

## An electrochemically tuneable cyclodextrin-based molecular adapter

Graeme Cooke,<sup>a,\*</sup> Patrice Woisel,<sup>\*,b</sup> François Delattre,<sup>b</sup> Marc Bria,<sup>c</sup> James F. Garety,<sup>a</sup> Shanika Gunatiliaka Hewage<sup>a</sup> and Gouher Rabani<sup>a</sup>

<sup>a</sup>WestCHEM Centre for Supramolecular Electrochemistry, Department of Chemistry, Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, UK

<sup>b</sup>Laboratoire de Synthèse Organique et Environnement, Université du Littoral Côte d' Opale, Dunkerque 59140, France

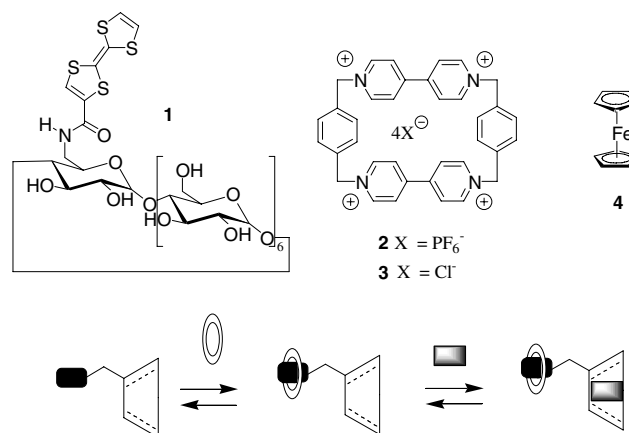
<sup>c</sup>CCM-RMN Lille 1, Université des Sciences et Techniques de Lille, Villeneuve d'Ascq, 59655, France

Received 26 April 2006; revised 10 June 2006; accepted 22 June 2006

Available online 14 July 2006

**Abstract**—We report the synthesis of a cyclodextrin-based molecular adapter which has the propensity to form an electrochemically tuneable ternary complex with cyclophanes **2** or **3** and ferrocene **4** in non-aqueous and aqueous environments, respectively.  
© 2006 Elsevier Ltd. All rights reserved.

In order to perform their wide ranging functions, biological surfaces are required to bind to a variety of guest species using a fairly limited number of surface-confined hosts. To successfully achieve this, Nature has developed molecular adapters that have allowed a range of initially non-complementary surface immobilised hosts to bind to guest species.<sup>1</sup> Although non-natural molecular adapters have been developed to interact with biological structures,<sup>2</sup> the application of molecular adapters as a means of modulating man-made surfaces and polymers in order to create new materials and devices has received little attention. To prepare a synthetic molecular adapter that has the propensity to both mimic their biological brethren, and in the longer term, provide a means of modifying non-natural polymers and surfaces, we report the synthesis of compound **1** which involves the juxtaposition of two important building blocks in supramolecular/materials chemistry: the tetra-thiafulvalene<sup>3</sup> (TTF) and the cyclodextrin<sup>4</sup> (CD) unit.<sup>5</sup> In particular, we report the synthesis of a CD-based molecular adapter unit that can simultaneously bind to cyclophanes **2** or **3**<sup>6</sup> and ferrocene **4**<sup>7</sup> in aqueous and non-aqueous environments (Fig. 1). Moreover, we have exploited the electrochemically controllable binding properties of cyclophanes **2** or **3**<sup>6</sup> to disassemble the ternary complex in solution.<sup>8</sup>



