CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200601040

Allosteric Tuning of the Intra-Cavity Binding Properties of a Calix[6]arene through External Binding to a Zn^{II} Center Coordinated to Amino Side Chains

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Abstract: Molecular recognition by calix[6]arene-based receptors bearing three primary alkylamino side chain arms (**1**) is described. Complexation of Zn^{II} ion provides the dinuclear μ-hydroxo complex $\mathbf{2}_G^{OH}$, XRD characterization of which, together with solution studies, provided evidence of its hosting of neutral polar organic guests G. Treatment of this complex with a carboxylic acid or a sulfonamide (XH) results in the formation of mononuclear species $\mathbf{3}_G^X$, one of which (X = Cl) has been characterized by XRD. A dicationic complex $\mathbf{3}_G^{RNH_2}$ is obtained upon treatment of $\mathbf{2}_G^{OH}$ with a mixture of an alkylamine and a strong acid. Each of these Zn^{II} complexes features a tetrahedral metal ion bound to the three amino arms of ligand **1** and to an exogenous ligand (either HO^-, X^-, or RNH_2) sitting outside of the cavity. As a result, the metal ion structures the calixarene core, constraining it in a cone conformation suitable for guest hosting. The receptor properties of these compounds have been explored in detail and are compared with those of the trisammonium receptor $\mathbf{1}_G^{3H^+}$, based on the same calixarene core, as well as those of the trisimidazole-based dicationic Zn funnel complexes. This study reveals very different host properties, in spite of the common hydrophobic, π-basic, and hydrogen-bonding acceptor properties of the calixarene cores. A harder external ligand produces a less polarized receptor that is consequently particularly sensitive to the hydrogen-bonding ability of its guest. The less electron-rich the apical ligand, and a fortiori the trisammonium host, the more sensitive the receptor to the dipole moment of the guest. All this stands in contrast with the funnel Zn complexes, in which the coordination link plays a dominant role. It is also shown that the asymmetry of an *exo*-coordinated enantiopure amino ligand is sensed by the guest. This supramolecular system nicely illustrates how the receptor properties of a hydrophobic cavity can be allosterically tuned by the environment.

Keywords: allosterism · calixarenes · host–guest systems · supramolecular chemistry · zinc

Introduction

Molecular recognition is a fundamental phenomenon in biology, and tuning of the affinity of a receptor for a ligand by the environment is key for the regulation of biological processes.[1] The effector can be, for example, a pH jump, the binding of a metal ion or a molecule, the phosphorylation of a proteic residue. In enzymes, for example, the binding of a substrate may be triggered by a change in the protonation state of a residue or in a metal oxidation state, or by the presence of a co-factor or co-substrate that affects the receptor properties at the active site. All these phenomena involve subtle modifications of the microenvironment defining the binding pocket.

This has inspired many chemists to design artificial receptors.[2,3] Being involved in the design of biomimetic receptors, we have developed the first supramolecular system that mimics metalloenzyme active sites by the selective binding of a neutral molecule to a metal center incorporated inside a calix[6]arene cone. The most representative system, de-

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picted in Figure 1, is based on a calixarene to which three imidazole arms (mimicking the histidine residues of the protein) have been covalently connected to the narrow rim through short methylene linkers (X_6Im_3). This allows the coordination of a metal ion such as Zn^{2+} in a tetrahedral geometry with an introverted labile site. With the hydrophobic neutral environment augmenting the Lewis acid character of the metal ion, the so-called funnel complexes[4] $(X_6Im_3Zn)^{2+}_G$ revealed themselves to be extremely sensitive to a large variety of exogenous ligands (G) presenting different donors (amines, alcohols, amides, carboxylic acids, nitriles, and even aldehydes) and shapes (the calixarene cavity can accommodate a long alkyl chain such as that depicted in Figure 1 as well as a phenyl group). Since the labile site is oriented toward the inside of the calix[6]arene structure, the hydrophobic pocket acts as a highly selective molecular funnel for neutral molecules. In many respects, this system resembles the Michaelis complexes of zinc enzymes.

More recently we have been studying non-metallic calixarene-based receptors that have highlighted the efficiency of combining a polyammonium site and a hydrophobic cavity to construct a receptor for neutral molecules that possess high dipole moments. Indeed, a calix[6]arene bearing three primary amino arms grafted onto the narrow rim (namely the calix[6]trisamine **1**) can be efficiently structured by strong acids such as trifluoroacetic acid (TFA) into a polarized receptor $\mathbf{1}^{3H^+}_G$ (Figure 1). Hence, upon protonation in an organic solvent of medium polarity, the three ammonium arms of calix[6]trisamine **1** become sealed together by the counter-anions. In chloroform, the resulting host $\mathbf{1}^{3H^+}_G$, featuring a hydrophobic π-basic cavity terminating in a tricationic protic site, displays an impressive affinity for polar neutral guests (G) such as ureas, amides, alcohols, or nitriles.[5,6,7] This efficiency is the result of the self-assembly of the ion-paired cap, which closes the cavity, freezes the calixarene core into a cone conformation, and stabilizes the neu-

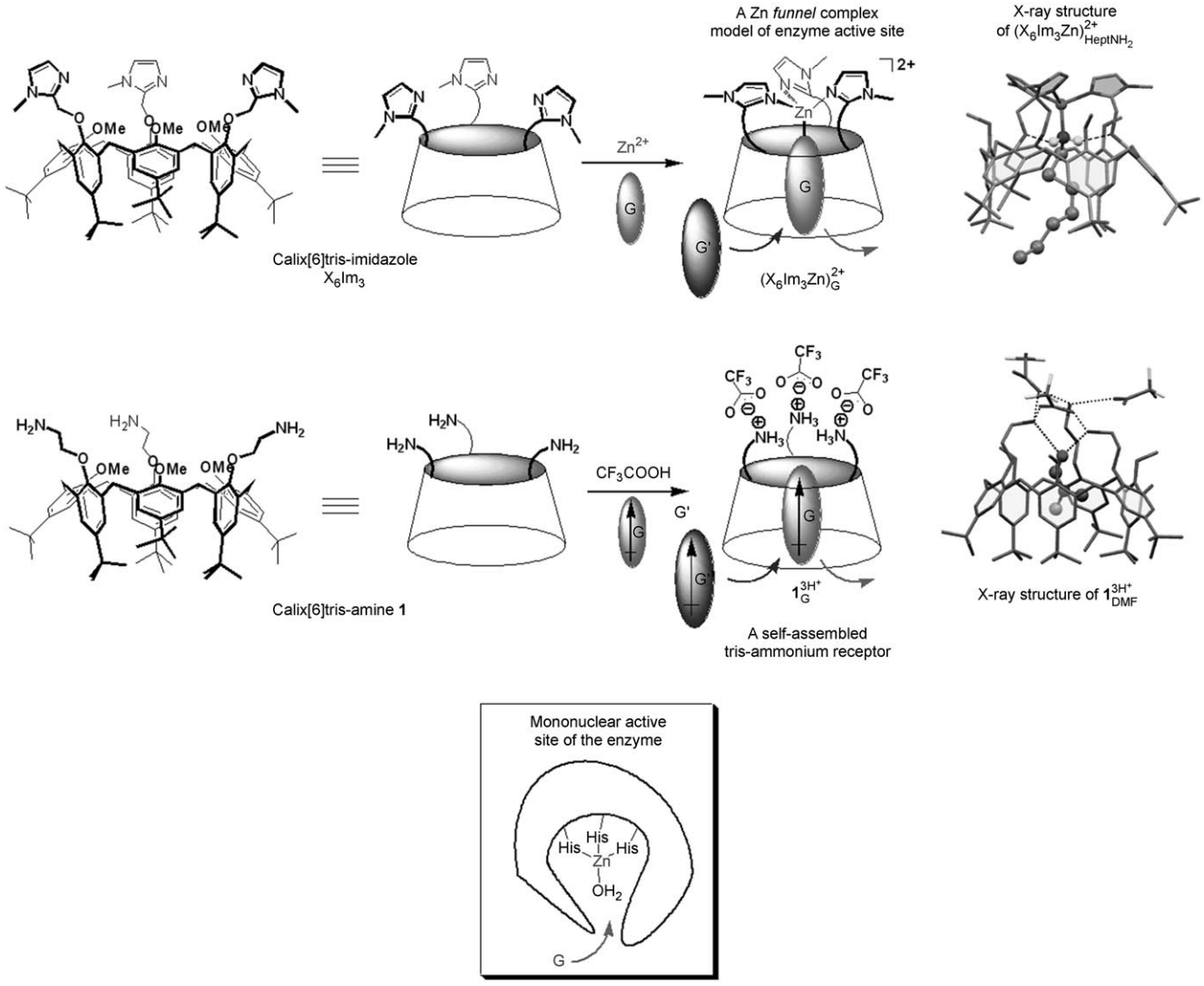


Figure 1. Molecular receptors based on calix[6]arenes bearing nitrogen donors at the narrow rim. Top: Zn funnel complex. Bottom: Ion-paired self-assembled trisammonium receptor.

tral guests through hydrogen bonding and charge–dipole interactions.

In this paper we describe the coordination of Zn^{II} to calix[6]trisamine **1**, which still produces tetrahedral complexes, but with different geometries from all previously described funnel complexes. Indeed, in this less sterically hindered system, the labile site is oriented toward the outside of the cavity, so the resulting calixarene cone acts as a polarized pocket in which the host properties are not dictated by the coordination link with a guest but can be efficiently tuned through external binding of either anionic or neutral ligands to the capping Zn^{II} ion.

