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Hydrogen bonding and CH/π interactions for the stabilization of biomimetic zinc complexes: first examples of X-ray characterized alcohol and amide adducts to a tetrahedral dicationic Zn center

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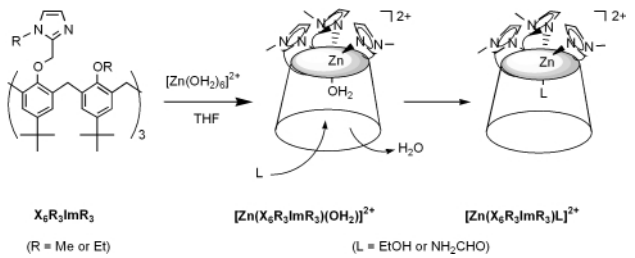
X-Ray analysis of two biomimetic $(N_3ZnL)^{2+}$ complexes with L = ethanol and formamide revealed that hydrogen bonding and CH/π interactions between the guest ligand L and the calix[6]arene host structure play a key role in their stabilization.

Recognition of the importance of zinc enzymes in biological processes is ever increasing. The active site of mononuclear enzymes often displays a pseudo-tetrahedral Zn^{2+} ion coordinated by three amino-acid residues and a labile water molecule. Among them, the recurrent tris(histidine) coordination set (as in Adamalysin II, Atrolysin C, Carbonic Anhydrase)[1] has motivated the design of synthetic analogues based on N_3 ligands. However, tetrahedral dicationic zinc complexes have proved difficult to stabilize. We have recently described a supramolecular system based on a *tert*-butylcalix[6]arene functionalized in alternating positions by three imidazole groups.[2–4] The neutral ligand $X_6Me_3ImMe_3$, which presents three *N*-methyl imidazole donors (ImMe) associated to a cavity that mimics the enzyme pocket, was shown to stabilize four-coordinated zinc species N_3ZnL^{2+} with various neutral molecules L, including amines, alcohols, amides, nitriles and even aldehydes. An amino and a nitrilo complex were characterized crystallographically.[2] We describe here two novel adducts $[Zn(X_6Me_3ImMe_3)L]^{2+}$, one with ethanol (L = EtOH) and the other with formamide (L = NH_2CHO). Their X-ray structures revealed that hydrogen bonding and CH/π interactions between the calix[6]arene host and the guests L play an important role in stabilizing of the complexes. To our knowledge, they provide the first examples of stable four-coordinated Zn dicationic complexes presenting a terminal aliphatic alcohol[5] or amide[6] ligand. Both compounds are strongly relevant to the enzyme/substrate complexes in mononuclear zinc biological systems.

As previously demonstrated by ^{1}H NMR spectroscopy, the water ligand in complex $[Zn(X_6Me_3ImMe_3)(H_2O)](ClO_4)_2$ is easily displaced by alcohols and amides (Scheme 1). We succeeded in growing X-ray quality crystals† of the ethanol adduct $[Zn(X_6Me_3ImMe_3)(EtOH)]^{2+}$ out of an acetone solution of the aqua complex to which 10 molar equivalents of EtOH were added. The molecular structure, displayed in Fig. 1, shows a tetrahedral complex where Zn^{2+} is wrapped by the three imidazole arms of the calixarene-based ligand. The average Zn–



Scheme 1 Synthetic scheme for the calix[6]arene-based biomimetic Zn complexes.

