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Calix[6]arenes and Zinc: Biomimetic Receptors for Neutral Molecules

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Abstract: A novel supramolecular system that acts as a biomimetic receptor for neutral guests is presented. The functionalization of *t*-butyl-calix[6]arene (X_6H_6) at the lower rim in alternate position by methyl (Me) and 2-methylene-1-methyl-1*H*-imidazole (Imme) yielded the new ligand $X_6Me_3Imme_3$. It provided a neutral tris(imidazole) coordination site associated with a conic cavity, thereby mimicking the active center of zinc proteins. Upon reaction with $Zn(ClO_4)_2(H_2O)_6$, an air-stable dicationic zinc−aqua complex $[Zn(X_6Me_3Imme_3)(H_2O)](ClO_4)_2$ was obtained. The highly acidic Zn^{2+} center was constrained in a tetrahedral environment with a labile site oriented toward the inside of the calix[6]arene structure. The hydrophobic pocket acted as a selective molecular funnel for neutral molecules. ^1H NMR spectroscopy studies showed the easy exchange of the aqua ligand for amines, alcohols, amides, or nitriles. The selectivity of the exchange process is based on both the guest's binding ability to the metal center and its shape and size. Two of these ternary complexes were characterized by X-ray diffraction analysis: $[Zn(X_6Me_3Imme_3)(NCC_2H_5)](ClO_4)_2$ and $[Zn(X_6Me_3Imme_3)(NH_2C_7H_{15})](ClO_4)_2$. Hydrogen bonds between the acidic protons of the coordinated guest and the calixarene phenoxyl group suggest an important role in the stabilization of these dicationic complexes that do not undergo deprotonation.

Introduction

Molecular recognition is a fundamental phenomenon in biology. It has inspired many organic chemists to design artificial receptors.[1] Recently, the construction of hosts with metal ions in the scaffold has allowed for the binding of many structurally sophisticated guests.[2] Clearly, however, there is still a need for neutral molecule receptors that would be simple, versatile, but also selective, giving rise to stable but reversible adducts. Recalling that the first stages of an enzymatic process involve the formation of an enzyme−substrate complex, we sought to design a model for the Michaelis complex in metallo-enzymes that combines the binding of a substrate to a biomimetic metal center with lipophilic host−guest interactions.

Zinc(II) ion is a biologically essential element. Recognition of its importance has been increasing as more enzymes containing zinc(II) in their active site have been discovered.[3] Of great interest in relation to several diseases, these enzymes are mainly involved in hydrolytic processes but also catalyze the reversible oxidation of alcohols. Hence, the enzyme active centers interact with a variety of functionalized molecules such as amides, carboxylic acids, and amines, as well as alcohols and aldehydes. Among the structurally characterized zinc enzymes, an active-site motif appears to be recurrent for a growing number of proteins. Indeed, carbonic anhydrase, matrix metalloproteases, Snake Venom metalloproteinases, *Bacillus cereus* β-lactamase II, and 6-Pyruvoyl tetrahydropterin synthase all possess a common feature in their active site: a mononuclear zinc center coordinated by three histidines and a water molecule. Despite the number of studies related to these proteins, the nature of the enzyme−substrate interaction is still controversial. Two alternatives have been proposed: either the substrate initially substitutes the water ligand upon binding to the metal center or it directly interacts with a zinc hydroxide species.[3] In recent years, several research groups have structurally modeled the coordination environment of the zinc center using a variety of ligands,[4] such as macrocyclic triamines,[5] tris(imidazolyl)-

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(1) (a) Lehn, J. M. *Supramolecular Chemistry*; VCH: Weinheim, 1995. (b) Reviews of molecular recognition. *Chem. Rev.* **1997**, *97*, 1232−1734.

(2) For a review concerning the selective recognition of organic molecules by metallohosts, see the following: Canary, J. W.; Gibb, B. C. In *Prog. Inorg. Chem., Vol. 45*; Karlin, K. D. Ed.; Wiley: New York, 1997; pp 1−81.

(3) (a) Lipscomb, W. N.; Sträter, N. *Chem. Rev.* **1996**, *96*, 2375−2433. (b) Auld, D. S. Metal Sites in Proteins and Models. In *Structure and bonding, Vol. 89*; Sadler, P. J., Ed.; Springer-Verlag: Berlin-Heidelberg, 1997; pp 29−50.

(4) For a recent review, see the following: Kimura, E.; Koike, T.; Shionoya, M. Metal Sites in Proteins and Models. In *Structure and bonding, Vol. 89*; Sadler, P. J., Ed.; Springer-Verlag: Berlin-Heidelberg, 1997; pp 1−28.

(5) (a) Kimura, E.; Shiota, T.; Koike, T.; Shiro, M.; Kodama, M. *J. Am. Chem. Soc.* **1990**, *112*, 5805−5811. (b) Zhang, X.; van Heldik, R.; Koike, T.; Kimura, E. *Inorg. Chem.* **1993**, *32*, 5749−5755.

(6) (a) Read, R. J.; James, M. N. G. *J. Am. Chem. Soc.* **1981**, *103*, 6947−6952. (b) Brown, R. S.; Curtis, N. J.; Huguet, J. *J. Am. Chem. Soc.* **1981**, *103*, 6953−6959. (c) Kimblin, C.; Allen, W. E.; Parkin, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1813−1815.

(7) (a) Alsfasser, R.; Powell, A. K.; Vahrenkamp, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 898−899. (b) Kitajima, N.; Hikichi, S.; Tanaka, M.; Moro-oka, Y. *J. Am. Chem. Soc.* **1993**, *115*, 5496−5508. (c) Alsfasser, R.; Ruf, M.; Trofimenko, S., Vahrenkamp, H. *Chem. Ber.* **1993**, *126*, 703−710. (d) Ruf, M.; Schell, F.-A.; Walz, R.; Vahrenkamp, H. *Chem. Ber./Recl.* **1997**, *130*, 101−104. (e) Bergquist, C.; Parkin, G. *Inorg. Chem.* **1999**, *38*, 422−423.

