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Biomimetic Cavity-Based Metal Complexes

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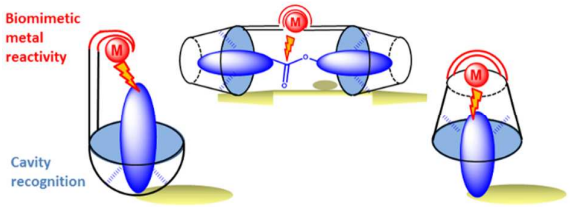


The biomimetic association of a metal ion with a cavity allows selective recognition, unusual redox properties and new reactivity patterns.

Abstract

The design of biomimetic complexes for the modeling of metallo-enzyme active sites is a fruitful strategy for obtaining fundamental information and a better understanding of the molecular mechanisms at work in Nature's chemistry. The classical strategy for modeling metallo-sites relies on the synthesis of metal complexes with polydentate ligands that mimic the coordination environment encountered in the natural systems. However, it is well recognized that metal ion embedment in the proteic cavity has key roles not only for the recognition events but also for generating transient species and directing their reactivity. Hence, this review focuses on an important aspect common to enzymes, which is the presence of a pocket surrounding the metal ion reactive sites. Through selected examples, the following points are stressed: (i) the design of biomimetic cavity-based complexes, (ii) their corresponding host-guest chemistry, with a special focus on problematics related to orientation and exchange mechanisms of the ligand within the host, (iii) cavity effects on the metal ion binding properties, including 1^{st}, 2^{nd}, 3^{rd} coordination sphere and hydrophobic effects and finally (iv) the impact these factors have on the reactivity of embedded metal ions. Important perspectives lie in the use of this knowledge for the development of selective and sensitive probes, new reactions, and green and efficient catalysts with bio-inspired systems.

Introduction

Metallo-enzymes are fascinating natural factories able to catalyze a great variety of reactions under very mild conditions and with a high chemo- and stereo-selectivity.[1] The design of small metal complexes that mimic molecular aspects of the active site is important for obtaining information about their fundamental mechanism. It also allows discovering new reactive species and/or new reactivity patterns associated with a metal ion. All this information may also lead to the development of bio-inspired systems displaying interesting and exploitable properties.[2] The classical way to design biomimetic complexes consists in using a ligand that mimics the natural environment of the metal ion at work in the enzyme.[3, 4] It can be a porphyrin for modeling heme enzymes or a tripodal ligand with N/O/S donors for mimicking amino-acid residues holding the metal ion in the active site. This will define the first coordination sphere. Such an approach has been proven to be very fruitful, allowing to obtain key information about the reactive species involved in the catalytic cycles. More recently, growing attention has been paid to second sphere effects that can direct the reactivity of the metal ion. Yet, another important aspect common to enzymes is the presence of a pocket surrounding the metal ion reactive sites. It allows substrate binding and preorganization, as well as product release. It also provides a well-defined 2nd coordination sphere, protects the metal center, and controls the nuclearity. Modeling these aspects requires the design of a ligand presenting both a biomimetic coordination core, and a pocket in its vicinity. In enzymes, this pocket is provided by the protein folding, which makes it very difficult to mimic with a small molecule. One possible approach consists in using a readily available macrocyclic structure that presents a defined cavity space, such as a calixarene or a cyclodextrin and functionalizing it with donors for metal ion binding..

This review focuses on this approach with the goal of presenting various fundamental aspects illustrated by selected examples. It will first present different strategies for the design of cavity-containing biomimetic metal complexes.[5-7] It will then discuss their associated host-guest chemistry and how it may allow orienting the ligand within the host and controlling the exchange mechanism. Different levels of coordination sphere effects associated with cavity effects will then be illustrated. Finally, examples of reactivity and catalytic activity specific to these systems will be presented and discussed.

1. Design of cavity-containing biomimetic metal complexes

The addition of a metal complex to a macromolecular cavity for the design of a supramolecular system proposing new structural and/or catalytic functions can be achieved in many different ways. Two limiting cases can be proposed: one or several pre-defined metal complexes are grafted onto a cavity, or the final metal complex results from the interaction of a metal ion with a cavity decorated with binding units. In the first case, the use of polydentate ligands is preferred in order to maintain the first coordination sphere in the final species. The cavity can be seen as a platform at the periphery of which one or several metal ions in a well-defined coordinating environment can be placed. In the second case, the ligand is directly built onto the cavity in order to obtain the best "communication" possible between labile coordination site(s) at the metal ion and the inner space of the cavity. In between these two cases, strategies combining the elements of these two extreme designs are possible. In this first section, we will discuss these different strategies based on some illustrative selected examples.

1.1 Grafting fully-formed complexes onto a cavity platform

The straightforward design of a cavity-containing metal complex consists in gathering *via* a covalent link one or several well-defined metal complexes and a molecular cavity. This generally enables the control over the nuclearity and the relative position of the metal ions around the cavity. The first building block, the metal complex, is preferentially composed of a polydentate (macrocyclic or not) ligand, which confers kinetic and thermodynamic stability to the final complex. The second partner, i.e. the cavity, should be easily functionalizable. For this reason, calixarenes[8] (and especially calix[4]arenes) and cyclodextrins [9-11] (CDs) are the most commonly reported macrocyclic cavities used. We will discuss two cases based on each of these two macrocycles that have a strong impact on the properties of the system. Indeed, these two cavities present an almost opposite behavior as far as host-guest recognition is concerned. The parent cyclodextrin is water-soluble and the hydrophobic effect drives the encapsulation of lipophilic substrates inside the CD in water. Many functionalized CD systems keep this interesting property. On the contrary, the parent calixarene is not water soluble. Important modifications of its structure must be done to provide a water-soluble molecule and this is not always compatible with its functionalization with a metal complex. Therefore, most of the calixarene-based metal complexes of this type are only soluble in organic solvents and the macrocycle can only be used as a platform, and not as a molecular receptor.

1.1.1 Calix[4]arene used as a platform. The functionalization of calix[4]arenes is well-documented. It makes this macrocyclic structure a good candidate as a molecular platform.[12] This strategy was employed by Reinhoudt *et al*. to produce a comprehensive study of the mechanism at work in some hydrolytic processes.[13-15] 2,6-bis(dimethylaminomethyl)pyridine or triazamacrocyclic ligands were attached onto the same platform (Fig. 1). Because the first coordination sphere defined by this type of ligands leaves at least one labile site on the metal center, the isolated metal complex (not attached to the cavity) is known to show catalytic activity (*via* the modulation of the p*Ka* value of water for instance, or the binding of the substrate). It is essential to keep the potential of binding and activating the reactants in the final system. It is thus possible to graft one, two or three polydentate ligands with a good control of the nuclearity in the final complex. Also, the position of the metal complexes on the platform can be changed (1,2 vicinal position or 1,3 distal position). Finally, the flexibility of the whole system is tunable by bridging the calixarene with a short covalent linker between two phenolic positions. As mentioned before, the calixarene cavity is not intended to play any role in the interaction between the substrate and the metal center. Hence, only the nature of the metal ions, their first coordination sphere and their relative positioning have an impact on the reactivity which will be discussed later in this review.

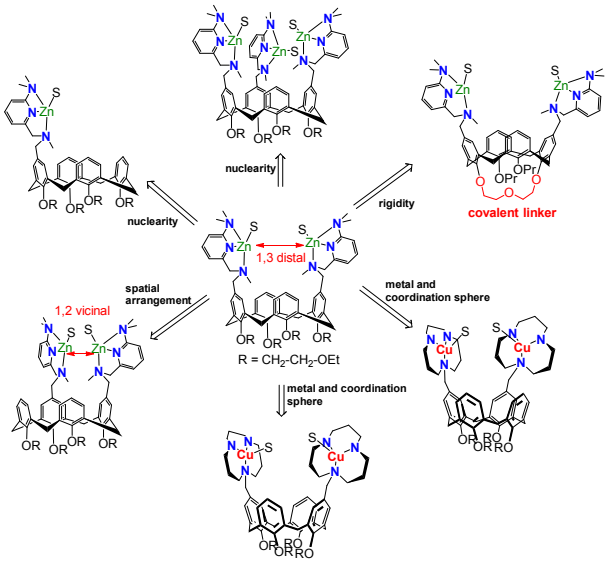


Fig. 1 Zinc and Copper complexes built on a calix[4]arene platform.

1.1.2 Non-innocent cavity; the case of the cyclodextrin receptor. Unlike calix[4]arene, CD can host an appropriately chosen substrate in water. The consequence of the

binding is the positioning of the substrate in close proximity to the reactive metal center.[16] In other words, the thermodynamic effect of substrate binding in the CD cavity has a kinetic impact on the activity of the metal catalyst (cf the Michaelis-Menten model). This approach is well illustrated with the triazacyclododecane (tacd) Zn^{II} complex linked to a β-CD (Fig. 2). In this case, the nature of the linker between the metal complex and the CD is an important factor since it is the key for the pre-organization.

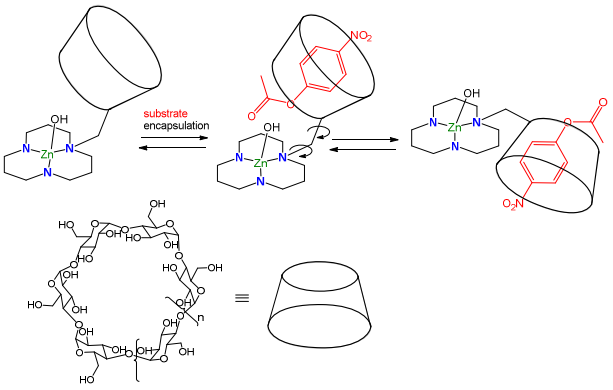


Fig. 2 Top: Biomimetic model using a CD cavity for substrate encapsulation in proximity of a (tacd)Zn^{II} complex. Bottom: Chemical structures of α-CD (n = 1) and β-CD (n = 2).

1.2 Bridging metal centers placed at the top of a cavity

As discussed above, several unsaturated metal complexes can be attached to a cavity and the possibility to modify their number is a tool to study and mimic the mechanism of some catalytic processes. In the resting state, solvent molecules (or residual water molecules in non-coordinating solvents) complete the coordination sphere before being displaced by the substrate or a reactant. The vacant position on the metal center can be used to bind a bridging ligand and direct the formation of a cluster otherwise difficult to obtain and stabilize (Fig. 3). Simultaneously, Collet *et al*. and Nolte *et al*. took advantage of a tri-thiol cyclotriveratrylene (CTV) ligand to form in high yield a metal complex containing a $[Fe_4S_4]$ cluster as a model of electron transfer proteins. [17, 18] Nolte *et al.* noticed that a ligand (Cl^- or *t*BuS^-) could complete the coordination sphere of the unique iron and that while the small chloride ligand was oriented inward the bowl, the bulky sulfide was oriented outward.

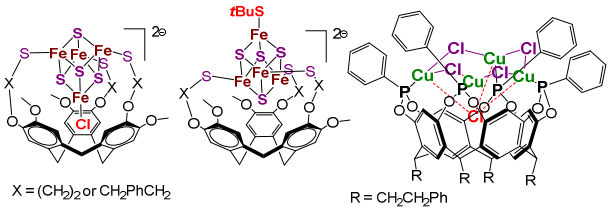


Fig. 3 Left: $[Fe_4S_4]$ cluster stabilized by a CTV ligand. Right: $[Cu_4Cl_4]$ cluster stabilized by a calixarene ligand.

Similarly, Puddephatt *et al.* could stabilize a $[Cu_4Cl_4]$ cluster with a tetraphosphonitocalixarene.[19] The XRD structure indicates that each chloride ion bridges two Cu^I ions. Moreover, the cluster is at the top of the bowl shaped complex and a fifth chloride atom is trapped inside this bowl weakly coordinated to three of the copper centers. This chloride can be displaced by an iodide which is large enough to coordinate to all four copper ions.

1.3 Monodentate ligands surrounding a cavity enable the formation of a well-defined species

The former strategy does not allow any binding of an exogenous ligand to the metal center. In order to leave an unsaturation, several monodentate ligands positioned on the edge of a cavity can be used to coordinate simultaneously a single isolated metal ion. In general, this strategy leads to a better control of the relative orientation of the metal center (more precisely the labile site(s) on the metal center) and the cavity. The adduct with a 1:1 stoichiometry can be anticipated by carefully modeling the system, which can be done by computer-aided modeling or with CPK type models. In this strategy, two cases can be discussed depending on the rigidity of the cavity. With a rather rigid macromolecule such as a CD or a resorcinarene, the relative position of the monodentate ligands in the apo-structure should fit with the spatial arrangement of the ligand around the metal center in the final structure. The covalent link between this monodentate ligand and the cavity is the only degree of freedom and is the key for a good design. With a flexible cavity such as calix[6]arene, the conformations of the molecule as a free ligand and in the complex are very different. Therefore, the design has to take into account not only the linker but also this conformational freedom.

1.3.1 Early example with a β-CD. This strategy was used by Tabushi *et al.* to propose a *Carbonic Anhydrase* model (Fig. 4).[20] It is based on a CD cavity selectively

functionalized by two histamine groups in A and C positions (the letter designates the position of the glucose units in the macrocycle). This ligand binds Zn^{II} in buffered water (pH = 7.5) with an estimated association constant of 4.5×10^{2} unit ? $L.mol^{-1}$ in the presence of excess imidazole. It is proposed that Zn^{II} is bound by the two imidazole ligands of the CD, by one exogenous imidazole and water molecules completing the coordination sphere. Rate increase for the hydration of CO_2 was observed but the role of the CD cavity was not discussed. A stronger interplay between the metal center and the cavity can be achieved with other systems.

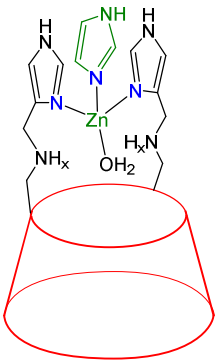


Fig. 4 Bis(histamino)-β-CD ligand used in a *Carbonic Anhydrase* model.

