Drastic effects of the second coordination sphere on neutral *vs.* anionic guest binding to a biomimetic Cu(II) center embedded in a calix[6]aza-cryptand†

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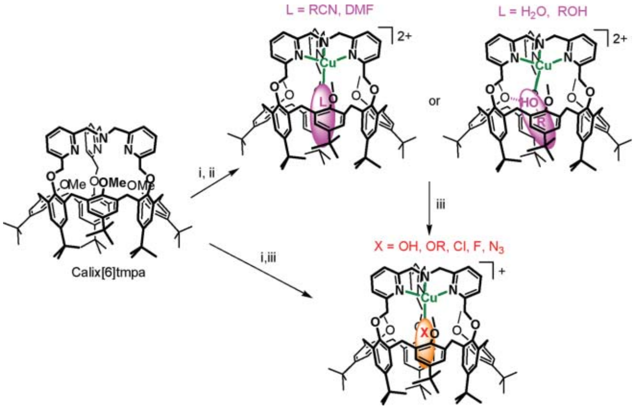
A calix[6]arene capped by a tmpa unit provides Cu(II) funnel complexes that, for the first time, accept not only neutral guest ligands but also anionic ones such as a hydroxide, which is due to a small conformational change in the calixarene cone.

In biology, the metal ion coordination properties are highly controlled by the protein framework. Whereas amino-acid residues such as His provide the first coordination sphere, the metal ion binding properties in enzymes are tuned by the protein backbone that defines the second coordination sphere as well as the entrance gate from the bulk to the active site.[1] Wanting to mimic these three aspects of the biological coordination, we have developed a set of ligands based on calix[6]arenes that are functionalized at the small rim by nitrogen arms. In this system, the aza-donors secure the first coordination sphere with one open binding site directed toward the center of the macrocycle cavity, and the calixarene small rim defines the second coordination sphere, whereas the aromatic units of the calixarene act as a hydrophobic funnel that selects and drives a guest molecule to the metal center.[2] In a recent paper,[3] we have described the synthesis of a new ligand, calix[6]tmpa, in which a tmpa [tris(2-methylpyridyl)amine] unit covalently caps the calixarene small rim. Here, we describe preliminary results relative to its Cu(II) complexes that display unique properties compared to all previously reported calix[6]arene-based funnel complexes.

Stoichiometric amounts of calix[6]tmpa and $Cu(ClO_4)_2(H_2O)_6$ were reacted in a 9 : 1 (v/v) THF–dichloromethane mixture to provide a blue cupric complex with a 1 : 1 : 2 ligand : Cu : ClO_4 stoichiometry. This accounts well for the formation of a dicationic mononuclear aqua complex $[Cu(calix[6]tmpa)(H_2O)]^{2+}$, with a 5-coordinate Cu(II) center as reported for the previously described calix[6]tris(imidazole)[4] and calix[6]tren-based Cu(II) complexes[5] (Scheme 1 top, L = H_2O).[6]

The electronic spectrum of the isolated aqua complex $[Cu(calix[6]tmpa)(H_2O)]^{2+}$ in pure CH_2Cl_2 displays a maximum absorption at 846 nm (ε = 220 M^{-1} cm^{-1}) with two shoulders at 700 and 685 nm, which is characteristic of the d–d transitions of a trigonal bipyramidal (TBP) copper(II) center. Progressive addition of an organic ligand L such as EtOH, MeCN or DMF to a 3 mM solution of this complex in CH_2Cl_2 produced a new set of spectra with isosbestic points, thus showing the exchange of the water ligand for the organic guest L.[7] Remarkably, whereas the addition of 50 equiv. of EtOH was required to obtain saturation of the spectrum, the nitrilo and amido adducts were quantitatively obtained upon the addition of only one equiv. of MeCN and DMF, respectively, under the same experimental conditions. These data highlight an impressive affinity of the Cu(II) center for these π-acceptor guests compared to water or EtOH.



Scheme 1 Synthesis of complexes $[Cu(calix[6]tmpa)(L)]^{2+}$ and $[Cu(calix[6]tmpa)(X)]^{+}$. i: $Cu(ClO_4)_2(H_2O)_6$, THF–CH_2Cl_2, ii: L, iii: base or X^-.

