A rotaxane of a 1,1′-disubstituted ferrocene and β-cyclodextrin

Philip J. Skinner, Stephanie Blair, Ritu Kataky and David Parker*

Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE
E-mail: david.parker@dur.ac.uk

Received (in Cambridge, UK) 14th January 2000, Accepted 3rd March 2000
Published on the Web 12th April 2000

The synthesis is reported of the first rotaxane involving a bound ferrocenyl moiety and β-cyclodextrin; cyclodextrin groups are used as stoppers; intermediate 1 : 1 adduct formation in d_8-THF was monitored by HR-DOSY methods ($K_d = 25$ mM, 293 K) and the product rotaxane, isolated in 11% yield, has been characterised by NMR, CD and MALDI-TOF MS.

The inclusion of ferrocene by β-cyclodextrin was first described in 1975,[1] and although the 1 : 1 complex is relatively weak ($K = 50$ M^{-1} (DMSO, 298 K)), it has been shown to facilitate electron transfer to suitable guest substrates, for example in the oxidation of NADH.[2] A conjugate of per-*O*-acetyl ferrocene linked in the 6-position to ferrocene carboxylic acid, has also been reported to catalyse the oxidation of benzyl alcohol to benzaldehyde in acetonitrile solution, a reaction which was postulated to occur *via* electron transfer from the ferrocenium cation to the co-complexed aryl guest.[3] Recently, we have described the use of per-*O*-alkylated cyclodextrins in a variety of electroanalytical applications with thin film devices, in which the lipophilic cyclodextrin serves to mediate transport of the analyte at the interface and through the film.[4] In enzyme-relay electrodes for acetylcholine, involving the use of acetylcholine esterase and 1,1′-bis(methoxymethyl)ferrocene as a charge relay, it was suggested that the very low limits of detection observed ($\leqslant 10^{-13}$ M) were a direct consequence of the presence of the lipophilic per-*O*-ethyl-β-cyclodextrin, which served to aid transport not only of the enzyme substrate but also of the ferrocenyl charge relay.[5] As a result of this work, we set out to examine complexes of per-*O*-methyl- and per-*O*-ethyl-β-cyclodextrin with ferrocene derivatives, and examine some conjugates linked *via* the primary face to an electron rich ferrocenyl group using an amide bond.

Support for the binding of ferrocene by per-*O*-methyl- and per-*O*-ethyl-β-cyclodextrin was gained from electrospray mass spectrometry and high resolution diffusion ordered ^{1}H NMR (HR-DOSY) experiments.[6] Previously, pulsed field gradient spin echo (PGSE) methods have been used to measure such diffusion coefficients, and hence allow evaluation of host–guest binding affinities.[7] Binding constants were assessed by measuring the diffusion coefficient for the host and guest separately and for known concentrations of the guest in the presence of the host cyclodextrin (500 MHz, 293 K), *i.e.* under fast exchange conditions.[6] The binding affinity for each guest was estimated to be 20 ($\pm$10) (ferrocene) and 160 ($\pm$30) M^{-1} (CD_3OD, 295 K) for the corresponding cobaltocenium complex with per-*O*-ethyl-β-cyclodextrin. Similar values (30 and 190 M^{-1} respectively) were measured with per-*O*-methyl-β-cyclodextrin as the host, and positive ion ESMS spectra (MeOH) confirmed the presence of a 1 : 1 complex in each case, with stronger molecular ions observed for the cationic guests. In the case of 1,1-bis(hydroxymethyl)ferrocene and per-*O*-methyl-β-cyclodextrin, the 1 : 1 adduct had a binding constant of 40 ($\pm$8) M^{-1} (*i.e.* $K_d = 25$ mM, 293 K, d_8-THF) in the relatively non-polar solvent THF (Fig. 1).