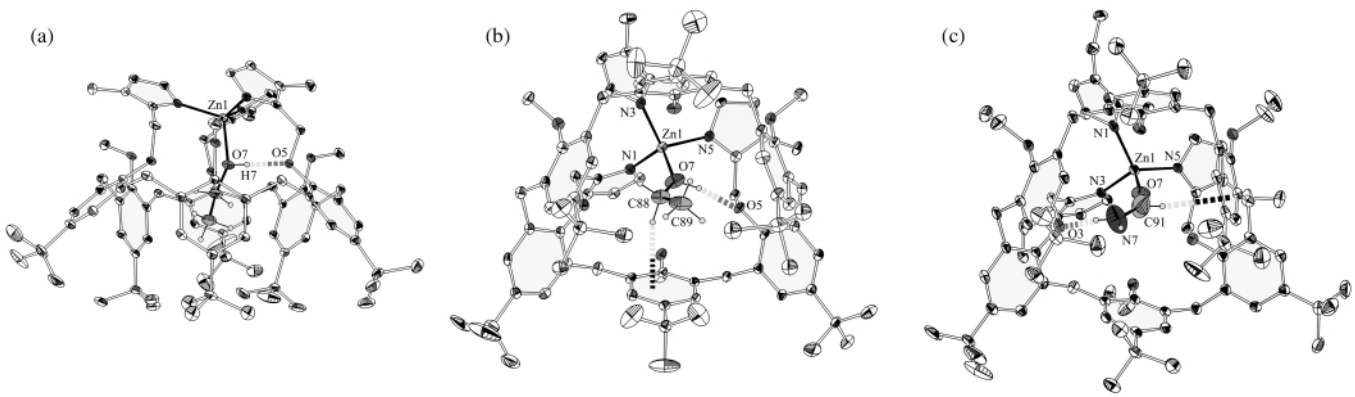


Fig. 1 Crystal structures† of Zn complexes: (a) and (b): $[Zn(X_6Me_3ImMe_3)(EtOH)]^{2+}$, side and top views, respectively. (c): $[Zn(X_6Et_3ImEt_3)(NH_2CHO)]^{2+}$, top view. The hydrogen atoms of the ethanol and formamide ligands could not be located experimentally but their location was calculated and is represented by a plain sphere of arbitrary radius. Other hydrogen atoms and solvents of crystallization are omitted for clarity as well as the perchlorate counter anions. Selected bond lengths (Å) and angles (°): $[Zn(X_6Me_3ImMe_3)(EtOH)](ClO_4)_2$, Zn(1)–N(1) 1.978(5), Zn(1)–N(3) 1.977(5), Zn(1)–N(5) 1.989(5), Zn(1)–O(7) 1.984(5), O(7)–C(88) 1.341(9), N(1)–Zn(1)–O(7) 110.4(2), N(3)–Zn(1)–O(7) 112.0(2), N(5)–Zn(1)–O(7) 99.2(2), N(1)–Zn(1)–N(3) 109.1(2), N(3)–Zn(1)–N(5) 108.0(2), N(1)–Zn(1)–N(5) 117.9(2); $[Zn(X_6Et_3ImEt_3)(NH_2CHO)](ClO_4)_2$, Zn(1)–N(1) 1.972(7), Zn(1)–N(3) 2.000(6), Zn(1)–N(5) 1.981(6), Zn(1)–O(7) 1.897(9), O(7)–C(91) 1.202(11), C(91)–N(7) 1.238(13), N(1)–Zn(1)–O(7) 105.2(3), N(3)–Zn(1)–O(7) 110.7(3), N(5)–Zn(1)–O(7) 107.3(3), N(1)–Zn(1)–N(3) 105.8(2), N(3)–Zn(1)–N(5) 111.1(2), N(1)–Zn(1)–N(5) 116.6(2), Zn(1)–O(7)–C(91) 169.6(10), O(1)–C(91)–N(7) 131.6(8).

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N_{Im} bond length (1.981 Å) is comparable to those of the related propionitrile adduct (1.996 Å) but shorter than in the heptylamine complex (2.007 Å).[2] A bound EtOH molecule is buried deeply inside the calixarene conic cavity. The Zn–O distance [1.984(5) Å] is similar to that of the only other reported four-coordinate Zn–alcohol complex [1.993(3) Å].[5] It is however significantly shorter than those reported for the Zn–alcohol adducts in Liver Alcohol Dehydrogenase (2.0–2.1 Å). This may be attributed to a different overall charge in the coordinated metal center, which is negative in the enzyme.[7] The ethanol OH group points selectively toward one of the OCH_2ImMe units. The corresponding shorter O···O distance (2.86 *vs.* 3.56 and 3.40 Å for the others) indicates the presence of a strong hydrogen bond. Also noteworthy is the position of the ethanol carbon skeleton in the π-basic cavity. The methyl group stands just in front of an aromatic anisole ring with a perpendicular C···Ar distance of 3.67 Å. The methylene group points toward another anisole moiety at a perpendicular C···Ar distance of 3.82 Å. These values are typical of CH/π interactions.[8]

The X-ray structure† of an amide adduct was obtained with a slightly modified ligand, $X_6Et_3ImEt_3$.‡ Single crystals of $[Zn(X_6Et_3ImEt_3)(NH_2CHO)]^{2+}$ were grown by Et_2O diffusion into a benzonitrile solution of the aqua precursor to which 20 molar equivalents of formamide were added. As in the other related structures, the tetrahedral Zn^{2+} ion is coordinated to all three imidazoles with a comparable averaged $Zn–N_{Im}$ bond length (1.984 Å). The amide ligand sits inside the calixarene cavity (Fig. 1) with a short Zn–O distance [1.897(9) Å],[6] which again reflects a highly acidic zinc center. Two additional anchorage points fix the guest molecule in the center of the cavity. On one side, a hydrogen bond hangs the NH_2 group next to one oxygen from the calixarene skeleton [d(N···O) = 3.08 Å and correspondingly, d(NH···O) = 2.29 Å]. In the opposite direction, a CH/π interaction draws the guest CH group in front of one of the aromatic rings of the host with a perpendicular C···Ar distance of 3.60 Å.

