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Supramolecular Modeling of Mono-copper Enzyme Active Sites with Calix[6]arene-based Funnel Complexes

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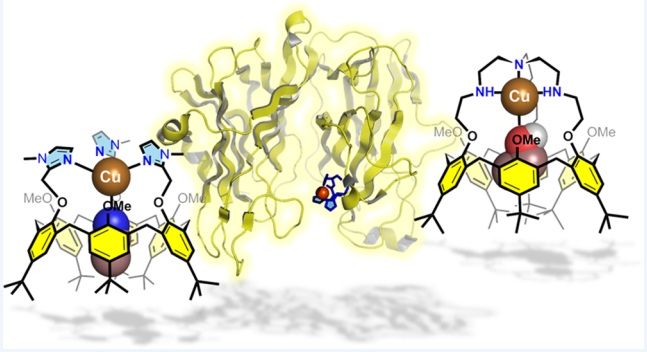
CONSPECTUS: Supramolecular bioinorganic chemistry is a natural evolution in biomimetic metallic systems since it constitutes a further degree of complexity in modeling. The traditional approach consisting of mimicking the first coordination sphere of metal sites proved to be very efficient, because valuable data are extracted from these examples to gain insight in natural systems mechanisms. But it does not reproduce several specific aspects of enzymes that can be mimicked by the implementation of a cavity embedding the labile active site and thus controlling the properties of the metal ion by noncovalent interactions. This Account reports on a strategy aimed at reproducing some supramolecular aspects encountered in the natural systems.



The cavity complexes described herein display a coordination site constructed on a macrocycle. Thanks to a careful design of the cavity-based ligands, complexes orienting their labile site specifically toward the inside of the macrocycle were obtained. The supramolecular systems are based on the flexible calix[6]arene core that surrounds the metal ion labile site, thereby constraining exogenous molecules to pass through the conic funnel to reach the metal center. Such an architecture confers to the metal ion very unusual properties and behaviors, which in many aspects are biologically relevant. Three generations of calix[6]-based ligands are presented and discussed in the context of modeling the monocopper sites encountered in some enzymes.

A wide range of phenomena are highlighted such as the impact that the size and shape of the access channel to the metal center have on the selectivity and rate of the binding process, the possible remote control of the electronics through small modifications operated on the cavity edges, induced-fit behavior associated with host−guest association (shoe-tree effect) that affects the redox properties of the metal ion and the electron exchange pathway, consequences of forbidden associative ligand exchange allowing a redox switch to drive an "antithermodynamic" ligand exchange, drastic effects of the full control of the second coordination sphere, and dioxygen activation in a confined chamber conducted to a selective and unusual four-electron redox process. All these findings bring new clues for better understanding the control exerted by the proteic environment on a metal center, allow the identification of new reaction pathways, and lead to new proposals for enzymatic catalytic cycle (such as the formation of an alkylhydroperoxide intermediate for mononuclear Cu-hydroxylases). The supramolecular systems may also be exploited for designing highly selective and sensitive probes for molecules of particular function and shape or to design new selective catalysts.

INTRODUCTION

In metallo-enzymes, the structure of the protein backbone not only preorganizes the coordination site for the metal ion but also provides a cavity and a corridor connecting it to the bulk.[1−3] This allows control of the reactivity of the metal ion and its interaction with exogenous molecules. The frequently encountered poly(histidine) motif has guided the concept of tripodal polyaza ligands able to reproduce the first coordination sphere of the metal.[4] Introduction of substituents next to the N-donors allows tuning of the steric hindrance around the metal center and, to some extent, its second coordination sphere (Figure 1).[5,6] However, this strategy faces a dilemma: small substituents fail to control the nuclearity of reactive metal ions, whereas high steric hindrance decreases access to exogenous molecules. A supramolecular approach consists of combining a metal ion and a

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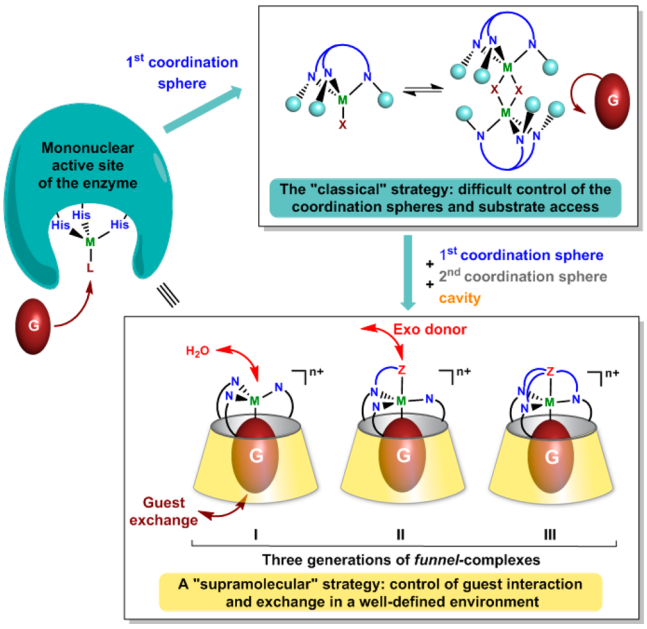

Figure 1. Modeling the active site of mononuclear enzymes with tripodal systems.

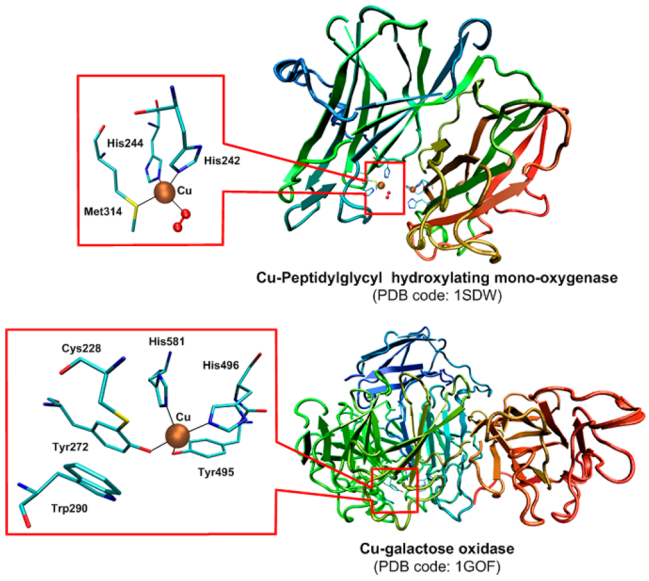

Figure 2. Schematic representations of the 3D structures of some copper enzymes with their active sites.

hydrophobic cavity: this may allow the control of not only the first and the second coordination spheres but also the substrate binding pocket and access channel that selects and drives exogenous molecules to the metal center.

