# Synthesis and Characterization of a Novel Calix[4]arene-Based Two-Coordinate Copper(I) Complex That Is Unusually Resistant to Dioxygen

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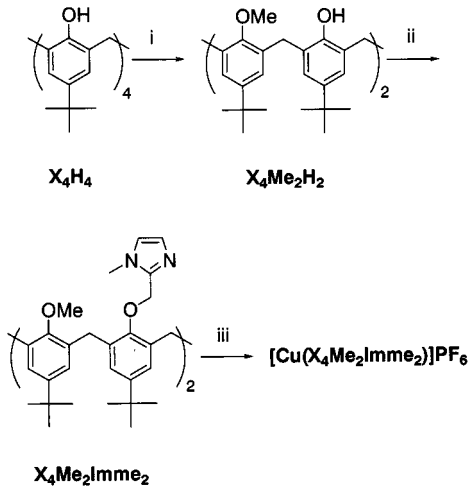
The ligand $X_4Me_2Imme_2$ was synthesized from *p-tert*-butylcalix[4]arene. Upon reaction with one equivalent of $Cu(NCMe)_4PF_6$, it led to the new two-coordinate copper(I) complex $[Cu(X_4Me_2Imme_2)]PF_6$ that was characterized by X-ray diffraction analysis. This complex revealed itself to be totally inert towards dioxygen in the solid state as well as in coordinating or protic solvents.

## Introduction

Copper is a very important metal ion in biological systems, playing a very diverse role in living organisms.[1] It is involved in biochemical oxido-reduction processes, in electron transfers, as well as in the reversible binding of small gaseous molecules such as $O_2$ (Hemocyanin) or the plant hormone ethylene. Because the active form in these systems involves copper(I), the coordination chemistry of low-coordinate $Cu^+$ compounds is essential to the understanding of the metal reactivity. Due to the lack of useful spectroscopic probes for the $Cu^I$ centers in native proteins, it is important to study its coordination chemistry with small artificial ligands.

Our main interest resides in the study of the chemical behavior of a metal ion in a biomimetic environment. For that purpose, we are trying to design supramolecular systems that allow the control of the metal nuclearity and reactivity. We recently showed that a calix[6]arene judiciously functionalized with three pyridine groups was particularly suited for stabilizing a cuprous ion in a tetrahedral mononuclear environment with a labile site included in a hydrophobic cavity. This was therefore a good model for type 2 centers in proteins.[2] We now describe the use of a calix[4]arene as a platform for the stabilization of a two-coordinate $Cu^I$ complex with two biomimetic imidazolyl pendant arms. This complex appeared to be extremely resistant to $O_2$ oxidation and was stable in air for weeks, even in a potentially coordinating or protic solvent.

The new bidentate ligand $X_4Me_2Imme_2$ was prepared in two steps, as depicted in Scheme 1. *t*Bu-calix[4]arene ($X_4H_4$) was first converted into its 1,3-dimethyl ether ($X_4Me_2H_2$)[3] and then treated with 2-chloromethyl-1-methyl-1*H*-imidazole in the presence of NaH to produce $X_4Me_2Imme_2$ in 90% yield. Its $^1H$ NMR spectrum exhibited broad ill-defined resonances at room temperature. This indicated that the calixarene was mobile and not fixed in a cone conformation.




Scheme 1. Synthesis of the calixarene-based ditopic ligand $X_4Me_2Imme_2$ and complexation of copper(I); reagents and conditions: (i) $K_2CO_3$, MeOTs, MeCN, reflux 24 hours, 89%; (ii) NaH, 2-chloromethyl-1-methyl-1*H*-imidazole, THF/DMF, reflux 4 hours, 90%; (iii) $[Cu(MeCN)_4]PF_6$, $CHCl_3$, 90%

The reaction of $X_4Me_2Imme_2$ with one equivalent of $Cu(NCMe)_4PF_6$ in chloroform gave rise to a new cuprous complex, which spontaneously precipitated out of the solution (Scheme 1). Its elemental analysis was in good agreement with a compound of formula $[Cu(X_4Me_2Imme_2)]PF_6$. The corresponding $^1H$ NMR spectrum was well resolved and suggestive of a complex possessing a twofold symmetry. Suitable crystals for X-ray diffraction analysis were grown from a cold solution in $CHCl_3$/MeCN. The crystal structure of $[Cu(X_4Me_2Imme_2)]PF_6$ (Figure 1) showed a mononuclear complex where $Cu^+$ is coordinated to both imidazole

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arms of the calix[4]arene-based ligand, which is in a cone conformation.

