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Awakening of a Ferrous Complex's Electronic Spin in an Aqueous Solution Induced by a Chemical Stimulus

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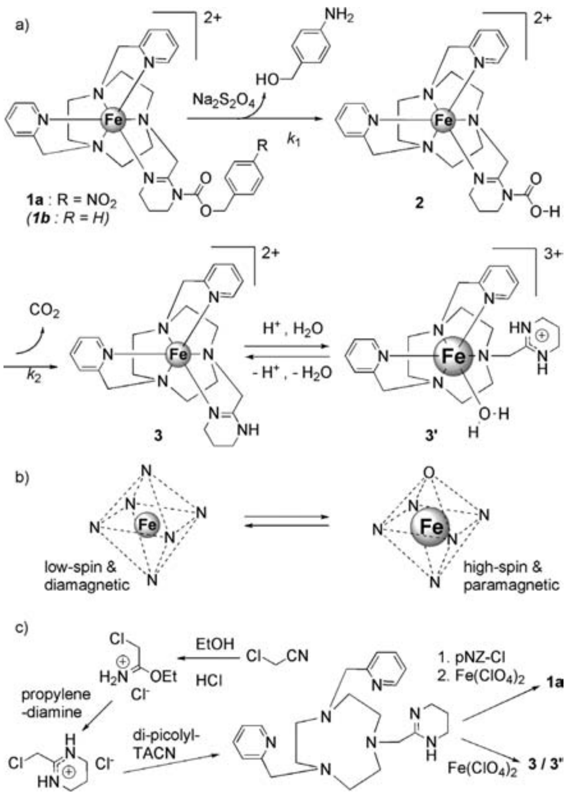
Supporting Information

ABSTRACT: A low-spin, macrocyclic iron(II) complex in an aqueous solution responds to the addition of a chemical reactant (dithionite) by transformation into a high-spin complex, detectable by measurement of the longitudinal relaxation time (T_1) of surrounding water hydrogen nuclear spins. The initial compound does not modify T_1 of pure water at concentrations as high as 4 mM. The response is pH-dependent, and the complex is robust at a variety of conditions.

The category of molecular switches may be divided into those that are reversible and those that are not. While the activity of the former is usually induced by light or a change in the pH, temperature, voltage, or ion presence,[1] the latter, irreversible ones ordinarily respond to a covalent chemical modification and thus fall into the realm of molecular probes. Today, probing particular chemical events (the making or breaking of a covalent bond) in real time or with little delay is arguably achieved mainly by optical detection, in view of the diversity of responsive, switchlike probes at our disposal. Among the other possible physical readouts, a change in the magnetic susceptibility is actively pursued in the design of new probes, whether they be molecular or nanoparticular[2] in nature.[3] One of the physical phenomena entertained as a possible basis for molecular computing[4,5] is the change in the magnetic susceptibility of certain materials. Crystalline samples of ferrous coordination complexes or polymers may show a more or less abrupt switch from a diamagnetic to a paramagnetic state, termed "spin crossover", upon heating or irradiation.[7]

We have previously proposed to exploit the fact that certain transition metals can adopt diamagnetic or paramagnetic spin states according to the nature of the surrounding ligand for the design of a magnetic switch that operates in a true off–on mode (Scheme 1b).[8−10] In the meantime, others reported on a dimethyl sulfoxide sample containing a nickel complex that partially changes its magnetic properties upon irradiation.[11] We now describe a diamagnetic iron(II) complex (**1a**) that irreversibly turns into a paramagnetic one (**3′**) in an aqueous solution at pH 3 when treated with a chemical stimulus (Scheme 1a), a process that can be monitored by measurement of the longitudinal relaxation time T_1 of the sample.

Scheme 1. (a) Mode of Action of 1a, (b) Dependence of the Spin State on the Coordination Motif, and (c) Synthesis of Central Target Compounds



The synthesis of **1a** and **1b** (Scheme 1c) begins with the preparation of a cyclic chloroacetamidine by published chemistry.[12] Its carbamylation with a chloroformate led to a synthon that turned out to be useless because of its high susceptibility to spontaneous hydrolysis. A more sequential strategy was thus chosen by reacting the cyclic chloroacetamidine directly with the remaining secondary amine on the previously reported macrocycle 1,4,7-triazacyclononane bearing two picolyl groups (DPTACN).[9,13] The thus-obtained hexadentate ligand is then either (a) directly complexed with

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iron(II) to furnish complex **3**/**3′** or (b) carbamylated with either *p*-nitrobenzylchloroformate (pNZ-Cl) or plain Cbz-Cl before being complexed with iron(II) to yield perchlorate salts of **1a** and **1b**, respectively. In a typical experiment, 200 mg of crystalline **1a** (Figure S1 in the Supporting Information, SI) can be harvested from 1 g of crude material. Monocrystals of **1a**, **1b**, and **3** were subjected to X-ray structural analysis (Figure 1; see the SI for further details).