Results and Discussion

Calix[6]trisamine **1** was prepared from the C_{3v} tris-*O*-methylated *t*Bu-calix[6]arene in an efficient two-step sequence by peralkylation with bromoacetamide in the presence of NaH and subsequent reduction of the triamide with BH_3/THF (77% overall yield).[8] Its properties as a N_3 donor for the coordination of a Zn^{II} ion were first investigated.

Synthesis and XRD characterization of a dinuclear μ-hydroxo complex: When ligand **1** was treated with one equivalent of $[Zn(H_2O)_6](ClO_4)_2$ and one equivalent of KOH in a CH_2Cl_2/MeOH mixture, the crystalline Zn^{2+} complex $\mathbf{2}^{OH}_{MeOH}$ was isolated in 60% yield (Scheme 1). Its elemental analysis was consistent with a 2:2:3 ligand/Zn/perchlorate stoichiometry, thereby suggesting the formation of a dinuclear species.

Single crystals of complex $\mathbf{2}^{OH}_{MeOH}$ were grown from a cold (4°C) $CHCl_3$ solution, and its XRD structure is displayed in Figure 2. Complex $\mathbf{2}^{OH}_{MeOH}$ consists of a dinuclear tricationic species in which two Zn^{II} ions are bridged by a single hydroxo ligand. The Zn···Zn distance [3.54 Å] is similar to those in other monobridged dinuclear Zn complexes and the zinc ions are in a tetrahedral geometry with classical Zn–$N_{av.}$ (2.03 Å) and Zn–O (1.911 Å) distances for hydroxo complexes.[9] The hydroxo ligand is weakly hydrogen bonded to one perchlorate ion [d(O,O) = 3.05 Å, not shown].

In comparison with bishydroxo complexes,[10] such a monobridged structure is relatively rare; its stabilization may be attributed to the constraining structure of the calixarene, which disfavors the formation of a double bridge.[11] The calixarene units contain a methanol molecule that is *not* coordinated to the metal ion [*d*(O8,Zn1) = 3.361 Å], but is hydrogen-bonded to one oxygen and one nitrogen atom of the calixarene structure [*d*(O8,O1) = 2.91 Å, *d*(O8,N2) = 3.02 Å]. Finally, the three amino arms encircling the Zn ion do not form a helix but adopt an asymmetric conformation with two coordinated arms presenting mutually opposed relative helical orientations (Figure 2, top view). Interestingly, this stereochemistry has also been observed in the X-ray structures of metal complexes obtained with a tren-capped calix[6]arene ligand.[12]

Synthesis and XRD characterization of a mononuclear complex: When Zn^{II} perchlorate was allowed to react with ligand **1** in a CH_2Cl_2/MeOH mixture in the absence of base, a complex with a different stoichiometry precipitated out of the solution ($\mathbf{3}^{ClO_4}_{MeOH}$, 60% yield; Scheme 1). Its elemental analysis indicated a 1:1:2 ligand/Zn/perchlorate ratio, thus supporting a mononuclear structure, while its solid-state IR spectrum displayed two distinct absorptions at 636 and 625 cm^{-1} for the perchlorate anions (instead of one at 624 cm^{-1} for $\mathbf{2}^{OH}_{MeOH}$), which suggested the coordination of one of them to the metal center.

All our attempts to grow single crystals of complex $\mathbf{3}^{ClO_4}_{MeOH}$ were unsuccessful, but addition of triethylammonium hydrochloride (dissolved in EtOH) to substitute the labile perchlorato ligand allowed the growth (by ether diffusion) of crystals suitable for XRD analysis out of a cold $CHCl_3$ solution of complex $\mathbf{3}^{ClO_4}_{MeOH}$. The molecular structure of complex $\mathbf{3}^{Cl}_{G}$ (with G = MeOH or EtOH) is displayed in Figure 3 and shows a mononuclear and monocationic Zn^{II} center in a tet-

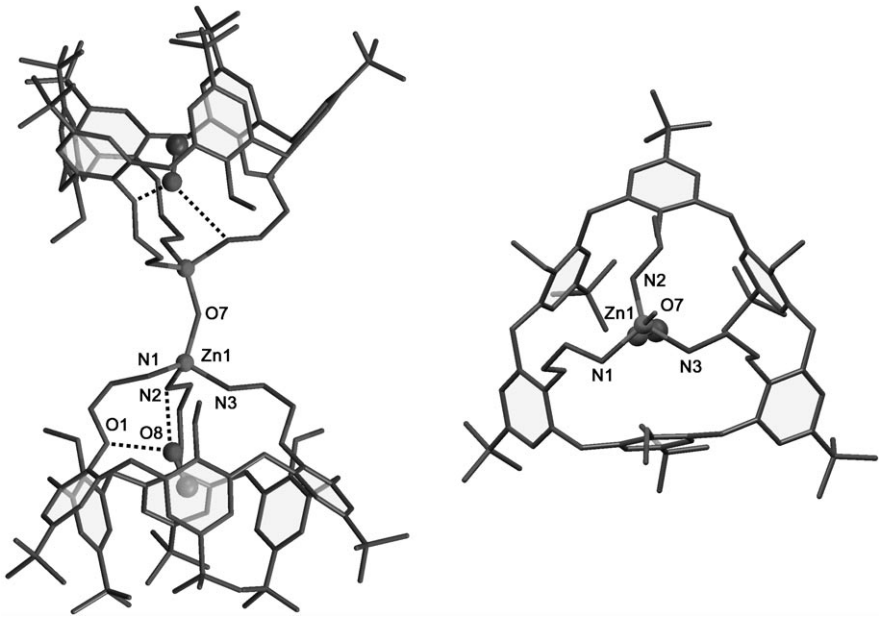
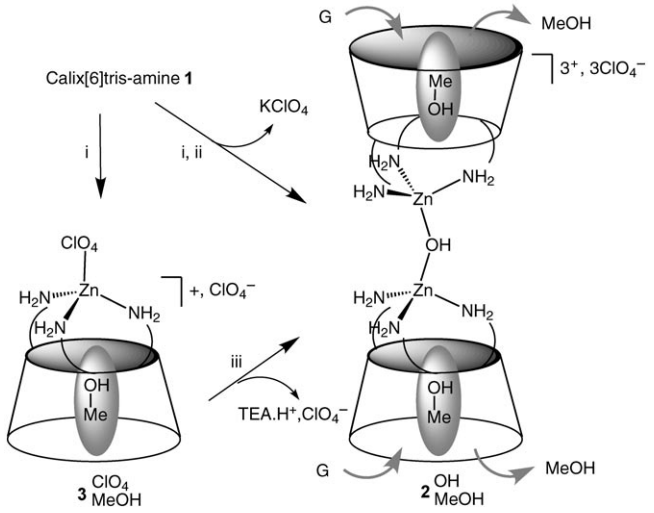


Figure 2. XRD structure of complex $\mathbf{2}^{OH}_{MeOH}$. The dashed lines depict H bonds. Hydrogen atoms, counter-ions, and solvent of crystallization have been omitted for clarity. Left: Side view of the dinuclear complex. Right: Top view of one Zn unit. Selected bond lengths [Å] and angles [°]: Zn1–N3 2.029(6), Zn1–N2 2.027(5), Zn1–N1 2.039(6), Zn1–O7 1.911(3), O7-Zn1-N1 121.8(3), O7-Zn1-N2 113.2(2), O7-Zn1-N3 106.8(6), N2-Zn1-N3 108.6(2), N2-Zn1-N1 104.6(2), N3-Zn1-N1 100.6(3), Zn1-O7-Zn2 135.8(3).



Scheme 1. Synthesis of Zn complexes $\mathbf{3}^{ClO_4}_{MeOH}$ and $\mathbf{2}^{OH}_{MeOH}$ and guest exchange resulting in complexes $\mathbf{2}^{OH}_{G}$ (G = alcohol, amide, nitrile, sulfoxide, ketone). i) $Zn[(H_2O)_6(ClO_4)_2$, $MeOH/CH_2Cl_2$. ii) KOH. iii) TEA, H_2O, $CHCl_3$.

