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FULL PAPER

Synthesis and structure of *N*-ferrocenylglycosylamines; redox chemistry of *O*-ferrocenylglycosides† and *N*-ferrocenylglycosylamines

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The *N*-ferrocenylamine–carbohydrate conjugates *N*,*N*-bis(ferrocenylmethyl)-*N*-(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)amine, *N*-(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)aminomethylferrocene and *N*,*N*-bis(ferrocenylmethyl)-*N*-[4-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-1-deoxy-β-D-glucopyranosyl]amine have been synthesized from $FcCH_2NMe_3^+I^-$ and the appropriate aminosugars. Deprotection using an ion exchange resin gave the analogous water soluble complexes. A short C–N bond at the anomeric carbon in the crystal structure of the first compound is attributed to an *exo*-anomeric n–σ* interaction between the *exo* C–N and *endo* C–O bonds. *N*-Ferrocenylmethylalkanolamines $FcCH_2NH(CH_2)_nOH$ and $(FcCH_2)_2N(CH_2)_nOH$ ($n = 2$ or 5) were synthesized in good yield using reductive amination reactions. Owing to the basicity of the *N*-ferrocenylamine component the electrochemistry is both solvent and pH dependent; protonation occurs in polar solvents and in all solvents with the first two compounds. Rapid oxidation to the non-protonated ferrocenium complexes occurs in aqueous solvents under physiological pH.

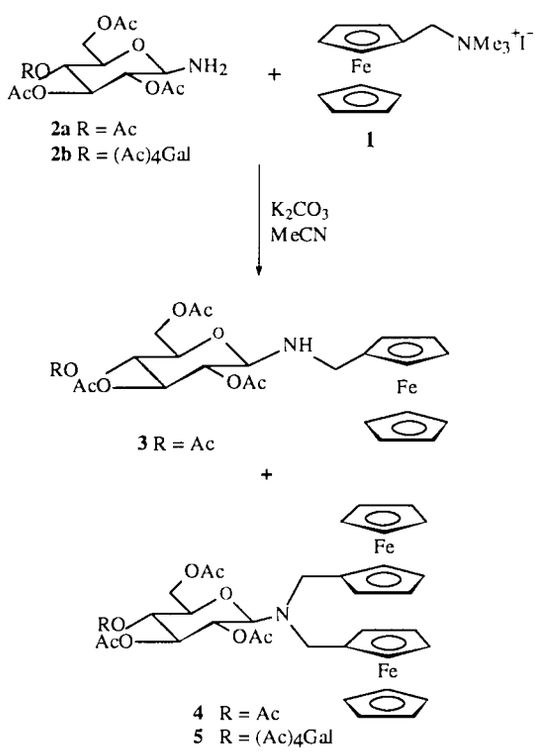
Introduction

Metallocene–carbohydrate conjugates offer a way of overcoming the hydrophobic character of neutral metallocene compounds which is a problem for biological studies. In addition, these conjugates can be used selectively to target specific sites and functions[2] and to label polysaccharides with heavy atoms.[3] The accompanying paper[1] describes the background literature for compounds where a ferrocene moiety is linked to a sugar *via* a heteroatom and successful synthetic strategies for the preparation of *N*-glycosyloxy-*N*-(hydroxyalkyl)aminomethylferrocenes. In an extension of this theme we wished to determine if a ferrocenylamine unit *N*-bound to the sugar *via* the anomeric carbon experienced a perturbation of its electronic properties and if steric perturbations of the carbohydrate occur with the proximity of a metallocene. In addition, the methodology for the use of ferrocenylamine–carbohydrate conjugates as bioprobes requires a knowledge of the redox behaviour under physiological conditions. The use of ferrocenyl compounds as sensors for sugars is well documented[4] but our emphasis is on probes for protein structure and function. This paper deals specifically with the synthesis and structure of *N*-ferrocenylamine–carbohydrates and *N*-ferrocenylalkanolamines. The redox chemistry of these compounds, and the *O*-bound compounds in the preceding paper,[1] is also reported.

Results and discussion

Preparation of *N*-ferrocenylamine–carbohydrate conjugates

Several routes to the *N*-ferrocenylamine–carbohydrate conjugates were explored but the nucleophilic displacement of trimethylamine from the methiodide $FcCH_2NMe_3^+I^-$ **1** by a protected aminosugar gave the best yields. Thus reaction of acetylated 1-amino-β-D-glucose[5] **2a** in acetonitrile, in the presence of K_2CO_3, produced a 2:3 mixture of the *N*-ferrocenyl-1-glycosylamines **3** and **4** (Scheme 1). Yields of **4** were optimised with longer reaction times but neither the reaction stoichiometry nor solvent changed the **3**:**4** yield ratio. Prepared by the same route was the lactose conjugate **5** (Scheme 1) and the *N*-ferrocenyl-2-glycosylamines **6** and **7** previously reported by Adam and Hall.[6] For reasons that are not obvious, acetylated 1-amino-β-D-lactose **2b** gave the bis-(ferrocene)–carbohydrate conjugate **5** exclusively.



Scheme 1

† Ferrocenylamine–carbohydrate conjugates. Part 2.[1] Electronic supplementary information (ESI) available: IR and ^{13}C NMR data. See http://www.rsc.org/suppdata/dt/a9/a908513k/

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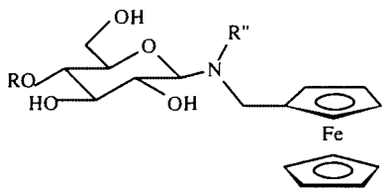
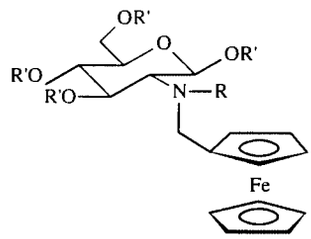


8 R = H, R" = H
9 R = H, R" = CH_2Fc
10 R = Gal, R" = CH_2Fc



IRA(OH^-) Resin, MeOH

6 R = H, R' = Ac
7 R = CH_2Fc, R' = Ac

11 R = H, R' = H
12 R = CH_2Fc, R' = H

Our goal of water solubility was attained by deprotection of the acetylated conjugates. Careful treatment of compounds **3**–**5** with IRA 400 (OH) resin in methanol over a period of a few days gave good yields of the fully deprotected conjugates **8**–**10**. Resin deprotection of **6** was also successful giving **11** in a quantitative yield whereas Adam and Hall report[6] that sodium methoxide *O*-deacetylation was unsuccessful.