Whereas the aqua complex displayed a rhombic EPR spectrum in a non-coordinating solvent such as CH_2Cl_2, the nitrilo adduct (L = MeCN) showed a strongly axial spectrum, with $g_\perp > g_\parallel$ (Fig. 1),† in agreement with a d_{z^2} configuration due to the trigonal bipyramidal geometry enforced by the tmpa chelating core.[8] Interestingly, similar axial EPR spectra with close parameters were obtained with other organonitriles RCN displaying quite different bulkiness properties (R = Et, Bu, Ph) as well as with DMF, whereas the coordination of EtOH produced a rhombic spectrum similar to that of the aqua complex (Fig. 1). Such a geometric distortion may be related to the establishment of a hydrogen bond between the OH group of the guest ligand and one oxygen atom belonging to the calixarene small rim, as observed in various XRD structures of other funnel complexes.[5,9–11]

Single crystals were grown out of a cold chloroform solution of the Cu(II) complex in the presence of traces of MeCN. Its XRD structure is displayed in Fig. 2 (top).†‡ It shows a strongly axial

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† Electronic supplementary information (ESI) available: Experimental details for the syntheses and EPR analyses, XRD data collection (CCDC 620319). See DOI: 10.1039/b613564a

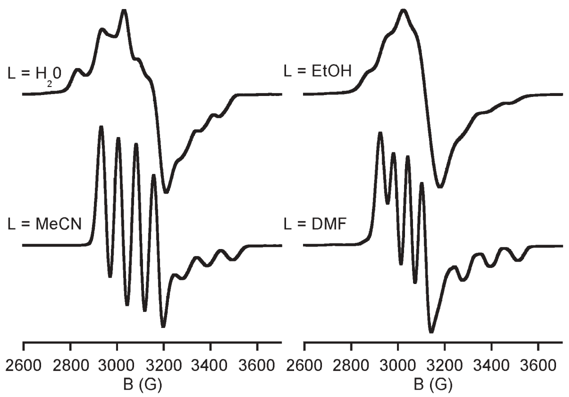

Fig. 1 EPR spectra (X band) of [Cu(calix[6]tmpa)(L)](ClO$_4$)$_2$ in frozen CH$_2$Cl$_2$ (100 K) with 10% (v/v) of guests. For L = H$_2$O: g_1 = 2.000, g_2 = 2.157, g_3 = 2.230, A_1 = 92, A_2 = 28, A_3 = 82; L = EtOH: g_1 = 2.008, g_2 = 2.149, g_3 = 2.236, A_1 = 73.5, A_2 = 39, A_3 = 107; L = MeCN: $g_\parallel$ = 1.998, $g_\perp$ = 2.182, $A_\parallel$ = 97, $A_\perp$ = 75; L = DMF: $g_\parallel$ = 1.999, $g_\perp$ = 2.206, $A_\parallel$ = 106.7, $A_\perp$ = 59 ($A \times 10^{-4}$ cm^{-1}).†

(τ = 0.96)[12] TBP Cu(II) center bound to the tmpa cap and to an acetonitrile molecule that sits aligned on the C_3 axis in the heart of the calixarene cavity.

The Cu–N$_{\text{MeCN}}$ bond length is significantly shorter than those reported for other tmpa-based Cu(II) complexes, whereas the Cu–N$_{\text{tmpa}}$ distances are longer.[8,13] In addition, the Cu(II) ion is much displaced from the equatorial basal plane (0.599 Å) toward the axial MeCN ligand. All of this accounts for a stronger Cu–MeCN bond in our calix-system compared to other tmpa-based Cu(II) complexes. Interestingly, the cone conformation adopted by the calix[6]arene core is different from that observed for all other funnel M(II) complexes,[2] including those based on calix[6]tren.[5,14] Indeed, the anisole *t*Bu substituents are classically in an *in* position relative to the cavity because of the projection of the amino arms toward the center to wrap the metal ion. Here, the geometrical constraint imposed by the rigid tmpa cap seems to preclude the *out* position of their linked aromatic units, thus leading to the converse relative alternate position of the aromatic units.[15] An interesting consequence of this is the modification of the second coordination sphere provided by the calixarene small rim. In this structure, the coordinating nitrogen atom of the guest is surrounded by CH$_2$ groups at a N···H distance of 2.82(1) Å, whereas the related oxygen atoms point their electron lone pair in the opposite direction. This stands in strong contrast with the other calix-Cu(II) complexes for which the same oxygen atoms direct their electron density toward the metal ion, as schematized in Fig. 2 (bottom).

