## Journal Name

### **RSCPublishing**

### ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012, Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

### Hydrogen Bonding Effects in Anion Binding Calixarenes

Naseem Qureshi,<sup>*a*</sup> Dimitri S. Yufit,<sup>*b*</sup> Kirsty M. Anderson,<sup>*b*</sup> Judith A. K. Howard<sup>*b*</sup> and Jonathan W. Steed\*<sup>*b*</sup>

A series of disubstituted urea, thiourea and dansyl amide calix[4]arene based anion receptors have been prepared and characterised by X-ray crystallography. The structures show a fine balance of intramolecular urea  $\alpha$ -tape, and urea...calixarene phenolic oxygen atom hydrogen bonding patterns. Both motifs are in competition with the anion binding behaviour of the compounds in solution.

### Introduction

Calixarenes have been used extensively as scaffolds for enzyme mimics,<sup>1</sup> HCl co-transporters,<sup>2</sup> and receptors for cationic, anionic and neutral guests.<sup>3-9</sup> As part of their work on calixarene-based membrane transporters and chemically modified field effect transistors (CHEMFETs) the Reinhoudt group developed a range of lipophilic di- and tetra(urea) calix [4] arene receptors of type 1 and  $2^{10}$  displaying significant selectivity for the biologically important<sup>11, 12</sup> chloride anion. Analogous tris(urea) calix[6]arenes are selective for tricarboxylates.<sup>13</sup> Monte Carlo modelling by Jorgensen and coworkers on the 1,3-difunctionalised bis(urea) calix[4]arene 1 (R = Ph) in which the urea groups are linked to the calixarene phenolic oxygen atoms by relatively long, flexible butylene spacers, suggests that the compound adopts a conformation involving an intramolecular urea-urea six-membered-ring hydrogen bond;<sup>14</sup>  $R_2^1(6)$  in graph set nomenclature<sup>15</sup> (Fig. 1a). Chloride binding then disrupts this interaction and the anion is bound in a cleft between the pair of urea functional groups (Fig. 1d). Subsequent X-ray crystallographic analysis on the related bis(thiourea) derivative 3a which possesses shorter ethylene linkers and no alkyl substituents on the calixarene 2- and 4position phenolic rings, reveals intramolecular OH---O interactions at the narrow ('lower') rim, intramolecular NH---O interactions from thiourea to phenolic oxygen (Fig. 1c) and intermolecular thiourea hydrogen bonding of the  $R_2^2(8)$  type (Fig. 1b).<sup>16</sup> A range of other more conformationally constrained cyclic calix[4]- and calix[6]arene derivatives has also been produced based in the pendant urea or thiourea template.<sup>17-21</sup> The presence of OH…O hydrogen bonding in calixarenes is known to rigidify the cone conformation<sup>22</sup> and hence potentially preorganise the anion binding pocket provided by the urea pendant groups. Additional preorganisation may also be offered by the shorter, less flexible ethylene spacer groups in **3a** as opposed to the longer butylene groups in compounds such as 1. However, a shorter linker may also favour the hydrogen bonding involving intramolecular interactions between one of the thiourea or urea NH groups (in an anti conformation) and the calixarene oxygen atoms, Fig. 1c. In order to probe the occurrence of these various hydrogen bonding modes and examine their influence on anion, and specifically chloride, affinity in these systems we have prepared the disubstituted pendant bis(urea) calix[4]arenes **3b** and **4**. We now report their structural and anion binding characteristics, along with their dansyl analogues **5** and **6**, which are designed as act as fluorescent chloride anion sensors.



Figure 1: Hydrogen bonding modes in bis(urea) calixarenes (a) intramolecular urea  $R_2^1(6)$ , (b) intermolecular  $R_2^2(8)$ , (c) amide or urea-calixarene  $R_2^2(7)$ , (d) urea-chloride double  $R_2^1(6)$ .

### **Results and discussion**

**Bis(urea)** Calixarenes

Disubstituted bis(urea) calixarenes of type **4** were prepared from reaction of the appropriate isocyanate with the known calixarene bis(2-aminoethyl) derivative.<sup>23</sup> During the course of this work a variety of nitrile intermediates were also characterised by X-ray crystallography – see supplementary information. Anion binding studies in acetone and chloroform solution with the *p*-tolyl derivative **4a** proved to be disappointing. Compound **4a** showed evidence for fluxional behaviour on the NMR spectroscopic timescale and exhibited poor solubility. As a result we turned our attention to compounds **4b** and **4c**.

Crystals of **4b** suitable for X-ray diffraction were obtained from acetonitrile/chloroform solution and proved to be of the mixed acetonitrile chloroform solvate **4b**·2MeCN·2CHCl<sub>3</sub>. The molecular structure shows the expected 1,3-disubstitution pattern and a pinched cone conformation.<sup>24, 25</sup> The calixarene cavity is occupied by one of the lattice acetonitrile molecules.



The structure exhibits intramolecular hydrogen bonding interactions involving the calixarene hydroxyl groups to the adjacent phenolic oxygen atoms (2.91 and 2.95 Å) as shown in Fig. 2a. The urea groups adopt an unusual anti conformation (as opposed to the expected syn conformation compatible with urea  $\alpha$ -tape hydrogen bonding<sup>26</sup>) and are involved in two different intermolecular modes of interaction. One urea group forms an intermolecular hydrogen bonding interaction of the  $R_2^2(8)$  type (Fig. 1b). The other forms a single, long and rather bent NH···O=C interaction (N···O 3.07 Å) to another urea group on a further molecule (Fig. 2b). The carbonyl oxygen atom of this urea acts as an acceptor for a CH…O hydrogen bond from an included molecule of acetonitrile. The urea  $\alpha$ -NH protons of both unique urea groups also form intramolecular interactions to the calixarene phenolic oxygen atoms (Fig. 1c and Fig. 2a). While this *anti* arrangement and formation of the  $R_2^2(8)$  is analogous to the thiourea derivative 3a, the absence of the  $R_2^1(6)$  motif is unusual in the oxygen analogues and may arise from the dominance of an intramolecular interaction to the

calixarene oxygen atoms, facilitated by the short ethylene spacer. The complex crystal packing arrangement also involves offset  $\pi$ - $\pi$  interactions between the napthyl groups on adjacent calixarenes and CH··· $\pi$  interactions involving the included chloroform, as well as intramolecular  $\pi$ -interactions to the calixarene aromatic rings.<sup>27</sup> Overall it seems evident that the intramolecular interactions shown in Fig 2a bring about the unusual *anti* urea conformation resulting in a complex series of intermolecular interaction for the urea  $\beta$ -NH protons. (a)



Figure 2: X-ray crystal structure of **4b**·2MeCN·2CHCl<sub>3</sub> showing (a) the  $R_4^4(14)$  intramolecular hydrogen bonding and (b) the intermolecular  $R_2^2(8)$  motif. CH hydrogen atoms omitted for clarity. Acetonitrile intracavity guests shown in spacefilling mode.

