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Preliminary Communication

Unexpected formation of novel benzofuranyl-substituted ferrocenes by action of *p*-benzoquinone on 1,1′-bis-acylferrocene

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Abstract

A Michael addition was found to occur between 1,1′-bis-(undecanoyl)ferrocene and *p*-benzoquinone in the presence of tetrafluoroboric acid leading to the formation of benzofuranyl ferrocene derivatives. Under similar conditions, the fluoroalkyl 1,1′-bis[11-(*F*-octyl)-undecanoyl]ferrocene and the acetylferrocene analogue are oxidized to their respective ferricinium ions.

Key words: Ferrocene; Benzoquinone; Perfluoroalkyl; Oxidation

Our goal is to develop amphiphilic analogues of metal complexes known to have a biological and/or a therapeutic activity. We therefore became interested in ferrocene and ferricinium derivatives, a class of organometallic potent antitumour agents [1] and, owing to their exceptional electrochemical behaviour, reliable mediators for several redox reactions [2]. The functionalization of the cyclopentadienyl ligands by long alkyl or by highly perfluoroalkylated side-chains is expected to increase the amphiphilic, hydrophobic and/or fluorophilic character of these complexes and therefore to facilitate their incorporation into drug carrier and delivery systems such as liposomes, or into injectable fluorocarbon emulsions to be used simultaneously as drug and artificial oxygen carriers.

During our attempts to prepare amphiphilic ferricinium salts by chemical oxidation of the corresponding ferrocenes, we found that an unexpected reaction occurs when the ferrocene derivative (**1a**) bears hydrogenated acyl side-chains. Indeed, when we tried to oxidize **1a** using *p*-benzoquinone in the presence of HBF_4 [3] (see Scheme 1), a complex mixture was formed from which we could isolate, reproducibly, the novel ferrocene derivatives **2a** and **3a** which account for 25% of the starting material along with unreacted **1a** (30%).

Both compounds **2a** and **3a** contain a benzofuranyl moiety in one of the side-chains connected to the cyclopentadienyl ring. They differ in the presence of a hydroxyl for **2a** and of an ethoxy group for **3a** on the benzene ring. No evidence for the formation of the expected ferricinium **4a** could be found: this compound either does not form or is most unstable. This behaviour contrasts strongly with that observed with the fluoroalkyl analogue **1b** and the acetylferrocene **1c**: indeed, the sole reaction which took place under the same conditions with **1b** and **1c**, was the expected conversion into their respective ferricinium salt **4b** (75%; the balance was unreacted **1b**) and **4c** (almost quantitative). Formation of the fluoroalkyl benzofuranyl (**2b** or **3b**) and benzofuranyl analogues (**2c** or **3c**) of **2a** or **3a** did not occur.

Thus, a solution of 0.50 g (0.96 mmol) of 1,1′-bis(undecanoyl)ferrocene **1a** in 15 ml of dry chloroform was

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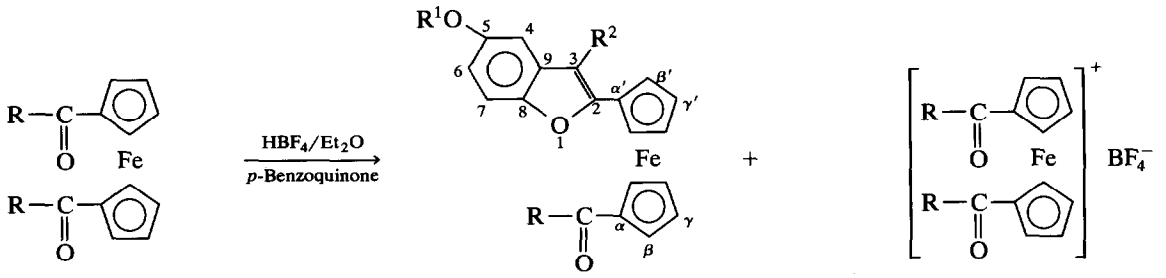


