ChemPubSoc Europe

DOI: 10.1002/chem.201505089

CHEMISTRY A European Journal Full Paper

Host–Guest Systems

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

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]cyclophane derivatives bearing peripheral amide groups were prepared according to two distinct synthetic strategies that depend on the connection pattern between the aryl units. NMR experiments combined with the X-ray structures of two tetraamide derivatives **4b** and **10** show that these cavitands adopt a 1,3-alternate conformation both in solution and 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 nonpolar solvents provided evidence for the selectivity of **10** to chloride anions in the halide series, with a corresponding association constant K_a reaching $2.5\times10^6\ M^{-1}$.

Introduction

The calixarene skeleton is one of the most popular scaffolds used in the design of simple to very sophisticated receptors in supramolecular chemistry because of 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 for the specific delivery of drugs.[3] The large structural diversity of calixarene derivatives rely on the numerous methods with which their skeleton can be changed or functionalized. When aromatic units are used to introduce functional groups such as in water-soluble *p*-sulfonatocalixarenes,[4] an important class of cavitands emerges wherein 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 have been the most intensively studied because their syntheses can be achieved by using 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 investigated in less detail so far.[8]

The introduction of nitrogen-bridging atoms has numerous consequences and leads to a number of potential applications. 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 noncovalent interactions.[10] N-Alkylation is a powerful tool to build more sophisticated receptors,[11] and this approach 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 because the N-atom can act as a 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 for 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 borne 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.

Although different synthetic strategies are now available to prepare azacalixarene derivatives, their binding properties remain rather scarce[8] and primarily concern host–guest complexes involving homoazacalixarenes[19] or cavitands incorporating heterocycles such as pyridines[20] or triazines[21] that con-

[a] Dr. G. Canard, J. A. Edzang, Z. Chen, Dr. O. Siri
Centre Interdisciplinaire de Nanosciences de Marseille (CINaM)
Aix Marseille Université, CNRS UMR 7325
13288 Marseille (France)
Fax: (+33) 491418916
E-mail: gabriel.canard@univ-amu.fr
olivier.siri@univ-amu.fr

[b] M. Chessé, Dr. M. Elhabiri
Laboratoire de Chimie Bioorganique et Médicinale
UMR 7509 CNRS-Université de Strasbourg
ECPM, 25 rue Becquerel, 67087 Strasbourg Cedex (France)

[c] Dr. M. Giorgi
Fédération des Sciences Chimiques de Marseille-Spectropole FR 1739
Aix Marseille Université
13397 Marseille (France)

Supporting information for this article and ORCID from one of the authors are available on the WWW under http://dx.doi.org/10.1002/chem.201505089.

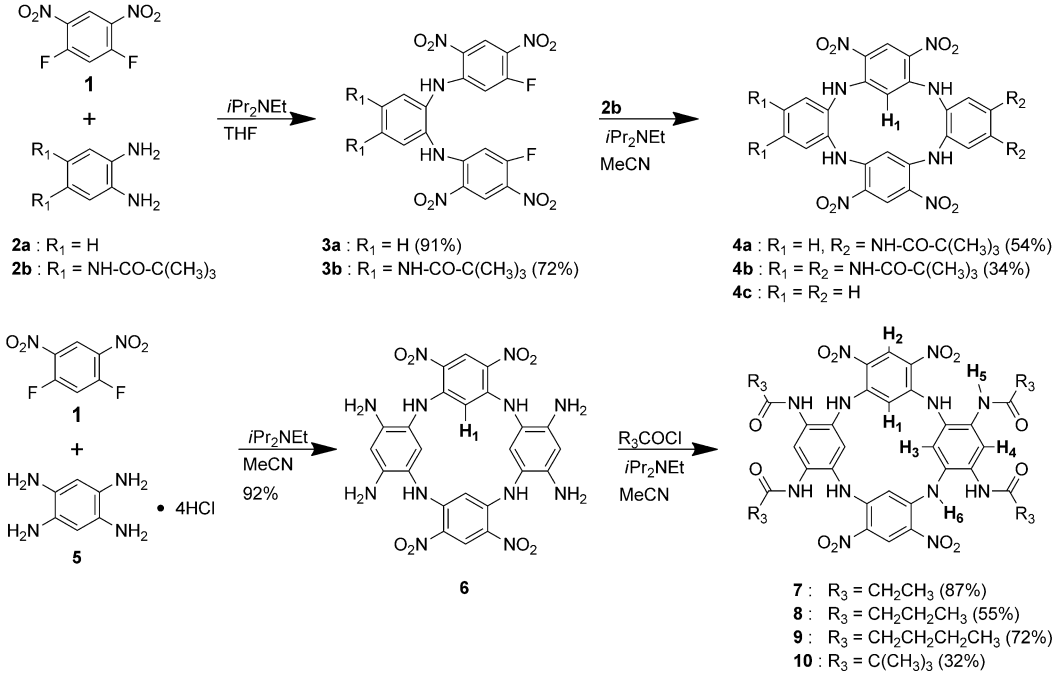
tribute to the recognition process. As far as tetraazacalix[4]arenes lacking heterocycles are concerned, only two examples of supramolecular host–guest complexes have been described; these examples show that the 1,3-alternate conformation was suitable to bind alkali metal ions[17] or a dichloromethane molecule.[22] One would expect that this distinctive conformation can be used as a scaffold to preorganize multiple supramolecular recognition moieties such as amide groups.

We disclose herein two distinct 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** were studied in detail both in solution and in the solid state because it forms host–guest complexes that precipitate in polar media (acetone, MeCN) that could be 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

In addition to the historical Buchwald–Hartwig aryl amination reactions,[8] the formation of azacalix[4]arenes can be achieved by 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 distinct 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-step procedure starting from **1** and allowing 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 respective [2+1] products **3a** and **3b** in good yields. Their ^{1}H NMR spectra ([D$_6$]DMSO) show a downfield NH signal at $\delta = 10.15$ and 10.14 ppm for **3a** and **3b**, respectively, in agreement with two NH···O$_2$N hydrogen-bonding interactions that restrict the rotation of these uncyclized precursors and induce their preorganization towards the subsequent macrocyclization.[13,18,24c–d] Compounds **3a** or **3b** were then reacted with **2b** in MeCN heated to reflux to give 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, whereas the direct condensation of equimolar amounts of **1** and **2b** af-



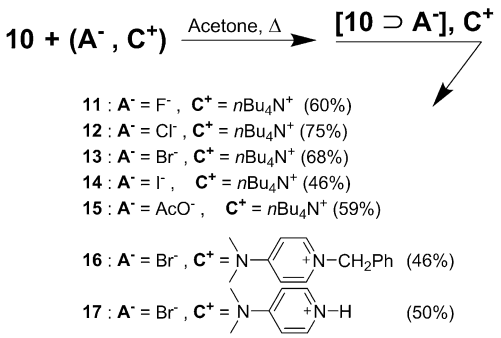
Scheme 1. Syntheses of azacalix[4]arene derivatives **4a**–**b** and **7**–**10** bearing peripheral amide groups.

forded a lower yield of **4b** together with uncyclized oligomers that were difficult to remove. The ^{1}H NMR spectra ([D$_6$]DMSO) of **4a** and **4b** reveal that these macrocycles adopt a 1,3-alternate 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 $\delta = 5.05$ and 5.23 ppm for H-1 protons of **4a** and **4b**, respectively. The synthesis of compound **4c**, lacking amide groups, was achieved by followed a previously described and analogous strategy starting from **1** and **2a**.[24d] Its unprecedented single-crystal X-ray structure is given here (Figure 3) and compared with that of **4b**.

