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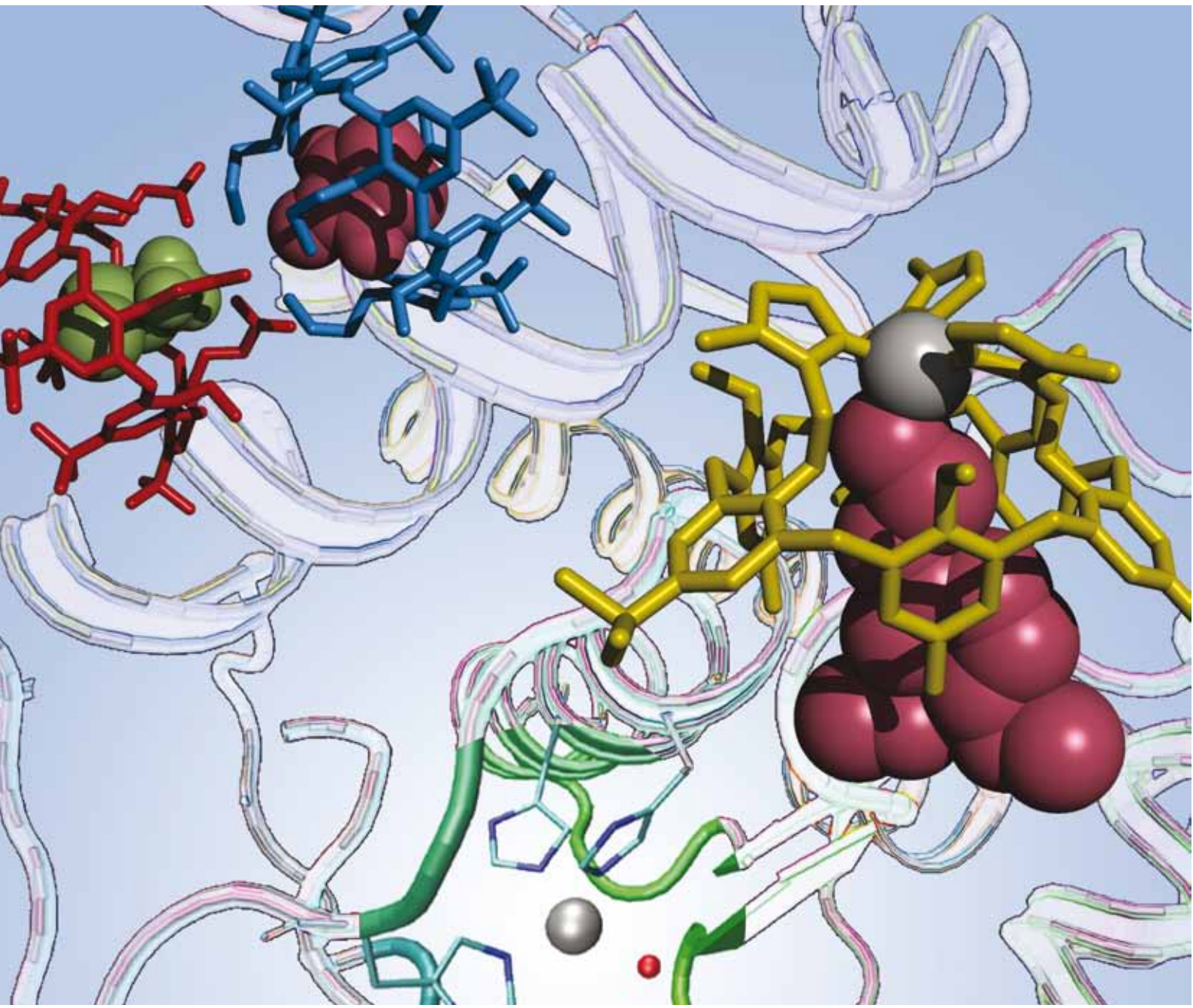

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Biomimetic and self-assembled calix[6]arene-based receptors for neutral molecules

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The selective recognition of substrates or cofactors is a key feature of biological processes. It involves coordination bonds, hydrogen bonding, charge/charge and charge/dipole interactions. In this Perspective, we describe how the calix[6]arene core can be functionalized and shaped to act as a biomimetic molecular receptor. The strategy relies on the selective introduction of three amino arms on alternate phenolic positions. Upon metal ion binding or self-assembly *via* multiple ion-pairing and H-bonding, these amino arms are projected towards each other, thus closing the calixarene small rim. The resulting cone-shaped receptors act as molecular funnels displaying high affinities for a variety of neutral guests. Their hosting properties can be finely tuned by changing the small or the large rim or by allosteric effects. Induced-fit processes are also often observed as the cavity can expand for large guests or shrink for small ones. Hence, the different families of calix[6]arene-based receptors presented here highlight the importance of having a flexible and polarized hydrophobic structure to accommodate the guest.

1 Introduction

In biology, molecular recognition is a fundamental process allowing capture and transmission of information, regulation, and selective chemical transformation. Specific protein-ligand binding arises from weak but multiple non-covalent interactions such as electrostatics, hydrogen bonding,[1] CH/π[2] and cation/π[3] interactions, coordination bonds,[4] as well as hydrophobic effects.[5,6] All these interactions must be strong enough to ensure selective binding and weak enough to allow reversibility. This is particularly stressed for enzymes: beside their catalytic activity, they first act as molecular funnels allowing substrate entrance to the active site and specific binding. Protein folding induces structuring of its backbone, which then defines the micro-environment at the active site together with the corridor connecting it to the bulk. In the case of metallo-enzymes, it also preorganizes the coordination core for the metal ion, while maintaining a free coordination site directed

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David Coquière

David Coquière obtained his PhD in 2006 under the supervision of Prof. O. Reinaud, at Paris Descartes University. Then, he moved to Groningen, The Netherlands, to join Prof. Feringa's group as a post-doctoral fellow for two years and worked on asymmetric catalysis based on biopolymer (DNA, protein) under the supervision of Dr Roelfes. He is now working in a biotech company at Lyon, France.

Stéphane Le Gac

Stéphane Le Gac completed his PhD in organic chemistry in 2006 under the supervision of Prof. I. Jabin, at Le Havre University. After a first postdoctoral period at the Free University of Brussels, Belgium, he joined the group of Prof. R. Nolte in Nijmegen, The Netherlands, where he is currently working as a postdoctoral fellow on the selective functionalization of chromophoric nanowires.

toward the substrate pocket. Part of the reactivity of the metal center is controlled as well by the proteic residues next to the metal ion, constituting a second coordination sphere.

Among the great variety of metallo-enzymes, interesting subfamilies present a mononuclear active site where a single metal ion is coordinated to a polyimidazole core.[7] For example, many metallo-proteases possess in their active site a mononuclear zinc center coordinated by three histidine residues and a water molecule (Fig. 1).[8] In proteases, the interaction with the substrate results in both selective recognition and activation for the nucleophilic attack of the general base assisted coordinated water. The activity of inhibitors is also often based on their ability to coordinate the metal ion at the active site. They then act as a ligand displacing the water molecule bound to Zn(II). Hence, recognition and activity are controlled by the microenvironment which defines the coordination spheres of the metal ion, key for its hydrolytic activity, together with the pocket allowing selective binding and acute positioning of substrates (and inhibitors).

Chemical modeling of metallo-enzymes is important for understanding the fundamental mechanisms involved in bio-catalytic cycles. It allows studying and evaluating the impact of the various factors that govern the interaction of the metal center with exogenous molecules, as small model compounds are relatively easily accessible and tunable. To be relevant to the active site, the model must first reproduce and control the first coordination sphere of the metal ion. Three important features are thus required: i) a polydentate ligand to mimic the geometry and the chemical nature of the amino-acid residues bound to the metal, ii) an appropriate environment to isolate the metal center and control the nuclearity of the system, and iii) a protected vacant site to allow coordination and exchange of exogenous ligands. The poly(histidine) motif, frequently encountered in metallo-enzymes, has guided the conception of a number of poly-aza ligands able to reproduce the first coordination sphere of the metal.[9] Few biomimetic complexes, however, have combined a metal ion and a hydrophobic cavity.[10,11]

Inspired by Nature, we are directing our efforts towards the elaboration of a biomimetic system that integrates the control of the second coordination sphere and the access to the metal center. Our strategy consists in the design of a half-open hydrophobic pocket, at the bottom of which a biomimetic metal-binding site is embedded. The role of the pocket is to define the microenvironment around the metal ion and act as a receptacle for selective guest binding with a funnel-shape allowing guest exchange (Fig. 1).

Ulrich Darbost

Ulrich Darbost obtained his PhD in 2004 under the supervision of Prof. I. Jabin, at Le Havre University. Then he moved to Montreal, Canada, to join Prof. J. D. Wuest's group as a post-doctoral fellow to work on molecular tectonics. He went back to France in 2006 and he is currently assistant professor at the University of Lyon, where he is carrying out research on calixarenes.

Ivan Jabin

Ivan Jabin was born in 1968 in France. He obtained his PhD in Organic Chemistry from the Pierre et Marie Curie University (ESPCI-UPMC) in 1996 and then spent two years as a post-doctoral fellow, first at Lehigh University (USA) and then at the Conservatoire National de Paris des Arts et Métiers (Paris, France). In 1998, he was named an assistant Professor of Chemistry at the University of Le Havre (France). After eight years, he joined the Free University of Brussels (Belgium) as a full Professor. His current research interests include the synthesis and study of new classes of molecular receptors. Ivan Jabin and Olivia Reinaud have been collaborating since 2000.

Olivier Sénèque

Olivier Sénèque obtained a PhD from the University of Paris XI under the supervision of Prof. Olivia Reinaud in 2002. Then he spent two postdoctoral years in the group of Pascale Delangle at the CEA-Greanoble before being appointed as a CNRS researcher in 2004. His current interest is focused on metallopeptides.

Olivia Reinaud

Olivia Reinaud completed a PhD in organic chemistry (1987, Dr M. Maumy, ESPCI-UPMC) and after a one-year postdoc in biochemistry (Dr D. Mansuy, Paris Descartes University), she was appointed CNRS researcher and developed novel biomimetic copper catalyzed processes (ESPCI). She took a two year sabbatical in inorganic chemistry (Delaware University, USA, Prof. K. Theopold). Upon return to France, she started a new project associating organic, inorganic and supramolecular chemistry with some "bio-inspiration". Since 2001, she has had a full Professorship at Paris Descartes. Her current research interest lies in "Supramolecular Bio-Inorganic Chemistry", dealing with biomimetic metal complexes based on calix[6]arene derivatives.