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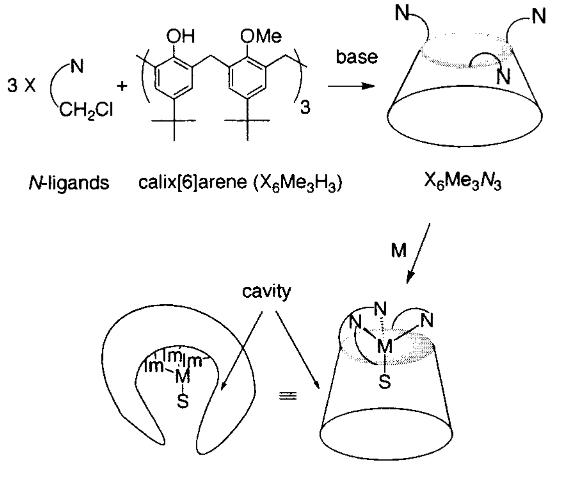
Scheme 1. General Strategy for the Design of the Calix[6]arene-Based Systems Acting as Biomimetic Molecular Funnels



A "funnel complex" modeling the mononuclear active site of enzymes

phosphines,[6] or the anionic tris(pyrazolyl)borates.[7] However, all these models focus on Zn−hydroxide complexes.[8] The synthesis and structural characterization of dicationic complexes, where Zn^{2+} is coordinated to a neutral N_3 site with a fourth neutral terminal ligand, remains a challenge. As a consequence, their potential to bind to different neutral organic molecules has not been exploited.

We have recently described a novel supramolecular system that models the active site of mononuclear copper enzymes (Scheme 1, M = Cu^+).[9] We have now extended our strategy to mononuclear zinc active sites (M = Zn^{2+}) that present a tris(histidine) coordination core. This new model takes advantage of the conic shape of a calix[6]arene properly functionalized with three imidazole groups that mimic the histidines of the enzyme active site. The geometry of the system is designed to constrain the metal center in a tetrahedral environment, orienting the fourth coordination site toward the inside of the hydrophobic cavity provided by the calixarene skeleton.

The corresponding zinc(II) complexes were characterized either by X-ray analysis and/or by ^{1}H NMR spectroscopy. These are rare, if not the first, examples of stable tetrahedral dicationic Zn complexes that possess a unique labile site and therefore display an unrivalled host/guest behavior toward neutral organic molecules.

Results

Synthesis and Characterization of an Aqua−Zinc(II) Complex. The new tridentate N ligand $X_6Me_3Imme_3$ was prepared from *t*-butyl-calix[6]arene,[10] which was converted to its 1,3,5-trimethyl ether[11] and then treated with 2-chloromethyl-1-methyl-*1H*-imidazole in the presence of NaH to yield the product as a high-melting solid. The reaction of the host molecule $X_6Me_3Imme_3$ with a stoichiometric quantity of $Zn(OH_2)_6(ClO_4)_2$ in THF yielded a complex with a 1:1 ligand/zinc ratio. The ^{1}H NMR spectrum of this new complex reflected a C_3 symmetry. The low-field shifts observed for the resonances of the imidazole protons attested to the coordination of the Zn^{2+} to all three imidazole cores. A 2D EXSY (exchange spectroscopy) study, recorded at 297 K with $\tau_m = 300$ ms, showed a correlation peak for free water and thus revealed the presence of an aqua ligand resonance at 3.63 ppm. Similar shifts ($\delta = 3.42-4.21$) have been reported for dicationic 5-coordinated aqua−Zn complexes,[12] whereas hydroxo−zinc complexes display a resonance for the coordinated OH group at a much higher field ($\delta = -0.06$).[13] In the present case, the δ value for the aqua ligand is the net result of two opposite effects: a downfield shift due to its coordination to Zn^{2+} and an upfield shift due to its location inside the π-basic aromatic calixarene cavity (vide infra). Hence, although similar to that of Brandsch's complexes,[12] this δ value reflects an increased acidity of the aqua ligand when zinc is 4-coordinated compared with when it is 5-coordinated. All these observations agree with the formation of a dicationic zinc complex in a tetrahedral environment due to the coordination of Zn^{2+} to the three imidazole groups and to a water molecule (Scheme 2).

X-ray Structure of a Nitrilo Adduct. We were able to grow single crystals by the slow diffusion of ether into a propionitrile solution of this zinc complex. The structure of $[Zn(X_6Me_3Imme_3)(EtCN)](ClO_4)_2$ was established by X-ray crystallographic analysis, displayed in Figure 1. The Zn(II) center resides in a regular tetrahedral N_4 ligand environment, close to C_{3v} symmetry. The three imidazole arms wrap the metal center, forming a chiral helix.[14] The propionitrile ligand is buried deep inside the cavity of the *t*-butyl-calix[6]arene macrocycle in a *cone* conformation.[15] The average value for the $Zn1-N_{Im}$ distances is 1.996 Å. This is close to those measured for the $\{Zn[tetrakis(N\text{-methylimidazole-}N')]\}^{2+}$ core (1.991 Å)[16] but significantly shorter than the values reported for tris(imidazolyl)phosphine-based Zn(II) complexes (2.048−2.11 Å).[6c] In the latter case, the zinc(II) complexes were monocationic due to a negatively charged fourth ligand. Thus, the shorter bond length observed here may be ascribed to an increased Lewis acidity of the zinc center when all four ligands are neutral. The distance between zinc and the propionitrile nitrogen atom, 1.985(6) Å, is also shorter than the ones previously reported.[17]

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[8] Furthermore, in all structurally characterized complexes, at least one ligand was anionic or the metal center was 5(or higher)-coordinate. Polynuclear complexes are also often produced. Hence, the coordination chemistry of the Lewis acidic Zn^{2+} center appears extremely difficult to control.

[9] (a) Blanchard, S.; Le Clainche, L.; Rager, M.-N.; Chansou, B.; Tuchagues, J.-P.; Duprat, A. F.; Le Mest, Y.; Reinaud, O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2732−2735. (b) Blanchard, S.; Rager, M.-N.; Duprat, A. F.; Reinaud, O. *New J. Chem.* **1998**, 1143−1146.

[10] Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1990**, *68*, 238−242.

[11] Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Uggozoli, F.; Ungaro, R.; Nieto, P. M.; Carramolino, M.; Cuevas, F.; Prados, P.; de Mendoza, J. *Synthesis* **1993**, 380−385.

[12] Brandsch, T.; Schell, F.-A.; Weis, K.; Ruf, M.; Müller, B.; Vahrenkamp, H. *Chem. Ber./Recl.* **1997**, *130*, 283−289.

[13] Looney, A.; Han, R.; McNeill, K.; Parkin, G. *J. Am. Chem. Soc.* **1993**, *115*, 4690−4697.