Microanalysis, mass spectra, ^{1}H and ^{13}C NMR and FTIR spectrometry and, in the case of **4**, a crystal structure were used to characterise the compounds. In the mass spectra fragments due to the dissociation of the acetylated sugar portion and those from the stable ion $FcCH_2^+$ accompanied those from dissociation of the molecular ion. Typical chemical shifts and splitting patterns were observed in the ^{1}H and ^{13}C NMR for the sugar and ferrocenyl units. An AB pattern due to the diastereotopic α-methylene protons was observed whenever the CH_2Fc unit was adjacent to a glycoside. ^{1}H NMR spectra were difficult to interpret as the sugar, CH_2Fc and Cp protons tended to overlap. With compounds **3**–**5**, **8**–**10** the anomeric proton is masked by the ferrocenyl protons, whereas the anomeric δ_H is readily assigned for **6** and **7** with $J_{1,2}$ 9 Hz being consistent with β stereochemistry[7] at the anomeric centre. ^{13}C and 2-D NMR spectra enabled the assignment of the $FcCH_2$ carbon(s) and C-1 and C-6 of the sugar. A useful diagnostic was δ_C for the anomeric carbon which is in the range 88.7–91.9 for *N*-1-glycosylamines and 92.4–101.2 for *O*-glycosides.[3]

Complexes **3**–**7** are soluble in organic solvents except hydrocarbons whereas the deprotected analogues **8**–**11** are soluble in chlorinated solvents, acetone, alcohols and water. Compound **9**, the least water-soluble of the deprotected glycosides, has a solubility of 1.8 g l^{-1} in water. However, all these complexes oxidise to the ferrocenium analogues in aqueous solutions in air; this oxidation is accelerated at pH < 6. This behaviour has been noted for other ferrocenylamines.[8] As a consequence the deprotected ferrocene–carbohydrate conjugates *will exist under physiological pH as the ferrocenium salts* (see below).

Crystal structure of compound 4

A perspective view of the molecule is given in Fig. 1, which shows the crystallographically determined absolute configuration and defines the atom numbering scheme. Table 1 lists pertinent bond length and bond angle data. The structure is that of a tertiary amine with the nitrogen atom, N(1), substituted by two methylferrocene moieties and a fully acetylated β-D-glucopyranose sugar residue. The sugar binds to N(1) through the anomeric C atom, C(1). The exocyclic C(1)–N(1) bond length is 1.428(8) Å. This is significantly shorter than the value of 1.469(14) Å obtained as an average of 1201 independent observations.[9] Bond contraction of this kind has been attributed to an *exo*-anomeric interaction between the *exo* C(1)–N(1) and *endo* C(1)–O(5) bonds. This could result from an *exo*-anomeric n–σ* interaction similar to that proposed by Bertolasi *et al.*[10] to account for a comparable C–N bond shortening in a series of 2-amino-1,3-oxazolidin-4-one derivatives. A projection along the C(1)–N(1) bond (Fig. 2) is consistent with an antiperiplanar arrangement of the lone pair on N(1) with respect to the C(1)–O(5) bond. This would favour overlap with the antibonding σ* orbital of the adjacent C(1)–O(5) vector.

The overall effect of such interactions is also signalled by a widening of the angles subtended at the amine N atom to between 111.0(5) and 115.5(5)°. The pyramidal arrangement about N(1) is distorted such that N(1) lies only 0.405(7) Å above the C(1), C(15), C(16) mean plane. Similar effects are also

Table 1 Selected bond lengths [Å] and angles [°] for compound **4**

C(1)–N(1)	1.428(8)	C(5)–C(6)	1.505(8)
C(1)–O(5)	1.439(6)	C(6)–O(6)	1.445(8)
C(1)–C(2)	1.532(8)	C(15)–C(60)	1.483(8)
C(2)–O(2)	1.450(7)	C(15)–N(1)	1.484(7)
C(2)–C(3)	1.516(8)	C(16)–N(1)	1.467(8)
C(3)–O(3)	1.444(7)	C(16)–C(70)	1.520(9)
C(3)–C(4)	1.511(9)	Fe(1)–C(60–64) (mean)	2.04(1)
C(4)–O(4)	1.438(7)	Fe(1)–C(65–69) (mean)	2.038(6)
C(4)–C(5)	1.535(9)	Fe(2)–C(70–74) (mean)	2.045(7)
C(5)–O(5)	1.418(7)	Fe(2)–C(75–79) (mean)	2.023(6)
N(1)–C(1)–O(5)	109.8(5)	O(5)–C(5)–C(4)	108.1(5)
N(1)–C(1)–C(2)	114.1(5)	N(1)–C(16)–C(70)	113.4(5)
O(5)–C(1)–C(2)	108.3(4)	C(1)–N(1)–C(16)	111.0(5)
C(3)–C(2)–C(1)	110.0(5)	C(1)–N(1)–C(15)	115.5(5)
C(4)–C(3)–C(2)	112.9(5)	C(16)–N(1)–C(15)	111.3(5)
C(3)–C(4)–C(5)	110.0(5)		

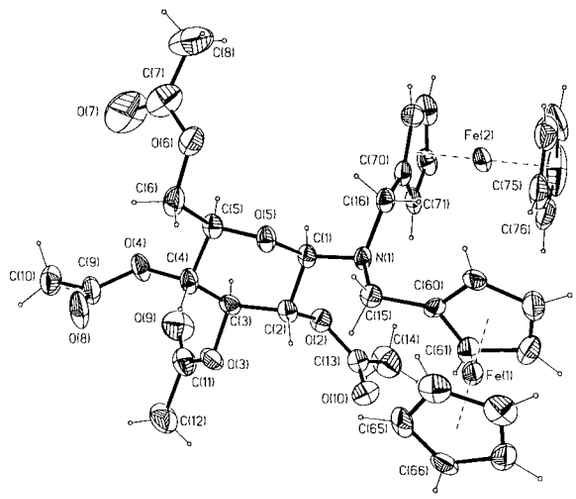


Fig. 1 Structure of compound **4** showing the atom numbering scheme. For clarity, numbering is shown only for the first two atoms of the consecutively numbered cyclopentadiene rings. Only one position of the disordered O(8) atom is displayed.