For the synthesis of the ferrocene–cyclodextrin conjugate, mono-6-amino-per-*O*-methyl-β-cyclodextrin, **1a** and the per-*O*-ethyl analogue **1b** were used as suitable precursors. Reaction with chloroacetyl chloride ($Et_3N/CH_2Cl_2/-10$ °C) yielded the corresponding α-halogenoamides **2a** and **2b** and alkylation with 1,1′-bis(hydroxymethyl)ferrocene (excess NaH, THF, -70 °C to 20 °C) afforded a mixture of two main products, in each case. Separation of the per-*O*-methylated reaction mixture by reverse-phase preparative HPLC ($MeOH/H_2O$) afforded a 3 : 1 (cyclodextrin/ferrocene) adduct (11% isolated yield, mp 108–110 °C) and a 2 : 1 conjugate (19%, mp 95–98 °C) as determined by ^{1}H NMR integration and microanalysis. Examination of the separated products by MALDI-TOF mass spectrometry revealed a molecular ion at 4623 and a daughter ion at 3176 for the 3 : 1 adduct; no other peaks were observed in the region 3176–4600. A parent ion at 3173 was observed for the 2 : 1 conjugate, with several fragments discerned at masses of less than 2500.[8] Such behaviour suggested that the 2 : 1 compound may be the simple ether **4a**, while the 3 : 1 adduct could be the rotaxane **3a**, formed *via* inclusion of the ferrocenyl moiety prior to ether bond formation, in which two further cyclodextrin moieties serve as 'stoppers'.

Support for this premise was provided by detailed NMR analysis: only one ^{13}C resonance was evident for the secondary amide carbonyl group in **3a** (δ 172.1, CD_3OD, 125.7 MHz). The ^{1}H NMR resonances of the ferrocenyl protons were rather broad in CD_3OD so the compounds were also examined in $CDCl_3$. ^{1}H NMR studies on **3a** in $CDCl_3$ revealed three amide NH protons around δ 6.90: for **4a** only 2 amide protons were revealed at δ 6.75 ($CDCl_3$). The ferrocenyl ring protons and $FcCH_2O$ protons resonated as three slightly broadened singlets for **4a** at δ 4.17, 4.22 and 4.35 respectively, each integrating to four protons. With the rotaxane, **3a**, a sharper but more complex multiplet pattern was observed in this solvent: 3 distinct resonances were observed for the $FcCH_2O$ protons at δ *ca.* 4.35, while the cyclopentadienyl protons resonated as a complex multiplet centered around δ 4.2. The local environmental differences experienced by the ferrocenyl protons adjacent to the primary or secondary cyclodextrin faces render the CH Cp ring protons diastereotopic and presumably give rise to the observed shift non-equivalence. A ^{1}H NMR ROESY experiment (500 MHz, 293 K, 1 s mixing time, CD_3OD) revealed cross peaks not only between the ferrocenyl ring CH protons at δ 4.32 (β to the CH_2O substituent) and the internal H^3 resonance of the cyclodextrin at δ 3.64 but also between the ferrocenyl CH_2O resonance at δ 4.42 and a cyclodextrin resonance at δ 3.95 (probably H^5 or H^6). Taken together such data are inconsistent with the only feasible alternate structure for **3a** wherein amide *N*-alkylation occurs giving a tertiary amide. The pres-