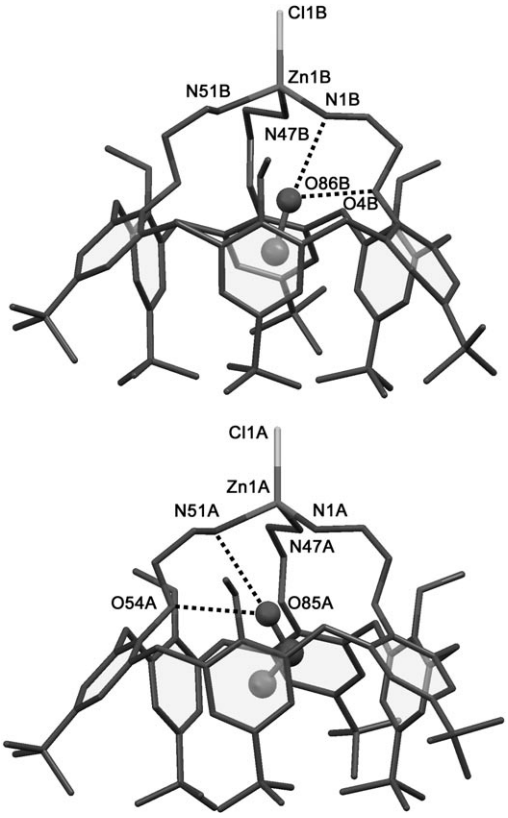


Figure 3. XRD structures of complexes $\mathbf{3}^{Cl}_{MeOH}$ (top) and $\mathbf{3}^{Cl}_{EtOH}$ (bottom). The H bonds are displayed in dark dashed lines. Hydrogen atoms and counter-ions have been omitted for clarity.[14] Selected bond lengths [Å] and angles [°]: Zn1A–N47A 2.010(4), Zn1A–N1A 2.030(4), Zn1A–N51A 2.052(4), Zn1A–Cl1A 2.160(2), Zn1B–N47B 2.024(4), Zn1B–N1B 2.018(6), Zn1B–N51B 2.081(5), Zn1B–Cl1B 2.164(2), N47A-Zn1A-N1A 106.9(2), N47A-Zn1A-N51A 101.6(2), N1A-Zn1A-N51A 107.2(2), N47A-Zn1A-Cl1A 112.3(2), N1A-Zn1A-Cl1A 113.9(2), N51A-Zn1A-Cl1A 114.3(1), N47B-Zn1B-N1B 107.2(2), N47B-Zn1B-N51B 100.2(2), N1B-Zn1B-N51B 106.2(2), N47B-Zn1B-Cl1B 115.6(2), N1B-Zn1B-Cl1B 115.7(2), N51B-Zn1B-Cl1B 110.6(2).

rahedral geometry, coordinated to the three amino arms and a chloride anion with classical Zn–$N_{av.}$ (2.04 and 2.03 Å for $\mathbf{3}^{Cl}_{MeOH}$ and $\mathbf{3}^{Cl}_{EtOH}$, respectively) and Zn–Cl (2.16 Å for both complexes) distances for chloro complexes.[13] Similarly to the case of $\mathbf{2}^{OH}_{MeOH}$, the calixarene cavity is occupied by an alcohol molecule (either MeOH or EtOH[14]) that is not coordinated to the metal center. The alcohol guest is stabilized through multiple hydrogen bonds with its host [$\mathbf{3}^{Cl}_{MeOH}$: d(O86B,O4B) = 2.93 Å, d(O86B,N1B) = 2.95 Å; $\mathbf{3}^{Cl}_{EtOH}$: d(O85 A,O54 A) = 2.89 Å, d(O85A,N51A) = 2.96 Å] and additional CH–π interactions [d(C···C=C) = 3.63 Å] in the case of G = EtOH. Unlike those in $\mathbf{2}^{OH}_{MeOH}$, the amino arms in the two complexes $\mathbf{3}^{Cl}_{MeOH}$ and $\mathbf{3}^{Cl}_{EtOH}$ adopt helical conformations around their metal centers, conferring C_3 symmetry on the hosts.

Solution study of $\mathbf{2}^{OH}_{MeOH}$ and $\mathbf{3}^{ClO_4}_{MeOH}$: Complex $\mathbf{2}^{OH}_{MeOH}$ did not appear to be base-sensitive: indeed, addition of nBu$_4$NOH (up to 4 equiv, 1 M in methanol) or triethylamine (TEA, 22 equiv) did not affect its NMR signature in $CDCl_3$. The conformational and host–guest properties of complex $\mathbf{2}^{OH}_{MeOH}$ in solution were investigated by NMR spectroscopy in $CDCl_3$, and its ^{1}H NMR spectrum at 293 K, displayed in Figure 4a, shows D_{3h} symmetry with a normal methoxy resonance at 3.93 ppm for the anisole units pointing away from the cavity. The two well separated tBu and H_{Ar} resonances indicate that the calixarene is in a flattened cone conformation, with its aromatic units alternatively in *in* and *out* positions relative to the cavity. The observed CH_2N downfield shift (δ = 3.31 ppm) supports the coordination of all three amino arms to the Zn ion. At 243 K, extra resonances in the high-field region pointed to the presence of a MeOH molecule in the calixarene cavity [a doublet at 0.39 ppm (CH_3OH) and a quadruplet at 0.84 ppm (CH_3OH)].[15] This MeOH guest was easily exchanged for EtOH, as was shown by the disappearance of the $MeOH_{in}$ resonances at 243 K and the concomitant appearance of two triplets at −1.73 and 1.01 ppm ($CH_3CH_2OH_{in}$ and $CH_3CH_2OH_{in}$, respectively) observable even at RT (see complex $\mathbf{2}^{OH}_{EtOH}$, Figure 4b and c).[16]

Whereas the substitution of the MeOH guest for a variety of polar molecules (amides, nitriles, DMSO, acetone, see below) could be observed, primary amines such as $PrNH_2$ displayed very low affinities for the calixarene cavity.[17] This contrasts with the previously reported Zn funnel complexes $(X_6Im_3Zn)^{2+}_{G}$ based on calix[6]trisimidazole (Figure 1), in which, under the same conditions, primary amines were stoichiometrically included because of the strong coordination link to the Lewis acidic Zn^{II} center. Additionally, the complexation-induced upfield shifts (CISs) of the RCH_2OH protons in $\mathbf{2}^{OH}_{G}$ (G = RCH_2OH) were much higher (ca. 1 ppm) than those measured in $(X_6Im_3Zn)^{2+}_{G}$ [see Table 1, Entries 6 and 7 for $\mathbf{2}^{OH}_{G}$ vs. $(X_6Im_3Zn)^{2+}_{G}$]. These two observations support the contention that in solution, as in the solid state, the guests are not coordinated to the Zn ion in complex $\mathbf{2}^{OH}_{G}$.

When $AcNH_2$ (4 equiv) and EtOH (3 equiv) were added to $CDCl_3$ solutions of $\mathbf{2}^{OH}_{MeOH}$, two sets of signals were ob-

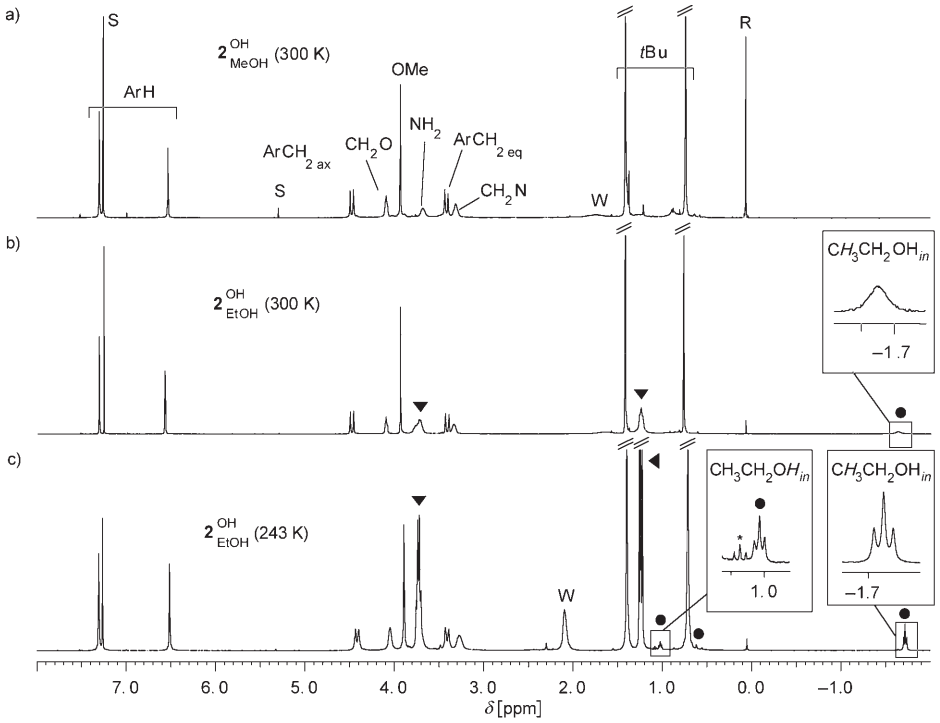


Figure 4. a) ^{1}H NMR spectrum (400 MHz) of complex $\mathbf{2}^{OH}_{MeOH}$ in $CDCl_3$ at 300 K. b) Spectrum obtained at 300 K after addition of EtOH (14 equiv). c) Spectrum obtained at 243 K: ▼ = $EtOH_{free}$, ● = $EtOH_{in}$, * = satellite peak of $CH_3CH_2OH_{free}$. Solvent, water, and reference have been labeled "S", "W", and "R", respectively.

served for each of these guests (two CH_3 signals for $AcNH_{2in}$ at −0.98 and −1.03 ppm and for $EtOH_{in}$ at −1.70 and −1.73 ppm). Further addition of EtOH (12 equiv) resulted mostly in an increase in the $EtOH_{in}$ signal at −1.73 ppm and a decrease in the $AcNH_{2in}$ signal at −0.98 ppm, the two other signals being less affected. This observation is consistent with the dimeric nature of the complex, which can host two different guests, giving rise to mixtures of three different species: $\mathbf{2}^{OH}_{EtOH,EtOH}$, $\mathbf{2}^{OH}_{EtOH,AcNH_2}$, and $\mathbf{2}^{OH}_{AcNH_2,AcNH_2}$. The solution structure of $\mathbf{2}^{OH}_{G}$ was further supported by T1 measurements,[18] which indicated a high molecular weight compound similar to a recently described self-assembled biscalix[6]arene adduct.[6]

All these NMR data indicate that the μ-hydroxo dinuclear structure of complex $\mathbf{2}^{OH}_{G}$ is maintained in solution, while the calixarene cavities, constrained by the coordination links at the narrow rim, play the role of good hosts for polar neutral guests in spite of the lack of a coordination link.