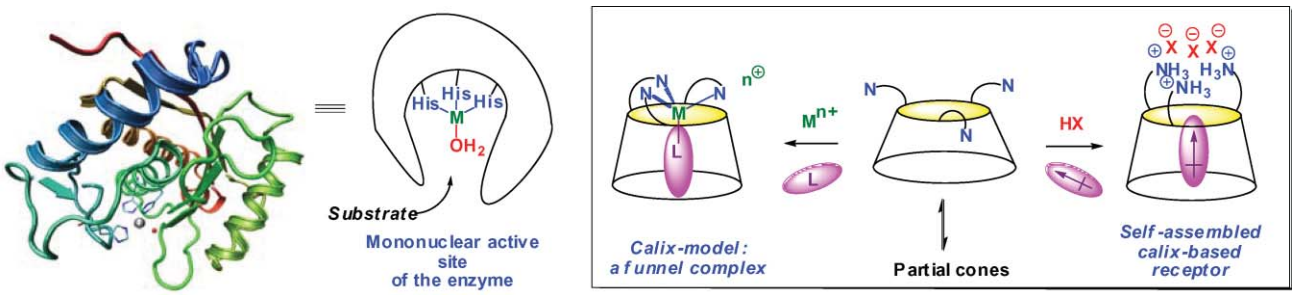

Fig. 1 Left: Schematic representations of the 3D structures of a mononuclear metallo-enzyme (Adamalysine, a Zn-matrix metallo-peptidase from snake venom, PDB code: 1IAG). Right: shaping the calix[6]arenes into a cone through two different strategies.

A possible way to construct such a biomimetic supramolecular system is to use readily available building blocks such as cyclodextrins (CDs),[12] cyclotriveratrylenes (CTVs),[13] resorcinarenes,[14] or calixarenes[15,16] (Fig. 2). These four classes of macrocyclic receptors display very different features in terms of shape, size, symmetry pattern, rigidity, and hosting properties.

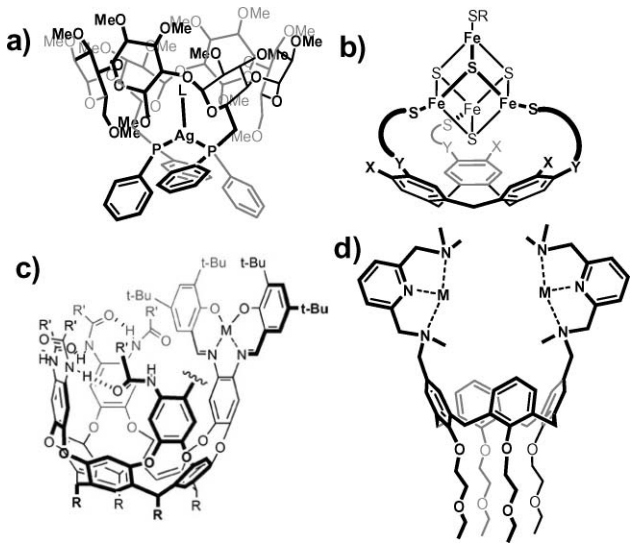

Fig. 2 Examples of bio-inspired systems based on metal centers appended to a hydrophobic cavity[18] with: (a) α-cyclodextrin,[19] (b) cyclotriveratrylene,[20] (c) resorcinarene,[21] and (d) calix[4]arene.[22]

- CTVs and resorcinarenes have a bowl shape, whereas CDs and calixarenes are conic, open at both sides.
- Various sizes of cyclodextrins and calixarenes are available and methodologies have been developed for appending aromatic units to transform resorcinarenes into deep cavitands.[14] Such modifications are more difficult with CTV which suffers from its smallness.
- Some hosts display a C_3 (CTV) or C_6 axis (α-CDs, calix[6]arenes), while others are C_{4v} symmetrical (resorcinarenes and calix[4]arenes).
- The first three classes present a rigid base whereas calixarenes are highly flexible.
- Natural CDs are water-soluble and work mainly through hydrophobic effects, whereas the other hosts mainly bind guests in non-polar solvents if not appended by water-solubilizing substituents.
- CDs display an aliphatic but polar inner core well adapted to electron-rich guest binding, whereas the three other macrocycles display π-rich aromatic walls favoring cation-π and London-type host–guest interactions.[17]

In order to associate metal ion interaction with inner cavity binding, a pocket large enough for hosting a molecule of the size of benzene is required, to which a tridentate coordination core can be appended with an introverted free coordination site. With the bowl-shape cavities, the metal core has to be grafted to one side-wall, which makes obtaining an introverted coordination site difficult. In contrast, the cone-shape offers the possibility of setting the metal core at the bottom of the cavity open at the other side to give rise to funnel-like systems. Although CDs appear to fit these specifications very well, their selective functionalization remains a very difficult task.[23] In contrast, a wide variety of methodologies have been described for calixarenes.[15] Calix[4]arene-based receptors are the most developed as they are easily constrained in a given conformation through small rim *per-O*-alkylation. However, their small rim is too narrow to allow an organic guest to go through. As a result, they have been mostly used as a platform for the preorganization of a binding site outside of the cavity, with no direct connection between the hydrophobic cone and the metal site (Fig. 2).[24] On the other hand, higher oligomers such as calix[6]arenes[25] are difficult to constrain into a cone as *O*-alkylation does not prevent the facile "through the annulus" ring inversion of their aromatic units. The resulting high flexibility of these macrocycles constitutes an obstacle for obtaining a receptor with a well-defined cavity.[26] One strategy to remedy this problem consists in grafting covalent bridges at one rim[27] and, in this regard, various calix[6]arene-based molecular receptors have been reported.[28,29] An alternative strategy, which is less synthetically demanding, is to use coordination chemistry for shaping the macrocycle. The calix[6]arene must be first functionalized at the small rim by three amino arms on alternate phenolic positions. Their binding to a metal ion then constrains the calix-core into a cone, leaving a single coordination site accessible for guest binding inside the funnel-like cavity[30] (Fig. 1). On this basis, a first generation of calix[6]arene-based ligands has been developed (Fig. 3). Their corresponding metal complexes were baptized "*funnel complexes*".[31,32]

More recently, we have discovered that the calix[6]-based ligand presenting three primary amino-arms can be shaped into a cone in the absence of any metal ion. Indeed, in this case, the protonated ethylammonium arms can be projected towards each other by self-assembly with anions, thus sealing the small rim of the calixarene

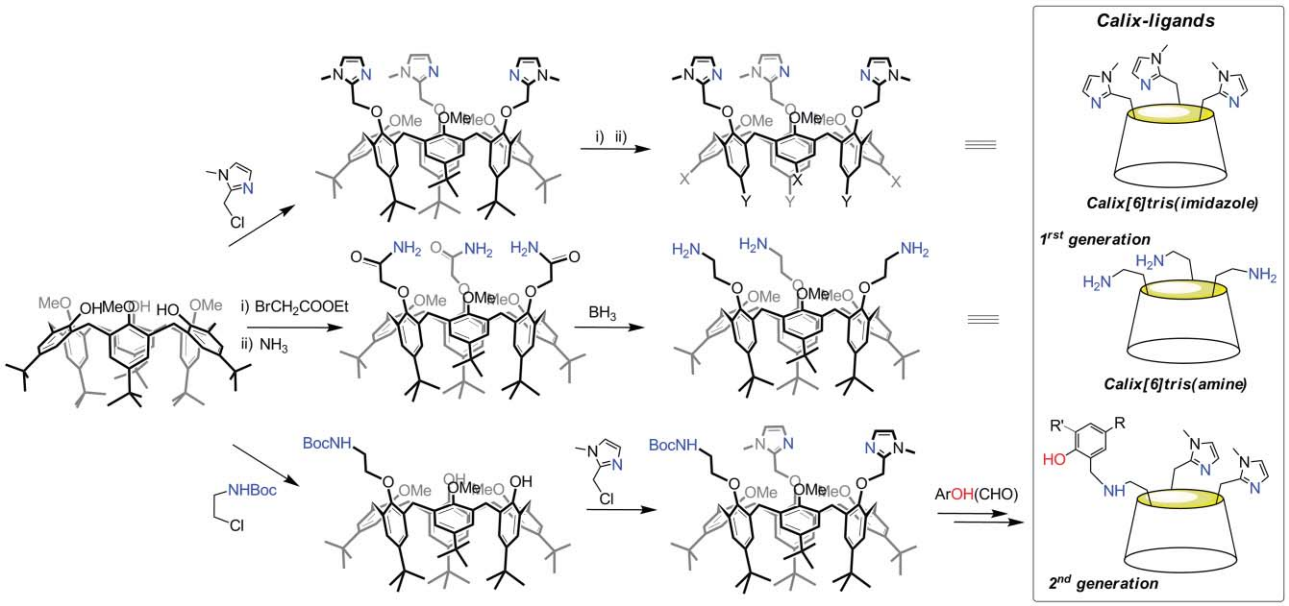

Fig. 3 Synthetic routes to the first and second generations of calix[6]triaza ligands (for more examples, see ref. 35 and 40). (i) and (ii) HNO_3 or HSO_3Cl (then hydrolysis or aminolysis). The X and Y substituents can be further derivatized (*e.g.* X = NO_2 → NH_2 → triazole). For calixarenes in cone conformation, the small rim is defined by the oxygen atoms of the phenolic units and the large rim by their *para*-substituents (*t*Bu, X, Y).

(Fig. 1).[33,34] The resulting highly polarized cavity also behaves as a remarkable receptor for neutral molecules with, however, different guest affinities from the metal-based ones.

Here, we describe the properties of receptors first rigidified through metal ion binding, then those obtained through self-assembly *via* multiple ion-pairing and H-bonding. The aim of this paper is not to present functional enzyme models, but rather to show how bio-inspired concepts led us to elaborate relatively simple tools for molecular recognition. In each case, we will show how the properties of the resulting funnel-like hosts can be tuned either at the small rim or at the large rim of the calixarene. Very interestingly, this highly versatile system exhibits allosteric properties where the flexibility of the calix[6]arene macrocycle is turned into an advantage. This provides receptors with exceptionally broad scope, which, by many ways, may be considered as biomimetic as it will be discussed throughout this Perspective.

