A Ferrous Center as Reaction Site for Hydration of a Nitrile Group into a Carboxamide in Mild Conditions

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The mild and efficient hydration of nitriles in ecological-friendly conditions, a challenging research area, still far from being achieved by synthetic chemists,[1–7] is known in biological systems: Nature has designed the so-called nitrile hydratases (NHases), which are metal-containing proteins that are key players in the process of assimilation of nitriles upon conversion to amides.[8,9] The presence of Co(III) or Fe(III) ions centers is essential to the activity of the enzyme, and a generally accepted hypothesis involves the interaction of the substrate and reagent with the metal site.[10–14] The detailed mechanism of the reaction, however, is far from being completely understood, especially the question as to whether water molecule or the nitrile, or both, coordinates to the metal in order to be activated.

In our efforts to develop electron-deficient iron complexes with tripodal tetraamine ligands,[15–17] we synthesized the cyanide-α-substituted tripod CNTPA, L_1 = (6-cyano 2-pyridylmethyl)bis(2-pyridylmethyle)amine, and report that under anaerobic and wet conditions, the dichloroferrous complex L_1FeCl_2 converts to L_2-$FeCl_2$, with L_2 = H2NCOTPA, (6-carboxamido 2-pyridylmethyl)-bis(2-pyridylmethyl)amine. Decomplexation of L_2FeCl_2 affords the free L_2 ligand, that has incorporated ^{18}O when H2^{18}O is used. This reaction represents to our knowledge the first example of the hydration of a nitrile carried out by a *ferrous (Fe(II))* center to yield the corresponding carboxamide. We also demonstrate that the nitrile group does not need to be coordinated to react with water.

The preparation of L_1 and L_1FeCl_2 follows straightforward procedures.[18,15] L_1FeCl_2 is a red thermally stable and moderately oxygen-sensitive compound displaying an Fe(II) => ligand MLCT transition at λ = 389 nm (ϵ = 1.96 × 10³ mmol·cm²) in its UV–vis spectrum in line with a tetradentate coordination mode of the ligand.[15,19] Both its ¹H NMR (well resolved paramagnetically shifted signals) and the molecular conductivity data (Λ = 13.8 S·mol⁻¹·cm² at 10⁻³ M) support a pseudo-octahedral geometry in solution.[15] IR spectroscopy shows ν_{CN} at 2238 cm⁻¹. Single crystals of L_1FeCl_2 could be obtained. As expected from solution studies, the ligand coordinates in a tetradentate fashion around the metal, and the two chloride ions complete the coordination sphere. The ORTEP diagram is displayed in Figure 1.

Contacts between the nitrile group and the iron and equatorial chloride are evidenced by d_{C18-Fe} = 3.54 Å, $d_{C19-Cl1}$ = 3.70 Å, and d_{N5-Cl1} = 3.69 Å. The $C_{18}C_{19}N_5$ segment is bent with $<C_{18}C_{19}N_5$ = 173.8°. This provides evidence for a repulsive interaction between the equatorial chloride ligands and the CN group, the latter being probably destabilized.

