Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3341–3347

TETRAHEDRON

Ferrocene incorporating host–guest dyads with electrochemically controlled three-pole hydrogen bonding properties

Graeme Cooke,[a,*] Hugues A. de Cremiers,[a,b] Florence M. A. Duclairoir,[a] Julie Leonardi,[a]
Georgina Rosair[a] and Vincent M. Rotello[b]

[a]*Department of Chemistry, The Centre for Biomimetic Design and Synthesis, School of Engineering and Physical Sciences, Heriot-Watt University, William H. Perkin Building, Riccarton, Edinburgh EH14 4AS, UK*
[b]*Department of Chemistry, University of Massachusetts at Amherst, Amherst, MA 01002, USA*

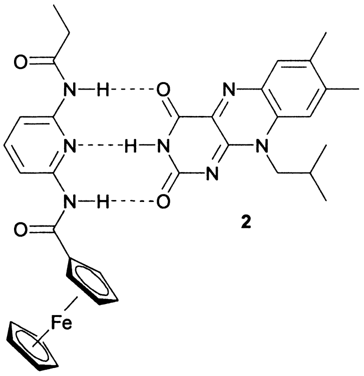
Received 4 November 2002; revised 17 February 2003; accepted 13 March 2003

Abstract—We describe the electrochemically controlled hydrogen bonding interactions between the isobutyl flavin/2,6-diferrocenylamidopyridine (**2·5**) and 9,10-phenanthrenequinone/1-ferrocenyl-3-hexylurea (**4·6**) dyads. Cyclic and square wave voltammetry studies have shown that the binding efficiencies between these moieties can be electrochemically actuated in non-polar (CH_2Cl_2 for **2·5**) or polar (DMF for **4·6**) organic solvents between three distinct states. © 2003 Elsevier Science Ltd. All rights reserved.

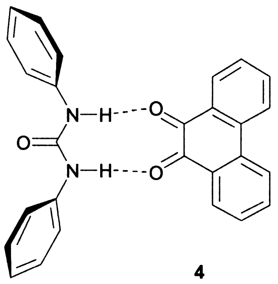
1. Introduction

The application of electrochemistry to modulate hydrogen bonded interactions between host–guest complexes is rapidly emerging as an important field within supramolecular chemistry.[1] The electrochemically controlled gain or loss of an electron by a redox-active host (or guest) can profoundly influence the electrostatic interactions between a hydrogen bonded host–guest dyad, leading to the development of systems with two[2] or multi-pole[3] binding properties. Systems with multi-pole binding properties will undoubtedly find new applications as responsive systems within the advanced materials and molecular electronics arenas, where their enhanced ability to control supramolecular structure and handle and process information at the molecular level can be exploited.[4] However, for pragmatic devices to be fabricated from these systems, two major improvements must occur. First, the disparate recognition efficiencies in their different redox states must be maximised in order that binary 'on' or 'off' binding can be achieved. The majority of studies reported to-date has focused upon the electrochemical modulation of hydrogen bonding efficiencies between weak and stronger states. Second, all of the electrochemically controlled hydrogen bonded systems with multi-pole binding properties reported to-date has been modulated in non-polar organic solvents. For future commercial exploitation to be assured, more environmentally robust host–guest systems must be produced with binding that can be actuated in polar environments.

Here, we report our first steps towards these goals, by modifying previously studied host–guest dyads **1·2** and **3·4**, respectively. In a previous communication we reported a three-pole hydrogen bonded switch fabricated between **1·2**,



1 **2**



3 **4**

Keywords: ferrocene; recognition; electrochemistry; hydrogen bonding.

* Corresponding author. Tel.: +131-451-8184; fax: +131-451-3180; e-mail: g.cooke@hw.ac.uk

