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Synthesis and Studies of a Water-Soluble and Air-Stable $\mathrm{Cu^{I}/Cu^{II}}$ Open-Shell *Funnel* Complex

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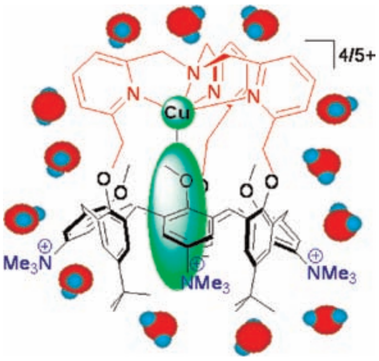
ABSTRACT



The derivatization of the large rim of a TMPA-capped calix[6]arene (TMPA = tris(2-pyridylmethyl)amine) with three trimethylammonium groups enables the water-solubilization of two air-stable Cu(I)/Cu(II) complexes. These two complexes present a vacant coordination site shielded from the aqueous environment by the calixarene core. The spectroscopic and electrochemical data recorded in pure water indicate that the host–guest properties of the funnel complex are retained in both oxidation states of the copper cation.

The construction of artificial metallo-enzymes aims at reproducing structural and functional properties of natural systems.[1] While these systems rely on extraordinary complicated machinery giving impressive kinetic features and exquisite thermodynamic selectivity,[2] the mimetic strategy has mainly focused on the first coordination sphere of the metal ion.[1d] More recently, we and others have started to implement the model compounds with structural elements mimicking the environment around the metal ion labile site. Hence, the importance of the second coordination sphere has been explored by introducing H-bond donors or acceptors in the vicinity of the metal ion.[3] It is also well recognized that the enzymatic pocket plays a key role for substrate selective binding (third coordination sphere). One approach to explore this aspect consists in associating the metal complex to a

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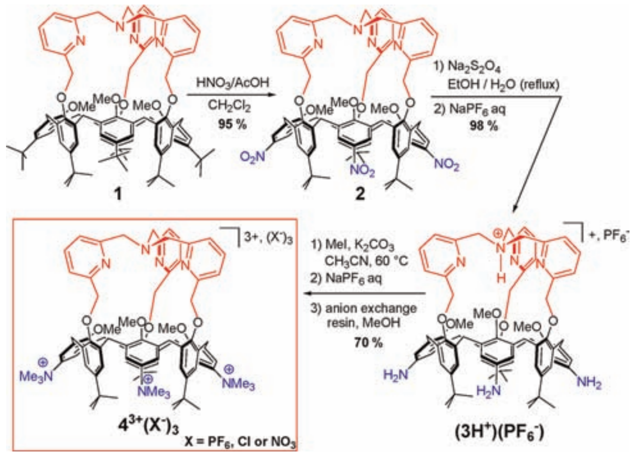
hydrophobic cavity.[4] In all these strategies, the addition of interaction sites remote from the metal center stabilizes the complex−substrate or complex−intermediate adducts. Consequently, noncovalent interactions have been identified as key partners for studying more accurately the influence of the many parameters found in enzymes.[5] Another parameter that obviously has a key role is the water solvent. Indeed, the hydrophobic effect,[6] ubiquitous when one looks at the processes in biological systems have not yet received a lot of attention from the biomimetic community working on metallo-enzyme models.[7]

The water-solubilization of promising artificial systems working in organic solvents remains a tantalizing goal.[8] We have recently proposed a strategy to water-solubilize a calix[6]arene ligand presenting three chelating imidazole units.[9] Interestingly, the behavior of this ligand is different in water and in an organic solvent. The hydrophobic effect has been clearly identified as the key driving force for the formation of a ternary complex between the ligand, a zinc cation, and a hydrophobic primary amine at an optimal pH of 7.8. The lack of stability of the zinc complex in absence of the hydrophobic guest prompted us to investigate the water-solubilization of a stronger cavity-based ligand. In the past few years, we have intensively studied the calix[6]TMPA ligand **1** (Scheme 1) (TMPA = tris(2-pyridylmethyl)amine).[10,11] Herein, we wish to report the synthesis of a water-soluble calix[6]TMPA ligand and the first data obtained with the corresponding Cu(I)/Cu(II) complexes studied in pure water.

