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Note

Products of hydrolysis of (ferrocenylmethyl)trimethylammonium iodide: Synthesis of hydroxymethylferrocene and bis(ferrocenylmethyl) ether

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Abstract

The attempted coupling of (ferrocenylmethyl)trimethylammonium iodide (**1**) with 1,4,7-(triformyl)-1,4,7,10-tetraazacyclododecane (**2**) in water led to the formation of the expected compound 1-(ferrocenemethyl)-4,7,10-(triformyl)-1,4,7,10-tetraazacyclododecane (**3**). In addition, hydrolysis of the ferrocenyl precursor **1** led to the formation of two other known compounds, hydroxymethylferrocene (**4**) and bis(ferrocenylmethyl) ether (**5**). An X-ray crystal structure determination of **4** revealed the presence of H-bonding between the hydroxyl groups of one molecule of **4** and the oxygen atom of an adjacent molecule resulting in a left-handed helical chain of molecules lying along the *b*-axis direction. The O···O distances are significantly shorter than those found in previously reported structures of hydroxymethylferrocene derivatives indicative of moderate strength H-bonding interactions. In the structure of **5**, the orientation of the ferrocenyl groups are staggered relative to a vector comprising the two carbons of the C–O–C linker.
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Keywords: Synthesis; Ferrocene derivatives; 1,4,7,10-Tetraazacyclododecane (cyclen); X-ray crystal structure; H-bonding; Hydrolysis products

1. Introduction

Our group has recently focused attention on the development of redox (bio)sensors using metal complexes for the possible electrochemical recognition of thymine derivatives [1] and the nitrate anion [2]. The ligand used in these studies was the previously reported 1-(ferrocenemethyl)-1,4,7,10-tetraazacyclododecane [3] (**6**) (Fig. 1) with the ferrocene (Fc) of **6** being used as the redox-active moiety. We also demonstrated that the complexation of **6** with Cu^{II} added a supplementary redox moiety that enabled a double electrochemical recognition of nitrate in acetonitrile and nitromethane [2]. A larger electrochemical shift was obtained upon the addition of nitrate for the $Cu^{II/I}$ centre than for $Fc^{0/+}$ due to coordination of the nitrate to the copper centre. These promising results led us to investigate a shorter synthetic pathway to **6** [2], than the previously published procedure [3], involving the formation of 1,4,7-tris-*tert*-butoxycarbonyl-10-(ferrocenylmethyl)-1,4,7,10-tetraazacyclododecane with the subsequent acidic cleavage of the *tert*-butoxycarbonyl (BOC) groups, Unfortunately, this method did not yield the desired product. Furthermore, during another attempt to prepare **3**, the unexpected formation of hydroxymethylferrocene (**4**) (also known as ferrocenemethanol) and bis(ferrocenylmethyl) ether (**5**) was observed (Fig. 1). Due to the importance of attaching ferrocene to molecules of biological interest or for electrochemical sensing, as recently underlined by Metzler-Nolte and van Staveren [4] and Tucker and Collinson [5], we report, in this paper, these results and the X-ray crystal structures of **4** and **5**.

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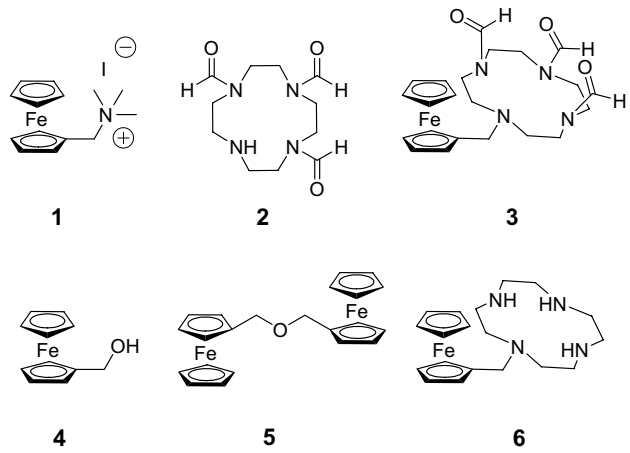


Fig. 1. Structures of compounds **1**–**6**.