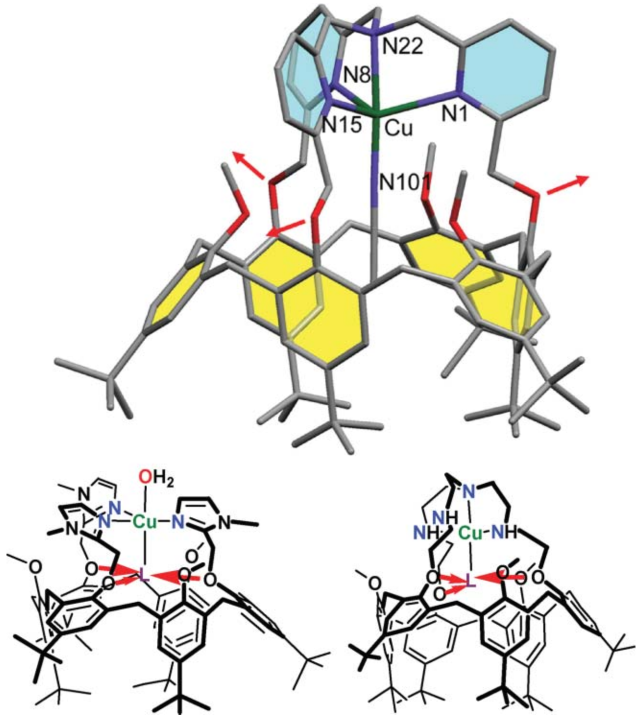

Fig. 2 Top: XRD structure of [Cu(calix[6]tmpa)(MeCN)](ClO$_4$)$_2$.†‡ Hydrogen atoms, counterions and solvent of crystallization were omitted for clarity. Selected bonds length [Å] and angles [°]: Cu–N101 1.916(5), Cu–N22 2.203(5), Cu–N1 2.301(6), Cu–N8 2.300(6), Cu–N15 2.381(5), N101–Cu–N22 176.0(2), N101–Cu–N1 104.9(2), N101–Cu–N8 106.5(2), N101–Cu–N15 102.6(2), N22–Cu–N1 75.3(2), N22–Cu–N8 76.5(2), N22–Cu–N15 73.78(19), N1–Cu–N8 118.3(3), N1–Cu–N15 110.6(3), N8–Cu–N15 112.3(3). Bottom: conformations adopted by the related calix[6]-tris(imidazole) and calix[6]tren-based Cu(II) dicationic complexes based on XRD analyses.[4,5]

The addition of a weak base [a few molar equiv. of 2,6-lutidine or triethylamine (TEA)] to a solution of [Cu(calix[6]tmpa)(L)]$^{2+}$ yielded a new complex, whose EPR signal and UV-vis-NIR spectra were identical in pure CH$_2$Cl$_2$ (L = H$_2$O) or in a CH$_2$Cl$_2$–DMF mixture (L = DMF). Under both conditions, the set of absorption spectra obtained upon the progressive addition of the base showed isosbestic points (Fig. 3), with the formation of the same new species. This new species is characterized by a wider absorption spectrum, with three relatively well separated d–d transitions at 672, 811 and 1062 nm and a LMCT at 311 nm (ε = 185, 142, 87 and 3800 M^{-1} cm^{-1}, respectively). The corresponding EPR spectrum remains characteristic of a d$_{z^2}$ configuration ($g_\perp > g_\parallel$) with, however, an $A_\parallel$ value (187 × 10^{-4} cm^{-1}) that is much larger than the one classically encountered for TBP Cu(II) centers

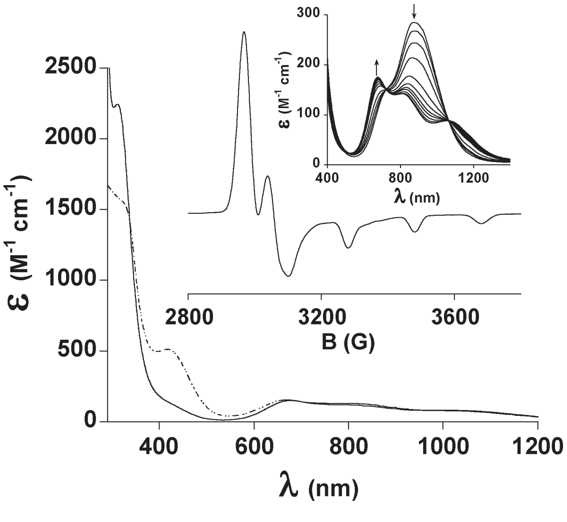

Fig. 3 UV-vis-NIR spectra (CH$_2$Cl$_2$, 293 K) of complex [Cu(calix[6]tmpa)(OH)](ClO$_4$) before (solid line) and after recrystallization in EtOH (dashed line). Inset: titration of [Cu(calix[6]tmpa)(DMF)](ClO$_4$)$_2$ by TEA, showing isosbestic points at 717 and 1061 nm, and EPR spectrum (X band) of complex [Cu(calix[6]tmpa)(OH)](ClO$_4$) in frozen CH$_2$Cl$_2$ (100 K): $g_\parallel$ = 1.994, $g_\perp$ = 2.207, $A_\parallel$ = 187.21, $A_\perp$ = 25.77 ($A \times 10^{-4}$ cm^{-1}).