0040–4020/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00423-X

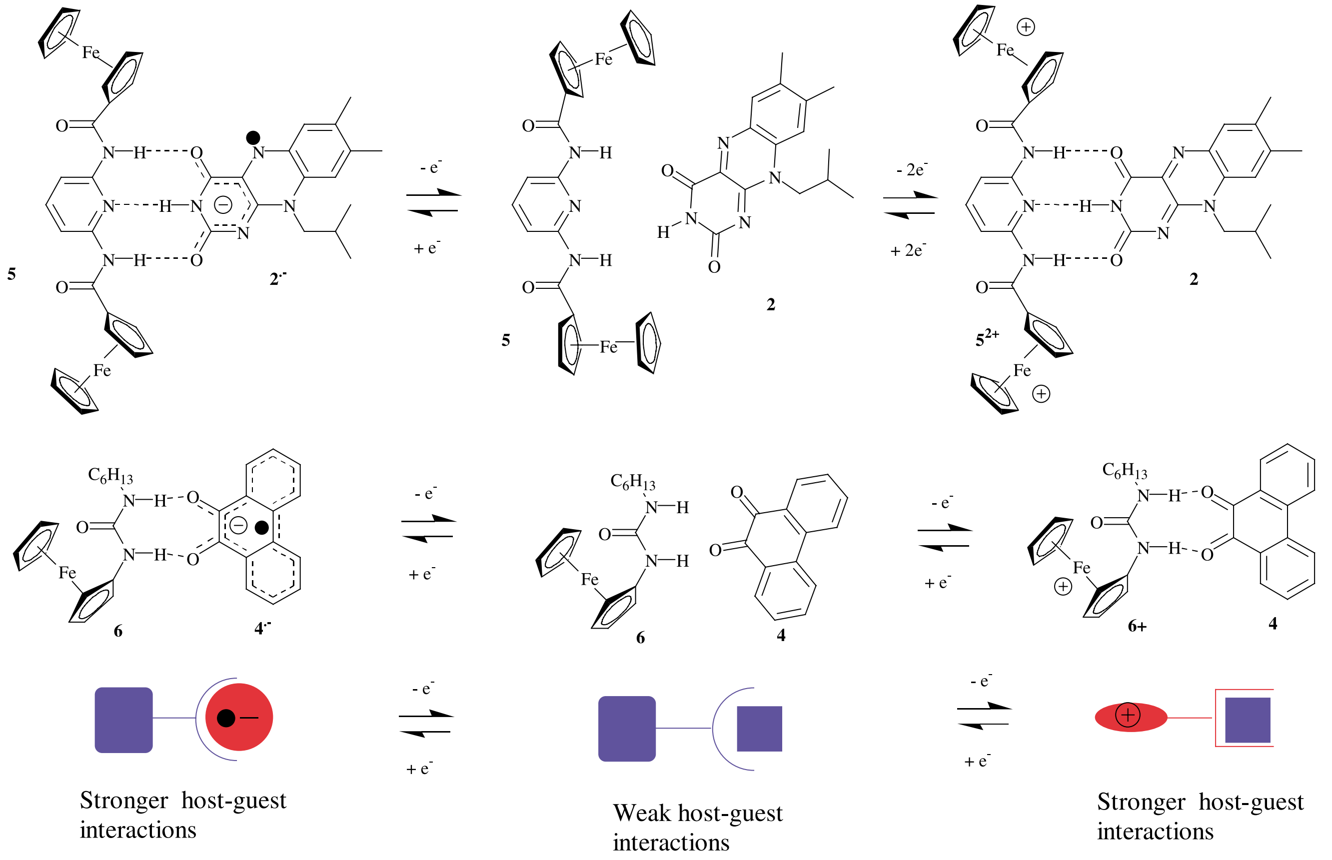
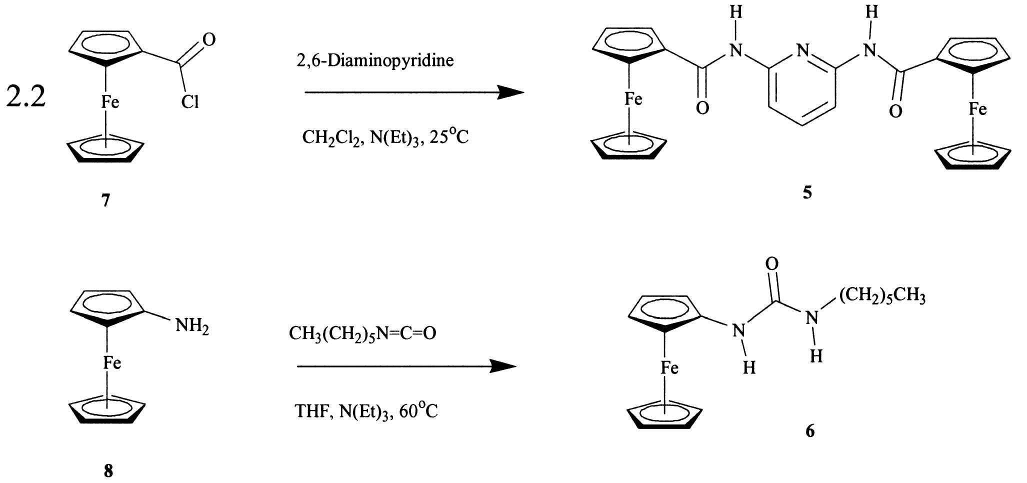


Figure 1. Schematic representation of ferrocene incorporating host–guest dyads with electrochemically controllable three-pole hydrogen bonding properties.

in which electrochemical oxidation of **1** or reduction of **2** could increase the hydrogen bonding efficiency by 4-fold and 50-fold, respectively.[3a] Furthermore, we also observed that the ferrocene unit causes a significant lowering of the binding efficiency of the neutral hydrogen bonded complex compared to that obtained for isobutylflavin **2** and diethylamidopyridine[2f] (K_a=45 and 537 M^{-1} in $CDCl_3$, respectively). Thus, the addition of a second ferrocene moiety to the diaminopyridine unit, as in **5**, should significantly lower the binding efficiency of the neutral complex, and thus allow us to achieve the goal of lowering the binding efficiency in the off state (Fig. 1). The diphenylurea/9,10-phenanthrenequinone **3**·**4** dyad is an attractive system to develop host–guest complexes with electrochemically controllable multi-pole binding in polar solvents, as it has been previously shown that the reduction of this complex to the **3**·**4**$^{\cdot-}$ species in DMF results in a significant increase in the binding efficiency.[2e] Thus, we reasoned that the addition of a redox-active ferrocene unit to the urea framework (e.g. **6**) should allow us to create hydrogen bonded host–guest dyad with **4** which displays binding efficiencies that can be electrochemically actuated



Scheme 1. Preparation of ferroreceptors **5** and **6**.