2 Synthesis

Tridentate *N*-ligands are readily obtained from p-*t*Bu-calix[6]arenes *O*-protected in alternate positions by three methyl groups (in some cases, other *O*R derivatives have been used). Their preparation is relatively straightforward, allowing grams scale syntheses. The calix[6]tris(imidazole) and tris(ethylamine) ligands depicted in Fig. 3 are representative members of this first generation of biomimetic calix[6]N_3-ligands. They present either aromatic or aliphatic *N*-donors, hence displaying different electronic and steric properties.[35,36,37] Once the amino-arms are grafted at the small rim, the calix-ligands can be selectively modified at the large rim. Indeed, the protonation of the *N*-arms in acidic medium deactivates the connected aromatic units towards electrophilic attack, allowing the selective *ipso*-substitution of the *t*Bu groups of the anisole aromatic units using HNO_3[38] or HSO_3Cl.[39] A combination of reactions leads to a great variety of patterns henceforth accessible at the large rim. The key point is to monitor the large rim reactivity through the small rim substitution pattern.

The second generation of ligands present a fourth donor (here *ArO*H) grafted onto one amino arm. Their synthesis requires the selective mono-functionalization of the trimethoxy-calixarene as schematized in Fig. 3.[41]

In solution, these calixarenes adopt a major cone conformation that is flattened due to the alternate positioning of the aromatic units in *in* and *out* positions relative to the cavity. However, the conformation is not locked and the aromatic units undergo pirouettes in solution, a process that is often slow on the NMR time scale, but always fast on the experiment time scale. As such, these compounds do not behave as hosts capable of binding a guest molecule in their cavity.

3 Shaping the cone through metal-ion binding

3.1 *Funnel* complexes: a practical guide

3.1.1 The Zn(II) "*funnel*" complexes. Complexation of one equivalent of Zn(II) to calix[6]tris(imidazole) ligands leads to the formation of four-coordinate mononuclear complexes where all three imidazoles wrap the metal dication in a helical way (Fig. 4). The apical binding site is oriented toward the center of the cavity and occupied by a guest ligand. The calixarene adopts a cone conformation that is locked since the aromatic units cannot undergo flipping around the methylene bridges of the calix-annulus due to the metal binding to the three nitrogen arms. Nevertheless, the aromatic units still stand alternatively in *in* and *out* positions relative to the cavity. This flattened conformation is the opposite of the one observed for the free ligand, as the anisole *t*Bu substituents now adopt an *in* position relative to the

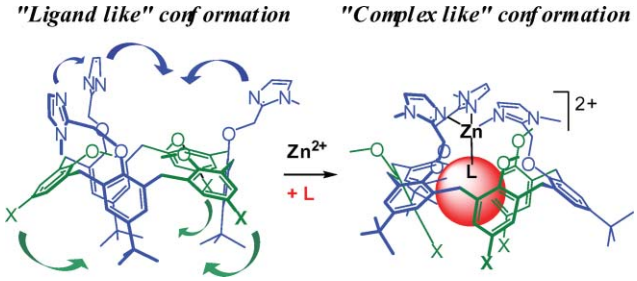

Fig. 4 Shaping the calix[6]arene core into a Zn(II) *funnel* complex.

three others. Altogether, they form a door controlling the cavity entrance.

3.1.2 A bis-aqua Zn(II) complex: modeling the active site of mono-Zn enzymes. Several chemical systems have been developed by various groups to reproduce the $[Zn(His)_3(OH_2)]^{2+}$ coordination core encountered in many hydrolytic Zn enzymes.[9] Surprisingly, dicationic zinc aqua model complexes have proven extremely difficult to stabilize and most classical models only succeeded in stabilizing Zn-hydroxo species because of the high Lewis-acidity of the Zn(II) center bound to only four neutral ligands. In strong contrast, the reaction of the calix[6]tris(imidazole) ligand with $Zn(H_2O)_6(ClO_4)_2$ in THF, readily yields a very stable dicationic zinc-aqua complex.[42] The complex actually presents two water molecules buried in the calixarene cavity, with only one of them coordinated to Zn. The second water molecule is suspended in the heart of the cavity by a very strong hydrogen bond to the aqua ligand and an OH/π stabilizing interaction. Each water molecule is also hydrogen-bonded to an oxygen atom belonging to the calixarene core, thus acting again as a second coordination sphere. A comparison with the active site of carbonic anhydrase shows surprising similarities (Fig. 5). The exceptional stability of this calixarene-based Zn-aqua complex is best illustrated by its reluctance to deprotonation in the presence of one molar equivalent of an amine. Instead, both water molecules are displaced by a primary amine yielding the 4-coordinate adduct depicted in Fig. 6. Such a behavior stands in contrast to the strong acidity expected from a water molecule coordinated to a dicationic tetrahedral zinc center and is well explained by the establishment of multiple stabilizing interactions within the calixarene cone, as it is observed in the enzyme.

This complex represents the first structural model for the Zn-aqua species found in enzymes and nicely illustrates the importance of the microenvironment. Here, the calix core constrains the

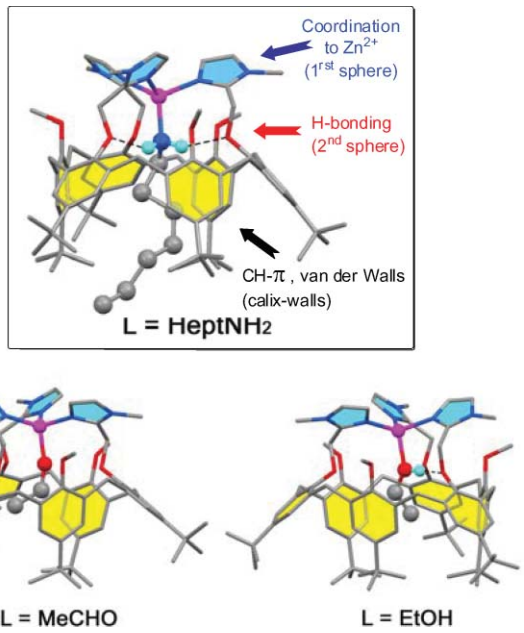

Fig. 6 XRD structures of dicationic Zn(II) *funnel* complexes.[31,44]

metal ion in a tetrahedral geometry, precluding a second guest as small as a water molecule to sit at the small rim. The corollary of this feature is that such a model will not allow mimicking the five-coordinate intermediate formed during enzymatic catalysis. Indeed, no hydrolytic activity has been observed. On the other hand, this model has allowed study of, for the first time, the binding properties of such a constrained Zn(II) center. The facile substitution of the two water guests by organic ligands highlights the exceptional affinity of the metal ion for a wide variety of exogenous donors, spanning from the basic amines to the weakly donating aldehydes (*vide infra*).

3.1.3 XRD structures: tetrahedral dicationic Zn(II) complexes. When crystallized out of a solution containing small organic coordinating molecules (L), ternary complexes can be isolated.[31,36,44] In each case, X-ray diffraction analysis shows a Zn(II) center in the regular tetrahedral environment provided by the tris(imidazole) core and the guest ligand L (Fig. 6). With protic guests such as amines, alcohols or primary amides, hydrogen bonds always connect their acidic protons to one or two calixarene phenoxyl units. The guest conformation often undergoes gauche interactions for an optimized filling of the calixarene cavity with stabilizing CH/π interactions between the guest alkyl chain

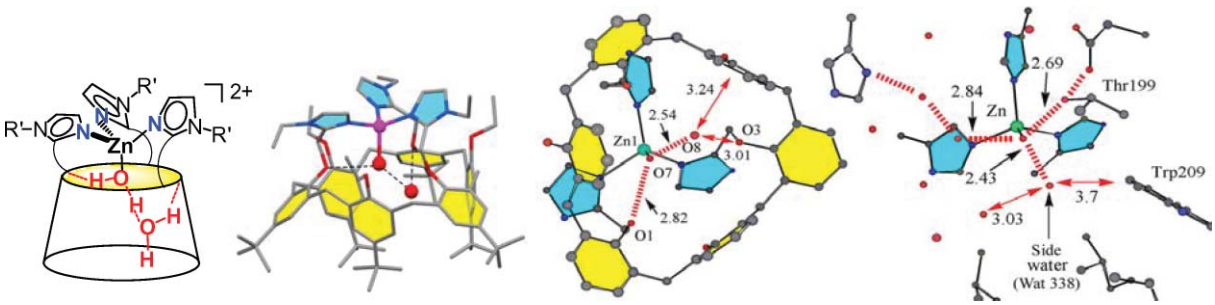

Fig. 5 XRD structures of, from right to left, the active site of carbonic anhydrase II (crystallized at pH 6)[43] and the calix-based model compound (bottom and side views, respectively).[42]

and the aromatic walls of the host. The XRD structure of the heptylamine complex displayed in Fig. 6 nicely illustrates all these features. The ethanol[44] and acetaldehyde[36] ternary complexes, which have been characterized by XRD as well as in solution, provide interesting models for substrate binding in liver alcohol dehydrogenase (LADH),[45] a zinc enzyme catalyzing the reversible dehydrogenation of alcohols to aldehydes *via* hydride transfer to NAD^+.