The methylsulfanylphenyl derivative 4c as a mixed acetone/methanol solvate of formula 4c·1.50CMe<sub>2</sub>·0.5MeOH was also characterised by X-ray crystallography. The cavity is occupied by a molecular of acetone and the molecule displays a similar pinched cone conformation with two intramolecular OH...O interactions from the calixarene phenolic groups, as observed for 4b. However, remarkably, the urea groups do not associate with the calixarene phenolic oxygen atoms and instead form the conventional urea  $\alpha$ -tape type  $R_2^1(6)$  motif (Fig. 3), analogous to the geometry calculated for 1 (R = Ph) by Monte Carlo methods.<sup>14</sup> The calculations for 1 suggest an unsymmetrical six-membered right with the NH group closest to the calixarene forming a markedly shorter hydrogen bond to the adjacent urea carbonyl group.<sup>14</sup> In the present experimental structure of 4c the six membered hydrogen bonded ring is relatively symmetrical and it is the distal urea NH group the forms the slightly shorter interaction, N····O=C distances 3.07

and 2.89 Å. However, these distances are likely to be dominated by crystal packing effects in these flexible compounds. The significant differences in the structures of **4b** and **4c** are not obviously related to the differences in the urea substituent groups and suggest that the alternative hydrogen bonding modes, and hence urea conformations, are finely balanced in this system in contrast to the usual predominance of the  $\alpha$ -tape  $R_2^1(6)$  arrangement.<sup>26</sup>



Figure 3: Urea  $R_2^1(6)$  tape hydrogen bonding in the structure of **4c**. CH hydrogen atoms omitted for clarity. Intracavity guests shown in spaceflling mode.

The anion binding properties of receptors 4b and 4c were examined in acetone solution using <sup>1</sup>H NMR spectroscopic titration. Significant chemical shift changes were observed on titration of both receptors with tetrabutylammonium chloride, bromide, acetate and nitrate. In the case of the interaction of 4c with Cl<sup>-</sup>, anion binding is evident in the chemical shift changes in the NH and OH resonances, initially at 8.31 and 8.65 ppm. The NH resonance moves downfield ( $\Delta \delta = 1.72$  ppm) giving a clean titration isotherm which can be readily fit to a 1:1 stoichiometric model. In contrast, the OH resonance undergoes a much less significant upfield chemical shift change ( $\Delta \delta = -$ 0.27 ppm after addition of one equivalent of anion). It is likely that the OH…O intramolecular hydrogen bonding at the calixarene narrow rim is retained in the chloride complex, while the urea intramolecular hydrogen bonding interaction observed in the crystal structure is replaced by a number of NH…Clhydrogen bonds.<sup>28, 29</sup> The OH…O interaction apparently becomes weaker as the conformation of the calixarene adapts to accommodate the anion guest. The second NH peak also undergoes a marked chemical shift change but becomes obscured by other resonances during the course of the titration. In the case of titration with acetate anion the chemical shift change is even more marked ( $\Delta \delta = 2.63$  and -0.32 ppm for the NH and OH resonances, respectively). Similar behaviour in terms of magnitude and direction of chemical shift changes were observed for the napthyl derivative 4b. Fitting the titration isotherm using HypNMR 2006<sup>30, 31</sup> yields the association constants given in Table 1. For 4c the selectivity order is  $Cl^- >$  $OAc^{-}$ ,  $> NO_{3}^{-} > Br^{-}$  and hence the receptor is weakly chloride selective. Receptor 4b exhibits generally slightly lower affinity, perhaps because of the intramolecular hydrogen bonding interactions to the calixarene oxygen atoms.

Table 1: Anion binding constants (log  $\beta_{11}$ , NBu<sub>4</sub><sup>+</sup> salts) for new receptors in acetone at 20 °C

| Receptor | Anion   |                 |                  |                              |  |  |
|----------|---------|-----------------|------------------|------------------------------|--|--|
|          | Cl-     | Br <sup>-</sup> | OAc <sup>-</sup> | NO <sub>3</sub> <sup>-</sup> |  |  |
| 4b       | 3.59(4) | -               | -                | 2.38(8)                      |  |  |
| 4c       | 3.91(3) | 3.41(3)         | 3.76(4)          | 3.03(1)                      |  |  |

Moving from urea (X=O) to thiourea (X=S) results in an increase in the C=X bond length and hence generally the observation of  $R_2^2(8)$  type hydrogen bonding patterns instead of the urea  $\alpha$ -tape  $R_2^1(6)$  motif.<sup>26, 32, 33</sup> This propensity is observed in the  $R_4^4(14)$  intramolecular hydrogen bonding, and  $R_2^2(8)$ intermolecular ribbon formation observed in the structure of thiourea derivative **3a** (Fig. 1b and 1c).<sup>16</sup> In general we anticipate that thiourea derivatives should favour this arrangement in contrast to the structure of 4c. By way of confirmation we prepared a close analogue of 3a, the bis(*m*tolylurea) derivative **3b**. This compound was also structurally characterised as the mixed chloroform/ethanol solvate and adopts a conformation closely related to 3a, exhibiting an anti conformation of the thiourea moieties. While the thiourea groups adopt an intramolecular  $R_4^4(14)$  interaction to the calixarene oxygen atoms analogous to 4b, the expected intermolecular  $R_2^2(8)$  ribbon analogous to **3a** is absent and is replaced by a solvent separated hydrogen bonded ring of graph set  $R_4^4(12)$  involving two well-ordered ethanol molecules (Fig. 4). The calixarene cavity is occupied by a disordered combination of ethanol and chloroform. While the details of the packing are thus rather different to the closely related 3a the dominance of intramolecular over intermolecular hydrogen bonding is consistent with the structure of 3a and 4b and is in contrast to the urea  $\alpha$ -tape structure of **4c**.



