Selective single crystal complexation of L- or D-leucine by *p*-sulfonatocalix[6]arene†

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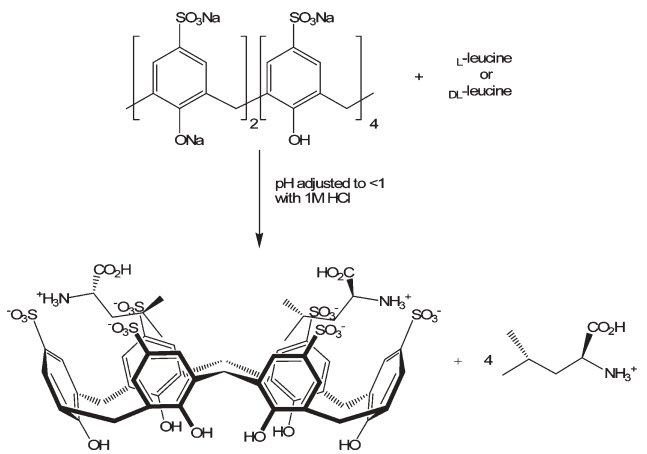
p-Sulfonatocalix[6]arene, organised in the 'double cone' conformation, has multi-guest capability binding either L- or D-leucine in a single crystal in a bi-layer type arrangement from a racemic mixture of the amino acid.

Water soluble calixarenes are a versatile family of molecules that have attracted much attention in recent years due to their ability to form host–guest arrangements either in solution or the solid state.[1] The biological activity of *p*-sulfonatocalix[*n*]arenes is a currently active area of research as they show several interesting properties. These include enzyme inhibition, ion channel blocking and anti-viral properties amongst others, and in this context investigation into their interaction with amino acids is warranted.[2] *p*-Sulfonatocalix[4]arene (SO_3[4]) typically adopts a truncated cone conformation which is particularly suited to forming bi-layer arrangements in the solid state.[3] A range of solid state amino acid complexes of SO_3[4] have been characterised by X-ray diffraction techniques either as molecular capsules or alternative bi-layer arrangements.[4–6] Two such examples show particular amino acids to traverse the traditional bi-layer or dramatically disturb the favourable arrangement, resulting in a new packing motif for the calixarene.[5,6] In contrast to SO_3[4], *p*-sulfonatocalix[6]arene (SO_3[6]) displays a greater degree of conformational flexibility and typically adopts an 'up-down' double partial cone conformation.[7–9] In this conformation, the molecule can act as a di-topic receptor to various guest molecules to form extended supramolecular arrays in the solid state. *p*-Sulfonatocalix[6]arene has recently been shown to adopt a 'double cone' solid state conformation in lanthanide crown ether complexes.[8] Coleman *et al.* have reported a series of studies demonstrating the complexation of several amino acids by *p*-sulfonatocalix[*n*]arenes both in solution (SO_3[4,6,8]) and the solid state (SO_3[4]).[5,6,10] The results suggest that SO_3[6] adopts a 'double cone' or 'taco' conformation but no structural evidence of this phenomenon has been reported to date. Herein we report the first structural authentication of an SO_3[6]/amino acid complex and show the capability of *p*-sulfonatocalix[6]arene to selectively complex L- or D-leucine in a single crystal from a racemic mixture.

Crystals of **1**, [(L-leucine + H^+)$_2$⊂*p*-sulfonatocalix[6]arene]-[L-leucine + H^+)$_4$]·3.25H_2O (or the D-isomer, see Notes and references) grew upon slow evaporation of an acidified solution (1 M HCl, pH < 1) containing Na_8SO_3[6] and a ten-fold excess of DL-leucine. The crystals are in an orthorhombic cell and the structural solution was performed in the chiral space group $P2_12_12_1$.‡ The asymmetric unit in **1** comprises one SO_3[6] molecule, six L-leucine molecules and three and a quarter waters of crystallisation that are disordered over eight positions. Two L-leucine molecules have a partial occupancy of 0.5 (one of which is only partially resolved). The SO_3[6]/L-leucine stoichiometry was confirmed to be 1 : 6 by ^{1}H NMR spectroscopy. The calixarene in **1** adopts the 'double cone' conformation whilst bearing host to two L-leucine molecules, Scheme 1, Fig. 1. The L-leucine molecules that are hosted by SO_3[6] are positioned such that the hydrophobic aliphatic tails reside in the cavities of the calixarene. The hydrophilic amino acid functional groups are positioned near the upper-rim sulfonate groups of the host. In addition to inclusion of the amino acids in the cavities of the calixarenes, the remaining L-leucine molecules occupy interstitial spaces within the extended structure. Although no hydrogen atoms were located on the amine or the majority of carboxylic acid functions of the L-leucine molecules, the pH of the mother liquor would likely ensure protonation of both. Four hydrogen bonding contacts are evident between oxygen atoms of the amino acids to closest sulfonate groups within the asymmetric unit and extended structure of **1** (CO···OS distances ranging from 2.508 and 2.654 Å), two examples of which are shown in Fig. 1. There are several hydrogen bonding contacts between protonated nitrogen atoms of the L-leucine molecules and SO_3[6] sulfonate groups (N···OS distances ranging from 2.656 to 2.927 Å).