**Figure 1.** Schematic diagram of the structure of a molecular adapter fabricated from **1**, **2** (**3**) and **4**.

Derivative **1** was conveniently synthesised from 4-fluorocarbonyl TTF<sup>9</sup> and 6-amino- $\beta$ -CD.<sup>10</sup> Cyclophanes **2** and **3** were synthesised using previously reported methods.<sup>11</sup> Surprisingly, derivative **1** possesses poor solubility in water (reasonable in water/DMSO, 9:1), however, good solubility was observed in pure DMSO. The <sup>1</sup>H NMR spectrum of **1** recorded in DMSO-*d*<sub>6</sub> at 298 K (Supplementary data) displays the characteristic resonances of the cyclodextrin moiety between 3 and 6 ppm and the TTF unit around 6 ppm. The <sup>13</sup>C spectrum shows clearly a chemical shift near 159 ppm belonging to the carbonyl

**Keywords:** Supramolecular chemistry; Pseudorotaxanes; Electrochemistry.

\* Corresponding author. Tel.: +44 141 330 5500; fax: +44 141 330 4888; e-mail: graeme.cooke@chem.gla.ac.uk

of the amide group. To obtain further evidence about the initial geometry of **1**, 2D-ROESY experiments were undertaken (Supplementary data), which indicate the absence of ROE cross-peaks between the H3 and H5 protons located inside the CD unit and the TTF protons, indicating unambiguously that the TTF unit is located outside the cavity and not inter- or intramolecularly complexed within the CD unit.

In order to probe the formation of the ternary complex, and thus proving that derivative **1** has the propensity to behave as a molecular adapter, we have explored the complex formation using  $^1\text{H}$  NMR spectroscopy in  $\text{DMSO-}d_6$  and  $\text{D}_2\text{O/DMSO-}d_6$  (9:1, v/v) (Table 1). For these studies the counter anion of the cyclophane played a vital role; the  $\text{PF}_6^-$  units of **2** conferred solubility in  $\text{DMSO-}d_6$ , whereas the  $\text{Cl}^-$  counter ions of **3** conferred solubility in  $\text{D}_2\text{O/DMSO-}d_6$ . The addition of derivative **1** to compounds **2** or **3** dissolved in  $\text{DMSO-}d_6$  and  $\text{D}_2\text{O/DMSO-}d_6$  (9:1, v/v), respectively, resulted in an emerald coloured solution, characteristic of TTF-based pseudorotaxanes of this type (**1.2**  $\lambda = 794$  nm,  $\text{DMSO}$ ; **1.3**  $\lambda = 778$  nm,  $\text{H}_2\text{O/DMSO}$  (9:1)).<sup>12</sup> For both systems, shifts were observed in the resonances for the TTF and cyclophane units, which are indicative of pseudorotaxane formation (Table 1). We have determined the association constants ( $K_a$ ) for the binary complexes formed between **1.2** and **1.3** in  $\text{DMSO}$  and  $\text{DMSO/H}_2\text{O}$  (9:1). Interestingly, the  $K_a$  for **1.2** in pure  $\text{DMSO}$  ( $K_a = 166 \pm 8 \text{ M}^{-1}$ ,  $\Delta G = 13 \text{ kJ mol}^{-1}$ ) is significantly lower than that of **1.3** in  $\text{DMSO/H}_2\text{O}$  (9:1) ( $K_a = 10800 \pm 540 \text{ M}^{-1}$ ,  $\Delta G = 23 \text{ kJ mol}^{-1}$ ), indicating that hydrophobic interactions are important for determining the stability of **1.3**.

The addition of ferrocene **4** to the binary complexes **1.2** or **1.3** dissolved in  $\text{DMSO-}d_6$  or  $\text{D}_2\text{O/DMSO-}d_6$  (9:1, v/v), respectively, did not significantly affect either the colour of the complex or the chemical shifts for the aromatic spectral region, indicating that, in both cases, electron rich **4** does not interact significantly with the electron deficient cyclophanes **2** or **3**. In contrast, the  $^1\text{H}$  NMR spectra of **1.2** and **1.3** upon the addition of

**4** to form supramolecular systems **1.2.4** and **1.3.4**, respectively, induced a shielding and broadening effect for the resonances corresponding to the inner protons (H3, H5) of the CD unit, suggesting the accommodation of the ferrocene into the cavity of the cyclodextrin (Supplementary data). In order to obtain further evidence for the inclusion of **4** inside the CD unit, 2D-ROESY experiments were carried out. For both ternary complexes **1.2.4** (Supplementary data) and **1.3.4** (Fig. 2), 2D-ROESY NMR spectra show cross-peaks arising from ROE interactions between the protons of **4** and the  $\beta$ -CD component protons of **1**, H3 and H5, thus confirming the formation of the ternary complexes **1.2.4** and **1.3.4** in aqueous and non aqueous media, respectively.

