X-ray and Solution Structures of the First Zn Funnel Complex Based on a Calix[6]aza-cryptand

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First insights into the coordinative behavior of a calix[6]tren ligand are presented. Reaction with zinc perchlorate led to a dicationic complex with the metal ion strongly bound to the tren cap. It presents a unique coordination site accessible for a small coordinating molecule that is controlled by the calixarene cavity. Hence, X-ray analysis and solution ^{1}H NMR studies evidenced a five-coordinate complex thanks to the coordination of a guest ligand, MeCN, included deep inside the calixarene cavity. Interestingly, the metal ion is bound in an asymmetrical environment in both the solid state and in solution. It is also particularly reluctant, and resistant, to anion binding.

Introduction

In nature, the control of the reactivity of a metallo site is performed by the structuring of the protein backbone in order to not only preorganize the coordination site for the metal ion, but also provide a cavity and a corridor connecting it to the bulk that controls the binding of exogeneous molecules and the reactivity of the metal ion.[1] Whilst exploring these supramolecular aspects of bioinorganic chemistry, we have developed a calixarene-based system that models mononuclear metallo-enzyme active sites.[2–4] In these systems, the binding of a zinc ion to a calix[6]arene bearing three nitrogenous arms allows the shaping of the molecular receptor. As a result, the first examples of stable tetrahedral dicationic Zn complexes were obtained. These so-called funnel complexes display unrivalled host/guest behavior toward neutral organic molecules due to the control exerted by the calixarene structure on the second coordination sphere of the metal ion and on the access to the metal center.[2] The highly flexible calix-based N_3 system appears, however, to suffer from two weaknesses: i) although highly disfavored, external binding of small molecules is not totally precluded, as evidenced in some particular cases,[4,5] and ii) the addition of a base such as triethylamine to the complex leads to decoordination and precipitation of metal hydroxides, particularly in an aprotic solvent, due to a weak chelate effect (two coordinating nitrogen centers are separated by 15 atoms). We have recently described the synthesis of a novel calix[6]aza-cryptand, namely calix[6]tren,[6] which appears to be a good candidate to remedy the weaknesses of the N_3-calix system (Scheme 1). Indeed, the tren structure offers a strong chelate effect and its tertiary nitrogen atom, which caps the narrow rim of the calixarene, closes the access in the *trans* position of the cavity for an exogenous molecule. This paper describes the first member of the calix-cryptand metal complexes family that fulfills both desired improvements of the supramolecular biomimetic system.

Results and Discussion

Complexation of zinc by calix[6]tren (**1**) was performed in a CH_2Cl_2/MeOH (1:1) mixture by reacting stoichiometric amounts of zinc perchlorate and the N_4 ligand. Under these conditions, the calix-tren Zn complex **2**⊃L (L = MeOH) was isolated in 69% yield (Scheme 1).

X-ray quality crystals of **2**⊃MeCN were grown by slow diffusion of diethyl ether into an acetonitrile solution of the complex. The crystal structure is displayed in Figure 1. As

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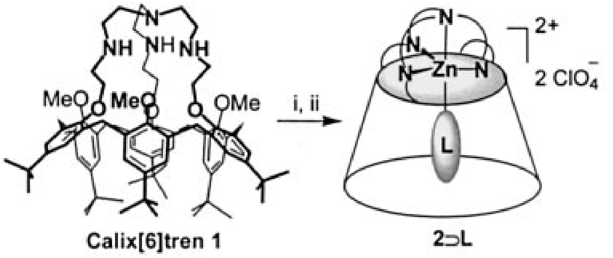

Scheme 1. Zn complexation of calix[6]tren **1**: i) $Zn(ClO_4)_2(H_2O)_6$, CH_2Cl_2/MeOH (L = MeOH); ii) MeCN (L = MeCN)