1.3.2 ”Funnel” complexes obtained with the calix[6]arene scaffold. Calix[6]arene can be selectively functionalized at the phenolic groups in alternate 1-, 3- and 5- positions. This allows the introduction of three monodentate donors at the small rim such as pyridine or imidazole units. The conformational freedom of the ligand dynamically distributes the three binding groups in several relative positions. The addition of a metal center such as Zn^{II} or Cu^{II} yields a mononuclear complex in which the calixarene adopts a cone conformation with the three nitrogen “arms” bound to the metal ion (Fig. 5). Metal coordination of the ligand shapes the cavity in an allosteric way. With Zn^{II}, the first coordination sphere adopts a pseudo-tetrahedral geometry and is composed of the three nitrogen donors and a guest ligand sitting inside the calixarene cavity. With Cu^{II}, an additional water molecule selectively binds to the metal center in the *exo* position, *trans* to the *endo* site, thus leading to 5-coordinate complexes. In both cases, the guest ligand, which can be a primary amine, alcohol, amide or nitrile, is exchangeable. Their affinity is governed not only by the coordination to the metal center but also by secondary interactions (mainly H-bonding and CH-π, see the next section) within the calixarene core. Interestingly, the complex retains a certain degree of flexibility which leaves the possibility for the host to adapt its shape and optimize the interaction with its guest in an *induced-fit* process. As a result, these complexes, called funnel complexes due to

the fact that the guest has to go through the calixarene cone to reach the metal center, behave as selective receptors for neutral molecules. The different levels of selectivity depend on the intrinsic donor ability of the guest ligand (amines are better ligands than alcohols), the steric hindrance at or nearby the coordinating atom (for instance primary amines are the best guest ligands, whereas secondary amines do not bind to the metal ion), and the shape of the ligand (linear ligands fit the cavity better than cyclic ones). Ligand exchange can be easily followed by different spectroscopies (^{1}H NMR, UV-vis, EPR) depending on the metal ion used. The softer Cu^I ion can adopt a 2- or 4- coordinate environment. A good σ-donor *N*-ligand such as *N*-Me-imidazole favors the linear N_2Cu geometry unless a strong π-acceptor ligand (CO for instance) is present, thus driving the complex to adopt a tetrahedral $N_3Cu(CO)$ binding mode. On the contrary, weaker pyridine arms favor a $N_3Cu(G)$ binding mode with a nitrile guest or a chloride (G, Fig. 5). These systems are interesting for the study of a metal complex in a constrained environment. [21-26] Several properties stemming from this particular molecular arrangement will be discussed later in this review.

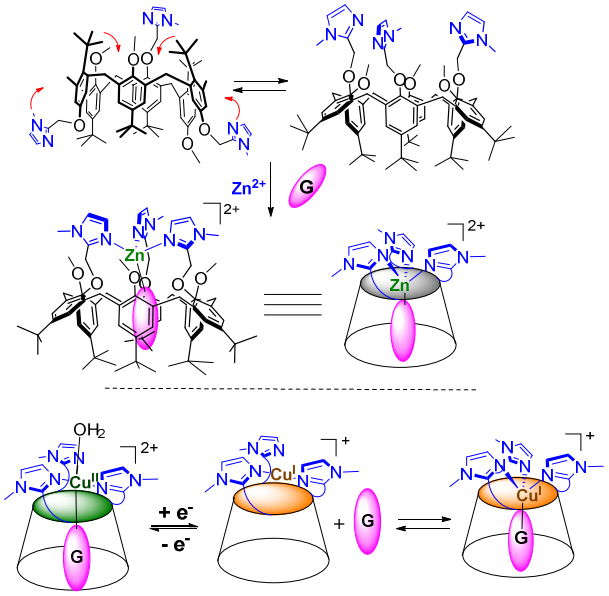


Fig. 5 Top: Illustration of the flexibility of the calix[6]arene ligands and formation of the Zn^{II} metal complex leading to the encapsulation of a guest (G). Bottom: Coordination sphere of the Cu^{II} and Cu^I metal complexes.

1.3.3 "Bowl" complexes obtained with the resorcinarene scaffold. The use of three monodentate imidazole binding units attached to a resorcinarene bowl-shaped cavity opens the coordination sphere of the metal center (Zn^{II} or Cu^{II}) while maintaining the

mononuclearity of the metal complex (Fig. 6).[27-30] In both Zn^{II}- and Cu^{II}-complexes, the metal ion is 5-coordinated. Two *cis* labile coordination sites are available for exogenous ligands. One site is directed toward the *endo* position and interacts strongly with the cavity. The other one is in *exo* position, exposed to the bulk solvent. This is a prerequisite for mimicking some hydrolytic zinc enzymes in which both the electrophilic substrate and the water molecule are activated by the metal center. The *endo* binding site is sensitive to the size of the ligand since acetate is the bulkiest carboxylate which can fit into the cavity. On the contrary, the *exo* binding site can be occupied by larger ligands. Coordination of Cu^{I} was also investigated. In a non-coordinating solvent and with a non-coordinating anion (such as PF_6^-), the copper ion binds linearly to two out of the three imidazoles in a dynamic fashion as in the case of the calixarene. In presence of chloride, acetonitrile or carbon monoxide, the tetrahedral $N_3Cu(L)$ geometry is obtained. This new ligand binding topology opens the way to potential selective reactivity of two cis-bound substrate(s)/reactant, as observed in enzymatic systems.

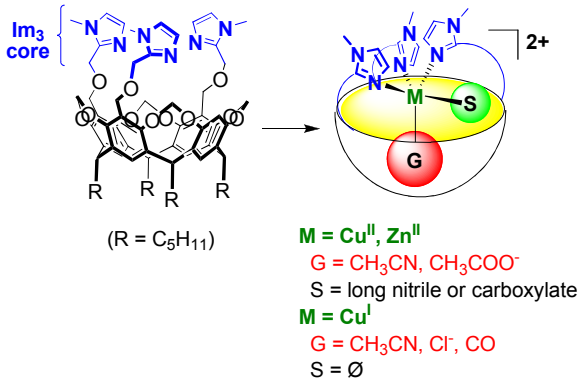


Fig. 6 Copper and Zinc complexes of a resorcinarene bowl-shaped ligand having two distinct (*endo* in red and *exo* in green) binding sites in *cis* position.

1.4 Use of both rims of the cavity: Non-equivalent metal centers around a cavity. Mixing "polydentate" and "monodentate" strategies

The strategies discussed so far for the design of polynuclear metal complexes position either a single or several identical metal centers on only one side of the functionalized cavity. By combining these two approaches, a calix[6]arene ligand was designed to give access to hetero-polymetallic complexes.[31, 32] At the small rim, three imidazole ligands bind an isolated Zn^{II} ion while three bi- or tri-dentate ligands placed at the large rim can coordinate metal ions of the same or different nature (Zn^{II} or Cu^{I}) (Fig. 7). The upper metal ion as previously discussed acts as an anchoring point for guest hosting in the calix cavity. In this strategy, it is

envisioned that the metal ions at the large rim can be employed as catalytic sites for the selective transformation of the substrate hung in the cavity.

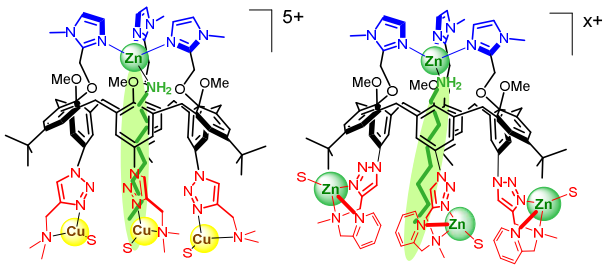


Fig. 7 Hetero-polynuclear metal complexes generated by the different environments at each rim of the calixarene (S = solvent, H_2O, OH^-).

1.5 Insulating the metal center: covalent capping of the cavity with a polydentate ligand

Polydentate donors insure a better metal-ligand interaction. They also restrict the number of labile binding sites of the metal center. When a cavity is covalently capped by a polydentate ligand through multiple covalent linkages, the corresponding complex benefits from the high preorganization of the system both for metal ion binding and guest ligand hosting. It also exacerbates the interaction between the labile coordination site and the cavity. Such systems with different polydentate ligands are discussed below.

1.5.1 Porphyrin capping ligand. A porphyrin is a strongly chelating planar ligand. Depending on the metal ion coordinated, its oxidation and electronic spin states, one or two axial ligands are present in the coordination sphere. Porphyrin metal complexes have been intensively used in supramolecular chemistry.[33] Different classes of macromolecules (calixarene, resorcinarene, cyclodextrin, glycoluril) have been capped by a porphyrin metal complex.[34] In the simplest case where only one side of the porphyrin is exposed to a cavity, the two axial positions become distinguishable, one being oriented towards the cavity, the other one being exposed to the solvent (Fig. 8). Depending on the size of the cavity, a suitable guest will preferentially bind the *endo* site with an enhancement of the association constant compared to the simple porphyrin. When the size of the ligand does not fit the dimensions of the cavity, *exo* binding is favored. A representative example combining a resorcinarene and a Zn-porphyrin was reported by Reinhoudt *et al*. In this study, the number (2 or 4) and length of the linkers between the two partners are varied. It was demonstrated that with long and flexible linkers, the system does not discriminate much between a pyridine and a 4-phenyl-

pyridine ligand. With a more rigid connection (4 short spacers), strong and selective binding was observed for small ligands such as *N*-methyl-imidazole or 4-methyl-pyridine with a 700-fold enhancement of the binding constant compared to uncapped porphyrin. Hence, tuning the size and rigidity of the hosting part of the system is the key to optimize the metal-ligand interaction in *endo* position.

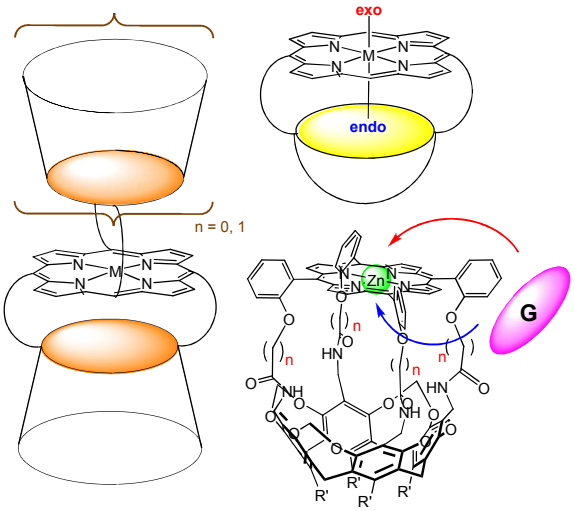


Fig.8 Left: schematic representation of a porphyrin ligand capping one or two molecular cavities. Right: a Zn-porphyrin complex capping a resorcinarene host and displaying a strong *endo*-selectivity for some small guest ligands (G).

1.5.2 Strict control of the *endo* coordination with calix[6]arene-based azacryptands. When embedded in a supramolecular system involving a cavity, the porphyrin metal complex can interact with a ligand in *exo* position, *trans* to the *endo* binding site. Such a *trans* coordination is also observed in the case of the tris-imidazole or tris-pyridine calix[6]arene-based systems. This means that a ligand for the metal center does not necessarily sit inside the cavity. *Endo* coordination can be guaranteed when the *exo* position is suppressed, which is the case with an azacryptand type ligand, wrapping a metal ion and leaving vacant site(s) only in *endo* position. This strategy was used with the calix[6]arene scaffold. Several poly-aza caps could be added on the calixarene structure: TREN [tris(2-aminoethyl)amine], TMPA [tris(2-pyridylmethyl)amine] and PN_3 [tris(2-aminophenyl)phosphine] (Fig. 9).[35-37] The capped calixarenes are more rigid than their tris-imidazole or tris-pyridine analogs and enforce all the donor atoms of the ligand to bind the metal ion. Also, the conformation of the calixarene, which has a strong impact on the binding properties (*vide infra*), will be impacted by the capping ligand. Zn^{II}, Cu^{II} and Cu^{I} metal

complexes of these ligands have been subject of intense studies. Ligand exchange takes place inside the calix cavity. Various important features specific to these systems will be discussed in the other sections of this review.

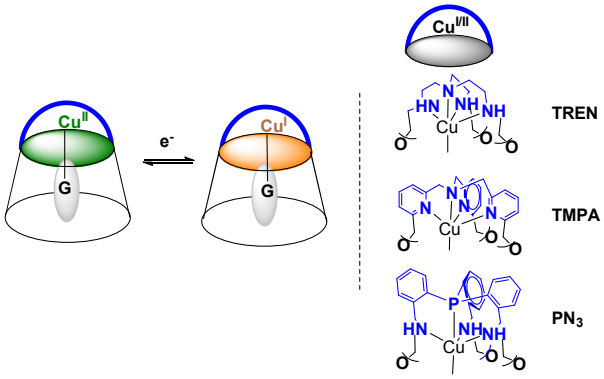


Fig. 9 Copper complexes of the aza-cryptand calix[6]arene family.

2. Host-Guest chemistry. Orientation and exchange mechanism of the ligand within the host

In the first section, which is dedicated to the design of the different cavity-containing metal complexes, the importance of the interplay between the binding sites on the metal center and in the cavity has already been pointed out. Obviously, cooperativity between these two sites is one of the reasons for which such an association is obtained. Some examples discussed above do not display this cooperativity. For instance, in the case of calix[4]arenes decorated with one or several metal complexes, the ligand on the labile coordination site is not forced to interact with the cavity (see Fig. 1). A similar design leading to a reversed situation, i.e. recognition of the ligand inside the cavity without metal ion binding, is illustrated by the CD functionalized by an aza-Zn^{II} complex displayed in Fig. 2. In this section, we will focus on cooperativity: how can it be achieved and what is the main driving force in this process. Besides these thermodynamic considerations, it is important to understand how the connection of a metal center to a cavity can affect the kinetics of the binding event.

2.1 Cavity binding vs. metal coordination: what is the driving force for recognition?

When the structure of the system enables the ligand to interact with both a metal center and a cavity, it is sometimes possible to unfold the contribution of each of the interacting parts. The

comparison of the thermodynamic parameters gives insight into the main factors contributing to the stabilization of the host-guest adduct.