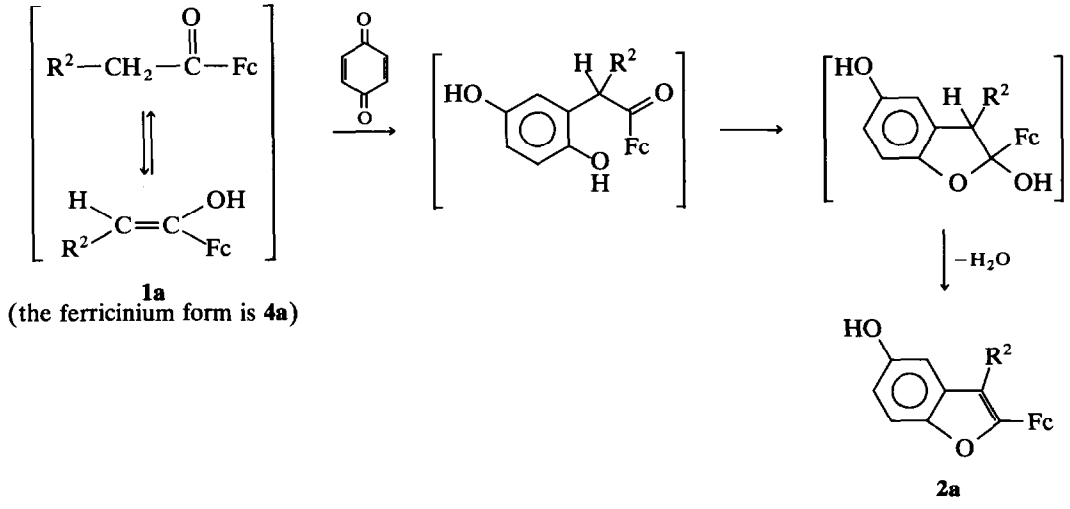
1a: R = $CH_3(CH_2)_9$
1b: R = $C_8F_{17}(CH_2)_{10}$
1c: R = CH_3

2a: R^1 = H; **3a**: R^1 = Et; R^2 = $CH_3(CH_2)_8$
2b, 3b: R^2 = $C_8F_{17}(CH_2)_9$ } not detected
2c, 3c: R^2 = H

4a not detected
4b (75%)
4c (100%)

Scheme 1.

0022-328X/94/$7.00
SSDI 0022-328X(93)24174-4

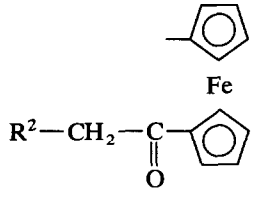


1a
(the ferricinium form is **4a**)

2a

$R^2 = CH_3(CH_2)_8$

Fc =



Scheme 2.

added dropwise under argon to a mixture of 0.21 g (1.94 mmol) of *p*-benzoquinone in 0.63 ml (3.87 mmol) of a 54% $HBF_4 \cdot Et_2O$ solution at −10°C. The resulting dark-brown solution was then stirred for 1 h at room temperature. Filtration [4*] and careful silica gel chromatography led to the isolation of **3a** as a red-orange oil (30 mg, ~ 5%), unreacted starting ferrocene (150 mg, 30%) and **2a** as red-orange crystals (120 mg, 20%). The same procedure when applied to **1b** or to the acetylferrocene **1c** afforded the ferricinium salts **4b** and **4c**, respectively, which precipitate from the reaction mixture [5*].

The elemental and spectral data (IR, ^1H, ^{13}C and ^{13}C-DEPT NMR) are fully consistent with the proposed structures for **2a** and **3a** [6*]. Thus, the same characteristic ^1H and ^{13}C patterns of the $CH_3(CH_2)_9$-$C(O)$–C_5H_4 (Cp) moiety found for **1a** [7*] are also found for **2a**: *e.g.* (i) a triplet for the $CH_2C(O)$ hydrogen atoms at 2.65 ppm, (ii) an A_2X_2 system for the Cp protons at 4.45 and 4.75 ppm and three ^{13}C lines at 80.0, 73.5 and 70.5 ppm for the Cα, Cβ and Cγ carbons, respectively, and (iii) a resonance at 205.1 ppm for the carbonyl carbon. Apart from these ^1H and ^{13}C NMR patterns, the ^1H NMR spectrum for **2a** also shows (i) a new triplet at 2.52 ppm consistent with the presence of CH_2 protons connected to a double bound, and (ii) a new A_2X_2 system located at 4.39 and 4.78 ppm. Three new ^{13}C lines at 77.9, 70.6 and 68.0 ppm for the Cα', Cβ' and Cγ' carbon atoms indicate a Cp ring bearing one substituent which is different from that of the other Cp ring. That this substituent is the benzofuranyl moiety as shown in **2a** is definitively confirmed by the presence of (i) three aromatic proton resonances in the ^1H NMR spectrum of **2a** – two doublets at 6.91 and 7.23 ppm corresponding respectively to H4 and H7, and one doublet of doublets at 6.78 ppm for H6 and (ii) three aromatic CH carbon resonances (104.2, 110.9 and 112.2 ppm) and five quaternary aromatic-type carbon resonances (151.8, 150.1 and 148.8 ppm for C2, C5 and C8; 131.3 and 115.8 ppm for C3 and C9) in the ^{13}C-DEPT NMR spectrum. These NMR data measured for the benzofuranyl moiety in **2a** are further consistent with those of other substituted benzofurans [8]. Compound **3a** displays nearly the same ^1H and ^{13}C NMR patterns as **2a**. However, (i) the absence of a ν(OH) vibration and OH resonance in the IR and ^1H NMR spectra of **3a**, (ii) the presence of the characteristic resonances of an OEt group in the ^1H and ^{13}C NMR spectra of **3a** and (iii) the downfield shift of the ^{13}C resonance of the C5