Surprisingly, complex $\mathbf{3}^{ClO_4}_{MeOH}$ presented a ^{1}H NMR spectrum (in $CDCl_3$) identical to that of complex $\mathbf{2}^{OH}_{MeOH}$, suggesting the spontaneous release of one equivalent of $HClO_4$ upon dissolution. Indeed, TEA was stoichiometrically protonated by $\mathbf{3}^{ClO_4}_{MeOH}$, and not by $\mathbf{2}^{OH}_{MeOH}$. Consistently with this, when a $CHCl_3$ solution containing complex $\mathbf{3}^{ClO_4}_{MeOH}$ was washed with water and TEA, complex $\mathbf{2}^{OH}_{MeOH}$ was isolated (Scheme 1).

Host–guest properties of the dinuclear μ-hydroxo complex $\mathbf{2}^{OH}_{G}$: The ability of complex $\mathbf{2}^{OH}_{G}$ (4 mM in chloroform) to host various neutral guests (G, up to 20 equiv) was analyzed by ^{1}H NMR spectroscopy at low temperature. Table 1 reports all the guests that have been detected in the calixarene cavity under these experimental conditions.

These NMR data highlight the fact that complex $\mathbf{2}^{OH}_{G}$ can host a wide variety of compounds: particularly amides and alcohols, but also a sulfoxide and a ketone. Moreover, complex $\mathbf{2}^{OH}_{G}$ exhibited shape selectivities, since no coordination of *i*BuOH, propane-1,2-diol, or $MeSO_2NH_2$ was detected under conditions in which *n*BuOH had been included. It also displays a strong preference for dipolar guests (a very low affinity for amines relative to alcohols, no inclusion of ethers under the same conditions). The CIS values for the guest protons are reported in Table 1 and are compared to those previously obtained with $\mathbf{1}^{3H^+}_{G}$ and $(X_6Im_3Zn)^{2+}_{G}$.[4b,5] In many cases, the highest CIS values (ca. −3 ppm) measured for $\mathbf{2}^{OH}_{G}$ corresponds to the β-position relative to the heteroatom that must point toward the Zn^{II} ion. This is quite similar to the situation with the funnel Zn complex $(X_6Im_3Zn)^{2+}_{G}$ but different from that with receptor $\mathbf{1}^{3H^+}_{G}$, in which the γ position clearly corresponds to the highest CIS values (see, in particular, entry 7 for *n*PrOH). This indicates that the shape of receptor $\mathbf{2}^{OH}_{G}$ resembles that of $(X_6Im_3Zn)^{2+}_{G}$ and that these two hosts should position their guests more centrally in their cavities than $\mathbf{1}^{3H^+}_{G}$, due to their more tightly linked amino arms, which push the guest back towards the entrance of the cavity. Indeed, a comparison of the XRD host–guest structures, displayed in Figures 1–3, highlights a "higher" position of the DMF guest in $\mathbf{1}^{3H^+}_{DMF}$.

***exo* Coordination of anionic or neutral ligands—NMR characterization of the corresponding mononuclear Zn complexes $\mathbf{3}^{PhCOO}_{G}$, $\mathbf{3}^{AcO}_{G}$, $\mathbf{3}^{MeSO_2NH}_{G}$, and $\mathbf{3}^{RNH_2}_{G}$**: Treatment of complex $\mathbf{2}^{OH}_{EtOH}$ with a protic donor such as a carboxylic acid or a sulfonamide (XH) was studied by ^{1}H NMR spectroscopy at low temperatures in $CDCl_3$ containing a few molar equivalent of EtOH. In each case a novel species was produced, as attested by the appearance of a different resonance in the high-field region for the ethanol guest, a modification of the peaks corresponding to the coordinating amino arms and

Table 1. NMR complexation-induced upfield shifts (CISs) in $CDCl_3$ (223 K or 243 K) observed on *endo*-complexation of neutral organic guests (G) by complex $\mathbf{2}_G^{OH}$ and comparison with the dicationic calix[6]trisimidazole Zn *funnel* complex $(X_6Im_3Zn)_G^{2+}$[4b] and trisammonium $\mathbf{1}_G^{3H^+}$.[5]

Entry	G	Host–guest complex	CISs (ppm)[a]			
			α	β	γ	δ
1	$AcNH_2$	$\mathbf{2}_G^{OH}$	–	−3.02	–	–
		$(X_6Im_3Zn)_G^{2+}$	–	−2.82	–	–
		$\mathbf{1}_G^{3H^+}$	–	−2.79	–	–
2	$EtCONH_2$	$\mathbf{2}_G^{OH}$	–	n.d.[b]	−2.56	–
		$\mathbf{1}_G^{3H^+}$	–	−2.04	−2.98	–
3	pyrrolidin-2-one	$\mathbf{2}_G^{OH}$	–	−2.74	−3.06[c]	–
4	DMF	$\mathbf{2}_G^{OH}$	−2.25	–	−2.92[d]	–
		$(X_6Im_3Zn)_G^{2+}$	−1.41	–	−2.82[d]	–
		$\mathbf{1}_G^{3H^+}$	−1.25	–	−3.28[d]	–
5	MeOH	$\mathbf{2}_G^{OH}$	−3.03	–	–	–
6	EtOH	$\mathbf{2}_G^{OH}$	−3.02[e]	−2.96	–	–
		$(X_6Im_3Zn)_G^{2+}$	−2.00	−2.78	–	–
		$\mathbf{1}_G^{3H^+}$	n.d.[b]	−3.03	–	–
7	*n*PrOH	$\mathbf{2}_G^{OH}$	−2.54[e]	−2.95	−2.71	–
		$(X_6Im_3Zn)_G^{2+}$	−1.60	−2.90	−2.53	–
		$\mathbf{1}_G^{3H^+}$	n.d.[b]	−3.05	−3.12	–
8	*n*BuOH	$\mathbf{2}_G^{OH}$	−2.43[e]	−2.75	−2.91	−1.94
9	DMSO	$\mathbf{2}_G^{OH}$	–	−3.22	–	–
		$(X_6Im_3Zn)_G^{2+}$	–	−2.75	–	–
		$\mathbf{1}_G^{3H^+}$	–	−3.00	–	–
10	MeCN	$\mathbf{2}_G^{OH}$	–	−3.23	–	–
		$(X_6Im_3Zn)_G^{2+}$	–	−2.76	–	–
		$\mathbf{1}_G^{3H^+}$	–	−3.36	–	–
11	MeCOMe	$\mathbf{2}_G^{OH}$	–	−2.99	–	–
12	*n*$PrNH_2$	$\mathbf{2}_G^{OH}$	−2.13	−2.78	−2.66	–

[a] Defined as $\Delta\delta = \delta(G_{in}) - \delta(G_{free})$. α, β, γ, δ refer to the relative positions of the protons with respect to the oxygen atom or to the nitrogen atom in the case of MeCN and $PrNH_2$. [b] Not determined due to overlapping of the host and guest signals. [c] Values determined for $CH_2CH_2CH_2$. The CH_2N resonance was not determined, due to overlapping of the host and guest signals. [d] Average value of the two nonequivalent methyl groups. [e] Determined through either COSY or NOESY experiments.

the aromatic protons (Figure 5, Scheme 2). T1 measurements[18] indicated that these new species have much lower molecular weights than $\mathbf{2}_{EtOH}^{OH}$, in agreement with the formation of mononuclear complexes ($\mathbf{3}_{EtOH}^{X}$).

Treatment of the complex $\mathbf{2}_{EtOH}^{OH}$ with $PhCO_2H$ (2 equiv) resulted in the quantitative formation of the new complex $\mathbf{3}_{EtOH}^{PhCOO}$. A single resonance in the high-field region (triplet at −1.67 ppm, Figure 5b) indicated that one equivalent of EtOH was still present in the cavity, while three new resonances in the aromatic area (6.40, 6.46, and 6.50 ppm) for the aromatic protons of the anisole units indicated a slight loss of symmetry. Three new signals in the low-field region (at 8.17, 7.82, and 7.52 ppm, next to those corresponding to free benzoate) attested to the external coordination of one equivalent of benzoate to the metal center. Hence, treatment of the hy-