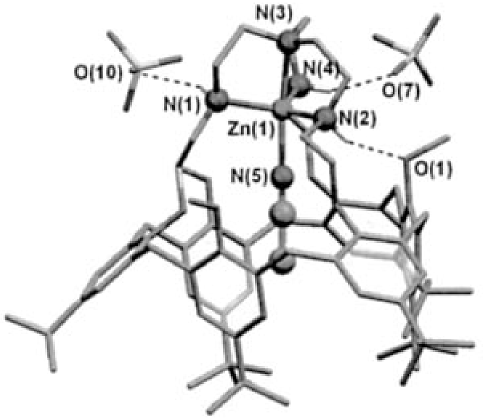

Figure 1. Crystal structures of **2**⊃MeCN; the location of the hydrogen atoms of the amino groups was calculated; other hydrogen atoms and solvents of crystallization have been omitted for clarity; selected bond lengths (Å) and angles (°): Zn(1)−N(4) 2.053(7), Zn(1)−N(2) 2.078(7), Zn(1)−N(1) 2.080(7), Zn(1)−N(5) 2.107(9), Zn(1)−N(3) 2.197(6); N(4)−Zn(1)−N(2) 124.8(3), N(4)−Zn(1)−N(1) 112.7(3), N(2)−Zn(1)−N(1) 118.0(3), N(4)−Zn(1)−N(5) 102.0(3), N(2)−Zn(1)−N(5) 89.4(3), N(1)−Zn(1)−N(5) 100.2(3), N(4)−Zn(1)−N(3) 84.4(3), N(2)−Zn(1)−N(3) 81.0(3), N(1)−Zn(1)−N(3) 83.6(3), N(5)−Zn(1)−N(3) 170.4(3); hydrogen bonding: N(1)···O(10) 3.07, N(4)···O(7) 3.01, N(2)···O(1) 3.07; N(1)···H···O(10) 131, N(4)···H···O(7) 157, N(2)···H···O(1) 156

attested by the presence of two counteranions, the Zn complex is dicationic. The metal ion is encapsulated in the calix[6]cryptand thanks to its coordination to the N_4 core of the tren cap and to a guest ligand (MeCN). The geometry is trigonal bipyramidal with some tetragonal distortion (τ = 0.76).[7] The average Zn−N distance for the trigonal base of the pyramid is 2.070 Å. This is slightly longer than found in the related tetrahedral calix-N_3 complexes,[2] in agreement with a decrease of the Zn Lewis acidity for a five-coordinate species compared to a four-coordinate one. In the axial position, the tertiary N atom capping the system is even more loosely bound to the metal ion [$d(Zn_1-N_3)$ = 2.197 Å] than the MeCN ligand [$d(Zn_1-N_5)$ = 2.107 Å]. The guest is deeply buried in the heart of the calixarene structure, with its methyl group pointing towards an aromatic ring at a perpendicular distance (3.8 Å) typical of CH-π interactions. Interestingly, weak hydrogen bonds are present between the capping secondary amino groups and either a perchlorate anion or a phenoxyl oxygen atom. Finally, the three amino arms wrapping the Zn ion do not form a helix, but adopt an asymmetric conformation with two coordinated arms presenting a relative helical orientation opposite to each other with opposite configurations at the nitrogen atoms.

The dicationic Zn complex **2**⊃MeCN has also been characterized in solution. When **2**⊃MeOH was dissolved in CD_3CN, a dissymmetrical ^1H NMR spectrum was obtained (Figure 2). Thanks to the sharpness of the spectrum, most resonances could be attributed by 2D NMR analyses (see the Exp. Sect. and Supporting Information). Compared to the free ligand, the methoxy protons are shifted downfield, which indicates that they have been expelled from the cavity by a coordinating guest. The dissymmetry of the NMR spectrum is due to the asymmetric conformation adopted by the cap due to the different configurations of the NH stereocenters, as depicted by the X-ray structure of **2**⊃MeCN.[8] When **2**⊃MeOH was dissolved in a non-coordinating solvent such as $CDCl_3$, in the presence of CH_3CN, the NMR spectrum was similar to that recorded in CD_3CN, although with an additional highfield-shifted singlet at δ = −1.11 ppm (220 K), thereby confirming the intra-cavity binding of the acetonitrile molecule. Increasing the temperature to above room temperature led to the coalescence of the calixarene resonances. At 390 K, in $Cl_2CDCDCl_2$, a C_{3v}-symmetric spectrum was obtained (see the Supporting Information). This phenomenon is explainable by the fast pyramidal inversion of the coordinated nitrogen atoms at high temperature, leading to an average C_{3v}-symmetrical conformation.

Finally, the nitrilo complex was not affected by the presence of chloride ions[9] nor by hydroxide.[10] This shows that the Zn ion is much more strongly coordinated by the calix-cryptand than it is by the calix-N_3 ligands. It also emphasizes the reluctance of these funnel complexes to bind anionic ligands due to repulsive interactions with the phenoxyl units of the calixarene structure.