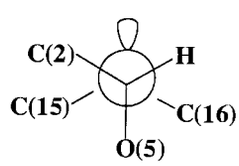


Fig. 2 The Newman projection along the C(1)–N(1) bond showing the antiperiplanar arrangement of the N(1) non-bonded electron pair with respect to the C(1)–O(5) bond.

apparent from the crystallographic data reported on the oxazolidine compounds.[10] A further contributing factor to these distortions may result from steric interactions between the bulky methylferrocene and sugar moieties.

Bond distances and angles in the ferrocene units are unremarkable; the cyclopentadiene rings are eclipsed in both cases. The rings are inclined at 2.5(4) [C(60)–C(64)/C(65)–C(69)] and 0.3(5)° [C(70)–C(74)/C(75)–C(79)]. In the solid state the two ferrocene systems are approximately orthogonal to one another with interplanar angles [C(60)–C(64)/C(70)–C(74)] 89.1(2) and [C(65)–C(69)/C(75)–C(79)] 88.7(2)°.

Ferrocenylalkanolamines

As peripheral OH groups may confer water solubility ferrocenylalkanolamines were synthesized for synthetic elaboration and electrochemical studies. Using the nucleophilic displacement procedure diethanolamine gave *N*-ferrocenylmethyldiethanolamine **13** and 5-aminopentan-1-ol gave the bis(ferrocenyl) pentanolamine **14** (Scheme 2) without the intermediacy of a monoferrocenyl derivative **15**. However, **15** was accessible *via* a reductive amination reaction[11] between ferrocenecarbaldehyde and 5-aminopentan-1-ol; the same reaction with ethanolamine gave both a monoferrocenyl **16** (prepared previously by Schlogel[12]) and bisferrocenyl compound **17** (Scheme 3). Microanalytical and spectral data were in accordance with the proposed structures. None of the *N*-ferrocenylalkanolamines was soluble in water at any pH although they were soluble in alcohols.

Redox chemistry

The ferrocenylamine–carbohydrate conjugates were developed to provide probes where the ferrocene–ferrocenium couple would be a redox attenna used to monitor structure and function in biological systems. An important consideration was whether the redox properties would be modified on going from a non-aqueous to aqueous environment. The electrochemistry of few neutral ferrocenyl complexes has been recorded in aqueous solution.[13,14] Accordingly, representative protected and deprotected *N*-glycosylamines, *O*-glycosides and *N*-ferrocenylalkanolamines were studied by cyclic and square wave voltammetry in dichloromethane, aqueous methanol and, where possible, water.

A typical chemically reversible one-electron oxidation process **A** centred on the ferrocene is observed (Fig. 3a) in *dichloromethane* in the cyclic and square wave voltammetry for the *N*-glycosylamines **3**, **6**–**9**, all *O*-glycosides of ferrocenylamines, and the *N*-ferrocenylalkanolamines. The current for the

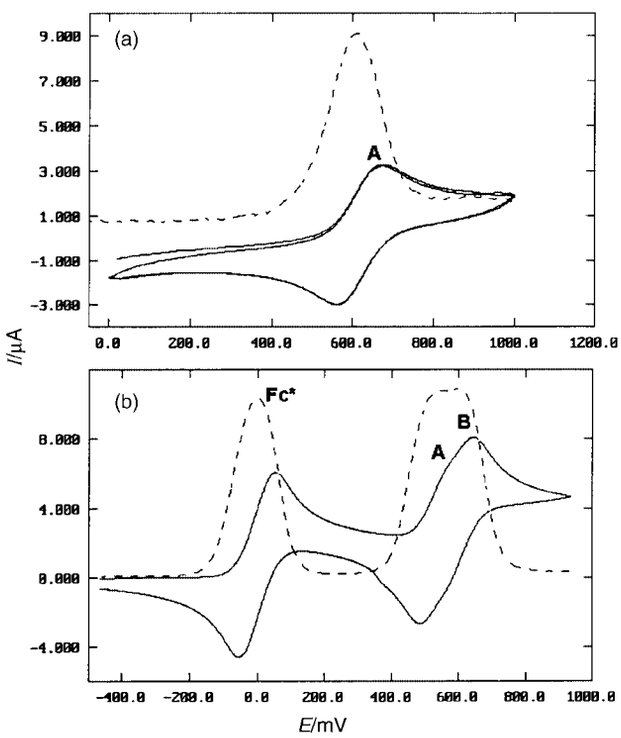
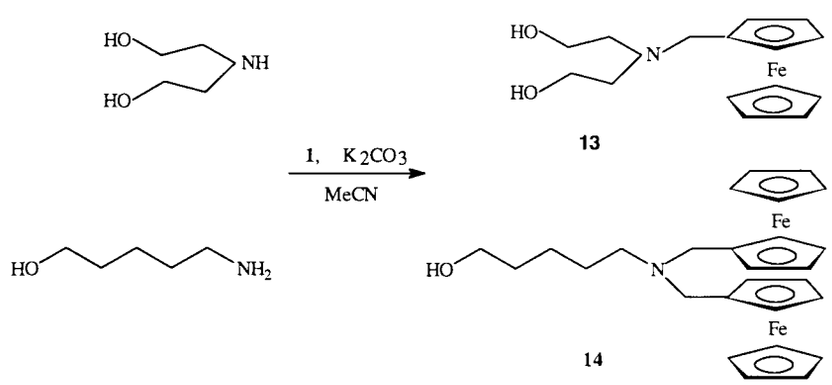
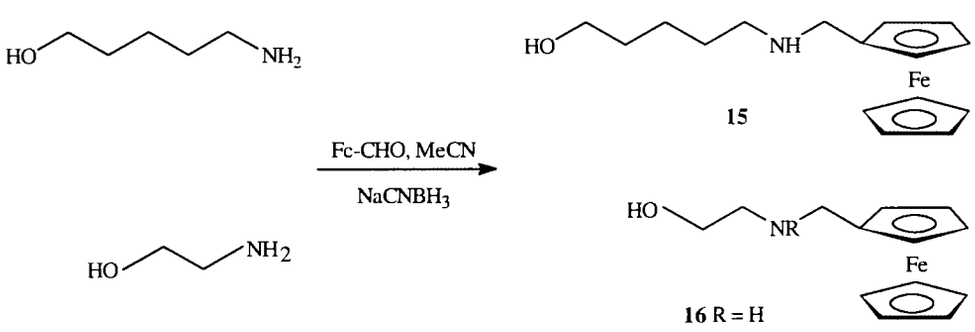