Upon crystal packing, the calixarenes form 'bi-layer type' helical chains along the *a* axis, Fig. 3. These chains pack through two unique interactions; one π-stacking interaction with an aromatic centroid···centroid distance of 3.793 Å; one CH···π interaction from a bridging methylene group to an aromatic ring of the



Scheme 1 Schematic representation of the SO_3[6]/L-leucine complex, **1**.

† Electronic Supplementary Information (ESI) available: Structural data for L-leucine hydrochloride monohydrate. See http://www.rsc.org/suppdata/cc/b4/b413821j/

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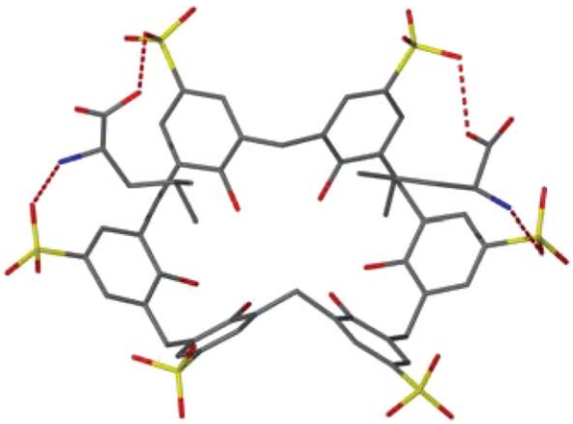

Fig. 1 Near aerial view of part of the inclusion complex **1** showing multi-guest inclusion, the double cone conformation of the calixarene, and the hydrogen bonding from the L-leucine molecules to sulfonate groups (disordered atoms, hydrogen atoms, other L-leucine molecules and water molecules omitted for clarity).

nearest calixarene with a CH···centroid distance of 2.617 Å, Fig. 2. This packing is similar to that formed when SO_3[6] forms a 'bis-molecular capsule' in the presence of 18-crown-6 and lanthanide(III) chloride.[8] The fact that SO_3[6] adopts a 'double cone' conformation may be attributable to the low pH employed, thereby maintaining the integrity of the hydrogen bonding regime at the base of the host. At slightly higher pH and in the presence of excess 18-crown-6 and lanthanide chloride, this regime is not formed and hydrogen bonding is evident from base phenoxy groups to water molecules positioned near the cavity of the crown ethers resulting in the alternative 'double-partial cone' conformation.[8]

Further analysis of the extended structure reveals that the remaining L-leucine molecules are in interstitial spaces in and around the bi-layer type arrangement of the calixarenes as shown in Fig. 3. In these positions, there are numerous hydrogen bonding contacts between protonated amine groups and symmetry equivalent SO_3[6] sulfonate groups.

Given that solid state complex formation is possible with L- or D-leucine (see Notes and references), complex formation with racemic or mixed pairs of amino acids may well be possible with the calixarene in the 'double cone' conformation, as may be bis-molecular capsule formation.

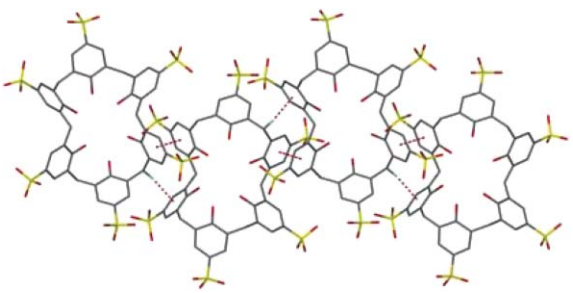

Fig. 2 Packing of SO_3[6] into helical chains in **1** showing pi-stacking and CH···π interactions (disordered atoms, L-leucine molecules, water molecules and some hydrogen atoms omitted for clarity).

