Selective recognition of small hydrogen bond acceptors by a calix[6]arene-based molecular container

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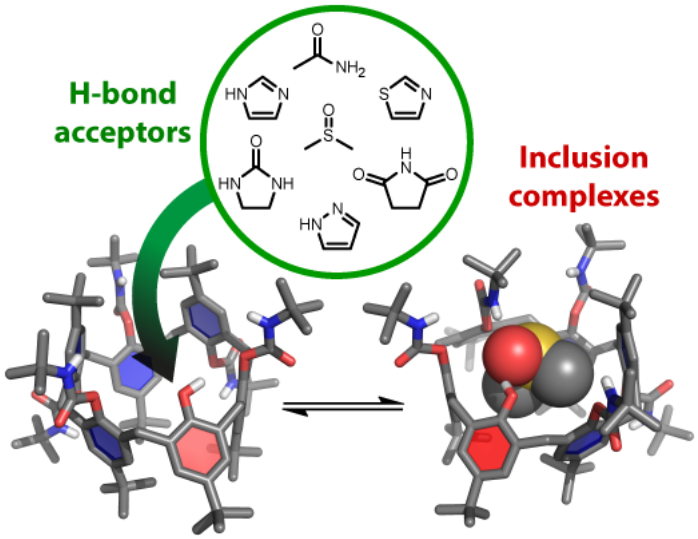
Graphical abstract (max 525 px width, no height limit)



Abstract (max 150 words)

Selective molecular recognition is of primary importance for applications such as sensing and separation of chemicals. This work describes the host-guest and crystallisation properties of a penta-carbamated calix[6]arene designed as a molecular container with a H-donating recognition group directed toward the heart of the cavity. As demonstrated by NMR spectroscopy and X-ray diffraction studies, this macrocyclic receptor can selectively recognise small H-bond acceptors through one or two hydrogen bonds, the guests nesting inside the polyaromatic cavity surrounded by eleven bulky *tert*-butyl groups.

Keywords (5 or 6)

Calixarenes; Host-guest; Inclusion complexes; Molecular recognition; Macrocycles

Introduction

Molecular receptors have attracted considerable attention over the past decades for their ability to sense (1,2), transform (3,4), transport (5,6) or separate (7,8) neutral or charged species. These molecular receptors can find various applications in catalysis (9,10), material science (11,12), medicine (13,14) and in environmental (15) or analytical (16) chemistry. Macrocyclic oligomers such as cyclodextrins (17), cucurbiturils (18), calixarenes (19), resorcinarenes (20), pillararenes (21) and hemicucurbiturils (22) are commonly used for the elaboration of cavitands that can serve as molecular receptors complexing guests into their cavity. Calixarenes present the advantage that many strategies have been developed for their selective modification (23). In this regard, we have previously described a general method for the iteroselective functionalisation of calix[4, 5, 6, or 8]arenes (24) and homooxacalixarenes (25). This so-called 'all-but-one' carbamation methodology consists of reacting the polyphenolic platform with *tert*-butyl isocyanate (*t*-BuNCO) under basic conditions in a non-polar solvent. With this one-step procedure, derivatives bearing *N*-*tert*-butylaminocarbonyl (Bac) groups on all but one phenol unit of the starting calixarene are obtained in high yield. According to this strategy, calix[6]arene **2** bearing five carbamated moieties was readily obtained from *p*-*tert*-butylcalix[6]arene **1** (Figure 1). We showed that this penta-functionalised calix[6]arene constitutes a key intermediate for the preparation of mono-functionalised calixarenes (25) and molecular containers (26). Receptor **2** displays a single H-bond donating phenolic moiety associated to a polyaromatic pocket protected by eleven bulky *tert*-butyl groups. We thus envisaged that this compound could behave as a molecular container (27) for small H-bond accepting guests. As a proof of concept, preliminary host-guest studies indicated that calixarene **2** was able to encapsulate DMSO in organic solvents (24).

Herein we describe the characterisation of **2** in the solid state as well as its unique host-guest properties toward neutral molecules possessing H-bond accepting groups.

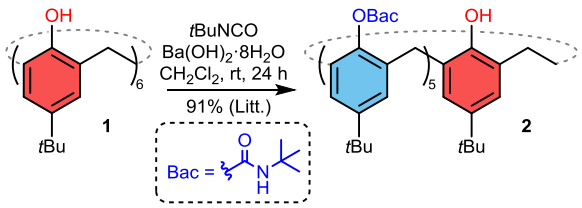


Figure 1. Synthesis of **2** through the one-step selective penta-carbamation of **1**.

