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Arylferrocenylmethanols: a new family of ferrocenes to be used as mediators in biosensors

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Arylferrocenylphenylmethanols, ArFcPhCOH, were prepared from the corresponding aryl ferrocenyl ketones, ArCOFc, prepared by Friedel–Crafts acylation. pK_a values of ArCOFc were determined in sulfuric acid. The electrochemical properties of ArFcPhCOH were investigated. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: ferrocenyl alcohols; ferrocenyl ketones; cyclic voltammetry; electrochemical sensors

INTRODUCTION

Ferrocene derivatives have found a number of applications in organic synthesis, as well as in materials science.[1] In the last 10 years the ferrocene/ferricenium cation system has found an interesting field of application as a mediator in biosensors. A biosensor is a system of two transducers, one of which (biochemical) provides selectivity and the other (physical) the signal.[2] A good mediator must fulfill a number of requisites:[3] it should be absorbed on the surface of the electrode, be retained on it, react rapidly with the reduced enzyme, be stable in the reduced and oxidized forms, be non-reactive with oxygen, and, finally, it must be non-toxic. Moreover, the regeneration of the oxidized form should occur at low voltage and be pH independent. The first successful enzyme electrode used 1,1′-dimethylferrocene absorbed on a graphite electrode, where glucose oxidase was chemically immobilized.[4] Several reports followed, among which was the amperometric enzyme electrode for the determination of hypoxanthine in fish flesh, which was based on a hydroxymethylferrocene-modified carbon paste electrode,[5] and the study of the kinetics of the reaction between ferrocenecarboxylic acid and glucose oxidase.[6] Although the ferrocene system represents a good choice for applications *in vivo*, because of its relatively low toxicity, ferrocenes-mediated enzyme electrodes suffer some drawbacks, such as relatively short lifetimes and loss of ferrocene, besides enzyme loss or denaturation.[7] Thus, in an attempt to improve the characteristics of biosensors, ferrocene-modified enzymes[8–12] and ferrocene-containing polymers were used.[13–25] Co-immobilization of both the enzyme and the ferrocene using various techniques was also used.[2,26–29]

Electropolymerization is a particularly suitable technique for preventing interferences and electrode fouling in biosensors.[30–41] Ferrocenes were used in biosensors of this type either by electropolymerizing a suitably substituted ferrocene,[42–50] by absorbing them on the electropolymerized film,[51–56] or by encapsulating them in polymers or in other matrices.[57–71]

We wish to report here the synthesis and characterization of a new family of arylferrocenylphenylmethanols, prepared to be adsorbed on electropolymerized materials, since their bulky and hydrophobic groups might ensure a good absorption of both the oxidized and reduced forms, their oxidation potentials might be finely tuned by changing the aryl substituent, and the tertiary alcoholic function does not interfere with oxidation of iron(II).

RESULTS AND DISCUSSION

Preparation of the substrates

A number of new arylferrocenylphenylmethanols have been prepared from aryl ferrocenyl ketones (according to Scheme 1) and characterized. Attempts to prepare ferrocenyl *p*-nitrophenyl and ferrocenyl *m*-nitrophenyl ketones failed, yielding only oxidation of ferrocene, as already observed.[72] Aryl ferrocenyl ketones, and the alcohols therefrom, pure enough for quantitative measurements (96–99% by gas chromatography (GC)) were obtained by column chromatography.

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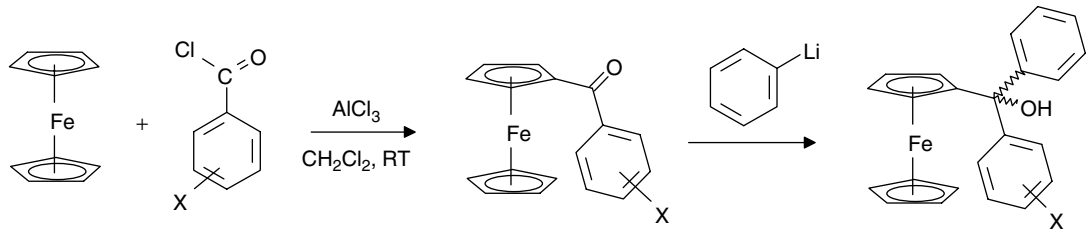


X = H, 4-OMe, 3-Me, 4-Me, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F

Scheme 1. Preparation of arylferrocenylphenylmethanols.

The mass spectra of both alcohols and ketones showed the molecular ion, with one exception, i.e. the 4-methoxy-substituted alcohol. The fragmentation pattern of aryl ferrocenyl ketones led to typical $FcCO^+$, Fc^+, and $CpFe^+$ fragments. Arylferrocenylphenylmethanols generally showed loss of Cp and Ph moieties.

Basicity of aryl ferrocenyl ketones

The pK_a values for the conjugate acids of aryl ferrocenyl ketones were determined on the basis of their spectral change in solutions of 45–70% H_2SO_4, at several wavelengths in the range 550–580 nm. The results are reported in Table 1. In order to evaluate the electronic effects of the substituents in the aryl ring on the basicity, empirical linear free energy relationships were considered. The best correlation was obtained with σ^+ values[73] (Fig. 1), in keeping with the formation of a cationic species. In fact, when Hammett σ values were used as the substituent constants, the values relative to *p*-OMe and *p*-Me groups lay largely out of the straight line generated by the other substituents. The reaction constant ρ is positive, as expected for K_a values. The value of ρ (0.66) is indicative of a scarce sensitivity of acidity on the presence of substituents on the aromatic ring. This fact has to be attributed to the leveling effect of the strongly electron-donating ferrocenyl group, which accounts for most of the stabilization of the protonated ketone.

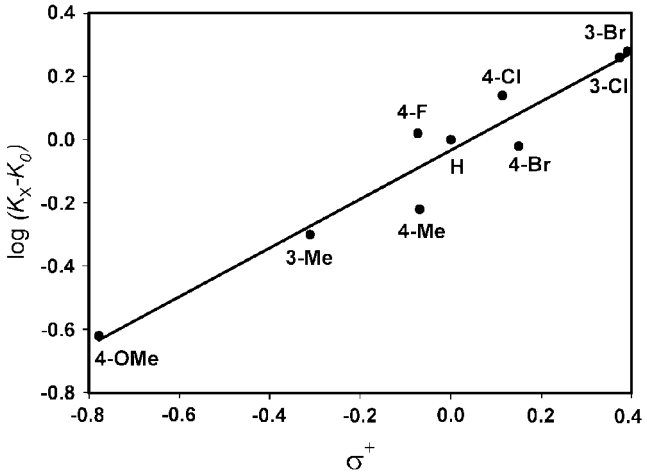
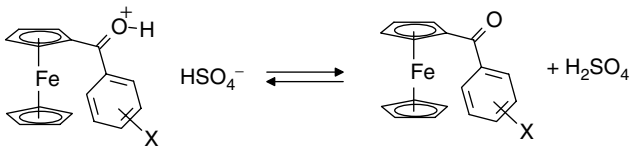


Figure 1. Linear free-energy relationship for the acidity of protonated ketones, ArFcC═OH^+.

