

Encapsulation of a $(\text{H}_3\text{O}_2)^-$ unit in the aromatic core of a calix[6]arene closed by two Zn(II) ions at the small and large rims†

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Received (in Cambridge, UK) 9th June 2006, Accepted 10th July 2006

First published as an Advance Article on the web 4th August 2006

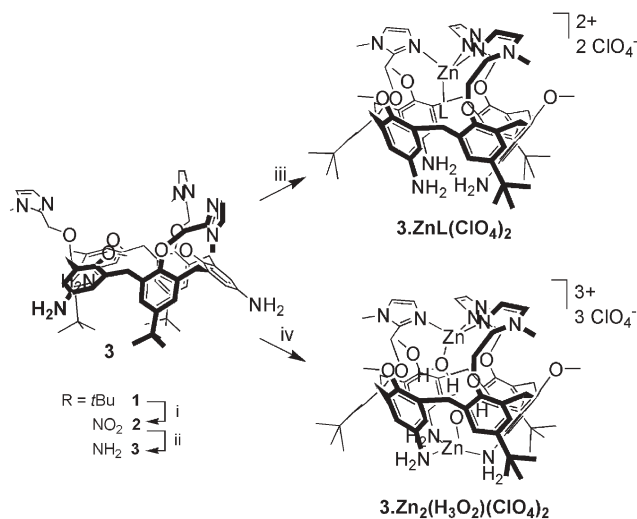
DOI: 10.1039/b608203c

The coordination of a first Zn(II) ion to a calix[6]arene presenting three imidazolyl arms at the small rim and three aniline moieties at the large rim allows the binding of a second Zn(II) ion while hosting a $(\text{H}_3\text{O}_2)^-$ unit in the aromatic cavity.

Calix[6]arenes are superb molecular platforms¹ offering a π -basic hydrophobic cavity that can act as a selective receptor for a variety of molecules, but only under the condition that they are conformationally constrained into a cone conformation. We have largely described a system that presents a biomimetic tris-imidazole core at the small rim²⁻⁴. This system allows efficient binding of a metal ion such as Zn(II) that acts as a glue, fixing at the same time three aromatic units of the calixarene core. As a result, the tetrahedral complex behaves as a remarkable receptor for small exogenous neutral ligands. Recently, we have discovered efficient methods allowing the selective functionalization of the calixarene large rim.^{5,6} This opened the possibility of synthesizing ditopic calixarene ligands. Here, we present the coordination properties of a calix[6]arene presenting a nitrogenous binding site at each rim.

Calixarene ligand **3** was obtained in two steps from the parent *t*Bu-substituted tris-imidazole calix[6]-ligand **1**.³ **1** was first selectively *ipso*-nitrated⁵ on the three anisole cores to provide calixarene **2**⁵ whose nitro substituents were subsequently reduced with hydrazine to give compound **3** (Scheme 1).†

In CDCl_3 or CD_3CN solutions, the ^1H NMR spectrum (250 MHz) of **3** is broad, presumably because of conformational motion that takes place at the NMR time scale analysis. This shows an increased mobility compared to the parent compound **1** due to the replacement of three bulky *t*Bu substituents by small amino-groups, which facilitate the flipping of the aromatic units through the calixarene annulus. In DMSO however, the ^1H NMR spectrum of **3** was well defined with sharp resonances (Fig. 1). The reduced number of peaks, together with the presence of two doublets for the calixarene bridging CH_2 groups, attests to a major cone conformation of C_{3v} symmetry. The high-field shifted methoxy and *t*Bu resonances ($\delta = 1.97$ and 0.87 ppm, respectively) indicate that these groups are directed toward the center of the aromatic core of the calixarene. Hence, in DMSO solution, ligand



Scheme 1 i) HNO_3/AcOH (1 : 1 v/v), CH_2Cl_2 , 80%; ii) hydrazine hydrate, Pd/C, EtOH, reflux, 72 h, 75%; iii) $\text{Zn}(\text{H}_2\text{O})_6(\text{ClO}_4)_2$, MeCN/ H_2O (2 : 1 v/v); iv) $\text{Zn}(\text{H}_2\text{O})_6(\text{ClO}_4)_2$, THF.†

3 adopts a flattened cone conformation with the aromatic units alternatively in *in* and *out* position relative to the cavity, as depicted in Scheme 1.

