Novel electrochemical sensors for neutral molecules

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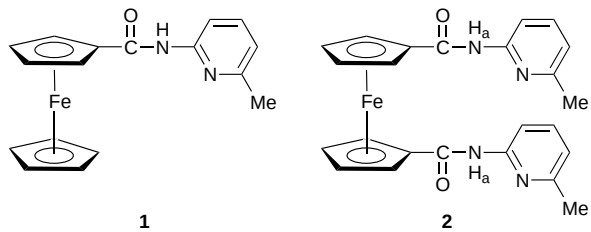
Two new ferrocene receptors bind to a series of neutral carboxylic acid guests *via* hydrogen bonding interactions; complexation induces a significant change in the electronic properties of the proximate ferrocene units, as evidenced by the recognition of these neutral guests by cyclic voltammetry.

Supramolecular compounds that undergo a change in their redox properties upon complexation are relevant to the development of molecular sensing and switching devices.[1] So far, research in this area has focused almost exclusively on redox-active receptor molecules that bind and sense either cations[2] or anions.[3] However, although the chemistry of neutral molecule recognition is well-developed,[1,4] there are only a few reports of systems where the binding of neutral guest molecules in solution has been followed electrochemically.[5,6] The recent interest in hydrogen bonded supramolecular systems containing metal centres,[7] combined with evidence that hydrogen bonding contributes to the magnitude of redox potentials in metalloproteins,[8] suggest that effective electrochemical sensing of neutral molecules, *via* hydrogen bonding interactions, is within reach. Here we report two new receptor compounds containing ferrocene units and give preliminary results on their interaction with a range of neutral carboxylic acids.



Two simple redox-active ferrocene compounds **1** and **2**, containing a mono- and bis-amido pyridine moiety respectively, have been synthesised in good yield from the reaction of either chlorocarbonylferrocene or 1,1′-bis(chlorocarbonyl)ferrocene with 2-aminopicoline in CH_2Cl_2 in the presence of base.

Complex formation between receptors **1** and **2** and a series of monocarboxylic acids **3a**–**c** and a dicarboxylic acid, glutaric acid **4**, is evidenced by changes to the ^{1}H NMR spectra of **1** and **2** in $CDCl_3$. For each receptor, the addition of excess substrate causes marked shifts in the signals corresponding to the amide and cyclopentadienyl protons. A complex of 1 : 1 stoichiometry between **2** and **4** is revealed by monitoring the downfield shift for the H_a proton of **2** ([**2**] ≈ 1 mM) upon addition of aliquots of **4** (Fig. 1).† The large shift of *ca*. 1.9 ppm is strong evidence for a hydrogen bonding interaction.[7a,10]

Titrations of **1** and **2** (1 mM, $CDCl_3$) with monoacids **3a**–**c** give complexes of 1 : 1 and 1 : 2 (Fc : acid) stoichiometry respectively, whereas a titration of **1** with diacid **4** proceeds *via* a dimeric complex of 2 : 1 (Fc : acid) stoichiometry to give a 1 : 1 complex upon the addition of excess guest. In agreement with the solution studies, an X-ray structure of a crystal grown by slow evaporation of a $CDCl_3$–Et_2O solution of **1** and excess **4** reveals a hydrogen bonded dimer (Fig. 2), consisting of two linked complexes of 1 : 1 stoichiometry [N(1)–H(1)–O(3) distance 2.92 Å, N(1)–H(1)–O(3) angle 166°; O(2)–H(2)–N(2) 2.65 Å, 171°; O(5)–H(5)–O(4) 2.63 Å, 167°].‡

This X-ray structure and the NMR studies suggest that the complex between **2** and **4** is likely to consist of an intermolecular four-point binding interaction, in which the guest is bridged between the two cyclopentadienyl rings. A similar geometry has been found by Hamilton[10] for related complexes between neutral terephthalate bis-amidopyridine derivatives and dicarboxylic acids.

Cyclic voltammetry studies in CH_2Cl_2 (1 mM) reveal that substrate complexation can be detected electrochemically (Table 1). The addition of excess monoacid (**3a**–**c**) to **1** causes small negative shifts ($\Delta E°$ = −20 to −25 mV) in the reversible redox wave of the receptor, whereas for receptor **2** the magnitude of the shift is approximately twice that amount ($\Delta E°$ = −55 to −60 mV). This indicates that the number of hydrogen bonds is approximately proportional to the shift in the redox potential. The shift of −20 mV found for **1** in the presence of excess **4** therefore denotes a 1 : 1 complex, which is in agreement with the NMR and X-ray studies. However, the significantly larger shift of −85 mV found for **2** with diacid **4** is likely to be a result of the effect of four strong hydrogen bonds, combined with the unique geometry of the complex. In this conformation the guest is bridged across the ferrocene unit, much closer to the redox-active iron centre.