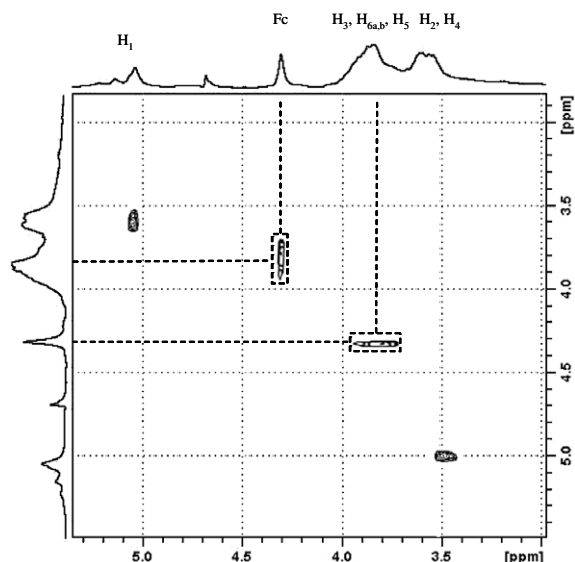
The solution electrochemistry of **1** has been studied using cyclic voltammetry (CV) and square wave voltammetry (SWV), and gave rise to two reversible oxidations at  $E_{1/2}^1 = +0.47 \text{ V}$  and  $E_{1/2}^2 = +0.70 \text{ V}$  in  $\text{DMSO}$  (0.1 M  $\text{Bu}_4\text{NPF}_6$ ) corresponding to the formation of  $1^{+}$  and  $1^{2+}$ , respectively.<sup>13</sup> Upon the addition of a 10-fold excess of **2** to the CV cell, to ensure effective complexation between host and guest,<sup>12</sup> the oxidation wave giving rise to the  $1^{+}$  species was immediately displaced by +30 mV, whilst the oxidation due to the formation of  $1^{2+}$  was largely unaffected ( $E_{1/2}^1 = +0.50 \text{ V}$  and  $E_{1/2}^2 = +0.70 \text{ V}$ ), suggesting that **1.2** reversibly decomplexes when the  $1^0$  guest experiences its first electrochemical oxidation to form the  $1^{+}$  state (Fig. 3).<sup>12</sup> Unfortunately, it was not possible to judge whether the same process was possible in an aqueous environment (pH = 7.0 buffer/ $\text{DMSO}$  (9:1)), due to the irreversible oxidation waves obtained for the TTF moiety. Furthermore, the investigation of the effect of the addition of **1** to a solution of **4** in  $\text{DMSO}$  or pH = 7.0 buffer/ $\text{DMSO}$  (9:1), had on the solution electrochemistry of the latter, was hampered by overlapping redox waves of the TTF and ferrocene moieties.

