Salt formation affects the conformational and assembly properties of \( p \)-carboxylatocalix[4]arenes†

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The conformational properties and self-assembly behaviour of the \( p \)-carboxylatocalix[4]arenes, when in the presence of a pyridine template, are well understood. Salt formation with these molecules, a process driven by the introduction of an amino group to the 2-position of the pyridine template, has dramatic consequences on both building block conformation and the resulting self-assembly.

The \( p \)-carboxylatocalix[\( n \)]arenes (\( p\text{CO}_2[\( n \)]s, where \( n \) represents the number of aromatic rings in the calixarene) have received relatively little attention as molecular building blocks in supramolecular chemistry. This is surprising when one considers a) their structural relation to the \( p \)-sulfonato analogues which have been studied extensively,1 b) the fact that the benzoate moiety has featured heavily in MOF formation2 and c) that well-established synthons may be used to drive self-assembly with carboxylic acids.3 Despite this these molecules show great promise for exploitation in areas such as targeted self-assembly4 (through careful choice of synthon employed) and the formation of novel metal–organic systems.5 The latter can be discrete \(^{a,c,d,f,h}\) or polymeric \(^{e,b}\) in nature, and we have recently shown that these can be designed so as to specifically contain inherently cavity-containing \( p\text{CO}_2[\( 4 \)]s.\(^{5,b}\)

The basic calix[4]arene (\( C[4] \)) framework adopts a cone conformation due to the presence of concerted H-bonding interactions at the polyphenolic lower-rim. This can be readily modulated through \( C[4] \) lower-rim alkylation to afford, amongst others, partially pinched-cone (via di-O-alkylation) and fully pinched-cone (via tetra-O-alkylation) conformers as shown in Fig. 1A; tetra-O-alkylation with methyl or ethyl chains allows for conformational inversion through the \( C[4] \) annulus, and chains greater or equal to propyl in length are known to lock the molecule in the fully pinched-cone conformation.\(^{6}\) Once the desired conformer (or structurally mobile \( C[4] \) for OMe and OEt derivatives) has been synthesised, the introduction of upper-rim carboxylic acid functionality is relatively straightforward.

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Fig. 1. A) Control over \( C[4] \) conformation by di- and tetra-O-alkylation at the lower-rim. B) Schematic of the Py–\( \text{CO}_2\text{H} \) heterosynthon. C) Head-to-head H-bonded capsule formed by crystallisation of a di-O-alkylated \( p\text{CO}_2[\( 4 \)] \) in the presence of a Py template.\(^{a,7}\) D) Schematic of the 2-aminopyridinium-carboxylate heterosynthon.
We have investigated the assembly of a range of $p$CO$_2$[4]s containing two or four lower-rim alkyl chains in the presence of pyridine (Py), picoline and ethylpyridine templates.

In the aforementioned series of studies we found that a) the components generally formed the expected Py⋯CO$_2$H heterosynthon shown in Fig. 1B, b) if a cavity is present (e.g. in a lower-rim di-O-alkyl $p$CO$_2$[4]) it will be occupied by a Py or Py derivative guest template, c) host–guest $p$CO$_2$[4]/Py (or Py derivative) arrangements dimerise to form capsules (Fig. 1C) and d) Py or Py derivative templates form the aforementioned heterosynthon but do not force access to the potential cavity of a lower-rim tetra-O-alkyl $p$CO$_2$[4] (fully pinched-cone conformation, Fig. S1†). Here we report interesting effects on the conformational properties of a series of tetra-O-alkyl $p$CO$_2$[4]s, as well as their assembly preferences, once salt formation has been performed via introduction of an amino group to the Py template (using 2-aminopyridine, 2-AP). This well-known heterosynthon was targeted for structural comparison with related Py⋯CO$_2$H driven assembly of $p$CO$_2$[4]s (compare Fig. 1B and D), and it was anticipated that deprotonation of the upper-rim would cause deviation from the fully pinched-cone conformation due to repulsion of CO$_2^-$ groups. We screened salt formation in methanol between 2-aminopyridine (2-AP) and the series of $p$-carboxylato-O-alkylcalix[4]arenes shown in Fig. 2; single crystals of salts formed for 1, 3 and 4, and the interesting structural features of these assemblies are described in order below.

