Copper Complexes as Functional Models for Dopamine β-Hydroxylase – Mechanistic Study of Oxygen Atom Transfer from Cu/O Species to Benzylic C−H Bonds[‡]

Ingrid Blain,[a] Michel Giorgi,[a] Innocenzo De Riggi,[b] and Marius Réglier*[a]

Keywords: Copper / Enzymes / Radicals / RPY2 ligand / Oxygen atom transfer / O-O activation

The mechanism of the oxygen atom transfer reaction mediated by copper-oxygen species has been studied through a substrate-binding ligand approach. Oxidations of copper 5-X-IndPY2 type complexes in which an electron donating (X = OMe) or withdrawing group (X = CN) substitutes the aromatic nucleus in position 5, lead to compounds **2b,c** and **3b,c** resulting from benzylic hydroxylations. With these complexes, where one of the benzylic positions is influenced by a *para* substituent (leading to **2b,c**) while the other suffers influence from the *meta* group (leading to **3b,c**), we observe that the ratio **2**:**3** > 1 is in favor of a certain electrophilicity of the copper/oxygen species responsible for the hydroxylations. While a concerted mechanism cannot be excluded, the results are in favor of a two-step mechanism involving radical species.

Introduction

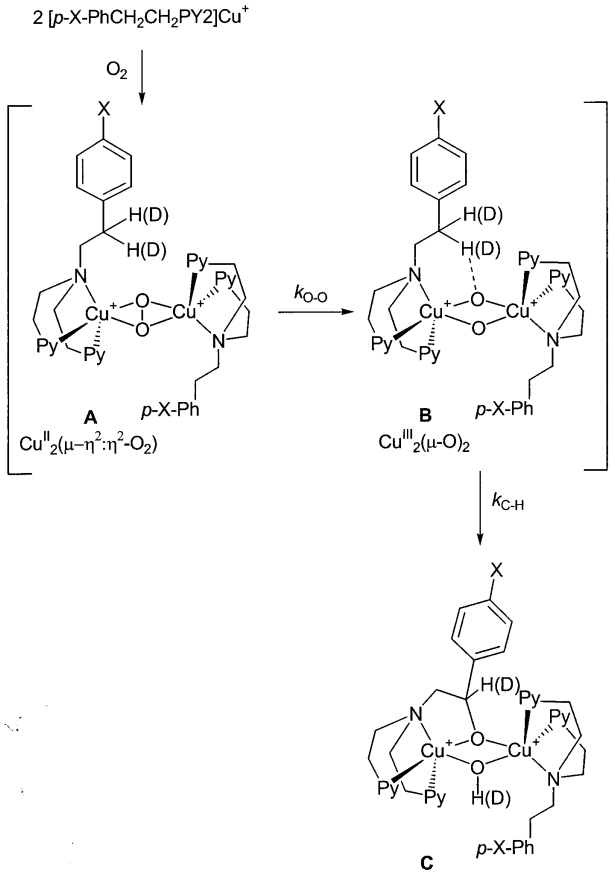
The mechanism of O_2 activation by copper-containing mono-oxygenases such as dopamine β-hydroxylase (DBH; benzylic hydroxylation of dopamine into noradrenaline) is of current interest.[1] Given that this enzymatic process involves the formation of highly reactive Cu/O radical species, which are responsible for hydrogen atom abstraction from the substrate, the Cu/O_2 chemistry has been the subject of recent investigations and considerable progress in the understanding of structural and spectroscopic aspects was made through biomimetic studies using copper complexes as active site models.[2,3] Recently, using the substrate-binding ligand approach,[4] Itoh and co-workers have described the first benzylic hydroxylation at the β-position of a tertiary amino group similarly to that of DBH.[5] This approach involved the study of copper complexes derived from RPY2-type ligands, in which a phenethylamine "substrate" is covalently bound to the tertiary amino group of the ligand, favoring conditions for an intramolecular oxygen atom transfer. An important feature of Itoh's hydroxylation is that not only does it occur during the reaction of the [PhenPY2]Cu^{I} complex with O_2 (condition I) but also under conditions close to the enzymatic reaction where the [PhenPY2]Cu^{II} complex is reduced first by benzoin before the reaction with O_2 (condition II). A detailed study of intermediates formed under condition I showed that upon reaction with O_2 the first step is the formation of the side-on $[L_2Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ species.[6] A detailed kinetic study including solvent, *p*-substituent and the kinetic deuterium isotope effects suggested the rate-determining step of the benzylic hydroxylation of the ligand to be the O−O bond homolysis of the μ-η^2:η^2-peroxodicopper(II) intermediate to give a bis(μ-oxo)dicopper species $[Cu_2^{III}(\mu\text{-}O)_2]^{2+}$ (Scheme 1: **A** → **B**).[7]

In order to get more information on the Oxygen Atom Transfer to the Ligand (OATL) involved in these reactions (Scheme 1: **B** → **C**), we studied the reaction of copper complexes derived from a RPY2 ligand in which a 2-aminoindane "substrate" is used.[8] Due to a five-membered ring structure fused to an aromatic nucleus, 2-aminoindane is a very promising substrate for studying the stereochemistry of the transfer of an oxygen atom. Indeed, 2-aminoindane possesses two benzylic stereogenic centers, each bearing two hydrogen atoms and the stereochemistry of aminoindanols obtained after hydroxylation (*cis* vs. *trans*) can be regarded as an indicator for the stereoselectivity of the oxygen atom transfer.[9] On the other hand, the two equivalent benzylic positions in 2-aminoindane can be differentiated by benzylic mono substitution with a deuterium atom (Scheme 2: **1a**). In this way, the process involving an insertion into a C−H bond competes with a process involving an insertion into a C−D bond. The ratio of compounds **2**:**3** (Scheme 2) resulting from these two processes is related to the deuterium kinetic isotope effect (DKIE) of the reaction.

