Supramolecular control of an organic radical coupled to a metal ion embedded at the entrance of a hydrophobic cavity

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A novel N_3ArO-calix[6]arene-based system is presented. It allows the formation of an aryloxy radical bound to a metal ion (Cu^{II} or Zn^{II}) that presents a free coordination site in a concave cavity. Its oxidative activity appears highly controlled by the supramolecular system hence providing a good model for radical enzymes such as Galactose oxidase.

We have previously shown that a calix[6]arene is a superb supramolecular platform for constraining a 4- or 5-coordinate metal ion in a mononuclear environment that preserves a binding site buried inside an enzyme-like pocket accessible to small molecules. When functionalized with three *N*-donor groups at the small rim, the calixarene-based ligands yielded good structural models for mono Zn or Cu (type 2) enzyme active sites.[1,2] In the context of radical-enzyme biomimetic chemistry,[3] the next step of sophistication of this supramolecular system appeared to us to be the introduction of a redox non-innocent binding site and the exploration of the reactivity of the corresponding complexes. Therefore, taking advantage of an available external fifth coordination site in the parent N_3-based complexes, we grafted a phenol to one of the *N*-arms of the calixarene. The expected role of the coordinated phenate was to mimic the redox-active tyrosinate residue, oxidizable into the tyrosinyl radical, found in some metallo-radical-enzymes, such as the copper enzyme Galactose oxidase (GAO).[4,5] In this Communication, we report on the synthesis, characterization and redox behavior of the first complexes of this novel calix[6]arene family.

The Cu^{II} complexes of the calix[6]arene-based N_3ArOH ligands L^1H and L^2H, nitro- and tBu$_2$-substituted respectively,[6] were obtained by reacting stoichiometric amounts of the ligands with $Cu(H_2O)_6(ClO_4)_2$ in EtOH (Scheme 1). Each isolated compound presented an EPR axial signal† characteristic of a mononuclear Cu^{II} complex in a square-based pyramidal geometry. Their UV-VIS spectra in different CH$_2$Cl$_2$/S mixtures were dominated by an intense band at 330–390 nm attributable to a $\pi \longrightarrow \pi^*$ transition. A PhO$^- \longrightarrow Cu^{II}$ charge transfer transition (LMCT) was observed at 500–600 nm and the d–d transition at 630–760 nm.[7–10] These spectroscopic data were co-solvent (S) dependant. As examples of specific importance for this study, the EPR and UV-VIS data recorded in CH$_2$Cl$_2$ shifted upon addition of MeCN or benzyl alcohol.‡ This supports the formation of mononuclear Cu^{II} complexes of general formula $[L^iCu(S)](ClO_4)$, where Cu is coordinated to the deprotonated tetradentate ligand L^i and to a neutral molecule, S being either H$_2$O, MeCN or PhCH$_2$OH.

The crystal structure of $[L^1Cu^{II}(MeCN)](ClO_4)$ is displayed in Fig. 1.§ The Cu^{II} ion is coordinated in a distorted square-based pyramidal (SBP, $\tau = 0.23$)[11] N_4O environment. The base

R = NO$_2$, R' = H : L_1H
R = R' = tBu : L_2H

$[L^iCu^{II}(S)]^+$ $[L^iCu^{II}(S)]_2^+$
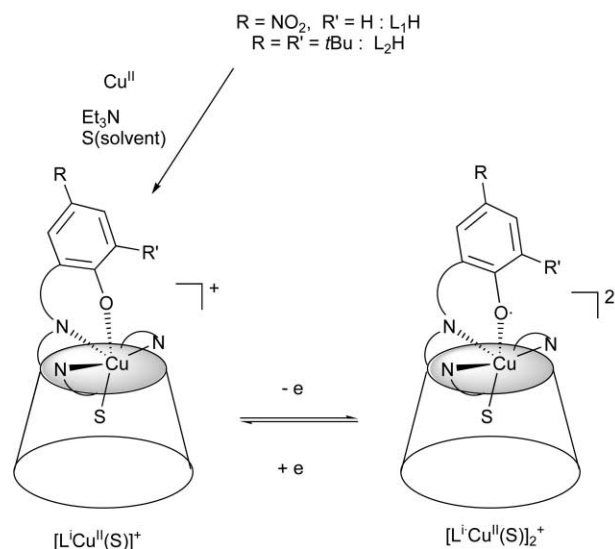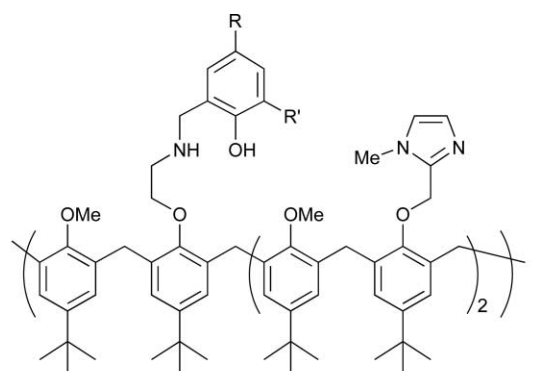
Scheme 1