Results and Discussion

Characterisation of calixarene 2 in the solid state. Crystallisation of compound **2** from organic solvents was found remarkably fast and easy. For instance, X-ray quality single crystals were obtained reproducibly in few minutes by simple evaporation of a solution of **2** in CH_2Cl_2 on a 10 mg scale. When the evaporation was prolonged for 16 h on a gram scale, it was possible to produce large elongated crystals (*i.e.* over 1 cm in length) of **2**. The X-ray diffraction patterns revealed that single crystals of **2** obtained from either CH_2Cl_2, $CHCl_3$ or $(CHCl_2)_2$ solutions exhibit static orientational disorder. Indeed, the electron density of the single phenolic unit is distributed over all six possible positions of the calixarene (Figure 2a and Table S27) with the observed electron density pattern resembling the result of an overlap of six different orientations of an 1,3-alternate conformation of compound **2** (Figure 2b and Table S28) (28). Due to this disorder, we were unable to determine what guest is included in the calixarene even though it is most likely the solvent of crystallisation or gases, similarly to previously reported calixarenes with related structures (26). Interestingly, in the crystal structure, the phenolic OH group of calixarene **2** is directed toward the heart of the polyaromatic pocket and is thus ideally placed for the intra-cavity

stabilisation of H-bond acceptors (Figure 2b). It is noteworthy that the presence of a single 1,3-alternate conformer in the solid state stands in contrast with what is observed in solution. Indeed, the ^{1}H NMR analysis of solutions of **2** in $CDCl_3$ showed the presence of numerous unidentified conformers in slow exchange on the chemical shift timescale at 298 K (see Figures S1-3). The fast and simple crystallisation of **2** suggests that the C_s symmetrical 1,3-alternate conformer of **2** packs easily as if it was a highly symmetric hexagonal prism (Figure 3). Indeed, we previously observed that related calix[6]arenes bearing twelve *tert*-butyl groups crystallise easily as hexagonal prisms maximizing intermolecular interactions and allowing close packing in the solid state (26,29).

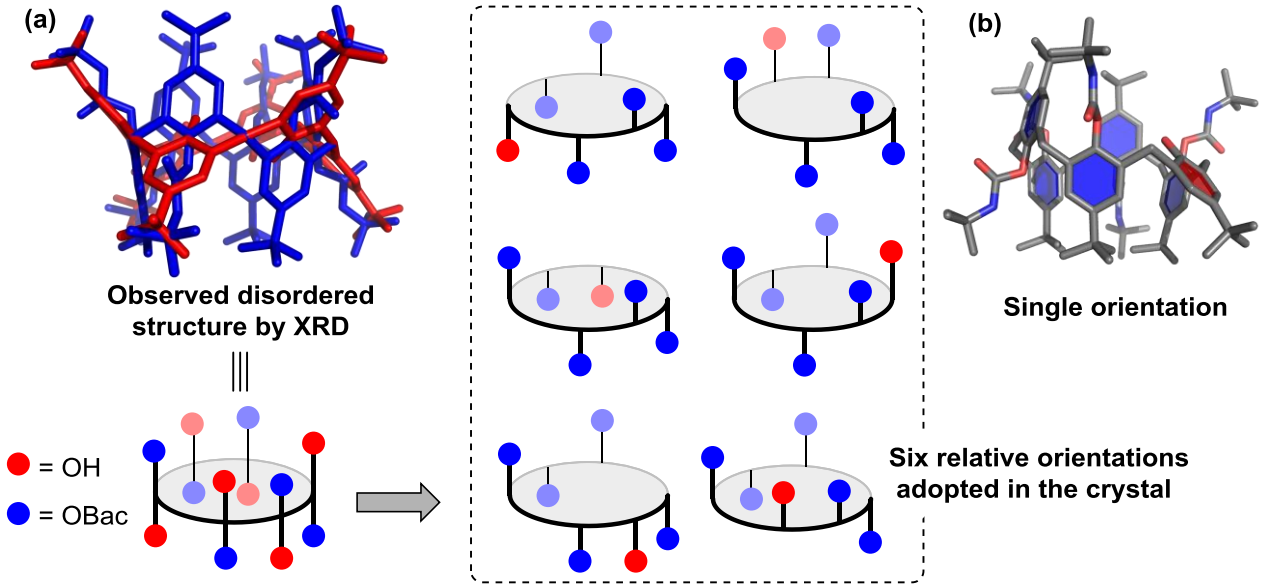


Figure 2. (a) Apparent XRD structure of calixarene **2** as a consequence of six possible orientations in the crystal cell. (b) Structure of calixarene **2** extracted from the disordered structure. Solvent molecules and hydrogen atoms are not displayed for clarity purpose.

