrobicyclic polyethers with bridgehead carbon atoms, see: A. C. Coxon and J. F. Stoddart, *J. Chem. Soc., Perkin Trans. 1*, 1977, 767–785.
- P. A. S. Smith, J. H. Hall and R. O. Kan, *J. Am. Chem. Soc.*, 1962, **84**, 485–489.
- M. A. Olson, A. Coskun, R. Klajn, L. Fang, S. K. Dey, K. P. Browne, B. A. Grzybowski and J. F. Stoddart, *Nano Lett.*, 2009, **9**, 3185–3190.
- (a) D. H. Busch and N. A. Stephenson, *Coord. Chem. Rev.*, 1990, **100**, 119–154; (b) S. Anderson, H. L. Anderson and J. K. M. Sanders, *Acc. Chem. Res.*, 1993, **26**, 469–475; (c) *Templated Organic Synthesis*, ed. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, 1999; (d) J. F. Stoddart and H.-R. Tseng, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 4797–4800; (e) D. H. Busch, *Top. Curr. Chem.*, 2005, **249**, 1–65; (f) K. E. Griffiths and J. F. Stoddart, *Pure Appl. Chem.*, 2008, **80**, 485–506.
- K. Mislow and M. Raban, *Top. Stereochem.*, 1967, **1**, 1–38.
- H. L. Frisch and E. Wasserman, *J. Am. Chem. Soc.*, 1961, **83**, 3789–3974.
- J. F. Stoddart, *Chem. Soc. Rev.*, 2009, **38**, 1802–1820.
- (a) D. M. Walba, *Tetrahedron*, 1985, **41**, 3161–3212; (b) G. A. Breault, C. A. Hunter and P. C. Mayers, *Tetrahedron*, 1999, **55**, 5265–5293; (c) J. S. Siegel, *Science*, 2004, **304**, 1256–1258.
- (a) G. Schill, *Catenanes, Rotaxanes and Knots*, Academic Press, New York, 1971; (b) *Catenanes, Rotaxanes and Knots—A Journey Through the World of Molecular Topology*, ed. C. O. Dietrich-Buchecker and J.-P. Sauvage, Wiley-VCH, Weinheim, Germany, 1999.
- S. A. Vignon and J. F. Stoddart, *Collect. Czech. Chem. Commun.*, 2005, **70**, 1493–1576.