Scheme 1. Synthesis of the Water-Soluble Calix[6]TMPA Ligand $\mathbf{4}^{3+}$



Synthesis of the Water-Soluble Calix[6]TMPA Ligand $\mathbf{4^{3+}}$**.** In order to modify as little as possible the coordination properties of the TMPA cap, the functionalization of the ligand with hydrophilic substituents was operated at the large rim of the calixarene core. It is worth to notice that the most challenging point was to find procedures that allowed purifications without the rescue of chromatography. Indeed, as soon as the TMPA cap is grafted onto the calixarene core, it becomes highly sensitive to silica and alumina and any attempt to purify the calix[6]TMPA derivatives on these phases led to their complete decomposition. The strategy relied on the selective *ipso*-nitration of **1** (Scheme 1).[12] As in the case of the tris(imidazole) derivative, the electrophilic substitution revealed selective of the anisole groups thanks to the deactivation of the pyridyl-connected aromatic units through protonation of the aza core under the experimental conditions. Hence, compound **2**, selectively nitrated in the *para* position of the methoxy groups, was obtained in excellent yield (Figures S1 and S3, Supporting Information). Reduction of the nitro groups was achieved with sodium dithionite ($Na_2S_2O_4$) in a refluxing EtOH/H_2O mixture.[13] Compound **3** was precipitated with an aqueous $NaPF_6$ solution as a monocationic compound (containing H^+ or Na^+) associated to a PF_6^- anion as identified by IR. The last step consisted of the permethylation of the three aniline moieties using excess of iodomethane in CH_3CN in the presence of K_2CO_3. Quite remarkably, the alkylation of either the tertiary amine or the pyridine rings was not observed. Such a surprising selectivity leading to the methylation of the a priori less nucleophilic aniline groups most likely stems from the rigidity of the scaffold. Grafting the TMPA unit onto the calix[6]arene macrocycle reduces the mobility of the pyridyl groups and orients all nitrogen lone pairs toward the inside of the cavity. As a consequence, they become inaccessible for electrophilic substitution with MeI.

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Hence, pure compound $\mathbf{4}^{3+}$ could be isolated by precipitation as a PF_6 salt with, as in the case of **3**, a proton or a sodium cation bound to the aza-cap.[14] $\mathbf{(4^{3+}H^+)(PF_6)_4}$ is not readily water-soluble. Water-solubilization (up to 10 mM) was achieved after anion metathesis using an anion-exchange resin charged with chloride or nitrate. During this quantitative step, $\mathbf{4}^{3+}$ was obtained as a free ligand (i.e., with no cation in the TMPA cap).[14]

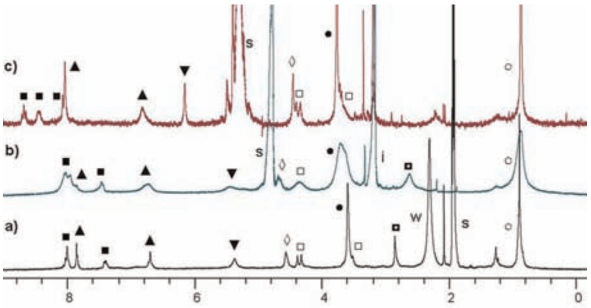

Figure 1. ^1H NMR (250 MHz, 300 K) spectra of (a) $\mathbf{(4^{3+}H^+)(PF_6)_4}$ (CD_3CN); (b) $\mathbf{(4^{3+})(Cl^-)_3}$ (D_2O); (c) $\mathbf{(4^{3+})(Cl^-)_3}$ in presence of an excess of HCl (D_2O): ■, H_{py}; ▲, HAr; ▼, OCH_2; ◊, NCH_2; □, $ArCH_2$; ◘, OCH_3; ●, $N^+(CH_3)^3$; ○, *t*Bu; s, solvent; i, internal reference; w, water.