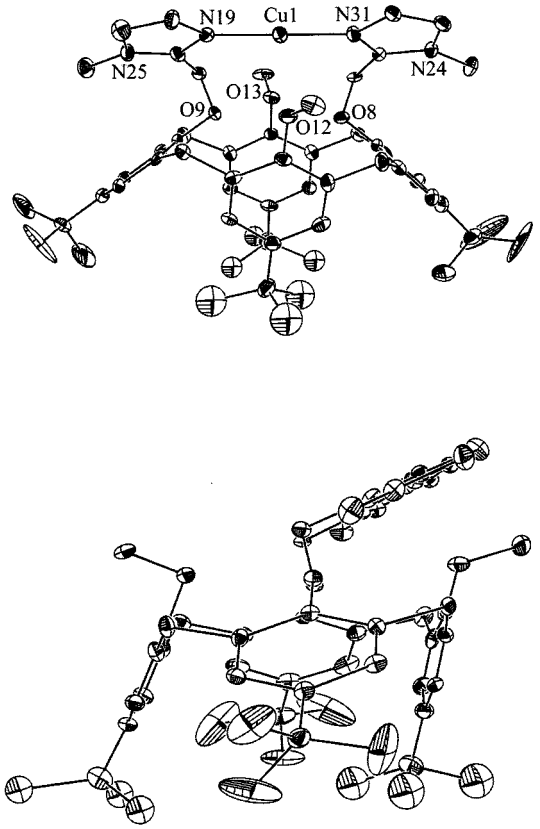


Figure 1. X-ray structure of $[Cu(X_4Me_2Imme_2)]PF_6$ (two different side views are displayed); selected atom distances (Å) and bond angles (°): Cu(1)−N(19) 1.87(1), Cu(1)−N(31) 1.867(9), N(19)−Cu(1)−N(31) 178.5(4); the counter ion and the solvent of crystallization have been omitted for clarity; for the same reason, only one occupancy site for each of the disordered *tert*-butyl groups is displayed

The Cu−N distances (1.87 Å) are similar to those previously reported for two-coordinate imidazole complexes.[4,5] The geometry at the metal center is almost linear (N−Cu−N = 178.5°) and the dihedral angle between the two imidazole rings is 3°, showing that they are almost coplanar. The plane of the imidazoles is bent on one side relative to the O13 oxygen, which is in close contact with the copper ion [Cu(1)···O(13) = 2.73 Å compared to Cu(1)···O(8) = 3.58 Å, Cu(1)···O(9) = 3.75 Å, Cu(1)···O(12) = 4.81 Å]. This may reflect a stabilizing electronic interaction between $Cu^+$ and one basic oxygen of the calixarene. In solution, however, the symmetrical $^1H$ NMR profile indicated that, if it exists at all, this interaction is averaged over both opposite phenoxyl groups and the coordination plane is probably flipping from one side to the other. $[Cu(X_4Me_2Imme_2)]PF_6$ exhibited an unusual stability towards dioxygen. In the solid state, it is indefinitely stable. In polar solvents such as DMSO or acetonitrile, or protic solvents like methanol, no oxidation of copper(I) has ever been observed, even if the solution is allowed to stand in an open flask for weeks.

