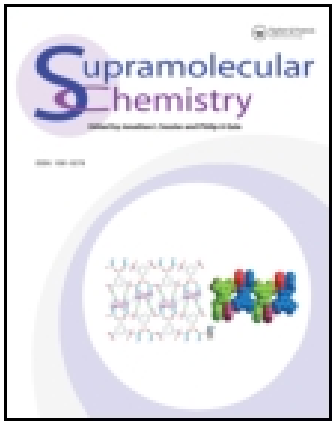


Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsch20

A tetraguanidinium macrocycle for the recognition and cavity expansion of calix[4]arene tetraoxoanions

Julián Valero[a] & Javier de Mendoza[a]
[a] Institute of Chemical Research of Catalonia (ICIQ), Avgda. Països Catalans 16, 43007 Tarragona, Spain
Published online: 06 Sep 2013.

To cite this article: Julián Valero & Javier de Mendoza (2013) A tetraguanidinium macrocycle for the recognition and cavity expansion of calix[4]arene tetraoxoanions, Supramolecular Chemistry, 25:9-11, 728-740, DOI: 10.1080/10610278.2013.835814

To link to this article: http://dx.doi.org/10.1080/10610278.2013.835814

Supramolecular Chemistry, 2013
Vol. 25, Nos. 9–11, 728–740, http://dx.doi.org/10.1080/10610278.2013.835814

A tetraguanidinium macrocycle for the recognition and cavity expansion of calix[4]arene tetraoxoanions

Julián Valero[1] and Javier de Mendoza*

Institute of Chemical Research of Catalonia (ICIQ), Avgda. Països Catalans 16, 43007 Tarragona, Spain

(*Received 5 June 2013; accepted 12 August 2013*)

Molecular containers have raised an increased interest over the last decade. These supramolecular architectures have found applications in catalysis, molecular sensing or as insulators for key intermediates, among others. In this study, we describe the synthesis and binding properties of a tetraguanidinium macrocycle which forms robust complexes with diverse calix[4]arene tetraoxoanions through hydrogen bonding and electrostatic interactions. The binding behaviour and affinity strength of these constructs have been measured by NMR and isothermal titration calorimetry. Besides, VT NMR experiments show that this novel cyclic tetracation is able to stabilise the cone conformation of these calix[4]arenes. Preliminary NMR-binding experiments between a tetraguanidinium calix[4]arenate and quinolinium or isoquinolinium salts suggest an effective increase in the cavity volume of these supramolecular constructs.

Keywords: bicyclic tetraguanidinium; macrocycle; calix[4]arenes; molecular recognition; host–guest interactions

Introduction

Nature uses clefts, well-defined pockets and solvent-hindered structures to direct and allow efficient molecular recognition. By size and shape discrimination, in addition to other essential interactions, biological systems are able to selectively bind target molecules. This enables membrane transport, delivery to a different organelle or diverse synthetic transformations, such as in enzymatic active sites, allosteric pockets or transmembrane pore channel proteins.

Inspired by these complex systems, synthetic molecular containers are based on the same fundamental principles that govern host–guest recognition at the biological level. Different pre-organised concave scaffolds such as resorcinarenes, calixarenes or cyclotriveratrylenes have been used as supramolecular baskets and capsules for binding, isolation and sensing of small molecules and ions (*1*), catalysis (*2*) or trapping of unstable intermediates (*3*).

Another significant group of molecular containers is based on the expansion of hollow cavitands to afford open void-like molecular architectures. Rebek and others explored this approach by deepening resorcinarenes-based self-assembled cavities (*4*). Recently, our group detailed different examples of calix[4]arene deep cavitands, in which the confined space was locked by either hydrogen bonding (*5*) or metal bridges (*6*) between their aromatic extended walls. These interactions prevented the molecules from adopting partially collapsed pinched conformations. These molecular vessels offer a solvent accessible space to reversibly encapsulate different guests inside without the dependence on the dynamic assembly of diverse components, due to the fact that encapsulation occurs with closed capsular-like structures.

Herein, we describe the construction of stable and robust open molecular containers based on the binding between different oxoanionic calix[4]arenes and the cationic macrocyclic tetraguanidinium ligand **1** in its two possible diastereomeric forms (Figure 1). Namely, ligand **1** stabilises the cone conformation of these calix[4]arenes by means of hydrogen bonding and ion pairing and expands the inner volume of the cavity allowing association with a guest that would otherwise not fit inside. To the best of our knowledge, this is the first example of a cavity expansion promoted by non-covalent reversible bonds to generate an open-shell construct.

Results and discussion

Design and synthesis

Macrocyclic tetraguanidinium hexafluorophosphate salt **1** was prepared after five synthetic steps starting from functionalised monoguanidines **2** and **3** (Scheme 1). *R,R*-thioacetyl monoguanidine **3** was coupled by nucleophilic attack of its thiolate to *S,S*-guanidine mesylate **2**, giving rise to *R,R-S,S*-diguanidinium **4**. Cleavage of the silyl groups and activation of the diol with methanesulphonic anhydride afforded dimesylate diguanidinium **6** in good

*Corresponding author. Email: jmendoza@iciq.es

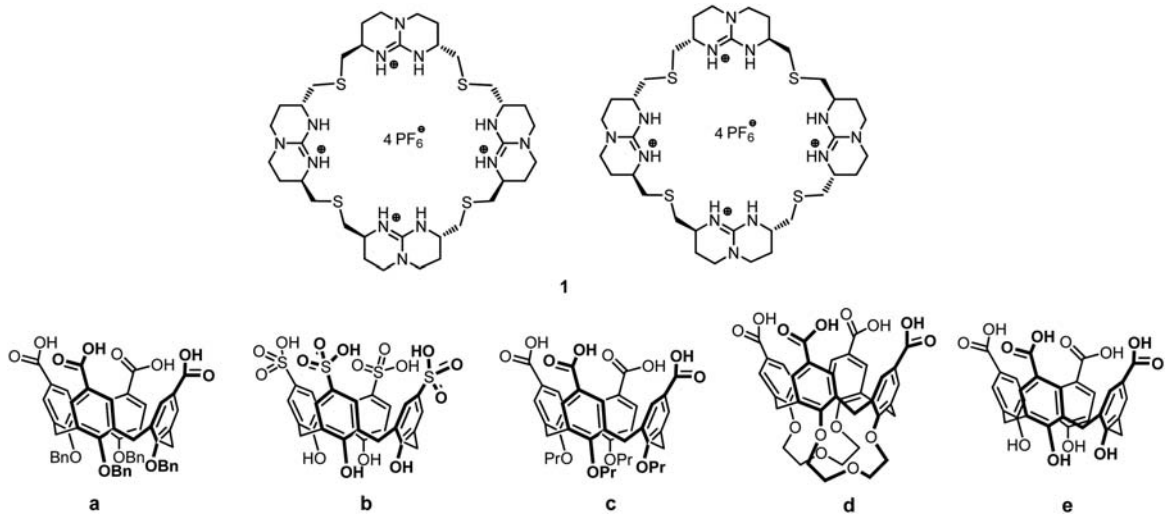
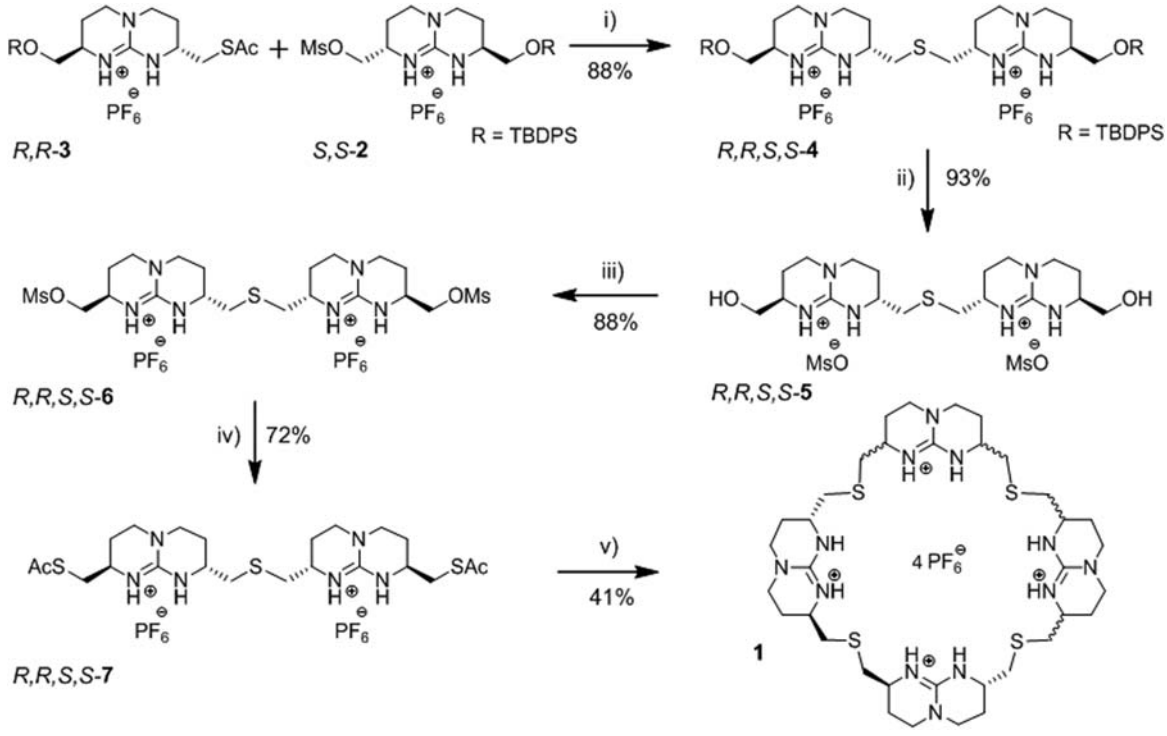


Figure 1. Tetraguanidinium macrocyclic ligand **1** (left, diastereoisomer *R,R-S,S-R,R-S,S*; right, diastereoisomer *R,R-S,S-S,S-R,R*), and calix[4]arene tetracarboxylic and sulphonic acids **a**–**e**.



