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Novel ferrocene receptors for barbiturates and ureas

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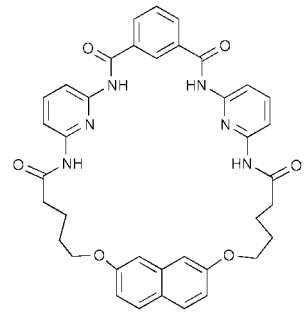
The complexation *via* complementary hydrogen bonds, of three novel ferrocene receptors with barbital, ethylene urea and trimethylene urea is described with the binding mode and stoichiometry clearly shown by NMR spectroscopy and X-ray crystallography.

As part of the continued interest in the development of novel molecular switches and sensors, redox-active receptors for inorganic cations and anions have been studied in much detail,[1] although reports of similar receptors for organic molecules, be they charged or neutral, are less common.[2] Interest in the development of functional receptors for organic molecules such as barbiturates arises due to their importance as sedatives and anticonvulsants,[3] whilst the detection of ureas is important with regard to possible applications in dialysis. Previous studies concerning the binding of barbiturates and ureas have largely focused on organic receptors that bind the neutral guest through hydrogen bonds.[4] In particular, Hamilton and coworkers have reported the complexation of barbiturates by both macrocyclic and acyclic receptors (*e.g.* **1** and **2**) containing two 2,6-diaminopyridine units linked *via* an isophthaloyl group.[4a,b] Here we report that a similar binding motif can be constructed through the incorporation of the redox-active ferrocene unit into the receptor framework.



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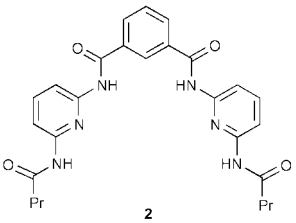

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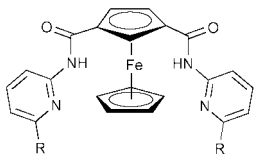
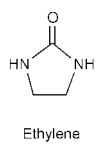
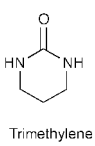


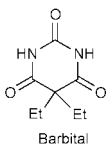
3 R = CH_3
4 R = NH_2
5 R = HNCOEt



Ethylene urea



Trimethylene urea



Barbital

The synthetic strategy involved the synthesis of ferrocene-1,3-dicarbonylchloride,[5] which was then reacted, in the presence of triethylamine, with either two equivalents of 2-amino-6-methylpyridine or with an excess of 2,6-diaminopyridine, to yield compounds **3** and **4** respectively. Further reaction of **4** with propionyl chloride, again in the presence of triethylamine, yielded compound **5**. These reactions thus produced a series of ferrocene receptors containing either two hydrogen bond donor groups (D) with two hydrogen bond acceptor groups (A) (receptor **3**) or four hydrogen bond donor groups with two hydrogen bond acceptor groups (receptors **4** and **5**).

The interaction of each ferrocene receptor with a range of neutral guests was monitored by ^{1}H NMR spectroscopy in dry $CDCl_3$. Downfield shifts in the resonances corresponding to the amide protons and also the proton in the 2-position of the disubstituted ferrocene Cp ring were observed. For example, this Cp-H resonance in receptor **5** underwent a downfield shift of +0.25 ppm upon the addition of one molar equivalent of barbital. The stoichiometry of each of the complexes was confirmed as 1:1 *via* Job plots derived from the NMR data, which displayed a maximum at 0.5 mole fraction of the receptor. The values of the binding constants for each complexation experiment were then determined using the EQNMR program (Table 1).[6]

