Spectacular induced-fit process for guest binding by a calix[6]arene Zn(II) *funnel complex*†

David Coquière,[a] Jérôme Marrot[b] and Olivia Reinaud*[a]

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The host properties of a calix[6]arene cone capped by a Zn(II) *tris*-imidazole core at the small rim and decorated by three NH_2 substituents at the large rim are described and compared to the *hexa-t*Bu parent complex. It is shown that the replacement of three bulky *t*Bu substituents by three hydrophilic and small NH_2 groups has three major impacts: the receptor is now soluble in aqueous media, it accepts large guests such as dimethyldopamine and, most interestingly, undergoes a spectacular induced-fit behavior for guest binding.

Introduction

Calixarenes are versatile platforms for building selective receptors.[1] In a cone conformation, they provide a π-basic cavity that allows the *endo*-binding of organic guests. In this perspective, calix[6]arenes are more appealing than calix[4]arenes due to their larger size. However, several obstacles must be overcome to obtain a good host: (i) their high flexibility, which contrasts with cyclodextrin hosts, must be restricted to constrain the macrocycle in a cone conformation,[2] (ii) the high number of phenol units makes their selective functionalization difficult, and (iii) the large rim *t*Bu substituents limit the cavity size and cause them to be insoluble in aqueous solvents.

For about ten years now, we have been working on and developing a system that provides efficient answers to these problems. In the so-called *funnel complexes*, the coordination of a metal ion at the small rim constrains the calix[6]arene macrocycle into a cone conformation, taking advantage of previously reported selective methodologies for grafting three coordinating "arms" in alternate position onto the small rim.[3] Recently, we have discovered efficient methodologies allowing the selective funtionalization of the large rim, for which very few methods exist.[4] Indeed, we have made use of the small rim functionalities to direct *ipso*-reactions such as nitration[5] and chlorosulfonylation[6] at the large rim.

Here, we report on the impact of a large rim modification on the properties of a "classical" *funnel complex* based on Zn(II) coordination into a *tris*-imidazole core at the small rim. Indeed, the parent *hexa-t*Bu derivative (**1**)[3] has been converted to a *tris*-amino derivative (**2**), thus presenting three NH_2 groups at the entrance of the cavity, in place of the *t*Bu door in the parent ligand. A comparison of the corresponding Zn(II) complexes (**4** and **3**, respectively) highlights three major novel properties: an appreciable increase in the water solubility of the receptor, a substantial increase in its capacity to accept large guests[7] and, most interestingly, a higher flexibility that gives rise to spectacular induced-fit phenomena for guest binding.

Results

Calix[6]arene **2** was obtained in two steps from the *tris*(imidazole) calix[6]-ligand **1** by (i) the selective *ipso*-substitution of three *t*Bu groups for nitro groups and (ii) the reduction of the nitro substituents to amino groups. Ligand **2** was then reacted with one equiv. of Zn(II) perchlorate to provide the corresponding dicationic mono-Zn complex **3** (Scheme 1).[8]

A novel Zn(II) dicationic aqua complex

The XRD molecular structure of complex **3** is displayed in Fig. 1.[9] It shows a calix[6]arene cone in a flattened pseudo C_{3v} symmetrical conformation. The Zn(II) metal center is in a tetrahedral environment (Td), being coordinated to the three *N*-methyl-imidazole arms [d(Zn,N) = 1.98–2.00 Å] grafted onto the calix[6]arene small rim, and to one guest water molecule [d(Zn,O88) = 2.04 Å]. The latter is hydrogen-bonded to one oxygen atom of the calixarene small rim [d(O88,O63) = 3.09 Å].[10] Interestingly, one aniline unit of the calixarene macrocycle is pointing much more into the cavity than the two others and therefore presents its aromatic core at a relatively short distance from the water guest [d(O88–centroid) = 3.48 Å] coherent with an OH–π interaction.[11] The nitrogen atom (N72) of this peculiar aniline unit is at relatively short distances from the two others (3.13 and 3.24 Å), whereas the others are more distant from each other (4.38 Å). All together, these amino functions form a door that closes the entrance to the calixarene cavity.