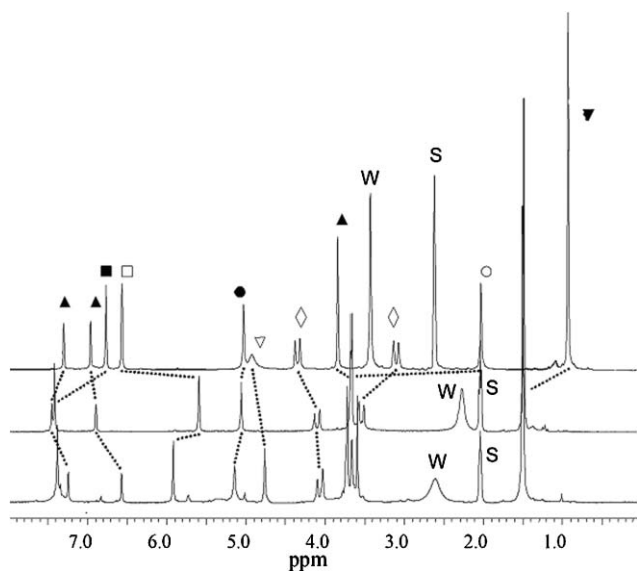


Fig. 1 ^1H NMR spectra (250 MHz, 300 K) of ligand **3** in DMSO *d*₆ (top) and isolated complexes **3·Zn(MeCN)(ClO₄)₂** (middle) and **3·Zn₂(H₃O₂)(ClO₄)₂** dissolved in CD_3CN (bottom). ▼ *t*Bu, ○ OCH₃, ▲ NCH₃ and H_{im}, ◇ CH₂Ar, ▽ NH₂, ● CH₂im, □ and ■ H_{Ar}.

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† Electronic supplementary information (ESI) available: experimental details for the syntheses, NMR analyses and XRD data collection (CCDC 610232). See DOI: 10.1039/b608203c

When one equiv. of Zn perchlorate was added to a MeCN–H₂O solution of ligand **3**, the corresponding mononuclear dicationic complex **3**·ZnL(ClO₄)₂ was formed. After evaporation of MeCN, the complex corresponding to L = H₂O was isolated (72% yield), as for all previously reported M(II) complexes based on parent ligand **1**.^{†,2,4} In contrast to free ligand **3**, this complex is soluble in a wide variety of solvents, including chloroform, acetonitrile, acetone and stable in mixed aqueous media such as MeCN–H₂O 1 : 4 v/v. The ¹H NMR spectra are sharp and characteristic of a C_{3v} symmetrical species (Fig. 1). As compared to free ligand **3**, some resonances appear to be significantly shifted, such as the methoxy and *t*Bu peaks that are shifted from 1.97 to 3.60 ppm and from 0.87 to 1.42 ppm, respectively. The aniline aromatic protons are also shifted from 6.51 to 5.54 ppm. This indicates an *in-out* inversion of the aromatic units of the calix[6]arene core with respect to the free ligand. These experimental results show that complex **3**·ZnL(ClO₄)₂ presents a cone conformation with a tetrahedral Zn²⁺ ion bound to the three imidazole arms and to an included guest ligand L, as described for the parent complexes **1**·ZnL(ClO₄)₂. Indeed, when recorded in CH₃CN, the ¹H NMR spectrum shows an additional resonance at 0.53 ppm attesting to the *in* coordination of one MeCN molecule within the aromatic core of the calixarene receptor. However, the observed up-field shift ($\Delta\delta = -1.44$ ppm) of the *endo*-coordinated MeCN guest is smaller than the one measured for the parent complex **1**·Zn(MeCN)(ClO₄)₂ (–2.76 ppm).³ This difference is ascribed to the replacement of the inductive electron donating *t*Bu groups of **1** by the amino substituents on the aromatic units of **3**.⁷

When the complexation of Zn perchlorate to ligand **3** was carried out in a non-coordinating solvent such as THF, a different species spontaneously crystallized out of the reaction medium and was isolated with a relatively low yield (*ca.* 20% by weight). The same compound was obtained in a 65% yield when four equiv. of Zn perchlorate were engaged in the synthesis. IR and elemental analyses of this new compound correspond to a **3**–Zn–ClO₄ 1 : 2 : 3 stoichiometry.[†] Single crystals were grown by ether diffusion into a CH₂Cl₂–CH₃CN solution of the complex. The XRD molecular structure is displayed Fig. 2.[†] It shows a calix[6]arene core with C_{3v} symmetry in a flattened cone conformation with two coordinated Zn(II) ions, one at each rim. The first one [Zn(1)] stands in the tris-imidazole core in a four-coordinate environment with the binding to an oxygen atom [O(30)] situated at the level of the small rim, off the threefold axis. The second one [Zn(2)] is also in a tetrahedral environment since bound to the three aniline NH₂ donors and to another oxygen atom [O(31)] that sits at a short distance from the first one [*d*[O(30),O(31)] = 2.20 Å]. According to the presence of three perchlorate anions per complex, the nature of these O-donors must be interpreted as a water molecule and a hydroxide ion, which are strongly hydrogen bonded. The Zn···O distances are 2.00 and 1.85 Å for Zn(1) and Zn(2), respectively. This indicates that, whereas Zn(1) is bound to a water molecule as in the parent “classical” mononuclear *funnel* complex in a non-coordinating environment,⁴ Zn(2) is coordinated to a hydroxide anion. As a result, a [H–O–H···OH][–] unit appears to be encapsulated in the aromatic cavity of the calixarene, closed at both rims by the Zn(II) ions 5.806 Å away from each other. An additional hydrogen bond between the water ligand and one oxygen of the calixarene skeleton [*d*[O(30),O(7)] = 2.62 Å] further stabilizes the assembly.