L_1FeCl_2 is thermally stable in anaerobic solution for days. The addition of 100 equiv of degassed water to a solution of L_1FeCl_2 resulted in minor yet detectable changes in the UV–visible
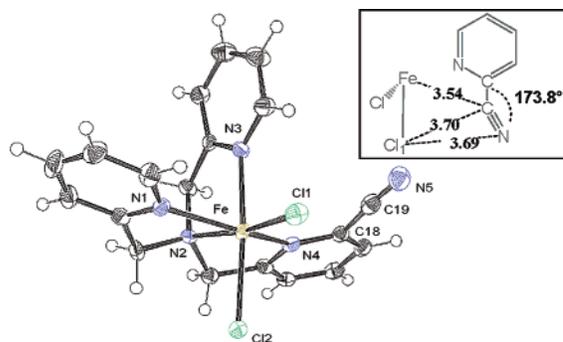
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Figure 1. ORTEP drawing of L_1FeCl_2. Selected bond lengths (Å) and angles (deg): Fe–N3 2.202(4); Fe–N1 2.215(4); Fe–N2 2.266(4); Fe–N4 2.312(4); Fe–Cl1 2.3496(15); Fe–Cl2 2.4324(15); N3–Fe–Cl2 166.97-(12); N1–Fe–N4 146.20(17); N2–Fe–Cl1 171.22(12); C18–C19–N5 178.8(6). The insert shows contacts between the iron center and C19, equatorial chloride Cl1 and the nitrile substituant, and tilting of the C18C19N5 segment.
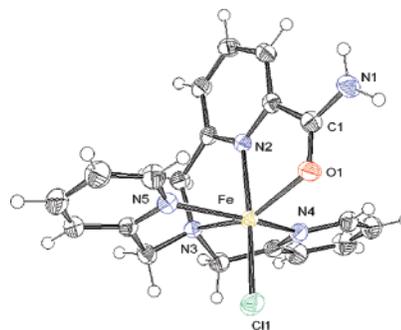

Figure 2. ORTEP drawing of the [L_2FeCl]⁺ cation. Selected bond lengths (Å) and angles (deg): Fe–N2 2.1339(16); Fe–O1 2.1443(16); Fe–N4 2.1913(18); Fe–N5 2.2195(19); Fe–N3 2.2430(18); Fe–Cl1 2.3328(6); O1–C1 1.259(3); N1–C1 1.329(3); N2–Fe–Cl1 173.00(5); N5–Fe–N4 151.37(7); N3–Fe–O1 150.97(6); N1–C1–O1 121.9(2).

spectrum over 24–40 h, the Fe(II) => ligand MLCT being shifted to λ = 396 nm (ϵ = 1.82 × 10³ mmol·cm²), with an isobestic point at λ = 412 nm. When the reaction temperature was lowered to 0 °C, no change could be detected, even in the presence of more added water.[20] In ¹H NMR, the formation of a new high-spin ferrous species over 24 h was observed. An amido carbonyl group was detected in IR with $\nu_{C=O}$ = 1679 cm⁻¹. The new L_2FeCl_2 complex could be obtained in a single-crystalline form. Its ORTEP diagram is displayed on Figure 2.

Obviously, the nitrile substituent has been converted into an amide group, with d_{C1O1} = 1.258 Å and d_{C1N1} = 1.329 Å. Unlike in L_1FeCl_2, the substituted pyridyl arm lies trans to the chloride, and the oxygen of the amide group coordinates to the iron center trans to the tertiary amine of the tripod with d_{O1-Fe} = 2.14 Å. The

Scheme 1. Proposed Mechanism for the Hydration of the Nitrile Substituent upon Addition of Water to L_1FeCl_2[a]
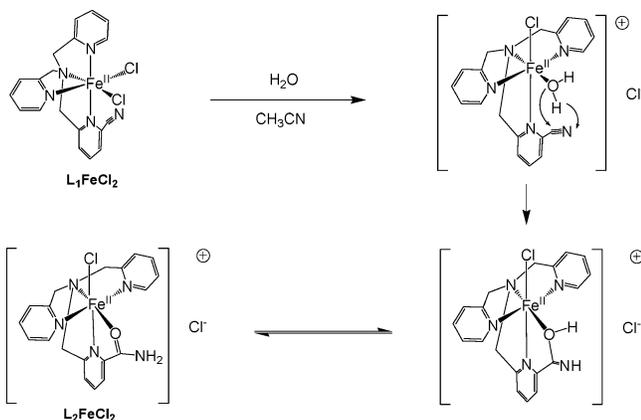
L_1FeCl_2

[a] Crystal structures are provided for L_1FeCl_2, L_2FeCl_2.

