Biomimetic Copper(I)–CO Complexes: A Structural and Dynamic Study of a Calix[6]arene-Based Supramolecular System

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Abstract: Four novel calix[6]arene-based cuprous complexes are described. They present a biomimetic tris(imidazole) coordination core associated with a hydrophobic cavity that wraps the apical binding site. Each differs from the other by the methyl or ethyl substituents present on the phenoxyl groups (OR^1) and on the imidazole arms (NR^2) of the calix[6]arene structure. In solution, stable CO complexes were obtained. We have investigated their geometrical and dynamic properties with respect to the steric demand. IR and NMR studies revealed that, in solution, these complexes adopted two distinct conformations. The preferred conformation was dictated only by the size of the OR^1 group. When R^1 was an ethyl group, the complex preferentially adopted a flattened C_3-symmetrical structure. The corresponding helical enantiomers were in conformational equilibrium, which, however, was slow on the ^1H NMR time scale at $-80\,^{\circ}C$. When R^1 was a methyl group, the low-temperature NMR spectra revealed the partial inclusion of one *t*Bu group. The complex wobbled between three dissymmetric but equivalent conformations. Hence, small differences in the steric demand of the calixarene's skeleton changed the geometry and dynamics of the system. Indeed, this supramolecular control was promoted by the strong conformational coupling between the metal center and the host structure. Interestingly, this was not only the result of a covalent preorganization, but also stemmed from weak interactions within the hydrophobic pocket. The vibrational spectra of the bound CO were revealed to be a sensitive gauge of this supramolecular behavior, similar to copper proteins in which allosteric effects are common.

Keywords: bioinorganic chemistry · calixarenes · copper · host–guest chemistry · N ligands · supramolecular chemistry

Introduction

The elaboration of artificial systems that mimic the active site of a metalloprotein[1, 2] is important for the understanding of the protein function[3] as well as for the development of new selective receptors and catalysts.[4–7] Supramolecular systems that combine a biomimetic coordination core with a cavity are an attractive topic for the chemist.[8–14] A possible way to construct them is to use readily available building blocks, such as cyclodextrins,[15] cyclotriveratrylenes,[16] resorcinarenes,[17, 18] or calixarenes[19–23] We chose to use a calix[6]arene for the following reasons: 1) its size allows the inclusion of organic molecules, 2) it can be easily functionalized, 3) its carbon skeleton is compatible with C_3 symmetry, and finally 4) the macrocycle is highly flexible. This last feature has been analyzed as a handicap for its use as a molecular host. Therefore, different research groups developed the synthesis of rigidified calix[6]arenes attained by means of a three-point covalent cap.[24–27] We have chosen a different strategy that is based on coordination chemistry. The selective functionalization of a calix[6]arene in alternate positions with three nitrogen arms affords a tridentate ligand that, upon binding to a metal ion, will cap the lower rim. The calixarene structure will become constrained in a cone conformation that is suitable to play the role of a biomimetic host. Our first success[28] was achieved with the synthesis and X-ray characterization of a so-called "*funnel complex*" that mimics the type II site of monocopper proteins.

Indeed, copper enzymes play a major role in many metabolic oxidative pathways[29–31]. More and more enzymes are now structurally characterized and often display a polyimidazole binding site. However, the functioning of these enzymes still remains mysterious. The active state is described as Cu^I, since the first step of the catalytic process is the binding of dioxygen.[30] Unfortunately, the mononuclear CuO_2 adducts

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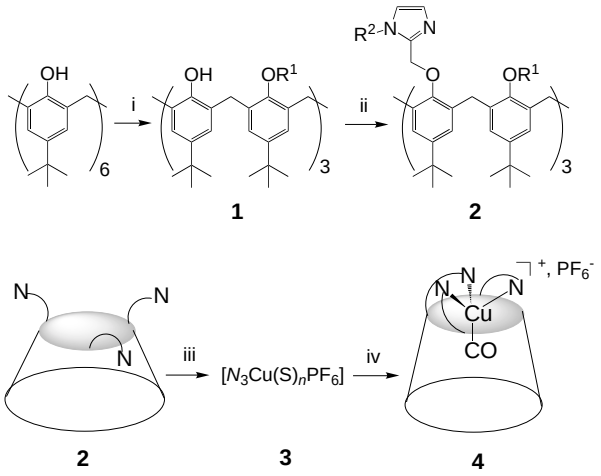
are not stable. In biomimetic systems, they have proven very difficult to isolate.[32–36] In enzymes, they rapidly evolve with the gain of one electron to generate the oxidative species that reacts with the substrate. Carbon monoxide, which is an analogue of O_2 but devoid of redox properties, is therefore often used as a tool to characterize the cuprous state of enzymes.[37–47] Our first model system was based on a calix[6]arene that contained a tris(pyridine) coordination site. The cuprous ion, wrapped by three amino groups, was constrained in a tetrahedral environment in a hydrophobic pocket that controlled the binding and exchange of an exogenous nitrilo ligand.[28] Surprisingly however, this system appeared unreactive towards CO. Therefore, we turned to a more biomimetic system, and replaced the pyridines with imidazole ligands.

We describe here the synthesis and properties of a novel series of calixarene-based cuprous complexes. These are derived from a tris(imidazole) coordination core and do provide stable CO adducts. We have investigated their geometrical and dynamic properties with respect to the steric demand of the ligands. IR and NMR studies revealed that minor changes in their carbon skeleton induced considerable differences in both the structure and the dynamic behavior of the copper(I) – CO complexes.

Abstract in French: *Une nouvelle famille biomimétique de complexes cuivreux dérivés de calix[6]arènes fonctionalisés est présentée. Elle est basée sur un site de coordination N_3 tris(imidazole) associé à une cavité hydrophobe qui enveloppe le site de liaison apical. Les quatre complexes décrits diffèrent les uns des autres par la nature, méthyle ou éthyle, des substituants présents sur les groupements phénoxyles (OR^1) ou sur les bras imidazoles (NR^2) de la structure calix[6]arène. En solution, des complexes CuCO stables ont été obtenus et leurs propriétés géométriques et dynamiques étudiées en regard de la demande stérique. Des études en spectroscopies IR et RMN ont révélé que, en solution, ces complexes peuvent adopter deux conformations différentes, la plus stable étant déterminée par la taille du groupement OR^1. Quand R^1 est un groupement éthyle, le complexe adopte préférentiellement une conformation cône aplatie présentant une symétrie C_3. Les deux formes énantiomères hélicoïdales correspondantes sont en équilibre conformationnel, lent à l'échelle de temps d'analyse de la spectroscopie RMN-^{1}H à $-80\,^\circ$C. Lorsque R^1 est un groupe méthyle, les spectres RMN obtenus à basse température ont mis en évidence l'auto-inclusion partielle de l'un des groupements tBu du calixarène. Le complexe oscille alors entre trois conformations dissymétriques mais équivalentes. Ainsi, de faibles différences d'encombrement stérique sur le squelette du calix[6]arène changent la géométrie et la dynamique du système. Ce contrôle supramoléculaire est dû au fort couplage existant entre le centre métallique et la structure hôte. Ceci est en fait le résultat non seulement d'une préorganisation covalente, mais aussi d'interactions faibles à l'intérieur de la cavité hydrophobe. Comme pour les protéines où les effets allostériques sont classiques, le spectre vibrationnel de CO coordonné s'est révélé être une sonde sensible à ce comportement supramoléculaire.*

