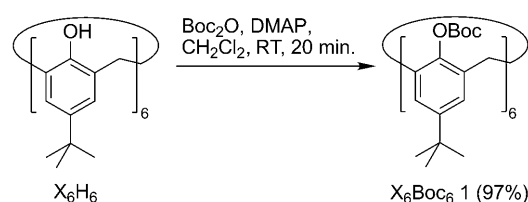


Induced-Fit Encapsulation by a 1,3,5-Alternate Calix[6]arene**

Mickaël Ménand, Axel Leroy, Jérôme Marrot, Michel Luhmer, and Ivan Jabin*

Calixarene-based building blocks are widely used for the elaboration of molecular receptors.^[1] Calixarenes are highly flexible, in contrast to other concave macrocyclic compounds such as cyclodextrins,^[2] cyclotrimeratrylenes,^[3] or resorcinarenes.^[4] The control of their conformation is thus crucial for the formation of receptors with well-defined cavities. Among the different oligomers, calix[4]arenes are the most developed since they are easily constrained in a cone or a 1,3-alternate conformation through the alkylation of their phenolic positions.^[5] Both conformations have proven to be powerful scaffolds for the elaboration of various host–guest systems.^[6] However, only rare examples describe the endo-complexation of organic guests by calix[4]arenes because of the smallness of their cavity.^[7] On the other hand, the larger calix[6]arenes are more difficult to constrain into a given conformation, since these oligomers display a higher flexibility because of the facile “through the annulus” ring inversion of their aromatic units.^[5] As a result, the parent *p*-*t*Bu-calix[6]arene (X_6H_6) is not able to complex organic guests. To date, strategies have been mostly developed for the rigidification of calix[6]arenes into the cone conformation since this conformation results in a concave hydrophobic pocket that is well-adapted to the binding of organic guests.^[8] However, seven other conformations, which differ in the *syn* or *anti* orientations of the aromatic units with respect to one another, are theoretically possible.^[9] While the partial cone,^[10] 1,2-alternate,^[11] 1,3-alternate,^[12] 1,4-alternate,^[13] and 1,2,3-alternate^[14] conformations are known, the 1,2,4-alternate and 1,3,5-alternate conformations have not been reported to date. The 1,3,5-alternate conformation is particularly attractive since it should display a highly symmetrical closed cavity and could constitute a useful platform for the introduction of two divergent functional domains in a spatially controlled manner.

Herein we describe the synthesis and host–guest properties of calix[6]hexa-Boc (X_6Boc_6) **1** (Boc = *tert*-butoxycarbonyl), which is the first calix[6]arene derivative reported to adopt such a 1,3,5-alternate conformation. Compound **1** was synthesized in high yield (97%) by following a standard procedure and thus can be easily obtained on a multigram scale from the commercially available X_6H_6 (Scheme 1).



Scheme 1. Synthesis of X_6Boc_6 **1**. DMAP = 4-dimethylaminopyridine.

Compound **1** is not soluble in most of the common organic solvents except CH_2Cl_2 and $Cl_2CHCHCl_2$. Single crystals were obtained by diffusion of Et_2O in a CH_2Cl_2 solution of **1** at 4 °C. X-ray diffraction analysis revealed a linear packing of calixarenes that display a 1,3,5-alternate conformation and encapsulate a CH_2Cl_2 molecule (Figure 1a).^[15] A detailed analysis based on the dihedral angles ϕ and χ ^[16] of these host–guest complexes $CH_2Cl_2@1$ indicates that two highly similar 1,3,5-alternate conformations of **1** are present in the same unit cell, and that both conformations accommodate a CH_2Cl_2 molecule. Indeed, besides the expected S_6 symmetrical conformation (**1**_{S6}: $\phi = \pm 100.2^\circ$ and $\chi = \pm 101.9^\circ$), a slightly

