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Design, synthesis and redox properties of two ferrocene-containing iron chelators

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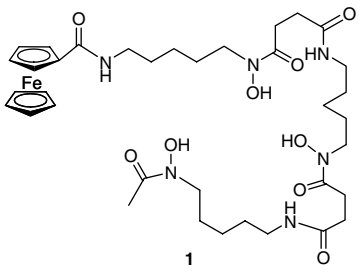
Abstract—Two ferrocene-containing iron(III) chelators were synthesized from desferrioxamine B and kojic acid and their electronic absorption and electrochemical properties were studied in acetonitrile in the absence and presence of ferric ions. The results show a complex behavior arising from the occurrence of competing redox and complexation processes. Such systems are a first step toward the generation of chemosensors for the electrochemical detection of iron(III) in a solution.

Iron plays numerous essential roles in life processes.[1] However, excess levels of this metal are deleterious to living organisms.[1] Therefore, Fe^{3+} sensing methods capable of providing quantification of the available iron pool in biological and environmental media are of considerable interest. The methods of detection described so far are not fully satisfactory because they require the destruction of the sample, lack the requisite sensitivity, or are not easily adaptable for high throughput assays and in vivo measurements.[2] A possibility to solve this problem is the use of spectrofluorimetric methods that offer valuable tools for real-time monitoring, sensitive determination, and in situ imaging of chemical and biochemical species. Fluorescently labeled siderophore-like chelators were reported to act as versatile and effective reporters of Fe^{3+}.[3] Recently, Hider and co-workers described a series of iron-specific fluorescent probes in which a fluorescent coumarin moiety forms a part of bidentate hydroxypyridinone or hydroxypyranone ligands.[4] Another way is the use of electrochemical methods. Compared to spectrofluorimetric methods, electrochemical detections receive particular attention due to their high sensitivity, easy instrumentation, low production cost, and miniaturization. These considerations led us to investigate the potential of molecular systems in which the Fe^{3+} chelating unit is instead connected to a redox signaling unit, such as ferrocene, for the electrochemical sensing of Fe^{3+}.

While ferrocene-based receptors were designed to allow the electrochemical detection of a great variety of metallic species,[5] there is no example to our knowledge of such systems that are capable to electrochemically respond to the presence of ferric ions in a solution.

In this context, we have decided to synthesize two ferrocene-containing siderophore-like prototype systems, **1** and **2**, and investigate their physico-chemical and electrochemical properties in the absence and presence of Fe^{3+} in acetonitrile.



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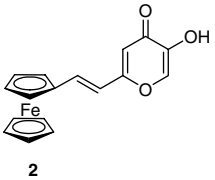

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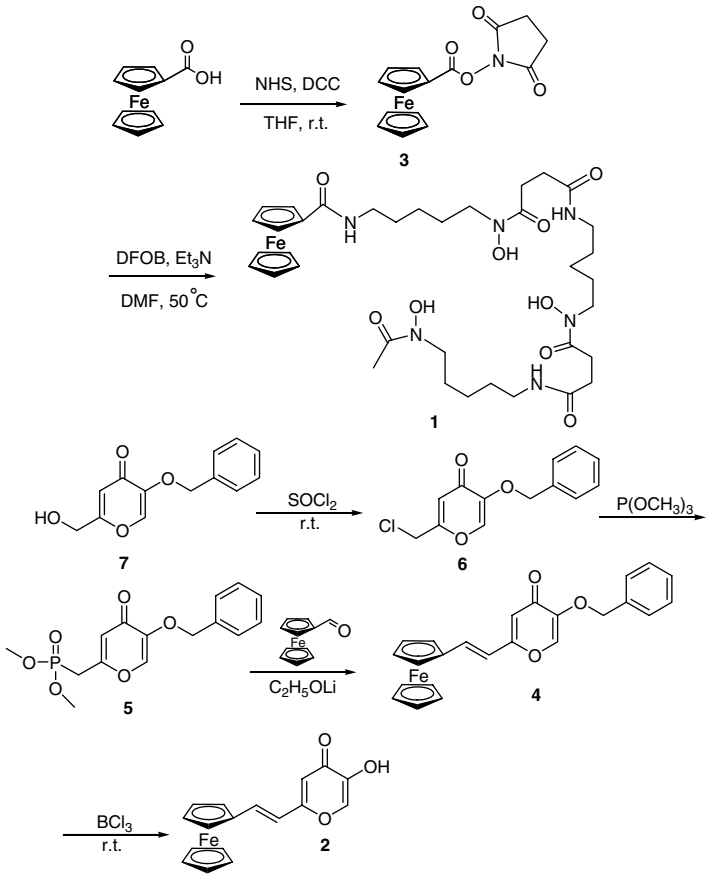
Fe^{3+} is known to be a strong one-electron oxidant capable of oxidizing pristine ferrocene into ferricinium ion in solution.[6] We were, therefore, interested in examining the interplay between chelation and redox phenomena occurring in solutions of **1** and **2** containing gradual amounts of ferric ions. In **1**, the ferrocenyl moiety is covalently bound to the terminal amino functionality of the hexadentate ligand desferrioxamine B (DFOB), a microbial trishydroxamate siderophore.[7] Here, Fe^{3+} complexation was anticipated to lead to the formation of a 1:1 metal/ligand complex, bearing a single ferrocene unit attached to the coordination center via a flexible link, similar to the case of the fluorescent DFOB derivatives reported by Shanzer and co-workers.[8] As a bidentate ligand, the hydroxypyranone[9] derivative **2** is expected to form a 1:3 metal/ligand complex featuring three ferrocene peripheral units. Moreover, this ligand was designed to provide a through bond communication between the redox and metal centers owing to the presence of the conjugated bridge.[5a]