[14] Both enantiomers were included in the unit cell. In solution, these were in conformational exchange. However, the exchange process was slow on the NMR time scale. A detailed spectroscopic study showed that the coordinating guest molecule experienced a chiral environment. This will be published elsewhere.

[15] The relative conformation of the phenolic units is different from what was previously observed in the calixarene-based copper(I) complex,[9] the reasons of which are under investigation.

[16] Chen, X.-M.; Huang, X.-C.; Xu, Z.-T.; Huang, X.-Y. *Acta Crystallogr., Sect. C* **1996**, *52*, 2482−2484.

[17] X-ray structures of nitrilo−zinc complexes appear to be rare. In the tetrahedrally coordinated $[ZnCl_2(MeCN)_2]$, d(Zn−N) = 2.046(3) Å [Bel'sky, V. K.; Streltsova, N. R.; Bulychev, B. M.; Storozhenko, P. A.; Ivankina, L. V.; Gorbunov, A. I. *Inorg. Chim. Acta* **1989**, *164*, 211−220]; for a 5-coordinated dicationic Zn complex, d(Zn−N) = 2.059(4) Å [Matthews, C. J.; Clegg, W.; Heath, S. L.; Martin, N. C.; Stuart Hill, M. N.; Lockhart, J. C. *Inorg. Chem.* **1998**, *37*, 199−207]; for 5-coordinated neutral complexes: d(Zn−N) = 2.114(4) Å [Castro, J. A.; Romero, J.; Garcia-Vasquez, J. A.; Macias, A.; Souza, A.; Englert, U. *Polyhedron* **1993**, *12*, 1391−1397] and d(Zn−N) = 2.087(4) Å [Becker, B.; Radacki, K.; Wojnowski, W. *J. Organomet. Chem.* **1996**, *521*, 39−49].

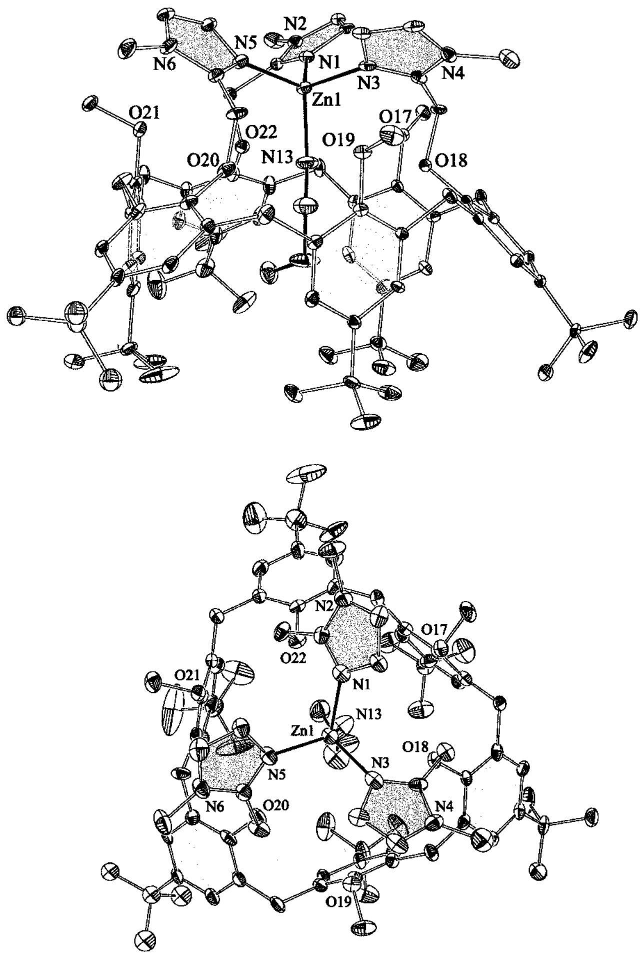
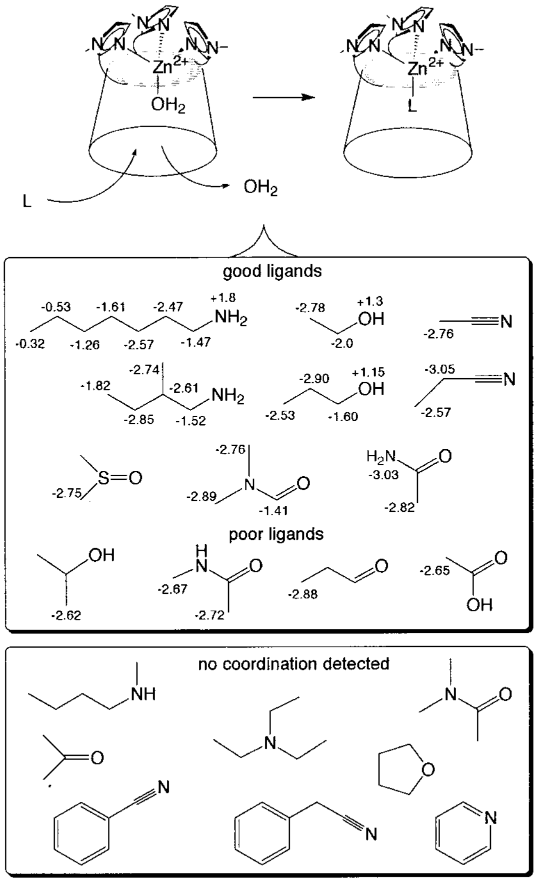


Figure 1. Crystal structure of $[Zn(X_6Me_3Imme_3)(NCEt)](ClO_4)_2$, showing ellipsoids at 20% probability. Hydrogen atoms, perchlorate counterions, and solvent of crystallization were omitted for clarity. There were two molecules per asymmetric unit that displayed only minor geometrical differences. Only one (Zn1) is represented. Top: side view. bottom: plan view. Selected bond lengths [Å] and angles [degrees]: Zn1−N1 2.005(9), Zn1−N3 1.99(1), Zn1−N5 1.994(7), Zn1−N13 1.985(6), N13−C133 1.36(3), N1−Zn1−N3 110.4(5), N1−Zn1−N5 108.7(4), N1−Zn1−N13 102.4(5), N3−Zn1−N5 107.4(5), N3−Zn1−N13 110.8(6), N5−Zn1−N13 116.9(4), Zn1−N13−C133 130.0(13), N13−C133−C134 124.4(22).