A possible way to construct a supramolecular system that combines a biomimetic coordination core and a cavity is to use readily available macrocycles such as cyclodextrins (CD) or calixarenes. Breslow was a pioneer, using cyclodextrins with a polydentate ligand attached.[7] However, in these systems, the metallo-site is not under the control of the cavity, since a single link does not allow directional control of the metal reactive site. Recently, we and others developed a strategy consisting of grafting several donors at the edge of a macrocycle so as to create a polydentate ligand that can fold on the top of the cavity upon coordination to a metal ion. The objective was to obtain a well-defined environment around the metal center with a labile coordination site inside of the cavity. Whereas Matt's group developed CD- and calix[4]arene-based P-ligands for organometallic catalysis,[8] we chose to use calix[6]arene-based N-ligands. Calix[6]arenes provide a cavity space large enough to play the role of a good host for organic molecules. However, the high flexibility of the calix[6]arene macrocycle, due to the facile ring inversion of their phenolic units, makes difficult their constraint in a cone conformation proper to play the role of the host. Hence, we developed two different strategies: one relies on the folding of the coordinating arms around the metal center, which rigidifies the calixarene core into its cone conformation; the other consists of the triple covalent linkage of a tripodal ligand to the calix small rim. Three generations of calix[6]arene-based ligands were developed, leading to the so-called funnel complexes (Figure 1).

The properties of the calix[6]arene-based funnel type ligands are presented and illustrated by copper complexes aimed at modeling the active site of copper enzymes (Figure 2).[9] Appropriate modeling of such redox enzymes requires the control of both oxidation states, Cu^{I} and Cu^{II}, which represents a challenge by itself, in view of their very different electronic and geometrical demands. Throughout selected examples, we try to show how the various cavity-based ligands can be tuned (flexibility, donor ability, second coordination sphere, guest access and hosting, gating) and what is their impact on the metal ion properties, environment, constraints, and host−guest and redox behavior.

DESIGN AND SYNTHESIS OF CAVITY-BASED LIGANDS

The first generation of calix[6]arene-based ligands presents either three aza-heterocyclic or three alkylamino pendant arms at the small rim. These tridentate N-ligands (calix[6]N_3) can be easily obtained by direct alkylation of the C_{3v} symmetrical *p*-*t*Bu-calix[6]arene O-protected in alternate positions by methyl groups (Figure 3). They form a large family of biomimetic N_3-ligands with different electronic and steric properties.[10]

Aiming at introducing a different donor group into the coordination sphere of the metal ion, a second generation of ligands, calix[6]N_3Z, was developed (Figure 4).[11] It presents a fourth donor group Z covalently linked to one nitrogenous arms. The key step for the ligand synthesis is a selective monoalkylation of the calix[6]arene small rim.

The next degree of sophistication consisted of the elaboration of ligands in which the three coordinating arms are covalently linked to each other. Three different capped calix[6]arenes (calix[6]tren,[12] calix[6]PN_3[13] and calix[6]tmpa[14]) were synthesized (Figure 5), the key step consisting in a [1 + 1] macrocyclization reaction between two tripodal partners.

The three generations of calixarene-based ligands can be selectively modified at different positions in order to associate various functions (Figure 6). Notably, methodologies for the selective removal of the OCH_3[15] or *t*Bu[16] groups of the parent ligands were developed.

FIRST GENERATION OF CALIX[6]-BASED FUNNEL COMPLEXES

Classically, Cu^{I} and Cu^{II} complexes complexes adopt a four-coordinate tetrahedral (Td) and a five-coordinate square-based pyramidal (SBP) environment, respectively. Indeed, with the first generation of calix[6]-ligands, both structures have been obtained as exemplified by DRX structures (Figure 7).

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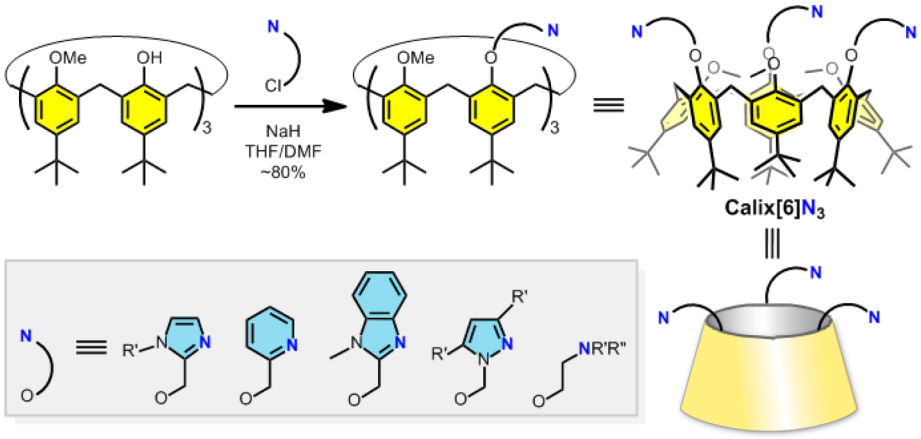

Figure 3. First generation of calix[6]arene-based N_3-ligands.

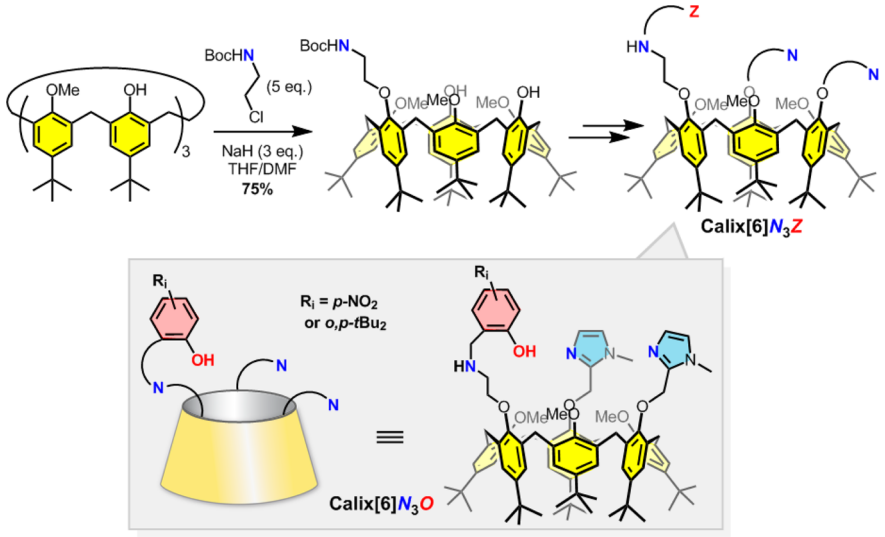

Figure 4. Second generation of ligands: Calix[6]arenes with mixed N/Z donor groups.