Ligand **1** was obtained by a classical two-step procedure (Scheme 1). Ferrocene carboxylic acid was activated via DCC-mediated condensation with *N*-hydroxysuccinimide to give the activated ester **3**. The latter was reacted in DMF with DFOB in the presence of triethylamine to give **1** as an orange solid (88% yield).[10] Kojic acid was reacted with benzyl bromide to afford 5-(benzyloxy)-2-(hydroxymethyl)-4*H*-pyran-4-one **7** according to the literature.[5a] After conversion of **7** to the chloride **6** with thionyl chloride and subsequent treatment of **6** with trimethylphosphite, phosphonate **5** was reacted with ferrocene carboxaldehyde under Wittig–Horner conditions to form the double bond in the precursor **4** (80% yield).[11] Deprotection of **4** with boron trichloride afforded **2** as a red solid (70% yield).[12]

The electronic absorption spectrum of free ligand **1** in DMF showed a transition band at 440 nm, characteristic of the ferrocene absorption (Fig. 1). Upon addition of gradual amounts of $Fe(ClO_4)_3$, the absorbance at 440 nm was observed to increase and to level off at one molar equivalent of added metal, which was attributed to the formation of the 1:1 Fe^{3+}/DFOB complex.[7] Beyond 1 equiv, a new absorption band was observed to emerge at lower energy (620 nm), and was assigned to the formation of the ferricinium ion.[13]

A similar behavior was noticed for **2** in the presence of Fe^{3+} in acetonitrile. However, the electronic absorption band ($\lambda_{max} = 482$ nm) of the ferrocene unit was red-shifted relative to that of **1** as a result of the presence of the π-conjugating bridge between ferrocene and hydroxypyranone subunits. Furthermore, addition of $Fe(ClO_4)_3$ up to 0.3 mol equiv led to the formation of the 1:3 metal/ligand complex ($\lambda_{max} = 517$ nm), the absorption of the ferricinium ion being observed only when the metal-to-ligand ratio was more than 1:3. These



Scheme 1. Synthesis of **1** (top) and **2** (bottom).

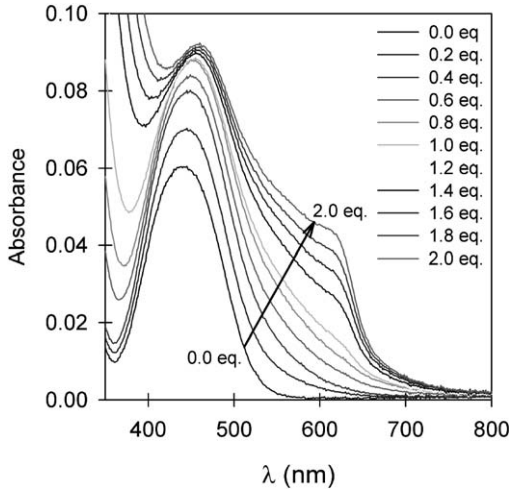


Figure 1. UV–vis spectra of a DMF solution of **1** (5×10^{-4} M) containing gradual amounts of $Fe(ClO_4)_3$ (0–2 equiv).

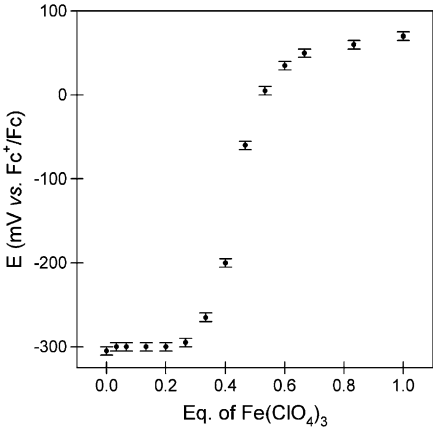


Figure 2. Open circuit potential (E) measured for a solution of **2** (5×10^{-4} M in 0.2 M nBu$_4$NPF$_6$/CH$_3$CN) as a function of added $Fe(ClO_4)_3$ (0–1 equiv).

results indicate that, for both ligands, oxidation of the pendant ferrocene moieties occurs only when an excess of metal is present in the solution. This is consistent with the high thermodynamic stability of ferric hydroxamates and the reduced oxidizing ability of Fe^{3+} in such species.[9]