Scheme 3. Ligand Exchange in the Cavity of the Zinc "Funnel Complexes"[a]

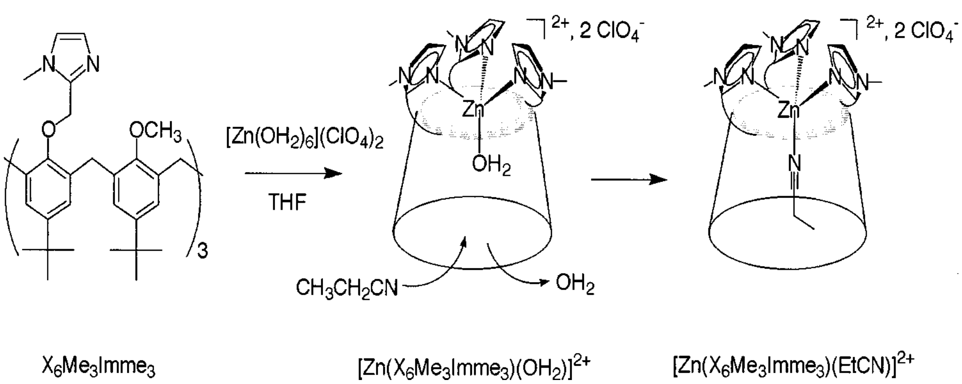


[a] The Δδ shifts observed by ^1H NMR spectroscopy for the guest ligand are indicated next to the corresponding atoms ($\Delta\delta = \delta_{\text{coordinated L}} - \delta_{\text{free L}}$. δ is the chemical shift; in some cases, $\delta_{\text{coordinated L}}$ could not be determined because of peaks overlapping).

^1H NMR Studies of the Host−Guest Behavior. The discovery that the aqua ligand of the calixarene-based zinc complex could easily be substituted for propionitrile in order to give a stable adduct prompted us to test the reactivity of this complex toward different neutral, potentially coordinating, molecules. For this reason, we undertook a series of ^1H NMR experiments: an exogenous substrate L (up to 60 molar equivalents) was added to a $CDCl_3$ solution of the aqua complex. Under these experimental conditions, there were 3−5 molar equiv of H_2O. The ^1H NMR spectrum was then recorded and analyzed.

Primary amines, alcohols, amides easily displaced the coordinated water molecule to form stable zinc complexes (Scheme 3). The ^1H NMR spectra of these new compounds, although different, displayed similar profiles, thereby indicating only little change in the conformation of the calixarene. They were all characteristic of a dicationic C_3 symmetric complex where the zinc ion was coordinated to the N_3 ligand and to the exogeneous neutral molecule. As shown by the important upfield shifts of

Scheme 2. Synthesis of the Novel Biomimetic Calix[6]arene-Based Zinc Complexes



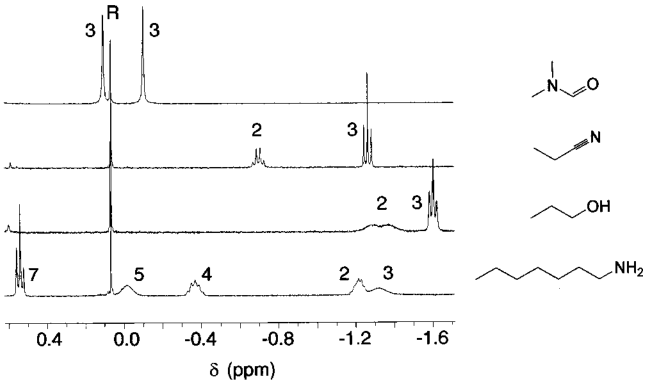


Figure 2. High-field region of the ^{1}H NMR spectra of $[Zn(X_6Me_3\text{-}Imme_3)(L)](ClO_4)_2$ in $CDCl_3$ at 297 K (400 MHz). From top to bottom, L = DMF, EtCN, PrOH, *n*-HeptNH$_2$. The relative protons' positions to the coordinating heteroatom (Y = N, O) are indicated with numbers. The reference peak is labeled "R".

Table 1. Equilibrium Constants K_{L/H_2O} for the Ligand Exchange (L vs H_2O) at the Zn^{2+} Center, in the Cavity of the Calixarene

substrate L	K_{L/H_2O}
heptylamine	>100
dimethyl sulfoxide	21 (5)
acetamide	28 (7)
dimethylformamide	4.0 (8)
N-methylacetamide	0.15 (9)
ethanol	20 (6)
propan-1-ol	1.3 (5)
propan-2-ol	0.04 (1)
acetonitrile	1.7 (5)
propionitrile	0.6 (3)

its protons, the latter sat inside the aromatic cavity. In most cases, the peaks of the included coordinated molecule were very sharp and well-defined (representative examples are displayed in Figure 2). This indicates that chemical exchange at the metal center was slow compared with the time scale of the NMR analysis. The proton resonances of the amino and hydroxo groups were also identified, displaying a coupling with the adjacent methylene protons. Hence, the exchange of the protons at the level of the coordinating heteroatom is substantially slower in comparison with the free molecules (L = RNH_2, ROH). This reflects the high hydrophobicity of the cavity around the guest molecule.

The relative capacity of these molecules to displace the coordinated water was evaluated. In some cases, it was possible to estimate from the integrations of the NMR spectra the constant K_{L/H_2O} (Table 1) defined in the following equilibrium:

$$[Zn(X_6Me_3Imme_3)(H_2O)]^{2+} + L \leftrightarrows [Zn(X_6Me_3Imme_3)(L)]^{2+} + H_2O$$

$$K_{L/H_2O} = [Zn(X_6Me_3Imme_3)(L)][H_2O]/[Zn(X_6Me_3Imme_3)(H_2O)][L]$$

(1) With primary amines, coordination to the metal center was stoichiometric and quantitative. For acetamide, ethanol, and DMSO, the binding to Zn^{2+} was ~20−30 times stronger than for water. DMF was also an excellent guest, that is, bound more strongly to the metal center than nitriles. Coordination to even weaker donor molecules, such as propionaldehyde and acetic acid, could also be detected. In these cases, however, the aqua species remained by far the dominant one. Finally, ether, THF, acetone did not yield any detectable coordinated species.

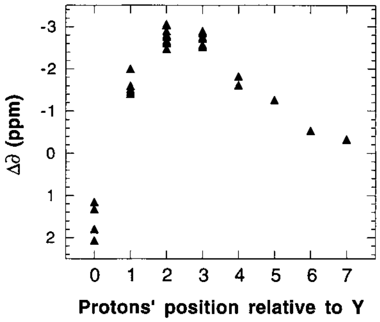


Figure 3. Plot of the Δδ shifts for the guest's protons as a function of their position relative to the coordinating atom (Y).