Table 1. pK_a values of aryl ferrocenyl ketones



X	10^4[ketone] (M)	H_2SO_4 (%)	pK_a
H	2.74	55–60	−3.32 ± 0.09
4-OMe	3.34	45–55	−2.7 ± 0.2
4-Me	4.14	55–60	−3.02 ± 0.02
3-Me	4.62	55–60	−3.10 ± 0.05
4-Br	3.20	55–60	−3.3 ± 0.1
3-Br	3.39	55–60	−3.60 ± 0.03
4-Cl	3.30	55–60	−3.46 ± 0.03
3-Cl	4.15	55–60	−3.58 ± 0.01
4-F	2.97	55–60	−3.34 ± 0.03

It was not possible to determine the pK_{R^+} values of arylferrocenylphenylmethanols following Deno's method,[74] because the alcohols were practically insoluble in H_2SO_4 solutions at concentrations too low to have appreciable amounts of protonation and soluble only when completely protonated (*ca* 40% H_2SO_4).

Electrochemical behavior

Arylferrocenylphenylmethanols showed reversible voltammograms in *N*,*N*-dimethylformamide (DMF) solution, with oxidation potentials independent of the electrode material and the scan rate (see Experimental). Redox potentials are reported in Table 2 and an example is shown in Fig. 2.

An attempt to correlate redox potentials with substituent rate constants (Hammett σ) showed no linear relationship (Fig. 3).

Two separate trends were observed for electron-donating and electron-withdrawing substituents (the dotted lines are a help to detect the trend). In both series, the oxidation is

Table 2. Redox potentials of arylferrocenylphenylmethanols, $XC_6H_4FcPhCOH$

X	E°, (V)
H	0.516 ± 0.001
4-OMe	0.485 ± 0.002
3-Me	0.509 ± 0.003
4-Me	0.505 ± 0.002
4-F	0.471 ± 0.002
3-Cl	0.507 ± 0.002
4-Cl	0.496 ± 0.001
3-Br	0.517 ± 0.002
4-Br	0.515 ± 0.003

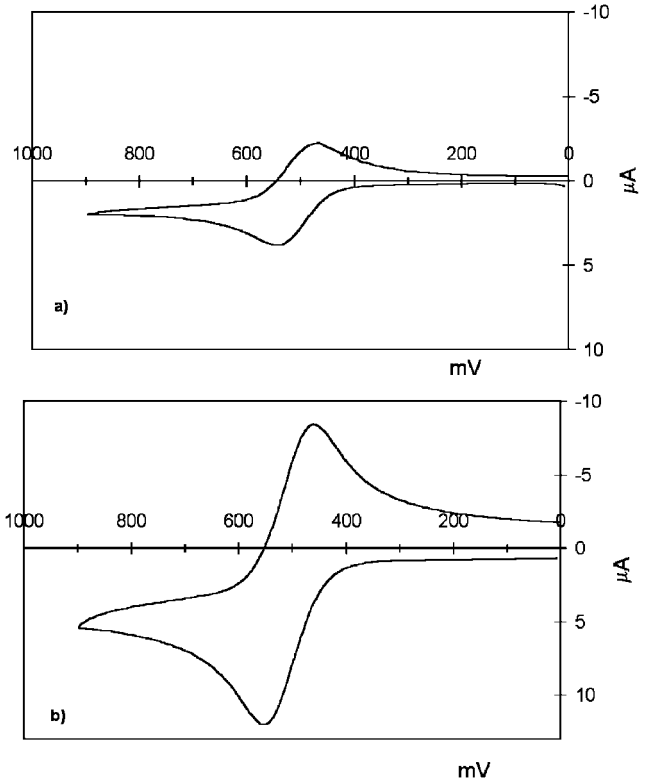


Figure 2. Cyclic voltammograms of ferrocenyl(4-methylphenyl) phenylmethanol in DMF (platinum electrode, TEAP) at different scan rates: (a) 20 mV s^{-1}; (b) 200 mV s^{-1}.

somewhat easier for a more electron-donating substituent. The observed substituent effect might be due to some influence other than the simple electronic effect. Nevertheless, the determination of the minimum energy conformation did not show any specific interaction between the substituent and the iron atom (Fig. 4), thus offering no support for the above hypothesis. The differences in redox potentials of the compounds examined are small (but within the experimental error) and the narrow range may be responsible for the lack of correlation.

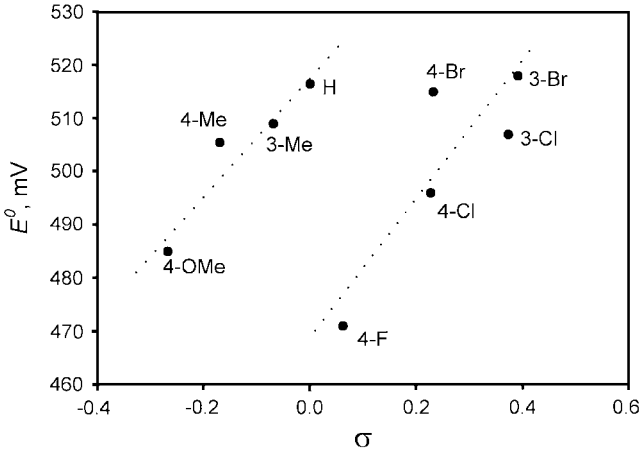


Figure 3. Oxidation potentials of ArFcPhCOH as a function of Hammett substituent constants.