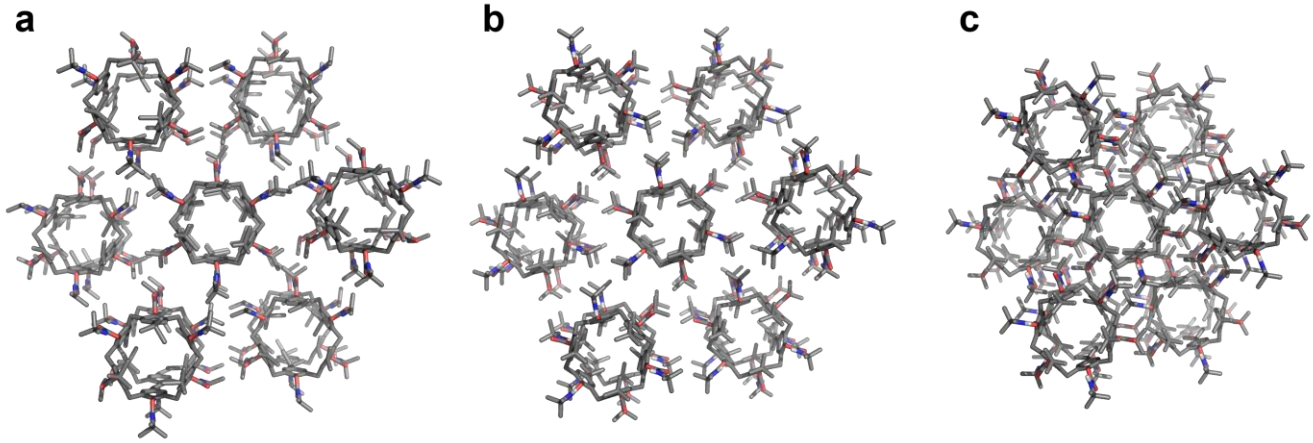


Figure 3. Packing observed in single crystals of **2** obtained from solutions in a) CH_2Cl_2, b) $CHCl_3$, and c) $(CHCl_2)_2$. A similar hexagonal packing is observed from all three solvents of crystallisation. **2** crystallised with interstitial solvent molecules from CH_2Cl_2 and $CHCl_3$ but not from $(CHCl_2)_2$. Solvent molecules and non-polar hydrogen atoms were removed for clarity. The structure of **2** is shown with six Bac groups due to orientational disorder (see the text). The high disorder led to challenging structure refinement but the observed packing is unaffected (see the SI).

Recognition properties of 2. Host **2** being quasi-insoluble in standard polar solvents, NMR binding studies were carried out in non-polar solvents. Due to the coexistence of multiple conformations in slow exchange on the NMR chemical shift time scale at 298 K, host **2** displays a complex ^{1}H NMR pattern in either $CDCl_3$, C_6D_6 or $(CDCl_2)_2$, with singlets below 0.1 ppm that are characteristic of self-included *t*Bu groups (Figure 4a for the ^{1}H spectrum in C_6D_6). However, upon the addition of a few equivalents of DMSO, a well-defined NMR signature corresponding to the 1:1 complex **2**⊃DMSO was observed (Figure 4b). A similar ^{1}H NMR spectrum was obtained either in $CDCl_3$, $(CDCl_2)_2$ or C_6D_6, indicating a similar mode of recognition in these three solvents (Figures S5). The complex was studied more thoroughly in C_6D_6 because the spectrum presented fewer overlapping signals (Figure 4b), thus facilitating a complete assignment of all the signals through 2D NMR (COSY, HSQC, HMBC, ROESY experiments) (Figures and Tables S6-S13) (30). The calixarene adopts an asymmetric conformation with a single inverted unit. The included DMSO molecule is stabilised through two H-bonds, one from the single OH group (singlet at 8.72 ppm) and one from a NH group of the receptor (singlet at 8.00 ppm). Moreover, both methyl groups of the guest are differentiated and high-field shifted, indicating their location in the heart of the polyaromatic cavity (complexation-induced shifts (CISs) = –1.43 and –1.90 ppm). An association constant K_a = 4.6 × 10^3 M^{-1} ±11% was determined for DMSO in C_6D_6 at 298 K through a titration experiment (see the SI).

