1,3-Alternate Tetra-amido-Azacalix[4]arenes as Selective Anion Receptors

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Gabriel Canard,*[a] Judicaelle Andeme Edzang,[a] Zhongrui Chen,[a] Matthieu Chessé,[b] Mourad Elhabiri,[b] Michel Giorgi,[c] and Olivier Siri*[a]

Abstract: Six tetraaza[1.1.1.1]cyclophanes derivatives bearing peripheral amide groups were prepared according to two distinctive synthetic strategies that depend on the connection pattern between aryl units. NMR experiments combined with the X-ray structures of two tetraamide derivatives **4b** and **10** show that these cavitands adopt an 1,3-alternate conformation either in solution or in the solid state. Consequently, the four amide groups of the aza[1.1.1.1]*m*,*m*,*m*,*m*-cyclophane isomer **10** can contribute to the same recognition process towards neutral water molecules or anion guests. NMR experiments, mass spectrometry analyses and single crystal X-ray structures confirm the anion-binding ability of this receptor. Absorption spectrophotometric titrations in non polar solvents evidenced the selectivity of **10** to chloride anions in the halide series with a corresponding association constant K_a reaching up to 2.5 × 10^6 M^{-1}.

Introduction

The calixarene skeleton is one of the most popular scaffold used in the design of simple to very sophisticated receptors in supramolecular chemistry owing to its tunable conformation arising from the high flexibility of the macrocycle framework.[1] Consequently, calixarenes can be found in various applied research areas such as catalysis[2] or the specific delivery of drugs.[3] The large structural diversity of calixarene derivatives rely on the numerous means to change or to functionalize their skeleton. If aromatic units are often used to introduce functional groups such as in water-soluble *p*-sulfonatocalixarenes,[4] an important class of cavitands has emerged where non-carbon bridging atoms are incorporated into the calixarene skeleton[5] providing additional opportunities to tune the ring size, the conformation and the binding properties of the corresponding macrocycle. Among the various types of heterocalixarenes, thiacalixarenes[6] incorporating sulfur-bridging atoms were the most intensively studied since their syntheses can be achieved by simple and versatile one-pot procedures. The special functionalities imparted by heteroatoms stimulated research progress in the field of other heterocalixarenes such as oxacalixarenes[7] and the emerging azacalixarenes which have been poorly investigated so far.[8]

Multiple consequences and applications relying on the introduction of nitrogen-bridging atoms have to be mentioned. Several supramolecular assemblies of azacalixarenes were shown to be built on interactions involving the bridging nitrogen atoms such as hydrogen bonds[9] or Se···N non-covalent interactions.[10] The *N*-alkylation is a powerful tool to build more sophisticated receptors[11] but can also be used to induce an inherent chirality[12] or to improve the macrocycle solubility.[13] Oxidation of azacalixarene derivatives can produce stable radical cations, high-spin diradicals or polycationic species since the N-atom can act as spin-bearing site and the nitrogen lone pair of each bridging atom is effectively conjugated with one or multiple neighboring aryl units.[14] This conjugation is responsible of the exclusive 1,3-alternate conformation adopted by tetraazacalix[4]arenes observed in all single crystal X-ray structures of such derivatives reported so far.[8,15] NMR studies and TD-DFT calculations have shown previously that this conformation can be frozen in solution when bulky groups are born by the nitrogen atoms[16] or when appropriate substituents such as methoxy[17] or nitro groups[18] are introduced on the aryl moieties of the tetraazacalix[4]arene backbone.

Even though different synthetic strategies are now available to prepare azacalixarene derivatives, their binding properties are still rather scarce[8] and primarily concern host-guest complexes involving homoazacalixarenes[19] or cavitands incorporating heterocycles such as pyridines[20] or triazines[21] that contribute to the recognition process. As far as tetraazacalix[4]arenes lacking heterocycles are concerned, only two examples of supramolecular host-guest complexes were described and showed that their 1,3-alternate conformation was suitable to bind alkali metal ions[17] or a dichloromethane molecule.[22] One would expect that this distinctive conformation can be used as a scaffold to pre-organize multiple supramolecular recognition groups such as amide ones.

We disclose here two distinctive synthetic strategies to introduce four amide groups on tetraaza[1.1.1.1]cyclophanes depending on the connection pattern between aryl units. The single crystal X-ray structures of two derivatives show, as expected, that their 1,3-alternate conformations produce a close spatial proximity between the appended amide groups allowing their involvement in a common recognition process. The anion complexation properties of one selected derivative **10**

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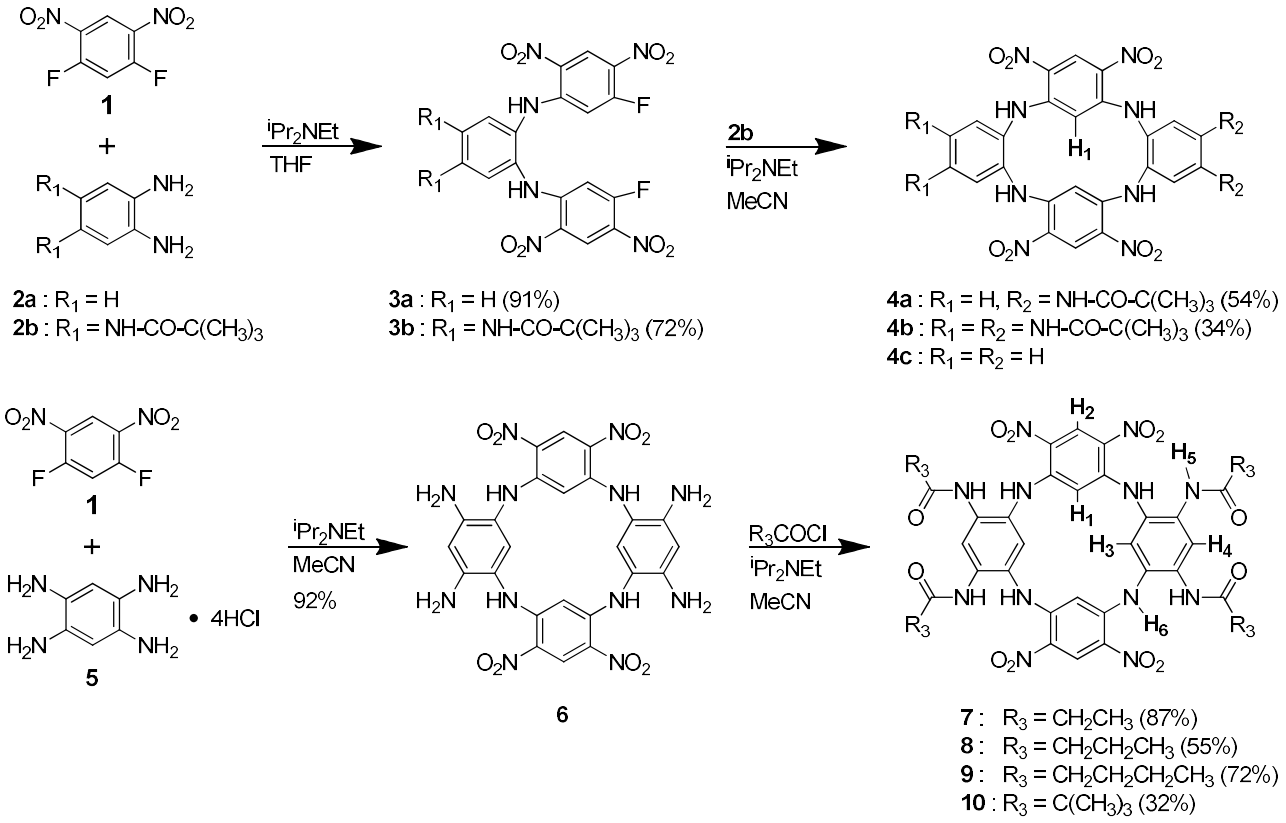
were thoroughly studied in solution and in solid state because it forms host-guest complexes precipitating in polar media (acetone, MeCN) that were characterized by several techniques including single crystal X-ray diffraction. Absorption spectrophotometric titrations show that this anion receptor displays a selectivity toward chloride anions resulting from the spatial arrangement of the four amide groups appended to the azacalix[4]arene scaffold. This contribution brings a significant advance in the applications of azacalix[4]arenes and shows that their 1,3-alternate conformation is a reliable tool to elaborate well-tailored supramolecular receptors.