of the pyramid is constituted by one imidazole, the nitrogen and the oxygen of the amino-phenolate arm and an acetonitrile molecule. The latter is deeply buried in the conic cavity of the calixarene, in *trans* position relative to the phenolate group. The second imidazole arm occupies the axial position, hence completing the pyramid. The Cu–N and Cu–O distances are similar to those reported for other Cu^{II} mononuclear complexes with the same N_3OS environment.[8,9,12,13] Lastly, the NH ligand is weakly hydrogen bonded to one methoxy group (O3) of the calixarene. The main structural characteristics of this complex are interestingly similar to those previously reported with the tris(imidazole)calix[6]arene-based system.[2a,c] Indeed
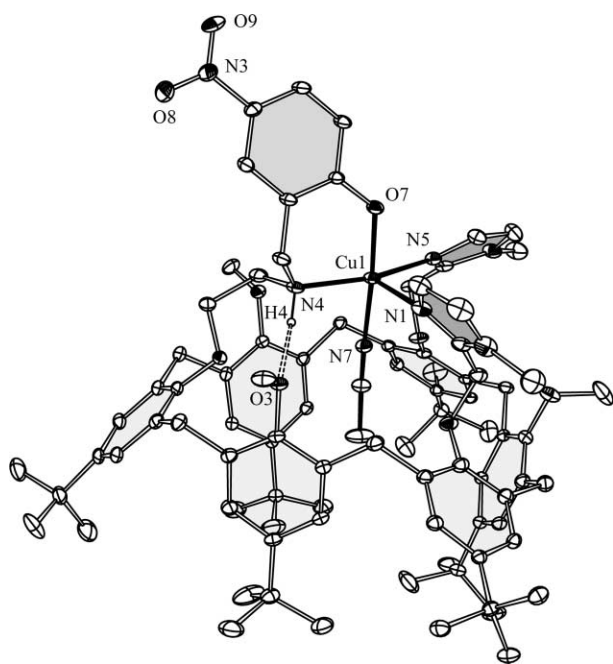

Fig. 1 Crystal structure of [L^{1}Cu^{II}(MeCN)](ClO$_4$) showing ellipsoids at 20% probability. Hydrogen atoms, perchlorate counterion and solvent of crystallization have been omitted for clarity. Selected bond length [Å] and angles [degrees]: Cu1–N1 2.227(4), Cu1–N4 2.034(4), Cu1–N5 2.050(4), Cu1–O7 1.919(3), Cu1–N7 2.008(4), N4–O3 3.064, N4–Cu1–N5 158.4(2), N4–Cu1–N7 86.0(2), N4–Cu1–O7 92.8(2), N4–Cu1–N1 106.7(2), N5–Cu1–N7 91.2(2), N5–Cu1–O7 87.2(2), N5–Cu1–N1 94.9(2), O7–Cu1–N7 172.4(2), O7–Cu1–N1 91.0(2), N7–Cu1–N1 96.6(2).

the [N_3Cu^{II}(H$_2$O)(RCN)]$^{2+}$ named complexes also displayed a 5-coordinate metal ion due to one intra-cavity labile co-ordination site, one external water ligand and three *N*-donors in the same relative positions. Most importantly of all, the phen-olate group of the new system now occupies the external site, thereby capping the cupric complex and leaving a single access-ible site for the coordination of an exogenous ligand S. This forces the labile ligand to be encapsulated in the cavity.

