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RESEARCH ARTICLE

Synthesis of a New Ligand Tris (2-pyridylmethyl) amine functionalized by a methoxy group and study of Dichloroferrous complexes, its reactivity to dioxygen both in the presence and absence of substrate

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ABSTRACT

The biomimetic oxidations at active sites of iron proteins involve peroxides, especially hydrogen peroxide which is a strong and very convenient reagent since it is inexpensive and does not release any toxic by-products. In many cases however, Mother Nature uses molecular dioxygen to carry out major oxidation reactions in particularly attractive conditions. The biomimetic interest of iron complexes in the tris (2-pyridylmethyl) amine series (TPA) is no longer to demonstrate. Various α-substituted TPA-based ligands were prepared with the idea to modulate the electronic properties at the metal centre. A new type of ligand MeOTPA was prepared and the effect of (MeO) in the oxygenation of complex was studied.

Keywords: Biomimetic, tris (2-pyridylmethyl) amine, iron(II), Molecular dioxygen activation.

1. INTRODUCTION

The catalysis of oxygen transfer to organic substrates is well known in biology and can be carried out by enzymes containing metalloproteins having an iron center of the heme type (cytochromes P-450 for example) or non-heme (methane monooxygenase by example) [1]. These reactions can be carried out using molecular oxygen. Another well studied enzyme in biological systems is tryptophan hydroxylase, which catalyzes a key step in serotonin biosynthesis and plays important roles in the circadian rhythms [2-8]. In this case, it must be fixed. Then there can either be formation of a hydroperoxo-reactive species or cleavage of the O-O bond. In the latter case, highly reactive metal – oxo compounds are formed [9]. Iron complexes with tris (2-pyridyl methyl) amine (TPA) tetradente ligands and some of its derivatives have been well studied over the past twenty years. Some of them show functional analogies with certain non-heme iron enzymes involved in the activation of oxygen [10]. However, in the majority of cases, hydroperoxides are used as

oxygen donating agents [11-18]. Molecular oxygen has been well used, however, but it only reacts with ferrous compounds already coordinated with substrates which activate the metal, such as catechols or thiolates [19-20]. The study of a series of dichloroferrous complexes with substituted TPA-type ligands was undertaken in the laboratory [21-22]. On the ligand, the α-substitution of nitrogen can induce trident coordination of the ligand (potentially tetradent). The complexes thus formed can react with molecular oxygen without particular activation, provided that the ligand is substituted by halogens. There is therefore here a double effect, steric and electronic.

One of the goals was to build artificial systems that are active to molecular oxygen. Ideally, this requires the presence of an oxygen binding site, an electron source (external or grafted) and a site protection matrix, the latter of the protein type, (riboflavin or nanotube for example). In any case, it is important to be able to have a set of functional complexes which also have an interesting reactivity. This is the context in which this study is situated. First, ligands of TPA structure monosubstituted was prepared by functional groups and added to series of this type of ligands [23-33] which has been will studied previously. Their synthesis will be described. Then the coordination chemistry of these ligands was observed, which was approached by the preparation of dichloroferrous complexes. One of the complexes prepared has been completely characterized and studied in solution. Finally, the reactivity of this complex to molecular oxygen was described first.

Following the same ideas, the study focused on complexes coordinated with ligands substituted by groups known to be electron donors. This is how the preparations of the methoxy-substituted ligand complexes first discussed in the present paper emerged.

2. METHODS AND MATERIALS

2.1. Synthesis of ligands

The synthesis of the DPA and TPA ligands was carried out according to published methods [1, 8] No particular difficulty was encountered.