This new copper(I) complex displays a geometry that is similar to previously reported two-coordinate copper(I) complexes with nitrogen donors.[4,5] Although the resulting linear geometry is known to disfavor $O_2$ and CO interaction,[4,5] our complex appeared to be unusually[4−6] resistant to oxidation with $O_2$ and did not coordinate CO. In contrast, the two-coordinate $Cu^I$ complexes obtained with various unidentate imidazole ligands were reported to undergo rapid autoxidation in air, especially in a protic solvent. Curiously[6], we also found that the presence of two imidazole rings rather than two pyridine rings provided an enhanced stability of the copper(I) complex toward oxidation. Indeed, the copper(I) complex $[Cu(X_4Me_2Pic_2)]PF_6$ derived from the corresponding pyridine-based calix[4]arene ligand[7] was extremely sensitive to $O_2$ and underwent autoxidation in air within seconds.

The following points can rationalize these observations:
i) the exceptional inertness of the $[Cu(X_4Me_2Imme_2)]^+$ complex compared to the complexes derived from unidentate imidazole ligands is attributable to the highly favorable preorganization provided by the calix[4]arene platform rather than to steric hindrance;
ii) the enhanced stability of $[Cu(X_4Me_2Imme_2)]^+$ compared to the analogous pyridine-based complex is due to electronic factors and may be explained by an increased orbital overlap between the imidazole-nitrogen atom and copper(I) that stabilizes the two coordinate form for the imidazole-ligated species compared to the pyridine, as previously discussed by Sorrel.[4]

In conclusion, we have described a novel copper(I) complex that, although coordinatively unsaturated, revealed itself to be resistant to oxidation in a protic aerated environment. This emphasizes the importance of preorganization of the metal binding site as one of the key features that allows the control of the $Cu^I$ reactivity. This may be reminiscent of biological systems, which either utilize copper(I) to bind or activate a small molecule[1] or stabilize it as in copper chaperones,[8] which transport and/or deliver $Cu^I$ to other proteins in the cells.[9]

## Experimental Section

**$X_4Me_2Imme_2$:** Under an argon atmosphere, a solution of $X_4Me_2H_2$ (500 mg, 0.74 mmol) in dry THF (10 mL) was introduced into a flask containing NaH (60% in oil washed twice with pentane; 0.9 g, 22 mmol) and the resulting mixture was stirred for 30 minutes. 2-Chloromethyl-1-methyl-1*H*-imidazole hydrochloride (0.74 g, 4.5 mmol) was added over a period of 5 minutes. After 4 hours at reflux, the solvents were removed under reduced pressure to a third volume and poured into water (110 mL). The crude precipitate was collected by filtration, washed with water (3 × 25 mL) and then chromatographed to give a white product which was dried under vacuum on KOH (580 mg, 90%). − M.p. 280 °C (dec.). − IR (KBr): $\tilde{\nu}$ = 1481, 1457, 1361, 1286, 1119, 1018, 978, 840 ($PF_6$) $cm^{-1}$. − ESI: *m/z* = 865.6 [$M^+$ + 1]. − $C_{56}H_{72}N_4O_4$ (864.6): calcd. C 77.78, H 8.33, N 6.48; found C 77.31, H 8.51, N 6.25.

**$[Cu(X_4Me_2Imme_2)]PF_6$:** To a solution of $X_4Me_2Imme_2$ (200 mg, 0.25 mmol) in $CHCl_3$ (1.4 mL) under an inert atmosphere was added dropwise $[Cu(NCMe)_4]PF_6$ (92 mg, 0.25 mmol). The mixture was stirred under argon. After 3 hours, the crude precipitate was

