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**Host–Guest Systems**

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

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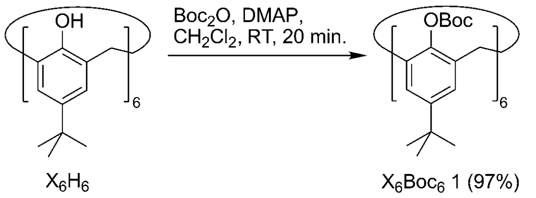
Calixarene-based building blocks are widely used for the elaboration of molecular receptors.[1] Calixarenes are highly flexible, in contrast to other concave macrocyclic compounds such as cyclodextrins,[2] cyclotriveratrylenes,[3] or resorcinarenes.[4] The control of their conformation is thus crucial 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 1 a).[15] A detailed analysis based on the dihedral angles $\phi$ and $\chi$[16] of these host–guest complexes $CH_2Cl_2@\mathbf{1}$ 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 ($\mathbf{1}_{S6}$: $\phi = \pm 100.2°$ and $\chi = \pm 101.9°$), a slightly

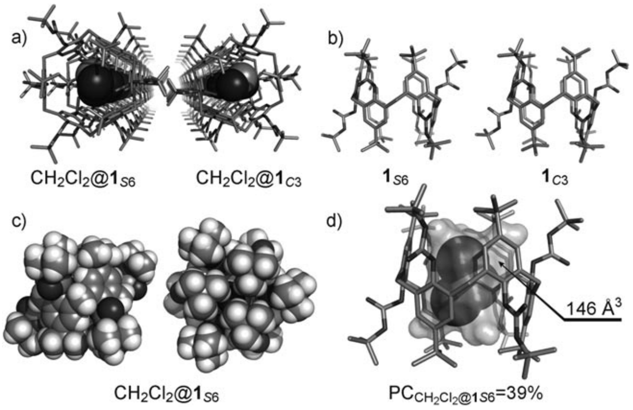


***Figure 1.*** a) Perspective view of the crystal packing of $CH_2Cl_2@\mathbf{1}_{S6}$ and $CH_2Cl_2@\mathbf{1}_{C3}$ (H atoms and free $CH_2Cl_2$ molecules are omitted for clarity). b) Side views of the X-ray structures of $\mathbf{1}_{S6}$ and $\mathbf{1}_{C3}$ (H atoms omitted). c) Side and top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

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distorted $C_3$ symmetrical conformation was observed ($\mathbf{1}_{C3}$: $\phi = +97.8°, -98.6°$ and $\chi = +102.9°, -102.4°$).

Both conformations of the calixarene have a barrel shape that is closed at each extremity by the *p-tert*-butyl groups ($t\mathrm{Bu}^{\mathrm{Cal}}$). This shape arises from the *anti* relationship of all the aromatic units (Figure 1 b). As a result, these two 1,3,5-alternate conformations of **1** behave as molecular capsules that completely surround their guest to form encapsulation complexes ($CH_2Cl_2@\mathbf{1}_{S6}$, Figure 1 c).[17] The inner volumes estimated using GRASP software[18] are 146 Å$^3$ and 142 Å$^3$ for $\mathbf{1}_{S6}$ and $\mathbf{1}_{C3}$, respectively[19] ($CH_2Cl_2@\mathbf{1}_{S6}$, Figure 1 d), which correspond to solid-state packing coefficients (PCs) of 39 % and 40 % for the included $CH_2Cl_2$ molecule ($V_{CH_2Cl_2} = 57$ Å$^3$). It is noteworthy that these PCs are slightly less than the optimal value of (55 ± 9) % described by Rebek and co-workers in the case of liquid-state molecular recognition.[19]

NMR studies of $X_6Boc_6$ **1** were carried out in order to investigate if the 1,3,5-alternate conformation could be observed in solution. Firstly, when the $^1$H NMR spectrum was recorded in 1,1,2,2-[D$_2$]tetrachloroethane ($C_2D_2Cl_4$), a solvent that is too large to be accommodated in the cavity, a complex NMR pattern with a high-field signal at $\delta = -1.61$ ppm was observed (Figure 2 a). An HSQC experiment was used to assign this signal to a self-included $t$Bu moiety of a Boc protecting group ($t\mathrm{Bu}^{\mathrm{Boc}}$).[20,21] Surprisingly, the spectrum remained essentially unchanged at high temperature (358 K).[22] The patterns of the $t\mathrm{Bu}^{\mathrm{Cal}}$ (1:2:2:1), $t\mathrm{Bu}^{\mathrm{Boc}}$ (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: $\delta = 4.07/3.34$ ($^2J = 16$ Hz, $\Delta\delta = 0.73$ ppm, *syn*), 3.56/3.49 ppm ($^2J = 14$ Hz, $\Delta\delta = 0.07$ ppm, *anti*), and a singlet signal ($\delta = 3.47$ ppm, *anti*) agrees with a 1,3-alternate conformation (see insets in Figure 2 a). 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 ($\delta = 27$ 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, $X_6Boc_6$ **1** adopts a 1,3-alternate conformation with a self-included $t\mathrm{Bu}^{\mathrm{Boc}}$ moiety (Boc@**1**, Scheme 2).[24]