Single crystals of the salt (5) formed between 1 and 2-AP were found to be in a monoclinic cell and structure solution was performed in the space group $P2_1/n$. The asymmetric unit in 5 consists of one molecule of 1 (with three of four upper-rim CO$_2$H groups deprotonated), four 2-AP molecules (three of which are protonated, H2-AP) and two and a half methanol molecules (the half being disordered by symmetry) of crystallisation (Fig. 3). The most noticeable feature upon inspection is that 1 unexpectedly adopts a partial pinched-cone conformation; as stated above, lower-rim OMe groups allow for conformational mobility, and crystallisation of 1 from 4-picoline affords a structure in which the calixarene adopts a partial-cone conformation with inversion of one aromatic ring. One of the aromatic rings of 1 in 5 is slightly splayed in comparison to the others within the framework. One H2-AP cation occupies the resulting host cavity, forming various intermolecular interactions as shown in Fig. 3; there are CH⋯π and π-stacking interactions between guest and host, occurring with respective H[42]⋯aromatic centroid and aromatic centroid⋯aromatic centroid distances of 2.6 Å and 3.975 Å. There is also an NH⋯OCO H-bonding interaction between the cationic guest and an upper-rim CO$_2^-$ group of 1 with an H[43A]⋯O[6] distance of 2.2 Å. Symmetry expansion around the guest in 5 results in formation of a H-bonded head-to-head dimer/capsule as shown in Fig. 4. This occurs through formation of the targeted heterosynthon shown in Fig. 1D, with an NH⋯OCO H-bonding interaction between H[38] and symmetry equivalent [s.e.] O[7] (H[43B]⋯O[7] s.e. distance of 1.8 Å), as well as an NH⋯OCO H-bonding interaction between H[43B] and O[8] s.e. (H[43B]⋯O[8] s.e. distance of 2.0 Å). The two remaining 2-AP cations in 5 also interact with upper-rim...
CO$_2^-$ groups of 1 through formation of the same heterosynth (Fig. 3); this occurs with two NH⋯OCO (respective H[45]⋯O[6] and H[52]⋯O[12] distances of 1.7 and 1.9 Å) and two HNH⋯OCO H-bonding interactions (respective H[50B]⋯O[5] and H[57B]⋯O[11] distances of 2.0 and 1.9 Å). The neutral 2-AP in the asymmetric unit interacts with two upper-rim CO$_2^-$ groups of 1 via two HNH⋯OCO interactions with H[64A]⋯O[6] and H[64B]⋯O[7] distances of 2.1 and 2.1 Å. The three methanol molecules of crystallisation form a range of OH⋯OCO and OH⋯O H-bonding interactions; these occur between neighbouring MeOH of crystallisation, or CO$_2$H/CO$_2^-$ groups of 1 (Fig. 3).

Further symmetry expansion of the asymmetric unit around the splayed/protonated upper-rim CO$_2$H group in 1 reveals an OCOH⋯OCO H-bonding interaction to an upper-rim CO$_2^-$ group of an s.e. molecule (Fig. 4); this unique OCOH⋯OCO interaction occurs with an H[9]⋯O[12] distance of 1.8 Å. Examination of the extended structure reveals that these capsules, linked by H-bonding interactions, pack in an anti-parallel bi-layer motif (Fig. S2†) akin to several previously reported for the Py derivative solvates of pCO$_2$[4]. The final noteworthy feature of 5 is that the closest distance between C atoms of the upper-rim CO$_2^-$ groups in 1 was found to be ~7.4 Å. This is significantly greater than values typically observed for the distance between upper-rim CO$_2$H groups in tetra-O-alkyl pCO$_2$[4]s where the lower-rim alkyl chain is greater or equal to propyl in length; the respective distances observed for 3 and 4 are ~4.1 and ~3.7 Å upon crystallisation from Py or the picolines.† Unfortunately we have been unable to crystallise 1 in a fully pinched-cone conformation to date so it is therefore not possible to make direct structural comparison between neutral and anionic forms, or draw conclusions relating to upper-rim charge repulsion and or associated cationic guest inclusion in this particular case.

Single crystals of the salt (6) formed between 3 and 2-AP were found to be in a triclinic cell and structure solution was performed in the space group P1.† The asymmetric unit in 6 is large and comprises two molecules of 3 (with all upper-rim CO$_2$H groups deprotonated), eight molecules of 2-AP (all of which are protonated and one of which is disordered over two positions), two molecules of methanol, six and a half water molecules and a disordered methanol/water of crystallisation (0.33 and 0.67 occupancies respectively). Simple inspection of 6 reveals that each calixarene cavity is occupied by a H2-AP cation, but to differing extents (Fig. 5). In the first of these there are two CH⋯π interactions observed between both the meta hydrogens of the H2-AP and aromatic rings on the anionic host (Fig. 5A); these occur with H[92]⋯aromatic centroid and H[94]⋯aromatic centroid distances of 3.1 and 2.8 Å respectively. As is the case in 5 there is concomitant HNH⋯OCO H-bonding between the cationic guest and an upper-rim CO$_2$ group of the host; this occurs with an H[95B]⋯O[7] distance of 2.2 Å. Any CH⋯π interactions in the second host/guest arrangement can be considered to be very long (Fig. 5B),† and as a result there is no evidence of analogous HNH⋯OCO H-bonding with the calixarene upper-rim. Rather the H2-AP cation forms an HNH⋯O H-bonding interaction with a water of crystallisation with an NH⋯O distance of 2.1 Å.