[‡] Aminoindanes in Oxygen Transfer Reactions, 3. − Part 2: ref.[8]; part 1: ref.[9]

[a] Chimie, Biologie et Radicaux Libres, UMR-CNRS 6517, Universités d'Aix-Marseille 1 et 3, Faculté des Sciences et Techniques de Saint Jérôme, case 432, av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France
Fax: (internat.) +33-4/9198-3208
E-mail: marius.reglier@lbs.u-3mrs.fr
[b] Synthèse, Catalyse et Chiralité, UMR-CNRS 6516, Université d'Aix-Marseille 3, Faculté des Sciences et Techniques de Saint Jérôme, ENSSPICAM, av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

  1434−1948/01/0101−0205 $ 17.50+.50/0

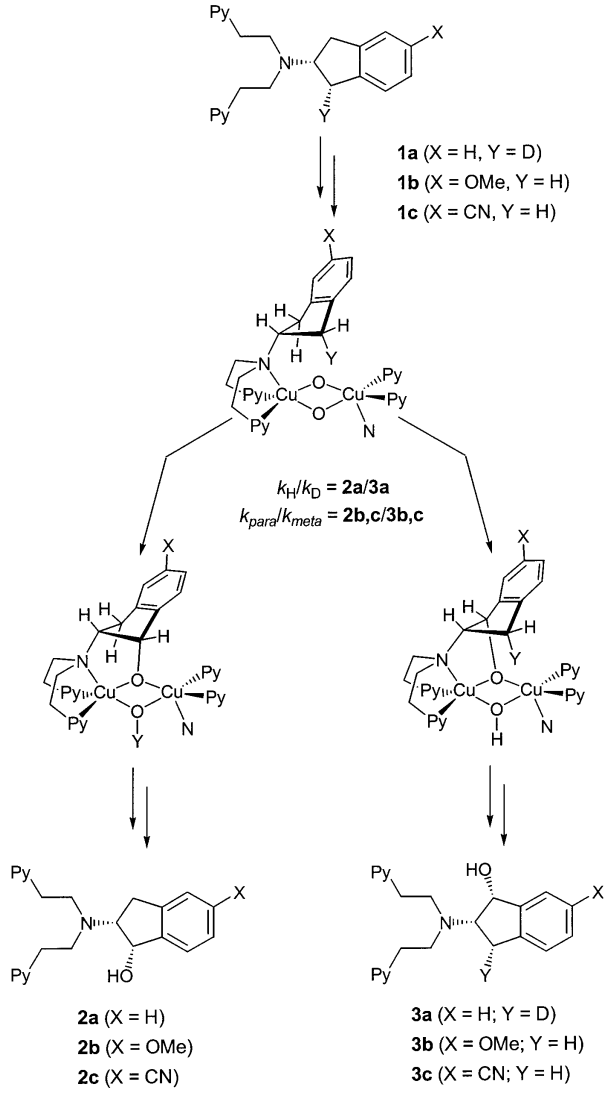


Scheme 1. Substrate-binding ligand approach

With copper complexes derived from ligand **1a** (Table 1, runs 1−2), we demonstrated that the oxygen atom transfer occurs with retention of configuration and we determined a DKIE of 11 and 7.6 for conditions I and II, respectively. In order to study the substituent effect on the oxygen atom transfer reaction and using the same strategy, we describe now the elaboration of new ligands **1b,c** in which an electron donating (OMe) or withdrawing group (CN) substitutes the aromatic nucleus in position 5. With these ligands, where one of the benzylic positions is influenced by a *para* substituent while the other suffers influence from the *meta* group, the oxygen atom transfer should be influenced by various electronic factors and the ratio of compounds **2**:**3** resulting from this transformation should give information on the k_{para}/k_{meta} ratio as well as the mechanism of the OATL process.

Results and Discussion

The ligands 5-X-IndPY2 **(1b,c)** and 7-X-TetralPY2 **(1d,e)** were synthesized by Michael addition of the corresponding primary amines to freshly distilled 2-vinyl pyridine in a methanol/acetic acid mixture. The copper(I) complexes [5-X-IndPY2]$CuPF_6$ and [7-X-TetralPY2]$CuPF_6$ were prepared by reaction of $[CH_3CN]_4CuPF_6$ and the corresponding ligands in dichloromethane. The corresponding copper(II) complexes [5-X-IndPY2]$Cu(CF_3SO_3)_2$ and [7-X-TetralPY2]$Cu(CF_3SO_3)_2$ were obtained in nearly quantitative yields by complexation of the ligands with $Cu(CF_3SO_3)_2$ in methanol. Recrystallization from dichloromethane using the diethyl ether vapor diffusion technique afforded blue crystals of [7-OMe-TetralPY2]$Cu(CF_3SO_3)_2$ which were suitable for X-ray diffraction analysis (Table 2, Figure 1).



Scheme 2. 2-Aminoindane in substrate-binding ligand approach

The oxidation of copper complexes derived from 5-X-IndPY2 ligands **1b,c** was performed in dichloromethane under conditions I and II. After demetallation of the resulting copper(II) complexes with 35% aqueous ammonia the oxidation products were analyzed by NMR spectroscopy. Under condition I, the oxidation led to a 1:1 mixture of the recovered ligands **1b,c** and the two hydroxylated ligands **2b,c** and **3b,c** (Table 1, runs 3 and 5). Under condition II, these two compounds **2b,c** and **3b,c** were also obtained but in quantitative yields (Table 1, runs 4 and 6). Because it was impossible to separate them by chromatography, their structure and the ratios were determined by NMR spectroscopic analysis of the mixture. To achieve this, the first task was the complete assignment of all protons and carbons by

Table 1. Oxidation of copper complexes derived from ligands 5-X-IndPY2 (**1b,c**) and 7-X-TetralPY2 (**1d,e**)

Runs	Ligands	Conditions[a]	Product distributions	**2:3**
1	*cis*-d-IndPY2 (**1a**)	I	**1a** (51%) + **2a** (45%) +**3a** (4%)	11.0
2		II	**2a** (88%) +**3a** (12%)	7.6
3	5-MeO-IndPY2 (**1b**)	I	**1b** (57%) + **2b** (33%) + **3b** (10%)	3.3
4		II	**2b** (81%) + **3b** (19%)	4.3
5	5-CN-IndPY2 (**1c**)	I	**1c** (58%) + **2c** (25%) + **3c** (17%)	1.5
6		II	**2c** (70%) + **3c** (30%)	2.3
7	TetralPY2 (**1d**)	I	**1d** (75%) + **3d** (25%)	–
8		II	**3d** (100%)	–
9	7-MeO-TetralPY2 (**1e**)	I	**1e** (75%) + **3e** (25%)	–
10		II	**3e** (100%)	–

[a] Condition I: 2 mM solution of copper(I) complex in dichloromethane placed under dioxygen atmosphere for one day. Condition II: 1.6 mM solution of copper(II) complex in dichloromethane reduced by benzoin (2 equiv.) in the presence of NEt_3 (2 equiv.) for two hours under argon, then placed under dioxygen atmosphere for one day.

