



Synthesis and electrochemical properties of a new range of strained 2-aza-[3]ferrocenophanes

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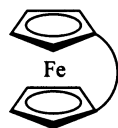
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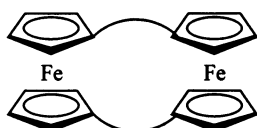
Abstract—The previously unreported 2-aza-[3]ferrocenophanes **3** and **4**, prepared from a preformed [5]ferrocenophane, act as electrochemical sensors either of Mg^{2+} , Zn^{2+} and Ni^{2+} cations (free ligand): a new redox peak appears in the CV shifted 310–360 mV or hydrogensulfate anion (protonated ligand) via a significant cathodic perturbation. © 2001 Elsevier Science Ltd. All rights reserved.

The most prevalent organometallic analogs of cyclophanes are the ferrocenophanes with bivalve-like structures, in which the two cyclopentadienyl rings of ferrocene are joined by an atomic or molecular bridge. In these sort of compounds many of the desirable characteristics of the parent ferrocene are retained and they are expected to show unique chemical properties owing to functionality of the side arm.

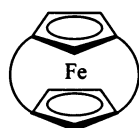
There have been many different classes of ferrocenophanes described, most of which possess exclusively carbon-based bridges with three modes of ring attachment:¹ mononuclear $[m]$ ferrocenophanes (type **I**), mononuclear multiply-bridged $[m]''$ ferrocenophanes (type **II**) and multinuclear $[m]'''$ ferrocenophanes (type **III**). Ferrocenophanes type **I** and **II** in which the bridge contains heteroatoms² have also been described.



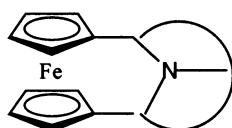
I



III



II



IV

Ferrocenophanes type **I** with either an unsaturated bridge or heteroatom have been exploited as monomers in ring-opening polymerizations (ROPS), which can be conducted under thermal, anionic or coordination-catalyzed conditions,³ to give conjugated polymers that contain repeating units of ferrocene in the backbone. Recently, quiral doubly-bridged ferrocenophanes type **II** have been used as catalysts in asymmetric synthesis,⁴ whereas much of the interest in multinuclear ferrocenophanes type **III** stems from the potential interactions between the metal centers, which might give rise to unique physical and chemical phenomena.⁵

However, this activity has been barely applied to ferrocenophanes bearing a nitrogen atom in the bridge, aza-[m]ferrocenophanes, in spite of the rich functionality on the side arm. To the best of our knowledge, it has only been reported the preparation of *N*-substituted 2-aza-[3]ferrocenophanes either from the reaction of 1,1'-ferrocenedimethanol with aryl isocyanates or arylamines in the presence of $\text{RuCl}_2(\text{PPh}_3)_2$ ⁶ or by condensation of [1,1'-ferrocenediylbis(methylene)]bispyridinium tosylate with methylamine.⁷

Following our work on the preparation of aza-heteroaryl substituted ferrocene derivatives displaying redox-switchable character,⁸ we now wish to report on the synthesis of a new range of ferrocenophanes containing an aza-substituted bridge in which all the atoms belong to a rigid aza-fused tricyclic ring system (type **IV**). This structure combines the typical 2-aza-[3]ferrocenophane framework with the unprecedented 2,8-disubstituted benzoquinoclidine ring.

