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Anion recognition and sensing by mono- and bis-urea substituted ferrocene receptors

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Abstract

New mono- and bis-urea substituted ferrocene receptors have been synthesised. Proton NMR anion coordination studies with chloride and dihydrogen phosphate reveal the presence of bulky *tert*-butyl ester group urea substitiuents disfavours $H_2PO_4^-$ complexation and amplifies the recognition of Cl^-. Electrochemical studies showed these urea ferrocene receptors electrochemically recognise $H_2PO_4^-$ and Cl^- and AcO^- via perturbations of the respective ferrocene oxidation wave.

Keywords: Anion binding; Electrochemical sensing; Urea

1. Introduction

The recognition and sensing of anionic guest species of biological and environmental importance by positively charged or neutral abiotic receptor molecules is an area of ever increasing research activity [1]. We [2–5] and others [6,7] have exploited the redox-active ferrocene moiety in the selective electrochemical sensing of anions in organic and aqueous media. In particular acyclic, macrocyclic and calixarene amide-functionalised ferrocene derivatives have all been shown to undergo cathodic perturbations of the respective metallocene redox couple in the presence of a variety of anions. Although the urea group has been exploited in the construction of anion receptors it has not to our knowledge been incorporated into redox active anionphores [8]. We report here the syntheses of new urea-functionalised ferrocene receptors whose anion coordination properties critically depend upon the presence of bulky *tert*-butyl ester urea appended substituents.

2. Synthesis of ferrocene urea receptors

The reactions of ferrocenemethylamine (**1**) with hexylisocyanate (**2**) and the branched isocyanate (**3**) [9] in dichloromethane afforded the new urea functionalised ferrocene receptors (**4**) and (**5**) in 72 and 61% yields, respectively (Scheme 1). Analogous reactions of 1,1′-bis(aminomethyl)ferrocene (**6**) [10] with two equivalents of the isocyanates gave the bis-urea substituted ferrocene receptors (**7**) and (**8**) in moderate yields (Scheme 2). All four urea-ferrocene receptors were characterised by ^1H, ^{13}C NMR, electrospray mass spectrometry and elemental analysis (Section 6).

3. ^1H NMR anion titration studies

Proton NMR anion titration experiments with chloride and dihydrogen phosphate anions were undertaken in deuterated acetonitrile solutions. In all cases the addition of Cl^- or $H_2PO_4^-$ produced significant downfield perturbations of the respective urea protons of the ferrocene receptors (Fig. 1). This suggests the anionic guest species is being complexed in the vicinity of the

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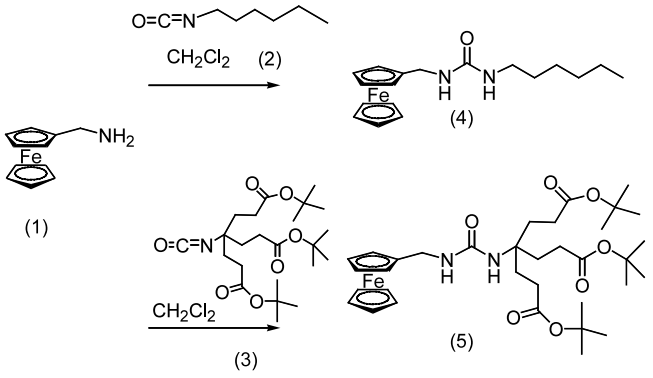
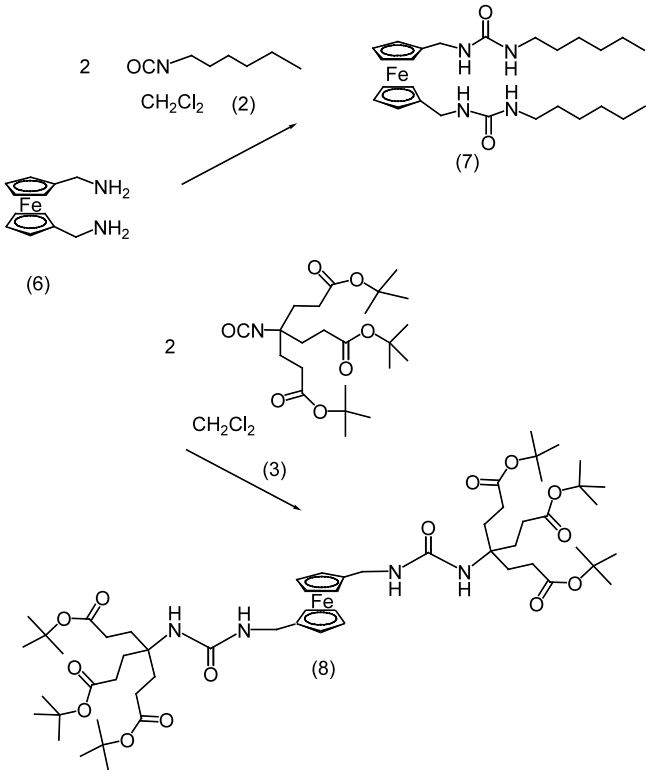