Here it is very interesting to compare this structure with the aqua Zn complex **4**[3c] based on the parent ligand **1** reported a few years ago (Scheme 1, Fig. 2).[12] In many ways, the structures resemble each other: a similar Td environment for the metal ion, similar coordination bond distances [d(Zn–N) = 1.98–2.01 Å and d(Zn–O_w) = 1.97 Å for complex **4**], alternate *in*/*out* positions of the aromatic units of the calixarene cone. A major difference, however, lies in the presence of a second water molecule in the

[a]*Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR CNRS 8601, Université Paris Descartes, 45 rue des Saints-Pères, 75006 Paris, France. E-mail: Olivia.reinaud@univ-paris5.fr*
[b]*Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles St-Quentin en Yvelines, 45 av. des Etats-Unis, 78035 Versailles cedex, France*

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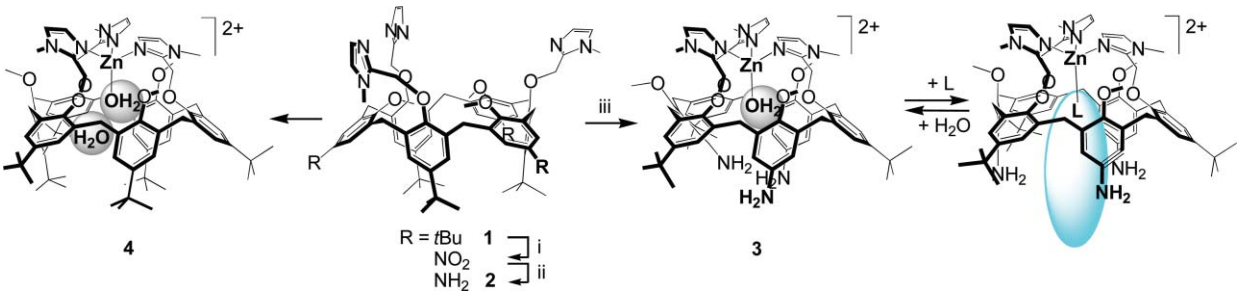

Scheme 1 Strategies for selective amino group introduction on the large rim and metallo host synthesis. (i) HNO_3–AcOH, 80%; (ii) hydrazine monohydrate, Pd/C, 75%; (iii) $Zn(H_2O)_6(ClO_4)_2$ (1 equiv.), CH_3CN–H_2O (2 : 1), 72%.

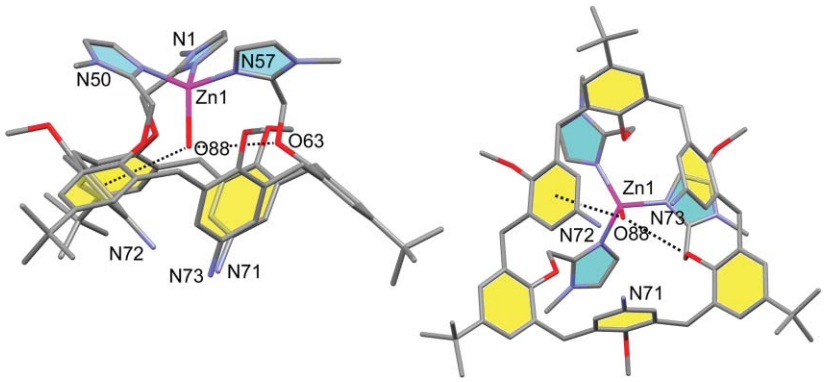

Fig. 1 XRD structure of complex **3**. Left: side view, right: bottom view. The dashed lines indicate the H_2O stabilizing interactions within the calixarene cavity. Hydrogen atoms and counter anions have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Zn1–N1 1.9980(17), Zn1–N57 1.9972(18), Zn1–N50 1.9766(17), Zn1–O88 2.041(2), N1–Zn1–N50 112.50(7), N1–Zn1–N57 104.05(7), N50–Zn1–N57 109.74(7), N1–Zn1–O88 110.25(8), N50–Zn1–O88 112.09(8), N57–Zn1–O88 107.81(8), O88 · · · O63 3.091, O88 · · · Ar 3.479.