Table 2. Crystallographic data for [7-MeO-TetralPY2]Cu$(CF_3SO_3)_2$

Crystal data	
Formula	$C_{27}H_{29}CuF_6N_3O_7S_2$
M_r	749.21
Crystal system	Monoclinic
Space group	$P2_1/c$
a [Å]	9.93(3)
b [Å]	12.80(4)
c [Å]	27.59(3)
β [°]	90.162(2)
V [Å^3]	3508(2)
$D_{calcd.}$ [g cm^{-3}]	1.42
Z	4
F(000) [e]	1532
μ (Mo-K_α) [cm^{-1}]	8.1
T [K]	298
Scan mode	ω/2θ
Scan width [°]	2.7 + 0.4 tanθ
$2\theta_{max}$ [°]	48.04
Measured refl.	6880
Unique refl.	6151
Refl. used for ref.	2212
Absorption correction	none
Ref. parameters	331
H atoms	included not refined
R[a]	0.088
R_w	0.163
w	unit
$(shift/e.s.d.)_{max}$	1.04
Goodness of fit	5.198
$\Delta\rho_{fin}$(max/min) [eÅ^{-3}]	0.84/-0.69

[a] We could not obtain a very good R value during the structure refinement because the diffracted intensities (high mosaicity and anisotropic shape of the samples) and the resolution (few intensities could be measured until 2θ = 48°) were low. As the absorption corrections did not give better results, we did not use them in the last refinement cycles.

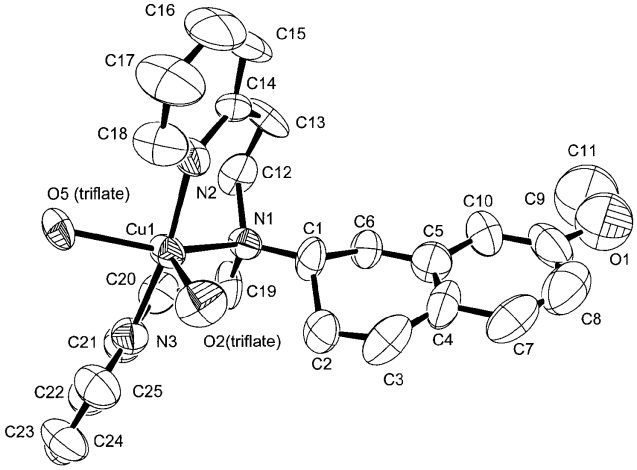
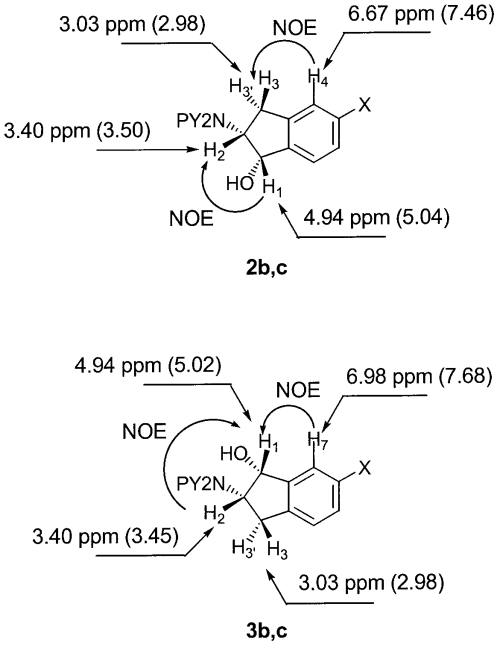


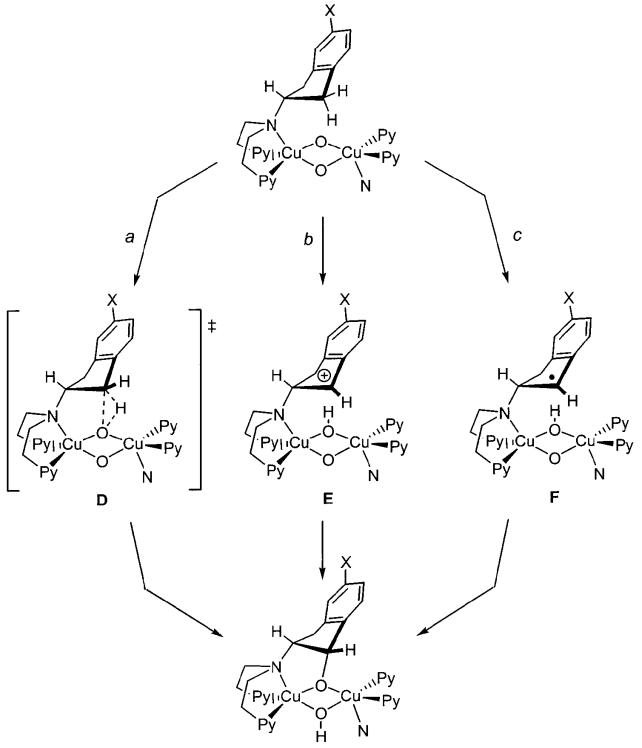
Figure 1. ORTEP representation of [7-MeO-TetralPY2]-Cu$(CF_3SO_3)_2$ at the 30% probability level; selected bond lengths in Å: Cu1−O2 2.23(2), Cu1−O5 2.15(5), Cu1−N1 2.08(3), Cu1−N2 2.05(2), Cu1−N3 1.98(2); selected bond angles in °: O2−Cu1−O5 97.6(12), O2−Cu1−N1 113.6(8), O2−Cu1−N2 85.3(8), O2−Cu1−N3 94.8(10), O5−Cu1−N1 148.7(13), O5−Cu1−N2 85.7(13), O5−Cu1−N3 85.0(13), N1−Cu1−N2 94.4(7), N1−Cu1−N3 94.2(9), N2−Cu1−N3 170.6(8)