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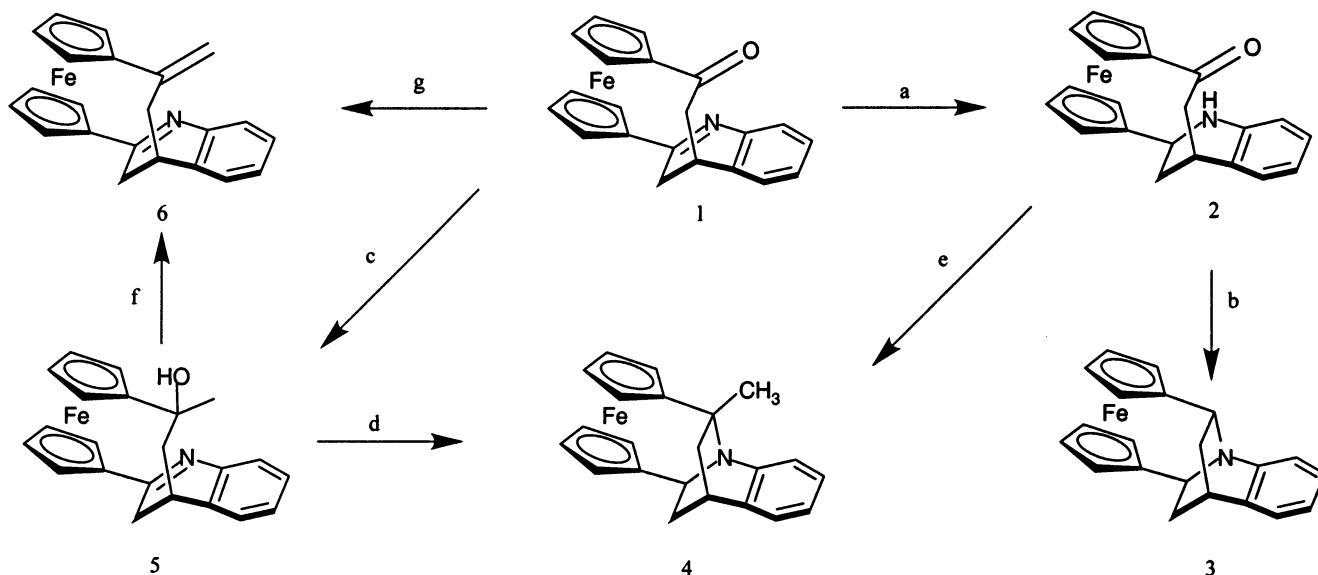
The starting material of choice was the ferrocene derivative **1** readily available in 39% overall yield from 1,1'-diacetylferrocene by sequential treatment with *o*-azidobenzaldehyde and tri-*n*-butylphosphane.⁹ Compound **1** can be considered as a [5]ferrocenophane bearing a 2,4-bridged dihydroquinoline ring or [4](2,4)dihydroquinolinophane containing a 1,1'-disubstituted ferrocene bridge. Our approach starts by selective reduction of the C=N double bond in **1** with NaBH₃CN in methanol in the presence of HBF₄ to give **2** in 80% yield. On treatment of **2** with LiAlH₄–AlCl₃ (3:1) in ether at room temperature we were surprised to discover that, rather than the expected fully reduced [5]ferrocenophane, the only product isolated from this reaction was the rigid 2-aza-[3]ferrocenophane **3**, which was recovered in almost quantitative yield (95%) by flash chromatographic separation over silica gel.¹⁰ Similar results were obtained when BH₃–Me₂S was used as reducing agent. Taking into account that this reagent has been successfully applied for the reduction of ferrocenyl ketones into ferrocenylalkyl alcohols,¹¹ we think that the formation of **3** probably involves initial reduction of the carbonyl group at the hydroxyl stage with concomitant cyclization by nucleophilic attack of the amino group on the α -position of ferrocene.¹²

The synthetic approach described above also allows the preparation of 1-methyl-2-aza-[3]ferrocenophane **4**. Methylation of **1** with MeLi afforded the alcohol derivative **5** in 70% yield, which by treatment with LiAlH₄–AlCl₃ gave **4** albeit in low yield (20%). However, **4** is much more conveniently obtained from **2** (40% yield after chromatography) by sequential treatment with MeLi and an excess of AlCl₃.