Figure 4: X-ray crystal structure of bis(*m*-tolylurea) derivative **3b** showing the intermolecular ethanol solvent-separated hydrogen bonded ribbon and an intramolecular  $R_4^4(14)$  interaction to the calixarene oxygen atoms. Calixarene CH hydrogen atoms omitted for clarity.

Due to increased acidity of the NH protons of the thiourea compared to urea (thiourea p*K*a = 21.0; urea p*K*a = 26.9),<sup>34</sup> the anion complexation was expected to be stronger. The increased acidity is evident from the <sup>1</sup>H-NMR spectrum of **3b** where the

NHb proton is shifted 0.26 ppm and the NHa proton 0.57 ppm to lower field compared to the urea analogue 4a. <sup>1</sup>H-NMR spectroscopic titration experiments were performed with  $TBA^{+}X^{-}$  (X = Cl, OAc, NO<sub>3</sub>) in acetone–d<sub>6</sub>. The <sup>1</sup>H-NMR resonances assigned to NHa, OH and NHb occur at 7.87, 8.08 and 6.75 ppm in the free host. The urea NHa proton shifts to 9.32 ppm ( $\Delta\delta = 1.45$  ppm) upon 1:1 chloride binding, log  $\beta_{11} = 3.16(6)$ . The OH peak moves from 8.08 ppm to 8.27 ppm  $(\Delta \delta = 0.19 \text{ ppm})$ . This chemical shift change is in the opposite direction to that observed for the oxygen analogues and suggests that intramolecular hydrogen bonding reinforces anion binding in this case. In the case of acetate anion, the NH resonances disappear suggesting deprotonation. The nitrate anion binds very weakly with chemical shift changes of the NH resonances still occurring on with addition of up to five equivalents of anion.

#### Fluorescent anion sensing

Given the affinity and modest chloride selectivity observed for receptors of type 4b and 4c we prepared the related dansyl amides 5 and 6 with, respectively, ethylene and butylene spacer groups linking the anion binding amide group with its appended chromophore to the calixarene scaffold. Compound 5 was characterised by X-ray crystallography which confirms that the dansylamide groups are substituted at 1,3-distal calixarene phenolic rings. The amide NH groups form a short intramolecular hydrogen bond (2.97 Å) to the oxygen atoms of the lower rim of the calixarene in a similar way to the structures of 3a, 3b and 4b but in contrast to 4c (Fig. 5). <sup>1</sup>H NMR spectroscopic titration of host 5 with TBA<sup>+</sup>X<sup>-</sup> (X = Cl, OAc, Br, F, NO<sub>3</sub>) in a range of solvents did not produce any significant chemical shift change, suggesting that the amide functionalities may be unavailable for interaction with guest anions as a result of the intramolecular hydrogen bonding interaction. In contrast, <sup>1</sup>H NMR spectroscopic titration of host 7 bearing the longer butylene spacer gave a significant anion response.



Titration with chloride in acetone– $d_6$  resulted in a shift in the NH peak from 6.83 ppm in the free host to 8.13 ppm at five equivalents. Other anion guests (OAc<sup>-</sup>, Br<sup>-</sup>, F<sup>-</sup> and NO<sub>3</sub><sup>-</sup>) have significantly less effect. Fitting the binding isotherm to a 1:1 model gave a relatively modest chloride binding constant of log  $\beta_{11} = 1.47(1)$ , reflecting the single NH hydrogen bonding group

of the amide as opposed to two NH groups of the urea moieties. However, the longer butylene spacer clearly disfavours the intramolecular hydrogen bonding and allows the compound to function as an anion receptor.



Figure 5: X-ray crystal structure of dansyl derivative **5** showing the intramolecular  $R_4^4(14)$  interaction to the calixarene oxygen atoms. Intracavity acetonitrile guest shown in spacefilling mode. Calixarene CH hydrogen atoms omitted for clarity.

The fluorescent response to chloride in compounds 5 and 6 was monitored by fluorescence titration in acetonitrile solution (see supplementary information figures S14 and S15). Both receptors are highly quenched in this medium, perhaps as a result of photo-induced electron transfer from the sulfonamide lone pair, even though this lone pair is expected to be delocalised. Addition of chloride results in significant fluorescence enhancement of the unstructured dansylamide monomer emission band in both compounds. For compound 5 there is no shift in the  $\lambda_{max}$  514 nm upon anion addition up to 500 molar equivalents and  $Cl^{-}$ . For the butylene complex 6 the emission enhancement is accompanied by a shift in the wavelength of the monomer emission band from 511 nm to 520 nm consistent with the chloride binding by this compound observed by NMR spectroscopy. Emission enhancement on anion binding has been observed in intramolecularly hydrogen bonded dansyl-based receptors for cyanide,35 however anioninduced quenching has been observed in other systems<sup>36, 37</sup> including calixarene-based hosts for N-acetyl aspartate.<sup>38</sup> The origins of the emission enhancement in both compounds is difficult to explain, particularly given the very weak binding of chloride anion by 5, but may reflect a change in the bulk ionic strength of the medium. The quantum yield of the dansyl moiety is known to be highly dependent on the medium in ways that are not fully understood.<sup>39</sup> Recent work has also shown that aggregation-induced emission can result in enhancement of dansyl fluorescence, however this is accompanied by a significant shift in emission wavelength.<sup>40</sup> Analogous titration with bromide, nitrate and acetate resulted in similar

### Conclusions

Intramolecular hydrogen bonding effects of both urea-to-urea and urea- or amide to calixarene types are in competition with

Table 1. Crystallographic data for new compounds.

methods and refined by full-matrix least squares on  $F^2$  for all data using SHELXTL software.<sup>42</sup> All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were located on the difference Fourier map and refined isotropically. Molecular graphics were produced using the programs X-Seed and POV-Ray.<sup>43, 44</sup> Crystal data are listed in Table 1.