($A_{\parallel} < 80 \times 10^{-4}$ cm^{-1}).[16] In contrast, these values resemble those reported for a tetrahedral hydroxo-Cu(II) complex coordinated to an N_3 ligand ($A_{\parallel}$ = 152 G, $g_{\parallel}$ = 2.00, $g_{\perp}$ = 2.24).[17] This new complex was isolated and its elemental analyses account well for a 1 : 1 : 1 ligand : Cu : ClO_4 ratio, thus confirming its monocationic nature. Interestingly, when recrystallized in EtOH, the isolated complex displayed a LMCT at 419 nm in CH_2Cl_2, whereas the d–d transitions were not affected (see Fig. 3). New lines in the $g < 2$ area of the EPR spectrum were also observed, thereby attesting to the appearance of a second species that resembles the first one. Similar experiments with the bulkier *i*PrOH did not show the formation of a second species. All these experiments substantiate the formation of a hydroxo-complex, [Cu(calix[6]tmpa)(OH)]$^+$, with its OH ligand sitting in the cavity, which can react with EtOH to yield the corresponding monocationic ethoxo-complex, [Cu(calix[6]tmpa)(OEt)]$^+$, but not with the bulkier *i*PrOH. This alkoxo ligand underwent hydrolysis in CH_2Cl_2 solutions exposed to air as spectra corresponding to the hydroxo-species were recovered after a few hours.[18]

Similar spectroscopic data were obtained upon the reaction of the dicationic complex [Cu(calix[6]tmpa)(L)]$^{2+}$ with either azide, chloride or fluoride anions, thus showing the formation of the corresponding monocationic complexes [Cu(calix[6]tmpa)(X)]$^+$. All EPR spectra obtained upon anion binding exhibit unusually large $A_{\parallel}$ ($>136 \times 10^{-4}$ cm^{-1}) values for a d_{z^2} cupric state. It is noteworthy that such EPR signatures are relatively rare for Cu(II). They must be related to the axial trigonal geometry with the binding of strong donors on the z axis.

In conclusion, the cupric complexes based on calix[6]tmpa revealed themselves to be very stable, the Cu(II) ion being strongly bound to the tmpa cap in a TBP geometry and displaying high affinities for neutral guest ligands that sterically fit into the calix-cavity. These aspects resemble those of the previously reported calix[6]tren-based Cu(II) complexes.[5] A major difference, however, stems from the second coordination sphere that provides a different electronic environment around the guest coordinated atom. Indeed, a small conformational change (compared to other funnel complexes) drives the oxygen atoms linked to the nitrogen arms to be oriented in the opposite direction, *i.e.* toward the bulk, thus leading to an inverted dipolar environment. As a result, the Cu(II) ion in the calix[6]tmpa environment readily binds a large variety of anions, whereas with the former systems,[5,14,19,20] anion binding in the cavity appeared strongly disfavored, most probably because of charge–dipole repulsion at the level of the small rim. Most interestingly, a hydroxo-complex is now stabilized in the mononuclear environment, constrained by the calixarene cavity that protects the potentially bridging guest ligand,[20] although allowing its selective exchange for an alkoxide. We are currently exploring the reactivity of these rare and interesting species that are highly biologically relevant to mononuclear active sites of metallo-enzymes.[1]

Notes and references

‡ Crystal data: $C_{92}H_{111}N_5O_{14}Cl_2Cu$, M_w = 1645.30, monoclinic, space group *C*2/*c*; dimensions: a = 42.363(3) Å, b = 19.886(2) Å, c = 22.794(2) Å, β = 102.349(3)°, V = 18758(2) Å^3; Z = 8; μ = 0.350 mm^{-1}; 291 801 reflections measured at 100 K; independent reflections: 16 511 [14 706 $F_o > 4\sigma(F_o)$]; data were collected up to a $2\theta_{max}$ value of 50° (100% coverage). Number of variables: 959; R_1 = 0.1578, wR_2 = 0.3934, S = 1.047; highest residual electron density 1.295 e Å^{-3} (all data R_1 = 0.1643, wR_2 = 0.3976). CCDC 620319. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613564a

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