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Synthesis and First Studies of the Host–Guest and Substrate Recognition Properties of a Porphyrin-Tethered Calix[6]arene Ditopic Ligand

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The synthesis and first host–guest investigations of a (Zn)porphyrin-tethered calixarene are described. The target compound was obtained by selective copper-catalyzed alkyne/azide cycloaddition at one position of a tris-azide-substituted calixarene using an alkyne-functionalized (Zn)porphyrin. After the complexation of zinc to the tris-imidazole site of the modified calixarene, the heteroditopic receptor showed a strong affinity for primary alkylamines, which formed host–guest complexes within the cavity. This process is in competition with the binding of the amine at the apical coordination site of the (Zn)porphyrin. The use of a diamine (primary) with a C_{12} aliphatic chain led to the formation of a heteroditopic complex, as evidenced by NMR and UV/Vis spectroscopy. This highlights the possibility of generating cooperative interactions between the three "actors" of the complex (calixarene <> guest <> porphyrin), a feature of great interest as it is reminiscent of the interactions governing enzymatic catalysis (recognition pocket <> substrate <> reactive center).

Introduction

In natural enzymatic systems, the preorganization of a substrate at the catalytic site is key to achieving high efficiency and selectivity for the chemical transformation. The active pocket selects and recruits the substrate, brings it into close vicinity with the reactive center, and orients it in an optimal fashion to promote the desired reaction.[1] Classically, the substrate bears motifs for the recognition at the active site on one side and another side is exposed to the reactive center. Multiple "weak" interactions allow for selective binding and positioning at the active site, typically a combination of electrostatic and hydrophobic interactions with a possible anchoring through coordination to a metal center. In this way, natural enzymatic systems can operate efficiently under mild reaction conditions and perform fast, substrate specific, and site-controlled chemical reactions even in highly diluted media. The construction of artificial systems that can mimic the catalytic properties of such naturally occurring catalysts is therefore of high fundamental and applicative importance. Indeed, this theme[2] has lured in the last three decades researchers from virtually all fields of chemistry (organic,[2] organic catalysis,[3] bioinorganic,[4] biomolecular,[5] supramolecular,[6] spectroscopic,[7] and theoretical chemistry[8]). In recent years, catalysts designed according to supramolecular strategies have been shown to display remarkable control of regio- and stereoselectivity as well as substrate recognition.[9]

In this context, molecular receptors such as cyclodextrin,[10] calixarene,[11] resorcinarene,[12] or cryptophane[13] derivatives are appealing platforms for building artificial enzymes. Calix[6]arenes are of particular interest: Owing to the large size and structural flexibility of their cavities, these funnel-shaped host molecules can accommodate a wide range of organic guests.[14] However, one drawback of this flexibility is that calix[6]arene molecules can readily "flip" in solution leading to the occurrence of multiple conformational isomers devoid of guest accommodation properties.[14a] Over the last decade we have successfully addressed this issue through the development of new families of functionalized calix[6]arenes. Macrocycle covalent capping and/or coordination chemistry at the small rim have been used to freeze the systems in the cone conformation that is required for host–guest interactions. These strategies simultaneously allow the affinity and selectivity of the so-designed receptors towards different kinds of guest molecules to be improved.[15] The tris(imidazole) systems designed according to this principle are particularly appealing as they are synthetically easily accessible and their metal complexes behave as remarkable receptors for linear guests bearing a coordinating group.

The coordination links at the small rim, associated with hydrogen bonding to the anisole moieties and CH–π interactions with the aromatic walls of the cone, are strong enough to anchor a primary amine, the alkyl chain of which is partly included in the cone and, depending on the length of the chain, partly outside. Upon host–guest complex for-

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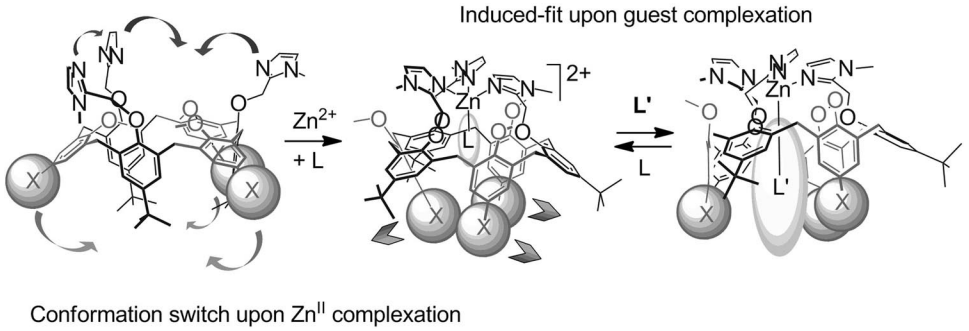


Figure 1. Changes in the conformations associated with zinc coordination at the small rim of a calixarene and inclusion of a small ligand (e.g. H_2O or MeCN; left) and of a bulkier ligand by the induced-fit process (right).

mation, the calixarene cavity reshapes to optimize its interaction with the guest molecule in a so-called induced-fit process (Figure 1). The resulting changes to the cavity structure can easily be monitored by NMR techniques.[15a,15d,16]

As well as introducing modifications at the small rim of calixarene systems to provide metal-ion binding and guest recognition, we also directed our efforts towards the appendage of various functionalities at the large rim. The discovery of the possibility of directing electrophilic substitution at the large rim by the substitution pattern at the small rim was a strategic breakthrough. This approach gives access to a wide variety of functionalities at the large rim.[17] In particular, the introduction of azido groups has allowed us to consistently expand the range of possible modifications at the large rim by using simple CuAAC (copper-catalyzed azide-alkyne cycloaddition) click methodologies.[19b] Interestingly, we have recently shown that the tris(imidazole) system can be used as a supramolecular protecting tool for a polytopic guest: One primary amino group of a linear triamine guest bearing two primary amines is anchored to the metal ion bound to the small rim imidazole site and the other can regioselectively react with an electrophile outside of the cavity.[18] This is a proof of concept that our systems can be used to efficiently direct chemical reactions selectively to the exposed extremity of guest molecules.

