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Oxidations

Solvent-Dependent Oxidation of a (Pyridylmethyl)amino Ligand by $FeCl_3$ To Give a Water-Soluble Blue Fluorophore**

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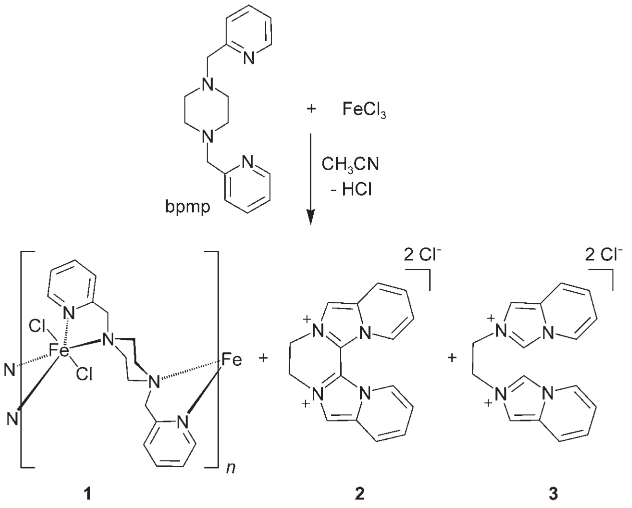
Dedicated to Professor Karl Wieghardt on the occasion of his 65th birthday

Recently, an increasing number of mononuclear iron complexes have been reported that represent effective bioinspired catalysts for the oxidation of hydrocarbons.[1,2] It has been shown that particularly active systems are obtained when polydentate (pyridylmethyl)amino ligands (for instance, tris(2-pyridylmethyl)amine,[2a,b] *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)ethylenediamine,[2c] 1,1-dipyridyl-*N,N*-bis(2-pyridylmethyl)methanamine,[2d] and bispidine derivatives[2e]) are employed. In this context, we have recently described[3] preliminary results concerning the coordination properties of the ligand 1,4-bis(2-pyridylmethyl)piperazine (bpmp)[4] in combination with Fe^{II} and Fe^{III} ions. It was found that treatment of two equivalents of $FeCl_3$ with bpmp in dichloromethane leads to the expected Fe^{III} complex $[(bpmp)FeCl_2][FeCl_4]$, with the bpmp ligand in a tetradentate coordination mode. Herein, we report the fundamental changes observed for the reaction of $FeCl_3$ and bpmp when acetonitrile, DMF, or DMSO are used as the solvents; redox chemistry, C–H activation, C–N bond formation, and C–C bond cleavage occur, which finally lead to a water-soluble blue fluorophore.

Treating bpmp with $FeCl_3$ in acetonitrile solution under argon initially led to a red solution from which a yellow solid slowly precipitated (within two days) that was identified as the Fe^{II} compound $[(bpmp)FeCl_2]_n$ (**1**, yield of crystalline product 27%, see Scheme 1), which had been isolated previously after the reaction of bpmp with $FeCl_2$.[3] Accordingly, a significant portion of the Fe^{III} source employed had been reduced in the conversion, and clearly bpmp represented the only oxidizable substance in solution, even though the nature of the product resulting from the electron loss was not obvious. Furthermore, another peculiar observation could be made. Upon addition of water to the reaction mixture and exposure of the vessel to daylight, a blue fluorescence could be noticed. Bearing in mind that Fe ions efficiently quench fluorescence, from the first it appeared unlikely that the fluorophore corresponded to an iron-containing compound. Hence, the fluorophore was anticipated to be derived from the oxidized ligand, and in order to identify it, the mother liquor that was separated from precipitated **1** was reinvestigated. This process led to the isolation of small amounts of pale yellow crystals, which were analyzed spectroscopically as well as by means of single-crystal X-ray crystallography,[5] and the result (Figure 1) was rather astonishing. In contact with $FeCl_3$, a portion of the original bpmp ligand molecules undergoes an eight-electron oxidation; during this process, they additionally lose six protons, and two new C–N bonds are formed, thus leading to the organic salt **2** (Scheme 1).



Scheme 1. The oxidation of bpmp with $FeCl_3$ in acetonitrile.

A second product, **3**, was identified, isolated, and investigated by single-crystal X-ray crystallography.[5] The result is shown in Figure 2, and it immediately becomes obvious that **3** is derived from **2** by formal addition of dihydrogen to the central C–C bond, leading to its cleavage (Scheme 1). This transformation represents a reduction reaction, and it is reasonable to assume that the two electrons and two protons required for this process stem from the formation of **2** and are transferred to molecules of **2** that have already formed. On dissolution in water, **2** and **3** show a strong fluorescence in UV light, that is, these are the pursued compounds.