Results and Discussion

Synthesis and characterization

Besides the historical Buchwald-Hartwig aryl amination reactions,[8] the formation of azacalix[4]arenes can be achieved using a catalyst-free approach based on successive nucleophilic aromatic substitutions (S_NAr)[11,13,18,21-24] between diaminobenzene derivatives as nucleophilic partners and electrophilic activated dihalogeno aryl units such as the 1,5-difluoro-2,4-dinitrobenzene **1** (Scheme 1). The use of this latter derivative is particularly efficient and has been successfully applied in the preparation of various oxa- and azacalix[4]arene derivatives.[13,18,21,22,24] Two distinctive synthetic strategies were used to introduce amide groups on tetraazacalix[4]arenes depending on the connection pattern between aryl units (Scheme 1). The tetraaza[1.1.1.1]*o*,*m*,*o*,*m*-cyclophanes **4a** and **4b** were prepared in a two steps procedure starting from **1** and allowing the access to unsymmetrical macrocycles. The reaction between 1,2-diaminobenzenes **2a** or **2b**[25] and **1** (0.5 equiv.) led to the formation of the [2+1] products **3a** and **3b** in good yields. Their ^{1}H NMR spectra (DMSO-d_6) show a downfield NH at δ 10.15 and 10.14 ppm for **3a** and **3b**, respectively, in agreement with two NH···O_2N hydrogen bonding interactions that restrict the rotation of these uncyclized precursors and induce their pre-organizations towards the subsequent macrocyclization. [13,18,24c-d] **3a** or **3b** were then reacted with **2b** in refluxing MeCN to give the tetraaza[1.1.1.1]*o*,*m*,*o*,*m*-cyclophanes **4a** and **4b** bearing two and four peripheral amide groups respectively. This stepwise procedure does not require chromatographic separations while the direct condensation of equimolar amounts of **1** and **2b** affords a lower yield of **4b** together with uncyclized oligomers that are difficult to remove. The ^{1}H NMR spectra (DMSO-d_6) of **4a** and **4b** reveal that these macrocycles adopt an 1,3-alternated conformation in solution, in which the intraannular aromatic protons H_1 (Scheme 1) are located inside the anisotropic shielding cone of the adjacent aromatic rings. This assumption is supported by the high-field chemical shifts at δ 5.05 and 5.23 ppm for H_1 protons of **4a** and **4b**, respectively. The synthesis of compound **4c** lacking amide groups has followed a previously described and analogous strategy starting from **1** and **2a**.[24d] Its unprecedented single crystal X-ray structure is given here (*vide infra*) and compared to the one of **4b**.



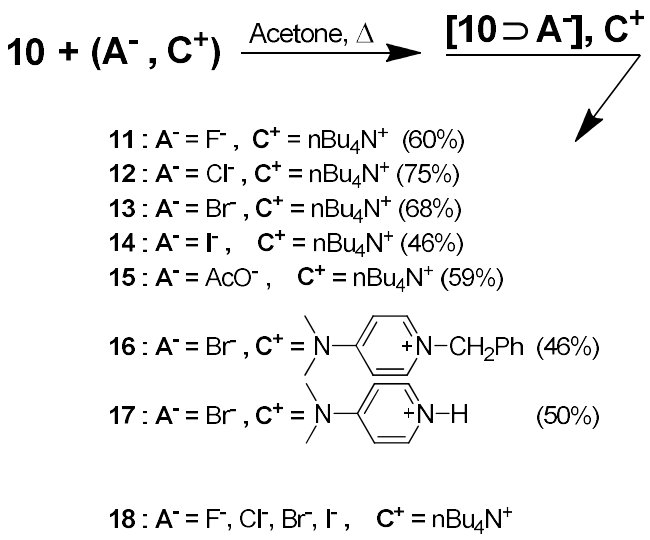
Scheme 1. Syntheses of azacalix[4]arene derivatives **4a-b** and **7-10** bearing peripheral amide groups.

The preparation of the symmetrical tetra-amido-tetraaza[1_4]*m*,*m*,*m*,*m*-cyclophanes **7**-**10** relies on a different two steps synthetic procedure that allows the access to numerous derivatives since the introduction of the amide groups is performed after the macrocyclization (Scheme 1). The condensation of **1** on the 1,2,4,5-tetra-aminobenzene (formed *in situ* by deprotonation of its tetra-hydrochloric salt **5**) gives, as previously described,[26] a high yield of the tetraamino-azacalix[4]arene **6**. The oxidation that usually affects electron-rich tetra-aminobenzene units[27] is here avoided through their connections with strong electron-withdrawing dinitro-aryl groups. The condensation between the tetra-amino derivative **6** with 4 to 10 equivalents of acyl chlorides in refluxing MeCN affords the tetra-amido-tetraazacalix[4]arenes **7**-**10** with yields ranging from 32 to 87%. The 1,3-alternate conformation of **6**, probed by the ^{1}H NMR singlet of its hydrogen atoms H_1 located at δ 4.98 ppm in DMSO-d_6, induces a spatial proximity between the four appended amine groups. Therefore, the lowest synthetic yield for **10** bearing four bulky amide groups is probably due to this geometrical orientation and remains low even if a higher excess of acyl chloride and/or a longer reaction time are used. The ^{1}H NMR spectra (DMSO-d_6) of **7**, **8**, **9** and **10** support their 1,3-alternated conformations in solution through the positions of their intraannular aromatic H_1 singlets chemical shifts at δ 5.42, 4.40, 5.33 and 5.61 ppm respectively (See the supporting information).

Host-guest species between 10 and anions

A preliminary investigation using UV-vis absorption and NMR spectroscopies revealed that all the cavitands **4b-c** and **7**-**10** interact with anions in solution. The strongest interactions, *i.e.* as probed by the largest variations of the UV-vis absorptions and ^{1}H NMR spectra, were observed using the *m*,*m*,*m*,*m*-cyclophanes derivatives **7**-**10**. The latter derivative **10** was chosen as the subject of a comprehensive and exhaustive study because it forms stable host-guest complexes with anions that precipitate in polar media (acetone, MeCN). Addition of tetra-*n*-butylammonium halide or acetate salts to a solution of the host **10** in acetone led to the precipitation of the host-guest complexes that is favored by increasing with the temperature. This straightforward procedure was used to prepare the host-guest complexes **11**-**17** with yields ranging from 46 to 75% (Scheme 2). Inclusion complexes **11**-**15** were prepared starting from the tetra-*n*-butylammonium salts of fluoride, chloride, bromide, iodide and acetate, respectively. 1-Benzyl-4-dimethylaminopyridinium bromide[28] and 4-dimethylaminopyridinium bromide[29] were also used to evaluate the potential effect of the cation's nature in the solids **16** and **17** and compared to the solid **13** (Scheme 2). A first analysis of the selectivity of **10** in the halide series was performed through the precipitation of the solid **18** prepared by refluxing the receptor **10** in a solution containing equimolar amounts of F^-, Cl^-, Br^- and I^- (Scheme 2).

Regardless the nature of the anion, the formation of [1+1] host-guest complexes was confirmed by elemental analyses of the solid **11**-**17** containing between 1 and 3 water molecules (See the experimental section). This anion complexation is also supported by the presence in the ESI spectra (anion mode) of peaks for **12**, **13** and **14** corresponding to the adducts [**10**⊃Cl]$^-$, [**10**⊃Br]$^-$ and [**10**⊃I]$^-$, respectively (Figure S1-S5 in the supporting information). In each mass spectrum of **11**-**17**, a peak corresponding to the deprotonated form of **10** [**10**-H]$^-$ can be seen, suggesting that an acid-base reaction occurs, in the gas phase, between the anion $\mathbf{A}^-$ and the host **10** and forms the neutral acid molecule **AH**. No peaks corresponding to the adducts [**10**⊃**A**]$^-$ where observed when the more basic acetate and fluoride anion are complexed while the dianionic form of **10** [**10**-2H]$^{2-}$ is detected. Among the adducts [**10**⊃**A**]$^-$ ($\mathbf{A}^-$ = Cl^-, Br^-, I^-) that can be seen on the mass spectrum of **18** (Figure S6), the highest intensity observed for [**10**⊃Cl]$^-$ seemingly indicates a selectivity towards the smaller and harder anions Cl^- and F^- in the halide series.



Scheme 2. Precipitation of the host-guest complexes **11**-**18**.

Further evidences were brought by the ^{1}H NMR spectra of diluted solution of **11**-**15** and **18** that were recorded and compared to the one produced by the receptor **10** upon identical conditions (Figure 1). The anion-complexation process induces the variation of the receptor signals chemical shifts in the low fields region. Little variations are affecting the 1-3-alternate conformation of the azacalix[4]arene **10** which is retained whatever the added anions as confirmed by the chemical shift of the intraannular proton H_1 decreasing from 5.61 ppm in **10** to 4.99 ppm in **12**. As expected, the highest shift amplitude concerns the interacting amide protons H_5 and the aromatic hydrogen atoms H_4 that are located close to the complexation site (Scheme 1). Consequently, the remote hydrogen atoms H_2 and H_3 are only slightly sensitive to the host-guest interaction. The shift amplitude is increasing with the hardness of the anion when the bulky iodide is replaced successively by bromide and chloride. This trend is not fully retained when fluoride and acetate are interacting and produce the disappearance of the signals corresponding to acidic protons borne by the nitrogen bridging groups (H_6). The close resemblance between the spectra of **12** (Cl^-) and **18** is again a piece of evidence of the selectivity of **10**

towards chloride anions in the halide series (Figure 1). The replacement of the ammonium counter-cation of **13** by pyridinium ions in **16** and **17** has no effect on the chemical shifts of [**10**⊃Br]$^-$ showing that the cation is not directly involved in the complexation process (see the supporting information).