Wanting to further exploit this property, we aimed to graft a catalytic moiety onto the large rim of the calixarene host. By this approach we hoped to promote the long-distance preorganization of the catalyst–substrate complex. The role of the tris(imidazole)–metal complex formed at the small rim is to anchor the coordinating substrate with its carbon skeleton partly caged within the calixarene cavity and its other extremity exposed to the distant catalytic site (Figure 2).

Metal complexes of porphyrins and related macrocyclic compounds are probably among the most widely studied compounds for applications in catalysis owing to their robustness, ease of synthesis and functionalization, and the versatility of their catalytic properties.[19] In addition, architectures featuring a porphyrin moiety covalently connected to a calixarene cavity are original because examples of this

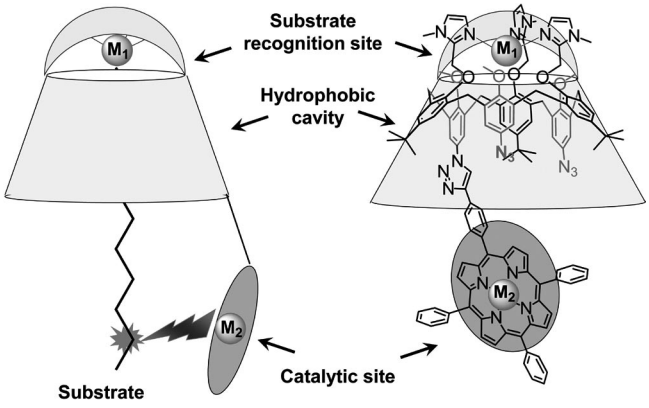


Figure 2. Design concept of a supramolecular ditopic catalyst (left) and the target complex Calix(M1)P(M2) described in this study, based on this design (right).

class of molecules have rarely been reported in the literature and then for completely different applications (molecular electronics).[20]

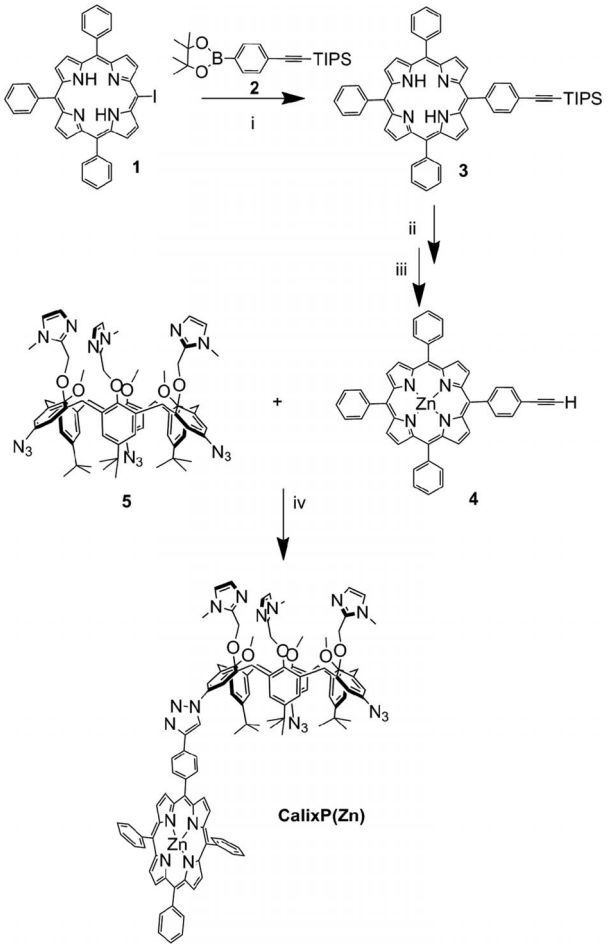
We thus decided to direct our attention towards the synthesis of a calixarene-tethered porphyrin as a first target compound (as depicted in Figure 2). This compound will be referred to as Calix(M1)P(M2) throughout the article, M1 and M2 being the metal cations complexed to the calixarene small rim and to the porphyrin macrocycle, respectively.

Results

Synthesis

The silyl-protected ethynylphenylboronic pinacolic ester **2**[21] and the triphenyliodoporphyrin **1**[22] (Scheme 1) were synthesized following literature methodologies and coupled by a Suzuki–Miyaura cross-coupling reaction. Cleavage of the silyl group followed by metalation of porphyrin **3** using $Zn(OAc)_2$ led to the alkyne-functionalized zinc porphyrin **4**, which was tethered in a last step to the tris-azide functionalized calixarene **5** by the CuAAC methodology. Several classic solvents, temperatures, and catalyst conditions were

tried. The best results were obtained when a biphasic dichloromethane/water (1:1, v/v) solvent mixture was used in combination with a $Cu(SO_4)$/sodium ascorbate catalyst, a system previously reported by Lee et al.[23] Under these conditions, the target molecule CalixP(Zn) could be isolated in an acceptable yield of 45% for the last step and with a remarkable selectivity for the monoadduct (Scheme 1). Indeed, under all of the click conditions that we tried, no analytical evidence (ESI-MS) was found for the formation of multi-addition products. This seemingly implies that the steric hindrance induced by the porphyrin macrocycle prevents further functionalization of the calixarene rim with bulky substituents. This selectivity is unprecedented to date in our systems prepared by CuAAC. It is of particular interest in the context of our target applications as the presence of more than one porphyrin unit at the calixarene large rim might lead to the undesired (as catalytically inactive) formation of intramolecularly bridged μ-oxo-porphyrin–metal complexes.[24] Moreover, it is important to note that the two remaining azido groups on the calixarene can potentially be involved in subsequent coupling steps with other chemical groups of potential interest, such as chiral entities, water-solubilizing moieties, and redox-active species.