Scheme 1. Synthesis of tetraguanidinium macrocycle **1**. Conditions: (i) 2.7 equiv. Cs_2CO_3, MeOH/ACN, N_2; (ii) MsOH, THF/H_2O; (iii) Ms_2O, NMM in CH_2Cl_2; (iv) $KSCOCH_3$, ACN, reflux; (v) 1 equiv. **6**, 2.7 equiv. Cs_2CO_3, (^{n}Bu)$_2$PhP polystyrene, in MeOH/ACN (high dilution conditions), 2 days, N_2.

yields. Thioacetylation of **6** resulted in dithiolate precursor **7**. Finally, coupling of diguanidinium dimesylate **6** with dithioacetylated diguanidinium salt **7** afforded tetraguanidine **1** (mixture of two diastereoisomers *R,R-S,S-R,R-S,S* and *R,R-S,S-S,S-R,R*) in a 21% overall yield.

The cyclisation step deserves several considerations. First, high dilution conditions were required to avoid formation of undesirable linear oligomeric or polymeric products. In this respect, it is worth mentioning that the configuration of each stereogenic centre in the molecule is relevant. Indeed, *R,R-S,S*-diguanidines (*meso*), despite their inherent flexibility, should provide the correct orientation of their reactive side arms pointing towards the same face of the molecule to allow formation of the macrocycle.

Separation of the two possible diastereoisomers was unsuccessful by HPLC. However, the thioether linkages between the different bicyclic guanidinium moieties should provide enough flexibility to accommodate well and orient the ion-pair interactions of both diastereomers with the corresponding calixarenate. Indeed, we expect a similar interaction and strength of binding due to the high preorganisation of these cyclic tetraguanidinium species. Thus, we decided to use this diastereomeric mixture to conduct the characterisation and subsequent binding experiments described here, although for clarity we used only the *R,R-S,S-R,R-S,S* isomer for the molecular models.

On the other hand, calix[4]arenes (**a**, **c**–**e**) were synthesised according to the literature precedents, whereas compound **b** was commercially available (see further details in the 'Experimental section') (Figure 1). Formylation of the corresponding *O*-alkyl calix[4]arenes, followed by oxidation with sulphamic acid and sodium chlorite, afforded tetracarboxylic compounds **a**, **c** and **d** in moderate to good yields. Subsequent *O*-debenzylation of compound **a** gave rise to calix[4]arene **e**.

NMR characterisation of the complexes

The ^{1}H NMR spectra of 1:1 mixtures of macrocyclic tetraguanidine **1** and the sodium salts of calix[4]arenes **a**–**c** revealed no significant chemical shifts with respect to the original calix[4]arene signals in a CD_3CN/D_2O (2:1) mixture. However, the broadening of the original proton signals of the independent species indicated that molecular assembly was likely taking place.

Molecular models of macrocyclic tetraguanidinium calix[4]arenate complexes pointed out that molecule **1** should sit on the anionic edge of the calix[4]arenes, compensating the four positive charges of **1** (Figure 2). Hence, it was expected to find nuclear Overhauser effect (nOe) contacts between the upper rim proton signals of the calix[4]arene and tetraguanidinium molecule **1**. Thus, NMR ROESY experiments were conducted. Indeed, after selective irradiation of the aromatic signals of calix[4]arene **c**, 1D ROESY showed nOe contacts with almost all signals of macrocyclic tetraguanidinium **1** (Figure 3).

Molecular modelling indicates that only the CH_2S and CH_α protons of macrocycle **1** should be within the optimal distance to display nOe contacts with the aromatic protons of the calix[4]arene. However, the β and γ methylene protons also showed nOe contacts, revealing that the inherent flexibility of macrocycle **1** could allow for the dynamic bending and twisting of some of the bicyclic guanidines of the ring, resulting in a closer proximity of these protons to the aromatic protons of the calixarene in the NMR timescale.

In addition, **1@a** and **1@b** were also characterised by mass spectrometry analysis (*7*) ($[M-H]^- = 1555.8$ and 1531.5 *m/z*, respectively; see Supplementary Material, available online). The masses of the individual species were also found in the gas phase, as a result of complex fragmentation.

To further investigate the structural features of these complexes in solution, NMR DOSY experiments were conducted (*8*, *9*). DOSY spectra of complexes **1@a** and **1@c** in a D_2O:CD_3CN (1:3) showed sharp DOSY peaks, respectively, pointing to a single complexed species in solution without scrambling between the free species in the NMR timescale (Figure 4).

Hydrodynamic radii of different complexes and free species in solution were determined both experimentally and theoretically. These data provide qualitative information about the complexation and validate the postulated model for the association. As illustrated in Table 1, theoretical hydrodynamic radii of the calix[4]arene carboxylate salts and macrocycle **1** are similar, and therefore, it was expected to observe similar values of the hydrodynamic radii as well as of the complexes. Indeed, the experimental hydrodynamic radii obtained for the complexes are in good fit with the calculated hydrodynamic radii. Two theoretical radii were considered depending on the conformation of the calix[4]arene **a**: 5.9 Å for the *cone* conformation and 6.5 Å for the *pinched cone*, which is the preferred conformation for this compound. Indeed, the experimental hydrodynamic radius (6.7 Å) is in good agreement with that extracted from the *pinched cone* model. This preferred conformation was also confirmed by preliminary X-ray crystallography data (not shown).

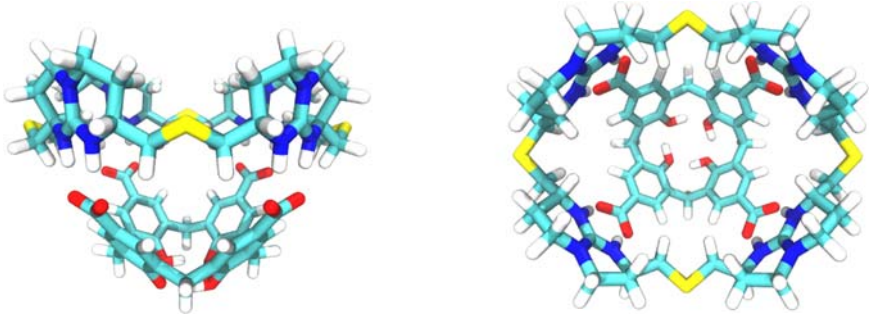


Figure 2. (Colour online) Side view (left) and top view (right) of the molecular model (MM3) of complex **1@e**.

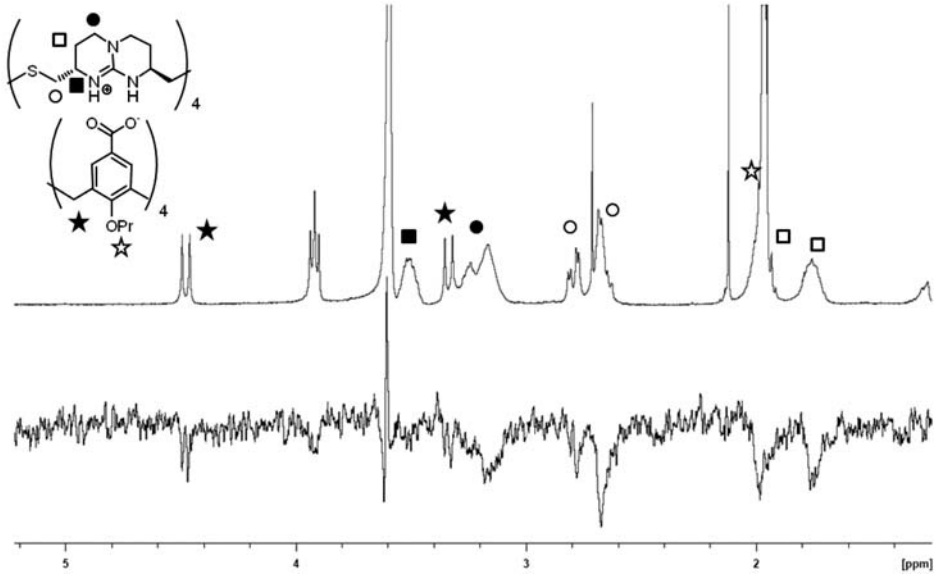


Figure 3. 1D ROESY experiment showing contacts between the aromatic part of calixarene **c** and **1**.