$\mathbf{4}^{3+}$ was characterized by HR-ESI MS and ^1H NMR spectroscopy in CD_3CN and D_2O (Figure 1). The ^1H NMR spectrum of $\mathbf{(4^{3+}H^+)(PF_6^-)_4}$ in CD_3CN shows sharp resonances and a signature of a molecule having a C_{3v} symmetry. A singlet at 3.60 ppm (N^+Me_3) accounts for the permethylation of the aniline. The NCH_2 resonance at 4.56 ppm is characteristic of a protonated calix[6]TMPA core.[10a] The ^1H NMR spectrum of $\mathbf{(4^{3+})(Cl^-)_3}$ dissolved in D_2O also attests to an average C_{3v} symmetry with broader resonances, however. This may be due to host–guest exchange of water molecules associated to acid–base equilibria within the nitrogen cap. Indeed, due to its basicity,[15] the TMPA unit is most probably partially protonated in pure D_2O. This is supported by the chemical shift of the NCH_2 protons which lies in the same range as the one expected for the protonated ligand (4.70 ppm in CD_3CN).[10a] When an excess of HCl was added into the aqueous solution, the resonances sharpened and the peaks of the pyridyl and OCH_2 protons shifted downfield. This indicates the acid–base equilibria displacement toward a single major species which is polyprotonated. The polyprotonation may lead to a stronger association of water molecules inside the cavity (via H-bond and charge-dipole interactions), thus changing the kinetics of the host–guest exchanges. Addition of KOH to the starting solution induced the precipitation of a solid. The ^1H NMR spectrum of this solid recorded in CD_3CN is consistent with the unprotonated form of the ligand (Figure S12, Supporting Information).

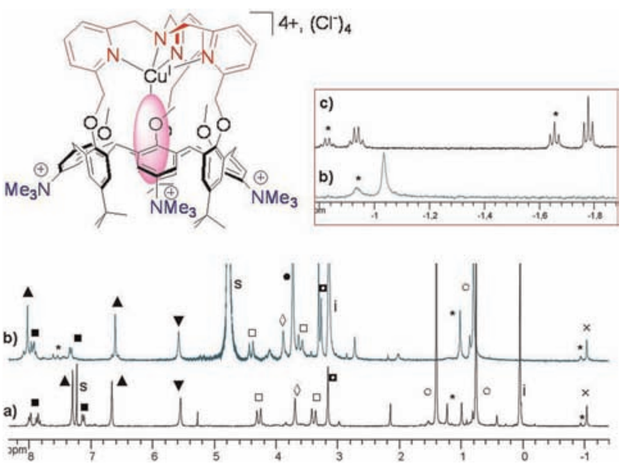

Figure 2. ^1H NMR spectra of (a) $[Cu^I\mathbf{1}(CH_3CN)](PF_6^-)$ (250 MHz, 300 K, $CDCl_3$); (b) $[Cu^I\mathbf{4}^{3+}(CH_3CN)](Cl^-)_4$ (250 MHz, 300 K, D_2O); (c) high-field region of $[Cu^I\mathbf{4}^{3+}(CH_3CH_2CN)](Cl^-)_4$ (500 MHz, 280 K, D_2O): ■, H_{py}; ▲, HAr; ▼, OCH_2; ◊, NCH_2; □, Ar CH_2; ◘, OCH_3; ●, $N^+(CH_3)_3$; ○, *t*Bu; ×, CH_3CN in; *, minor conformation; s, solvent; i, internal reference.

Hence, a water-soluble version of calix[6]TMPA was efficiently synthesized through a three-step procedure allowing to avoid chromatographic purification.

