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[14] X-ray crystal data for **14** at 295 K ($C_{54}H_{84}N_2Si_4$, $M_r = 436.8$): monoclinic, space group $P2_1/n$ (no. 14), $\rho_{calcd} = 0.996\,\mathrm{g\,cm^{-3}}$, $Z = 2$, $a = 13.320(4)$, $b = 7.766(2)$, $c = 28.722(5)$ Å, $\beta = 101.30(2)°$, $V = 2913.5(13)$ Å^3. Nonius CAD4 diffractometer, $Cu_{K\alpha}$ radiation, $\lambda = 1.5418$ Å. A single crystal with linear dimensions of ca. $0.20 \times 0.07 \times 0.04$ mm was grown in a capillary from hexane at 273 K. A semi-empirical absorption correction, based on psi scans was applied to the data ($T(\mathrm{max}) = 0.99$, $T(\mathrm{min}) = 0.89$). The structure was solved by direct methods (SIR92) and refined by full-matrix least-squares analysis (SHELXL97), using an isotropic extinction correction, and $w = 1/[\sigma^2(F_o^2) + (0.078\,P)^2 + 1.792\,P]$, where $P = (F_o^2 + 2F_c^2)/3$. All heavy atoms were refined anisotropically and H atoms isotropically. H-atom positions are based on stereochemical considerations. Final $R(F) = 0.049$, $wR(F^2) = 0.137$ for 305 parameters and 2536 reflections with $I > 2\sigma(I)$ and $3.14 < \theta < 54.97°$ (corresponding R values based on all 3630 reflections are 0.079 and 0.166, respectively). CCDC-182715 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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A Structural and Functional Model of Galactose Oxidase: Control of the One-Electron Oxidized Active Form through Two Differentiated Phenolic Arms in a Tripodal Ligand

Fabrice Thomas,* Gisèle Gellon, Isabelle Gautier-Luneau, Eric Saint-Aman, and Jean-Louis Pierre

Galactose oxidase (GOase) is a type II copper protein (68 kDa) that catalyzes the oxidation of primary alcohols to aldehydes with the concomitant reduction of molecular oxygen.[1] Its crystal structure[2] reveals a unique mononuclear copper site with two nitrogen (from histidine imidazole groups) and two oxygen (from one axial and one equatorial tyrosine group) donor atoms, plus an exogenous water or acetate molecule in a distorted square-pyramidal coordination. The enzyme exists in three well-defined oxidation levels: the EPR-silent active form (cupric ion antiferromagnetically coupled to the equatorial tyrosyl radical), an intermediate form, and the reduced copper(I) form [Eq. (1)].

$$\mathrm{Cu^{II} - Tyr^{+\cdot}} \overset{e^-}{\rightleftharpoons} \mathrm{Cu^{II} - Tyr} \overset{e^-}{\rightleftharpoons} \mathrm{Cu^{I} - Tyr} \qquad (1)$$

The axial tyrosine group is involved in protonation–deprotonation processes during the catalytic cycle (Scheme 1b).

Among the structural models of the active site of GOase described,[3] only a few contain two phenolic arms and involve the $[N_2O_2]$ copper coordination sphere of the enzyme.[4] Some of the functional models of GOase involve salen-type ligands and exhibit interesting catalytic activity only with activated alcohols as substrates.[5] The best results have been obtained by Wieghardt et al. with a very nice set of complexes in which the redox chemistry during the catalytic cycle is ligand-based.[6–7] Another interesting model developed by Wieghardt and co-workers involves true GOase chemistry but is not, strictly speaking, a structural model.[8]

We have previously described a model, unfortunately not functional, involving an axial phenoxyl radical associated with a Cu^{II} center possessing a $[N_2O_2]$ coordination sphere. It was built from a tripodal ligand (Scheme 1a).[9] With a model close to ours, the phenoxyl radical species was obtained spontaneously by disproportionation.[10]

We present here a structural and functional model of galactose oxidase. Our strategy was based on the differentiation of the two phenolic arms in the tripodal ligand