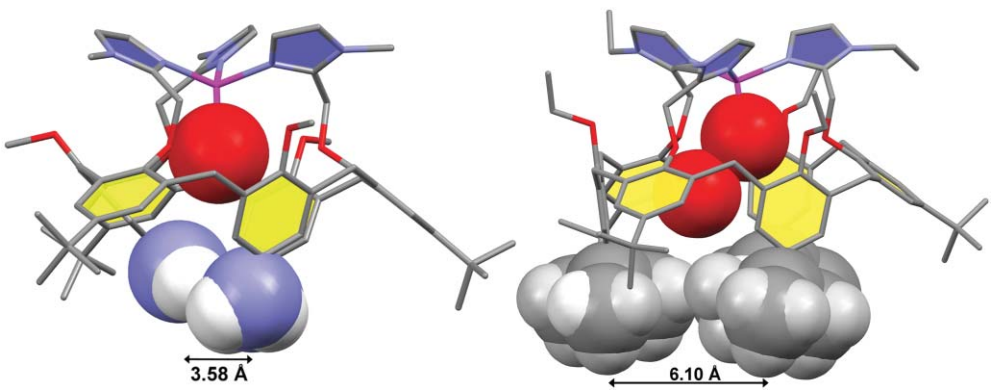

Fig. 2 Comparison of the calixarene cores of the Zn–aqua complexes **3** (left) and **4** (right),[3c] with space-filling representation of the guest water molecules and the large rim inner substituents evidencing a different cavity space. Hydrogen atoms and counter anions have been omitted for clarity.

hexa-*t*Bu derivative **4**, which, in the case of **3**, is lacking. The role attributed to the second water molecule is: (i) to stabilize the coordinated one through a strong hydrogen bond [d(O,O) = 2.54 Å], thus establishing a bridge to an anisole unit through an OH–π interaction, and (ii) to fill the cavity, hence stabilizing the overall structure and avoiding a major distortion of the calixarene core that would have been induced by the partial inclusion of a bulky *t*Bu group.[13] In complex **3**, the stabilization of the water ligand is ensured by a direct OH–π interaction with the bent aniline unit that shrinks the cavity size, thus adapting it to the smallness of the guest ligand. This is shown by the average distances between the nitrogen atoms in complex **3** (3.58 Å), which are much shorter than the 6.10 Å separating the central *t*Bu C atoms that lie in the *in* position of complex **4**. Hence, when stacked together, the bulky *t*Bu groups define a larger cavity space, whereas in complex **3**, the small amino substituents allow an increased flattening of the calixarene cone, leading to a smaller cavity volume, well adapted to a single guest water molecule.

Host–guest properties

Comparative ^{1}H NMR spectra of ligand **2** and its zinc complex **3** in various solvents are displayed in Fig. 3. Each spectrum is sharp and characteristic of an average C_{3v} symmetrical flattened