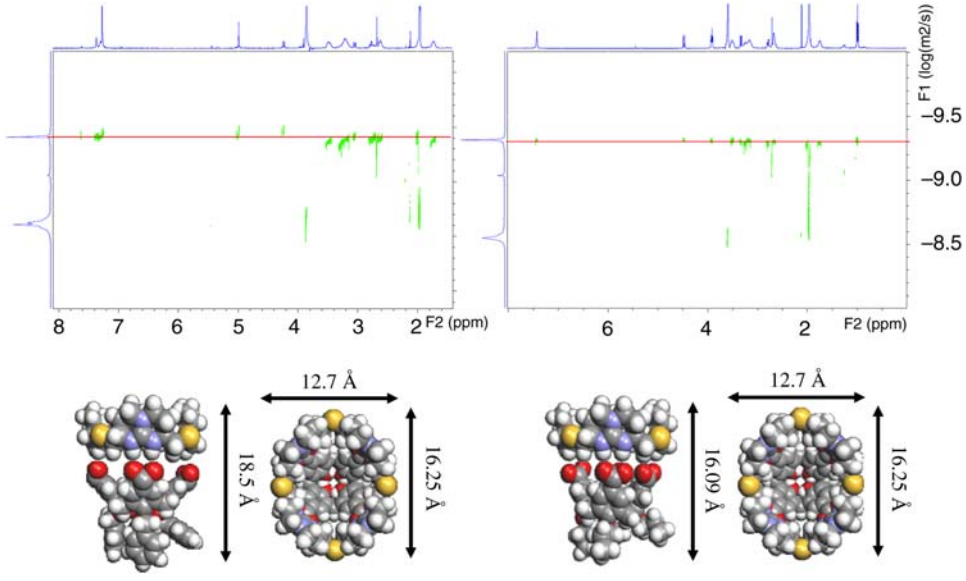


Figure 4. (Colour online) DOSY spectra of **1@a** (left) and **1@c** (right) measured in D_2O:CD_3CN (1:3) with the corresponding molecular models used to calculate their theoretical R_h.

Table 1. Theoretical and experimental hydrodynamic radius extracted from the molecular models and DOSY experiments, respectively.

	*R*calc (Å)	*R*exp (Å)
Tetraguanidinium **1**	5.6	5.1
Calix (OBn) **a**	5.9/6.5	6.7
Calix (OPr) **c**	5.6	–
Complex **1@a**	8.1	8.9
Complex **1@c**	7.5	7.8

Conformational study of the tetraguanidinium calix[4]arenate complexes in solution

Calixarenes can adopt different conformations due to the inherent flexibility of the phenol rings around the methylene bridges (*10*). In particular, calix[4]arenes with bulky substituents such as **a** and **c** (i.e. benzyl or propyl chains at the lower rim) show a restricted conformation, whereas the aryl moieties of calix[4]arenes **b** and **e**, with hydroxyl groups at the lower rim, can unrestrictedly rotate. These hydroxyl

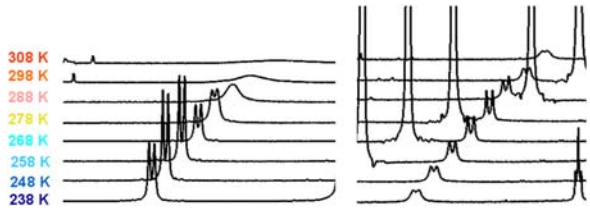


Figure 5. Example of a variable temperature ^{1}H NMR experiment monitoring the protons in the methylene bridge of calix[4]arene **b** with **1** (right) and without **1** (left).

groups provide an intramolecular hydrogen-bonding array that predominantly stabilises the *cone* conformation. However, in the presence of polar solvents, hydrogen bonding is disrupted and consequently, the ^{1}H NMR signal of the methylene protons appears as a broad singlet indicating a statistical distribution of the different conformations due to a rapid exchange between the conformers.

The macrocyclic tetraguanidinium compound **1** should stabilise the cone conformation of otherwise flexible calix[4]arenes, providing a strong and robust complex which should prevent or slow down the conformational exchange. Each bicyclic guanidinium may face a negatively charged group of the calix[4]arene, hereby influencing its orientation through electrostatic and hydrogen-bonding interactions. Therefore, the association should increase the inversion energy barriers which can be measured by the determination of coalescence temperatures using variable temperature ^{1}H NMR experiments.

To conduct these experiments, tetrabutylammonium salts of the anionic calix[4]arenes **b** and **e** were formed to enhance their solubility in organic solvents. Hence, mixtures of CD_3CN:CD_3OD (6:4) which tolerate a wide range of temperatures (from −45 to 55°C) were used in the variable temperature NMR experiments.

As shown in Figure 5, the methylene protons of calix[4]arene **b** appeared as a broad signal at room temperature, accounting for a rapid interconversion between different conformers in solution. Upon cooling, the *cone* conformation was stabilised, and thus, the proton signal became a doublet at 278 K. Conversely, at room temperature in the presence of tetraguanidinium ligand **1**, the calix[4]arene **b** adopted a more stable *cone* conformation which should facilitate the complexation with this polycationic molecule. Consequently, the doublet signal was observed up to 318 K (the upper temperature limit for this solvent system). A similar trend was observed for calix[4]arene **e**.

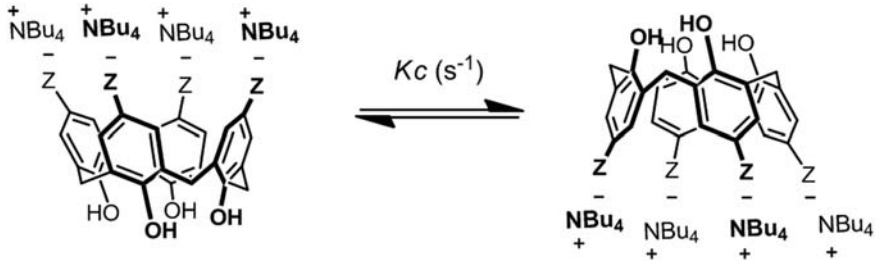
Gutsche et al. (Gutsche and Bauer *11* and van Hoorn et al. *12*) described a method to assess conformational mobilities in calix[*n*]arenes by means of dynamic ^{1}H NMR spectroscopy (see Supplementary Material, Figure S1, available online). Applying this methodology, conformational barriers of calix[4]arene inversions with and without ligand **1** were deduced from the coalescence temperatures extracted from the variable temperature ^{1}H NMR data.

Table 2 summarises the data obtained from these experiments. In general, tetrabutylammonium calix[4]arene salts display lower coalescence temperatures (T_c) than the corresponding tetraguanidinum calix[4]arenate complexes. The numbers (together with those shown in Table 3) were calculated assuming an accuracy of ±5°C for the value of T_c; ±15 Hz for the value of $\Delta\nu$ and ±1 Hz for the value of J_{AB}. It is also estimated that $\Delta G^{\neq}$ values are accurate to ±0.4 kcal mol^{-1}.

However, T_c values are higher than 328 K for the tetraguanidinium calix[4]arenate complexes, and therefore, free energy interconversion barriers cannot be accurately determined as the solvent mixture employed (CD_3CN/CD_3OD) does not allow to reach this temperature (see the corresponding NMR spectra in Supplementary Material, Figures S2 and S3, available online).

In DMSO, the upper limit of the temperature range increases, but extrapolation from previous experiments

Table 2. Calculated values for the coalescent constant (K_c) and $\Delta G^{\neq}$ in the system depicted.



In CD_3CN/CD_3OD	T_c (K)	$\Delta\nu$	J_{AB}	K_c (s^{-1})	$\Delta G^{\neq}$ (±0.4 kcal mol^{-1})
Calix **b** ($Z = SO_3^-$)	308–318	280	12.5	626.4	14.36
Calix **e** ($Z = CO_2^-$)	308–318	255	12.9	570.5	14.42
Complex **1@b**	>328	271	12.9	609.0	–
Complex **1@e**	>328	273	12.5	608.7	–

Table 3. Calculated values for the coalescent constant (K_c) and $\Delta G^{\neq}$ in DMSO.

In DMSO	T_c (K)	$\Delta\nu$ (Hz)	J_{AB} (Hz)	K_c (s^{-1})	$\Delta G^{\neq}$ (± 0.4 kcal mol^{-1})
Calix **b** ($Z = SO_3^-$)	298–308	280	12.5[a]	626.4	13.9
Calix **b** + 4 equiv. **8**	298–308	280	12.5[a]	626.4	13.9
Calix **b** + 2 equiv. **4**	298–308	280	12.5[a]	626.4	13.9
Complex **1@b**	>408	232.5[b]	12.45[b]	520.6	>19.1
Calix **e** ($Z = CO_2^-$)	318–328	200	12.95[a]	438.6	15.3
Calix **e** + 4 equiv. **8**	318–328	200	12.95[a]	438.6	15.3
Calix **e** + 2 equiv. **4**	368–378	200	12.95[a]	438.6	17.4
Complex **1@e**	388–398	210	12.8	471.4	18.4

[a] Extrapolated from the experiment conducted in CD_3CN/MeOD (6/4).
[b] These numbers correspond to the last complex observed.

made in CD_3CN/CD_3OD mixture was necessary for parameters such as J_{AB} and $\Delta\nu$, as the lower temperature limit of DMSO does not allow their direct measurement (see the corresponding NMR spectra in Supplementary Material, Figures S4–S9, available online).

