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Bio-inspired Calix[6]Arene–Zinc Funnel Complexes

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The Future of Supramolecular Chemistry

Supramolecular chemistry concerns the reversible assembly of discrete entities through the establishment of multiple weak interactions between the different components. As these phenomena are fundamental in the biological world, nature has been a major source of inspiration for chemists involved in the supramolecular field. Two main routes have now been opened. One concerns the construction of new edifices through auto-assembly. These can be nanosized and are aimed at becoming the base for innovating technologies. The other is the control of recognition processes. Early work with Pedersen crown ethers mimicking valinomycin has allowed the selective recognition of a simple cation. This has been developed thereafter for either charged or neutral molecules, often of biological interest such as phosphates, ammoniums ions, and so on. The next step, as in natural systems, is to associate a catalytic activity to these recognition processes. This belongs to the field of biomimetic chemistry, in which Breslow has been a pioneer with his cyclodextrin-based models of hydrolytic enzymes. Yet another sophistication in this field is the introduction of a metal ion as a central actor in the supramolecular system. Indeed, catalysis by transition metal ions is often encountered in natural systems. Bioinorganic chemistry comprises two aspects: the study of biological systems and their modelling by coordination compounds. In contrast to bioorganic chemistry, however, little has been done in the supramolecular field. Biomimetic inorganic chemistry is mainly focused on mimicking the first sphere coordination environment of the metal ion. Little information is available concerning the influence, or even the control, that the microenvironment provided by a protein can have on the reactivity of the metal. Exploration of this aspect involves two major steps. The first is the control of metal ion binding, including recognition events, through the establishment of weak but decisive interactions between the metal–ligand adduct and its environment. The second is the implementation of a catalytic process that can be as efficient and selective as the biological model. Whereas the first aspect is beginning to emerge, the second, which is by far the most challenging, still belongs to the future. This is a tremendously exciting aspect of Supramolecular Chemistry.

Olivia Reinaud was born in 1960 in France. She studied Physics and Chemistry first at Orsay University (Paris XI), then at Pierre et Marie Curie University (Paris VI) and finally at the Ecole Supérieure de Physique et Chimie Industrielles de la ville de Paris (ESPCI). Her PhD thesis concerned the development of new synthetic routes to quinonoid compounds of biological interest, using bio-inspired copper catalysed oxidation methodologies in the group of Drs M. Maumy and P. Capdevielle. She then spent a year as a postdoc fellow in the lab of Dr D. Mansuy at René Descartes University (Paris V) and studied the biochemical aspects of oxidative processes related to the metabolism of linoleic acid by leucocytes. Rejoining her former lab at the ESPCI as a CNRS researcher, she then developed novel biomimetic copper-catalysed processes. In order to complete her experience, she took a 2-year sabbatical and worked at Delaware University (USA) with Professor K. Theopold on the stepwise activation of dioxygen by cobalt trispyrazolyl borate complexes. Upon her return to France, she started a new project associating organic, inorganic and supramolecular chemistry with some "bio-inspiration". After 4 years at the Ecole Nationale Supérieure de Chimie de Paris (ENSCP), she ended up back in her postdoc lab, at René Descartes University. She switched her CNRS position for a Professor position in 2001. Her current research interest now lies in the field entitled "Supramolecular Bio-Inorganic Chemistry", mainly dealing with biomimetic metal complexes based on calixarene derivatives.

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A bio-inspired supramolecular system is presented. A calix[6]arene possessing three imidazolyl arms on alternate phenolic positions binds a zinc ion. The resulting complex contains a hydrophobic pocket, which has a flattened conic shape. The system behaves as a selective molecular funnel for neutral guests that bind the metal centre. The exceptional stability of these tetrahedral dicationic complexes is exemplified by the acetaldehyde ternary adduct that was analysed by X-ray crystallography. The ligand is deeply buried in the heart of the calixarene cavity, pointing its methyl group selectively towards the centre of one of the aromatic walls, thereby establishing a stabilizing CH/π interaction. Protic guests undergo hydrogen bonding with the phenolic oxygens of the calixarene structure. The selectivity of the binding in the cavity is based on both the affinity of the donor atom of the guest ligand for the zinc ion and the relative host–guest geometries. The helical shape of the tris-imidazolyl groups binding the metal centre is the base of the chirality of the system. The twisted calix[6]arene structure of the zinc *funnel complexes* is shown to provide a new example of a cavity suitable for host–guest chiral induction.

Keywords: Zinc; Calixarene; Biomimetic; Host–guest; Coordination; N_3-ligand

INTRODUCTION

In the biological world, proteins act as highly efficient and selective chiral receptors. Recognition processes are based on non-covalent interactions such as hydrogen bonding, electrostatic and the weaker but multiple CH/π and cation/π interactions. Many proteins also contain metal ions, which may have a structural role. They can also be directly involved in recognition processes or even act as a catalyst leading to the selective transformation of an organic substrate. Recognition through host–guest assemblies is one of the bases of supramolecular chemistry [1–6]. Many macrocyclic receptors have been studied in recent years, either natural such as cyclodextrins [7,8] or artificial with the cryptophanes [9], cyclophanes and carcerands [1–6]. Some of them are chiral and are able to display an enantioselective response to a chiral guest.[†] Indeed, chiral recognition represents a growing but still challenging field.