Fig. 3 Cyclic and square wave voltammograms of (a) compound **6** and (b) **4** in CH_2Cl_2, Pt, 0.1 M $^nBu_4NPF_6$, 100 mV s^{-1}.



Scheme 2



Scheme 3

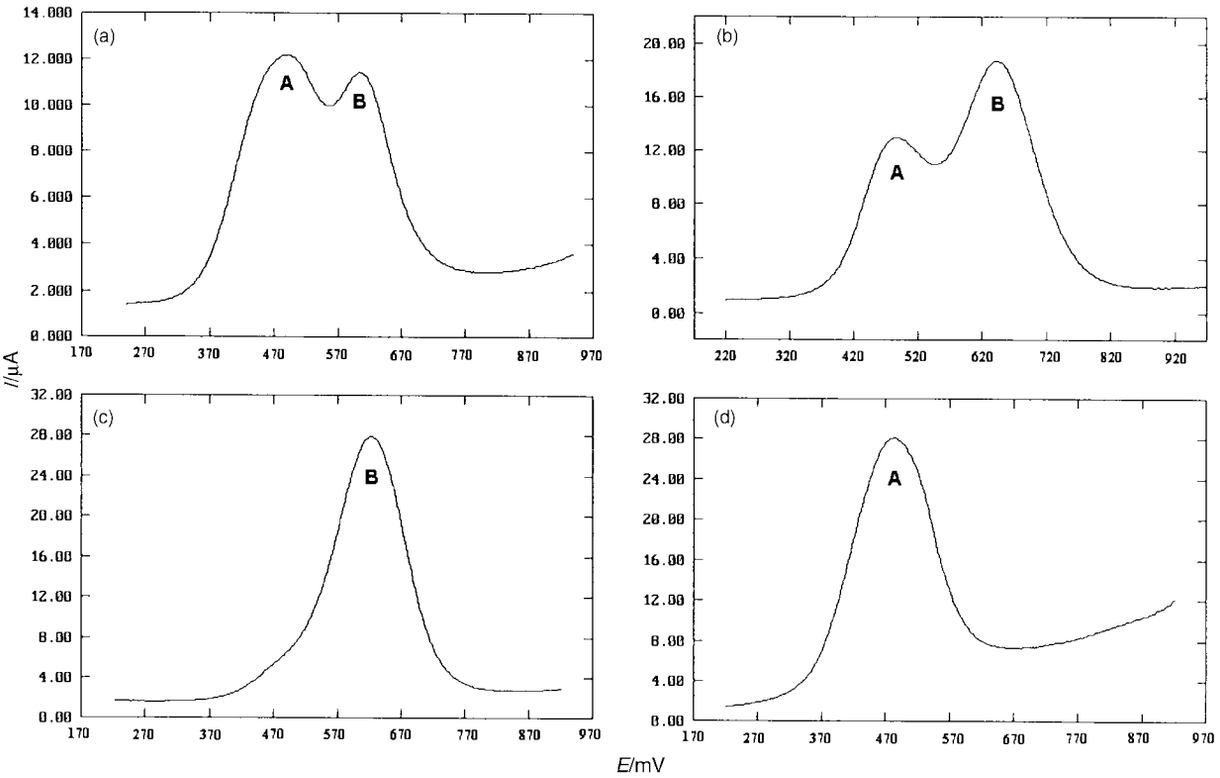


Fig. 4 Square wave voltammograms of (a) compound **9**; (b) **9H**$^+$, (c) **9** after the addition of 2 mol equivalents of 0.1 M $HClO_4$ and (d) **9** after the addition of 10 mol equivalents of Bu_4NOH, all in water–MeOH, Pt, 0.1 M Et_4NClO_4, 100 mV s^{-1}.

Table 2 Electrochemical data

	$E_{1/2}$ (CH_2Cl_2)[a]/V		$E_{1/2}$ (aq MeOH)[b]/V	
Compound	**A**	**B**	**A**	**B**
3	0.55		0.48	0.60
4	0.54	0.59	0.47	0.60
4H$^+$				0.60
5	0.54	0.60		
6	0.55			
7	0.54		0.48	0.61
8	0.51	0.60	0.45	
9	0.56		0.49	
9H$^+$				0.62
14	0.54			
18[c]			0.48	0.65
19[c]			0.48	
20[c]			0.48	0.65