Results

Four different calix[6]arene-based ligands with a tris(imidazole) core were synthesized according to the procedure depicted on Scheme 1. They differ from each other in the methyl or ethyl substituents present on the phenoxyl moieties



Scheme 1. Ligand synthesis and complexation of copper(I). **a**: $R^1 = Me$, $R^2 = Me$; **b**: $R^1 = Me$, $R^2 = Et$; **c**: $R^1 = Et$, $R^2 = Me$; **d**: $R^1 = Et$, $R^2 = Et$. i) R^1I, K_2CO_3, acetone; ii) 2-chloromethyl-1-R^2-*1*H-imidazole, NaH, THF/DMF; iii) $[Cu(MeCN)_4]PF_6$, THF; iv) CO, $CDCl_3$ or CD_2Cl_2.

(OR^1) and in the imidazole groups (NR^2). In the first step, the *tert*-butylcalix[6]arene[48] was protected in alternate positions by the reaction of iodomethane[49] or iodoethane[50] in the presence of K_2CO_3 in acetone. The remaining phenolic positions of the 1,3,5-tris-alkylated products (**1**) were then treated with either 2-chloromethyl-1-methyl-*1*H-imidazole[51] or 2-chloromethyl-1-ethyl-*1*H-imidazole[52] in the presence of NaH to fix the three nitrogenous arms. The structures of the resulting ligands **2**, with OR^1 and NR^2 groups, were analyzed by NMR spectroscopy. Ligands **2a** ($R^1 = Me$, $R^2 = Me$), **2b** ($R^1 = Me$, $R^2 = Et$), and **2d** ($R^1 = Et$, $R^2 = Et$) exhibited ^{1}H NMR spectra that are characteristic[28, 53, 54] of a major cone conformation. All OR^1 groups were projected towards the inside of the π-basic calixarene cavity, as shown by their corresponding high-field δ_H shift values. The related *t*Bu-phenoxyl groups, identified by HMBC experiments ($\delta(t\mathrm{Bu}^1) = 1.3 - 1.4$),[55] were in *out* positions relative to the center of the molecule. In contrast, the ^{1}H NMR spectrum of **2c** ($R^1 = Et$, $R^2 = Me$) showed broad, ill-defined, multiple peaks. This indicates that this ligand did not adopt a simple cone structure in solution.

The targeted copper(I) complexes **3** were obtained in good yield by dissolving stoichiometric quantities of ligands **2** and $[Cu(MeCN)_4]PF_6$ in THF. Precipitation with pentane yielded colorless polycrystalline compounds **3** that can be described as $[N_3Cu(S)_n]PF_6$ (where N_3 stands for one of the tripodal ligands **2**, and S is a molecule of solvent or water). Complex **3a** ($R^1 =$ Me, $R^2 = Me$) was poorly soluble in chlorinated solvents; however, the presence of an ethyl group on the other ligands improved the solubility of the complexes considerably. They were all subjected to ^{1}H NMR analysis. Complex **3b** ($R^1 =$

Me, $R^2 = Et$), however, was the only one to display an interpretable spectrum in $CDCl_3$. Although poorly defined, it was consistent with a mononuclear C_3-symmetrical structure. The spectra of the three other complexes gave little information because of the extremely broad resonance signals. This may be caused by some chemical exchange process that proceeds on the NMR time scale. The addition of a small coordinating molecule, such as acetonitrile, did not yield well-defined spectra, as opposed to the tris(pyridine)-based copper(I) system.[28]

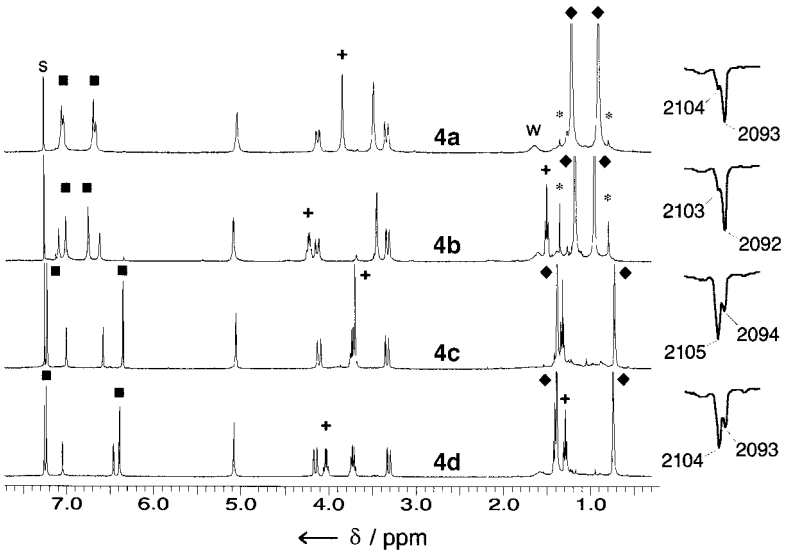


Figure 1. IR and ^1H NMR characterization of Cu–CO adducts **4** at room temperature in $CDCl_3$ at 400.13 MHz. H_{Ar}: ■; NR^2: +; *t*Bu: ◆. Peaks that could account for the coexistence of a minor conformation (see text) are indicated by ∗. Solvent and water are labeled "s" and "w", respectively. IR stretching frequencies (ν_{CO}) are reported in cm^{-1} (right).

However, bubbling CO into the solution induced drastic changes in all NMR profiles, which indicates the formation of novel, yet highly soluble species **4**. The NMR spectra became well-defined and presented a reduced number of narrow peaks. Each of them integrated for three or six groups of equivalent protons, in accordance with a C_3-symmetrical molecule. Whereas for free ligands **2** both sets of imidazole protons had almost identical chemical shifts (they were separated by less than 0.06 ppm), in the new species **4** they were separated by 0.3–0.6 ppm. This provides evidence of the coordination of Cu^+ to the imidazole arms of ligands **2**. Displacement of the chemical shifts from the methoxy (or ethoxy) protons to lower fields compared to free ligands, indicated that these OR^1 groups were repelled outside of the cavity. As a consequence, the corresponding three *t*Bu-phenoxyl groups were stacked in the *in* position relative to the π cavity ($\delta(t\mathrm{Bu}^1) = 0.7-0.9$), which was the exactly reverse situation of free ligands **2**. All these observations are consistent with a trigonal geometry at the cuprous ion which results from its coordination to the three imidazole groups of ligands **2**. The calixarene adopts a cone conformation with its phenoxyl moieties in alternate *in* and *out* positions, as reflected by the difference in chemical shifts between the two sets of *t*Bu protons.