homo- and heteronuclear correlation experiments (COSY gradient, HMQC and HMBC). Then two dimensional NOESY sequences revealing several interesting Nuclear Overhauser Effects (NOE) allowed us to attribute the fine structure of compounds **2b,c** and **3b,c** (Scheme 3). First of all, an NOE between protons H_1 and H_2 allowed the assignment of the *cis* stereochemistry of the 1,2-amino alcohol. In order to attribute the structure of the major compound, we first localized on the ^{1}H NMR spectra protons in the *ortho* position of the X substituent (numbered H_4 for **2b,c** and H_7 for **3b,c**). In both cases these protons show an NOE with the two benzylic protons H_3 for the major isomers, while the minor isomers show an NOE with proton H_1. These results indicate unambiguously that the major isomers correspond to the *para*-hydroxy compounds **2b,c**, and the minor isomer to the *meta*-hydroxy compounds **3b,c**. Integration of protons corresponding to **2b,c** and **3b,c** gave the *para*/*meta* ratios reported in Table 1.

In compounds **1b,c**, whatever the nature of the substituent (OMe vs. CN) and under reaction conditions I or II, hydroxylation preferentially occurs in the *para* position. The effects are more important for the electron donating OMe group (**2b**/**3b** = 3.3 and 4.3) than for the electron-withdrawing CN (**2c**/**3c** = 1.5 and 2.3). This is in favor of a certain electrophilicity of the copper/oxygen species responsible for the hydroxylations. In one of our previous studies, the higher DKIE observed under condition I compared to that of condition II (11 vs. 7.6) was rationalized as the occurrence of two different copper-oxygen intermediates.[10] Though being low, the differences observed in the **2**:**3** ratios confirm once again this former interpretation. Under condition I, the occurrence of a bis(μ-oxo)dicopper



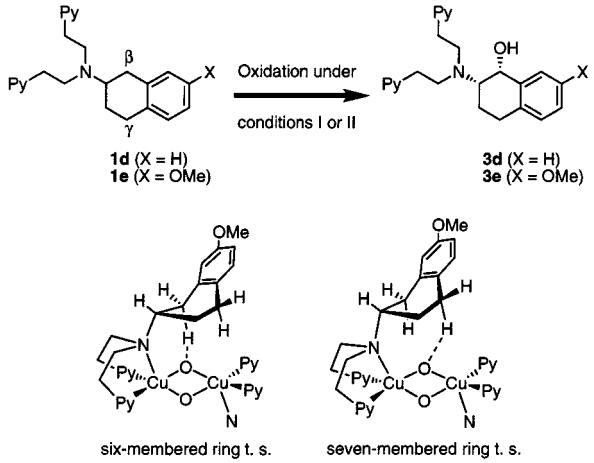
Scheme 3. Some Nuclear Overhauser Effects observed with compounds **2b,c** and **3b,c**. Chemical shifts are reported for X = MeO and in parenthesis for X = CN



Scheme 4. Possible mechanisms for the oxygen atom transfer

species $[Cu_2^{III}(\mu\text{-}O)_2]^{2+}$ is now well accepted as the principal active species in oxygen atom transfer. But in the presence of benzoin (condition II), the structure of the active copper/oxygen species is less clear and several structures can be proposed. Among them, species involving the mixed valence $[Cu^{II}Cu^{III}(\mu\text{-}O)_2]^{2+}$ intermediates or the oxygen radical species $[Cu^{II}-O^{\bullet}]^{+}$ ($\equiv [Cu^{III}-O^{-}]^{+}$) are very attractive.[10] Possible pathways consistent with these structures and an intramolecular oxygen atom insertion into the benzylic C−H bond are presented in Scheme 4. The high **2**:**3** ratios observed with 5-OMe-IndPY2 ligand (Table 1, runs 3 and 4) could be in favor of a hydride abstraction (Scheme 4, pathway *b*) and a carbocation intermediate **E**. Although these values indicate transition-state stabilization by an electron donating group, they are small compared with values normally observed in reactions involving benzylic carbocation intermediates. Moreover, with the 5-CN-IndPY2 ligand, we would expect a more marked effect in favor of the *meta* product **3c**. Indeed, according to the Hammet equation $\log(k/k_0) = \sigma\rho$,[11] values of $\log(k_{para}/k_{meta})$ can be estimated by the expression $\rho(\sigma_p-\sigma_m)$. Considering that for reactions involving benzylic carbocation intermediates, the ρ value is less than −2, we would expect a k_{para}/k_{meta} ratio of 6 and 0.6 for MeO and CN groups, respectively.[12] These results, which seem to be unfavorable to the intermediacy of **E**, could be in favor of a concerted mechanism (Scheme 4: pathway *a*) where a positive minimal charge development in the transition state may be envisaged. However, initial radical formation (Scheme 4: pathway *c*) by a hydrogen atom abstraction by the Cu−O core seems to be more reasonable, since Mayer has recently shown that metal-oxo complexes can oxidize hydrocarbons by a hydrogen-atom abstraction mechanism which is attributed to their thermodynamic affinity for a hydrogen atom ($\equiv H^+ + e^-$).[13] This proposal is all the more reasonable as similar values of the k_{para}/k_{meta} ratio are often seen in radical-generating systems. Indeed, for benzylic H abstraction of *p*- or *m*-substituted toluenes by *t*BuOO$^{\bullet}$ (*t*BuO$^{\bullet}$) radical the ratios k_{para}/k_{meta} were found to be 3.14[14] and 1.3[14] (1.0[15]) for OMe and CN groups, respectively.[16]

All of our results and those described in the literature, concern hydroxylation occurring in the β position of a tertiary amino group of the ligand. In order to study the factors that govern the oxygen atom transfer, we decided to examine the hydroxylation of ligands derived from 2-aminotetralin compounds. Like 2-aminoindane, 2-aminotetralin possesses two benzylic carbons but one is in the β position while the second is in the γ position with respect to the amino group. Moreover, the γ position can be activated by a OMe substituent in position 7 of the aromatic ring and it would be interesting to know whether this activation would be enough for directing the hydroxylation towards this benzylic position. Under both oxidation conditions, hydroxylation takes place at the β benzylic carbon even when an OMe substituent is present in position 7 of the aromatic ring (Table 1, runs 7−10). This is evident from the ^{1}H NMR spectrum, which shows a doublet at δ = 4.65 (**3d**) and 4.60 (**3e**) with coupling constants ^3J = 3.4 Hz characteristic for a *cis* stereochemistry.[17] Our results demonstrate that the six-membered transition state is more favorable than the seven-membered one even when an OMe