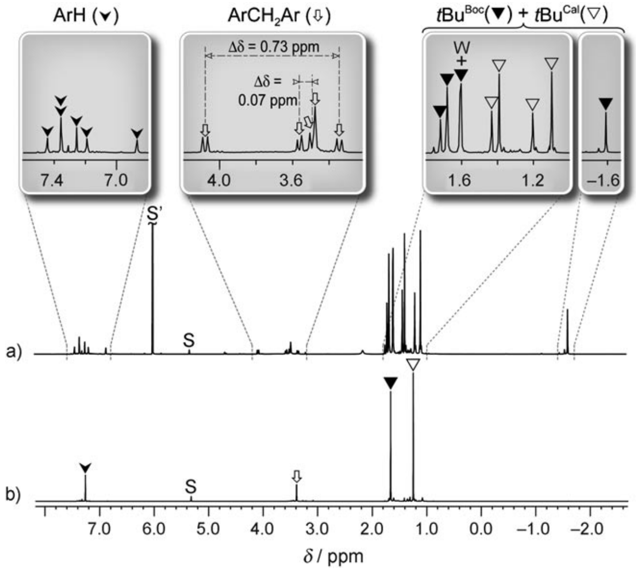
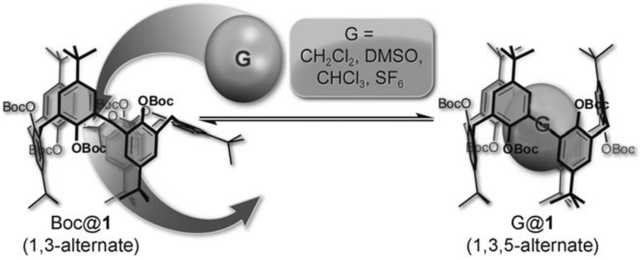


**Figure 2.** $^1$H NMR spectra (600 MHz, 298 K) of $X_6Boc_6$ **1** a) in $C_2D_2Cl_4$ and b) in $CD_2Cl_2$. The inset show the ArH, $ArCH_2Ar$, and $t$Bu regions. W: water, S and S′: residual solvents.



**Scheme 2.** Induced-fit encapsulation of neutral guests (G) by host **1**.

The progressive addition of $CD_2Cl_2$ to a solution of **1** in $C_2D_2Cl_4$ led to the appearance and intensity increase of a set of four singlet signals in the $^1$H NMR spectrum. These signals indicated the formation of a new, high-symmetry species in slow exchange with the introverted Boc@**1**.[21] In pure $CD_2Cl_2$, this new species was almost the only product observed (Figure 2 b). 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 **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 $t\mathrm{Bu}^{\mathrm{Boc}}$, 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 $t\mathrm{Bu}^{\mathrm{Boc}}$ 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 Å$^3$ (i.e., $SF_6$, $CDCl_3$, and [D$_6$]DMSO: PCs = 44, 50, and 54 %, respectively) led to the corresponding $S_6$ symmetrical host–guest complexes G@**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 Boc@**1** and G@**1** revealed weak interactions (i.e., $K = 0.07$, 0.08, 0.8, and 0.9 $\mathrm{M}^{-1}$ at 298 K for $CDCl_3$, [D$_6$]DMSO, $CD_2Cl_2$, and $SF_6$ respectively).[21] Finally, the NMR spectrum of Boc@**1** in $C_2D_2Cl_4$ was not affected by the addition of large amounts of smaller neutral molecules such as

$CD_3OD$, EtOH, or $CD_3CN$ (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 $C_2D_2Cl_4/CD_3CN$ mixture was saturated with tetramethylammonium picrate ($TMA^+Pic^-$, 86 equivalents) ($V_{TMA+} = 101\ Å^3$, 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 −0.34 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 ($K = 10\,\text{M}^{-1}$ 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]

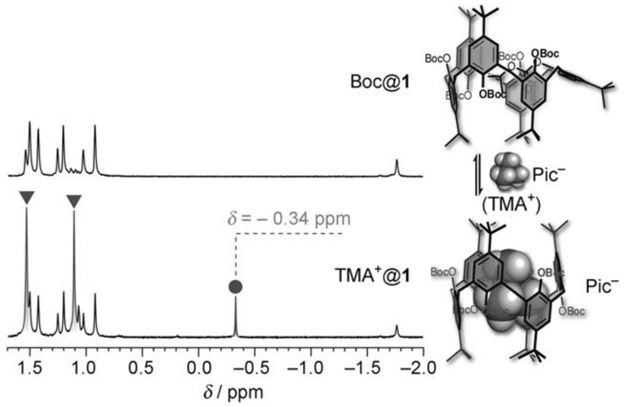


***Figure 3.*** $^1H$ NMR spectra (298 K) of the high-field region of **1** a) in $C_2D_2Cl_4/CD_3CN$ (2:1) and b) saturated with $TMA^+Pic^-$. ▼: **1** in 1,3,5-alternate conformation; ●: complexed $TMA^+$ ion.

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 $t\text{Bu}^{\text{Boc}}$ 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 $t\text{Bu}^{\text{Boc}}$ group. Nevertheless, the association constants cover more than two orders of magnitude ($K = 0.07$ to $10\,\text{M}^{-1}$), the optimal value being obtained with the $TMA^+$ ion that can establish specific interactions (CH–π 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 $X_6Boc_6$ **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 $145\ Å^3$ 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*

$X_6Boc_6$ **1**: $Boc_2O$ (1.96 g, 8.99 mmol) and *N,N*-dimethyl-4-aminopyridine (46 mg, 0.38 mmol) were successively added to a solution of $X_6H_6$ (1.00 g, 1.03 mmol) in $CH_2Cl_2$ (25 mL) and the mixture was stirred at room temperature for 20 min. After evaporation of $CH_2Cl_2$ under vacuum, the resulting white solid was washed with $CHCl_3$ (10 mL) and dried under vacuum to afford $X_6Boc_6$ (1.56 g, 97%).

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[25] Increasing the proportion of $CD_3CN$ in the solution led to the precipitation of **1**.