IR studies in solution indicated the presence of two CO stretching bands at about 2100 cm^{-1} that disappeared when argon was bubbled through the solution. The most energetic one was predominant for **4c** ($R^1 = Et$, $R^2 = Me$) ($\tilde{\nu} =$ 2105 cm^{-1}) and **4d** ($R^1 = Et$, $R^2 = Et$) (2104 cm^{-1}), whereas the less energetic was less intense (2094 and 2093 cm^{-1}, respectively). For **4a** ($R^1 = Me$, $R^2 = Me$) and **4b** ($R^1 = Me$, $R^2 = Et$), it was exactly the reverse (Figure 1). This indicates that the coordination of CO to Cu^+ led to the simultaneous formation of two species. One of these was predominant in the methoxy compounds **4a**, **b**, the other in the ethoxy compounds **4c**, **d**. Each of them, however, corresponded to a four-coordinate complex with the binding of all three imidazole groups and a CO molecule because: 1) the carbonyl stretching frequencies in complexes **4** fall in the range of values reported for N_3CuCO structures ($\tilde{\nu} = 2045-2102$ cm^{-1} for nonfluorinated ligands),[56–67] 2) bis(imidazole)Cu^+ complexes have been described as stable species that do not react with CO,[68, 69] 3) N_2CuCO complexes are rare and present ν_{CO} values above 2112 cm^{-1},[68, 70] and 4) binding of more than one CO molecule to Cu^+ has only been observed in the gas phase or in solution in the presence of only extremely weak donors.[71]

The relative intensity of the carbonyl stretching frequencies was neither concentration dependent in CO nor in complex **4**. It was not dependent on the nature of the NR^2 groups. Rather, the preferred species was dictated by the nature and the size of the calixarene OR^1 groups.[72] This suggests that the major and minor species correspond to different conformational isomers. Indeed, geometrical differences as a result of subtle changes in the steric demand on the ligand are observable in the ^1H NMR spectra (Figure 1). Among the remarkable differences are:

- The ethoxy compounds **4c, d** exhibit narrower peaks than **4a, b**.
- In **4c, d**, the difference in chemical shifts between both sets of *t*Bu groups or phenyl protons ($\Delta\delta = 0.65$ ppm and 0.85 ppm, respectively) is more important than for **4a, b** ($\Delta\delta \approx 0.30$ and 0.35 ppm, respectively).
- The NMe or NEt resonances are shifted upfield in the ethoxy compounds **4c, d** compared to the methoxy compounds **4a, b**.

Variable-temperature ^1H NMR study: We have conducted low-temperature ^1H NMR studies. Once again, two very different behaviors were observed.

In the ethoxy family **4c, d**, the C_3 symmetry of the molecule was retained as the solutions were cooled (Figure 2). The $ArCH_2Ar$ doublets, as well as the OCH_2Im and H_{Ar} singlets were split into pairs of equal intensity, whereas the other

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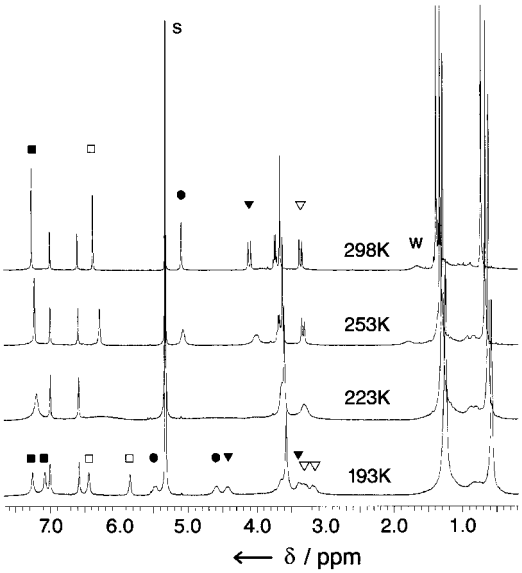
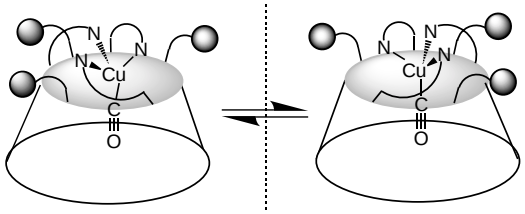


Figure 2. Variable-temperature ^{1}H NMR spectra of **4c** in CD_2Cl_2 at 400.13 MHz. [A similar behavior was observed for **4d** (data not shown)]. From all the coalescence processes, an enantiomerization barrier of 9.2(2) kcal mol^{-1} was determined from the relationship[82] $k_c = 2.22\sqrt{\delta\nu^2 + 6J^2}$AB. H_{Ar}: ■□; OCH_2Im: ●; $ArCH_{ax}H_{eq}Ar$: ▼; $ArCH_{ax}H_{eq}$-Ar: ▽. Solvent and water are labeled "s" and "w", respectively.

peaks were not. As previously described for the related pyridine-based system,[73] these complexes can exist as a pair of enantiomers that are in conformational equilibrium. The interconversion between them, fast at room temperature, becomes slower than the NMR time scale at $-80\,^\circ$C. In this situation of slow exchange, the ^{1}H NMR spectroscopy distinguishes the diastereotopic protons corresponding to one helical enantiomer. Nondiastereotopic protons, that is the imidazolyl, R^1, R^2, *t*Bu groups, were almost unaffected by temperature changes. Hence, the main exchange phenomenon that affects this system was the interconversion between two enantiomeric helices, a process that respects the C_3 symmetry (Scheme 2).



Scheme 2. Enantiomeric equilibrium for complexes **4c, d** (R^1 = Et) (conformation **A**).

The methoxy family **4a, b** family displayed a completely different ^{1}H NMR pattern at low temperatures (Figure 3). As the temperature decreased, most peaks started to broaden. This shows that the whole molecule was involved in the observed exchange phenomenon. Interestingly, however, the phenyl and *t*Bu groups were influenced more than the imidazole protons. This indicates that the dynamic exchange affected the calixarene skeleton more than the coordination

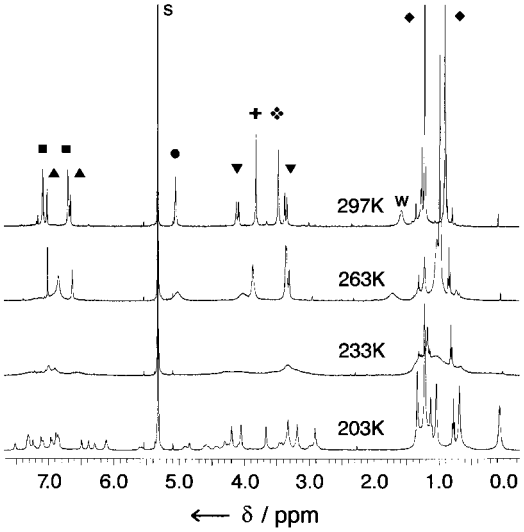


Figure 3. Variable-temperature ^{1}H NMR spectra of **4a** in CD_2Cl_2 at 400.13 MHz.[A similar behavior was observed for **4b** (data not shown)]. H_{Ar}: ■; H_{Im}: ▲; OCH_2Im: ●; NCH_3: +; OCH_3 ❖; $ArCH_{ax}H_{eq}Ar$: ▼; *t*Bu: ◆. Solvent and water are labeled "s" and "w", respectively.