Conclusion

We have described the first member of a novel family of biomimetic complexes based on an N_4-calix-cryptand. In this system, the Zn ion is strongly coordinated by the three tren NH moieties in an asymmetrical environment with the tren tertiary nitrogen atom capping the edifice. As a result, the calix-tren ligand forces the metal ion to complete its coordination sphere through the binding of a guest ligand that is deeply included in the calixarene cavity, leaving no access for an external binding in the position *trans* to the guest. The strong chelate effect provided by the tren cap confers on the complex an increased robustness compared to the parent calix-N_3 system as it does not collapse under strongly basic conditions. Hence, this calix-cryptand exerts a remarkable control on the first and second coordination sphere of the metal ion.

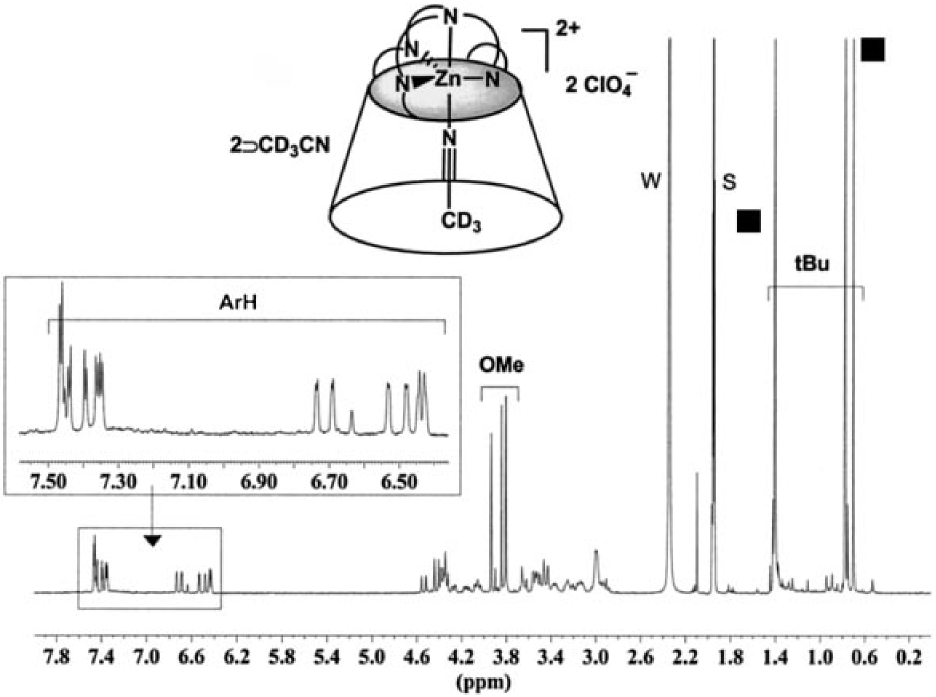

Figure 2. ^{1}H NMR spectrum (400 MHz, room temp., CD_3CN) of complex **2**⊃CD_3CN; residual solvent and water peaks have been labeled "S" and "W" respectively

Experimental Section

General Remarks: CH_2Cl_2 was distilled from CaH_2 under argon. ^{1}H and ^{13}C NMR spectra were recorded either with a Bruker Avance 400 or a Bruker Avance 300 specrtometer. Traces of residual solvent or poly(dimethylsiloxane) (R) were used as internal standard. ^{1}H and ^{13}C resonances corresponding to anisole moieties are labelled with a superscripted 1 (e.g. $t\mathrm{Bu}^1$, ArH^1, $\mathrm{C}^1{}_{\mathrm{Ar}}$) and the others are are labelled with a superscripted 2. They were assigned by HMBC and HMQC experiments. IR spectra were recorded on a Perkin−Elmer IRFT Paragon 1000 apparatus. Elemental analyses were performed at the Service de Microanalyse, (I.C.S.N., Gif sur Yvette, France).