Single crystals of the complex **2**⊃DMSO were grown by slow evaporation of a solution of **2** in a $(CHCl_2)_2$/DMSO 1:1 mixture. The XRD structure is in good agreement with what is observed in solution by NMR: i) host **2** displays an asymmetric conformation with an inverted aromatic unit (31) and ii) the included DMSO is recognised through H-bonding interactions into the polyaromatic pocket (Figure 4c-d). The X···O length and angle of the H-bonds are 2.6 Å and 144° for the O–H···O=S, and 3.0 Å and 161° for the N–H···O=S. These values are consistent with H-bonds of moderate strength (32). The XRD structure clearly shows that the phenolic unit is tilted towards the inside of the cavity to facilitate the H-bonding to the guest. As a result, the DMSO molecule is fully encapsulated in the polyaromatic cavity and is isolated from the external medium thanks to the surrounding bulky *tert*-butyl groups. In other words, host **2** behaves as a molecular container that can stabilise guests thanks to a flexible H-donating phenolic unit.

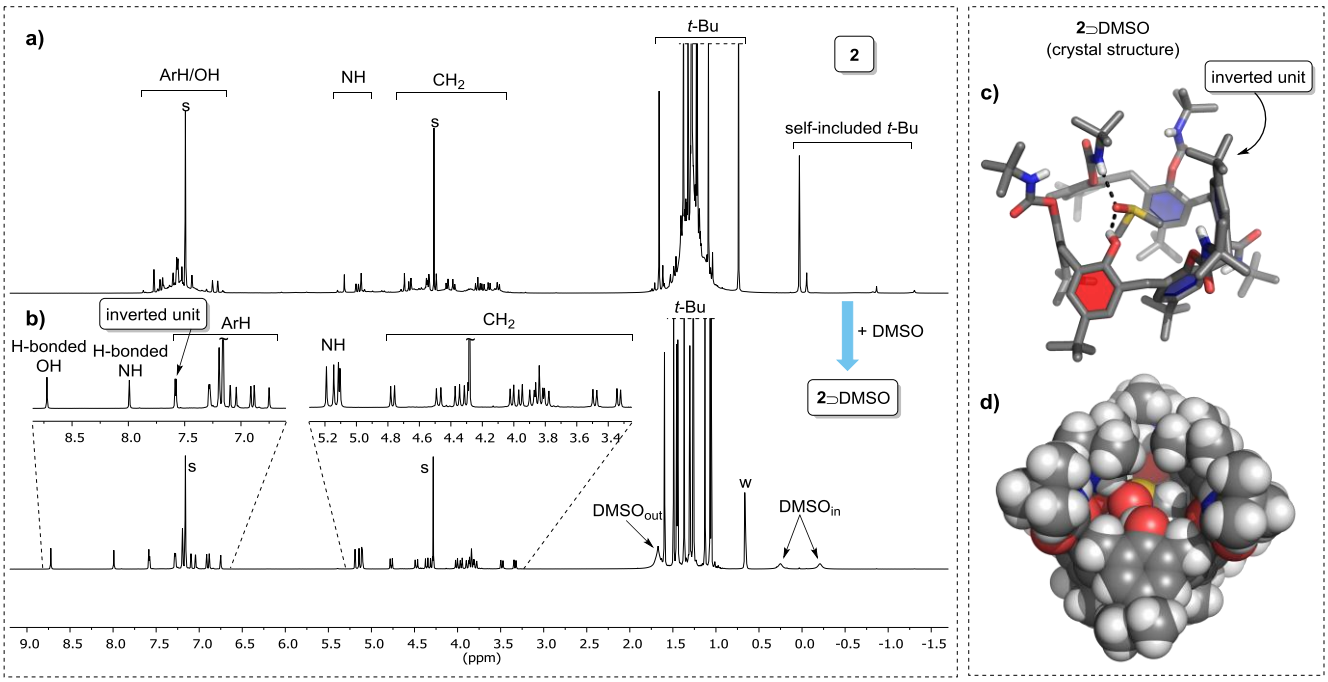


Figure 4. Left: ^{1}H NMR spectra (C_6D_6, 600 MHz, 298 K) of a) host **2** and b) **2**⊃DMSO inclusion complex after addition of DMSO (3 equiv.); s = residual solvents; w = residual water. Right: X-ray structure of **2**⊃DMSO in c) stick model and d) space-filling model showing the encapsulated DMSO isolated from the environment. H-bonds are shown by dashed lines. External solvent molecules and non-polar hydrogen atoms in the stick model were removed for clarity purpose.