2.2. Synthesis of 2-methoxy-6-Methylpyridine [30]

6.10 g (153mmoles) of 60% NaH are washed with hexane and the mineral oil is extracted several times under argon until obtaining NaH without oil (pure NaH). 12 g (70mmoles) of 2-Bromo-6-Methylpyridine are dissolved in 80 ml of DMF, the solution is added to the NaH gradually over 15 minutes. The temperature of

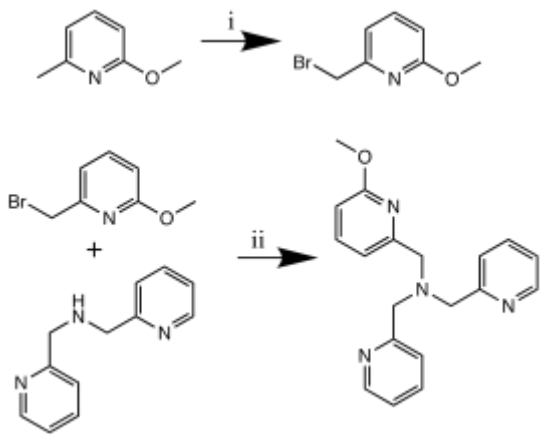

Figure1: i) NBS, AIBN, CCl_4, reflux for 15h,
ii) Na_2CO_3 in CH_3CN reflux for 16h.

the medium is adjusted to 0°C using an ice bath under argon. The medium becomes very thick and the temperature does not exceed 0°C. 6.1 cm3 (153 mmol) of methanol are added gradually over 5 minutes. The reaction mixture is refluxed for 3 hours at 80°C. The solution obtained is allowed to cool to room temperature. The product is extracted several times with ether. At the end, the transparent pale yellow solution obtained is washed several times with distilled water. Then, the organic phase is dried over $MgSO_4$ then filtered and evaporated. This transparent pale yellow liquid is distilled under reduced pressure (P=15 mmHg). The fraction of the desired product was collected between 80 and 85°C, it is a colorless liquid.

RMN1H, ($CDCl_3$ δ ppm): 7.35-7.31, (1Hγ, m) 6.62-6.60 (1Hβ, d, J=6); 6.48-6.45 (1Hβ',d, J=9); 3.86,(s, 3H,OCH_3); 2.28, (s, 3H,CH_3).

2.3. Synthesis of 2-methoxy-6-Bromomethylpyridine [30]

Into a solution of 2-methoxy-6-methyl pyridine (12g, 97.5 mmoles) in 200ml of carbon tetrachloride CCl_4 are introduced 20.82 g of N-bromosuccinimide (117.3 mmoles) and 675 mg of azobisisobutyronitrile (2.79 mmoles). The reaction mixture is brought to reflux (90°C.) for 5 hours. At the end, the solution was evaporated to dryness. The product was taken up in 200 ml of toluene. The precipitate which forms is filtered off and the yellow solution is concentrated. The product is purified by chromatography column on silica mounted in toluene. The separation is followed by thin layer chromatography (TLC). This is the third fraction that contains the desired product. The product 2-methoxy-6-Bromomethylpyridine is a transparent liquid obtained with a yield of 50% (mass obtained: 9.85 g)

RMN1H: ($CDCl_3$, δ ppm) 7.54-7.47, (t, 1H) 6.96-6.96 (d, 1H); 6.64-6.61 (d, 1H); 4.43, (s, 2H); 3.91(s, 3H).

2.4. Synthesis of Bis (pyridin-2-ylmethyl) amine (DPA) [31]

5 g (39.2 mmoles) of picolyl chloride are dissolved in 120 ml of ethanol. 8.84 g (81.8 mmoles) of 2-aminomethylpyridine are then added. The reaction mixture is refluxed for 12 hours at 85°C. The solution obtained is taken up in an aqueous solution of K_2CO_3, then dichloromethane was added. The organic phase is then washed and then dried over $MgSO_4$, filtered and evaporated. The product is distilled under 1 to 2 mmHg and two fractions are collected: one distilling between 45 and 55°C (2-aminomethylpyridine) and the others is distilling between 139-141°C (Bis (pyridin-2-ylmethyl) amine) with an efficiency of 80%.