The preparation of the symmetrical tetraamido-tetraaza[1.1.1.1]*m*,*m*,*m*,*m*-cyclophanes **7**–**10** relies on a different two-step synthetic procedure that allows access to numerous derivatives because the introduction of the amide groups is performed after the macrocyclization (Scheme 1). The condensation of **1** on the 1,2,4,5-tetraaminobenzene (formed in situ by deprotonation of its tetra-hydrochloric salt **5**) gives, as previously described,[26] a high yield of 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 tetraamino derivative **6** with 4 to 10 equivalents of acyl chlorides in MeCN heated to reflux afforded tetraamido-tetraazacalix[4]arenes **7**–**10** with yields ranging from 32 to 87%. The 1,3-alternate conformation of **6**, probed by monitoring the ^{1}H NMR singlet of its hydrogen atoms H-1 located at $\delta = 4.98$ ppm in [D$_6$]DMSO, 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 when a higher excess of acyl chloride and/or a longer reaction time is used. The ^{1}H NMR spectra ([D$_6$]DMSO) of **7**, **8**, **9**, and **10** support their 1,3-alternate conformations in solution through the positions of their intraannular aromatic H-1 singlet chemical shifts at $\delta = 5.42$, 4.40, 5.33, and 5.61 ppm, respectively (see the Supporting Information).

Host–Guest Species Generated from 10 and Anions

A preliminary investigation using UV/Vis absorption and NMR spectroscopies revealed that all the cavitands **4a**, **4b**, and **7**–**10** interact with anions in solution. Based on the largest variations of the UV/Vis absorptions and ^{1}H NMR spectra, the strongest interactions were observed with *m*,*m*,*m*,*m*-cyclophanes derivatives **7**–**10**. 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 host **10** in acetone led to the precipitation of the host–guest complex in a process that was favored by increased temperature. This straightforward procedure was used to prepare 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 nature of the cation in the solids **16** and **17** and compared with 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 heating to reflux a solution containing receptor **10** and equimolar amounts of F^-, Cl^-, Br^- and I^-. (Scheme 2).



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

Regardless of 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 MS (ESI; negative 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**]$^-$ were observed when the more basic acetate and fluoride anion were complexed, whereas the dianionic form of **10** [**10**−2H]$^{2-}$ was 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.

Further evidence was gained by analysis of the ^{1}H NMR spectra of dilute solutions of **11**–**15** and **18**, which were recorded and compared with that of receptor **10** under identical conditions (Figure 1). The anion complexation process induces variation of the chemical shifts of the receptor signals in the low-field region. The 1,3-alternate conformation of azacalix[4]-arene **10** is retained and is only slightly affected by the nature of the interacting anion, 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 (Scheme 1) that are located close to the complexation site (Scheme 1). Consequently, the remote hydrogen atoms H-2 and H-3 are barely sensitive to the host–guest interaction. The shift amplitude increases with increasing

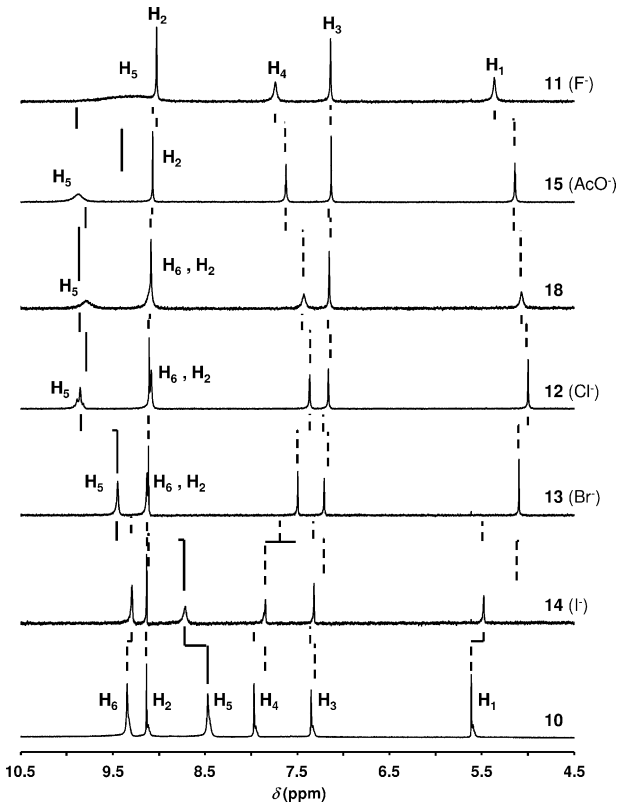


Figure 1. Partial ^{1}H NMR spectra of dilute solutions of **10**–**15** and **18** (in [D$_6$]acetone). The numbering scheme is detailed in Scheme 1.

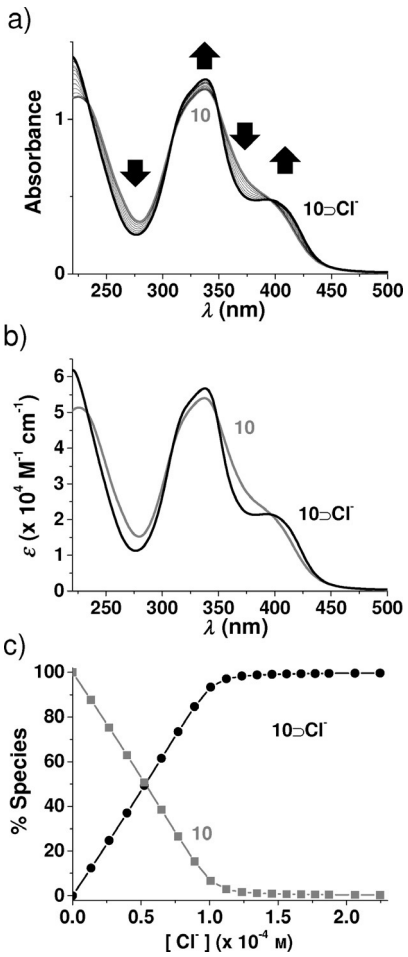


Figure 2. a) Spectrophotometric titration of **10** ([**10**] = 1.098×10^{-4} M) with 0–2.5 equivalents of [(*n*Bu$_4$)N]Cl in 1,2-dichloroethane. b) Electronic spectra of **10** and of the host–guest complex **10**⊃Cl$^-$. c) Distribution diagram between **10** and **10**⊃Cl$^-$ during the spectrophotometric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

hardness of the anion when the bulky iodide is replaced by bromide and chloride. This trend is not fully retained when fluoride and acetate interact, and leads to 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 evidence for 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).