Scheme 1. Reagents and conditions: i) DMF/toluene (1:1, v/v), $[Pd_2dBa_3]\cdot CHCl_3$, PPh_3, Cs_2CO_3, 60 h, 90 °C, 55%; ii) NBu_4F (1 M in THF), CH_2Cl_2, 20 h, room temp., 100%; iii) $Zn(OAc)_2$, CH_2Cl_2/MeOH (1:1, v/v), room temp., 1 h, 92%; iv) $CuSO_4$, sodium ascorbate, CH_2Cl_2/H_2O (1:1, v/v), 20 h, room temp., 45%.

Compound CalixP(Zn) and its bimetallic derivative were characterized by ESI-MS, UV/Vis, and ^1H NMR spectroscopy (see the Supporting Information for details). In the following, we will particularly focus on the results of the NMR and UV/Vis experiments that were carried out to gain insight into the host–guest properties of the molecule.

NMR Experiments

Mono- and Bimetallic Zinc Complexes CalixP(Zn) and Calix(Zn)P(Zn)

The NMR spectrum of the metal-free calixarene, CalixP(Zn), recorded in $CD_3CN/CDCl_3$ (1:1, v/v), shows a very broad, ill-defined signature, especially in the calixarene region. The bluish purple solution appeared slightly cloudy and showed a very strong diffusion when exposed to light, which is characteristic of the formation of molecular aggregates.[25] Upon the addition of 1 equiv. of $[Zn(H_2O)_6(ClO_4)_2]$, the solution immediately turned burgundy-red and limpid, and the proton signals sharpened considerably. As a result, a clean signature was obtained for the Calix(Zn)-P(Zn) complex (Figure 3a and b) similar to those obtained for analogous calixarene–tris(imidazole)Zn^{II} complexes that have been desymmetrized at the large rim (with a typical split of proton signals as a consequence of symmetry breakdown).[26] This suggests that, in the absence of Zn^{II} at the imidazole site, the aggregation observed for CalixP(Zn) is due to intermolecular apical coordination of the imidazole nitrogen to the porphyrin metal ion (see Figure 7c for an illustration).

Host–Guest Study of the Bimetallic Complex Calix(Zn)-P(Zn) with Monotopic Guests

Guest inclusion in calix[6]arene receptors is classically evidenced by important shielding of the guest proton signals, generally observed in the negative range of chemical shift, and concomitant downfield shifts of the aromatic calixarene signals due to cavity opening.[15a,15d,16]

Addition of increasing amounts of propylamine or heptylamine to the Calix(Zn)P(Zn) complex led to the appearance of distinctive sets of resonances at negative δ shifts. These correspond to the cavity-included alkylamine, the protons of which are exposed to the intense shielding effect of the aromatic sidewalls. Concomitant marked changes in the chemical shifts of the calixarene proton signals (Figure 3, see the Supporting Information for the whole titration experiment and assignments) are the result of conformational modifications induced by the hindering effect of the amine guest, as depicted earlier: A swing of the aromatic walls takes place as revealed by the downfield shifts of the protons that sit in an in-position relative to the cavity (H_{ArN3} and $H_{Artriaz}$, Figure 4) with concomitant upfield shifts of the connected methoxy groups; the OCH_2 linkers

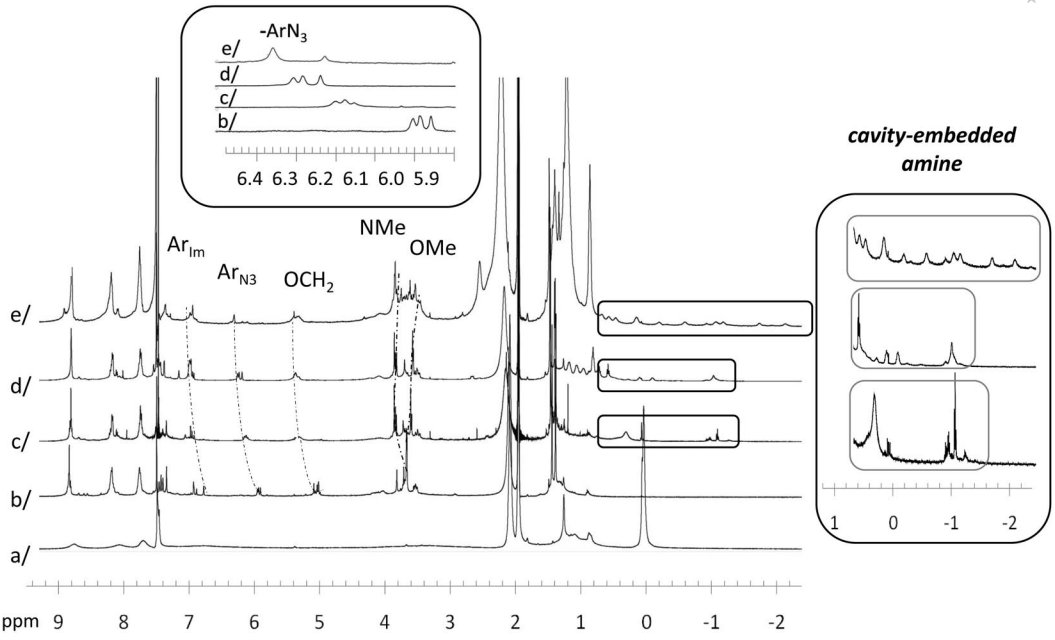


Figure 3. ^{1}H NMR spectra [$CD_3CN/CDCl_3$ (1:1 v/v), 500 MHz, 300 K] of compounds **a**–**e** (as depicted in Figure 4); the dotted line shows the evolution of some characteristic chemical shifts. Inset: close-up of the H_{ArN3} shift region.

at the small rim are also pushed outwards to allow the sp^3 N atom of the amine to bind (instead of the less sterically demanding sp N of a nitrile). Notably, these host changes were more pronounced in the case of the complex formed between Calix(Zn)P(Zn) and heptylamine as a result of a stronger interaction between the calixarene large rim and the longer alkyl chain (see Figures 3 and 4).

