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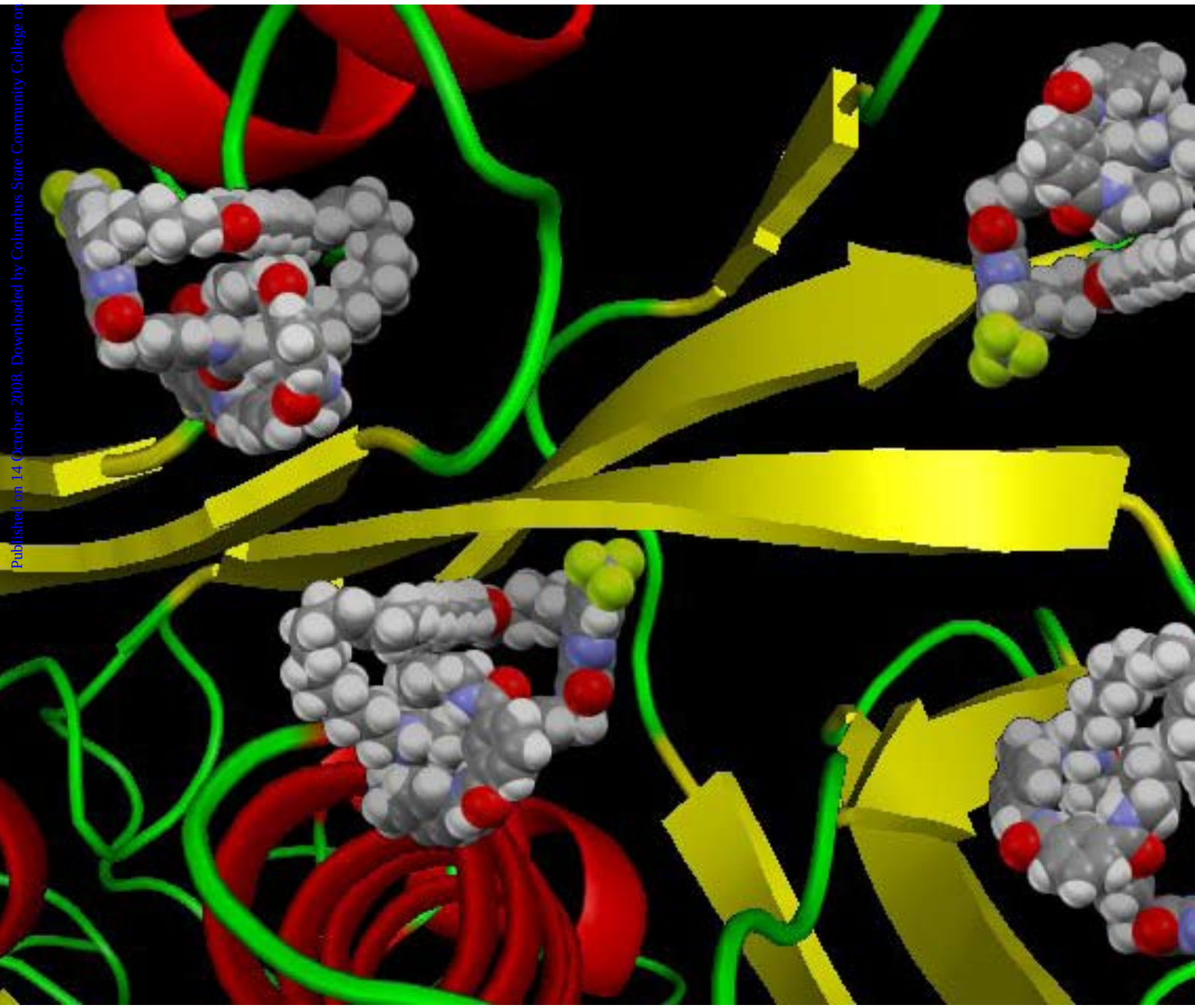