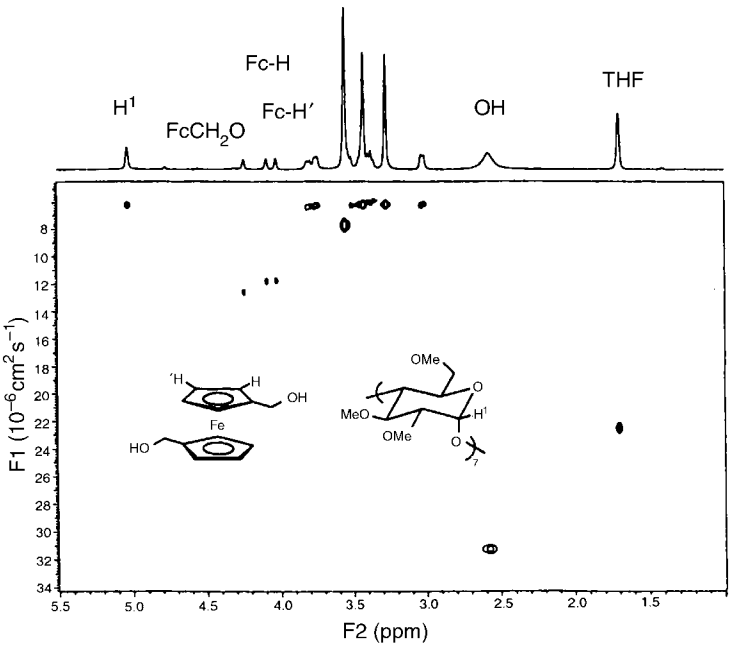
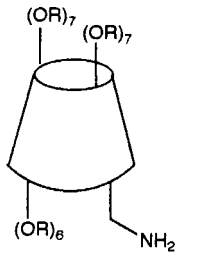
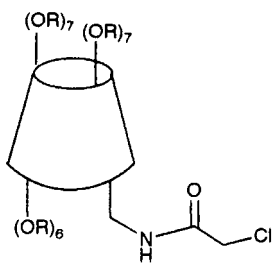


Fig. 1 HR-DOSY ^{1}H NMR spectrum obtained using the 'bppse' pulse sequence[6] showing the diffusion-ordered spectrum for a 1 : 1 mixture of per-*O*-methyl-β-cyclodextrin and 1,1′-bis(hydroxymethyl)ferrocene (10 mM, d_8-THF, 295 K, 500 MHz). Under the same conditions, the unbound ferrocenyl derivative gave *D* values of 14.1 and 13.6 × 10^{-6} cm^2 s^{-1} for the $FcCH_2O$ and each ring CH resonance.



1 a R = Me
b R = Et



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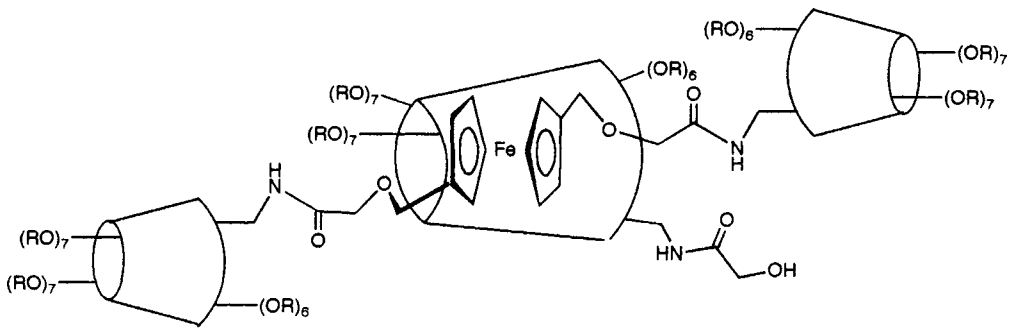
ence of the $NHCOCH_2OH$ functionality in the rotaxane was inferred from MS and ^{13}C data (*e.g.* absence of additional CH_2Cl resonance at δ *ca.* 41 in ^{13}C and in ^{1}H NMR at δ 4.1), and is presumably formed by hydrolysis of the α-halogenamide during product isolation.