Considering the stoichiometry, the maximum theoretical yield that can be expected for **2** and **3** after an equimolar reaction between $FeCl_3$ and bpmp amounts to only 12.5–16.7% (depending on the ratio of **2** to **3**), and this calculation does not consider that part of the ligand employed will function as HCl scavenger. However, provided with the

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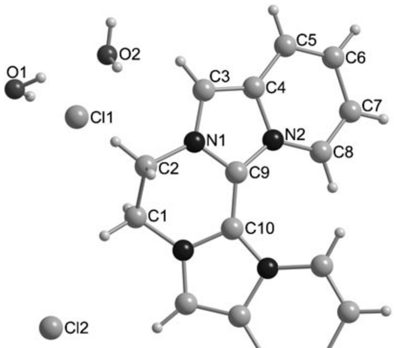


Figure 1. Molecular structure of the dication of **2** with the chloride anions and two cocrystallized water molecules. Selected bond lengths [Å] and angles [°]: C1-C2 1.519(3), C2-N1 1.471(3), N1-C3 1.358(3), C3-C4 1.380(3), C4-C5 1.417(3), C5-C6 1.363(3), C6-C7 1.432(3), C7-C8 1.354(3), C8-N2 1.392(3), N2-C4 1.410(3), N2-C9 1.355(3), C9-N1 1.351(3); C9-C10 1.428(3); C1-C2-N1 107.6(2), C2-N1-C9 120.5(2), C2-N1-C3 128.5(2), N1-C9-C10 118.5(2), N1-C9-N2 107.1(2), N1-C3-C4 106.9(2), C3-C4-N2 106.5(2), C3-C4-C5 134.1(2), C4-C5-C6 119.0(2), C4-N2-C9 108.4(2), C4-N2-C8 121.1(2), C5-C6-C7 120.1(2), N2-C4-C5 119.4(2), C6-C7-C8 121.6(2), C7-C8-N2 118.6(2), C8-N2-C9 130.3(2), N2-C9-C10 134.0(2).

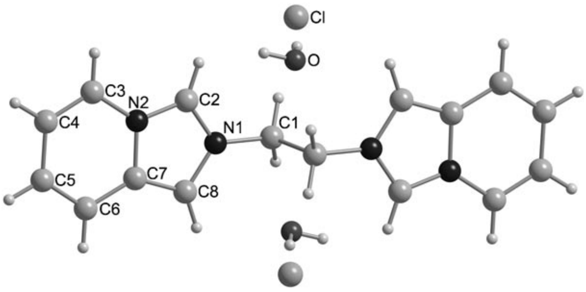


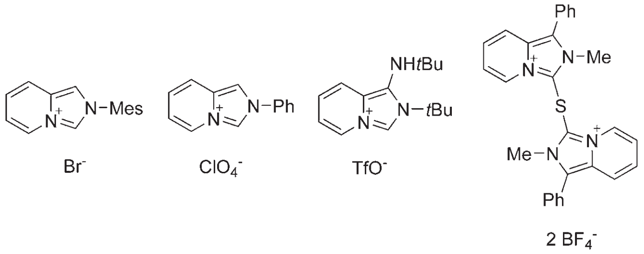
Figure 2. Molecular structure of the dication of **3** with the chloride anions and two cocrystallized water molecules. Selected bond lengths [Å] and angles [°]: C1-N1 1.466(3), N1-C2 1.335(3), N1-C8 1.370(2), C2-N2 1.343(3), N2-C3 1.394(3), N2-C7 1.401(2), C3-C4 1.347(3), C4-C5 1.427(3), C5-C6 1.356(3), C6-C7 1.422(3), C7-C8 1.371(3); C1-N1-C2 123.7(2), C1-N1-C8 125.6(2), N1-C2-N2 107.3(2), N1-C8-C7 106.5(2), C2-N2-C7 108.9(2), C2-N2-C3 128.4(2), N2-C7-C8 106.5(2), N2-C7-C6 118.4(2), N2-C3-C4 117.7(2), C3-C4-C5 121.4(2), C4-C5-C6 121.2(3), C5-C6-C7 118.6(2), C6-C7-C8 135.1(2).

knowledge that the synthesis of **2** requires eight oxidizing equivalents, the reaction was repeated with an eightfold excess of $FeCl_3$. The purification procedure then required the initial precipitation of all iron ions left in solution by addition of aqueous Na_2CO_3, removal of all volatile components, extraction of the organic salts from the residue (mainly NaCl and excess Na_2CO_3), and finally column chromatography and recrystallization. While determining the ideal conditions, it was found that both **2** and **3** are not indefinitely stable in solution; they slowly decompose to unknown products. This instability, as well as the extensive isolation procedure (repeated extraction of vast amounts of solid and loss of material during chromatography and recrystallization) leads to isolated yields that—despite being significantly improved relative to the equimolar reaction—are still comparatively low (5 %), considering the initially expected yields.