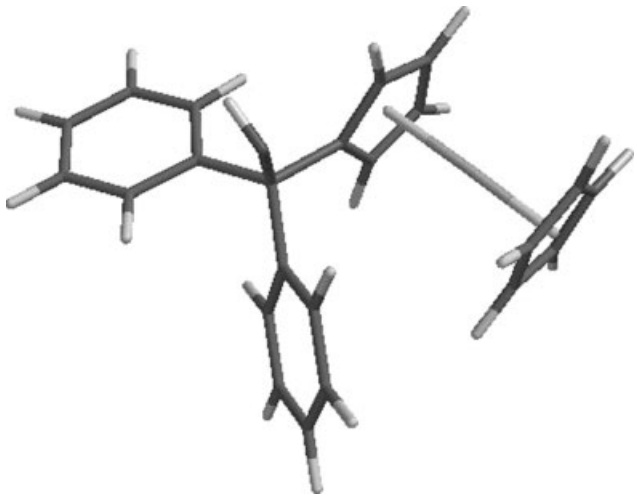


Figure 4. Minimum energy conformation of $FcPh_2COH$, as determined by TITAN, ver. 1.0.5 (Wavefunction, USA). Similar results were obtained with compounds bearing substituents in *meta* and *para* positions.

The voltammetric reversible behavior of arylferrocenylphenylmethanols in solution rendered these species suitable for use in electrochemical sensors. Unfortunately, electrodes coated with electropolymerized polymers presented no electrochemical activity due to the ferrocenyl alcohols, probably because the bulky redox-active species was unable to reach the electrode through the polymer. On the other hand, attempts to include the ferrocenyl alcohols in the polymer, performing the electropolymerization in the presence of the redox-active species, gave very complicated voltammetric waves, probably due to a coupling reaction between the alcohol and the monomer during the electropolymerization process. In this case, it is necessary to separate the electropolymerization step from the trapping step, because

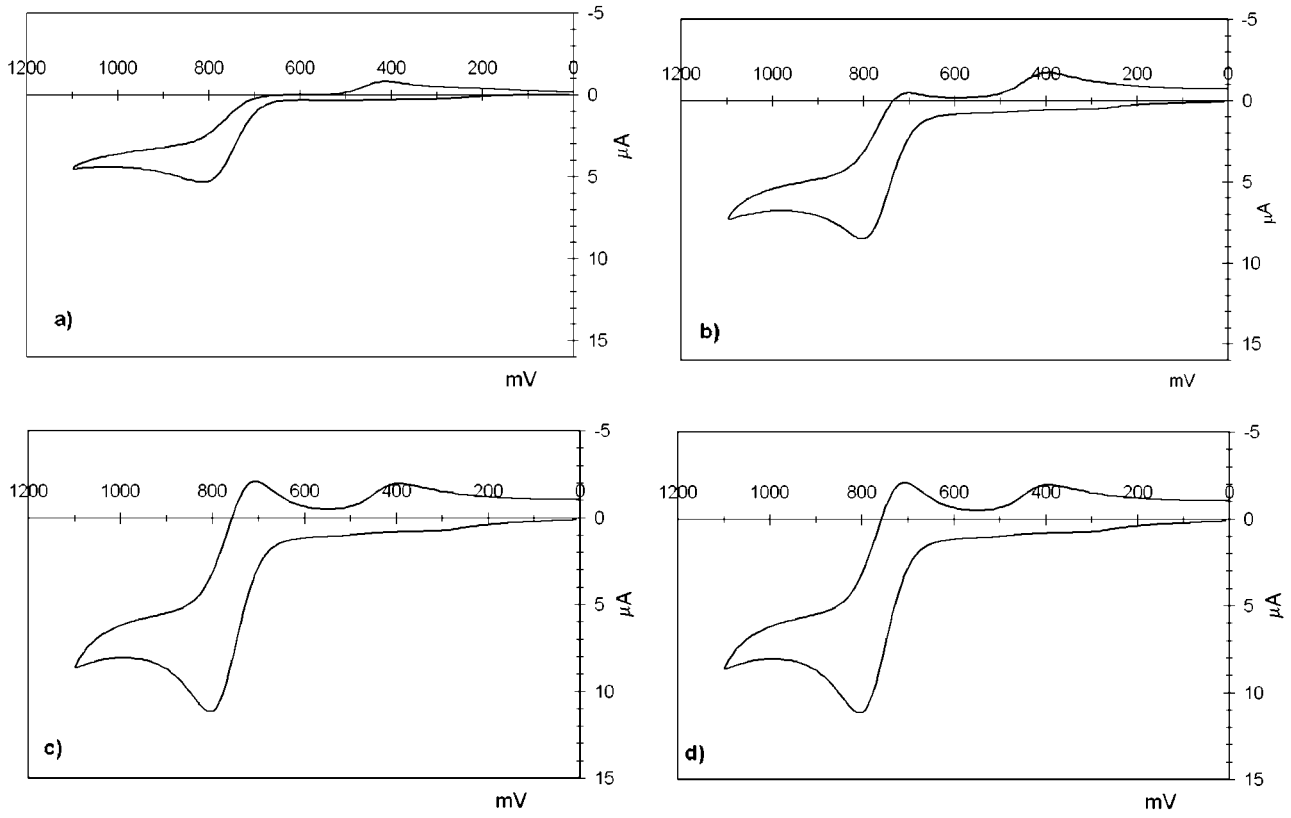


Figure 5. Cyclic voltammograms of ferrocenyl phenyl ketones in DMF (platinum electrode, TEAP) at different scan rates: (a) $v = 20$ mV s^{-1}; (b) $v = 100$ mV s^{-1}; (c) $v = 200$ mV s^{-1}; (d) $v = 400$ mV s^{-1}.

the monomer and the mediator show quite different behaviors in water and in aprotic solvents and the oxidation of the monomer involves the oxidation of the mediator (see the oxidation peak potential) and the related coupling reactions.

With aryl ferrocenyl ketones, the oxidation reaction of iron(II) was followed by a second reaction, yielding a new electroactive species. At low scan rates (Fig. 5) the reduction wave of the ferricenium cation disappeared, whereas the reduction wave of the second species appeared. At high scan rates, the side-reaction has no time to occur and the reduction wave of the ferricenium cation is observed.

CONCLUSIONS

A new family of arylferrocenylphenylmethanols was prepared and characterized. They showed a reversible electrochemical behavior, but they could not be used to prepare electrochemical sensors coated with polymers. Nevertheless, their electrochemical characteristics are promising and might be exploited for a different type of electrochemical sensor. A better way to immobilize these compounds on the probe surface has to be investigated.