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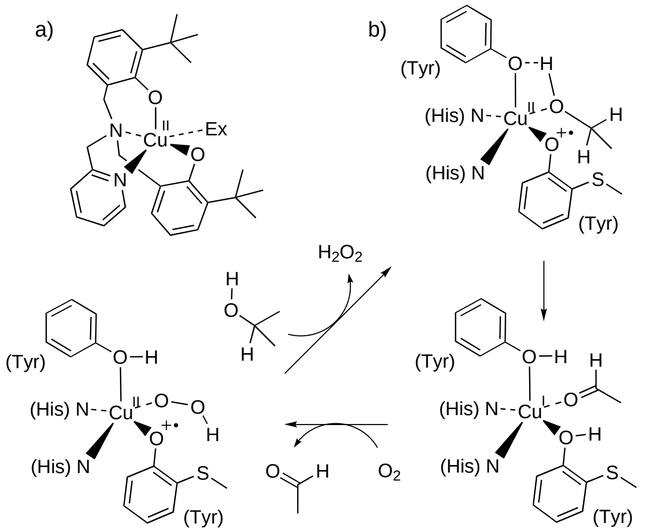
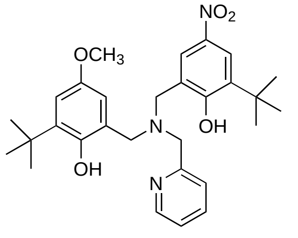


Scheme 1. a) Our previous model (Ex represents an exogenous ligand) and b) the simplified reaction mechanism of GOase.

LH$_2$,[11] to allow the geometric control of the one-electron oxidized active form. One of *tert*-butyl phenolic arms bears an electron-withdrawing nitro group and the other an electron-donating methoxy group.



LH$_2$

$[Cu^{II}(LH)(OAc)]$ is obtained upon mixing LH$_2$ and copper(II) acetate in the absence of base, while the dimeric complex $[Cu^{II}_2(L)_2]$ is obtained in presence of two equivalents of base and copper(II) perchlorate. $[Cu^{II}_2(L)_2]$ is converted into $[Cu^{II}(LH)(OAc)]$ upon addition of $N(Et)_3HCH_3CO_2$ ($K_D = 10^4\,M^{-1}$).

The X-ray structure analysis of $[Cu^{II}(LH)(OAc)]$ (Figure 1) reveals a mononuclear complex in which the copper(II) ion resides within a square-pyramidal geometry.[12] The crystal structure unambiguously provides evidence of the geometric control of the two different phenolic arms. The electron-donating effect of -OCH$_3$ relative to -NO$_2$ makes deprotonation of the hydroxy group harder: The weak $Cu^{II}\cdots OH(Ar)$ bond occupies the more labile position, that is axial. After dissolution of the crystalline material into a CH_3CN/CH_2Cl_2 (1:1) solution, the EPR spectrum reveals only one species: no isomerization into a complex involving axial nitrophenol moieties occurs. The g_{zz}/A_{zz} ratio is characteristic for a copper center within a square-planar geometry with an axial coordinated phenol group. The electronic spectrum shows an absorption at 500 nm ($\varepsilon = 760\,M^{-1}cm^{-1}$), which is attributed to the nitrophenolate-to-copper charge transfer, while the band at 392 nm is assigned to the π–π* transition of this nitrophenolate moiety. $[Cu^{II}(LH)(OAc)]$ was not deprotonated upon addition of $N(Et)_3$ in excess, probably due to intramolecular hydrogen bonding (O1–H1···O7).

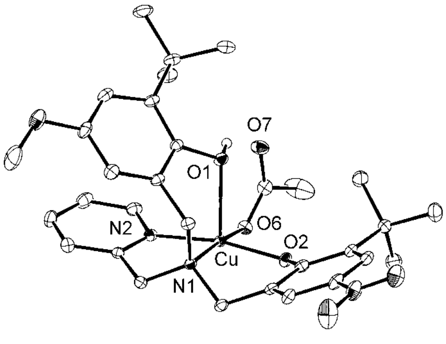


Figure 1. Structure of $[Cu^{II}(LH)(OAc)]$ (ORTEP view; ellipsoids drawn at the 30% probability level). Selected bond lengths [Å] and angles [°]: Cu-O1 2.399(2), Cu-O2 1.912(2), Cu-O6 1.955(2), Cu-N1 2.024(3), Cu-N2 1.990(3); O1-Cu-O2 98.30(8), O1-Cu-O6 99.59(8), O1-Cu-N1 88.03(9), O1-Cu-N2 92.39(9), O2-Cu-O6 87.49(9), O2-Cu-N1 94.4(1), O2-Cu-N2 169.0(1), O6-Cu-N1 171.8(1), O6-Cu-N2 93.1(1), N1-Cu-N2 83.6(1).