Symmetry expansion of the asymmetric unit around the upper-rim of both calixarenes reveals that, irrespective of the degree of cavity occupation by the H2-AP guests described above, formation of H-bonded head-to-head dimers akin to those found in 5 occurs via formation of the targeted heterosynth.† In both cases this is facilitated by analogous HNH⋯OCO and NH⋯OCO H-bonding interactions as shown in Fig. 6 (capsule shown for expansion of the arrangement
shown in Fig. 5B). There are two NH⋯OCO hydrogen-bonding interactions between both H-bonded head-to-head dimers with respective H[90]⋯O[6]s.e. and H[97]⋯O[22]s.e. distances of 1.8 and 1.9 Å. Additionally there are two HNH⋯OCO H-bonding interactions with respective H[95A]⋯O[5] and H[10A]⋯O[20] distances of 2.0 and 1.9 Å.

Five of the remaining H2-AP cations in the asymmetric unit (including one of which is disordered over two positions) interact with upper-rim CO2− groups via one HNH⋯OCO and one NH⋯OCO H-bonding interaction in each case. The NH⋯OCO H-bonding interactions have distances ranging from 1.7–1.9 Å, while the HNH⋯OCO interactions range from 1.9–2.0 Å (Fig. 5). The final H2-AP cation in the asymmetric unit interacts with the remaining upper-rim CO2− group via only one NH⋯OCO H-bonding interaction with an H[118]⋯O[10] distance of 1.7 Å (Fig. 5A). The additional solvent of crystallisation (MeOH/H2O) forms a wide range of H-bonding interactions, but inspection shows that none appear to dictate extended assembly in an influential manner (as is the case for the cationic H2-AP template). Examination of the extended structure of 6 reveals that the components assemble as capsules within a wave-like bi-layer motif as shown in Fig. S3.†

As stated above, the average closest distance between C atoms of upper-rim CO2H groups in 3 (when crystallised in neutral form from Py or the picolines) was found to be ~4.1 Å.4e Examination of the analogous distances between C atoms of the upper-rim CO2− groups in 6 reveals that these are significantly greater with respective C[41]⋯C[43] and C[85]⋯C[87] distances of ~6.7 and ~7.1 Å (average distance of ~6.93 Å, Fig. 7).

Single crystals of the salt (7) formed between 4 and 2-AP were found to be in a monoclinic cell and structure solution was performed in the space group C2/c.† The asymmetric unit in 7 comprises one half of a molecule of 4 (with upper-rim CO3H groups deprotonated) and two 2-AP molecules (both of which are protonated, Fig. 8).

The most noticeable feature upon inspection is that the H2-AP cations do not occupy the cavity presented by the calixarene, nor do they force access within this particular structure. One H2-AP cation in 7 forms the targeted heterosynthron7 with the splayed symmetry unique upper-rim calixarene CO2− group via one NH⋯OCO and one HNH⋯OCO H-bonding interaction; this occurs with respective H[25]⋯O[3] and H[31A]⋯O[4] distances of 1.9 Å and 1.7 Å. The remaining H2-AP cation is disordered over two positions and was modelled at 50% occupancy in each. In one position this interacts with the pinched upper-rim calixarene CO2− group via one NH⋯OCO and one HNH⋯OCO hydrogen-bonding interaction; this occurs with respective H[113]⋯O[5] and H[10C]⋯O[6] distances of 1.9 Å and 2.5 Å. Symmetry expansion of the asymmetric unit around the other position reveals two HNH⋯OCO hydrogen-bonding interactions between the...
Work continues in further tailoring the assembly behaviour of cases, or the increase in cleft size relative to the neutral forms relating to poor solubility based on the short lower-rim alkyl studied in two out of three cases, with the other forming a. The more basic template fully deprotonated the calixarenes extended this template chemistry to include salt and related 3716 to assume that the presence of the H2-AP cations markedly 43 to 4.8 Å, representing a significant increase in the size of the cavity present (Fig. 9). Given that cavity occupation by a H2-AP cation is not observed, we propose that in the presence of pyridine supramolecular building blocks in the presence of pyridine –alkyl– groups on the half-calixarene; this is difficult to state for the latter as there is disorder present in this region of the structure.

Conclusions

The p-carboxyphthalalix[4]arenes have been shown to be versatile supramolecular building blocks in the presence of pyridine (or pyridine derivative) templates through exploitation of a) the Py−·CO2H heterosynth and b) the availability of a cavity for template/guest occupation. Here we have extended this template chemistry to include salt and related heterosynthon formation through the use of 2-aminoypyridine. The more basic template fully deprotonated the calixarenes studied in two out of three cases, with the other forming a tri-rather than tetra-anionic building block, a feature possibly relating to poor solubility based on the short lower-rim alkyl group present. Given the observation of cavity accessibility in two cases, or the increase in cleft size relative to the neutral forms of 3 and 4 (structural comparison possible), it is reasonable to assume that the presence of the H2-AP cations markedly influences both conformational and assembly properties of the lower-rim tetra-O-alkyl-p-carboxyphthalalix[4]arenes in general. Work continues in further tailoring the assembly behaviour of these useful hosts through targeted heterosynthon formation with a view to controlling the formation of nanoscale spherical and tubular architectures.

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Notes and references


8 Compound 1 is poorly soluble in most solvents and we propose that the degree of protonation may relate to this.