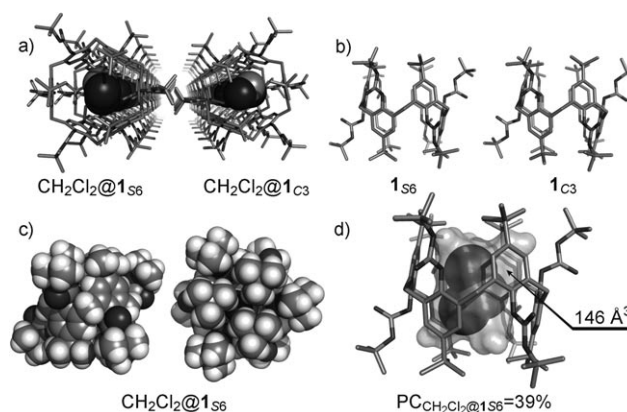


Figure 1. a) Perspective view of the crystal packing of $CH_2Cl_2@1_{S6}$ and $CH_2Cl_2@1_{C3}$ (H atoms and free CH_2Cl_2 molecules are omitted for clarity). b) Side views of the X-ray structures of **1**_{S6} and **1**_{C3} (H atoms omitted). c) Side and top views of the X-ray structure of $CH_2Cl_2@1_{S6}$. d) Side view of $CH_2Cl_2@1_{S6}$ (H atoms omitted) with transparent cavity surface.

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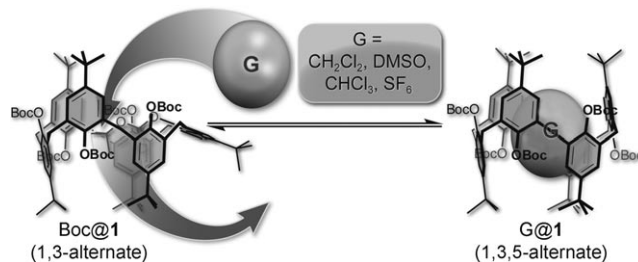
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distorted C_3 symmetrical conformation was observed ($\mathbf{1}_{C_3}$: $\phi = +97.8^\circ, -98.6^\circ$ and $\chi = +102.9^\circ, -102.4^\circ$).

Both conformations of the calixarene have a barrel shape that is closed at each extremity by the *p*-*tert*-butyl groups ($t\text{Bu}^{\text{Cal}}$). This shape arises from the *anti* relationship of all the aromatic units (Figure 1b). As a result, these two 1,3,5-alternate conformations of $\mathbf{1}$ behave as molecular capsules that completely surround their guest to form encapsulation complexes ($\text{CH}_2\text{Cl}_2 @ \mathbf{1}_{S_6}$, Figure 1c).^[17] The inner volumes estimated using GRASP software^[18] are $146 \text{ \AA}^3$ and $142 \text{ \AA}^3$ for $\mathbf{1}_{S_6}$ and $\mathbf{1}_{C_3}$, respectively^[19] ($\text{CH}_2\text{Cl}_2 @ \mathbf{1}_{S_6}$, Figure 1d), which correspond to solid-state packing coefficients (PCs) of 39% and 40% for the included CH_2Cl_2 molecule ($V_{\text{CH}_2\text{Cl}_2} = 57 \text{ \AA}^3$). It is noteworthy that these PCs are slightly less than the optimal value of $(55 \pm 9)\%$ described by Rebek and co-workers in the case of liquid-state molecular recognition.^[19]

NMR studies of $\text{X}_6\text{Boc}_6 \mathbf{1}$ were carried out in order to investigate if the 1,3,5-alternate conformation could be observed in solution. Firstly, when the ^1H NMR spectrum was recorded in 1,1,2,2-[D_2]tetrachloroethane ($\text{C}_2\text{D}_2\text{Cl}_4$), a solvent that is too large to be accommodated in the cavity, a complex NMR pattern with a high-field signal at $\delta = -1.61 \text{ ppm}$ was observed (Figure 2a). An HSQC experiment