From Table 1 it is clear that there is a correlation between the number of the hydrogen bonds and the value of the binding constant. Receptor **3** forms the most stable complex *via* four hydrogen bonds with trimethylene urea, suggesting that ethylene urea is too small for the cavity formed by these receptors. Interestingly, **3** only forms a weak complex with barbital which is a similar size to trimethylene urea. This reflects the fact that there are two carbonyl groups on the barbital guest, which are not involved directly in hydrogen bonding but nevertheless are adjacent to a hydrogen bond, leading to unfavourable diagonal secondary electrostatic interactions.[7] In a related manner, trimethylene urea forms weaker complexes with receptors **4** and **5** compared to receptor **3**. The additional hydrogen bond donor groups on **4** and **5** are not directly involved in hydrogen bond formation but still contribute to unfavourable diagonal secondary electrostatic interactions with the adjacent hydrogen bonds. As expected, the highest binding constants, *via* the formation of six hydrogen bonds, are observed between barbital and receptors **4** and **5**. In fact, **4** binds more strongly than **5**, where the difference beween these two receptors arises at the hydrogen bond donor groups in position R, being amines or amides respectively. A related effect has previously been reported with ferrocene receptors used in anion recognition studies.[8]

Single crystals suitable for study by X-ray crystallography were obtained *via* the diffusion of diethyl ether into a chloroform solution of barbital and **5**.‡ The structures in Fig. 1 show that, as expected, barbital is complexed in a 1:1 stoichiometry through complementary hydrogen bonds. The hydrogen bond lengths in Table 2 show that the closest contacts are between barbital and the amide groups at the position R (*i.e.* N3 and N3′). The two bonds to the apical O3 atoms of the guest in fact are, in fact, very long for a hydrogen bond. However, it

Table 1 Binding constants (M^{-1}) for complexes **3**–**5**, as determined from ^{1}H NMR titration experiments ($CDCl_3$, 298 K)

Receptor	Ethylene urea	Trimethylene urea	Barbital
3	250 ± 5	600 ± 20	195 ± 6
4	—[a]	110 ± 2	3200 ± 242
5	—[a]	25 ± 2	2150 ± 127

[a] Weak binding with several complexes formed in solution.

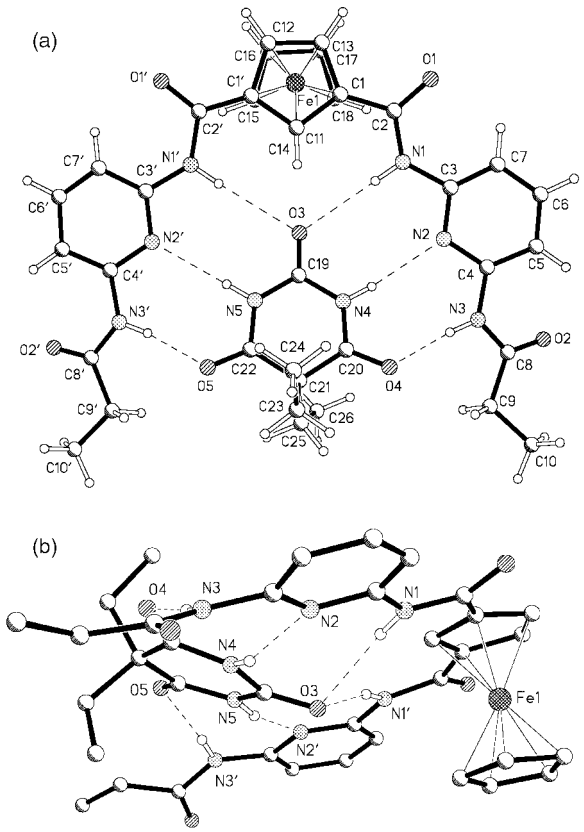


Fig. 1 (a) Top and (b) side views of the X-ray structure of [**5**:barbital].