In both cases, however, more than 1 equiv. of the amine was required to quantitatively form the host–guest complex (between 1.5 and 2 equiv.). This observation is ascribed to the competition between the coordination of the amine at the (Zn)tris(imidazole) site and its apical ligation to the (Zn)porphyrin. The latter is evidenced by the characteristic change in the color of the sample from burgundy-red to greenish blue (see also the UV/Vis studies reported below), which took place upon addition of the amine, and confirmed by the small variations in the chemical shifts experienced by the porphyrinic protons (Figure 5). Hence, apical coordination to the zinc porphyrin occurs by a fast equilibrium exchange with the free amine on the NMR timescale, whereas the exchange is slow at the cavity site. Both phenomena are competitive, which indicates similar magnitudes of the binding constants at the two sites, but a preference is nonetheless observed for the calixarene site (because, upon addition of excess amine, shifts are still observed for the porphyrinic protons after the signals of the "free" calixarene have fully disappeared).

The Calix(Zn)P(Zn)/heptylamine host–guest complex is stable enough to be isolated by precipitation with pentane. When redissolved in a deuteriated solvent, the upfield-shifted signature of the *endo*-bound heptylamine remained intact.

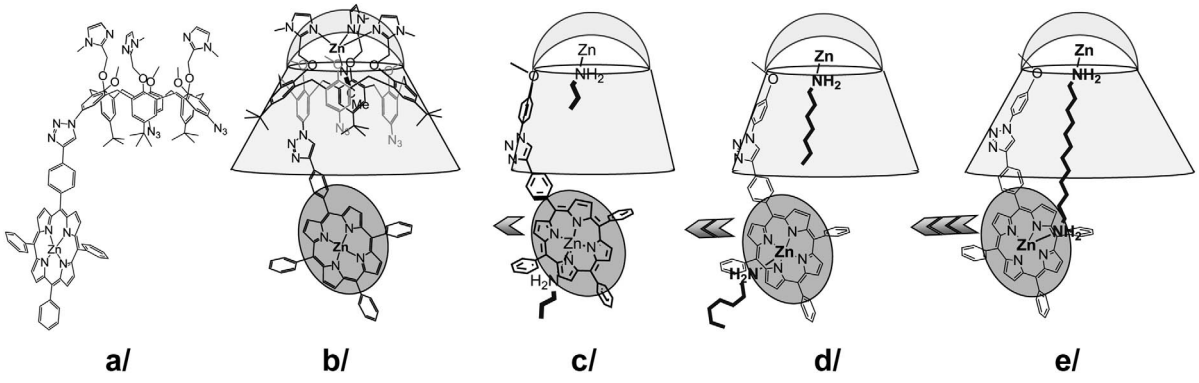


Figure 4. Various molecules and complexes investigated in the NMR study; the size of the arrow reflects the cavity opening that results from the inclusion of amine as a guest. a) CalixP(Zn), b) Calix(Zn)P(Zn), c) Calix(Zn)P(Zn)/propylamine, d) Calix(Zn)P(Zn)/heptylamine, e) Calix(Zn)P(Zn)/dodecyldiamine.

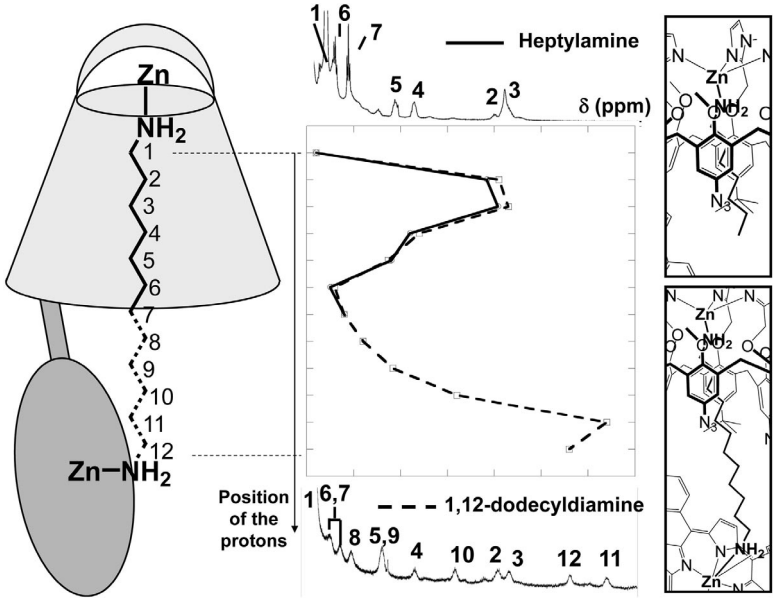


Figure 5. Variation of the chemical shifts of the guest protons as a function of their position in complexes Calix(Zn)P(Zn)/heptylamine and Calix(Zn)P(Zn)/1,12-dodecyldiamine Intense shielding effects are observed for the methylene groups situated in the calixarene cavity and in the porphyrin vicinity [the ^{1}H NMR spectra were recorded in $CD_3CN/CDCl_3$ (1:1, v/v) at 500 MHz, 300 K].

