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Novel Biomimetic Calix[6]arene-Based Copper(II) Complexes

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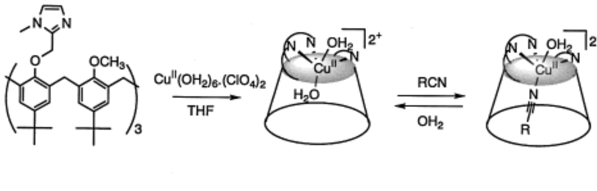
Mononuclear copper enzymes constitute an important class of proteins[1] that perform highly efficient and selective transformations on organic molecules. Therefore, it is important to develop chemical systems that allow the specific chemistry at a monocopper site to be modeled.[2] The main difficulty stems from the necessity to simultaneously control (i) the complex nuclearity and (ii) the access to the metal center for the substrate. Thanks to the design of calixarene-based N_3 ligands, we have recently[3] described a novel supramolecular model for the cuprous type II site of enzymes. The geometry of the system was designed to constrain the metal in a mononuclear environment, orienting a labile site toward the inside of the hydrophobic cavity provided by the calixarene skeleton. Because copper enzymes are involved in redox processes,[1] it was most important to explore the coordination of Cu^{II} to these calixarene-based ligands. Here, we describe the structure and host−guest behavior of the first cupric complexes derived from a novel calixarene-based ligand presenting a neutral trisimidazole core.

The new N_3 ligand $X_6Me_3Imme_3$[4] reacted with a stoichiometric amount of copper(II) perchlorate in THF to produce a blue cupric complex **1**. Its elemental analysis was in accord with a 1:1 ligand/Cu complex of formula $Cu(X_6Me_3Imme_3)(OH_2)_2(ClO_4)_2$.[4] In dichloromethane, it displayed a tetragonal EPR spectrum with $g_\perp = 2.07$ and $g_\| = 2.28$ ($A_\| = 162 \times 10^{-4}$ cm^{-1}) and a d−d transition at 644 nm. These data are typical of mononuclear five-coordinate species with a distorted, square-based pyramidal geometry (SBP).[5] When synthesized with cupric triflate instead of perchlorate, the complex displayed similar spectroscopic properties. This suggests that these anions do not coordinate the metal center. Therefore, we propose the formation of a mononuclear, dicationic calixarene-based complex with three imidazole groups and two water molecules in the Cu^{II} coordination sphere (Scheme 1).

The addition of acetonitrile to a dichloromethane solution of complex **1** induced considerable modifications of the spectroscopic data. The $g_\|$ value increased to 2.31, and $A_\|$ decreased to 135×10^{-4} cm^{-1}. The d−d absorption underwent a red shift to 758 nm. These spectroscopic changes reflect an interaction between MeCN and the metal center with a distortion of the tetragonal geometry toward trigonal bipyramidal (TBP).[5] The addition of propionitrile or allylnitrile also induced significant changes to both the EPR and visible spectra, whereas the more bulky benzylnitrile was ineffective.[4] This suggests that complex **1** possesses an exchangeable coordination site that selectively interacts with small molecules.

Scheme 1



$X_6Me_3Imme_3$ **1** **2**: R = Me

Eq. 1 : $K_{MeCN} = [2][H_2O]/[1][MeCN]$

The formation of nitrilo adducts was studied by spectrophotometric titration in CH_2Cl_2 saturated with water.[4] Typical spectral data are shown in Figure 1. The presence of isosbestic points attested to the formation of a unique species. A Hill plot yielded a straight line with a slope $n = 1$, indicating the formation of an adduct with a 1:1 stoichiometry. The calculated equilibrium constant for the aqua substitution reaction by acetonitrile (Scheme 1) was $K_{MeCN} = 4.0(5) \times 10^{-2}$. For propionitrile and allylnitrile, corresponding K_{EtCN} and $K_{AllylCN}$ were $1.5(3) \times 10^{-2}$ and $0.8(3) \times 10^{-2}$, respectively. With the bulkier benzylnitrile, since no adduct could be detected under the same experimental conditions, the corresponding K_{BnCN} was estimated to be lower than 10^{-4}. Hence, the size and shape of the nitrile alkyl chain affected not

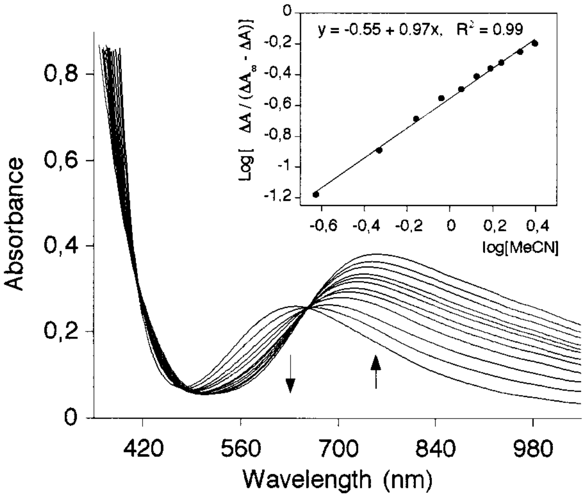


Figure 1. Titration of **1** with MeCN at 23 °C. Spectra were obtained upon successive addition of aliquots of MeCN (5 μL) to the complex (6.4 mM) in CH_2Cl_2 (400 μL) saturated with water (140 mM). The inset shows the corresponding Hill plot.