Safety Note: ***Caution!*** *Although we have not encountered any problem, it is noted that perchlorate salts of metal complexes with organic ligands are potentially explosive and should be handled only in small quantities with appropriate precautions.*

Zn-calix[6]tren Complex 2: Methanol (2.5 mL), dichloromethane (3 mL) and triethylamine (0.011 mL, 0.082 mmol) were added to a flask containing $Zn(ClO_4)_2(H_2O)_6$ (30.6 mg, 0.082 mmol) and calix[6]tren (**1**; 102 mg, 0.082 mmol) under an inert atmosphere. The reaction mixture was stirred at room temperature for 30 min. After concentration to a third of the volume by bubbling argon through the solution, a crystalline product was obtained. It was separated from the solvent by centrifugation, washed with cold methanol and dried under vacuum to give **2**⊃MeOH (88 mg, 69%) as a white solid. M.p. 275 °C (decomp.). ^{1}H NMR (400 MHz, CD_3CN, room temp.): δ = 0.70 (s, 9 H, $t\mathrm{Bu}^1$), 0.77 (s, 9 H, $t\mathrm{Bu}^1$), 0.78 (s, 9 H, $t\mathrm{Bu}^1$), 1.40 (s, 27 H, $t\mathrm{Bu}^2$), 2.90−3.66 (m, 24 H, $\mathrm{NHC}H_2\mathrm{CH_2N}$ + $\mathrm{NHCH_2C}H_2\mathrm{N}$ + $\mathrm{OCH_2C}H_2\mathrm{N}$ + Ar-α$\mathrm{CH_{eq}}$), 3.80 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.02−4.55 (m, 12 H, $\mathrm{O}CH_2\mathrm{CH_2NH}$ + Ar-α$\mathrm{CH_{ax}}$), 6.43 (br. s, 1 H, ArH^1), 6.44 (br. s, 1 H, ArH^1), 6.48 (d, J = 2 Hz, 1 H, ArH^1), 6.53 (d, J = 2 Hz, 1 H, ArH^1), 6.69 (d, J = 2 Hz, 1 H, ArH^1), 6.73 (d, J = 2 Hz, 1 H, ArH^1), 7.35 (d, J = 2 Hz, 1 H, ArH^2), 7.36 (d, J = 2 Hz, 1 H, ArH^2), 7.39 (d, J = 2 Hz, 1 H, ArH^2), 7.44 (d, J = 2 Hz, 1 H, ArH^2), 7.46 (d, J = 2 Hz, 1 H, ArH^2) ppm. ^{1}H NMR (300 MHz, 390 K, $Cl_2CDCDCl_2$): δ = 0.69 (s, 27 H, $t\mathrm{Bu}^1$), 1.33 (s, 27 H, $t\mathrm{Bu}^2$), 3.00−3.40 (m, 24 H, $\mathrm{C}H_2\mathrm{N}$ + $\mathrm{C}H_2\mathrm{O}$), 3.47 (d, J = 15 Hz, 6 H, Ar-α$\mathrm{CH_{eq}}$), 3.86 (br. s, 9 H, OCH_3), 4.31 (d, J = 15 Hz, 6 H, Ar-α$\mathrm{CH_{ax}}$), 6.53 (s, 6 H, ArH), 7.25 (s, 6 H, ArH) ppm. ^{13}C NMR (75 MHz, CD_3CN, room temp.): δ = 29.4, 29.5, 30.0, 30.3, 30.7, 31.0 (Ar-α$\mathrm{C}H_2$); 31.5, 31.6 [$\mathrm{C}^1(\mathrm{C}H_3)_3$]; 31.8 [$\mathrm{C}^2(\mathrm{C}H_3)_3$]; 34.5(5), 34.5(7), 34.6(2) [$C^1(\mathrm{CH_3})_3$]; 34.9(4), 34.9(8) [$C^2(\mathrm{CH_3})_3$]; 46.9, 48.5, 48.9 ($\mathrm{NH}C\mathrm{H_2CH_2N}$); 49.6, 51.1, 51.5 ($\mathrm{OCH_2}C\mathrm{H_2NH}$); 51.7, 52.0, 52.3 ($\mathrm{NHCH_2}C\mathrm{H_2N}$); 61.4, 61.5, 62.1 ($OCH_3$); 71.7, 73.4(6), 73.5(0) ($\mathrm{O}C\mathrm{H_2CH_2NH}$); 123.0, 123.3, 123.9(8), 124.0(2), 124.7, 125.2 ($\mathrm{C}^1{}_{\mathrm{Ar}}\mathrm{H}$); 129.1(0), 129.1(4), 129.2, 129.4, 129.9, 130.1 ($\mathrm{C}^2{}_{\mathrm{Ar}}\mathrm{H}$); 132.0, 132.6, 132.9, 133.3, 133.6, 133.8, 133.9, 134.0, 135.3(5), 135.4(1) ($C_{\mathrm{Ar}}\mathrm{CH_2}$); 146.4, 146.5, 146.6 ($\mathrm{C}^1{}_{\mathrm{Ar}}$); 147.6, 147.8, 147.9 ($\mathrm{C}^2{}_{\mathrm{Ar}}$); 152.8 ($\mathrm{C}^2{}_{\mathrm{Ar}}\mathrm{O}$ + $\mathrm{C}^1{}_{\mathrm{Ar}}\mathrm{O}$), 153.2 ($\mathrm{C}^1{}_{\mathrm{Ar}}\mathrm{O}$ + $\mathrm{C}^2{}_{\mathrm{Ar}}\mathrm{O}$), 153.4 ($\mathrm{C}^1{}_{\mathrm{Ar}}\mathrm{O}$), 154.4 ($\mathrm{C}^2{}_{\mathrm{Ar}}\mathrm{O}$) ppm. IR (KBr): $\tilde{\nu}$ = 1637, 1482, 1120, 624 (Cl−O) cm^{-1}. $[\mathrm{Zn}(\mathrm{C_{81}H_{114}N_4O_6})(\mathrm{CH_3OH})](\mathrm{ClO_4})_2\cdot0.5\mathrm{H_2O}$ (1545.1): calcd. C 63.74, H 7.76, N 3.63; found C 63.69, H 7.65, N 3.46.