* Reference number with asterisk indicates a note in the list of references.

carbon (155.2 ppm) with respect to that measured for **2a** (151.7 ppm) confirms that the hydroxyl in **2a** has been replaced by an ethoxy group in **3a**.

Compounds **2a** and **3a** are most likely formed as a result of a Michael addition of ketone **1a** (in its enolic form) to *p*-benzoquinone [9], as depicted in Scheme 2. This Michael addition could occur either to the ferrocene **1a** or to its ferricinium salt **4a**, which would then be formed *in situ* in a first step of the reaction mechanism: the intermediate formation of **4a** cannot be excluded in view of the reaction products in the case of the fluorinated and unsubstituted analogues **1b** and **1c** of **1a**. Due to its higher lipophilic character as compared to that of **4b** and **4c**, **4a** is likely to be much more soluble in the reaction medium and consequently more reactive towards benzoquinone than the almost insoluble **4b** or the unsubstituted **4c**. The mechanism of formation of the ethoxy derivative **3a** is currently not understood [10*].

To our knowledge, **2a** and **3a** constitute the first examples of a benzofuranyl substituted organometallic complex. Furthermore, there have been only few reports, in "organic chemistry", on Michael addition of enolates derived from aldehydes or ketones on quinones [9]. The complexity of this reaction and the lack of regioselectivity has limited its potential uses for the preparation of benzofurans which could be obtained in high yields only when silyl enol ethers were used [9]. Further work is now needed in order to understand fully the mechanisms of formation of **2a** and **3a** and the role of the acyl side-chains in **1** in directing the course of the reaction of **1** with *p*-benzoquinone.

References and notes

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4 Filtration led to the separation of a black powder whose IR spectrum is identical to that of the product resulting from the action of HBF_4 on *p*-benzoquinone.

5 **4b** and **4c** are insoluble in most common organic solvents. IR (Nujol, cm^{-1}): **4b** 3120 (=CH); 1703 (CO); 1200 (CF); 1072, 1050 (BF_4^-); **4c** 1687 (CO).