Comparatively little has been reported so far on the use of the calixarene cavity, although these cyclic phenolic oligomers can be easily functionalized [14–17]. This stems from the fact that, on one hand, the conic cavity provided by calix[4]arenes is too small to play the role of a good host for organic molecules. On the other hand, the increased flexibility of higher oligomers such as calix[6]arenes constitutes an obstacle for obtaining a receptor with a cavity. Indeed, these molecules are difficult to constrain in a cone conformation due to the facile ring inversion of their phenolic units. We have recently shown [18] that this could be achieved through the use of coordination chemistry with adequately functionalized structures. This strategy led us to describe a novel family of calix[6]arene-based zinc complexes that act as remarkable receptors for neutral molecules [19,20]. In this paper, we present a synthetic overview of this supramolecular biomimetic system, with a special focus on the role that the metal ion and the cavity play for the exceptional stability and selectivity displayed by the metallo-host compounds. New results relative to the chirality of the host–guest relationship demonstrate that the guest experiences the intrinsic chirality of the host. Conversely, an optically active guest can transmit its chirality to the calixarene structure.

RESULTS AND DISCUSSION

The ligand $X_6Me_3Imme_3$ was constructed from *p-tert*-butylcalix[6]arene by selective alternate alkylation of the phenolic units [19]. The first step involves the methylation of three phenolic units in alternate position. The second step is the alkylation of the remaining phenol moieties by three 2-methylene-*N*-methylimidazole groups, thereby providing the tripodal N_3 ligand on grams scale. The resulting calixarene is *per*-alkylated and contains three imidazolyl arms. ^{1}H NMR studies have shown that, in solution, it adopts a major cone conformation with C_{3v} symmetry [19]. The methoxy groups point towards the inside of the cavity with all three imidazolyl arms being rejected outside. For the free ligand, the phenolic units undergo free rotation around the methylene groups of the calixarene skeleton, leading to a facile cone–cone interconversion.

Shaping the Cavity

The calixarene $X_6Me_3Imme_3$ behaves as an N_3 ligand capable of binding a unique metal ion in close proximity to the small rim (Scheme 1). Upon reaction with $[Zn(H_2O)_6](ClO_4)_2$, it forms a dicationic 4-coordinated zinc–aqua species, which has been recently structurally characterized by X-ray crystallography [21]. The molecular structure shows that the Zn^{2+} ion is bound to the three nitrogen arms, thereby constraining the calixarene in a cone conformation and offering a concave hydrophobic pocket (Fig. 1). The phenolic units adopt an alternate

[†]Studies related to chiral induction from guest to host in supramolecular assemblies are still rare. See [10–13]

in and *out* position relative to the centre of the cavity, which is the opposite of that observed for the free ligand. The anisol groups form a gate at the entrance of the cavity, their *t*Bu substituents being in the *in* position. This appeared to be a constant for all zinc complexes of this family (*vide infra*). It is interesting to note that the relative position adopted for the Zn^{2+} systems is opposite to that adopted by the Cu^{+} complexes obtained with the tris-pyridine-based calixarene ligand [18]. This is probably related to a stronger electrostatic interaction between the dicationic zinc ion and the oxygen atoms of the calixarene structure in comparison with the monocationic cuprous ion. This is shown in the comparative X-ray structure of the metal complexes obtained with the same guest molecule (L = propionitrile). Indeed, the metal–oxygen distances are 0.3 Å shorter in the "zinc" conformation [19], compared with the "cuprous" conformation [18]. The average distances between the metal ion and the *t*Bu lying in *in* position are $d(\mathrm{Zn},\ \mathrm{C}_{t\,\mathrm{Bu}}) = 8.07$ Å and $d(\mathrm{Cu},\ \mathrm{C}_{t\,\mathrm{Bu}}) = 8.57$ Å. As a result, the Zn–calixarene is flatter and the cavity shortened. This is an interesting case of induced fit leading to the control of the cavity shape by a metal ion (see Fig. 1).