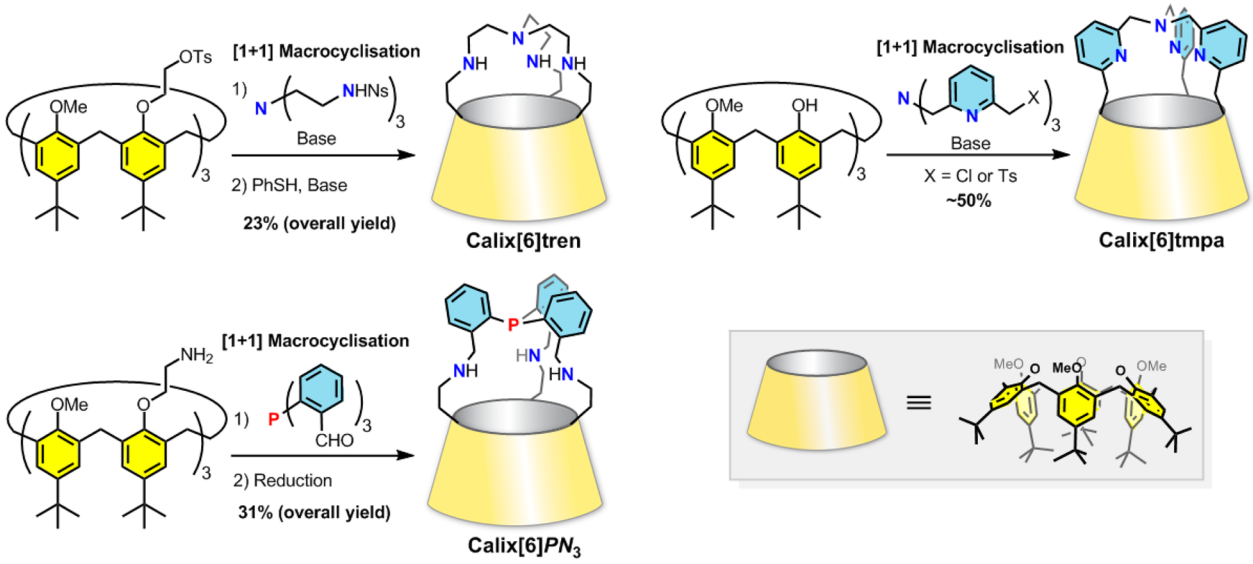

Figure 5. Third generation of ligands: The calix[6]azacryptands.

The tris(pyridine) ligand stabilizes Cu^{I} in a Td environment with a bound RCN guest buried inside the cavity.[17] The tris(imidazole) ligand yields highly stable SBP Cu^{II} complexes with either nitrilo, alcohol, or amido guests, in endo position and an additional capping water ligand that binds outside the cavity, in exo position.[18]

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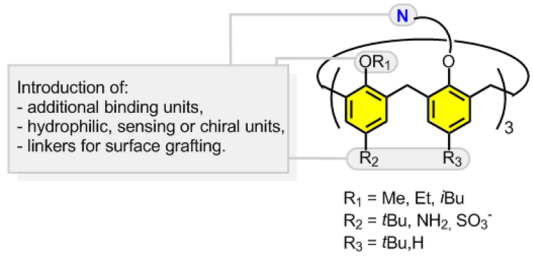

Figure 6. Tunability of the supramolecular environment.

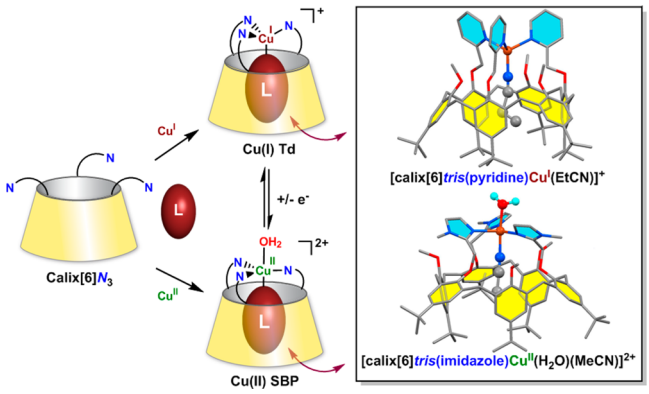

Figure 7. General scheme for the complexation of Cu^{I} and Cu^{II} by the calix[6]N_3 ligands and representative XRD structures.

Remote Control of the Metal Ion Properties

Large Rim Substituents: Impact on the Thermodynamics and Kinetics of RCN Guest Exchange. The mechanism of the guest exchange at the cuprous center has been thoroughly explored with two tris(pyridine)-based calixarene ligands and was shown to follow a dissociative pathway (Figure 8). Compounds **a** and **b** differ by the substitution pattern of their large rim.[19] As **b** presents an enlarged cavity with a wider opening due to the removal of three *t*Bu substituents, the recognition pattern for MeCN vs PhCN by **a** and **b** is inverted, the relative affinity constants differing by 3 orders of magnitude. The *t*Bu gate also strongly affects the kinetics of the exchange process as shown by a 100-fold increase of the rate (for MeCN) as it is removed. The corresponding lower activation enthalpy and higher activation entropy show that, with **a**, bumping into the *t*Bu door is part of the exchange process. Hence, these supramolecular systems highlight the impact of the channel size and shape on the selectivity and rate of the binding process, which mimics the hydrophobic corridor giving access to a metallo-enzyme active site.

Small Rim Substituents: Impact on Metal− and Guest−Ligand Communication. Carbon monoxide is classically used as a probe to characterize the cuprous state of enzymes. With the calix[6]tris(imidazole) ligand, the Cu^{I} complex is conformationally ill-defined because the metal is essentially two-coordinate. Upon exposure to CO, due to its π-acceptor character, the system rigidifies and a stable tetrahedral complex is obtained with coordination of all three imidazoles.[20] Interestingly, as the CO ligand is not large enough to fill the cavity, the Cu^{I}−CO complex undergoes self-inclusion of one *t*Bu group, thus swinging between three nonsymmetric but equivalent conformations (Figure 9). This process can be monitored by the OR_1 substituents at the calixarene small rim: the simple replacement of methoxy groups by ethoxy restricts its mobility to a swing