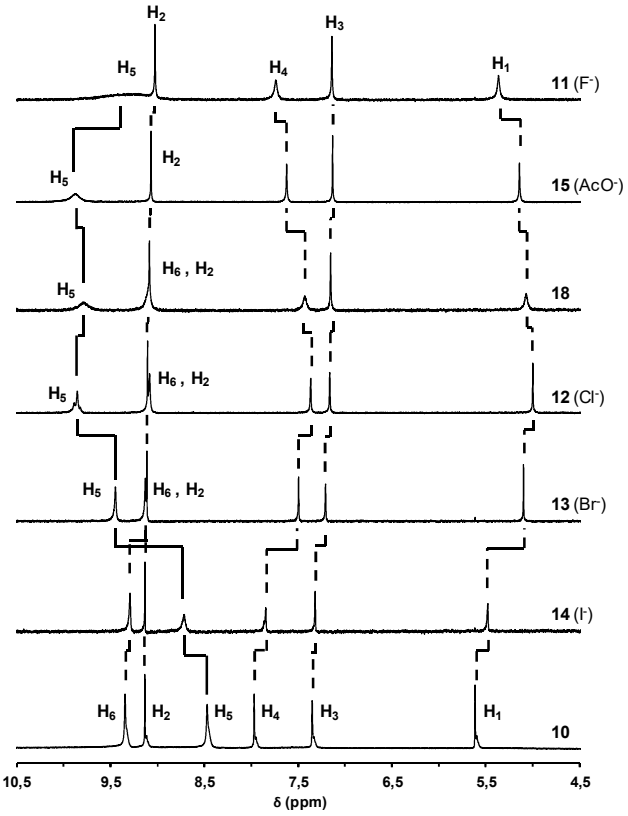


Figure 1. Partial ^{1}H NMR spectra of diluted solutions of **10**-**15** and **18** (in acetone-d_6). The numbering scheme is detailed on Scheme 1.

Since the host-guest complexes between **10** and anions **A**$^-$ are only slightly soluble in polar media, their association constants were measured through absorption spectrophotometric titrations in an apolar solvent, i.e. 1,2-dichloroethane (Figure 2 and Figures S7-S11 in the supporting information). The absorption spectrum of the host **10** is characterized by an intense absorption in the UV region (340 nm) together with a shoulder lying at a lower energy (400 nm). Previous TD-DFT calculations were performed on similar derivatives[18b] and showed that these bands originate from π-π* transitions of the electronically independent 1,5-diamino-2,4-dinitro-benzene units, those of the diamido-substituted benzene rings being centred at much higher energies. Consequently, the anion complexation process produces only little modifications of the shape and intensity of the UV-vis spectrum of the receptor. Indeed, when a solution of anions (F^-, Cl^-, Br^-, I^-, AcO^- or HSO_4^-) is added to a solution of **10**, the intensity of the main absorption is slightly decreasing while its shoulder is slightly red-shifted.

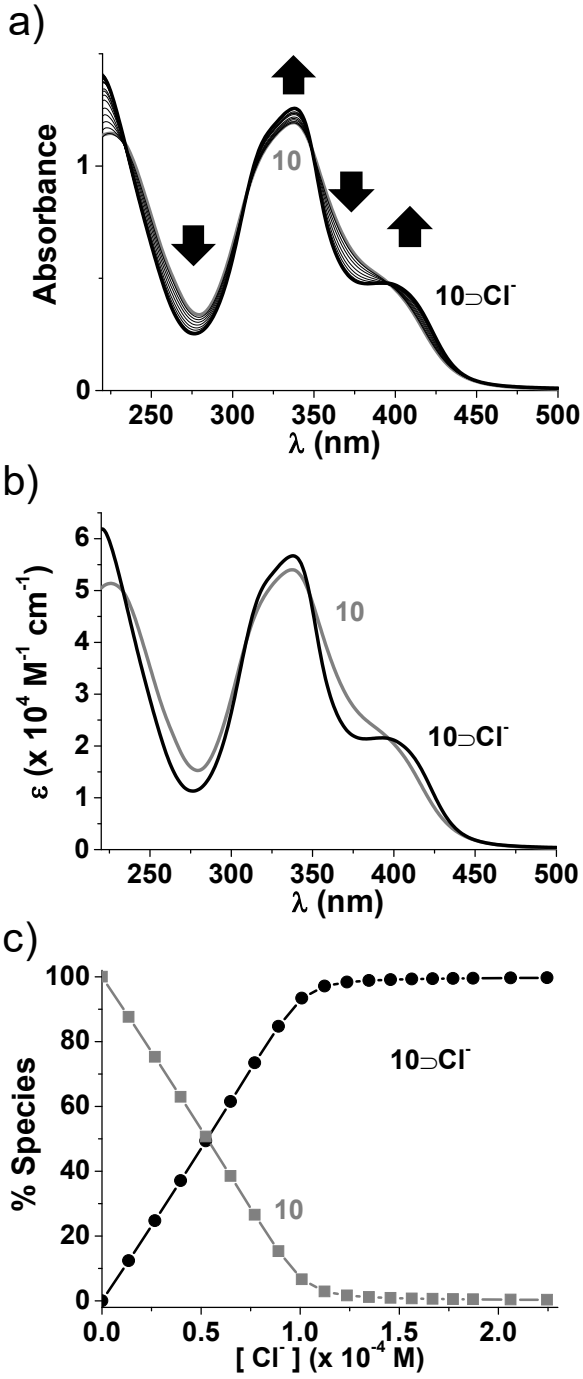


Figure 2. a) Spectrophotometric titration of **10** ([**10**] = 1.098 × 10^{-4} M) by 0-2.5 equivalents of [(*n*Bu$_4$)N]Cl in 1,2-dichloroethane. b) Electronic spectra (corrected from dilution effects) of **10** and of the host-guest complex **10**⊃**Cl**$^-$. c) Distribution diagram between **10** and **10**⊃**Cl**$^-$ during the spectrophotometric titration.

Nevertheless, the noticeable spectral amplitudes recorded along these titrations combined to the presence of four isosbestic points (Figure 2) substantiate the speciation model previously established by ESI-MS, ^{1}H NMR and elementary analyses and confirm the exclusive formation of [1+1] host-guest complexes involving **10** and one anion. These absorption spectrophotometric data were statistically

processed assuming the equilibrium (1) for the 6 different anions by using nonlinear least-squares techniques (see the experimental section in the supporting information).

$$\mathbf{10} + \mathbf{A}^- \rightleftharpoons [\mathbf{10}\supset\mathbf{A}^-] \quad K_a \qquad (1)$$

The six corresponding formation constants are listed in Table 1 and evidence a marked capacity of host **10** towards anions recognition together with a substantial size discrimination capacity. The highest association constant values were calculated to be close to 10^6 M^{-1} and are reached for the hardest anions F^-, AcO^- and Cl^- while those measured for the bulkier anions such as Br^- or I^- are more than two orders of magnitude lower. The latter anion HSO_4^- was chosen as a guest able to interact concomitantly with the four pendant amide groups of the receptor but its corresponding host-guest formation constant was only superior to that measured for iodide. As suspected before, an improved induced-fit between the receptor cavity and the chloride ion is clearly seen. The corresponding formation constant is more than two times higher than that of fluoride and more than ten times higher than the association constant measured for bromide. This unexpected selectivity probably originates from the spatial arrangement of the four interacting amide groups produced by the 1,3-alternate conformation of the azacalixarene receptor (see below).

It has to be noted that the influence of the water on the binding process of Cl^- and Br^- was further evaluated through new absorption spectrophotometric titrations conducted in C2H5Cl2/H2O (99.9:0.1 v/v) (Figures S12 and S13 in the supporting information). No significant effect of the water content was observed as shown by the very close binding constants that were measured under these new experimental conditions (log K10⊃Br^- = 5.2(4) in the presence of water versus log K10⊃Br^- = 5.1(2) in the absence of water; log K10⊃Cl^- = 6.3(2) in the presence of water versus log K10⊃Cl^- = 6.4(4) in the absence of water).

Table 1. Formation constants of **10**⊃$\mathbf{A}^-$ at 298 k in 1,2-dichloroethane.

A^-	F^-	Cl^-	Br^-	I^-	AcO^-	HSO_4^-
log K_a	6.0 (4)	6.4 (4)	5.1 (2)	3.6 (2)	5.7 (2)	4.0 (1)
K_a^{X-}/K_a^{I-}	251	631	32	1	126	2.5
Size (pm)[a]	133	181	196	220	-	-

[a] according to ref [30]

Single crystal X-ray structures of the cavitands 4b, 4c and 10, and of the host-guest complexes 11, 13 and 15.

Diffracting single crystals were grown and were suitable for an X-ray diffraction study of compounds **4b**, **4c**, **10**, **11**, **13** and **15** (Figures 3-6 and Figures S14-S17 in the Supporting Information). Details of the experimental structure determinations are given in the Supporting Information with the corresponding structural data (Table S1 and S2). Two structurally similar but interacting molecules of **15** are found in the corresponding asymmetric unit while those of **4b**, **4c**, **10** (**10a** and **10b**) and **13** consist of a single host or host-guest molecule. The structure of the receptor **10** is described thanks to two different single crystals grown using different experimental conditions and named **10a** and **10b**.