core. A well-defined spectrum was obtained at $-70\,^\circ$C. Assignment of the resonances was made on the basis of 2D-COSY, NOESY, EXSY and saturation-transfer experiments. Three distinct peaks were assigned to the OMe groups (δ = 2.86, 3.19, 3.67), as well as for NMe (δ = 3.33, 4.05, 4.20). The $ArCH_2Ar$ protons were represented by twelve doublets, the *t*Bu groups by five singlets, (one accounted for 18 protons, the others for 9 each), etc. Interestingly, one *t*Bu group (δ = 0.07) and one NOESY-correlated phenyl proton (δ = 4.84) were shifted upfield compared to the others. This indicates that a *t*Bu group is partially included in the empty space left by the small CO ligand in the π-basic calixarene cavity. Exchange experiments conducted at $-70\,^\circ$C showed correlations between all groups of protons that were equivalent at 25 °C (Figure 4). Hence, the C_3 symmetry observed at room

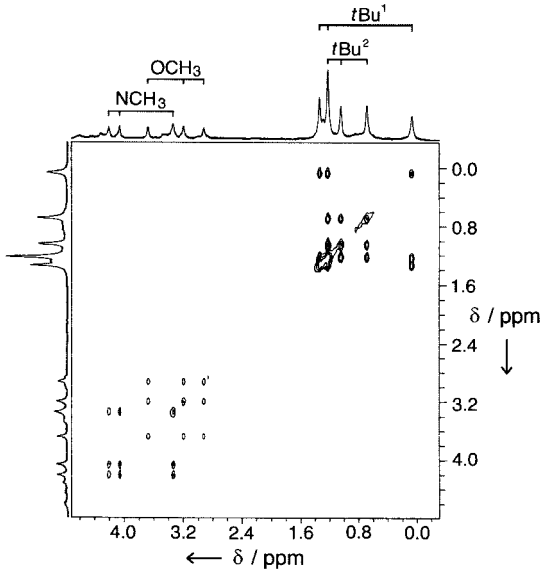
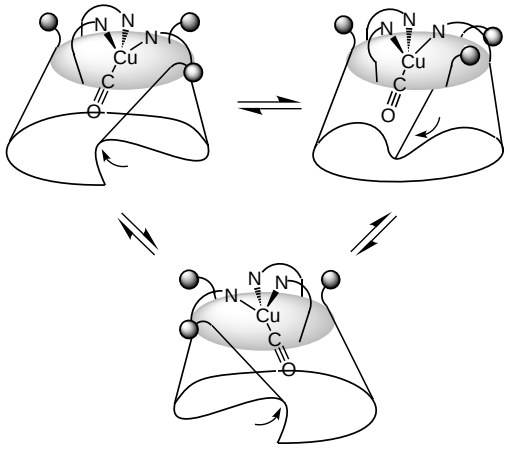


Figure 4. Selected area of the 2D-EXSY spectrum obtained for complex **4a** in CD_2Cl_2 at $-70\,^\circ$C.[55]

temperature was merely a pseudosymmetry that resulted from a fast internal *t*Bu exchange that averaged three dissymmetrical but equivalent conformations (Scheme 3). On the other hand, no EXSY correlation was observed between the sets of axial and equatorial methylene protons of the calixarene skeleton, which exchanged only 6 by 6. In this system, as in the former one, the cone inversion was inhibited, at least on the time scale of these NMR experiments.



Scheme 3. Dynamic behavior of complexes **4a, b** ($R^1 = Me$) (conformation **B**).

In conclusion, two different conformations (**A** and **B**) are accessible to Cu–CO complexes **4**. Conformation **A** is a flattened cone with the *t*Bu groups pointing alternatively *in* and *out* of the calixarene cavity. It presents a C_3 symmetry and the corresponding helical enantiomers are in conformational equilibrium with each other (Scheme 2). On the other hand, in conformation **B**, the partial inclusion of one *t*Bu group breaks the symmetry of the system, which now wobbles in between three equivalent conformations (Scheme 3). Whereas the ethoxy compounds **4c, d** preferentially adopt conformation **A**, the methoxy compounds **4a, b** prefer conformation **B**. In both cases, however, all conformers coexist as shown by the presence of two IR carbonyl stretching bands for each compound and minor peaks on the NMR spectra of the methoxy compounds **4a, b** that could account for conformation **A** (see Figure 1).

Discussion

CuCO complexes: CO is a well known ligand for cuprous ions and has been used to characterize the Cu^I state in proteins. Since they present a poly(imidazole) binding site, many N_xCuCO model complexes ($x = 2-4$) have been studied.

In proteins that contain a tris(imidazole) coordination core for the cuprous center, such as hemocyanins,[37] amine oxidases,[39] peptidylglycine monooxygenase,[38] cytochrome *c* oxidase,[43, 45] and other proteins belonging to the heme-copper family,[40–42, 44] the reported stretching frequency of the CO adducts[37–45] lie in the range 2043 – 2063 cm^{-1}. The only model complexes that exhibit such low values are those derived from nonchelating imidazoles (2059 – 2067 cm^{-1}),[68] or from the anionic tris(pyrazolyl)borate ligand.[57, 58, 62, 63] On the other hand, for complexes obtained with the neutral tris(imidazolyl)methoxymethane ($\nu_{CO} = 2080\ cm^{-1}$)[59] and tris(imidazolyl)phosphane ($\nu_{CO} = 2083 - 2086\ cm^{-1}$)[60] tripods, the CO stretches are more energetic. Complexes **4**, although structurally very similar to the biological systems, display ν_{CO} values that are $\approx 40\ cm^{-1}$ higher. Since the presence of a *N* substituent does not greatly influence the value of ν_{CO},[68] a possible explanation lies in the geometrical constraint. Indeed, a chelating system cannot optimize the orbital overlap between the ligating nitrogens and the metal as a free system does. The lower the $N-\sigma$ donation is, the smaller the π-back donation from Cu^+ to CO and the weaker the Cu–(CO) bond strength. This hypothesis is substantiated by the comparison between [(1,2-dimethylimidazole)$_3$CuCO] (2062 cm^{-1}),[68] **4a, b** (2092 cm^{-1}) and **4c, d** (2102 cm^{-1}). Whereas the ligand electronic properties are a priori equivalent, the series expands for almost all the range reported for N_3CuCO complexes, following a decrease in structural freedom. The more flexible **4a, b** allows the metal to adopt a better geometry for the CO binding than in **4c, d**.

These observations allow us to propose an explanation for the inertness of the tris(pyridine) calixarene-based copper(I) complex toward CO. Indeed, pyridine being a lower σ donor and better π acceptor than imidazole, the corresponding CuCO adducts are less stable. The [tris(2-picoline)Cu(CO)] complex presents a stretch ($\nu_{CO} = 2085\ cm^{-1}$)[68] at a higher frequency than its imidazole analogue. Again, ν_{CO} increases for a chelating system, such as tris(pyridyl)methoxymethane tripods (2093 – 2102 cm^{-1}).[61] With the calixarene-based ligand, the expected increase of 40 cm^{-1} relative to 2-picoline, as a result of steric constraint, would give values ($> 2125\ cm^{-1}$) that could only account for a very weak Cu–(CO) bond.