Studies are in progress to cross-link the ferrocene derivatives using different cross-linkers,[75] or else to incorporate these kinds of mediator in carbon paste as an electrode material.[76] An alternative strategy might be to anchor the ferrocenyl alcohols onto the electrode surface by means of a long flexible chain.[77]

EXPERIMENTAL

Gas chromatographic analyses were carried out with a Carlo Erba HRGC 5300 Mega Series instrument, equipped with a 2 m 3% OV-17 or a 30 m × 0.25 mm capillary column.

Bruker WP80 and AM400 spectrometers were used to obtain ^{1}H and ^{13}C NMR spectra, respectively, as $CDCl_3$ solutions with tetramethylsilane as the internal standard.

GC–mass spectrometry (MS) analyses were performed with a Hewlett-Packard 5970B system, equipped with a Hewlett-Packard gas chromatograph (12 m × 0.2 mm capillary column). Direct inlet (electronic impact (EI) 50 eV) mass spectra were obtained with a VG Quattro spectrometer.

IR spectra were recorded with a Perkin–Elmer 983 spectrophotometer, in CCl_4 as the solvent. All the compounds exhibited peaks at 1002 and 1106 cm^{-1}, typical of monosubstituted ferrocenes.[78] UV measurements were carried out with a Hewlett-Packard 8452A diode array spectrophotometer.

An AMEL polarographic system Model 433A (AMEL, Milan, Italy) was used for voltammetric studies and for

polymer electrosynthesis. Amperometric measurements were carried out with a 559 HPLC Detector from AMEL. Currents were recorded using a LINSEIS L6512 recorder (LINSEIS, Selb, Germany). The platinum, gold and glassy carbon (GC) electrodes (nominal surface area 0.071 cm^2) were from AMEL.

Materials

Reagent-grade solvents (Carlo Erba) and substances (Aldrich) were used when commercially available without further purification. Tetrahydrofuran (THF) was dried according to a reported procedure.[79]

Arylferrocenyl ketones

Arylferrocenyl ketones were prepared by Friedel–Crafts acylation.[80] In a typical experiment, 58 mmol aroyl chloride and 58 mmol $AlCl_3$ in 100 ml CH_2Cl_2 were added dropwise, stirring at room temperature under nitrogen atmosphere, to a 60 mmol CH_2Cl_2 solution of ferrocene. After stirring overnight at room temperature, the mixture was poured into aqueous NH_4Cl, extracted with CH_2Cl_2, washed with water to neutrality, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, eluent 40–70 °C petroleum ether with increasing amounts of diethyl ether). The following ketones were prepared.

Ferrocenyl 4-methoxyphenyl ketone

Yield, 84%, >99% pure (GC). M.p., 66–68 °C (lit. 80–82 °C,[81] 84.5–85 °C[82]). Anal. Found: C 67.82; H 5.38. Calc.: C, 67.5; H, 5.0%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.2 (s, 5H, unsubstituted Cp ring), 4.5 (complex, 2H, H_α of substituted Cp ring), 4.9 (complex, 2H, H_β of substituted Cp ring) 6.96, 7.92, $J = 8.8$ Hz (AA′BB′ pattern, 4H, aromatic protons), 3.8 (s, 3H, OMe). ^{13}C NMR data are listed in Table 3. MS (EI, 50 eV), m/z: clusters (iron isotopes) around 320 (M^+, MF, 320.17), 305 ($M^+ - Me$), 259 ($M^+ - Cp$), 212 ($FeCO^+$), 184 (Fc^+), and 121 ($CpFe^+$), and peaks at 135 ($ArCO^+$) and 107 (Ar^+).

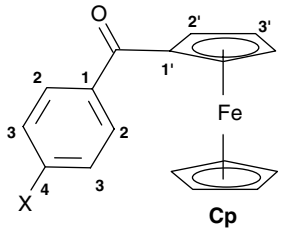
Ferrocenyl 3-methylphenyl ketone

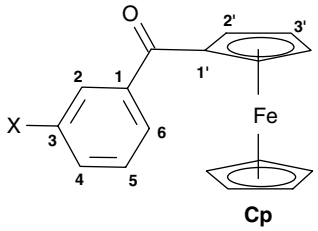
Yield, 85%, >99% pure (GC). M.p., 49–50 °C (lit. 63–64 °C[81]). Anal. Found: C 70.81; H 5.62. Calc.: C, 71.1; H, 5.3%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.2 (s, 5H, unsubstituted Cp ring), 4.5 (complex, 2H, H_α of substituted Cp ring), 4.9 (complex, 2H, H_β of substituted Cp ring) 7.3–7.8 (complex, 4H, aromatic protons), 2.4 (s, 3H, Me). ^{13}C NMR data are listed in Table 3. MS (EI, 50 eV), m/z: clusters (iron isotopes) around 304 (M^+, MF, 304.17), 288 ($M^+ - Me$), 214 ($FeCO^+$), 185 (Fc^+), and 121 ($CpFe^+$), and peaks at 119 ($ArCO^+$) and 91 (Ar^+).

Ferrocenyl 4-methylphenyl ketone

Yield, 75%, >98% pure (GC). M.p., 110–111 °C (lit. 129–130 °C[81]). Anal. Found: C 70.97; H 5.74. Calc.: C, 71.1; H, 5.3%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.1 (s, 5H, unsubstituted Cp ring), 4.5 (complex, 2H, H_α of substituted Cp ring), 4.9 (complex, 2H, H_β of substituted Cp ring) 7.22, 7.75, $J = 8.8$ Hz (AA′BB′ pattern, 4H, aromatic protons), 2.3 (s, 3H, Me). ^{13}C

Table 3. ^{13}C NMR spectra (δ, ppm) of aryl ferrocenyl ketones in $CDCl_3$[a]





	4-F[b]			4-OMe	4-Me	4-Br	4-Cl	3-Me	3-Br	3-Cl
C1	135.99			132.37	137.11	138.52	137.76	137.93	141.56	141.53
C2	130.57	130.48	$^3J_{CF} = 8.7$ Hz	113.42	128.27	129.68	129.53	128.59	131.23	128.28
C3	115.38	115.16	$^2J_{CF} = 21.8$ Hz	130.41	128.85	131.51	128.53	139.83	122.37	134.73
C4	166.05	163.54	$J_{CF} = 252.5$ Hz	162.43	141.99	126.25	138.08	132.18	134.37	131.44
C5								127.98	129.90	129.62
C6								125.25	126.65	126.52
CO	197.41			197.32	198.55	197.85	197.72	199.18	197.43	197.73
C1′	78.12			78.78	78.50	77.87	77.93	78.31	77.72	77.71
C2′	72.57			72.08	72.29	72.76	72.72	72.39	72.86	72.85
C3′	71.49			71.48	71.49	71.45	71.46	71.50	71.50	71.49
Cp	70.24			70.13	70.16	70.29	70.28	70.17	70.34	70.33
X				55.39	21.52			21.37		

[a] Assigned from comparison with ^{13}C NMR spectra of ferrocenes and calculated chemical shifts.[83]
[b] J_{CF} values are in agreement with expected values.[84]

NMR data are listed in Table 3. MS (EI, 50 eV), m/z: clusters (iron isotopes) around 304 (M^+, MF, 304.17), 288 ($M^+ - Me$), 214 ($FeCO^+$), 185 (Fc^+), and 121 ($CpFe^+$), and peaks at 119 ($ArCO^+$) and 91 (Ar^+).

