Solution and solid state interplay of isomeric 4′-(pyridyl)-3,2′:6′,3″-terpyridines with *p*-sulfonatocalix[4]arene

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p-Sulfonatocalix[4]arene, **1**, forms inclusion complexes with the three isomeric 4′-(pyridyl)-3,2′:6′,3″-terpyridines in acidic aqueous medium. Both 4′-(2-pyridyl)-, **3**, and 4′-(3′-pyridyl)-3,2′:6′,3″-terpyridine, **4**, form 1 : 1 host–guest complexes in the solid state, in which the terminal 4′-(pyridyl) ring resides in the cavity of the calixarene. In the case of 4′-(4-pyridyl)-3,2′:6′,3″-terpyridine, **5**, a molecular capsule is formed in which two calixarenes encapsulate one terpyridine guest molecule, with the terminal pyridine ring being *exo* to the calixarene cavities. NMR spectroscopy indicates that association between *p*-sulfonatocalix[4]arene and each terpyridine guest occurs in solution at elevated temperature (333 K) as a prelude to crystallisation of the inclusion complexes.

Introduction

Cavitand based materials

Self-assembly has become a powerful paradigm in building up molecular architectures as an entry to new materials and molecular devices.[1] Oligopyridines, in particularly the terpyridines, are widely used as supramolecular tectons for this purpose[2] and recently they have also gained prominence as scaffolding groups in medicinal chemistry for the development of new anticancer and antimicrobial agents.[3] A challenge for utilising these compounds as therapeutics is to address the issue of solubility, which is often a key factor limiting their potential applications *in vivo*. In attempting to address this issue, we and others have focused on using water-soluble *p*-sulfonatocalix[*n*]arenes as 'molecular containers' for the inclusion of guest molecules[4–11] and as new surfactants to water-solubilise biomolecules such as carotenoids.[5] These host molecules are in general easy to synthesise and are widely available. A recent review on the biochemistry of *p*-sulfonatocalix[*n*]arenes[6] emphasises the breadth of recent interest in this field and highlights the potential for these molecules to act as hosts for applications in drug delivery as well as for the diagnosis of disease.

The sulfonated calixarene with the smallest cavity, *p*-sulfonatocalix[4]arene, **1** (Fig. 1), has been widely studied as a host molecule. This is mainly because of its ability to include guest molecules within its cone-shaped hydrophobic cavity en route to the forming of new materials. Guest molecules include biologically significant amino acids and nucleotide bases,[7] small organic molecules and ions,[8] globular shaped organic molecules[4] and transition metal complexes.[4,9,11] While **1** usually forms 'bilayer' structures in the solid state,[4] giant tubules,[10] superhelices[11] and spheroidal arrays[10,12] are accessible where the calixarenes arrange themselves in a 'head to head' fashion often through the assembly of molecular capsules around a central guest molecule. These giant spheroids adopt either icosahedral,[10] or cuboctahedral[12] geometries and have been touted as inorganic virus mimics due to their large internal volumes and similar geometries. While the interior of the spheres are occupied by aquated metal ions, encapsulation of drug molecules within the spheres is a fundamental goal of this research, in addition to retaining their structural integrity in solution for drug delivery.

We have recently focused on developing libraries of terpyridines using green chemistry[13] for therapeutic applications. Herein we investigate the inclusion and host–guest chemistry of selected terpyridines, namely 4′-(pyridyl)-terpyridines **3–5** (Fig. 1), with *p*-sulfonatocalix[4]arene, **1**, in water. In this context we note the ability of **1**, and higher sulfonated calixarenes, to encapsulate and solubilise β-carotene,[5] in

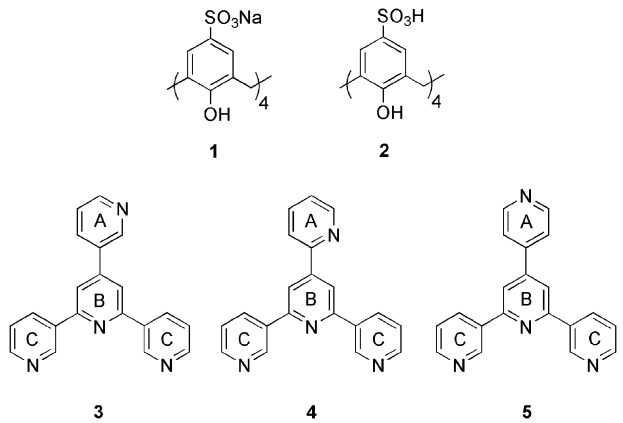

Fig. 1 Host and guest molecules featuring in this study; rings A, B and C in the guest molecules are defined.

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aqueous solution, as well as crown ethers and related molecules.[4,12] We also note that related 4,4″-terpyridines form molecular capsules with calix[4]resorcinarene.[14] In addition to isolating and structurally characterising crystalline inclusion complexes, we endeavour here to gain insight into the nature of the host–guest complexes in solution at elevated temperature prior to crystallisation.