Table 2 Hydrogen bond lengths and anglesin the X-ray structure of [**5**:barbital]

	Separation (D···A/Å	Angle (DHA)/°
N1–O3	3.434(7)	174.2
N1′–O3	3.494(7)	164.7
N4–N2	3.105(8)	156.6
N5–N2′	3.116(8)	165.3
N3–O4	2.865(7)	174.4
N3′–O5	2.892(8)	171.5

is clear that in solution, these two hydrogen bonds are formed since both resonances for the amide protons of the receptor undergo large downfield shifts upon addition of barbital. In fact, unambiguous assignment of the two resonances corresponding to these two pairs of amide protons was achieved through NOE experiments, allowing the observation that in the presence of 1.5 equiv. of barbital, the resonance for the amide protons adjacent to the Cp-ferrocene ring shifted by +0.9 ppm compared to a larger shift of +1.19 ppm for the resonance for the amide protons at position R. These findings are therefore in agreement with the solid state results in that the strongest amide hydrogen bonds are those that are the furthest away from the ferrocene unit. It is interesting to note that a similar trend in bond lengths was found in the crystal structure of the same guest with the macrocyclic host **1**.[4b] Furthermore, in both structures, the guest is oriented at an angle with respect to the plane formed by the 1,3-arms of the host (**1**:barbital = 27°,[4b] **5**:barbital = 38°).

The nature of the spacer group affects the binding constant with barbital. For Hamilton's analagous acyclic receptor **2**, where the spacer is a 1,3-isophthalic acid group,[4a] the binding constant with barbital in $CDCl_3$ is approximately one order of magnitude higher than that between **5** and barbital (K = 2.08 × 10^4 and 2.15 × 10^3 M^{-1} respectively). A likely explanation for this difference is that the angle between the 1,3-arms in the ferrocene host is larger (the angle geometry is 144 and 120° respectively for five and six-membered rings) which results in the guest having to position itself even closer to the spacer group, with its protuding Cp–H proton, to form hydrogen bonds of any reasonable length. However, additional electronic effects can not be completely ruled out since the Cp unit should lower the acidity of the proximate amide hydrogens, as it is more electron donating than benzene. To examine this effect further, electrochemical measurements were undertaken to assess the effect of oxidising the ferrocene unit on the binding strength. Receptor **5** undergoes a reversible oxidation in dry CH_2Cl_2 at 298 K [E = 0.41 V *vs.* ferrocene internal reference, where E = (E_{pa} + E_{pc})/2], corresponding to the Fe^{II}/Fe^{III} redox couple. Upon addition of excess barbital, a modest cathodic shift of −20 (±5) mV in this redox couple was observed, reflecting a slightly stronger binding of the guest upon oxidation of the ferrocene unit,§ as found previously with related hydrogen bonding ferrocene receptors.[2a] Therefore, the introduction of a positive charge and the resulting electron withdrawing effect from the spacer group would appear to increase the hydrogen bonding strength, although this effect is not as pronounced as when the guest is bridged between the two Cp rings.[2a,b] In conclusion, we have shown that a series of ferrocene compounds can form discrete complexes with a range of biologically relevant molecules through hydrogen bonding interactions. Further binding studies with these and other related receptors are currently underway.

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Notes and references

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‡ *Crystal data* for the 1:0.5 solvate of receptor **5**-barbital with $CDCl_3$; orange blocks from $CDCl_3$–Et_2O, T = 150 K, $C_{36.56}H_{40.50}Cl_{1.50}FeN_8O_7$, M = 812.29, monoclinic, a = 11.281(2), b = 26.560(5), c = 13.995(3) Å, β = 107.39(3)°, U = 4001.5(14) Å^3, space group $P2_1/n$, Z = 4, D_c = 1.348 Mg m^{-3}, μ(MoKα) = 0.789 mm^{-1}, crystal size = 0.10 × 0.07 × 0.07 mm^3, Final R [on 6173 $F > 2\sigma(F^2)$] = 0.0841 and wR (on F^2) = 0.1740. CCDC 154652. See http://www.rsc.org/suppdata/cc/b0/b009820p/ for crystallographic data in .cif or other electronic format.

§ Reference electrode Ag/AgCl; scan rate 100 mV s^{-1}; for other conditions used, see reference 2*b*. Although a clear negative shift in the redox couple was observed upon complexation, the small magnitude of this shift along with the slight increase in peak separation (E_{pa} − E_{pc} (±5 mV); **5**, 75 mV; **5**: barbital, 85 mV; ferrocene internal reference, 70 mV) made the binding enhancement difficult to quantify without a computer simulation.

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