3-Bromophenyl ferrocenyl ketone

Yield, 97%, >96% pure (GC). M.p., 95–97 °C (lit. 101–102 °C[81]). Anal. Found: C 54.94; H 3.61. Calc.: C, 55.3; H, 3.6%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.2 (s, 5H, unsubstituted Cp ring), 4.6 (complex, 2H, H_α of substituted Cp ring), 4.8 (complex, 2H, H_β of substituted Cp ring) 7.2–8.2 (complex, 4H, aromatic protons). ^{13}C NMR data are listed in Table 3. MS (EI, 50 eV), m/z: clusters (bromine and iron isotopes) around 367 (M^+, MF, 369.04), 288 ($M^+ - Br$), 212 ($FeCO^+$), 185 ($ArCO^+$ and Fc^+), and 121 ($CpFe^+$), and peaks at 155, 157 (Ar^+).

4-Bromophenyl ferrocenyl ketone

Yield, 12%, >99% pure (GC). M.p., 117–119 °C (lit. 123–124 °C[81]). Anal. Found: C 55.17; H 3.51. Calc.: C, 55.3; H, 3.6%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.1 (s, 5H, unsubstituted Cp ring), 4.6 (complex, 2H, H_α of substituted Cp ring), 4.9 (complex, 2H, H_β of substituted Cp ring) 7.60, 7.76, $J = 8.8$ Hz (AA′BB′ pattern, 4H, aromatic protons). ^{13}C NMR data are listed in Table 3. MS (EI, 50 eV), m/z: clusters (bromine and iron isotopes) around 367 (M^+, MF, 369.04), 288 ($M^+ - Br$), 213 ($FeCO^+$), 185 ($ArCO^+$ and Fc^+), and 121 ($CpFe^+$), and peaks at 155, 157 (Ar^+).

3-Chlorophenyl ferrocenyl ketone

Yield, 93%, >96% pure (GC). M.p., 96–98 °C (lit. 81–82 °C[81]). Anal. Found: C 62.68; H 3.93. Calc.: C, 62.9; H, 4.0%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.2 (s, 5H, unsubstituted Cp ring), 4.6 (complex, 2H, H_α of substituted Cp ring), 4.9 (complex, 2H, H_β of substituted Cp ring) 7.3–8.0 (complex, 4H, aromatic protons). ^{13}C NMR data are listed in Table 3. MS (EI, 50 eV), m/z: clusters (chlorine and iron isotopes) around 323 (M^+, MF, 324.58), 288 ($M^+ - Cl$), 212 ($FeCO^+$), 185 (Fc^+), and 121 ($CpFe^+$), and peaks at 139, 141 ($ArCO^+$) and 111, 113 (Ar^+).

4-Chlorophenyl ferrocenyl ketone

Yield, 90%, >97% pure (GC). M.p., 115–116 °C (lit. 121–122 °C[81]). Anal. Found: C 63.00; H 4.08. Calc.: C, 62.9; H, 4.0%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.2 (s, 5H, unsubstituted Cp ring), 4.6 (complex, 2H, H_α of substituted Cp ring), 4.9 (complex, 2H, H_β of substituted Cp ring) 7.45, 7.85, $J = 8.8$ Hz (AA′BB′ pattern, 4H, aromatic protons). ^{13}C NMR data are listed in Table 3. MS (EI, 50 eV), m/z: clusters (chlorine and iron isotopes) around 324 (M^+, MF, 324.58), 288 ($M^+ - Cl$), 259 ($M^+ - Cp$), 212 ($FeCO^+$), 185 (Fc^+), and 121 ($CpFe^+$), and peaks at 139, 141 ($ArCO^+$) and 111, 113 (Ar^+).

Ferrocenyl 4-fluorophenyl ketone

Yield, 94%, >96% pure (GC). M.p., 108–110 °C (lit. 117–118 °C[81]). Anal. Found: C, 66.41; H, 4.18. Calc.: C, 66.3; H, 4.3%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.2 (s, 5H, unsubstituted Cp ring), 4.6 (complex, 2H, H_α of substituted Cp ring), 4.9 (complex, 2H, H_β of substituted Cp ring) 7.0–8.0 (pattern para complicated by H–F coupling, 4H, aromatic protons). ^{13}C NMR data are listed in Table 3. MS (EI, 50 eV), m/z: clusters (iron isotopes) around 308 (M^+, MF, 308.13), 289 ($M^+ - Cl$), 214 ($FeCO^+$), 185 (Fc^+), and 121 ($CpFe^+$), and peaks at 123 ($ArCO^+$) and 95 (Ar^+).

Arylferrocenylphenylmethanol

Arylferrocenylphenylmethanols were prepared following the general reaction of aryllithiums with ketones.[85] In a typical experiment, 4.8 mmol phenyllithium in 3 ml anhydrous THF was slowly added to a solution of 4 mmol aroylferrocene in 20 ml THF, stirred under nitrogen, at room temperature. After 30 min, the reaction mixture was poured into aqueous NH_4Cl, extracted with CH_2Cl_2, washed with water to neutrality, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, eluent 40–70 °C petroleum ether with increasing amounts of diethyl ether up to 100%). The following alcohols were prepared.

Ferrocenyldiphenylmethanol

Yield, 68%, >99% pure (GC). M.p., 131–133 °C. Anal. Found: C 74.86; H 5.55. Calc.: C, 75.0; H, 5.5%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.0–4.3 (complex, 9H, superposition of substituted and unsubstituted Cp rings), 7.3 (complex, 10H, aromatic protons), 3.4 (s, 1H, OH). ^{13}C NMR data are listed in Table 4. MS (EI, 50 eV), m/z: clusters (iron isotopes) around 368 (M^+, MF, 368.25), 303 ($M^+ - Cp$), 285 ($M^+ - Cp - OH$) 229 ($M^+ - Cp - Ph$), and 152 ($M^+ - Cp - 2Ph$). IR, ν (cm^{-1}): $\nu_{OH} = 3533$.