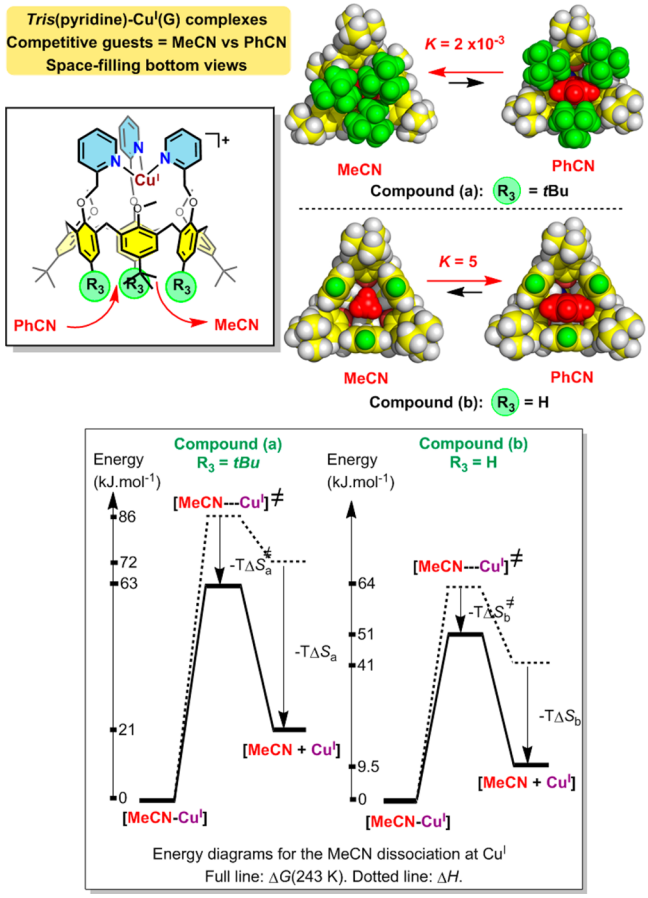

Figure 8. Control of the ligand exchange at the cuprous center by the "R_3 door" of the calix[6]arene.

between two helical enantiomers, as in the case of the nitrilo complexes. Interestingly, this small change in the steric demand, which occurs relatively far from the metal center, significantly affects the electronic properties of Cu, as shown by ν_{CO} absorptions.

Shoetree Effect and Impact on the Redox Behavior of the Calix[6]N_3-Cu Funnel Complexes

Classically, the Cu^{II}/Cu^{I} redox process involves a structural reorganization between five- and four-coordinate species (Figure 7). Indeed, in noncoordinating solvents, the electrochemical behavior of the Cu-calix[6]N_3 complexes is totally irreversible, indicating major structural restrictions. In contrast, in MeCN solution, owing to CH−π weak interactions between MeCN and the calix[6] core, the guest ligand acts as a shoetree molecule, inducing a conformational adaptation of the calixarene along the redox cycle, analogous to *induced fit* behaviors in biological systems (Figure 10).[21]

The redox process can be accounted for by a square-scheme mechanism (Figure 10) with two different routes of electron transfer, implying two redox potentials, E_A° or E_B°. For pyridine donors, the retracting effect of the MeCN-shoetree toward Cu favors strained tetrahedral geometry, *even for* Cu^{II}. Consequently, in this *entatic state*, the potential is unusually high (pathway B) and the metal is strongly oxidizing ($E_{1/2} = E_B^\circ$).[22] The complex electrocatalytically oxidizes phenols.[23] Conversely, with the imidazole donors, the retracting effect of the MeCN ligand has less influence and five-coordination is favored, leading to a much weaker oxidant following the classical pathway A ($E_{1/2} = E_A^\circ$).

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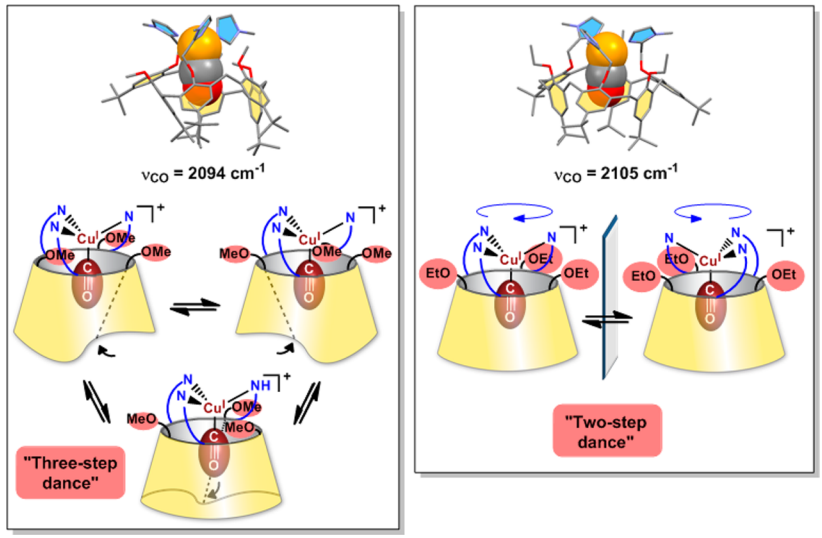
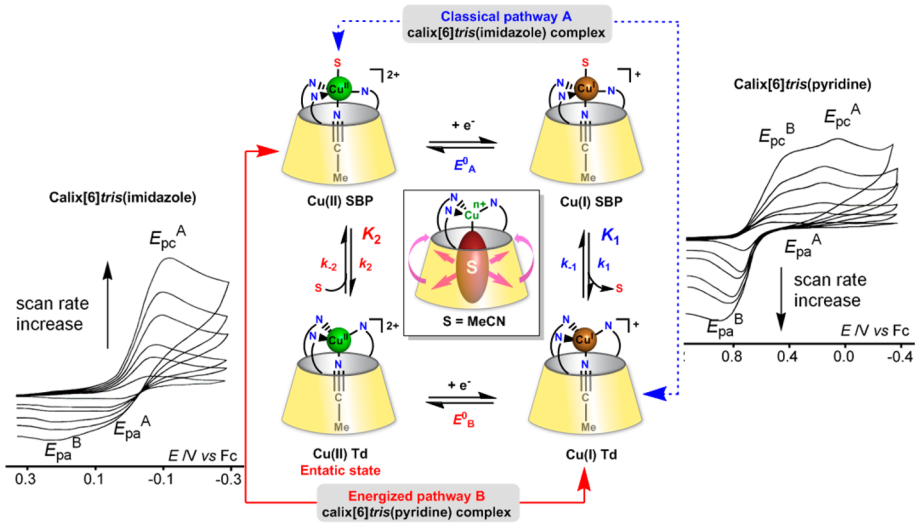


Figure 9. Coupled electronic and conformational properties of [calix[6]tris(imidazole)Cu^{I}(CO)]$^{+}$ complexes controlled by the small rim OR_1 substituents.