Finally, the shift of the CO stretches from conformation **A** to conformation **B** is indicative of a relationship between the geometry at the metal center and the cavity. The geometrical distortion in conformation **B** is transmitted from the lower rim to the ligating tripod and allows a stronger binding of CO. This is an interesting example of geometrical control, not only through covalent pre-organization, but also by weak interactions within the hydrophobic pocket.[74]

Conformations and molecular modeling: The calixarene structure obviously plays a major role in the properties of our complexes. The helical C_3-symmetrical conformation adopted by the ethoxy complexes **4c, d** is characterized by a pronounced alternate *in*/*out* position of the phenoxyl units, thus offering a flat and relatively closed cavity. As shown by the NMR studies, the OR^1 groups are pushed far away from the coordination core. This drives the corresponding *t*Bu-phenoxyl to bend into the *in* position relative to the calixarene cavity. The three other *t*Bu groups related to the nitrogenous arms are thus repelled into the *out* position. Previous molecular modeling experiments on other calixarene-based complexes[73, 75] led to a good agreement with the crystal structures obtained by X-ray analysis.[28, 76] Therefore, we

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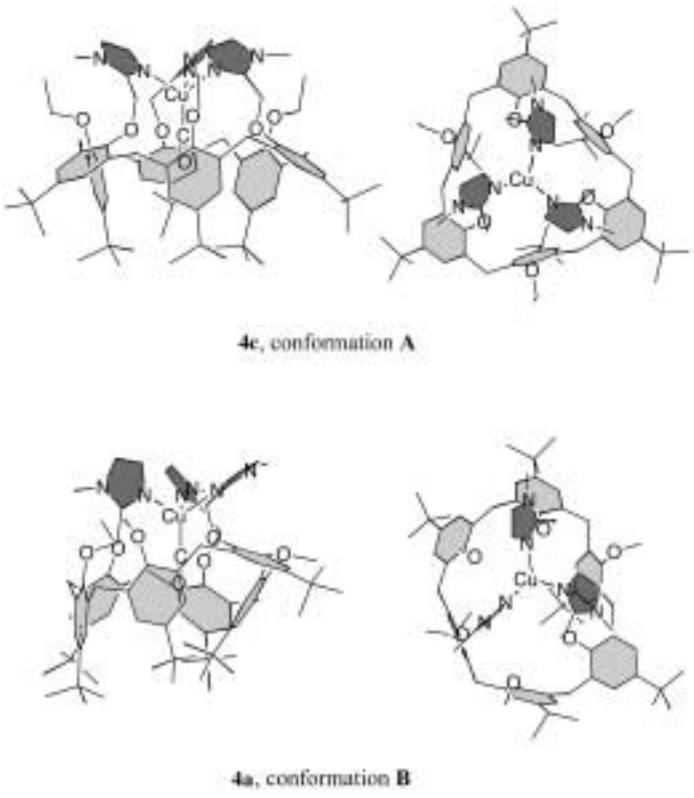

Figure 5. Energy-minimized structures of **4**. Left: viewed from the side; right: viewed from above.[77]

have G conducted calculations for compounds **4**.[77] Figure 5 (top) displays the conformation of lowest energy that was found for all of them. This model agrees with conformation **A**, which is preferentially adopted by the ethoxy compounds **4c, d**. For the methoxy compounds **4a, b** it was possible to locate an extra conformation that is dissymmetric and has an energy comparable to conformation **A** ($\Delta E_{cf} = 1 - 1.5$ kcal mol^{-1}). In agreement with conformation **B** described in Scheme 3, the computed model displayed in Figure 5 (bottom) shows the partial inclusion of one *t*Bu in the π cavity of the calixarene and two OMe substituents that are close to the coordination core. Interestingly, this new conformation did not correspond to a minimum of energy for **4c, d**. This is most likely to result from the steric repulsion between the OEt groups and the coordination site, which drives compounds **4c, d** to prefer conformation **A** where the OEt/core interaction is minimized.[78] Lastly, conformations that present the apical CO ligand outside of the calixarene cavity have also been explored and ruled out because of their much higher energies ($\Delta E_{cf} > 40$ kcal mol^{-1}).

Dynamics: The ethoxy complexes **4c, d**, for which conformation **A** is the most stable, mainly exist as pairs of enantiomers whose interconversion can be frozen on the NMR time scale at low temperature. The chirality of the related calixarene-based tris(pyridine)Cu^{I} complexes was previously observed in solution in the specific case of an anionic guest, Cl^-.[73] With the neutral MeCN ligand, the former system did not show any diastereotopic splitting of the proton resonances, even at low temperature. Hence, the results obtained with the imidazole-based system may be considered as a new step toward chiral recognition, even if the interconversion activation energy is still too low to allow separation of enantiomers.

The major conformation adopted by the methoxy complexes **4a, b** is totally dissymmetric, in spite of the linearity of the guest molecule, CO, which is compatible with the symmetry of the host. There are previously reported examples of cuprous complexes based on C_3 facial-capping N_3 ligands that display a seemingly symmetric NMR spectrum,[59, 61–63, 79] whereas X-ray analysis revealed a dissymmetric structure.[80] This was related either to the bulkiness of a good ligand, such as PPh_3, that prevents coordination of one nitrogenous arm, or to the formation of dimeric structures which result from the lack of a fourth exogeneous coordinating molecule. In these cases, fast exchange as a result of the labile cuprous ion accounted for the apparent symmetry observed in solution for three-coordinate species. Our case is different. The dynamics of the system are not directly related to the Cu^+ coordination sphere, but to supramolecular effects that arise from the necessary filling of the calixarene cavity. The four-coordinate methoxy complexes **4a, b** alternate between three equivalent dissymmetric conformations, thereby displaying a motion that resembles a three-step waltz.

Conclusions

Few biomimetic complexes have combined a metal ion and a hydrophobic cavity.[13] Supramolecular models, however, are very important for the detailed understanding of the functioning of natural systems. Recognition mechanism, chemoselectivity, and allosteric control are indeed monitored by the interaction of the substrate with the protein.