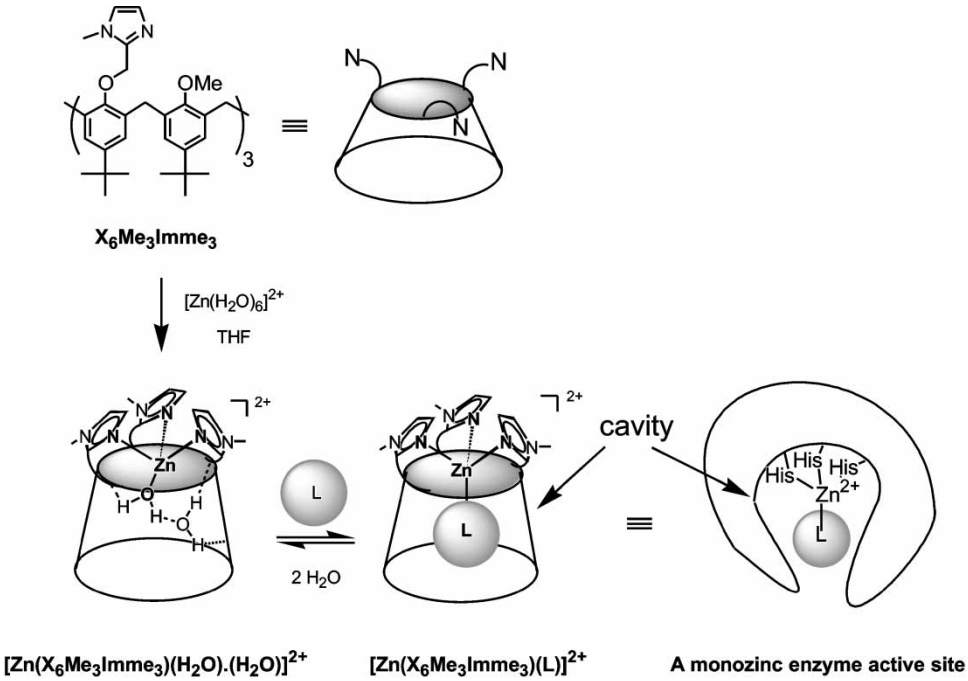
Coordination of a Guest

In the structure of the zinc–aqua complex, the fourth coordination site of the Zn ion is occupied by a water molecule. This water ligand is strongly hydrogen-bonded to a second water molecule that is suspended in the heart of the hydrophobic cavity of the calixarene. The exceptional stability of this quaternary edifice is due to a sophisticated hydrogen bond network that connects the metal ion to two oxygens of the phenolic units and to an aromatic wall through an OH/π interaction [21].

This calix[6]arene-based zinc complex acts as a highly sensitive receptor for neutral molecules. Indeed, a wide variety of organic molecules L such as amines, alcohols, amides and nitriles can substitute both the water ligand and the water guest to yield novel four-coordinated stable Zn complexes $[Zn(X_6Me_3Imme_3)(L)]^{2+}$ (Scheme 1). Solid-state and solution studies indicated that the organic guest is deeply buried in the centre of the cavity provided by the calixarene skeleton. The relative stability of the ternary adducts follows the affinity of Zn for the coordinating atom. As a general tendency, amines are better coordinated than alcohols and amides, which are better bound than nitriles and carboxylic acids.

In all X-ray structures depicting one of these complexes, hydrogen bonds between the protic guest ligand and the phenoxyl moieties were observed [19,22]. Alcohols and primary amines are hydrogen-bonded to one or two, respectively, phenoxyl oxygens linked to a nitrogenous arm. Formamide, bound to the zinc ion through its carbonyl group, is orientated to also connect its amino group to one of the phenoxyl units bearing an imidazole arm through the establishment of a stabilizing hydrogen bond.

CH/π interactions between the guest and the aromatic walls of the calixarene also play a major role



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

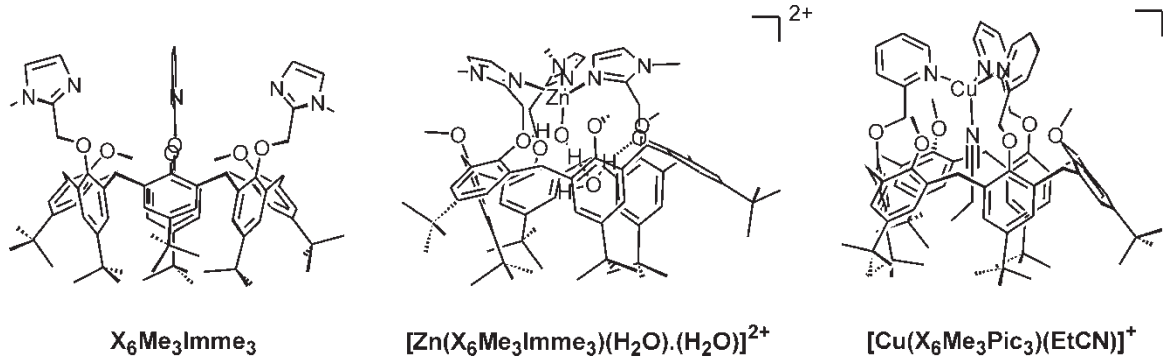


FIGURE 1 Schematic drawing of the structure of a ligand, a Zn(II) complex and a Cu(I) complex according to various X-ray data [18–20,22].