With the full characterisation of the complex **2**⊃DMSO in hands, we next moved to the evaluation of the recognition properties of **2** toward other small charged or neutral species. For this, ^{1}H NMR binding studies were conducted in chlorinated solvents (*i.e.* $CDCl_3$ and/or $(CDCl_2)_2$). No significant interaction was observed for charged species (*i.e.* various anions and NMe_4^+), 1,8-octanediol (5 equiv.), acetic acid (7 equiv.), acetone (20 equiv.) and sulfolane (20 equiv.) (Figure 5). However, similarly to what was observed in the case of DMSO, addition of a slight excess of imidazole or thiazole to host **2** gave rise to a predominant set of sharp ^{1}H signals corresponding to 1:1 inclusion complexes (Figures S2 and S3). In the case of acetamide, 2-imidazolidinone (Imi), succinimide and pyrazole, mixtures of complexes were obtained, as indicated by the appearance of multiple sets of ^{1}H peaks in different ratio (Figures S1-S3). This result may be rationalised by a slow exchange on the chemical shift timescale of inclusion complexes differing by the conformation adopted by host **2** or, possibly, by additional exo-complexation. In the case of amines, complexes with complicated ^{1}H NMR spectra were initially observed but new species were progressively observed over time. This result was attributed to the degradation of host **2** through the deprotonation of the carbamate NH groups by the basic amines (Figure S4). All these NMR data show that receptor **2** selectively interacts with small molecules bearing strong H-bond accepting groups such as sulfoxides, azoles, amides, imides, ureas and amines.

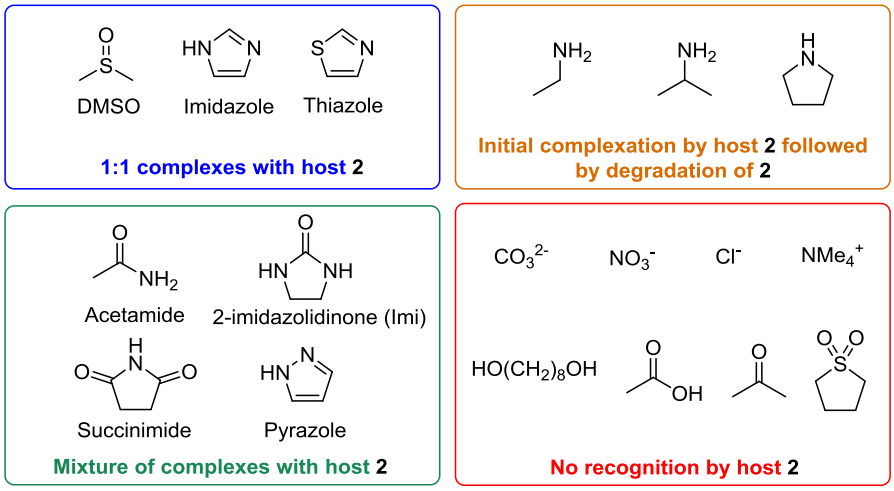


Figure 5. Small neutral and charged species evaluated by ^{1}H NMR spectroscopy ($CDCl_3$ and/or $(CDCl_2)_2$) as potential guests for host **2**. Charged species were tested as the following salts: K_2CO_3, Cs_2CO_3, $TBA^+NO_3^-$, $NMe_4^+Cl^-$, $NMe_4^+BARF^-$ and the samples were heated at 50°C for two days without noticeable change.