Results and discussion

Synthesis of host–guest complexes

Molecules **3–5** were synthesised in poly(ethylene glycol) (PEG) as part of a programme targeting libraries based on using benign reaction media.[13] Hot aqueous solutions (pH ~ 2) of the isomeric terpyridines **3–5** were combined, in separate experiments, with hot (pH ~ 2) solutions of the sodium salt of *p*-sulfonatocalix[4]arene **1**. A series of experiments was attempted, in which ratios of 2 : 1, 1 : 1, and 0.5 : 1 were employed for **3–5** : **1**. On addition of the guest, the mixtures became turbid, and on cooling microcrystalline white precipitates were deposited. In the case of mixtures containing **3** and **5**, colourless crystals with a 2 : 1 ratio of **3**, **5** : **1** also formed in addition to the precipitated material on further standing (24 h). Other attempts failed to afford X-ray quality crystalline material, apart from the 1 : 1 mixture of **1** and **4**.

Crystal structure of complex 1·3

The inclusion complex crystallised as colourless plates in the triclinic space group $P\bar{1}$, with the asymmetric unit comprised of two molecules of **1** and three terpyridine molecules (Fig. 2). Three of the four pyridine rings (rings A and C) in each terpyridine molecule are protonated, with the exception being the nitrogen atom on the central pyridine ring (B). The absence of chloride ions within the structure dictates that charge balance is through deprotonation of one of the calixarene phenolic units, which has been observed elsewhere for a range of inclusion complexes involving **1**.[4,7–12] Numerous water molecules are present in the crystal lattice. However the poor X-ray data was not sufficient to allow all hydrogen atoms on these molecules to be located.

Both calixarenes adopt the expected 'pinched cone' conformation, with the cavity in each being occupied by the pyridine ring A of molecule **3**. Each of the perched host–guest supermolecules {calixarene ∩ terpyridine}, designated hereafter as motifs are superficially similar, although there are slight differences in the alignment of the guest within the cavity. In both cases, the pyridine ring A is centrally located within the cavity and has interplanar angles of 86.22° (Motif 1) and 79.04° (Motif 2) with the plane defined by the methylene carbons of the calixarene. The included terpyridine guest molecules exhibit several differences, most notably regarding the distortion of the planes of the included pyridine ring A and the central ring B from planarity. Rings A and B in the two {calixarene ∩ terpyridine} motifs show considerable distortion from planarity (interplanar angle 61.3° Motif 1, 56.8° Motif 2), compared with 39.9° for the interplanar angle between the 2,2′-bipyridinium rings in the related solid state complex with **1**.[15] No interactions between the protonated nitrogen atom and the calixarene are evident, although the two C–H protons of **3** are directed towards the centroids of opposite calixarene phenyl rings with distances C–H···centroid 2.65 Å, 2.63 Å (Motif 1), and C–H···centroid 2.57 Å, 2.49 Å (Motif 2). This contrasts with the [2,2′-bipyridinium · **1**] complex, in which the guest is inserted into the cavity and stabilised through the formation of C–H···π interactions with two juxtaposed calixarene phenyl rings.[15] The 4′-bipy A ring of **3** which protrudes into the cavity makes an interplanar angle with the central aromatic ring B of 57.9° in Motif 1, and 62.9° in Motif 2. The analogous angle in the 2,2′-bipyridinium–calix[4]arene complex is 48.9°.[15]

The pyridine rings external to the calixarene cavity are oriented differently in the two {calixarene ∩ terpyridine} host–guest complexes, with Motif 1 having the nitrogen atoms positioned on the same side of the molecule (*cis*, *cis* arrangement). This differs in Motif 2, in which one ring is rotated by

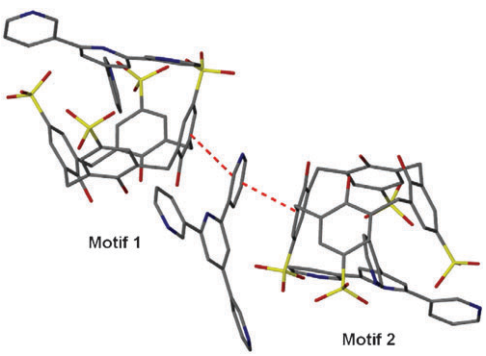

Fig. 2 The asymmetric unit of complex **1** · **3**. Water molecules and hydrogen atoms have been omitted for clarity. The broken lines show π-stacking.

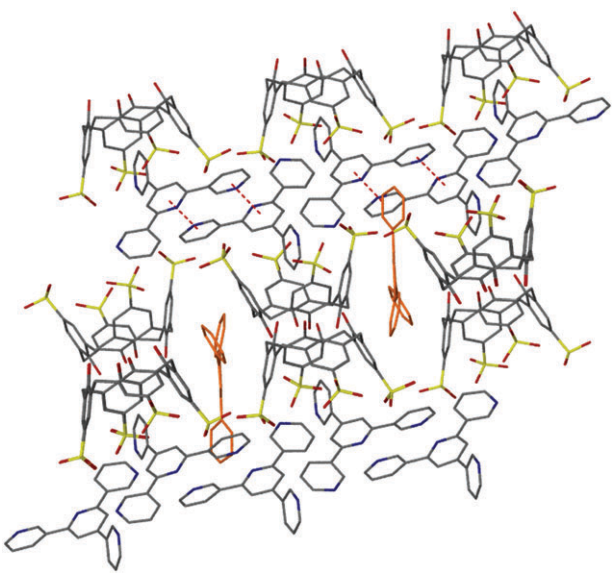

Fig. 3 A view of the bilayer structure in **1** · **3** viewed down the *a* axis. Terpyridine molecules inserted into the calixarene bilayer arrangement are shown in orange (water solvent molecules are omitted for clarity). Broken lines depict overlaying of the terpyridines linking the calixarene bilayers.