(2) Steric hindrance at the level of the coordinating atom (Y) and its 1-position appeared to be a major factor of selectivity. Secondary (*N*-methylbutylamine), tertiary (Et_3N), and aromatic (pyridine) amines did not yield any detectable coordinated species. Coordination of 2-propanol was 30 times weaker than that of 1-propanol.

(3) Whereas benzo- and benzyl-nitrile appeared too sterically encumbered to yield a stable adduct, a methyl substituent in the 2-position (as in DMF) or a long alkyl chain did not preclude coordination at the metal center. Indeed, 2-methylbutylamine and heptylamine quantitatively and stoichiometrically replaced the bound water molecule. However, ethanol was more strongly coordinated than 1-propanol.

A classification of the affinity of the calixarene-encapsulated zinc ion for different coordinating molecules may be proposed as follows:

Primary amines ($K_{Y/H_2O} > 10^2$) > primary alcohols and amides > nitriles > secondary amides and alcohols, carboxylic acids, aldehydes, ≫> secondary, tertiary and aromatic amines, ethers and ketones ($K_{Y/H_2O} < 10^{-2}$).

Mapping the Guest Molecule. The ^{1}H NMR proved to be a powerful tool to monitor the presence of a coordinating molecule (L) inside the cavity. The upfield shifts (Δδ) measured for its protons were dependent on their spatial position in the aromatic cavity of the calixarene. These have been reported in Scheme 3 and plotted in Figure 3 as a function of their relative position to the coordinating heteroatom (Y = N or O). An excellent correlation was obtained for all molecules that were analyzed. The protons at 2- and 3-positions shifted most (−2.5 to −3.0 ppm), indicating that they sit right in the center of the aromatic cavity. Those in the 1-position shifted less upfield (Δδ = −1.4 to −2.0). Those directly bound to the coordinating atom Y underwent a downfield shift (Δδ = + 1.2 to + 2.1). This reflects an additional electronic effect as a result of the coordination at the highly acidic metal center which induces an opposite downfield shift. In the case of acetamide, the important upfield shift observed for NH_2 (Δδ = −3.03 ppm) points out that its coordination occurred through the oxygen binding. For *N*-methyl acetamide, the Δδ values were plotted into the graph of Figure 3 in both hypotheses: coordination at the carbonyl (Y = O) or at the nitrogen (Y = N) [the *N*-methyl protons (a doublet) are in the 3- and 1-position relative to Y, respectively]. The first hypothesis was the only one to give data that match those reported for the other guests. Therefore, these observations show that, as expected, coordination of amides preferentially occurs through the oxygen binding.

Hence, NMR analysis not only allowed identification of the coordinating molecule but also provided cartography of the geometry that this supramolecular system adopts. For the zinc−heptylamine complex, all methylene protons of the included alkyl chain appeared as well-separated resonances whose

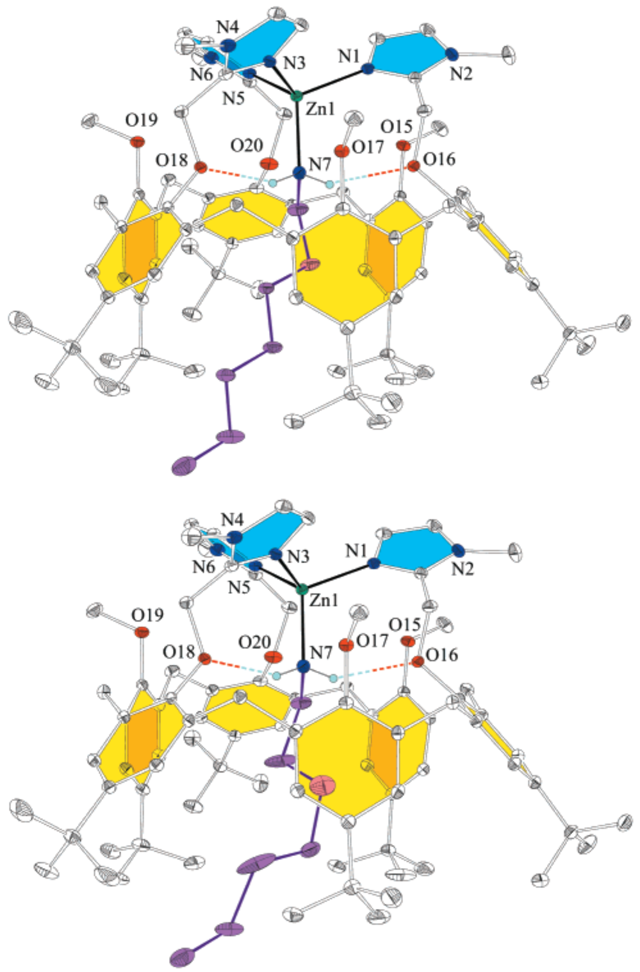


Figure 4. Crystal structure of [Zn($X_6Me_3Imme_3$)(n-$HeptNH_2$)](ClO_4)$_2$, showing ellipsoids at 20% probability. Side views. Top: major conformation (70%, the included heptylamine ligand is colored in purple). Bottom: minor conformation (30%, heptylamine is colored in pink). The amino hydrogen atoms were located experimentally and are represented by spheres of arbitrary radius. Other hydrogen atoms, perchlorate counterions, and solvents of crystallization are omitted for clarity. Selected bond lengths [Å] and angles [degrees]: Zn−N1 2.005(2), Zn−N3 2.021(2), Zn−N5 1.996(5), Zn−N7 2.01(2), N1−Zn−N3 109.3(1), N1−Zn−N5 108.1(2), N1−Zn−N7 111.1(3), N3−Zn−N5 106.1(2), N3−Zn−N7 101.9(4), N5−Zn−N7 119.7(3).

assignments were made on the basis of a $^1H-^1H$ COSY experiment. Interestingly, the relatively low upfield shifts of the two terminal carbons' protons suggested that they were extended out of the cavity.