	E^0_A /V vs Fc	k^0_A /cm s^{-1}	E^0_B /V vs Fc	k^0_B /cm s^{-1}	K_1	k_1 /s^{-1}	k_{-1} /s^{-1}	K_2	k_2 /s^{-1}	k_{-2} /s^{-1}
Calix[6]*tris* (pyridine)	+0.26(0)	1 10^{-3}	+0.65(0)	1 10^{-3}	8 10^{5}	2 10^{4}	0.025	0.16	11.2	70
Calix[6]*tris* (imidazole)	+0.00(5)	2 10^{-3}	+0.16(0)	1.5 10^{-3}	1.7	4.3	2.5	4.1 10^{-3}	367	8.9 10^{4}

Kinetic and thermodynamic parameters from CVs fitting of calix[6]N_3-Cu complexes by Digisim©.

Figure 10. Supramolecular shoetree concept illustrated by a square-scheme mechanism for rationalizing the $Cu^{II/I}$ geometrical reorganization through two different pathways.

Interestingly, subtle long-range modulation of the supramolecular shoetree effect was highlighted by structural host modifications, through variation of substituents at the small or large rim of the cone (R_1, Figures 6 and 11). In the tris(pyridine) family, removal of three *t*Bu groups at the large rim induces a total loss of reversibility by CV. Such an effect is ascribable to a weakened shoetree effect. Conversely, substitution of a methyl group by a bulkier isobutyl moiety at the small rim of the tris(imidazole) series leads to a more reversible process. Bulky OR_1 groups are proposed to freeze a conformation in which the three R_3 = *t*Bu are projected into the cavity. The shoetree MeCN blocked in the cavity only allows a single redox process restricted to pathway A.[22]

Oxidative Properties vs Exogenous Substrates

All calix[6]tris(imidazole) and -tris(pyridine)Cu^{I} complexes are unreactive toward O_2. This stands in strong contrast with most unprotected classical models that readily react with O_2. The absence of reactivity cannot be correlated to the redox potential of the complexes, as previously evidenced with classical models.[4] In the present case, the calix[6] cone, hampering dimerization processes, erases the O_2 reactivity driven by formation of Cu_2O_2 intermediates.[4] With H_2O_2 as an oxidant, calix[6]tris(pyridine)-Cu^{II} oxidizes ethanol to acetaldehyde and acetic acid and benzene to phenol and benzoquinone (Figure 12). Similar although lower reactivity was observed with calix[6]tris(imidazole)-Cu^{II}. Host–guest studies and comparison with complexes deprived of cavity

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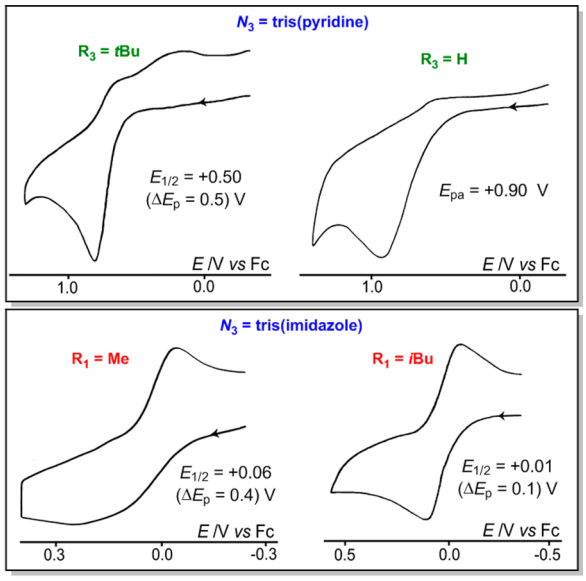

CVs in MeCN under N_2. Supporting salt: NBu_4PF_6; v = 0.1 V s^{-1}, Pt electrode.

Figure 11. Remote control of the redox behavior of $[calix[6]N_3Cu^{I}]^{+}$ complexes.

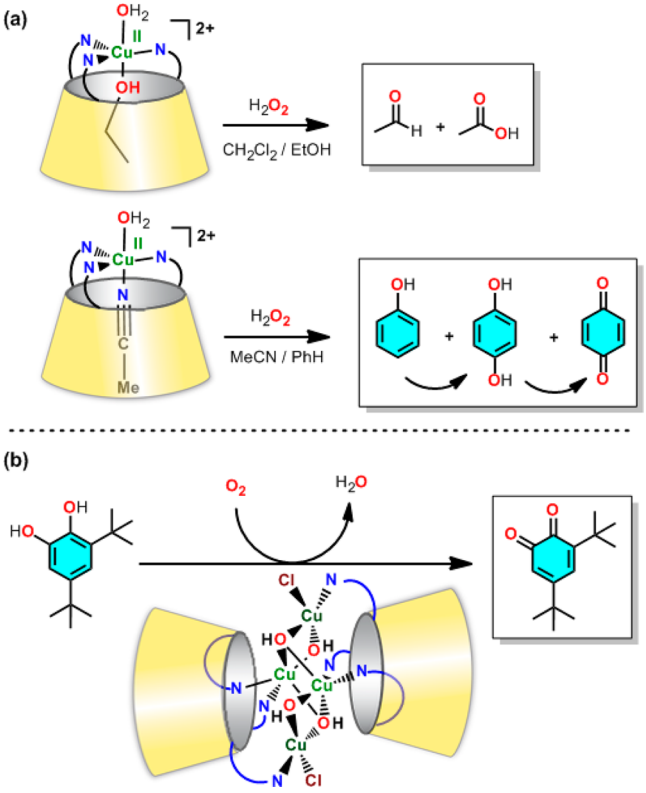

Figure 12. (a) Reactions catalyzed by calix[6]tris(pyridine)-Cu^{II} with H_2O_2. (b) Catecholase activity of the tetranuclear cluster.

are consistent with the oxidation of embedded substrates, although not directly demonstrated. The formation of a Cu^{II}–OOH species was suggested by UV–vis spectroscopy analysis with an absorption at 375 nm ascribed to a HOO → Cu^{II} ligand to metal charge transfer (LMCT). In the presence of chloride ions, a tetranuclear cluster was generated and displayed catecholase activity. Given the cluster structure, reactivity is assumed to take place outside the calixarene cavity, already occupied by an imidazole arm.[24] In that case, the calixarene cores just help maintain an unusual nuclearity.