6 **2a** ($C_{38}H_{52}FeO_3$): Anal. Calc.: C 74.50, H 8.55. Found: 74.30, H 8.53. IR (KBr, cm^{-1}): 1650 (C=O); 1610 (C=C); 3100 (=CH); 3360 (OH). ^1H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, $^3J_{H,H}$ = 6.5 Hz, 6H, CH_3); 1.26 (br s, 26H, $(CH_2)_nCH_3$); 1.57 (m, 4H, $COCH_2CH_2$ and $=CCH_2CH_2$); 2.56 (t, $^3J_{H,H}$ = 7.5 Hz, 2H, $=CCH_2$); 2.69 (t, $^3J_{H,H}$ = 7.5 Hz, 2H, $O=CCH_2$); 4.39 (t, $^3J_{H,H}$ = 1.9 Hz, 2H, Hβ'); 4.45 (t, $^3J_{H,H}$ = 1.9 Hz, 2H, Hβ); 4.75 (t, 2H, Hγ); 4.78 (t, 2H, Hγ'); 5.78 (br s, 1H, OH); 6.82 (dd', $^3J_{H6H7}$ = 8.7 Hz, $^4J_{H6H4}$ = 2.5 Hz, 1H, H6); 6.95 (d, $^4J_{H6H4}$ = 2.5 Hz, 1H, H4); 7.27 (d, $^3J_{H6H7}$ = 8.7 Hz, 1H, H7). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.1 (s, CH_3); 22.6, 24.0, 24.4, 29.3, 29.4, 29.45, 29.5, 29.55, 29.8, 31.9 (all s, $(CH_2)_8$); 39.8 (s, $CH_2C=O$); 68.0 (s, Cβ'); 70.5; 70.6 (s, Cγ,γ'); 73.5 (s, Cβ); 77.9 (s, Cα'); 80.0 (s, Cα); 104.2, 110.9, 112.2 (s, C4,6,7); 115.8 (s, C3); 131.3 (s, C9); 148.8, 150.1 (s, C2,8); 151.7 (s, C5); 205.1 (s, CO).
3a ($C_{40}H_{56}FeO_3$): IR (KBr, cm^{-1}): 1675 (C=O); 1610 (C=C); 3100 (=CH). ^1H NMR (200 MHz, $CDCl_3$): δ 0.86, 0.87 (both t, $^3J_{H,H}$ = 7 Hz, 3H, 3H, CH_3); 1.27 (br s, 26H, $(CH_2)_nCH_3$); 1.47 (t, $^3J_{H,H}$ = 7 Hz, 3H, OCH_2CH_3); 1.57 (m, 4H, $COCH_2CH_2$, $=CCH_2CH_2$); 2.51 (t, $^3J_{H,H}$ = 7.5 Hz, 2H, $=CCH_2$); 2.71 (t, $^3J_{H,H}$ = 7.6 Hz, 2H, $O=CCH_2$); 4.10 (q, $^3J_{H,H}$ = 7 Hz, 2H, OCH_2); 4.39 (t, $^3J_{H,H}$ = 1.9 Hz, 2H, Hβ'); 4.43 (t, $^3J_{H,H}$ = 1.9 Hz, 2H, Hβ); 4.75 (t, 2H, Hγ); 4.78 (t, 2H, Hγ'); 6.87 (dd', $^3J_{H6H7}$ = 8.7 Hz, $^4J_{H6H4}$ = 2.5 Hz, 1H, H6); 6.94 (d', $^4J_{H6H4}$ = 2.5 Hz, 1H, H4); 7.32 (d, $^3J_{H6H7}$ = 8.7 Hz, 1H, H7). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.1, 14.2 (s, CH_3); 15.1 (s, OCH_2CH_3); 22.0 to 32.0 (all s, $(CH_2)_8$); 39.9 (s, $CH_2C=O$); 64.4 (s, CH_2O); 68.1 (s, Cβ'); 70.5, 70.6 (s, Cγ,γ'); 73.3 (s, Cβ); 77.8 (s, Cα'); 80.2 (s, Cα); 103.0, 111.0, 112.5 (s, C4,6,7); 116.0 (s, C3); 131.1 (s, C9); 149.0, 150.1 (s, C2,8); 155.2 (s, C5); 204.3 (s, CO).

7 **1a**: IR (KBr, cm^{-1}): 1680 (CO); 3100 (=CH). ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (t, $^3J_{H,H}$ = 6.5 Hz, 6H, CH_3); 1.25 (br s, 28H, $(CH_2)_nCH_3$); 1.66 (m, 4H, $COCH_2CH_2$); 2.62 (t, $^3J_{H,H}$ = 7.5 Hz, 4H, $COCH_2$); 4.45 (t, $^3J_{H,H}$ = 1.9 Hz, 4H, Hβ); 4.75 (t, $^3J_{H,H}$ = 1.9 Hz, 2H, Hγ). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.1 (s, CH_3); 22.8, 24.5, 29.5, 29.4, 29.6, 29.7, 29.8, 32.0 (all s, $(CH_2)_8$); 39.8 (s, $CH_2C=O$); 70.7 (s, Cγ); 73.5 (s, Cβ); 80.6 (s, Cα); 203.8 (s, CO).

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10 Neither the chloroform we used (it was free from ethanol and was washed several times with water, then dried over $MgSO_4$ and finally distilled over P_2O_5) nor the work-up procedure (as shown by thin-layer chromatography, **3a** is already present in the reaction medium) can account for the formation of the ethoxy derivative **3a**. The ethoxy group in **3a** most likely arises from a side-reaction which involves the other solvent we used, diethyl ether.