2.5. Synthesis of (bis (2-methylpyridine) [(6-methoxy-2-methylpyridine)] amine) (MeOTPA)

1 g (4.95 mmol) of 2-bromomethyl-6-methoxy-pyridine and 0.985 g (4.95 mmol) of DPA are introduced into a flask. 1 equivalent of Na_2CO_3 or 836 mg and approximately 150 ml of ethanol are added. The reaction mixture is refluxed for 14 hours at 95°C. The solution is evaporated and distilled water is added in order to solubilize the remaining Na_2CO_3, dichloromethane to solubilize MeOTPA. The

medium is decanted, the recovered organic phase is dried over $MgSO_4$ and then filtered. The filtrate is then purified by chromatography on an alumina column mounted with DCM containing 7% methanol. MeOTPA has an orange-brown color (Yield: 1.346g = 85%).

Analyse elementary:

Calculated for $C_{19}H_{20}N_4O$. C: 71,23; H:6,29; N: 17,49.
Calculated for $(C_{19}H_{20}N_{4O})_2+H_2O$:C:69,28; H: 6,43;N:17,10.
Obtained for $(MeOTPA)_2.H_2O$.C: 69,27; H:6,409; N:16,56.
RMN 1H (300 MHz, $CDCl_3$):δ (ppm) 3,78 (s, 2H,CH_2); 3,85 (s, 4H,2xCH_2); 3,94 (s, 3H,CH_3); 6,53-6.50 (d, 1H); 6.97-7,001 (d, 1H); -7.03-7,10 (m, 2H); 7,40-7.50 (t, 2H); 7,55-7.62 (m, 3H); 7,74 (m, 1H); 8,46 (d, 2H, α-pyridine).

RMN 13C:163(C-OMe); 159(2xC); 156(C); 148(2CH); 138(CH); 136(2CH); 122(2CH); 121(2CH); 115(CH); 108(CH); 60(2C,CH_2); 59(2 CH_2); 53(CH_3).

2.6. Procedure for determining the molar conductivity of a complex

4 ml of degassed dry acetonitrile are introduced into the measuring cell, and the relative conductivity of the blank is measured (A). The relative conductivity of the sample dissolved in 4 ml of the same solvent is then measured (B). The conductivity of the compound is obtained by subtracting B–A. The molar conductivity is obtained by the ratio (B–A)/Complex concentration.

In the case of Bis-catTPAFeCl_2, the ligand is first introduced into the cell. The metallation is carried out in situ, by adding a stoichiometric quantity of $FeCl_2$ which is excessively measured.