Control tests with mono- and diguanidinium calix[4]arene salts were conducted to evaluate their effect in the conformational stability of the complexes. Addition of stoichiometric amounts (4 equiv.) of a bicyclic guanidinium monomer **8** (see formula in Supplementary Material, Figure S2, available online) did not influence the interconversion rate (Table 3), the calix[4]arene carboxylate salts showing similar coalescence temperatures as the tetrabutylammonium salts. Interestingly, diguanidine **4** had an effect on the conformational barrier of calix[4]arene tetracarboxylate **e** but not on tetrasulphonate **b**. This accounts for slower kinetic off-rates for guanidinium cations with carboxylates than with sulphates, in agreement with thermodynamic data reported for similar complexes (*13*). This trend is also observed with macrocyclic tetraguanidinium ligand **1** [complex **1@e** showed higher coalescence temperatures (up to 408 K) than the **1@b** adduct (ca. 393 K)].

In conclusion, binding of tetraguanidinium multivalent ligand **1**, and to a lesser extent diguanidine **4**, stabilises the conformation of oxoanionic calix[4]arenes by hindering the mobility of their aryl moieties. This effect is not attributable to the intrinsic interaction of four 'monovalent' guanidine ligands with anionic calix[4]arenes as demonstrated by control experiments. The higher conformational stabilisation of the calix[4]arene carboxylates over the corresponding sulphonates indicates that a stronger interaction results in a structurally more stable complex. Indeed, as the number of guanidinium moieties increases, the strength of the interaction should also increase, both by effective molarity and by the cooperativity effect.

This structural behaviour in solution is essential to allow molecular recognition at these interfaces, because stabilisation of the *cone* conformations allows for the formation of robust and well-defined void-like structures which are able to bind other guest molecules even at high temperatures.

Isothermal titration calorimetry studies

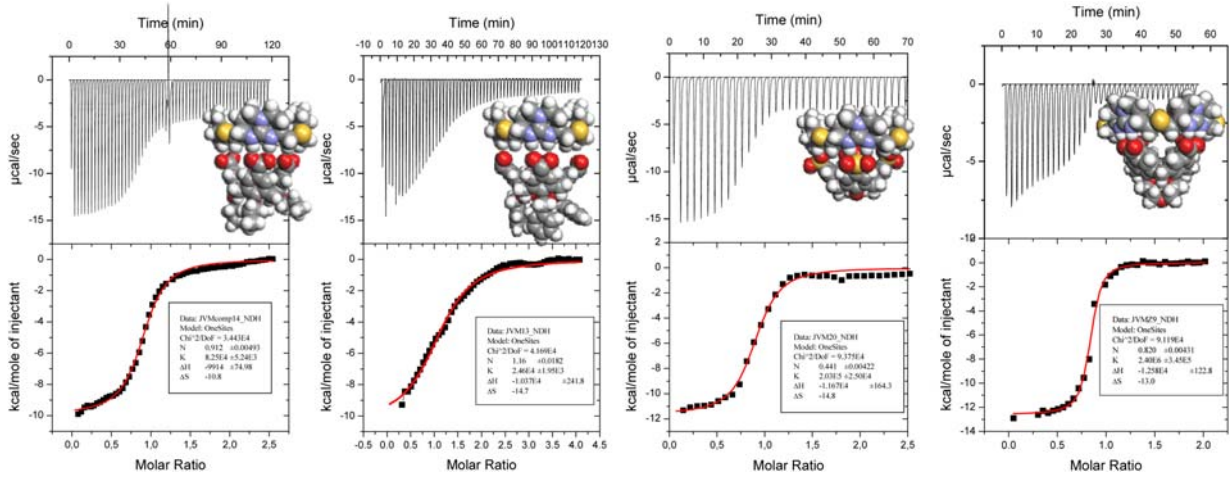
Isothermal titration calorimetry (ITC) was used to assess quantitatively and qualitatively the thermodynamic factors of the binding between macrocyclic tetraguanidinium ligand **1** and tetraoxoanionic calix[4]arenes. The experiments were carried out in a tetrahydrofuran (THF)/H_2O (3:1) mixture to allow solubilisation of the more hydrophilic sodium calix[4]arenate salts **a**–**d**.

High binding constants (within the range of 10^4–$10^6\,M^{-1}$, see Table 4) were determined even in the presence of polar solvents such as water, accounting for a robust and cooperative enthalpically driven interaction. Hence, the binding is dominated by hydrogen bonding and ion-pair formation. Conversely, the entropic factor, which mainly depends on disorder in the molecular assembly process, solvation effects and solvent-shell reorganisation upon complexation, has only a minor contribution in these systems.

As previously discussed, molecular modelling and VT ^1H NMR experiments suggested that the preferred calix[4]arene conformation to maximise the interaction with macrocyclic tetraguanidinium ligand **1** is the *cone* conformation.

In fact, the highly preorganised calix[4]arene **d** showed an association constant with ligand **1** up to two orders of magnitude higher than the more flexible calix[4]arenes **a** and **c**. This molecule, bearing bridges between vicinal phenols at the lower rim, displays a restricted *cone* conformation (*14*) which facilitates the interaction with **1**. Tetrasulphonatocalix[4]arene **b** should also show a preferred cone conformation due to the intramolecular hydrogen-bonding array between the phenolic groups of the lower rim. However, in polar media, this array is less stable. Indeed, the binding constant drops by one order of magnitude due to the weaker sulphonate–guanidinium interaction and also due to the fact that this molecule is conformationally less robust than calix[4]arene **d**. Indeed, compounds **a** and **c** preferentially display a *pinched* conformation which results in weaker binding to the tetraguanidinium ligand **1** ($K_a = 2.5 \times 10^4$ and $8.3 \times 10^4\,M^{-1}$, respectively). This *pinched* disposition of the aryl moieties prevents interaction with the macrocyclic

Table 4. ITC profiles and thermodynamic data obtained by ITC measurements.



	Complex **1@a**	Complex **1@b**	Complex **1@c**	Complex **1@d**
K_a (M^{-1})	2.46×10^4	2.03×10^5	8.25×10^5	2.45×10^6
ΔH (kcal mol^{-1})	− 10.4	− 9.9	− 11.7	− 12.6
ΔS (cal mol^{-1} K^{-1})	− 14.7	− 10.8	− 14.8	− 12.9
ΔG (kcal mol^{-1})	− 6.0	− 6.7	− 7.3	− 8.8

Notes: Stoichiometry of the complexes (1:1). Errors ≤ 10%.

tetraguanidine, and thus, lack of a correct preorganisation in a conical shape translates into a lower association constant.

Finally, titrations with bicyclic guanidinium monomer **8** and dimer **5**, respectively, did not produce any significant heat exchange in the presence of tetracarboxylic calix[4]arene **a** (see Supplementary Material, Figure S10, available online). This highlights the requirement of having multivalent systems such as ligand **1** to allow complexation even in highly competitive polar solvents.

Guest complexation in calix[4]arene-tetraguanidinium expanded cavities

As shown in previous molecular models, complexation of the tetraguanidinium ligand **1** with oxoanionic calix[4]arenes may result in the increase in the inner volume of these molecular containers.

To demonstrate the ability of calixarene-guanidinium expanded cavities to effectively include and bind guest molecules, titration experiments of **1@d** with two different quinolinium iodide salts (**9** and **10**) (Figure 6) were carried out. For this purpose, we selected the most robust tetraguanidinium calix[4]arenate complex (**1@d**) in terms of binding and structural stability.

Host–guest interactions between calixarenes and ammonium salts have been extensively reported (*15*). Their inclusion is mainly driven by cation–π, CH–π and π–π contacts, although hydrophobic effects should also be taken into account in polar solvents (Figure 7).

Figure 6. 2-Methylisoquinolinium and 1-ethyl-2-methylquinolinium iodide salts **9** and **10**.

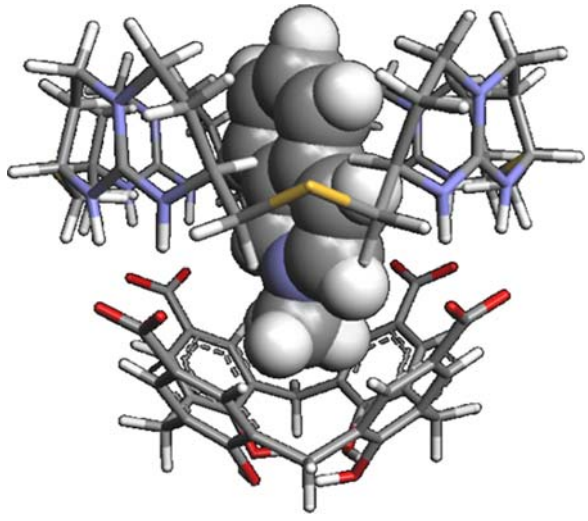


Figure 7. Molecular model (MM3) of guest encapsulation complex **9**@[**1@e**].