3.1.4 NMR studies: mapping the cavity. ^{1}H NMR spectroscopy has proven to be a powerful tool to monitor the presence of a coordinating molecule (L) inside the cavity.[31] Studies in $CDCl_3$ showed the easy exchange of the guest ligand with only little change in the C_{3v} flattened cone conformation of the calixarene, in agreement with the XRD data. With the *hexa-t*Bu-calix[6]tris(imidazole) ligand, the peaks of the included coordinated molecule are usually very sharp and well separated from those of the unbound species. This indicates that chemical exchange at the metal center is slow on the NMR analysis timescale. The up-field shifts ($\Delta\delta$) measured for the guest protons, due to the shielding effect of the π electron ring current, are dependent on their spatial position in the aromatic cavity of the calixarene (Fig. 7). An excellent correlation between their position relative to the coordinating heteroatom and the corresponding $\Delta\delta$ is observed for all guests.[31]

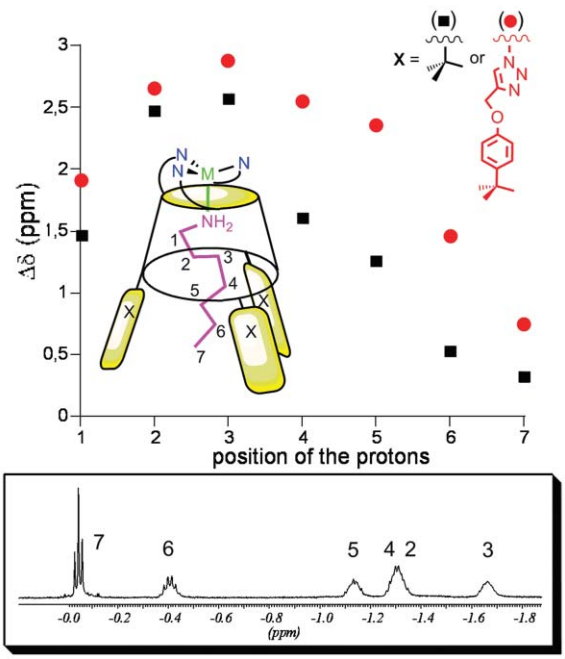

Fig. 7 Representative high-field shifted ^{1}H signature of an included guest (L = $CH_3(CH_2)_6NH_2$, $CDCl_3$, 300 K, 500 MHz) with mapping of the corresponding $\Delta\delta$ shifts as a function of the large rim substitution pattern.[31,58]

3.1.5 Chirality: the calix-core conveys chiral information. Due to their helical shape caused by the folding of their arms, these *funnel* complexes are chiral. In solution however, both enantiomers are in equilibrium.[46] Sterically hindered *N*-donors have the highest enantiomerization barrier (>70 kJ/mol). The helicity, which originates from the metal binding of the three amino arms, is transmitted to the calixarene core. The cavity becomes twisted, hence providing a chiral environment that ultimately is experienced by the guest. Conversely, a chiral guest can control the equilibrium between the two helical forms of the complexes, thereby transmitting its own chirality to the whole calixarene-based system (Fig. 8).[36]

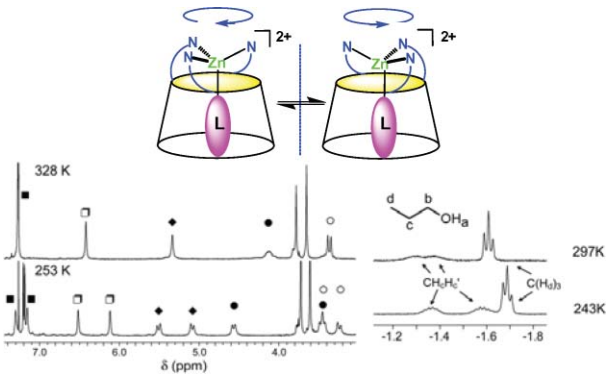

Fig. 8 Diastereotopic differentiation of the host {left, calix[6]-tris(imidazole)} and guest (right, L = EtOH) ^{1}H NMR resonances (400 MHz, $CDCl_3$) upon freezing the equilibrium between the helical enantiomers.[36]

3.2 *Funnel* complexes in action

3.2.1 Hosting properties: a highly selective receptor for neutral molecules. The relative capacity of organic molecules to bind to the Zn(II) center was evaluated by ^{1}H NMR spectroscopy through competition experiments in a non-coordinating solvent (Fig. 9). The equilibrium constants $K_{L'/EtOH}$ show that the selectivity of the inner-cavity binding is based on i) the σ-donor property of the guest ligand, ii) the possible establishment of hydrogen bonds between the guest and the small rim and iii) the relative host/guest geometries.

⇒ With primary amines, coordination to the metal center is stoichiometric and quantitative at mM concentrations. Amides and alcohols are also excellent guests, better than nitriles. Coordination of aldehydes and carboxylic acids is much weaker, although detected. Neither ether nor ketone yields detectable coordinated species.

⇒ Steric hindrance at the level of the coordinating atom and at its α position is a major factor of selectivity: whereas primary amines are the best ligands, secondary amines do not coordinate the metal center at all! Coordination of 1-propanol is 30 times stronger than 2-propanol.

⇒ Either a methyl substituent in the 2-position or a long alkyl chain does not preclude coordination at the metal center. However, benzo- and benzyl-nitrile are too sterically demanding to yield a stable adduct with the *hexa-t*Bu ligand.

⇒ Finally, the calix-cavity is surprisingly reluctant to host anions in spite of the presence of the dicationic metal center. Adding halides or hydroxides[47] in excess either leads to decoordination or it induces a rearrangement of the calixarene macrocycle to give dimers and trimers with the coordinated bridging anion outside the cavity. A recent study[48] has highlighted the role of the oxygen-rich small rim: in the conformation adopted by the tris(imidazole)-based complexes, all six oxygen atoms of the

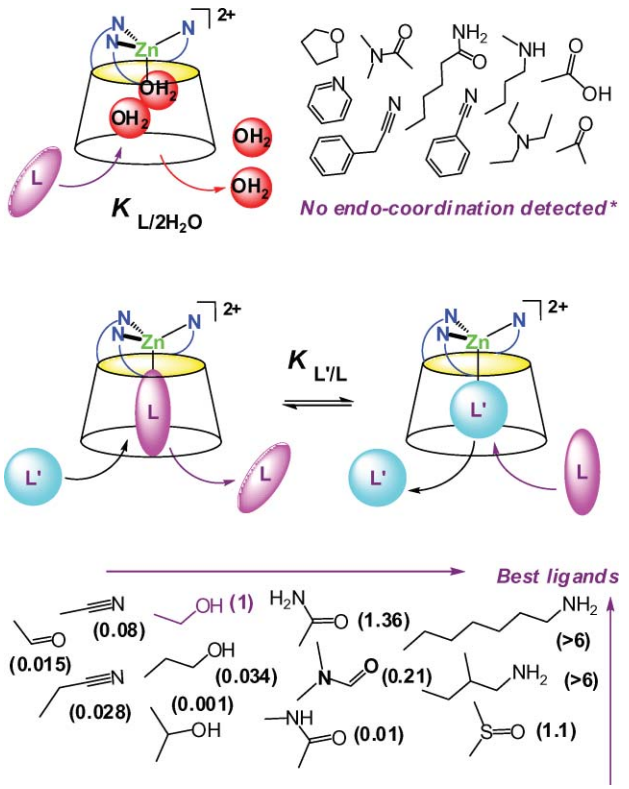

Fig. 9 Ligand exchange at the Zn(II) center of the *funnel* complexes based on the *hexa*-*t*Bu-calix[6]tris(imidazole) ligand. The equilibrium constants $K_{L'/EtOH}$ (exchange of L = EtOH for L′ at 298 K in $CDCl_3$) are given in parentheses.[31,42] *$K_{EtOH/2H2O}$ = 0.4 mol.L^{-1}. When no endo-coordination can be detected, $K_{L/2H2O} < 10^{-5}$ mol.L^{-1}.

macrocycle point their lone pairs towards the cone axis, at the level of the coordinating atom. If an anion were to occupy that position, a strong electrostatic repulsion would result and lead to the destabilization of the host–guest adduct.

3.2.2 Large rim tuning.

Opening the cavity. As schematized in Fig. 4, the *para*-substituents of the anisole units are oriented in an *in* position relative to the cavity, thus constituting a door that closes the entrance of the host. Removing these three bulky *t*Bu groups[49] or replacing them by smaller ones allows the cavity to host larger guests. For example, the tris(anilino) derivative[50] (corresponding to X = NH_2 in Fig. 4) accepts much larger guests, *e.g.* dimethyldopamine, tryptamine, benzylamine, than the parent compound (X = *t*Bu), for which endo-coordination of these bulky amines has never been detected.

Induced fit: recognition processes benefits from flexibility. Most interestingly, the replacement of the *t*Bu door by three small NH_2 substituents at the large rim has revealed a spectacular induced-fit behavior for guest binding. This is well illustrated by the comparison of the XRD structures shown Fig. 10.

With dimethyldopamine or benzylamine as a guest, the XRD structure evidences aniline walls standing almost parallel to each other to allow the large aromatic core of the guest to fit in. Surprisingly, the XRD structure of the related aqua complex revealed a single guest molecule in the cavity. This stands in contrast to the *hexa*-*t*Bu analog that hosts a second water guest to optimize the cavity filling. In the aniline-host, the stabilization of the acidic 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. In contrast, when stacked together, the bulky *t*Bu groups define a larger cavity space, thus requiring the hosting of a second water molecule to stabilize the structure (see Fig. 10, right). In other words, the increased flexibility allows the optimization of non-covalent attractive 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 with small as well as with large guests. Such a behavior stands in strong contrast to cyclodextrin[51] or resorcinarene-based[52] receptors, which, due to their rigidity, can display strong binding to organic guests, at the very condition however that there is a good fit between the guest size and the cavity size (described as the 55% rule by Rebek).[53] 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 the calix[6]-based 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. The importance of such a behavior has been well recognized for drug-receptor complexes, as well as for enzyme-substrate complexes in some cases.[54] Indeed, 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 face the efficient binding of a wide variety of substrates within the same active pocket. It has been recently recognized that this class

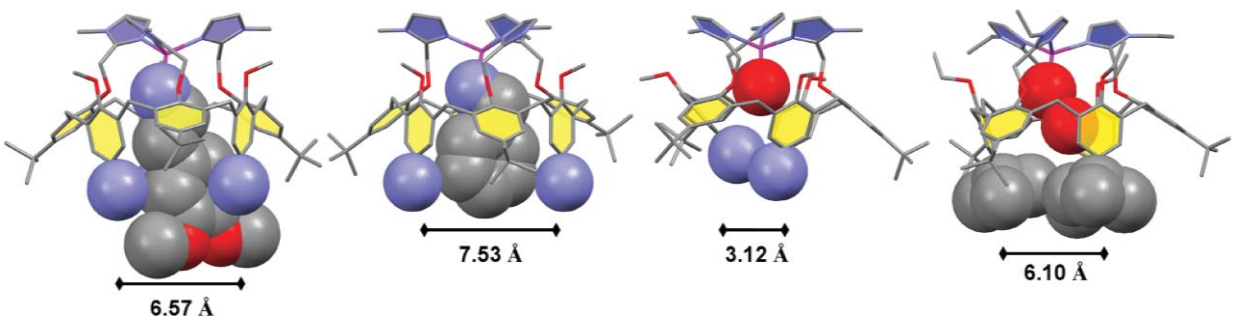

Fig. 10 Induced fit process undergone by the tris(aniline) derivative that allows larger and smaller guests to bind compared to the parent *t*Bu compounds, as illustrated by XRD structures. From left to right: the dimethyldopamine, benzylamine and mono-aqua Zn(II) complexes[50] and the bis-aqua derivative based on the *hexa*-*t*Bu ligand for comparison.[42]

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.[55]

Ditopic receptors. Para-substituents can also be involved in molecular recognition. The Zn(II) *funnel* complex based on the same tris(aniline) ligand for example, displays a high propensity to interact at the level of the large rim aniline door with a variety of cations, such as a second metal ion,[56] a single proton or an ammonium,[57] thus giving rise to stable tricationic structures. Thanks to the establishment of multiple hydrogen bonds at the level of the tris-aniline door, this receptor is able to discriminate between mono- and polyamines, *e. g.* it binds much better 1,3-propyldiamine than butylamine, provided, however, the former is monoprotonated. The remarkable selectivity of this multipoint recognition system is best illustrated by the regio-selective binding of a dissymmetrical triamine, as illustrated in Fig. 11.