in the stabilization of these dicationic complexes [22]. This has been observed in all the X-ray structures as well: methyl and methylene groups of the guest invariably point selectively towards the centre of one of the aromatic units of the calixarene. This gives rise to unusual *syn* conformations adopted by an included alkyl chain to optimize both the filling of the cavity and the CH/π interactions [19]. Acetaldehyde, which does not possess any protic moiety, leads to the formation of a stable adduct in spite of the fact that it presents a very weak donor group. The corresponding complex could be fully characterized in solution (by NMR and IR) as well as in the solid state by X-ray crystallography (see Experimental). The equilibrium constant K_{MeCHO/H_2O}, defined in Table I, lies in between those previously reported for propionitrile and *N*-methylacetamide in the same system [21], thereby attesting to the remarkable stability of the acetaldehyde adduct.

The molecular structure obtained by X-ray crystallography is displayed in Fig. 2. It shows a tetrahedral complex where Zn^{2+} is wrapped by the three imidazole arms of the calixarene-based ligand with a bound MeCHO molecule deeply buried inside its conic cavity. 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 (1.983 Å). The acetaldehyde ligand is bound to the metal in a *cis* fashion and sits inside the calixarene cavity. The Zn–O distance [1.882(8) Å] is significantly shorter than in the other previously reported zinc–aldehyde complexes (2.00–2.24 Å) [23], thereby reflecting a strongly acidic zinc centre. Once again, a CH/π interaction is observed between the guest methyl group and one of the anisole rings of the host with a perpendicular C···Ar distance of 3.25 Å. In the acetaldehyde complex, the absence of hydrogen bond appears to be partly overcome by the optimization of the CH/π contacts. This is indeed reflected by the relatively shorter distance between the guest methyl group and the interacting anisole ring in the acetaldehyde adduct compared with the ethanol adduct for example, in which the perpendicular C···Ar distance is longer (3.67 Å) [22].

To our knowledge, this provides the first example of a stable dicationic Zn complex presenting a terminal aliphatic aldehyde ligand. All other previously reported tetrahedral Zn–aldehyde complexes were stabilized with chelate aldehydes and anionic ligands [23]. Furthermore, these were only obtained with aromatic aldehydes to prevent their degradation. Our system did not induce any polymerization or disproportionation of acetaldehyde. Hence, the calixarene cavity not only stabilizes adducts with a donor as weak as MeCHO but also protects the guest against side-reactions.

Finally, the relative topologies of the host and the guest is the base of a remarkable discrimination. The calixarene structure is narrow next to the metal ion. As a result, a substituent placed on the coordinating atom greatly destabilizes the adducts. For example, secondary and tertiary amines do not bind the zinc ion. The α-position is also more sterically encum-

TABLE I Equilibrium constants K_{L/H_2O} and $K'_{L/DMF}$ for ligand exchange (L vs. H_2O and vs. DMF, respectively) at the Zn^{2+} centre, in the calixarene cavity at 298 K [21] $[Zn(X_6Me_3Imme_3)(DMF)]^{2+} + L \rightleftharpoons [Zn(X_6Me_3Imme_3)(L)]^{2+} + DMF$ $K'_{L/DMF} = [[Zn(X_6Me_3Imme_3)(L)]^{2+}][DMF]/[[Zn(X_6Me_3Imme_3)(DMF)]^{2+}][L]$ $[Zn(X_6Me_3Imme_3)(H_2O)\cdot(H_2O)]^{2+} + L \rightleftharpoons [Zn(X_6Me_3Imme_3)(L)]^{2+} + 2H_2O$ $K'_{L/H_2O} = [[Zn(X_6Me_3Imme_3)(L)]^{2+}][H_2O]^2/[[Zn(X_6Me_3Imme_3)(H_2O)\cdot(H_2O)]^{2+}][L]$ and $K_{L/H_2O} = K'_{L/DMF} \times K_{DMF/H_2O}$

Substrate (L)	K_{L/H_2O} (mol × L^{-1})	$K'_{L/DMF}$
Heptylamine	>2	>25
2-Methylbutylamine*	>2	>25
2-Butylylamine*	0.78 (6)	9 (1)
Dimethyl sulfoxide	0.43 (6)	5.3 (5)
Acetamide	0.52 (6)	6.4 (6)
Dimethylformamide	0.082 (5)	1
N-Methylacetamide	0.004 (1)	0.05 (1)
Ethanol	0.39 (4)	4.7 (2)
Propan-1-ol	0.013 (2)	0.16 (2)
Propan-2-ol	0.0004 (1)	0.005 (1)
Acetonitrile	0.031 (5)	0.38 (4)
Propionitrile	0.011 (2)	0.13 (2)
Acetaldehyde*	0.006 (2)	0.07 (2)

*This work.