X-ray Structure of the Heptylamine−Zinc Complex. The geometry of this complex was confirmed by X-ray analysis, displayed in Figure 4. As for the nitrilo complex, the Zn^{2+} center resides in a regular tetrahedral N_4 ligand, provided by the $(Im)_3$ moiety and the heptylamine ligand. The average value for the three $Zn-N_{Im}$ distances (2.007 Å) is similar to that measured in the parent propionitrile complex. The amino ligand sits inside the conic cavity of the *t*-butyl-calix[6]arene. Two different conformations were experimentally determined for its alkyl chain. Both exhibit a gauche interaction between the nitrogen and the γ-carbon [the (N,γ-C) dihedral angles are 68 and 71°]. In the minor conformation, an additional gauche interaction was observed between the β- and ϵ-carbons [the (β-C,ϵ-C) dihedral angle is 53°]. Hence, it appears that the observed guest's conformations correspond to an optimized filling of the calixarene conic cavity. Finally, the NH_2 protons were experimentally identified. Each of them points toward an oxygen atom of the calixarene. Their distances to these oxygen atoms (O18 and O16) are 2.047 and 2.152 Å, respectively, and the corresponding (N•••O) distances are 2.923 and 2.925 Å, respectively. Thus, a hydrogen-bond network between the coordinating guest and the host cavity further stabilizes the ternary complex.

Discussion

Most of the previously reported zinc-based receptors concerned coordination of amines and, to a lesser extent, nitriles.[2,18] These were generally based on tetradentate ligands (porphyrins or polyamines) and therefore gave rise to five- or six-coordinate species upon binding to the guest molecule. In contrast, in our system the calixarene-based ligand is only tridentate and allows stabilization of tetrahedral dicationic zinc complexes. Thus, the exceptional sensitivity of the aqua species to weak donors may be ascribed to the very high Lewis acidity of the metal center in such an environment. Also significant is that the geometry of the calixarene-based system apparently disfavored the coordination of a fifth molecule to the metal center, and the Zn complex rather underwent substitution of its labile aqua ligand.

The stability of these complexes, and more particularly those of the aqua and the alcohol adducts, may be surprising if one compares it with that of other $N_3Zn(ROH)$ systems. Indeed, they do not undergo deprotonation to yield the corresponding alkoxo or hydroxo derivatives as was the case for the closely related tris(imidazolyl)phosphine system.[6c] It is important to note that, upon adding a primary amine, the water ligand of the calixarene-based complex is substituted rather than deprotonated. Furthermore, whereas a secondary amine (one equivalent) did not displace the water ligand, neither did it deprotonate it. The high stability of these dicationic complexes also stands in contrast with the tris(pyrazolyl)hydroborato (Tp) system. With these anionic ligands, mononuclear hydroxo complexes[7c−e,13] could be stabilized thanks to the introduction of bulky substituents on the pyrazole groups. The corresponding aqua species, however, appeared even more difficult to isolate. The first example, $[Tp^{t-Bu,Me}ZnOH_2]^+$, was obtained through protonation of the hydroxo complex, employing a sterically encumbered proton donor.[19] The X-ray structure revealed that a strong hydrogen bond between the water ligand and the counteranion stabilizes the whole edifice. The authors made an analogy with the zinc water ligand at the active site of carbonic anhydrase, which also participates in a hydrogen bond with Thr-199.[20] The hydrogen-bond network displayed in Figure 4 between the heptylamine ligand and the phenoxyl groups of the calixarene structure is also suggestive of an important stabilizing effect for the complex when the included coordinating molecule bears acidic protons.

Finally, the relative stability of the alcohol versus water adducts in our system stands in contrast with the other related

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[18] Representative examples of Zn-based supramolecular receptors for neutral molecules: (a) Bonar-Law, R. P.; Sanders, J. K. M. *J. Chem. Soc., Chem. Commun.* **1991**, 574−577. (b) Imai, H.; Uemori, Y. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1793−1797. (c) Imai, H.; Kyuno, E. *Inorg. Chem.* **1990**, *29*, 2416−2422. (d) Haskard, C. A.; Easton, C. J.; May, B. L.; Lincoln, S. F. *Inorg. Chem.* **1996**, *35*, 1059−1064. (e) Mizutani, T.; Murakami, T.; Ogoshi, H. *Tetrahedron. Lett.* **1996**, *37*, 5369−5372. (f) Froidevaux, J.; Ochsenbein, P.; Bonin, M.; Schenk, K.; Maltese, P.; Gisselbrecht, J.-P.; Weiss, J. *J. Am. Chem. Soc.* **1997**, *119*, 12362−12363. (g) Huang, X.; Rickman, B. H.; Borhan, B.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1998**, *120*, 6185−6186. (h) For a rare example of carbohydrate recognition, see: Mizutani, T.; Kurahashi, T.; Murakami, T.; Matsumi, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1997**, *119*, 8991−9001.

[19] Bergquist, C.; Parkin, G. *J. Am. Chem. Soc.* **1999**, *121*, 6322−6323.

[20] Christianson, D. W.; Fierke, C. A. *Acc. Chem. Res.* **1996**, *29*, 331−339, and references therein.

biomimetic systems. Most Zn complexes involving coordination by an alcohol or amide were stabilized by a chelate effect due to the introduction of a pendant arm between the weak donor and the nitrogen-based ligand.[4,21] The structure of a Tp-based zinc complex with a bound methanol has been reported. In this case, however, the zinc ion is 5-coordinate and the bound methanol molecule is stabilized by a hydrogen bond with the proximate anionic ligand.[12] In fact, the only available comparison for the relative stability of alcohols versus water coordination in biomimetic zinc chemistry are Tp zinc alkoxides. They were described as "extremely water sensitive", undergoing a facile hydrolysis in contact with air.[7c] The equilibrium constant for the ethanolysis of $[\mathrm{Tp}^{t\text{-Bu,Me}}]\mathrm{ZnOH}$ was reported to be $\sim 10^{-3}$.[7e] In contrast, with the calixarene-based ligand, the complex with the bound ethanol is more stable than that with water. This is obviously due to an important stabilizing interaction between the small alkyl chain of the included molecule and the hydrophobic conic cavity of calixarene.