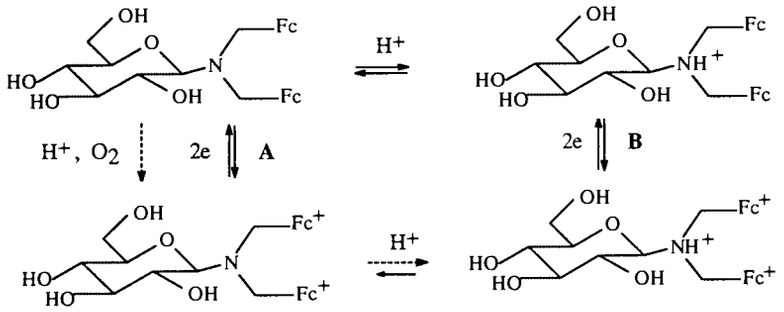
[a] In dichloromethane, referenced against decamethylferrocene, square wave data, Pt. [b] In 50% aqueous methanol, referenced against decamethylferrocene, square wave data, Pt. [c] *N*-[2-(β-D-glucopyranosyloxy)alkyl]-*N*-methylaminomethylferrocene;[1] alkyl is ethyl **18**, propyl **19**, pentyl **20**.

i/V response in these compounds is directly related to the number of ferrocenyl groups. All $E_{1/2}$ for **A** are close to that of ferrocene measured under the same conditions but the slow electrode kinetics gave large ΔE_p (cyclic) or peak widths (square wave). There were no significant differences in $E_{1/2}$ within the group of compounds studied (typical data are given in Table 2) and it is clear that the carbohydrate moiety is electronically 'neutral' with respect to the ferrocenyl redox centre.

The electrochemistry of these compounds was also studied in polar solvents to discover whether there were any solvent effects in the absence of peripheral OH groups. Decamethylferrocene was used as the reference as it is known[14–16] to be solvent-insensitive. In methanol, $E_{1/2}$ for couple **A** showed a small but significant shift to cathodic potentials; for example, $E_{1/2}$ for **3** is 0.55 V in dichloromethane and 0.48 V in methanol. However, in 50% aqueous methanol $E_{1/2}$ for **3** is also 0.49 V; the importance of using a solvent-insensitive reference is well illustrated by this system as $E_{1/2}$ for **3** is 0.47 and 0.26 V against SCE in dichloromethane and aqueous methanol respectively. A solvent shift of 50 mV from dichloromethane to aqueous methanol was also noted with $(OC)_9Co_3C$–carbohydrate complexes[3] indicating that the generic solvent interaction is with the carbohydrate portion of the molecule rather than with the ferrocenyl couple.

Surprisingly, the electrode response was different for compounds **4** and **5** where there are two ferrocenyl redox centres. For these compounds, in dichloromethane and aqueous methanol, *two* chemically reversible oxidation processes (**A** and **B**) were observed in both the cyclic and square wave voltammograms (Fig. 3b). The difference in potential between **A** and **B**, and the relative currents, were solvent dependent. These two one-electron processes are unlikely to arise from communication between the two ferrocenyl redox centres. A plausible explanation was thought to be protonation, which from previous work[8] on ferrocenylamines was known to influence their electrochemistry. In support of this explanation it was observed that **3** and the deprotected conjugates **11**–**13** in *aqueous methanol or water* (Fig. 3a) also displayed **A** and **B** (Table 2), the relative currents varying with substrate.

To gain further insight into these electrode processes the pH dependence of the electrochemistry was studied in some detail in aqueous methanol, and hydrochloride salts of each compound prepared. Taking compound **9** as a representative system $E_{1/2}$ [**A**] and $E_{1/2}$ [**B**] are 0.47 V and 0.60 V respectively (potentials are from fitted square wave data) in 1 mmol aqueous methanol solutions (Fig. 4a). The salt **9H**$^+$ shows the same profile in this solvent and in water (Fig. 4b) and intermediate stages in the equilibrium can be seen in the *i*/V scans depending on the pH; solutions of **9H**$^+$ are also *oxidised rapidly in air*. As expected, the potential for the $Fc^{+/0}$ oxidation of the cation **9H**$^+$ (at **B**) is more positive than $Fc^{+/0}$[**9**] (at **A**) and the difference in $E_{1/2}$ of 0.13 V is similar to that found in between the free base and salts of simple ferrocenylamines.[8] Upon the addition of a two mole equivalents of acid to **9** a single two-electron revers-



Scheme 4

ible wave **B** is seen at the same potential as **B** for $\mathbf{9H^+}$, and a very small current due to residual **A** (Fig. 4c). Wave **A** disappears completely after 10 mole equivalents of acid are added. Conversely, the addition of 10 mole equivalents of OH^- gives one broad two-electron wave **A** (Fig. 4d).

All other glycosides showed evidence in their electrochemistry of protonation to varying degrees and the general redox pathway (using **9** as the substrate) is summarised in Scheme 4. These electrochemical observations reinforce the proposition[8] that tertiary ferrocenylamines are strong bases and that the electrochemistry of these compounds can wrongly be assigned unless the pH dependence is studied. The pH of a 0.1 mmol aqueous solution of **9** is 9.24. An approximate pK_a of 9.0 was derived from the ratio of the currents for the protonated and non-protonated conjugates in the square wave voltammmogram. This is similar to the pK_a of dialkylferrocenylamines[8] and may be compared with the pK_a for 2-glucosamine of 7.66 at 25 °C.[17] In contrast, the pK_a values for ferrocenylamines where the *N*-substituent can interact directly with a ferrocenyl unit are smaller by several orders of magnitude.[8] Qualitative estimates of the basicity from the electrochemical data are *N*,*N*-diferrocenyl-1-glycosylamines > *N*-ferrocenyl-1-glycosylamines > *N*,*N*-diferrocenyl-2-glycosylamines > *N*-ferrocenyl-2-glycosylamines > *O*-ferrocenyl 1-glycosides.[1] The high basicity of the *N*-ferrocenyl-1-glycosylamines is unexpected given that an anomeric effect should reduce the electron density on the tertiary nitrogen and destabilise the salt.

As already noted aqueous solutions of ferrocenylamine–carbohydrate conjugates and their salts rapidly oxidise to ferrocenium compounds in air. Nonetheless, voltammetry of these solutions show that it is the *ferrocenium* derivative of the *non-protonated* conjugate, not the protonated, which is produced (Scheme 4). This is not unreasonable given the high charge on a protonated ferrocenium cation.

