A bridged pyrrolic *ansa*-ferrocene. A new type of anion receptor

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Reaction of an activated bis(pyrrolyl)ferrocene with 2,2′-(ethylenedioxy)bis(ethylamine) under standard amide-forming conditions gives rise to a novel *ansa*-ferrocene system that acts as a redox-based sensor for F$^-$ and H$_2$PO$_4$$^-$ anions.

The construction of metallocene-based anion sensors constitutes an area of active research.[1] In general, successful systems reported in the literature have consisted of a redox active metallocene 'marker' covalently linked to an anion recognition subunit and in this context a wide range of anion binding agents have been employed. One set of anion chelating agents that appears attractive in terms of anion sensor development, but which, apparently, has yet to be explored, is polypyrroles.[2] Pyrrole-containing species, both cyclic and acyclic, often possess H-bond donating characteristics that, depending on the details of structure, can make them effective and selective as anion binding agents both in solution and in the solid state. We thus thought that combining a suitable pyrrolic anion binding entity with a ferrocene marker group could give rise to a new type of anion sensing device. Here, we report the first successful test of this hypothesis. Specifically, we describe the synthesis, solid state characterization, and solution phase anion binding behavior of the *ansa*-ferrocene system **1**; this system acts as an effective redox-based sensor for F$^-$ and H$_2$PO$_4$$^-$.

The synthesis of **1** and its acyclic control **2**, is summarized in Scheme 1. Here, the key precursor **4** was obtained starting from an isomeric mixture of cyclopentadienyl functionalized pyrroles **3**.[3,†] Deesterification of **4** under reductive conditions led to the corresponding diacid **5**. Reaction with 2,2′-(ethylenedioxy)bis(ethylamine) under standard amide-forming conditions then gave the desired *ansa*-ferrocene system **1**, with the acyclic analog **2** being prepared from 2-methoxyethylamine in a similar way.

The *ansa*-ferrocene **1** was characterized *inter alia* by X-ray diffraction analyses. Diffraction-grade single crystals of **1** were obtained by slow diffusion of a CH$_2$Cl$_2$ solution of **1** into hexanes in the case of the solvent-free structure (Fig. 1), and by slow evaporation of a CH$_2$Cl$_2$–hexanes solution at −10 °C in the case of the water-containing structure (Fig. 2). The resulting structures revealed a *trans*-type arrangement about the ferrocene subunit and the presence of an internal 'pocket' that, depending on the anion size, might be expected to accommodate either one or two negatively charged substrates.‡ In the absence of a bound guest, this suggested propensity towards substrate binding is accommodated in the solid state *via* a dimerization process, wherein amide and oxygen atoms from one macrocyclic subunit are bound, *via* H-bonding interactions, to the pyrrolic and amido NH portions of another macrocycle (Fig. 1).§

Interestingly, the second structure alluded to above (Fig. 2) actually provided a more concrete 'hint' that receptor **1** can accommodate a substrate in its binding pocket. In this case a single water molecule is found to be bound within the macrocyclic cavity.‡ A second water molecule, not constrained within the cavity, is found H-bonded to the encapsulated water and to an amide oxygen of an adjacent macrocycle.

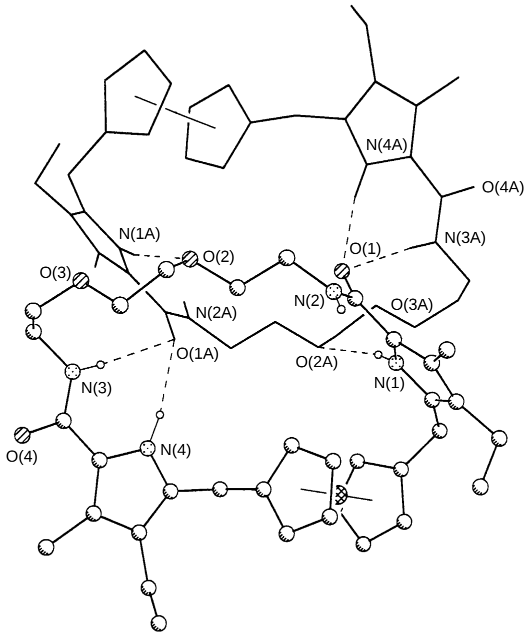
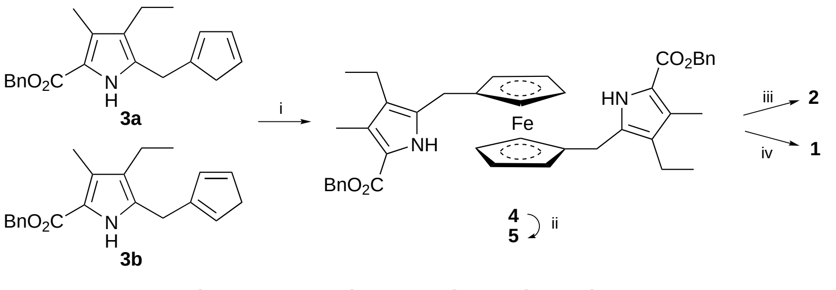