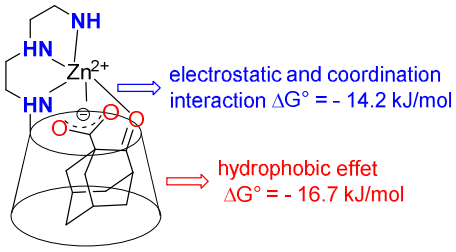
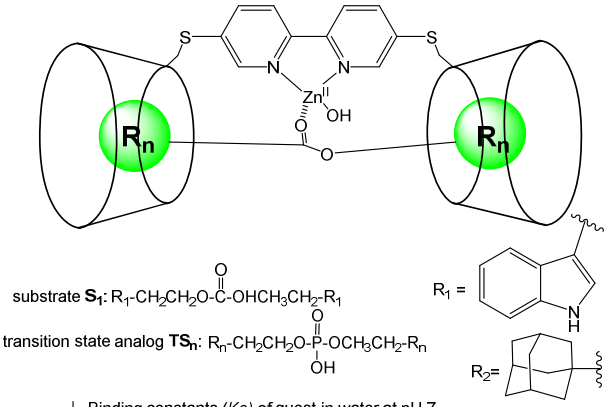


Fig. 10 Early example of a β-CD Zn^{II} complex associating the hydrophobic effect for guest inclusion and the interaction of the ligand with a metal center.

An important aspect associated with host-guest recognition in water is the hydrophobic effect, where the driving force for host-guest inclusion is not only based on electrostatic interactions (enthalpy), but also benefits from entropy gain due to expulsion/freedom of water molecules. This was particularly well illustrated with cyclodextrin-based receptors, and the seminal work of Breslow in the field of artificial-enzymes.[11] Wanting to explore the relationship between metal coordination and cavity binding with CDs, Tabushi *et al.* reported a study[38] where a β-CD, monofunctionalized by a polyethylene polyamine coordinates a Zn^{II} ion in the vicinity of the hydrophobic cavity. They showed that the metallo-host binds 2-oxo-1-adamantane carboxylate 330 times stronger than a simple β-CD. Such a binding enhancement was observed only with hydrophobic anions of the types $-CO_2^{(-)}$,$-SO_3^{(-)}$, and $ArO^{(-)}$, while the apo-hosts are only 2-3 times more effective than β-CD. The additivity in the energetics associated with metal ion binding and host inclusion with anionic ligands displaying a hydrophobic scaffold (e.g. adamantane) is explicited in Fig. 10.

Breslow *et al.* studied substrate binding and transition state analogs in a hydrolytic enzyme model composed of two hydrophobic CD cavities bridged by a Zn^{II}-bipyridine metal complex (Fig. 11).[39] The design was carefully thought to avoid product inhibition and achieve some turn-overs. The binding of polytopic guests, either a substrate ($\mathbf{S_1}$) or a transition state analog ($\mathbf{TS_i}$), was investigated in presence and absence of a metal ion. Each guest presents two lypophilic groups (adamantyl or indyl) at its extremities and a central function prone to metal ion interaction (diestercarbonate or phosphate, neutral or anionic at pH 7, respectively). In the absence of Zn^{II}, $\mathbf{S_1}$ and $\mathbf{TS_1}$ displayed similar affinities for the host (with a binding constant value of ca. 10^6 in water at pH 7). However, in the presence of Zn^{II}, the affinity for

the phosphate ligand **TS$_1$** was higher by one order of magnitude compared to **S$_1$**, highlighting the role of the metal-ligand interaction in the overall binding. The importance of the metal-ligand interaction is also evidenced by the fact that the binding to the metallated host was 50-fold stronger than to the apo-host for the two phosphate ligands **TS$_1$** and **TS$_2$** while with the weaker donor carbonyl ligand in **S$_1$**, only a 5-fold binding enhancement was observed. These results clearly emphasize the leading role of the two CDs in the recognition process and the existence of a weaker secondary interaction due to the metal center when the substrate presents a good anionic ligand. Yet, this secondary interaction allows for the selectivity between the carbonate and phosphate ligands. Most importantly, it shows that the transition state analog is more stabilized than the ground state forecasting a great catalytic activity for this system. Indeed, rate increases by a factor of 10^4-10^5 for ester hydrolysis were observed together with turnovers.



	Binding constants (*Ka*) of guest in water at pH 7		
guest	*Ka*	*Ka* with Zn(II)	*Ka*(Zn)/*Ka*
S$_1$	1.43 10^6	7.70 10^6	5
TS$_1$	1.00 10^6	5.47 10^7	55
TS$_2$	2.05 10^7	1.02 10^9	50

Fig. 11 Breslow's model for the study of hydrolytic reactions and binding constants for different substrates.

The opposite situation consists in giving the metal-ligand interaction the leading role in the overall binding process. In the previous example, the hydrophobic effect drives the recognition of the lipophilic substrate in the CD dimer. In organic solvent, this driving force is suppressed, since solvent molecules strongly compete for guest hosting and consequently most cavities do not spontaneously encapsulate a guest unless a poorly competitive solvent can be found. For instance, in the absence of a metal ion, the calix[6]arene ligand having three

imidazole ligands at the small rim (see Fig. 5) does not bind a primary amine in organic solvent. As mentioned before, this is due to the absence of a solvophobic driving force. In that case, the presence of the metal ion is mandatory to observe an interaction between the ligand and the calixarene cavity.

In between these two limiting cases, a more balanced situation for the contributions of the binding by the metal ion or by the cavity is also often encountered. Rebek *et al.* studied a resorcinarene-porphyrin system and the recognition of a pyridine ligand (targeting the metal ion) functionalized by an adamantyl group (targeting the resorcinarene cavity, Fig. 12) in toluene.[40] The driving force was found to be $\Delta G° = -40$ kJ/mol at 295 K. Using the monotopic host analogs deprived of a cavity or a Zn porphyrin moiety, they found that the contribution due to the metal-pyridine bond is $\Delta G° = -22$ kJ/mol, while the contribution due to the cavity alone does not exceed -12.5 kJ/mol (at 273 K). The addition of these two separate contributions reveals a positive cooperativity of the two binding sites in the hybrid receptors.

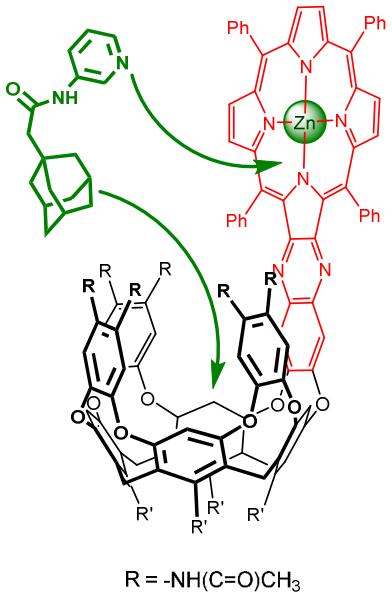


Fig. 12 Cooperativity effect in a Zn-porphyrin-resorcinarene system studied by Rebek *et al.*

Another example of positive cooperativity was reported by Nau et *al.* in a ternary {tetrasulfonato calix[4]arene-Zn^{II}-azoalkane} system in water (the ligand being a bicyclic azoalkane, Fig. 13).[41] In this case, the metal-ligand interaction is very weak (K_{met} = 4 M^{-1}) while recognition by the cavity alone is much stronger (K_{cav} = 1000 M^{-1}). The metal complex binds the ligand with an association constant K = 4000 M^{-1}. The increase in binding in the

presence of Zn^{II} highlights a synergistic effect. The XRD structure of the ternary complex showed the partial encapsulation of the ligand in the hydrophobic calixarene, coordination to the Zn^{II} ion and interaction (mainly electrostatic) between the calixarene and the metal ion.

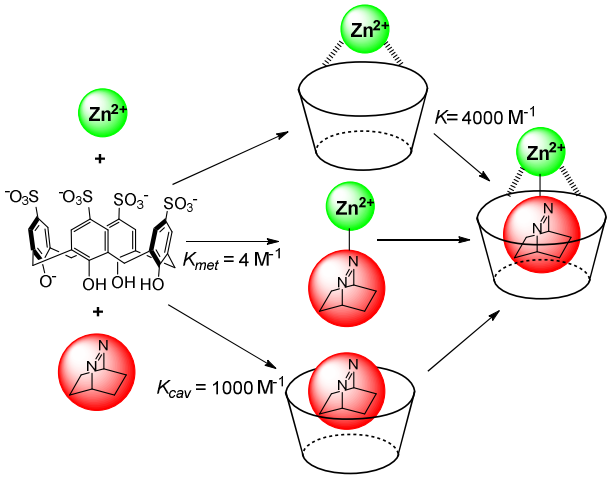


Fig. 13 Selected binding constants in ternary complexes.

2.2 Multipoint recognition with two metal centers around a cavity

Ligand recognition is in general due to the cooperativity between its coordination to the metal center and its interaction with the cavity. With a more sophisticated design, one (or several) binding site(s) can be appended. The resulting new interactions (metal-ligand, H-bonds, electrostatic…) are expected to increase not only the binding affinity for a suitable ligand but also the selectivity. This is well illustrated by a calix[6]arene-based Zn^{II} complex. A Zn^{II} porphyrin moiety was grafted at the large rim of the calixarene, thus offering a new binding site, and a ditopic recognition process was observed with a diamine (Fig. 14).[42] Comparison of this ditopic ligand with a mono amine evidenced a higher stabilization (by two orders of magnitude) as anticipated by the presence of the second coordination site.

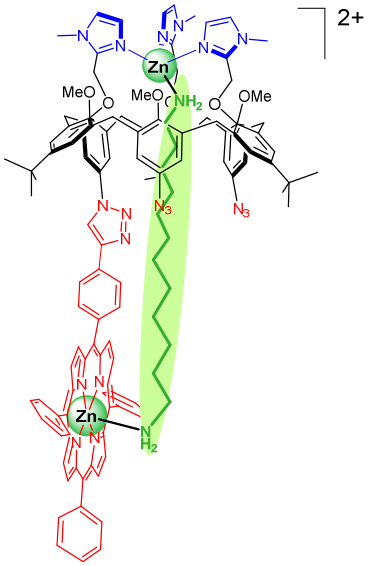


Fig. 14 Dinuclear metal complexes for the ditopic recognition of a diamine.

2.3 Guest-triggered switch of metal coordination

In flexible systems, the recognition of a guest affects the conformation of the host *via* an *induced-fit* process. The nature of this *induced-fit* modification can vary and trigger some reorganization of the metal coordination pattern in a polytopic system.

2.3.1 Translocation of a metal ion. A calixarene presenting three imidazole binding groups at the small rim and three tridentate ligands at the large rim preferentially binds one Zn^{II} ion in a N_6 environment proposed by two ligands at the large rim (Fig. 15, top). Addition of heptylamine induced a clean and drastic structural change. It triggered the translocation of the Zn^{II} ion from the large rim to the small rim with concomitant recognition of heptylamine in the calixarene cavity.[32] The translocation is thermodynamically favored by several factors: i) formation of a N_3Zn(heptylamine) complex at the small rim, ii) stabilization of the ligand by secondary interactions with the calixarene core (H-bond and CH-π, discussed in the next section) and iii) disruption of the N_6 metal complex at the large rim prompted by the long alkyl chain of the guest ligand. This last point was evidenced by the fact that the smaller propylamine ligand did not yield a clean translocation but produced a mixture of species.

2.3.2 Modification of the nuclearity. A related system reveals different behavior upon ligand binding.[31] In this case, the calixarene is functionalized by three bidentate ligands (aminomethylene-triazol groups, Fig. 15, bottom) at the large rim. In the presence of one

equivalent of Zn^{II} and three equivalents of Cu^{I}, a hetero-dinuclear complex is the thermodynamically favored species in solution, with the regioselective coordination of one Zn^{II} ion at the small rim and of one (out of three) Cu^{I} ion at the large rim. Once again, this arrangement can be disrupted by the addition of the long heptylamine guest. Its coordination to Zn^{II} through the calixarene cavity hinders the copper complex at the large rim. Therefore, the cooperative binding of all three triazole groups is precluded and each bidentate donor chelates independently a copper ion, leading to a tetranuclear complex.

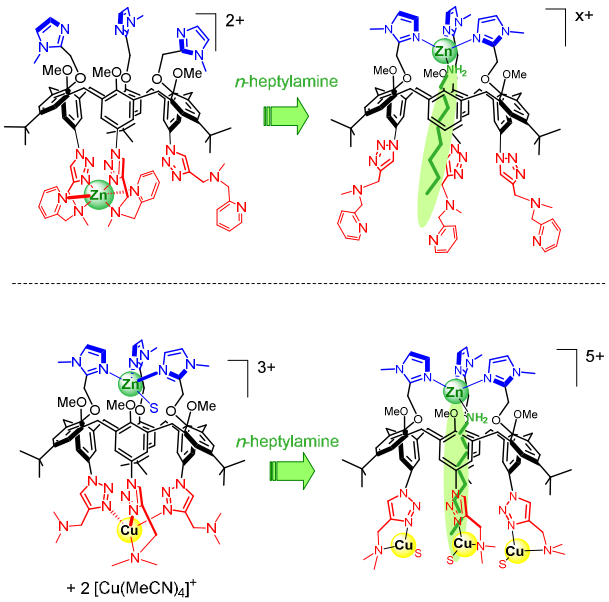


Fig. 15 Top: Guest-triggered Zn^{II} translocation. Bottom: Guest-triggered switch of nuclearity and coordination sphere.

2.4 Mechanisms of ligand exchange and gate effect

2.4.1 Embedment of the metal center in a cavity favors a dissociative guest-exchange mechanism. When one labile site at the metal center is strongly interlocked within the cavity, i.e. is buried inside the cavity, an associative mechanism for guest exchange can be forbidden for simple geometrical reasons. Therefore, ligand exchange necessitates first the decoordination of the guest. Such a dissociative mechanism was experimentally demonstrated for the exchange of an acetonitrile ligand in calix[6]arene-based Cu^{I} complexes (Fig. 16).[43] Indeed, the rate limiting step was shown to be first order in copper complex and independent of the concentration in acetonitrile, and associated with a large and positive activation entropy that advocates for a dissociative mechanism.

The calixarene structure was then modified at its large rim where three *t*Bu substituents were removed (Fig. 16). These substituents play a crucial role since they are oriented inwards relative to the cavity. Indeed, they both reduce the size of this cavity and act as a gate at its entrance, with two major consequences: i) the relative affinity displayed by the Cu^{I} host for acetonitrile vs the larger guest benzonitrile is inversed; ii) the exchange rate of the acetonitrile guest is increased by two orders of magnitude. The last effect was found to be due to a lower enthalpy of activation and a higher entropy of activation. This underlines the role of the *t*Bu groups in the mechanism of guest exchange: they act as a door that must be opened in a process concomitant to the metal-ligand bond cleavage.