On the other hand, dehydration of **5** under acid conditions (10-camphorsulfonic acid or CF₃COOH/AcOH) afforded **6** in 80% yield. This compound was also prepared in 30% yield directly from **1** by reaction with [cyclo-dibromodi-*m*-methylene(*m*-tetrahydrofuran)triazine] (Nysted's reagent) in the presence of TiCl₄.¹³ While it may be surprising that the exocyclic olefin in **6** does not isomerize into the endocyclic olefin under the acidic conditions employed for its preparation, analysis of molecular models reveals the endocyclic isomer is much more strained than the exocyclic isomer (Scheme 1).

First, the electrochemical behavior of ferrocenophanes **3** and **4**, as well as in the presence of variable concentrations of HBF₄, was investigated. The cyclic voltammograms (CVs) of **3** and **4** display a single anodic process with features of electrochemical reversibility ($E^{\circ'} = 0.410$ and 0.450 V versus SCE, respectively) with no subsidiary amine oxidation being observed. Upon protonation by addition of 1 equiv. of HBF₄ in acetonitrile to a solution of compounds **3** and **4** in acetonitrile, the redox potential of the ferrocene nucleus was shifted anodically in each case. For compound **3** the potential shift on protonation was 390 mV and, consequently, the binding-enhancement factor (BEF) is 2.5×10^{-7} and the reaction-coupling efficiency (RCE) is 3.9×10^6 . For compound **4** these values were 320 mV, 3.9×10^{-6} , and 2.6×10^5 , respectively.

The high values of the redox potential shift on protonation are in good agreement with the linear relationship [$y = (-2.7 \times 2.1x) \times 10^2$] between the inverse iron–nitrogen separation (x) and the shifts of the potentials (y) found upon protonation of several types of aza-substituted ferrocenes.⁷



Scheme 1. Synthesis of ferrocenophanes **3** and **4**. (a) NaBH₃CN, HBF₄, EtOH, rt; (b) LiAlH₄–AlCl₃ (3:1), Et₂O, rt or BH₃–Me₂S, Et₂O, rt; (c) MeLi (2 equiv.), Et₂O, –30°C to rt; (d) LiAlH₄–AlCl₃ (3:1), Et₂O, rt; (e) (i) MeLi (2 equiv.), Et₂O, –30°C to rt, (ii) AlCl₃, rt; (f) 10-camphorsulfonic acid, toluene, reflux or CF₃COOH/AcOH, THF, rt; (g) Nysted's reagent TiCl₄, THF, –50°C to rt.

Recognition properties of the redox-active compounds **3** and **4** were also evaluated by CV.¹⁴ Whereas no perturbation of the CV of **3** was observed upon addition of Li⁺ and Ca²⁺ cations, significant modifications of the CVs could be observed upon addition of Mg²⁺, Zn²⁺ and Ni²⁺ cations. On addition of Mg(ClO₄)₂ a second redox peak appeared in the CV, anodically shifted by ca. 350 mV. This ‘two-wave’ behavior is diagnostic of a large value for the equilibrium constant for cation binding by the neutral ligand¹⁵ (Fig. 1). Further addition of Mg²⁺ up to 16 equiv. had no effect on the CV; however, after H₂O addition the CV was identical to that obtained before the addition of Mg(ClO₄)₂. The presence of the methyl group in **4** slightly decreased the strength of binding of Mg²⁺ ($\Delta E^{\circ'} = 330$ mV). Notably, compounds **3** and **4** showed an identical affinity for Zn²⁺ and Ni²⁺, which required a considerably higher concentration of Ni²⁺ (14 equiv.) than the other cations before the original ferrocene redox peak was lost. Data comparing the redox behavior of these ligands in the presence of Mg²⁺, Zn²⁺ and Ni²⁺ cations are collected in Table 1.