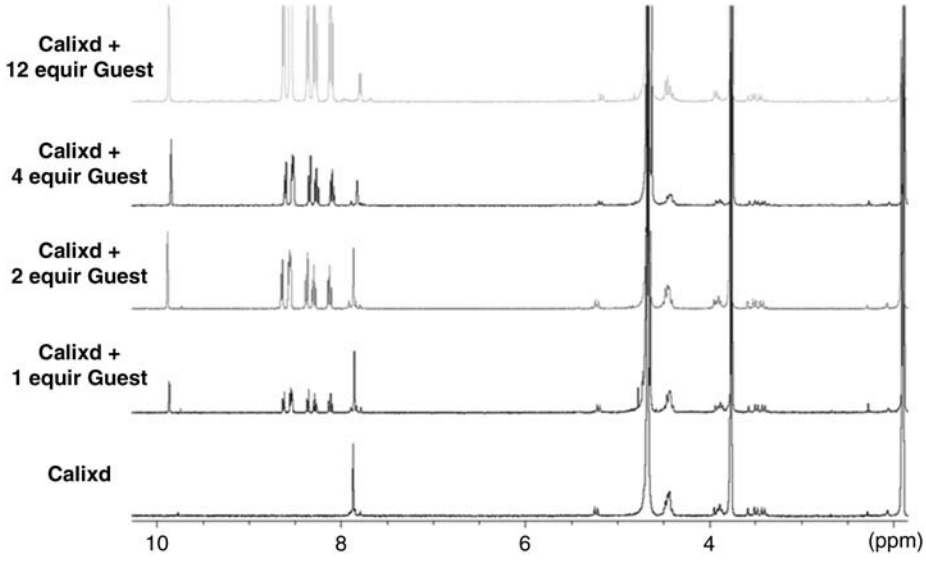


Figure 8. ^{1}H NMR titration (in 3:1 THF-d_8/D_2O mixture) of the selected guest **9** with oxoanionic calix[4]arene **d**.

In terms of size, it is likely that 2-methylisoquinolinium guest **9** should not allow an effective complexation with a simple calix[4]arene. Indeed, no binding was observed by ^{1}H NMR titration experiments between calix[4]arenate **d** and quinolinium **9** (Figure 8) in the absence of tetraguanidinium. Also, no appreciable changes in the spectra were observed upon adding guest **10** to a solution containing macrocyclic tetraguanidine **1**.

^{1}H NMR titration experiments with guest **9** in the presence of the supramolecular tetraguanidinium calix[4]arenate host **1@d** (Figure 9) in a (3:1) THF-d_8/D_2O mixture revealed upfield shifting of the guest proton signals, accounting for a molecular encapsulation process. As illustrated in Figure 11, the addition of an excess of ammonium guest resulted in the appearance of new broad signals, which corresponds in chemical shift with the free 2-methylisoquinolinium guest in solution. The data strongly support slow exchange equilibrium between the free and the bound guest (*16*). The broadness of the signals did not allow an accurate integration for the association constant determination.

As shown in Figure 10, nOe cross peaks between these two bound and free species confirmed the existence of a chemical exchange due to guest inclusion.

^{1}H NMR titrations in a (3:1) THF-d_8/D_2O mixture with 1-ethyl-2-methylquinolinium iodide guest **10** were also

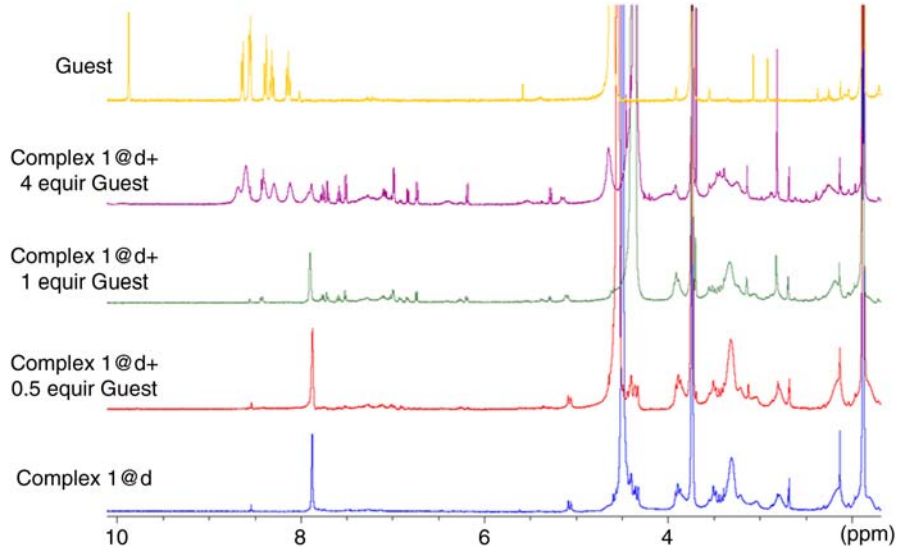


Figure 9. ^{1}H NMR titration (in 3:1 THF-d_8/D_2O mixture) of guest **9** with complex **1@d**.

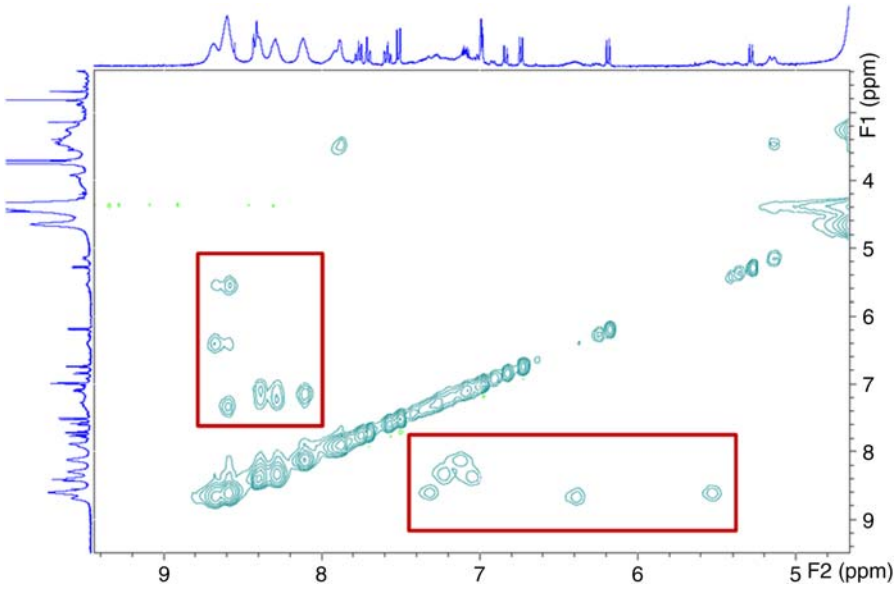


Figure 10. NOESY spectrum showing exchange cross peaks between free and bound guest (**9**) signals.

performed to explore the possibility of this bulkier molecule to be included into **1@d** complex. Indeed, the spectra showed well-defined upfield shifted signals accounting for the complexation of **10** (Figure 11). When an excess guest was added, a new set of signals corresponding to the free species appeared, clearly indicating a slow exchange process on the NMR timescale.

The chemical exchange observed in the NOESY spectrum (Figure 12) confirmed this two-state (free and bound) behaviour for guest **10**.

Conclusions

We have shown that the cavity of a calix[4]arene containing anionic functions at the upper rim (such as carboxylates or sulphates) can be expanded by complexation with a macrocycle that is complementary in size and binding sites. For this purpose, we employed a tetraguanidinium macrocycle that can provide well-oriented hydrogen bonds and strong electrostatic interactions in apolar solvents. The resulting expanded cavity is able to complex large guests such as quinolinium salts that

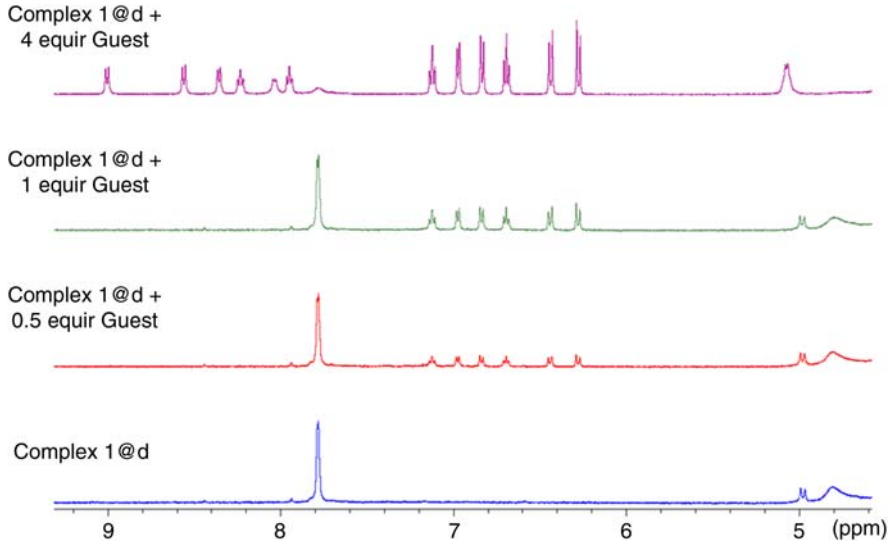


Figure 11. ^{1}H NMR titration (in 3:1 THF-d_8/D_2O mixture) of guest **10** with complex **1@d**.