Conclusions

Upon coordination to a Zn^{2+} ion, the novel ligand X_6Me_3-$Imme_3$ gave rise to a remarkable biomimetic receptor for neutral organic molecules. Indeed, the corresponding aqua complex acts as a molecular funnel for lipophilic guests as a result of: (i) the tris*(*imidazole) donor set that wraps the metal center, thereby capping the cone of the calix[6]arene, (ii) the neutral environment that exacerbates the acidic character of Zn^{2+}, (iii) the hydrophobic calixarene cavity,[22,23] which controls the exchange processes at the metal center, and (iv) the presence of hydrogen-bond acceptors that can stabilize an acidic guest. The selectivity of this very sensitive but stable receptor is based on *both* the chemical nature of the guests and their size and shape. In all these respects, this system resembles the Michaelis complex of zinc enzymes. Finally, this novel supramolecular system may lead to the design of selective chemical sensing agents.

Experimental Section

General Procedures. All solvents and reagents were obtained commercially. DMF was stored over 4-Å molecular sieves under Argon. THF was distilled over sodium/benzophenone under Argon. $CHCl_3$ was distilled over $CaCl_2$ under Argon. ^1H NMR spectra were recorded at 400 MHz on a Bruker Avance 400 spectrometer. Traces of residual solvent or poly(dimethylsiloxane) (R) were used as an internal standard. IR spectra of $CHCl_3$ solution of ligand and complex were recorded on a Bomen MB 100 IR−FT spectrometer equipped with an InSb detector and a Spectratech ultramicro cavity (1 mm). Elemental analyses were performed at the Institut de Chimie des Substances Naturelles, 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.*

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris[(1-methyl-2-imidazolyl)methoxy]calix[6]arene ($X_6Me_3Imme_3$). Under an argon atmosphere, a solution of $X_6Me_3H_3$ (5,11,17,23,29,35-hexa-*tert*-butyl-37,39,41-trimethoxycalix[6]aren-38,40,42-triol)[11] (2.06 g, 2.03 mmol) in dry THF (40 mL) was introduced into a flask containing NaH (60% in oil, washed with pentane; 2.43 g, 60.8 mmol), dry THF (40 mL), and DMF (20 mL). The mixture was stirred for 20 min and 2-chloromethyl-1-methyl-*1H*-imidazole hydrochloride[24] (3.38 g, 20.3 mmol) was added over a period of 10 min. After 3 h of refluxing, the solvents were removed under reduced pressure to a quarter of the volume and water (300 mL) was poured into the solution. The resulting precipitate was collected by filtration, dried under vacuum, washed with pentane, and finally dried under vacuum overnight. The crude product (2.5 g, 96%) was pure enough to be used for the synthesis of zinc complexes without further purification. For microanalysis purposes, a sample (281 mg) was filtered on silica gel (CH_2Cl_2/MeOH (95:5) as eluent) and dried overnight under vacuum (0.01 mmHg, 50 °C) to give a white solid (241 mg, 84%). mp: 270 °C (decomp). ^1H NMR ($CDCl_3$): δ 0.77 (27H, s, *t*Bu), 1.37 (27H, s, *t*Bu), 2.14 (9H, s, OCH_3), 3.20 (6H, d, $J = 15$ Hz, Ar-αCH_{eq}), 3.88 (9H, s, NCH_3), 4.45 (6H, d, $J = 15$ Hz, Ar-αCH_{ax}), 5.01 (6H, s, Im-αCH_2), 6.62 (6H, s, Ar*H*), 6.91 (6H, s, Im*H*), 6.97 (6H, s, Im*H*), 7.22 (6H, s, Ar*H*). IR ($CHCl_3$): ν 1484, 1463, 1363, 1286, 1116, 1104, 993, 977 cm^{-1}. Anal. Calcd for $X_6Me_3Imme_3 \cdot H_2O$: C, 76.68; H, 8.39; N, 6.39. Found: C, 76.72; H, 8.24; N, 6.23.

$[Zn(X_6Me_3Imme_3)(H_2O)](ClO_4)_2$. Under an argon atmosphere, dry THF (1.5 mL) was added into a flask containing $Zn(H_2O)_6(ClO_4)_2$ (35.3 mg, 0.095 mmol) and $X_6Me_3Imme_3$ (123 mg, 0.095 mmol). The mixture was stirred for 10 min, filtered over Celite, and concentrated to a third of the volume. Precipitation with heptane (5 mL) yielded a white powder, which was dried under vacuum (0.01 mmHg): 130.4 mg, 87%. For elemental analysis, a sample was recrystallized from CH_2Cl_2/Et_2O and dried overnight under vacuum (0.01 mmHg). mp: 280 °C (decomp). ^1H NMR ($CDCl_3$): δ 0.72 (27H, s, *t*Bu), 1.39 (27H, s, *t*Bu), 3.35 (6H, d, $J = 15$ Hz, Ar-αCH_{eq}), 3.63 (11H, s, $OCH_3 + H_2O$), 3.71 (9H, s, NCH_3), 3.7−4.8 (6H, sl, Ar-αCH_{ax}), 5.32 (6H, s, Im-αCH_2), 6.37 (6H, s, Ar*H*), 7.24 (12H, s, Im*H* + Ar*H*). IR ($CHCl_3$): ν 3335 (H_2O), 1483, 1461, 1364, 1294, 1102 (ClO_4), 988, 976 cm^{-1}. Anal. Calcd for $[Zn(X_6Me_3Imme_3)(H_2O)](ClO_4)_2 \cdot H_2O \cdot CH_2Cl_2$: C, 60.66; H, 6.83; N, 4.99. Found: C, 60.77; H, 6.72; N, 4.83 (presence of solvent molecule was confirmed by ^1H NMR analysis).

Crystal Structure Analysis of $[Zn(X_6Me_3Imme_3)(EtCN)](ClO_4)_2$. X-ray-quality crystals were grown by slow diffusion of diethyl ether into a propionitrile solution of the complex.

$[C_{176}H_{226}O_{12}N_{14}Zn_2]4ClO_4 \cdot 4H_2O$. MW = 3288.33, colorless crystal (0.2 × 0.2 × 0.3 mm), triclinic *P*1 space group, a =18.2411(8) Å, b = 22.9074(8) Å, c = 24.7429(12) Å, α = 90.442(2)°, β = 77.707(2)°, γ = 78.950(2)°, V = 9901.9(1) Å^3, Z = 2, ρ_{calcd} = 1.55 g cm^{-3}, μ(MoKα) = 25.1 cm^{-1}, 26 346 reflections collected at 175 K (Nonius KappaCCD diffractometer) in the 1−23° θ range, 25 801 unique, 1316 parameters refined on F using 14 101 reflections [maxus][25] to final R indices: R1 [$F > 3\sigma(F)$] = 0.125, wR1 ($w = 1/\sigma2$) = 0.1339. The crystals were poorly shaped, highly sensitive to desolvation, and weakly diffracting, giving low-resolution data and high *R* values. Most of the *t*Bu groups of the calixarene ligand are disordered and could be refined isotropically on two positions using distance restraints. The last Fourier difference gave four peaks of density which have been assumed as

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[21] Recently, a tetrahedral alcohol complex has been described, using the anionic tris(2-mercapto-1-arylimidazolyl)hydroborato ligand: Kimblin, C.; Bridgewater, B. M.; Churchill, D. G.; Parkin, G. *J. Chem. Soc., Chem. Commun.* **1999**, 2301−2302.