SECOND GENERATION OF CALIX[6]-BASED FUNNEL COMPLEXES

Appending a Redox Functionality to the Calix Ligand: Supramolecular Modeling of Galactose Oxidase

In this second generation of ligand (Figure 4), one amino arm of the calix ligand is covalently linked to a fourth donor that can act as a hemilabile arm controlling endo binding.[25] When the donor is redox-active, such as a phenoxide, it can promote the oxidation of a substrate, as in galactose oxidase (GAO).[26] In the calix[6]N_3ArO-Cu^{II} complexes (Figure 13), the phenoxide

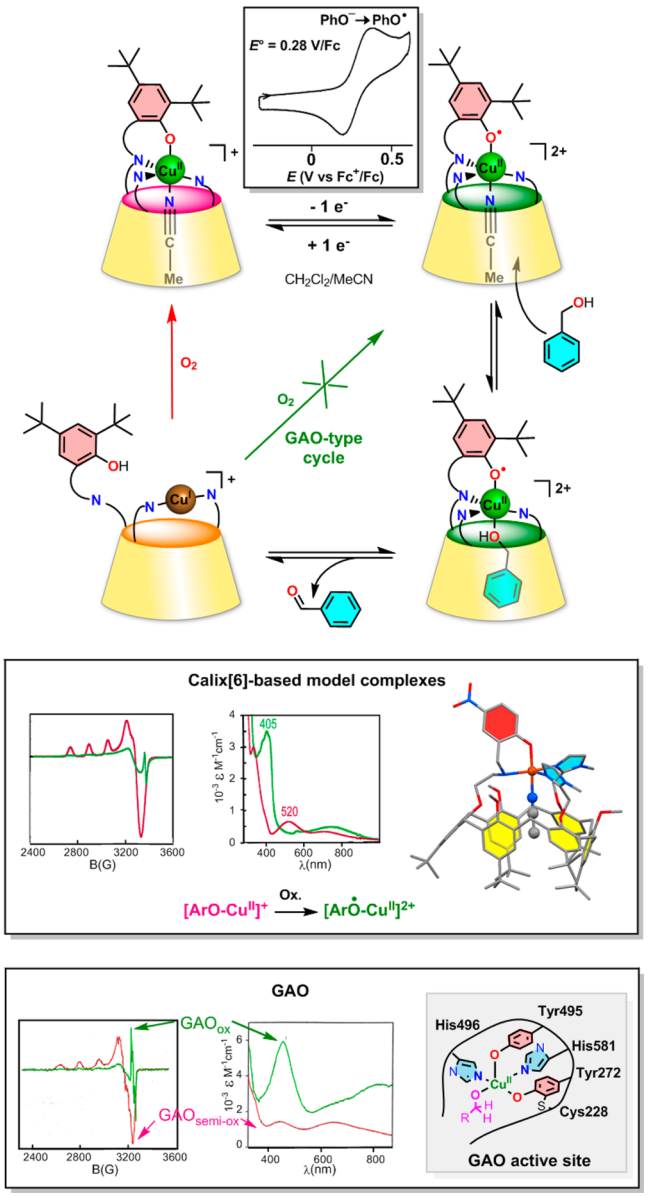

Figure 13. Modeling the active site of GAO. (top) Proposed mechanism for BnOH oxidation by electrogenerated $ArO^{\bullet}$-Cu^{II} (inset, low-temperature CV). (bottom) EPR and UV–vis spectra of Cu^{II} centers and XRD structure of the $[calix[6]N_3ArOCu^{II}(MeCN)]^{+}$ complex.

donor substitutes the capping water molecule present in the first generation of Cu^{II} complexes (Figure 7), which leaves a single site for the coordination of an exogenous ligand in endo position.[27] Electro- or chemical oxidation at low temperature with MeCN as a guest leads to a phenoxyl radical ($ArO^{\bullet}$) bound to

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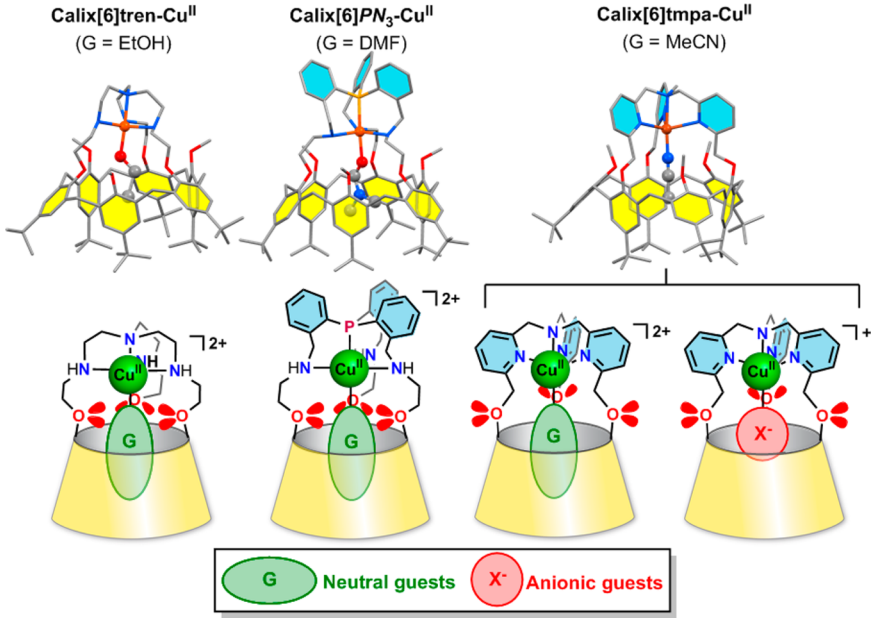

Figure 14. XRD structures of Cu^{II}-funnel complexes with various guests and supramolecular control of guest binding.

Cu^{II} (E° = 0.32 V vs Fc^+/Fc). Its spectroscopic features are very similar to those of the oxidized active form of GAO: strong $ArO^\bullet$ $\pi \rightarrow \pi^*$ transition at 405 nm and vanishing of the Cu^{II} EPR signal due to $ArO^\bullet-Cu^{II}$ antiferromagnetic coupling.

Remarkably, this Cu^{II}–phenoxyl radical complex stoichiometrically oxidizes benzylic alcohol into benzaldehyde, which contrasts with its Zn^{II} analog that is stable for hours at RT. Indeed, if the substrate sits inside the cavity, only $[ArO^\bullet-Cu^{II}]^{2+}$, not $[ArO^\bullet-Zn^{II}]^{2+}$, can mediate the two-electron redox process. These specific features mimic the protecting effect of the protein cavity relative to the substrate as well as the redox activity of metal-radical enzyme. Unfortunately, reoxidation by dioxygen regenerates the Cu^{II}–phenolate complex and not the Cu^{II}–phenoxyl radical necessary to obtain turnovers as with GAO: the reactivity control is lost at the Cu^{I} state, which is assignable to the high flexibility of the calix[6] core.