Scheme 1.



Scheme 2.

urea group of the receptor via favourable hydrogen bonding interactions. Interestingly, as Fig. 1 and Fig. 2 illustrate, both urea protons of each receptor were perturbed to similar extents on anion addition. EQNMR [11] analysis of the resulting titration curves, (for example Fig. 2) gave stability constant values for 1:1 stoichiometric complexes for both mono- and 1,1′-bis-substituted urea appended ferrocene derivatives (Table 1). Job plot analyses also confirmed 1:1 anion:receptor stoichiometric binding with (**7**) and (**8**), which implies the two urea groups of each receptor bind the anion in a cooperative fashion. Table 1 shows that as a consequence of an additional urea group both bis-substituted receptors (**7**) and (**8**) bind Cl^- and $H_2PO_4^-$ significantly

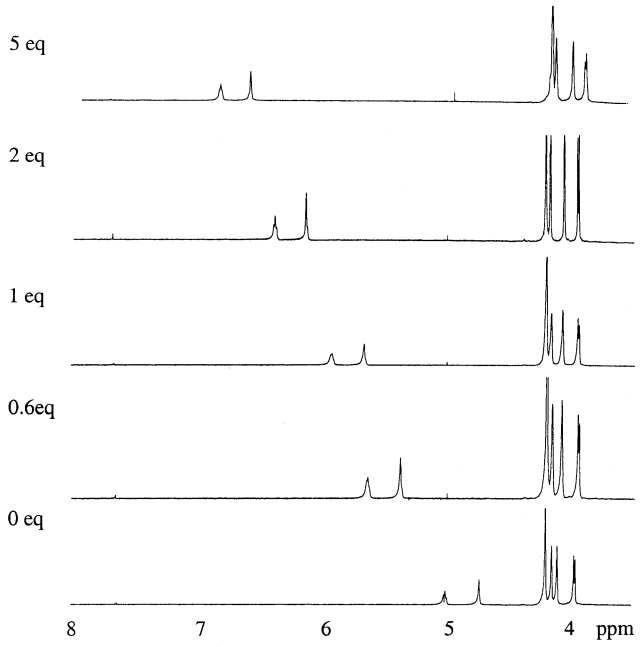


Fig. 1. ^1H NMR spectra of (**5**) upon addition of 0, 0.6, 1, 2, 5 equivalents of chloride anions in CD_3CN solution.

more strongly than the mono-substituted receptors. It is noteworthy that the presence of the tertiary carbon α- to the urea group, appended with *tert*-butyl ester moieties in (**5**) and (**8**), has a profound effect on the anion selectivity preferences exhibited by these receptors. In particular Table 1 reveals the bis-hexyl urea ferrocene receptor (**7**) selectively complexes $H_2PO_4^-$ over Cl^- whereas in contrast the bis-*tert*-butyl ester urea derivative (**8**) exhibits the reverse selectivity trend $Cl^- > H_2PO_4^-$. With the mono-substituted urea receptors, whereas (**5**) preferentially binds Cl^-, (**4**) does not discriminate between the anionic guest species.

The anion selectivity preferences $H_2PO_4^- > Cl^-$ shown by (**7**) may be attributed to the relative basicities of the respective anions. However, with (**8**) the bulky *tert*-butyl ester substituents may serve to sterically hinder complexation of the larger $H_2PO_4^-$ guest. It is difficult to rationalise the increased strength of Cl^- binding exhibited by (**5**) and (**8**).

4. Electrochemical investigations

The electrochemical properties of the receptors were investigated by cyclic and square wave voltammetry in acetonitrile with NBu_4BF_4 as supporting electrolyte. Table 2 shows all receptors undergo a reversible one electron oxidation process at potentials similar to ferrocene itself.