1,3-alternate conformation (see insets in Figure 2a). This very rare conformation was further confirmed by ^{13}C NMR and HSQC experiments, which showed that one of the three pairs of equivalent ArCH_2Ar methylenic carbon atoms appears at a higher field ($\delta = 27 \text{ ppm}$) than the two other signals ($\delta = 34$ and 35 ppm).^[21] These values are consistent with *syn* and *anti* relationships respectively.^[13] Thus, all these results indicate that, in the absence of a suitable guest, $\text{X}_6\text{Boc}_6 \mathbf{1}$ adopts a 1,3-alternate conformation with a self-included $t\text{Bu}^{\text{Boc}}$ moiety ($\text{Boc} @ \mathbf{1}$, Scheme 2).^[24]



Scheme 2. Induced-fit encapsulation of neutral guests (G) by host $\mathbf{1}$.

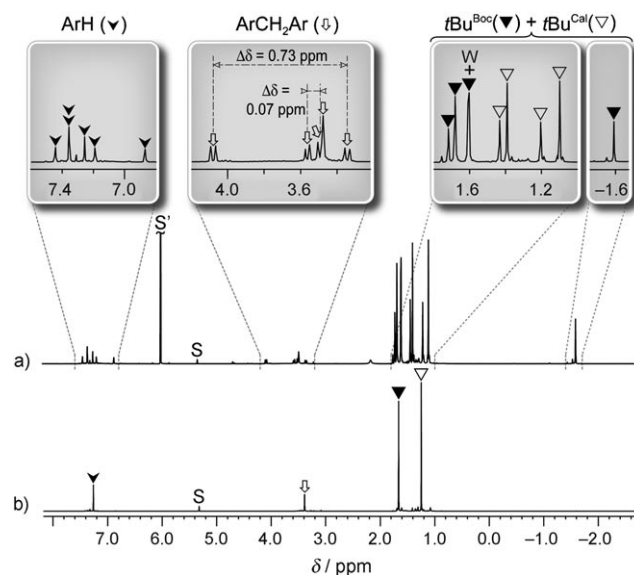


Figure 2. ^1H NMR spectra (600 MHz, 298 K) of $\text{X}_6\text{Boc}_6 \mathbf{1}$ a) in $\text{C}_2\text{D}_2\text{Cl}_4$ and b) in CD_2Cl_2 . The inset show the ArH, ArCH_2Ar , and $t\text{Bu}$ regions. W: water, S and S': residual solvents.

was used to assign this signal to a self-included $t\text{Bu}$ moiety of a Boc protecting group ($t\text{Bu}^{\text{Boc}}$).^[20,21] Surprisingly, the spectrum remained essentially unchanged at high temperature (358 K).^[22] The patterns of the $t\text{Bu}^{\text{Cal}}$ (1:2:2:1), $t\text{Bu}^{\text{Boc}}$ (1:2:2:1), and ArH (1:1:1:1:1:1) signals are characteristic of a C_s symmetrical conformation. Analysis of the ArCH_2Ar signals reveals the *syn/anti* relationships between the adjacent aromatic units.^[23] Hence, the 1:1:1:2:1 pattern that consist of two pairs of doublet signals: $\delta = 4.07/3.34$ ($^2J = 16 \text{ Hz}$, $\Delta\delta = 0.73 \text{ ppm}$, *syn*), $3.56/3.49 \text{ ppm}$ ($^2J = 14 \text{ Hz}$, $\Delta\delta = 0.07 \text{ ppm}$, *anti*), and a singlet signal ($\delta = 3.47 \text{ ppm}$, *anti*) agrees with a