The seven different crystal structures share a common feature which is the 1,3-alternate conformation of the tetraaza[1_4]cyclophane backbone. This unique and stabilized conformation probably originates from the combination of two distinct features of the 1,5-diamino-2,4-dinitro-benzene units that are found in each compound. The first one is the sp^2 hybridation adopted by all the nitrogen bridging atoms that are conjugated with their adjacent dinitrobenzene rings. This conjugation is corroborated by the N-C average bond length (1.36 Å) between the bridging nitrogen atoms and the electron-withdrawing dinitrobenzene ring which is significantly shorter than the one with the other aromatic unit (1.43 Å). Each nitro group is essentially planar with its attached aromatic ring as illustrated by the nitro oxygen atoms deviation from the benzene ring ranging from 0.01 to 0.43 Å and averaging 0.12 Å in the seven X-ray structures. This orientation allows the formation of intramolecular hydrogen bonds between one oxygen atom of the nitro group and the acidic hydrogen atom borne by the bridging nitrogen located at the *ortho* position (Figure 3) with bond lengths ranging from 2.01 to 2.06 Å and averaging 2.04 Å. These strong intramolecular hydrogen bonds are increasing the macrocycle inversion barrier and thus stabilizing the 1,3-alternate conformation. Using the classification of Tsue *et al.*[8a], the conformation retained in all structures follows the clip-like type and defines two cavities between aryl groups whose sizes and shapes will be here describes using the four structural parameters d_1, θ_1, d_2 and θ_2 (Figure 3) that are listed in Table 2. d_1 is the distance between the centroids of the two isolated and almost parallel benzene rings defining the angle θ_1 while d_2 will describe the corresponding distance between the two conjugated dinitro-benzene forming the angle θ_2.

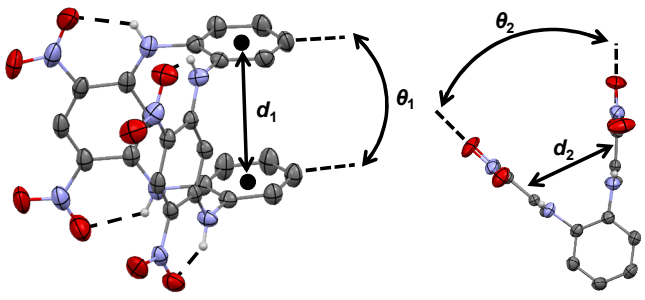


Figure 3. Two views of the single crystal X-ray structure of **4c** showing the structural parameters d_1, d_2, θ_1 and θ_2 (aromatic hydrogen atoms and solvent molecules are omitted for the sake of clarity). The dashed lines show the intramolecular $NO_2\cdots HN$ hydrogen bonds.

The connection of the two dinitro-benzene rings by *ortho*-phenylenediamine moieties in **4c** induces a short distance d_1 of 4.80 Å between the two simple benzene rings that are almost parallel (θ_1 = 4°). This close arrangement

(d_1 = 4.62 Å and θ_1 = 5°) is retained when four bulky amide groups are introduced in **4b** (Figure 4). In this compound, the two adjacent amide groups of a single aryl unit are forming a strong C=O···H-N intermolecular hydrogen bond with a O···H length of *ca.* 2.00 Å (Figure 4c). This interaction is reinforced by a concomitant weak C=O···H-C hydrogen bond (Figure 4c). Therefore, in the structure of **4b** only two amides NH are likely to interact with a guest. The participation of the four amide groups in a single recognition process will be facilitated if such intermolecular interactions are not enabled by a higher distance between the two amides groups born by an identical aryl unit as in the structure of its isomeric receptor **10**.

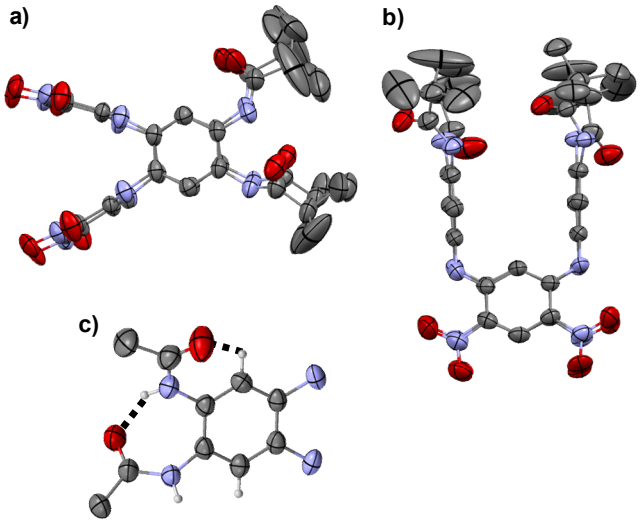


Figure 4. a) and **b)** Two views of the single crystal X-ray structure of **4b** (hydrogen atoms and solvent molecules are omitted for the sake of clarity). **c)** Partial view showing intramolecular hydrogen bonds involving the amide groups.

The modification of the substitution pattern in **10** produces a higher distance d_2 of 7.33 Å between the two dinitro-benzene rings. Actually, the two different structures of **10** (**10a** and **10b**) show that this receptor forms already host-guest complexes with two water molecules whatever the experimental conditions we chose to get diffracting single crystals (Figure 5 and S14). This affinity towards water molecules is due to the formation of a well define hydrogen bond network between the four amide groups of the receptor **10** and the two hosted molecules. Since these networks are similar in **10a** and **10b** only the structure of **10a** will be detailed below.

The four amide groups of the receptor **10** are involved in the host-guest process through their participation in strong hydrogen bonds involving either their carbonyl CO functions or their N-H groups interacting respectively with the water hydrogen or oxygen atoms (Figure 5c). Each water molecule forms a C=O···H-O-H hydrogen bond with one aryl unit concomitantly to a N-H···OH_2 hydrogen bond with the opposite and almost parallel aryl unit. This supramolecular network is completed by a fifth hydrogen bond between the two guest water molecules. The two remaining carbonyl groups form two intramolecular hydrogen bonds with the N-H bridging groups while the two remaining N-H amide groups interact with external acetone solvent molecules. Even if the connecting dinitro-aryl fragments are identical in **4b** and **10**, the complexation of two water molecules induces a higher distance between the two tetra-amido units d_1 that increases from 4.80 Å in **4b** to 5.05 Å in **10a**.

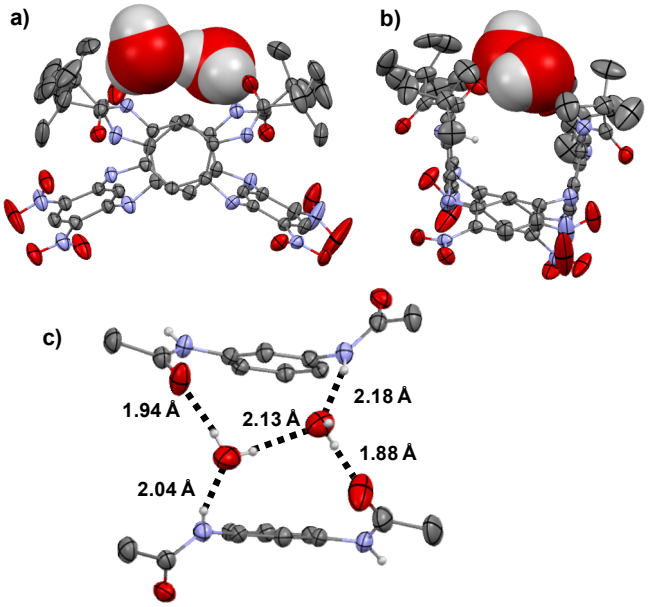


Figure 5. a) and **b)** Two views of the first single crystal X-ray structure of **10 (10a)** (hydrogen atoms and external solvent molecules are omitted for the sake of clarity). The guest water molecules are shown by space-filling model. **c)** Partial view showing the hydrogen bond network involving the amide groups and the water guest molecules.

Surprisingly, this distance becomes shorter (d_1 = 4.63 Å or 4.70 Å) when the acetate ion is complexed and replaces one of the two guest water molecules in the X-ray structure of **15**. The corresponding asymmetric unit contains two slightly different host-guest complexes **15a** and **15b** that interact with each other through weak intermolecular interactions but are forming almost identical hydrogen bond networks with their guests (Figures 6 and S15). The introduction of a charged anionic guest induces a new orientation of the four amide groups that are interacting with the two guests only through hydrogen bonds involving their N-H amide groups. This reorientation is accompanied by four stabilizing hydrogen bonds formed by the four carbonyl groups and the four NH bridging groups with NH···OC bond length values close to 2.60 Å. In the cavity, the four strong intermolecular N-H···O hydrogen bonds are completed in the structure of **15** by a fifth hydrogen bond taking place between the two guests (Figure 6).