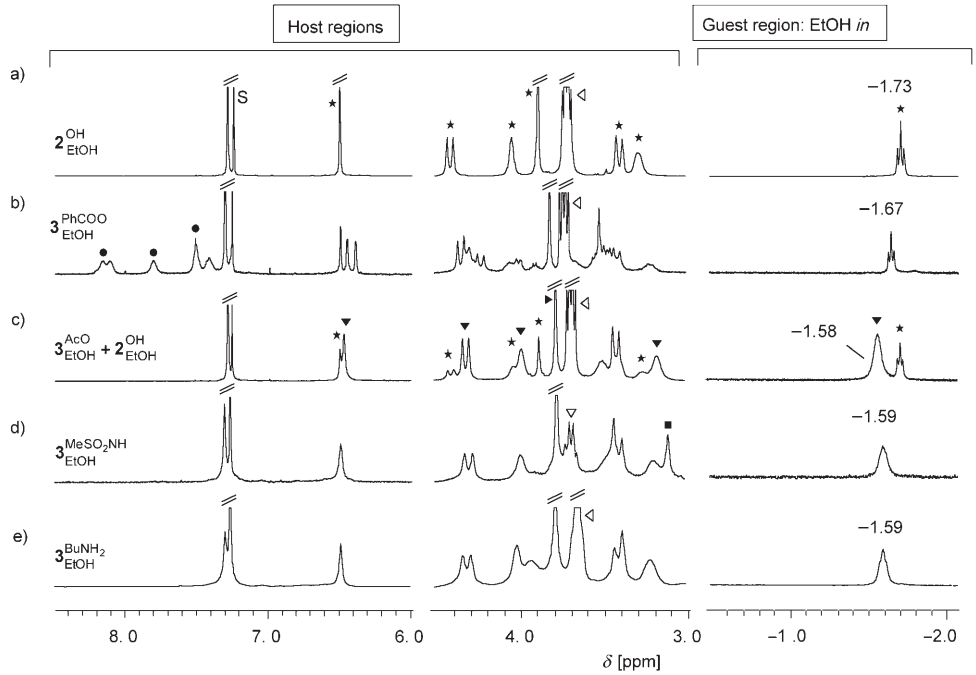
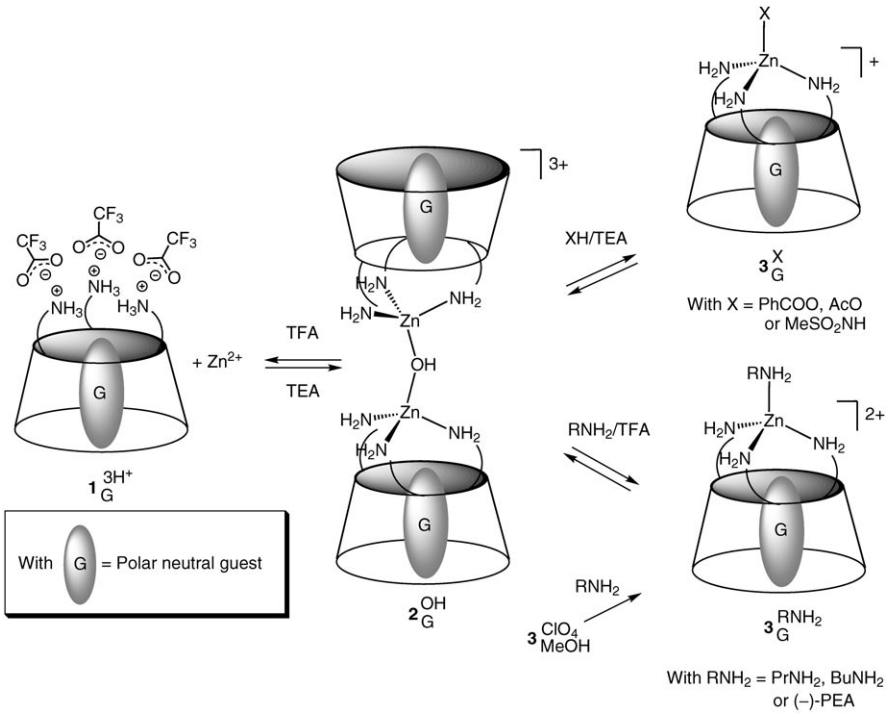


Figure 5. ^1H NMR spectra (400 MHz) in $CDCl_3$ at 243 K (left: aromatic region of the host; center: CH_2 region of the host; right: guest region). a) Complex $\mathbf{2}_{EtOH}^{OH}$ in a $CDCl_3$ solution containing ca. 9 equiv of EtOH. b) +$PhCO_2H$ (2 equiv). c) +AcOH (10 equiv) and TEA (14 equiv). d) +$MeSO_2NH_2$ (2 equiv) and TEA (8 equiv). e) +$BuNH_2$ (13 equiv) and TFA (1 equiv). ∗ = $\mathbf{2}_{EtOH}^{OH}$; ● = $PhCOO^-$ coordinated, ▼ = $\mathbf{3}_{EtOH}^{AcO}$, ▽ = $EtOH_{free}$, ■ = $MeSO_2NH_{2\,free}$. Solvent has been labeled "S".



Scheme 2. Interconversion between different host–guest species in chloroform.

droxo complex with benzoic acid gave rise to a novel complex, $\mathbf{3}_{EtOH}^{PhCOO}$, which is not C_{3v}-symmetrical, probably because of steric crowding at the metal core (Scheme 2).

With the less acidic acetic acid or methanesulfonamide, the substitution of the hydroxide ligand required the addition of these acids together with TEA, so treatment of $\mathbf{2}_{EtOH}^{OH}$ with AcOH/TEA (20 and 100 equiv)[19] or with $MeSO_2NH_2$/TEA (2 and 8 equiv) produced the corresponding mononuclear complexes $\mathbf{3}_{EtOH}^{AcO}$ and $\mathbf{3}_{EtOH}^{MeSO_2NH}$, respectively. In each case the guest EtOH resonance was slightly shifted relative to $\mathbf{2}_{EtOH}^{OH}$ (Figure 5c,d). The calixarene core is characterized by two single resonances for its H_{Ar} protons, which indicates that it remains C_{3v} symmetrical, thanks to the small size of the external binding anion. Interestingly, when the exchange was not complete, species $\mathbf{3}_{EtOH}^{X}$ and $\mathbf{2}_{EtOH}^{OH}$ were distinctly observed at 243 K, which means that external exchange of the binding anion was slower than the NMR timescale, as illustrated in Figure 5c.

It was also possible to stabilize a mononuclear dicationic state for the Zn^{II} complex with the aid of the coordination of a strong neutral donor such as a primary amine in the apical position (Scheme 2). Indeed, when RNH_2 (with R = *n*Pr or *n*Bu, >13 equiv) and EtOH were added to complex $\mathbf{3}_{MeOH}^{ClO_4}$ in $CDCl_3$, the novel compound $\mathbf{3}_{EtOH}^{RNH_2}$ was produced. The same compound was obtained on treatment of $\mathbf{2}_{EtOH}^{OH}$ with the amine after the addition of 1 equiv of TFA (see Figure 5e for R = *n*Bu). The high-field shifted triplet of the ethanol guest was observed at −1.58 or −1.59 ppm in $\mathbf{3}_{EtOH}^{PrNH_2}$ and $\mathbf{3}_{EtOH}^{BuNH_2}$, respectively. Very interestingly, when a chiral primary amine [(*S*)-(−)-1-phenylethylamine (PEA)] was coordinated to the Zn^{II} ion, a splitting of the ArCH_2 and CH_2N resonances of the calixarene core was observed as well as the resonance of the guest (δ = −0.52 and −0.54 ppm for G = DMSO, instead of one at −0.57 ppm for complex $\mathbf{3}_{DMSO}^{BuNH_2}$; see Figure 6 for $\mathbf{3}_{DMSO}^{PEA}$). This indicates that the calixarene methylenic protons and the guest methyl groups had become diastereotopic, so the external coordination of a chiral ligand to the metal center transforms the calixarene into a chiral pocket that is sensed by the guest.

Tuning and comparing the host properties of the different molecular receptors: A comparative ^{1}H NMR study of the host properties of receptors $\mathbf{2}_{G}^{OH}$, $\mathbf{3}_{G}^{AcO}$, $\mathbf{3}_{G}^{MeSO_2NH}$, and $\mathbf{3}_{G}^{BuNH_2}$ was conducted at 223 K in $CDCl_3$. For each experiment, a solution

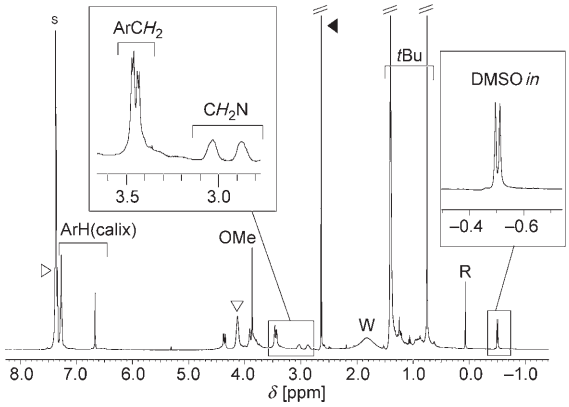


Figure 6. ^{1}H NMR (500 MHz) spectrum of complex $\mathbf{3}_{DMSO}^{PEA}$ recorded at 273 K in $CDCl_3$. ▼ = $DMSO_{free}$, ▽ = (−)-PEA. Solvent, water, and reference have been labeled "S", "W", and "R", respectively.

containing EtOH and another neutral substrate G was added to complex $\mathbf{2}_{MeOH}^{OH}$ to yield the corresponding basic species $\mathbf{2}_{EtOH}^{OH}$ and $\mathbf{2}_{G}^{OH}$. Subsequent addition of either XH/TEA (with XH = AcOH or $MeSO_2NH_2$) or $BuNH_2$/TFA then provided a mixture of complexes $\mathbf{3}_{EtOH}^{X}$ and $\mathbf{3}_{G}^{X}$ or $\mathbf{3}_{EtOH}^{BuNH_2}$ and $\mathbf{3}_{G}^{BuNH_2}$, respectively. A ^{1}H NMR spectrum was recorded after each step, and integration of the free and bound substrates (EtOH and G) gave the ratio of the corresponding complexes (see the Experimental Section). The relative affinities of the receptors for EtOH, DMF, DMSO, $AcNH_2$, and MeCN are reported in Table 2 and compared with those previously reported for the trisammonium[5] $\mathbf{1}_{G}^{3H^+}$ and the funnel Zn complex $(X_6Im_3Zn)_G^{2+}$.[4b] It is noteworthy that the

Table 2. Relative affinities of complexes $\mathbf{2}_G^{OH}$, $\mathbf{3}_G^{AcO}$, $\mathbf{3}_G^{MeSO_2NH}$, and $\mathbf{3}_G^{BuNH_2}$ for G = EtOH, DMF, DMSO, $AcNH_2$, and MeCN measured by ^1H NMR spectroscopy at 223 K in $CDCl_3$ and comparison with the dicationic Zn *funnel* complex[4b] $(X_6Im_3Zn)_G^{2+}$ and trisammonium[5] $\mathbf{1}_G^{3H^+}$.