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A flavin-based [2]catenane†

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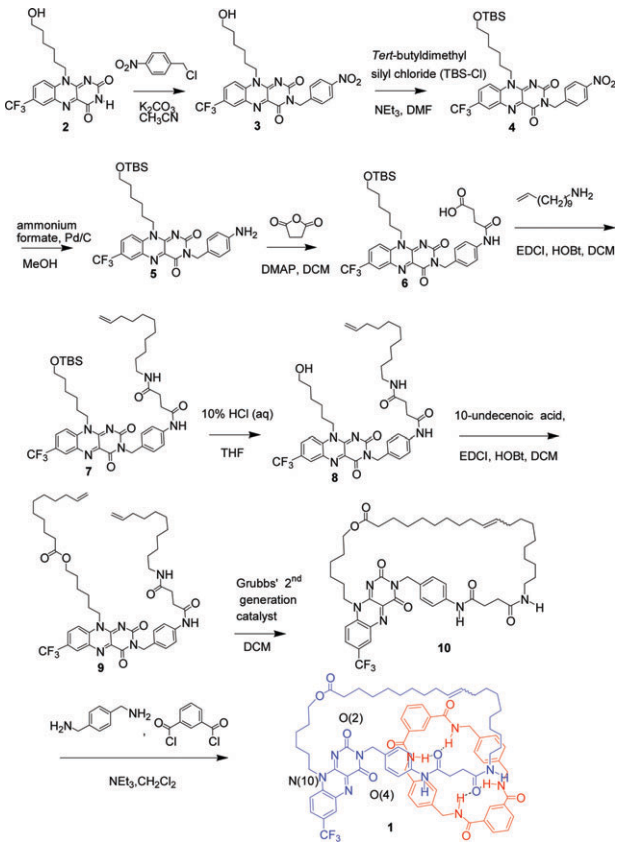
We report the synthesis, solid-state and preliminary solution properties of a flavin-based [2]catenane.

Controlled molecular motion processes are ubiquitous in nature and have inspired chemists to create synthetic analogues in the form of molecular machines.[1] By virtue of their topology, molecular machines fabricated from catenanes (mechanically interlocked macrocycles) can undergo controlled rotational motion under the influence of an external stimulus (*e.g.* electrochemistry).[2] As a consequence catenane-like architectures are attractive systems for the development of biomimetic and synthetic rotary motors[3] and components for molecular electronics.[4]

Molecular machines fabricated from hydrogen bonded interlocked structures have emerged as important systems for the development of chemically, photochemically and electrochemically controllable assemblies.[5] Although a range of moieties have been incorporated into these architectures to facilitate controlled molecular motion, there still remains scope for the development of systems containing new molecular components. Flavin units, in view of their interesting electrochemically controllable hydrogen bonding properties,[6] and their ability to have their recognition, redox[7] and optical properties tuned by synthetic manipulation, nominate these units as excellent building blocks for the formation of functional interlocked structures.[8] In this communication, we report the synthesis, solid-state structure and preliminary solution properties of flavin-based [2]catenane **1**.

Catenane **1** was synthesized as described in Scheme 1 and the ESI.† Compound **2** was readily N-alkylated with 4-nitrobenzyl chloride to yield compound **3** in 68% yield. The hydroxyl group was protected with *tert*-butyldimethylsilyl chloride to afford derivative **4** in 96% yield. The nitro group was then reduced using ammonium formate and palladium on carbon to yield derivative **5**. This compound was then reacted with succinic anhydride to yield compound **6**. Compound **7** was readily synthesised from **6** by reaction with 10-undecenamine in the presence of EDCI–HOBt. Deprotection of the silyl group of **7** to yield alcohol **8** was readily achieved under standard conditions. Compound **8** was subsequently converted to alkene derivative **9** in good yield by esterification with 10-undecenoic acid. Macrocycle **10** was conveniently synthesized using a ring-closing metathesis reaction catalysed by Grubbs' second generation catalyst. A remarkably high yield of 50% was obtained for the formation of the 43-atom macrocycle. ^{1}H NMR spectroscopy indicated that the ratio of the *cis* : *trans* isomers was approximately 1 : 4. Catenane **1** was conveniently synthesized from **10** using a standard clipping methodology in 26% yield.