2.7. Common procedure for the metallation of all ligands with ferrous chloride

The principle of this reaction is to oppose one

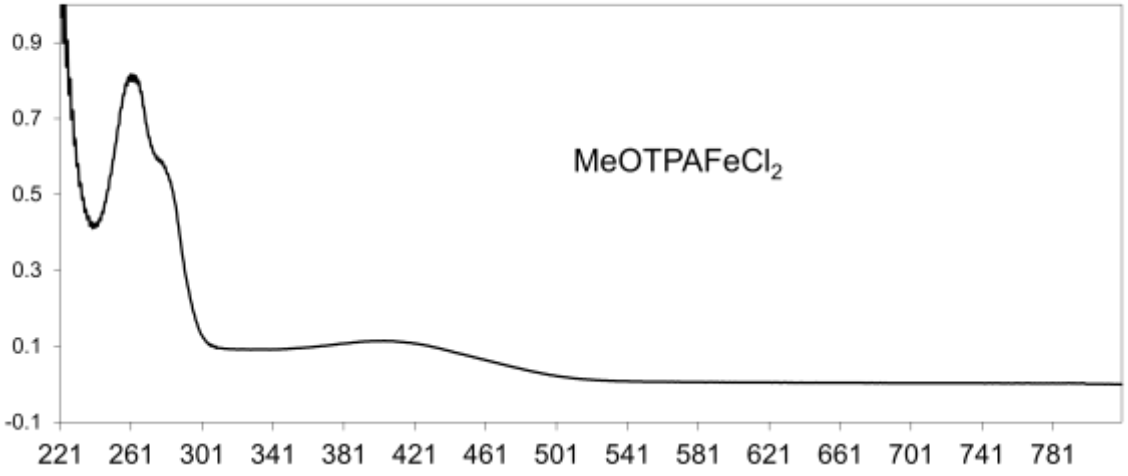

Figure 2: The UV-visible spectrum for the MeOTPAFeCl_2 complex

equivalent of ferrous chloride to one equivalent of ligand. In practice, a slight excess of ligand (5 to 10%) is used: this allows complete complexation of the metal, and the excess ligand is easy to remove by washing with ether or THF. This reaction takes place in the absence of Schlenck tube air. The solvents used are all distilled and degassed before use. The filtrations are carried out under overpressure by means of filter cannulas.

2.8. Synthesis of ligand MeOTPA

The MeOTPA ligands are synthesized according to the conventional method used in the laboratory, the synthesis of a mono-substituted tris (2-pyridylmethyl) amine (TPA) ligand is a second-order nucleophilic substitution reaction carried out from bis (2-pyridylmethyl) amine (DPA)) and the appropriate brominated reagent, here 6-methoxy-2-bromomethyl pyridine, in the presence of a base (Figure 1). They are generally characterized by 1 H NMR, 13C, and elemental analysis.

2.9. Complexation of (MeO)TPA

The ligands, the syntheses of which have been described above, were metallized with anhydrous ferrous chloride, specially prepared in the laboratory for this purpose. Commercial ferrous chloride is indeed very often hydrated and contaminated with small amounts of ferric salts which give it, at best, a pale brown color. Anhydrous $FeCl_2$ is a perfectly white solid.

$$L + FeCl_2 \xrightarrow[5h\ minimum,Ar]{THF\ ou\ CH_3CN} LFeCl_2$$

The generic reaction is very simple and involves the use of one equivalent of ligand relative to the metal salt, under strictly anhydrous conditions and under an argon atmosphere. The solvents are thus freshly distilled over appropriate desiccants, and before use, undergo extensive cryogenic degassing. The methodology used is that known as the “Schlenck technique”.

In principle, and for practical reasons of further processing, a 10% excess of ligand is opposed to ferrous chloride. The yields of clean isolated

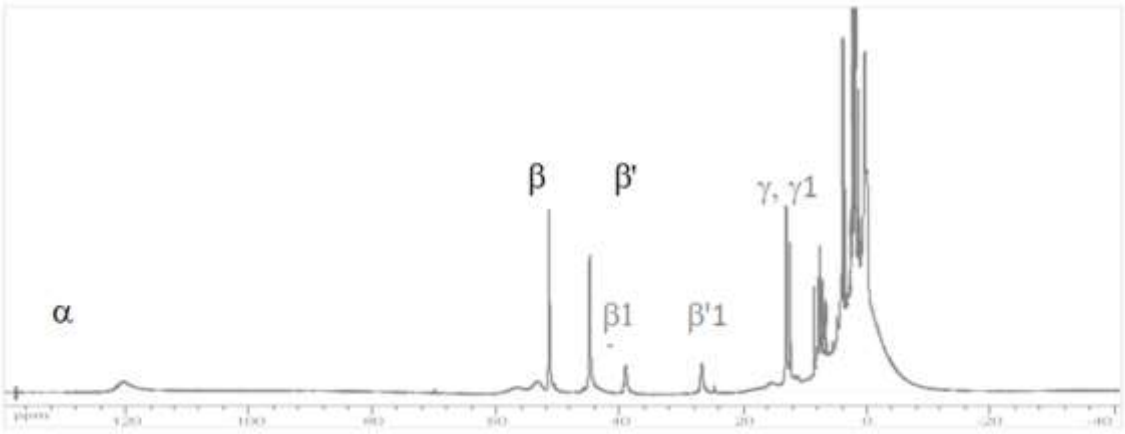

Figure 3: The 1H NMR spectrum for the MeOTPA$FeCl_2$ complex

products are generally between 80 and 90%. It is very probable that the reaction is quantitative, but more or less important quantities of compound are lost during the treatment, which is here entirely carried out under an inert atmosphere. In the solid state, the compounds are handled quickly out of the Schlenck tube for a few seconds, for example using an inverted argon funnel.