We have described the synthesis of a series of novel calix[6]arene-based Cu^{I} complexes with a systematic variation of the ligand skeleton. As in their biological models, the cuprous ion is coordinated to a neutral tris(imidazole) core and combines a structural role with the binding of an exogenous molecule. Contrary to the tris(pyridine) analogues,[28] stable mononuclear tetrahedral complexes are obtained upon coordination of CO. This emphasizes that important electronic differences do exist between imidazole and pyridine. The calixarene structure also plays a major role in the properties of our complexes. It provides a hydrophobic cavity around the apical binding site, into which an exogenous ligand can enter. We previously showed that the conical pocket could influence the conformation of the included guest molecule for the optimized filling of the cavity.[76] Here, because the CO ligand is not big enough to fill the pocket, the calixarene can auto-include one of its *t*Bu groups. This process is controlled by the size of the O substituents (R^1): if it is bulky (ethyl rather than methyl), a symmetrical conformation (**A**) is preferred. Hence, the complexes behave as two distinct families (methoxy **4a, b** and ethoxy **4c, d**) which possess different dynamic properties. The resulting differences in the steric demand also induced significant modifications of the electronic properties of the metal center. Interestingly, the accountable small ligand change (**2a, b** versus **2c, d**) occurs relatively far away from both the cavity and the metal ion. The

calixarene structure conveys the conformational modifications from one end of the molecule to the other. This supramolecular behavior, promoted by the strong conformational coupling between the metal center and the host structure, is reminiscent of allosteric effects common in biological systems, such as protein folding or substrate binding.[38, 39, 43, 45, 81] Furthermore, as in copper proteins, the vibrational spectrum of the bound CO revealed it to be a sensitive gauge of the coordination structure of the Cu^+ ion.[74]

Finally, this work provides a nice example of conformational assignment for host–guest complexes in solution. Knowledge of the relative orientation of the host–guest structures in complexes, particularly when weak noncovalent interactions operate, is important for the development of functional supramolecular materials, such as those for catalytic or analytical purposes.

Experimental Section

General procedures: All solvents and most reagents were obtained commercially. DMF was stored over 4 Å molecular sieves under argon. THF was distilled over sodium/benzophenone under argon. ^{1}H and ^{13}C NMR spectra were recorded either on a Bruker Avance 400 or on a Bruker AC 200 spectrometer. Standard HMQC and HMBC experiments were used for peaks assignments.[55] Traces of residual solvent were used as an internal standard. Exchange experiments (NOESY and EXSY) were recorded with $\tau_m = 300$ ms. Solution (chloroform) IR spectra were obtained on a Bomen MB 100 FTIR spectrometer equipped with a InSb detector and a Spectratech ultramicro cavity (1 mm). Solid state measurements (KBr pellets) were carried on a Perkin–Elmer 783 IR spectrophotometer. Elemental analyses were performed at the Institut de Chimie des Substances Naturelles (France). For this purpose, the products where dried for at least one night under vacuum at 60–70 °C.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-triethoxycalix[6]aren-38,40,42-triol (1, R = OEt): This compound was obtained by a modification of a previously described synthesis[50]: *tert*-butylcalix[6]arene[48] (5 g, 5.15 mmol), K_2CO_3 (2.13 g, 15.5 mmol), EtI (1.65 mL, 20.6 mmol), and acetone (375 mL) were stirred for 48 h at 70 °C in a 500 mL round glass flask, with thick walls, and firmly closed with a screw cap. Potassium acetate (2.4 g, 24.5 mmol) was then added to the mixture, which was stirred for 30 min before removal of the solvent under reduced pressure. The residual solid was dissolved in chloroform (400 mL) and washed with 10% aq. HCl. The aqueous phase was further extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic phases were washed with water (2 × 200 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was finally chromatographed (silica gel, CH_2Cl_2/AcOEt 995/5; $R_f = 0.37$) to give the desired tris(ethylated) calixarene as a white solid. Yield = 33%; m.p. 162 °C.

General procedure for the synthesis of ligands 2: All ligands **2** were obtained by reacting **1** (R = OMe[49] or R = OEt[50]) with either 2-chloromethyl-1-methyl-*1H*-imidazole[51] or 2-chloromethyl-1-ethyl-*1H*-imidazole[52] in the presence of excess NaH in a THF/DMF mixture. The experimental procedures were the same as previously described[76] for ligand **2a**. Quantities, yields and characterizations are given below.

Synthesis of 5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-triethoxy-38,40,42-tris[(1-methyl-2-imidazolyl)methoxy]calix[6]arene (2c): Compound **1** (R = Et; 500 mg, 0.47 mmol), NaH (60% in oil, washed with pentane, 600 mg, 15.0 mmol), and 2-chloromethyl-1-methyl-*1H*-imidazole hydrochloride (950 mg, 5.7 mmol). Yield 90%. For microanalysis purposes, the product was filtered on silica gel (CH_2Cl_2/MeOH 9/1, $R_f = 0.4$). M.p. 175 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$, 298 K; only the prominent peaks are given): $\delta = -0.38$, 0.46, 0.83, 0.97, 1.00, 1.29, 2.94, 3.34, 3.79, 4.30, 4.34, 4.94, 6.69, 6.99, 7.14. The relative intensities of the regions: $\delta = \{-0.38$ to 2.4$\}$, $\{2.8–5.2\}$, $\{6.5–7.2\}$ are 21:7:4; ^{13}C NMR (100.6 MHz): $\delta = 29.7–34.1$, 122.1, 127.8, 133.2, 143.4, 146.0; IR (KBr): $\tilde{\nu} = 1605$, 1587, 1480, 1418, 1365, 1289, 1200, 1120, 1040, 990, 738 cm^{-1}; $C_{87}H_{114}O_6N_6 \cdot 2$MeOH (1404): calcd: C 76.14, H 8.76, N 5.99; found: C 76.31, H 8.58, N 5.51.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris[(1-ethyl-2-imidazolyl)methoxy]calix[6]arene (2b): Compound **1** (R = Me; 1.0 g, 0.98 mmol), NaH (60% in oil, washed with pentane; 1.15 g, 29 mmol), and 2-chloromethyl-1-ethyl-*1H*-imidazole hydrochloride (1.02 g, 5.9 mmol). Yield 97%. The product could be further purified by recrystallization from hot acetonitrile. M.p. 260 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$, 298 K): $\delta = 0.77$ (s, 27H; tBu^2), 1.38 (s, 27H; tBu^1), 1.53 (t, ^3J(H,H) = 7.3 Hz, 9H; NCH_2CH_3), 2.11 (s, 9H; OCH_3), 3.24 (d, ^2J(H,H) = 15.2 Hz, 6H; Ar-αCH_{eq}), 4.27 (q, ^3J(H,H) = 7.3 Hz, 6H; NCH_2CH_3), 4.46 (d, ^2J(H,H) = 15.2 Hz, 6H; Ar-αCH_{ax}), 5.01 (s, 6H; Im-αCH_2), 6.62 (s, 6H; ArH^2), 6.98 (d, ^3J(H,H) = 1.0 Hz, 3H; ImH), 6.99 (d, ^3J(H,H) = 1.0 Hz, 3H; ImH), 7.24 (s, 6H; ArH^1); ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): $\delta = 16.5$ (NCH_2CH_3), 29.5 (Ar-αCH_2), 31.1 ($C^2(CH_3)_3$), 31.7 ($C^1(CH_3)_3$), 33.8 ($C^2(CH_3)_3$), 34.1 ($C^1(CH_3)_3$), 41.4 (NCH_2CH_3), 60.0 (OCH_3), 66.9 (Im-αCH_2), 120.0 (C_{Im}H), 123.6 (C^2_{Ar}H), 128.1 (C_{Im}H and C^1_{Ar}H), 133.0 (C_{Ar}-CH_2), 133.6 (C_{Ar}-CH_2), 143.7 (C_{Im}), 145.9 (C^2_{Ar}), 146.2 (C^1_{Ar}), 151.4 (C^2_{Ar}-OCH_2-Im), 154.3 (C^1_{Ar}-OMe); IR (KBr): $\tilde{\nu} = 3660$, 3560, 3410 (H_2O),1608, 1587, 1489, 1367, 1295, 1200, 1018, 990, 752 cm^{-1}; $C_{87}H_{114}O_6N_6 \cdot 1.5H_2O$ (1367): calcd: C 76.45, H 8.63, N 6.15; found: C 76.46, H 8.42, N 6.14.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-triethoxy-38,40,42-tris[(1-ethyl-2-imidazolyl)methoxy]calix[6]arene (2d): 1 (R = Et; 0.80 g, 0.75 mmol), NaH (60% in oil, washed with pentane; 0.70 g, 2.9 mmol), and 2-chloromethyl-1-ethyl-*1H*-imidazole hydrochloride (1.05 g, 5.8 mmol). This yields 95% of a white product that can be further purified by filtration on silica gel (CH_2Cl_2/MeOH 9/1; $R_f = 0.7$). M.p. 155 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$, 298 K): $\delta = 0.37$ (br, 9H; OCH_2CH_3), 0.80 (s, 27H; tBu^2), 1.32 (s, 27H; tBu^1), 1.50 (t, ^3J(H,H) = 7.3 Hz, 9H; NCH_2CH_3), 2.85 (br, 6H; OCH_2CH_3), 3.34 (d, ^2J(H,H) = 14.7 Hz, 6H; Ar-αCH_{eq}), 4.22 (q, ^3J(H,H) = 7.3 Hz, 6H; NCH_2CH_3), 4.35 (d, ^2J(H,H) = 14.7 Hz, 6H; Ar-αCH_{ax}), 4.86 (s, 6H; Im-αCH_2), 6.67 (br, 6H; ArH^2), 6.98 (s, 3H; ImH), 7.02 (s, 3H; ImH), 7.19 (s, 6H; ArH^1); ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): $\delta = 14.5$ (OCH_2CH_3), 16.6 (NCH_2CH_3), 30.1 (Ar-αCH_2), 31.3 ($C^2(CH_3)_3$), 31.7 ($C^1(CH_3)_3$), 34.0 ($C^2(CH_3)_3$), 34.2 ($C^1(CH_3)_3$), 41.3 (NCH_2CH_3), 66.9 (Im-αCH_2), 68.2 (OCH_2CH_3), 119.9 (C_{Im}H), 124.0 (C^2_{Ar}H), 127.9 (C_{Im}H), 128.3 (C^1_{Ar}H), 133.1 (C_{Ar}-CH_2), 133.2 (C_{Ar}-CH_2), 144.0 (C_{Im}), 145.0 (C^2_{Ar}), 145.8 (C^1_{Ar}), 151.5 (C^2_{Ar}-OCH_2-Im), 153.2 (C^1_{Ar}-OEt); IR (KBr): $\tilde{\nu} = 1608$, 1590, 1470, 1200, 1038, 992, 736 cm^{-1}; $C_{90}H_{120}O_6N_6 \cdot$MeOH (1414): calcd: C 77.30, H 8.84, N 5.94; found: C 77.79, H 8.89, N 5.47.