The host–guest complexes between **10** and anions **A**$^-$ are only slightly soluble in polar media, therefore their association constants were measured through absorption spectrophotometric titrations in 1,2-dichloroethane as an apolar solvent (Figure 2 and Figure S7–S11 in the Supporting Information). The absorption spectrum of 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, with those of the diamido-substituted benzene rings being centered at much higher energies. Consequently, the anion complexation process produces only small 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$_4^-$) was added to a solution of **10**, the intensity of the main absorption decreases slightly and its shoulder is slightly redshifted.

Nevertheless, the noticeable spectral amplitudes recorded along these titrations reveal the presence of four isosbestic points (Figure 2), which substantiates the speciation model previously established by ESI-MS, ^{1}H NMR and elementary analyses and confirms the exclusive formation of [1 + 1] host–guest complexes involving **10** and a single anion. These absorption spectrophotometric data were statistically processed assuming the equilibrium (1) for the six investigated anions by using nonlinear least-squares techniques (see the experimental section in the Supporting Information).

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

The six corresponding formation constants, listed in Table 1, evidence a marked capacity of host **10** towards the recognition of anions together with a substantial size discrimination capacity. The highest association constant values were calculated to be close to 10^6 M^{-1}, which were determined for the hardest

Table 1. Formation constants of **10**⊃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].

anions F^-, AcO^-, and Cl^-, whereas those measured for bulkier anions such as Br^- or I^- were more than two orders of magnitude lower. Anion HSO_4^- was chosen in this approach, as a guest that was 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 twenty 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).

The influence of the water on the binding process of Cl^- and Br^- was further evaluated through absorption spectrophotometric titrations conducted in $C_2H_5Cl_2/H_2O$ (99.9:0.1 v/v) (Figure 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 experimental conditions [$\log K_a$ **10**⊃Br^- = 5.2(4) in the presence of water versus $\log K_a$ **10**⊃Br^- = 5.1(2) in the absence of water; $\log K_a$ **10**⊃Cl^- = 6.3(2) in the presence of water versus $\log K_a$ **10**⊃Cl^- = 6.4(4) in the absence of water].

Single-Crystal X-ray Structures of Cavitands 4b, 4c, and 10, and of the Host–Guest Complexes 11, 13, and 15

Diffracting single crystals of **4b**, **4c**, **10**, **11**, **13**, and **15** were grown and were suitable for X-ray diffraction study (Figures 3, 4, 5, and 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, whereas those of **4b**, **4c**, **10** (**10a** and **10b**) and **13** consist of a single host or host–guest molecule. The structure of receptor **10** is described based on analysis of two different single crystals grown under different experimental conditions and named **10a** and **10b**.

The seven different crystal structures share a common feature: the 1,3-alternate conformation of the tetraaza[1,1,1,1]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 feature 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 bond length to the other aromatic unit (1.43 Å). Each nitro group is essentially planar with its attached aromatic ring, as illustrated by the deviation of the nitro oxygen atoms from the benzene ring, which ranges from 0.01 to 0.43 Å and averages 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

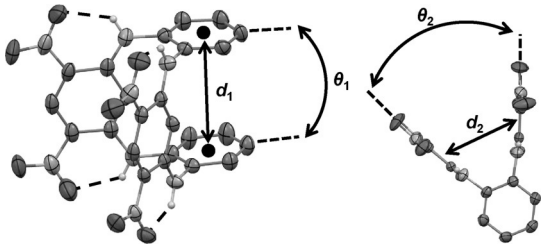


Figure 3. Two views of the single-crystal X-ray structure of **4c** showing the structural parameters d_1, d_2, θ_1, and θ_2 (aromatic hydrogen atoms and solvent molecules are omitted for clarity). The dashed lines show the intramolecular NO_2···HN hydrogen bonds.

averaging 2.04 Å. These strong intramolecular hydrogen bonds increase the macrocycle inversion barrier and thus stabilizes the 1,3-alternate conformation. By 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, the sizes and shapes of which will be described herein by using the four structural parameters d_1, θ_1, d_2 and θ_2, (Figure 3) listed in Table S3 in the Supporting Information, where d_1 is the distance between the centroids of the two isolated and almost parallel benzene rings defining the angle θ_1, and d_2 describes the corresponding distance between the two conjugated dinitro-benzene groups forming the angle θ_2.

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 ($\theta_1 = 4°$). This close arrangement ($d_1 = 4.62$ Å and $\theta_1 = 5°$) 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 form a strong C=O···H–N intermolecular hydrogen bond with a O···H length of approximately 2.00 Å (Figure 4c). This interaction is reinforced by a concomitant weak C=O···H–C hydrogen bond (Figure 4c). Therefore, only two amides NH are likely to interact with a guest in the structure of **4b**. 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 borne by an identical aryl unit, as in the structure of its isomeric receptor **10**.

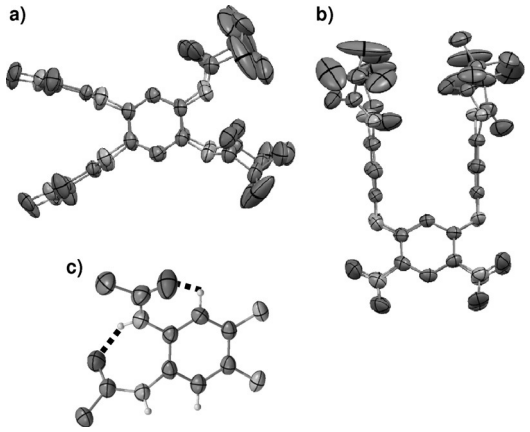


Figure 4. a) and b) Two views of the single-crystal X-ray structure of **4b** (hydrogen atoms and solvent molecules are omitted for clarity). c) Partial view showing intramolecular hydrogen bonds involving the amide groups.