Host–Guest Study of the Bimetallic Complex Calix(Zn)-P(Zn) with a Ditopic Guest

Inclusion of dodecyldiamine inside the cavity of Calix(Zn)P(Zn) led to changes in the chemical shifts similar to those observed with propyl- and heptylamine with the appearance of a set of protons in the negative region characteristic of the cavity-included alkyl chain and shifts for the calixarene proton resonances attesting a wider opening of the cavity walls (see Figures 4, 5, and in the Supporting Information Figure SI18). 2D NMR experiments allowed the assignment of each of the methylene protons of the diamine alkyl chain, which are differentiated by their well-defined spatial positioning relative to both the calixarene host and the porphyrin moiety. As shown in Figure 5, the upfield shifts undergone by the first seven methylene groups are superimposed on those measured for heptylamine. This shows a similar positioning relative to the cavity, with C-7 (the less shifted) situated at the entrance of the calix cone. The next four methylene groups then experience a strongly increasing upfield shift, which denotes their proximity to the porphyrin core. Finally, the last one, which is in the α position with respect to the amino group, has a less-shifted resonance as a result of its coordination to the Zn porphyrin. As one may anticipate, the shifts in the resonances recorded for the aromatic protons of the calixarene cavity, particularly those in the *ortho* position of the azido group (H_{ArN3}), are more marked for the longer dodecyldiamine than with propyl- and heptylamine, which indicates more pronounced conformational changes, as shown in Figure 4.

As mentioned above, the exchange process for propyl- or heptylamine at the (Zn)porphyrin site is fast relative to the NMR timescale. This is illustrated by a progressive shift of the resonances of the porphyrinic β protons of Calix(Zn)-P(Zn) upon the gradual addition of the amine due to coalescence of the signals of the free and axially bound zinc porphyrin (Figure 6). This is not true for the addition of dodecyldiamine: The β protons of the free and axially bound porphyrin appear as two distinct sets of signals. This indicates that the equilibrium of the apical coordination of the amine to the zinc porphyrin of Calix(Zn)P(Zn) is now taking place by a slow exchange on the NMR timescale. This can be attributed to a multipoint binding process: The overall kinetics for the formation of the ditopic complex between dodecyldiamine and Calix(Zn)P(Zn) is controlled by the rate-limiting step of the process, that is, the inclusion of the guest molecule into the calixarene cavity. In other words, the slow-exchange character of this host–guest process is somehow "transferred" to the apical complexation of one extremity of the diamine to the zinc porphyrin.

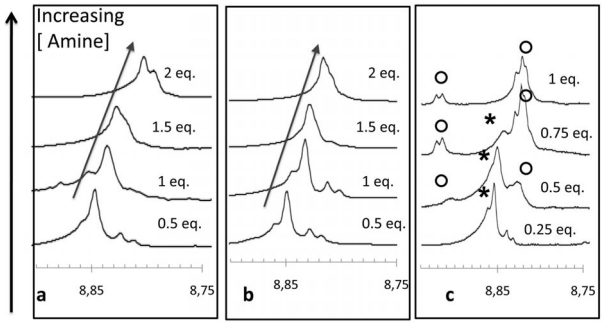


Figure 6. Variation in the chemical shifts of the porphyrin β-protons upon addition of: a) propylamine (fast exchange); b) heptylamine (fast exchange); c) dodecyldiamine (slow exchange) [the ^{1}H NMR spectra were recorded in $CD_3CN/CDCl_3$ (1:1, v/v), 500 MHz, 300 K].

Competition Experiment between Mono- and Diamines for Calix(Zn)P(Zn) Binding

^{1}H NMR competition experiments between propylamine and dodecyldiamine for 1:1 complex formation with Calix(Zn)P(Zn) were also undertaken in $CD_3CN/CDCl_3$ (1:1, v/v; Figure SI20). The experiments showed that for Calix(Zn)P(Zn)/dodecyldiamine/propylamine in a ratio of 1:1:1, Calix(Zn)P(Zn)/dodecyldiamine was the only adduct that could be detected at the NMR resolution. For a Calix(Zn)P(Zn)/dodecyldiamine/propylamine ratio of 1:1:60, about 50% each of the Calix(Zn)P(Zn)/propylamine and Calix(Zn)P(Zn)/dodecyldiamine adducts coexisted in solution. These last results clearly underline a much stronger affinity for the bidentate guest and thereby for a ditopic coordination mode (see the Supporting Information) with an estimated value of 17 M for the equilibrium constant (1) and 120 for equilibrium (2) in $CD_3CN/CDCl_3$ (1:1) at 300 K (DA = 1,12-dodecyldiamine).

$$\text{Calix(Zn)P(Zn)(PrNH}_2)_2 + \text{DA} \leftrightarrows \text{Calix(Zn)P(Zn)(DA)} + 2\text{PrNH}_2 \quad (1)$$

$$\text{Calix(Zn)P(Zn)(PrNH}_2) + \text{DA} \leftrightarrows \text{Calix(Zn)P(Zn)(DA)} + \text{PrNH}_2 \quad (2)$$

UV/Vis Experiments

Monometallic Complex CalixP(Zn): Oligomer Formation

All UV/Vis experiments were conducted in distilled chloroform (see the Supporting Information for the spectra of all porphyrin derivatives and complexes formed in this work). At 0.5 μM CalixP(Zn) showed a sharp Soret band centered at 425 nm (ε = 330000 $M^{-1}cm^{-1}$) and two Q bands at 555 (ε = 16500) and 604 nm (ε = 7200 $M^{-1}cm^{-1}$), a classic signature of zinc-metalated porphyrins. The positions of the Soret and Q bands were strongly redshifted upon increasing the solution concentration to reach maximal absorption wavelengths of 432 (8 nm shift), 564 (10 nm shift), and 605 nm (4 nm shift) at 60 μM (Figure 7a). The same experiment performed with CalixP(2H), the free base analogue of CalixP(Zn) (see the Supporting Information for preparation, characterization, and UV/Vis measurements), did not show any concentration-dependent variation of the absorption signature. The evolution observed with CalixP(Zn) is in agreement with the expected effect of coordination of a nitrogenated ligand to a zinc porphyrin,[27] which of course cannot take place with the free base porphyrin.