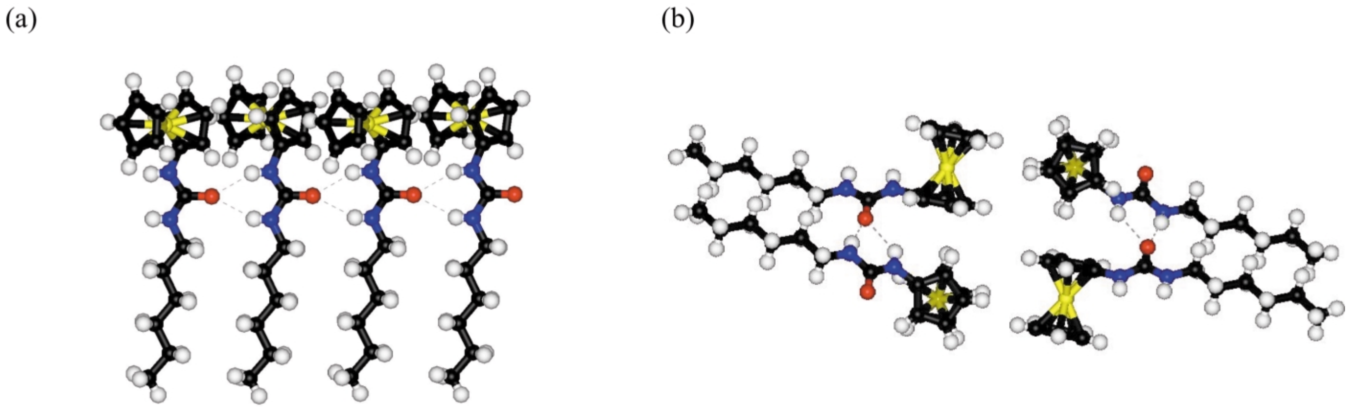


Figure 2. X-Ray crystal structure of four molecules of **6** showing: (a) the hydrogen bonded tape-like architecture and (b) the orthogonal arrangement of the ferrocene moieties within the double sheet.

between three distinct states by either oxidation of the ferrocene host or reduction of the phenanthrenequinone guest moiety.[5]

2. Results and discussion

2.1. Synthesis

Ferroreceptor **5** was conveniently prepared in high yield from the reaction of 2,6-diaminopyridine and ferrocenecarbonyl chloride **7**[6] under basic conditions (Scheme 1). Column chromatography (silica gel, CH_2Cl_2/ethyl acetate 9:1 v/v) readily afforded compound **5** in 40% yield. Ferrocene host **6** was synthesised by heating ferrocenylamine[7] **8** and 1.2 equiv. of hexylisocyanate in THF at 60°C for 2 days in the presence of triethylamine. Compound **6** was readily isolated using column chromatography (silica gel, dichloromethane /ethyl acetate 9:1 v/v) to afford the pure host unit in 70% yield.

2.2. X-Ray crystal structure of 6

Slow evaporation of a CH_2Cl_2/ethyl acetate (9:1, v/v) solution of **6** gave crystals of sufficient quality to allow X-ray crystallography to probe the solid-state structure of this compound (Fig. 2). The crystal structure shown in Figure 2(a) reveals a tape-like architecture whereby, each molecule forms four $NH\cdots O{=}C$ hydrogen bonds to two adjacent molecules of the tape. It is noteworthy that within the tape the ferrocene units adopt an orthogonal stacked architecture, presumably help to accommodate these bulky units within the supramolecular structure. The stacks themselves are arranged as a double sheet of ferrocene units, with the hydrogen bonded side chains arranged either side of these double sheets (Fig. 2(b)).

2.3. Solution binding studies

Hydrogen bond formation between **2** and **5** was confirmed by changes in the ^1H NMR spectra. Addition of aliquots of ferroreceptor **5** to a solution of flavin **2** in $CDCl_3$ resulted in a small downfield shift (~0.2 ppm) in the resonance of H(3) of the flavin, consistent with the formation of a low-affinity hydrogen bonded complex. The resulting curve was fitted to a 1:1 binding isotherm, which provided an association constant (K_a) of 5 (±5) M^{-1}.[2f] As anticipated, this is considerably lower than that of K_a obtained for the 1:1 hydrogen bonded complex of **1·2** (K_a=45 M^{-1}),[3a] presumably due to the second bulky ferrocene unit further masking the hydrogen bonding site of **5**. ^1H NMR dilution measurements performed on compound **6** indicated that substantial self-aggregation occurs in $CDCl_3$.[2d,e] An interesting feature of the NMR spectra of **6** when measured in $CDCl_3$ was the urea proton adjacent to the ferrocene unit gave rise to larger shifts than the adjacent urea proton upon dilution. However, when measurements were repeated in DMF-d_7 significant concentration dependence was not observed, indicating that the competitive nature of this polar solvent greatly diminishes the self-aggregation of **6**, thereby allowing the K_a for **4·6** to be estimated as 1(±5) M^{-1} using NMR titration experiments in DMF-d_7.