Conclusion

The synthetic routes to ferrocenylamine–conjugates described in this and the accompanying paper[1] can be used to prepare a wide variety of water-soluble, potentially bioactive, ferrocenyl drugs and bioprobes. This avenue is being explored. Furthermore, co-ordination to Pt^{II} gives an additional series of bioactive molecules which will be described elsewhere.[18] An important observation from a biological perspective was not only the reversibility of the $[Fc]^{+/o}$ couple in aqueous media, but also the rapid oxidation of the conjugates in air to the non-protonated ferrocenium species. This highlights the fact that under physiological pH they will be in equilibrium with the non-protonated ferrocenium salts. This may have a significant impact on their mode of action in a cell and hence the mechanism of oxidation of the ferrocenylamines in aqueous solution needs to be explored.

Experimental

General reactions, procedures and equipment are described in the accompanying paper.[1] Silica gel 60 column chromatography was employed where the separation of reaction products by silica gel column chromatography was difficult. Compounds **1**,[19] **2**[5] and 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose[20] were prepared by literature methods and other reagents purchased from Aldrich. The complexes **6** and **7** were prepared by a similar method to that given by Adam and Hall.[6] The protonated salts were prepared[8] by bubbling HCl gas through a diethylether solution of the respective *N*-ferrocenylglycosylamine from which they precipitated. Electrochemical measurements were performed with a three-electrode cell employing a polished platinum microelectrode using a computer controlled EG & G PAR 273A potentiostat/galvanostat at scan rates 0.05–10 V s^{-1}. The supporting electrolyte was 0.1 M tetraethylammonium perchlorate in water and aqueous methanol, and tetrabutylammonium hexafluorophosphate in dichloromethane; the substrate was $\approx 1 \times 10^{-3}$ M. In dichloromethane the potentials were referenced against decamethylferrocene ($E_{1/2}[\text{ferrocene}]^{+/0} = 0.55$ V uncorrected for junction potentials) and in water and aqueous methanol against SCE ($E_{1/2}[\text{ferrocene}]^{+/0} = 0.47$ V) with decamethylferrocene as an internal reference. All potentials in the text are referenced to decamethylferrocene. pK_a Values in aqueous acetone were obtained as described previously.[8]

Reaction of (ferrocenylmethyl)trimethylammonium iodide 1 with glycosylamines and alkanolamines

***N*,*N*-Bis(ferrocenylmethyl)-*N*-(2,3,4,6-tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)amine 4.** Compound **1** (1.80 g, 4.7 mmol) was added to a mixture of **2a** (0.65 g, 19 mmol) and sodium carbonate (0.57 g, 5.4 mmol) in dry acetonitrile (40 ml). The mixture was heated to reflux for 16 h, filtered, and the solvent removed *in vacuo*. The residue was dissolved in dichloromethane and washed with water (3 × 100 ml) to remove any remaining methiodide salt. The organic layer was dried ($MgSO_4$) solvent stripped and the yellow oil separated by silica gel chromatography; 2:1:1 hexane–dichloromethane–ethyl acetate to elute the first two bands and then ethyl acetate to elute the third fraction. Crystallisation of the second fraction from dichloromethane–hexane gave orange crystals of **4** (27%). $[\alpha]_D^{20} = -75°$ (*c* 0.4% CH_2Cl_2) (Found: C, 57.99; H, 5.61; N, 1.86. $C_{36}H_{41}Fe_2NO_9$ requires C, 58.16; H, 5.55; N, 1.88%); $\delta_H(CDCl_3)$ 1.98, 2.00, 2.02, 2.12 (4 × 3 H, 4 × s, 4 × OAc), 3.40 (2 H, d, *J* 14 Hz, CH_2Fc), 3.46 (1 H, m, 5-H), 3.75 (2 H, d, *J* 14, CH_2Fc), 4.03–4.16 (20 H, m, 18 of ferrocene, 1-H and 6-H), 4.22 (1 H, dd, *J* 5 and 12.5, 6-H), 5.02 (1 H, t, *J* 9.5, 4-H), 5.10 (1 H, t, *J* 9, 2-H) and 5.26 (1 H, t, *J* 9 Hz, 3-H).

***N*-(2,3,4,6-Tetra-*O*-acetyl-1-deoxy-β-D-glucopyranosyl)aminomethylferrocene 3.** Crystallisation of the third band from methanol from the above reaction gave compound **3** as orange crystals (18%) (Found: C, 52.45; H, 5.19; N, 2.46%; M^+ *m*/*z* 545. $C_{25}H_{31}FeNO_9 \cdot 0.5CH_2Cl_2$ requires C, 52.10; H, 5.49; N, 2.38%; *M* 545); $\delta_H(CDCl_3)$ 1.65 (1 H, br s, NH), 2.00, 2.02, 2.05, 2.10 (4 × 3 H, 4 × s, 4 × OAc), 3.48 (1 H, d, *J* 13, 1 of CH_2Fc) 3.63 (1 H, dq, *J* = 2 and 11, 5-H), 3.76 (1 H, d, *J* 13, 1 of CH_2Fc), 4.09, 4.13, 4.15 (10 H, m, 9 of Fc and 1-H), 4.28 (2 H,

dd, *J* 4.5 and 12.5, 6-H_2), 4.89 (1 H, t, *J* 9, 2-H), 5.06 (1 H, t, *J* 9.5, 4-H) and 5.24 (1 H, t, *J* 9.5 Hz, 3-H).