| Compound                                | 3b                                                                                   | 4b                                                                                                          | <b>4</b> c                                                                                                                                 | 5                                                                                                 |
|-----------------------------------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Formula                                 | $\begin{array}{c} C_{64}H_{80}N_4O_4S_2 \cdot CHCl_3 \cdot \\ 3C_2H_5OH \end{array}$ | C <sub>70</sub> H <sub>80</sub> N <sub>4</sub> O <sub>6</sub> ·2CH <sub>3</sub> CN·<br>1.5CHCl <sub>3</sub> | C <sub>64</sub> H <sub>80</sub> N <sub>4</sub> S <sub>2</sub> O <sub>6</sub> ·0.5<br>CH <sub>3</sub> OH·1.5C <sub>3</sub> H <sub>6</sub> O | C <sub>72</sub> H <sub>88</sub> N <sub>4</sub> O <sub>8</sub> S <sub>2</sub> ·4CH <sub>3</sub> CN |
| Formula weight                          | 1228.30                                                                              | 1334.54                                                                                                     | 1168.58                                                                                                                                    | 1365.80                                                                                           |
| Crystal system                          | Monoclinic                                                                           | Monoclinic                                                                                                  | Monoclinic                                                                                                                                 | Triclinic                                                                                         |
| Space group                             | C2/c                                                                                 | $P2_1/c$                                                                                                    | $P2_{1}/c$                                                                                                                                 | <i>P</i> -1                                                                                       |
| a, Å                                    | 28.3148(6)                                                                           | 12.6122(5)                                                                                                  | 19.5803(5)                                                                                                                                 | 12.1816(3)                                                                                        |
| b, Å                                    | 15.8506(3)                                                                           | 30.9836(12)                                                                                                 | 20.1679(5)                                                                                                                                 | 24.5969(7                                                                                         |
| c, Å                                    | 18.2260(4)                                                                           | 18.6901(7)                                                                                                  | 18.2981(5)                                                                                                                                 | 26.7522(7)                                                                                        |
| α, °                                    | 90.00                                                                                | 90.00                                                                                                       | 90.00                                                                                                                                      | 102.923(10)                                                                                       |
| β, °                                    | 118.09(1)                                                                            | 92.349(10)                                                                                                  | 111.82(3)                                                                                                                                  | 95.542(10)                                                                                        |
| γ, °                                    | 90.00                                                                                | 90.00                                                                                                       | 90.00                                                                                                                                      | 98.546(10)                                                                                        |
| Volume/Å <sup>3</sup>                   | 7216.3(3)                                                                            | 7297.4(5)                                                                                                   | 6708.2(3)                                                                                                                                  | 7655.6(4)                                                                                         |
| Z                                       | 4                                                                                    | 4                                                                                                           | 4                                                                                                                                          | 4                                                                                                 |
| $\rho$ (calc.), mg/mm <sup>3</sup>      | 1.131                                                                                | 1.215                                                                                                       | 1.157                                                                                                                                      | 1.185                                                                                             |
| μ, mm <sup>-1</sup>                     | 0.181                                                                                | 0.235                                                                                                       | 0.134                                                                                                                                      | 0.129                                                                                             |
| F(000)                                  | 2640                                                                                 | 2828                                                                                                        | 2516                                                                                                                                       | 2928                                                                                              |
| Reflections collected                   | 43374                                                                                | 54294                                                                                                       | 55928                                                                                                                                      | 85996                                                                                             |
| Independent refl., R <sub>int</sub>     | 8708, 0.0464                                                                         | 14329, 0.0926                                                                                               | 14623, 0.1568                                                                                                                              | 35131, 0.0544                                                                                     |
| No. of parameters                       | 420                                                                                  | 861                                                                                                         | 782                                                                                                                                        | 1822                                                                                              |
| Final $\mathbf{R}_1$ [I>2 $\sigma$ (I)] | 0.0962                                                                               | 0.0852                                                                                                      | 0.0936                                                                                                                                     | 0.0600                                                                                            |
| $wR_2$ (all data)                       | 0.2708                                                                               | 0.2330                                                                                                      | 0.2441                                                                                                                                     | 0.1502                                                                                            |
| $GOF \text{ on } F^2$                   | 1.071                                                                                | 1.004                                                                                                       | 1.056                                                                                                                                      | 1.031                                                                                             |

anion binding in this series of disubstituted calixarenes. As a result the compounds exhibit unusual conformational characteristics which offer potential opportunities in anion sensing by conformational switching processes.<sup>41</sup>

Structural characterisation of a range of simple calix[4]arene anion receptors has revealed a finely balanced interplay between intramolecular and intermolecular hydrogen bonding, with intermolecular interactions to the calixarene phenolic oxygen atoms significantly interfering with anion affinity. Increasing the tether length offers a way to decouple the anion binding functionality from the calixarene scaffold, although the consequent increased flexibility must reduce receptor preorganisation.

### **Experimental**

### X-ray Crystallography

Suitable single crystals were grown by slow evaporation and mounted using silicon grease on a thin glass fibre. Crystallographic measurements were carried out on a Bruker SMART CCD 6000 and Rigaku R-AXIS Spider IP diffractometer using graphite monochromated Mo-K $\alpha$  radiation  $\lambda = 0.71073$  Å). The standard data collection temperature was 120 K, maintained using an open flow N<sub>2</sub> Cryostream (OxfordCryosystems) device. Integration was carried out using the Bruker SAINT and Rigaku FS Process packages. Data sets were corrected for Lorentz and polarisation effects and for the effects of absorption. Structures were solved using direct

### Titrations

<sup>1</sup>H-NMR titrations were carried out at room temperature using a Varian Inova-500 spectrometer operating at 500 MHz (Durham University). All chemical shifts are reported in ppm relative to TMS as an internal reference. A solution of the host species of known concentration typically 0.5 - 1.5 mM, was made up in an NMR tube using the appropriate deuterated solvent (0.5 ml). Solution of the anions, as TBA salts, were made up in volumetric flasks (2.0 ml) with a concentration five times greater than that of the host. The guest solution was typically added in 10 µl aliquots, representing 0.1 equivalents of the guest with respect to the host. Larger aliquots were used in some cases where no inflection of the trace was evident. Spectra were recorded after each addition and the trace was followed simultaneously. Results were analysed using the curve fitting programme HypNMR.<sup>30, 31</sup>

Fluorescence spectroscopic titrations were carried out in acetonitrile solution using a PE LS55 Spectrometer at the concentrations stated. See supplementary information.