Cu(I) Complex in Water. The Cu(I) complex was synthesized by mixing an equimolar amount of CuCl and $\mathbf{(4^{3+})(Cl^-)_3}$ in a 5:1 MeOH/CH_3CN mixture at room temperature. The resulting complex, $[Cu^I\mathbf{4}^{3+}(CH_3CN)](Cl^-)_4$, was isolated as a yellow solid. This complex is soluble in water (up to 10 mM) and its ^1H NMR spectrum in D_2O is very similar to the one obtained with the parent organo-soluble complex[11] (see Figure 2a,b). Indeed, the spectra indicate that in water, like in chloroform, the cuprous complex based on a calix[6]TMPA ligand (**1** an $\mathbf{4}^{3+}$, respectively) adopts two different conformations in equilibrium. A major one, as attested by the set of the most intense resonances, is C_{3v} symmetrical, whereas the minor one (26% in D_2O vs 13% in $CDCl_3$) is of lower symmetry, which has been attributed to an upside-down inverted anisole unit.[11] For both conformations, a resonance at ca. −1 ppm indicates the encapsulation of one CH_3CN guest inside the calixarene cone. No free CH_3CN could be detected, which attests to the very high affinity of the Cu(I) complex for CH_3CN in D_2O as it was noticed in

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(14) See the Supporting Information for details.

(15) For a simple TMPA ligand, three successive protonation constants have been reported with log K = 6.3, 4.5, and 2.7. See:Mareque-Rivas, J. C.; Prabaharan, R.; Torres Martin de Rosales, R. *Chem Commun.* **2004**, 76–77.

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(17) The first open-shell water stable Cu(I) complex was obtained with a tris(imidazole)–calix[6]arene ligand substituted by three sulfonato groups at the large rim. The ligand however did not allow the characterization of the Cu(II) complex in water, the solubility of which was poor due to charge–charge neutralization (between the three sulfonato substituents and the cupric center):Rondelez, Y.; Bertho, G.; Reinaud, O. *Angew. Chem., Int. Ed.* **2002**, *41*, 1044–1046.

an organic solvent. When 2.5 equiv of propionitrile was added into the D_2O solution of the acetonitrilo complex, disappearance of the peak at −1 ppm and appearance of two new resonances (for the major species) at −0.93 ppm and −1.78 ppm (see Figure 2c, inset) attested to guest exchange and formation of the propionitrilo complex. The "empty-cavity" Cu(I) complex was obtained by reduction of the corresponding Cu(II) complex (vide infra for its synthesis) with sodium ascorbate. $[\mathrm{Cu}^{\mathrm{I}}\mathbf{4}^{3+}](\mathrm{NO_3}^-)_4$ presents a much broader NMR signature, which can be explained by the larger conformational flexibility due to the lack of guest molecule bound to the metal center.

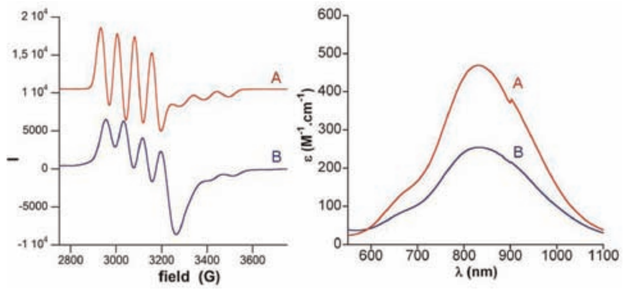

Figure 3. EPR spectra at 100 K (left) and UV−vis spectra at 300 K (right) of $[\mathrm{Cu}^{\mathrm{II}}\mathbf{1}(\mathrm{CH_3CN})](\mathrm{ClO_4}^-)_2$ in CH_2Cl_2 (A) and $[\mathrm{Cu}^{\mathrm{II}}\mathbf{4}^{3+}(\mathrm{CH_3CN})](\mathrm{NO_3}^-)_5$ in H_2O (B).