***N*,*N*-Bis(ferrocenylmethyl)-*N*-[4-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-acetyl-1-deoxy-β-D-glucopyranosyl]aminoe 5.** Compound **2b** as for **4** gave **5** as a yellow solid (41%) (Found: C, 55.21; H, 5.45; N, 1.43%; M^+ *m*/*z* 737. $C_{48}H_{57}Fe_2NO_{17}$ requires C, 55.88; H, 5.57; N, 1.36%; *M* 737); *m*/*z* (FAB) 760 (MNa^+); 737 (M^+) and 199 ($FcCH_2^+$) $\delta_H(CDCl_3)$ 1.95, 1.97, 2.03, 2.04, 2.06, 2.14, 2.17 (7 × 3 H, 7 × s, 7 × OAc), 3.33 (2 H, d, *J* 13, CH_2Fc), 3.37 (1 H, partially obscured m, 5-H), 3.70 (1 H, partially obscured m, 4-H), 3.71 (2 H, d, *J* 13, CH_2Fc), 3.84 (1 H, t, *J* 7.5, 5′-H), 4.00–4.16 (22 H, m, 18 Fc, 1-H, 6-H_2, 1 of 6′-H), 4.40 (1 H, dd, *J* 2 and 12, 1 of 6′-H), 4.46 (1 H, d, *J* 8, 1′-H), 4.93 (1 H, dd, *J* 3.5 and 10.5, 3′-H), 5.05–5.10 (2 H, m, 2-H, 2′-H), 5.25 (1 H, t, *J* 9.5, 3-H) and 5.33 (1 H, d, *J* 4 Hz, 4′-H).

***N*,*N*-Bis(2-hydroxyethyl)aminomethylferrocene 13.** As for compound **6** from diethanolamine; 5:1 ethyl acetate–methanol as eluent gave **18** as orange crystals (78%) (Found: C, 57.10; H, 6.58; N, 4.22%; M^+ *m*/*z* 303. $C_{15}H_{21}FeNO_2{\cdot}2CH_2Cl_2$ requires C, 57.02; H, 6.74; N, 4.38%; *M* 303); $\delta_H(CDCl_3)$ 2.21 (2 H, br s, 2 × OH), 2.66 (4 H, t, *J* 5.5, 2 and 2′-H_2), 3.61 (4 H, t, *J* 5.5 Hz, 1-H_2), 3.63 (2 H, s, CH_2Fc), 4.12 (5 H, s, C_5H_5) and 4.15 (4 H, m, α and β ferrocene protons).

***N*,*N*-Bis(ferrocenylmethyl)-*N*-(5-hydroxypentyl)amine 14.** As for the preparation of compound **4** aminopentanol using 4:1 ethyl acetate–methanol as eluent gave **14** as a yellow oil (53%) (Found: C, 62.19; H, 6.43; N, 2.67%; M^+ *m*/*z* 499. $C_{27}H_{33}Fe_2NO{\cdot}0.33CH_2Cl_2$ requires C, 62.22; H, 6.43; N, 2.66%; *M* 499); $\delta_H(CDCl_3)$ 1.22–1.40 (2 H,m, 3-H_2), 1.40–1.60 (4 H, m, 2-H_2 and 4-H_2), 2.37 (2 H, br t, *J* 7, 5-H_2), 3.54 (4 H, s, 2 × CH_2Fc), 3.59 (2 H, t, *J* 6 Hz, CH_2OH), 4.10 (10 H, s, 2 × C_5H_5), 4.16 (4 H, t, *J* 1.5, 4 × Fc) and 4.23 (4 H, t, *J* 1.5, 4 × Fc).

O-Deacetylation of conjugates

***N*-(1-Deoxy-β-D-glucopyranosyl)aminomethylferrocene 8.** Compound **3** (167 mg, 0.31 mmol) was dissolved in methanol (5 ml) and Amberlite IRA 400(OH) resin (250 mg) added. The mixture was stirred for 5 days, filtered and the solvent removed *in vacuo*. Preparative thin layer chromatography with 2:2:6 hexane–methanol–dichloromethane give **8** as a yellow oil (29%) (Found: C, 51.61; H, 6.14; N, 3.52%; M^+ *m*/*z* 377. $C_{17}H_{23}FeNO_5{\cdot}0.25CH_2Cl_2$ requires C, 51.61; H, 5.90; N, 3.49%; *M* 377); $\delta_H(CDCl_3)$ 3.15–3.85 (11 H, br m, 5 sugar protons, CH_2Fc and 4 × OH), 4.05–4.27 (11 H, m, Fc and 2 sugar protons, including C_5H_5, s, at 4.13).

***N*-(1-Deoxy-β-D-glucopyranosyl)-*N*,*N*-bis(ferrocenylmethyl)-amine 9.** Deprotection of compound **4** as for **3** gave **9** as a yellow oil (59%) (Found: C, 58.39; H, 5.94; N, 2.68%; M^+ *m*/*z* 575. $C_{28}H_{33}Fe_2NO_4$ requires C, 58.46; H, 5.78; N, 2.44%; *M* 575); δ_H ($CDCl_3$) 2.78 (4 H, br s, 4 × OH), 3.35–3.50 (2 H, m, sugar protons), 3.55–3.80 (7 H, sugar protons and 2 of the CH_2Fc protons), 3.80–4.05 (1 H, m, sugar proton), 4.10 (5 H, s, C_5H_5), 4.14 (6 H, m, 6 α and β Fc protons) and 4.23 (3 H, m, 2 α and β Fc protons and 1 sugar proton).

***N*,*N*-Bis(ferrocenylmethyl)-*N*-[4-(β-D-galactopyranosyl)-1-deoxy-β-D-glucopyranosyl]amine 10.** Compound was deprotected as described for **3**; eluent 9:1 ethyl acetate–methanol gave **10** as an orange oil (72%). Sequential deprotection could be observed by TLC (hexane–methanol–dichloromethane, 1:1:3), where the R_f value became lower as deprotection progressed (Found: M^+ *m*/*z* 737. $C_{34}H_{43}Fe_2NO_{10}$ requires 737); δ_H ($CDCl_3$) 3.10–4.06 (23 H, m, 12 sugar protons, 2 × CH_2Fc, 7 × OH), 4.08–4.24 (18 H, m, 2 × C_5H_5, 8 × Fc protons) and 4.25–4.42 (2 H, m, 2 × sugar protons).