180° placing the nitrogen atom on the opposite side to that in the other two rings (*cis*, *trans* arrangement).

The asymmetric unit consists of two {calixarene ∩ terpyridine} motifs separated by another molecule of **3** (Fig. 2). The extended structure shows the presence of bilayers, Fig. 3, which are remarkably different to the usual bilayers in complexes of the same calixarene. The calixarenes are arranged in an up–down fashion, and are separated by molecules of **3** which are thus embedded in the bilayer. Indeed, each C ring is π-stacked to two calixarenes from each of the motifs, Fig. 2 and 3. The centroid···centroid distances are 3.40 and 3.83 Å, Motifs 1 and 2 for ring C shown sandwiched between two calixarenes in Fig. 2, and 3.59 and 3.66 Å for the corresponding distances for the other C ring, Fig. 3. The interplay of **1** and included **3** relates to the torsion mobility of **3** along the C–C bonds connecting the peripheral pyridine rings to the central ring, with dihedral angles for rings C relative to ring B at 56.8 and 61.3°. For the same included terpyridine there is no π-stacking associated with ring A or ring B and calixarenes or any other guest molecules. Interestingly ring C protrudes out of the bilayer thereby imparting greater hydrophobic character to the surface of the bilayer. An additional intermolecular π-stacking interaction joins adjacent 'up–down' calixarene pairs running in the *a* direction, with a close centroid···centroid contact of 3.87 Å. The bilayer arrangement incorporating molecules other than calixarenes is unusual and has only been reported in a few instances for positively charged guest molecules.[16] The linking of the calixarene bilayers occurs through the pairing up of two {calixarene ∩ terpyridine} motifs. This occurs through the B and C rings of **3** in Motif 1 partly overlaying rings C and B of **3** in Motif 2 in the adjacent bilayer (centroid···centroid distances 3.77, 3.80 Å). No other interactions between molecules of **3** within the terpyridine layer are evident.

Crystal structure of complex 1·4

The inclusion complex crystallised in the monoclinic space group *C*2/*c*, with the asymmetric unit containing a 1 : 1 ratio of **1** and **4**. Eight disordered water molecules are also present, albeit with the poor X-ray data preventing location of the hydrogen atoms in these molecules. The terpyridine molecule is included within the cavity of **1** *via* the terminal 4′-(2-pyridyl) ring A, which is disordered with equal occupancy over two positions (Fig. 4a). As in complex **1**·**3**, the nitrogen atoms on rings A and C are protonated, and those on the C rings of **4** are in a *cis*, *trans* conformation, with one nitrogen centre on the same side as the nitrogen atom in the central B ring, and the other on the opposite side. The nitrogen atom on ring B is not protonated, and in the absence of chloride ions the discrepancy in charge balance can be addressed by the presence of oxonium ions or through protonation of a sulfonate group, as reported in other supramolecular arrays containing **1**.[4,7–12]

The packing of the {calixarene ∩ terpyridine} motifs in **1**·**4** is strikingly different to that in **1**·**3**, with the calixarenes not packed into a bilayer arrangement. Each calixarene is associated with one terpyridine molecule, which protrudes into the cavity, and two neighbouring calixarenes, in addition to two *exo*-cavity terpyridine molecules. Pairs of {calixarene ∩ terpyridine} motifs related by an inversion centre are 'molecular-capsule' like in arrangement shrouding in part two terpyridine molecules (Fig. 4b). Such 'molecular-capsules' have been noted for smaller pairs of amino-acids and related molecules where the shrouding is more effective.[7] The calixarenes in 'molecular-capsules' are related to each other by 180° along an 'axis' through the centre of the two calixarenes with molecules of **4** skewed relative to this axis by 14.7°. As in complex **1**·**3**, the guest molecule interacts with the calixarene cavity through C–H···π interactions (C_4–H···centroid 2.77 Å, C_5–H···centroid 2.53 Å) with the 1,3-pair of calixarene phenyl rings.

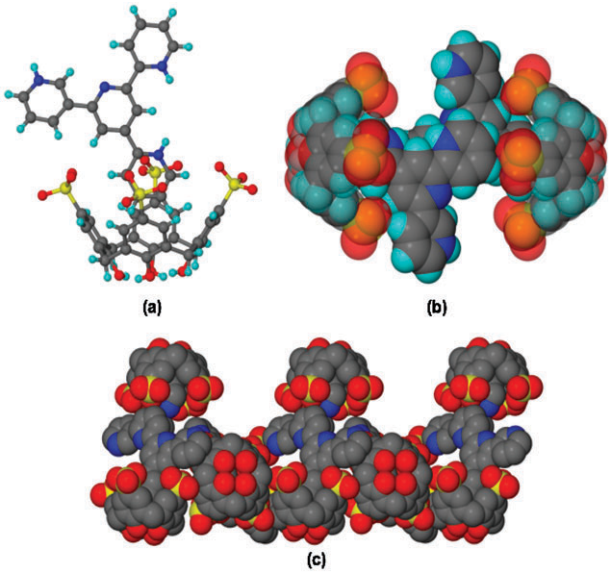

Fig. 4 (a) The 1 : 1 motif in complex **1**·**4**. (b) The dimeric arrangement of terpyridines within the confines of a 'molecular capsule'. (c) The zig-zag strand of {calixarene ∩ terpyridine} motifs, with the complementing strand is omitted for clarity; 'molecular capsular' sets are at an angle of 87.3° from each other.