General procedure for the synthesis of complexes 3 Under an argon atmosphere, dry THF (2 mL) was added to a flask containing the ligand (**2**, 100 mg) and a stoichiometric amount of $[Cu(NCMe)_4]PF_6$. After 1–4 h, either a white precipitate spontaneously appeared or pentane (5 mL) was added to induce precipitation of the product. The solid was then separated from the solvent, washed with pentane (2 × 2 mL), and dried under vacuum. The yield was 80–90%.

3a (R^1 = Me, R^2 = Me): M.p. > 260 °C (decomp); IR (KBr): $\tilde{\nu} = 3650$, 3560, 3480, 3410 (H_2O), 1605, 1587, 1485, 1460, 1420, 1398, 1365, 840 (PF_6^-), 565 (PF_6^-) cm^{-1}; $C_{84}H_{108}O_6N_6CuPF_6 \cdot 3H_2O$ (1560): calcd: C 64.66, H 7.36, N 5.39; found: C 64.69, H 7.21, N 5.69;

3b (R^1 = Me, R^2 = Et): M.p. > 260 °C (decomp); ^{1}H NMR (200.13 MHz, $CDCl_3$, 298 K): $\delta = 0.79$ (s, 27H; tBu), 1.16 (br, 36H; tBu and NCH_2CH_3), 1.91 (br, 9H; OCH_3), 3.35 (br, 6H; Ar-αCH_{eq}), 4.14 (br, 6H; NCH_2CH_3), 4.51 (br, 6H; Ar-αCH_{ax}), 5.05 (s, 6H; Im-αCH_2), 6.65 (s, 6H; ArH), 7.00 (br, 6H; both ImH), 7.17 (br, 6H; ArH); IR (KBr): $\tilde{\nu} = 3650$, 3560, 3480, 3415 (H_2O), 1608, 1588, 1488, 1368, 1300, 1200, 1122, 1010, 845 (PF_6^-), 565 (PF_6^-) cm^{-1}; $C_{87}H_{114}O_6N_6CuPF_6 \cdot 2H_2O$ (1584): calcd: C 65.95, H 7.51, N 5.30; found: C 65.51, H 7.39, N 5.45.

3c (R^1 = Et, R^2 = Me): M.p. > 260 °C (decomp); IR (KBr): $\tilde{\nu} = 3660$, 3560, 3490, 3415 (H_2O), 1608, 1590, 1485, 1368, 1295, 1200, 1035, 845 (PF_6^-), 565 (PF_6^-) cm^{-1}; $C_{87}H_{114}O_6N_6CuPF_6 \cdot$THF $\cdot H_2O$ (1634): calcd: C 66.71, H 7.62, N 5.13; found: C 66.45, H 7.28, N 4.98.

3d (R^1 = Et, R^2 = Et): M.p. > 260 °C (decomp); IR (KBr): $\tilde{\nu} = 3650$, 3565, 3480, 3415 (H_2O), 1607, 1588, 1470, 1368, 1300, 1200, 1120, 1040, 845 (PF_6^-), 565 (PF_6^-) cm^{-1}; $C_{90}H_{120}O_6N_6CuPF_6 \cdot 2H_2O$ (1626): calcd: C 66.46, H 7.68, N 5.17; found: C 66.44, H 7.55, N 5.25.

Formation and characterization of CO adducts 4: In an NMR tube, complexes **3** were weighed (≈10 mg) and solvent added (either $CDCl_3$ or CD_2Cl_2). CO gas was then bubbled through the solution for two minutes. In the specific case of **3a**, which was only poorly soluble, introduction of CO induced an almost instantaneous dissolution of the complex to give **4a**.

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Conversely, bubbling argon through a solution of **4a** caused rapid precipitation of **3a**.