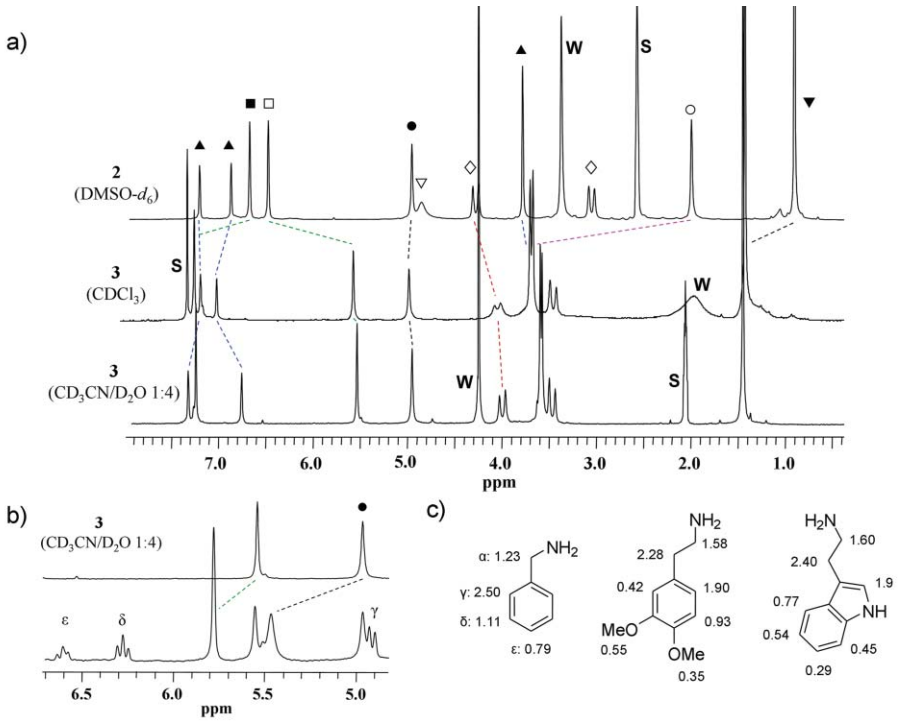

Fig. 3 (a) ^{1}H NMR profiles (250 MHz) of ligand **2** and its Zn(II) complex **3** in various solvents[8] (5 mM), (b) ^{1}H NMR signature of the benzylamine guest in a CD_3CN–D_2O 1 : 4 solvent mixture, and (c) values of the high field shifts [$\delta\Delta$ (ppm)] measured for three bulky guest amines hosted by **3**. ▼ $(CH_3)_3C$, ○ OCH_3, ▲ NCH_3 and H_{Im}, ◊ CH_2Ar, ● CH_{2Im}, □ H_{ArNH2} and ■ $H_{Ar/Bu}$; greek characters: guest protons; S: solvent; W: water.

cone conformation. As classically observed for such calix[6]arene-based ligands,[3,5–8,14] the methoxy resonance appears at a relatively high-field (1.97 ppm, Fig. 3a, upper spectrum), which indicates that they are oriented toward the center of the calixarene cavity. After Zn complexation, this methoxy resonance is displayed at a "normal" shift (*ca.* 3.5–3.6 ppm depending on the solvent,[8] see Fig. 3a, lower spectra), thus attesting to a switch in the alternate flattened cone conformation. Indeed, in order to coordinate the zinc dication, the imidazole arms must be projected toward the C_3 axis (*in* position), thus pushing the methoxy groups into the *out* position. Such a switch of the pendulum (as schematized in Scheme 1) is further attested by the large modification of the H_{Ar} resonances belonging to the calixarene core: independent of the solvent in which the complex has been dissolved, the aniline walls display H_{Ar} protons at a very high field (5.0 ppm, *in* position), whereas the aromatic units bearing *t*Bu groups at the large rim see their H_{Ar} protons at a low field (*ca.* 7.2 ppm). The *t*Bu δ shift changes (0.97 ppm for the ligand in DMSO *vs.* 1.4 ppm for the complex either in $CDCl_3$ or in a MeCN–D_2O mixture) further substantiates the conformational switch.

As previously reported[3] for the parent Zn complex **4**, the addition of a variety of small ligands (DMF, acetamide, DMSO, EtOH, aminopropanol, heptylamine) to complex **3** leads to their encapsulation in the calixarene cone. This was attested by the appearance of new peaks in the high field area (see the ESI†), with very little change to the resonances of the calixarene core, the conformation of which was barely affected. Hence, complex **3** displays similar host properties for small guest molecules compared with host **4**.[3] However, two major differences in their behavior were observed.

- First, complex **3** is soluble and stable in aqueous solvents. Indeed, the ^{1}H spectrum recorded in a 1 : 4 mixture of CD_3CN–D_2O shows a profile that can almost be superimposed on that recorded in $CDCl_3$ (Fig. 3a).[8] This indicates that the cone is maintained thanks to the strong complexation of the Zn(II) ion. With host **4**, the first drop of water added to an acetonitrile solution of the complex induced its precipitation. This shows that the replacement of three *t*Bu groups with three NH_2 moieties has a strong impact on the solubility properties of the complex and allows its solubilisation in an 80% aqueous medium at 10 mM concentration.
- Second, complex **3** can host much bulkier guests than **4** does. This is best illustrated by its higher affinity for benzylamine, dimethyldopamine or decarboxylated tryptamine when compared with **4**, which either did not host these guests or underwent decoordination of Zn(II) from the calixarene core. With host **3**, their *endo*-binding was cleanly observed upon the addition of one equiv. of these amines to the complex (*ca.* 5 mM) in any solvent: $CDCl_3$, MeCN or aqueous medium. A representative signature is shown Fig. 3b together with the ^{1}H high-field shifts observed for the bulky guests, attesting to their inclusion in the aromatic macrocycle. As for host **3**, the highest up-field shifts are observed for the protons situated in the β and γ positions relative to the coordinated amino group (see Fig. 3c), which indicates a similar positioning of the Zn–guest ligand adduct relative to the host calixarene skeleton. Interestingly, in the case of these bulky ligands, and in contrast with the above mentioned small guests, their inclusion in the calixarene core induces strong modifications of the host resonances. As illustrated by Fig. 3b, the aromatic protons that are in an *in* position (H_{ArNH2}) together