# 5,11,17,23-Tetra-t-butyl-25,27-bis[[*N-m*-tolyl-thioureido]oxy]-26,28-dihydroxycalix[4]arene (3b).

5,11,17,23-tetra-t-butyl-25,27-bis[(aminoethyl)oxy]-26,28dihydroxycalix[4]arene<sup>23</sup> (0.500 g, 6.80 x  $10^{-4}$  mol) was reacted with *m*-tolyl isothiocyanate (0.203 g, 1.36 x  $10^{-3}$  mol) in 25 ml of chloroform. The mixture was stirred for 20 h resulting in the formation of a crude product which was washed 5 ml of hexane, diethyl ether, petroleum ether and propanol to get a pure product.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 700 MHz): 1.10 (18H, s, Bu<sup>t</sup>), 1.20 (18H, s, Bu<sup>t</sup>), 1.96 (6H, s, CH<sub>3</sub>), 3.22 (4H, d, *J* = 14 Hz, ArCH<sub>2</sub>Ar), 3.75 (4H, d, J = 14 Hz, ArCH<sub>2</sub>Ar), 4.08 (4H, m, CH<sub>2</sub>), 4.17 (4H, t, J = 7 Hz, OCH<sub>2</sub>), 6.79 (2H, d, J = 7 Hz, Ar), 6.86 (2H, br, NH), 6.90 (4H, s, Ar), 6.92 (4H, s, Ar), 7.03 (2H, t, J = 7 Hz, Ar), 7.07 (2H, d, J = 7 Hz, Ar), 7.77 (2H, br, NH), 7.93 (2H, t, Ar) and 8.00 (2H, s, OH); <sup>13</sup>C{<sup>1</sup>H}-NMR (CDCl<sub>3</sub>, 700 MHz): 21.00 (s, CH<sub>3</sub>), 31.09 (s, Bu<sup>t</sup>), 31.53 (s, Bu<sup>t</sup>), 32.24 (s, ArCH<sub>2</sub>Ar), 33.78 (s, ArCH<sub>2</sub>Ar), 34.16 (s, CH<sub>2</sub>), 46.21 (s, CCH<sub>3</sub>), 74.91 (s, OCH<sub>2</sub>), 122.91 (s, Ar), 125.47 (s, Ar), 125.96 (s, Ar), 126.38 (s, Ar), 127.75 (s, Ar), 129.00 (s, Ar), 133.11 (s, Ar), 136.31 (s, Ar), 140.02 (s, Ar), 142.57 (s, Ar), 148.03 (s, Ar), 148.29 (s, Ar), 149.29 (s, Ar) and 182.26 (s, CS); Anal. for C<sub>64</sub>H<sub>80</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>·H<sub>2</sub>O calc. C 73.10, H 7.67, N 5.32, found C 72.76, H 7.67, N 4.85 %; IR (cm<sup>-1</sup>) 3283, 2985, 1657, 1484, 1199 and 1034; ESI-MS 1055.5 (C<sub>64</sub>H<sub>80</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>+Na).

# 5,11,17,23–Tetra-t-butyl-25,27-bis[[(*N*-p-tolylureido)-ethyl]oxy]-26,28-dihydroxycalix[4]arene (4a).

5,11,17,23-tetra-t-butyl-25,27-bis[(aminoethyl)oxy]-26,28-

dihydroxycalix[4]arene<sup>23</sup> (0.700 g,  $9.49 \times 10^{-4}$  mol) was mixed with *p*-tolyl isocyanate (0.51 g,  $3.80 \times 10^{-3}$  mol) in 50 ml of chloroform solvent. The reaction mixture was refluxed for more than 12h resulting in a formation of crude product, which was washed with slight amount of diethyl ether and hexane solvent to get a pure product.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): 1.15 (18H, s, Bu<sup>t</sup>), 1.27 (18H, s, Bu<sup>t</sup>), 2.25 (6H, s, CH<sub>3</sub>), 3.41 (4H, d, J = 12 Hz, ArCH<sub>2</sub>Ar), 3.86 (4H, m, CH<sub>2</sub>), 4.12 (4H, t, J = 8 Hz, OCH<sub>2</sub>), 4.19 (4H, d, J = 12 Hz, ArCH<sub>2</sub>Ar), 6.66 (2H, br, NH), 6.99 (4H, s, Ar), 7.01 (4H, s, Ar), 7.04 (2H, s, Ar), 7.08 (2H, s, Ar), 7.12 (2H, s, Ar), 7.14 (2H, s, Ar), 7.16 (2H, br, NH) and 7.28 (2H, s, OH).

### 5,11,17,23–Tetra–t-butyl-25,27-bis[[(*N*-napthylureido)ethyl]oxy]-26, 28- dihydroxycalix[4]arene (4b).

5,11,17,23-tetra-t-butyl-25,27-bis[(aminoethyl)oxy]-26,28-

dihydroxycalix[4]arene<sup>23</sup> (0.200g,  $2.72 \times 10^{-4}$  mol) was mixed with naphthyl isocyanate (0.092 g,  $5.44 \times 10^{-3}$  mol) in 10 ml chloroform solvent at 0 <sup>o</sup>C. The reaction mixture was stirred for 1h resulting in a formation of crude product and washed with slight amount of diethyl ether, hexane and petroleum ether to get a pure product.