4a (R^1 = Me, R^2 = Me): ^{1}H NMR (400.13 MHz, $CDCl_3$, 297 K): δ = 0.89 (s, 27H; *t*Bu^1), 1.21 (s, 27H; *t*Bu^2), 3.31 (d, ^2J(H,H) = 14.8 Hz, 6H; Ar-αCH_{eq}), 3.48 (s, 9H; OCH_3), 3.83 (s, 9H; NCH_3), 4.12 (d, ^2J(H,H) = 14.8, Hz 6H; Ar-αCH_{ax}), 5.04 (s, 6H; Im-αCH_2), 6.65 (s, 3H; ImH), 6.77 (s, 6H; ArH^1), 7.03 (s, 3H; ImH), 7.06 (s, 6H; ArH^2); ^{1}H NMR (400.13 MHz, CD_2Cl_2, 203 K): δ = 0.07, 1.22, 1.33 (s, 9H each; *t*Bu^2), 0.68, 1.04, 1.22 (s, 9H each; tBu^1), 2.86, 3.19, 3.67 (s, 3H each; OCH_3), 3.33, 4.05, 4.20 (s, 3H each; NCH_3), 2.90/3.32, 3.00/3.40, 3.18/4.42, 3.32/4.08, 3.44/4.27, 3.44/4.57 (br, 1H each; Ar-αCH_{eq}/Ar-αCH_{ax}), 5.59/6.11, 4.91/4.60, 4.29/4.29 (br, 1H each; Im-αCH/Im-αCH),4.84, 6.29, 6.85, 7.23, 7.31, 7.31 (s, 1H each; ArH^2), 6.11, 6.85, 6.94, 7.08, 7.31, 7.51 (s, 1H each; ArH^1), 6.38, 6.49, 6.78 (s, 1H each; ImH), 6.85, 6.96, 7.11 (s, 1H each; ImH); ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): δ = 29.5 (Ar-αCH_2), 31.4 (C(C^1H_3)$_3$), 31.5 (C(C^2H_3)$_3$), 34.0 ($C^1(CH_3)_3$), 34.2 ($C^2(CH_3)_3$ and NCH_3), 61.0 (OCH_3), 66.1 (Im-αCH_2), 122.1 (C_{Im}H), 124.1 (C^1_{Ar}H), 127,5 (C^2_{Ar}H), 127.9 (C_{Im}H), 132.0 (C_{Ar}-CH_2), 132.6 (C_{Ar}-CH_2), 145.7 (C^1_{Ar}-*t*Bu), 145.9 (C_{Im}), 146.2 (C^2_{Ar}-*t*Bu), 152.8 (C^1_{Ar}-OMe), 153.7 (C^2_{Ar}-OCH_2).

4b (R^1 = Me, R^2 = Et): ^{1}H NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 0.94 (s, 27H; *t*Bu^1), 1.16 (s, 27H; *t*Bu^2), 1.49 (t, ^3J(H,H) = 7.2 Hz, 9H; NCH_2CH_3), 3.32 (d, ^2J(H,H) = 14.8 Hz, 6H; Ar-αCH_{eq}), 3.44 (s, 9H; CH_3), 4.14 (d, ^2J(H,H) = 14.8 Hz, 6H; Ar-αCH_{ax}), 4.22 (q, ^3J(H,H) = 7.2 Hz, 6H; NCH_2CH_3), 5.08 (s, 6H; Im-αCH_2), 6.61 (s, 3H; ImH), 6.75 (s, 6H; ArH^1), 7.01 (s, 6H; ArH^2), 7.09 (s, 3H; ImH).

4c (R^1 = Et, R^2 = Me): ^{1}H NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 0.73 (s, 27H; *t*Bu^1), 1.32 (t, ^3J(H,H) = 7.0 Hz, 9H; OCH_2CH_3), 1.37 (s, 27H; *t*Bu^2), 3.70 (d, ^2J(H,H) = 15.2 Hz, 6H; Ar-αCH_{eq}), 3.67 (s, 9H; NCH_3), 3.72 (q, ^3J(H,H) = 7.0 Hz, 6H; OCH_2CH_3), 4.13 (d, ^2J(H,H) = 15.2 Hz, 6H; Ar-αCH_{ax}), 5.06 (s, 6H; Im-αCH_2), 6.37 (s, 6H; ArH^1), 6.57 (s, 3H; ImH), 7.00 (s, 3H; ImH), 7.23 (s, 6H; ArH^2); ^{1}H NMR (400.13 MHz, CD_2Cl_2, 193 K): δ = 0.57 (s, 27H; *t*Bu), 0.73 (br, 9H; OCH_2CH_3), 1.24 (s, 27H; *t*Bu), 3.19 and 3.40 (br d, 3H each; Ar-αCH_{eq}), 3.31 and 4.42 (br d, 3H each; Ar-αCH_{ax}), 3.57 (s, 9H; NCH_3), 3.65 (br, 6H; OCH_2CH_3), 4.59 and 5.47 (br, 3H each; Im-αCH_2), 5.84 and 6.44 (s, 3H each; ArH), 6.58 (s, 3H; ImH), 7.00 (s, 3H; ImH), 7.08 and 7.26 (s, 3H each; ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): δ = 16.1 (OCH_2CH_3), 30.3 (Ar-αCH_2), 31.3 (C(C^1H_3)$_3$), 31.6 (C(C^2H_3)$_3$), 33.8 ($C^1(CH_3)_3$), 34.0 (NCH_3), 34.3 ($C^2(CH_3)_3$), 64.8 (Im-αCH_2), 68.5 (OCH_2CH_3), 121.8 (C_{Im}H), 122.7 (C^1_{Ar}H), 128.1 (C_{Im}H), 128.2 (C^2_{Ar}H), 131.7 (C_{Ar}-CH_2), 132.6 (C_{Ar}-CH_2), 145.3 (C^1_{Ar}-*t*Bu), 146.0, 146.2 (C_{Im} and C^2_{Ar}-*t*Bu), 151.8 (C^1_{Ar}-OEt), 154.7 (C^2_{Ar}-OCH_2Im).

4d (R^1 = Et, R^2 = Et): ^{1}H NMR (400.13 MHz, $CDCl_3$, 298 K): δ = 0.73 (s, 27H; *t*Bu^1), 1.28 (t, ^3J(H,H) = 6.6 Hz, 9H; OCH_2CH_3), 1.38 (s, 27H; *t*Bu^2), 1.40 (t, ^3J(H,H) = 7.2 Hz, 9H; NCH_2CH_3), 3.31 (d, ^2J(H,H) = 15.2 Hz, 6H; Ar-αCH_{eq}), 3.71 (q, ^3J(H,H) = 6.6 Hz, 6H; OCH_2CH_3), 4.03 (q, ^3J(H,H) = 7.2 Hz, 6H; NCH_2CH_3), 4.15 (d, ^2J(H,H) = 15.2 Hz, 6H; Ar-αCH_{ax}), 5.08 (s, 6H; Im-αCH_2), 6.39 (s, 6H; ArH^1), 6.46 (s, 3H; ImH), 7.05 (s, 3H; ImH), 7.23 (s, 6H; ArH^2).

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[78] Considering that: 1) the calculated values are only steric energies, 2) we can admit an uncertainty of a few kcal mol^{-1}, 3) special effects, such as π stacking are not taken into account, these results are indicative of a more important steric crowding in conformation **B** for compounds **4c, d** than for **4a, b**, and not of inaccessible conformation **B** to family **4a, b**..
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