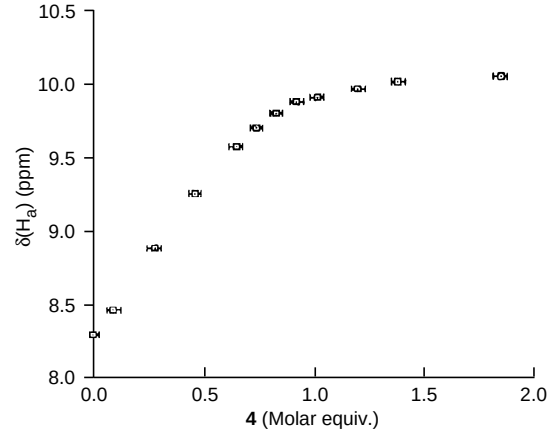


Fig. 1 ^{1}H NMR shift value of the H_a proton of **2** in $CDCl_3$ as a function of molar equivalents of glutaric acid **4**

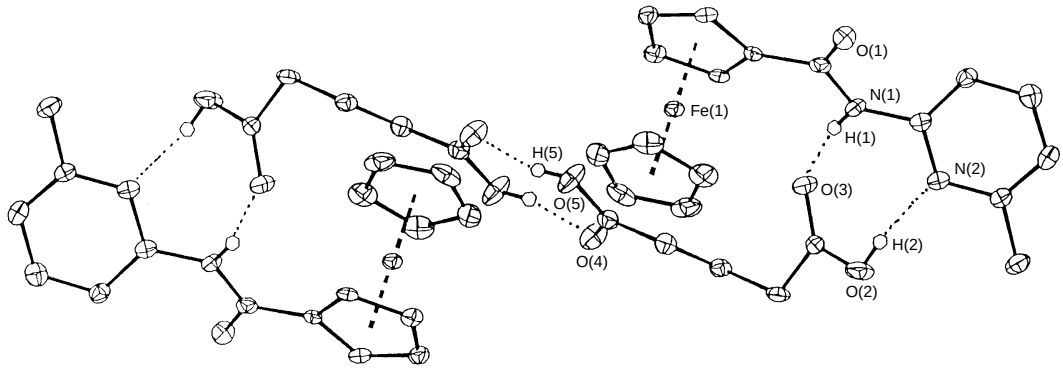


Fig. 2 Crystal structure of [**1**·**4**]$_2$ (the dotted lines indicate strong hydrogen bonds between the two species and also between a pair of acid molecules

Table 1 Electrochemical data[a] for compounds **1** and **2** in CH_2Cl_2 in the absence and presence of neutral guest substrates **3a**–**c** and **4**

		$\Delta E°$/V[c]			
Compound[b]	$E°$/V	**3a**	**3b**	**3c**	**4**
1	+0.24	−20	−20	−25	−20
2	+0.44	−60	−55	−55	−85

[a] Cyclic voltammograms were carried out at a scan rate of 200 mV s^{-1} in CH_2Cl_2 containing tetrabutylammonium perchlorate (TBAP) as supporting electrolyte (0.1 M), ferrocene as internal reference (*ca.* 1 mM) and the appropriate ferrocene receptor (1 mM) at room temp. The following electrode system was used: Pt wire working electrode, Pt wire counter electrode and Ag wire pseudo-reference electrode. [b] Redox potentials ($E°$) were referenced to ferrocene as an internal standard where $E° = 0.5 (E°_{pa} - E°_{pc})$. The confidence limit is ±10 mV. For each voltammogram, the reversibility of the redox wave matched that of the ferrocene internal reference ($\Delta E°_p$ = 70–100 mV). [c] The cathodic shift (mV) of the reversible redox couple of **1** or **2** upon addition of excess substrate.

In all cases, negative shifts in the redox waves of **1** and **2** are observed, which indicates that complexation increases the electron density at the iron centre. This is most likely a result of complexation delivering more electron density to the amide nitrogen. However, an attempt to monitor the change in the amide carbonyl stretch of 2 ($\nu_{C=O}$ 1668 cm^{-1}, KBr disc) using IR spectroscopy was hampered because of overlap by the carboxylic acid peaks of each guest. At any rate, there is no evidence of shifts being induced by protonation of the pyridine units, which would be the case if binding is of the zwitterionic form; addition of H$^+$ leads to large positive shifts in the redox waves of **1** and **2**.[9]

The $\Delta E°$ values reflect the difference in substrate binding strength between the two redox states of each complex.[11] In this case, the negative shifts indicate that each guest is bound more strongly once the ferrocene unit is oxidised. Such a trend is consistent with a positive charge on the ferrocene unit increasing the acidity of the amide N–H bond of the receptor.[12] However, recent quantitative studies on related systems[7b] show that the strength of hydrogen bonding may in fact increase or decrease upon the introduction of a postive charge at an adjacent metal centre. The direction and magnitude of this change appears to be strongly dependent upon the type of donor–acceptor system and the degree of conjugation between the metal centre and the binding site.

As far as we are aware, this system represents the most significant change in the redox properties of a supramolecular receptor compound that is induced by the complexation of a *neutral* guest. In other examples, the effect has either been smaller,[5] or has involved systems in which the guest, and not the host, is redox-active.[6] Studies are currently underway to fully explain the nature of this redox response in these and other related systems.

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Footnotes and References

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† The near complete complexation of **2** for a 1 : 1 molar ratio at millimolar concentrations suggests a stability constant between **2** and **4** of ⩾ 10^4 M^{-1}. Comprehensive studies are now in progress to evaluate the stability constants between **1** and **2** and a range of carboxylic acid guests.[9]

‡ *Crystal data* for **1**·**4**: $C_{22}H_{24}FeN_2O_5$, orange crystals from $CDCl_3$–Et_2O, M = 452.28, triclinic, a = 7.4380(10), b = 7.596(2), c = 18.211(4) Å, α = 82.58(3), β = 79.99(3), γ = 86.10(3)°, U = 1003.7(4) Å^3, space group $P\bar{1}$, Z = 2, D_c = 1.497 Mg m^{-3}, μ(Mo-Kα) = 0.789 mm^{-1}, crystal size 0.14 × 0.12 × 0.10 mm. Final R [on 2194 $F > 4\sigma(F_o)$] = 0.0426 and wR (on all F^2) = 0.1045. CCDC 182/546.

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