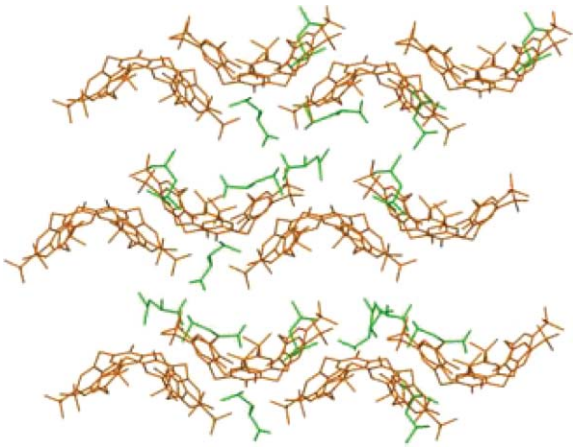

Fig. 3 Partial packing diagram of **1** showing the bi-layer type arrangement of calixarenes (orange) and the L-leucine molecules (green) that occupy interstitial spaces in the extended structure (disordered atoms, hydrogen atoms, water molecules and cavity held L-leucine molecules are omitted for clarity).

In conclusion we have reported that *p*-sulfonatocalix[6]arene selectively complexes L- or D-leucine in addition to elucidating the first structure of an SO_3[6]/amino acid complex that shows multi-guest inclusion in the calixarene. Although there are few examples of SO_3[6] adopting the 'double cone' or 'taco' conformation, the results suggest that the calixarene prefers this conformation (at least in the solid state) at low pH (<3). Future studies will investigate inclusion of other amino acids and/or mixtures of amino acids with the larger and more conformationally flexible *p*-sulfonatocalix[*n*]arenes (where $n > 5$).§

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Notes and references

‡ *Crystal data.* $C_{78}H_{120.50}N_6O_{39.25}S_6$, M = 1962.66, orthorhombic, a = 18.5302(8), b = 21.3013(8), c = 24.4166(11) Å, U = 9637.7(7) Å^3, μ = 0.231 mm^{-1}, T = 100 K, space group $P2_12_12_1$ (no. 19), Z = 4, Mo-Kα radiation (λ = 0.71073 Å), final GOF = 1.216, R_1 = 0.09, 102169 reflections measured, 17229 unique (R_{int} = 0.1411) which were used in all calculations. The final $\omega R(F^2)$ was 0.2378 (all data). Although complex **1** is shown to form with L-leucine, selective complexation of either hand is possible (Absolute structure parameter = 0.09(10)). Three L-leucine molecules were refined isotropically whilst two disordered sulfonate groups were refined with constrained thermal parameters. CCDC 248963. See http://www.rsc.org/suppdata/cc/b4/b413821j/ for crystallographic data in .cif or other electronic format.

§ *p*-Sulfonatocalix[6]arene was synthesised by literature methods[11] whilst DL-leucine and L-leucine were purchased from Aldrich and used as supplied. X-Ray crystallographic studies were performed on a Bruker-Nonius X8 rotating anode (operating at 4.2 kW). *Synthesis of [(L-leucine + H^+)$_2$⊂p-sulfonatocalix[6]arene][L-leucine + H^+)$_4$]·3.25H_2O, **1**.*1 M hydrochloric acid was added to a solution containing octa-sodium *p*-sulfonatocalix[6]arene (20 mg, 11.5 μmol) and DL-leucine (16 mg, 115 μmol) until the

pH was <1. As the solution concentrated, crystals of two morphologies that were suitable for X-ray diffraction studies formed. They were found to be complex **1** and L-leucine hydrochloride, the structural data for which is given in the ESI (CCDC 249862).† Although several data sets were collected for complex **1**, none showed the presence of D-leucine as the guest. Although some ambiguity surrounds the formation of crystals containing D-leucine, the crystals of either the L- or D-complex can only form in one hand. Notably, crystals of **1** were also isolated from an optically pure solution containing L-leucine but it has not yet been possible to grow crystals from a pure D-leucine solution. Complex **1**; NMR δ_H (D2O): 7.54 (12H, s, ArH), 3.96, (12H, s, CH_2), 1.54 (18H, m, CH, CH_2), 0.65, (dd, CH_3).

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