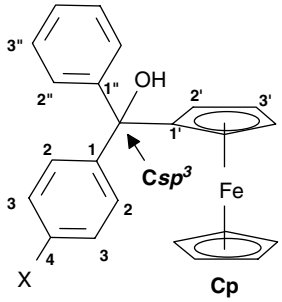
Ferrocenyl(4-methoxyphenyl)methanol

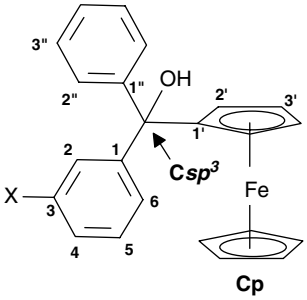
Yield, 63%, >99% pure (GC); oil. Anal. Found: C 72.13; H 5.76. Calc.: C, 72.4; H, 5.6%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.0–4.4 (complex, 9H, superposition of substituted and unsubstituted Cp rings), 6.7–7.5 (complex, 9H, superposition of Ar and Ph protons), 3.8 (s, 3H, OMe), 3.3 (s, 1H, OH). ^{13}C NMR data are listed in Table 4. MS (EI, 50 eV), m/z: clusters (iron isotopes) around 368 ($M^+ - Me$, MF, 398.29), 365 ($M^+ - OMe$), 315 ($M^+ - Cp - OH$) 259 ($M^+ - Cp - Ph$), and 121 ($CpFe^+$). IR, ν (cm^{-1}): $\nu_{OH} = 3532$.

Ferrocenyl(3-methylphenyl)phenylmethanol

Yield, 70%, >99% pure (GC). M.p., 79–81 °C. Anal. Found: C 75.83; H 6.08. Calc.: C, 75.4; H, 5.8%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.0–4.4 (complex, 9H, superposition of substituted and unsubstituted Cp rings), 7.0–7.6 (complex, 9H, superposition of Ar and Ph protons), 2.4 (s, 3H, Me), 3.5 (s, 1H, OH). ^{13}C NMR data are listed in Table 4. MS (EI, 50 eV), m/z: clusters (iron isotopes) around 382 (M^+, MF, 382.28), 317 ($M^+ - Cp$), 299 ($M^+ - Cp - OH$), 244 ($M^+ - Cp - Ph$), and 229 ($M^+ - Cp - Ar$). IR, ν (cm^{-1}): $\nu_{OH} = 3532$.

Table 4. ^{13}C NMR spectra (δ, ppm) of arylferrocenylphenylmethanols in $CDCl_3$[a]





	4-F[b]			4-OMe	4-Me	4-Br	4-Cl	H	3-Me	3-Br	3-Cl
C1	142.92			139.52	144.18	146.08	145.58	147.28	146.88	149.28	149.03
C2	128.76	128.68	$^3J_{CF} = 8.0$ Hz	128.21	126.96	128.87	128.47	127.33	127.63	130.10	127.18
C3	114.25	114.03	$^2J_{CF} = 23.9$ Hz	112.75	127.38	130.50	128.47	127.76	136.08	121.83	133.47
C4	162.85	160.40	$J_{CF} = 245.6$ Hz	157.32	136.21	120.81	132.60	127.05	126.93	128.97	126.85
C5									127.23	129.83	128.63
C6									126.62	126.99	126.85
C1″	146.75			147.28	147.12	146.40	146.49	147.28	146.93	146.20	146.19
C2″	127.95			126.96	126.96	126.88	127.55	127.33	127.35	126.91	126.93
C3″	129.81			127.40	128.12	127.53	127.55	127.76	127.45	127.59	127.52
C4″	126.84			126.66	126.93	126.69	126.90	127.05	124.22	126.86	125.35
C sp^3	99.25			99.66	99.50	98.89	98.99	99.68	99.42	98.89	98.77
C1′	77.00			77.06	77.32	77.00	77.00	77.64	77.31	77.00	77.00
C2′	68.39			68.27	68.26	68.32	68.50	68.66	68.21	68.58	68.47
				68.30	68.63	68.92			68.25		
C3′	68.68			68.61	68.67	68.55	68.57	69.01	65.54	68.58	68.54
Cp	68.54			68.53	68.52	68.55	68.57	68.86	68.48	68.58	68.54
X				55.17	20.98				21.55		

[a] Assigned from comparison with ^{13}C NMR spectra of ferrocenes and calculated chemical shifts.[83]
[b] J_{CF} values are in agreement with expected values.[84]

Ferrocenyl(4-methylphenyl)phenylmethanol
Yield, 49%, >99% pure (GC). M.p., 97–98 °C. Anal. Found: C 75.83; H 6.06. Calc.: C, 75.4; H, 5.8%. ^1H NMR ($CDCl_3$) δ (ppm): 4.0–4.4 (complex, 9H, superposition of substituted and unsubstituted Cp rings), 7.0–7.6 (complex, 9H, superposition of Ar and Ph protons), 2.4 (s, 3H, Me), 3.4 (s, 1H, OH). ^{13}C NMR data are listed in Table 4. MS (EI, 50 eV), m/z: clusters (iron isotopes) around 382 (M^+, MF, 382.28), 317 ($M^+ - Cp$), 244 ($M^+ - Cp - Ph$), and 229 ($M^+ - Cp - Ar$). IR, ν (cm^{-1}): $\nu_{OH} = 3531$.

(3-Bromophenyl)ferrocenylphenylmethanol
Yield, 61%, >99% pure (GC). M.p., 75–77 °C. Anal. Found: C 61.46; H 4.38. Calc.: C, 61.8; H, 4.3%. ^1H NMR ($CDCl_3$) δ (ppm): 4.0–4.4 (complex, 9H, superposition of substituted and unsubstituted Cp rings), 7.1–7.3 (complex, 9H, superposition of Ar and Ph protons), 3.5 (s, 1H, OH). ^{13}C NMR data are listed in Table 4. MS (EI, 50 eV), m/z: clusters (bromine and iron isotopes) around 446 (M^+, MF, 447.15), 381 ($M^+ - Cp$), 310 ($M^+ - Cp - Ph$), 228 ($M^+ - Cp - Ar$), 152 ($M^+ - Cp - Ph - Ar$), and 121 ($CpFe^+$). IR, ν (cm^{-1}): $\nu_{OH} = 3528$.