[22] Due to the high flexibility of the calix[6]arene macrocycle, the capacity of its aromatic cavity to act as a molecular host has been scarcely used. Most previous studies concerned the complexation with ammonium and tetra(alkyl)-ammonium cations: (a) Chang, S.-K.; Hwang, H.-S.; Son, H.; Youk, J.; Kang, Y. S. *J. Chem. Soc., Chem. Commun.* **1991**, 217−218. (b) Chang, S.-K., Jang, M. J.; Han, S. Y.; Lee, J. H.; Kang, M. H.; No, K. T. *Chem. Lett.* **1992**, 1937−1940. (c) Araki, K.; Shimizu, H.; Shinkai, S. *Chem. Lett.*, **1993**, 205−208. (d) Inoue, Y.; Liu, Y.; Tong, L.-H.; Shen, B.-J.; Jin, D.-S. *J. Am. Chem. Soc.* **1993**, *115*, 10637−10644. (e) Odashima, K.; Yagi, K.; Tohda, K.; Umezawa, Y. *Anal. Chem.* **1993**, *65*, 1074−1083. (f) Han, S.-Y.; Kang, M.-H.; Jung, Y. E.; Chang, S.-K. *J. Chem. Soc., Perkin Trans. 2* **1994**, 835−839. (g) Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032−4034. (h) Ahn, S.; Chang, S.-K.; Kim, T.; Lee, J. W. *Chem. Lett.* **1995**, 297−298. (i) Magrans, J. O.; Ortiz, A. R.; Molins, M. A.; Lebouille, P. H. P.; Sànchez-Quesada, J.; Prados, P.; Pons, M.; Gago, F.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1712−1715.

[23] Recent reviews on calixarenes: (a) Gutsche, C. D. *Calixarenes Revisited, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, UK, 1998. (b) Wieser, C.; Dieleman, C. B.; Matt, D. *Coord. Chem. Rev.* **1997**, *109*, 93−161. (c) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713−1734. (d) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713−745.

[24] Reese, C. B.; Pei-Zhuo, Z. *J. Chem. Soc., Perkin Trans. 1* **1993**, *19*, 2291−2302.

[25] Mackay, S.; Gilmore, C. J.; Edwards, C.; Tremayne, M.; Stewart, N.; Shackland, K. ≪ *maXus: a computer program for the solution and refinement of crystal structures from diffraction data* ≫, University of Glasgow, Scotland, UK; Nonius BV, Delft, The Netherlands; and MacScience Co. Ltd., Yokohama, Japan, 1998.

oxygen atoms of water molecules. Because of the high disorder observed on the molecule, the hydrogen atoms could not be introduced in theoretical positions and were not included in the calculations.

Selected bond lengths [Å] and angles [degrees] for the second molecule (Zn2) of the asymmetric unit: Zn2−N7 2.03(2), Zn2−N9 2.01(2), Zn2−N11 2.02(2), Zn2−N14 2.00(2), N14−C150 1.24(4), N7−Zn2−N9 109.9(4), N7−Zn2−N11 110.8(5), N7−Zn2−N14 99.8(5), N9−Zn2−N11 108.0(5), N9−Zn1−N14 111.4(5), N11−Zn2−N14 116.8(5), Zn2−N14−C150 135.0(14), N14−C150−C151 131.7(24).

Crystal Structure Analysis of [Zn($X_6Me_3Imme_3$)(*n*-$C_7H_{15}NH_2$)](ClO_4)$_2$. X-ray-quality crystals grew out of an acetonitrile solution of the complex.

[$C_{91}H_{125}O_6N_7Zn_1$]2ClO_4·CH_3CN. MW = 1800.47, colorless crystal (0.1 × 0.3 × 0.4 mm), triclinic $P1$ space group, a =14.5244(4) Å, b = 15.8190(5) Å, c = 23.3483(6) Å, $\alpha = 90.340(1)°$, $\beta = 104.163(1)°$, $\gamma = 108.724(1)°$, V = 4905.3(4) Å^3, Z = 2, ρ_{calcd} = 1.22 g cm^{-3}, μ(MoKα) = 3.719 cm^{-1}, 17 093 reflections collected at 175 K (Nonius Kappa CCD diffractometer) in the 1−25.45° θ range, 16 909 unique, 1195 parameters refined on F using 13 728 reflections [maxus][25] to final R indices: R1 [F > 3σ(F)] = 0.054, wR1 ($w = 1/\sigma2$) = 0.092. The crystals were very thin and highly sensitive to desolvation. The two ClO_4 counterions are disordered and could be refined by assuming some oxygen atoms on several occupation sites. Three CH_3CN molecules cocrystallized with the complex. The heptylamine molecule coordinated to the zinc was disordered and could be refined on two different sites with multiplicity 0.7 and 0.3, respectively. No special restraints were applied. Most of the hydrogen atoms were found by Fourier difference, including those of the nitrogen atom of the heptylamine moiety.

Determination of Equilibrium Constants For calculation of equilibrium constants, a 6.3(1) mM solution of [Zn($X_6Me_3Imme_3$)(OH_2)](ClO_4)$_2$ in $CDCl_3$ was prepared. Exogenous substrate (L) was added to the NMR tube in various proportions. ^{1}H NMR spectra were recorded at 300 K and equilibrium constants were determined by integration of the ArH, NMe, OMe, *t*Bu, and/or coordinated ligand and free ligand regions of the spectra. For some ligands, K_{L/H_2O} was directly obtained. In the case of good ligands (heptylamine, ethanol, dimethyl sulfoxide, acetamide, and acetonitrile), 20 equivalents of DMF were added first, $K_{L/DMF}$ was measured, and K_{L/H_2O} was calculated using the value found for K_{DMF/H_2O}. Under these experimental conditions, the measured water content was usually 3−5 molar equivalents.

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