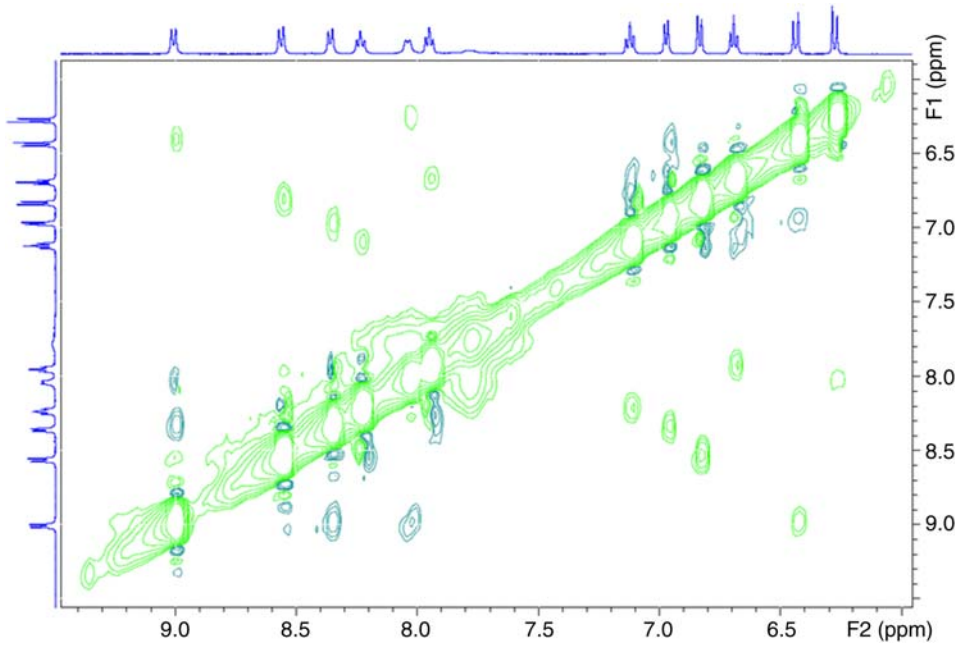


Figure 12. NOESY spectrum showing exchange cross peaks between free and bound guest (**10**) signals.

could not be accommodated in simple calixarene scaffolds. This constitutes a new strategy based on the self-assembly to build up large containers for host–guest interactions.

Experimental section

Materials and methods

Synthesis

All commercially available reagents (Aldrich, Fluka, Acros, NovaBiochem, Panreac) were used without further purification. Anhydrous solvents were obtained from a solvent purification system. All reactions were carried out under nitrogen atmosphere unless specified.

Chromatography

Thin layer chromatography (TLC) was performed on pre-coated TLC plates SIL G-25 UV_{254} (Macherey-Nagel, Düren, Germany) glass supported with UV detection at 254 nm and/or bromocresol green stain (in EtOH and 1 N NaOH mixture). Column chromatography was done using silica gel (Chromagel SDS 40–60 mm) following the procedure described by W.C. Still. HPLC chromatograms were recorded on Agilent Technologies 1100 (UV detector) analytical HPLC C18 Symmetry300 and SunFire C18 columns (4.6 × 150 mm, 5 μm). For semi-preparative HPLC, an LC 18 column Symmetry (10 × 150 mm, 5 μm) was used. The mobile phase consisted of CH_3CN/H_2O mixture containing 0.05 or 0.1% trifluoroacetic acid. The solvents were provided by Scharlau and Carlo Erba (HPLC gradient grade).

Analysis

NMR spectra were recorded on a Bruker Advance 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) equipped with a *z*-gradient 5-mm broadband observe probe with ATM Ultrashield spectrometer. Deuterated solvents used are indicated in each case. Chemicals shifts (δ) are expressed in ppm, and are referred to the residual peak of the solvent. Mass spectra were recorded in a Waters LCT Premier (electrospray ionisation or atmospheric pressure chemical ionisation mode), Waters GCT (electronic impact and chemical ionisation modes) or Bruker MALDI-TOF spectrometers. Calorimetric measurements were made in an isothermal titration microcalorimeter Microcal VP-ITC. The operating temperature range varies from 2°C up to 80°C with a noise level of 1 nanocal s^{-1} (4 nanowatts).

Synthesis

Calix[4]arenes **a**, **c**, **d** and **e** were synthesised according to described procedures (*17*). Calix[4]arene tetrasulphonic acid **b** was commercially available.

*(2S,8S)-2-(*tert*-butyldiphenylsilanyloxymethyl)-8-methanesulphonyloxymethyl-3,4,6,7,8,9,-hexahydro-2H-pyrimido[1,2-a]pyrimidin-1-ium hexafluorophosphate (**2**)*

To a solution of mono-deprotected guanidine (PF_6^-) (1.23 g, 2.11 mmol) in dry CH_2Cl_2 (25 ml) were added

Ms_2O (1.84 g, 10.55 mmol) and N-methylmorpholine (NMM) (1.87 ml, 16.87 mmol), and the mixture was stirred for 4 h at room temperature. After evaporation of the solvent, the resulting solid was dissolved in CH_2Cl_2 (100 ml) and washed with a 0.1 N NH_4PF_6 solution (2 × 50 ml). The organic layer was filtered over cotton and concentrated at reduced pressure. Purification by silica gel column chromatography (CH_2Cl_2/MeOH, 98:2) afforded the corresponding mesylate **2** (1.23 g, 88%) as a white solid. M.p. 60–61°C. $[\alpha]_D^{25} + 78$ ($c = 0.8$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 4H, CH_{Ar}), 7.50–741 (m, 6H, CH_{Ar}), 6.28 (s, 1H, NH), 6.12 (s, 1H, NH), 4.33 (dd, $J = 4.5$ and 10.3 Hz, 1H, CH_2OMs), 4.19 (dd, $J = 6.5$ and 10.3 Hz, 1H, CH_2OMs), 3.86–3.79 (m, 1H, CH_α), 3.72–366 (m, 2H, CH_2OSi), 3.63–3.56 (m, 1H, CH_α), 3.43–3.27 (m, 4H, $CH_{2\gamma}$), 3.11 (s, 3H, CH_{3MsO}), 2.15–1.87 (m, 4H, $CH_{2\beta}$), 1.08 (s, 9H, $CH_{3t\text{-}Bu}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7 (C_{guan}), 135.6, 135.5, 132.6, 132.5, 130.1, 130.1, 128.0 (CH_{Ar}, C_{Ar}), 69.5 (CH_2OMs), 65.4 (CH_2OSi), 50.2, 47.8 (CH_α), 45.4, 45.0 ($CH_{2\gamma}$), 37.2 (CH_{3MsO}), 26.8 ($CH_{3t\text{-}Bu}$), 22.5, 22.0 ($CH_{2\beta}$), 19.2 ($C_{t\text{-}Bu}$). HR-MS calcd for $[C_{26}H_{38}N_3O_4SSi]^+$ 516.2352; found 516.2354.