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 already forms host–guest complexes with two water molecules irrespective of the experimental conditions used to obtain diffracting single-crystals (Figure 5 and S14). This affinity towards water molecules is due

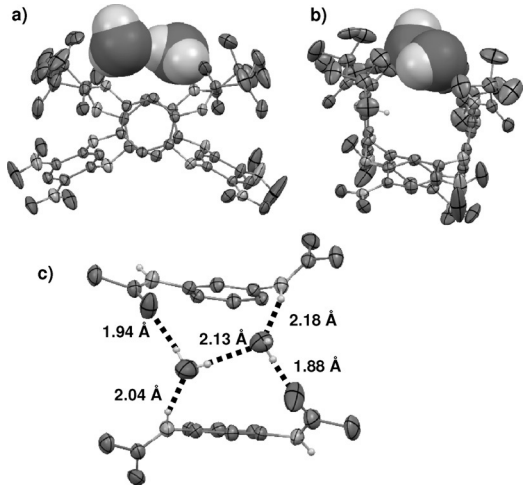


Figure 5. a) and b) Two views of the first single-crystal X-ray structure of **10** (**10a**) (hydrogen atoms and external solvent molecules are omitted for clarity). The guest water molecules are shown by space-filling model. c) Partial view showing the hydrogen-bond network involving the amide groups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

to the formation of a well-define hydrogen-bond network between the four amide groups of receptor **10** and the two hosted molecules. Given that these networks are similar in **10a** and **10b**, only the structure of **10a** will be detailed below.

The four amide groups of 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 whereas the two remaining N-H amide groups interact with external acetone solvent molecules. Although the connecting dinitroaryl fragments are identical in **4b** and **10**, the complexation of two water molecules induces a higher distance between the two tetraamido units d_1 that increases from 4.80 Å in **4b** to 5.05 Å in **10a**.

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 form almost identical hydrogen-bond networks with their guests (Figure 6 and S15). The introduction of a charged anionic

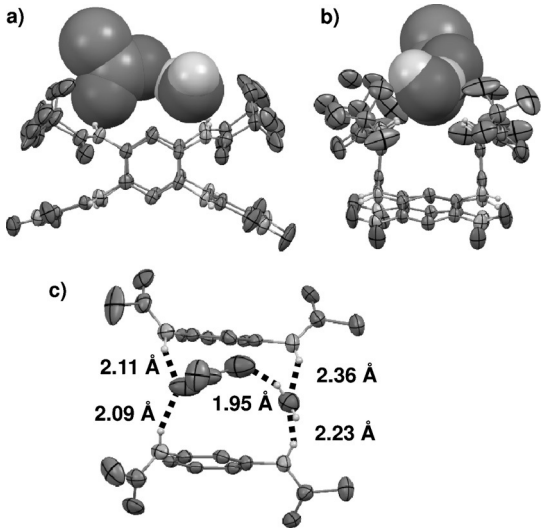


Figure 6. a) and b) Two views of the first host–guest complex contained in the asymmetric unit of the single-crystal X-ray structure of **15** (**15a**) (the ammonium cation, the hydrogen atoms and the external solvent molecules are omitted for clarity). The guest acetate ion and water molecule are shown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

guest induces a new orientation of the four amide groups that interact 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).

The structures of **11** and **13** suffer from partial disorder (Figure S16 and S17). For example, the guest fluoride ion of **11**

was shown to occupy four different fitted positions in the cavity, whereas the bromide ion in **13** occupies alternatively one of the two possible positions between opposite N-H amide groups (Figure S16 and S17). Nevertheless, we are confident that the corresponding structural qualities are high enough to ensure that the corresponding host–guest processes use 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 ion 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 S3 in the Supporting Information). If the higher affinity of receptor **10** for the hardest anions is the 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.

Conclusion

The 1,3-alternate conformation of calix[4]arenes has been considered as the "smart" and valuable one because it has been used as the basis for numerous cryptands with practical applications.[31] In the calix[4]arene family, two strategies are usually used to stabilize this particular conformation. The first approach relies on the introduction of bulky substituents, whereas the second approach requires the fabrication of "straps" upon one or two of the resulting cavities. We describe herein that such structural modifications are not required to produce, in solution, the inflexible 1,3-alternate conformation of up to six different tetraaza[1,1,1,1]cyclophanes. For example, heating DMSO solutions of either **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 isopropyl substituents, the corresponding inversion barrier reaches a value higher than 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 binding 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 likely reaches an optimum arrangement when a chloride is incorporated in the macrocyclic cavity. The interaction of tetraamide receptors **7**–**10** with other guests is under investigation, as is the introduction and application of other 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 (nBu$_4$NI. 98%, Alfa Aesar; (nBu$_4$N)CH$_3$CO$_2$, 98%, Alfa Aesar; nBu$_4$NF, 98%, Alfa Aesar; nBu$_4$NBr, 99+%, Acros Organics; nBu$_4$NCl, 98%, Acros Organics; (nBu$_4$N)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 NMR spectra were recorded with a Bruker Avance 400 Ultrashield or a JEOL ECS400 NMR spectrometer. Chemical shifts are given in ppm relative to residual peaks of [D$_6$]acetone (δ = 2.05 ppm) or [D$_6$]DMSO (δ = 2.50 ppm). UV/Vis absorption spectra were measured with a Shimadzu UV-2401 (PC) instrument or with a Varian Cary 5000. HRMS (ESI) and MS (ESI) analyses were performed with a QStar Elite (Applied Biosystems SCIEX) spectrometer or a SYNAPT G2 HDMS (Waters) spectrometer. These two instruments were equipped with an electrospray ionization source.

All stock solutions used for spectrophotometric titrations were prepared by weighing appropriate amounts of the solid samples using a Mettler Toledo XA105 Dual Range (0.01/0.1 mg - 41/120 g) and complete dissolution in 1,2-dichloroethane was achieved by using an ultrasonic bath. The concentrations of the stock solutions of **10** (ca. 2.20×10^{-4} M) and the *n*-tetrabutylammonium salts (ca. $1.31–1.67\times10^{-3}$ M) were calculated by quantitative dissolution of solid samples in 1,2-dichloroethane. The absorption spectrophotometric titrations of the tetraazacalix[1,1,1,1]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$_4$NX (X = Br$^-$, I$^-$, F$^-$, Cl$^-$, HSO$_4^-$, and CH$_3$CO$_2^-$) were added to 500 μL of the receptor with microliter Hamilton syringes (#701 and #750). Care was taken to ensure that complete equilibration was attained. The corresponding absorption UV/Vis spectra were recorded from 220 to 600 nm with 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 program, which adjusts 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 by using the Hyss program.[37]