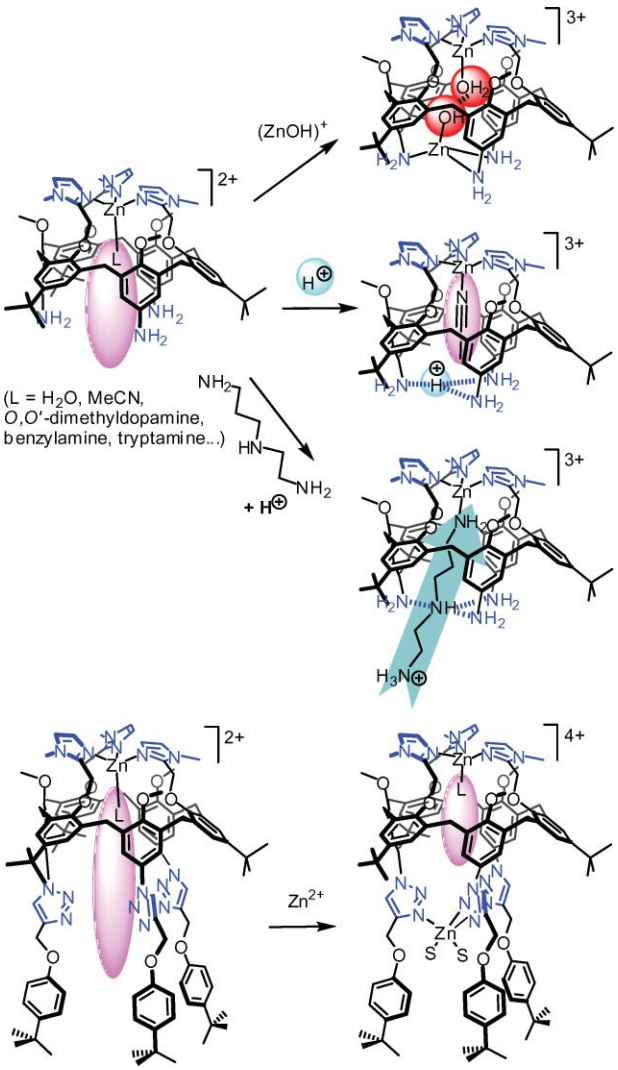

Fig. 11 Illustration of the capacity of the large rim substituents to act as a second binding core.[56–58]

Extending the hydrophobic cone. The aniline moieties of the above described ligand can be easily "clicked" with a variety of alkynes *via* their azido derivatives.[58] The resulting calixarenes substituted by three triazol groups at the large rim provide host complexes with an extended cavity. This was evidenced by the comparative shielding effect of the cavity between the mono zinc complex of calixarenes depicted in Fig. 7. Such a methodology has also opened routes toward dinuclear complexes as the triazole site can bind a second metal ion as depicted in Fig. 11.

3.2.3 Small rim tuning: implementation of an acid–base control for guest binding. The second generation of ligands (Fig. 3) was developed in order to introduce an additional functionality to the metal complexes.[59,40] The ligands present a fourth donor group covalently linked to one nitrogenous arm, which provides an additional cap to the system. This fourth donor can play the role of a redox-active function, such as a phenoxide, and participate in the oxidation of a substrate, hence providing a good functional model of the radical copper enzyme, galactose oxidase.[60] It can also act as a hemi-labile arm and control the inner binding.[61] Indeed, with ligand calix[6]N_3Ar*O*H (schematized in Fig. 12), three different protonation states for the corresponding Zn(II) complexes have been characterized: [Zn(II)N_3Ar*O*H]$^{2+}$, [Zn(II)N_3Ar*O*]$^+$ and [Zn(II)(OH)N_3Ar*O*]. Whereas the dicationic 5-coordinate species is very sensitive to guest binding, the mono-cationic complex binds a guest ligand with a lower affinity due to a decrease of the Zn(II) Lewis acidity.

The neutral species can be obtained upon reaction with a base to yield a hydroxo complex or with an anion such as a chloride that coordinates the metal center from the outside of the calixarene cavity. The simultaneous binding of two anionic donors induces an impressive conformational reorganization of the system. One imidazole arm is released by the metal center. The other one undergoes self-inclusion into the π-basic calixarene cavity, thus precluding any guest inclusion. As a result, the calix[6]N_3Ar*O*H-based Zn(II) complexes act as an acid–base switch for guest binding. Several aspects of this system appear reminiscent of Zn-peptidases of the astacin and serralysin families.[8] For these enzymes, in addition to the three histidine residues, a side chain tyrosine coordinates the metal ion and its role has been questioned. This model system suggests that one role is to accurately control the activity of the enzymes as the pH varies, acting as an off-switch upon a pH rise.

3.3 Zn complexes with the calix[6]tris(ethylamine) ligand: exo-binding for endo tuning

When the aromatic imidazole donors are replaced by three primary ethylamino-arms, the corresponding Zn(II) complexes present quite different features. The Zn(II) ion remains in a tetrahedral environment thanks to its coordination to the calix-N_3 core and to an exogenous donor, thus constraining the calix core into a cone. A major difference, however, stems from the decrease of steric hindrance at the nitrogenous sites, which now allows external binding of exogenous ligands to Zn. Primary amines, carboxylates, sulfonamides and chloride are now external donors that cap the system from the outside. With hydroxide, an OH-bridged dinuclear species is produced (Fig. 13).[62] In all cases, the flattened cone of the calixarene remains accessible to a guest, which, however, cannot coordinate the metal center like in the tris(imidazole) system. Here, the intra-cavity binding only involves non-covalent electrostatic features: charge–dipole and CH–π interactions become essential for efficient hosting of

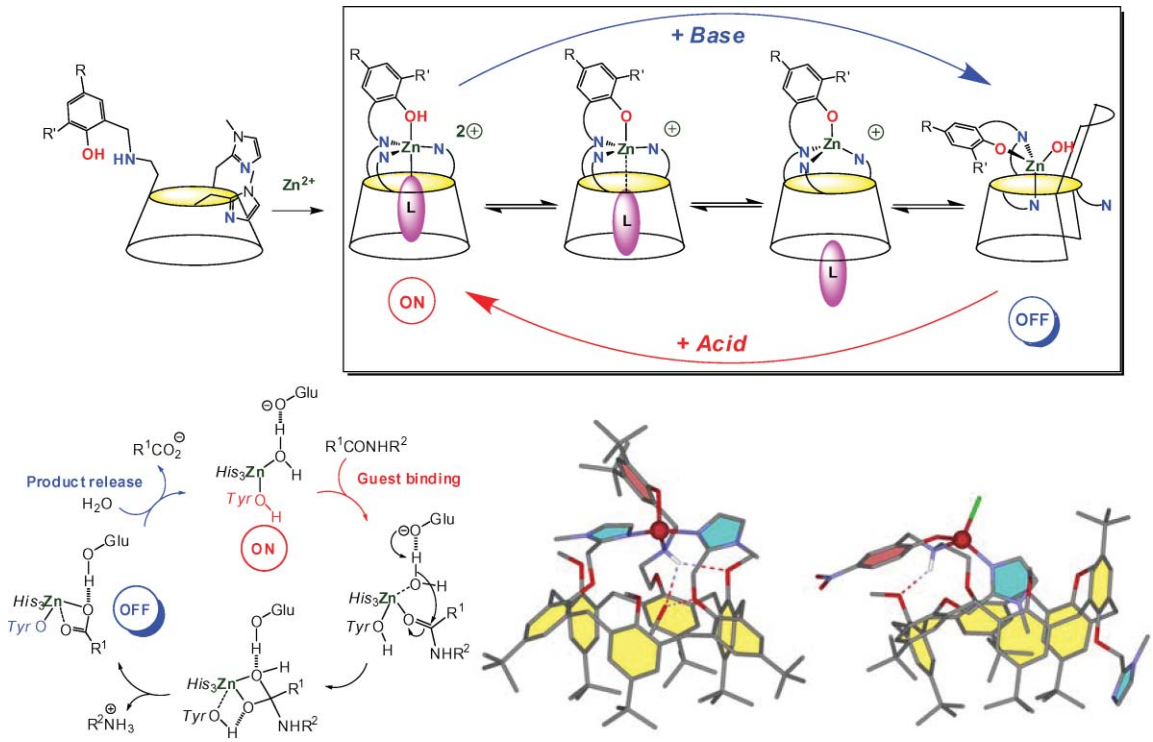

Fig. 12 Acid–base switch for guest binding by the calix[6]N_3Ar*O*H based Zn(II) complexes. Bottom, from left to right: proposed mechanism for the peptidase activity of astacyn and serralysin Zn-enzyme families, XRD structures of the monocationic phenoxide complex with a non-coordinated MeOH guest and the neutral chlorophenoxide complex presenting a self-included imidazolyl arm.[61]