**Table 1.** The  $^1\text{H}$  NMR chemical shifts ( $\delta$  and  $\Delta\delta$ ) for **1** and its complexes with **2** or **3** and **4** in  $\text{DMSO-}d_6$  and  $\text{D}_2\text{O/DMSO-}d_6$  (9/1)

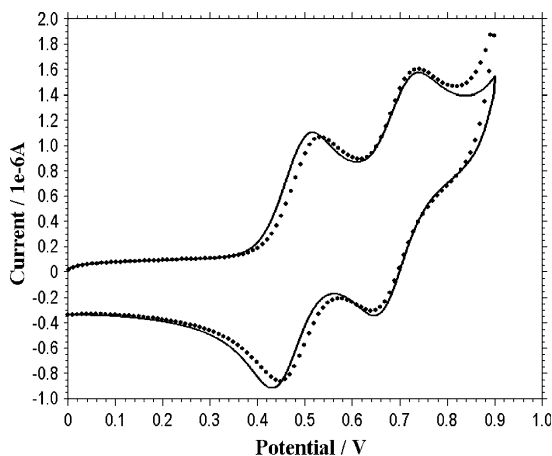
Compound or complex	$\alpha$ -Bipy	$\beta$ -Bipy	$\text{C}_6\text{H}_4$	5-TTF	4',5'-TTF
<b>2</b> <sup>a</sup>	9.49	8.69	7.73	—	—
<b>1</b> <sup>a</sup>	—	—	—	7.47	6.72
<b>[1.2]</b> <sup>a</sup>	9.39	8.44	7.75	7.21	6.17
$\Delta\delta$	(−0.10)	(−0.25)	(+0.02)	(−0.26)	(−0.55)
<b>[1.2.4]</b> <sup>a</sup>	9.38	8.44	7.75	7.15	6.29
$\Delta\delta$	(−0.11)	(−0.25)	(+0.02)	(−0.32)	(−0.43)
<b>3</b> <sup>b</sup>	8.98	8.16	7.49	—	—
<b>[1.3]</b> <sup>b</sup>	9.17	8.11	7.67	6.07	7.67
$\Delta\delta$	(+0.19)	(−0.05)	(+0.18)	—	—
<b>[1.3.4]</b> <sup>b</sup>	9.15	8.09	7.65	6.08	7.65
$\Delta\delta$	(+0.17)	(−0.07)	(+0.16)	—	—

<sup>a</sup> Recorded in  $\text{DMSO-}d_6$ .

<sup>b</sup> Recorded in  $\text{D}_2\text{O/DMSO-}d_6$  (9/1). Concentration of each component ( $\sim 1 \times 10^{-2} \text{ M}$ ).



**Figure 2.** Partial ROESY NMR spectrum of the ternary complex **[1.3.4]** in  $\text{D}_2\text{O/DMSO-}d_6$  (9/1) ( $\sim 1 \times 10^{-2} \text{ M}$ ).

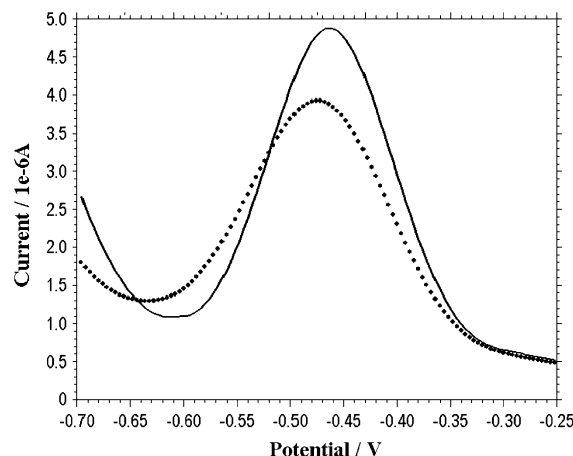


**Figure 3.** Cyclic voltammograms of **1** (—) ( $\sim 2 \times 10^{-4}$  M) and upon the addition of excess **2** (···) ( $\sim 2 \times 10^{-3}$  M) in DMSO. Scan rate =  $100 \text{ mV s}^{-1}$ .