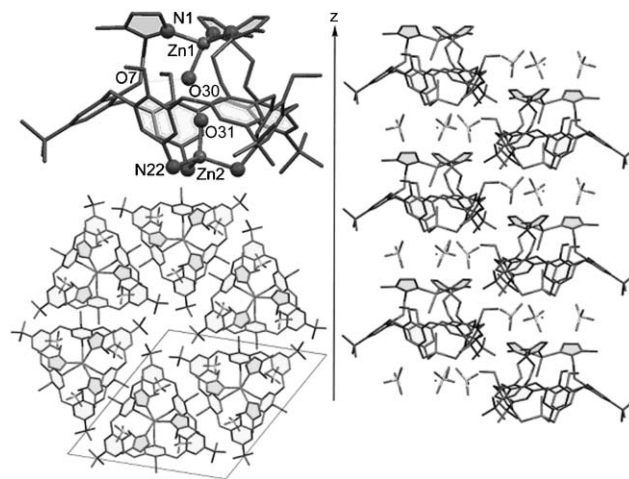


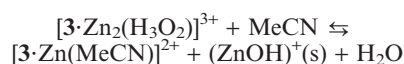
Fig. 2 XRD structure of the dinuclear Zn(II) complex based on ligand **3**.[†] Left: side view of the molecular structure (top), top view of three unit cells (bottom). Right: linear axial arrangement of the calixarene cores in the crystal. Atom O30 has been found disordered over three equivalent sites. Only one is shown.

The aniline aromatic units are *in* directed with their OMe substituents away from the calixarene core. The other three aromatic units, forced by the coordinated imidazole arms, adopt an *out* position with their *t*Bu groups strongly projected towards the external medium.

Interestingly, all calixarene complexes in the crystal undergo the same helical twisting of the imidazole groups around the Zn(II) center. This shows that the crystal is chiral and enantiomerically pure. The complexes are perfectly stacked above each other in an head-to-tail manner, with three perchlorate ions and a water molecule sandwiched in between.⁸ All Zn ions are aligned along the *z* axis. As shown in Fig. 2 (right), three unit cells form an elegant pseudo hexagonal rosette. According to the Cambridge Data Base, this complex represents the first example of a tetrahedral Zn(II) ion coordinated to aniline donors. Actually, the only XRD structure reporting a Zn ion bound to aniline donors shows an octahedral complex with a cryptand-like N₆ ligand exhibiting longer Zn–NH₂Ar bonds (2.20–2.23 Å).⁹ It is thus quite remarkable that ligand **3** allows the coordination of an acidic Zn²⁺ center to rather weak ArNH₂ donors.

In order to test the stability of this *a priori* weak coordination link, a ¹H NMR solution study was undertaken. In contrast to the mononuclear complex, the isolated dinuclear solid is insoluble in chloroform. In CD₃CN however, the ¹H NMR spectrum revealed two distinct species of C_{3v} symmetry. One has been identified as the above-described mononuclear complex **3**·Zn(MeCN)(ClO₄)₂. The other one, although presenting similar characteristics (methoxy and *t*Bu peaks at 3.53 and 1.41 ppm, respectively, denoting the same *in-out* alternate position of the aromatic rings), displays different resonances. In particular, the imidazole proton resonances are up-field shifted (7.25 and 6.56 ppm vs. 7.45 and 6.84 ppm), whereas the CH₂Im groups and H_{ArNH2} protons undergo down-field shifts (5.12 and 5.89 ppm vs. 5.00 and 5.46 ppm, respectively). The addition of Zn perchlorate to the same CD₃CN solution increased the intensity of the resonances corresponding to the second species.[†] An associated NH₂ resonance is observed at 4.74 ppm, which is consistent with a

decrease of their proton lability due to the N-coordination to a second Zn ion. All these results indicate that the new resonances belong to the dinuclear complex, $[3 \cdot \text{Zn}_2(\text{H}_3\text{O}_2)]^{3+}$, that is sufficiently stable to partially survive in a coordinating solvent such as MeCN. Recording the NMR spectrum at lower temperatures showed a reversible increase of the di-/mono-nuclear ratio. A careful analysis of the data in the 345–285 K range, measuring the relative concentration of each species by integration of characteristic resonances, showed equilibrium between both complexes. As it was supposed to be dependent on the water concentration, the experiment was repeated with different amounts of water. Indeed, a Hill plot based on the equilibrium given below, gives a straight line with an excellent correlation.†