Scheme 5. 7-X-TetralPY2 ligands **1d,e** in oxygen atom transfer reaction

substituent activates the γ benzylic position (Scheme 5). It might be hazardous to consider the Cu−O core as an oxygen centered radical, however, we can see here a similarity to Barton's reaction where an intramolecular δ C−H bond activation by an alkoxy radical takes place.[18]

Conclusion

Several examples of OATL are described in the literature demonstrating that the substrate binding ligand approach gives valuable information about the active species involved in the copper−dioxygen activation. However, two problems remain. The first one concerns the mechanism of the oxygen atom transfer. The question is to determine whether the oxygen atom transfer occurs in a concerted pathway or in a two step process involving radical intermediates. For the moment, it is difficult to answer this fundamental question. More experiments are needed, notably using a radical clock fixed on the tertiary amino group of the ligand. The second problem concerns the catalytic aspect of the oxygen atom transfer. Few examples of oxygen atom transfer from a copper center to an exogenous substrate are known.[19,20] To achieve this, the substrate association in the copper coordination sphere still remains to be solved.[21] We think this will be an exciting challenge for the organic chemist.

Experimental Section

General: Solvents were freshly distilled under Ar (MeOH/Mg, Et_2O/Na-benzophenone ketyl, CH_3CN/CaH_2 and CH_2Cl_2/P_2O_5). Deoxygenation of solvents and solutions was carried out by 3 vacuum/purge cycles. Preparations and handling of air sensitive compounds were carried out using standard Schlenk techniques. Commercial starting materials were used without further purification, except for 2-vinylpyridine, which was distilled prior to use. 2-Amino-5-methoxyindane was prepared in two steps from 5-methoxy-1-indanone by a procedure described in the literature.[22] 2-Amino-5-cyanoindane was prepared in six steps from 5-bromo-1-indanone.[23] 2-Aminotetralin and 2-amino-7-methoxytetralin were obtained by reductive amination of the corresponding 2-tetralones.[24] NMR spectra were recorded at 25 °C on Bruker AC-200 or AMX-400 spectrometers. Chemical shifts are reported in ppm as δ values downfield from an internal standard of TMS. Homo- and heteronuclear correlations were obtained by COSY gradient, HMQC and HMBC techniques with a 5 mm reverse probehead using a *z* field gradient. 2D-NOESY experiments were performed with a 5 mm $^1H/^{13}C$ DUAL probehead.

Ligands 1b−e: To absolute MeOH were added 2-vinylpyridine, primary amine and acetic acid. After refluxing for several days, MeOH was evaporated and 15% NaOH was added. The product was extracted with CH_2Cl_2 and the organic layer dried over Na_2SO_4. Evaporation of CH_2Cl_2 under reduced pressure (18 Torr) left the crude product. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 95:5) afforded the pure ligands (Table 3).

1b: ^1H NMR (200 MHz, $CDCl_3$): δ = 2.65−2.85 (m, 2 H), 2.90−3.10 (m, 10 H), 3.65−3.80 (m, 1 H), 3.75 (s, 3 H), 6.60−6.75 (m, 2 H), 7.00−7.20 (m, 5 H), 7.55 (td, *J* = 7.5 and 1.7 Hz, 2 H), 8.50 (ddd, *J* = 4.8, 1.7 and 1 Hz, 2 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 36.1 (CH_2-ind), 36.2 (2 CH_2), 37.3 (CH_2-ind), 51.5 (2 CH_2), 55.4 (CH_3O), 63.6 (CHN), 110.0 (CH-aryl), 112.2 (CH-aryl), 121.1 (2 CH-pyr), 123.4 (2 CH-pyr), 125.0 (CH-aryl), 133.8 (C-aryl), 136.2 (2 CH-pyr), 143.2 (C-aryl), 149.3 (2 CH-pyr), 158.7 (C-aryl), 160.7 (2 C-pyr).

1c: ^1H NMR (200 MHz, $CDCl_3$): δ = 2.70−3.10 (m, 12 H), 3.75 (m, 1 H), 7.20 (d, *J* = 8.2 Hz, 1 H), 7.30−7.40 (m, 6 H), 7.55 (td, *J* = 7.5 and 1.7 Hz, 2 H), 8.50 (ddd, *J* = 5.5, 1.7 and 1 Hz, 2 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 35.8 (2 CH_2), 36.4 (CH_2-ind), 40.0 (CH_2-ind), 51.2 (2 CH_2), 62.7 (CHN), 109.9 (C-aryl), 119.4 (CN), 121.2 (2 CH-pyr), 123.4 (2 CH-pyr), 125.2 (CH-aryl), 127.9 (CH-aryl), 130.5 (CH-aryl), 136.3 (2 CH-pyr), 143.0 (C-aryl), 147.6 (C-aryl), 149.2 (2 CH-pyr), 160.2 (2 C-pyr).

1d: ^1H NMR (200 MHz, $CDCl_3$): δ = 1.50−1.70 (m, 1H), 2.00−1.85 (m, 1H), 2.95−3.05 (m, 13 H), 6.96−7.10 (m, 8H), 7.54 (td, *J* = 7.5 and 1.7 Hz, 2 H), 8.51 (ddd, *J* = 4, 1.7 and 1 Hz, 2 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 25.0 (CH_2-tetral), 29.7 (CH_2-tetral), 32.3 (CH_2-tetral), 38.0 (2 CH_2), 50.9 (2 CH_2), 56.9 (CHN), 121.1 (2 CH-pyr), 123.6 (2 CH-pyr), 125.5 (CH-aryl), 125.6 (CH-aryl), 128.5 (CH-aryl), 129.4 (CH-aryl), 136.1 (2 CH-pyr), 136.3 (2 C-aryl), 149.1 (2 CH-pyr), 160.7 (2 C-pyr).