Compared to DMSO, weaker binding was observed for imidazole and thiazole. In the case of thiazole, the observation of the inclusion complex as the major calixarene-based species required a large excess of the guest (>30 equiv.) and a low temperature (223 K). Association constants were calculated as K_a = 208 M^{-1} ±13% for **2**⊃imidazole ($CDCl_3$, 298 K) and 21 M^{-1} ±19% for **2**⊃thiazole ($CDCl_3$, 223 K) (see the SI). Similarly to **2**⊃DMSO, the ^{1}H NMR spectra of the complexes **2**⊃imidazole and **2**⊃thiazole are consistent with an asymmetric conformation of the receptor. The complete assignment of the NMR spectra recorded for **2**⊃imidazole in $CDCl_3$ at 223 K showed that the receptor adopts the same conformation than in **2**⊃DMSO with a single inverted unit (Figures S14-S20). Besides, the presence of all five carbamate NH signals in the chemical shift range of 4.8–5.3 ppm and the phenolic

OH signal at 10.51 ppm indicates that a single H-bond O–H···N is involved in the binding of imidazole as opposed to two H-bonds for DMSO (Figure 4b). This is a direct consequence of a single lone electron pair available on the imidazole nitrogen to accept the H-bond in contrast to the two lone pairs on the oxygen of DMSO. This smaller number of H-bonds could explain in part the weaker binding of imidazole compared to DMSO. The CISs for the three CH protons of imidazole range from –2.8 to –3.3 ppm, which is consistent with a complexation inside the polyaromatic cavity of the calixarene.

Despite the formation of more than one complex upon mixing **2** and Imi, one predominant asymmetric species was observed in $CDCl_3$ (Figure S21). Slow exchange on the chemical shift timescale between bound and free Imi was reached at 248 K (600 MHz). The methylene groups of the complexed Imi are differentiated and are high-field shifted (CISs = –3.22 to –3.43 ppm), showing their inclusion in the polyaromatic cavity of the calixarene. Interestingly, the NH groups of the included Imi are also high-field shifted (CIS = –3.29 ppm) (33). Such a high CIS value indicates that these NH are also inside the polyaromatic cavity and are not involved in H-bonds. Imi is thus only recognised as a H-bond acceptor in contrast with all the previously reported cases of Imi recognition by calix[6]arene-based receptors (34,35,36,37). The modes of recognition for the other guests were not characterised due to the complex mixture of species present in solution.

The critical role played by the phenolic OH of calixarene **2** as an H-bond donor for guest binding can be explained by its ideal positioning at the edge of the polyaromatic pocket as well as by the lack of competing intramolecular H-bonding interactions. Indeed, in contrast with most calix[6]arene-based receptors bearing phenolic units, the nearby oxygen atoms on calixarene **2** are bonded to electron-withdrawing carbonyls, which limits the self-association through intramolecular H-bonding (Figure 6). While the five carbonyl groups on the molecule are good H-bonds acceptors, no O–H···O=C hydrogen bonding is observed in the different crystal structures obtained, which is likely caused by the steric crowding of the eleven *tert*-butyl groups decorating the macrocycle. The intermolecular H-bond donating capability of the single phenol group of penta-carbamated calix[6]arene **2** is therefore enhanced compared to partially alkylated calixarenes which are most commonly described (38).

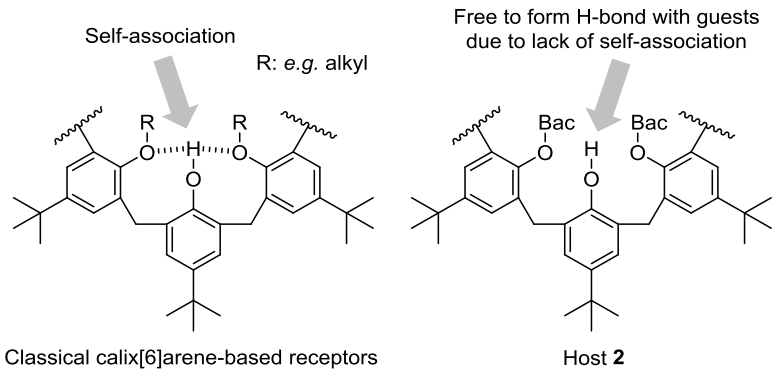


Figure 6. Difference in intermolecular H-bond donating potential between partially alkylated calixarenes and **2**.

Conclusions

The penta-carbamated host **2** behaves as a molecular container displaying a flexible H-donating phenolic door that can interact with small H-bond accepting guests such as sulfoxides, ureas, amides, imides and azoles. As revealed by NMR spectroscopy and XRD studies, the guests are stabilised by one or two H-bonds into the

polyaromatic cavity of the host and are isolated from the external environment thanks to the presence of the multiple bulky *tert*-butyl groups.

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Disclosure statement

The authors declare no competing financial interest.

Data availability

The crystal structures of **2** and **2**⊃DMSO are available at the Cambridge Crystallographic Data Centre: CCDC 1959492 and 1952601.

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