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Synthesis and Redox Properties of Ferrocene Derivatives containing an Oleyl Group†

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The synthesis and electrochemical characteristics of (*Z*)-octadec-9-enoylferrocene, (*Z*)-octadecen-9-ylferrocene and ferrocenylmethyl (*Z*)-octadec-9-enoate, potential redox mediators in lipid-based biosensors, are reported.

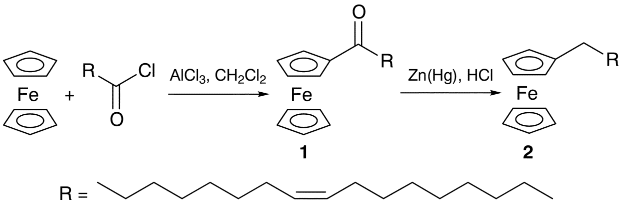
An important application of ferrocene (Fc) and its derivatives is in the construction of electrochemical biosensors.[1] However, a large share of the Fc-based bioelectrodes undergo rather fast deterioration through the leakage of the low molecular weight ferricinium ions (Fc^+). On the other hand, there is evidence[1g] that this problem can be overcome when the bioactive layer on the electrode surface is formed by self-assembling of the amphiphilic Fc derivatives.

Our previous studies[2] have demonstrated that the *Pn*3*m* cubic liquid-crystalline phase of aqueous glyceryl monooleate is suitable for the bioactive layer formation in biosensors where the electrochemically inactive lipid phase serves as a stable matrix for enzymes. Since the continuous lipid bilayer is distinctive of the *Pn*3*m* cubic phase,[3] it seems possible to transform this matrix into the redox active one by the appropriate chemical modification of the headgroup in the lipid molecule.

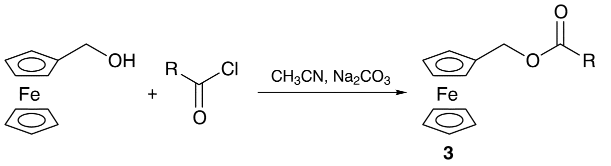
Considering the foregoing, we report on the synthesis of Fc derivatives containing (*Z*)-octadec-9-enoyl and related substituents. In addition, the redox properties and the diffusion coefficients of these compounds in organic solvents were determined and compared with those of Fc, ferrocenylmethanol (FcM) and ferrocenemonocarboxylic acid (FcMA).

Results and Discussion

The Fc derivatives were synthesized starting with a direct acylation of Fc (Scheme 1). Investigation of acylation has shown similarities between Fc and benzene[4] confirming the compound's aromatic character although its resistance to alkylation shows marked difference from benzene. Acylation of Fc was effected with (*Z*)-octadec-9-enoyl (oleoyl) chloride and aluminium chloride in a usual Friedel–Crafts manner giving the desired product **1** in a high yield. The subsequent reduction of carbonyl group with zinc amalgam in strong aqueous acids is referred to as the Clemmensen reduction.[5] The reaction medium usually consisted of 20–30% hydrochloric acid, and a large excess of zinc metal has to be employed. The zinc was normally amalgamated by shaking with 5–10% mercury(II) chloride solution immediately before using. The reaction proceeded rather smoothly to give **2** in a high yield.



Scheme 1



Scheme 2

Ferrocenylmethyl(*Z*)-octadec-9-enoate **3** (Scheme 2) was prepared by esterification of FcM with oleoyl chloride in the presence of solid sodium carbonate. The reaction was controlled by TLC and gave an oily product with a moderate yield after repeated purification by column chromatography.

Redox conversion of compounds **1–3**, Fc, FcM and FcMA was studied by cyclic voltammetry (CV) on the gold electrode in organic solvents containing 0.1 M $NaClO_4$.

The CV curves of the new compounds exhibit clearly expressed oxidation and reduction peaks of the headgroup Fc^+/Fc^0 redox couple. At the same potential (E) scan rate (ν), the separation of the anodic and cathodic peak potentials ($\Delta E_p = E_{pa} - E_{pc}$) depends on the solvent ($CH_3CN \leqslant$ MeOH $\leqslant$ DMSO $\approx$ DMF $\leqslant$ EtOH $<$ Pr^nOH $<$ Bu^nOH) and on the compound structure (**2** < **1** < **3**). The ΔE_p value of all compounds is higher than 60 mV for all sweep rates employed (0.02–0.2 $V\,s^{-1}$). This result indicates that the redox conversion is electrochemically quasi-reversible.[6] Besides, since the peak-currents of the anodic and cathodic processes for the compounds under discussion are linearly dependent on $\nu^{1/2}$, the heterogeneous redox process is determined by molecular diffusion.[6]