Scheme 1 Synthesis of catenane **1**.

Low resolution fast-atom bombardment mass spectrometry confirmed the [2]catenane structure for **1** ([M+] = 1409) (see ESI†). Slow crystallization of **1** from ethanol/chloroform provided crystals of sufficient quality for X-ray structure determination (Fig. 1).‡ The data clearly proves the interlocked nature of the proposed catenane structure. The smaller macrocycle forms hydrogen bonds to the carbonyl oxygen

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† Electronic supplementary information (ESI) available: Full synthetic details for the preparation of **1**–**10**, NMR spectra of **1** and **10**, crystallographic methods and electrochemistry details. CCDC 697887. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b813779j

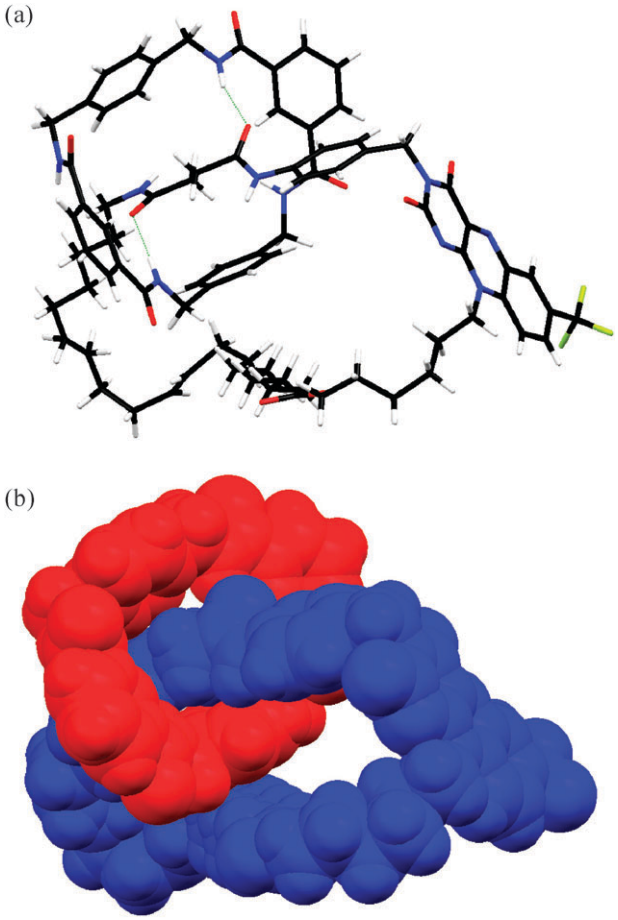

Fig. 1 X-Ray crystal structure of catenane **1** depicted using: (a) a stick representation (hydrogen bonding interactions are highlighted in light green) and; (b) a spacefill model. The structures are visualised using Mercury 1.4.2.[15]

atoms of the succinamide group of the larger flavin-based macrocycle. Interestingly, only two hydrogen bonds were indicated between two of the NH groups of the smaller macrocycle and the succinamide carbonyl groups of the flavin-based macrocycle. The remaining NH moieties of the smaller macrocycle participate in inter-catenane hydrogen bonding.