THIRD GENERATION OF CALIX[6]-BASED FUNNEL COMPLEXES

In the first two generations, the flexibility of the calix[6] core is related to a low chelate effect because the nitrogen donors are separated by 17 atoms, which weakens metal complexation. Indeed, the complexes readily undergo structural rearrangements into multinuclear species in the presence of bridging anions. Such a behavior represents an obstacle for studying the intrinsic reactivity of a mononuclear site. In the third generation of calix ligands (Figure 5), the covalently capped structure provides a strong chelate effect, precludes any bimetallic interaction, and enforces exogenous coordination in endo position through the funnel.

Full Control of the First and Second Coordination Spheres: Impact on Cu^{II} Binding Properties

Such a controlled environment allowed us to evaluate the impact the first (donor cap) and second spheres (the oxygen-rich calixarene small rim providing H-bonding sites and dipolar interactions) as well as cavity effects (CH–π interactions within the cavity, shape selectivity). The strong chelate effect provided by this family of ligands (Figure 14) is illustrated by the stabilization of the Cu^{II} redox state in the PN_3 environment, despite a mismatch between the hard and soft characters of Cu^{II} and the P-donor, respectively.[28] Surprisingly, the corresponding Cu^{I} complex is completely inert toward O_2, which stands in strong contrast with the N_4 environment provided by the tren cap (vide infra).

Analyses of competitive guest binding also highlighted a spectacular and specific affinity of calix[6]tmpa-Cu^{II} for MeCN, despite its weak donor ability. This gives evidence of a strong effect of the cavity leading to selectivity based on guest shape as the tmpa unit strongly rigidifies the calix[6] core.[29] Indeed, a careful analysis of the calix conformation showed a major difference between the systems capped by the flexible tren[30] or PN_3[28] units and the tmpa ligand (Figure 14). In the first cases, the calixarene adopts a flattened cone conformation with the phenoxyl units connected to the nitrogenous arms pointing their lone pair toward the donor atom of the guest ligand. In contrast, the tmpa core induces the same three units to stand in the opposite direction, the corresponding oxygen atoms orienting their dipoles toward the outside. As a result, the electron-rich environment provided by the small rim in the tren and PN_3 cases prevents coordination of anions, whereas the tmpa–Cu^{II} complex readily binds hydroxide, alkoxides, azides, and halides. Such contrasted behaviors illustrate the importance of the second coordination sphere generated by the macrocyclic environment. It also highlights the dramatic impact of a conformational change of the molecular microenvironment on the metal ion properties. This echoes the regulatory role of proteic conformational changes for many biochemical processes.

Supramolecular Redox Control and Blocking of an Associative Process and Redox Driven Ligand Interconversion

The important shifts of $E_{1/2}$ (370–450 mV) toward higher values observed for the calix[6]tmpa system, compared with the simple tmpa core, highlights the important effect that a hydrophobic funnel-shape cavity can have on the thermodynamic properties (Figure 15).[31] Guest ligand interconversion during the $Cu^{II/I}$ redox process was illustrated by competitive experiments with DMF and MeCN. Indeed, the Cu^{II} state displays a higher affinity

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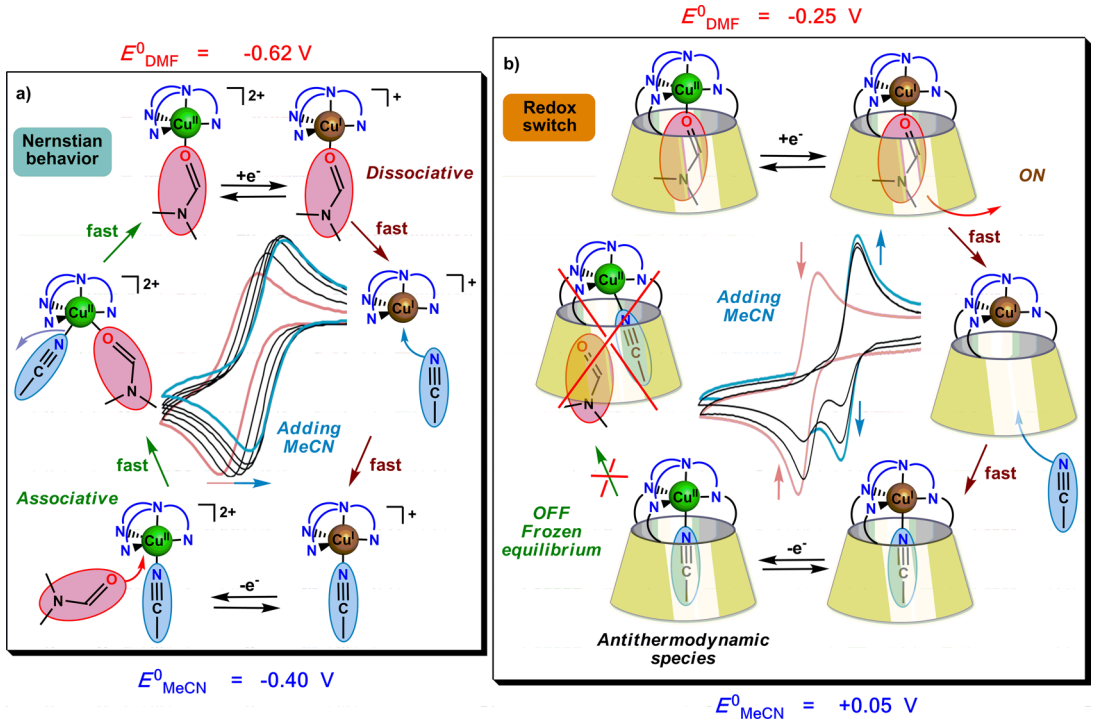

Figure 15. Ligand exchange coupled to electron exchange as evidenced by CV: (a) tmpa, no cavity; (b) funnel complex.