The one-electron oxidized forms of $[Cu^{II}(LH)(OAc)]$ and $[Zn^{II}(LH)(OAc)]$ (diamagnetic complex prepared for comparative studies) were generated electrochemically. The cyclic voltammogram of $[Cu^{II}(LH)(OAc)]$ (Figure 2, insert) as well as $[Zn^{II}(LH)(OAc)]$ exhibits in the anodic region a fully reversible one-electron (as judged by coulometric titration) redox couple at +0.075 V versus Fc/Fc$^+$.

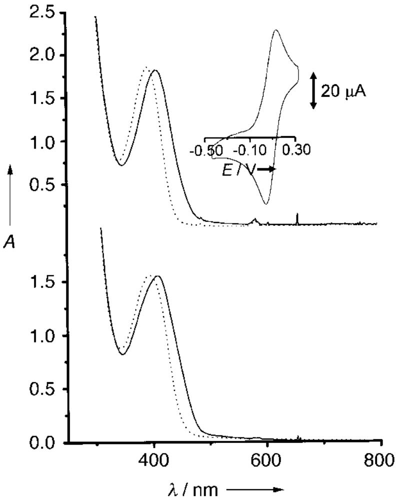


Figure 2. UV/Vis absorption spectra in CH_2Cl_2/CH_3CN (1:1) + tetrabutylammonium perchlorate (TBAP; 0.1 M) of $[Cu^{II}(LH)(OAc)]$ (top, (···)), $[Zn^{II}(LH)(OAc)]$ (bottom, (···)) and the electrochemically generated radicals $[Cu^{II}(LH)(OAc)]^{\bullet+}$ (top, (——)), $[Zn^{II}(LH)(OAc)]^{\bullet+}$ (bottom, (——)); $[Cu^{II}(LH)(OAc)] = 90\,\mu M$, $[Zn^{II}(LH)(OAc)] = 100\,\mu M$. Insert: CV curve of $[Cu^{II}(LH)(OAc)]$, 1 mM in CH_2Cl_2/CH_3CN (1:1) + TBAP (0.1 M); scan rate: 0.1 V s^{-1}; E/V versus Fc/Fc$^+$.

Exhaustive electrolysis at +0.15 V was performed directly in the UV/Vis spectrophotometer. At one exchanged electron, the absorption at 392 nm shifts to 410 nm for both $[Cu^{II}(LH)(OAc)]$ and $[Zn^{II}(LH)(OAc)]$ (Figure 2, $\varepsilon = 19\times10^3$ and $17\times10^3\,M^{-1}cm^{-1}$, respectively). Similar results obtained with the two complexes attest that oxidation is ligand-based. The UV/Vis features of the oxidized species are close to those previously described for phenoxyl radicals.[13] On the other hand, while $[Zn^{II}(LH)(OAc)]^{\bullet+}$ is EPR-active,[14] $[Cu^{II}(LH)(OAc)]^{\bullet+}$ is EPR-silent (Figure 3): This indicates a significant overlap between the $d_{x^2-y^2}$ magnetic orbital of Cu^{II} and the half-occupied π orbital of the phenoxyl radical leading to an ($S = 0$) ground state.

