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A Calix[6]azacryptand Ligand with a Sterically Protected Tren-based Coordination Site for Metal Ions

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ABSTRACT: A new calix[6]azacryptand ligand has been prepared in six steps starting from 1,3,5-trismethoxy-calix[6]arene. An X-ray study shows that this ligand has a sterically protected tren-based binding site at the bottom of a polyaromatic bowl and ether sites around its rim. It binds Zn^{2+} to give a complex in which zinc is in a trigonal bipyramidal geometry with a water bound in one apical position and two additional hydrogen-bonded waters that fill the calixarene cavity.

Complexes that contain a tris(2-aminoethyl)amine (tren) ligand, or the triamido(3-) version derived from tren, have been known and elaborated for fifty years.[1] Molybdenum complexes that contain a tren(3-) ligand in which a 3,5-(2,4,6-triisopropylphenyl)$_2$C$_6$H$_3$ (HIPT) group is bound to each tren amido nitrogen (Mo[(HIPTNCH$_2$CH$_2$)$_3$N] or Mo(HIPTN$_3$N) complexes) were shown for the first time, in 2003, to catalyze the reduction of molecular nitrogen to ammonia in the presence of [2,6-lutidinium][B(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_4$] with decamethylchromocene in heptane at room temperature and pressure;[2] approximately four equivalents of nitrogen are reduced before the catalyst decomposes. The Mo(HIPTN$_3$N) catalyst system has been studied extensively over the last dozen years both experimentally[3] and computationally.[4] All evidence suggests that the efficacy of nitrogen reduction is limited by protonation of the amido nitrogens and ultimate loss of (HIPTNHCH$_2$CH$_2$)$_3$N. It might be possible to prevent loss of the parent tren ligand by connecting the "arms" to give a relatively rigid tren(3-) complex. This approach was partially tested recently.[5] However, a Mo complex was not prepared and tested for dinitrogen reduction, in part because it was felt that the particular macrocyclic ligand may not be rigid enough to prevent its loss from the metal upon being protonated at the amido nitrogen atoms, and the ligand was difficult to synthesize in quantity.

A calix[6]arene-based ligand having a tren unit capping the small rim (Figure 1a) was first described in 2003.[6] This so-called calix[6]tren features a tetraazamacrocyclic core that can bind various metal ions (e.g. Zn^{2+}, Cu^{n+}) and a polyaromatic superstructure that prevents the formation of polynuclear species.[7] Exogenous neutral ligands such as alcohols or amines can bind to the metal center inside the cavity.[8] In order to access a rigid macrocyclic tren-based ligand on a practical scale, we envisioned the synthesis of a calix[6]azacryptand ligand in which the tren unit was attached to the large rim of the calixarene core (Figure 1b). A smaller 18-membered macrocycle would then connect the tren and calixarene subunits, and passage of exogenous ligands through the small rim of the calixarene (24-membered macrocycle) therefore might be restricted.[9] It also should be noted that the tren ligand shown in Figure 1b has *N*-aryl bonds instead of *N*-alkyl bonds and the *N*-aryl groups are linked to one another through a similar aryl unit, thus creating a relatively rigid and sterically protected binding pocket at one end of a cavity lined with six aryl rings. A trianionic version of the ligand shown in Figure 1b bound to molybdenum might be more likely to survive under the conditions required for catalytic reduction by Mo(HIPTN$_3$N) complexes. A synthesis and preliminary metalation results of the ligand shown in Figure 1(b) are reported here.

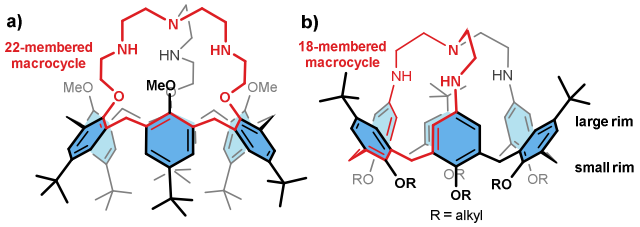
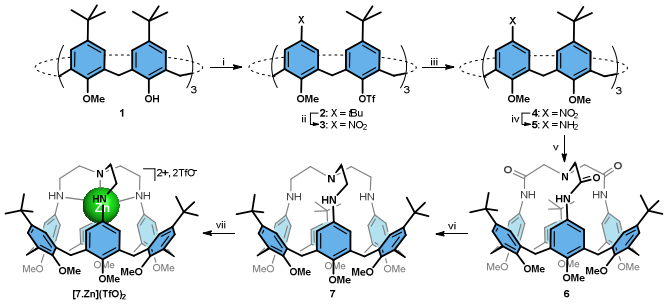


Figure 1. Structures of (a) the previously reported calix[6]tren ligand and (b) the target ligand.