2. Experimental

2.1. Materials

All chemicals were of reagent grade purity or better, and used as obtained from the commercial suppliers. Deionised water was distilled prior to use.

2.2. Instrumentation

^{1}H and ^{13}C NMR spectra were recorded at 30 °C in deuterated solvents using either Bruker AC200, Bruker DPX300 or Avance DRX400 Bruker spectrometers. The residual solvent resonances were used as the internal reference for spectra recorded in non-aqueous solvents. Low resolution electrospray mass spectra were obtained with a Micromass Platform II Quadrupole Mass Spectrometer fitted with an electrospray source. The capillary voltage was set at 3.5 eV and the cone voltage at 35 V.

2.3. Synthesis

2.3.1. (Ferrocenylmethyl)trimethylammonium iodide (1) and 1,4,7-(triformyl)-1,4,7,10-tetraazacyclododecane (2)

These compounds were synthesised and characterised as described by Lindsay and Hauser [6] and Sisti et al. [3], respectively. The products gave clean ^{1}H and ^{13}C NMR spectra that were consistent with the literature and product composition.

2.3.2. 1-(Ferrocenemethyl)-4,7,10-(triformyl)-1,4,7,10-tetraazacyclododecane (3), hydroxymethylferrocene (4) and bis(ferrocenylmethyl) ether (5)

Compound **1** (4.23 g, 11.0 mmol) and **2** (2.82 g, 11.0 mmol) were refluxed in deoxygenated water (90 mL) for 15 h. After cooling to room temperature, the orange solution was extracted with CH_2Cl_2 (3 × 100 mL) and the solvent of the combined organic phases was removed under vacuum to give an orange solid. Purification was achieved by column chromatography on silica with 20:1 CH_2Cl_2:MeOH. Four main compounds, hydroxymethylferrocene (**4**) ($R_f = 1$), bis(ferrocenylmethyl) ether (**5**) ($R_f = 0.95$), 1-(ferrocenemethyl)-4,7,10-(triformyl)-1,4,7,10-tetraazacyclododecane (**3**) ($R_f = 0.48$) and (ferrocenylmethyl)trimethylammonium iodide (**1**) ($R_f = 0.24$) were isolated (recovered) in yields of 12% (0.29 g), 20% (0.45 g), 30% (1.50 g) and 26% (1.11 g), respectively. The spectroscopic data for **1** (^{1}H NMR) [7], **3** (^{1}H and ^{13}C NMR, ESI MS) [2], **4** (^{1}H NMR) [7] and **5** (^{1}H NMR) [8] were in agreement with those reported previously. Crystals of **4** suitable for X-ray crystallography were grown by slow evaporation of an isopropanol and chloroform (1:1 v/v) solution of **4**. Crystals of **5** suitable for X-ray crystallography were grown by slow evaporation of a solution of **5** in acetonitrile.

2.4. X-ray crystallography

Intensity data for **4** (0.08 × 0.05 × 0.04 mm) and **5** (0.3 × 0.15 × 0.05 mm) were measured at 123 K on a Bruker X8 Apex CCD fitted with a graphite–monochromated Mo-Kα radiation (0.71073 Å) source. The data was collected to a maximum 2θ value of 50° and processed using the Bruker Apex II software. (Collection and refinement parameters are summarised in Table 1). Both structures were solved using the direct method and expanded using standard Fourier routines in the SHELX-97 [9,10] software package. The structure of **4** was solved in the space group *C*2. All hydrogens (except H2A) were placed in idealised positions while all non-hydrogen atoms were refined with anisotropic thermal parameters. The structure of **5** was solved in the space group *P*2/*n*. All hydrogens were placed in idealised positions while all non-hydrogen atoms were refined with anisotropic thermal parameters.