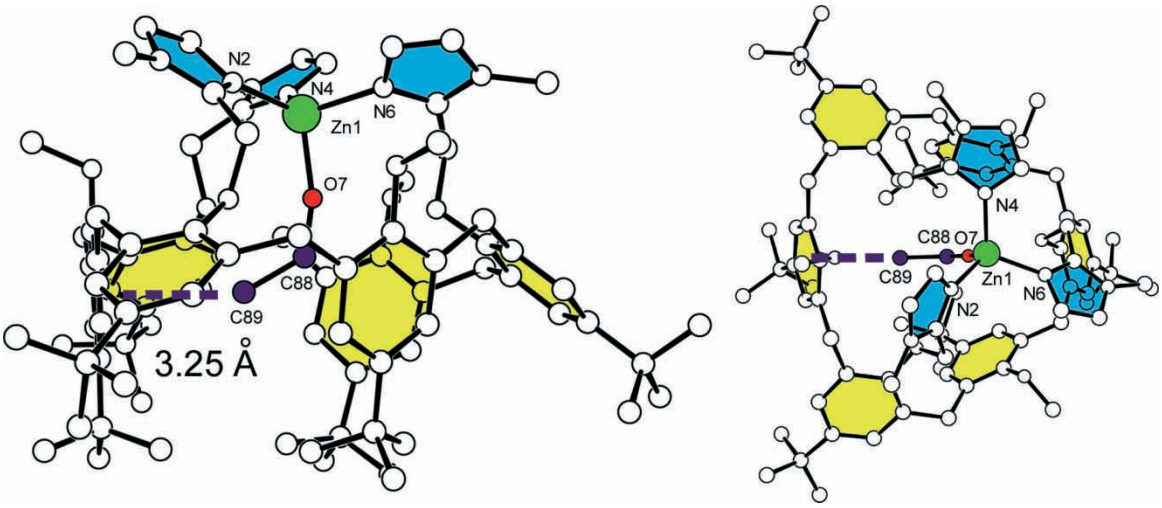


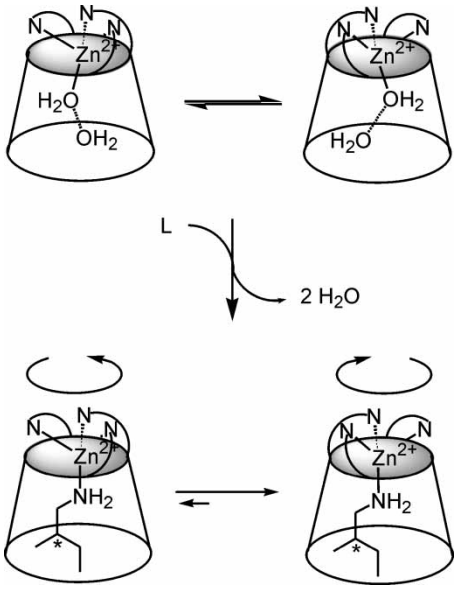
FIGURE 2 Crystal structure of complex $[Zn(X_6Me_3Imme_3)(MeCHO)](ClO_4)_2$. Left and right: side and top views, respectively. Hydrogen atoms and solvents of crystallization are omitted for clarity. Selected bond lengths (Å) and angles (°): Zn1–N2 1.969(6), Zn1–N4 1.994(6), Zn1–N6 1.987(6), Zn1–O7 1.882(8), O7–C88 1.301(6), N2–Zn1–O7 113.0(3), N4–Zn1–O7 108.5(5), N6–Zn1–O7 98.5(4), N2–Zn1–N4 109.4(2), N4–Zn1–N6 112.82, N2–Zn1–N6 114.3(2). (See colour plate 2 at the end of this issue.)

bered than the β-position. Indeed, the Zn ion displays more affinity for 2-methylbutylamine than for 2-butylamine. *n*-Propanol is bound 30 times stronger than *i*-propanol (see Table I).

A Chiral Receptor

A ^{1}H NMR study at 400 MHz in $CDCl_3$ revealed that with an achiral guest L, complexes $[Zn(X_6Me_3Imme_3)(L)]^{2+}$ exist as a pair of enantiomers that are in conformational equilibrium (Scheme 2).‡ At room temperature, the exchange process between the two helical forms can be either fast or slow on an NMR timescale, depending on the nature of the guest [26]. Above the coalescence temperature, T_c, the ^{1}H NMR spectra of the complexes are characteristic of averaged C_{3v} symmetric species in a flattened cone conformation. They display only three singlets for H^1_{Ar} (~7.2 ppm), H^2_{Ar} (~6.3–6.7 ppm) [27] and OCH_2 (~5.2–5.5 ppm) and two doublets for the bridging methylenes (~4.1 and 3.3 ppm). Below T_c, these diastereotopic protons are differentiated, giving rise to two doublets for H^1_{Ar} and H^2_{Ar} and three AB systems for OCH_2 and the bridging methylenes (Fig. 3). This indicates that the helical chirality that originates in the metal centre is transmitted to the whole calixarene host structure that twists around the C_3 symmetry axis.