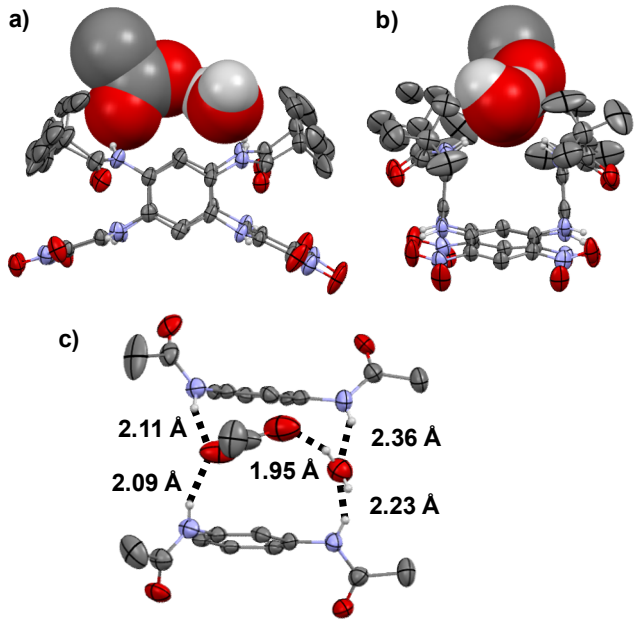


Figure 6. a) and **b)** Two views of the first host-guest complex contained in the asymmetric unit of the single crystal X-ray structure of **15 (15a)** (the ammonium cation, the hydrogen atoms and the external solvent molecules are omitted for the sake of clarity). The guest acetate ion and water molecule are shown by space-filling model. **c)** Partial view showing the hydrogen bond network involving the amide groups and the guest anion and water molecule.

The structures of **11** and **13** suffered from partial disorder (Figures S16 and S17). For example, the guest fluoride ion of **11** was shown to occupy four different fitted positions in the cavity while the bromide ion in **13** occupies alternatively one of the two possible positions between opposite N-H amide groups (Figures S16 and S17). Nevertheless, we are confident that the corresponding structural qualities are high enough to ensure that the corresponding host guest processes are using a similar complexation mode based on hydrogen bond networks involving the four N-H amide groups and two guests that are the anion and a water molecule. It has to be noted that the replacement of the acetate anion by a bromide or a fluoride one has no effect on the interplanar distances d_1 and d_2 which are roughly the same in the structures of **11**, **13** and **15** (Table 2). If the higher affinity of the receptor **10** for hardest anions is the presumable result of the formation of more stable intermolecular hydrogen bonds, its selectivity towards chloride probably originates from a perfect size match between the guests and the arrangement of the four amide groups at the edges of the cavity of the azacalixarene scaffold.

Conclusions

The 1,3-alternate conformation of calix[4]arenes has been considered as the "smart" and valuable one since this conformation proved to be the basis of numerous cryptands with practical applications.[31] In the calix[4]arene family, two strategies are usually used to stabilize this particular conformation. The first one relies on the introduction of bulky substituents while the second one requires the fabrications of straps upon one or two of the resulting cavities. We described herein that such structural modifications are not required to produce, in solution, the inflexible 1,3-alternate conformation of up to six different tetraaza[1_4]cyclophanes. For example, heating up to 410 K DMSO solutions of **4b** or **10** up to 410 K did not produce any changes of their respective ^{1}H NMR spectra. Moreover, it has been shown that if the four amide groups of **10** are replaced by iso-propyl substituents, the corresponding inversion barrier reaches a value superior to 85 kJ.mol^{-1}.[18a]

Consequently, the stable and "smart" 1,3-alternate conformation can be used as a scaffold to organize multiple supramolecular recognition sites. The present contribution illustrates such applications through the incorporation in the tailored receptor **10** of four peripheral amide groups that participate in a single and identical host-guest process towards anions or water molecules. This receptor proved to be particularly efficient in the bind of micromolar to submicromolar amounts of hard anions such as fluorides or acetates and showed an unexpected selectivity for chloride anions. This supramolecular recognition is due to the appearance of a well defined network of intermolecular hydrogen bonds that reaches likely an optimum arrangement when a chloride is incorporated in the macrocyclic cavity. The interaction of tetra-amide receptors **7**-**10** with others guests is presently investigated as well as the introductions and applications of others supramolecular recognition groups on the azacalixarene scaffold.

Experimental Section

General Remarks: All reagents were used as received. Absorption spectrophotometric titrations analyses were carried out using spectroscopic grade 1,2-dichloroethane (Merck, 99.8% or Carlo Erba, 99.8% for spectroscopy). The *n*-tetrabutylammonium salts (*n*Bu_4NI 98% Alfa Aesar, (*n*Bu_4N)CH_3CO_2 98% Alfa Aesar, *n*Bu_4NF 98% Alfa Aesar, *n*Bu_4NBr 99+% Acros Organics, *n*Bu_4NCl 98% Acros Organics and (*n*Bu_4N)HSO_4 99% Acros Organics) were purchased from commercial sources and used without further purification. All solutions were protected from daylight to avoid any photochemical degradation. Flash column chromatography was performed on silica gel 60 (230-400 mesh).

^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 400 Ultrashield or on a JEOL ECS400 NMR spectrometer. Chemical shifts are given in ppm relative to residual peaks of acetone-d_6 (δ = 2.05 ppm) or DMSO-d_6 (δ = 2.50 ppm). UV-vis absorption spectra were measured with a Shimadzu UV-2401 (PC) instrument or with a Varian Cary 50. High Resolution Mass Spectrometry (HRMS-ESI) and Mass Spectrometry (ESI-MS) analyses were performed on a QStar Elite (Applied Biosystems SCIEX) spectrometer or on a SYNAPT G2 HDMS (Waters) spectrometer. These two instruments are equipped with an electrospray ionization source.

All stock solutions used for spectrophotometric titrations were prepared by weighing appropriate amount of the solid samples using a Mettler Toledo XA105 Dual Range (0.01/0.1 mg - 41/120 g) and the complete dissolution in 1,2-dichloroethane was achieved using an ultrasonic bath. The concentrations of the stock solutions of **10** (~ 2.20×10^{-4} M) and the *n*-tetrabutylammonium salts (~ 1.31-1.67×10^{-3} M) were calculated by quantitative dissolution of solid samples in 1,2-dichloroethane. The absorption spectrophotometric titrations of

the tetraazacalix[1$_4$]arene **10** (2.20×10^{-4} M) with the *n*-tetrabutylammonium salts were carried out in a Hellma quartz optical cell (2 mm). The stock solutions of the ammonium salts were further diluted between 5 to 10 times and microvolumes of the diluted solutions of nBu$_4$N***X*** (***X*** = Br$^-$, I$^-$, F$^-$, Cl$^-$, HSO_4^- and $CH_3CO_2^-$) were added to 500 µL of the receptor with microliter Hamilton syringes (#701 and #750). Special care was taken to ensure that complete equilibration was attained. The corresponding absorption UV-vis spectra were recorded from 220 nm to 600 nm on an Agilent Cary 5000 spectrophotometer maintained at 25.0(2) °C by the flow of a Cary Varian Dual Cell Peltier accessory. The spectrophotometric data were processed with the Specfit programs, which adjust the stability constants and the corresponding extinction coefficients of the species formed at equilibrium. Specfit[32-34] uses factor analysis to reduce the absorbance matrix and to extract the eigenvalues prior to the multiwavelength fit of the reduced data set according to the Marquardt algorithm.[35, 36] Distribution curves of the various species were calculated using the Hyss program.[37]

The intensity data of the X-ray-quality crystals of **10b**, **4b** and **4c** were collected on a Bruker–Nonius KappaCCD diffractometer using MoKα radiation (λ= 0.71073 Å). For these compounds, data collection was performed with COLLECT,[38] cell refinement and data reduction with DENZO/SCALEPACK.[39] The intensity data for compounds **11**, **15**, **13** and **10a** were collected on a Rigaku Oxford Diffraction SuperNova diffractometer using CuKα radiation (λ=1.54184 Å). For these compounds, data collection, cell refinement and data reduction were performed with CrysAlis^{Pro} (Rigaku Oxford Diffraction). The structures were solved with SIR92,[40] SHELXS[41] or SHELXL-2013[41] was used for full matrix least squares refinement. The hydrogen atoms were found experimentally for compounds **11** (except for the water molecules), for the amines of compound **13**, for compound **10a** (except for the methyl groups) and for the water molecules of compound **10b**, the remaining H-atoms were introduced at geometrical positions. All hydrogen Uiso parameters were fixed to 1.2Ueq(parent atom) for the aromatics or amines and to 1.5Ueq(parent atom) for the remaining ones. CCDC-1430290 (**15**), CCDC-1430291 (**13**), CCDC-1430292 (**10a**), CCDC-1430294 (**11**), CCDC-1430295 (**4c**), CCDC-1430296 (**10b**) and CCDC-1430297 (**4b**) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request:cif.