2.4. Electrochemical studies

With host–guest complexation verified for **2·5** and **4·6**, we next investigated the role of electrochemistry to modulate binding properties of these systems using CV and SWV studies. CV studies on compound **5** gave rise to a reversible single electron oxidation with $E_{1/2}$=+0.78 mV (versus the decamethylferrocene/decamethylferrocenium redox couple=0 V). Addition of excess **2** to a solution of **5**,

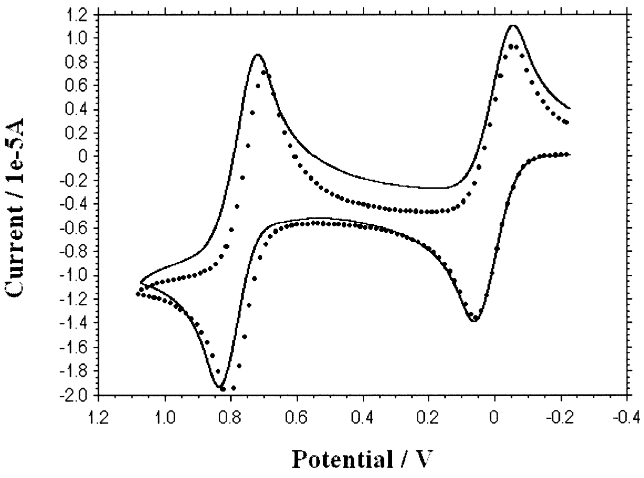


Figure 3. Cyclic voltammograms of **5** (~1×10^{-3} M) (continuous line) and in the presence of excess **2** (4×10^{-2} M) (dotted line) (CH_2Cl_2, decamethylferrocene/decamethylferrocenium).

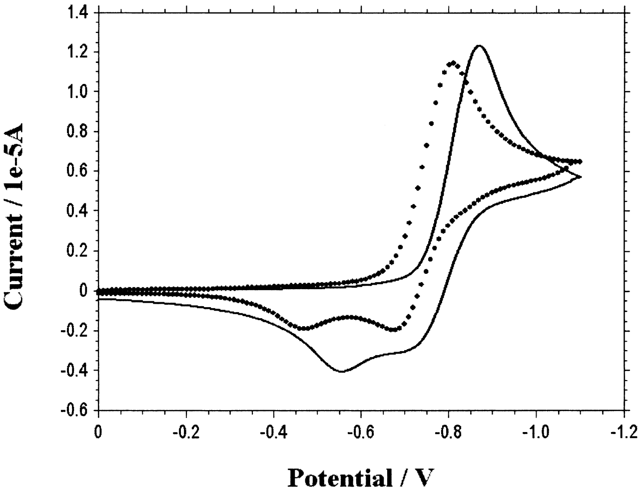


Figure 4. Cyclic voltammograms of **2** (~8×10^{-4} M) (continuous line) and in the presence of excess **5** (~2×10^{-2} M) (dotted line) (CH_2Cl_2, Ag/AgCl).

immediately resulted in a −24 mV shift in the oxidation potential of the ferrocene moiety of receptor **5** (Fig. 3). This negative shift indicates a stabilization (1.11 kcal/mol) of the ferrocenium states of receptor **5**, and hence corresponds to the flavin unit becoming more than six times more strongly bound to **5** ($\mathbf{2}\cdot\mathbf{5}^{2+}$, K_a=33 M^{-1}). CV studies of flavin **2** show a single, one electron reduction peak and two separate re-oxidation peaks (Fig. 4).[2f] Addition of excess **5** provides a significant reduction (+40 mV) in the voltage for both the reduction wave potential and $E_{1/2}$ for the reversible redox couple, indicating a substantial (0.92 kcal/mol) stabilization of the radical anion of **2**, which results in an approximately 5-fold increase in the binding strength of the complex ($\mathbf{2}^{\cdot-}\cdot\mathbf{5}$, K_a=24 M^{-1}). In line with previously reported data for the hydrogen bonded complex of **2** with 2,6-diethylamidopyridine, the wave corresponding to the re-oxidation of the flavin radical anion is enhanced.[2f] However, the wave due to re-oxidation of the flavohydroquinone anion to the neutral flavin is not fully suppressed and is shifted by approximately 50 mV to a more positive potential (versus the decamethylferrocene/decamethylferrocenium redox couple=0 V).