In most cases, we found that the exchange rate of the coordinated guest was slow on the NMR timescale at room temperature. As a result, the corresponding resonances could be observed directly. Important upfield shifts due to the anisotropy of the calixarene aromatic walls attested to their inclusion in the cavity. For guests bearing methylene protons, the surrounding helical environment resulted in the splitting of their resonances, providing, however, that the temperature was low enough to slow down the conformational exchange process between the two helical host enantiomers. Two representative examples are shown in Fig. 4. In the case of propionitrile, whereas the ^{1}H NMR signature for the included methylene protons is a quadruplet at room temperature, it is split into two broad signals at 243 K. For 1-propanol, the $CH_cH_{c'}$ protons are



SCHEME 2 Formation of helical zinc complexes.

‡Although we previously reported a similar phenomenon with Cu(I) complexes, we were never able to observe it with an organic guest such as a nitrile. See [24,25].

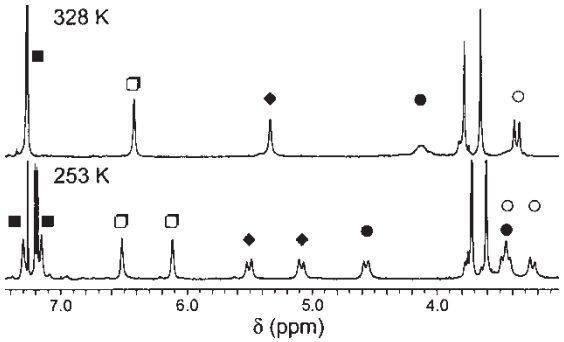


FIGURE 3 ^{1}H NMR spectra (400 MHz) of complex $[Zn(X_6Me_3Imme_3)(H_2O)](ClO_4)_2$ in $CDCl_3$. H^1_{Ar} : ■, H^2_{Ar} : ❐, OCH_2: ◆, $ArCH_{ax}CH_{eq}Ar$: ●, $ArCH_{ax}CH_{eq}Ar$: ○,. The *t*Bu region is not shown. The coalescence temperature T_c for H^2_{Ar} and OCH_2 is 293 K. The $\Delta G^{\neq}$ at T_c value for the coalescence process is 13.7 (2) kcal × mol^{-1}.

already differentiated at 298 K and exhibit two well resolved multiplets at 243 K. The signals for $CH_bH_{b'}$ and OH_a change from a quadruplet and a triplet at 298 K to a multiplet and a doublet of doublet at 243 K, respectively. This demonstrates that the guest experiences the chiral environment provided by the twisted host.

These observations prompted us to look at the effect of a chiral guest [10–13]. (*S*)-(−)-2-Methylbutylamine (= R*NH_2; 1.1 equivalent) was added to a $CDCl_3$ solution of the tris(imidazole)–zinc complex, and the ^{1}H NMR spectrum was recorded at 298 K. The resonances in the high-field region and their integrations attested to the quantitative coordination of the amino ligand inside the calixarene cavity. Signals of the host structure were broad at 298 K. However, when the temperature was lowered to 253 K, both the host and the guest exhibited two sets of signals, thereby demonstrating the formation of two diastereoisomeric supramolecular structures of the general formula $[Zn(X_6Me_3Imme_3)(R^*NH_2)]^{2+}$ (Fig. 5).

A ratio of 3:2 was obtained for these species from integration of the spectra. This shows that a chiral guest can control the equilibrium between the left-handed and right-handed helical form of the zinc complexes (Scheme 2) [28,29]. Owing to the geometry of the system, direct interaction between the guest ligand and the imidazolyl arms cannot be responsible for the induced diastereoselection. It thus appears that this effect is mainly due to weak interactions within the calixarene structure, i.e. hydrogen bonds and CH/π interactions between the included guest molecule and the twisted phenoxyl walls of the host [22,30]. Interestingly, enough, the same experiment conducted with (*S*)-(−)-2-butylamine did not yield any detectable diastereoisomeric excess. This means that the above-observed chiral selection is not due to a direct interaction between the ligand and the chiral metal centre. Rather, it is attributable to the helical shape of the calixarene skeleton that is more pronounced in the centre of the cavity than it is next to the metal ion, at the small rim.