Fig. 1 View of the H-bound dimer of **1** obtained in the solid state. One molecule is shown in ball-and-stick form while a second related by 1 − *x*, 1 − *y*, −*z* is shown in wireframe form. Dashed lines are indicative of a H-bonding interaction. With the exception of the amide- and amino-H all other H atoms are omitted for clarity.

The solution phase anion-binding properties of **1** and **2** were studied by carrying out ^{1}H NMR spectroscopic titrations. Stability constants were then calculated using the EQNMR



Scheme 1 Syntheses of the receptor systems **1** and **2**. *Reagents*: i, TlOEt, THF then FeCl$_2$; ii, Pd/C–H$_2$, THF; iii, BOP, NEt$_3$, DMF, H$_2$NCH$_2$CH$_2$OMe; iv, BOP, NEt$_3$, DMF, H$_2$NCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$NH$_2$.

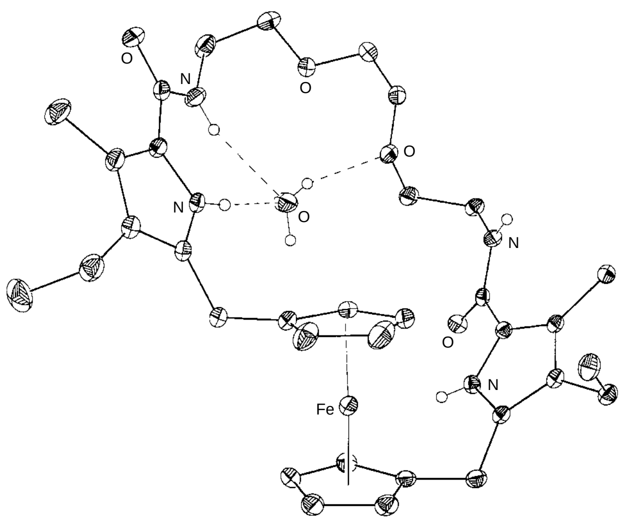


Fig. 2 Solid state structure of **1**·$2H_2O$ (the second water molecule, not contained in the cavity, has been omitted for clarity). Thermal ellipsoids are scaled to the 30% probability level. H atoms shown are drawn at an arbitrary scale. With the exception of the amide and amino hydrogens all other H atoms are omitted for clarity.

computer program.[4] As summarized in Table 1, it was determined that **1** and **2** bind both $H_2PO_4^-$ and Cl^- anions with high affinity in acetonitrile. Although the relevant interactions are clearly weaker, effective anion binding was also observed when Br^- and HSO_4^- anions were tested as substrates. The reduced affinities observed for Br^- and HSO_4^- are ascribed to the lower basicity of these anions and a set of correspondingly weaker H-bond interactions.[1]

Not surprisingly, **2** displays overall affinity constants that are weaker for all of the anions tested. Given the fact that identical functionality is present in both **1** and **2**, this disparity in anion affinity is easily interpreted in terms of the greater preorganization (and lower flexibility) presumed to pertain in receptor **1**.