The progressive addition of CD_2Cl_2 to a solution of $\mathbf{1}$ in $\text{C}_2\text{D}_2\text{Cl}_4$ led to the appearance and intensity increase of a set of four singlet signals in the ^1H NMR spectrum. These signals indicated the formation of a new, high-symmetry species in slow exchange with the introverted $\text{Boc} @ \mathbf{1}$.^[21] In pure CD_2Cl_2 , this new species was almost the only product observed (Figure 2b). This very simple pattern is highly consistent with the S_6 symmetrical 1,3,5-alternate conformation observed in the solid state. No broadening of the ArCH_2Ar signal was observed at low temperatures (from 298 K to 238 K),^[21] thus confirming that the singlet signal arises from an *anti* relationship of the aromatic units of $\mathbf{1}$ and not from a rapid conformational exchange on the NMR timescale. This impressive solvent-dependent conformational behavior is compatible with the encapsulation of dichloromethane through the ejection of the self-included $t\text{Bu}^{\text{Boc}}$, which led to the host–guest complex observed in the solid state (Scheme 2). Thus, to some extent, the aromatic unit that bears the self-included $t\text{Bu}^{\text{Boc}}$ group can be seen as a rotating molecular door that can control access to the cavity. This induced-fit process shows that the flexibility of calix[6]arenes can be advantageous as these hosts are able to dramatically change their conformation in order to bind a guest. Similarly, the addition of other neutral guests (G) with sizes that are a priori well-adapted to a cavity of approximately $145 \text{ \AA}^3$ (i.e., SF_6 , CDCl_3 , and $[\text{D}_6]\text{DMSO}$: PCs = 44, 50, and 54%, respectively) led to the corresponding S_6 symmetrical host–guest complexes $\text{G} @ \mathbf{1}$ (Scheme 2). In all cases, the “in and out” guest exchange was slow on the NMR timescale. The association constants K measured for the host–guest equilibria between $\text{Boc} @ \mathbf{1}$ and $\text{G} @ \mathbf{1}$ revealed weak interactions (i.e., $K = 0.07, 0.08, 0.8$, and 0.9 M^{-1} at 298 K for CDCl_3 , $[\text{D}_6]\text{DMSO}$, CD_2Cl_2 , and SF_6 respectively).^[21] Finally, the NMR spectrum of $\text{Boc} @ \mathbf{1}$ in $\text{C}_2\text{D}_2\text{Cl}_4$ was not affected by the addition of large amounts of smaller neutral molecules such as

CD₃OD, EtOH, or CD₃CN (PCs = 27, 34, and 34% respectively). Thus, host **1** shows remarkable size selectivity.

The recognition properties of host **1** toward guests of suitable size and able to develop additional noncovalent π -cationic interactions were investigated. When a solution of **1** in a 2:1 C₂D₂Cl₄/CD₃CN mixture was saturated with tetramethylammonium picrate (TMA⁺Pic⁻, 86 equivalents) ($V_{\text{TMA}^+} = 101 \text{ \AA}^3$, PC = 69%), the corresponding ¹H NMR spectrum showed a mixture of TMA⁺@**1** and Boc@**1** (ca. 60:40) in slow exchange on the NMR timescale.^[25] The new host–guest complex TMA⁺@**1** exists in the expected *S*₆ symmetrical 1,3,5-alternate conformation. The ¹H NMR spectrum of TMA⁺@**1** shows a high-field signal at $\delta = -0.34 \text{ ppm}$, which was identified (by using HSQC and NOESY) as one equivalent of an included TMA⁺ ion (Figure 3).^[21] The association constant for this interaction

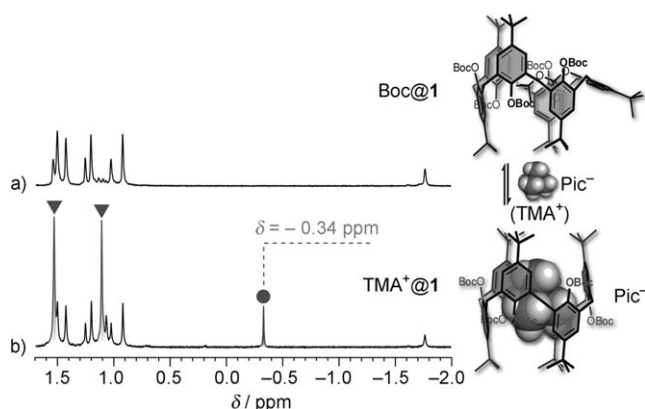


Figure 3. ¹H NMR spectra (298 K) of the high-field region of **1** a) in C₂D₂Cl₄/CD₃CN (2:1) and b) saturated with TMA⁺Pic⁻. ▼: **1** in 1,3,5-alternate conformation; ●: complexed TMA⁺ ion.