A plot of the maximal absorption wavelength versus sample concentration shows a well-defined pattern with an initial fast evolution and a plateau value reached at high concentration in a curve that is reminiscent of a binding isotherm (Figure 7b). This provides evidence that intermolecular coordination takes place between the calixarene free imidazoles and the metalloporphyrin to form supramolecular oligomeric structures (shown in Figure 7c), as anticipated from the extreme signal broadening observed in the NMR experiments. However, the expected dispersity of the oligomer distribution prevents fitting of the obtained curve to simple existing models.

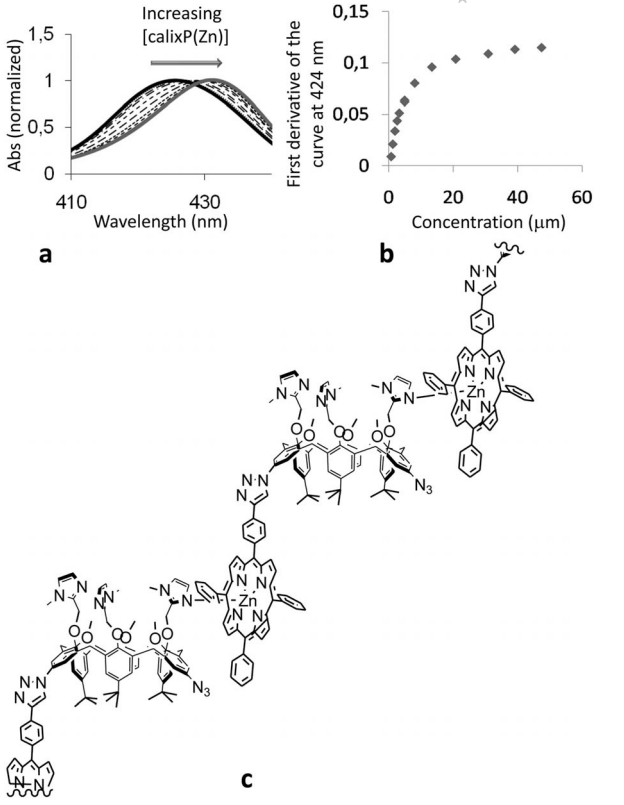


Figure 7. a) Normalized UV/Vis spectra in the Soret region of CalixP(Zn) at different concentrations (0.5–50 μM in $CHCl_3$) showing the effect of dilution on the Soret maximal absorption wavelength. b) Plot of the Soret maximum absorption wavelength (first derivative method) vs. concentration (using a first derivative variation method on the normalized curves allows for a precise detection of variations in the absorption maxima). c) Putative structure of the supramolecular polymer accounting for the observed UV/Vis evolution.

Host–Guest Studies of the Bimetallic Complex Calix(Zn)-P(Zn) with a Monotopic Guest

The bis(zinc) complex Calix(Zn)P(Zn) shows a spectrum that is overall similar to that of its mononuclear coordinated analogue CalixP(Zn) at low concentration with absorption maxima at 424 (ε = 330000), 552 (ε = 15700), and 595 nm (ε = 5100 $M^{-1}cm^{-1}$).

To determine the host–guest properties of Calix(Zn)-P(Zn) towards primary amines, we first performed a series of titrations with propylamine. As mentioned above, primary amines can bind to two sites (the two Zn^{II} metallic centers) of Calix(Zn)P(Zn). By recording the spectral changes of the porphyrin visible electronic transitions upon addition of a monotopic primary amine, it was possible to determine the sequence of binding events of the amine to Calix(Zn)P(Zn). Three cases can be distinguished.

1) The binding constant for the binding of propylamine to the Zn metal center located inside the cavity (K_c) is several orders of magnitude higher than that of the metalloporphyrin (K_P). In this case, no (or little) variation of the porphyrin bands should be observed until the calixarene cavity is saturated (when ca. 1 equiv. of amine is added) and

the second binding event to the porphyrin should then take place. As a consequence, the titration curve should have a sigmoidal shape.

2) The binding constant K_P is several orders of magnitude higher than K_c. The titration curve would then be virtually unaffected by the presence of the calixarene cavity and a binding constant similar to that measured in the absence of a calixarene guest should be obtained.

3) The binding constants K_c and K_P have a similar order of magnitude. Competition between the two binding sites would then take place resulting in a lower value of the apparent binding constant relative to analogous measurements in the absence of the cavity.[28]

Thus, Calix(Zn)P(Zn) was titrated with propylamine (see Figures 8 and 9) and the results compared with those obtained with a porphyrin precursor of the molecule (porphyrin **4**, see the Supporting Information for the titration experiment of this porphyrin), which gives a good estimation of K_P. Because we had to carry out the measurements at a concentration that was lower than that required for NMR, we tried to minimize as much as possible competitive effects of the solvent for the coordination to the calixarene-complexed zinc. Hence, pure chloroform was preferred to the chloroform/acetonitrile (1:1, v/v) mixture used in NMR experiments. Fitting of the results to a 1:1 binding model[29] using a LAB Fit program and Hill's plot linearization afforded a binding constant for the binding of the amine to the Zn porphyrin of Calix(Zn)P(Zn) [$K_{app}(PrNH_2) = 1.8 \times 10^3$ M^{-1}] that is one order of magnitude lower than that measured for the reference porphyrin **4** [$K_a(\mathbf{4}\cdot PrNH_2) = 1.9 \times 10^4$ M^{-1}]. This is clearly indicative of competition between the two binding events (to the Zn porphyrin and to the Zn metal center inside the cavity), with a significantly higher value of the binding constant at the metal center inside the cavity. From the ratio $K_{app}(PrNH_2)/K_a(\mathbf{4}\cdot PrNH_2)$, a minimal value of $K_c = 2.5 \times 10^4$ M^{-1} could be estimated (see the Supporting Information), which is indeed slightly higher than $K_P \approx 1.9 \times 10^4$ M^{-1}.