Table 1
Crystallography data for **4** and **5**

Crystal	**4**	**5**
Empirical formula	$C_{11}H_{12}FeO$	$C_{22}H_{22}Fe_2O$
M (g mol^{-1})	216.06	414.10
Crystal system	Monoclinic	Monoclinic
Space group	*C*2	*P2n*
a (Å)	30.705(3)	12.5115(9)
b (Å)	6.0459(5)	5.7867(5)
c (Å)	15.687(2)	24.587(2)
V (Å^3)	2793(5)	1737.2(2)
Z	12	4
T (K)	123(2)	123(2)
λ (Å)	0.71073	0.71073
D_c (g cm^{-3})	1.541	1.583
μ (MoKα) (mm^{-1})	1.571	1.676
No. data measured	12,833	12,304
Unique data (R_{int})	4111(0.055)	3055(0.073)
Observed data [$I > 2(\sigma)I$]	3743	2613
Final R_1, wR_2 (observed data)	0.0424[a], 0.0721[b]	0.0793[a], 0.1726[b]
Final R_1, wR_2 (all data)	0.0484, 0.0765	0.0911, 0.1785
ρ_{min},ρ_{max}/e Å^{-3}	−0.361, 0.503	−0.650, 0.930

[a] $R1 = \sum \|F_0| - |F_c\| / \sum |F_0|$.
[b] $wR2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$.

3. Results and discussion

3.1. Synthesis

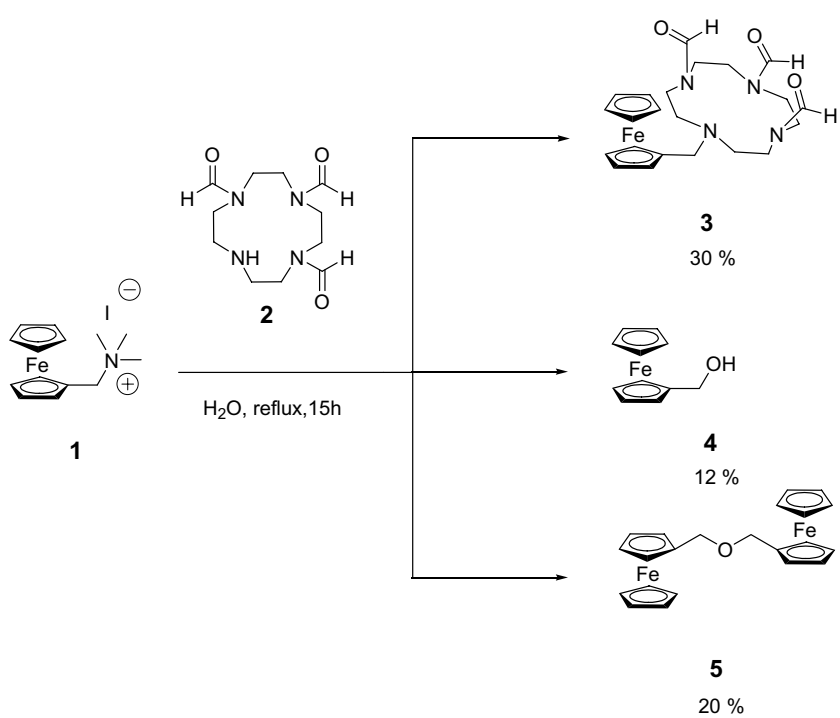
Sisti et al. recently reported the synthesis of 1-(ferrocenemethyl)-4,7,10-(triformyl)-1,4,7,10-tetraazacyclododecane (**3**) [3]. Their method involved the coupling of the two known compounds (ferrocenylmethyl)trimethylammonium iodide [6] (**1**) and 1,4,7-(triformyl)-1,4,7,10-tetraazacyclododecane (**2**) in DMF in the presence of K_2CO_3. To avoid the use of the high boiling and environmentally unfriendly solvent DMF, the same coupling reaction was successfully attempted by our group in deoxygenated water, without the use of a base [2]. Compound **3** was obtained in a slightly higher yield than previously reported [3]. However, during one of our preliminary attempts, which utilised the same reaction time and lower concentration of reagents, two other known compounds, hydroxymethylferrocene [6] (**4**) and bis(ferrocenylmethyl) ether [11] (**5**) were obtained in a reasonable yield, in addition to the desired product **3**, as summarised in Scheme 1. Some unreacted starting material (**1**, 26%) was also recovered.