Figure 1. X-ray structural analysis (ORTEP plots) of perchlorate salts of **1a** (left) and **3** (right).

The structures of ferrous complexes **1a** and **3** (Figure 1), as well as **1b** (Figure S2 in the SI) are characterized by their binary and cationic nature and the cagelike ligand that surrounds the metal center. Notably, the carbamyl−amidine−iron unit lies roughly in one plane. All six coordination sites on the ligand are nitrogen atoms, with half being of the imine type (sp^2-configured) and the other half being of the amine type (sp^3). All six Fe−N bonds are approximately 2.0 Å long, thus indicating the low-spin state of the ferrous metal center in the crystal compared to a high-spin state that would exhibit coordination bonds of substantially greater length (2.2 Å).[14] Boosted by what is generally referred to as the "macrocyclic effect",[15] the ligand field exercised by the six nitrogen atoms is evidently strong enough to pair all six d electrons. The structures also have parameters very similar to those of the reported low-spin complex $[Fe(TPTACN)]^{2+}$, including a comparable conformation of all six five-membered chelate rings.[16] The ^1H NMR signals (see the SI) of **1a** (aqueous sample of freshly dissolved crystals) and the magnetic moment of 0.5 μ_B determined by Evans' method (Figure S4 in the SI) confirmed the low-spin state in solution.[9,17−19] This value does not change during heating to, e.g., 48 or 72 °C, hence also ruling out the presence of a spin-crossover compound.[6]

The choice of the trigger group is inspired by well-established protective group chemistry[20] and by the simplicity of its removal,[21] with the expectation that the same does not interfere with signal generation. When an aqueous sample (0.2 mM) of **1a** at approximately neutral pH (6.5) is treated with an excess of solid sodium dithionite, liquid chromatography−mass spectrometry (LCMS) monitoring shows the complete disappearance of the starting material within a few minutes (Figure 2a) and the formation of a new compound that has a retention time and a mass spectrum similar to those of an authentic sample of complex **3**. This transition is accompanied with a color change from light yellow to light orange (Figure S5 in the SI). Because this transition does not have an impact on the water hydrogen longitudinal relaxation time ($T1$), as would be expected if **3** were paramagnetic, we titrated (from pH 6.5 to 2.0) an authentic sample of **3** monitored by T_1 measurement to study any potential change in the magnetic susceptibility. Figure 2b indicates that **3** can indeed become fully paramagnetic at pH 3, a trend that is reversible. The transition from long to short relaxation times occurs at roughly pH 4.5, a value that may be interpreted as the pK_a value of the amidine moiety in the presence of the ferrous metal center. The pK_a value of a noncoordinated amidine moiety is approximately at 12.5 in water.[22] The phenomena of protonation versus metal coordination of the amidine moiety clearly enter into competition at pH 4.5. The paramagnetic nature of **3′** at pH 3 can also be deduced from its magnetic moment of 4.5 μ_B (Figure S4 in the SI), which approaches the value of 5.5 μ_B predicted for a fully paramagnetic mononuclear ferrous complex[6] and obtained for a closely related reference compound.[9] When the magnetic moments of **1a** and **3′** are compared, the delicate dependence of the adoption of a high-spin or a low-spin state on the presence of an N6 or N5O1 coordination motif becomes apparent (Scheme 1b).[23]

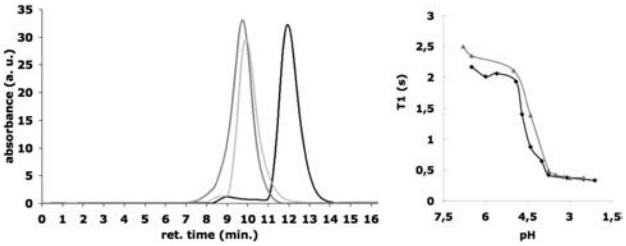

Figure 2. Left: HPLC−UV−MS monitoring (430 nm) of the incubation of aqueous **1a** (0.2 mM, dissolved crystals) with an excess of $Na_2S_2O_4$ at pH 6.5: before $Na_2S_2O_4$ addition (black); 5 min after addition (gray); authentic sample of **3**/**3′** (light gray). Right: Titrations of two independently synthesized samples of aqueous **3** (4 mM) with dilute HCl monitored by T_1 at 500 MHz/11.7 T.