As an alternative strategy for disrupting pseudorotaxane formation between **1** and **2** or **3**, we exploited the well-documented ability of reducing the cyclophane to its diradical dicationic state to induce pseudorotaxane dethreading.<sup>6</sup> For example, the addition of excess **1** to a solution of **2** in DMSO ( $0.1 \text{ M Bu}_4\text{NPF}_6$ ) resulted in the immediate negative shift in the first reduction wave of **2**. The half-wave potential of the second reduction wave was largely unaffected, indicating the pseudorotaxane dethreads when the cyclophane is first reduced. When SWV experiments were undertaken for **3** in pH = 7.0 phosphate buffer/DMSO (9:1), a pseudoreversible redox wave was obtained for the first reduction wave, and an irreversible reduction wave for the second redox wave, presumably due to precipitation onto the working electrode surface. However, scanning between 0 and  $-0.6 \text{ V}$  resulted in a pseudoreversible redox wave, that underwent a  $-20 \text{ mV}$  (recorded using SWV) shift upon addition of **3**, indicating that the pseudorotaxane dethreads upon reduction of **3** to its diradical dication state.

With electrochemically controllable recognition shown for the binary complexes formed between **1** and **2** or **3** in non-aqueous and aqueous solution, respectively, we turned our attention to whether the ternary complexes **1.2.4** and **1.3.4** could also be disassembled by reduction of the cyclophane moiety. To a solution of **2** or **3** in DMSO or pH = 7.0 buffer/DMSO (9:1), respectively, were added 5 equiv of **1** and then **4**, respectively. The addition of the ferrocene unit had minimal effect on the initial induced shift ( $\sim -15$  to  $-20 \text{ mV}$ ) resulting from the addition of **1** (Fig. 4). Thus, we are confident that the electrochemically induced dethreading observed for **1.2** or **1.3** is also shared by their corresponding ternary complexes **1.2.4** and **1.3.4**.

In conclusion, we have shown that derivative **1** has the propensity to form a ternary complex with derivatives **2** or **3** and **4** in aqueous and non-aqueous environments. Moreover, we have shown that the ternary complex can be disassembled by the electrochemical reduction of the tetracationic cyclophane moiety. The ability to form



**Figure 4.** Square wave voltammogram of **3** (—) ( $\sim 2 \times 10^{-4}$  M) and upon the addition of excess **1** and **4** (···) recorded in DMSO/H<sub>2</sub>O (9:1).

and subsequently disassemble the ternary complex paves the way for the reversible modification of appropriately functionalised biomolecules, synthetic polymers and surfaces. Our endeavours in these areas will be reported in due course.

### Acknowledgements

G.C. gratefully acknowledges the EPSRC for funding.

### Supplementary data

Details of the synthesis of **1** and characterization of the complexes with **2–4**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.116.

### References and notes

- Scott, J. D.; Pawson, T. *Sci. Am.* **2000**, 282, 72.
- For examples of small molecules acting as molecular adapters for biomolecules see: (a) Gu, L.-Q.; Braha, O.; Conlan, S.; Cheley, S.; Bayley, H. *Nature* **1999**, 398, 686; (b) Sanchez-Quesada, J.; Ghadiri, M. R.; Bayley, H.; Braha, O. *J. Am. Chem. Soc.* **2000**, 122, 11757; (c) Gu, L.-Q.; Serra, M. D.; Vincent, J. B.; Vigh, G.; Cheley, S.; Braha, O.; Bayley, H. *PNAS* **2000**, 97, 3959.
- For examples of review articles which focus upon the applications of TTF within supramolecular chemistry see: (a) Segura, J. L.; Martín, N. *Angew. Chem., Int. Ed.* **2001**, 40, 1372; (b) Nielsen, M. B.; Lomholt, C.; Becher, J. *Chem. Soc. Rev.* **2000**, 29, 153; (c) Jørgensen, T.; Hansen, T. K.; Becher, J. *Chem. Soc. Rev.* **1994**, 23, 41.
- For examples of reviews of cyclodextrins in supramolecular chemistry see: (a) Harada, A. *Adv. Polym. Sci.* **1997**, 133, 141; (b) Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, 98, 1959; (c) Harada, A. In *Large Ring Molecules*; Semlyen, A. J., Ed.; Wiley: Chichester, 1996; (d) Harada, A. *Acc. Chem. Res.* **2001**, 34, 456; (e) Haider, J. M.; Prokramenou, Z. *Chem. Soc. Rev.* **2005**, 34, 120; (f) Wenz, G.; Han, B.-H.; Müller, A. *Chem. Rev.* **2006**, 106, 782.