The synthesis of the targeted ligand required the regioselective introduction of a tren unit on the calix[6]arene large rim with the tren being linked to the calixarene at the 1, 3, and 5 positions. To this aim, we exploited the classical strategy that consists of introducing deactivating substituents on the phenolic rings (1,3,5) in order to reduce the reactivity of three rings toward electrophilic aromatic substitutions.[10] This strategy allows the 1,3,5 functionalization pattern to be transferred from the small rim to the large rim. Triflate groups were chosen as the deactivating substituents since they are also protecting groups that can be cleaved easily under basic conditions.[11] Therefore, the known 1,3,5-trismethoxy-calix[6]arene **1** was treated with triflic anhydride in the presence of pyridine to afford the tristriflate derivative **2** in high yield (Scheme 1). Regioselective nitration of the aromatic units that are not deactivated produced the trisnitrated calix[6]arene **3** in 86% yield and subsequent treatment with iodomethane under basic conditions led to the *in situ* cleavage of the triflate groups and the methylation of the resulting phenolate groups in 94% yield.[12] Reduction of the nitro groups of **4** yielded intermediate **5** in 94% yield. The key macrocyclization reaction was then carried out under conditions that were optimal for the synthesis of closely

related compounds.[13] Compound **5** was thus treated with nitrilotriacetic acid in the presence of an excess of PyBOP and triethylamine, leading to calix[6]cryptamide **6** in 45% yield after flash chromatography; the relatively high yield of **6** is undoubtedly a consequence of the preorganization of the aniline groups in **5**. Reduction of the amide groups with BH_3·THF finally gave the target calix[6]azacryptand **7** in 75% yield from **6**. The overall yield of **7** from **1** (23%) allows preparation of this ligand on a gram scale.

Scheme 1. Synthesis of the calix[6]tren-based ligand **7** and of the corresponding Zn^{2+} complex. i) Tf_2O, pyridine, DCM, rt, 3 h, 95%; ii) HNO_3/AcOH, DCM, rt 5 h, 86%; iii) MeI, NaH, THF/DMF, rt, 2 h, 94%; iv) Pd/C, H_2N-NH_2.H_2O, EtOH, reflux, 7 days, 85%; v) $N(CH_2COOH)_3$, PyBOP, Et_3N, DMF/$CHCl_3$, 50 °C, 20 h, 45%; vi) BH_3.THF, THF, reflux 8 h, then rt for 10 h, 75%, vii) $Zn(TfO)_2$, MeCN, 1 week at rt, then 5 h at 60 °C, 85%.



Crystals of **7** suitable for X-ray diffraction were obtained by evaporation of a solution of **7** in dichloromethane. The calixarene skeleton is found in a flattened cone conformation, as shown by the values of the dihedral angles between adjacent aromatic rings (Figure 2). The flattened conformation is a consequence of the rigid tren-based cap directing the aniline units toward the inside of the cavity. Consequently, the three other aromatic units project the *t*-Bu groups outside the cone. The methoxy groups borne by the latter partially close the entrance to the poly-aromatic cavity from the small rim.

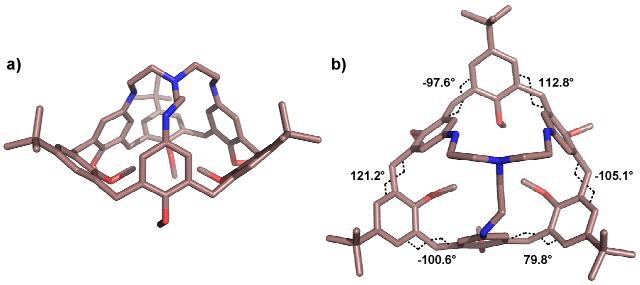


Figure 2. X-ray structure of ligand **7**; (a) side view; (b) top view showing selected dihedral angles. Solvent molecules and all H-atoms are omitted.