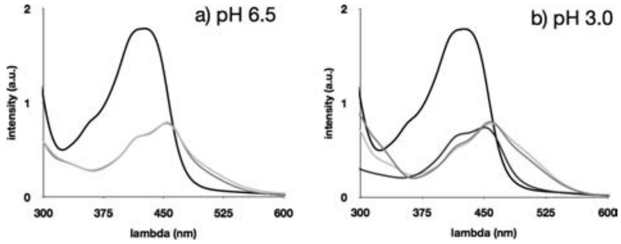

Figure 3. UV spectra of the incubation of aqueous **1a** (0.5 mM, dissolved crystals) with $Na_2S_2O_4$. (a) At pH 6.5 and 22 °C: **1a** before $Na_2S_2O_4$ addition (black), **1a** immediately after $Na_2S_2O_4$ addition (gray), and an authentic sample of **3**/**3′** (light gray). (b) At pH 3.0: **1a** before $Na_2S_2O_4$ addition (black), **1a** after $Na_2S_2O_4$ addition at 22 °C (dark gray), the same sample after 90 min at 100 °C (medium gray), and an authentic sample of **3**/**3′** (light gray).

The alternative approach of the addition of dithionite at pH 3 rather than 6.5 does not change the color or T_1. Thorough UV analysis (Figure 3) turns out to be the most effective means to follow the reaction in view of the intense metal-to-ligand charge-transfer band at roughly 400 nm of **1a** ($\varepsilon \approx 10\,000$), which is also characteristic for the low-spin reference compound $[Fe(TPTACN)]^{2+}$ ($\varepsilon \approx 13\,000$).[16] UV spectra taken at both pH values revealed that the two immolative processes—elimination of iminoquinone methide (k_1), followed by that of carbon dioxide (k_2)—are only very fast at pH 6.5, while the second step is comparatively slow at pH 3 (see Scheme 1a). Only reflux of the reaction mixture for 90 min leads to a UV spectrum largely identical with that of an authentic sample of **3′** (Figure 3b), while the UV spectrum initially obtained from incubation at room temperature indicates a new species that can only correspond to the intermediate carbamic acid **2**. These data lead us to conclude that during LCMS monitoring the mass analyzer cannot distinguish between **2** and **3**/**3′** (presumably because of the high source temperature), while UV analysis can. Indeed, elimination of CO_2 from amidinecarbamic acids is also achieved by heating in other reports.[24]

A new T_1 determination of a sample of **1a** before and after treatment with dithionite at pH 3 was attempted at reflux for 90 min. These conditions ultimately demonstrated the capacity of **1a** to act as a switch from a diamagnetic to a paramagnetic species in an aqueous solution (Figure 4). In terms of T_1 modification, the presence of 4 mM **1a** is invisible; i.e., the corresponding aqueous solution behaves as if no compound were present, while the presence of reacted **1a** leads to a significant modification of T_1. This same T_1 value is obtained when **1a** is incubated at pH 6.5 and room temperature for 5 min before the pH is adjusted to 3.0. It also corresponds to the values of the titration experiment of **3** described in Figure 2b.

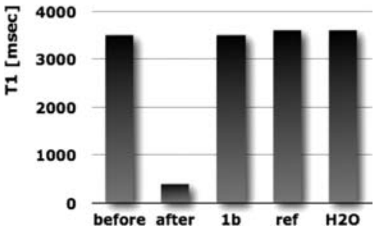

Figure 4. **1a** (4 mM, dissolved crystals) at pH 3.0 acting as an irreversible switch from a diamagnetic to a paramagnetic species as determined by T_1 measurement. before = **1a** (4 mM) before dithionite incubation (citrate buffer at pH 3). after = same sample of **1a** after incubation at 100 °C for 3 h. **1b** = 4 mM, dissolved crystals. ref: low-spin reference compound $[Fe(TPTACN)]^{2+}$ (dissolved powder sample).

Last, the robustness of complex **1a** was examined. Treatment of **1a** at pH 3.0 and reflux for 90 min but in the absence of dithionite (negative control) results in a sample that produces a UV and MS spectrum identical with that of the starting material (Figure S6 in the SI). Likewise, LCMS monitoring (see Figure S7) of a sample at pH 3 or 6.5, at room temperature, and under air for 2 or 3 days does not show any signs of the formation of **3**/**3′**, of decomplexation, or of oxidation. This highlights the stability of the carbamyl link toward spontaneous hydrolysis as well as the kinetic inertness of the low-spin coordination motif toward substitution[25] and oxidation.[26]

In conclusion, ferrous complex **1a** is robust. Dithionite converts it instantly to free amidine **3** at pH 6.5 and room temperature. Conversely, at pH 3.0, where the free amidine exists as paramagnetic **3′**, only the nitrobenzyl group departs swiftly; complete CO_2 departure requires reflux to 100 °C for 90 min. At these conditions, the corresponding aqueous solution turns from a purely diamagnetic state to a paramagnetic one, a process that changes the longitudinal relaxation time of water hydrogen atoms from that of pure water to a significantly reduced value. The example set by the behavior of **1a** may stimulate further investigations that benefit fields such as electron spin resonance imaging or molecular magnetic resonance imaging.[27]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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