Cyclic voltammetry (CV) of the free ligands shows a reversible redox system at 0.04 and 0.10 V (vs Fc^+/Fc) for **1** in 0.2 M nBu$_4$NPF$_6$/DMF and **2** in 0.1 M LiClO$_4$/CH$_3$CN, respectively. The positive shift observed relative to pristine ferrocene could be attributed to the electron-withdrawing effect of the carbonyl group.[6] Surprisingly, the addition of Fe^{3+} to the solution of **1** or **2** did not lead to any significant change in the position of the ferrocene-centered redox wave. The absence of electrochemical transduction in ligand **1** can be rationalized by the fact that the ferrocene probe is remote from the coordination center. Moreover, the 1:1 metal/ligand complex is neutral, which is expected not to induce any electrostatic destabilization of the ferricium cation, in contrast to the case of other ferrocene-containing receptors.[5a] The behavior of the conjugated system **2** remains yet not fully understood. It appears that the ferrocene probe does not respond to a binding event at the hydroxypyranone moiety, although both subunits are connected via a conjugated bridge.

These results led us to investigate the influence of the addition of ferric ions on the open circuit potential (OCP), that is, the potential at which there is no current. The potential measured is a mixed potential, a function of all species present in solution and their concentrations. The measurement of the OCP can be used to elaborate a potentiometric sensor. Titration of a solution of pristine ferrocene with $Fe(ClO_4)_3$ was observed to induce a continuous positive shift of the OCP value from the first metal solution aliquot, which is the result of the Fe^{3+} promoted oxidation of ferrocene. In the case of **1** and **2**, a similar effect was observed only when the metal-to-ligand ratio was more than 1:1 and 1:3, respectively (Fig. 2). These results are in agreement with those obtained by electronic absorption spectroscopy. They clearly indicate that Fe^{3+} coordination is the favored process unless there is no excess of free metal in the solution.

In conclusion, we have designed, synthesized, and characterized two ferrocene-containing chelators that are sensitive to Fe^{3+}. Although CV proved to be poorly sensitive to the binding events in the solution, these ligands represent a first, simple approach toward potentiometric chemosensors for Fe^{3+}. To achieve this goal, more work is to be directed to optimizing the coupling mechanism between the redox active moiety and the guest binding site. At this stage, ligands **1** and **2** allow to monitor the OCP change in response to Fe^{3+} complexation. This effect stems from the oxidation of the ferrocene probe which occurs beyond a metal concentration threshold. In this respect, ligands **1** and **2** could be useful for the generation of alerting or dosimeter devices capable of signaling Fe^{3+} concentration jumps.

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10. Characterization of **1**. Mp: 181–184 °C. ^{1}H NMR (DMSO-d_6) δ: 1.19–1.48 (m, 18H, 9*CH_2), 1.95 (s, 3H, CH_3CO), 2.25 (4H, CH_2CONH), 2.56 (4H, CH_2CONOH), 2.99 (4H, CH_2NHCO), 3.14 (2H, CH_2NHCOFc), 3.47 (m, 6H, CH_2NOH), 4.13 (s, 5H, H_{Fc}), 4.31 (s, 2H, H_{Fc}), 4.76 (s, 2H, H_{Fc}), 7.77 (s, 2H, NHCO), 7.94 (s, 1H, NHCOFc), 9.61 and 9.65 (2s, 2H and 1H, NOH); ^{13}C NMR (DMSO-d_6) δ: 20.2, 23.4, 23.5, 25.9, 26.0, 27.5, 28.7, 29.1, 29.8, 38.3, 38.4, 40.1, 40.2, 45.7, 46.7, 46.9, 47.0, 67.9, 69.1, 69.6, 76.8, 168.5, 169.9, 171.1, 171.8.
11. Characterization of **4**. Mp: 123–5 °C. ^{1}H NMR ($CDCl_3$) δ: 4.16 (s, 5H, H_{Fc}), 4.41 (d, 4H, H_{Fc}), 5.05 (s, 2H, CH_2O), 6.20 (d, 1H, J = 16.00 Hz, $H_{ethylenic}$), 6.14 (d, J = 15.80 Hz, 1H, $H_{ethylenic}$), 7.35–7.41 (m, 5H, H_{arom}), 7.52 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 68.0, 69.6, 70.7, 71.9, 79.9, 111.9, 116.0, 127.8, 128.3, 128.7, 135.0, 137.0, 140.9, 161.7, 175.2. HRMS (FAB^+): calculated for $C_{24}H_{20}FeO_3$ $(M+H)^+$ 413.0752, found 413.0756.
12. Characterization of **2**. Mp: 192 °C. ^{1}H NMR ($CDCl_3$) δ: 4.18 (s, 5H, H_{Fc}), 4.39 (d, 4H, H_{Fc}), 6.11 (d, 1H, J = 15.80 Hz, $H_{ethylenic}$), 6.19 (d, J = 16.00 Hz, 2H, $H_{ethylenic}$ and H), 7.50 (s, 1H). RMN ^{13}C ($CDCl_3$) δ: 68.3, 69.5, 70.2, 80.2, 112.0, 116.0, 136.1, 137.0, 140.9, 161.2, 174.8. HRMS (FAB^+): calculated for $C_{24}H_{20}FeO_3$ $(M+H)^+$ 323.0292; found 323.0301.
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