The formation of the expected product **3** and the side-compound **4** can be rationalised as follows. Compound **3** was most likely to have been obtained via nucleophilic attack of the non-formyl-protected nitrogen atom of **2** on the methylene carbon of **1** and compound **4** was probably formed by the hydrolysis of **1**. This hypothesis is supported by the fact that the first reported synthesis of **4** was performed through refluxing **1** in an aqueous 1 M NaOH solution [6]. In our case, the presence of the amine **2** may make the reaction mixture sufficiently basic for the hydrolysis of **1**–**4** to take place. The formation of **5** could involve attack by the oxygen atom of **4** at the methylene carbon of **1**, whilst the other would involve a similar attack on another molecule of **4** rather than a mechanism involving a carbocation [8,12–14].

The formation of **3**–**5** gives a useful indication of the synthetic behaviour of **1**. Surprisingly, despite the fact that the commercially available precursor of **1**, (dimethylaminomethyl)ferrocene, is significantly cheaper than ferrocenecarboxylic acid (which is the most commonly used precursor to attach the ferrocenyl moiety to biomolecules or molecules of biological interest) [4], to the best of our knowledge, only a few reports described the use of **1** for such a purpose [15–21]. In our opinion, the potential of **1** is for the moment underestimated and its reactivity with biomolecules needs to be explored more thoroughly, especially because the coupling can be easily achieved in water. Despite being known for a long time, the X-ray structures of compounds **4** and **5** have not been previously reported. We have determined their structures and in the process identified some interesting features which are described below.

3.2. X-ray crystal structures

Compound **4** crystallised in the monoclinic space group *C*2 with three molecules in the asymmetric unit. The molecular structure, a packing view, selected bond distances and bond angles as well as a summary of the hydrogen bonds in **4** are presented in Figs. 2 and 3, and Tables 2 and 3,



Scheme 1. Summary of the formation of **3**–**5**.

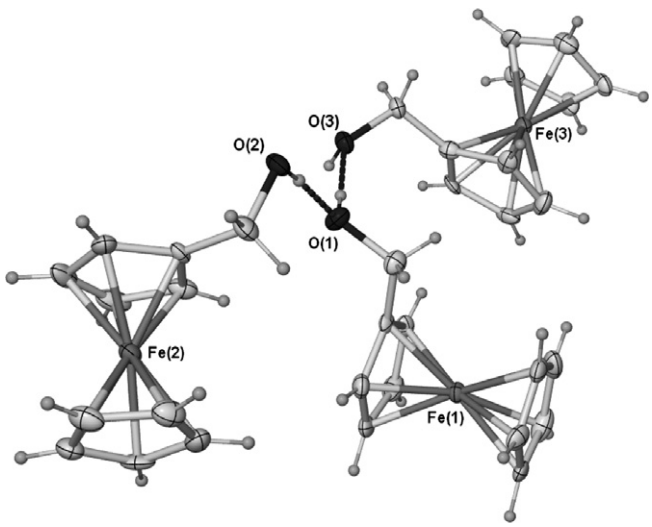


Fig. 2. Thermal ellipsoid plot of the three unique molecules of **4** showing the H-bonding between adjacent molecules (ellipsoids drawn at 50% probability).

respectively. The structure of each unique molecule in **4** in itself does not present any surprises with all bond length and angle values quite similar to those reported for the related compound, 1-ferrocenyl-1-phenylethanol [22]. For instance, the Fe–C distances in the three ferrocenyl moieties range between 2.029(5) and 2.054(6) Å. But, interestingly, two of the three unique ferrocene groups (containing Fe(1) and Fe(3)) have quasi eclipsed cyclopentadienyl groups (Cp) (the torsion angles are determined as the angle between the C–H bond of one Cp and the C–H bond of the other Cp of the ferrocene). The largest torsion angles for ferrocenes containing Fe(1) and Fe(3) are 6.0 and 4.2°, respectively, whilst the other ferrocene group containing Fe(2) is quite staggered (the largest torsion angle being 19.2°).