Organic synthesis: 1-Benzyl-4-dimethylaminopyridinium bromide,[28] 4-dimethylaminopyridinium bromide,[29] 4,5-Diamino-1,2-bis(2,2-dimethylpropionamido)benzene (**2b**),[25] 4,6,17,19-tetranitro-2,8,15,21-tetraazacalix[4]arene (**4c**)[24d] and 4,6,16,18-tetranitro-10,12,22,24-tetraamino-2,8,14,20-tetraazacalix[4]arene (**6**)[26] were prepared and purified according to literature procedures.

***N*^{1},*N*^{2}-bis(5-fluoro-2,4-dinitrophenyl)benzene-1,2-diamine 3a:** A solution of 1,5-difluoro-2,4-dinitrobenzene **1** (2.52 g, 12.35 mmol, 2 equiv.) in THF (50 mL) was cooled with an ice-water bath before a solution of benzene-1,2-diamine **2a** (666 mg, 6.16 mmol, 1 equiv.) and *N*-ethyldiisopropylamine (2.6 mL, 14.9 mmol, 2.4 equiv.) in THF (50 mL) was added dropwise. The mixture stirred during 3 hours at 0 °C and then during 48 hours at room temperature. The completion of the reaction was detected by a TLC on silica (AcOEt/Cyclohexane 50:50). The solvent was removed under vacuum before acetone (100 mL) was added. The resulting suspension was heated to reflux for 5 minutes and the solvent was removed under vacuum. The resulting solid was washed with EtOH (3 x 25 mL) and dried under vacuum to yield **3a** (2.66 g, 5.58 mmol, 91%). M. p. 232-234 °C ;^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ = 10.15 (brs, 2H, NH), 8.82 (d, ^4J (H, F) = 8.0 Hz, 2H, Ar-H), 7.62-7.54 (m, 4H, Ar-H), 6.98 ppm (d, ^3J (H, F) = 14.0 Hz, 2H, Ar-H); ^{13}C NMR (62 MHz, DMSO-d_6, 25 °C): δ = 158.5 (d, ^1J (C, F) = 263.3 Hz), 147.6 (d, ^2J (C, F) = 13.3 Hz), 134.0, 129.0, 128.5, 128.1 (d, ^4J (C, F) = 0.9 Hz), 126.8, 126.2 (d, ^2J (C, F) = 10.0 Hz), 104.2 ppm (d, ^2J (C, F) = 26.9 Hz); $C_{18}H_{14}F_2N_7O_8$ (476.30): calcd. C 45.39, H 2.12, N 17.64; found C 45.92, H 2.21, N 17.13; ESI-MS ([M+NH$_4$]$^+$): 494.0; calcd. for $C_{18}H_{14}F_2N_7O_8^+$: 494.1.

***N*^{1},*N*^{2}-bis(5-fluoro-2,4-dinitrophenyl)-4,5-bis(2,2-dimethylpropionamido)-benzene-1,2-diamine 3b:** A solution of **2b** (154.3 mg, 0.503 mmol, 1 equiv.) and *N*-ethyldiisopropylamine (0.2 mL, 1.1 mmol, 2.2 equiv.) in THF (6 mL) was added dropwise to a solution of **1** (225 mg, 1.1 mmol, 2.2 equiv.) in THF (6 mL) at 0°C. The mixture was stirred during 3 hours at 0 °C and at room temperature for 66 hours. The completion of the reaction was detected by a TLC (silica, AcOEt/Cyclohexane 50:50). The solvent was then removed under vacuum. The crude product was dissolved in a minimum amount of absolute EtOH. The solvent was then concentrated to 5% of its original volume before water (20 mL) was added. The resulting suspended solid was filtered, washed successively with hot water (10 mL), EtOH (10 mL) and Et$_2$O (5 mL) before it was dried under vacuum to yield pure **3b** (243 mg, 0.360 mmol, 72%). M. p. 256-258 °C;^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ = 10.14 (brs, 2H, NH), 9.07 (brs, 2H, NH), 8.96 (d, ^3J (H, F) = 8.0 Hz, 2H, Ar-H), 7.88 (s, 2H, Ar-H), 7.21 (d, ^3J (H, F)= 13.8 Hz, 2H, Ar-H), 1.33 ppm (s, 18H, C(CH$_3$)$_3$); ^{13}C NMR (62 MHz, DMSO-d_6, 25 °C): δ = 177.0, 158.5 (d, ^1J (C, F) = 263.2 Hz), 147.8 (d, ^2J (C, F) = 13.5 Hz), 131.0, 130.6, 128.1, 126.8, 126.2 (d, ^2J (C, F) = 9.9 Hz), 124.7, 104.3 (d, ^2J (C, F) = 26.7 Hz), 38.9, 27.1 ppm; $C_{28}H_{28}F_2N_8O_{10}$ (674.57): calcd. C 49.85, H 4.18, N 16.61; found: C 49.47, H 4.29, N 16.43; ESI-MS ([M+H]$^+$): 675.1; calcd. for $C_{28}H_{29}F_2N_8O_{10}^+$: 675.2.

4,6,17,19-tetranitro-11,12-bis(2,2-dimethylpropionamido)-2,8,15,21-tetraazacalix[4]arene 4a: A solution of **3a** (1.06 g, 2.26 mmol, 1.05 equiv.) and **2b** (650 mg, 2.12 mmol, 1 equiv.) in acetonitrile (30 mL) was stirred before *N*-ethyldiisopropylamine (1.2 mL, 6.93 mmol, 3.3 equiv.) was added dropwise. The mixture was heated to reflux during 22 hours before it was at 0 °C for 1 hour. The resulting precipitated solid was filtered, washed successively with acetonitrile (40 mL), hot water (40 mL) and Et$_2$O (20 mL), and then dried under vacuum to yield pure **4a** (840 mg, 1.13 mmol, 54%). M. p. >300 °C ;^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ = 9.26 (brs, 2H, NH), 9.19 (brs, 2H, NH), 9.15 (brs, 2H, NH), 8.76 (s, 2H, Ar-H), 7.39 (s, 2H, Ar-H), 7.33-7.22 (m, 4H, Ar-H), 5.05 (s, 2H, Ar-H), 1.27 ppm (s, 18H, C(CH$_3$)$_3$); ^{13}C NMR (62 MHz, DMSO-d_6, 25 °C): δ = 176.7, 147.3, 147.2, 136.1, 132.5, 131.1, 130.9, 129.0, 127.4, 126.7, 124.1, 124.1, 98.8, 39.0, 27.1 ppm; $C_{34}H_{34}N_{10}O_{10}$ (742.69): calcd. C 54.98, H 4.61, N 18.86; found: C 54.91, H 4.62, N 18.64; ESI-MS ([M+NH$_4$]$^+$): 760.3; calcd. for $C_{34}H_{38}N_{11}O_{10}^+$: 760.2.

4,6,17,19-tetranitro-11,12,24,25-tetra(2,2-dimethylpropionamido)-2,8,15,21-tetraazacalix[4]arene 4b: A solution of **3b** (151 mg, 0.224 mmol, 1 equiv.) and **2b** (71 mg, 0.232 mmol, 1.04 equiv.) were dissolved in acetonitrile (4 mL) was stirred before *N*-ethyldiisopropylamine (0.1 mL, 0.578 mmol, 2.6 equiv.) was added dropwise. The mixture was heated to reflux for 46 hours and then cooled to room temperature. The solvent was removed under vacuum. The resulting solid was washed with EtOH (2 x 30 mL) and dried under vacuum to yield pure **4b** (71 mg, 0.075 mmol, 34%). M. p. >300 °C ;^{1}H NMR (250 MHz, DMSO-d_6, 25 °C): δ = 9.21 (brs, 4H, NH), 8.91 (brs, 4H, NH), 8.78 (s, 2H, Ar-H), 7.44 (s, 4H, Ar-H), 5.23 (s, 2H, Ar-H), 1.23 ppm (s, 36H, C(CH$_3$)$_3$); $C_{44}H_{52}N_{12}O_{12}$ (940.96): calcd. C 56.16, H 5.57, N 17.86; found: C 55.92, H 5.61, N 17.56. ESI-MS ([M+NH$_4$]$^+$): 958.4; calcd. for $C_{44}H_{56}N_{13}O_{12}^+$: 958.4.

4,6,16,18-tetranitro-10,12,22,24-tetra(propionamido)-2,8,14,20-tetraazacalix[4]arene 7: A solution of azacalixarene **6** (100 mg, 0.16 mmol, 1 equiv.) and propionyl chloride (0.12 mL, 1.3 mmol, 8 equiv.) in acetonitrile (200 mL) was stirred under argon during 1 hour at room temperature before *N*-ethyldiisopropylamine (0.23 mL,

1.3 mmol, 8 equiv.) was added dropwise. The mixture was refluxed overnight. The reaction was monitored by TLC (cyclohexane/ethyl acetate, 2:3, Rf = 0.2). The solvent was evaporated to dryness. The residue was triturated in water and filtered. A recrystallization from $CHCl_3$ afforded pure **7** compound as a yellow solid (94 mg, 0.11 mmol, 87%). M. p. 225-228°C ;^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 9.50 (brs, 4H, Ar-NH-Ar), 9.32 (brs, 4H, NH-CO), 9.02 (s, 2H, Ar-H), 8.04 (s, 2H, Ar-H) 7.24 (s, 2H, Ar-H), 5.42 (s, 2H, Ar-H), 2.22 (q, ^3J (H, H) = 7.4 Hz, 8H, -CH_2-CH_3), 0.95 ppm (t, ^3J (H, H) = 7.4 Hz, 12H, -CH_2-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): δ = 172.61, 147.32, 133.97, 127.92, 127.56, 126.97, 124.78, 119.56, 94.77, 28.68, 9.36 ppm; HRMS-ESI: ([M+NH_4]$^+$): 846.2910 ([M+Na]$^+$): 851.2465; calcd. for $C_{36}H_{40}N_{13}O_{12}^+$: ([M+$NH_4$]$^+$): 846.2914 and $C_{36}H_{36}N_{12}NaO_{12}^+$ ([M+Na]$^+$): 851.2468.