In order to gain insight into the structure of catenane **1** in solution, the ^{1}H NMR spectra of **1** and precursor macrocycle **10** were recorded. It has been previously been shown that this technique offers a useful tool for studying the positional integrity of interlocked structures of this type, as aromatic ring currents in the *p*-xylylene rings result in significant upfield shifts in the resonances of the portion if the axle/wheel covered by this macrocycle.[9] Catenane **1** displayed sufficient solubility in chloroform and DMSO to allow us to compare the solution-based structure in a non-polar ($CDCl_3$) and relatively polar (DMSO-*d6*) solvent. In $CDCl_3$ the chemical shifts of the succinamide methylene protons of **1** were positioned significantly more upfield than the corresponding protons of macrocycle **10** (Fig. 2).[10] Furthermore, ^{1}H NMR spectroscopy suggests that no other co-conformers exist, suggesting good positional integrity of the smaller macrocyle over the succinamide station of catenane **1** in $CDCl_3$. However, in DMSO-*d6*,

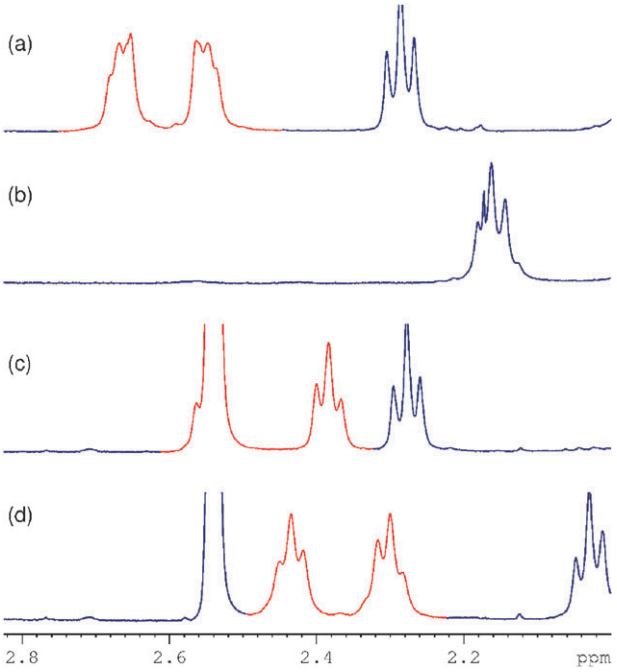

Fig. 2 Partial ^{1}H NMR spectra of **1** and **10** showing: (a) spectrum of **10** in $CDCl_3$; (b) spectrum of **1** in $CDCl_3$; (c) spectrum of **10** in DMSO-*d6* (one methylene signal overlaps with the solvent peak); (d) spectrum of **1** in DMSO-*d6*. Succinamide methylene protons are highlighted in red.

which is a competitive solvent for hydrogen bonding interactions, large shifts for the succinamide methylene protons were not observed suggesting that the DMSO actively competes for the succinamide binding site of the flavin-based macrocycle (Fig. 2). The ^{1}H and 2D COSY NMR spectra suggest that the smaller macrocycle resides over the alkyl chain adjacent to the N(10) of the flavin unit of the larger macrocycle in this solvent (see ESI†).

It is well established in the literature that three-point hydrogen bonding between the imide moiety of the flavin and diaminopyridine (DAP) derivatives results in significant stabilisation (typically −150 mV) of the flavin radical anion (**Fl**$^{\bullet-}$) state. Therefore, DAP-based hosts are attractive systems to model the role hydrogen bonding interactions have in modulating the redox properties of flavin moieties in flavoenzymes.[6,11] However, DAP systems do not adequately replicate the geometry of the enzyme–cofactor interactions as the enzyme spatially distributes the complementary hydrogen bonding units in a semicircular array, while DAP constrains the hydrogen bonding donor (D) and acceptor (A) moieties of its DAD array to one face of the ADA hydrogen bonding motif of the imide moiety of flavin. The unfavourable secondary interactions, inherent in the geometrically constrained DAD–ADA arrays of this type, greatly diminish the efficiency of the recognition process.[12] More significantly, the increase in electron density of O(2) and O(4) of the flavin unit upon reduction accentuates these unfavourable interactions by increasing negative charge density on the heteroatoms, and hence the repulsive forces between these atoms and the complementary DAD sites of DAP. This diminishment of recognition between reduced flavin and DAP limits the ability