The ^{1}H NMR spectrum of calix[6]azacryptand **7** in $CDCl_3$ is characteristic of a C_{3v}-symmetric and relatively rigid calix[6]arene in a cone conformation; two well-defined doublets at 3.45 ppm and 4.47 ppm are observed for the ArCH_2 protons.[14] Moreover, the significant high-field shift of the Ar*H* signal of the aniline units ($\delta_{ArHaniline}$ = 5.65 ppm) as well as the down-field shift of the OMe resonance of the other three aromatic units (δ_{OMe} = 2.54 ppm) suggest that the calixarene core adopts a solution structure that is similar to that observed in the solid state.

In order to obtain early results on the metal complexation properties of **7** that can be compared to the parent calix[6]tren system, we next investigated its ability to coordinate Zn^{2+}. Preliminary NMR studies showed that the reaction between **7** and a stoichiometric quantity of $Zn(TfO)_2$ is relatively slow in acetonitrile (one week at 22 °C, then 60 °C for 5 h; Scheme 1). In THF the reaction mixture was heated to 70 °C for 24 h. An X-ray structural study of the resulting [**7**.Zn]$(TfO)_2$ complex shows that the Zn^{2+} ion is bound to the N_4 core of the tren cap and one water molecule and has a trigonal bipyramidal (TBP) geometry (τ = 0.93)[15] (Figure 3a). The flattened cone conformation adopted by the calixarene skeleton is similar to that found for **7** itself. The Zn-O bond length (Zn1-O1w = 2.019(2) Å), which is significantly longer than Zn-O distances reported for Zn-OH complexes (1.85-1.86 Å),[16] along with the presence of two triflate anions[14] clearly suggests that the cation has a 2+ charge and that the exogenous apical ligand is water. It is noteworthy that the calixarene core may play a role in stabilizing the water ligand toward deprotonation (*vide infra*).[17] The average Zn-N distance to equatorial nitrogen atoms in the TBP is 2.08 Å. The capping tertiary amino group is relatively loosely bound to the metal ion as shown by its larger distance to the metal ion (Zn1-N4 = 2.269(3) Å). All Zn-N bond lengths in [**7**·Zn]$(TfO)_2$ are slightly longer than those reported for the Zn^{2+} derivative of the calix[6]tren ligand shown in Figure 1a.[8] In addition to one coordinated water, two other water molecules are found in the polyaromatic corridor. The three water molecules are held together through H-bonding interactions (average d(O-O) = 2.64 Å; Figure 3a); three additional H-bonding interactions with oxygen atoms belonging to the calixarene core also contribute to the stabilization of this chain of water molecules. The three waters fill the calixarene cavity and force three OMe groups to point away from the cavity. The water molecule standing at the entrance of the cavity is also positioned to be H-bonded to a triflate counter-anion.[14] As found for known tren-based Zn-complexes, the three nitrogen stereocenters that arise from coordination of the aniline groups to the metal center possess different configurations (i.e. *R*,*R*,*S* or *S*,*S*,*R*); only this heterochiral C_1 complex is present in the crystal lattice (in its racemic form). As far as the zinc coordination is concerned, the [**7**·Zn]$(TfO)_2$ complex resembles the active site of zinc enzymes[18] in that the Zn^{2+} ion is stabilized within a polyaza environment, displays a coordination site for one exogenous ligand (here water), and is buried at the end of a tunnel through which the metal center is accessed (Figure 3b).

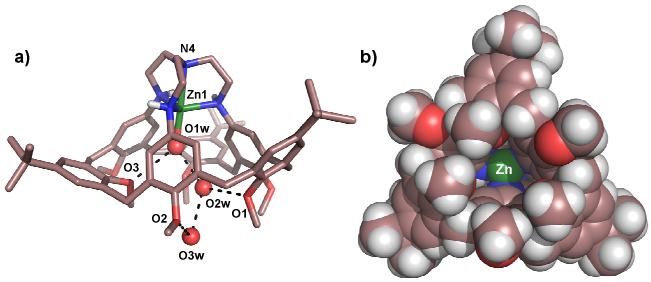


Figure 3. X-ray structure of [**7**·Zn]$(TfO)_2$; (a) side view, all H-atoms (except those of the NH groups) are omitted for clarity; (b) bottom view showing the poly-aromatic corridor that provides access to the metal center (the three guest water molecules are omitted). The two triflate counter-anions and minor components of disordered atoms are omitted for clarity and only the *R*,*R*,*S* enantiomer of the Zn-complex is displayed (see SI for a full description of [**7**·Zn]$(TfO)_2$).