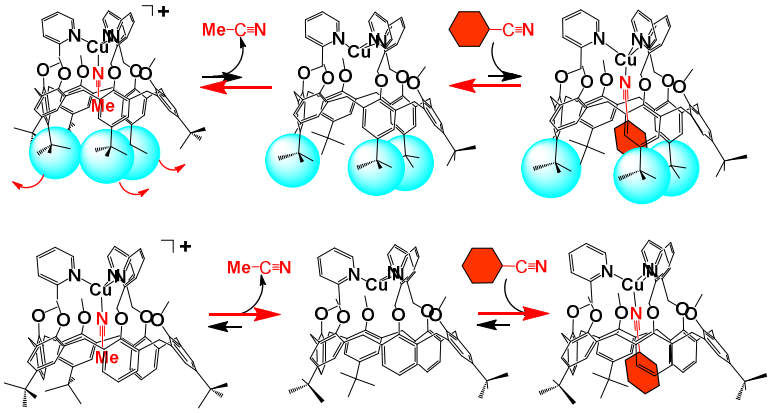


Fig. 16 Dissociative guest exchange mechanism in two Cu^{I} calixarene-based complexes.

The same exchange reaction was investigated for a Cu^{I}-containing molecular basket (Fig. 17).[44] Coordination of three pyridine ligands appended to a C_{3v} symmetrical scaffold to a cuprous ion folds the structure and creates a basket-like architecture. Two mechanisms for the entrance of an acetonitrile guest molecule inside an empty basket were envisaged. In the first one, the rate limiting step is the decoordination of a pyridine arm which opens the structure and favors the encapsulation of the acetonitrile. In the second one, the acetonitrile slips into the empty cavity without disruption of the copper coordination sphere. Experimental data together with DFT calculations are actually in agreement with the second scenario. The slight expansion of the basket required for the entrance (or escape) is energetically much less demanding than the decoordination of one pyridine arm.

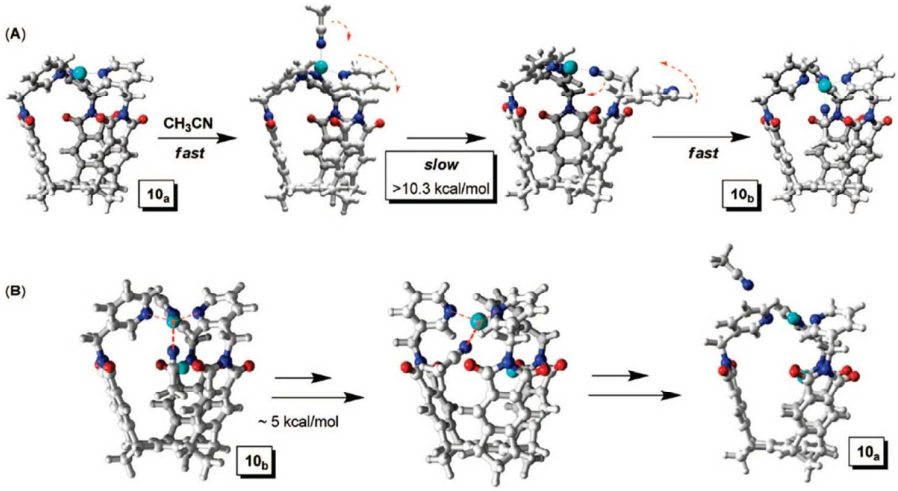


Fig. 17 Gated (A) and slippage (B) mechanisms for the entrance of a CH_3CN guest in a molecular Cu^I basket (Reprinted with permission from Reference 44. Copyright 2008 American Chemical Society).

2.4.2 Trapping of an intermediate (two-step dissociative mechanism). The dissociative mechanism is a common feature of systems in which the metal center has one labile coordination site buried in the heart of a cavity. The reaction pathway for guest exchange can be decomposed in two steps: first, cleavage of the metal-guest bond, second the expulsion of the guest ligand from the cavity (Fig. 18). This mechanism supposes the existence of an intermediate species where the metal-guest bond is broken, but in which the ligand still occupies the cavity. Not all systems allow this observation. With the calix[6]-TREN Cu^I complex, such an intermediate could be observed thanks to the well-defined cavity (relatively rigid and closed by *t*Bu doors) that can transiently entrap a non-bonded guest.[45]

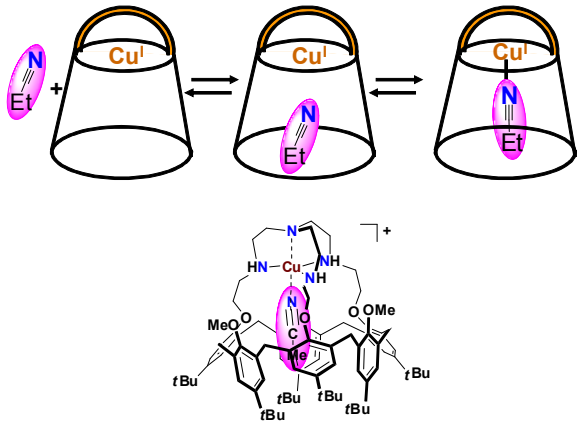


Fig. 18 Schematic representation of the intermediate (middle) observed during the dissociation of a guest of a cuprous complex.

3. 1st, 2nd, 3rd coordination sphere effects, cavity effects

The goal of the design of biomimetic metal complexes is to construct an environment for the metal ion(s) that will reproduce specific features encountered in metallo-enzymes. Different levels of sophistications can be considered, namely the first, second and third coordination spheres.

- The design of a polydentate ligand that reproduces the first coordination sphere of the catalytic metal ion is a prerequisite for obtaining essential properties: strong binding of the metal center with simultaneous presentation of labile sites available for substrate(s)/reactant(s) interaction, a well-defined geometry, and appropriate electronic properties conferring the adequate Lewis acidity and redox potential. Modeling heme enzymes requires the synthesis of a porphyrin ligand. Non-heme enzymes often present a cofacial triad of amino-acid residues that can be mimicked by a poly-aza ligand. In that case, a tripodal ligand is preferred over a linear polydentate one, since it will better reproduce the geometry at the metal center, with cofacial coordination.[3, 4]

- The second coordination sphere allows tuning the reactivity of the metal ion through secondary interactions with its ligands. The classical strategy to mimic such aspects consists in appending an H-bond donor or acceptor (or acid/base) to the tripodal ligand.[46] This may lead to the stabilization of a transient species, or conversely to the activation of an intermediate, thus orienting its reactivity. This has been well illustrated with dioxygen metal complexes and their partially reduced derivatives that can be H-bonded to the distal or proximal oxygen atom, thus leading to different reactivity patterns.[47]

- The third sphere is further away and more difficult to mimic, although obviously important in enzyme active sites. Indeed, it has been long recognized that the enzymatic pocket is key for substrate affinity and selectivity, and conversely product release. More recently, it has been also shown that it plays key roles for water molecule positioning, especially when water is the reactant, or for proton transfer generally associated with redox processes.[48] Such effects are best mimicked with macrocyclic ligands presenting a cavity surrounding the metal ion, hence defining the 1st, 2nd and also 3rd coordination spheres, and

providing what will be named "cavity effects" due to embedment of the metal ion in a pocket that can host an exogenous ligand (substrate/reactant/product or an analog of one of these).

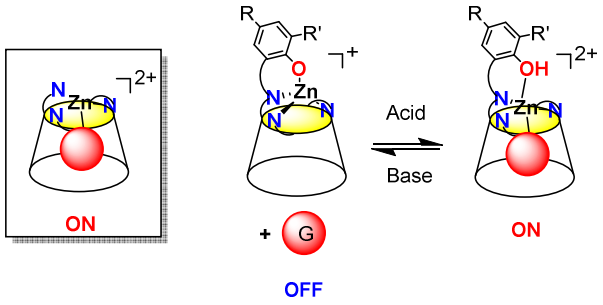
- Finally, one fundamental characteristic of enzymes is their ability to function under physiological conditions, thus in an aqueous environment. Water as a solvent is also a highly competitive medium for all electrostatic interactions involving charges, dipoles and H-bonding, which are keys for reactivity, selectivity and efficiency.[49] Most of the biomimetic complexes aimed at reproducing a specific feature observed in the active site are not water-soluble compounds. There are several reasons for this. First, in enzymes, the metal center is buried in the heart of the protein that defines a medium resembling an organic solvent more than water. Second, it is very difficult to control the reactivity of a metal center in water due to its propensity to form hydro/oxo species that readily undergo dimerization if not polymerization and precipitation. Third, the synthesis of a ligand allowing simultaneously metal ion coordination, protection against water, and water-solubilization is a difficult task, from both a design and synthetic point of view.

Here, we will present selective examples of cavity-based complexes that best highlight specific features related to the different coordination spheres and cavity effects. In spite of the number of cavity-based complexes, only few have been structurally characterized at the atomic level, which is a prerequisite to identify unambiguously these effects.

3.1 1st sphere effect: tuning the Lewis acidity of a metal ion – models for Zn-sites of proteases

In mononuclear Zn proteases, two major patterns of coordination environment can be observed: one with a triad of amino-acids, generally $(His)_3$ or $(His)_2Glu$ (or Asp), and one with an additional Tyr thus providing a tetradentate donor site.[50] The first coordination sphere of Zn^{II} is completed by a water molecule, which, in the presence of substrate, is activated for hydrolysis, but which can also be displaced by inhibitors for example. Fig. 19 presents two model compounds for these families of enzymes, which are based on the calix[6]arene scaffold. They allow a direct comparison of Zn^{II} funnel complexes presenting different 1st coordination spheres, whereas the surrounding environment is defined by the same cavity. The first model,[25] based on a tris-imidazole core mimicking the $(His)_3$ triad, presents a Zn^{II} center surrounded by only three neutral *N*-donors in a pyramidal fashion. This design leaves a single site for binding a guest ligand in the calixarene cavity to complete the tetrahedral geometry. As a result, the Zn^{II} center displays a high Lewis acidity and a high propensity to bind weak neutral donor, (an alcohol, nitrile, or even an aldehyde). Comparatively, the Zn^{II}

complex within the $N_3ArO^{(-)}$ environment provided by the other ligand[51] displays a much lower Lewis acidity, and as a consequence, a lower affinity for exogenous donors. This is well illustrated by the coordination of alcohols: with the N_3Zn system, they readily coordinate the metal ion (at mM concentration in chloroform), whereas, under the same experimental conditions, with the $N_3ArO^{(-)}$Zn complex, they are just included in the cavity by polarization effects, without coordination to the metal ion. This highlights a much weaker binding when implementing an anionic donor into the first coordination sphere of Zn^{II}. Interestingly, it was shown that when this extra phenol-based donor is in its neutral form, the metal ion recovers a Lewis acidity similar to that of the N_3 dicationic system.[25] This reveals the possible tuning of substrate/reactant/product binding through the transient deprotonation/protonation of the Tyr residue of the proteases of the astacin family. From this observation, a detailed mechanism has been proposed, highlighting the specific additional features of these proteases resulting from the implementation of a Tyr residue at the active site. Indeed, it is well-known that these enzymes have a relatively narrow pH window for their activity.



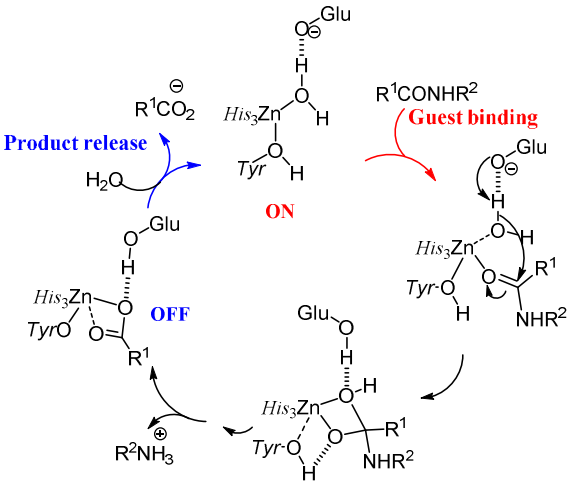


Fig. 19 Top: Acid-base switch process in Zn^{2+} calix-complexes. Bottom: Proposed mechanism for the peptidase activity of astacin and serralysin, in view of the acid-base switch process of the model.[51]

3.2 2nd coordination sphere: stabilization of a Td aqua-Zn^{2+} complex, model of carbonic anhydrase

Several biomimetic complexes have been developed by various groups to reproduce the specific $[Zn(His)_3(OH_2)]^{2+}$ coordination core encountered in many hydrolytic Zn enzymes.[52] 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, with the calix[6]tris(imidazole) ligand, a very stable dicationic zinc-aqua complex was obtained for the first time.[53] The complex presents two water molecules buried in the calixarene cavity, with only one of them coordinated to Zn^{II} (Fig. 20). Each water molecule is hydrogen-bonded to an oxygen atom belonging to the calixarene small rim, thus acting as a 2nd coordination sphere. 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 (3rd sphere effect). A comparison with the active site of carbonic anhydrase shows surprising similarities (Fig. 20, right). The exceptional stability of this calixarene-based Zn^{II}-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. Such a behavior is well explained by the establishment of multiple stabilizing interactions within the calixarene cone, as it is observed in the enzyme. Conversely, the corresponding hydroxo Zn^{II} species is destabilized by repulsive electrostatic interactions with the 2nd sphere oxygen atoms of the calixarene small rim. This complex represents the first structural model for the Zn^{II}-aqua species found in enzymes and convincingly underlines the importance of the microenvironment. Here, the calix core constrains the 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 was observed. On the other hand, this model has allowed studying, for the first time, the binding properties of such a constrained Zn^{II} center.