The 'molecular-capsules' are associated with a slipped overlaying of ring B for each terpyridine and one ring C of each terpyridine, with the closest centroid···centroid distance at 4.20 Å and the closest C···C, C···N contacts at 3.71, 3.90, 3.70 Å in accordance with π-stacking interactions. Each 'molecular-capsule' is associated with two adjacent near-orthogonal 'molecular-capsules', rotated by 87.3°, as defined by the plane of the methylene carbon atoms (Fig. 4c). This is associated with π-stacking interactions involving **4** in one 'molecular-capsule' with calixarenes in adjacent 'molecular-capsules'. This involves the other pyridine rings C, *i.e.* rings C which not involved in intra-'molecular-capsule' π-stacking. The centroid···centroid distance for the inter-'molecular-capsule' π-stacking is 3.65 Å. In this way, a chain of alternating 'molecular capsules' propagates through the crystal in the *c* direction.

The packing of the chains of 'molecular-capsules' results in channels within the crystal lattice, which also run in the direction of the *c* axis (Fig. 5). Disordered water molecules occupy the channels in a way defined primarily by the polar OH moieties of the water molecules, and sulfonate groups of

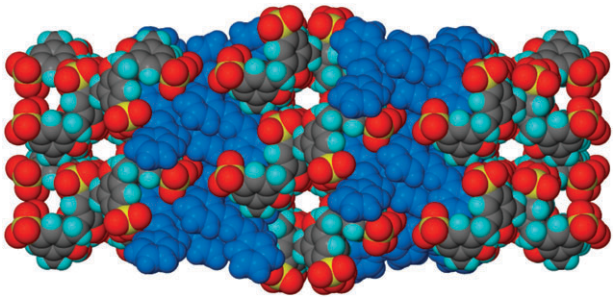

Fig. 5 A view down the *c* axis of **1**·**4** highlighting the channels within the lattice (occupying water molecules are omitted for clarity). Terpyridine molecules are blue.

the calixarenes. This makes these otherwise voids largely hydrophilic, and is similar to that recently reported for a supramolecular array of the related *p*-sulfonatocalix[8]arene,[17] although the diameter of the channel is substantially smaller (approx 6.2 Å *cf.* 12 Å in the calix[8]arene array).

Crystal structure of complex 1·5

The complex crystallises in the monoclinic space group $C2/c$, with the asymmetric unit comprised of two molecules of **1** and two and a half molecules of **5**. Twelve disordered water molecules are present, again with the data quality not sufficient for locating the associated hydrogen atoms. The terpyridine molecules are in the *cis*, *cis* conformation, with two of them showing considerable disorder about the terminal 4′-(4-pyridyl) ring A, with each having partial occupancy over two positions. All three of the nitrogen centres for the terminal pyridine rings (A and C) are protonated, in contrast to central ring B, and charge balance within the system is likely to arise through the presence of oxonium ions or by protonation–deprotonation of one of the calixarenes,[4,7–12] as for complex **1**·**4**.

The calixarenes form 'molecular-capsule' like arrangements with their cavities directed towards each other (Fig. 6), but now involve only one terpyridine, **5**, rather than two such molecules in the structure of **1**·**4**. Molecules of **5** confined in part in the 'molecular-capsules' have each C ring penetrating a cavity, with the terminal A ring not included and pointing orthogonally to the principal axis of the capsule. As for the previous structures, the arm of the terpyridine in the cavity is associated with CH···π interactions between the protons on C_4 and C_5 and the 1,3-pair of calixarene phenyl rings with two sets of short contacts involving each calixarene at 2.60, 2.98 and 2.58, 2.88 Å. A close contact between N–H group and a sulfonate oxygen atom (N···O 2.90 Å) is also evident, suggestive of hydrogen bonding between the two.

The 'molecular-capsules' pack together in a different way relative to the aforementioned complex which is also based on 'molecular-capsules'. Moreover, the calixarenes are in a 'up–down' bilayer arrangement (Fig. 6) but this is distinctly different from that seen in the majority of bilayer structures,[4] including that for complex **1**·**3** which, like the present structure, also has terpyridines embedded in the bilayers. A salient feature of the structure is a slippage within the bilayer arrangement in respect to the hydrophilic and hydrophobic domains giving rise to an overall 'corrugated' bilayer arrangement, and the calixarenes are unusually well separated from each other through bilayer intercalation of terpyridine molecules. In particular, the *exo* terpyridine molecules have a profound influence on the positioning of the 'molecular-capsules'. Calixarene–terpyridine and terpyridine–terpyridine π-stacking interactions are prevalent within the structure. Each calixarene adopts the expected 'pinched cone' conformation, with the 1,3-pair of 'pinched-in' phenyl rings each overlaying with ring C of a terpyridine. One of these terpyridines (centroid···centroid distance 3.48 Å) has its primary axis (through the N-centres of ring A and ring B) aligned approximately parallel with the primary axis of the 'molecular-capsule', and forms a link with an adjacent 'molecular-capsule' through an identical π-stacking interaction from the other ring C to the calixarene (Fig. 7). In addition, both C rings in this terpyridine partially overlay and form face–edge interactions with phenyl rings of two other calixarenes, with their cavities facing downwards (centroid···C distance 3.33 Å). The other terpyridine molecule is cofacially aligned (ring C) with the opposite phenyl ring of the calixarene. Although the rings are not directly overlayed they are reminiscent of another face–edge interaction (centroid···C distance 3.53 Å). Ring A