5. For examples of covalently linked TTF and CD derivatives see: (a) Bras, Y. L.; Sallé, M.; Leriche, P.; Mingo-  
taud, C.; Richomme, P.; Møller, J. *J. Mater. Chem.* **1997**,  
7, 2393; (b) Sallé, M.; Bras, Y. L.; Andreu, R.; Leriche, P.;  
Mingotaud, C.; Gorgues, A. *Synth. Met.* **1998**, 94, 47.
6. Anelli, P. L.; Ashton, P. R.; Ballardine, R.; Balzani, V.;  
Delgado, M.; Gandolfi, M. T.; Goodnow, T. T.; Kaifer,  
A. E.; Philp, D.; Pietraszkiewicz, M.; Prodi, L.; Redding-  
ton, M. W.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.;  
Vicent, C.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, 114,  
193.
7. (a) Harada, A.; Takahashi, S. *J. Chem. Soc., Chem.*  
*Commun.* **1984**, 645; (b) Harada, A.; Takahashi, S. *J.*  
*Chem. Soc., Dalton Trans.* **1988**, 729.
8. For recent examples of synthetic ternary complexes see: (a)  
Kim, H.-J.; Heo, J.; Jeon, W. S.; Lee, E.; Kim, J.;  
Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem.,*  
*Int. Ed.* **2001**, 40, 1526; (b) Jeon, W. S.; Kim, E.; Ko, Y.  
H.; Hwang, I.; Lee, J. W.; Kim, S.-Y.; Kim, H.-J.; Kim, K.  
*Angew. Chem., Int. Ed.* **2005**, 44, 87.
9. Cooke, G.; Rotello, V. M.; Radhi, A. *Tetrahedron Lett.*  
**1999**, 40, 8611.
10. Hamasaki, K.; Ueno, A.; Toda, F. *J. Am. Chem. Soc.*  
**1993**, 115, 5035.
11. Ashton, P. R.; Ballardine, R.; Blazani, V.; Boyd, S. E.;  
Credi, A.; Gandolfi, M. T.; Gómez-López, M.; Iqbal, S.;  
Philp, D.; Preece, J. A.; Prodi, L.; Ricketts, H. G.;  
Stoddart, J. F.; Tolley, M. S.; Venturi, M.; White, A. J. P.;  
Williams, D. J. *Chem. Eur. J.* **1997**, 3, 152.
12. (a) Devonport, W.; Blower, M. A.; Bryce, M. R.;  
Goldenberg, L. M. *J. Org. Chem.* **1997**, 62, 885; (b)  
Ashton, P. R.; Balzani, V.; Becher, J.; Credi, A.; Fyfe, M.  
C. T.; Mattersteig, G.; Menzer, S.; Nielsen, M. B.; Raymo,  
F. M.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *J. Am.*  
*Chem. Soc.* **1999**, 121, 3951.
13. All electrochemical experiments were performed using a  
CH Instruments 620A electrochemical workstation. The  
electrolyte solution (0.1 M) was either prepared from  
recrystallised Bu<sub>4</sub>NPF<sub>6</sub> and spectroscopic grade DMSO  
or a pH = 7.0 buffer and DMSO mixture (9:1). A three  
electrode configuration was used with a platinum disk  
working electrode, a Ag/AgCl reference electrode and a  
platinum wire as the counter electrode. All electro-  
chemical data were recorded under a nitrogen atmo-  
sphere. Upon the addition of the guest, the solution  
was stirred for 1 min, and the resulting solution purged  
with nitrogen prior to recording the electrochemical  
data.