X-ray Crystallographic Study: X-ray quality crystals of **2**⊃MeCN were grown by slow diffusion of diethyl ether into an acetonitrile solution. M_w = 1545.1, monoclinic, colorless crystal (0.5 × 0.3 × 0.3 mm^3), a = 33.7660(6) Å, b = 14.7500(3) Å, c = 37.6960(9) Å, β = 97.255(7)°, V = 18624.1(7) Å^3, space group $C2/c$, Z = 8, ρ = 1.102 g·cm^{-3}, μ(Mo-K_α) = 3.79 cm^{-1}, 9382 reflections measured at 193 K (Bruker-Nonius KappaCCD diffractometer[11]) in the 0.54−27.83° θ range, 8901 unique, 969 parameters refined on F^2

using 8901 reflections [Shelxl][12] to final indices $R[F^2 > 4\sigma F^2] = 0.1292$, $wR = 0.4056$ [$w = 1/[\sigma^2(F_o^2) + (0.35P)^2 + 40.0P]$ where $P = (F_o^2 + 2F_c^2)/3$]. Some remaining densities outside the calixarene complex were attributed to diffused and highly disordered water molecules. One of the two perchlorate counteranions was found to be disordered and was split on two sites with occupancies equal to 0.5. One *tert*-butyl group was treated in the same way. All hydrogen atoms were introduced in theoretical positions, included in the calculations but not refined. The last residual Fourier positive and negative peaks were equal to 0.930 and −0.933 respectively.
CCDC-244803 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Supporting Information: See also the footnote on the first page of this article. ^1H NMR spectra of **2** (recorded at 293 K, 330 K, 360 K and 390 K in $Cl_2CDCDCl_2$). ^{13}C NMR, COSY and HMQC spectra of complex $\mathbf{2}\supset CD_3CN$ (recorded at room temp. in CD_3CN) and ^1H NMR spectra of $\mathbf{2}\supset CH_3CN$ (recorded at 290 K and 220 K in $CDCl_3$).

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[8] The use of $Zn(OTf)_2$ or $Zn(picrate)_2$ salts led also to a similar dissymmetrical ^1H NMR spectrum in CD_3CN. In the case of the zinc picrate complex, integration of the picrate signal confirmed the presence of two equivalents of anion versus calixtren.

[9] When $ZnCl_2$ was added to a CD_3CN solution of **1**, the ^1H NMR spectrum of the resulting Zn complex was identical to the one obtained from Zn perchlorate. The same procedure with the previously reported calix-N_3 system[2] led to the formation of dimeric species (unpublished data). With Cu, the presence of chloride gave rise to a tetranuclear complex.[5]

[10] The addition of four equivalents of tetrabutylammonium hydroxide (0.1 M solution in toluene/methanol) or a large excess of TEA (up to 126 equiv.) did not affect the NMR spectrum of the complex, even in $CDCl_3$. With the classical calix-N_3 based complexes,[2] addition of hydroxides or TEA in $CDCl_3$ led to instantaneous precipitation of $Zn(OH)_2$.

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