1e: ^1H NMR (200 MHz $CDCl_3$): δ = 1.55 (qd, *J* = 11.7 and 6.5 Hz, 1 H), 1.85−2.00 (m, 1 H), 2.65−2.76 (m, 4 H), 2.90−3.07 (m, 9 H), 3.72 (s, CH_3O), 6.53 (d, *J* = 2.7 Hz, 1 H), 6.62 (dd, *J* = 8.2 and 2.7 Hz, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 7.03−7.12 (m, 4 H), 7.52 (td, *J* = 7.6 and 1.7 Hz, 2 H), 8.48 (ddd, *J* = 5.8, 1.7 and 1 Hz, 2 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 26.0 (CH_2-tetral), 28.9 (CH_2-tetral), 32.5 (CH_2-tetral), 38.0 (2 CH_2), 50.9 (2 CH_2), 55.2 (CH_3O), 57.0 (CHN), 112.0 (CH-aryl), 113.9 (CH-aryl), 121.1 (2 CH-pyr), 123.6 (2 CH-pyr), 128.4 (C-aryl), 129.4 (CH-aryl), 136.1 (2 CH-pyr), 137.4 (C-aryl), 149.2 (2 CH-pyr), 157.4 (C-aryl), 160.6 (2 C-pyr).

Copper(II) Complexes: To a solution of $Cu(CF_3SO_3)_2$ in MeOH was added dropwise a solution of the ligand in MeOH. This mixture was then stirred for 30 min. MeOH was evaporated in vacuo and Et_2O was added. The precipitate was filtered off, washed with Et_2O and dried in vacuo to give the copper(II) complexes as blue solids (Table 4).

General Procedure for the Oxidation of Copper(I) Complexes by O_2 (Condition I): To a solution of $[CH_3CN]_4CuPF_6$ (100 μmol) in degassed CH_2Cl_2 (50 mL) was added dropwise a solution of ligand **1b−e** (100 μmol) in CH_2Cl_2 (50 mL). The mixture was allowed to stir under Ar for 1 h, and then exposed to O_2 atmosphere for 24

Table 3. Preparation of ligands **1b−e**

Ligands	**1b**	**1c**	**1d**	**1e**
Primary amines	2-amino-5-MeO-indane 540 mg (3.3 mmol)	2-amino-5-CN-indane 126 mg (0.8 mmol)	2-aminotetralin 438 mg (3 mmol)	2-amino-7-MeO-tetralin 332 mg (1.9 mmol)
Vinylpyridine	3.5 mL (33 mmol)	1.7 mL (15.7 mmol)	6.5 mL (60 mmol)	4.1 mL (38 mmL)
MeOH	8 mL	2 mL	16 mL	8 mL
AcOH	0.75 mL	0.36 mL	1.37 mL	4.1 mL
Yields	374 mg (1 mmol, 30%).	156 mg (0.42 mmol, 53%)	226 mg (0.63 mmol, 21%)	220 mg (0.57 mmol, 30%)

Table 4. Preparation of copper(II) complexes [RPY2]Cu(CF_3SO_3)$_2$

Copper(II) complexes	[5-MeOIndPY2] Cu(CF_3SO_3)$_2$	[5-CNIndPY2] Cu(CF_3SO_3)$_2$	[TetralPY2] Cu(CF_3SO_3)$_2$	[7-MeOTetralPY2] Cu(CF_3SO_3)$_2$
Ligands	**1b** (400 mg, 1 mmol)	**1c** (370 mg, 1 mmol)	**1d** (360 mg, 1 mmol)	**1e** (390 mg, 1 mmol)
Cu(CF_3SO_3)$_2$	350 mg (0.97 mmol)	350 mg (0.97 mmol)	350 mg (0.97 mmol)	350 mg (0.97 mmol)
MeOH	15 mL	15 mL	15 mL	15 mL
Yields	700 mg (952 µmol, 95%)	680 mg (931 µmol, 93%)	690 mg (959 µmol, 96%)	710 mg (947 µmol, 95%)
Analysis	$C_{26}H_{27}N_3CuS_2O_7F_6$ (735.17) calcd. C 42.48, H 3.70, N 5.72 found C 42.58, H, 3.62, N 5.81	$C_{26}H_{24}N_4CuS_2O_6F_6$ (730.16) calcd. C 42.77, H 3.31, N 7.67 found C 42.82, H 3.35, N 7.72	$C_{26}H_{27}N_3CuS_2O_6F_6$ (719.17) calcd. C 43.42, H 3.78, N 5.84 found C 43.38, H 3.72, N 5.93	$C_{27}H_{29}N_3CuS_2O_7F_6$ (749.20) calcd. C 43.29, H 3.90, N 5.61 found C 43.38, H 3.72, N 5.55

h. Then, CH_2Cl_2 was evaporated in vacuo and Et_2O was added and the precipitate obtained was centrifuged, washed with Et_2O and dried in vacuo to give a mixture of copper(II) complexes. This mixture was dissolved in CH_2Cl_2 (20 mL), washed with 35% NH_4OH (5 mL), brine (3 × 5 mL) and dried over Na_2SO_4. Evaporation of CH_2Cl_2 under reduced pressure (18 Torr) gave the crude product. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 90:10) afforded the recovered ligands **1b−e** and a mixture of compounds **2b,c** and **3b,c** (**3d,e**).

General Procedure for the Oxidation of Copper(II) Complexes by O_2 in the Presence of Benzoin (Condition II): To a solution of copper(II) complex (100 µmol) in degassed CH_2Cl_2 (6 mL) were added benzoin (200 µmol) and NEt_3 (200 µmol). This mixture was stirred under Ar for 2 h and then exposed to O_2 atmosphere for 24 h. CH_2Cl_2 was evaporated in vacuo and Et_2O was added. The precipitate obtained was centrifuged, washed with Et_2O and dried in vacuo to give a mixture of copper(II) complexes. This mixture was dissolved in CH_2Cl_2 (20 mL), washed with 35% NH_4OH (5 mL), brine (3 × 5 mL) and dried over Na_2SO_4. Evaporation of CH_2Cl_2 under reduced pressure (18 Torr) gave the crude product. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 90:10) afforded compounds **2b,c** and **3b,c** (**3d,e**).