The solids obtained are generally sufficiently soluble in nitriles to be able to be studied in solution in this type of solvent. The methodology used for their characterization is simple and consists of using the following techniques:

a) UV- visible and conductimetry

The presence of a well-defined MLCT-type absorption at λ = 403 nm with a relatively strong intensity (ε= 1652.1 $mmmol^{-1}.cm^2$) (table 1) strongly suggests a tetradent coordination mode for this ligand, involving the three pyridines [22] (figure 2).

b) RMN 1H

This spectrum is characteristic of a strong spin Fe(II) species, with a pseudo-octahedral geometry, in which the ligand coordinates in a tetradent manner [22, 33]. The two fine and intense signals correspond to the β and β' 'protons of non-pyridines; those of weaker intensity, to protons β and β'of substituted pyridine (figure 3). It can also be compared with the spectra of the derivatives of the mono and difluorinated ligands. The methylene protons appear in the form of broad signals between 40 and 60 ppm.

c) Radiocrystallographic structure

Crystallization of the solid originating from the metallation of the ligand was carried out by the usual methods under an inert atmosphere.

Table 1: The value of absorption in UV- visible spectrum and the conductimetry of complex $MeOTPAFeCl_2$

$MeOTPAFeCl_2$	
Distances	Angles
Fe-N3 2.215(2)Å	N3 Fe N4 109.25(9)° N3 Fe N1 73.72(8)°
Fe-N4 2.233(2)Å	N4 Fe N1 74.07(8)° N3 Fe Cl2 95.30(6)°
Fe-N1 2.316(2)Å	N4 Fe Cl2 91.50(6)° N1 Fe Cl2 157.15(6)°
Fe-Cl2 2.3612(8)Å	N3 Fe Cl1 82.11(6)° N4 Fe Cl1 157.32(7)°
Fe-Cl1 2.4986(8)Å	N1 Fe Cl1 91.26(6)° Cl2 Fe Cl1 107.31(3)°
Fe-Cl1 2.5091(8)Å	N3 Fe Cl1 161.85(6)° N4 Fe Cl1 83.51(7)°
Cl1-Fe 2.5091(8)Å	N1 Fe Cl1 98.54(6)° Cl2 Fe Cl1 97.25(3)°
Fe-Fe=3.789 Å	Cl1 Fe Cl1 81.67(3)° Fe Cl1 Fe 98.33(3)°

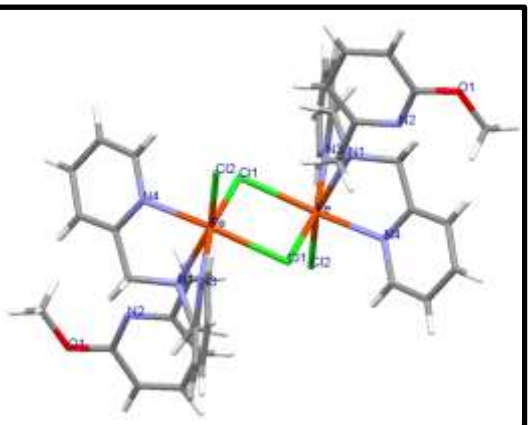

Figure 4: Mercury representation of the metallation product of (MeO) TPA by $FeCl_2$

The following parameters were considered:

Triclinic system, space group P-1. Mesh parameters: a= 89.7860(9) Å, b =10.4530 (10) Å, c=11.0840 (15) Å, α=65.887(3)°, β=78.897(4)°, γ=71.118(3)°. Z=1, V=976.80(19) Å3. The mercury diagram is shown in figure 4.

Surprisingly, the compound which crystallizes is the μ-dichloro-bridged binuclear complex. The ligand coordinates here tridentally, the decoordinated arm being the one superseded by the methoxyl function (table 2).