	Relative affinities for G[a],[b], referred to EtOH				
G	EtOH	MeCN	DMF	DMSO	$AcNH_2$
μ [D]	(1.67)	(3.92)	(3.82)	(3.96)	(3.7)
complex $\mathbf{2}_G^{OH}$	1	< 0.004[c]	0.003	0.16	2.5[d]
complex $\mathbf{3}_G^{MeSO_2NH}$	1	–	0.007	0.73	20
complex $\mathbf{3}_G^{AcO}$	1	< 0.009[c]	–	0.69	16
complex $\mathbf{3}_G^{BuNH_2}$	1	–	0.02	2.9	42
trisammonium $\mathbf{1}_G^{3H^+}$	1	0.05	1.3	3.5	35
complex $(X_6Im_3Zn)_G^{2+}$	1	0.08	0.21	1.1	1.4

[a] Errors estimated $\pm 10\%$. [b] Defined as $[G_{in}]/[EtOH_{in}] \times [EtOH_{free}]/[G_{free}]$.[20] [c] $MeCN_{in}$ could not be detected by ^1H NMR. [d] In this particular case, $[AcNH_{2in}]$ corresponds to the included $AcNH_2$ of $\mathbf{2}_{EtOH,AcNH_2}^{OH}$ and $\mathbf{2}_{AcNH_2,AcNH_2}^{OH}$. Similarly $[EtOH_{in}]$ is related to $\mathbf{2}_{EtOH,AcNH_2}^{OH}$ and $\mathbf{2}_{EtOH,EtOH}^{OH}$.[20]

CIS values observed with these neutral guests[15] were very similar for all the Zn complexes and quite different from those obtained with the trisprotonated receptor $\mathbf{1}^{3H^+}$.

The data collected in Table 2 first show that acetamide is the best ligand for all receptors, and MeCN the weakest. They also show that the relative affinities are highly dependent on the nature of the receptor: the reported data for the relative DMF/EtOH affinities, for example, are spread over an impressively wide range of almost three orders of magnitude. The common features of all these receptors are the calixarene cavity, which allows CH–π interactions with the guest alkyl chain, and H-bonding to the aryl ether oxygen atoms with the protic guests. Differences obviously stem from the nature of the cap, which indeed variously provides a coordination link within the Zn funnel complex, strong H-bonding donors for the trisammonium, or a variable charge–dipole interaction due to the charge on the cap, which is either tri-, di-, or monocationic. MeCN, for example, is relatively better bound to the funnel receptor, which is due to its coordination link to the metal center [with Cu^{II} in place of Zn^{II} this value is even higher (0.33)].[4c] The trisammonium compound presents the highest relative affinities for guests possessing high dipole moments and oxygen atom donors, such as DMF and DMSO, while $AcNH_2$ is the "winner" guest for all receptors, with a particularly strong affinity for the tri- and dicationic receptors. Indeed, this guest combines a high dipole moment, a good hydrogen bond donor (NH_2), and a good acceptor (CO).

Very interestingly, the natures of the external ligands greatly influence the relative affinities of the neutral guests for Zn complexes **2** and **3**. Complex $\mathbf{2}_G^{OH}$, which possesses the more basic external ligand, presents smaller relative affinities for MeCN, DMF, and DMSO. Indeed, with these polar aprotic guests the stabilization of the host–guest adducts is due mainly—besides CH–π interactions—to the charge–dipole interaction between the metal center and the polar guest, so the smaller the positive charge at the metal center, the less stabilizing the effect of the charge–dipole interaction. Replacing the hydroxide by the less basic acetato ligand indeed raises the relative affinities for DMSO and acetamide, while replacing the oxygen donor by the nitrogen donor of a deprotonated sulfonamide also increases these values, which are the highest when the apical anionic ligand is substituted for a neutral one (for example, $BuNH_2$).

All these results show allosteric control of the host properties of the calix[6]trisamine **1** through small modifications at the level of the amino arms, which are ca. 3 Å away from the calixarene narrow rim. Interestingly, this can be exploited to switch the guest by effecting a modification to the environment. To illustrate this point, we carried out an NMR experiment in which host–guest systems $\mathbf{2}_G^{OH}$ and $\mathbf{1}_G^{3H^+}$ were quantitatively interconverted through the acid/base-mediated Zn decoordination/coordination process (Figure 7, Scheme 2).[21] Thus, when a chloroform solution of complex $\mathbf{2}_G^{OH}$ contains a 100:6 molar ratio of DMF/EtOH, EtOH is the winner guest, as $\mathbf{2}_{EtOH}^{OH}$ is observed together with only traces of $\mathbf{2}_{DMF}^{OH}$ ($< 5\%$). Addition of TFA then results in the exclusive formation of the trisammonium receptor $\mathbf{1}_{DMF}^{3H^+}$, with the replacement of DMF for EtOH in the cavity. Addition of TEA restored the Zn receptor, $\mathbf{2}_{EtOH}^{OH}$, thus resulting in the expulsion of DMF and back-inclusion of EtOH.

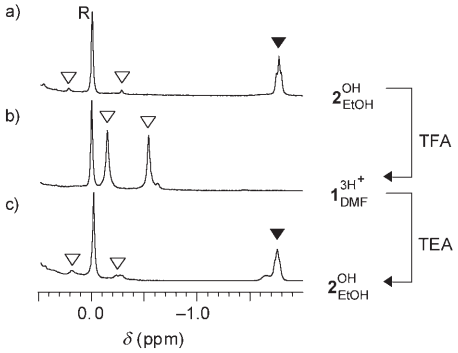


Figure 7. Reversible switching of the EtOH guest for DMF governed by the acidic/basic conditions. a) High-field region of the ^1H NMR spectrum (300 MHz, 223 K) of a $CDCl_3$ solution of $\mathbf{2}_{EtOH}^{OH}$ in the presence of EtOH and DMF (6 and 100 equiv, respectively). b) After addition of TFA (6 equiv). c) After subsequent addition of TEA (30 equiv).[22] ▼ = $EtOH_{in}$, ▽ = DMF_{in}. Reference has been labeled "R".

Conclusion

The Zn funnel complexes previously obtained with aromatic amino arms exhibit four-coordinate tetrahedral zinc dicationic centers that selectively coordinate neutral guests sitting inside the cavity. Because of the reduced steric hindrance provided by the primary amino arms of calix[6]trisamine **1**, the corresponding tetrahedral Zn^{II} complex preferentially coordinates the fourth donor externally. As a result, a dinuclear species ($\mathbf{2}_G^{OH}$) bridged by a single hydroxo ligand is obtained upon treatment with zinc perchlorate. This complex is particularly robust, as it did not yield a bis-hydroxo-

dinuclear Zn complex, as has been described with the classical N_3 ligands, or undergo decoordination of the metal ion when exposed to an excess of base. The basic hydroxide ligand of $\mathbf{2}_G^{OH}$ reacts with carboxylic acids and sulfonamides to provide monocationic mononuclear Zn^{II} complexes $\mathbf{3}_G^{RCOO}$ and $\mathbf{3}_G^{RSO_2NH}$ with *exo*-coordinated carboxylato and sulfonamidato ligands, respectively. Application of a strong but neutral donor such as a primary amine also results in the formation of a mononuclear complex, $\mathbf{3}_G^{RNH_2}$, which is dicationic. All these different species, mono- or dinuclear, behave as good and selective *endo*-receptors for neutral polar guests. The characterization of the multiple-species-based calix[6]trisamine **1** (the previously reported trisammonium $\mathbf{1}_G^{3H^+}$ and the Zn complexes $\mathbf{2}_G^{OH}$, $\mathbf{3}_G^{RCOO}$, $\mathbf{3}_G^{RSO_2NH}$, and $\mathbf{3}_G^{RNH_2}$) provided a unique opportunity to compare their host properties directly. On the one hand, in all of them, part of the stabilization of the host–guest adducts is due to CH–π interactions and possible hydrogen bonding with the calixarene core. On the other hand, this study highlights efficient tunability of the host–guest affinity through external binding (HO^-, $RCOO^-$, $MeSO_2NH^-$, or RNH_2) to the Zn center. The higher the positive charge capping the calixarene narrow rim, the more polarized the cavity and the more efficient the binding of dipolar molecules. As a consequence, substitution of the external apical ligand for a better or weaker donor changes the host properties of the complex. A harder external ligand results in a less polarized receptor that will consequently be particularly sensitive to the hydrogen-bonding ability of the guest, while a less electron-rich apical ligand, and a fortiori the neutral one (RNH_2), will make the receptor more sensitive to the dipole moment of the guest, which will become the major point of discrimination with the tricationic trisammonium receptor $\mathbf{1}_G^{3H^+}$. All this stands in contrast with the funnel Zn complexes, in which the coordination link plays a dominant role. Interestingly, the asymmetry of an external enantiopure amino ligand is transmitted to the calixarene core, thus providing a chiral environment sensed by the guest.

