Thiacalix[4]tube: synthesis, X-ray crystal structure and preliminary binding studies†

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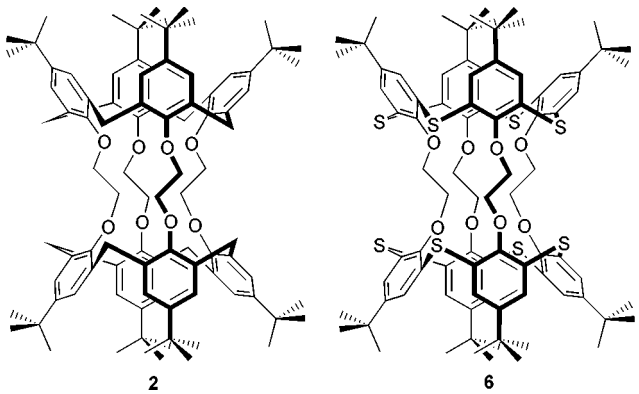
The calix[4]tube family of ionophores has been extended to encompass the slightly larger thiacalix[4]tube. ^{1}H NMR and crystallographic studies show the ligand to adopt a flexible C_{2v} flattened cone arrangement. However, in contrast to the parent calix[4]tube, preliminary binding studies show no selectivity for potassium, in agreement with the absence of a template effect in tube formation and molecular modelling studies.

Since the first reported synthesis of thiacalix[4]arene (**1**) in 1997,[1,2] considerable interest has been focused on both its derivatisation[3,4] and metal complexation[5,6] properties. Thiacalix[4]arene ideally complements the existing calixarene family,[7] providing a macrocycle with a slightly larger annulus than calix[4]arene combined with four sulfur donor atoms, which have been shown to co-ordinate transition metal cations.[3,8,9]

We have recently reported a new class of cryptand-type ionophores, the calix[4]tube **2**, based on a bis(calix[4]arene) scaffold that displays exceptional selectivity for potassium over all group 1 metal cations.[10] Extending this system to incorporate thiacalix[4]arene units would provide a cavity of slightly larger dimensions, which may lead to a new ionophore with contrasting metal co-ordination properties.

Akdas *et al.*[11] have developed selective conditions for the preparation of the lower rim substituted thiacalix[4]arene tetraacetate (**3**) in the cone conformation, which offers the opportunity of further functionalisation at the narrow rim.[12] Careful $LiAlH_4$ reduction of **3** in ether allows the isolation, in 48% yield, of the tetraalcohol **4**, which retains the cone conformation. This compound can be effectively converted (62% yield) to the tetratosylate **5** on treatment with tosylchloride and triethylamine. This useful precursor can be further treated with *t*-butyl thiacalix[4]arene (**1**) in the presence of potassium carbonate in refluxing xylene to yield the desired symmetrical thiacalix[4]tube (**6**) in 10% yield. (Scheme 1)



2 **6**

The ^{1}H and ^{13}C NMR spectra (Fig. 1) of the thiacalix[4]tube **6** indicate, by a doubling of all resonances (a and a′, *etc.*), that the two calix[4]arene units are fixed in a C_{2v} flattened cone arrangement and are linked by two independent types of ethylene linkages in a similar manner to the uncomplexed calix[4]tube **2**.[10] However, all the resonances are broad at room temperature and an ideal spectrum is only observed at 0 °C. The temperature dependence of the ^{1}H NMR signals is shown in Fig. 2. Significant broadening occurs over the temperature range −20 to 55 °C with a gradual tendency towards coalescence and a C_{4v} symmetrical structure, that results in the proton NMR spectrum simplifying from 6 to 3 resonances. Of particular interest is the 30–50 °C region where further resonances appear in the spectrum, this can be postulated to relate to a second favourable arrangement of the ethylene region that can be attained at higher temperatures. This flexibility is aptly demonstrated by the rate of exchange between the two possible C_{2v} arrangements of the calix[4]arene subunits, through the intermediate C_{4v} cone; k_{exch} calculated from EXSY ^{1}H NMR data[13] for the thiacalix[4]tube **6** is 9.25 s^{-1} at 273 K in comparison to 0.9 s^{-1} at 328 K for the potassium selective calix[4]tube **2**.

X-Ray quality single crystals of thiacalix[4]tube were grown by slow diffusion of diisopropyl ether into a chloroform solution. The structure in the solid state is shown in Fig. 3 and is consistent with the low temperature NMR studies in solution. The conformation of the cage can be quantified by the –O–CH_2–CH_2–O torsion angles and the angles made by the phenyl rings with the plane of the four linking sulfur atoms. Two of the torsion angles are 0°, consistent with the 2/*m* symmetry of the molecule. The other two are ±165.2°. The angles made by the phenyl rings with the 4S plane are 88.1 and 42.7°.