Table 2
Selected bond distances (Å) and bond angles (°) for **4**

Fe(1)–C(Cp)	2.029(5)–2.047(5)	Fe(1)–C(10)–C(11)	123.2(3)
C(10)–C(11)	1.499(7)	C(10)–C(11)–O(1)	113.2(4)
C(11)–O(1)	1.434(6)	Fe(2)–C(21)–C(22)	125.7(3)
Fe(2)–C(Cp)	2.028(5)–2.054(6)	C(21)–C(22)–O(2)	110.9(4)
C(21)–C(22)	1.492(6)	Fe(3)–C(32)–C(33)	126.0(4)
C(22)–O(2)	1.451(6)	C(32)–C(33)–O(3)	111.7(4)
Fe(3)–C(Cp)	2.031(5)–2.054(5)		
C(32)–C(33)	1.491(7)		
C(33)–O(3)	1.450(5)		

Table 3
Hydrogen bonds for **4** (Å and °)

D–H . . . A[a]	d(D–H)[a]	d(H . . . A)[a]	d(D . . . A)[a]	∠(DHA)[a]
O(1)–H(1A) . . . O(3)	0.84	1.80	2.633(5)	174.8
O(2)–H(2A) . . . O(1)	0.88(6)	1.81(6)	2.679(5)	177(5)
O(3)–H(3A) . . . O(2)[b]	0.84	1.86	2.675(5)	164

[a] D = donor, A = acceptor.
[b] Symmetry transformation used to generate equivalent atoms: x, $1 + y$, z.

An interesting feature of the structure of **4** is the hydrogen bonding formed by each hydrogen atom of the hydroxyl groups and an oxygen atom of the adjacent molecule giving rise to a left-handed helicoidal chain that projects in the b-axis direction (Fig. 3). The non-centrosymmetric space group $C2$ defines the presence of only a single handedness of the chains. Each alcohol functional group is involved in two intermolecular hydrogen bonds, acting both as a hydrogen atom donor and acceptor. Similar H-bonded chains have been observed in hydroxymethylferrocenes similar to **4** [23–25]. However, the O···O separations of 2.635(5)–2.679(5) Å found in **4** are significantly shorter than in the other derivatives (e.g.,