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(4) See Supporting Information for experimental details, spectroscopic characterization, and X-ray structure determination of new compounds.

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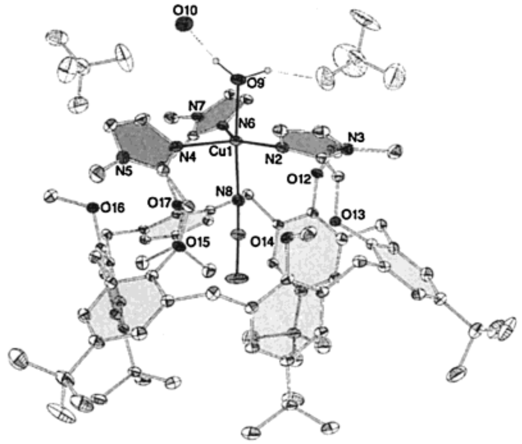

Figure 2. Crystal structure of complex [Cu($X_6Me_3Imme_3$)(NCMe)](ClO_4)$_2$·(OH_2) (**2**). The hydrogen atoms of the aquo ligand were located experimentally and are represented by plain spheres of arbitrary radius. Other hydrogen atoms and solvents of crystallization are omitted for clarity. Selected bond lengths [Å] and angles [deg]: Cu1−O9, 2.015(2); Cu1−N2, 2.008(3); Cu1−N4, 2.189(3); Cu1−N6, 2.030(3); Cu1−N8, 1.992(3); O9−Cu1−N2, 85.6(1); O9−Cu1−N4, 90.5(1); O9−Cu1−N6, 88.5(1); O9−Cu1−N8, 175.3(1); N2−Cu1−N4, 105.5(1); N2−Cu1−N6, 145.8(1); N2−Cu1−N8, 90.4(1); N4−Cu1−N6, 108.2(1); N4−Cu1−N8, 93.1(1); N6−Cu1−N8, 93.4(1).

only the geometry of the system but also its stability. This suggests that water substitution selectively occurred in the cavity, as depicted in Scheme 1.

Single crystals were obtained by the slow diffusion of diethyl ether into an acetonitrile solution of **1**. The X-ray structure of [Cu($X_6Me_3Imme_3$)(OH_2)(NCMe)](ClO_4)$_2$·OH_2 (**2**) is displayed in Figure 2. The copper ion is in a distorted tetragonal N_4O environment, provided by the N_3 ligand, an acetonitrile (Cu−N, 1.992(3) Å) buried inside the calixarene cavity, and a water molecule (Cu−O, 2.015(2) Å) that sits outside. The calixarene adopts a cone conformation close to C_3 symmetry with all three methoxy groups projected outside the cavity.[6] Whereas two Cu−imidazole bond distances (2.008(3), 2.030(3) Å) have values similar to those reported for five-coordinate Cu^{II} compounds,[7,8] the third one is considerably longer (Cu−N, 2.189(3) Å). The corresponding loosely tied imidazole can be regarded as the apical donor site of a square-based pyramid. The corresponding τ value[9] is 0.492 and reflects a geometry between SBP ant TBP. The aquo ligand is hydrogen-bonded to another H_2O (H···O, 1.712 Å) and to one perchlorate (H···O, 1.893 Å). The associated water molecule is most probably hydrogen-bonded to the second perchlorate (O···O, 2.75 Å; aquo H atom not found). This extensive hydrogen bond network reflects the very high acidity of the water ligand because of its coordination to the dicationic metal center. These results confirm that complex **1** underwent a regioselective exchange process to produce **2**. Indeed, substitution of one of the aquo ligands for the more lipophilic acetonitrile molecule preferentially occurred inside the hydrophobic cavity, not outside.

We have here described the synthesis and structural characterization of the first member of a new family of calix[6]arene-based copper(II) complexes. The metal center is in a neutral five-coordinate environment provided by (i) three imidazole groups that mimic the trishistidine coordination site of enzymes, (ii) a water ligand that sits outside of the cavity and is stabilized by a hydrogen-bonding network, and (iii) a second aquo ligand that is buried inside the hydrophobic cavity and can be selectively exchanged for lipophilic molecules. The calixarene hydrophobic pocket protects the metal center against dimerization and *simultaneously* acts as a molecular funnel for organic molecules.[10−12] For all these reasons, this novel supramolecular system provides a unique model for the active site of type II copper proteins. We are currently exploring its reactivity.

Supporting Information Available: Synthetic procedures, characterization, and crystallographic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The three imidazole arms wrapping the metal center form a chiral helix. Both enantiomers were included in the unit cell.[4] The relative conformation of the phenolic units is different from what was previously observed in the case of the copper(I) complex.[3]

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