In conclusion, this supramolecular system illustrates how the receptor properties of a hydrophobic cavity can be finely tuned by the environment (presence of metal ions, coordinating species, protons, etc.). From a biomimetic point of view, these results may be highly relevant to enzymes, the active site host properties of which (formation of Michaelis–Menten complexes) are most often dependent on the pH, the presence and redox state of a metal ion, the co-binding of second molecule, etc. All these allosteric effectors allow fine tuning of the affinity of the protic site for its substrate and product.

Experimental Section

General procedures: CH_2Cl_2 was distilled over CaH_2 under argon. ^1H NMR spectra were recorded at 500, 400, or 300 MHz and ^{13}C NMR spectra were recorded either at 75 or 50 MHz. Traces of residual solvent or poly(dimethylsiloxane) (R) were used as internal standard. All reactions were performed under an inert atmosphere. Elemental analyses were performed at the Laboratoire de Microanalyse Organique (IRCOF, France) and 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.*

$[Zn(1)(MeOH)(ClO_4)](ClO_4)$ ($\mathbf{3}_{MeOH}^{ClO_4}$): Methanol (30 mL) and dichloromethane (80 mL) were added to a flask containing $[Zn(H_2O)_6](ClO_4)_2$ (0.545 g, 1.46 mmol) and calix[6]trisamine **1** (1.46 g, 1.28 mmol). After removal of the resulting precipitate, the reaction mixture was stirred at room temperature for 10 min and was then concentrated to a third of the volume by bubbling argon through the solution. The resulting precipitate was separated from the solvent, washed with pentane, and dried under vacuum, yielding the complex $\mathbf{3}_{MeOH}^{ClO_4}$ (1.10 g, 60%) as a white solid. M.p. 270°C (decomp); IR (KBr): $\tilde{\nu}$ = 3296, 3241, 636, 625 cm^{-1}; elemental analysis calcd (%) for $[Zn(C_{75}H_{105}N_3O_6)(CH_3OH)](ClO_4)_2$: C 63.35, H 7.62, N 2.92; found: C 63.55, H 7.44, N 3.10.

$[Zn_2(1)_2(MeOH)_2(OH)](ClO_4)_3$ ($\mathbf{2}_{MeOH}^{OH}$): This complex formed spontaneously upon dissolution of complex $\mathbf{3}_{MeOH}^{ClO_4}$ in chloroform in the presence of traces of H_2O. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.74 (s, 27H; *t*Bu), 1.41 (s, 27H; *t*Bu), 3.31 (br s, 6H; CH_2N), 3.42 (d, J = 15 Hz, 6H; $ArCH_{eq}$), 3.68 (br s, 6H; NH_2), 3.93 (s, 9H; OCH_3), 4.10 (br s, 6H; CH_2O), 4.47 (d, J = 15 Hz, 6H; $ArCH_{ax}$), 6.53 (s, 6H; Ar*H*), 7.30 ppm (s, 6H; Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.0, 31.1, 31.6, 33.8, 34.3, 42.6, 60.9, 73.0, 122.9, 128.3, 132.2, 132.9, 145.2, 146.4, 152.0, 152.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3606, 3311, 3242, 623 cm^{-1}.

Compound 2: Two different synthetic procedures allowed the isolation of pure $\mathbf{2}_{MeOH}^{OH}$

Procedure A: Methanol (0.5 mL) and dichloromethane (2.5 mL) were added to a flask containing $[Zn(H_2O)_6](ClO_4)_2$ (31.0 mg, 0.083 mmol) and calix[6]trisamine **1** (96 mg, 0.084 mmol), the reaction mixture was stirred at room temperature for 30 min, and a KOH solution (1 M in MeOH, 84 μL, 0.084 mmol) was added in 10 μL portions. After 15 h at room temperature, the resulting precipitate ($KClO_4$) was removed by centrifugation and methanol (2 mL) was added to the solution. After concentration to a third of the volume by bubbling argon through the solution, a crystalline product was obtained, separated from the solvent, and dried under vacuum, to give the dinuclear complex $\mathbf{2}_{MeOH}^{OH}$ (70 mg, 60%) as a white solid. M.p. 275°C (decomp); IR (KBr): $\tilde{\nu}$ = 3675 to 3345, 3303, 3258, 624 cm^{-1}; elemental analysis calcd (%) for $[Zn_2(C_{150}H_{210}N_6O_{12})(CH_3OH)_2(OH)](ClO_4)_3(H_2O)_2$: C 64.38, H 7.93, N 2.96; found: C 64.25, H 7.93, N 2.92.

Procedure B: Chloroform (1 mL) and triethylamine (5 μL, 0.062 mmol) were added to a flask containing $\mathbf{3}_{MeOH}^{ClO_4}$ (30 mg, 0.021 mmol). After 15 minutes at room temperature, the reaction mixture was washed three times with distilled water (1 mL), the organic layer was stirred on molecular sieves and filtered through celite, and the solvent was removed. The crude compound was recrystallized from dichloromethane/methanol to afford $\mathbf{2}_{MeOH}^{OH}$ (25 mg, 86%) as a white powder.

^1H NMR determination of the "relative affinities" reported in Table 2:[20] In a typical procedure, DMSO (76 equiv) and EtOH (38 equiv) were successively added to a $CDCl_3$ solution of complex $\mathbf{2}_{MeOH}^{OH}$. A ^1H NMR spectrum was recorded at 223 K and showed the guest resonances of the two *endo*-complexes $\mathbf{2}_{EtOH}^{OH}$ and $\mathbf{2}_{DMSO}^{OH}$, together with the signals corresponding to the free EtOH and DMSO. The integrations of the methyl groups of the free and included EtOH and DMSO were used to calculate the relative affinity, defined as $[DMSO_{in}]/[EtOH_{in}] \times [EtOH_{free}]/[DMSO_{free}]$ (errors estimated ±10%).

X-ray structure analysis of complex $\mathbf{2}_{MeOH}^{OH}$: X-ray quality crystals were grown at 4°C from a $CHCl_3$ solution in which complex $\mathbf{2}_{MeOH}^{ClO_4}$ was dissolved in the presence of a large excess of TEA and trace of water.

Crystal data: $[C_{150}H_{210}O_{13}N_6Zn_2]\cdot 3\,ClO_4\cdot 3\,CHCl_3\cdot 2\,H_2O$, M_w = 3128.48, orthorhombic, colorless crystal ($0.6\times0.3\times0.2$ mm^3), a = 46.8870(3), b = 19.2130(3), c = 20.6100(10) Å, V = 18566.3(1) $Å^3$, space group *Pccn*, Z = 4, ρ = 1.119 $g\,cm^{-3}$, $\mu(Mo_{K\alpha})$ = 4.9 cm^{-1}, 17143 reflections mea-

sured at 223 K (Bruker–Nonius KappaCCD diffractometer)[23] in the 0.43–26.04° θ range, 15954 unique, 987 parameters refined on F^2 with use of 15954 reflections [Shelxl][24] to final indices $R[F^2>4\sigma F^2] = 0.129$, $wR = 0.339$ [$w = 1/[\sigma^2(F_o^2)+(0.1099P)^2+4.0995P]$ where $P = (F_o^2+2F_c^2)/3$].

Refinement details: the dinuclear compound $\mathbf{2}^{OH}_{MeOH}$ co-crystallized with four molecules of disordered chloroform with occupancies equal to 0.5, one disordered molecule of chloroform, three ClO_4^- counter-ions, and two disordered molecules of water. No hydrogen atoms were found experimentally. The last residual Fourier positive and negative peaks were equal to 1.05 and −0.66, respectively.

X-ray structure analyses of complexes $\mathbf{3}^{Cl}_{MeOH}$ and $\mathbf{3}^{Cl}_{EtOH}$: A colorless crystal of dimensions $0.15\times0.08\times0.04$ mm^3 was mounted with Paratone-N oil (Hampton Research) coating and immediately placed in a nitrogen cold stream. X-ray intensity data were collected at 100 K on a Bruker–Nonius X8-APEX2 CCD area-detector diffractometer with use of $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Four sets of narrow data frames (90 s per frame) were collected at different values of θ for one and three initial values of ϕ and ω, respectively, with use of 0.5° increments of ϕ or ω. Data reduction was accomplished by use of SAINT V7.03.[25] The substantial redundancy in data allowed a semiempirical absorption correction (SADABS V2.10)[25] to be applied, on the basis of multiple measurements of equivalent reflections. The structure was solved by direct methods, developed by successive difference Fourier syntheses, and refined by full-matrix, least-squares on all F^2 data with the aid of SHELXTL V6.14.[26] Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms. Several disordered molecules were initially modeled as discrete ClO_4^- counter-ions but were ultimately removed from the structure. The data set was corrected with the program PLATON/SQUEEZE.[27]

Crystal data: $[C_{76.50}H_{107.75}O_8N_3Cl_{1.25}Zn]$, $M_w = 1307.09$, triclinic, space group $P\bar{1}$; dimensions: $a = 17.763(2)$, $b = 22.293(3)$, $c = 23.722(3)$ Å, $\alpha = 93.538(5)$, $\beta = 107.585(5)$, $\gamma = 99.724(5)$°, $V = 8762(2)$ Å^3, $Z = 4$; total reflections collected: 63277; independent reflections: 24226 (7367 $F_o > 4\sigma(F_o)$); data were collected up to a $2\theta_{max}$ value of 46° (99.3% coverage). Number of variables: 1597; $R_1 = 0.1316$, $wR_2 = 0.3108$, $S = 1.045$; highest residual electron density 1.06 e Å^{-3}.