*(2S,8S)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-8-[(2R,8R)-8-(*tert*-butyldiphenylsilanyloxymethyl)-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-2-ylmethylsulphanylmethyl-1-ium hexafluorophosphate]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium hexafluorophosphate (**4**)*

A mixture of compound *R,R*-**3** (751 mg, 1.17 mmol), mesylate *S,S*-**2** (774 mg, 1.17 mmol) and Cs_2CO_3 (761 mg, 2.34 mmol) was dissolved in 20 mL of degassed (3:1) CH_3CN/MeOH at 0°C under N_2, and the solution was stirred for 4 h. The solvent was evaporated under vacuum at room temperature. The crude was dissolved in CH_2Cl_2 (20 ml) and washed with aqueous 1 N NH_4PF_6 (2 × 15 ml). The organic phase was filtered over cotton and concentrated to dryness to give a crude residue which was purified by silica gel (with KPF_6) column chromatography (CH_2Cl_2/MeOH, 96:4), affording symmetric diguanidinium **4** (1.20 g, 88%) as a white solid. M.p. 84–86°C. $[\alpha]_D^{25} + 3$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 2H, NH), 8.05 (s, 2H, NH), 7.71–7.55 (m, 8H, CH_{Ar}), 7.50–7.33 (m, 12H, CH_{Ar}), 3.73 (dd, $J = 4.7$ and 9.8 Hz, 2H, CH_2O), 3.67–3.50 (m, 5H, CH_2O, CH_α), 3.48–3.10 (m, 9H, CH_α,$CH_{2\gamma}$), 3.00 (dd, $J = 2.7$ and 13.5 Hz, 2H, CH_2S), 2.59 (dd, $J = 10.8$, 13.5 Hz, 2H, CH_2S), 2.18–1.69 (m, 8H, $CH_{2\beta}$), 1.06 (s, 18H, $CH_{3t\text{-}Bu}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2 (C_{guan}), 135.6, 135.6, 132.8, 132.7, 129.9, 127.9, 127.9 (CH_{Ar}, C_{Ar}), 65.2 (CH_2O), 49.7, 48.3 (CH_α), 45.1, 44.7 ($CH_{2\gamma}$), 38.5 (CH_2S), 26.9 ($CH_{3t\text{-}Bu}$), 26.2, 22.6 ($CH_{2\beta}$), 19.2 ($C_{t\text{-}Bu}$). HR-MS calcd for $[C_{50}H_{69}N_6O_2SSi_2]^+$873.4741; found 873.4754.

*(2S,8S)-2-Hydroxymethyl-8-[(2R,8R)-8-hydroxymethyl-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-2-ylmethylsulphanylmethyl-1-ium hexafluorophosphate]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium mesylate (**5**)*

A solution of **4** (1.20 g, 1.03 mmol) and MsOH (1.46 mL, 22.53 mmol) in a mixture of THF/H_2O (3:1, 40 ml) was heated overnight at 76°C. The solvent was evaporated, and the acid mixture was diluted in water and washed with CH_2Cl_2 (2 × 50 ml). The aqueous phase was partially evaporated under reduced pressure. Afterwards, $KHCO_3$ was added until a neutral pH was reached. The water was evaporated, and the crude was dissolved in a mixture of CH_2Cl_2/MeOH (1:20, 50 ml). The resulting precipitate was filtered off. The polarity of the solvent mixture was gradually reduced until pure CH_2Cl_2. The solvent was then evaporated to afford compound **5** (573 mg, 93%) as a pale yellow powder. ^{1}H NMR (400 MHz, MeOD) δ 3.78 (dd, $J = 4.0$ and 11.7 Hz, 2H, CH_2O), 3.68–3.48 (m, 6H, CH_2O, CH_α, $CH_{2\gamma}$), 3.60–3.40 (m, 10H, CH_α, $CH_{2\gamma}$), 3.01 (dd, $J = 3.9$ and 13.8 Hz, 2H, CH_2S), 2.75 (dd, $J = 8.0$ and 13.8 Hz, 2H, CH_2S), 2.19–2.08 (m, 2H, $CH_{2\beta}$), 2.07–1.84 (m, 6H, $CH_{2\beta}$).^{13}C NMR (100 MHz, MeOD) δ 152.1 (C_{guan}), 65.0 (CH_2O), 51.7 (CH_α), 46.4 ($CH_{2\gamma}$), 36.6 (CH_2S), 26.7, 23.5 ($CH_{2\beta}$). ESI-MS *m/z* 397.3 $(M - HCl - Cl^-)^+$, 199.1 $(M - 2Cl^-)^{2+}$. HR-MS calcd for $[C_{18}H_{33}N_6O_2S]^+$397.2386; found 397.2381.

*(2S,8S)-2-Methanesulphonyloxymethyl-8-[(2R,8R)-8-methanesulphonyloxymethyl-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-2-ylmethylsulphanylmethyl-1-ium hexafluorophosphate]-3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidin-1-ium hexafluorophosphate (**6**)*

Compound **5** (610 mg, 1.04 mmol) and NMM (1.84 ml, 16.59 mmol) were mixed in dry CH_2Cl_2 (25 ml) under N_2 at 0°C, and the mixture was stirred for 5–10 min. Then, Ms_2O (1.81 g, 10.37 mmol) was added, and stirring was continued for 24 h. The solution was directly washed with a 0.1 N NH_4PF_6 solution (2 × 15 ml). The organic layer was filtered over cotton and left slowly to evaporate. A white precipitate was filtered off affording **6** (771 mg, 88%) as a yellowish oil. ^{1}H NMR (400 MHz, CD_3CN) δ 6.60 (s, 2H, NH), 6.50 (s, 2H, NH), 4.32 (dd, $J = 4.1$ and 10.5 Hz, 2H, CH_2O), 4.15 (dd, $J = 7.1$ and 10.5 Hz, 2H, CH_2O), 3.87–3.77 (m, 2H, CH_α), 3.61–3.51 (m, 2H, CH_α), 3.44–3.29 (m, 8H, $CH_{2\gamma}$), 3.12 (s, 6H, CH_{3MsO}), 2.83 (dd, $J = 5.4$ and 14.0 Hz, 2H, CH_2S), 2.64 (dd, $J = 8.4$ and 13.9 Hz, 2H, CH_2S), 2.17–2.05 (m, 4H, $CH_{2\beta}$), 1.94–1.80 (m, 4H, $CH_{2\beta}$).^{13}C NMR (100 MHz, CD_3CN) δ 150.4 (C_{guan}), 70.4 (CH_2O), 47.5, 47.4 (CH_α), 44.8, 44.4 ($CH_{2\gamma}$), 36.4 (CH_{3MsO}) 35.3 (CH_2S), 24.6, 21.3 ($CH_{2\beta}$). HR-MS calcd for $[C_{20}H_{38}N_6O_6S_3PF_6]^+$699.1657; found 699.1630.

*(2S,8S)-2-(Acetylthiomethyl)-8-[(2R,8R)-8-(acetylthiomethyl)-2,3,4,6,7,8-hexahydro-1H-pyrimido[1,2-a]pyrimidin-9-ium-2-yl)methylthio)methyl)-2,3,4,6,7,8-hexahydro-1H-pyrimido[1,2-a]pyrimidin-9-ium hexafluorophosphate (**7**)*

A mixture of **6** (250 mg, 0.296 mmol) and potassium thioacetate (203 mg, 1.776 mmol) in CH_3CN (20 ml) was stirred and refluxed overnight. Then, the solution was evaporated under vacuum, dissolved in CH_2Cl_2 and washed with a 0.1 N NH_4PF_6 solution (2 × 20 ml). The organic layer was filtered over cotton and evaporated giving a crude residue which was purified by silica gel (with KPF_6) column chromatography (CH_2Cl_2/MeOH, 98:2 (96:4), affording **7** (171 mg, 72%) as a brownish oil. ^{1}H NMR (400 MHz, CD_3CN δ 6.15 (bs, 4H, NH), 3.63–3.49 (m, 4H, CH_α), 3.44–3.28 (m, 8H, $CH_{2\gamma}$), 3.14–3.03 (m, 4H, CH_2SCO), 2.78 (dd, J = 5.8 and 13.7 Hz, 2H, CH_2S), 2.62 (dd, J = 7.9 and 13.7 Hz, 2H, CH_2S), 2.40 (s, 6H, CH_3COS), 2.15–2.03 (m, 4H, $CH_{2\beta}$), 1.90–1.78 (m, 4H, $CH_{2\beta}$). ^{13}C NMR (100 MHz, CD_3CN) δ 195.1 (SCO), 150.2 (C_{guan}), 47.6, 47.4 (CH_α), 44.8, 44.5 ($CH_{2\gamma}$), 37.5 (CH_2SCO), 35.3 (CH_2S), 30.8 (CH_3COS), 24.6, 21.5 ($CH_{2\beta}$). ESI *m/z* 659.4 $(M - PF_6^-)^+$, 513.6 $(M - PF_6^- - HPF_6^-)^+$.

*Compound **1***

A solution of compound **7** (95 mg, 0.118 mmol), caesium carbonate (173 mg, 0.531 mmol) and $(^nBu)_2PhP$ polystyrene resin (323 mg, 0.260 mmol) in dry MeOH (40 mL) was stirred under inert atmosphere for 20 min. Then, a solution of compound **6** in MeCN (100 ml) was added dropwise, and the final mixture was stirred for 2 days. The phosphine resin was filtered off, and the solvent was evaporated under vacuum, dissolved in CH_2Cl_2 and washed with a 0.1 N NH_4PF_6 solution (3 × 30 ml). The organic phase was filtered over cotton and concentrated to dryness to give a crude residue which was purified by silica gel (with KPF_6) column chromatography (CH_2Cl_2/MeOH, 100:0 (94:6), affording cyclic tetraguanidinium **1** (60 mg, 41%) as a pale yellow solid. ^{1}H NMR [400 MHz, CD_3CN: D_2O (3:1)] δ 3.58–3.45 (m, 8H, CH_α), 3.41–3.25 (m, 16H, $CH_{2\gamma}$), 2.91–2.77 (m, 8H, CH_2S), 2.68–2.52 (m, 8H, CH_2S), 2.15–2.02 (m, 8H, $CH_{2\beta}$), 1.87–1.67 (m, 8H, $CH_{2\beta}$). ^{13}C NMR (100 MHz, CD_3CN) δ 151.2, 151.1 (C_{guan}), 48.4, 48.2, 47.5 (CH_α), 45.0, 44.9, 44.8 ($CH_{2\gamma}$), 37.8, 37.5, 36.3 (CH_2S), 25.7, 25.4, 25.3, 22.5 ($CH_{2\beta}$). MALDI *m/z* 789.6 $(M - PF_6^- - 3HPF_6^-)^+$. HR-MS calcd for $[C_{36}H_{61}N_{12}S_4]^+$789.4019; found 789.4458.