The effect of anion complexation on the electrochemical properties of these urea-ferrocene derivatives was also investigated. Following the addition of $H_2PO_4^-$,

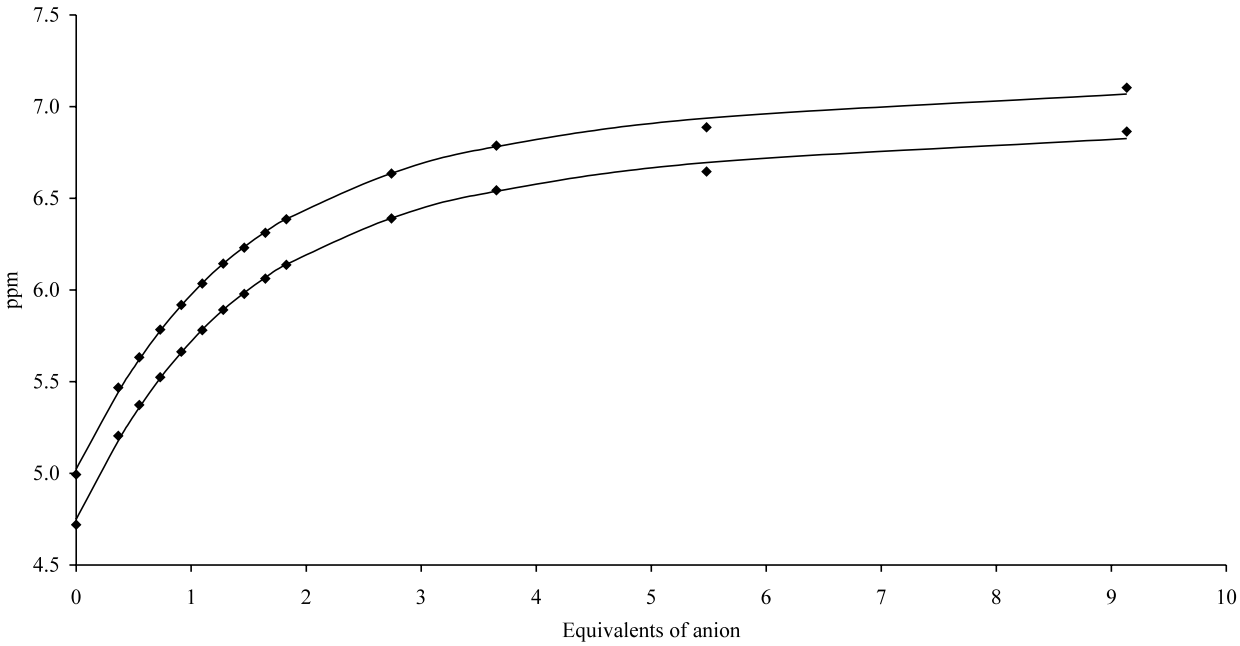


Fig. 2. ^{1}H NMR titration profile of both urea protons of (**5**) upon addition of chloride in CD_3CN solution.

Table 1
Stability constants calculated using EQNMR in CD_3CN solution

Receptor	K_a/M^{-1}	
	Cl^-	$H_2PO_4^-$
(**4**)	60	50
(**5**)	120	30
(**7**)	350	1150
(**8**)	880	150

Errors < 10%.

AcO^-, Cl^-, significant cathodic shifts of up to $\Delta E =$ 150 mV with $H_2PO_4^-$ were observed in the respective ferrocene oxidation potential (Table 2) and the electrochemical response remained reversible. As previously noted with amide-ferrocene receptors [12] the bound anion effectively stabilises the positively charged ferrocenium moiety facilitating the oxidation redox process. Interestingly Table 2 shows in all cases $H_2PO_4^-$ and AcO^- cause larger perturbations than Cl^-, a trend commonly observed in simple amide functionalised ferrocene receptors [12].

5. Conclusion

A series of new mono- and bis-urea substituted ferrocene receptors have been prepared and characterised. Proton NMR anion coordination investigations with chloride and dihydrogen phosphate revealed all receptors form 1:1 stoichiometric complexes in acetonitrile solution. Stability constant determinations showed the presence of bulky *tert*-butyl ester group substituents significantly disfavours complexation of the larger $H_2PO_4^-$ anion, whilst enhancing the recognition of Cl^-. Electrochemical investigations show these urea ferrocene receptors can electrochemically sense Cl^- and $H_2PO_4^-$ and AcO^- via significant cathodic perturbations of the respective ferrocene oxidation wave.