The intensity data of the X-ray-quality crystals of **10b**, **4b**, and **4c** were collected with a Bruker-Nonius KappaCCD diffractometer using Mo Kα 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 with a Rigaku Oxford Diffraction SuperNova diffractometer using Cu Kα 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] or SHELXS[41] and SHELXL[41] was used for full matrix least squares refinement was used for full matrix least squares refinement. The hydrogen atoms were found experimentally for **11** (except for the

water molecules), for the amines of **13**, for **10a** (except for the methyl groups), and for the water molecules of **10b**; the remaining H-atoms were introduced at geometrical positions. All hydrogen Uiso parameters were fixed to 1.2 Ueq(parent atom) for the aromatics or amines and to 1.5 Ueq(parent atom) for the remaining hydrogen atoms. CCDC 1430290 (**15**), 1430291 (**13**), 1430292 (**10a**), 1430294 (**11**), 1430295 (**4c**), 1430296 (**10b**), and 1430297 (**4b**), contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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 reported 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 was stirred for 3 h at 0 °C and then for 48 h at RT. Completion of the reaction was determined by TLC analysis on silica (EtOAc/cyclohexane, 50:50). The solvent was removed under vacuum before acetone (100 mL) was added. The resulting suspension was heated to reflux for 5 min and the solvent was removed under vacuum. The resulting solid was washed with EtOH (3×25 mL) and dried under vacuum to give **3a** (2.66 g, 5.58 mmol, 91%). M.p. 232–234 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ = 10.15 (br s, 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, [D$_6$]DMSO, 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; MS (ESI): *m/z* calcd for $C_{18}H_{14}F_2N_7O_8^+$: 494.1 $[M+NH_4]^+$; found: 494.0.

***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 for 3 h at 0 °C and at RT for 66 h. Completion of the reaction was determined by TLC analysis (silica; EtOAc/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_2O (5 mL) then dried under vacuum to give pure **3b** (243 mg, 0.360 mmol, 72%). M.p. 256–258 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ = 10.14 (br s, 2H; NH), 9.07 (br s, 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, [D$_6$]DMSO, 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; MS (ESI): *m/z* calcd for $C_{28}H_{29}F_2N_8O_{10}^+$: 675.2 $[M+H]^+$; found: 675.1.

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 for 22 h, then stirred at 0 °C for 1 h. The resulting precipitated solid was filtered, washed successively with acetonitrile (40 mL), hot water (40 mL), and Et_2O (20 mL), and then dried under vacuum to give pure **4a** (840 mg, 1.13 mmol, 54%). M.p. > 300 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ = 9.26 (br s, 2H; NH), 9.19 (br s, 2H; NH), 9.15 (br s, 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, [D$_6$]DMSO, 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; MS (ESI): *m/z* calcd for $C_{34}H_{38}N_{11}O_{10}^+$: 760.2 $[M+NH_4]^+$; found: 760.3.

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) was 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 h and then cooled to RT. The solvent was removed under vacuum. The resulting solid was washed with EtOH (2×30 mL) and dried under vacuum to give pure **4b** (71 mg, 0.075 mmol, 34%). M.p. > 300 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ = 9.21 (br s, 4H; NH), 8.91 (br s, 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; MS (ESI): *m/z* calcd for $C_{44}H_{56}N_{13}O_{12}^+$: 958.4 $[M+NH_4]^+$; found: 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 for 1 h at RT before *N*-ethyldiisopropylamine (0.23 mL, 1.3 mmol, 8 equiv) was added dropwise. The mixture was heated to reflux overnight. The reaction was monitored by TLC (cyclohexane/EtOAc, 2:3; R_f = 0.2). The solvent was evaporated to dryness and the residue was triturated in water and filtered. A recrystallization from $CHCl_3$ afforded pure **7** (94 mg, 0.11 mmol, 87%) as a yellow solid. M.p. 225–228 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 9.50 (br s, 4H; Ar-NH-Ar), 9.32 (br s, 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_2CH$_3$), 0.95 ppm (t, ^3J(H,H) = 7.4 Hz, 12H; CH$_2$CH_3); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 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/z* calcd for $C_{36}H_{40}N_{13}O_{12}^+$: 846.2914 $[M+NH_4]^+$ and $C_{36}H_{36}N_{12}NaO_{12}^+$: 851.2468 $[M+Na]^+$; found: 846.2910 and 851.2465.

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 for 1 h at RT before *N*-ethyldiisopropylamine (0.17 mL, 1.0 mmol, 4 equiv) was added dropwise. The mixture was heated to reflux overnight. 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. Chromatography on silica gel (MeOH/CH_2Cl_2, 1:9; R_f = 0.34) followed by a crystallization from a mixture of CH_2Cl_2 and *n*-hexane afforded pure **8** (120 mg, 0.13 mmol, 55%) as a yellow solid. M.p. > 300 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 9.58 (br s, 4H; Ar-NH-Ar), 9.34 (br s,

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; $COCH_2$), 1.52 (m, 8H; CH_2CH_3), 0.88 ppm (t, ^3J(H,H) = 7.3 Hz, 12H; CH_3); HRMS (ESI): *m/z* calcd for $C_{40}H_{48}N_{13}O_{12}^+$: 902.3540 $[M+NH_4]^+$; found: 902.3539.

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 for 1 h at RT before *N*-ethyldiisopropylamine (0.11 mL, 0.66 mmol, 4 equiv) was added dropwise. The mixture was heated to reflux overnight. 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. Chromatography on silica gel (MeOH/CH_2Cl_2, 1:9; R_f = 0.47) followed by crystallization from a mixture of CH_2Cl_2 and *n*-hexane afforded pure **9** (112 mg, 12 μmol, 72%) as a yellow solid. M.p. > 300 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 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; $COCH_2$), 1.43 (m, 8H; $COCH_2CH_2$), 1.92 (m, 8H; CH_2CH_3), 0.80 ppm (t, ^3J(H,H) = 7.3 Hz, 12H; CH_3); HRMS (ESI): *m/z* calcd for $C_{44}H_{56}N_{13}O_{12}^+$: 958.4166 $[M+NH_4]^+$; found: 958.4167.

4,6,16,18-Tetranitro-10,12,22,24-tetra(2,2-dimethylpropionamido)-2,8,14,20-tetraazacalix[4]arene (**10**): A solution of 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 for 1 h at RT before *N*-ethyldiisopropylamine (0.55 mL, 3.1 mmol, 10 equiv) was added dropwise. The mixture was heated to reflux overnight. The reaction was monitored by TLC (cyclohexane/EtOAc, 2:3; R_f = 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 give **10** (94 mg, 0.10 mmol, 32%) as a yellow solid. M.p. > 260 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO, 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, [D$_6$]acetone, 25 °C): δ = 9.34 (brs, 4H; Ar-NH-Ar), 9.13 (s, 2H; Ar-H), 8.47 (brs, 4H; NHCO), 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/z* calcd for $C_{44}H_{56}N_{13}O_{12}^+$: 958.4166 $[M+NH_4]^+$; found: 958.4166.