4,6,16,18-tetranitro-10,12,22,24-tetra(butylamido)-2,8,14,20-tetraazacalix[4]arene 8: A solution of azacalixarene **6** (150 mg, 0.25 mmol, 1 equiv.) and butyryl chloride (0.10 mL, 1.0 mmol, 4 equiv.) in acetonitrile (50 mL) was stirred under argon during 1 hour at room temperature before *N*-ethyldiisopropylamine (0.17 mL, 1.0 mmol, 4 equiv.) was added dropwise. The mixture was refluxed overnight. The solvent evaporated to dryness. The residue was dissolved in CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated under vacuum. A chromatography on silica gel (MeOH / CH_2Cl_2, 1:9, Rf = 0.34) followed by a crystallization from a mixture of CH_2Cl_2 and *n*-hexane afforded the pure compound **8** as a yellow solid (120 mg, 0.13 mmol, 55%). M. p. >300 °C ;^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 9.58 (brs, 4H, Ar-NH-Ar), 9.34 (brs, 4H, NH-CO), 9.01 (s, 2H, Ar-H), 7.99 (s, 2H, Ar-H) 7.24 (s, 2H, Ar-H), 5.40 (s, 2H, Ar-H), 2.24 (t, ^3J (H, H) = 6.5 Hz, 8H, CO-CH_2), 1.52 (m, 8H, CH_2-CH_3), 0.88 ppm (t, ^3J (H, H) = 7.3 Hz, 12H, CH_3); HRMS-ESI: ([M+NH_4]$^+$): 902.3539; calcd. for $C_{40}H_{48}N_{13}O_{12}^+$: 902.3540.

4,6,16,18-tetranitro-10,12,22,24-tetra(pentylamido)-2,8,14,20-tetraazacalix[4]arene 9: A solution of azacalixarene **6** (100 mg, 16 µmol) and valeroyl chloride (79 µL, 0.66 mmol, 4 equiv.) in acetonitrile (150 mL) was stirred under argon during 1 hour at room temperature before *N*-ethyldiisopropylamine (0.11 mL, 0.66 mmol, 4 equiv.) was added dropwise. The mixture was refluxed overnight. The solvent was evaporated to dryness. The residue was dissolved in CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated under vacuum. A chromatography on silica gel (MeOH / CH_2Cl_2, 1:9, Rf = 0.47) followed by a crystallization from a mixture of CH_2Cl_2 and *n*-hexane afforded the pure compound **9** as a yellow solid (112 mg, 12 µmol, 72%). M. p. >300 °C ;^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 9.56 (brs, 4H, Ar-NH-Ar), 9.31 (brs, 4H, NH-CO), 9.01 (s, 2H, Ar-H), 7.92 (s, 2H, Ar-H) 7.22 (s, 2H, Ar-H), 5.33 (s, 2H, Ar-H), 2.24 (t, ^3J (H, H) = 7.1 Hz, 8H, CO-CH_2), 1.43 (m, 8H, CO-CH_2-CH_2-), 1.92 (m, 8H, -CH_2-CH_3), 0.80 ppm (t, ^3J (H, H) = 7.3 Hz, 12H, CH_3); HRMS-ESI: ([M+NH_4]$^+$): 958.4167; calcd. for $C_{44}H_{56}N_{13}O_{12}^+$: 958.4166.

4,6,16,18-tetranitro-10,12,22,24-tetra(2,2-dimethylpropionamido)-2,8,14,20-tetraazacalix[4]arene 10: A solution azacalixarene **6** (190 mg, 0.31 mmol) and trimethylacetyl chloride (0.38 mL, 3.1 mmol, 10 equiv.) in acetonitrile (200 mL) was stirred under nitrogen during 1 hour at room temperature before *N*-ethyldiisopropylamine (0.55 mL, 3.1 mmol, 10 equiv.) was added dropwise. The mixture was refluxed overnight. The reaction was monitored by TLC (cyclohexane/ethyl acetate, 2:3, Rf = 0.35). The solvent was evaporated to dryness and the residue was dissolved in CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$, filtered and evaporated under vacuum. The crude residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate, 2:3) to yield **10** as a yellow solid (94 mg, 0.10 mmol, 32%). M. p. >260 °C ;^{1}H NMR (250 MHz, DMSO-d_6, 25 °C) : δ = 9.30 (brs, 4H, Ar-NH-Ar), 9.00 (brs, 6H, Ar-H, NH-CO), 7.57 (s, 2H, Ar-H), 7.41 (s, 2H, Ar-H), 5.61 (s, 2H, Ar-H), 1.09 ppm (s, 36H, $C(CH_3)_3$); ^{1}H NMR (250 MHz, acetone-d_6, 25 °C) : δ = 9.34 (brs, 4H, Ar-NH-Ar), 9.13 (s, 2H, Ar-H), 8.47 (brs, 4H, NH-CO), 7.98 (s, 2H, Ar-H), 7.35 (s, 2H, Ar-H), 5.61 (s, 2H, Ar-H), 1.18 ppm (s, 36H, $C(CH_3)_3$); $C_{44}H_{52}N_{12}O_{12}\cdot 2H_2O$ (976.99): calcd. C 54.09, H 5.78, N 17.2; found C 54.35, H 5.31, N 17.10; HRMS-ESI: ([M+NH_4]$^+$): 958.4166; calcd. for $C_{44}H_{56}N_{13}O_{12}^+$: 958.4166.

Host-guest complex 11: A solution of tetra-amido-tetraazacalixarene **10** (10 mg, 10 µmol) and tetra-*n*-butylammonium fluoride (2.7 mg, 10 µmol, 1 equiv.) in acetone (1.5 mL) was refluxed for 24 hours. The resulting precipitate was filtered, washed with acetone and dried under vacuum to yield the host-guest complexe 11 (7.4 mg, 6.1 µmol, 60%). M. p. (dec.) >100 °C ;^{1}H NMR (250 MHz, acetone-d_6, 25 °C) : δ = 9.02 (s, 2H, Ar-H), 7.74 (s, 2H, Ar-H), 7.14 (s, 2H, Ar-H), 5.36 (s, 2H, Ar-H), 3.44 (t, ^3J (H, H) = 8.6 Hz, 8H, N-CH_2-), 1.86 (m, 8H, N-CH_2-CH_2), 1.45 (m, 8H, -CH_2-CH_3), 1.15 (s, 36H, CO-C$(CH_3)_3$), 0.98 ppm (t, ^3J (H, H) = 7.3 Hz, 12H, CH_3); $C_{60}H_{88}FN_{13}O_{12}\cdot 3H_2O$ (1256.47): calcd. C 57.35, H 7.54, N 14.49 found C 57.39, H 7.05, N 14,31; ESI-MS: m/z 469.3 ([M-2H]$^{2-}$), 939.4 ([M-H]$^-$); calcd. for $C_{44}H_{50}N_{12}O_{12}^{2-}$ ([M-2H]$^{2-}$) 469.2 calcd. for $C_{44}H_{51}N_{12}O_{12}^-$ ([M-H]$^-$) 939.5.

Host-guest complex 12: A solution of tetra-amido-tetraazacalixarene **10** (18 mg, 19 µmol) and tetra-*n*-butylammonium chloride (5.8 mg, 21 µmol, 1.1 equiv.) in acetone (1.5 mL) was refluxed for 24 hours. The resulting precipitate was filtered, washed with acetone and dried under vacuum to yield **12** (18 mg, 14 µmol, 75%). M. p. > 300 °C ;^{1}H NMR (250 MHz, acetone-d_6, 25 °C) : δ = 9.86 (brs, 2H, NH-CO), 9.10 (s, 2H, Ar-H), 9,08 (brs, 4H, Ar-NH-Ar), 7.36 (s, 2H, Ar-H), 7.16 (s, 2H, Ar-H), 4.99 (s, 2H, Ar-H), 3.49 (t, ^3J (H, H) = 8.6 Hz, 8H, N-CH_2-), 1.83 (m, 8H, N-CH_2-CH_2-), 1.45 (m, 8H, -CH_2-CH_3), 1.13 (s, 36H, CO-C$(CH_3)_3$), 0.98 ppm (t, ^3J (H, H) = 7.31 Hz, 12H, CH_3); $C_{60}H_{88}ClN_{13}O_{12}\cdot H_2O$ (1236.89): calcd. C 58.26, H 7.33, N 14.72; found C 58.42, H 7.39, N 14.48; ESI-MS: 939.4 ([M-H]$^-$), 975.4 ([M+Cl]$^-$); calcd. for $C_{44}H_{51}N_{12}O_{12}^-$ ([M-H]$^-$) 939.5 calcd. for $C_{44}H_{52}ClN_{12}O_{12}^-$ ([M-H]$^-$) 975.4.