2b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (dd, *J* = 15 and 7 Hz, 1 H), 2.98−3.09 (m, 5 H), 3.10−3.25 (m, 4 H), 3.40 (m, 1 H), 3.75 (s, CH_3O), 4.94 (d, *J* = 5 Hz, 1 H), 6.71−6.75 (m, 2 H), 7.08 (ddd, *J* = 7, 5 and 1 Hz, 2 H), 7.12 (d, *J* = 8 Hz, 2 H), 7.33 (d, *J* = 9 Hz, 1 H), 7.55 (td, *J* = 8 and 2 Hz, 2 H), 8.50 (bd, *J* = 5 Hz, 2 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 34.3 (CH_2-Ind), 34.4 (2 CH_2), 49.9 (2 CH_2), 55.4 (CH_3O), 67.0 (CHN), 72.7 (CHOH), 110.3 (CH-aryl), 112.9 (CH-aryl), 121.5 (2 CH-pyr), 123.7 (2 CH-pyr), 126.5 (CH-aryl), 135.6 (C-aryl), 136.6 (2 CH-pyr), 143.4 (C-aryl), 149.4 (2 CH-pyr), 160.0 (2 C-pyr), 160.5 (C-aryl).

2c: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95−3.00 (m, 5 H), 3.02 (m, 1 H), 3.08−3.20 (m, 4 H), 3.50 (m, 1 H), 5.04 (d, *J* = 5.4 Hz, 1 H), 7.05−7.10 (m, 4 H), 7.45−7.50 (m, 3 H), 7.53 (td, *J* = 8 and 2 Hz, 2 H), 8.46 (dd, *J* = 5 and 1.6 Hz, 2 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 34.4 (CH_2-Ind), 34.5 (2 CH_2), 49.6 (2 CH_2), 66.3 (CHN), 73.4 (CHOH), 119.2 (CN), 123.6 (2 CH-pyr), 112.1 (C-aryl), 121.4 (2 CH-pyr), 126.1 (CH-aryl), 128.4 (CH-aryl), 131.2 (CH-aryl), 136.5 (2 CH-pyr), 142.8 (C-aryl), 148.7 (C-aryl), 149.1 (2 CH-pyr), 159.6 (2 C-pyr).

3b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (dd, *J* = 15 and 7 Hz, 1 H), 2.98−3.09 (m, 5 H), 3.10−3.25 (m, 4 H), 3.40 (m, 1 H), 3.76 (s, CH_3O), 4.94 (d, *J* = 5 Hz, 1 H), 6.88 (dd, *J* = 8 and 2 Hz, 1 H), 6.98 (d, *J* = 2 Hz, 1 H), 7.20−7.00 (m, 1 H), 7.08 (ddd, *J* = 7, 5 and 1 Hz, 2 H), 7.12 (d, *J* = 8 Hz, 2 H), 7.55 (td, *J* = 8 and 2 Hz, 2 H), 8.50 (bd, *J* = 5 Hz, 2 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 33.1 (CH_2-Ind), 34.4 (2 CH_2), 49.9 (2 CH_2), 55.5 (CH_3O), 66.9 (CHN), 73.7 (CHOH), 110.3 (CH-aryl), 115.5 (CH-aryl), 121.5 (2 CH-pyr), 123.7 (2 CH-pyr), 125.6 (CH-aryl), 135.6 (C-aryl), 136.6 (2 CH-pyr), 143.4 (CH-aryl), 149.4 (2 CH-pyr), 159.2 (C-aryl), 160.0 (2 C-pyr).

3c: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95−3.00 (m, 5 H), 3.02 (m, 1 H), 3.08−3.20 (m, 4 H), 3.45 (m, 1 H), 5.02 (d, *J* = 5.8 Hz, 1 H), 7.05−7.10 (m, 4 H), 7.28 (d, *J* = 8 Hz, 1H), 7.45−7.50 (m, 1 H), 7.53 (td, *J* = 8 and 2 Hz, 2 H), 7.68 (d, *J* = 1 Hz, 1 H), 8.46 (dd, *J* = 5 and 1.6 Hz, 2 H). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 34.0 (CH_2-Ind), 34.5 (2 CH_2), 49.6 (2 CH_2), 66.4 (CHN), 73.2 (CHOH), 110.6 (CH-aryl), 119.2 (CN), 121.4 (2 CH-pyr), 123.6 (2 CH-pyr), 125.6 (CH-aryl), 129.1 (CH-aryl), 132.6 (CH-aryl), 136.5 (2 CH-pyr), 144.8 (C-aryl), 147.4 (C-aryl), 149.1 (2 CH-pyr), 159.6 (2 C-pyr).

3d: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.00 (m, 1 H), 2.62−3.10 (m, 10 H), 3.10−3.30 (m, 1 H), 4.65 (d, *J* = 3.4 Hz, 1 H), 6.98−7.10 (m, 5 H), 7.10−7.20 (m, 2 H), 7.35 (m, 1 H), 7.50 (td, *J* = 7.5 and 2 Hz, 2 H), 8.48 (dd, *J* = 5 and 1 Hz, 2 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.9 (CH_2-tetral), 29.5 (CH_2-tetral), 35.8 (2 CH_2), 49.7 (2 CH_2), 61.6 (CHN), 68.34 (CHOH), 121.2 (2 CH-pyr), 123.6 (2 CH-pyr), 126.0 (CH-aryl), 127.6 (CH-aryl), 128.2 (CH-aryl), 130.6 (CH-aryl), 136.3 (2 CH-pyr), 137.4 (2 C-aryl), 149.0 (2 CH-pyr), 160.0 (2 C-pyr).

3e: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.95 (m, 2 H), 2.60−3.30 (m, 11 H), 3.80 (s, CH_3O), 4.60 (d, *J* = 3.4 Hz, 1 H), 6.75 (dd, *J* = 8.6 and 2.8 Hz, 1 H), 6.90 (d, *J* = 2.8 Hz, 1 H), 7.10−6.95 (m, 5 H), 7.50 (td, *J* = 7.5 and 2 Hz, 2 H), 8.50 (dd, *J* = 5, 2 and 1 Hz, 2 H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.2 (CH_2-tetral), 28.7 (CH_2-tetral), 35.9 (2 CH_2), 49.8 (2 CH_2), 55.4 (CH_3O), 61.6 (CHN), 68.5 (CHN), 114.2 (C-aryl), 114.8 (CH-aryl), 121.2 (2 CH-pyr), 123.6 (2 CH-pyr), 128.5 (C-aryl), 129.2 (C-aryl), 136.3 (2 CH-pyr), 138.5 (C-aryl), 149.1 (2 CH-pyr), 157.9 (C-aryl), 160.2 (2 C-pyr).