Further support for the rotaxane structure was provided by circular dichroism studies. The chiral β-cyclodextrin cavity has previously been shown to induce weak, negative CD bands in bound aryl guests.[2,9] Indeed in the complexation of the ferrocenecarboxylate anion at pH 9.2 by β-cyclodextrin, a negative induced CD (ICD) was observed, supporting an



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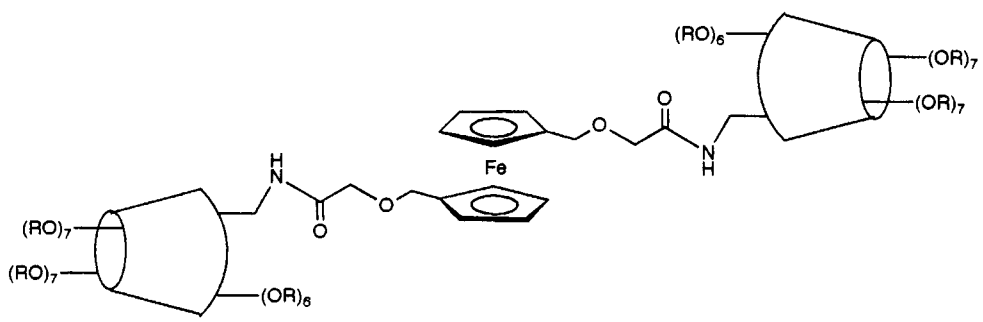

4 a R = Me
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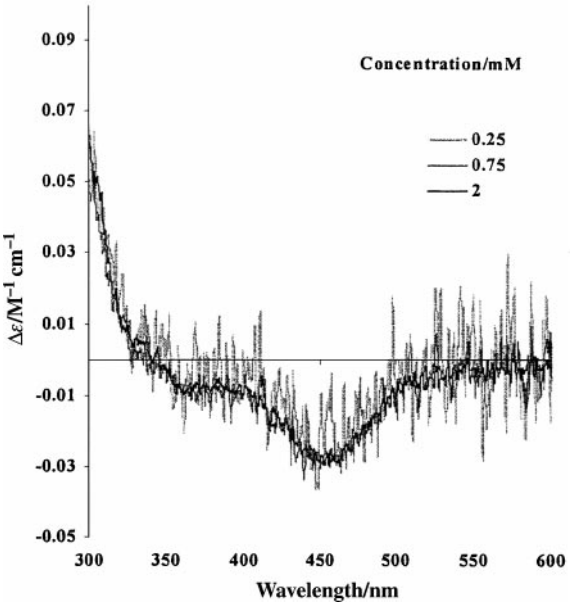

Fig. 2 Circular dichroism spectra for **3a** in methanol highlighting the ferrocenyl chromophore (298 K) at 0.25, 0.75 and 2.0 mM concentration.

orientation of the ferrocenyl guest in which the Cp–Fe–Cp axis is parallel to the central axis of the cavity.[2] A negative induced CD band at 460 nm was observed for **3a** in methanol whose intensity ($\Delta\varepsilon = -0.03$ M^{-1} cm^{-1}) was independent of sample concentration (0.25 to 2 mM) (Fig. 2). In the concentration range 0.5 to 10 mM, an induced CD was not discerned for the intermolecular association of a 1 : 1 mixture of 1,1′-bis(methoxymethyl)ferrocene with per-*O*-methyl-β-cyclodextrin in methanol, nor for **4a** itself: ferrocenyl binding is presumably too weak under these conditions to give an observable CD signal.

Some preliminary electrochemical experiments have been carried out with **3a** in EtOH or MeCN solution. Reversible oxidation in MeCN solution at a glassy carbon electrode occurred at +224 mV (*vs.* SCE, 0.1 M NEt_4Cl) generating a ferrocenium cation characterised *in situ* spectroelectrochemically by formation of a characteristically intense charge-transfer band at 620 nm. The observed redox couple is anodically shifted by 63 mV compared to 1,1′-bis(methoxymethyl)ferrocene and is also shifted with respect to **4a** ($E_{1/2}$ = +175 mV). The rotaxane **3a** was stable in solution (CD_3OD, MeCN) for prolonged periods, whereas the 2 : 1 adduct **4a** was observed (^1H NMR) to degrade slowly, both in solution and on storage in air.