<sup>1</sup>H-NMR (Acetone, 700 MHz): 1.03 (18H, s, Bu<sup>t</sup>), 1.27 (18H, s, Bu<sup>t</sup>), 2.43 (4H, d, J = 14 Hz, ArCH<sub>2</sub>Ar), 3.87 (4H, m, CH<sub>2</sub>), 4.05 (4H, t, OCH<sub>2</sub>), 4.25 (4H, d, J = 14 Hz, ArCH<sub>2</sub>Ar), 7.14 (4H, s, Ar), 7.17 (2H, d, J = 7 Hz, Naph), 7.22 (4H, s, Ar), 7.26 (2H, d, J = 7 Hz, Naph), 7.30 (2H, br, NH), 7.37 (2H, t, J = 7 Hz, Naph), 7.47 (2H, d, J = 7 Hz, Naph), 7.75 (2H, d, J = 7 Hz, 14 Hz, Naph), 7.84 (2H, m, Naph), 7.93 (2H, brm, Naph), 8.16 (2H, br, NH), and 8.67 (2H, s, OH); <sup>13</sup>C{<sup>1</sup>H}-NMR (Acetone, 700 MHz): 28.70 (s, CH<sub>2</sub>), 28.81 (s, Bu<sup>t</sup>), 28.92 (s, Bu<sup>t</sup>), 29.03 (s, ArCH<sub>2</sub>Ar), 29.14 (s, ArCH<sub>2</sub>Ar), 76.10 (s, OCH<sub>2</sub>), 121.75 (s,

Naph), 121.85 (s, Naph), 123.45 (s, Naph), 125.19 (s, Naph), 125.30 (s, Naph ), 125.40 (s, Naph), 125.58 (s, Ar), 125.95 (s, Ar), 127.45 (s, Ar), 127.60 (s, Naph), 128 (s, Naph), 142.32 (s, Ar), 147.67 (s, Ar), 149.31 (s, Ar), 150.03 (s, Ar), 150.14 (s, Ar), 156.35 (s, Naph), 156.45 (s, Naph) and 156.54 (s, Naph); Anal. for  $C_{70}H_{80}O_6N_4$ ·0.2 CHCl<sub>3</sub> calc. C 76.84, H 7.37, N 5.11, found C 77.14, H 7.67, N 4.80; IR (cm<sup>-1</sup>) 3357, 2960, 1645, 1548, 1483 and 1047; ESI-MS 1072.38 ( $C_{70}H_{80}O_6N_4$ -H+Na).

# 5,11,17,23–Tetra–t-butyl-25,27-bis[[(*N*-3-methylsulfanylphenylureido)ethyl]oxy]-26,28-dihydroxycalix[4]arene (4c).

5,11,17,23-tetra-t-butyl-25,27-bis[(aminobutyl)oxy]-26,28-

dihydroxycalix[4]arene<sup>23</sup> (0.500g, 6.80 x 10-4 mol) was mixed with 3-methylsulfanylphenyl isocyanate (0.225g,  $1.36x10^{-3}$  mol) in 30 ml of chloroform. The reaction mixture was monitored by TLC while stirring for 4 h. The crude product was washed through slight amount of diethyl ether and hexane solvent to get pure product.

<sup>1</sup>H-NMR (Acetone, 700 MHz): 1.05 (18H, s, But), 1.27 (18H, s, But), 2.34 (6H, s, SCH3), 3.49 (4H, d, J = 14 Hz, ArCH2Ar), 3.93 (4H, m, J = 7, 14 Hz, CH2), 4.07 (4H, t, J = 7 Hz, OCH2), 4.24 (4H, d, J = 14 Hz, ArCH2Ar), 6.80 (2H, d, J = 7 Hz, Ar), 6.84 (2H, br, NH), 7.06 (2H, t, J = 7, 14 Hz, Ar), 7.11 (2H, d, J = 7 Hz, Ar), 7.19 (4H, s, Ar), 7.23 (4H, s, Ar), 7.43 (2H, s, Ar), 8.30 (2H, br, NH) and 8.66 (2H, s, ArOH). <sup>13</sup>C{<sup>1</sup>H}-NMR (Acetone, 700 MHz): 15.28 (s, SCH3), 30.75 (s, But), 31.37 (s, But), 31.85 (s, ArCH2Ar), 31.70 (s, ArCH2Ar), 39.85 (s, CH2), 76.53 (s, OCH2), 115.4 (s, Ar), 115.6 (s, Ar), 116.6 (s, Ar), 119.2 (s, Ar), 125.4 (s, Ar), 125.8 (s, Ar), 127 (s, ArOH) and 150 (s, CO); Anal. calc. for  $C_{64}H_{80}N_4O_6S_2 \cdot 0.25CHCl_3 C$  70.45, H 7.38, N 5.12, found C 70.47, H 7.39, N 5.0 %; IR (cm<sup>-1</sup>) 3339 (vbr, OH & NH), 2958 (w, CH, str.), 1657 (w, CO), 1537 NH), 1480, 1193; Mass Spectrum ESI 1087.5 (s,  $(C_{64}H_{80}N_4O_6S_2-H+Na)$ , 1064.3  $(C_{64}H_{80}N_4O_6S_2-H)$ .

# 5,11,17,23-Tetra-t-butyl-25,27-bis[[(*N*-dansylureido)-ethyl]oxy]-26,28-dihydroxycalix[4]arene (5).

5,11,17,23-tetra-t-butyl-25,27-bis[(aminoethyl)oxy]-26,28-

dihydroxycalix[4]arene<sup>23</sup> (0.200 g,  $2.72 \times 10^{-4}$  mol) was mixed with dansyl chloride in water and sodium hydrogen carbonate solution (1:1 v/v: 8 ml). The reaction mixture was stirred at room temperature for 2 h resulting in a formation of crude product which was washed with small amount of diethyl ether and hexane to get a pure product.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 700 MHz): 1.12 (18H, s, Bu<sup>t</sup>), 1.21 (18H, s, Bu<sup>t</sup>), 2.89 (12H, s, NCH<sub>3</sub>), 3.01 (4H, m, CH<sub>2</sub>), 3.27 (4H, d, J = 14 Hz, ArCH<sub>2</sub>Ar), 3.81 (4H, t, J = 7, OCH<sub>2</sub>), 6.98 (4H, s, Ar), 6.99 (4H, s, Ar), 7.11 (2H, m, Naph), 7.29 (4H, m, Naph), 7.49 (2H, d, Naph), 7.50 (2H, br, NH), 7.83 (2H, t, J = 7 Hz, Naph), 8.10 (2H, d, J = 7 Hz, Naph), 8.39 (2H, d, J = 7 Hz, Naph), 8.55 (2H, d, J = 7 Hz, Naph) and 8.60 (2H, s, OH); <sup>13</sup>C{<sup>1</sup>H}-NMR (CDCl<sub>3</sub>, 700 MHz): 30.97 (s, Bu<sup>t</sup>), 31.10 (s, Bu<sup>t</sup>), 31.45 (s, CH<sub>2</sub>), 32.45 (s, CH<sub>2</sub>), 42.20 (s, NCH<sub>3</sub>), 45.80 (s, CH<sub>2</sub>), 76.11 (s, OCH<sub>2</sub>), 114.6 (s, Naph), 124 (s, Naph), 125.80 (s, Ar), 126