The formal potentials ($E^{\circ\prime}$) of the redox couples in the above-mentioned solvents, determined using the relationship $(E_{pa}+E_{pc})/2$, are given in Table 1. From the data obtained it can be seen that $E^{\circ\prime}$ increases in the following order: **2** < FcM < Fc ⩽ **3** < FcMA < **1**. Moreover, the $E^{\circ\prime}$ values linearly increase (correlation coefficients are in the range of 0.981–0.995) with an increase in the Hammet σ_p con-

Table 1 Formal redox potentials (in mV *vs.* SCE) of Fc and its derivatives obtained at the Au electrode in the solutions containing 0.1 M $NaClO_4$

	$E^{\circ\prime}$ mV *vs.* SCE					
Solvent (ε)	Fc	FcM	FcMA	**1**	**2**	**3**
DMSO (46.7)	450	426	651	670	401	456
CH_3CN (37.5)	335	319	552	576	270	320
DMF (36.7)	486	451	—	—	421	496
MeOH (32.6)	364	364	595	619	306	386
EtOH (24.3)	389	374	608	648	339	408
Pr^nOH (20.7)	419	408	649	662	368	444
Bu^nOH (17.1)	443	421	647	657	374	431

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Table 2 Diffusion coefficients and heterogeneous electron transfer rate constants of Fc and its derivatives in acetonitrile at 25 °C

Compound	$D/10^{-6}$ cm^2 s^{-1}	$k_s/10^{-3}$ cm s^{-1}
Fc	24[10]	9.3 ± 0.4
FcM	19.4 ± 0.1	8.6 ± 1.8
FcMA	11[10]	5.5 ± 0.4
1	6.3 ± 0.7	7.0 ± 0.6
2	7.7 ± 1.0	11.1 ± 1.7
3	7.6 ± 0.8	4.1 ± 0.4

stant of the substituent [σ_p: –0.17 (Me) < –0.01 (CH_2OH) < 0 (H) < 0.05 (CH_2CO_2Me) < 0.47 (CO_2H) < 0.50 (COMe)]. Interestingly, the same trend has been observed in the case of Fc derivatives containing palmitoyl group.[7] These results indicate that the decrease in the electron density in the Fc moiety makes the substance more resistant towards oxidation. The sensitivity of $E^{\circ\prime}$ to the influence of substituent, expressed by the slope of $E^{\circ\prime}$–σ_p dependence, is practically independent on the solvent.

In general, a clearly defined dependence of $E^{\circ\prime}$ on the solvent relative permittivity (ε) was not observed in this study. However, in the case of protic solvents, the $E^{\circ\prime}$ values become more positive as ε increases. For aprotic solvents, this shift is observed in accordance with the solvent order CH_3CN < DMSO < DMF, which is the same as in the case of decamethylferrocene.[8]

The diffusion coefficients (D) were determined in acetonitrile chronamperometrically (E step from 0.0–0.7 V for FcM, **2** and **3**, and from 0.3–0.8 V for compound **1**) by applying the Cottrell equation.[6] The heterogeneous rate constants (k_s) of the quasi-reversible redox conversion were calculated by the Nicholson method.[9] Both constants are given in Table 2. It can be seen that D of the novel compounds are about 2–3 times lower than those of the model ferrocenes, but the k_s values of compounds **1** and **2** are almost the same as in the case of unsubstituted Fc.

Experimental

The IR spectra were measured as liquid films on a Specord 75 IR spectrophotometer (Carl Zeiss, Germany). The ^{1}H and ^{13}C NMR spectra were recorded on a BS-587A 80 MHz Tesla spectrometer. The UV–VIS spectra were recorded on a Specord UV–VIS spectrophotometer (Carl Zeiss, Germany) using spectral grade *n*-heptane. Cyclic voltammograms were recorded with a PA-3 polarograph (Laboratorni Pristroje, Czechoslovakia). Chronoamperometric measurements were carried out using a home-made potentiostat and an A-1600B signal analyzer (Hitachi, Japan). All electrochemical experiments were performed in a three-electrode circuit using a glass cell (10 cm^3) thermostatted at 25 °C. A saturated calomel electrode (SCE) was used as a reference. A platinum plate (0.75 cm^2) served as the auxiliary electrode. The working electrode was a gold disc (0.189 cm^2) soldered in a glass tube. All electrochemical measurements were conducted in quiescent, argon-purged (30 min) solutions containing 0.1 M $NaClO_4$ as a supporting electrolyte. Fc, FcM and FcMA were purchased from Aldrich and were used without further purification. All solvents were HPLC grade. TLC was carried out on Silufol aluminium sheets coated with silica gel, and silica gel L 100/160 (Lachema, Czech Republic) was used for column chromatography.