Host-guest complex 13: A solution of tetra-amido-tetraazacalixarene **10** (15 mg, 16 µmol) and tetra-*n*-butylammonium bromide (5.65 mg, 17 µmol, 1.1 equiv.) in acetone (2 mL) was refluxed for 24 hours. The resulting yellow precipitate was filtered off, washed with acetone and dried under vacuum (14 mg, 11 µmol, 68%). M. p. > 300 °C ;^{1}H NMR (250 MHz, acetone-d_6, 25 °C) : δ = 9.45 (brs, 4H, NH-CO), 9.13 (brs, 4H, Ar-NH-Ar), 9.11 (s, 2H, Ar-H) 7.49 (s, 2H, Ar-H), 7.21 (s, 2H, Ar-H), 5.09 (s, 2H, Ar-H), 3.49 (t, ^3J (H, H) = 8.6 Hz, 8H, N-CH_2-), 1.84 (m, 8H, N-CH_2-CH_2-), 1.48 (m, 8H, -CH_2-CH_3), 1.14 (s, 36H, CO-C$(CH_3)_3$), 0.98 ppm (t, ^3J (H, H) = 7.3 Hz, 12H, CH_3); $C_{60}H_{88}BrN_{13}O_{12}\cdot 1.5H_2O$ (1290.35): calcd. C 55.85, H 7.11, N 14.11; found C 55.97, H 7.11, N 13.90; ESI-MS: 939.4 ([M-H]$^-$), 1021.4 ([M+Br]$^-$); calcd. for $C_{44}H_{51}N_{12}O_{12}^-$ ([M-H]$^-$) 939.5, calcd. for $C_{44}H_{52}BrN_{12}O_{12}^-$ ([M+Br]$^-$) 1021.4.

Host-guest complex 14: A solution of tetra-amido-tetraazacalixarene **10** (7 mg, 7.4 µmol) and tetra-*n*-butylammonium iodide (3 mg, 8.1 µmol, 1.1 equiv) in acetone (1.5 mL) was refluxed overnight. The resulting yellow precipitate was filtered and dried under vacuum (4.6 mg, 3.5 µmol, 46 %). M. p. > 300 °C ;^{1}H NMR (250 MHz, acetone-d_6, 25 °C): δ = 9.30 (brs, 4H, NH-CO), 9.13 (s, 2H, Ar-H), 8.72 (brs, 4H, Ar-NH-Ar), 7.84 (s, 2H, Ar-H), 7.32 (s, 2H, Ar-H), 5.47 (s, 2H, Ar-H), 3.50 (t, ^3J (H, H) = 8.6 Hz, 8H, N-CH_2-), 1.81 (m, 8H, N-CH_2-CH_2-), 1.46 (m, 8H, -CH_2-CH_3), 1.17 (s, 36H, -CO-C$(CH_3)_3$), 0.98 ppm (t, ^3J (H, H) = 7.3 Hz, 12H, CH_3); $C_{60}H_{88}IN_{13}O_{12}\cdot H_2O$ (1328.35): calcd. C 54.25, H 6.83, N 13.71; found C 54.65, H 6.91, N 13.60; ESI-MS: 939.4 ([M-H]$^-$), 1067.1 ([M+I]$^-$); calcd. for $C_{44}H_{51}N_{12}O_{12}^-$ ([M-H]$^-$) 939.5, calcd. for $C_{44}H_{52}IN_{12}O_{12}^-$ ([M+I]$^-$) 1067.1.

Host-guest complex 15: A solution of tetra-amido-tetraazacalixarene **10** (20 mg, 21 µmol) and tetra-*n*-butylammonium acetate (6.2 mg, 21 µmol, 1 equiv.) in acetone (2 mL) was refluxed for 24 hours. The resulting yellow precipitate was filtered off, washed with acetone and dried under vacuum to yield **15** (16 mg,

12 µmol, 59%). M. p. (dec.) > 165 °C ; ^{1}H NMR (250 MHz, acetone-d_6, 25 °C): δ = 9.90 (brs, 4H, Ar-NH-Ar) 9.08 (s, 2H, Ar-H), 7.72 (s, 2H, Ar-H), 7.15 (s, 2H, Ar-H), 5.34 (s, 2H, Ar-H), 3.44 (t, ^3J (H, H) = 8.3 Hz, 8H, N-CH_2-), 1.79 (m, 8H, N-CH$_2$-CH_2), 1.41 (m, 8H, -CH_2-CH$_3$), 1.15 (s, 36H, CO-C(CH$_3$)$_3$), 0.98 ppm (t, ^3J (H, H) = 7.3 Hz, 12H, CH_3); $C_{62}H_{91}N_{13}O_{14}\cdot H_2O$ (1260.49): calcd. C 59.08, H 7.44, N 14.45; found C 59.11, H 7.59, N 14.30; ESI-MS: 939.5 ([M-H]$^-$); calcd. for $C_{44}H_{51}N_{12}O_{12}^-$ ([M-H]$^-$) 939.5.

Host-guest complex 16: A solution of tetra-amido-tetraazacalixarene **10** (20 mg, 21 µmol) and *N*-benzyl-4-(dimethylamino) pyridinium bromide (6.2 mg, 21 µmol, 1 equiv.) in acetone (2 mL) was refluxed for 24 hours under argon. The resulting precipitate was filtered, washed with acetone and dried under vacuum (12 mg, 10 µmol, 46%). M. p. > 300 °C ; ^{1}H NMR (250 MHz, acetone-d_6, 25 °C): δ = 9.44 (s, 4H, NH-CO), 9.13 (brs, 4H, Ar-NH-Ar), 9.12 (s, 2H, Ar-H), 8.45 (d, ^3J (H-H) = 7.9 Hz, 2H, Ar-H$_{py}$), 7.50 (s, 2H, Ar-H), 7.44 (m, 5H, Ar-H), 7.20 (s, 2H, Ar-H), 7.16 (d, ^3J (H-H)= 7.9 Hz, 2H, Ar-H$_{py}$), 5.56 (s, 2H, N$^+$-CH_2-), 5.08 (s, 2H, Ar-H), 3.34 (s, 6H, N-(CH$_3$)$_2$), 1.14 ppm (s, 36H, -C(CH$_3$)$_3$); $C_{58}H_{69}BrN_{14}O_{12}\cdot 2H_2O$ (1270.20): calcd. C 54.84, H 5.79, N 15.44; found C 54.67, H 5.61, N 15.32; ESI-MS: 939.4 ([M-H]$^-$), 1021.3 ([M+Br]$^-$); calcd. for $C_{44}H_{51}N_{12}O_{12}^-$ ([M-H]$^-$) 939.5, calcd. for $C_{44}H_{52}BrN_{12}O_{12}^-$ ([M+Br]$^-$) 1021.4.

Host-guest complex 17: A solution of tetra-amido-tetraazacalixarene **10** (12 mg, 12 µmol) and *N*-hydrogeno-4-(dimethylamino) pyridinium bromide (2.6 mg, 12 µmol, 1 equiv.) in acetone (1.5 mL) was refluxed for 24 hours under argon. The resulting precipitate was filtered off, washed with acetone and dried under vacuum to yield **17** (7.4 mg, 6 µmol, 50%). M. p. > 300 °C ; ^{1}H NMR (250 MHz, acetone-d_6, 25 °C): δ = 9.19 (brs, 4H, NH-CO), 9.18 (brs, 4H, Ar-NH-Ar), 9.12 (s, 2H, Ar-H), 8.29 (d, ^3J (H, H) = 7.7 Hz, 2H, Ar-H$_{py}$), 7.6 (s, 2H, Ar-H), 7.25 (s, 2H, Ar-H), 7.10 (d, ^3J (H, H) = 7.7 Hz, 2H, Ar-H$_{py}$), 5.25 (s, 2H, Ar-H), 3.34 (s, 6H, N(CH$_3$)$_2$, 1.15 ppm (s, 36H, CO-(CH$_3$)$_3$); $C_{51}H_{63}BrN_{14}O_{12}\cdot 3H_2O$ (1198.09): calcd. C 51.13, H 5.80, N 16.37; found C 51.46, H 5.71, N 16.55; ESI-MS: 939.4 ([M-H]$^-$), 1021.3 ([M+Br]$^-$); calcd. for $C_{44}H_{51}N_{12}O_{12}^-$ ([M-H]$^-$) 939.5, calcd. for $C_{44}H_{52}BrN_{12}O_{12}^-$ ([M+Br]$^-$) 1021.4.

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