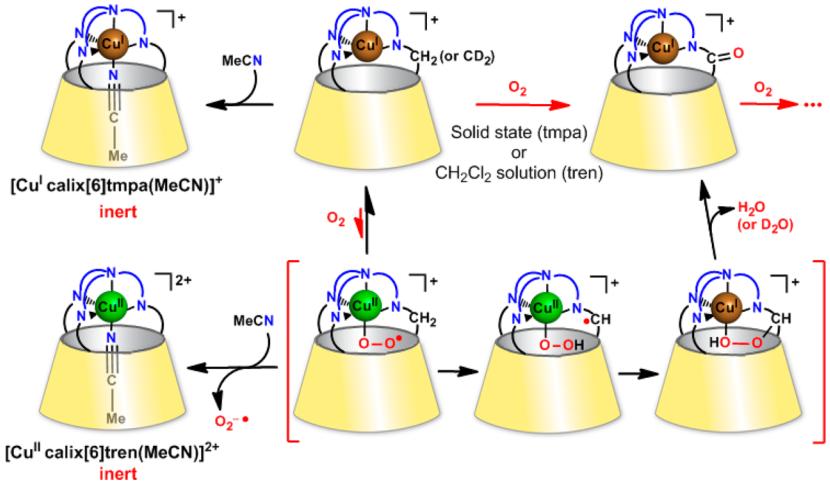

Figure 16. Proposed mechanism for dioxygen activation by the calix[6]azacryptand Cu^{I}-complexes.

for the better σ-donor (DMF), while Cu^{I} favors π-acceptor (MeCN) binding. With classical complexes deprived of cavity, the competitive guests are exchanged through an associative mechanism at Cu^{II} and a dissociative mechanism at Cu^{I}, both of which are fast processes. As a result, a Nernstian potential shift is observed, responding thermodynamically to the composition of the solution. With calix[6]azacryptands, the associative exchange at Cu^{II} is frozen, because two guests cannot fit into the cavity simultaneously.[31] At the Cu^{I} state, the dissociative ligand exchange is fast, and the more stable Cu^{I}(MeCN) is the only observed species. After reoxidation to the Cu^{II} state, the transient Cu^{II}(MeCN) complex is "trapped" on the electrochemical time scale, although thermodynamically less stable than Cu^{II}(DMF): the redox switch $Cu^{II} \rightarrow Cu^{I} \rightarrow Cu^{II}$ switches a good ligand for Cu^{II} for a weak one. The redox potential hence no more corresponds to the thermodynamic equilibrium in the solution but to the guest nature. This can be seen as an "antithermodynamic" process.[30]

Dioxygen Activation in an Insulating Cavity

The calix[6]azacryptands allow remarkable control of both Cu^{I} and Cu^{II}. This system represents a very unique probe for O_2 activation at an isolated Cu^{I} center, because the putative $[CuO_2]^{+}$ intermediate is fully embedded into the cavity and cannot lead to dimers, as with the classical models (Figure 1). The nature of the cap highly influences the reactivity. $[Calix[6]PN_3Cu^{I}]^{+}$ is completely inert to O_2. While $[calix[6]tmpaCu^{I}]^{+}$ is stable in aerated solutions, it readily reacts *in the solid state* through a four-electron oxidation of the ligand, which is a rarely observed reactivity pattern (Figure 16).[32] This four-electron oxidation leads to an ester derivative resulting from the insertion of an oxygen atom into a methylene group linking the cap to the calix

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core. Kinetic studies support a diffusion-controlled process with fast H-abstraction.

The intramolecular kinetic isotope effect values (21 at RT up to 29 at 277 K), activation enthalpies, and pre-exponential factors are suggestive of tunneling, which reveals strong preorganization and constrained environment as in natural systems.[26] The more reactive $[calix[6]trenCu^{I}]^{+}$ complex shows the same four-electron reactivity pattern *in solution* in a noncoordinating solvent, also leading to an oxygenated cap.[33] Interestingly, this oxygenating process is completely inhibited by MeCN: the very fast one-electron reaction between O_2 and calix[6]tren-Cu^{I} (solution conditions) yields the unmodified Cu^{II} complex. A transient superoxo complex undergoes fast substitution by MeCN leading to release of superoxide in the solvent. Conversely, in the case of calix[6]-tmpa (solid state and solution conditions), the corresponding MeCN−Cu^{I} complex is stable in air for months.

These examples demonstrate the possibility to activate O_2 at a single Cu^{I} center, yielding a reactive species that can oxidize a substrate without external electron input. This supports the idea that, in the Cu-mono-oxygenases that hydroxylate a CH_2 moiety, the $[CuO_2]^{+}$ adduct is the species responsible for the C−H bond cleavage. It also suggests that an alkylperoxo adduct is transiently formed (Figure 16).[34] The example of calix[6]tren shows that, without electron input, the reaction can run catalytically through a four-electron redox process.[33]

CONCLUSION

The supramolecular approach for modeling metal sites in enzyme, as described in this Account, focuses on cavity aspects, that is, embedment of the labile guest and thus potentially reactive metal site in a cavity. Important highlights relative to the supramolecular control of the metal ion properties have been obtained. The funnel shaped cavity surrounding the metal ion labile site controls both the thermodynamics and the kinetics of ligand exchange, thereby mimicking the hydrophobic substrate channel giving access to a metallo-enzyme active site. The mechanism of ligand exchange itself is strongly affected by the presence of the cone: this is exemplified by the enforced dissociative process when Cu^{II} is embedded in a calix-cryptand, which gives rise to unusual behavior such as a redox switch leading to an "antithermodynamic" ligand exchange. Long range information transmission has been emphasized: small changes at the calix small rim result in different steric demand transmitted to the cavity modifying its conformation and dynamic behavior around the guest ligand, which in turn affect the metal center and modulate its electronic properties. The supramolecular control of the coordination of copper allows the tuning of the redox properties of the cavity complexes, along the electron transfer, with the control of not only the redox potentials but also the electron exchange pathway. An interesting phenomenon was evidenced, where the guest ligand acts as a shoetree molecule, inducing a conformational adaptation of the calix[6] core, analogous to induced fit behavior in biological systems, generating in one case a redox entatic state. With the calix-cryptands, the covalently capped structure provides a strong chelate effect, precludes any bimetallic interaction, and enforces exogenous ligation through the funnel, thus leading to the full control of both first and second coordination spheres. This can be used to obtain metal complexes with unusual properties, for example, a Lewis acidic Cu^{II} center more prone to bind neutral molecules than anions. In an insulating cavity, it has been demonstrated that it is possible to activate O_2 at a single Cu^{I} center to yield a reactive species that can oxidize catalytically a substrate without external electron input through a four-electron pathway. This led to the proposal that an alkylperoxo adduct is transiently produced, which might be relevant to Cu-mono-oxygenases themselves.

As a whole, the supramolecular strategy appears as mandatory to reproduce this wide range of bioreminiscent behaviors. It offers many perspectives. Indeed, the remarkable hosting properties of the funnel complexes may be exploited for the design of sensitive and selective probes for small molecules of specific shape and functionality. The discovery of new redox behaviors and reactivity patterns also open doors toward the development of new catalysts with unusual reactivity and selectivity. We are currently exploring water-soluble systems and other cavities that define different constraints on the metal center (e.g., bowl complexes).[35] Also, we are advancing toward applications by immobilization at an electrode surface.

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