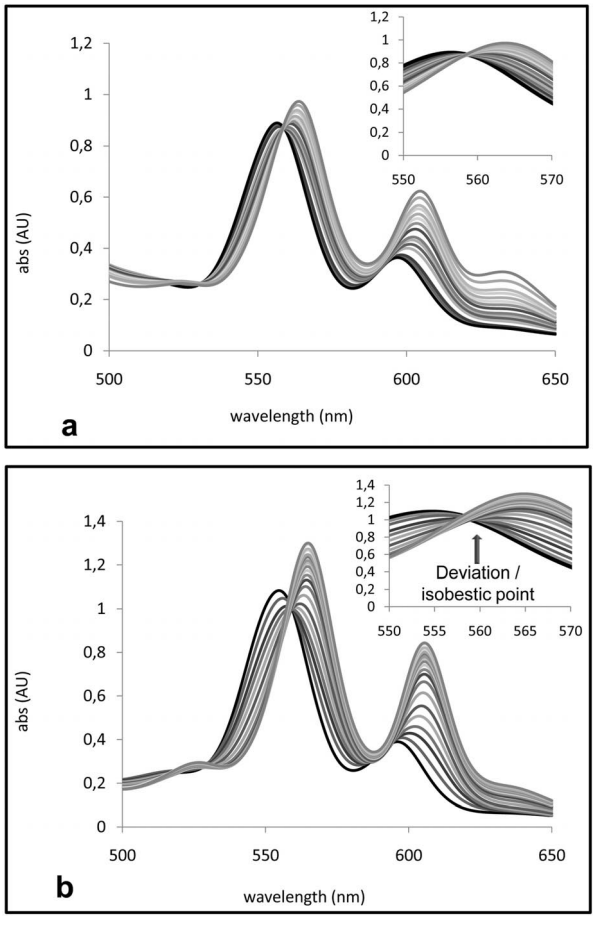


Figure 8. a) UV/Vis titration of Calix(Zn)P(Zn) (0.36 mM in $CHCl_3$) with propylamine. b) UV/Vis titration of Calix(Zn)P(Zn) (0.36 mM in $CHCl_3$) with dodecylamine (inset: deviation from isosbestic behavior observed upon addition of over 2 equiv. of guest).

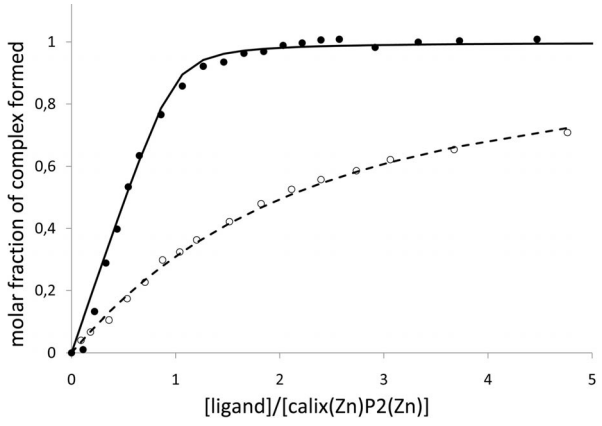


Figure 9. Data (circles) and 1:1 binding isotherm fits (lines) corresponding to the binding event of propylamine [dotted line: $K_{app}(PrNH_2) = 1.8 \times 10^3$ M^{-1}] and dodecyldiamine [plain line: $K_{app}(DA) = 1.4 \times 10^5$ M^{-1}].

Host–Guest Studies of Bimetallic Complex Calix(Zn)-P(Zn) with a Ditopic Guest

The formation of the complex with the ditopic guest dodecyldiamine was also investigated by UV/Vis spectrophotometry. A 0.36 mM solution of Calix(Zn)P(Zn) was titrated with dodecyldiamine and the evolutions of the Q bands were monitored (Figure 8b). Fitting of the evolution to a 1:1 binding isotherm (Figure 9) allowed us to make a rough estimation of the apparent binding constant [$K_{app}(DA) \approx 1.4 \times 10^5$ M^{-1}], which is almost two orders of magnitude higher than that for propylamine. This confirms that an entropic effect strongly facilitates the apical binding of the ditopic ligand to the zinc porphyrin (Figure 10). It can also be seen that a small drift of the isosbestic point progressively takes place upon addition of excess dodecyldiamine. Such a deviation from ideal isosbestic behavior may correspond to competing 2:1 dodecyldiamine–Calix(Zn)P(Zn) complex formation with each zinc center of Calix(Zn)P(Zn) being coordinated to a different ligand molecule. This may account for the unusual profile of the titration curve upon addition of excess ligand (i.e., an important increase in the

molar extinction coefficients of both Q bands without a significant change in their absorption wavelength), which hampers fitting of the curve.

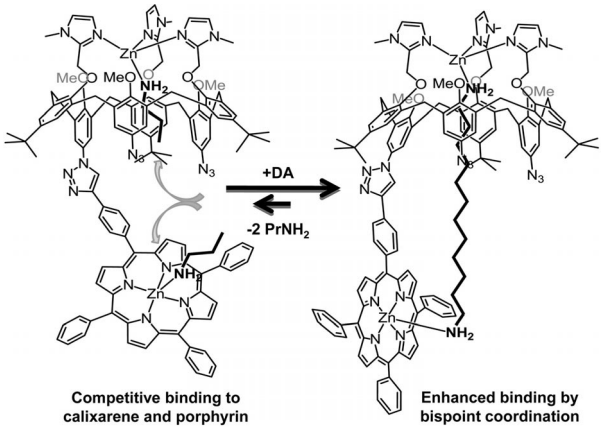


Figure 10. Binding modes for monoamines (left) and dodecyldiamine (right). DA = 1,12-dodecyldiamine.