The calculated positive enthalpy $[\Delta H^\circ = +29(2) \text{ kJ mol}^{-1}]$ accounts for the binding of the second metal ion in the calixarene core (in competition with the solvent MeCN), whereas the highly positive entropy value $[\Delta S^\circ = +120(7) \text{ J K}^{-1} \text{ mol}^{-1}]$ is in agreement with an increased ordered state when two metal ions are bound to one calixarene ligand **3**. Addition of large quantities of water [a good O-donor for Zn(II)] led to the progressive displacement of the di-/mono-nuclear equilibrium in favour of the latter.† After addition of a third volume of water, the mononuclear complex remained the only detectable species in solution. Lastly, adding a good guest ligand³ to the mixture such as a primary alkylamine (L = heptylamine) or an alcohol (L = EtOH) led to the selective and quantitative formation of the mononuclear species $[3 \cdot \text{Zn}(\text{L})]^{2+}$ hosting the organic ligand L, to the detriment of the dinuclear one hosting the $(\text{H}_3\text{O}_2)^-$ unit.

We have herein described a rare example of a Zn_2 complex bridged by a $(\text{H}_3\text{O}_2)^-$ unit. Its stability is related to its encapsulation in the hydrophobic π -basic calixarene core that disfavors a second deprotonation event that is classically observed with the “simple” tripodal N_3 ligand-based systems.¹⁰ Such an unusual coordination behavior is also attributable to the geometrical constrain set by the calixarene skeleton that presents distant binding sites too far away from each other to allow a μ -hydroxo complex to form. The XRD structure of the dinuclear complex also emphasizes the remarkable preorganization for a second metal ion binding, since the water molecule coordinated to the first Zn site stabilizes, through hydrogen bonding, the hydroxide bound to the second Zn ion. The coordination of the second metal ion is also favored by the alternate positioning of the aromatic units of the calixarene that presents its ArNH_2 groups directed toward the C_{3v} axis, in an ideal geometry for metal ion coordination, in spite of the very weak donor set constituted by three ArNH_2 moieties.

Interestingly, a $[\text{Zn}(\text{H}_3\text{O}_2)\text{Zn}]^{3+}$ core has been proposed to be the active species of hydrolytic multinuclear Zn enzymes.¹¹ Such model complexes are particularly rare and were obtained with

anionic ligands that either are highly bulky¹² or present a deprotonated pyrazole moiety spanning the Zn ions.¹³ The calix-complex actually represents the first example of such a unit stabilized by neutral ligands.¹⁴ This study thus shows the importance of the preorganization and second coordination sphere in the selective stabilization of such a species.

We are currently exploring the possible coordination of other metal ions, replacement of the $(\text{H}_3\text{O}_2)^-$ core by other bridging units, as well as the modification of the large rim donor set.

Notes and references

‡ Crystal data: $\text{C}_{72}\text{H}_{87}\text{Cl}_3\text{N}_9\text{O}_{21}\text{Zn}_2$, $M_w = 1651.60$, hexagonal, space group $P6_3$; dimensions: $a = b = 18.9573(7) \text{ \AA}$, $c = 12.5640(7) \text{ \AA}$, $V = 3910.3(3) \text{ \AA}^3$; $Z = 2$; $\mu = 0.793 \text{ mm}^{-1}$; 61565 reflections measured at 100 K; independent reflections: 3394 [$2561 F_o > 4\sigma(F_o)$]; data were collected up to a $2\theta_{\text{max}}$ value of 44.94° (99.9% coverage). Number of variables: 336; $R_1 = 0.1031$, $wR_2 = 0.2737$, $S = 1.060$; highest residual electron density 0.792 e \AA^{-3} (all data $R_1 = 0.1342$, $wR_2 = 0.3044$). CCDC 610232. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b608203c

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- In chloroform, the addition of a variety of guests L gives rise to the corresponding $3 \cdot \text{ZnL}^{2+}$ complexes. The related study will be the subject of a different paper.
- Such a head-to-tail arrangement is quite unusual as compared to all other mononuclear Zn dicationic *funnel* complexes, which usually undergo a head-to-head stacking and present two enantiomeric complexes in the unit cell (see ref. 2–4). This must be related to the presence of positive charges at both calixarene rims in the present case.
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- Indeed, the O...O distance in the $\text{Zn}(\text{H}_3\text{O}_2)\text{Zn}$ core is much shorter in the present case than in the three other XRD structures (2.40–2.46 Å, see ref. 12,13). This denotes a much stronger hydrogen bonding.