Table 1 Relevant electrochemical data and stability constants for anion complexes formed from receptors **1** and **2**

	Receptor 1				Receptor 2			
Anion[a]	$K_a{}^b$/dm^3 mol^{-1}	$E_{1/2}{}^c$/ mV	ΔE^d/ mV	BEF[e]	$K_a{}^b$/dm^3 mol^{-1}	$E_{1/2}{}^c$/ mV	ΔE^d/ mV	BEF[e]
None	N/A	396	—	N/A	—	424	—	N/A
F^-	$>10^5$	316	80	—[f]	$>10^5$	368	56	—[f]
Cl^-	9031	372	24	2.5	1260	388	36	4.1
Br^-	857	388	8	1.4	66	404	20	2.2
HSO_4^-	889	380	16	1.9	258	392	32	8.8
$H_2PO_4^-$	11305	260	136	199.0	4181	280	144	271.7

[a] $NBu^n{}_4{}^+$ salts. [b] Association constants for anion binding; recorded in CD_3CN; errors < 15%; determined from $\Delta(\delta)$/ppm NH(amide). [c] Determined in acetonitrile containing 0.1 M $NBu^n{}_4PF_6$ as the supporting electrolyte. Solutions of **1**/**2** were 5×10^{-4} M and potentials were determined with reference to Ag/AgCl, 10 Hz frequency in square wave voltammetry. [d] Cathodic shift observed after the addition of 5 molar equiv. of added anion. [e] Enhancement factor (BEF) for anion coordination after oxidation. [f] Since a 2 : 1 binding mode pertains the BEF could not be defined.

As was revealed by Job plots, different binding stoichiometries are observed (for both **1** and **2**) depending on the size of the anion. In particular, F^- was determined to bind in a 2 : 1 ratio while all other anions tested were found to be bound in a 1 : 1 fashion.

The above findings led us to consider whether systems **1** and **2** could be used to detect the presence of various anions electrochemically through the species specific perturbation of the ferrocene–ferrocenium (Fc/Fc^+) redox couple. As reflected by the data summarized in Table 1, it was found that this could in fact be done. Specifically, the addition of an added, non-electrolyte anion was found to induce a cathodic shift in the reversible Fc/Fc^+ couple seen in both **1** and **2**. These studies, carried out in acetonitrile to allow the calculation of binding enhancement factors,[5] also served to highlight the facts that (*i*) among the five test anions studied, the response factor for both **1** and **2** is greatest for $H_2PO_4^-$ anion followed by F^- and Cl^- and (*ii*) the purely electrochemical sensitivity (*i.e.* $\Delta E_{1/2}$) of these two systems is similar.

In conclusion, the employment of a 1,1′-dipyrrole substituted ferrocene as a building block in an *ansa*-ferrocene type anion system leads to the generation of receptors that not only display unusually high affinities for the 1 : 1 binding of Cl^- and $H_2PO_4^-$ relative to other systems in literature[1] but also allows the detection of these species *via* electrochemical means.

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Footnotes and References

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† All compounds gave spectroscopic and analytical data consistent with the proposed structures.

‡ *Crystal data*: for $C_{34}H_{44}N_4O_4Fe$: yellow crystals, triclinic, $P\bar{1}$, a = 9.248(2), b = 11.622(2), c = 15.681(3) Å, α = 70.168(13), β = 74.160(14), γ = 89.070(13)°, U = 1519.7(6) Å^3, Z = 2, μ = 5.42 cm^{-1}, D_c = 1.37 g cm^{-3}. For $C_{68}H_{88}FeN_8O_8 \cdot 2H_2O$. Yellow clusters, crystal size = 0.17 × 0.36 × 0.99 mm, triclinic, $P\bar{1}$, Z = 2, a = 9.8278(7), b = 13.015(1), c = 14.049(1) Å, α = 79.044(6), β = 73.254(4), γ = 76.547(6), U = 1658.9(3) Å^3, D_c = 1.33 g cm^{-3}, F(000) = 708. CCDC 182/675.

§ The solution and gas phase behavior of **1** was studied by vapor pressure osmometry (VPO) and electrospray mass spectrometry (ESMS), respectively. In solution only weak dimerization could be detected (calc. for $C_{34}H_{44}FeN_4O_4$ 628.6, found: 831). Similarly, only a weak peak of the dimer (2% compared to 100% for the monomer) was observed in ESMS.

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