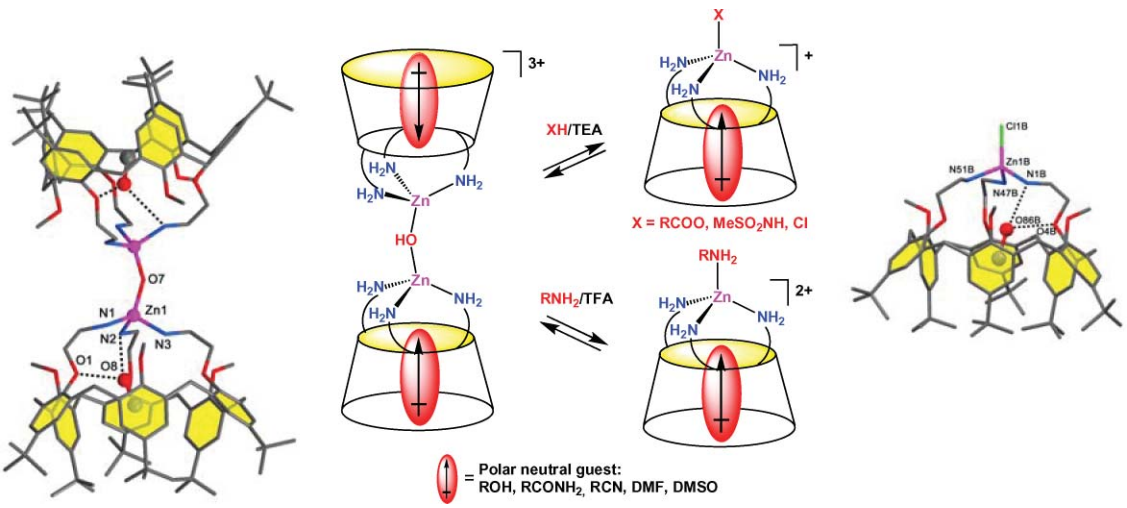

Fig. 13 Left: XRD structure of the dinuclear μ-hydroxo complex with included MeOH molecules. Middle: the different Zn(II) complexes obtained from the calix[6]tris(ethylamino) ligand in chloroform. Right: XRD structure of the mononuclear monocationic complex with a chloride as an external donor and an included MeOH molecule.[62]

polar neutral guests, with possible additional hydrogen bonding to the calixarene small rim. Interestingly, protic guests such as EtOH are not deprotonated by the basic hydroxo-complex, but rather undergo inclusion into the calix-cone as neutral guests. Quite remarkably in this system, the external donor bound to the metal center closing the cavity becomes an allosteric tool for tuning the hosting properties of the complexes (*vide infra* Table 1). Indeed, the stronger the external donor, the less polarized the receptor that will consequently be particularly sensitive to hydrogen bonding guest. The less electron-rich the external ligand, the more sensitive the receptor to the guest dipole moment. This supramolecular system nicely illustrates how the host properties of a hydrophobic cavity can be fine tuned by an allosteric effector (the external ligand in this case), which is reminiscent of natural systems and their propensity to undergo allosteric control.

Table 1 Relative affinities of various mono-, di- and tri-cationic calix[6]tris(ethylamino)-based hosts for G = EtOH, DMF, DMSO, $AcNH_2$, IMI and MeCN measured by ^1H NMR spectroscopy (223 K, $CDCl_3$) and comparison with the dicationic calix[6]tris(imidazole) Zn(II) *funnel* complexes[62]

	Relative affinities for the guest, referred to EtOH[a,b]					
Guest	EtOH	MeCN	DMF	DMSO	$AcNH_2$	IMI[c]
Dipole moment (D)	(1.67)	(3.92)	(3.82)	(3.96)	(3.7)	(3.86)
{Zn-OH[tris(ethylamino)]}$^+$⊃**G**	1	nd[d]	0.003	0.16	2.5	nd[d]
{Zn-$NHSO_2$Me[tris(ethylamino)]}$^+$⊃**G**	1	—	0.007	0.73	20	—
{Zn-OAc[tris(ethylamino)]}$^+$⊃**G**	1	nd[d]	—	0.69	16	—
{Zn-NH_2Bu[tris(ethylamino)]}$^{2+}$⊃**G**	1	—	0.02	2.9	42	—
{3 CF_3COO^-,[tris(ethylammonium)]$^{3+}$}⊃**G**	1	0.05	1.3	3.5	35	520
{Zn-**G**[tris(imidazole)]}$^{2+}$	1	0.08	0.21	1.1	1.4	nd[d]

[a] Errors estimated ±10%. [b] Defined as $[G_{in}]/[EtOH_{in}]\times[EtOH_{free}]/[G_{free}]$. [c] T = 263K. [d] Not detected.

4 Shaping the cone through self-assembly

In the course of our research, we became interested in developing metal-free receptors for neutral molecules. The binding of neutral molecules by a metal-free cavity may be driven by the hydrophobic effect in water. In organic solvents however, additional multiple electrostatic interactions are required for an efficient binding, such as charge–charge or charge–dipole interactions and H-bonding. These can be provided by additional groups grafted at the edge of the cavity. It is noteworthy that the combination of ammonium groups to a hydrophobic cavity for the binding of neutral molecules has been scarcely studied, while the converse situation, *i.e.* the binding of ammonium guests by neutral receptors, is well established.[63,29] Having in hand the calix[6]tris(ethylamine) derivative, we planned to study its protonated form as a host for neutral molecules.

4.1 [1+3+1] self-assembly with counter anions

In contrast to the more preorganized calix[4]arenes,[64] calix[6]arenes have been scarcely studied in self-assembly processes, which is mostly due to their high flexibility.[65,66] In this regard, the calix[6]tris(ethylamine) compound proved to be a powerful building block for the design of sophisticated self-assembled receptors in organic solvents.[33,67] Indeed, its protonation by a strong acid such as trifluoro acetic acid (TFA) produces ethylammonium arms which assemble in chloroform with the counter anions to form a supramolecular ion-paired cap that locks the calixarene core into the cone conformation (Fig. 14, pathway 1). This rigidified structure presents a hydrophobic, π-basic cavity polarized by a tricationic, protic site. As revealed by NMR studies in $CDCl_3$, this very simple receptor displays a high affinity for polar neutral molecules such as alcohols, ureas, amides or sulfoxydes, leading to [1+3+1] self-assemblies, while endo-bound ethers, ketones or halogeno-alkanes have never been observed. X-ray structures show that the efficiency of the recognition process results from the combination of a strong charge–dipole interaction between the polar guests and the polycationic cap (the guests directing its dipole moment along the C_3 axis of the calixarene core), stabilizing CH–π interactions within the hydrophobic cavity and hydrogen bonding at the small rim and within the cap. As in the case of the Zn complexes, the cavity acts as a funnel which discriminates between guests of different shapes. Hence, as compared to all other guests, a very high affinity is observed for imidazolidin-2-one (IMI) since this molecule has the strongest complementarity in terms of size, shape and electronic structure with the calixarene host. These results emphasize the efficiency of combining, in close proximity, a poly-ammonium site and a hydrophobic cavity to build up receptors for polar neutral molecules.

4.2 [1+1+1] or [1+1+2] self-assemblies with tris(carboxylic) acid partners

The strategy relying on the supramolecular capping of the cavity *via* ion-pairing was further explored to construct more elaborated assemblies, with a particular emphasis on ditopic receptors in which the flexibility of the calixarene could be used for allosterism purposes.

With well-preorganized tripodal tris(carboxylic) acids as complementary subunits, discrete [1+1+1] self-assembled ternary structures have been obtained with the calix[6]tris(ethylamino) building-block, at the very condition however that a guest molecule is accommodated in the calixarene cavity (Fig. 14).[68] Indeed, as shown by NMR studies ($CDCl_3$), this highly selective self-assembly of the three subunits is directed by polar neutral guests through an induced-fit process: the inclusion of the guest (i) triggers off the expulsion of the methoxy groups from the cavity, (ii) rigidifies the calixarene core and (iii) increases the pre-organization and the directionality of the ammonium arms involved in the assembly of the ion-paired complex. Remarkably, these [1+1+1] self-assemblies display a high stability in polar and protic solvents, ternary complexes obtained with very rigid tris(acid) partners being stable even in pure methanol (Fig. 14, pathway 2). When capping the calixarene with a chiral cyclotriveratrylene (CTV) derivative, an enantioselective recognition process inside the calixarene cavity is possible through a supramolecular transmission of the chirality. Indeed, enantiomers of chiral guests such as (±)-4-methylimidazolidin-2-one can be discriminated with stereoselectivities up to 30% (Fig. 14, pathway 3). Mostly because of its small size, the filling of the CTV cavity by a second guest molecule is not observed. However, the use of a concave CTV partner enlarged by amido arms leads to an ion-paired ditopic receptor which can accommodate simultaneously two IMI molecules, one in the calixarene cavity and one in the CTV cavity (Fig. 14, pathway 4). DOSY and EXSY NMR experiments have shown that the two distinct cavities of the self-assembled receptor display different binding properties. Indeed, very different