*(2S,8S)-2,8-Bis-(hydroxymethyl)-3,4,6,7,8,9-hexahydro-2H-pyrimido-[1,2-a]-pyrimidin-1-ium chloride (**8**)*

A solution of silyl-protected bicyclic guanidinium chloride (3 g, 5.1 mmol) in 3 N HCl/CH_3CN (1:2, 75 ml) was stirred at room temperature for 2 days. The solvent was removed, and the resulting crude was dissolved in H_2O (50 mL) and washed with CH_2Cl_2 (4 × 50 ml). The aqueous phase was evaporated under reduced pressure affording **8** (1.16 mg, 97%) as a white solid. M.p. 178–180°C. $[\alpha]_D^{25}$ −64 (c = 0.5, H_2O). ^{1}H NMR (400 MHz, D_2O) δ 3.46 (m, 2H, CH_2O), 3.35 (m, 2H, CH_2O), 3.32 (m, 2H, CH_α), 3.26–3.13 (m, 4H, $CH_{2\gamma}$), 1.86–1.66 (m, 4H, $CH_{2\beta}$). ^{13}C NMR (100 MHz, D_2O) δ 151.2 (C_{guan}), 64.3 (CH_2OSi), 48.8 (CH_α), 45.0 ($CH_{2\gamma}$), 22.7 ($CH_{2\beta}$). ESI *m/z* 200.13 $[(M - Cl^-)^+$, 100%].

^{1}H NMR complexation host–guest studies

These experiments were conducted by mixing equimolar amounts of the host and the guest in the solvents specified earlier. All trials were made at the millimolar range concentration.

Variable temperature ^{1}H NMR experiments

These experiments required the formation of the tetrabutylammonium salt of the corresponding calix[4]arene for solubility. After adding 4 equivalents of 1 M tetrabutylammonium hydroxide solution to 1 equiv. of calix[4]arene tetracarboxylate, the mixture was evaporated until dryness. Then, another equiv. of tetraguanidinium salt was added, and the resulting powder was dissolved in the methanol/acetonitrile mixture as previously described.

ITC studies

The general conditions for the performance of these experiments consist of previously dissolving all the species in THF/H_2O (8:2), and adding a 4-mM solution of oxoanionic calix[4]arene (syringe) over a 0.5-mM solution of the cyclic tetraguanidine at 25°C.

Host–guest encapsulation experiments

These experiments were conducted in (3:1) THF-d_8/D_2O in the millimolar range (between 2 and 10 mM), successively adding different amounts of quinolinium or isoquinolinium guests (**9** and **10**) to tetraguanidinium calixarenate (**1@d**) complex.

Acknowledgements

The Ministry of Economy and Competitivity (MINECO, Spain) (Projects CTQ2008-00183 and CTQ2011-28677), the ICIQ Foundation and Consolider Ingenio (Grant 2010 CSD 2006-0003) are kindly acknowledged. The authors also thank the group members Dr A. Durana, Dr E. da Silva, Elena Galán and Dr V. Martos for providing some of the calix[4]arenes and their corresponding precursors described in this study.

Note

1. Current address: LIMES Institute, Chemical Biology and Medicinal Chemistry Unit, c/o Kekulé Institute of Organic Chemistry and Biochemistry, Gerhard-Domagk-Strasse 1, 53121 Bonn, Germany.

References

(1) (a) Rebek, J. Jr. *Chem. Commun.* **2000**, 637–643; (b) Biros, S.M.; Rebek, J. Jr. *Chem. Soc. Rev.* **2007**, *36*, 93–104; (c) Schmuck, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 5830–5833; (d) Ballester, P. *Chem. Soc. Rev.* **2010**, *39*, 3810–3830.

(2) (a) Vriezema, D.M.; Comellas Aragonès, M.; Elemans, J.A. A.W.; Cornelissen, J.J.L.M.; Rowan, A.E.; Nolte, R.J.M. *Chem. Rev.* **2005**, *105*, 1445–1489; (b) Lützen, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1000–1002; (c) Koblenz, T.S.; Wassenaar, J.; Reek, J.N.H. *Chem. Soc. Rev.* **2008**, *37*, 247–262; (d) Lützen, A. *ChemCatChem* **2010**, *2*, 1212–1214.

(3) Mal, P.; Breiner, B.; Rissanen, K.; Nitschke, J.R. *Science* **2009**, *324*, 1697–1699.

(4) (a) Tucci, F.C.; Renslo, A.R.; Rudkevich, D.M.; Rebek, J. Jr. *Angew. Chem. Int. Ed.* **2000**, *39*, 1076–1079; (b) Menozzi, E.; Onagi, H.; Rheingold, A.L.; Rebek, J. Jr. *Eur. J. Org. Chem.* **2005**, 3633–3636; (c) Ajami, D.; Rebek, J. Jr. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16000–16003; (d) Lledó, A.; Rebek, J. Jr. *Chem. Commun.* **2010**, *46*, 8630–8632.

(5) Botana, E.; Nättinen, K.; Prados, P.; Rissanen, K.; de Mendoza, J. *Org. Lett.* **2004**, *6*, 1091–1094.

(6) (a) Botana, E.; Da Silva, E.; Benet-Buchholz, J.; Ballester, P.; de Mendoza, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 198–201; (b) Botana, E.; Lubinu, M.C.; Da Silva, E.; Espinet, P.; de Mendoza, J. *Chem. Commun.* **2010**, *46*, 4752–4754.

(7) Zadmard, R.; Kraft, A.; Schrader, T.; Linne, U. *Chem. Eur. J.* **2004**, *10*, 4233–4239.

(8) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 520–554.

(9) (a) Timmerman, P.; Weidmann, J.-L.; Jollife, K.A.; Prins, L.J.; Reinhoudt, D.N.; Shinkai, S.; Frish L.; Cohen, Y. *Perkin Trans.* **2000**, *2*, 2077–2089; (b) Giuseppone, N.; Schmitt, J.-L.; Allouche, L.; Lehn, J.-M. *Angew. Chem. Int. Ed.* **2008**, *120*, 2267–2271; (c) Oliva, A.I.; Gómez, K.; González, G.; Ballester, P. *New J. Chem.* **2008**, *32*, 2159–2163; (d) Metselaar, G.A.; Sanders, J.K.M.; de Mendoza, J. *Dalton Trans.* **2008**, 588–590.

(10) (a) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P.M.; Sánchez, C. *J. Org. Chem.* **1991**, *56*, 3372–3376; (b) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955–4962.

(11) (a) Gutsche, C.D.; Bauer, L.J. *J. Am. Chem. Soc*. **1985**, *107*, 6052–6059; (b) Kanamathareddy, S.; Gutsche, C.D. *J. Org. Chem.* **1994**, *59*, 3871–3879; (c) Stewart, D.R.; Gutsche, C.D. *J. Am. Chem. Soc.* **1999**, *121*, 4136–4146.

(12) van Hoorn, W.P.; Briels, W.J.; van Duynhoven, J.P.M.; van Veggel, F.C.J.M.; Reinhoudt, D.N. *J. Org. Chem.* **1998**, *63*, 1299–1308.

(13) Jadhav, V.D.; Herdtweck, E.; Schmidtchen, F.P. *Chem. Eur. J.* **2008**, *14*, 6098–6107.

(14) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454–1457.

(15) (a) Abraham, W. *J. Incl. Phen. Macrocycl. Chem.* **2002**, *43*, 159–174; (b) Mutihac, L.; Lee, J.H.; Kim, J.S.; Vicens, J. *Chem. Soc. Rev.* **2011**, *40*, 2777–2796.

(16) (a) Saito, S.; Nuckolls, C.; Rebek, J. Jr. *J. Am. Chem. Soc.* **2000**, *122,* 9628–9630; (b) Trembleau, L.; Rebek, J. Jr. *Science* **2003**, *301*, 1219–1220.

(17) (a) Sansone, F.; Barboso, S.; Casnati, A.; Fabbi, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 897–905; (b) Sansone, F.; Barboso, S.; Casnati, A.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **1999**, *40*, 4741–4744; (c) Zhou, H.; Wang, D.; Baldini, L.; Ennis, E.; Jain, R.; Carie, A.; Sebti, S.M.; Hamilton, A.D. *Org. Biomol. Chem.* **2006**, *4*, 2376–2386; (d) Martos, V.; Bell, S.C.; Santos, E.; Isacoff, E.Y.; Trauner, D.; de Mendoza, J. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 10482–10486.