with the methylene groups connecting the *tris*-imidazole core to the macrocycle, undergo a down-field shift of *ca.* 0.3 and 0.5 ppm, respectively. This shows that each aromatic unit straightens up to a position that is more parallel to the C_3 axis, thus opening the cavity entrance and increasing the cavity space to allow the guest ligand to fit in. This interestingly denotes an induced fit process by which the cavity adapts to its guest, folding-in when water is the *endo* ligand, and unfolding to accommodate larger guests.

The XRD molecular structures of complex **3** with dimethyldopamine and benzylamine as the guest ligands are displayed in Fig. 4.[15] As in the case of the aqua complex, the calix[6]arene core is in a pseudo C_{3v} symmetry with a tetrahedral Zn(II) ion bound to the imidazole arms and to the guest ligand. In each case, the coordinated primary amino function is stabilized through two hydrogen bonds with the oxygen atoms belonging to two *t*BuAr units [d(N···O) = 2.92–3.01 Å].[14] The guests are further stabilized by CH···π interactions[11,16] with the aromatic walls of the calixarene [d(C89···centroid) = 4.02 Å each, d(C90···centroid) = 3.77 Å, d(C92···centroid) = 4.10 Å and d(C96,N69) = 3.57 Å for the dopa adduct], (see Fig. 4).

Here, the XRD structures show an important modification of the cone conformation compared to the aqua complex depicted in Fig. 1. Indeed, the aniline units are now almost parallel to the C_3 axis and the average distance between aniline nitrogen atoms has increased from 3.48 Å for the aqua complex to 6.57 Å and 7.53 Å for the dopa and benzylamine complexes, respectively. Such a change in the cone shape was obviously induced by the inclusion of the voluminous guest, necessitating the wide opening of the cavity door, as well as the increase in the cavity space.

Discussion and conclusion

In conclusion, this study shows that an *a priori* minor structural change at the large rim of a receptor has a major impact on his properties. Not only does it increase its water solubility and allow larger guests to fit in the cavity, but it also confers interesting adaptive properties to the cavity. Indeed, the replacement of the *t*Bu door by small NH_2 groups increases the degree of freedom of the aromatic units to rotate one relative to the other. This allows the calixarene to tune its cavity space for a best fit to the guest size, which can range from a single water molecule to the large dopa derivative. The increased flexibility also allows the optimization of non-covalent stabilizing interactions within the cavity *i.e.* hydrogen-bonds, OH–π and CH–π interactions with the aromatic walls of the more or less flattened cone core. Such a behavior stands in strong contrast with cyclodextrin[17] or