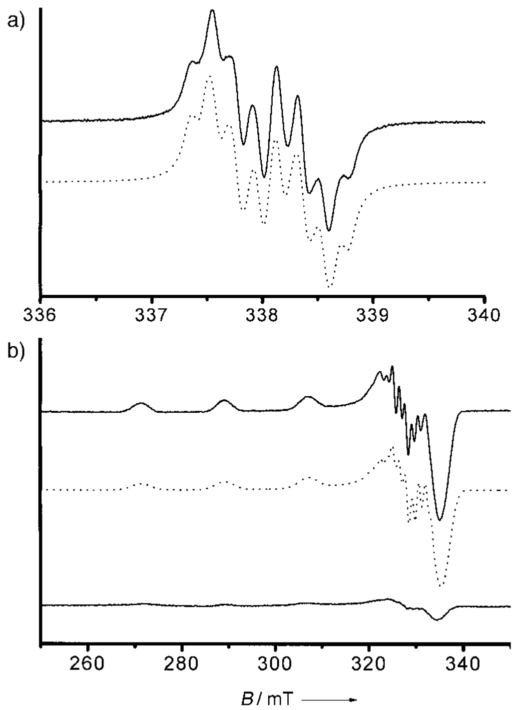


Figure 3. X-band EPR spectra of: a) the electrochemically generated [Zn^{II}(LH)(OAc)]$^{\bullet+}$ in CH_2Cl_2/CH_3CN (1:1) + TBAP 0.1 M (experimental (——), simulation (···)). [Zn^{II}(LH)(OAc)]$^{\bullet+}$ = 3 mM, $T = 22\,°C$, frequency: 9.4901 GHz, 2 mW; modulation: 0.0987 mT, 100 KHz. b) [Cu^{II}(LH)(OAc)] (experimental (——), simulation (···)) and [Cu^{II}(LH)(OAc)]$^{\bullet+}$(bottom): CH_2Cl_2/CH_3CN (1:1) + TBAP (0.1 M); [Cu^{II}(LH)(OAc)]$^{\bullet+}$ = [Cu^{II}(LH)(OAc)] = 3 mM, $T = 100$ K, frequency: 9.4112 GHz, 20 mW; modulation: 0.1756 mT, 100 KHz.

Even though the axial phenol is substituted by an electron-donating group, its remaining protonation makes its substitution insufficient to lower its redox potential below the redox potential of the deprotonated nitrophenolate. Moreover, the fully reversible redox process observed on the electrolysis time scale suggests that no chemical reaction, for example protonation–deprotonation, is associated with the electron transfer as expected for the oxidation of a protonated phenol.[15] The radical is thus located on the equatorial nitrophenolate group.

Oxidation of benzyl alcohol by [Cu^{II}(LH)(OAc)] and O_2 (in the presence of catalytic amounts of KOH) was monitored by GC. After two days 220 turnovers were achieved. A lag time during the first few hours indicates that [Cu^{II}(LH)(OAc)] is not the active species; the active species is more likely the radical [Cu^{II}(LH)(OAc)]$^{\bullet+}$, generated by aerobic oxidation. Use of $PhCD_2OH$ instead of $PhCH_2OH$ increased the lag time (only 50 turnovers/2 days). This isotopic effect indicates that the rate-limiting step during oxidation of alcohol is the C−H bond breakage as for GOase.

Use of the electrochemically generated [Cu^{II}(LH)(OAc)]$^{\bullet+}$ leads to oxidation of benzyl alcohol at a higher rate (220 turnovers in 2 h, 300 turnovers in one day). Using unactivated primary alcohols, 40 turnovers in one day were obtained for oxidation of the sterically hindered neopentyl alcohol, and 80 turnovers in one day for the oxidation of ethanol (aldehydes were titrated by a method previously developed by Wieghardt and co-workers).[7] Secondary alcohols (cyclohexanol or 2-hexanol) are not oxidized: no trace of ketone could be detected by GC after one week of reaction. The model thus reproduces the chemoselectivity of the enzyme. H_2O_2 was not detected after catalysis due to its fast disproportionation in basic medium (2 mM KOH or $N(Et)_3$). However, mixing together LH_2 and CuCl in a glove box (formation of a Cu^{I} complex) leads, upon exposure to air, to the formation of one equivalent of H_2O_2 (detected by a method developed by Wieghardt and co-workers).[7]