Host–guest complex 11: A solution of tetraamido-tetraazacalixarene **10** (10 mg, 10 μmol) and tetra-*n*-butylammonium fluoride (2.7 mg, 10 μmol, 1 equiv) in acetone (1.5 mL) was heated to reflux for 24 h. The resulting precipitate was filtered, washed with acetone and dried under vacuum to give the host–guest complex **11** (7.4 mg, 6.1 μmol, 60%). M.p. (dec.) > 100 °C; ^{1}H NMR (250 MHz, [D$_6$]acetone, 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; NCH_2), 1.86 (m, 8H; NCH_2CH_2), 1.45 (m, 8H; CH_2CH_3), 1.15 (s, 36H; $COC(CH_3)_3$), 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; MS (ESI): *m/z* calcd for $C_{44}H_{50}N_{12}O_{12}^{2-}$: 469.2 $[M-2H]^{2-}$ and for $C_{44}H_{51}N_{12}O_{12}^-$: 939.5 $[M-H]^-$; found: 469.3 and 939.4.

Host-guest complex 12: A solution of tetraamido-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 heated to reflux for 24 h. The resulting precipitate was filtered, washed with acetone and dried under vacuum to give **12** (18 mg, 14 μmol, 75%). M.p. > 300 °C; ^{1}H NMR (250 MHz, [D$_6$]acetone, 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; NCH_2), 1.83 (m, 8H; NCH_2CH_2), 1.45 (m, 8H; CH_2CH_3), 1.13 (s, 36H; $COC(CH_3)_3$), 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; MS (ESI): *m/z* calcd for $C_{44}H_{51}N_{12}O_{12}^-$: 939.5 $[M-H]^-$ and for $C_{44}H_{52}ClN_{12}O_{12}^-$: 975.4 $[M+Cl]^-$; found 939.4 and 975.4.

Host–guest complex 13: A solution of tetraamido-tetraazacalixarene **10** (15 mg, 16 μmol) and tetra-*n*-butylammonium bromide (5.65 mg, 17 μmol, 1.1 equiv) in acetone (2 mL) was heated to reflux for 24 h. The resulting yellow precipitate was filtered off, washed with acetone, and dried under vacuum to give **13** (14 mg, 11 μmol, 68%). M.p. > 300 °C; ^{1}H NMR (250 MHz, [D$_6$]acetone, 25 °C): δ = 9.45 (brs, 4H; NHCO), 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; NCH_2), 1.84 (m, 8H; NCH_2CH_2), 1.48 (m, 8H; CH_2CH_3), 1.14 (s, 36H; $COC(CH_3)_3$), 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; MS (ESI): *m/z* calcd for $C_{44}H_{51}N_{12}O_{12}^-$: 939.5 $[M-H]^-$, and for $C_{44}H_{52}BrN_{12}O_{12}^-$: 1021.4 $[M+Br]^-$; found: 939.4 and 1021.4.

Host–guest complex 14: A solution of tetraamido-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 heated to reflux overnight. The resulting yellow precipitate was filtered and dried under vacuum to give **14** (4.6 mg, 3.5 μmol, 46%). M.p. > 300 °C; ^{1}H NMR (250 MHz, [D$_6$]acetone, 25 °C): δ = 9.30 (brs, 4H; NHCO), 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; NCH_2), 1.81 (m, 8H; NCH_2CH_2), 1.46 (m, 8H; CH_2CH_3), 1.17 (s, 36H; $COC(CH_3)_3$), 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; MS (ESI): *m/z* calcd for $C_{44}H_{51}N_{12}O_{12}^-$: 939.5 $[M-H]^-$, and for $C_{44}H_{52}IN_{12}O_{12}^-$: 1067.1 $[M+I]^-$; found: 939.4 and 1067.1.

Host–guest complex 15: A solution of tetraamido-tetraazacalixarene **10** (20 mg, 21 μmol) and tetra-*n*-butylammonium acetate (6.2 mg, 21 μmol, 1 equiv) in acetone (2 mL) was heated to reflux for 24 h. The resulting yellow precipitate was filtered off, washed with acetone and dried under vacuum to give **15** (16 mg, 12 μmol, 59%). M.p. (dec.) > 165 °C; ^{1}H NMR (250 MHz, [D$_6$]acetone, 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; NCH_2), 1.79 (m, 8H; NCH_2CH_2), 1.41 (m, 8H; CH_2CH_3), 1.15 (s, 36H; $COC(CH_3)_3$), 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; MS (ESI): *m/z* calcd for $C_{44}H_{51}N_{12}O_{12}^-$: 939.5 $[M-H]^-$; found: 939.5.

Host–guest complex 16: A solution of tetraamido-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 heated to reflux for 24 h under argon. The resulting precipitate was filtered, washed with acetone, and dried under vacuum to give **16** (12 mg, 10 μmol, 46%). M.p. > 300 °C; ^{1}H NMR (250 MHz, [D$_6$]acetone, 25 °C): δ = 9.44 (s, 4H; NHCO), 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; MS (ESI): *m/z* calcd for $C_{44}H_{51}N_{12}O_{12}^-$: 939.5 $[M-H]^-$, and for $C_{44}H_{52}BrN_{12}O_{12}^-$: 1021.4 $[M+Br]^-$; found 939.4 and 1021.3.

Host–guest complex 17: A solution of tetraamido-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 heated to reflux for 24 h under argon. The resulting precipitate was filtered off, washed with acetone, and dried under vacuum to give **17** (7.4 mg, 6 μmol, 50%). M.p. > 300 °C; ^{1}H NMR (250 MHz, [D_6]acetone, 25 °C): δ = 9.19 (br s, 4H; NHCO), 9.18 (br s, 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; MS (ESI): *m/z* calcd for $C_{44}H_{51}N_{12}O_{12}^-$: 939.5 $[M-H]^-$, and for $C_{44}H_{52}BrN_{12}O_{12}^-$: 1021.4 $[M+Br]^-$; found: 939.4 and 1021.3.

Acknowledgements

J. A. E gratefully acknowledges the Agence Nationale des Bourses du Gabon (ANBG) for financial support. This work was supported by the Centre National de la Recherche Scientifique and the Ministère de la Recherche et des Nouvelles Technologies (PhD grant to Z. C.). We also thank Valérie Monnier and Christophe Chendo for the analyses by mass spectrometry (Spectropole, Marseille).

Keywords: anions · calixarenes · conformation analysis · host–guest systems · macrocycles

[1] a) C. D. Gutsche, *Calixarenes: An Introduction*, The Royal Society of Chemistry, Cambridge, **2008**; b) N. Le Poul, Y. Le Mest, I. Jabin, O. Reinaud, *Acc. Chem. Res.* **2015**, *48*, 2097 – 2106; c) J.-N. Rebilly, B. Colasson, O. Bistri, D. Over, O. Reinaud, *Chem. Soc. Rev.* **2015**, *44*, 467 – 489.