Discussion

The main contribution to the "cooperative" ditopic binding of a bidentate ligand is of entropic origin. For a large part it can be explained by the concept of effective molarity (EM),[30] which describes the relative ease of an intramolecular reaction compared with its intermolecular counterpart under otherwise identical conditions. Considering the ditopic coordination of a bidentate ligand to a single metal site, the so-called chelate effect, when one site of the bidentate ligand coordinates to the metal, the local concentration of the second site increases, which statistically favors its subsequent binding.[30a,31] For relatively short spacers (i.e., 2–4 carbon linker chains), this statistical entropic effect largely overcomes the entropic cost that is associated with the limitation of rotational freedom of the molecule due to immobilization of the binding sites.[32] However, the longer the spacer chain, the smaller EM becomes, down to a limit at which the intermolecular pathway is preferred.[32b,33] When not one, but two metal coordination sites are involved in the ditopic binding process, and when these metal sites are distant, the situation becomes even more complicated. If the spacer chain is too short, the ligand will not be able to coordinate simultaneously the two metal sites. If the chain is too long, the effect of EM will vanish and monotopic (2:1 complex formation) rather than ditopic (1:1 complex formation) coordination of the bidentate ligand will be observed.

A solution to overcoming this issue involves the introduction of rigid elements into the ligand such as unsaturated linear or cyclic fragments.[32a,34] Alternatively, one can precisely adjust the distance between the two metal sites involved in the coordination to the size of the spacer that separates the two coordinating sites of the ditopic ligand.[35] The complexes designed according to this strategy are sometimes referred to as "molecular rulers", the entropic cost being counterbalanced by the perfect size fit between the ligand and distant metal sites. Another option involves stabilizing a given orientation of the ligand molecule (i.e., restricting its rotational freedom) by introducing steric constraints around this molecule. Such a strategy, which involves creating a preferred orientation in the system, is a major process in natural enzymatic systems. This is precisely the effect that we promote here: as the tris(imidazole) zinc center is buried at the bottom of the calix funnel, access to its labile site is controlled by the large rim of the cavity. Upon binding to the small rim, the calixarene funnels the alkyl chain of the guest towards the porphyrin site. In the case of dodecyldiamine, 7 out of the 12 carbons of the guest alkyl chain are included in the funnel. As a result, the conformational mobility of the alkyl chain is highly restricted by the cone and by the large-rim substituents that form the door controlling the cavity entrance. Hence, the door opens just enough to allow the alkyl chain to sit through it with optimized van der Waals interactions (induced-fit process). After the seventh carbon, the chain can regain conformational freedom, but only through its five remaining methylene groups. In fact, this is enough to allow an entropically favored interaction with the proximal porphyrin. This generates an enhancement (ca. two orders of magnitude) of the association constant associated with ditopic complex formation.

Conclusions

We have successfully designed a new calix[6]arene derivative bearing a tridentate imidazole metal coordination site at its small rim and a single porphyrin ligand appended to its large rim. By using NMR and UV/Vis techniques we have shown that this calixarene derivative behaves as a ditopic ligand. Indeed, in addition to the metalated porphyrin, the tris-imidazole site readily coordinates one Zn^{II} cation. This rigidifies the calix[6]arene, locking it into a cone conformation, and concomitantly provides a new coordination site controlled by the calixarene cavity. The corresponding dinuclear complex Calix(Zn)P(Zn) is then able to accommodate 1 equiv. of a primary amine inside the calixarene cavity. Although in competition with binding to the (Zn)porphyrin site, it has been shown that the calix site is the thermodynamically favored one. As previously observed with related systems,[15a,15d,16] the funnel-shaped calix cone undergoes guest binding through an induced-fit process. Increasing the size of the amino alkyl chain from C_3 to C_{12} progressively opens the funnel to allow best host–guest fitting and its possible externalization. With the long-chain (C_{12}) diamine ligand, we showed that it was possible to form a ditopic complex between the two different Zn^{II} coordination sites of the molecule. This ditopic binding is associated with a higher binding constant than that of monoamines. Such an effect, which must be of entropic origin (increase of the effective molarity), is quite remarkable in view of the length of the alkyl chain playing the role of spacer and the flexibility and mobility of the calix-based

ligand. Indeed, even with this bimetallic system, the appended porphyrin is free to rotate and balance relative to the axis of the cone, as observed by NMR spectroscopy. The key to the possible ditopic recognition as seen in this study is the cone shape of the calixarene host. In other words, in the system depicted herein, Calix(Zn)P(Zn), the extremity of a long-chain guest can be preorganized and placed in close proximity with the appended porphyrin metal center as a result of a directional effect of the funnel-shaped calixarene cavity. Such a process is reminiscent of many enzyme active sites: The pocket-binding site for the substrate protects and orients it towards the reactive site, thus giving rise to the chemo-, regio-, and stereoselectivity. Another beneficial effect of the calixarene cavity lies in the observed change in the bidentate ligand exchange kinetics compared with that of the monodentate ones: Upon ditopic complexation, a slow equilibrium exchange is clearly evidenced at the apical site of the porphyrin. Indeed, the average time spent by one amino group of one diamine molecule in the vicinity of the porphyrin moiety is greatly enhanced by its anchoring to the small rim of the calixarene. Such a remarkable slowing down of the exchange kinetics of a nitrogen ligand on a porphyrin center, as a result of stabilizing supramolecular interactions, has to date been rarely reported[36] and in only one instance with a guest as floppy as dodecyldiamine.[35] Our hope is that the concepts introduced in this article, namely the possibility of preorganizing thermodynamically and kinetically a substrate (mimicked by the amine in this study, but could be an alcohol, an amide, or a nitrile) next to a potentially reactive center (here, the metalloporphyrin) owing to the directionality inherent to a calixarene host, will be exploitable for the development of efficient site-selective catalysts based on a similar framework. The synthesis and examination of the catalytic properties of a (Mn)porphyrin analogue of our system, Calix(Zn)P(Mn), are currently under investigation.

Experimental Section

For experimental details see the Supporting Information.

Supporting Information (see also the footnote on the first page of this article): Synthetic procedures, characterization of products and complexes, NMR and UV/Vis titrations and other experimental details.

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