X-ray Structure Analysis: Crystal data for [7-OMe-TetralPY2]-$Cu(CF_3SO_3)_2$ together with details of the X-ray diffraction experiment, are reported in Table 4.

Crystallographic data for the structure reported in this paper has been deposited at the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-137161. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033, E-mail: deposit@chemcrys.cam.ac.uk].

Acknowledgments

This research was supported by the *CNRS* and the *French Ministry of Universities*. The authors are grateful to Dr. A. Heumann for a number of enlightening discussions.

[1] J. P. Klinman, *Chem. Rev.* **1996**, *96*, 2541−2561; W. Kaim, J. Rall, *Angew. Chem.* **1996**, *108*, 47−64; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 43−60.

[2] K. D. Karlin, S. Kaderli, A. D. Zuberbühler, *Acc. Chem. Res.* **1997**, *30*, 139−147.

[3] N. Kitajima, Y. Moro-Oka, *Chem. Rev.* **1994**, *94*, 737−757.

[4] M. Réglier, E. Amadéi, E. H. Alilou, F. Eydoux, M. Pierrot, B. Waegell, *Bioinorganic Chemistry of Copper* (Eds.: K. D. Karlin, Z. Tiecklar), Chapman and Hall, **1993**, 348−362.

[5] S. Itoh, T. Kondo, M. Komatsu, Y. Ohshiro, C. Li, N. Kanehisa, Y. Kai, S. Fukuzumi, *J. Am. Chem. Soc.* **1995**, *117*, 4714−4715.

[6] References for $L_2Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)^{2+}$ species with L = RPY2: I. Sanyal, M. Mahroof-Tahir, S. Nasir, P. Ghosh, B. I. Cohen, Y. Gultneh, R. Cruse, A. Farooq, K. D. Karlin, S. Liu, J. Zubieta, *Inorg. Chem.* **1992**, *31*, 4322−4332; ref.; $HB(3,5\text{-}i\text{Pr}_2\text{pz})_3$, N. Kitajima, K. Fujisawa, Y. Moro-Oka, K. Toriumi, *J. Am. Chem. Soc.* **1989**, *111*, 8975−8976; $P(2,4\text{-}i\text{Pr}_2\text{im})_3$: T. N. Sorrel, W. E. Allen, P. S. White, *Inorg. Chem.* **1995**, *34*, 952−960; $i\text{Pr}_3$-tacn: S. Mahapatra, J. A. Halfen, E. C. Wilkinson, L. Que Jr., W. B. Tolman, *J. Am. Chem. Soc.* **1994**, *116*, 9785−9786.

[7] S. Itoh, H. Nakao, L. M. Berreau, T. Kondo, M. Komatsu, S. Fukuzumi, *J. Am. Chem. Soc.* **1998**, *120*, 2890−2899.

[8] I. Blain, P. Bruno, M. Giorgi, E. Lojou, D. Lexa, M. Réglier, *Eur. J. Inorg. Chem.* **1998**, 1297−1304.

[9] A. A. Mitrochkine, F. Eydoux, G. Gil, M. Réglier, *Eur. J. Org. Chem.* **1998,** 1171−1176.

[10] I. Blain, M. Giorgi, I. De Riggi, M. Réglier, *Eur. J. Inorg. Chem.* **2000**, 393−398.

[11] C. D. Johnson, *The Hammett Equation*; Cambridge University Press: Cambridge, U. K. **1973**.

[12] For the MeO group, $\sigma_p = -0.27$ and $\sigma_m = 0.12$ and for the CN group $\sigma_p = 0.66$ and $\sigma_m = 0.56$: C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165−195.

[13] K. Wang, J. M. Mayer, *J. Am. Chem. Soc.* **1997**, *119*, 1470−1471; J. M. Mayer, *Acc. Chem. Res.* **1998**, *31*, 441−450.

[14] J. A. Howard, J. H. B. Chenier, *J. Am. Chem. Soc.***1973**, *95*, 3054−3055.

[15] H. Sakurai, A. Hosomi, *J. Am. Chem. Soc.* **1967**, *89*, 458−460.

[16] Recently, a recent report confirmed the electropilicity of copper−oxygen core: S. Itoh, M. Taki, H. Nakao, P. L. Holland, W. B. Tolman, L. Que, Jr., S. Fukuzumi, *Angew. Chem. Int. Ed.* **2000**, *39*, 398−400.

[17] D. W. Patrick, L. K. Truesdale, S. A. Biller, K. B. Sharpless, *J. Org. Chem.* **1978**, *43*, 2628−2638.

[18] D. H. R. Barton, *Pure Appl. Chem.* **1968**, *16*, 1. R. H. Hesse, *Adv. Free Radical Chem.* **1969**, *3*, 83.

[19] H. V. Obias, Y. Lin, N. N. Murthy, E. Pidcock, E. I. Solomon, M. Ralle, N. J. Blackburn, Y.-M. Neuhold, A. D. Zuberbühler, K. D. Karlin, *J. Am. Chem. Soc.* **1998**, *120*, 12960−12961.

[20] M. A. Lockwood, T. J. Blubaugh. M. Coler, S. Lovell, J. M. Mayer, *Angew. Chem. Int. Ed.* **1999**, *38*, 225−227.

[21] R. J. M. Klein Gebbink, C. F. Martens, P. J. A. Kenis, R. J. Jansen, H.-F. Nolting, V. A. Solé, M. C. Feiters, K. D. Karlin, R. J. M. Nolte *Inorg. Chem.* **1999**, *38*, 5755−5768.

[22] I. Blain, Ph. D. Dissertation, Univ. of Aix-Marseille III, **1998**.

[23] J. G. Cannon, J. A. Perez, R. K. Bhatnagar, J. P. Long, F. M. Sharabi, *J. Med. Chem*. **1982**, *25*, 1442−1446.

[24] J. A. Howard, J. H. B. Chenier, *J. Am. Chem. Soc.* **1973**, *95*, 3054.

Received April 12, 2000
[I00143]