($K = 10 \text{ M}^{-1}$ at 298 K) is appreciably larger than the values measured for the neutral guests and indicates that the overall process of TMA⁺ inclusion is exergonic.^[21] The first-order dissociation rate constant of TMA⁺@**1** was determined by 1D-EXSY experiments and found to be 0.22 s^{-1} at 298 K, which corresponds to a residence time of 4.6 s.^[21]

All these results highlight a rare case of a reversible encapsulation process based on a covalently assembled host with a rotating molecular door. Indeed, except in the case of cryptophanes and hemicarcerands, reversible encapsulation is usually achieved with self-assembled molecular capsules^[17] rather than capsules built from covalent bonds. Moreover, the recognition process between **1** and charged or neutral species displays several unique features. Firstly, weak association constants were found while slow “in and out” guest exchanges were observed in all cases. Moreover, a slow dissociation rate was determined in the case of the TMA⁺ ion. These data reveal that the displacement of the guest by a *t*Bu^{Boc} group should possess a large activation barrier that is likely due to the important sterical crowding engendered by the multiple *t*Bu groups and thus to the restricted flexibility of the host. The weakness of the binding is clearly due to the competition between the guest encapsulation and the highly favorable

self-inclusion of a *t*Bu^{Boc} group. Nevertheless, the association constants cover more than two orders of magnitude ($K = 0.07$ to 10 M^{-1}), the optimal value being obtained with the TMA⁺ ion that can establish specific interactions ($\text{CH}-\pi$ and π -cationic) with the aromatic surface of the cavity. With neutral molecules, the binding process is mostly directed by the volume of the guest, and, in accordance with Rebek’s rule,^[19] a good fit is observed with PCs that range from 39 to 54%.

In summary, the readily available X₆Boc₆ **1** possesses unique conformational and host properties. Its skeleton is flexible enough for the encapsulation of small molecules through an induced-fit process that involves the conformational flip of an aromatic unit reminiscent of the rotation of a door. In the resulting encapsulation complexes, the calix[6]-arene skeleton adopts a 1,3,5-alternate conformation with an internal cavity of approximately $145 \text{ \AA}^3$ that can accommodate either charged or neutral species. In addition, the conformational mobility of the calixarene is highly restricted by the presence of multiple *t*Bu groups and, as a result, a rare case of weak binding with large barriers to guest exchange is observed. These results effectively illustrate the efficiency of the strategy that uses a highly flexible platform that can be appropriately rigidified as a starting point, rather than a rigid platform for the elaboration of host–guest systems that display induced-fit guest binding. This approach may open up interesting perspectives such as the design of 1,3,5-alternate calix[6]arenes that display stronger association constants, tuning of the rotating molecular door, grafting of water-soluble groups, and the development of molecular platforms able to provide multivalent interactions in two divergent regions.

Experimental Section

X₆Boc₆ **1**: Boc₂O (1.96 g, 8.99 mmol) and *N,N*-dimethyl-4-aminopyridine (46 mg, 0.38 mmol) were successively added to a solution of X₆H₆ (1.00 g, 1.03 mmol) in CH₂Cl₂ (25 mL) and the mixture was stirred at room temperature for 20 min. After evaporation of CH₂Cl₂ under vacuum, the resulting white solid was washed with CHCl₃ (10 mL) and dried under vacuum to afford X₆Boc₆ (1.56 g, 97%).

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