Proton NMR spectra of [**7**·Zn]$(TfO)_2$ are complex. Addition of 1 equivalent of $Zn(TfO)_2$ to **7** in CD_3CN led to a NMR spectrum corresponding to the protonated ligand, **7**·H^+.[19,20] However, the spectrum evolved when the solution was left at room temperature for a week and **7**·H^+ disappeared after heating the sample at 60 °C

for 5 h.[14] A mixture of several new species exhibiting complex NMR patterns was observed at this point (Figure 4a), with the major NMR profile being characteristic of an asymmetric C_1 complex;[8] we propose that the major profile corresponds to the zinc-aqua complex that was characterized in the solid state.[20] When the spectrum was recorded at 348 K, only a broadening of the resonances belonging to this major species was observed. We conclude from these experiments that metalation with $Zn(TfO)_2$ is relatively slow, possibly as a consequence of the tren binding pocket being relatively isolated from the external medium. When a spectrum of $[\mathbf{7}\cdot Zn](TfO)_2$, previously synthesized in acetonitrile, was recorded in CD_3OD, the sample clearly contained a mixture of species.[20] A much simpler spectrum consistent with a product having C_3-symmetry is obtained upon heating a CD_3OD solution of $[\mathbf{7}\cdot Zn](TfO)_2$ at 50 °C for 5 days in presence of ten equivalents of triethylamine (Figure 4b) or in CD_3OD without adding triethylamine in 1.5 days at 60 °C. There are several possible structures for this C_3-symmetric product, so an x-ray structural study is likely to be required .

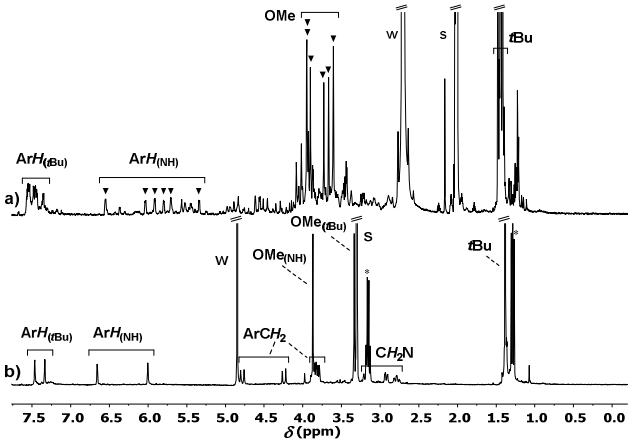


Figure 4. ^1H NMR (300 MHz) spectra at 298 K obtained: (a) upon addition of 1 equiv of $Zn(OTf)_2$ to **7** in CD_3CN after 5 days at 25 °C followed by heating the solution at 60 °C for 5 h; (b) upon dissolution of $[\mathbf{7}\cdot Zn](OTf)_2$ in CD_3OD, heating at 50 °C for 24 h, and adding 10 equiv of Et_3N and heating at 50 °C for 5 days (400 MHz): w: water; s: residual solvent, *: Et_3N.

In conclusion, we have relatively efficiently synthesized the new calix[6]azacryptand **7** from **1** in six steps. A Zn^{2+} ion can be bound in the buried tren-based binding site, access to which is controlled by a polyaromatic tunnel presenting H-bond donor groups around the rim. A coordination site for exogenous ligands remains in the apical position of the TBP geometry. The metal center in $[\mathbf{7}\cdot Zn](TfO)_2$ can communicate with the external medium through a relay of water molecules filling the interior tunnel in the calixarene core. Future studies will be aimed at evaluating the binding of other metal ions to **7** or its trianionic derivative, including transition metal ions, as well as studying the host-guest and catalytic properties of the resulting metal complexes.

ASSOCIATED CONTENT

Supporting Information

Crystallographic details for both X-ray structural studies. Experimental details for the synthesis of all new compounds. 1D and 2D NMR spectra of all new compounds and NMR complexation studies. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interests.

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(19) The same NMR spectrum was obtained upon addition of picric acid (*ca.* 1 equiv) to a CD_3CN solution of ligand **7**.

(20) No evidence for coordination of acetonitrile was obtained in an NMR study conducted in $CDCl_3$, indicating that the major C_1 species observed in CD_3CN more likely corresponds to the aqua-complex rather than to the acetonitrile complex. Moreover, it is the zinc-aqua complex that was observed in the solid state, while the complex was synthesized and crystallized in acetonitrile.

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