The redox behavior of the N_3ArO systems has been scrutin-ized in CH$_3$CN at room temperature (rt) and in CH$_2$Cl$_2$/CH$_3$CN (2/1 mixture) at −45 °C. By CV, both L^{1}H and L^{2}H ligands displayed irreversible oxidation peaks. The Cu^{II} com-plex based on L^{1}H also showed evidence of complicated oxid-ative behavior, and the CV of its Zn analog was not simplified, hence attesting to the high reactivity of the corresponding oxidized species.[9,14] In strong contrast, the Cu complex derived from ligand L^{2}H displayed at rt a fully reversible oxidation system, $E^{\circ\prime}$ = 0.32 V (*vs.* Fc$^+$/Fc) (ΔE_p = 60 mV, $i_{pa}/i_{pc} \approx 1$). A sluggish reduction process was also observed and is ascribed to the Cu^{II}/Cu^{I} couple with a slow reorganization at the electron exchange (Fig. 2).[13] The electrogenerated oxidized form ($n \approx 1$ e$^-$) of complex [L^{2}Cu^{II}(MeCN)]$^+$ was not stable at rt at the electrolysis time scale (1–2 h). At low temperature, the electro-chemical characteristics are only slightly modified and the elec-tron exchange slower [$E^{\circ\prime}$ = 0.30 V (ΔE_p = 240 mV) ($n \approx 1$ e$^-$)]; upon electro- or chemical [CAN (ceric ammonium nitrate), 1 equiv./Cu] oxidation, the solution turned from purple to green. CV and RDEV (rotating disk electrode voltammetry) showed the formation of the oxidized redox form, [L$^{2\bullet}$Cu^{II}(MeCN)]$^{2+}$, which was stable for a few hours at −45 °C. The UV-VIS spectrum (Fig. 2) of the oxidized complex revealed an intense phenoxyl $\pi \rightarrow \pi^*$ transition at 405 nm (ε = 3500 M^{-1} cm^{-1}), disappearance of the LMCT PhO$^-$ $\rightarrow$ Cu^{II} band at 520 nm (ε = 650 M^{-1} cm^{-1}) and a shift of the d–d transition from 720 nm (ε = 330 M^{-1} cm^{-1}) to 750 nm (ε = 500 M^{-1} cm^{-1}). The EPR spectra showed a 60 ± 5% loss of intensity with a broad Cu^{II} residual signal associated with the isotropic signature of a
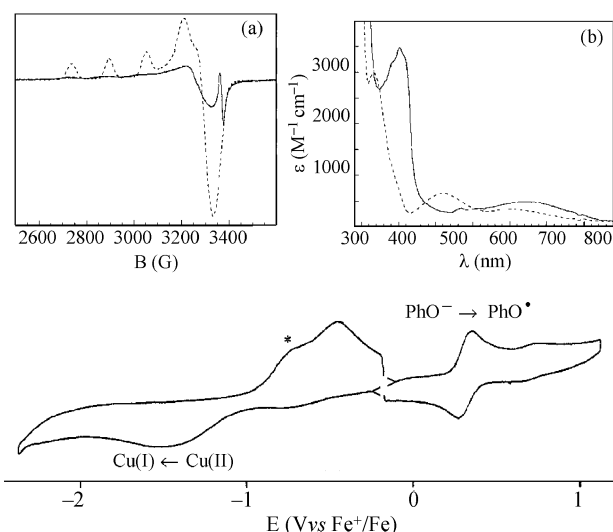

Fig. 2 Cyclic voltammetry of [L^{2}Cu^{II}(MeCN)]$^+$, at 25 °C in CH$_3$CN (Bu$_4$NPF$_6$ 0.2 M, Pt electrode, 100 mV s^{-1} scan rate; oxidation and reduction recorded as two separate scans). *: Redissolution peak of metallic Cu.[13b] Inset (a) and (b) respectively: EPR (150 K) and UV-VIS spectra of the complex before (- - -) and after (—) electrolysis at 0.5 V in CH$_2$Cl$_2$/CH$_3$CN (2/1), at −45 °C (Bu$_4$NPF$_6$ 0.2 M).

phenoxyl radical at $g \approx 2.0052$ (Fig. 2) likely resulting from an imperfect Cu^{II}–PhO$^\bullet$ antiferromagnetic coupling.