This conformation is very similar to that observed in the *t*-octyl calix[4]tube[14] in which the torsion angles are −0.5, 161.6, 0.5 and −154.9°. Here the cage contains a crystallographic centre of symmetry but again the two carbon atoms that make up the *trans* torsion angles are disordered over two sites. In contrast, the *t*-butyl calix[4]tube **2** has torsion angles of 161.2, −47.8, −161.2 and 47.8°; the tube again contains a crystallographic centre of symmetry but without disorder.

† Electronic supplementary information (ESI) available: full experimental details, including synthesis and characterisation of **4** and **5**, and the crystallographic study of **6**. See http://www.rsc.org/suppdata/nj/b1/b106094p/

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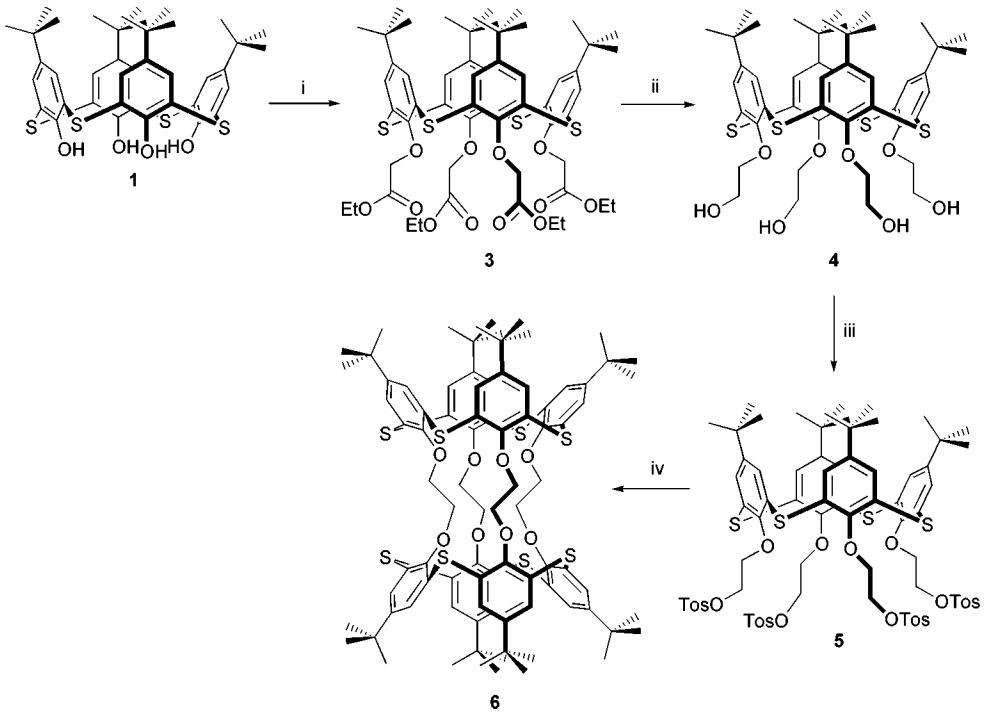

Scheme 1 Synthesis of thiacalix[4]tube (**6**). *Reagents and conditions*: (i) $BrCH_2CO_2Et$, Na_2CO_3, acetone, reflux, 71%; (ii) $LiAlH_4$, Et_2O, 48%; (iii) tosyl chloride, Et_3N, 62%; (iv) **1**, K_2CO_3, xylene, reflux, 4 days, 10%.

Preliminary alkali metal cation binding studies were undertaken using electrospray ionisation mass spectrometry (ESI-MS). This method has recently attracted much interest for the evaluation of host–guest complexation and alkali metal cation selectivity with calixcrown systems.[15,16] The thiacalix[4]tube **6** was pre-treated with a mixture of alkali metal iodides in chloroform–methanol (4 : 1) to give a host : guest ratio of 1 : 20. Disappointingly, Fig. 4 shows that significant complex [**6** + M^+] peaks were observed for both sodium and potassium, together with smaller rubidium and caesium peaks, which suggests that the thiacalix[4]tube exhibits poor selectivity for these cationic guest species. This observation is in stark contrast to **2**, which displays remarkable selectivity for potassium cations.