(4-Bromophenyl)ferrocenylphenylmethanol
Yield, 89%, >99% pure (GC). M.p., 101–103 °C. Anal. Found: C 61.93; H 4.46. Calc.: C, 61.8; H, 4.3%. ^1H NMR ($CDCl_3$) δ (ppm): 4.0–4.4 (complex, 9H, superposition of substituted and unsubstituted Cp rings), 7.1–7.3 (complex, 9H, superposition of Ar and Ph protons), 3.5 (s, 1H, OH). ^{13}C NMR data are listed in Table 4. MS (EI, 50 eV), m/z: clusters (bromine and/or iron isotopes) around 448 (M^+, MF, 447.15), 381 ($M^+ - Cp$), 308 ($M^+ - Cp - Ph$), 228 ($M^+ - Cp - Ar$), 186 (Fc^+). IR, ν (cm^{-1}): $\nu_{OH} = 3530$.

(3-Chlorophenyl)ferrocenylphenylmethanol
Yield, 57%, >99% pure (GC). M.p., 99–100 °C. Anal. Found: C 68.46; H 4.86. Calc.: C, 68.6; H, 4.8%. ^1H NMR ($CDCl_3$) δ (ppm): 4.0–4.4 (complex, 9H, superposition of substituted and unsubstituted Cp rings), 7.1–7.3 (complex, 9H, superposition of Ar and Ph protons), 3.5 (s, 1H, OH). ^{13}C NMR data are listed in Table 4. MS (EI, 50 eV), m/z: clusters (chlorine and iron isotopes) around 402 (M^+, MF, 402.71), 337 ($M^+ - Cp$), 319 ($M^+ - Cp - OH$), 264 ($M^+ - Cp - Ph$), 228 ($M^+ - Cp - Ar$), 152 ($M^+ - Cp - Ph - Ar$). IR, ν (cm^{-1}): $\nu_{OH} = 3530$.

Table 5. Electrochemical data from cyclic voltammetries of arylferrocenylphenylmethanols, $XC_6H_4FcPhCOH$, in DMF containing 0.1 M TEAP

		Gold		Platinum		Glassy carbon[a]	
X	v (mV s^{-1})	i_{pc}/i_{pa}	$E°$ (mV)	i_{pc}/i_{pa}	$E°$ (mV)	i_{pc}/i_{pa}	$E°$ (mV)
H	20	0.933	516	0.918	520	0.948	516
	50	0.942	520	1.000	516	0.966	516
	100	1.005	516	1.039	516	1.000	516
	200	1.031	516	1.008	516	1.000	516
4-OMe	20	0.964	484	1.000	484	0.984	488
	50	0.983	488	1.024	484	1.018	484
	100	0.983	484	1.009	484	0.996	488
	200	1.000	488	1.018	480	1.000	484
3-Me	20	0.946	508	0.978	508	0.982	508
	50	1.044	508	0.985	508	1.010	512
	100	1.065	508	1.011	504	1.025	512
	200	1.027	504	1.023	508	0.994	520
4-Me	20	1.027	508	1.028	504	0.926	504
	50	1.025	504	1.018	506	0.953	504
	100	1.037	504	0.994	504	1.010	516
	200	1.036	504	1.036	504	0.985	504
4-F	20	0.865	472	0.765	468	0.879	472
	50	0.843	476	1.088	470	0.897	472
	100	0.905	476	0.958	468	0.961	472
	200	0.947	472	1.079	472	1.000	468
3-Cl	20	1.014	508	0.973	508	0.994	504
	50	1.036	508	0.991	508	1.000	504
	100	0.988	508	0.968	504	0.989	508
	200	1.000	508	1.009	508	1.012	508
4-Cl	20	0.988	492	0.974	496	0.945	496
	50	0.984	496	0.992	496	0.964	496
	100	1.035	496	0.988	496	0.995	500
	200	1.078	492	1.017	496	0.977	498
3-Br	20	0.868	512	1.015	520	1.006	516
	50	1.043	516	1.000	522	0.891	520
	100	0.958	516	1.060	520	1.025	516
	200	1.000	516	1.005	516	1.018	516
4-Br	20	0.868	514	1.060	518	0.987	512
	50	0.827	514	0.981	524	0.992	512
	100	1.000	514	0.987	520	0.994	512
	200	1.052	512	1.019	520	0.949	512

(4-Chlorophenyl)ferrocenylphenylmethanol

Yield, 89%, >99% pure (GC). M.p., 104–106 °C. Anal. Found: C 68.43; H 4.94. Calc.: C, 68.6; H, 4.8%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.0–4.4 (complex, 9H, superposition of substituted and unsubstituted Cp rings), 7.1–7.3 (complex, 9H, superposition of Ar and Ph protons), 3.5 (s, 1H, OH). ^{13}C NMR data are listed in Table 4. MS (EI, 50 eV), m/z: clusters (chlorine and iron isotopes) around 402 (M^+, MF, 402.71), 337 ($M^+ - Cp$), 264 ($M^+ - Cp - Ph$), 228 ($M^+ - Cp - Ar$). IR, ν (cm^{-1}): $\nu_{OH} = 3530$.

Ferrocenyl(4-fluorophenyl)phenylmethanol

Yield, 87%, >99% pure (GC). M.p., 108–110 °C. Anal. Found: C 71.32; H 5.31. Calc.: C, 71.5; H, 5.0%. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.0–4.4 (complex, 9H, superposition of substituted and unsubstituted Cp rings), 6.9–7.6 (complex, 9H, superposition of Ar and Ph protons), 3.5 (s, 1H, OH). ^{13}C NMR data are listed in Table 4. MS (EI, 50 eV), m/z: clusters (iron isotopes) around 386 (M^+, MF, 386.24), 321 ($M^+ - Cp$), 303 ($M^+ - Cp - OH$), 247 ($M^+ - Cp - Ph$), and 226 ($M^+ - Cp - Ar$). IR, ν (cm^{-1}): $\nu_{OH} = 3530$.

pK_a determination

The equilibrium constants for the protonation of aryl ferrocenyl ketones were obtained spectrophotometrically, as previously reported for other ferrocenyl ketones.[86] Solutions of aryl ferrocenyl ketones (1–2 M) were prepared in 95% EtOH. 0.1 ml of the stock solution was added to 3 ml H_2SO_4 of different concentrations, up to 70%. The UV–visible spectrum was recorded in the range 280–700 nm. For each ketone, the absorption spectra were recorded at several H_2SO_4 concentrations, up to 70%. The complete conversion to the protonated form was obtained when no further spectral change occurred upon increase in acid concentration. The evaluation of the equilibrium constant was carried out according to the equation $H_0 = pK_a - \log I$,[87] where $I = [BH^+][B]$, with $[BH^+]$ being the concentration of the protonated species and [B] that of the ketone. Absorbances at a number of wavelengths, chosen where large changes occurred, were used to calculate $\log I$. The results, which are the average of several runs, are reported in Table 1.