This work highlights the opportunities that are available for rotaxane formation of 1,1′-disubstituted ferrocenyl derivatives, with modified cyclodextrins. Further studies are in progress to define the scope and utility of rotaxanes **3a** and **3b**[10] and related ferrocenyl–cyclodextrin conjugates for a range of electroanalytical applications.

Experimental

Synthesis of 3a and 4a

1,1′-Bis(hydroxymethyl)ferrocene (0.10 g, 0.40 mmol) was dissolved in anhydrous tetrahydrofuran (10 cm^3) under argon and chilled to −70 °C. Sodium hydride (0.30 g, 12.5 mmol) was added and the solution allowed to warm to room temperature and stirred for 1 hour. The solution was chilled to −70 °C and mono-6-(chloromethylcarbamoyl)-6-deoxy-per-*O*-methyl-β-cyclodextrin (1.36 g, 0.91 mmol) in anhydrous tetrahydrofuran (8 cm^3) added. The solution was allowed to warm to room temperature and stirred under argon for 3 days. Solvent was removed under reduced pressure and the residual solid purified by preparative HPLC (Hypersil semi-prep. column, 95% MeOH/5% H_2O) to give the rotaxane **3a** (0.16 g, 0.034 mmol, 11%, t_r = 11.2 min) and **4a** (0.24 g, 0.076 mmol, 19%, t_r = 5.7 min) as pale yellow solids.

3a: mp: 108–110 °C; $R_f = 0.73$ (10% MeOH/90% CH_2Cl_2, silica); *m/z* (MALDI-TOF+, linear): 4623 ($C_{204}H_{352}FeN_3O_{108}$ requires 4628). Found: C, 51.9; H, 7.42; N, 0.88. $C_{204}H_{352}FeN_3O_{108}\cdot 4H_2O$ requires C, 52.1; H, 7.12; N, 0.89%. $\delta_H(CDCl_3)$: 6.93 (1H, br t, N*H*CO), 6.88 (2H, br t, N*H*CO), 5.23–5.10 (21H, m, C(1)–*H*), 4.38, 4.37, 4.35 (4H, s + q, Fc-C*H′H*O), 4.24 (4H, m, Fc-H^2), 4.22 + 4.17 (2H + 2H, m + m, Fc-H^3), 4.05–3.20 (316 H, m, of which 3.63, 3.49 and 3.37 are for OCH_3). ν_{max} (MeOH): 433 nm (ε 229 M^{-1} cm^{-1}).

4a: mp: 95–98 °C; $R_f = 0.73$ (10% MeOH/90% CH_2Cl_2, silica); *m/z* (MALDI-TOF+, linear): 3173 ($C_{140}H_{239}FeN_2O_{72}$ requires 3156). Found: C, 50.3; H, 7.52; N, 1.23. $C_{140}H_{239}FeN_2O_{72}\cdot 8H_2O$ requires C, 50.7; H, 7.71; N, 0.84%. $\delta_H(CDCl_3)$: 6.75 (2H, br t, N*H*CO), 5.20–5.12 (14H, m, C(1)–*H*), 4.35 (4H, s, Fc-CH_2O), 4.22 (4H, br s, Fc-H^2), 4.17 (4H, s, Fc-H^3), 3.97–3.10 (212H, m, of which 3.65, 3.50 and 3.40 are for OCH_3).

Compounds **3b** and **4b** were prepared analogously in a combined yield of 64%.

Acknowledgements

We thank BBSRC and EPSRC for support and the EPSRC National Chiroptical Service for CD spectra (Dr G. Siligardi, King's College London).