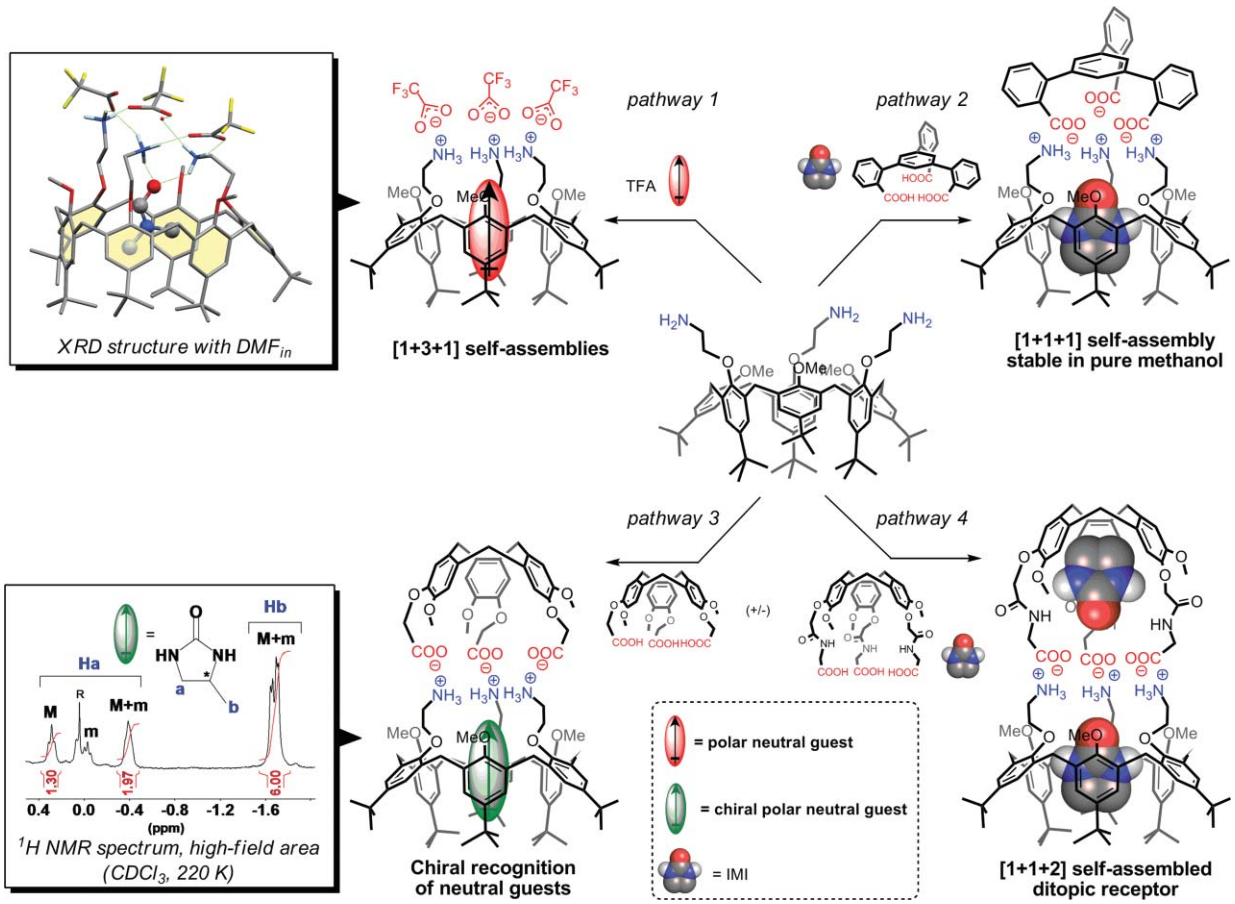

Fig. 14 Examples of self-assembled receptors obtained from the calix[6]tris(ethylamino) building block.[33,67,68] NMR spectrum inset: "M" and "m" stand for "Major" and "minor" diastereomers, respectively. R = Reference.

residence times have been found for IMI: 4 s and less than 10^{-3} s in the calix and CTV cavities, respectively, indicating that the calixarene subunit leads to a much better recognition of the neutral guest. This can be rationalized by the fact that, in contrast to the rigid CTV subunit, the flexible calixarene structure can undergo conformational changes upon complexation to optimize the host–guest interactions through induced-fit processes. As pointed out with the Zn-funnel complexes, the flexibility of the calix[6]arene skeleton represents clearly an advantage.

4.3 [1+1+1+1] self-assemblies with two calix[6]arene subunits

The next degree of sophistication in the elaboration of self-assembled receptors consisted in the use of two distinct calixarene building-blocks. Triple ion-pairing of a calix[6]tris(acid) with the calix[6]tris(ethylamine) subunit leads, in chloroform, and in the presence of appropriate guests (an ammonium and a neutral polar molecule, respectively), to [1+1+1+1] self-assembled quaternary complexes (Fig. 15).[69] In this system, the calix[6]tris(acid) itself behaves as an efficient endo-receptor for ammonium guests once structured by a supramolecular cap with exo-ammonium.[70] Such a behavior is actually the converse picture of that observed for the calix[6]tris(ethylamino) with TFA. The recognition process between the four organic partners involves several cooperative events: (i) the triple proton exchange between the two calix subunits leads to polarized cavities with opposite binding properties, (ii) the two guests act as shoe-trees that direct the self-assembly process, (iii) the rigidification of a calixarene induced by the inclusion of a first guest is efficiently sensed by the other calixarene host and the binding of the second guest is favored, denoting a positive heterotropic allosteric control. The formation of these [1+1+1+1] self-assemblies is a very selective process since no other species is detectable by NMR. The XRD structure of the quaternary complex with IMI and propyl ammonium as the guests highlights the remarkable host–guest complementarities in terms of size, shape and electronic structure, leading to an optimized hydrogen bonding network (Fig. 15, inset). Moreover, the self-assembled complexes have been found resistant to the addition of a large amount of protic solvents such as methanol. In conclusion, this is a rare and interesting case of allosterically coupled double induced-fit process that involves multiple recognition levels that are chemically (acid/base) and conformationally (host/guest) coupled. It is also reminiscent to biological processes where carboxylate and ammonium groups are classical effectors for recognition or self-assembly. For instance, the activity of arginyl-tRNA synthetase for tRNA aminoacylation involves a mutual induced fit process triggered by the recognition of the tRNA by the enzyme, in which both partners undergoes conformational changes of crucial importance for the enzyme activity.[71]

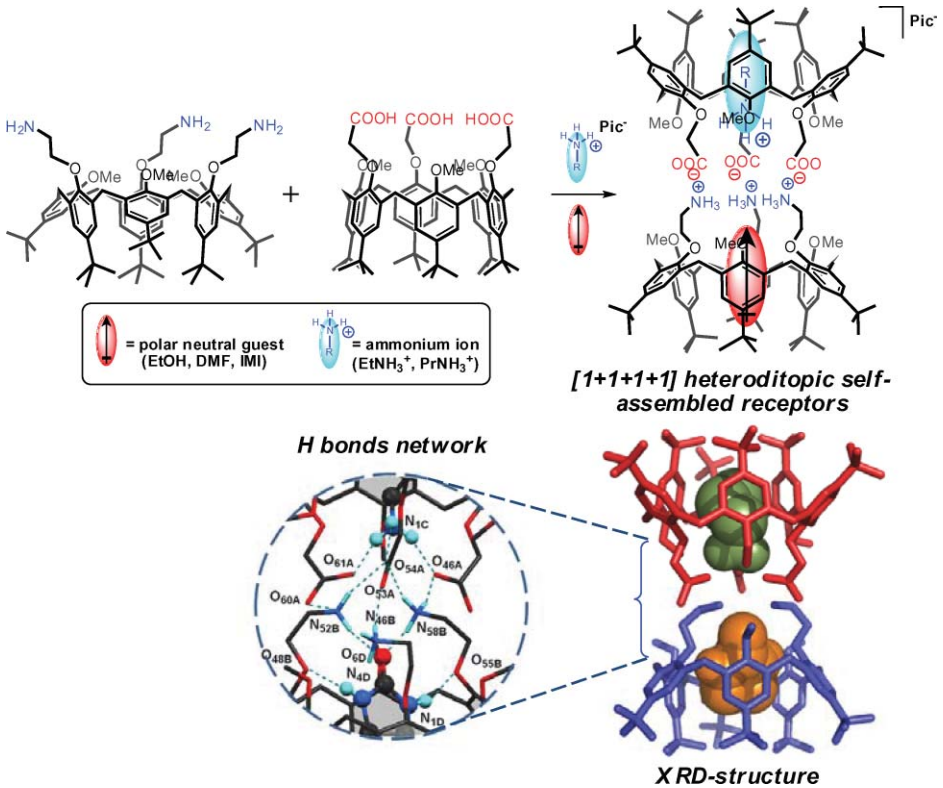

Fig. 15 Top: example of [1+1+1+1] self-assemblies obtained with two complementary calix[6]arene subunits.[69] Bottom: XRD structure of a self-assembled quaternary complex with IMI and propylammonium as guests.

5 Comparison of the host–guest properties of the calix[6]N_3-based receptors

The *Zn(II) funnel* complexes obtained with aromatic amino arms exhibit a 4-coordinate tetrahedral zinc center that selectively coordinates a neutral guest sitting inside the dicationic cavity. Due to the reduced steric hindrance provided by the primary amino arms of calix[6]tris(ethylamine), the corresponding tetrahedral Zn(II) complex preferentially coordinates the fourth donor in an external position. The primary amino arms can also be efficiently self-assembled through multiple ion pairing and H-bonding with counter anions. All these different species behave as good and selective endo-receptors for polar neutral guests. However, a comparison of their hosting properties reveals interesting differences. To illustrate this point, the relative affinities of some of these receptors for EtOH, DMF, DMSO, IMI, $AcNH_2$ and MeCN are reported in Table 1.

The data first show that the relative affinities are highly dependent on the capping system. For example, the relative affinities DMF/EtOH spread over an impressively wide range, almost three orders of magnitude. A common feature of all these receptors is the calixarene cavity that allows CH/π interactions with the guest alkyl chain and H-bonding between the arylether oxygen atoms and the protic guests. Differences stem from the nature of the cap. Indeed, the latter provides an endo-coordination link within the tris(imidazole)-based Zn(II) *funnel* complex, strong H-bonding donors for the tris(ammonium), and a variable charge–dipole interaction within the tri-, di- or mono-cationic cap. For example, MeCN is relatively stronger bound to the tris(imidazole)-based Zn(II) *funnel* receptor, due to its coordination link to the metal center. The tris(ammonium) host presents the highest relative affinities for guests possessing a high dipole moment and an oxygen atom as H-bond acceptor, such as IMI, DMF and DMSO. For the tris(amine)-based Zn(II) complexes, the external ligand (HO^-, $RCOO^-$, $MeSO_2NH^-$ or RNH_2) allows tuning the charge–dipole interaction for the host–guest adduct deprived of a coordination link. Indeed, the higher the positive charge capping the calixarene narrow rim, the more polarized the cavity and the more efficient binding of dipolar molecules. For all receptors, $AcNH_2$ is an excellent guest as it combines a high dipole moment, a hydrogen-bond donor (NH_2) and a hydrogen-bond acceptor or coordination link (C=O). Finally, IMI is by far the "winner" guest for self-assembled tris(ammonium) receptors as they allow four complementary H-bonding to the urea moiety (as illustrated in Fig. 15). Quite remarkably, IMI is not recognized by any of the Zn-complexes.

These results show that a small modification at the level of the amino arms, which are *ca.* 3 Å away from the calixarene small rim, affects strongly the host properties. This can be exploited to switch the guest by implementing a modification to the environment. Such a feature is illustrated by the acid–base mediated Zn(II) decoordination-coordination process with tris(ethylamino)-based receptors in the presence of the competitive guests EtOH and DMF. In a chloroform solution, the endo-bound EtOH Zn(II) complex can be quantitatively and reversibly replaced for the endo-bound DMF tris(ammonium) host through addition of acid.