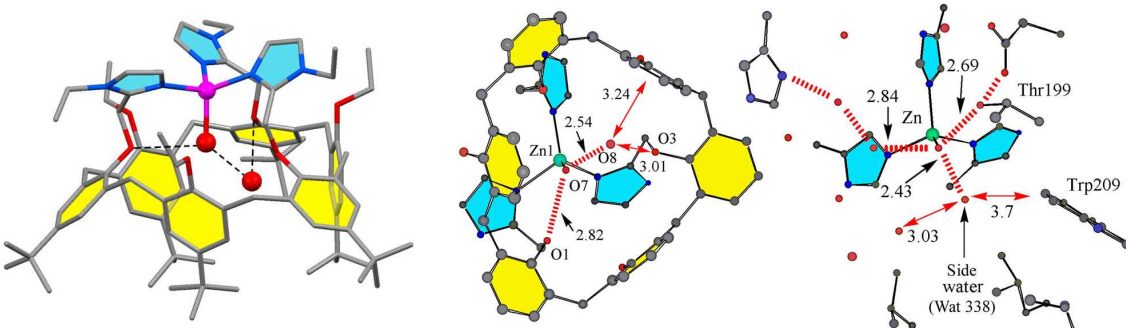


Fig. 20 Left: XRD structures of the first dicationic Zn^{II}-aqua complex; hydrogen bond networks in the calixarene-based aqua-complex (middle) and in carbonic anhydrase (right). Distances are given in Å.

3.3 1st and 2nd coordination spheres: tuning the guest ligand affinity of a Mono-Cu^{II} complex, models of copper monoxygenase active sites

Cu^{II} complexes based on calix[6]arene aza-cryptands constitute an interesting case for the study of 1st and 2nd sphere effects. The complexes depicted in Fig. 21 are mimics of mono-nuclear copper centers encountered in mono-oxygenases. Comparison of their binding properties towards guest ligands evidenced various effects. With the TREN cap, the affinity order relative to neutral donors reflects the σ-donor ability of the ligand: nitriles (MeCN) < alcohols (EtOH) < amides (DMF).[54] With the PN_3 cap, the affinity order between EtOH and MeCN is reversed and DMF affinity is massively enhanced, due to a LMCT involving the $P(Ar)_3$ moiety.[55] This is due to 1st sphere effects. With the TMPA cap, MeCN is preferred, which suggests a substrate shape selectivity that can be related to a specific conformation of the calixarene macrocycle due to its capping by the more rigid TMPA core (cavity effect).[56]

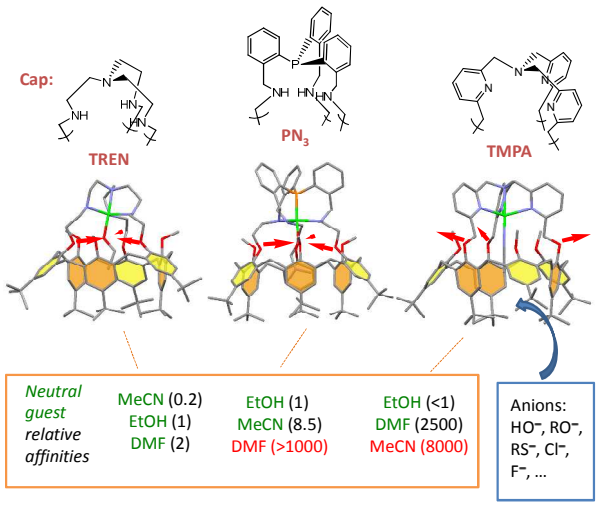


Fig. 21 Supramolecular control of neutral and anionic guest binding at Cu^{II} (the relative affinities for neutral guests are indicated in brackets). XRD structures of calix[6]TREN-, PN_3- and TMPA-based Cu^{II} complexes are represented with EtOH, DMF and MeCN as guests, respectively.

Even more surprising is the reluctance of cupric complexes of calix[6]TREN and PN_3 to bind anions, and consequently, they behave as selective hosts for neutral donors, as mentioned above. In contrast, the calix-TMPA Cu^{II} complex exhibits a classical behavior, with a high propensity to anion binding. Such behaviors cannot be explained by 1st sphere effects. A comparative analysis of the conformation adopted by the calixarene core with the three different aza-caps actually shows that with the TREN and PN_3-based complexes [as in the case of tris(imidazole), *vide supra*], all six oxygen atoms of the macrocycles point their lone pairs towards the cone axis, at the level of the coordinating atom, which results in a strong electrostatic repulsion with anions. With the more rigid TMPA cap, the connected oxygen atoms are forced to point their lone pairs outwards, thus decreasing the electronic shielding and making anion binding possible.[56] Such a behavior highlights the drastic effect of the 2nd coordination sphere. It also nicely illustrates the dramatic impact a conformational change of the molecular microenvironment around the metal center can have on the metal ion properties, which echoes the regulatory role of proteic conformational changes for many biochemical processes.

3.4 2nd, 3rd (and further) sphere effect: host-guest binding through multipoint recognition; selective recognition/positioning of a multifunctional guest

As illustrated above with the Zn^{II} aqua complex based on a calixarene-ligand (Fig. 20), the 3rd sphere is of the most importance: the second water guest is itself in interaction with various parts of the calixarene core, thus playing the role of the 3rd sphere. Indeed, a cavity surrounding the coordination site of the metal ion interacts with the guest at various levels through CH-π[25] and OH-π[53] interactions. The ligand can be modified at the large rim of the calixarene in order to add new interacting groups placed beyond the 3rd coordination sphere. For instance, three amino groups were selectively introduced at the anisole units. The resulting Zn^{II} complex 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,[57] a single proton or an ammonium, thus giving rise to stable tricationic structures (Fig. 22).[22, 58] 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.[59] The remarkable selectivity of this multipoint recognition system is best illustrated by the regioselective binding of a dissymmetrical triamine, as shown in Fig. 22.

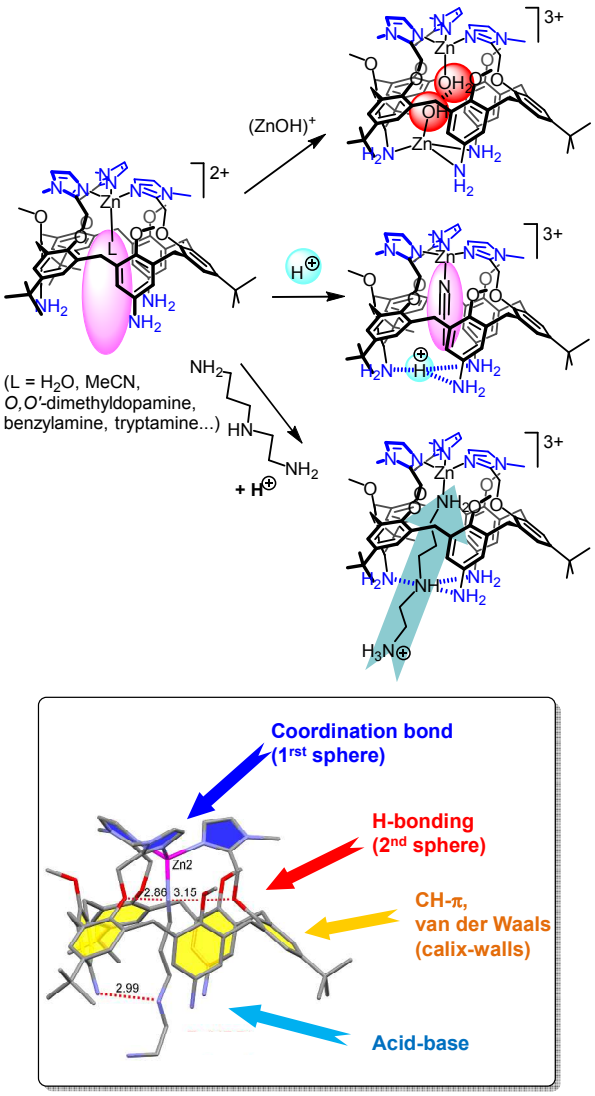


Fig. 22 Top: Illustration of the capacity of the large rim substituents to act as a second binding core. Bottom: XRD structure of a Zn^{II} funnel complex with a guest tri-amine; illustration of various level of coordination sphere interaction for the control of the binding process.

3.5 Cavity effects

3.5.1 Strengthening, selecting and orienting exogenous ligand interaction.

The energetics of a metal-ligand bond spread over a large range, but are often of higher energy than the non-covalent interactions involved in molecular recognition events. Hence, a

cavity appended in the vicinity of a metal ion can strengthen, select and orient exogenous ligand interaction. A nice illustration is provided by a deep cavitand to which a phenanthroline donor was grafted on one of its walls, at the edge of the vase-shaped cavity (Fig. 23). The N_2 donor, due to its rigid skeleton and its short covalent link to the benzymidazole wall, has restricted orientations, basically one *endo*, and one *exo* with respect to the cavity. The addition of an exogenous donor such as DABCO (1,4-diazabicyclo[2.2.2]octane) that is both a good ligand and a good guest for the cavity through multiple CH-π interactions, was shown to i) drive the Zn–phenanthroline complex to sit in *endo* position, in order to bring the DABCO guest into the cavity, and ii) strengthen the host-guest interaction (by a factor ≥ 5 in CD_2Cl_2 with the $ZnCl_2$ complex).[60]

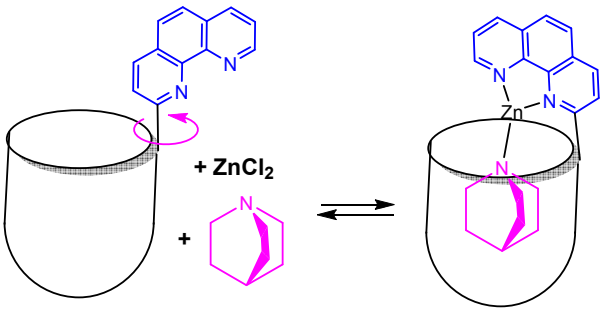


Fig. 23 Enforced orientation of the Zn^{II} complex through DABCO inclusion in Rebek's deep cavitand

3.5.2 Hydrophobic effect in water.

Synergistic binding in water: formation of ternary complexes with a hydrophobic cavity-ligand, Zn^{II} and a hydrophobic guest. A tricationic version of the calix[6]arene-based tris(imidazole) ligand allowed the direct comparison of its coordination and host-guest properties in water and in organic solvents (CH_3CN, $CHCl_3$). Depending on the counterions, this ligand is soluble in organic solvents (PF_6 salt) or in water (NO_3 salt). In organic medium, the ligand behaves like the parent compound, *i. e.* it binds Zn^{II} to form a mononuclear species and can accommodate primary amines in the cavity. On the contrary, it does not bind Zn^{II} in the highly competitive water medium. However, in the presence of a hydrophobic primary amine (such as heptylamine), a ternary complex (calix/Zn/amine) is readily formed at physiological pH, hence stabilizing the neutral form of the amino guest with a spectacular pseudo p*K*a shift of ca. 7 units (Fig. 24).[61] The hydrophobic effect is clearly evidenced by the

fact that this ternary complex is not formed in presence of hydrophilic amines (such as propylamine).

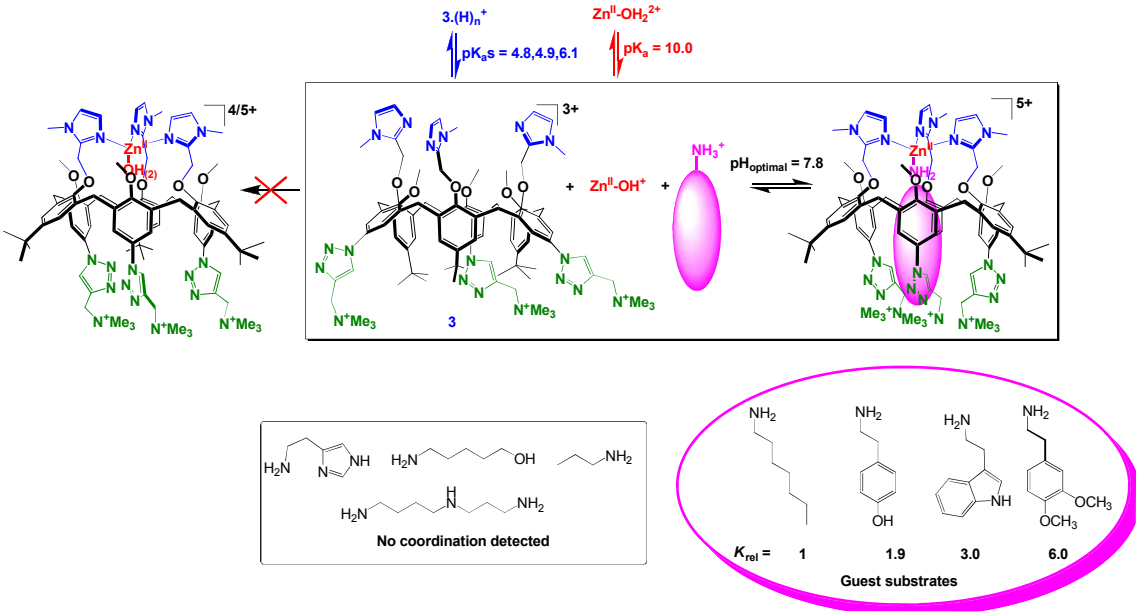


Fig. 24 Water-soluble biomimetic receptors – Illustration of the synergistic interaction of the calixarene ligand, hydrophobic amines and Zn^{II} for the complex formation. K_{rel} is defined as K(guest-amine)/K(heptylamine).

3.5.3 Cavity effect on the electronic properties of the metal. The supramolecular environment can also affect the electronic properties of the metal. This can be probed using CO as a ligand with cuprous complexes, as coordination to the metal involves CO π-back donation, which can be evaluated by measuring the CO vibration (ν_{CO}).