Electrode polishing

The bare electrodes consisted of platinum or gold and glassycarbon disks sealed in a Tygon tube. The working electrode surfaces were polished with alumina powder (Al_2O_3, Buehler, Evanston, IL, USA) of various particles sizes (1, 0.3 and 0.05 μm) before use. After a careful rinsing with distilled water, the electrodes were pre-treated by potential cycling in 0.5 M H_2SO_4 from −0.2 to +1.2 V (versus saturated calomel electrode (SCE)) at a scan rate of 20 mV s^{-1}, until no changes were observed in the cyclic voltammograms.[88]

Electrochemical measurements

Cyclic voltammetry (CV) studies of arylferrocenylmethanols (10^{-3} M) and of aryl ferrocenyl ketones (10^{-3} M) were carried out in DMF solutions using 10^{-4} M tetraethylammonium perchlorate (TEAP) as the supporting electrolyte. An SCE, modified for DMF solutions,[89] was used as the reference electrode. Different scan rates were used: 20, 50, 100 and 200 mV s^{-1} in the scan range between 0 and 1 V. Before each CV scanning, the solutions were deaerated by bubbling nitrogen for 20 min. Reproducible $E^{1/2}$ values were obtained with the different working electrodes and with the different scan speeds (Table 5). An example voltammogram is given in Figure 3.

Arylferrocenylphenylmethanols showed a reversible behavior, with i_{pa}/i_{cp} values close to unity in all cases (i_{pa} and i_{pc} being the anodic and cathodic peak currents respectively), thus indicating the absence of side reactions due to electronic transfer and the absence of electroactive species other than the ferrocene/ferricenium couple.[90]

The behavior of aryl ferrocenyl ketones was different, the oxidation reaction of which was followed by a second reaction leading to the formation of a new electroactive species. With a low scan speed, the reduction wave of the ferricenium cation disappears, and the reduction wave of the new species is present (Fig. 4).

Preparation of the sensor

1,2-Benzenediamine (1,2-DAB) and 1,3-benzenediamine (1,3-DAB) were electropolymerized on the different solid electrodes by CV as previously described.[32] The scan rate was 2 or 5 mV s^{-1}, and the potential was continuously cycled until a minimum constant value of current, after further cycling, was observed. All the solutions of monomers had been deaerated for 15 min with nitrogen before the electropolymerization.

Electrochemical measurements on the electrodes

10 μl of a 10 mM solution of ferrocenyldiphenylmethanol ($FcPh_2COH$) in absolute EtOH was applied on the electrode surface and the solvent was allowed to dry. Two further 10 μl portions of $FcPh_2COH$ solution were added in the same way. The electrode surface was then rinsed with distilled water and allowed to dry at 4 °C. A voltammetric measurement was performed in the range 0.0–1.0 V versus SCE[30] in a phosphate buffer (pH 6.5). $FcPh_2COH$ showed no electrochemical activity with any of the electrodes.

Several attempts were made in order to obtain inclusion of the ferrocene substrate in the polymer film during electrodeposition, as reported in the following.

- 20 cycles at 2 mV s^{-1} in the range 0–800 mV in DMF, 0.1 mM TEAP, 5 mM 1,2-DAB or 1,3-DAB, 5 mM $FcPh_2COH$. The oxidized ferrocene precipitated and the polymeric film did not form.
- 20 cycles at 2 mV s^{-1} in the range 0–800 mV in phosphate buffer (pH 6.5), 5 mM 1,2-DAB or 1,3-DAB, 5 mM $FcPh_2COH$. The signal relative to the alcohol oxidation appeared, but no electropolymerization occurred.
- 50 cycles at 2 mV s^{-1} in the range 0–800 mV in DMF, 0.1 mM TEAP, 5 mM 1,2-DAB or 1,3-DAB, 5 mM $FcPh_2COH$. No electropolymerization occurred.
- 20 cycles at 2 mV s^{-1} in the range 0–800 mV in phosphate buffer (pH 6.5), 5 mM 1,2-DAB or 1,3-DAB, 5 mM $FcPh_2COH$. No signal was observed.

Attempts were made to perform electropolymerization after the absorption of the substrate on the electrodes (three 10 μl portions of 1 or 10 mM solutions in absolute ethanol), as described in the following.

- 40 cycles at 2 mV s^{-1} in the range 0–800 mV in phosphate buffer (pH 6.5), 5 mM 1,2-DAB or 1,3-DAB. The signal of the monomer was too low and decreased very slowly, with no electrodeposition.
- 50 cycles at 2 mV s^{-1} in the range 0–800 mV in phosphate buffer (pH 6.5), 5 mM 1,2-DAB or 1,3-DAB. The efficiency of electropolymerization was too low.
- 60 cycles at 2 mV s^{-1} in the range 0–800 mV in phosphate buffer (pH 6.5), 5 mM 1,2-DAB or 1,3-DAB. The electrodeposition occurred, but the subsequent voltammetric experiment in the range 0–1 V in phosphate buffer yielded a very complex voltammetric wave, different from

that of $FcPh_2COH$, probably due to a coupling reaction of the alcohol with the monomer.

- Electropolymerization at constant potential (200 mV) for 2 h in phosphate buffer (pH 6.5), 5 mM 1,2-DAB or 1,3-DAB gave the same result as the previous run.
- Ten cycles at 2 mV s^{-1} in the range 0–800 mV in phosphate buffer (pH 6.5), 5 mM 1,2-DAB or 1,3-DAB. No signal corresponding to $FcPh_2COH$ was observed.
- Five cycles at 2 mV s^{-1} in the range 0–800 mV in phosphate buffer (pH 6.5), 5 mM 1,2-DAB or 1,3-DAB. No signal corresponding to $FcPh_2COH$ was observed.

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