Qualitative ^{1}H NMR complexation experiments with **6** and potassium cations in $CDCl_3$–CD_3OD (4 : 1) also confirmed the thiacalix[4]tube to be a poor ionophore for this metal cation; only very small shifts ($\Delta\delta \leqslant 0.05$) were observed in the spectra. These preliminary co-ordination chemistry results may account for the poor yield (10%) of the thiacalix[4]tube cage-forming step (Scheme 1), suggesting that formation of the

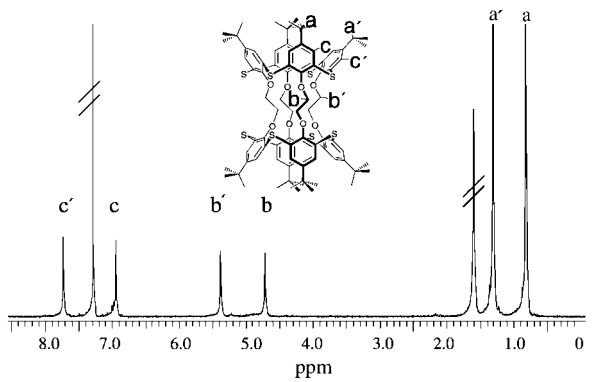

Fig. 1 NMR spectrum for thiacalix[4]tube (**6**) in $CDCl_3$ at 0 °C.

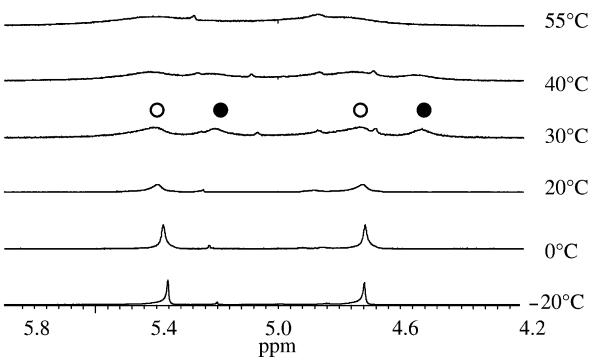

Fig. 2 A section of the ^{1}H NMR spectrum for thiacalix[4]tube (**6**) in $CDCl_3$ over a range of temperatures, showing broadening of the original signals for the ethylene linkage (○) and transient appearance of signals (●), indicating a second species at elevated temperature.

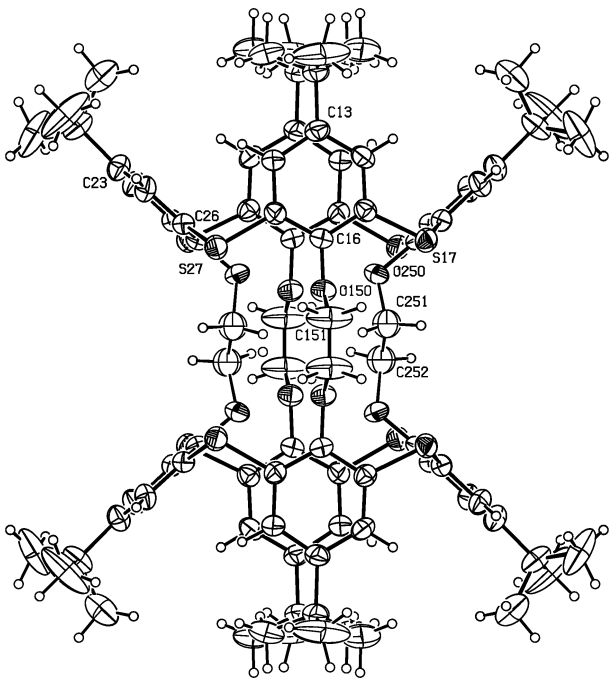

Fig. 3 The structure of **6** with ellipsoids at 15%. One ordered molecule is shown.

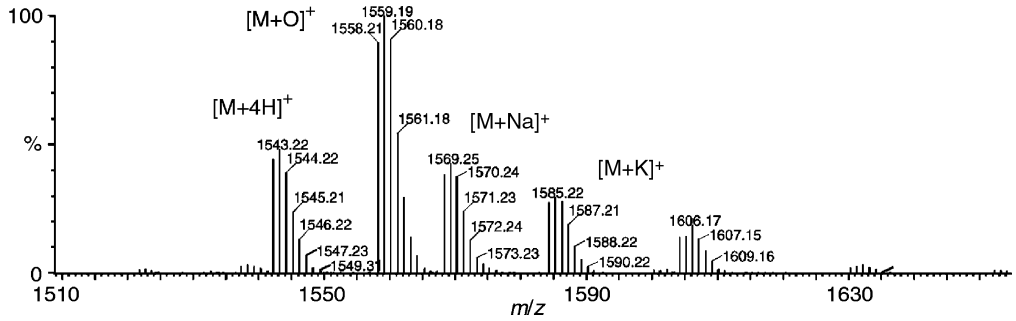

Fig. 4 Electrospray mass spectrum of thiacalix[4]tube (**6**) after pre-complexation with 20 equiv. of sodium, potassium, rubidium and caesium as the iodides in chloroform–methanol (4 : 1). These competition selectivity experiments were complicated by the *in situ* oxidation of the thiacalix[4]tube under the electrospray ionisation MS conditions.

thiacalix[4]tube is not potassium cation template driven as is the case with the parent calix[4]tube **2**.