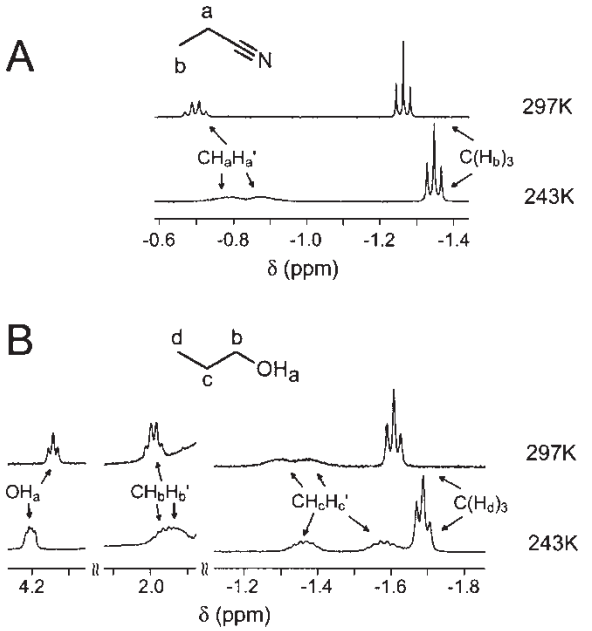


FIGURE 4 ^{1}H NMR signals (400 MHz) of the included guests of complexes $[Zn(X_6Me_3Imme_3)(L)]^{2+}$, $2ClO_4^-$ in $CDCl_3$ with L = EtCN (A) and L = *n*PrOH (B).

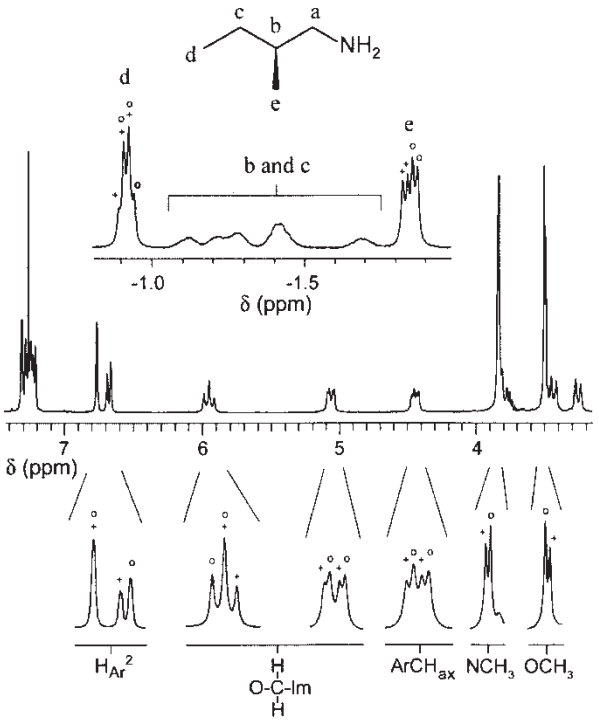


FIGURE 5 ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 253 K) of the two diasteroisomeric complexes $[Zn(X_6Me_3Imme_3)(R^*NH_2)]^{2+}$, $2ClO_4^-$ (R*NH_2 = (*S*)-(−)-2-methylbutylamine), denoted as + and o. The host *t*Bu and the guest CH_2(a) and NH_2 resonances are not shown.

Biomimetism

This is the first time that dicationic tetrahedral zinc complexes have been characterized. The exceptional stability of these species is highly reminiscent of monozinc active sites in hydrolytic enzymes [31]. Indeed, the zinc–aqua complex [21] provides a unique structural model for the active site of carbonic anhydrase [31,32], which displays a tetrahedral zinc ion bound to three histidine residues and a water molecule. The hydrogen bond network is remarkably similar. In particular, the distance separating the water ligand from its hydrogen-bonded partner is intriguingly short in both the natural system and its synthetic supramolecular model.

The ethanol and acetaldehyde ternary complexes also provide interesting models for substrate binding in Liver Alcohol Dehydrogenase (LADH), a zinc enzyme that catalyses the reversible dehydrogenation of alcohols to aldehydes *via* hydride transfer with NAD^+ [31]. They present stabilizing interactions similar to those reported for the enzyme. Indeed, it is also well known that these interactions can help in stabilizing an enzyme–substrate complex. In the specific case of LADH, it was shown that Phe-93 can interact with alcohol substrates [33] or sulfoxide-based inhibitors [34,35]. It is worth noticing that in agreement with the LADH mechanism, the affinity order for the binding guest is EtOH > MeCHO. However, the relatively small differences between the binding constants are coherent with what might be expected for a reversible reaction.

CONCLUSION

In conclusion, the binding of a zinc ion to a calix[6]arene bearing three coordinating arms allows the shaping of a molecular receptor. The resulting calix[6]arene-based tris(imidazole)–zinc complexes are chiral supramolecular edifices. They act as selective receptors for neutral molecules thanks to the establishment of weak stabilizing interactions between the host and the guest, as in natural systems. Indeed, the system is highly reminiscent of the Michaelis complexes in zinc enzymes. The selectivity of the binding is based on both the affinity of the ligand for the zinc ion and the relative topologies of the included guest and the flattened cone calixarene structure. The chirality originates from the helical metal binding of the three imidazolyl arms covalently grafted on the calix[6]arene. The helicity is then transmitted to the calixarene cavity that becomes twisted, thereby providing a chiral environment that ultimately is experienced by the guest. Conversely, this study shows that a chiral guest can control the equilibrium between the two helical forms of the complexes, thereby transmitting its own chirality to the whole calixarene-based system. These results are very promising in the perspective of chiral recognition, as they demonstrate that a calix[6]arene skeleton can convey chiral infomation [10–13]. Optimization of the host–guest interaction for a good chiral induction from the guest to the host may lead to a supramolecular system that behaves as an amplifier of chirality. Synthesis of chiral calixarene ligands may give rise to enantioselective receptors with the perspective of obtaining an asymmetric reaction chamber that could control a catalytic event. We are currently working on both of these aspects.