(s, Ar), 127.8 (s, Naph), 128.5 (s, Naph), 129.80 (s, Naph), 133.50 (s, Ar), 136.31 (s, Naph), 143.04 (s, Ar), 148.18 (s, Naph), 148.50 (s, Ar) and 149 (s, Ar); Anal. for  $C_{72}H_{88}O_8S_2N_4$  calc. C 71.97, H 7.38, N 4.66, found C 71.77, H 7.37, N 4.69 %; IR (cm<sup>-1</sup>) 3258, 2954, 2870, 1708, 1462 and 1442; ESI-MS 1224.4 ( $C_{72}H_{88}O_8S_2N_4$ +Na).

### 5,11,17,23-tetra-t-butyl-25,27-bis[[(N-

### dansylureido)butyl]oxy]-26,28-dihydroxycalix[4]arene (6).

5,11,17,23-tetra-t-butyl-25,27-bis[(aminobutyl)oxy]-26,28-

dihydroxycalix[4]arene<sup>23</sup> (0.724 g, 9.16 x  $10^{-4}$  mol) was mixed with dansyl chloride in water and sodium hydrogen carbonate solution (1:1 v/v: 8 ml). The reaction mixture was stirred at room temperature for 2.5 h resulting in a formation of crude product which was washed with 3 ml of diethyl ether and hexane to give a pure product.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 700 MHz): 0.827 (18H, s, Bu<sup>t</sup>), 1.24 (18H, s, Bu<sup>t</sup>), 1.63 (4H, pt, *J* = 6.4, 13.2 Hz, CH<sub>2</sub>), 1.77 (4H, pt, *J* = 6.4, 14, 20 Hz, CH<sub>2</sub>), 2.84 (12H, s, NCH<sub>3</sub>), 3.180 (4H, m, CH<sub>2</sub>), 3.21 (4H, d, J = 13.2 Hz, ArCH<sub>2</sub>Ar), 3.75 (4H, t, J = 6.3, 12.4 Hz, OCH<sub>2</sub>), 4.11 (4H, d, *J* = 12.8 Hz, ArCH<sub>2</sub>Ar), 6.04 (2H, br, NH), 6.70 (4H, s, Ar), 7.00 (4H, s, Ar), 7.20 (4H, t, J = 7.6, 14 Hz, Naph), 7.42 (2H, t, J = 8, 16 Hz, Naph), 7.47 (2H, s, OH), 8.22 (2H, d, *J* = 7.2 Hz, Naph), 8.29 (2H, d, *J* = 7.2 Hz, Naph) and 8.46 (2H, d, J = 8 Hz, Naph);  ${}^{13}C{}^{1}H$ -NMR (CDCl<sub>3</sub>, 700 MHz): 25.70 (s, CH<sub>2</sub>), 25.85 (s, CH<sub>2</sub>), 30.65 (s, Bu<sup>t</sup>), 31.25 (s, Bu<sup>t</sup>), 31.60 (s, ArCH<sub>2</sub>Ar), 31.80 (s, ArCH<sub>2</sub>Ar), 42.28 (s, CH<sub>2</sub>), 45.80 (s, NCH<sub>3</sub>), 76 (s, OCH<sub>2</sub>), 124.59 (s, Ar), 125 (s, Ar), 125.40 (d, Ar), 126 (s, Naph), 126.75 (s, Ar), 128.01 (s, Naph), 128.12 (s, Naph), 129.20 (s, Naph), 129.85 (s, Naph), 131.80 (s, Ar), 148.20 (s, Ar), 148.20 (s, Ar) and 148.90 (s, Ar); Anal. for C<sub>76</sub>H<sub>96</sub>O<sub>8</sub>S<sub>2</sub>N<sub>4</sub> calc. C 72.58, H 7.69, N 4.45, found C 71.57, H 7.52, N 4.10; IR (cm<sup>-1</sup>) 3673, 3311, 2953, 1575, 1484, 1311, 1073; ESI-MS 1279.6 (C<sub>76</sub>H<sub>98</sub>O<sub>8</sub>S<sub>2</sub>N<sub>4</sub>-H+Na).

### Acknowledgements

We thank Durham University, the Higher Education Commission of Pakistan, Charles Wallace Trust Pakistan and Dr. Wali Muhammad Trust for partial funding.

#### Notes and references

<sup>*a*</sup> Department of Chemistry, Karakoram International University, Gilgit-Baltistan 15100 Gilgit Pakistan E-Mail: ngq18@hotmail.com.

<sup>b</sup> Department of Chemistry, Durham University, South Road, Durham DH1 3LE. E-mail: jon.steed@durham.ac.uk

Electronic Supplementary Information (ESI) available: NMR titration plots, fluorescence spectra and X-ray crystal structures of synthetic intermediates. Crystallographic data have been deposited with the CCDC in CIF format. Deposition numbers CCDC: 1003765-1003769 and 1003934-1003936. See DOI: 10.1039/b000000x/

- 1. C. D. Gutsche, *Calixarenes Revisited*, Royal Society of Chemistry, Cambridge, 1998.
- V. Sidorov, F. W. Kotch, G. Abdrakhmanova, R. Mizani, J. C. Fettinger and J. T. Davis, J. Am. Chem. Soc., 2002, 124, 2267-2278.
- P. Schmitt, P. D. Beer, M. G. B. Drew and P. D. Sheen, Angew. Chem. Int. Ed. Engl., 1997, 36, 1840-1842.
- 4. P. Lhotak, Top. Curr. Chem., 2005, 255, 65-95.