Subsequent addition of base restores the Zn(II) receptor, thus leading to the expulsion of DMF and back inclusion of EtOH (Fig. 16).[62]

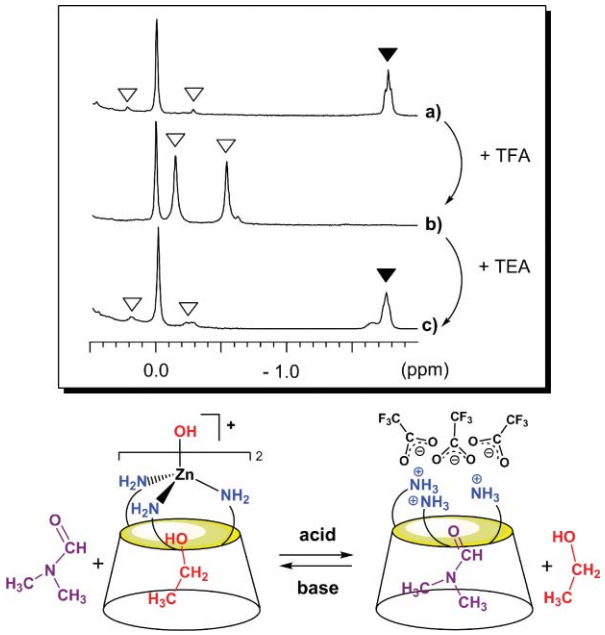

Fig. 16 Reversible switch of the EtOH guest for DMF monitored by the acid–base conditions.[62] Inset: a) high-field region of the ^{1}H NMR spectra (300 MHz, 223 K) of a $CDCl_3$ solution of the {Zn-OH[tris(ethylamino)]}$^+$ complex in the presence of EtOH and DMF (6 and 100 equiv., respectively); b) after addition of TFA (6 equiv.); c) after subsequent addition of TEA (30 equiv.). ▼: $EtOH_{in}$, ▽: DMF_{in}.

Hence, this supramolecular system nicely illustrates how the hosting properties of a hydrophobic cavity can be finely tuned by the environment (presence of metal ions, coordinating species or protons). Again, such a behavior is quite reminiscent of natural systems. In enzymes for example, substrate binding at the active site and formation of Michaelis–Menten complexes are often dependent on the pH, the presence and redox state of a metal ion, the co-binding of a cofactor or a second substrate. All these allosteric effectors allow the fine tuning of the affinity of the proteic site for its substrate and product.

6 Conclusion

Calix[6]arenes are unique scaffolds to obtain modular receptors for neutral molecules. Their size is better adapted for molecule inclusion than calix[4]arenes but these larger oligomers are highly flexible and more difficult to rigidify. The macrocycle presents two sites for modular architecture: a phenolic small rim and the aromatic walls' *para*-substituents defining the large rim. Keys for obtaining a good receptor for polar neutral molecules are: i) the macrocycle constraint into a cone conformation, and ii) polarization of the cavity. These two requirements can be fulfilled either through metal coordination or self-assembly with anions at the level of the small rim. Indeed, three amino-arms grafted on phenol moieties in alternate positions are used for closing the cavity at one end, leaving the large rim open for guest entrance.

6.1 Three different types of receptors can be obtained (Fig. 17)

Funnel Zn(II) complexes with imidazole arms (or other aromatic donors). In this system, the tetrahedral metal ion presents its fourth coordination site in the *endo*-position. As a result, a coordination link between the Lewis acidic metal ion and the guest donor plays an essential role in the recognition process.
Exo-bound Zn(II) complexes with ethylamino arms in which no coordination link is available for the guest. Here, the role of the Zn(II) ion is to shape and polarize the cone while the fourth, *exo*-ligand is used as an allosteric input.
Ion-paired self-assemblies with three primary ammonium arms that highly polarize one end of the cone and offer additional hydrogen-bond donors to the guest.

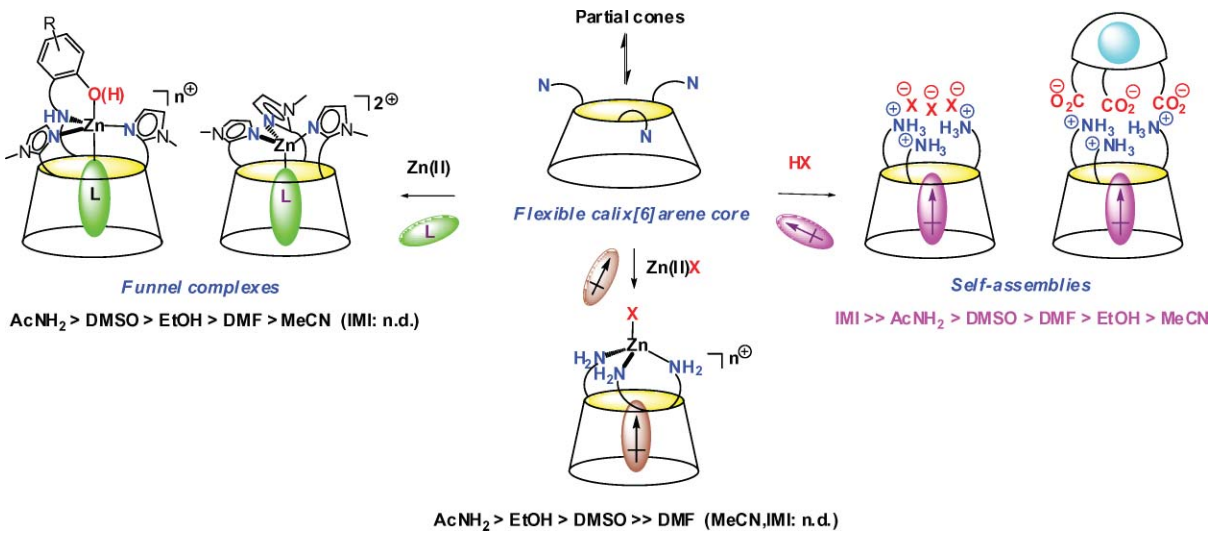

Fig. 17 Three different types of receptors are obtained, depending on the nature of the amino-arms, the presence or absence of a metal ion (Zn(II)) and the acidity of the medium (n.d.: not detected).

6.2 Comparative features of these receptors

Common features. *The calix cavity* is constrained in a flattened cone conformation well adapted for guest inclusion. The aromatic units adopt alternate *in* and *out* positions relative to the C_3 axis. The pocket is hydrophobic, π-basic and polarized by the positively charged cap. It also presents H-bond acceptors at the small rim (the phenoxyl moieties). The cavity size is relatively large (compared to a calix[4]arene), which allows the selective hosting of a variety of neutral guests.

The large rim entrance is tuned by the substitution pattern of the phenolic units in the *para*-position. While six bulky *t*Bu substituents constitute an aperture that regulates the access to the cavity, the removal of half of them largely opens it. Interestingly, the nature of these substituents modulates the physical and chemical properties of the whole structure without altering the guest interaction within the cap, at the small rim level.

The macrocycle flexibility allows the host to adapt to the guest shape and size, leading to induced fit processes.

Differing features. *The guest interaction within the cap*: a coordination link for the *funnel* complexes, H-bond donors in the tris(ammonium)-based self-assemblies, a mono-, di- or tri-cationic charge at the small rim lead to different electrostatic interactions with the guest dipole.

Tunability: for the *funnel* complexes, an additional proton sensitive capping donor such as a phenol allows us to tune the receptors′ sensitivity for a given guest; for Zn(II)-complexes displaying *exo*-binding, the nature of the *exo*-ligand tunes the polarization of the cavity; for tris(ammoniums), the nature of the self-assembled poly-anionic site controls the host–guest induced fit process and allows the implementation of a second hosting site.

6.3 Biomimicry

The ability of these hosts to mimic specific aspects of biological receptors has been emphasized. Indeed, all three systems display features that stress the importance of the micro-environment.

• In hydrolytic Zn enzymes, the metal ion plays the role of a Lewis acid for the activation of a water molecule and the substrate. Our modeling ambitions have been directed toward mononuclear sites integrating a free access for exogenous binding, which are particularly difficult to reproduce due to the propensity of mono-Zn(II) complexes to undergo dimerization. Hence, another key role of the calix structure is to control the nuclearity of the complex. Coordination of the tris(imidazole) ligand to Zn(II) led to the characterization of the first dicationic tetrahedral Zn(II) complexes. Their exceptional stability stems from the second coordination sphere at the small rim, which provides hydrogen bond acceptors (ArO) that relieve the Brønstedt acidity of the coordinated guest. It is also due to stabilizing interactions between the π-basic cavity and the alkyl group of the guest (CH–π interactions). These complexes have provided the first model for the dicationic aqua complex in Zn-enzymes and mimic nicely the Michaelis–Menten adducts, behaving as selective funnels for small neutral coordinating molecules. Implementation of a phenol moiety to the first coordination sphere allows driving of the host affinity for a given guest to the acidity of the medium.

• For the non-metal-based receptors, the self-assembled tris(ammonium) system highlights the importance and efficiency of polarizing a hydrophobic cavity for molecular recognition. Whereas neutral calixarenes display a poor affinity for organic guests when no hydrophobic effect is involved (ie. in an organic solvent, even when covalently constrained into a cone shape), the tris(cationic) ones described herein proved to be receptors displaying exceptional affinities for dipolar organic guests. In other words, a hydrophobic environment, when highly polarized, constitutes an exceptional tool for molecular recognition for neutral dipolar molecules, a phenomenon that is obviously key for ligand–protein interactions in biology.

• Also importantly, the flexibility of the calix[6]arene core has been shown to be an advantage: a wide range of neutral guests of different size can be recognized, spanning from a small water molecule to the much larger tryptamine or dopamine derivative. Indeed, the host can adapt to the guest for optimizing the inner cavity stabilizing interactions. This allows good recognition of a wide range of guests and induced-fit processes that are frequently encountered in biological systems.

In conclusion, all three systems behave as remarkable thermodynamically and kinetically tunable hosts, allowing allosteric control and induced-fit processes. As the bonds shaping the cone are relatively weak (coordination links and/or electrostatics), one hosting system can be reversibly switched for another (*e.g.* acid-based input for the tris(ethylamino)-based Zn(II) receptor or N_3ArO(H) *funnel* complex). All these properties evidence the versatility of the calix[6]arene hosts, opening a number of perspectives. Indeed, beside fundamental research for a better understanding of the key interactions governing molecular recognition, coordination and reactivity in biological systems, novel nano-devices for selective catalysis, detection, sensing or even vectorization may be developed.

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