Reactivity in the presence of substrate

Zinc amalgam was used as the Fe (III)/Fe (II) reducing agent to regenerate reactive species during the reaction. In a schlenck tube, prepare a solution of known concentration of complex dissolved in acetonitrile, add cyclohexane, a few drops of zinc amalgam, and bubble oxygen. After one to two hours, a grayish solution is obtained, the acetophenone is added in a known quantity and the whole is filtered through Celite. Acetophenone is used as a reference for the analysis of GC gas chromatography results.

3. RESULTS AND DISCUSSION

UV-visible spectroscopy clearly shows the tetradent character of the ligand; 1H NMR shows a very usual spectrum in which the protons β and β' appear to belong to the substituted pyridine bound to the metal. Molar conductimetry is not very informative: both the

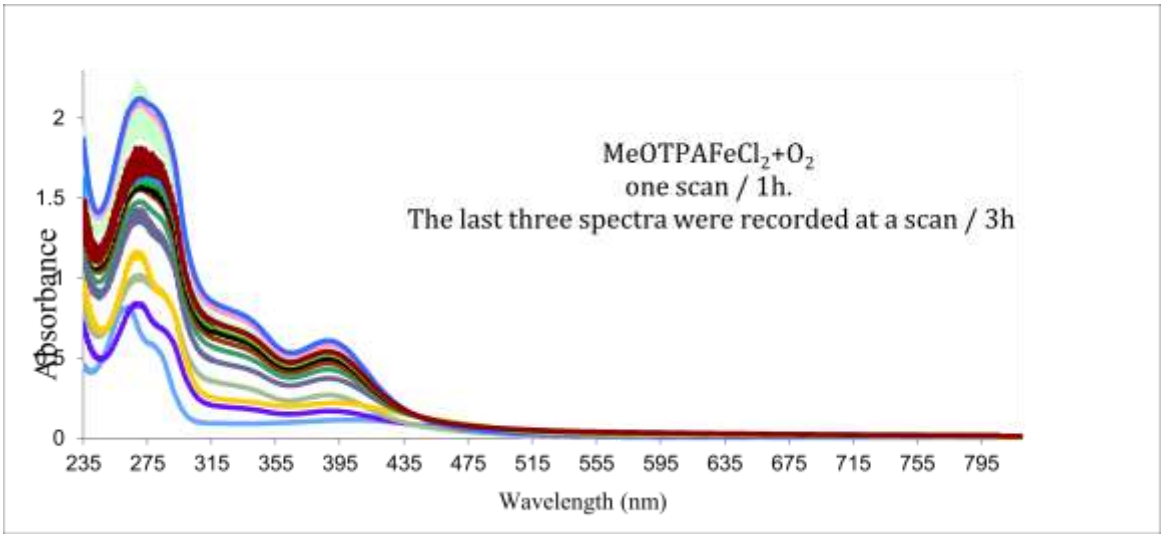

Figure 5: Monitoring by UV-visible spectroscopy of the oxygenation reaction of the MeOTPAFeCl2 complex.