6. Experimental

6.1. General methods

All elemental analyses were carried out by the Inorganic Chemistry Laboratory Microanalysis Service.

Table 2
Electrochemical data and cathodic shifts observed in the respective Fc/Fc^+ couple upon addition of ten equivalents of anion in CH_3CN/0.1 M $TBABF_4$ using an $Ag/AgNO_3$ reference electrode

Receptor	Fc/Fc^+ couple $E_{1/2}$ (V)	$H_2PO_4^-$ ΔE (mV)	AcO^- ΔE (mV)	Cl^- ΔE (mV)
(**4**)	0.07	115	95	60
(**5**)	0.07	110	140	30
(**7**)	0.09	150	115	50
(**8**)	0.10	a	a	60

a: insufficient compound.

NMR spectra were recorded on a Bruker AM300 NMR spectrometer. Electrochemical experiments were conducted on a Princeton Applied Research Potentiostat/Galvanostat Model 273. ESMS was carried out in the Inorganic Chemistry Laboratory.

6.2. Syntheses

6.2.1. Ferrocene urea (**4**)

Ferrocenemethylamine (0.14 g, 0.65 mmol) and hexylisocyanate (0.09 g, 0.65 mmol) were dissolved in CH_2Cl_2 (10 ml) and refluxed for 1.5 h. The solvent was removed in vacuo to give a red oil. The receptor was precipitated out of solution using Et_2O/C_6H_{12}. The product was filtered, and dried under vacuum to give an orange solid (0.16 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (t, 3H, $^3J = 6.3$ Hz, CH_2CH_3), 1.27 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.47 (m, 2H, $NHCH_2CH_2$), 3.19 (m, 2H, $NHCH_2CH_2$), 4.10 (m, 11H, Fc*H* and $FcCH_2$), 4.93 (br m, 1H, N*H*), 5.08 (br m, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.46 (*C*H$_3$), 22.99 (*C*H$_2$), 26.99 (*C*H$_2$), 30.63 (*C*H$_2$), 31.94 (*C*H$_2$), 40.00 (*C*H$_2$), 40.93 (Fc*C*H$_2$), 68.21 (Fc*C*–H), 68.29 (Fc*C*–H), 68.81 (Fc*C*–H), 86.35 (Fc*C*–C), 158.45 (*C*O). Microanalysis Calc. for $C_{18}H_{26}N_2OFe$ C, 63.2%; H, 7.7%; N, 8.2%. Found: C, 63.2%; H, 7.7%; N, 8.2%. ESMS: M^+ *m*/*z* 342.

6.2.2. Ferrocene urea (**5**)

Ferrocenemethylamine (0.11 g, 0.5 mmol) and isocyanate **3** (0.23 g, 0.5 mmol) were dissolved in CH_2Cl_2 (10 ml) and refluxed for 1 h. The solvent was subsequently removed and the receptor was precipitated out with Et_2O/C_6H_{12}, to afford a pale yellow solid (0.20 g, 61%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 27H, C*H*$_3$), 1.95 (t, 6H, $^3J = 7.5$ Hz, C*H*$_2$CO), 2.24 (t, 6H, $^3J = 7.5$ Hz, $NHCH_2CH_2$), 3.98 (d, 2H, $^3J = 5.1$ Hz, $FcCH_2$), 4.19 (m, 9H, Fc*H*), 4.31 (br m, 1H, $FcCH_2NHCO$), 4.80 (br s, 1H, CON*H*). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 28.64 (*C*H$_3$), 30.45 (*C*H$_2$), 31.16 (*C*H$_2$), 40.94 (Fc*C*H$_2$), 56.92 (HN*C*(CH$_2$)$_3$), 68.63 (Fc*C*–H), 68.74 (Fc*C*–H), 69.20 (Fc*C*–H), 80.94 (*C*(CH$_3$)$_3$), 86.11(Fc*C*–C), 158.22 (*C*O), 173.18 (*C*O). Microanalysis Calc. for $C_{34}H_{52}N_2O_7Fe$ C, 62.2%; H, 8.0%; N, 4.3%. Found: C, 62.3%; H, 7.7%; N, 4.0%. ESMS: M^+ *m*/*z* 657, MNa^+ *m*/*z* 680.