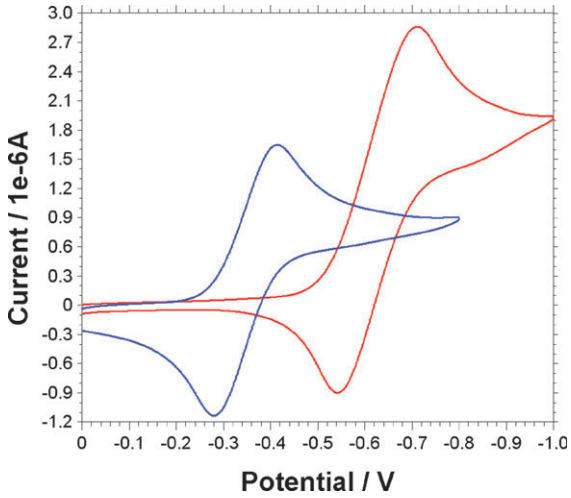

Fig. 3 Cyclic voltammograms of **1** (blue) and **10** (red) ($\sim 7 \times 10^{-4}$ M) recorded in CH_2Cl_2 (0.1 M Bu_4NPF_6). Scan rate 50 mV s^{-1}.

of DAP hosts to efficiently modulate flavin redox potentials, and hence to effectively model flavoenzyme behaviour. Thus, there remains considerable scope for the development of biomimetic flavin-based host–guest systems that more accurately replicate the ability of the apoenzyme of flavoenzymes to modulate the redox potential of the flavin cofactor.

In catenane **1**, reduction of the flavin moiety to the corresponding $\mathbf{Fl}^{\bullet-}$ state should increase the electronegativity of O(2) and O(4), and therefore could provide an effective hydrogen bonding site for complementary moieties within the catenane architecture.[13] Therefore, for catenane **1**, we anticipated that the electrochemical generation of the $\mathbf{Fl}^{\bullet-}$ species should occur at a significantly lower potential than **10**.[6,11] To test this hypothesis, we have investigated the solution electrochemistry of **1** and **10** using cyclic voltammetry (CV) in CH_2Cl_2 (Fig. 3 and ESI). Macrocycle **10** gave a single reversible redox wave ($E_{1/2} = -0.62$ V) corresponding to the formation of the $\mathbf{Fl}^{\bullet-}$ species. When the CV of catenane **1** was recorded, a reversible redox wave was observed at a significantly lower potential ($E_{1/2} = -0.35$ V) than that obtained for **10**. This +270 mV stabilisation of the $\mathbf{Fl}^{\bullet-}$ state suggests that the flavin moiety becomes hydrogen bonded to a complementary moiety of the catenane upon reduction of the flavin unit of **1**.[14]

In conclusion, we have devised effective methodology for synthesising a flavin-based [2]catenane. In the solid state and chloroform solution, the smaller macrocycle is positioned over the succinamide station of the flavin containing macrocycle. Cyclic voltammetry studies indicate that the catenane architecture of **1** results in a significant stabilisation of the $\mathbf{Fl}^{\bullet-}$, presumably due to intra-catenane hydrogen bonding interactions. A detailed study of the molecular machine and device properties of derivative **1** and its analogues is underway in our laboratory, and results from these investigations will be published in due course.

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Notes and references

‡ Selected crystal data for **1**. $C_{84}H_{107}F_3N_{10}O_{14}$, $M = 1537.80$, monoclinic, $a = 13.9514(5)$, $b = 29.1721(10)$, $c = 20.3132(7)$ Å, $\beta = 102.463(3)^\circ$. $U = 8072.5(5)$ Å^3, $T = 150$ K, space group $P2_1/c$ (no. 14), $Z = 4$, 33 859 reflections measured, 10 751 unique ($R_{int} = 0.0482$) which were used in all calculations. The final $R1$ was 0.065 and w$R2$ was 0.189 (all data).†

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