CCDC 227284 ($\mathbf{2}^{OH}_{MeOH}$) and -613414 ($\mathbf{3}^{Cl}_{MeOH}$ and $\mathbf{3}^{Cl}_{EtOH}$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

Part of this work was supported by the Région Haute-Normandie. We thank Michel Giorgi (Univ. Paul Cézanne, France) for the X-ray structure analysis of complex $\mathbf{2}^{OH}_{MeOH}$.

[1] J. M. Berg, J. L. Tymoczko, L. Stryer, *Biochemistry* (Ed.: W. H. Freeman), New York, 5th ed., **2002**.

[2] a) J. M. Lehn, *Supramolecular Chemistry*, VCH, Weinheim, **1995**; b) reviews on molecular recognition: *Chem. Rev.* **1997**, *97*, 1232–1734.

[3] For a review concerning the selective recognition of organic molecules by metallohosts, see: J. W. Canary, B. C. Gibb, *Prog. Inorg. Chem.* **1997**, *45*, 1–81.

[4] For leading references, see: a) S. Blanchard, L. Le Clainche, M.-N. Rager, B. Chansou, J.-P. Tuchagues, A. F. Duprat, Y. Le Mest, O. Reinaud, *Angew. Chem.* **1998**, *110*, 2861–2864; *Angew. Chem. Int. Ed.* **1998**, *37*, 2732–2735; b) O. Sénèque, M.-N. Rager, M. Giorgi, O. Reinaud, *J. Am. Chem. Soc.* **2000**, *122*, 6183–6189; c) L. Le Clainche, M. Giorgi, O. Reinaud, *Inorg. Chem.* **2000**, *39*, 3436–3437; d) Y. Rondelez, M.-N. Rager, A. F. Duprat, O. Reinaud, *J. Am. Chem. Soc.* **2002**, *124*, 1334–1340; e) O. Sénèque, M. Giorgi, O. Reinaud, *Supramol. Chem.* **2003**, *15*, 573–580; f) O. Sénèque, M. Campion, B. Douziech, M. Giorgi, Y. Le Mest, O. Reinaud, *Dalton Trans.* **2003**, 4216–4218.

[5] U. Darbost, M. Giorgi, N. Hucher, I. Jabin, O. Reinaud, *Supramol. Chem.* **2005**, *17*, 243–250.

[6] S. Le Gac, J. Marrot, O. Reinaud, I. Jabin, *Angew. Chem.* **2006**, *118*, 3195–3198; *Angew. Chem. Int. Ed.* **2006**, *45*, 3123–3126.

[7] For other examples of polarization of a calix[6]arene by protonation of its aza-cap for the selective and efficient binding of neutral dipolar guests, see: a) U. Darbost, X. Zeng, M. Giorgi, I. Jabin, *J. Org. Chem.* **2005**, *70*, 10552–10560; b) E. Garrier, S. Le Gac, I. Jabin, *Tetrahedron: Asymmetry* **2005**, *16*, 3767–3771.

[8] Its ^{1}H NMR spectrum was characteristic of a major flattened cone conformation with C_{3v} symmetry. The methoxy groups of **1** are in an *in* position relative to the cavity, as indicated by their high-field resonance ($\delta_{OMe} = 2.66$ ppm), whereas the amino arms are turned out in an *out* position. For the detailed synthesis and spectroscopic characterization of **1**, see: U. Darbost, M. Giorgi, O. Reinaud, I. Jabin, *J. Org. Chem.* **2004**, *69*, 4879–4884.

[9] Monohydroxo-bridged dinuclear Zn complexes with tetrahedral geometries have been reported with sterically bulky aromatic ligands. For representative examples, see: a) R. Alsfasser, H. Vahrenkamp, *Chem. Ber.* **1993**, *126*, 695–701; b) B. S. Hammes, X. Luo, M. W. Carrano, C. J. Carrano, *Inorg. Chim. Acta* **2002**, *341*, 33–38 and references therein. For an example obtained with an alkylamine, see: c) A. Mondal, G. Mostafa, A. Ghosh, N. R. Chaudhuri, W.-T. Wong, *Polyhedron* **1998**, *17*, 1217–1221.

[10] Pioneering work in Zn enzyme modeling: a) R. S. Brown, N. J. Curtis, J. Huguet, *J. Am. Chem. Soc.* **1981**, *103*, 6953–6959; b) H. Slebocka-Tilk, J. L. Cocho, Z. Frakman, R. S. Brown, *J. Am. Chem. Soc.* **1984**, *106*, 2421–2431. Recent reviews: c) E. Kimura, E. Kikuta, *J. Biol. Inorg. Chem.* **2000**, *5*, 139–155; d) G. Parkin, *J. Chem. Soc. Chem. Commun.* **2000**, 1971–1985; e) H. Vahrenkamp, *Acc. Chem. Res.* **1999**, *32*, 589–596; for a recent review, see: f) G. Parkin, *Chem. Rev.* **2004**, *104*, 699–767.

[11] Complex $\mathbf{2}^{OH}_{MeOH}$ displayed an exceptional stability since the addition of a strong base (up to 4 equiv) did not cause the formation of a bishydroxo complex or the decoordination of the metal ion.

[12] a) U. Darbost, X. Zeng, M.-N. Rager, M. Giorgi, I. Jabin, O. Reinaud, *Eur. J. Inorg. Chem.* **2004**, 4371–4374; b) U. Darbost, M.-N. Rager, S. Petit, I. Jabin, O. Reinaud, *J. Am. Chem. Soc.* **2005**, *127*, 8517–8525; c) G. Izzet, B. Douziech, T. Prangé, A. Tomas, I. Jabin, Y. Le Mest, O. Reinaud, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 6831–6836.

[13] Classically, d(Zn···Cl) = 2.25 Å. See: a) A. G. Orpen, L. Brammer, F. H. Allen, O. Kennard, D. G. Watson, R. Taylor, *J. Chem. Soc. Dalton Trans.* **1989**, *12*, S1–S83. In a calix/ZnCl complex it was 2.23 Å, see: b) O. Sénèque, M.-N. Rager, M. Giorgi, T. Prangé, A. Tomas, O. Reinaud, *J. Am. Chem. Soc.* **2005**, *127*, 14833–14840.

[14] In the case of $\mathbf{3}^{Cl}_{EtOH}$, different positions (50% each) were experimentally determined for the oxygen atom of the EtOH guest. Only one is shown in Figure 3.

[15] See Supporting Information.

[16] The methylene signal of the EtOH guest was hidden by one of the *t*Bu groups but was identified at 0.71 ppm thanks to 2D NOESY measurements and homodecoupling NMR experiments.

[17] After the addition of a large molar excess of $PrNH_2$ (34 equiv), only broad signals corresponding to its partial inclusion were detected at low temperature (i.e., signals at −1.77, −1.32, and −0.52 ppm for $CH_3CH_2CH_2NH_2$, $CH_3CH_2CH_2NH_2$, and $CH_3CH_2CH_2NH_2$, respectively, $CDCl_3$, 263 K).

[18] All groups of protons belonging to the calixarene skeleton of $\mathbf{2}^{OH}_{EtOH}$ displayed $T1$ values 25 to 140% higher than for the monocalixarene species $\mathbf{3}^{PrNH_2}_{EtOH}$ and $\mathbf{3}^{AcO}_{EtOH}$ (see Supporting Information). Because of its high molecular weight, complex $\mathbf{2}^{OH}_{EtOH}$ was found in the $\omega\tau_c>1$ regime (over the extreme narrowing limit) with negative NOE crosspeaks at 500 MHz ($\tau_m = 800$ ms). See ref. [6] for a related study.

[19] In contrast, when the stronger trifluoroacetic acid and a large excess of TEA were added to a solution of $\mathbf{2}^{OH}_{EtOH}$, no new species was de-

tected by ^{1}H NMR. This result clearly shows that the acetato ligand is coordinated to the metal center.
[20] Except in the case of $\mathbf{2}_G^{OH}$, the obtained values correspond to the ratio of the association constants.
[21] Quantitative interconversion of the two host–guest systems $\mathbf{2}_G^{OH}$ and $\mathbf{1}_G^{2H^+}$ through an acid/base-induced Zn decoordination/coordination process was detected with various guests G (see Supporting Information for G = EtOH, Scheme 2).
[22] See Supporting Information for the complete spectra.
[23] Bruker–Nonius, Kappa CCD Reference Manual, Nonius B. V., P.O. Box 811, 2600 Av, Delft (The Netherlands), **1998**.
[24] G. M. Sheldrick, SHELXL97, Program for the refinement of crystal structures, University of Göttingen (Germany), **1997**.
[25] APEX2 version 1.0–8, Bruker AXS, Madison, WI, **2003**.
[26] SHELXTL version 6.14, Bruker AXS, Madison, WI, **2001**.
[27] P. van der Sluis, A. L. Spek, *Acta Crystallogr. Sect. A* **1990**, *46*, 194–201.

Received: July 19, 2006
Published online: December 4, 2006