filtered, washed with heptane and dried under vacuum (KOH) to give a white solid (196 mg, 91%). M.p. 340 °C (dec.). − $C_{56}H_{72}N_4O_4CuPF_6{\cdot}2H_2O$ (1108): calcd. C 60.65, H 6.86, N 5.05; found C 60.90, H 6.62, N 4.95 − IR (KBr): $\tilde{\nu}$ = 1481, 1457, 1361, 1286, 1119, 1018, 978, 840 ($PF_6$) $cm^{-1}$. − $^1H$ NMR ([D$_6$]DMSO, 400 MHz, $T$ = 298 K): δ = 0.72 (s, 18 H, *t*Bu), 1.29 (s, 18 H, *t*Bu), 2.98 (s, 6 H, OMe), 3.03 (s, 4 H, $CH_{2eq}$), 3.59 (s, 10 H, NMe and $CH_{2ax}$), 5.46 (s, 4 H, O−$CH_2$), 6.31 (s, 4 H, ArH), 7.19 (s, 4 H, ArH), 7.39 (s, 2 H, ImH), 7.48 (s, 2 H, ImH). The assignment of the signal corresponding to $CH_{2ax}$ was achieved upon warming the sample to 50 °C: $^1H$ NMR ([D$_6$]DMSO, 400 MHz, $T$ = 323 K): δ = 0.75 (s, 18 H, *t*Bu), 1.29 (s, 18 H, *t*Bu), 3.01 (s, 6 H, OMe), 3.03 (s, 4 H, $CH_{2eq}$), 3.59 (s, 6 H, NMe), 3.66 (s, 4 H, $CH_{2ax}$), 5.45 (s, 4 H, O−$CH_2$), 6.35 (s, 4 H, ArH), 7.18 (s, 4 H, ArH), 7.39 (s, 2 H, ImH), 7.50 (s, 2 H, ImH) − $^{13}C$ NMR ([D$_6$]DMSO, 100 MHz, $T$ = 298 K): δ = 30.2 (Ar-α*C*H2), 30.8 (C*C*H$_3$), 31.5 (C*C*H$_3$), 33.3 (*C*CH$_3$ and N*C*H$_3$), 34.0 (*C*CH$_3$), 62.3 (O*C*H$_3$), 65.5 (Imme-α*C*H$_2$), 123.5 ($C_{Imme}$H), 124.6 ($C_{Ar}$H), 125.8 ($C_{Ar}$H), 127.4 ($C_{Imme}$H), 131.1 ($C_{Ar}$−$CH_2$), 135.6 ($C_{Ar}$−$CH_2$), 143.7 ($C_{Ar}$), 146.2 ($C_{Ar}$), 147.2 ($C_{Imme}$), 153.0 ($C_{Ar}$), 153.3 ($C_{Ar}$).

**X-ray Crystallographic Study**

**[Cu ($X_4Me_2Imme_2$)]$PF_6$:** [($C_{56}H_{72}N_4O_4$)Cu]$PF_6$: $M$ = 1072, monoclinic, colorless crystals (0.3 × 0.2 × 0.2 mm) $a$ = 17.552(1) Å, $b$ = 16.955(1) Å, $c$ = 21.860(1) Å, α = 90°, β = 100.44(1)°, γ = 90°, $V$ = 6434.1(1) Å$^3$, space group $P21/c$, $Z$ = 4, $\rho_{calcd.}$ = 1.54 g·cm$^{-3}$, μ(Mo-$K_\alpha$) = 15.5 $cm^{-1}$, 9420 reflections collected at 298 K (Nonius KappaCCD diffractometer) in the 1−25° θ range, 9074 unique, 715 parameters refined on $F$ using 5545 reflections [maXus][10] to final indices: $R1$ [$F > 3\sigma(F)$] = 0.087, $wR1$ ($w = 1/[\sigma^2(F) + 0.03F^2]$) = 0.099.

The complex and its counter ion co-crystallize with two molecules of chloroform in the asymmetric unit. During the refinement process, a disorder of position was observed for two *t*Bu groups. In each of them, the three terminal carbon atoms were split over two distinct sites with occupancy factors for the major and minor site, respectively, of 0.5−0.5 for one *t*Bu and 0.8−0.2 for the second *t*Bu. No hydrogen atoms were therefore introduced or refined on these disordered substituents.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Data Center as supplementary publication no. CCDC-138488. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[7] The ligand $X_4Me_2Pic_2$ (where Pic stands for Picolyl) was obtained according to the same synthetic scheme as for $X_4Me_2$-$Imme_2$ but replacing 2-chloromethyl-1-methyl-1*H*-imidazole with 2-chloromethyl-pyridine.

[8] In copper chaperones, the metal center is either trigonally or digonally coordinated to cysteines.

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