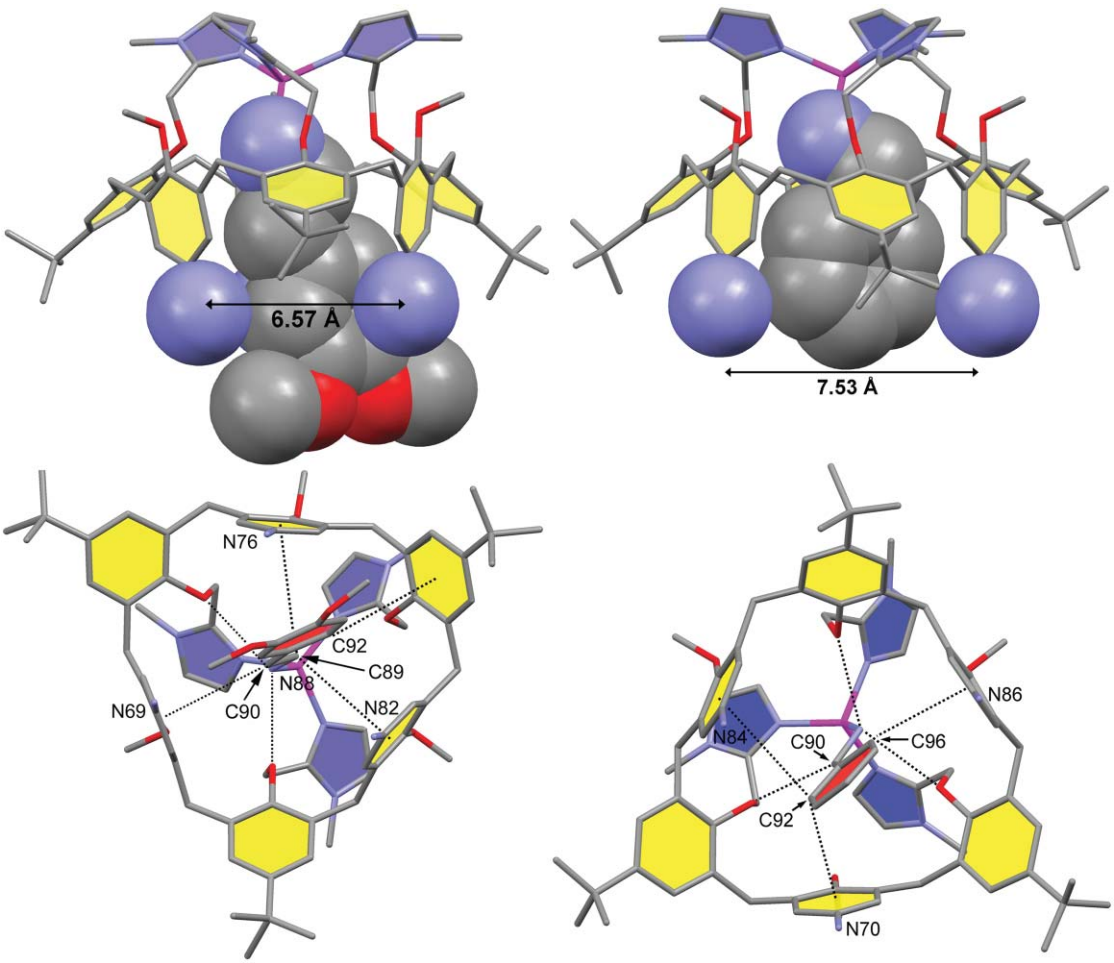

Fig. 4 XRD structures of complex **3** with bulky guest ligands L. Left: L = dimethyldopamine; right: L = benzylamine. Hydrogen atoms and counter anions have been omitted for clarity.

resorcinarene-based[18] receptors, which, due to their rigidity, can display strong binding to organic guests, but only on the condition that there is a good fit between the guest size and the cavity size (described as the 55% rule by Rebek and Mecozzi).[19] Hence, a rigid receptor presents a disadvantage as only a restricted number of guests will display a strong affinity for the receptor: only those whose size fits with the 55% rule. In our system, the high, but controlled, flexibility of the host turns out to be an advantage, with a cavity that adapts to the size and nature of the guest for an optimized host-guest binding energy.

From a biomimetic point of view, it is first worth noting that dicationic 4-coordinate Zn(II)aqua complexes, which model the active species of a number of hydrolytic enzymes, are rare species, difficult to stabilize with a simple tridentate ligand due to the high acidity of the coordinated water molecule. Complex **4** was the first example of its kind. Complex **3** displayed in Fig. 1 and 2, provides another example that illustrates the importance of the second coordination sphere for the stabilization of the dicationic core. It is also interesting to relate this system to enzyme–substrate complexes. Highly specific enzymes generally display a relatively rigid pocket for the selective recognition of a unique substrate. In contrast, enzymes that contribute to the metabolism of drugs and xenobiotics, such as cytochromes P-450, must carry out the efficient binding of a wide variety of substrates within the same active pocket. It has been recently recognized that this class of P-450 enzymes has indeed a very flexible proteic backbone that allows the active pocket to shrink or expand depending on the substrate size.[20]

We are now currently exploring the specific recognition properties that the presence of an amino door with acid–base properties can bring to our calix[6]arene-based versatile receptors.

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