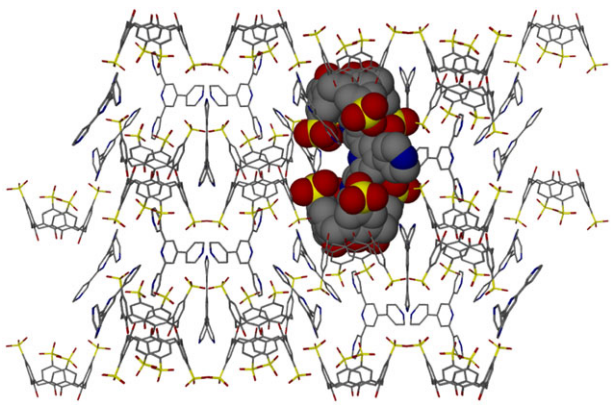

Fig. 6 Projection of complex **1**·**5** down the *a* axis represented with stick bonds, except for a 'molecular-capsule' arrangement which is shown in space filling; the 'corrugated bilayer' of calixarenes propagates in the *c* direction.

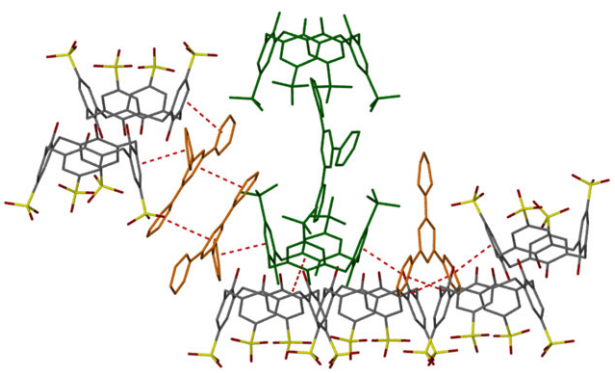

Fig. 7 The arrangement of neighbouring calixarenes and guest molecules around a central capsule (green) in complex **1**·**5**; dotted lines indicate π-stacking interactions, with terpyridines depicted in orange.

and the other C ring are held in a near-planar fashion (least-squares plane angle 4.8°) and overlay with a second terpyridine molecule, rotated 180° to it, creating face–edge interactions (distances of 3.52 and 3.54 Å). This second terpyridine interacts with two neighbouring calixarenes, in a face–edge fashion through rings A and C (centroid ring A···C 3.44 Å, centroid ring C···edge 3.71 Å). Formation of the stacking network through the *exo*-calixarene cavity terpyridine molecules sets the calixarenes at two different levels through the lattice. When viewed down the *a* direction, the calixarenes alternate between the standard 'up–down' arrangement, while along the *c* axis the arrangement is different, such that pairs of calixarenes in the same orientation alternate in the sequence {'up–up', 'down–down', 'up–up',···} such that an unusual 'corrugated bilayer' is formed along the *c* axis.

NMR studies

Terpyridines **3–5** are sparingly soluble in water, unless at low pH whereby protonation of the nitrogen centres occurs. Under similar conditions to the experiments on the binding of **1** with crown ethers and azacryptates,[12] we endeavoured to probe the inclusion behaviour of **3–5** under similar conditions to that which leads to the formation of the solid-state inclusion complexes **1**·**3**, **1**·**4** and **1**·**5**. By doing so, we hoped to determine whether binding of these terpyridines occurs in acidic aqueous solutions of **1**, prior to the formation of inclusion complexes on cooling.

Stock solutions (10 mM) of the tetrasulfonic acid **2**,[18] and each terpyridine **3–5**[13] were made in D_2O, with the pD adjusted to ~1 by the addition of concentrated DCl. In each of the experiments, ^{1}H NMR spectra were recorded at 333 K in order to closely resemble the conditions of the crystallisation experiments and to minimise the precipitation of complexes from solution.

Complexation of 2 with 3 and 4. The free guest **3** gave a sharp, well-resolved ^{1}H NMR spectrum at 333 K. Using conditions of Job's method of continuous variation,[19] a series of samples were made which contained both components, host **2** and guest **3** in varying amounts, but such that the volume, and concentration of the total species in solution (10 mM) remained constant. ^{1}H NMR spectra were recorded for each sample in the series, monitoring the level of chemical shift change in the guest as the host/guest ratios were varied (Fig. 8). The four signals of lowest intensity in the guest (spectrum **a**) correspond to the protons on ring A of the guest, and are labelled as shown in the figure caption. As shown in Fig. 8, the addition of the calixarene **2** results in a marked upfield shifting of these protons, with the proton H_5A (*) on ring A showing the greatest magnitude in chemical shift with $\Delta\delta \sim 2.5$ from the free guest to a host/guest ratio of 9 : 1 (spectrum **j**). Protons H_4A (▲) and H_6A (■) show a similar trend, although the upfield shifting of H_2A (**x**) is much less pronounced. The protons attached to rings B and C also show similar behaviour on addition of **2**, although the magnitude of the chemical shift differences between free and complexed guest is smaller than for ring C.