- 5. S. E. Matthews and P. D. Beer, Supramol. Chem., 2005, 17, 411-435.
- D. B. Qin, X. S. Zeng, Q. S. Li, F. B. Xu, H. B. Song and Z. Z. Zhang, Chem. Commun., 2007, 147-149.
- J. N. Babu, V. Bhalla, M. Kumar, R. K. Puri and R. K. Mahajan, New J. Chem., 2009, 33, 675 - 681.
- F. Sansone, L. Baldini, A. Casnati and R. Ungaro, *New J. Chem.*, 2010, 34, 2715-2728.
- O. Hudecek, J. Budka, H. Dvorakova, P. Curinova, I. Cisarova and P. Lhotak, *New J. Chem.*, 2013, 37, 220-227.
- J. Scheerder, M. Fochi, J. F. J. Engbersen and D. N. Reinhoudt, J. Org. Chem., 1994, 59, 7815-7820.
- E. J. Thomas, S. E. Gabriel, M. Makhlina, S. P. Hardy and M. I. Lethem, Am. J. Physiol.-Cell Physiol., 2000, 279, C1578-C1586.
- 12. C. J. E. Haynes and P. A. Gale, Chem. Commun., 2011, 47, 8203-8209.
- J. Scheerder, J. F. J. Engbersen, A. Casnati, R. Ungaro and D. N. Reinhoudt, *J. Org. Chem.*, 1995, **60**, 6448-6454.
- N. A. McDonald, E. M. Duffy and W. L. Jorgensen, J. Am. Chem. Soc., 1998, 120, 5104-5111.
- J. Bernstein, R. E. Davis, L. Shimoni and N.-L. Chang, Angew. Chem. Int. Ed. Engl., 1995, 34, 1555-1573.
- 16. B.-T. Zhao, Y. Liu and H.-Y. Zhang, J. Mol. Struct., 2004, 691, 25-31.
- G. Tumcharern, T. Tuntulani, S. J. Coles, M. B. Hursthouse and J. D. Kilburn, Org. Lett., 2003, 5, 4971-4974.
- E. J. Cho, B. J. Ryu, H. M. Yeo, Y. J. Lee and K. C. Nam, *Bull. Korean Chem. Soc.*, 2005, 26, 470-472.
- S. Moerkerke, S. Le Gac, F. Topić, K. Rissanen and I. Jabin, *Eur. J. Org. Chem.*, 2013, 2013, 5315-5322.
- D. Cornut, J. Marrot, J. Wouters and I. Jabin, Org. Biomol. Chem., 2011, 9, 6373-6384.
- A. Arduini, A. Credi, G. Faimani, C. Massera, A. Pochini, A. Secchi, M. Semeraro, S. Silvi and F. Ugozzoli, *Chem Eur. J.*, 2008, 14, 98-106.
- 22. C. D. Gutsche, *Calixarenes*, Royal Society of Chemistry, Cambridge, 1989.
- E. M. Collins, M. A. McKervey, E. Madigan, M. B. Moran, M. Owens, G. Ferguson and S. J. Harris, J. Chem. Soc.-Perkin Trans. 1, 1991, 3137-3142.
- J. Scheerder, R. H. Vreekamp, J. F. J. Engbersen, W. Verboom, J. P. M. van Duynhoven and D. N. Reinhoudt, *J. Org. Chem.*, 1996, **61**, 3476-3481.
- 25. B. R. Cameron and S. J. Loeb, Chem. Commun., 1997, 573-574.
- 26. M. C. Etter, Acc. Chem. Res, 1990, 23, 120-126.
- B. L. Schottel, H. T. Chifotides and K. R. Dunbar, *Chem. Soc. Rev.*, 2008, **37**, 68-83.
- L. J. Prins, D. N. Reinhoudt and P. Timmerman, *Angew. Chem. Int. Ed.*, 2001, 40, 2383-2426.
- 29. V. Bohmer, O. Mogck and W. Vogt, Tetrahedron, 1996, 52, 8489-8496.
- C. Frassineti, S. Ghelli, P. Gans, A. Sabatini, M. S. Moruzzi and A. Vacca, *Anal. Biochem.*, 1995, 231, 374-382.
- 31. P. Gans, University of Leeds, Leeds, 2006.
- 32. S. J. Kim, M.-G. Jo, J. Y. Lee and B. H. Kim, Org. Lett., 2004, 6, 1963-1966.
- 33. R. Custelcean, Chem. Commun., 2008, 295-307.
- S. Nishizawa, P. Bühlmann, M. Iwao and Y. Umezawa, *Tetrahedron Lett.*, 1995, 36, 6483-6486.
- 35. Y. M. Chung, B. Raman, D.-S. Kim and K. H. Ahn, *Chem. Commun.*, 2006, 186-188.
- K. R. Dey, B. M. Wong and M. A. Hossain, *Tetrahedron Lett.*, 2010, 51, 1329–1332.
- P. Anzenbacher, K. Jursíková and J. L. Sessler, J. Am. Chem. Soc., 2000, 122, 9350-9351.
- 38. G.-Y. Qing, Z.-H. Chen, F. Wang, X. Yang, L.-Z. Meng and Y.-B. He, *Chinese J. Chem.*, 2008, 26, 721-728.
- 39. S. R. Holmes-Farley and G. M. Whitesides, Langmuir, 1986, 2, 266-281.
- 40. Y.-B. Ruan, A. Depauw and I. Leray, Org. Biomol. Chem., 2014.
- K. J. Wallace, W. J. Belcher, D. R. Turner, K. F. Syed and J. W. Steed, J. Am. Chem. Soc., 2003, 125, 9699-9715.
- 42. G. M. Sheldrick, Acta Crystallogr. Sect. A, 2008, 64, 112-122.
- 43. L. J. Barbour, J. Supramol. Chem., 2001, 1, 189-191.
- 44. J. L. Atwood and L. J. Barbour, Cryst. Growth Des., 2003, 3, 3-8.

### **Graphical Abstract**

The interplay of anion binding, intra- and intermolecular hydrogen boning patterns in a range of receptors and sensors for chloride anion are discussed.