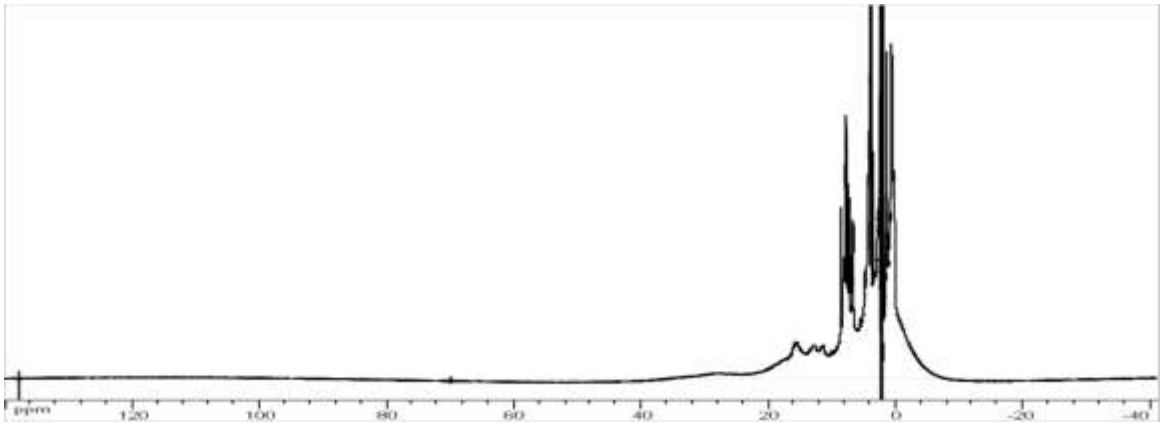

Figure 6: The 1H NMR spectrum of the oxygenation reaction product of the (MeO) TPAFeCl$_2$ complex

presumed mononuclear species in solution and the crystalline product are neutral.

A methoxy function is not larger than a bromine atom, but as known that in the latter case a mononuclear is obtained [22]. It can be argued that the pyridine substituted by a methoxy group, which is richer in electrons, is less acceptor than a simple pyridine, and that its coordination to a discontinued metal could be less favored. The thermodynamically stable product obtained after a few days of crystallization would be the binuclear complex of octahedral geometry with μ-dichloro bridge.

3.1. Oxygenation of (MeO) TPAFeCl$_2$

UV-visible tracking

The products exhibit a white to yellow-orange color depending on the case and are generally obtained with yields of between 80 and 85%. It is easy to see that the oxygenation reaction of (MeO) TPAFeCl$_2$ is slow and gradual. The spectrum no longer changes after about 20 hours, and the absorptions observed at λ = 332 nm and λ = 390 nm are characteristic of the presence of a diferric μ-oxo species of symmetrical structure. Figure 5 reports the observed spectroscopic changes.

1H NMR data

Full kinetics for this reaction was recorded but after 36 hours no more starting material is detected in the tube. The main signals of the final product appear between δ = 5 and 35 ppm and exhibit large line widths. The cropping of the observation window and the large width at half height suggests the presence of a ferric entity whose ground state approaches a

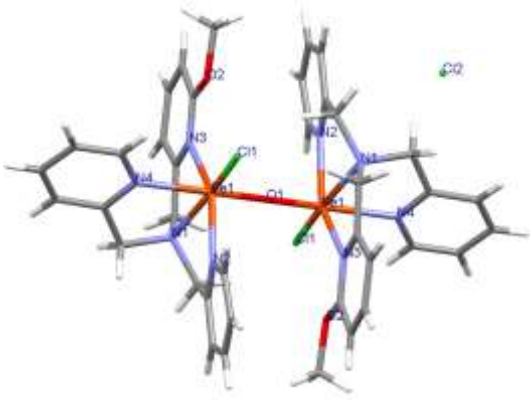

Figure 7: Mercury representation of the cation [((OMe) TPAFeCl) $_2$-O] $^{++}$

diamagnetic state (Figure 6).

3.2. Structure of the final compound

An oxygenated solution of the starting material was covered with diethyl ether. After a few days, single crystals appeared, and the radiocrystallographic structure could be resolved. Here are the mesh parameters:

Triclinic system, space group P-1. a = 9.8800 (11) Å, b =10.1200 (13) Å, c =12.9470 (18) Å ; α=80.09(5)°, β=68.74(5)°, γ=67.86(5)°, V=1116.6(2), Z=1.

A Mercury diagram is shown in Figure 7. The compound which crystallizes is a diferric, μ-oxo-bridged bicationic binuclear species, the ligand tetradently coordinating. The main metal-ligand distances and angles (Table 2).