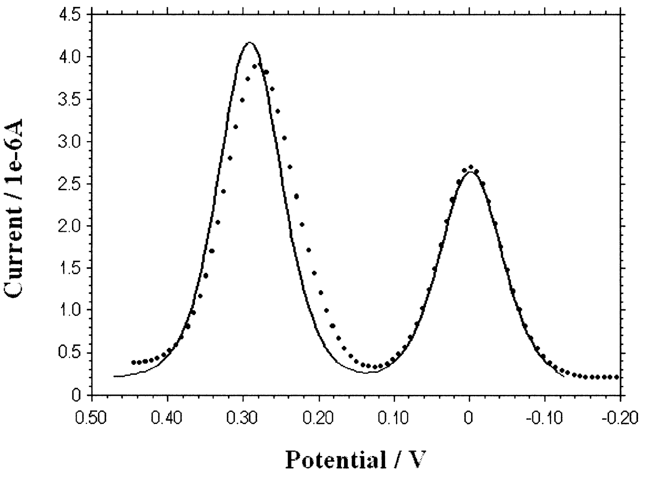


Figure 5. Square wave voltammograms of **6** (~5×10^{-4} M) (continuous line) and in the presence of excess **4** (~5×10^{-2} M) (dotted line) (DMF, decamethylferrocene/decamethylferrocenium).

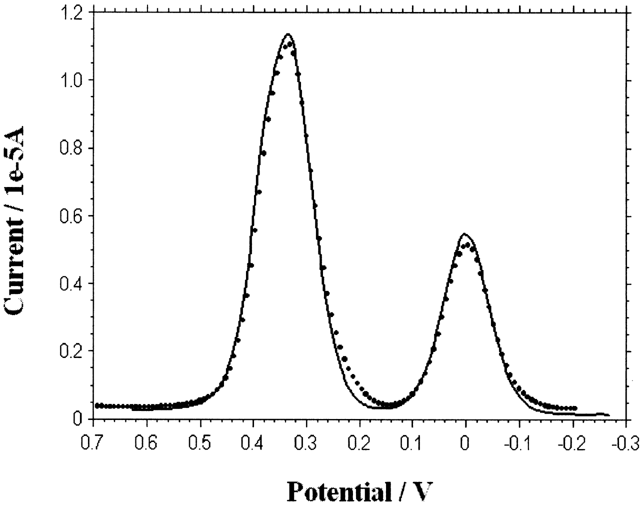


Figure 6. Square wave voltammograms of **6** (~1×10^{-3} M) (continuous line) and in the presence of excess **4** (~9×10^{-2} M) (dotted line) (CH_2Cl_2, decamethylferrocene/decamethylferrocenium).

CV studies of **6** performed in DMF or DCM gave rise to a reversible oxidation wave at $E_{1/2}$=+0.29 mV and $E_{1/2}$=+0.35 m, respectively. To study the effect that oxidation of the ferrocene moiety of **6** has upon the hydrogen bonding efficiency with **4**, an excess of the latter was added to a solution of **6** in DMF, and the CVs and SWVs were recorded. A −15 mV shift in the oxidation potential of the ferrocene moiety of **6** was observed (Fig. 5) which corresponds to a stabilization (0.34 kcal/mol) of the ferrocenium state of **6**, indicating a 2-fold increase in the binding strength of the complex ($\mathbf{4}\cdot\mathbf{6}^{+}$, K_a=2 M^{-1}). In CH_2Cl_2, virtually no shift in the oxidation potential of **6** was observed upon the addition of **4**, presumably due to the competitive self-aggregation of **6** preventing effective host–guest complexation with **4** (Fig. 6). In order to provide further evidence for the proposed self-aggregation of **6** in CH_2Cl_2, we have measured the half-wave potential of this compound at various concentrations (Fig. 7). A small positive shift (15 mV) in the half-wave potential of **6** was observed upon increasing the concentration from 10^{-4} M to

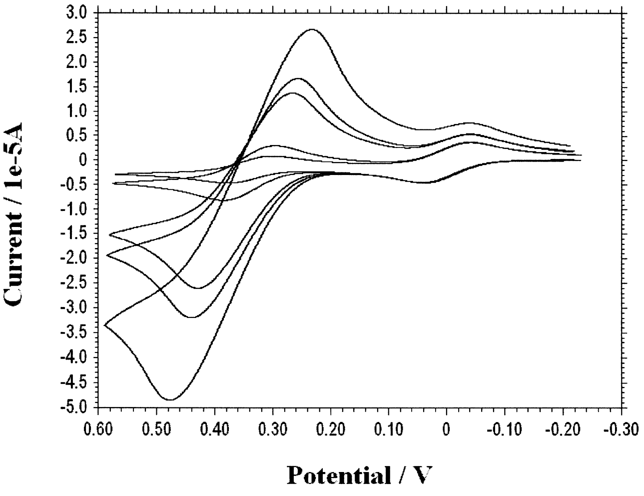


Figure 7. Cyclic voltammograms of **6** recorded at various concentrations in CH_2Cl_2 (versus decamethylferrocene/decamethylferrocenium). (Smallest peak current concentration of **6**=~4×10^{-4} M; largest peak current concentration of **6**=~6×10^{-3} M).