[Cu^{II}(LH)(OAc)]$^{\bullet+}$ is moderately stable at 25 °C in THF ($k_{dec} = 0.0175\ s^{-1}$).[16] Addition of an excess of benzyl alcohol under an anaerobic atmosphere increased k_{dec}, while quantitative formation (relative to the catalyst) of benzaldehyde was evidenced by GC. Monoexponential decay was fitted to obtain the observed pseudo-first-order constants $k_{dec}^{[Cu^{II}(LH)(OAc)]}$. The plot of $k_{dec}^{[Cu^{II}(LH)(OAc)]} - k_{dec}$ versus benzyl alcohol concentration shows a linear dependence (second-order rate constant $k_{Cu} = 0.0271(5)\ M^{-1}s^{-1}$) indicating that one benzyl alcohol is oxidized by one [Cu^{II}(LH)(OAc)]$^{\bullet+}$ complex[17] and thus the catalyst formally stores two oxidative equivalents, that is the phenoxyl/phenolate and the Cu^{II}/Cu^{I} couples.

In summary, the complex presented here may be considered as both a structural and functional model of GOase. It involves a similar [N_2O_2] coordination sphere around the Cu^{II} center. The one-electron oxidized form (Cu^{II}–phenoxyl radical) reproduces the magnetic control observed in the active form of the enzyme. It is also a good model for the chemistry and chemoselectivity of GOase, that is the oxidation of primary alcohols into aldehyde, with formation of H_2O_2. Finally, the complex [Cu^{II}(LH)(OAc)]$^{\bullet+}$ could be considered as a new possible intermediate in the catalytic pathway of GOase: the axial phenol is protonated and the equatorial phenoxyl antiferromagnetically coupled to the cupric center.

Experimental Section

[(Cu^{II})$_2$(L)$_2$]: LH_2 (173 mg) was treated with two equivalents of $N(Et)_3$ in CH_3CN (10 mL) prior to addition of $Cu(ClO_4)\cdot 6H_2O$ (118 mg). After 3 h a dark brown precipitate formed, which was filtered and washed with diethyl ether. Elemental analysis calcd (%) for $C_{64}H_{87}N_7Cu_2O_{13}\cdot 1/2\,CH_3CN\cdot 3/2\,H_2O$: C 59.76, H 6.33, N 7.68, Cu 10.72; found: C 59.75, H 6.31, N 7.49, Cu 9.88; FAB+ MS: *m/z*: 1139 ([(Cu^{II})$_2$(L)$_2$]). Single crystals of [$Cu^{II}_2(L)_2$]$\cdot 2\,CH_3CN$ and [$Cu^{II}_2(L)_2$] were obtained by recrystallization from CH_3CN/CH_2Cl_2 (1:1) or CH_3OH/CH_2Cl_2 (1:1). UV/Vis (CH_2Cl_2): λ_{max} (ε) = 296 (11.4×10^3), 391 (28.1×10^3), 500sh nm (5.1×10^3 L mol^{-1}cm^{-1}).

[Cu^{II}(LH)(OAc)]: LH_2 (100 mg) and $Cu(OAc)_2$ (40 mg) were dissolved in CH_3CN/CH_2Cl_2 (1:1). After one night CH_2Cl_2 was evaporated under vacuum. The solution was allowed to stand for three days at −20 °C. Green microcrystals of [Cu^{II}(LH)(OAc)] were collected by filtration. Elemental analysis calcd (%) for $C_{31}H_{39}N_3CuO_7\cdot 1\,CH_2Cl_2\cdot 1/2\,CH_3CN$: C 53.95, H 5.83, N 6.67, Cu 8.65; found: C 54.97, H 5.83, N 6.63, Cu 8.75; EPR (9.41 GHz, 100 K, CH_3CN/CH_2Cl_2): g_{xx}: 2.042; g_{yy}: 2.059; g_{zz}: 2.256; A_{xx}: 1 mT; A_{yy}: 2.5 mT; A_{zz}: 17.8 mT; A_N: 1.3 mT; FAB+ MS: *m/z*: 569 ([Cu^{II}(LH)]); UV/Vis (CH_3CN/CH_2Cl_2): λ_{max} (ε) = 298 (10.3×10^3), 393 (20.0×10^3), 500 sh (0.76×10^3), 600 sh nm (0.51×10^3 L mol^{-1}cm^{-1}).