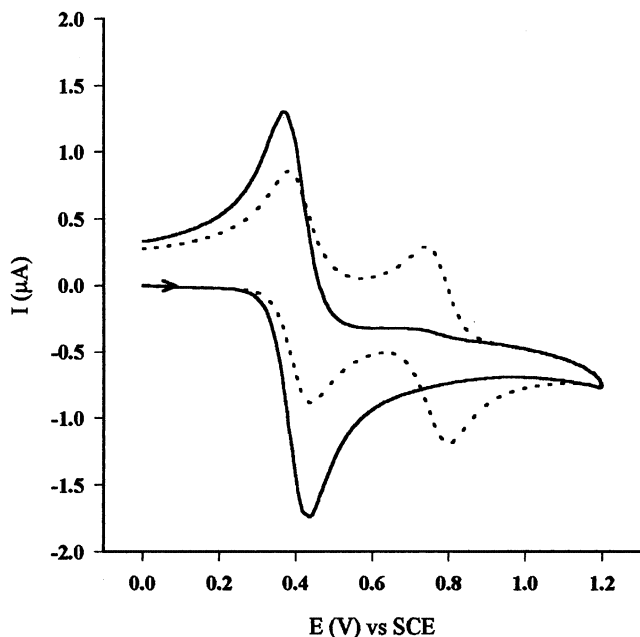


Figure 1. Cyclic voltammogram of **3** in CH₃CN (—) and after the addition of Mg(ClO₄)₂ (1 equiv.) (···).

Table 1. Cyclic voltammetric data

Ligand	$E^{\circ'}_{\text{free}}$ (V) ^a	$E^{\circ'}_{\text{complex}}$ (V) ^a	$\Delta E^{\circ'}$ (mV)	K_1/K_2^b
3/Mg	0.410	0.760	350	8.2×10^5
3/Zn	0.410	0.740	330	5.6×10^5
3/Ni	0.410	0.740	330	5.6×10^5
4/Mg	0.450	0.790	330	5.6×10^5
4/Zn	0.450	0.760	310	1.7×10^5

^a Data from acetonitrile solutions at a scan rate of 200 V s⁻¹ versus SCE. CV recorded from 0 to 1 V.

^b The equilibrium constants K_1 and K_2 correspond to the complexation processes by the neutral and oxidized forms of the ligand.

Additionally, as ligands **3** and **4** act as bases when protonated, they may also be used to detect anions. In this context, the synthesis of receptors containing ferrocene as functional antennae to detect anion binding has only recently been reported.¹⁶ In the protonated species **3**·HBF₄, readily prepared as a crystalline solid by addition of 1 equiv. of HBF₄ to a solution of **3** in chloroform, all signals are downfield shifted in relation to the free ligand **3**. In an initial study, this charged species **3**·HBF₄ was used to investigate its ability to sense electrochemically anion binding. Following the addition of dihydrogenphosphate and hydrogensulfate anions elicited different electrochemical responses. For dihydrogenphosphate anions a new reversible redox wave evolved, which was shifted cathodically from the original ferrocene redox potential. The evolving peak appeared at virtually the same potential as that for the free ferrocenophane **3**. A control experiment with the addition of K₂CO₃/H₂O to the final solution causing no further change in the redox behavior showed that this response was equivalent to deprotonation. However, significant modification of the CV of **3**·HBF₄ was observed upon addition of hydrogensulfate anion. The ferrocene oxidation wave shifted 60 mV cathodically (with 5 equiv. guest), indicative of oxidation being facilitated by the proximate coordination of a negative charge. Similar electrochemical findings have recently been reported with charged transition-metal-coordinated ferrocene phosphine amides as receptors.^{16d}

In conclusion, we have developed a synthetic route for the preparation of a new class of 2-aza-[3]ferrocenophanes **3** and **4** from the readily available [5]ferrocenophane **1**. Initial electrochemical investigations show that **3** and **4** can electrochemically sense various cations (Mg²⁺, Zn²⁺, Ni²⁺) and, when protonated, hydrogensulfate anions. This may also be of interest for electrochemically modifying reactions in which the coordination of these cations plays a pivotal role. In addition, ferrocenophane **6** represents a new kind of functionalized [5]ferrocenophane bearing an unsaturated side chain, which could permit the generation of conjugated oligomeric ferrocenes. We are currently further exploring the properties of these promising new classes of ferrocenophanes.

Acknowledgements

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