All these spectroscopic data support the formation of a Cu^{II}-phenoxyl species [L$^{2\bullet}$Cu^{II}(MeCN)]$^{2+}$, which resembles that observed in GAO[5] and its models.[4,15] Upon raising the temper-ature to rt, it was predominantly (>70%) converted back to the initial purple complex (≈30 min), thereby indicating the concomi-tant oxidation of a component of the electrochemical medium.

For comparison, the CV of the [L^{2}Zn(MeCN)]$^+$ complex displayed a single reversible system [$E^{\circ\prime}$ = 0.19 V (ΔE_p = 80 mV)] (Fig. 3). At rt, after electro-oxidation ($n \approx 1$ e$^-$), the solution turned from colorless to dark green. The reduction (RDEV) wave together with the unchanged CV indicated the formation of [L$^{2\bullet}$Zn]$^{2+}$. Its UV-VIS spectrum showed phenoxyl $\pi \rightarrow \pi^*$ transitions at 394 nm (ε = 2000 M^{-1} cm^{-1}) and 408 nm (ε = 2200 M^{-1} cm^{-1}) with a weaker absorption at 686 nm (ε = 200 M^{-1} cm^{-1}), all typical of a phenoxyl radical. The rt EPR spectrum revealed a two line signal at g = 2.0048 (LW = 3.13 G) character-istic of a Zn-coordinated ArO$^\bullet$, coupled with only one out of
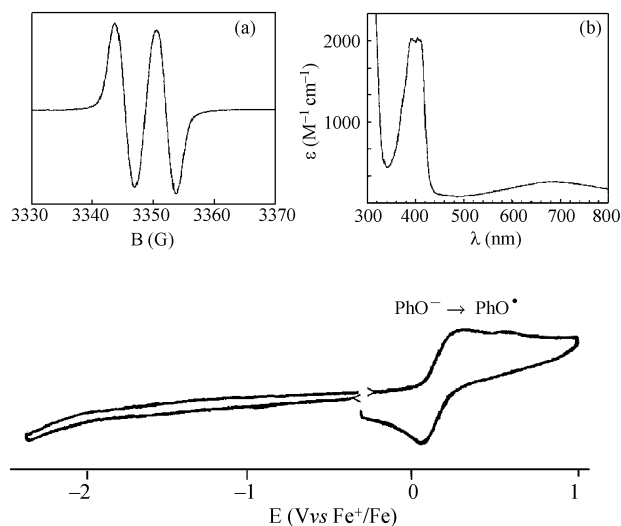

Fig. 3 Cyclic voltammetry of [L^{2}Zn(MeCN)]$^+$, at 25 °C in CH$_3$CN (Bu$_4$NPF$_6$ 0.2 M, Pt electrode, 100 mV s^{-1} scan rate; oxidation and reduction recorded as two separate scans). Inset (a) and (b) respectively: EPR and UV-VIS spectra of the complex after an electrolysis at 0.5 V in a CH$_2$Cl$_2$/CH$_3$CN (2/1), at 25 °C (Bu$_4$NPF$_6$ 0.2 M).

the two benzylic protons (A^H = 6.65 G).[10,16] This [L²˙Zn]²⁺ radical complex was remarkably stable for hours at rt.

In order to compare the reactivity of these complexes to that of GAO, which performs the two electron oxidation of an alcohol into an aldehyde, we tested their redox activity towards benzyl alcohol (BzOH). Addition of BzOH to a solution of [L²Cu]²⁺ maintained at −45 °C under argon initiated spectroscopic changes. With concurrent bleaching of the LMCT and d–d UV-VIS transitions, the solution slowly turned from green to yellow (*ca.* 1 h) and became EPR silent. From this, the formation of a Cu¹ derivative was inferred and the concomitant formation of a stoichiometric amount of benzaldehyde was evidenced by GC-MS [0.9(1) equiv.].¶ In contrast, no reaction between benzyl alcohol and [L²˙Zn]²⁺ occurred under the same conditions. In view of the closeness of its redox potential to that of the Cu¹¹ complex, the unreactivity of [L²˙Zn]²⁺ indicates that the oxidation of BzOH by [L²˙Cu]²⁺ does not follow an outer sphere mechanism but is mediated by its coordination to Cu. These observations stem from the fact that, in this supramolecular system, the only accessible binding site ‡ is buried inside by the calixarene cavity.‖ These results are then consistent with an inner-cavity process through which only [L²˙Cu¹¹]²⁺, not [L²˙Zn]²⁺, can mediate the two-electron oxidation of BzOH into PhCHO. We are currently exploring this very attractive hypothesis further.