[Zn^{II}(LH)(OAc)]: $Zn(OAc)_2$ (40 mg) was added to an ethanolic solution (5 mL) of LH_2 (100 mg); the mixture was stirred for 3 h and then filtered, extracted by CH_2Cl_2, washed, and dried over Na_2SO_4. [Zn^{II}(LH)(OAc)] was obtained as a yellow powder. Elemental analysis calcd (%) for $C_{31}H_{39}N_3ZnO_7\cdot 1\,H_2O$: C 57.36, H 6.37, N 6.47, Zn 10.07; found: C 57.38, H 6.34, N 6.41, Zn 9.70; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.34, 1.42 (s, 18H; 2*t*Bu), 2.17 (s, 3H; CH_3 acetate), 3.74, 3.82, 3.87, 3.89 (s, 9H; 3 CH_2, 1 OCH_3), 6.52, 6.81, 7.15, 7.92 (d, 4H; CH phenol), 8.15, 8.69 (d, 2H; CH pyridine), 7.33, 7.75 ppm (t, 2H; CH pyridine). FAB+ MS: *m*/*z*: 569 ([Zn^{II}(LH)]); UV/Vis (CH_3CN:CH_2Cl_2): λ_{max} (ε) = 316 (5.2×10^3), 392 nm (16.7×10^3 $L\,mol^{-1}\,cm^{-1}$).

Caution: Perchlorates are potentially explosive and should be handled with special care.

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[12] Crystal data for [$Cu^{II}(C_{29}H_{36}N_3O_5)(C_2H_3O_2)$]·1/2 CH_2Cl_2, $M_w = 671.68$, monoclinic, space group $P2_1/n$, $a = 13.104(1)$, $b = 14.327(1)$, $c = 17.760(1)$ Å, $\beta = 96.2(3)°$, $V = 3315(1)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.346\ g\,cm^{-3}$, $T = 120$ K, $\mu Mo_{K\alpha} = 0.788\ mm^{-1}$. A dark green platelet ($0.3 \times 0.2 \times 0.1$ mm) was mounted on a Kappa CCD Nonius diffractometer equipped with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) and a cryostream cooler. A total of 20358 reflections were collected and corrected for Lorentz and polarization effects. Crystal structural solution (direct methods) and refinement (by full-matrix least-squares on *F*) was performed by using the teXsan analysis package. All non-hydrogen atoms were refined with anisotropic thermal parameters. Only the phenol hydrogen atom was located on the Fourier-difference map and blocked on the carrier oxygen. All the other hydrogen atoms were generated on idealized positions, riding on the carrier atoms with isotropic thermal parameters. Of 8679 unique reflections ($R_{int} = 0.045$), 4892 were observed ($F = 4\sigma(F)$) and used in the full-matrix least-squares refinement of 145 variables. $R = 0.044$, $R_w = 0.059$, GOF = 1.90, max./min. residual peaks were 0.46/−0.54 e Å^3. CCDC-178422 ([Cu^{II}(LH)(OAc)]), CCDC-178423 ([$Cu^{II}_2(L)_2$]), and CCDC-178424 ([$Cu^{II}_2(L)_2$]·2 CH_3CN) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).

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[14] The hyperfine coupling constants determined from computer simulation indicate that the spin density is mainly located at the benzylic methylene group ($A_H = 0.600$ mT, $A_H = 0.175$ mT) and the nitro group ($A_N = 0.175$ mT). Based on the assumption that a McConnell-type angle dependent relationship for the hyperfine coupling to the benzylic proton exists, the magnitude of A_H depends on $\cos^2\theta$ ($90-\theta$ being the dihedral angle between the more strongly coupled proton of the methylene and the phenoxyl ring, see: A. Sokolowski, J. Müller, T. Weyhermüller, R. Schnepf, P. Hildebrandt, K. Hildenbrand, E. Bothe, K. Wieghardt, *J. Am. Chem. Soc.* **1997**, *119*, 8889) giving a θ value of 29° in good agreement with the dihedral angle (27°) obtained from the X-ray structure of [Cu^{II}(LH)(OAc)], showing that complexes are similar and the radical is equatorial.

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