The ability of calixarene to undergo a host–guest relationship with organic molecules has already been described in terms of CH/π interaction.[8,9] It has also been recognized that these interactions can help in stabilizing an enzyme–substrate complex.[8,10] In the specific case of Liver Alcohol Dehydrogenase,[7] Phe-93 interacts with sulfoxide-based inhibitors that coordinate the zinc dication.[11,12] The reported distances (3.7–3.8 Å) are very similar to that (3.67 Å) described above for the methyl group of the ethanol ligand. More important however, are the interactions of the calixarene aromatic structure with the CH groups that are directly connected to the O-atom coordinating the metal center (OCH_2– and O=C*H*– for L = EtOH and NH_2CHO, respectively). Indeed, these hydrogen atoms have an exacerbated acidic character that should increase the stabilizing effect of the interactions with π systems. Again, an interesting comparison can be made with the X-ray structure of LADH reporting a tetrahedral Zn center that binds EtOH in close contact with Phe-93.[7] The distance from the ethanol $–CH_2–$ hydrogen atom closest to the center of the aromatic ring is 3.15 Å in the enzyme. For the calixarene-based Zn model complexes, we found 2.92 Å for $–CH_2OH$ (L = EtOH) and 2.70 Å for –C*H*=O (L = NH_2CHO). The distance from the Zn ion to the center of the same phenyl rings is, in each case, 5.45, 5.41, 5.42 Å, respectively. Hence, this can be viewed as a metal ligand aromatic cation/π interaction, as recently suggested in a study concerned precisely with metalloproteins.[10] Finally, hydrogen bond networks have often been observed in enzyme active sites and in particular for the zinc-bound alcohol and Ser-48 in LADH.[13]

In conclusion, we have structurally characterized two novel dicationic tetrahedral Zn complexes that display unusual and remarkable stability. Both the ethanol and the formamide adducts are interesting structural models for the species involved in the catalytic cycle of Zn peptidases or LADH as these enzymes present similar stabilizing interactions. It is worth noting that these new data suggest that a sulfur-rich coordination core as in LADH is not a specific requirement for the stabilization of tetrahedral zinc–alcohol complexes, but might rather be necessary for substrate activation toward hydride transfer. We are currently studying the reactivity of these so-called *Zn funnel complexes*.

Notes and references

† The crystals were measured on a Nonius KappaCCD diffractometer. The structures were solved by direct methods and refined using the program SHELXL97. As usual with this series of compounds, the crystals were very sensitive to desolvation. The hydrogen atoms were added at idealized positions. In the calculations, they were treated as riding atoms and the U_{iso} were free to refine, except for the two hydrogens bonded to the nitrogen of the amide ligand. For these latter, the U_{iso} were fixed at 1.5 × U_{eq} of the nitrogen atom before the last cycles of refinement. *Crystal data* for $[Zn(X_6Me_3ImMe_3)(EtOH)](ClO_4)_2{\cdot}Me_2CO$: $C_{89}H_{120}N_6O_{16}Cl_2Zn$, M_w = 1666.24, triclinic, space group $P1$, a = 13.639(1), b = 16.006(1) c = 22.799(1) Å, α = 88.68(1), β = 78.12(1), γ = 68.24(1)°, V = 4515.8(5) Å^3, Z = 2, D_c = 1.225 g cm^{-3}, μ(Mo-Kα) = 0.396 cm^{-1}, 13013 reflections measured at 173 K, 1039 parameters refined on F^2 using 12869 unique reflections to final indices $R[F^2 > 4\sigma F^2]$ = 0.112, wR = 0.307 [w = $1/[\sigma^2(F_o^2) + (0.2P)^2 + P]$ where P = $(F_o^2 + 2F_c^2)/3$]. One Bu^t and one counter ion oxygen were split on two distinct sites with multiplicities of 0.7 and 0.3 because of static disorders. The final residual Fourier positive and negative peaks were equal to 0.70 and −0.78, respectively.

For $[Zn(X_6Me_3ImMe_3)(NH_2CHO)](ClO_4)_2{\cdot}2PhCN$: $C_{105}H_{133}N_9O_{15}Cl_2Zn$, M_w = 1897.47, monoclinic, space group $P2_1/c$, a = 23.752(1), b = 16.1345(8) c = 27.385(1) Å, β = 96.394(3)°, V = 10429.4(8) Å^3, Z = 4, D_c = 1.208 g cm^{-3}, μ(Mo-Kα) = 3.52 cm^{-1}, 13101 reflections measured at 193 K, 1316 parameters refined on F^2 using 12808 unique reflections to final indices $R[F^2 > 4\sigma F^2]$ = 0.119, wR = 0.278 [w = $1/[\sigma^2(F_o^2) + (0.1116P)^2 + 45.5085P]$ where P = $(F_o^2 + 2F_c^2)/3$]. The final residual Fourier positive and negative peaks were equal to 0.82 and −0.58, respectively.

CCDC 145474 and 161215. See http://www.rsc.org/suppdata/cc/b1/b102322p/ for crystallographic data in .cif or other electronic format.

‡ In ligand $X_6Et_3ImEt_3$, the *O*- and *N*-methyl substituents of $X_6Me_3ImMe_3$ are replaced by ethyl groups. Its synthesis was described in ref 3. The corresponding aqua complex $[Zn(X_6Et_3ImEt_3)(H_2O)](ClO_4)_2$ was obtained following the synthetic procedure described in ref 2.

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