Calix-tris(imidazole)Cu^{I} binds CO, yielding a Td environment involving the three imidazole arms. Depending on its substitution pattern at its small rim, the calixarene adopts either a C_{3v} symmetrical cone conformation or a non-symmetrical conformation presenting a partially included *t*Bu substituent.[24] A ν_{CO} shift is observed between the two conformations, evidencing the interdependence of the metal ion electron density and its supramolecular environment. Likewise, the tris(imidazole)Cu^{I}(CO) complex obtained with the resorcinarene-based bowl ligand displays a different ν_{CO} value (Fig. 25).[27] This emphasizes the impact of the microenvironment on the electronic properties of a metal ion and its ligand(s). Such behavior was also observed in cytochrome c oxidase, which evidenced the coordination flexibility at the copper site in the apolar binding pocket.[62]

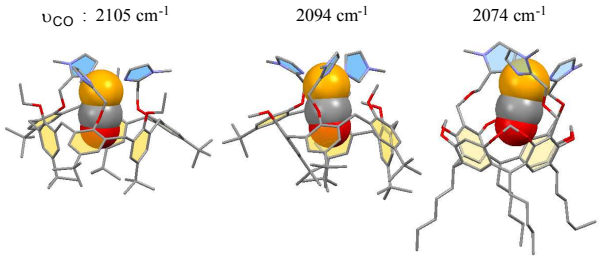


Fig. 25 Coupled conformational and electronic properties in the tris(imidazole)Cu^{I} core controlled by the bulkiness of small rim substituents (left and middle) or by the nature of the cavity (right).[24, 27]

Nolte's group developed a series of models of [4Fe-4S] clusters in order to study the effect of the environment on the redox properties of the metal ion. For this purpose, they semi-encapsulated [4Fe-4S] clusters in a CTV (cyclotriveratrylene) platform bearing thiol arms (Fig. 3). The length of the arms was varied to tune the distance between the platform and the cluster. As the length increased, the half wave potential of the 2+/1+ core reduction becomes more negative, showing that the local environment modulates redox properties.[63]

Likewise, inclusion of a small molecule model of the [FeFe]-Hydrogenase active site within *β*-CD was reported and the corresponding XRD structure obtained (Fig. 26). The *β*-CD not only helps to solubilize the complex in water, but also provides a hydrophobic environment around the metal centers. As a result, a small structural change was observed with a CO ligand slightly tilted, together with a 80 mV negative shift of the Fe-cluster reduction potential. Such an effect was previously reported for ferrocene and a Fe-porphyrin complex, also embedded in CDs.[64, 65]

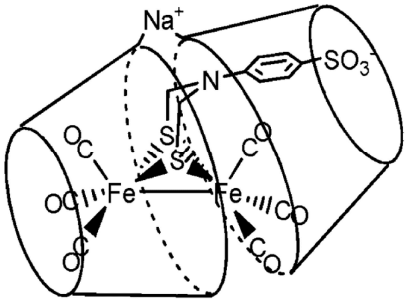


Fig. 26 Schematized representation of a Fe cluster embedded in a pair of CDs.

4. Reactivity

In natural systems, the constraints of the metal environment and the surrounding pocket greatly impact the reactivity of the metal center. Entatic states can be stabilized, reactive species protected and specific catalytic kinetic profiles (Michaelis-Menten) are observed. Reactivity control is optimized by first and further coordination sphere interactions, leading to remarkable selectivity. Such unusual reactivity patterns could be observed from the interaction of a metal reactive site and molecular cavity receptors and will be presented in the following sections.

4.1 Cavity effects: mutual influence of guest exchange and electron exchange

The design of calix[6]arene-based complexes, in which the metal center is buried at the bottom of the cavity and displays a labile coordination site oriented inside the hydrophobic pocket, generates unusual interlocking of host-guest phenomena and metal properties when it comes to redox processes. Indeed, the guest interacts both with the metal center by coordination (and thus impacts its redox properties) and with the cavity through 2nd and 3rd sphere interactions. Therefore, redox processes and guest exchange become interdependent.

4.1.1 Host-guest interactions control electron exchange pathways. Copper ions have different geometric requirements depending on their oxidation state. A square-based pyramid (SBP) geometry suits the d^9 Cu^{II} ion through a Jahn-Teller distortion, whereas the soft d^{10} Cu^{I} ion adopts preferentially a 4-coordinate environment within the Td geometry. A redox switch thus involves a significant reorganization of the coordination sphere. Two pathways are possible, involving either a 5-coordinate Cu^{I} intermediate (pathway A, Fig. 27), or a Td Cu^{II} species of high energy (pathway B). Due to the high flexibility of the soft Cu^{I} ion, pathway A is classically followed, whereas pathway B requires the transient formation of a high energy Cu^{II} species. In contrast to unconstrained environments provided by simple polydentate ligands, when embedded in a calix[6]arene-based tris(pyridine) ligand, the Cu ion follows pathway B during redox changes. Indeed, the binding arms are relatively weak donors and copper interaction with its guest MeCN is strengthened by the calixarene cavity. Consequently, the 3rd sphere cavity-guest interactions generate a local retracting force on the metal, which stabilizes the Td environment for Cu^{II} and favors pathway B (Fig. 27).[66]

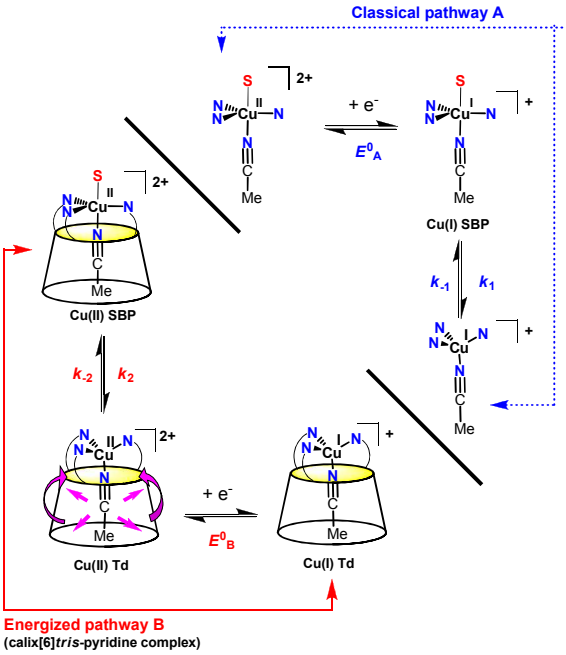


Fig. 27 The two possible electron-transfer pathways for copper complexes associated with a SBP geometry at Cu^{II} and Td geometry at Cu^{I}. The structure of the calixarene is displayed in Fig.16.

4.1.2 The cavity precludes associative guest exchange: trapping of intermediates upon redox switch. When the two competing ligands MeCN and DMF are present in a solution containing a copper complex, the Lewis-acidic Cu^{II} state preferentially binds the better donor ligand DMF whereas the π-accepting MeCN is preferred by the electron-rich Cu^{I} ion. Upon redox switch, guest exchange is thus expected. In 5-coordinate Cu^{II} complexes, guest-exchange is in general associative, whereas it is dissociative at the Cu^{I} state. In calix[6]arene-based funnel complexes cis-coordination of two guest ligands is precluded by the cone-shaped cavity. As a result, ligand exchange is forced through a dissociative path,[54] which is reflected by the significant slowing down of the ligand exchange (MeCN *vs* DMF) triggered by the redox switch from Cu^{I} to Cu^{II}. This phenomenon thus allowed to detect by electrochemistry the transient "antithermodynamical" adduct $[Calix\text{-}TMPACu^{II}(MeCN)]^{2+}$, which cannot be observed in the case of the TMPA ligand deprived of cavity (Fig. 28).[67]

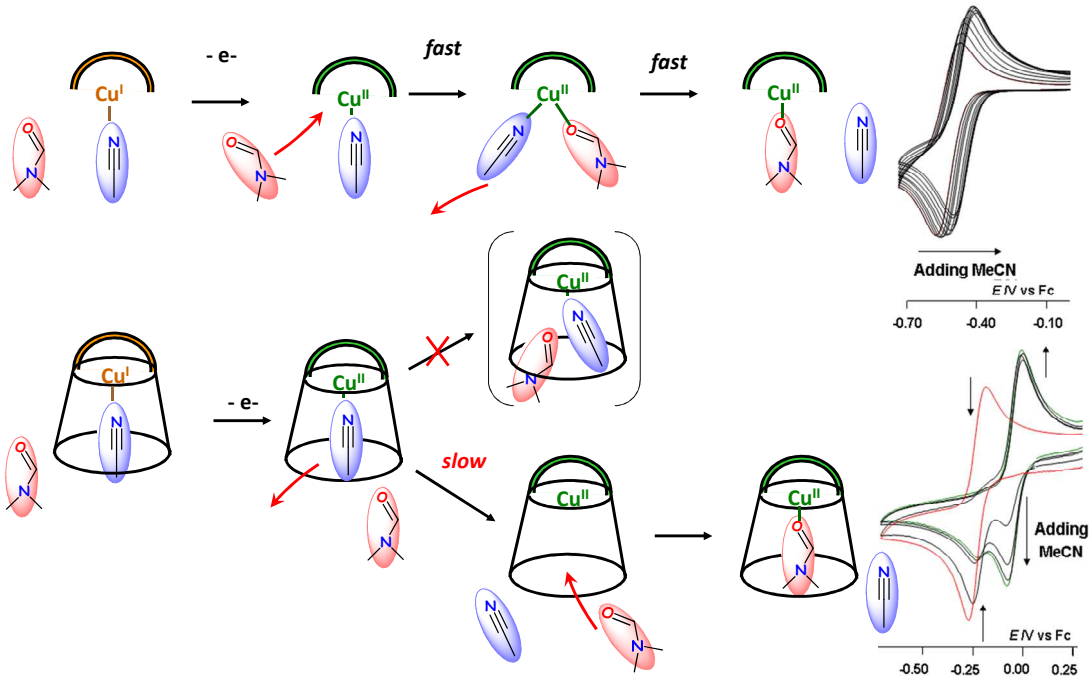


Fig. 28 Redox-triggered guest exchange (DMF *vs* MeCN) in copper complexes of TMPA (top) and Calix[6]-TMPA (bottom). See Fig. 21 for the molecular structures.

4.2 Interaction with dioxygen

4.2.1 Protection of reactive species. Interaction of a metal ion with O_2 to generate reactive species is a key step in the catalytic cycle of many redox metalloenzymes. Reaction of a mononuclear metal site with O_2 yields in a first instance a metal-superoxo species, which can either act directly as an oxidizing agent or be an intermediate towards another activated form of O_2. The protein pocket stabilizes such adducts by preventing dimerization and limiting access to solvent. Such patterns were mimicked by complexes associated with a cavity. Lang *et al*. reported the structure of a calix[4]arene Mn^{III}-superoxo complex in which $O_2^{\bullet -}$ is stabilized by the ammonium groups of the scaffold (charge-charge interactions) and the electron-poor aromatic walls (CH-π interactions), leading to an unusual linear arrangement (Fig. 29a).[68] The cavity can also be closed, as in the Fe porphyrin system of Kobayashi which is capped on one side by a calix[4]arene. Using a bulky axial ligand, interaction with dioxygen is enforced within the cavity. The metal-superoxo adduct is thus stabilized for 5.5 h at 25°C in CH_2Cl_2 (Fig. 29b).[69] The strategy was applied in aqueous medium by Kano *et al*., by encapsulating an iron porphyrin in β-cyclodextrins.[70] Using dimers of CDs bridged by a pyridine moiety (axial ligand for iron), the Fe^{III}-$OO^{\bullet}$ adduct was found to

be stable for up to 30 h at 25°C (TPPSFe/CD_2py, Fig. 29c). In natural systems (cytochromes P450), (P)Fe^{III}-$OO^{\bullet}$ is further reduced to (P)Fe^{III}-OOH, which in turn leads to ($P^{\bullet+}$)Fe^{IV}=O by heterolytic O-O bond cleavage. Using TPPSFe^{III}-OH/CD_2py as a precursor and H_2O_2 as an oxidant,[71] Kano observed the hydroperoxo species Fe^{III}-OOH and stabilized a Fe^{IV}=O species for 7 h at 25°C (Fig. 29d). Unlike the case of cytochrome P450, this species results from the homolytic cleavage of the O-O bond. However, (P)Fe^{IV}=O is encountered in the peroxidase cycle (known as "compound II").

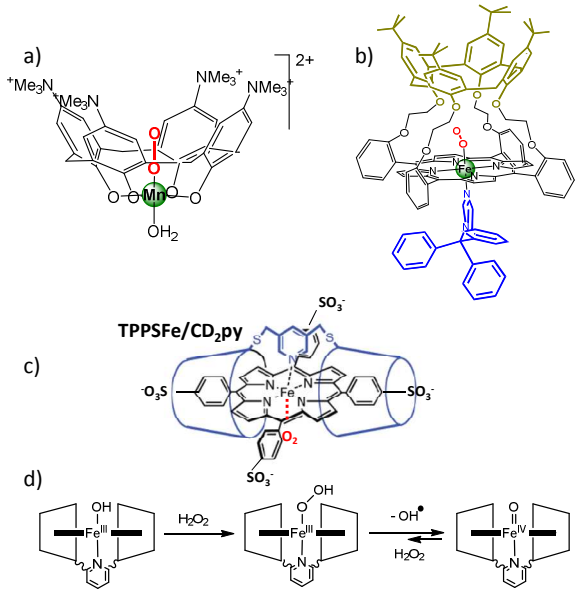


Fig. 29 Protection of reactive species by their supramolecular environment: Mn^{III}-superoxo species in a calix[4]arene scaffold (a); Fe^{III}-superoxo porphyrin species in a resorcinarene pocket (b); and a bis-cyclodextrin environment (c); stabilization of an Fe^{IV}=O porphyrin complexes in a bis-cyclodextrin environment (d).

4.2.2 The cavity as a preorganizing platform. Interaction of O_2 with mononuclear Cu^{I} complexes first leads to a Cu^{II}-superoxo intermediate on its way to the formation of the more stable dinuclear peroxo species. Some natural systems are also able to activate O_2 with three copper centers. In an attempt to study O_2 interaction at trinuclear sites, Karlin *et al.* reported a trinuclear Cu^{I} cluster derived from a CTV (cyclotriveratrylene) platform functionalized by three TMPA ligands (Fig. 30).[72] Upon oxygenation in THF at -80°C, UV-vis and resonance Raman studies showed the spectroscopic signature of both a mononuclear

Cu^{II}-$OO^{\bullet}$ and two dinuclear trans-peroxo species, the latter being ascribed to intra- and intermolecular adducts: at high concentration, only the intermolecular one remains, however the mononuclear Cu^{II}-$OO^{\bullet}$ is still present, which is remarkable, as it is usually an intermediate on the way to the trans-peroxo dinuclear adduct. With the TMPA fragment deprived of CTV, only the trans-peroxo species was detected in these conditions. This illustrates that the organization of complexes on a cavity platform (through steric hindrance, protective environment…) can impact the nature of reactive species.