These results indicate that, as expected, at high host/guest ratios (spectra **h–j**) the terpyridine should be fully complexed

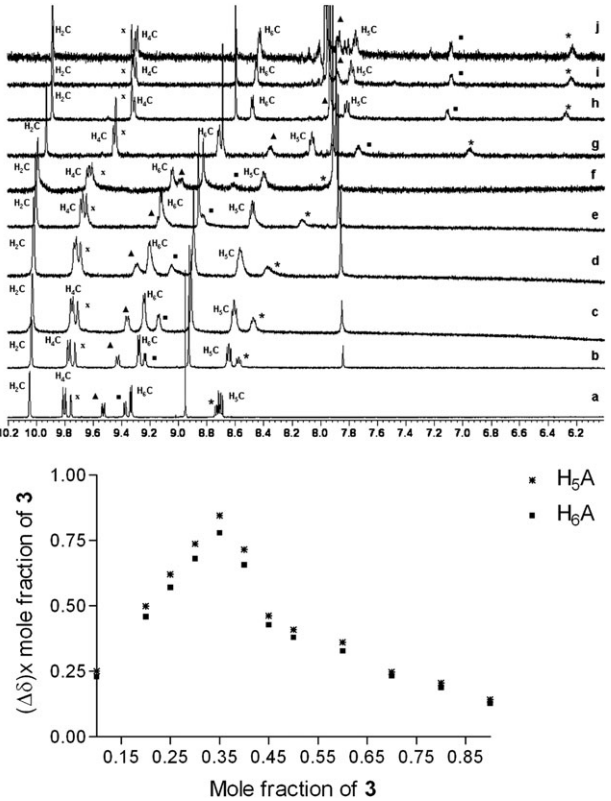

Fig. 8 ^{1}H NMR stack plot of varying ratios of **2**/**3** (top). Proton labels: H_2A (**x**), H_4A (▲), H_5A (*), H_6A (■). Spectrum **a** represents 10 mM **3**, spectrum **j** is 1 mM **3**:9 mM **2**. The signal at ~7.8 ppm in spectrum **b** is due to **2** (1 mM). The Job plot (bottom) shows the behaviour for protons H_5A and H_6A on addition of **2**.

by **2**, and that each terpyridine must be complexed by two or more host molecules (calixarene/terpyridine stoichiometry ≥ 2 : 1). The Job plot (Fig. 8) shows a clear maximum at a guest mole fraction of 0.35, which represents a 2 : 1 calixarene/terpyridine stoichiometry complex between **2** and **3** in solution which is consistent with the change in chemical shift of all protons in **3** on exposure to the calixarene. This contrasts with the solid state structure of **1**·**3**, which is a 1 : 1 inclusion complex. At lower calixarene/terpyridine ratios, the signals broaden considerably, and are intermediate in chemical shift between the fully complexed and uncomplexed terpyridine regime which is indicative of dynamic solution behaviour.

Terpyridine **4** also shows similar inclusion behaviour when exposed to calixarene **2**. The Job plot indicates a clear maximum at a mole fraction of 0.35, which corresponds to a 2 : 1 calixarene/terpyridine complex stoichiometry in solution, identical to that seen in **3**. As in **3**, the protons of all pyridine rings in **4** shift on exposure to varying ratios of **2**, consistent with interaction of multiple sites in the terpyridine with the calixarene cavity.

Complexation of 2 with 5. The solid state structure of complex **1**·**5** indicates a calixarene/terpyridine stoichiometry of 2 : 2.5 in the asymmetric unit. Inclusion by **2** involves 'molecular-capsule' formation, with one terpyridine sandwiched between two calixarenes and the other guest molecules

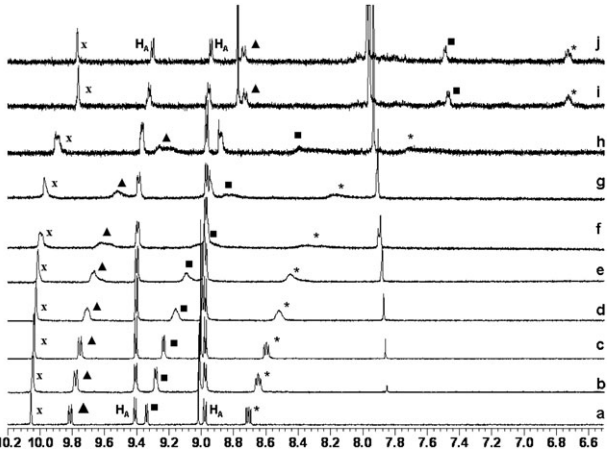

Fig. 9 ^{1}H NMR stack plot of varying ratios of **2**/**5**. Spectrum **a** represents 10 mM **5**, spectrum **j** is 1 mM 5:9 mM host **2**. The signal at ~7.8 ppm in spectrum **b** is due to **2**.

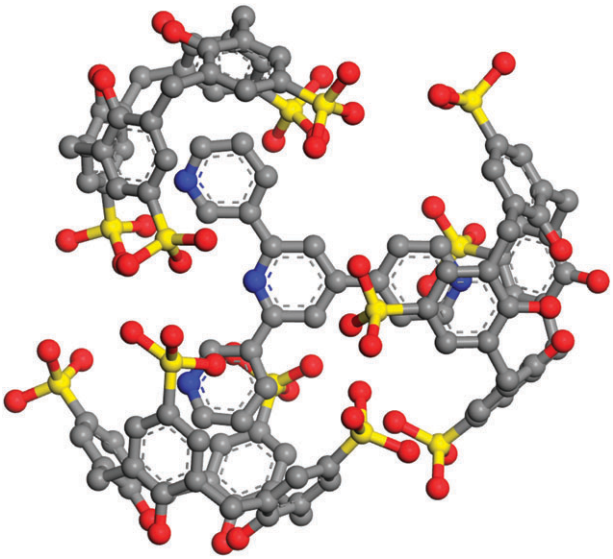

Fig. 10 A representation of the gas phase interaction of a third molecule of **1** with the 'molecular-capsule' in complex **1**·**5**. Computational results obtained using Accelrys software programs. Dynamics calculations performed with the Discover program using the cvff forcefield, *ab initio* calculations performed with the Discover program, and graphical displays generated with Materials Studio.