***N*-(2-Deoxy-D-glucopyranosyl)aminomethylferrocene 11.** Deprotection of compound **6** as for **3** gave **11** as a yellow oil (76%) (Found: MH^+ *m*/*z* 378. $C_{17}H_{23}FeNO_5$ requires 377); δ_H ($CDCl_3$) 2.78 (4 H, br s, 4 × OH), 3.35–3.50 (2 H, m, sugar protons), 3.55–3.80 (7 H, sugar protons and 2 of the CH_2Fc protons), 3.80–4.05 (1 H, m, sugar proton), 4.10 (5 H, s, C_5H_5), 4.14 (6 H, m, 6 α and β Fc protons) and 4.23 (3 H, m, 2 α and β Fc protons and 1 sugar proton).

Reductive amination reactions

***N*-(5-Hydroxypentyl)aminomethylferrocene 15.** Sodium cyanotrihydroborate (0.35 g, 5.57 mmol) was added to a solution of ferrocenecarbaldehyde (0.20 g, 0.93 mmol) and 5-amino-1-pentanol (0.39 g, 3.74 mmol) in dry acetonitrile (50 ml). The mixture was stirred at room temperature for 24 h then a further portion of sodium cyanotrihydroborate (0.20 g, 3.18 mmol) was added and stirring continued for 24 h. Dichloromethane (50 ml) was added, the organic layer washed with saturated aqueous sodium hydrogencarbonate (2 × 50 ml) and saturated aqueous sodium chloride (50 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The orange oil was purified by silica gel column chromatography using 5:1 ethyl acetate–hexane to elute the first two bands (FcCHO and imine), then 7:1 ethyl acetate–methanol to elute **15** as an orange oil (0.111 g, 39%) (Found: C, 58.74; H, 7.21; N, 4.49%; M^+ *m*/*z* 301. $C_{16}H_{23}FeNO{\cdot}0.4CH_2Cl_2$ requires C, 58.76; H, 7.16; N, 4.18%; *M* 301); $\delta_H(CDCl_3)$: 1.20–1.35 (2 H, m, 3-H_2), 1.40–1.55 (4 H, m, 2-H_2 and 4-H_2), 1.85 (1 H, br s, NH), 2.29 (2 H, br t, *J* 7, 5-H), 3.41 (2 H, s, CH_2Fc), 3.59 (2 H, t, *J* 6, 1-H), 4.09 (5 H, s, C_5H_5), 4.12 (2 H, t, *J* 1.5, α or β Fc protons) and 4.17 (2 H, t, *J* 1.5 Hz, α or β Fc protons).

***N*,*N*-Bis(ferrocenylmethyl)-*N*-(2-hydroxyethyl)amine 17.** As for the preparation of compound **15** from ethanolamine; eluent 2% acetic acid in dichloromethane. The first fraction gave **17** as a yellow powder (35%) (Found: C, 50.20; H, 6.23; N, 3.34. $C_{13}H_{17}FeNO{\cdot}2CH_3CO_2H{\cdot}0.5CH_2Cl_2$ requires C, 49.84; H, 6.21; N, 3.32%); $\delta_H(CDCl_3)$ 2.25 (1 H, br s, NH or OH), 2.52 (2 H, t, *J* 5, 2-H), 3.45 (2 H, s, CH_2Fc), 3.48 (2 H, t, *J* 5, 1-H), 4.10, (5 H, s, C_5H_5), 4.14, (2 H, t, *J* 1, α or β Fc protons) and 4.16 (2 H, t, *J* 1 Hz, α or β Fc protons).

***N*-(2-Hydroxyethyl)aminomethylferrocene 16.** From the preparation of compound **17**, the second fraction was obtained by eluting with 2% acetic acid in ethyl acetate in small yield as a yellow powder; the relative yield of **16**:**17** was erratic (Found: C, 62.64; H, 5.98; N, 3.21%; M^+, *m*/*z* 457. $C_{24}H_{27}Fe_2NO$ requires C, 63.05; H, 5.95; N, 3.09%; *M* 457); $\delta_H(CDCl_3)$ 2.54 (2 H, t, *J* 5.5, 2-H), 3.47 (4 H, s, CH_2Fc), 3.49 (2 H, t, *J* 5.5, 1-H), 4.10 (10 H, s, C_5H_5), 4.15 and 4.16 (8 H, overlapping t, *J* 3 Hz, α and β Fc protons).

X-Ray data collection, reduction and structure solution for compound 4

Crystal data for compound **4** are given in Table 3. The compound was recrystallised from CH_2Cl_2–hexane and an orange block was used for data collection on a Siemens R3m/V, four circle, fully automated diffractometer. Data were processed and empirical absorption corrections applied using SHELXLTL.[21] The structure was solved by direct methods, SHELXS 97,[21] and refined by full matrix least squares on F^2 using SHELXL 97.[21] All non-hydrogen atoms were refined anisotropically with hydrogen atoms included as fixed contributions to F_c with fixed isotropic thermal parameters. Refinement of the Flack parameter[22] [$x = 0.01(3)$] indicated that the parameters represented the correct absolute structure for the chiral molecule. High and increasing thermal parameters for the O(8) atom of the acetyl residue at C(4) indicated possible disorder. This was resolved by

Table 3 Crystal data and structure refinement for compound **4**

Chemical formula	$C_{36}H_{41}Fe_2NO_9$
Formula weight	743.40
Crystal system	Monoclinic
Space group	$P2_1$
μ/mm^{-1}	0.895
a/Å	10.692(4)
b/Å	10.746(4)
c/Å	15.212(4)
β/°	98.56(2)
V/Å	1728.3(10)
Z	2
T/K	168(2)
D_c/Mg m^{-3}	1.428
Reflections collected	4371
Independent reflections	3217 [R(int) = 0.0435]
Final $R1$, $wR2$ [$I > 2\sigma(I)$]	0.0433, 0.0940
[all data]	0.0682, 0.1060

refining two unique positions for this atom with occupancy factors f and f' refined such that $f' = 1 - f$. The final value of f refined to 0.65(12).

CCDC reference number 186/1888.

See http://www.rsc.org/suppdata/dt/a9/a908513k/ for crystallographic files in .cif format.

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