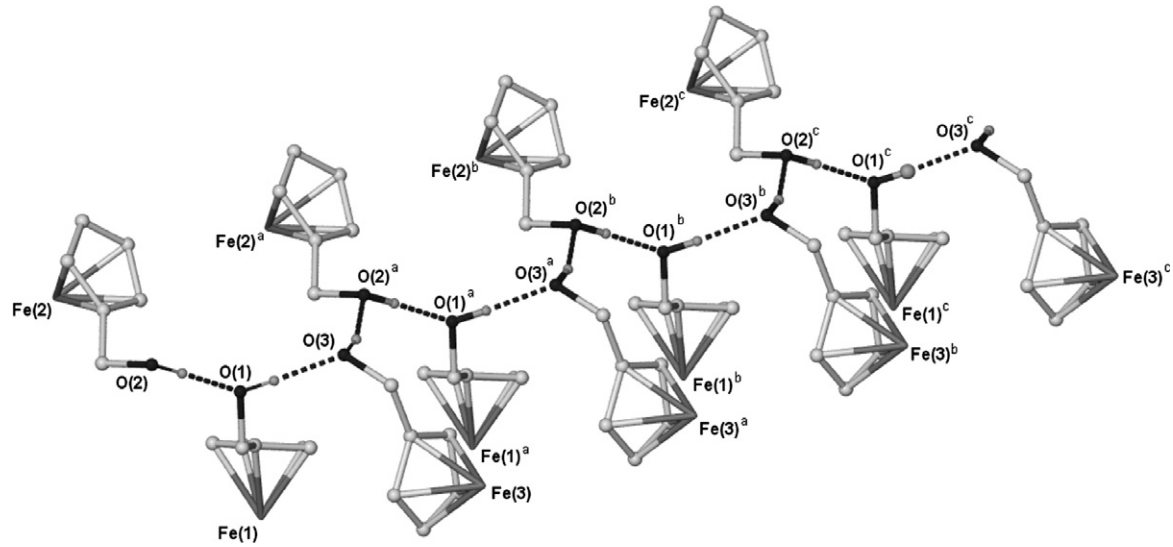


Fig. 3. A representation of **4** showing the H-bonded helicoidal chain lying along the b-axis direction. The unsubstituted Cp rings and hydrogen atoms, except those involved in hydrogen bonding, were omitted for clarity, ([a]x, $1 + y$, z; [b]x, $2 + y$, z; [c]x, $3 + y$, z).

2.751(3) Å for *rac*-[2-(diphenylphosphino)ferrocenyl]methanol [25]; 2.835(4)–2.866(4) Å for [1′(diphenylphosphino)ferrocenyl]methanol [24]; 2.746(3)–2.751(3) Å for *rac*-(hydroxymethyl)bromoferrocene [23]; 2.734–2.734 Å for octamethylferrocenyl methanol [26]). Balavoine et al. described a two-dimensional network in another hydroxymethylferrocene derivative, (*R*)-((*E*)-2-(4-nitrophenyl)-ethenyl)(hydroymethyl)ferrocene [27]. However, the H-bonding network was not only due to the atoms of the hydroxyl groups but also to one of the oxygen atoms of a nitro group present in their molecule. Nevertheless, the O···O separation between the oxygen atoms of the alcohol functional group in their ferrocenyl derivative (2.807 Å) was much larger than in **4**.

Compound **5** crystallised in the monoclinic space group *P*2/*n* with two half-molecules in the asymmetric unit (Fig. 4). The structure is typical with all distances and angles falling in the expected range. It is, however, interesting to compare the structure of **5** with that of its close analogue; di(octamethylferrocenylmethyl) ether [26]. Both structures are quite similar with the exception of larger Cp–CH_2–O angles in **5** (Table 4, cf 106.2°, 108.0° for di(octamethylferrocenylmethyl) ether [26]) whilst it would be expected that the bulkiness of the methyl groups in di(octamethylferrocenylmethyl) ether would result in larger angles. Another significant difference is the angle between

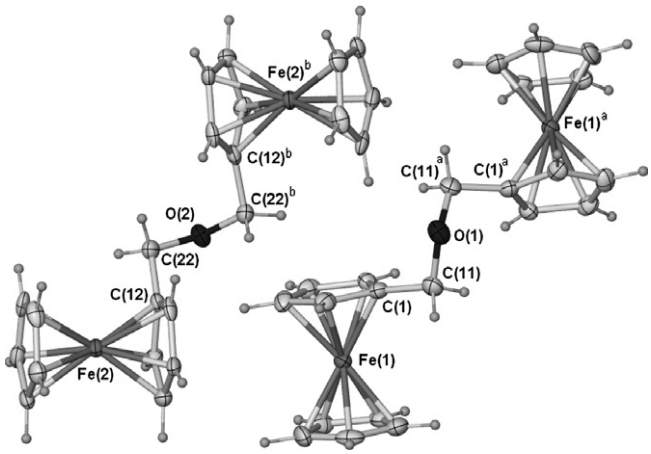


Fig. 4. Thermal ellipsoid plot of **5** (ellipsoids drawn at 50% probability). Complete molecules were generated by symmetry equivalents; [a]3/2−*x*, *y*, 1/2−*z*; [b]1/2−*x*, *y*, 1/2−*z*.

Table 4
Selected bond distances (Å) and bond angles (°) for **5**

Fe–C(Cp)	2.022(9)–2.048(8)
C(Cp)–C(CH_2O)	1.486(12), 1.498(11)
C(CH_2O)–O(CH_2O)	1.445(10), 1.441(9)
Fe–C(Cp)–C(CH_2O)	127.4(6), 126.8(6)
C(Cp)–C(CH_2O)–O(CH_2O)	111.9(6), 111.7(6)
C(CH_2O)–O–C(CH_2O)	113.7(9) [a], 112.8(9)[b]
Fe···Fe	7.398(2)[a], 7.478(2)[b]

[a] 3/2−*x*, *y*,1/2−*z*.
[b] 1/2−*x*, *y*, 1/2−*z*.