[2] a) D. M. Homden, C. Redshaw, *Chem. Rev.* **2008**, *108*, 5086 – 5130; b) Z.-Y. Li, J.-W. Chen, Y. Liu, W. Xia, L. Wang, *Curr. Org. Chem.* **2011**, *15*, 39 – 61; c) D. Sémeril, D. Matt, *Coord. Chem. Rev.* **2014**, *279*, 58 – 95.

[3] a) X. Ma, Y. Zhao, *Chem. Rev.* **2015**, *115*, 7794 – 7839; b) M. Giuliani, I. Morbioli, F. Sansone, A. Casnati, *Chem. Commun.* **2015**, *51*, 14140 – 14159.

[4] a) J. L. Atwood, L. J. Barbour, M. J. Hardie, C. L. Raston, *Coord. Chem. Rev.* **2001**, *222*, 3 – 32; b) F. Perret, A. N. Lazar, A. W. Coleman, *Chem. Commun.* **2006**, 2425 – 2438; c) D.-S. Guo, K. Wang, Y. Liu, *J. Inclusion Phenom. Macrocyclic Chem.* **2008**, *62*, 1 – 21; d) D.-S. Guo, Y. Liu, *Acc. Chem. Res.* **2014**, *47*, 1925 – 1934; e) K. Flídrová, S. Böhm, H. Dvořáková, V. Eigner, P. Lhoták, *Org. Lett.* **2014**, *16*, 138 – 141.

[5] a) B. König, M. H. Fonseca, *Eur. J. Inorg. Chem.* **2000**, 2303 – 2310; b) M. Vysotsky, M. Saadioui, V. Böhmer, in Calixarenes 2001 (Eds.: Z. Asfari, V. Böhmer, J. Harrowfield, J. Vicens, M. Saadioui), Kluwer Academic Publishers, Dordrecht, **2001**, pp. 250 – 265.

[6] a) P. Lhoták, *Eur. J. Org. Chem.* **2004**, 1675 – 1692; b) N. Morohashi, F. Narumi, N. Iki, T. Hattori, S. Miyano, *Chem. Rev.* **2006**, *106*, 5291 – 5316; c) R. Kumar, Y. O. Lee, V. Bhalla, M. Kumar, J. S. Kim, *Chem. Soc. Rev.* **2014**, *43*, 4824 – 4870; d) F. Botha, V. Eigner, H. Dvořáková, P. Lhoták, *New J. Chem.* **2016**, DOI: 10.1039/C5NJ02427G.

[7] a) W. Maes, W. Dehaen, *Chem. Soc. Rev.* **2008**, *37*, 2393 – 2402; b) C.-F. Chen, *Chem. Commun.* **2011**, *47*, 1674 – 1688; c) Y. Jiang, C.-F. Chen, *Eur. J. Org. Chem.* **2011**, *2011*, 6377 – 6403; d) Y.-X. Ma, Y. Han, C.-F. Chen, *J. Inclusion Phenom. Macrocyclic Chem.* **2014**, *79*, 261 – 281.

[8] a) H. Tsue, K. Ishibashi, R. Tamura, *Top. Heterocycl. Chem.* **2008**, *17*, 73 – 96; b) M.-X. Wang, *Chem. Commun.* **2008**, 4541 – 4551; c) M.-X. Wang, *Acc. Chem. Res.* **2011**, *44*, 182 – 195.

[9] a) H. Tsue, K. Ishibashi, S. Tokita, H. Takahashi, K. Matsui, R. Tamura, *Chem. Eur. J.* **2008**, *14*, 6125 – 6134; b) M. Xue, C.-F. Chen, *Chem. Commun.* **2011**, *47*, 2318 – 2320.

[10] Y. Yi, S. Fa, W. Cao, L. Zeng, M. Wang, H. Xu, X. Zhang, *Chem. Commun.* **2012**, *48*, 7495 – 7497.

[11] J. M. Caio, T. Esteves, S. Carvalho, C. Moiteiro, V. Félix, *Org. Biomol. Chem.* **2014**, *12*, 589 – 599.

[12] K. Ishibashi, H. Tsue, H. Takahashi, R. Tamura, *Tetrahedron: Asymmetry* **2009**, *20*, 375 – 380.

[13] M. Touil, J.-M. Raimundo, M. Lachkar, P. Marsal, O. Siri, *Tetrahedron* **2010**, *66*, 4377 – 4382.

[14] a) S. I. Hauck, K. V. Lakshmi, J. F. Hartwig, *Org. Lett.* **1999**, *1*, 2057 – 2060; b) A. Ito, Y. Ono, K. Tanaka, *Angew. Chem. Int. Ed.* **2000**, *39*, 1072 – 1075; *Angew. Chem.* **2000**, *112*, 1114 – 1117; c) X. Z. Yan, J. Pawlas, T. Goodson, III, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 9105 – 9116; d) K. Ishibashi, H. Tsue, N. Sakai, S. Tokita, K. Matsui, J. Yamauchi, R. Tamura, *Chem. Commun.* **2008**, 2812 – 2814; e) I. Kulszewicz-Bajer, V. Maurel, S. Gambarelli, I. Wielgus, D. Djurado, *Phys. Chem. Chem. Phys.* **2009**, *11*, 1362 – 1368; f) D. Sakamaki, A. Ito, K. Furukawa, T. Kato, M. Shiro, K. Tanaka, *Angew. Chem. Int. Ed.* **2012**, *51*, 12776 – 12781; *Angew. Chem.* **2012**, *124*, 12948 – 12953; g) D. Sakamaki, A. Ito, K. Furukawa, T. Kato, K. Tanaka, *J. Org. Chem.* **2013**, *78*, 2947 – 2956; h) P. Bujak, I. Kulszewicz-Bajer, M. Zagorska, V. Maurel, I. Wielgus, A. Pron, *Chem. Soc. Rev.* **2013**, *42*, 8895 – 8999; i) D. Sakamaki, A. Ito, T. Matsumoto, K. Tanaka, *RSC Adv.* **2014**, *4*, 39476 – 39483.

[15] a) A. Ito, Y. Ono, K. Tanaka, *New J. Chem.* **1998**, *22*, 779 – 781; b) H. Tsue, K. Ishibashi, H. Takahashi, R. Tamura, *Org. Lett.* **2005**, *7*, 2165 – 2168.

[16] M. Vale, M. Pink, S. Rajca, A. Rajca, *J. Org. Chem.* **2008**, *73*, 27 – 35.