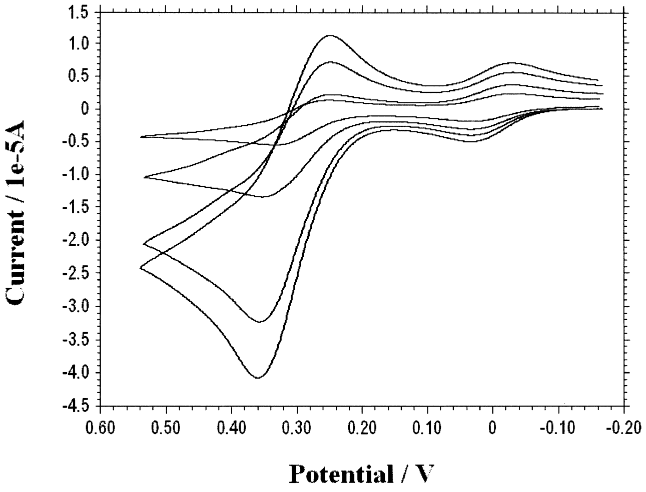


Figure 8. Cyclic voltammograms **6** recorded at various concentrations in DMF (versus decamethylferrocene/decamethylferrocenium). (Smallest peak current concentration of **6**=~4×10^{-4} M; largest peak current concentration of **6**=~5×10^{-3} M).

10^{-3} M, which is in accordance with the self-aggregation of **6** in CH_2Cl_2. When the oxidation potential of **6** was measured at similar concentrations in DMF, a negligible shift in half-wave potential was observed, which is consistent with limited self-aggregation in this solvent (Fig. 8).[8]

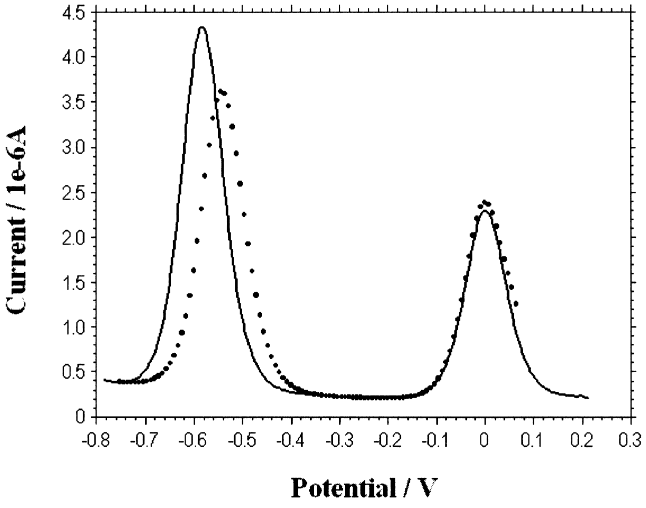


Figure 9. Square wave voltammograms of **4** (~6×10^{-4} M) (solid line) and in the presence of excess **6** (~2×10^{-2} M) (dotted line) (DMF, decamethylferrocene/decamethylferrocenium).

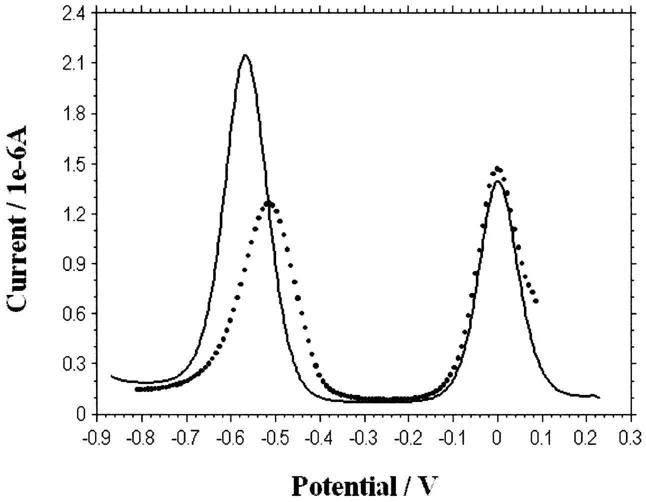


Figure 10. Square wave voltammograms of **4** (~3×10^{-4} M) (solid line) and in the presence of excess **6** (~1×10^{-2} M) (dotted line) (CH_2Cl_2 decamethylferrocene/decamethylferrocenium).

The effect the addition of **6** has on the stabilisation of the radical anion state of **4** was studied using SWV and CV. The addition of excess **6** to a solution of **4** in DMF gave rise to a +43 mV shift in the reduction potential (Fig. 9), indicating a stabilization (1 kcal/mol) of the radical anion state of **4**, corresponding to a 5-fold increase in the binding strength of the complex ($\mathbf{4}^{\cdot -}\cdot\mathbf{6}$, K_a=5.3 M^{-1}). When the experiments were repeated in CH_2Cl_2, preventing solvation of the radical anion state of **4**, a slightly larger shift of +55 mV was observed (Fig. 10). This result is in contrast to the CV data obtained for **6** upon the addition of excess **4** in CH_2Cl_2, where no shift in the ferrocene redox couple was observed, and suggests that the $\mathbf{4}^{\cdot -}$ state disrupts the intermolecular hydrogen bonding between **6** to allow effective recognition to occur. It is noteworthy that in both solvents the shifts of the reduction wave of **4** following the addition of **6** are somewhat lower than those reported for the addition of 1-phenyl-3-propylurea (+66 and +156 mV in DMF and CH_2Cl_2, respectively),[2d,e] presumably due to the bulky ferrocene moiety partially masking the hydrogen bonding site of **6**.[3a]