When the reaction is performed in MeCN with a 1:8 stoichiometry (bpmp/$FeCl_3$), **3** is always formed with a higher yield than **2** (ca. 2:1), while in DMF or DMSO the only fluorescent product isolated is **2**, independent of the bpmp/$FeCl_3$ ratio.

How are **2** and **3** formed? Certainly the reaction is triggered by initial binding of Fe^{III} ions to the ligand. It is reasonable to assume[6] that subsequently an electron is removed from one of the amino N atoms, which leads to a bpmp radical cation and an Fe^{II} center. The radical cation is prone to eliminate an H atom (or $H^+ + e^-$), most likely from one of the methylene groups in the vicinity of the amino radical cation. This process should lead to an iminium ion, which could undergo coupling to the pyridyl N atom before a further electron is released; continued cascade-type coupled electron–proton losses finally result in the products **2** and **3**. The question is why this kind of reaction proceeds in acetonitrile, DMF, and DMSO, while in dichloromethane typical coordination chemistry is observed, that is, Fe^{III} simply binds to bpmp, and no electron transfer occurs. To address this question, cyclovoltammetric investigations were performed, which gave conclusive results: the oxidation potential of bpmp in dichloromethane lies 0.15 V higher than in acetonitrile (and 0.12 V and 0.35 V higher than in DMF and DMSO, respectively), which seems to prohibit the electron transfer in the chlorinated solvent.[7]

Finally, we turned our attention to the two fluorophores. While to our knowledge the structural motif of **2** is unique, there are some imidazolium-based compounds[8] that at least resemble **3**, and some of those were also identified as fluorophores (Scheme 2).



Scheme 2. Imidazolium-based compounds related to **3**.

Such compounds usually emit between 250 and 450 nm, that is, in the green–blue range. Still, water-soluble blue fluorophores are of much interest, for instance, with respect to markers and probes but also in the context of two-photon absorptions.[9] We have therefore investigated the physical properties of **2**. The UV/Vis absorption spectrum shows two peaks at 398 and 420 nm, while the fluorescence spectrum, obtained after excitation at 398 nm, shows two corresponding peaks at 442 and 468 nm (Figure 3). The quantum yield was determined to be 0.43 ($\varepsilon_{max} = 18200\ L\,mol^{-1}\,cm^{-1}$; $k_{rad} = 4.56 \times 10^7\ s^{-1}$, corresponding to $\tau_{rad} = 21.9$ ns). Compound **2** thus represents a comparatively strong fluorophore.

Currently, we are derivatizing the ligand system to see whether the reaction cascade leading to **2** and **3** can be stopped at some stage, which would provide some mechanistic information. Furthermore, the role of the iron salt will

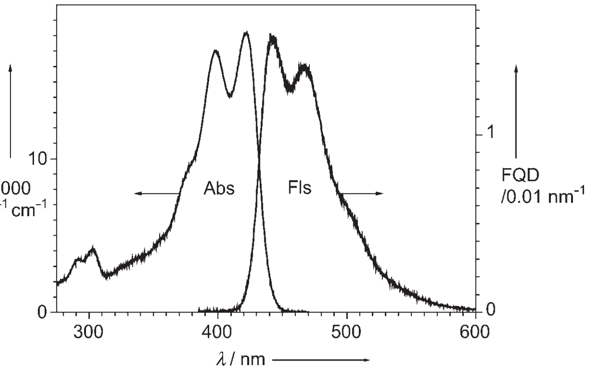


Figure 3. Absorption and fluorescence spectra of **2** in water; FQD = fluorescence quantum distribution.

be studied. Is it possible to replace FeCl$_3$ by other oxidants or to find conditions under which the reaction can even be performed electrochemically? Can the reaction be triggered starting from Fe^{II} with external oxidants? The results should lead to a more general understanding concerning the characteristics of certain classes of (pyridylmethyl)amino-based ligands.