Table 2: Main metal-ligand distances and angles

[((MeO)TPAFeCl)$_2$O]$^{++}$	
Distances	Angles
	O1 Fe1 N2=94.0(3)°
	O1 Fe1 N1=93.1(3)°
Fe1-O1=1.7947(19)Å	N2 Fe1 N1=75.0(5)°
	O1 Fe1 N3=88.0(3)°
Fe1-N2=2.167(12)Å	N2 Fe1 N3=151.2(5)°
	N1 Fe1 N3=76.2(5)°
Fe1-N1=2.205(12)Å	O1 Fe1 N4=167.0(3)°
	N2 Fe1 N4=91.5(4)°
Fe1-N3=2.209(13)Å	N1 Fe1 N4=77.0(4)°
	N3 Fe1 N4=81.6(4)°
Fe1-N4=2.229(10)Å	O1 Fe1 Cl1=100.71(12)°
Fe1-Cl1=2.307(4)Å	N2 Fe1 Cl1=93.6(4)°
	N1 Fe1 Cl1=162.8(3)°
O1-Fe1=1.7947(19)Å	N3 Fe1 Cl1=114.3(4)°
	N4 Fe1 Cl1=90.7(3)°
	Fe1 O1 Fe1=180.0°

This structure is directly comparable with that obtained from the parent compound TPAFeCl$_2$, [15-29]. The two ligands are located trans to each other to the Fe-O-Fe segment. The tertiary amine of the ligand is located in the trans position of the coordinate chloride (Figure 7).

3.3. Reactivity in the presence of substrate

The oxygenation mechanism of the complexes, shows that at some point an intermediate Fe (IV) - oxo species is formed. This species is very oxidizing, during the reaction in the absence of substrate, it reacts with a complex molecule to form a μ-oxo diferric species. It would therefore be conceivable that such a species in the presence of a substrate, such as cyclohexane, is capable of transferring oxygen to lead to the formation of an oxidized substrate.

The oxidation of cyclohexane to cyclohexanone has already been studied with, ferrous chloride salt, and complexes of TPA and the results were compared with complexes substituted by

methoxy groups. It is therefore a matter of reacting the three complexes with cyclohexane in the presence of O_2.

Table 3: The turnover of catalysis of conversion of cyclohexane to cyclohexanone

	$FeCl_2$	$TPAFeCl_2$	$MeOTPAFeCl_2$
TON	=0.4	=8	=29

The first signal appears at 4.1 minutes and corresponds to the acetonitrile peak, which is the most intense. Then a few seconds later follows the cyclohexane signal, a low intensity peak. At around 6.6 minutes, the appearance of cyclohexanone is observed, a very weak peak and at the end of 11.6 minutes the reference signal, acetophenone, appears. The relationship below makes it possible to calculate the concentration of cyclohexanone and therefore the TON turn over number (table 3):

cyclohexanone= 1.2[acetophenone]xAire(cyclohexanone) / Aire (acetophenone)

TON = [cyclohexanone] / [catalyst]

4. CONCLUSION

A series of TPA ligand substituted by methoxy groups was synthesized, characterized and complexed with $FeCl_2$. These types of ligand are the electrodonner ligands. The desire to create such a ligand is not trivial, in fact we are synthesized this ligand trying to demonstrate the defiant reactivity between electrodonner and the electro-deficient ligand, which has been study very will (the more the metal center of the complex has a strong Lewis acid character, for a given geometry). This comparison will demonstrate the different speed of O_2 coordination on the complex.

The complexes are then prepared and characterized by different spectroscopic techniques, thus making it possible to predict their geometry in solution and in the solid state for $MeOTPAFeCL_2$. The compound $MeOTPAFeCl_2$ exhibits equilibrium of mon and binuclear complexes in solid state and in solution. This leads to the study of the reactivity of the complexes in the presence of the substrate, cyclohexane. As observed that this reaction was catalytic, indeed several cycles are observed.

It is now imperative to improve the efficiency of this reaction that is to limit the deactivation of the catalyst. The incorporation of the complex in a protective matrix: i solid (zeolite, nanotube), or biological polymer (protein), this would seem to be an effective way to remedy the problem.

5. ACKNOWLEDGEMENT

NA

6. CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

7. SOURCE/S OF FUNDING

No source of funding

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