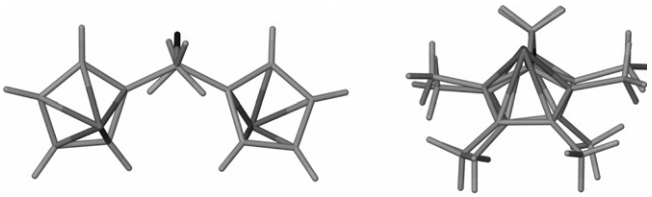


Fig. 5. Projection along a vector comprising the two carbons of the C–O–C linker: left in **5** right in di(octamethylferrocenylmethyl) ether [26].

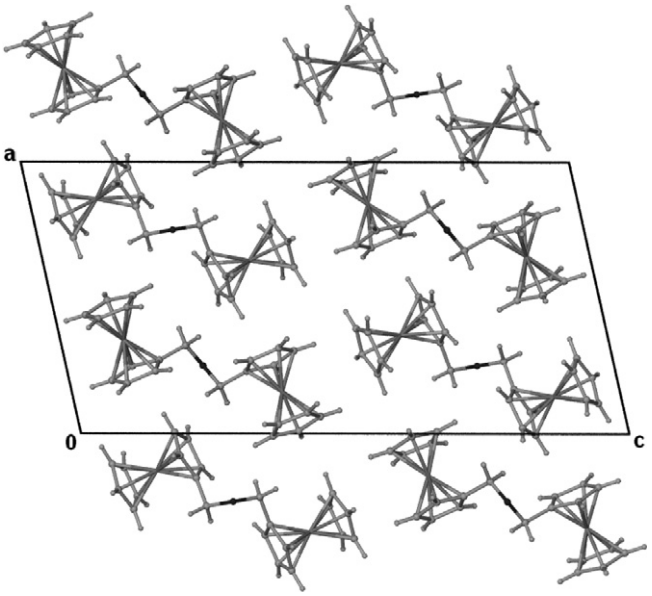


Fig. 6. Packing diagram of **5** as viewed down the *b*-axis.

the twol linked Cp rings (Fig. 4). Two angles of 33.8(4)° and 33.1(2)° are measured for **5** whilst the interplanar angle for di(octamethylferrocenylmethyl) ether is 82.4°. It is also interesting to point out that the ferrocenyl moieties in **5** are staggered when a projection along a vector comprising the two carbons of the C–O–C linker is drawn, whereas they are quasi eclipsed in di(octamethylferrocenylmethyl) ether (Fig. 5). Furthermore, the distance between the Fe centres is less in **5** (7.398–7.478 Å) than in di(octamethylferrocenylmethyl) ether (8.644 Å). A packing diagram of **5** (Fig. 6) shows the alternating perpendicular and parallel orientation of the ferrocenyl moieties within the crystal.

4. Conclusion

Two known compounds, namely hydroxymethylferrocene (**4**) and bis(ferrocenylmethyl) ether (**5**), have been isolated during the synthesis of 1-(ferrocenemethyl)-4,7,10-(triformyl)-1,4,7,10-tetraazacyclododecane (**3**). The X-ray structures of **4** and **5** were determined and, in the case of **4**, an interesting hydrogen-bonded helicoidal chain arrangement of hydroxymethylferrocene units was observed. The O···O separation was found to be significantly shorter than in similar examples previously reported.

The isolation of **3** and **4** during this reaction performed in water is a useful indication of the synthetic behaviour of **1** for (bio)organometallic chemists in search of an alternative to ferrocenecarboxylic acid for the attachment of the ferrocenyl moiety to (bio)molecules.

5. Supplementary material

CCDC 641127 and 641128 contain the supplementary crystallographic data for **4** and **5**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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