Molecular modelling studies have been carried out in an effort to rationalise the above findings. Calculations were undertaken to compare the pathway of a potassium cation through the thiacalix[4]tube **6** with that previously established for calix[4]tube **2**. In the case of calix[4]tube **2**, we showed *via* molecular dynamics calculations that K^+ entered the cage along the central axis of the calixarene, then located at an intermediate position close to the phenyl rings before proceeding to the centre of the cage, triggering the necessary conformational change of the central $O–CH_2–CH_2–O$ torsion angles from *tgtg* to *gggg*. This latter conformation then accommodates the K^+ ion in an approximate cubic eightfold co-ordination environment.

Our molecular dynamics calculations show that the mechanism for insertion of the K^+ ion in the thiacalix[4]tube **6** is equivalent to that found for the parent tube. However the size of the metal co-ordination sphere is significantly larger in that the optimum M–O distance (obtained by molecular mechanics calculations using our published method[17]) is 2.96 Å, compared to a calculated distance of 2.82 Å and an experimental distance in the crystal structure of 2.759(6) to 2.809(6) Å for calix[4]tube **2**. Indeed, a search of the Cambridge Crystallographic Databases for K–O (crown ether) distances showed a mean K–O distance of 2.85 Å for 1689 observations (17 outliers were ignored). This mismatch in size may be the reason that the K^+ ion does not remain in the cryptand region but readily withdraws and may also account for the poor binding ability of the thiacalix[4]tube **6**.

In summary, synthetic procedures for the preparation of calix[4]tubes have been successfully extended to the preparation of a thiacalix[4]tube. This adopts the same unusual flattened cone arrangement in both solution and crystalline states although exchange between the two extremes is fairly rapid at room temperature. Such fluxionality, combined with the absence of an apparent templation effect and molecular modelling results, tend to account for the lack of selective potassium binding of this new ionophore.

Experimental

General details and full characterisation of **4** and **5** are provided in the ESI, as well as details of the crystallographic study.

Thiacalix[4]tube (6)

Tetrakis[(4-methylphenyl)sulfonyloxyethoxy]-*p*-*tert*-butylthiacalix[4]arene (**5**; 400 mg, 0.27 mmol) and *p*-*tert*-butylthiacalix[4]arene (**1**; 192 mg, 0.27 mmol) were heated at reflux in xylene (20 ml) in the presence of K_2CO_3 (183 mg, 1.33 mmol) for 4 days. The solvent was evaporated, the residue redissolved in chloroform and then washed with water. After drying the solvent was evaporated and the crude material precipitated from chloroform–methanol. The white solid was recrystallised from chloroform–acetone to yield the thiacalix[4]tube **6** (10%). ^{1}H NMR (500 MHz [D]$CHCl_3$ 18 °C): δ 0.78 [s, 36H; $(CH_3)_3$], 1.26 [s, 36H; $(CH_3)'_3$], 4.67 (s, 8H; OCH_2), 5.33 (s, 8H; OCH'_2), 6.90 (s, 8H; Ar*H*), 7.69 (s, 8H; Ar*H*′); ^{13}C NMR (75 MHz, [D]$CHCl_3$, 18 °C): δ 30.76 [$(CH_3)_3$], 31.39 [$(CH_3)'_3$], 33.81 [$C(CH_3)_3$], 34.29 [$C(CH_3)'_3$], 74.06 ($OCH_2 + OCH'_2$), 128.25 (ArH + *Ar*H′), 130.97 (ArH + *Ar*H′), 133.04 ($ArCH_2$), 134.55 ($ArCH'_2$), 145.86 (*Ar*CH + *Ar*CH′), 158.34 (*Ar*O), 161.36 (*Ar*O′); MS (MALDI): m/z 1541.52 $[M - 4H]^+$.

Crystal data. $6 \cdot 4H_2O \cdot 3CH_2Cl_2$, $C_{91}H_{118}Cl_{16}O_{12}S_8$, $M = 1937.04$, monoclinic, space group $C2/m$, $a = 20.72(2)$, $b = 19.67(3)$, $c = 12.796(15)$ Å, $\beta = 101.48(1)°$, $U = 5111(11)$ Å^3, $Z = 2$.

CCDC reference number 170661. See http://www.rsc.org/suppdata/nj/b1/b106094p for crystallographic data in CIF or other electronic format.

Acknowledgements

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