Scheme 2. Hydration of the Nitrile Substituent of L_1 = CNTPA Leading to L_2 = H$_2$NCOTPA, upon Temporary Complexation to Iron Dichloride in Wet Conditions[a]
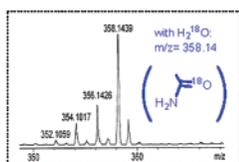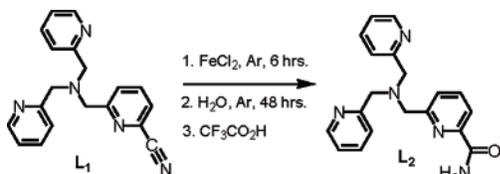
[a] Insert: ESMS, when H$_2$^{18}O is used; m/z = 358.14 for L_2(^{18}O) + Na$^+$.

complex is thus cationic, the uncoordinated chloride ion lying far away from the metal center with d_{FeCl} = 6.28 Å.

L_1 as a free ligand is indefinitely stable in the presence of water, and L_1FeCl_2 also is indefinitely stable, but in the absence of water. Thus, coordination of water to the ferrous center must occur prior to any further reaction, as displayed in Scheme 1. The first step corresponds to the dissociation of the chloride from the metal in the presence of water, followed by coordination of water. In L_2-$FeCl_2$ the fact that the substituted pyridyl arm lies trans to the chloride, that is, at a different position than in the starting material L_1FeCl_2, strongly suggests rearrangement of the coordination polyhedron, and coordination of water at the metal site as a necessary step in the conversion of L_1 to L_2. The detection of an isobestic point in UV−vis during hydration reaction impeded detection of any intermediate.

Treatment of L_1FeCl_2 with H$_2$O during 48 h at room temperature followed by acidification with CF_3CO_2H under inert atmosphere resulted in complete bleaching of the medium. Extraction of the organic phase under standard conditions with CH_2Cl_2 afforded L_2 as a white solid together with variable amounts (however, never more than 20% based on NMR) of L_1. L_2 was characterized by ^{1}H and ^{13}C NMR, IR, and mass spectroscopy. In the ^{13}C NMR, the δ_{CN} = 117.3 ppm resonance was replaced by a new signal at δ_{CO} = 167.0 ppm, and IR displayed a new absorption at ν_{CO} = 1685

cm^{-1}. MS yielded the molecular ion at m/z = 334.15 (L_2H^+) and 356.14 (L_2Na^+) as the main signal. As displayed in Scheme 2, the use of H$_2$^{18}O resulted in incorporation of ^{18}O in L_2 with m/z = 336.16 ($L_2[^{18}O]H^+$) and 358.14 ($L_2[^{18}O]Na^+$).

The involvement of a ferrous center in non-redox chemistry to promote the conversion of functional groups is unusual.[21,22] To our knowledge, the present communication is the first reported example of hydration of a nitrile function by a *ferrous complex*. In addition, we demonstrate that the smooth hydration reaction does not necessarily require the nitrile to be coordinated, but activated in the vicinity of a metal-coordinated water molecule. Enhanced Lewis acidity at the metal center might also contribute to what could be described as an anchimer effect, leading to nitrile hydration by a simple "outer-sphere mechanism".[9,14] Comparative studies with complexes of the same ligand with other transition metals are currently under investigation in our laboratory.

Supporting Information Available: All synthetic details, including the preparation and characterization of all compounds mentioned; experimental details for the hydration reaction. For the two reported structures, the crystallographic files in CIF format have been deposited. This material is available free of charge via the Internet at http:// pubs.acs.org.

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(20) Addition of a large excess of water resulted in precipitation of the starting material in the UV−vis cuvette.
(21) See for instance: Jain, R.; Hao, B.; Liu, R.-P.; Chan, M. K. *J. Am. Chem. Soc.* **2005**, *127*, 4558−4559.
(22) With a *diferric* complex, see: Hazell, A.; Jensen, K.; McKenzie, C. J.; Toftlund, H. *Inorg. Chem.* **1994**, *33*, 3127−3134.

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