In conclusion, this novel calixarene-based system is unique in that it associates a metal ion, an organic radical and a hydrophobic cavity leading to a supramolecular redox-active assembly. An X-ray structure along with the electrochemical and spectroscopic studies confirmed that the metal ion is capped by the aryloxyl donor, leaving a single coordination site accessible to exogeneous molecules located in the calix cavity. A comparative study of the Cu¹¹ and Zn¹¹ complexes showed that only the former was capable of oxidizing benzylic alcohol. Hence, this supramolecular system not only displays spectroscopic, redox and oxidative properties quite reminiscent of the enzyme Galactose oxidase but also integrates specific features reproducing the protecting effect of the protein cavity relative to the substrate receptor site.[5]

Acknowledgements

Notes and references

† Solid complexes issued from the synthesis with L¹H: $g_\perp$ = 2.06, $g_\parallel$ ($A_\parallel$/G) = 2.26 (156); with L²H: $g_\perp$ = 2.05, $g_\parallel$ ($A_\parallel$/G) = 2.25 (150). All EPR parameters were directly measured from the spectra.
‡ EPR and UV-VIS data of [L²Cu(S)](ClO₄) in different CH₂Cl₂/S = 1/1 (v/v) mixtures

S	$g_\perp$	$g_\parallel$ ($A_\parallel$/G)	λ_{max}/nm (ε/M⁻¹ cm⁻¹)
—ᵃ	2.05	2.25 (150)	335 (2830), 560 (530), 720 (460)
PhCH₂OH	2.07	2.31 (134)	324 (2160), 519 (520), 670 (230)
MeCN	2.06	2.27 (156)	333 (3060), 520 (650), 720 (330)

ᵃH₂O is the guest ligand.

§ Monocrystals were obtained by slow diffusion of pentane into a solution of the complex in a 1/1 toluene/CH₂Cl₂ mixture in the presence of a few equivalents of CH₃CN. Crystallographic data for [L¹Cu(MeCN)]-(ClO₄): C₉₇.₅H₁₂₅Cl₂CuN₇O₁₄, M_W = 1753.49, triclinic, green crystal (0.4 × 0.4 × 0.3 mm³), a = 15.9658(3) Å, b = 15.9740(3) Å, c = 22.8602(5) Å, α = 86.1316(7)°, β = 74.1236(8)°, γ = 61.927(8)°, V = 4935.1(2) Å³, space group P-1, Z = 2, ρ = 1.18 g cm⁻³, μ(Mo Kα) = 3.37 cm⁻¹, 15658 unique reflections in the 1–25° θ range, 1059 parameters refined on F^2 using 15658 reflections [Shelxl] to final indices $R[F^2 > 4\sigma F^2]$ = 0.092, $wR[w = 1/[\sigma^2(F_o^2) + (0.1211P)^2 + 14.0952P], P = (F_o^2 + 2F_c^2)/3]$ = 0.233. The

complex co-crystallized with a disordered CH₂Cl₂ solvate, a disordered water molecule and an unidentified fragment that we assigned as a disordered toluene solvate. The last residual Fourier positive and negative peaks were equal to 1.082 and −1.085 respectively. CCDC reference number 215663. See http://www.rsc.org/suppdata/dt/b3/b308255e/ for crystallographic data in CIF or other electronic format.
¶ The experiment was run in a CH₂Cl₂/MeCN 2:1 v/v mixture; [Cu] = 1.5 mM. 10% in volume of BzOH was added. The yield in PhCHO corresponds to the average value of three independent experiments. Under these experimental conditions, no extra production of benzaldehyde could be evidenced upon bubbling O₂ which only partially restored the spectral features of the [L²Cu¹¹(MeCN)]⁺ complex. We are now exploring the catalytic activity of the complex in the presence of a base.
‖ As evidenced in the X-ray structure (Fig. 1), the accessible binding site is controlled by the calixarene cavity. Modeling studies (with Dreiding and CPK models, or BIOSIM software) clearly indicate that (i) external binding of BzOH to the metal ion is highly disfavored due to sterical overcrowding, particularly in the case of the *t*Bu-substituted phenate (L²), (ii) the system is highly flexible and can easily adopt a conformation where the intra-cavity ligand is *cis* to the phenate.

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