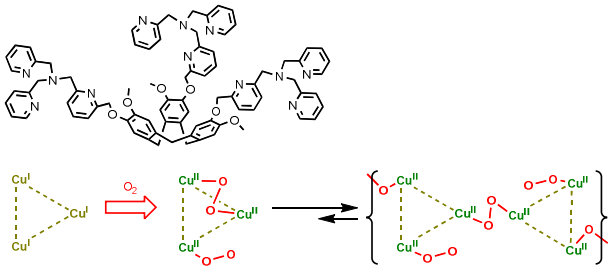


Fig. 30 Trinuclear Cu^{I} complex derived from a Tris-TMPA-CTV scaffold. Interaction with O_2 generates both a mononuclear Cu^{II}-superoxo and dinuclear trans-peroxo species.

4.3 Hydrolytic catalysis

Metalloenzymes involved in hydrolytic processes use Zn^{II} as a Lewis acid to enhance, by coordination, the electrophilicity of C=O or P=O bonds and/or the nucleophilicity of bound water. Some of them involve several metal centers for this purpose (alkaline phosphatase). Reinhoudt *et al*. developed calix[4]arene-based models to study the impact of the first coordination sphere (Lewis acidity of Zn^{II}), the number of metal centers involved and their relative orientation (Fig. 1).[14,15] On the one hand, the mononuclear complex of the L^{pyNMe2} family (Fig. 31a), was found 6 times more efficient than its counterpart deprived of a cavity in the intramolecular transesterifictaion of (2-hydroxylpropyl)nitrophenylphosphate, hence evidencing a beneficial role of the calix[4]arene environment. On the other hand, they found an increased activity by a factor of 50 in the dinuclear $L^{pyNMe2}_{distal}Zn_2$ and of 70 in the trinuclear $L^{pyNMe2}Zn_3$ complexes, which was assigned to a better substrate binding and preorganization. This was further illustrated by the dinuclear vicinal complex $L^{pyNMe2}_{vicinal}Zn_2$ which is far less efficient than its distal counterpart.[73]

Flexibility and adaptability to the substrate are also key elements: the more constrained arrangement of Zn centers in $L^{pyNMe2}_{distal/bridged}Zn_2$ lowers the activity with respect to $L^{pyNMe2}_{distal}Zn_2$ by a factor of 8 (Fig. 1). The authors thus proposed a mechanism for $L^{pyNMe2}_{distal}Zn_2$

involving activation of P=O by one Zn center and of the nucleophilic alcohol group by a second one (Fig. 31a).

Dinuclear bis-(Me-imidazole)Cu^{II} systems ($L^{bisMeIm}_{distal}Cu_2$) were also studied but showed 1st order kinetics and likely involved double phosphoryl activation (Fig. 31b). Addition of second sphere interactions via ammonium groups ($L^{bisMeIm}_{bisNH3+}Cu_2$) stabilizes the substrate and changes the mechanism, leading to Michaelis-Menten kinetics (Fig. 31c).

Other dinuclear examples based on triazacyclododecane (tacd) Cu^{II} complexes were reported in which, this time, the vicinal arrangement is more favorable than the distal one, illustrating the subtle necessary match between catalyst and substrate for optimal activity (Fig. 31d,e).[14]

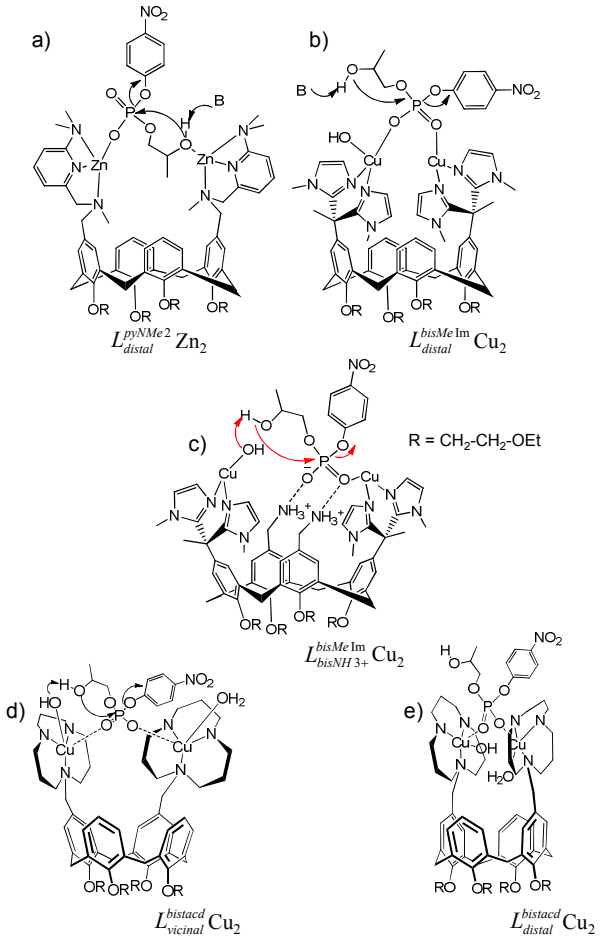


Fig. 31 Substrate activation proposal derived from kinetic studies of various polynuclear hydrolytic complexes based on calix[4]arene scaffolds.

The cavity can also be used as a receptor for substrate binding. Rebek *et al.* reported a Zn(salen) complex tethered onto a resorcinarene deep cavitand scaffold (Fig. 32).[74] The cavity

is a good receptor for trimethylammonium "knobs" in CH_2Cl_2 and thus recognizes p-nitrophenyl choline carbonate. The carbonate moiety is preorganized next to the Zn center and its hydrolysis is enhanced by a factor 5 with respect to free Zn(salen).

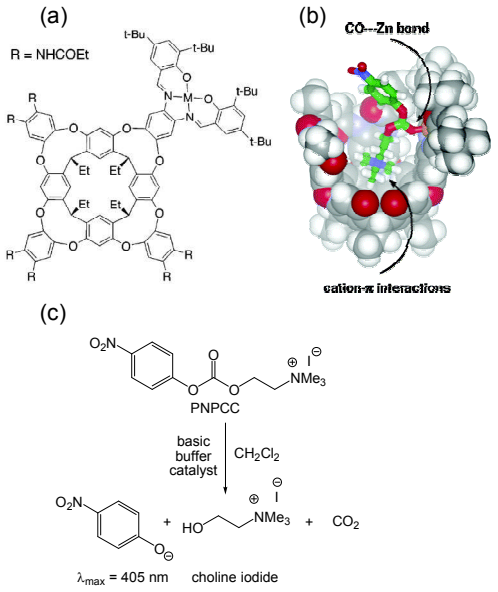


Fig. 32 Hydrolysis of p-nitrophenylcholine carbonate by a Zn(salen) complex grafted onto a deep cavitand scaffold. The ammonium group of the substrate is recognized by the resorcinarene cavity (model in the center is reprinted with permission from Reference 74. Copyright 2004 American Chemical Society).

The strategy can be transposed in water using cyclodextrin receptors. Appending a (tacd)Zn^{II} complex onto a CD (Fig. 2) cavity induces significant rate enhancements in ester hydrolysis (2 orders of magnitude). However, no turnovers were obtained due to the inhibition by the product trapped in the cavity.[16] To circumvent this problem, Breslow developed a (bipy)Cu^{II} complex appended to two CDs (Fig. 11). The substrate is now anchored by two cyclodextrins, as confirmed by kinetic studies. After hydrolysis, each product is bound to a single CD, and readily displaced by a new substrate, as the binding affinity is enhanced by bis-point recognition. Such a design strategy circumvents the classical product inhibition issue in supramolecular catalysis.[39]

4.4 Oxidation reactivity

4.5.1 Intramolecular oxidation. Metal species derived from the reaction with dioxygen are usually reactive oxidizing intermediates. A common pattern is that intramolecular (ligand) oxidation is much more favored than exogenous substrate oxidation. Indeed, the ligand is already preorganized towards the active species, unlike external substrate for which an entropic cost has to be paid to get them in its vicinity. Therefore, a first proof of reactivity is often observed with the oxidation of the ligand.

In the late 90's, Gutsche's group observed the aerobic oxidation of the ligand of a dinuclear Cu^{I} complex tethered onto a calix[4]arene platform to yield a monohydroxylated product at a specific position (the tether connection).[75] A 2-electron oxidizing intermediate (dinuclear μ–η_2,η_2 copper peroxo species) was postulated, in agreement with other models and with the site of oxidation (Fig. 33a). Such an adduct was fully characterized on a parent system grafted onto a diphenylglycoluryl molecular basket (MB), and led to the oxidative deamination of one of the polydentate groups (Fig. 33b).[76]

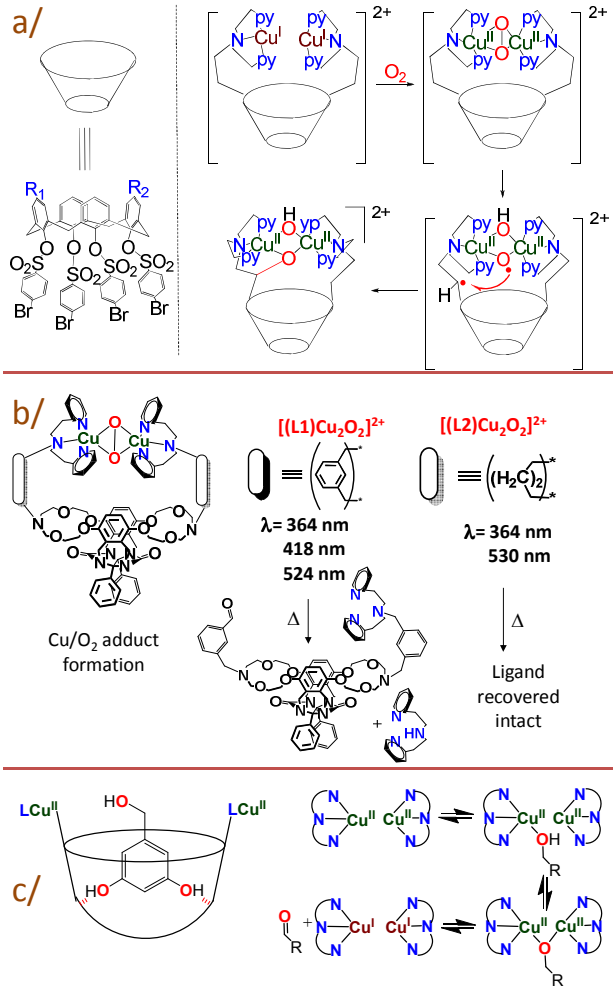


Fig. 33 Oxidation reactions carried out by dinuclear copper complexes tethered onto calix[4]arene (a) and diphenylglycoluryl scaffolds (b and c).

Whereas dinuclear Cu/O_2 species are readily obtained without necessary preorganization, mononuclear Cu-superoxo species are difficult to isolate on their way to dimerization, making their intrinsic reactivity difficult to distinguish from that of a dinuclear species. The strategy of the Reinaud's group consists in confining a mononuclear copper center at the bottom of a calix[6]arene cavity (Fig. 21), preventing dimerization while maintaining a labile site at the metal ion prone to O_2 interaction.[21] With the calix[6]TREN-based Cu^I complex, two successive 4-electron oxidations of the cap (ether to ester conversion) were observed in a non-coordinating solvent (CH_2Cl_2), while superoxide release was attested in MeCN (Fig. 34).[77] This suggests the initial formation of a Cu^{II}-$OO^{\bullet}$ species, which either releases superoxide upon ligand exchange with the solvent MeCN, or, in non-coordinating solvent, carries out H atom abstraction from the cap. After a rebound step, the resulting

alkylhydroperoxide evolves toward the keto product by releasing a water molecule. This supramolecular system is the first example of a 4-electron oxidation achieved by an isolated mononuclear Cu center. It is also relevant to the reactivity of mononuclear Cu enzymes (PHM, DβH…): these systems carry out 2-electron-(only) oxidations, but in order to achieve this, a second distant copper ion injects an electron at the active site during the catalytic cycle. The present model supports the idea that an electron input is not necessary to achieve the oxidation of the substrate, but could be used to break the O-O bond of a transient alkylhydroperoxide product in the later steps of the mechanism.

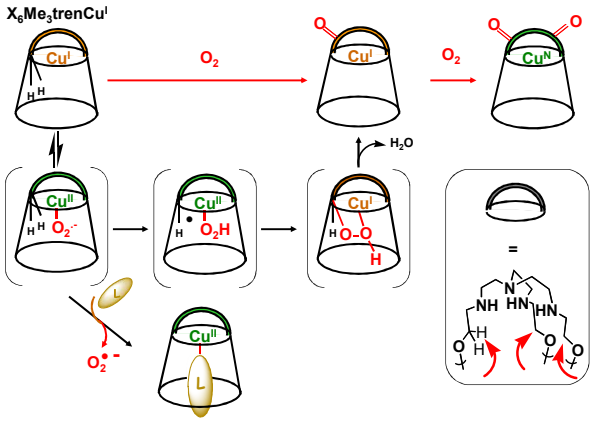


Fig. 34 Proposed mechanism for the reactivity of CalixtrenCu^{I} towards O_2 leading to the release of superoxide in a coordinating solvent (MeCN) and 4-electron oxidation of the ligand in non-coordinating ones (CH_2Cl_2).