(*Z*)-*Octadec*-9-*enoylferrocene* (**1**).—A mixture of 2 g (10.8 mmol) of Fc and 1.44 g (10.8 mmol) of aluminium chloride in 20 ml of dry methylene dichloride was cooled in an ice-bath, and 3.56 ml (10.8 mmol) of oleyl chloride in 5 ml of dry methylene dichloride was added during 1 h. The reaction mixture was stirred for 2 h at 40 °C and then poured into ice. After the organic phase had been separated and washed, methylene dichloride was removed under reduced pressure and the residue was chromatographed on a silica gel column to give 3.5 g (73%) of oil; ν_{max}/cm^{-1} 3098, 3008, 2928, 2858, 1672; UV–VIS, λ_{max}/nm (ε_{max}, dm^3 mol^{-1} cm^{-1}) 321 (1300), 357sh (≈640), 451 (370); δ_H (CCl_4, HMDSO) 0.83 (t, 3 H, CH_3), 1.2 (m, 22 H, CH_2), 1.95 (m, 4 H, CH_2C=), 2.52 (t, 2 H, CH_2CO), 4.04 (s, 5 H, C_5H_5), 4.44 (d, 4 H, C_5H_4CO), 5.21 (m, 2 H, CH=); δ_C ($CDCl_3$, TMS) 13.9 (CH_3), 22.7, 24.6, 27.3, 29.3, 29.7, 39.7 (all CH_2), 53.1 (CO*C*H_2), 60.1, 69.3, 69.7, 72.0 (C_5H_4 and C_5H_5), 129.6, 130.4 (CH=CH) (Found: C, 73.85; H, 9.08. $C_{28}H_{42}FeO$ requires C, 74.65; H, 9.39%).

(*Z*)-*Octadec*-9-*enylferrocene* (**2**).—A solution of 3.5 g (7.7 mmol) of **1** in 10 ml of an ethanol and dioxane mixture was added dropwise to a refluxing mixture of concentrated hydrochloric acid (7 ml) and amalgamated zinc (from 70–100 mmol of granulated zinc) over a period of 1 h. After refluxing for 3–4 h, the mixture was cooled, filtered and extracted with chloroform. The orange oil was chromatographed on a silica gel column using chloroform as eluent which afforded, after evaporation, 2.9 g (88%) of oil; ν_{max} cm^{-1} 3098, 3010, 2928, 2858, 1464; UV–VIS, λ_{max} nm (ε_{max} dm^3 mol^{-1} cm^{-1}): 325sh (≈240), 435 (120); δ_H (CCl_4, HMDSO) 0.83 (t, 3 H, CH_3), 1.2 (m, 24 H, CH_2), 1.92–2.23 (m, 4 H, CH_2C=), 2.73–2.87 (m, 2 H, $CH_2C_5H_4$), 3.88 (d, 9 H, $C_5H_4FeC_5H_5$), 5.21 (m, 2 H, CH=). δ_C ($CDCl_3$, TMS) 14.1 (CH_3), 22.7, 25.7, 27.3, 29.4, 29.6, 29.7, 29.9, 31.2, 32.0 (all CH_2), 67.0, 68.1, 68.4 (C_5H_4 and C_5H_5), 127.9, 129.7, 129.9 (*ipso*-C_5H_4 and CH=CH) (Found: C, 75.08; H, 10.42. $C_{28}H_{44}Fe$ requires C, 74.05; H, 10.16).

Ferrocenylmethyl (*Z*)-*octadec*-9-*enoate* (**3**).—To a 5 ml solution of 100 mg (0.5 mmol) FcM and 117 mg (0.55 mmol) sodium carbonate in acetonitrile was added 0.18 ml (0.55 mmol) of oleoyl chloride. After stirring for 2 h at room temperature, acetonitrile was removed under reduced pressure, and the residue was dissolved in chloroform, washed with water and chromatographed repeatedly on a silica gel column to give 90 mg (41%) of oily product; ν_{max} cm^{-1}: 3098, 3008, 2933, 2860, 1740; UV–VIS, λ_{max} nm (ε_{max} dm^3 mol^{-1} cm^{-1}) 324 (150), 440 (180); δ_H ($CDCl_3$, HMDSO) 0.88 (m, 3 H, CH_3), 1.26 (m, 22 H, CH_2), 1.99 (m, 4 H, CH_2C=), 2.34 (m, 2 H, CH_2CO), 3.44–3.51 (m, 2 H, $CH_2C_5H_4$), 4.12–4.24 (m, 9 H, $C_5H_4FeC_5H_5$), 5.34 (m, 2 H, CH=); δ_C ($CDCl_3$, TMS) 10.7 (CH_3), 13.8, 22.5, 22.7, 23.6, 27.0, 29.1, 29.3, 29.5, 29.6, 30.2, 31.7 (all CH_2), 38.6 (CO*C*H_2), 68.0, 68.2, 68.5, 69.2 (C_5H_4 and C_5H_5), 128.6, 128.8, 129.8, 130.6 (*ipso*-C_5H_4 and CH=CH) (Found: C, 69.23; H, 7.85. $C_{29}H_{44}O_2Fe \cdot H_2O$ requires C, 69.87; H, 9.30).

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