EXPERIMENTAL

Methods

Characterization of the Zn–acetaldehyde Adduct in Solution

Formation of the ternary adduct with acetaldehyde was observed by ^1H NMR spectroscopy when 10 molar equivalents of acetaldehyde were added to a 6.4 mM solution of the zinc–aqua complex $[Zn(X_6Me_3Imme_3)(H_2O)\cdot(H_2O)](ClO_4)_2$ in $CDCl_3$. At room temperature, coordinated MeCHO is in fast exchange with free MeCHO. However, at 243 K, the exchange process becomes slower than the NMR timescale, and the resonances of coordinated MeCHO can be detected: $\delta_{CHO} = 7.50$ ppm and $\delta_{CH3} = -0.68$ ppm). The IR spectrum of complex $[Zn(X_6Me_3Imme_3)(MeCHO)](ClO_4)_2$ in a $CDCl_3$ solution displays a band at 1691 cm^{-1} for coordinated MeCHO ($\nu = 1725\ cm^{-1}$ for free MeCHO).

Measurement of Equilibrium Constants with Chiral Amines

Chiral amines were introduced in a 4.9 mM solution of the zinc–aqua complex $[Zn(X_6Me_3Imme_3)(H_2O)\cdot(H_2O)](ClO_4)_2$ in $CDCl_3$. In the case of 2-butylamine, the equilibrium constant $K_{2\text{–butylamine}/H_2O}$ was calculated by integration of NMR spectra recorded with various concentration of amine. In the case of 2-methylbutylamine, even with less than one equivalent of amine, the formation of the amine adduct appeared quantitative. So, a minimum value for $K_{2\text{-methylbutylamine}/H_2O}$ ($2\ L \times mol^{-1}$) was assessed.

Crystal Structure Analysis of $[Zn(X_6Me_3Imme_3)(MeCHO)](ClO_4)_2$

Single crystals of this complex were grown out of a CH_2Cl_2/MeCHO mixture with a toluene layer. Diffraction data were measured on a Nonius KappaCCD diffractometer [36]. The structure

was solved by direct methods and refined using the program SHELXL97 [37]. $C_{101}H_{120}N_6O_{15}Cl_4Zn$, $M_w = 1865.28$, monoclinic, colourless crystals ($0.4 \times 0.3 \times 0.2\,mm^3$), $a = 22.7987(5)$ Å, $b = 16.2190(8)$ Å, $c = 26.494(1)$ Å, $\beta = 93.796(2)°$, $V = 9775(1)$ Å^3, space group $P21/c$, $Z = 4$, $\rho = 1.267\,g\,cm^{-3}$, $\mu(MoK\alpha) = 4.26\,cm^{-1}$, 16,412 reflections measured at 157 K in the 2–25° θ range, 15,852 unique, 1187 parameters refined on F^2 using 11,369 reflections to final indices $R/F^2 > 4\sigma F^2] = 0.121$, $wR = 0.297$ [$w = 1//\sigma^2(Fo^2) + (0.1559P)^2 + 28.8804P$], where $P = (Fo^2 + 2Fc^2)$ [3]. Classical numerical or empirical absorption corrections were not applied to the data: we found that the scaling procedure proposed by the data reduction program that we used was sufficient to perform a reasonable pseudo-correction of the reflections. The crystals were very sensitive to desolvation. The complex cocrystallized with a CH_2Cl_2 and two toluene (highly disordered) solvates. One *t* Bu and one counterion chloride were split on two distinct sites with equal multiplicities because of static disorders. The acetaldehyde ligand was determined through a last series of Fourier difference. The latter gave only three peaks of density of appropriate height, correctly positioned in the hydrophobic cage. The medium quality of the data led us to refine the acetaldehyde moiety as a rigid body block. The last residual Fourier positive and negative peaks were equal to 0.759 and −0.942, respectively.

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[26] For example, $T_c(H^2_{Ar})$ was 320 K and 293 K for EtOH and H_2O, respectively. For MeCN and EtCN, T_c was below 293 K.
[27] H^1_{Ar} and H^2_{Ar} designate protons of aromatic rings bearing imidazole and methyl groups, respectively.
[28] This corresponds to an estimated *de* of 20% for the process of chirality transmission, which is significant for standards of host–guest chemistry, especially for a non-optimized cavity filling [10–13].
[29] We cannot yet determine which one of the two helical form is favoured by (*S*)-(−)-2-methylbutylamine.
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