3. Conclusions

In conclusion, we have fabricated hydrogen bonded host–guest dyads whose binding can be electrochemically actuated between three distinct states by oxidation of the ferrocene host or reduction of the guest moiety. For the **2·5** host guest dyad, the addition of two ferrocene units to the 2,6-diaminopyridine core significantly reduced the binding efficiency of the neutral complex, thereby allowing us to achieve the goal of reducing the hydrogen bonding efficiency of the off state. However, the bulky nature of the ferrocene units was apparently also detrimental to the redox enhancement of binding upon reduction of the flavin unit, as lower redox modulation of hydrogen bonding efficiency was observed for **2·5** compared with **1·2** for this redox process. With host–guest system **4·6**, we have taken the first steps to create three-pole hydrogen bonded systems that can be actuated in polar solvents. We are currently synthesising analogous systems to improve the weak redox enhanced binding observed in these systems and our results will be reported in due course.

4. Experimental

4.1. General methods

Melting points are uncorrected. NMR experiments were performed on a Bruker AC 200 with TMS used as internal standard. IR spectra were recorded on a Perkin–Elmer RX FT-IR spectrometer. Flavin **2**[9] and ferrocene derivative **8**[6] were synthesised using the previously reported procedures.

4.1.1. 2,6-Diferrocenylamidopyridine (5). To a solution of 2,6-diaminopyridine (1.0 g, 9.2 mmol) and chlorocarbonylferrocene (5.0 g, 20 mmol) in dry dichloromethane (150 mL), was added NEt_3 (5 mL) dropwise over 10 min. The reaction mixture was stirred at room temperature for 48 h under an inert atmosphere, then water (100 mL) was added. The lower organic layer was removed and the aqueous layer was further extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue obtained was purified using column chromatography (silica gel, CH_2Cl_2/ethyl acetate 9:1 v/v as eluent), to afford **5** as a yellow solid. Yield: 2.0 g (40%). Mp 222–224°C; ^1H NMR (200 MHz, $CDCl_3$): δ 4.30 (10H, s), 4.46 (4H, q, J=3 Hz), 4.84 (4H, t, J=3 Hz), 7.77 (1H, t, J=8 Hz), 7.80 (2H, br s), 8.01 (2H, d, J=8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 68.33, 69.93, 71.23, 75.29, 109.02, 140.82, 149.59, 168.84; MS m/z (EI): 533 (M^+, 30%). IR (KBr, cm^{-1}): ν 3419, 3288, 3092, 1661, 1584, 1506, 1440, 1300, 1260, 1244, 1140, 798, 492. Anal. calcd for $C_{27}H_{23}Fe_2N_3O_2$: C, 60.82; H, 4.35; N, 7.88; found C, 60.72; H, 4.32; N, 7.77.

4.1.2. 1-Ferrocenyl-3-hexylurea (6). A solution of ferrocenylamine (0.5 g, 2.49 mmol), hexylisocyanate (0.35 g, 2.74 mmol) and NEt_3 (5 mL) was heated at 60°C for 48 h in dry THF (150 mL) under an inert atmosphere. The solution was then evaporated to dryness, and the crude residue obtained was purified using column chromatography (silica gel, CH_2Cl_2/ethyl acetate 9:1 v/v as eluent), to afford **6** as a yellow solid. Yield: 0.57 g (70%). Mp 104–107°C; ^1H NMR (200 MHz, $CDCl_3$: δ 0.92 (t, 3H), 1.28 (s, 6H), 1.48 (m, 2H), 3.20 (q, 2H, J=6.6 Hz), 4.05 (s, 2H), 4.22 (s, 5H), 4.33 (s, 2H), 5.16 (t, 1H), 6.10 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.94, 22.49, 26.49, 30.07, 31.42, 40.22, 64.01, 65.71, 69.35, 157.17; MS (EI): m/z=328 (M^+, 30%). IR (KBr, cm^{-1}): ν 3327, 3102, 2921, 2856, 1633, 1575, 1482, 1253, 1104, 1022, 807, 650, 486. Anal. calcd for $C_{17}H_{24}N_2FeO$: C, 62.19; H, 7.32; N, 8.54; found C, 62.20; H, 7.46; N, 8.48.

4.2. Electrochemistry

All electrochemical experiments were performed using a CH120A electrochemical workstation. The 0.1 M electrolyte solutions were prepared from re-crystallised Bu_4NPF_6 using spectroscopic grade dichloromethane or dimethylformamide and purged with nitrogen prior to use. A three electrode configuration was used with a Pt working electrode, a platinum wire as the counter electrode and either a Ag/AgCl or a Ag wire pseudo reference electrode. Decamethylferrocene was used as an internal standard when a silver wire pseudo reference electrode was used, and the redox potentials values are based upon the decamethylferrocene/decamethylferrocenium redox couple=0 V. Scan rate 100 mV/s. T=25°C. It is noteworthy that in all cases the Ag/AgCl reference electrode gave rise to larger shifts (20–30%) in redox potentials compared to the decamethylferrocene/decamethylferrocenium redox couple following the addition of the guest. All of the thermodynamic parameters derived from the $\Delta E_{1/2}$ or ΔE values were calculated form the data obtained using the Ag pseudo reference electrode. The redox-based modulation of recognition was calculated from the estimated K_a for the neutral complex using a thermodynamic cycle which can be expressed mathematically using: $K_a(red)/K_a(ox) = \exp((nF/RT)(E_{1/2}(\text{bound}) - E_{1/2}(\text{unbound})))$. K_a(red) and K_a(ox) are the association constants in the reduced and oxidized forms, and $E_{1/2}$(bound) and $E_{1/2}$(unbound) are the half-wave redox potentials in the receptor bound and unbound states.[1c]