residing exterior to the molecular capsule. As in the case of the previous terpyridines, the addition of calixarene **2** results in large chemical shift changes in the ^{1}H NMR spectrum, in particular for those protons attached to the C rings of the terpyridine (Fig. 9). Protons H_5C(*) and H_6C(■) experience the largest upfield chemical shift change, which is consistent with them being in closest proximity to the calixarene cavity as in the crystal structure of **1**·**5**. Protons H_2 (**x**), H_4 (▲) and H_3B also shift upfield on addition of **2**. As the calixarene/terpyridine ratio increases, the ring C protons also broaden considerably, such that at calixarene/terpyridine ratios of 1 : 1–7 : 3 (spectra **f–h**) (within a 1 : 1 complex regime) they almost merge with the baseline and are poorly resolved. Addition of excess **1** results in sharpening of these signals, such that the spectrum at a H : G ratio of 9 : 1 is fully resolved.

In the crystal structure of **1**·**5**, ring A shows no interaction with the inner walls of the 'molecular capsule'. While H_3B shows some upfield shift on complexation with **2** the protons on ring A show little change as the concentration of **2** increases, except at high calixarene/terpyridine ratios (spectra **i**, **j**). The signal centred at ~9.4 ppm experiences an ~0.07 ppm upfield shift from a calixarene/terpyridine ratio of 6 : 4 (spectrum **g**) to 8 : 2 (spectrum **i**), with the other H_A multiplet (~8.9 ppm) also shifted upfield by ~0.014 ppm over the same range. The Job plot of the interaction of **5** with **2** shows a maximum occurring at a mole fraction of **5** between 0.2 and 0.25, corresponding to a solution calixarene/terpyridine stoichiometry of 4 : 1 or 3 : 1. At high calixarene/terpyridine ratios, the shift in protons H_A may be due to inclusion within another molecule of **2**, giving a 3 : 1 complex in which all of the sulfonate groups of **2** intermesh to bind the structure together. Such a structure would also be favoured on electrostatic grounds, due to the pyridyl nitrogen centres being protonated at the low pD value (~1). Molecular modelling studies (MS Discover) suggest a good fit for the docking of the third calixarene allowing formation of the 3 : 1 complex, with the minimised energy of the complex forming a triangular cluster of the calixarenes around the central guest and interacting through either penetration of the cavity by ring A or through hydrogen bonding of the protonated ring A nitrogen centre with a calixarene sulfonate group, Fig. 10.[20]

Conclusions

These studies have shown that, in aqueous solution and at elevated temperature, the three isomeric 4′-(pyridyl)terpyridines **3–5** associate with *p*-sulfonatocalix[4]arene to form inclusion complexes in solution as a prelude to their crystallisation at lower temperature. For the 3′-, and 2′-pyridyl isomers **3** and **4**, ^{1}H NMR studies indicate that 2 : 1 calixarene/terpyridine complexes form in solution at 333 K, while the 4′-isomer **5** interacts differently with three calixarene molecules associating with each terpyridine molecule. Cooling mixtures of each terpyridine and **1** affords crystalline inclusion complexes, with **3** and **4** as 1 : 1 complexes. Terpyridine **5** forms a 'molecular-capsule' on crystallisation with **1**, with the calixarenes forming an unusual 'corrugated bilayer' structure within the crystal lattice. π-Stacking interactions are a dominant feature in each of the inclusion complex structures, either for terpyridines in the calixarene cavities, or those included in bilayers. This relates to the flexibility of the dihedral angle of the outer pyridine rings C relative to the central ring B. The ability to incorporate terpyridines in bilayers, effectively imparting hydrophobic character on the surface of otherwise hydrophilic bilayer is also noteworthy. Overall, the results further highlight the remarkable versatility of *p*-sulfonatocalix[4]arene as a tecton in building up new materials, along with the importance of differentiating solution and solid state interplay with guest/included molecules.

Notes and references

The terpyridines **3–5**,[13] calix[4]arene tetra-*p*-sulfonic acid **2**,[18] and *p*-sulfonatocalix[4]arene tetrasodium salt **1**[16] were prepared according to published procedures. **Complex 1 · 3**: A hot solution of **3** (9.2 mg, 2.98×10^{-5} mol) in dilute HCl (pH ~2, 1 mL) was added to a hot solution of **1** (12.4 mg, 1.49×10^{-5} mol) in dilute HCl (pH ~ 2, 2 mL). On cooling, a large amount of white microcrystalline precipitate formed, in addition to colourless crystals which formed on the surface of the solution. These were removed and subjected to X-ray diffraction studies. **Complex 1 · 4**: A hot solution of **4** (3.7 mg, 1.2×10^{-5} mol) in concentrated HCl (1 mL) was added to a hot solution of **1** (10 mg, 1.2×10^{-5} mol). Colourless microcrystals appeared on cooling. After leaving overnight, some larger crystals were deposited which were suitable for X-ray diffraction. **Complex 1 · 5**: A hot solution of **5** (8.0 mg, 2.54×10^{-5} mol) in dilute HCl (pH ~ 2, 2 mL) was added to a hot solution of **1** (10.6 mg, 1.27×10^{-5} mol) in dilute HCl (pH ~ 2, 2 mL). Crystalline material suitable for X-ray diffraction deposited on cooling, in addition to microcrystalline precipitate.