4.5.2 Exogenous substrate oxidation. Cavities can be used as a platform to organize a metal active site for exogenous substrate oxidation. Indeed, with the diphenylglycoluryl molecular basket above described, Nolte's group attempted to orient the reactivity towards bound guests (1,3-dihydroxybenzene moieties), which led to unidentified products. However, they validated the supramolecular strategy by studying the oxidation of benzyl alcohols with dinuclear Cu^{II} complexes (Fig. 33c).[78] Indeed, substrates displaying the mono or 1,3-diphenol recognition patterns showed enhancements of the reaction rate (oxidation into aldehydes) of up to 4 orders of magnitude, thanks to the preorganization of the benzylalcohol moiety next to the Cu centers. With the calix[6]arene-based system, Reinaud's group reported catecholase activity for a tetranuclear Cu complex obtained with bridging chloride anions (Fig. 35a).[79] In this complex however, the cavities are occupied by one of the imidazole donor grafted at the calixarene rim, which prevents their acting as a receptor. The occupation of the cavity by the

coordinating arm arises from its reluctance to bind anions (2nd sphere effects, *vide supra*, section III.3). In the absence of chloride or base, the cavity remains accessible and was used to oxidize ethanol to acetaldehyde and acetic acid, and toluene to phenol, hydroquinone, and benzoquinone (Fig. 35b). For this purpose, the peroxide shunt (Cu^{II} and H_2O_2 as an oxidant) was used. A Cu^{II}-OOH intermediate species was detected by UV-vis spectroscopy.[80]

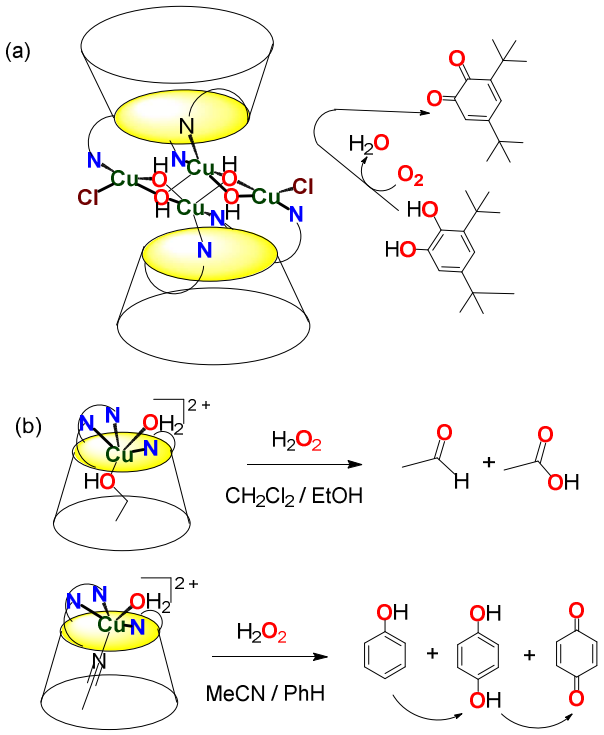


Fig. 35 Oxidation reactivity of copper complexes based on calix[6]arenes with three nitrogen donors [(a) N = *N*-methyl-imidazole, see Fig. 5, (b) N = pyridine see Fig. 16].

A mimic of galactose oxidase is presented in Fig. 36. In this calix[6]arene-based system, a redox active donor was added to the tri-nitrogen core (see Fig. 5 and 36).[81] Upon electrochemical or chemical oxidation at low temperature, a Cu^{II}-phenoxy radical species was obtained and characterized by UV-vis and EPR spectroscopies, which is reminiscent of the active form of galactose oxidase. Like the natural system, the model is able to oxidize benzylalcohol to benzaldehyde. Steric protection of the oxidizing radical Cu^{II} species together with substrate preorganization into the calix cavity allow controlling the oxidative reactivity of the complex, leading selectively to a two-electron oxidation of the alcohol substrate rather than its one-electron oxidation which results in the classical competitive pinacol coupling process. Unfortunately, and unlike the natural system, reoxidation of the resulting Cu^{I} species

by O_2 proceeds through a one-electron pathway, thus leading to the unreactive Cu^{II}/phenolate state and the active form is not regenerated. This was ascribed to the lack of control of the coordination environment at the Cu^{I} state.

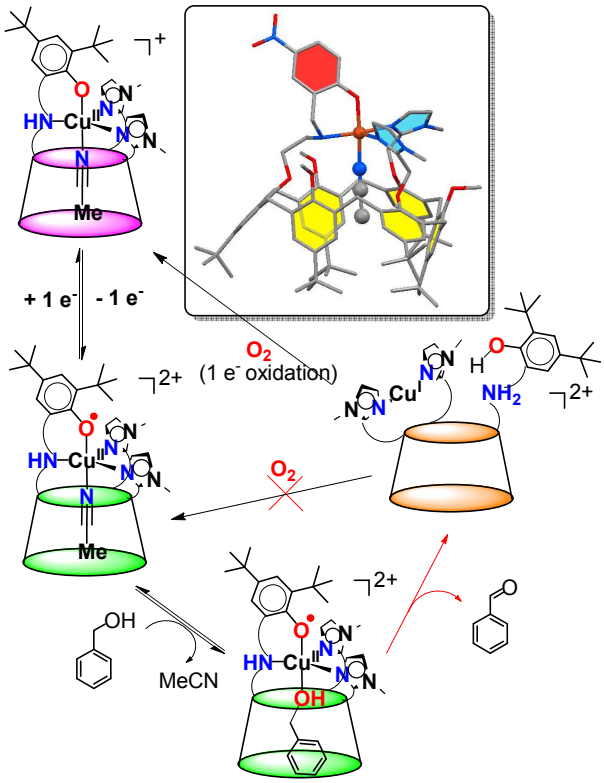


Fig. 36 Calix[6]arene-based model of galactose oxidase.

4.5.3 Host-guest recognition and chemoselectivity. Systems derived from CDs allow working in aqueous medium and can take advantage of the hydrophobic effect to preorganize lipophilic substrates next to an active site. A P450 mimic bearing two CDs grafted on each side of an iron porphyrin was compared to a sulfonato water-soluble iron porphyrin concerning its ability to epoxidize substrates in the presence of PhIO, an oxene donor used to generate Fe^{IV}=O species (Fig. 37).[82] Unlike the above described copper systems, porphyrins strongly bind the iron ion whatever its oxidation state (Fe^{II} to Fe^{IV}). The CD-tethered system was thus compared to a simple sulfonato porphyrin. With cyclohexene as a substrate, a strong difference in reactivity was observed, with 55% yield for the CD-tethered system, whereas the sulfonato porphyrin yielded less than 2% product. The low yield with free porphyrin was ascribed to competitive deactivation pathways: in the absence of steric protection, reactive Fe^{IV}=O intermediates readily react with their reduced precursor to form

Fe^{III}-μ-oxo dimers devoid of oxidative power. Such a dimerization process is prevented by CDs (like in the enzymes).

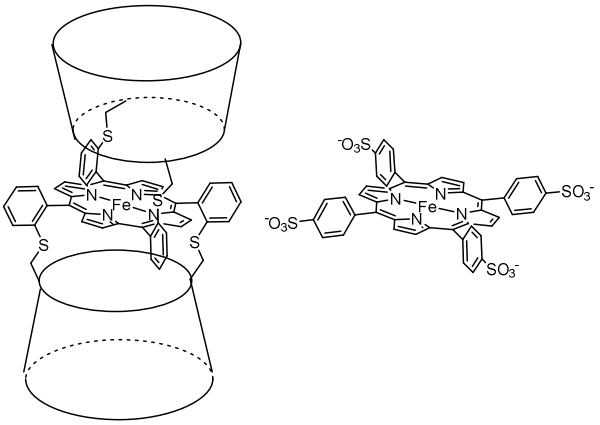


Fig. 37 Structures of two water-soluble Fe-porphyrin species used in epoxidation of cyclohexene. The first (left) is protected by water-solubilizing cyclodextrins which also act as receptors for cyclohexene, the second (right) is made soluble by sulfonato groups.

4.5.4 Host-guest recognition and oxidation stereoselectivity. The previous strategy can be modified to generate processive oxidation catalysts. Indeed, the former capping receptor cavity (CD) must be replaced by a ring-shaped cavity bearing the catalyst on its walls. This was achieved by Nolte's group using a Mn^{III}-porphyrin complex capping a molecular basket based on diphenylglycoluryl.[83] Using a bulky axial pyridyl ligand which can only sit in exo position, reaction with PhIO generates a Mn^{V}=O species oriented towards the inside of the ring (Fig. 38). Polybutadiene can then thread through the ring and get polyoxidized. Oxidation kinetics showed that complete epoxidation (TON = 8000) is achieved within 96 h. The different selectivities in cis/trans epoxide formation observed with pyridines able to fit within the ring indicate that, in the case of 4-*t*Bu-pyridine, the substrate threads through the ring.

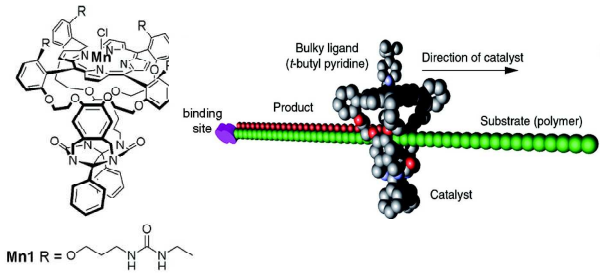


Fig. 38 Structure of Nolte's processing oxidation catalyst. The polymer substrate threads through the catalyst ring and is oxidized within the cavity (model on the right is reprinted with permission from Reference 83. Copyright 2010 American Chemical Society).

4.5.5 Host-guest recognition, regio- and stereo-selectivity. The former examples displayed either a single reactive site (C=C bond) or several sites which were all oxidized in the course of catalysis. A specific feature of metalloenzymes is their regio- and stereo-selectivity as in the case of cytochrome P450cam, which hydroxylates camphor with remarkable regio-and stereo-selectivity. For this purpose, the substrate is strongly anchored and oriented in front of the reactive site. The strategy of the natural system was used by Breslow *et al.* in the design of a Mn-porphyrin catalyst substituted by four CD receptors at each meso positions of the porphyrin (Fig. 39).[84, 85] A steroid substrate, functionalized by tert-butyl-phenyl groups on each extremity was regio- and stereoselectively hydroxylated. This was ascribed to bispoint recognition of the *t*Bu-Ph groups of the substrate by two '*trans*' CDs which led to an arrangement in which a specific site of the substrate is preferentially exposed to the Mn=O species. Indeed, changing the anchoring points of the substrate led to a looser host-guest adduct and a mixture of 6 oxidation products.

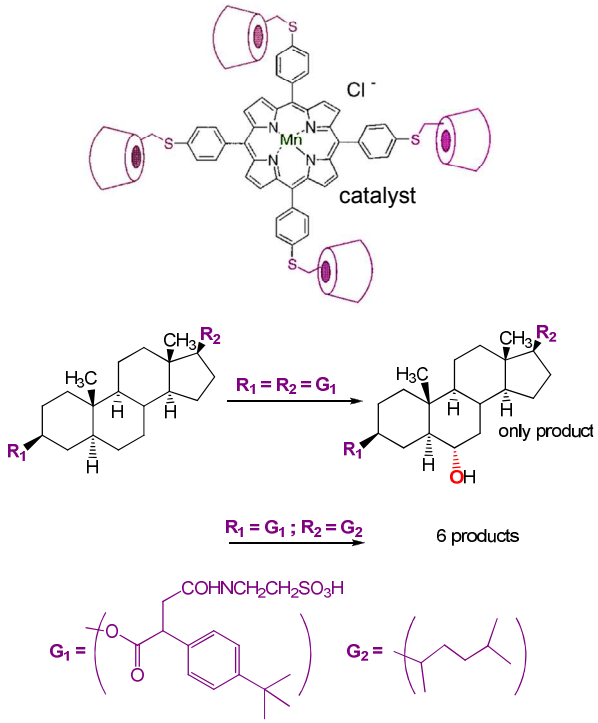


Fig. 39 Breslow's cyclodextrin-appended Mn-porphyrin catalyst. Strong binding of the substrate in the CD receptors yields a single product obtained regio- and stereoselectively. Weak anchoring leads to a mixture of products.

Conclusion and Perspectives

Supramolecular bioinorganic chemistry is the natural evolution of biomimetic metallic systems as it constitutes a further degree of complexity in modeling. The traditional approach consisting in modeling the 1st coordination sphere of metal sites proved to be very efficient, as valuable data could be extracted from these examples to gain insight into the mechanisms of natural systems. But they fail to reproduce several specific features of enzymes that must be mimicked by the implementation of non-covalent interactions. A possible strategy relies on the synthesis of cavity-based complexes, subject of this review.

The design of biomimetic cavity-based complexes relies essentially on two different strategies: one consists in grafting one or several polydentate ligands, each of them providing a biomimetic binding site for a metal ion; the other aims at building a coordination site from grafting several donors on the macrocycle defining the cavity. These two designs lead to very different systems presenting different advantages and limitations. The first strategy allows varying the number of metal ion binding sites and relies on well-known coordination chemistry associated with the grafted ligand. It faces problems correlated to the relative orientation of the metal reactive site and the host. For a good control, several covalent linkers between the donors and the cavity are required, which is more synthetically demanding. The second strategy is difficult to set up due to the high geometrical constrain of the donors for obtaining the adequate geometry. However, it allows the insulation of the metal ion and the full control of the nuclearity. This has been turned to good account for the development of biomimetic mononuclear complexes such as the so-called *funnel* and *bowl* complexes.

The associated host-guest properties also face difficulties essentially due to solvent competition. In organic solvents, efficient guest hosting requires a driving force that can be electrostatic with charged species, or a coordination link to the metal ion. In water, the host-guest association can benefit from hydrophobic effect for guest embedment. Most interestingly, when the metal labile site is surrounded by a cavity open to the solvent, the metal complex becomes a highly sensitive and selective receptor for guest ligands.

A judiciously appended cavity also allows tuning the metal ligand properties, with possible implementation of a switch control, and may enforce specific behavior such as

dissociative mechanism for ligand exchange, entrapment of intermediates, energized states, interlocked cavity and electronic effects. A poly-functionalized scaffold also allows setting up rare processes such as translocation of a metal ion controlled by guest binding.

The exploration of their reactivity may lead to the discovery of new reaction patterns. Indeed, weak interactions play key roles in reactivity: the same 1st coordination sphere motif can be found in many enzymes; however, very different catalytic activities are displayed due to various long distance interactions. The presence of a cavity mimicking the active site pocket gives rise to well-defined 2nd (and further) coordination spheres, which orient the reactivity of the metal ion, protect and stabilize intermediates, and promote the transient formation of unusual reactive species. It also allows maintaining an apolar environment around the metal ion in spite of the water solvent. This last point is obviously the key for hydrolytic processes and electron transfers.

All along this review, we have shown that building cavity-based complexes, which is a very challenging task, is a fruitful strategy that allows obtaining new fundamental information about Nature's chemistry. Indeed, biomimetics allows learning the "how" of selective recognition, reactivity and catalysis. Of course, important perspectives lie in the use of this knowledge for the development of selective and sensitive probes, new reactions, and green and efficient catalysts with bio-inspired systems.

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