4.3. X-Ray crystallographic study of 6

Crystals suitable for X-ray crystallography were grown from a solution of **6** in CH_2Cl_2/ethyl acetate (9:1 v/v) that was left to slowly evaporate over the course of several days. Selected crystal data for **6**: $C_{17}H_{24}N_2FeO$, M=328.23, monoclinic, a=21.609(4), b=8.003(2), c=9.4710(10) Å, V=1627.1(5) Å^3, T=160 K, space group=P2(1)/c, Z=4, μ=0.927 mm^{-1}, 3894 total reflections, 2843 unique [R(int)=0.1100], R=0.0839, wR=0.2128 for $I>2\sigma(I)$. Crystallographic data for **6** have been deposited with the Cambridge Crystallographic Data Centre (CCDC reference number 189247).

Acknowledgements

We gratefully acknowledge support from the EPSRC (FMAD), The EPSRC National Mass Spectrometry Service Centre, Swansea, The Royal Society and the National Science Foundation (US) (VMR).

References

1. For recent reviews containing aspects of supramolecular electrochemistry see: (a) Kaifer, A. E.; Gómez-Kaifer, M. *Supramolecular Electrochemistry*; Wiley/VCH: Weinheim, 1999. (b) Boulas, P. L.; Gomez-Kaifer, M.; Echegoyen, L. *Angew. Chem. Int. Ed.* **1998**, *37*, 216–247. (c) Rotello, V. M.; Niemz, A. *Acc. Chem. Res.* **1999**, *32*, 44–52. (d) Kaifer, A. E. *Acc. Chem. Res.* **1999**, *32*, 62–71. (e) Tucker, J. H. R.; Collinson, S. R. *Chem. Soc. Rev.* **2002**, *31*, 147–156. (f) Cooke, G.; Rotello, V. M. *Chem. Soc. Rev.* **2002**, *31*, 275–286.
2. (a) Carr, J. D.; Lambert, L.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A.; Tucker, J. H. R. *Chem. Commun.* **1997**, 1649–1650. (b) Carr, J. D.; Coles, S. J.; Hursthouse, M. B.; Light, M. E.; Tucker, J. H. R.; Westwood, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 3296–3299. (c) Collinson, S. R.; Gelbrich, T.; Hursthouse, M. B.; Tucker, J. H. R. *Chem. Commun.* **2001**, 555–556. (d) Ge, Y.; Lilienthal, R. R.; Smith, D. K. *J. Am. Chem. Soc.* **1996**, *118*, 3976–3977. (e) Ge, Y.; Miller, L.; Ouimet, T.; Smith, D. K. *J. Org. Chem.* **2000**, *65*, 8831–8838. (f) Breinlinger, E.; Niemz, A.; Rotello, V. M. *J. Am. Chem. Soc.* **1995**, *117*, 5379–5380. (g) Goldenberg, L. M.; Neilands, O. *J. Electroanal. Chem.* **1999**, *463*, 212–217. (h) Boyd, A. S. F.; Cooke, G.; Duclairoir, F. M. A.; Rotello, V. M. *Tetrahedron Lett.* **2003**, *44*, 303–306.
3. (a) Bourgel, C.; Boyd, A. S. F.; Cooke, G.; de Cremiers, H. A.; Duclairoir, F. M. A.; Rotello, V. M. *Chem. Commun.* **2001**, 1954–1955. (b) Goodman, A.; Breinlinger, E.; Ober, M.; Rotello, V. M. *J. Am. Chem. Soc.* **2001**, *123*, 6213–6214.
4. 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*, 3951–3957.

5. For examples of ferrocene containing ureas and thioureas that can undergo electrochemically controlled recognition with inorganic anions see: (a) Beer, P. D.; Davis, J. J.; Drillsma-Milgrom, D. A.; Szemes, F. *Chem. Commun.* **2002**, 1716–1717. (b) Alonso, B.; Casado, C. M.; Cuadrado, I.; Morán, M.; Kaifer, A. E. *Chem. Commun.* **2002**, 1778–1779.
6. Pauson, P. L.; Watts, W. E. *J. Chem. Soc.* **1963**, 2990–2996.
7. Knox, G. R.; Pauson, P. L.; Willison, D.; Solčaniova, E.; Tomas, S. *Organometallics* **1990**, *9*, 301–306.
8. While some solvent mediated decomposition was observed electrochemically in DMF, there was no visible change in the redox potential for the quasi-reversible oxidation/reduction of **6** upon repeated cycling at a particular scan rate.
9. Niemz, A.; Imbriglio, J.; Rotello, V. M. *J. Am. Chem. Soc.* **1997**, *119*, 887–892.