Crystal structure determinations. The X-ray diffracted intensities were measured using monochromatised Mo-Kα (λ = 0.71073 Å) radiation on an Oxford Diffraction Xcalibur CCD diffractometer (complexes **1 · 3** and **1 · 4**), or a Bruker ASX CCD diffractometer (complex **1 · 5**). Data were corrected for Lorentz and polarization effects and absorption corrections applied using multiple symmetry equivalent reflections. The structure were solved by direct method and refined on F^2 using SHELX-97 crystallographic package, with diagrams prepared using the X-Seed interface.[21] A full matrix least-squares refinement procedure was used, minimizing $w(F_o^2 - F_c^2)$, with $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$. Agreement factors ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$ and GOF $= \{\Sigma[w(F_o^2 - F_c^2)^2]/(n - p)\}^{1/2}$ are cited, where n is the number of reflections and p the total number of parameters refined). All non-hydrogen atoms of the non-disordered groups were refined anisotropically, while the disordered non-hydrogen atoms were refined isotropically. The positions of hydrogen atoms were calculated from geometrical considerations. The hydrogen atomic parameters were constrained to the bonded atoms during the refinement.

Crystal structure of complex 1 · 3†. $C_{28}H_{20}O_{16}S_4^{4-}$, $C_{28}H_{19}O_{16}S_4^{5-}$, $3(C_{20}H_{17}N^{3+})$, $26(H_2O)$: $C_{116}H_{142}N_{12}O_{58}S_8$, M = 2888.90, $F(000)$ = 3028 e, Triclinic, $P\bar{1}$, Z = 2, T = 100(2) K, a = 17.195(1), b = 17.804(3), c = 23.132(2) Å, α = 78.326(9), β = 86.573(4), γ = 68.775(9)°, V = 6464.0(13) Å^3; D_c = 1.484 mg m^{-3}; $\sin\theta/\lambda_{max}$ = 0.6475; N(unique) = 25823 (merged from 109 967, R_{int} = 0.066, R_{sig} = 0.120), N_o ($I > 2\sigma(I)$) = 14 332; R = 0.1382, w$R2$ = 0.2007 (A,B = 0.189, 51.04), GOF = 1.022; $|\Delta\rho_{max}|$ = 1.31(14) e Å^{-3}.

Crystal structure of complex 1 · 4‡. $C_{28}H_{20}O_{16}S_4^{4-}$, $(C_{20}H_{17}N_4^{3+})$, $8(H_2O)$: $C_{48}H_{53}N_4O_{24}S_4$, M = 1198.18, $F(000)$ = 5000 e, Monoclinic, $C2/c$, Z = 8, T = 100(2) K, a = 49.471(2), b = 11.382(1), c = 21.920(1) Å, β = 115.321(4) °, V = 11 157(1) Å^3; D_c = 1.427 g cm^{-3}; $\sin\theta/\lambda_{max}$ = 0.5964; N(unique) = 9860 (merged from 83 737, R_{int} = 0.0543, R_{sig} = 0.0295), N_o ($I > 2\sigma(I)$) = 9425; R = 0.1391, w$R2$ = 0.3170 (A,B = 0.14, 120.0), GOF = 1.086; $|\Delta\rho_{max}|$ = 1.4(1) e Å^{-3}.

Crystal structure of complex 1 · 5§. $4(C_{28}H_{20}O_{16}S_4^{4-})$, $5(C_{20}H_{17}N_4^{3+})$, $24(H_2O)$: $C_{212}H_{198}N_{20}O_{88}S_{16}$, M = 4946.86, $F(000)$ = 10 280 e, Monoclinic, $C2/c$, Z = 4, T = 153 K, a = 17.349(2), b = 33.402(4), c = 42.855(5) Å, β = 93.069(2) °, V = 24 798(5) Å^3; D_c = 1.325 g cm^{-3}; $\sin\theta/\lambda_{max}$ = 0.5946; N(unique) = 21 192 (merged from 77 928, R_{int} = 0.070, R_{sig} = 0.094), N_o ($I > 2\sigma(I)$) = 7728; R = 0.2234, w$R2$ = 0.4862 (A,B = 0.18, 750.0), GoF = 0.985; $|\Delta\rho_{max}|$ = 1.8(2) e Å^{-3}.

NMR Experiments. Stock solutions of calix[4]arene tetrasulfonic acid **2** (10 mM) and each terpyridine guest **3–5** (10 mM) were made in D_2O, with pD ~ 1 (adjusted by addition of DCl). ^{1}H NMR spectra were recorded at 333 K in 5 mm NMR tubes on a Bruker AV 500 MHz spectrometer, and are referenced to the residual water peak at 4.79 ppm. A series of samples were made in which the stock solutions of calixarene and guest were mixed in various ratios. In this way, the total concentration of calixarene and guest was kept constant at 10 mM, and only the calixarene/terpyridine ratio was varied. ^{1}H NMR spectra were recorded for each sample, and the chemical shifts of the terpyridines were analysed by Job's method of continuous variation,[19] by plotting the inclusion complex formation as a function of the mole fraction of terpyridines in each sample.

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