Experimental Section

2 and **3**: A solution of FeCl$_3$ (9.67 g, 59.6 mmol) in MeCN (30 mL) was added dropwise to a solution of bpmp (2.00 g, 7.45 mmol) in MeCN (30 mL) under argon. The reaction mixture was stirred at room temperature for two weeks. After removing all volatiles in vacuum, the residue was dissolved in water (50 mL) and treated with a solution of Na$_2$CO$_3$ (7.90 g, 74.5 mmol) in water (50 mL). The resulting precipitate was separated by filtration, and all water was removed from the filtrate in vacuum. The residue was extracted with methanol (3 × 5 mL), and the combined extracts were concentrated to a volume of 2 mL. This solution was employed for column chromatography with neutral Al$_2$O$_3$ as the stationary phase and ethanol, methanol, water, and mixtures of these solvents with increasing polarity as the mobile phase. A fraction containing only **2** and **3** (140 mg, ratio ca. 1:2) could be separated, and removing all volatiles yielded the two fluorophores as a yellow solid.

Single crystals of **2** and **3** could be grown by slow evaporation of the solvent from an ethanolic solution of the fluorophores as obtained from column chromatography.

When the same experiment is performed in DMSO with a reaction time of three days, pure **2** can be isolated in 5 % yield.

2: Elemental analysis (%) calcd for **2**·2 H$_2$O, $C_{16}H_{18}Cl_2N_4O_2$: C 52.04, H 4.91, Cl 19.20, N 15.17; found: C 51.95, H 5.11, Cl 18.98, N 15.32. ^{1}H NMR (400 MHz, D$_2$O, 25 °C): $\delta = 8.49$ (m, 4H; N-C*H*-CH, N-CH-C*H*), 8.00 (m, 2H; N-CH-C$_{quat}$), 7.48 (m, 4H; C$_{quat}$-CH, C$_{quat}$-CH-C*H*), 5.06 ppm (s, 4H; CH$_2$). ESI-MS (methanol) *m/z* calcd for $[C_{16}H_{14}Cl_2N_4]^{2+}$: 131.0604; found: 131.0602.

3: ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): $\delta = 6.97$ (m, 2H; N-CH-N), 5.93 (m, 2H; N-C*H*-CH), 5.48 (s, 2H; N-CH-C$_{quat}$), 5.31 (m, 2H; C$_{quat}$-C*H*-CH), 4.90 (m, 2H; C$_{quat}$-CH-C*H*), 4.77 (m, 2H; N-CH-C*H*), 2.79 ppm (s, 4H; CH$_2$). ESI-MS (methanol) *m/z* calcd for $[C_{16}H_{16}Cl_2N_4]^{2+}$: 132.0682; found: 132.0680.

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[5] Data for the X-ray structure analyses: **2** × 2 H$_2$O: $C_{16}H_{18}Cl_2N_4O_2$, $M_r = 369.24$, triclinic, space group $P\bar{1}$, $a = 6.799(1)$, $b = 10.256(2)$, $c = 12.993(2)$ Å, $\alpha = 111.463(8)$, $\beta = 93.785(9)$, $\gamma = 103.935(9)°$, $V = 806.4(2)$ Å^3, $Z = 2$, $T = 100(2)$ K, $F_{000} = 384$, $\mu = 0.420$ mm^{-1}, $\Theta = 3.54$–$30.51°$, 13436 reflections collected, 4865 independent reflections [$R_{int} = 0.0728$], GoF = 1.063, $R = 0.0487$, $wR_2 = 0.1043$, largest diffraction peak and hole 0.574/−0.380 e Å^{-3}. **3** × 2 H$_2$O: $C_{16}H_{20}Cl_2N_4O_2$, $M_r = 371.26$, triclinic, space group $P\bar{1}$, $a = 6.886(1)$, $b = 8.008(1)$, $c = 9.206(1)$ Å, $\alpha = 65.64(1)$, $\beta = 69.29(1)$, $\gamma = 82.29(1)°$, $V = 432.6(1)$ Å^3, $Z = 1$, $T = 100(2)$ K, $F_{000} = 194$, $\mu = 0.392$ mm^{-1}, $\Theta = 3.69$–$27.49°$, 1964 reflections collected, 1964 independent reflections [$R_{int} = 0.0000$], GoF = 1.077, $R = 0.0331$, $wR_2 = 0.0834$, largest diffraction peak and hole 0.364/−0.244 e Å^{-3}. The data for **2** and **3** were collected on a STOE IDPS2T diffractometer using Mo$_{K\alpha}$ radiation, $\lambda = 0.71073$ Å. The structures were solved by direct methods (SHELXS-97), refined versus F^2 (SHELXL-97) with anisotropic temperature factors for all non-hydrogen atoms.[10] All hydrogen atoms were added geometrically and refined using a riding model. CCDC-600366 (**2**) and CCDC-600367 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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