References

1 B. Siegel and R. Breslow, *J. Am. Chem. Soc.*, 1975, **97**, 6869.
2 T. Matsue, D. H. Evans, T. Osa and N. Kobayashi, *J. Am. Chem. Soc.*, 1985, **107**, 3411; the d–d transitions of ferrocene are polarised along the axis parallel to the cyclopentadienyl rings: D. R. Scott and R. S. Becker, *J. Chem. Phys.*, 1961, **35**, 516; D. Nielson, D. Boone and H. Eyring, *J. Phys. Chem.*, 1972, **76**, 511.
3 I. Suzuki, Q. Chen, Y. Kashiwagi, T. Osa and A. Ueno, *Chem. Lett.*, 1993, 1719.
4 R. Kataky and D. Parker, *Chem. Commun.*, 1997, 141.
5 R. Kataky and D. Parker, *Analyst*, 1996, **121**, 1829.
6 M. D. Pelta, H. Barjat, G. A. Morris, A. L. Davis and S. J. Hammond, *Magn. Reson. Chem.*, 1998, **36**, 706: the bipolar pulse pair stimulated echo sequence (bppse) was used in the HR-DOSY experiments to assess ferrocene binding. Limiting *D* values (the mean of three independent measurements) for per-*O*-methyl-β-cyclodextrin were 6.3×10^{-6} cm^2 s^{-1} (d_8-THF, 10 mM, 293 K) compared to 14.1 and 13.6×10^{-6} cm^2 s^{-1} for the ring CH and CH_2O resonances of 1,1′-bis(hydroxymethyl)ferrocene under the same concentration. Values of *D* in CD_3OD were about 30% lower than in d_8-THF. Complexes gave intermediate *D* values, allowing the calculation of binding affinities, *K*(±15%). In comparison, the binding affinities of acetylcholine with per-*O*-ethyl- and per-*O*-methyl-β-cyclodextrin were measured to be 275(±45) and 100(±15) M^{-1} respectively (CD_3OD, 293 K); in these cases the utility of the HR-DOSY method is highlighted as no chemical shift change of the NMe_3 singlet (δ_H 3.21) occurs on complexation, in this solvent.
7 (*a*) O. Soderman and P. Silbs, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1994, **26**, 480; (*b*) O. Mayzel and Y. Cohen, *J. Chem. Soc., Chem. Commun.*, 1994, 1901; (*c*) A. Gafni and Y. Cohen, *J. Org. Chem.*, 1997, **62**, 120.
8 **3a:** Calculated mass ($C_{204}H_{352}FeN_3O_{108}$) 4628 [$M^+$]; loss of a cyclodextrin moiety gave a fragment at 3171. For the per-*O*-ethyl analogue, MALDI-TOF analysis showed peaks for **3b** at 5464 ($C_{264}H_{472}FeN_3O_{108}$; 5469) and for **4b** at 3716 [M^+] ($C_{180}H_{318}FeN_2O_{72}$; 3716). A threaded structure for **4a** and **4b** was considered, but was inconsistent with the absence of an

induced CD in the ferrocenyl chromophore (2 mM, 295 K, MeOH) and with the observed NMR behaviour in $CDCl_3$.

9 (*a*) S. Monti, G. Köhler and G. Grabner, *J. Phys. Chem.*, 1993, **97**, 13011; (*b*) M. Kodaka, *J. Phys. Chem.*, 1998, **102**, 8101; (*c*) I. Tinoco, *Adv. Phys. Chem.*, 1962, **4**, 113; (*d*) H. Shimizu, A. Kaito and M. Hatano, *J. Am. Chem. Soc.*, 1982, **104**, 7059.

10 For a recent review of cyclodextrin rotaxanes and catenanes: S. A. Nepogodiev and J. F. Stoddart, *Chem. Rev.*, 1998, **98**, 1959; a ferrocenyl unit bearing a β-*N*,*N*-dimethylammonium unit has been used as a stopper, in a cyclodextrin rotaxane, in which a cyclodextrin is threaded onto a long chain alkyl group: R. Isnin and A. Kaifer, *J. Am. Chem. Soc.*, 1991, **113**, 8188.