[17] H. Tsue, K. Ishibashi, S. Tokita, K. Matsui, H. Takahashi, R. Tamura, *Chem. Lett.* **2007**, *36*, 1374 – 1375.

[18] a) H. Konishi, S. Hashimoto, T. Sakakibara, S. Matsubara, Y. Yasukawa, O. Morikawa, K. Kobayashi, *Tetrahedron Lett.* **2009**, *50*, 620 – 623; b) R. Haddoub, M. Touil, Z. Chen, J.-M. Raimundo, P. Marsal, M. Elhabiri, O. Siri, *Eur. J. Org. Chem.* **2014**, 745 – 752; c) J. L. Katz, B. A. Tschaen, *Org. Lett.* **2010**, *12*, 4300 – 4303.

[19] a) K. Niikura, E. V. Anslyn, *J. Chem. Soc. Perkin Trans. 2* **1999**, 2769 – 2775; b) P. Thuéry, M. Nierlich, J. Vicens, B. Masci, H. Takemura, *Eur. J. Inorg. Chem.* **2001**, 637 – 643; c) C. Kaewtong, B. Pulpoka, *J. Inclusion Phenom. Macrocyclic Chem.* **2009**, *65*, 129 – 136; d) H. Takemura, Y. Yonebayashi, T. Nakagaki, T. Shinmyozu, *Eur. J. Org. Chem.* **2011**, 1968 – 1971.

[20] a) Y. Miyazaki, T. Kanbara, T. Yamamoto, *Tetrahedron Lett.* **2002**, *43*, 7945 – 7948; b) M.-X. Wang, X.-H. Zhang, Q.-Y. Zheng, *Angew. Chem. Int. Ed.* **2004**, *43*, 838 – 842; *Angew. Chem.* **2004**, *116*, 856 – 860; c) H.-Y. Gong, X.-H. Zhang, D.-X. Wang, H.-W. Ma, Q.-Y. Zheng, M.-X. Wang, *Chem. Eur. J.* **2006**, *12*, 9262 – 9275; d) E.-X. Zhang, D.-X. Wang, Q.-Y. Zheng, M.-X. Wang, *Org. Lett.* **2008**, *10*, 2565 – 2568; e) Y.-X. Fang, L. Zhao, D.-X. Wang, M.-X. Wang, *J. Org. Chem.* **2012**, *77*, 10073 – 10082.

[21] M. Xue, C.-F. Chen, *Org. Lett.* **2009**, *11*, 5294 – 5297.

[22] M. Touil, M. Elhabiri, M. Lachkar, O. Siri, *Eur. J. Org. Chem.* **2011**, 1914 – 1921.

[23] a) J. Clayden, S. J. M. Rowbottom, W. J. Ebenezer, M. G. Hutchings, *Org. Biomol. Chem.* **2009**, *7*, 4871 – 4880; b) J. Clayden, S. J. M. Rowbottom, M. G. Hutchings, W. J. Ebenezer, *Tetrahedron Lett.* **2009**, *50*, 3923 – 3925.

[24] a) J. L. Katz, B. J. Geller, R. R. Conry, *Org. Lett.* **2006**, *8*, 2755 – 2758; b) E. Hao, R. Fronczek Frank, M. G. H. Vicente, *J. Org. Chem.* **2006**, *71*, 1233 – 1236; c) M. Touil, M. Lachkar, O. Siri, *Tetrahedron Lett.* **2008**, *49*, 7250 – 7252; d) R. Haddoub, M. Touil, J.-M. Raimundo, O. Siri, *Org. Lett.* **2010**, *12*, 2722 – 2725; e) N. P. Bizier, J. P. Vernamonti, J. L. Katz, *Eur. J. Org. Chem.* **2012**, *2012*, 2303 – 2307; f) N. Manganaro, G. Lando, C. Gargiulli, I. Pisagatti, A. Notti, S. Pappalardo, M. F. Parisi, G. Gattuso, *Chem. Commun.* **2015**, *51*, 12657 – 12660.

[25] C. Seillan, P. Braunstein, O. Siri, *Eur. J. Org. Chem.* **2008**, 3113 – 3117.

[26] Z. Chen, M. Giorgi, D. Jacquemin, M. Elhabiri, O. Siri, *Angew. Chem. Int. Ed.* **2013**, *52*, 6250 – 6254; *Angew. Chem.* **2013**, *125*, 6370 – 6374.

[27] a) O. Siri, P. Braunstein, M.-M. Rohmer, M. Bénard, R. Welter, *J. Am. Chem. Soc.* **2003**, *125*, 13793 – 13803; b) H. Audi, Z. Chen, A. Charaf-Eddin, A. D'Aléo, G. Canard, D. Jacquemin, O. Siri, *Chem. Commun.* **2014**, *50*, 15140 – 15143.

[28] S. B. Bulgarevich, D. V. Bren, D. Y. Movshovic, P. Finocchiaro, S. Failla, *J. Mol. Struct.* **1994**, *317*, 147 – 155.

[29] S. Manivannan, S. Dhanuskodi, K. Kirschbaum, S. K. Tiwari, *Cryst. Growth Des.* **2006**, *6*, 1285 – 1290.

[30] R. D. Shannon, *Acta Crystallogr. Sect. A* **1976**, *32*, 751 – 767.

[31] L. Baklouti, J. Harrowfield, B. Pulpoka, J. Vicens, *Mini-Rev. Org. Chem.* **2006**, *3*, 355 – 384.

[32] H. Gampp, M. Maeder, C. J. Meyer, A. D. Zuberbühler, *Talanta* **1985**, *32*, 95 – 101.
[33] H. Gampp, M. Maeder, C. J. Meyer, A. D. Zuberbühler, *Talanta* **1985**, *32*, 257 – 264.
[34] H. Gampp, M. Maeder, C. J. Meyer, A. D. Zuberbühler, *Talanta* **1986**, *33*, 943 – 951.
[35] D. W. Marquardt, *J. Soc. Ind. Appl. Math.* **1963**, *11*, 431 – 441.
[36] M. Maeder, A. D. Zuberbühler, *Anal. Chem.* **1990**, *62*, 2220 – 2224.
[37] L. Alderighi, P. Gans, A. Ienco, D. Peters, A. Sabatini, A. Vacca, *Coord. Chem. Rev.* **1999**, *184*, 311 – 318.
[38] Nonius *COLLECT.* **2001**, Nonius BV, Delft, The Netherlands.
[39] Z. Otwinowski, W. Minor in *Methods in Enzymology* (Eds.: C. W. Carter Jr, R. M. Sweet), Academic Press, New York, **1997**, *276*, pp. 307 – 326.
[40] A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435.
[41] G. M. Sheldrick, *Acta Crystallogr. Sect. C* **2015**, *71*, 3 – 8.

Received: December 18, 2015
Published online on March 3, 2016