Addition of CH_3CN regenerates the acetonitrilo complex (Figure S13, Supporting Information). Finally, in the presence or absence of a nitrilo guest, no sign of decomplexation or oxidation of the cuprous species was observed after standing in pure water under air for days. This indicates that the Cu(I) complex is resistant to both disproportionation and O_2 oxidation in spite of the existence of an exchangeable site.

Cu(II) Complex in Water. The synthesis of the copper(II) complex was carried out by mixing $(\mathbf{4}^{3+})(\mathbf{NO_3}^-)_3$ and 1 equiv of $\mathrm{Cu}^{\mathrm{II}}(\mathrm{NO_3})_2(\mathrm{H_2O})_3$ in MeOH to provide $[\mathrm{Cu}^{\mathrm{II}}\mathbf{4}^{3+}(\mathrm{S})](\mathrm{NO_3}^-)_5$ isolated as a green powder (S being a water molecule or a bound anion). As for the Cu(I) complex, the metal center displayed a high affinity for acetonitrile. When dissolved in water, the addition of a stoichiometric amount of MeCN produced EPR and UV−vis spectra similar to the those recorded for the organo-soluble acetonitrilo Cu(II) complex based on ligand **1** in CH_2Cl_2 (Figure 3 and Figures S14 and S15, Supporting Information). The UV−vis spectrum exhibited a broad absorption peak with a maximum at 832 nm and two shoulders, one of higher energy and one of lower energy. The EPR data were characterized by $g_{//} < g_{\perp}$, which is typical of a Cu(II) cation in a trigonal bipyramidal geometry. All these features accounts for a five-coordinated Cu(II) complex with a metal ion bound to the four nitrogen atoms of the TMPA cap and one acetonitrile guest, namely $[\mathrm{Cu}^{\mathrm{II}}\mathbf{4}^{3+}(\mathrm{MeCN})]^{5+}$.[10b] The electrochemical potential of $[\mathrm{Cu}^{\mathrm{II}}\mathbf{4}^{3+}(\mathrm{CH_3CN})](\mathrm{NO_3}^-)_5$ measured in $H_2O/NaNO_3$ with 0.1% CH_3CN (20 mol. equiv. vs Cu) is $E_{1/2} = +0.53$ V vs NHE ($\Delta E_p = 100$ mV). This value can be compared to those recorded for the Cu(II) complexes based ligand **1** and the TMPA ligand deprived of calixarene cavity (Table S1 and Figure S16, Supporting Information). The first observation is the decrease of $E_{1/2}$ when swapping from an organic solvent (CH_2Cl_2 or CH_3CN) to water ($\Delta E_{1/2} = 350$ mV and 290 mV, respectively[14]). It likely results from the better stabilization of a dicationic vs monocationic state as the medium polarity increases.[14] On the other hand, this $E_{1/2} = +0.53$ V value contrasts markedly with that measured in water for the complex deprived of cavity $E_{1/2} = -0.04$ V. This nicely illustrates the insulating effect of the calixarene cavity from the media and highlights the spectacular ability of a hydrophobic embedment to tune the redox potential of a metal ion in water.

In conclusion, the water-soluble calix[6]arene-based ligand $(\mathbf{4}^{3+})$ presented here is a very rare example (if not the first) of an artificial structure capable of stabilizing in pure water a copper ion featuring a coordinative unsaturation in both +I and +II oxidation states.[16,17] Preliminary data suggest that the major structural and functional properties observed in organic solvents are maintained for both complexes: mononuclear embedment, exogenous ligand-binding, host−guest exchange, impressive affinity for small nitriles despite of the highly competitive medium, protection from auto-oxidation. This opens the route for specifically addressing the influence of water in the molecular recognition of hydrophobic guests and in biomimetic redox processes.

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

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The authors declare no competing financial interest.