6.2.3. Ferrocene urea (**7**)

1,1′-Bis(aminomethyl)ferrocene (0.053 g, 0.21 mmol) and hexylisocyanate (0.06 g, 0.4 mmol) were dissolved in CH_2Cl_2 (10 ml) and refluxed for 1 h. The solvent was subsequently removed and the receptor was recrystallised with Et_2O/C_6H_{12} to yield the pure product (0.04 g, 24%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, 6H, $^3J =$ 6.6 Hz, CH_2CH_3), 1.29 (m, 16H, $CH_2CH_2CH_2$-CH_2CH_3,), 1.48 (t, 4H, $^3J = 5.7$ Hz, $NHCH_2CH_2$), 3.19 (obs q, 4H, $^3J = 6.9$ Hz, $NHCH_2CH_2$), 4.09–4.13 (ov m, 12H, $FcCH_2NH_2$ and Fc*H*), 5.24 (b, 1H, N*H*CO), 5.35 (b, 1H, N*H*CO). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.13 (*C*H$_3$), 22.67 (*C*H$_2$), 26.70 (*C*H$_2$), 30.35 (*C*H$_2$), 31.66 (*C*H$_2$), 38.92 (*C*H$_2$), 40.38 (Fc*C*H$_2$), 67.55 (Fc*C*–H), 68.27 (Fc*C*–H), 88.15 (Fc*C*–C), 159.06 (*C*O). Microanalysis Calc. for $C_{26}H_{42}N_4O_2Fe$ C, 62.2%; H, 8.5%; N, 11.2%. Found: C, 62.1%; H, 8.4%; N, 11.1%. ESMS: M^+ *m*/*z* 499, MNa^+ *m*/*z* 522.

6.2.4. Ferrocene urea (**8**)

1,1′-Bis(aminomethyl)ferrocene (0.05 g, 0.2 mmol) and isocyanate **3** (0.19 g, 0.4 mmol) were dissolved in CH_2Cl_2 (10 ml) and refluxed for 1 h. The solvent was subsequently removed and the receptor was recrystallised with Et_2O/C_6H_{12} to yield the pure product (0.01 g, 44%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 54H, C*H*$_3$), 1.96 (t, 12H, $^3J = 4.2$ Hz, C*H*$_2$CO), 2.27 (m, 12H, $NHCH_2CH_2$), 4.06–4.14 (m, 12H, $FcCH_2NH$ and Fc*H*), 5.21 (br m, 2H, N*H*CH$_2$), 5.28 (br s, 2H, N*H*). Microanalysis Calc. for $C_{58}H_{93}N_4O_{14}Fe$ C, 61.9%; H, 8.3%; N, 4.9%. Found: C, 62.0%; H, 8.5%; N, 4.8%. ESMS: M^+ *m*/*z* 1123, MNa^+ *m*/*z* 1150.

7. Anion coordination studies: NMR titrations

^{1}H NMR titrations were carried out in acetonitrile-d_3 solutions of compounds (**4**), (**5**), (**7**), (**8**). In a typical titration, 5×10^{-6} mol of receptor were dissolved in 0.5 ml acetonitrile-d_3 and equivalents of the anion added as n-$Bu_4N^+X^-$ ($X = Cl^-$, $H_2PO_4^-$) in acetonitrile-d_3 (0.1 M^{-1}) solution. The shifts of the resonances of the protons involved in anion coordination were then recorded and plotted as a function of the amount of anion added. Stability constant values were determined using the computer program EQNMR [11].

8. Anion coordination studies: electrochemistry

The electrochemical properties of (**4**), (**5**), (**7**), and (**8**) were investigated using cyclic and square wave voltammetry in acetonitrile with (n-Bu$_4$)NBF_4 as the supporting electrolyte. The working electrode used was a 5 mm glassy carbon disk, the counter electrode consisted of a platinum mesh and an $Ag/AgNO_3$ reference electrode was used. Cyclic and square wave voltammograms were also recorded after addition of ten equivalents of anionic guests as 0.1 M solutions of (n-Bu$_4$)NH_2PO_4, (n-Bu$_4$)NOAc and (n-Bu$_4$)NCl in CH_3CN solution with (n-Bu$_4$)NBF_4 as the supporting electrolyte.

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