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2-Methylresorcinarene: a very high packing coefficient in a mono-anion based dimeric capsule and the X-ray crystal structure of the tetra-anion†

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Mono- and tetra-deprotonated 2-methylresorcinarene anions (1 and 2) as their *trans*-1,4-diammoniumcyclohexane $(TDAC)^{2+}$ inclusion complexes are reported. The mono-anion forms a fully closed dimeric capsule $[1{\cdot}H_2O{\cdot}MeOH]_2^{2-}$ with a cavity volume of 165 Å^3 and $(TDAC)^{2+}$ as the guest with an extremely high packing coefficient, PC = 84.2%, while the tetra-anion forms a close-packed structure with two structurally isomeric tetra-anions 2a and 2b with a 50 : 50 ratio in the crystal lattice.

Resorcinarenes are stable π-rich cavity containing host systems in the C_{4v} crown conformation.[1] Since the 1980's, resorcinarenes and their cavitand analogues have played a key role in molecular recognition processes in a multitude of host–guest systems.[2] The easy synthesis and selective functionalization either at the upper rim hydroxyl groups or the 2-position on the aromatic rings, and the lower rims have made them a very useful and accessible family of host compounds.[2] With the C_{4v} vase shaped cavity, resorcinarenes manifest selective guest complexation and in some cases encapsulation through a multitude of weak non-covalent interactions such as cation···π, C–H···π and π···π interactions.[3] In addition, the hydroxyl groups form strong hydrogen bonds with *exo*- or *endo*-complexed guests in the solid state.[3] The construction of hydrogen bond based host–guest systems using resorcinarenes has been well-studied with alcohols,[4] sugars,[5] steroids,[6] as well as with heterocyclic five- and six-membered ring compounds.[7]

Treating core resorcinarenes with even weak bases[8] leads to the formation of deprotonated species in which the increased π-character of the resorcinarene cavity can be used for more efficient molecular recognition processes by enhancing the weak interactions.[9] In resorcinarenes, the acidity of the first proton is greater than that of the second and so on, and the cavity attains maximum stability upon tetra-deprotonation, retaining its crown C_{4v} conformation, and being stabilized by stronger circular intramolecular O–H···O$^-$ hydrogen bonds. The tetra-deprotonated resorcinarenes *viz.* tetraphenolate anions are known to exist in alkaline media, and are reported to have remarkably high binding constants towards alkyl ammonium salts when compared to the neutral non-deprotonated resorcinarenes.[10] The strong electrostatic interactions between the π-delocalized negatively charged macrocyclic cavity and cationic guests have been reported to lead to high binding constants.[9] Schneider and co-workers demonstrated the hydrolysis of acetylcholine to choline in the resorcinarene tetraphenolate cavity by ^{1}H NMR, supporting the hydrolysis mechanism with molecular models.[11] Other biological molecules have also been hosted by the resorcinarene tetraphenolate.[12]

Although the resorcinarene tetraphenolate is known in solution, the crystal structure of it has remained elusive. Along these lines, we have previously reported the structures of mono- and di-deprotonated core resorcinarenes using mono- and diamine bases in the solid state.[13] In this contribution, we report the preparation, X-ray crystal structures and the electrospray ionization mass spectrometry (ESI-MS) characterization of mono- (**1**) and tetra-anions (**2**) as their *trans*-1,4-diammoniumcyclohexane, $(\mathbf{TDAC})^{2+}$, complexes obtained by reacting 2-methylresorcinarene, **2-MeC2**, and *trans*-1,4-diaminocyclohexane, **TDAC**, as shown in Fig. 1.

Single crystals of the complexes $(\mathbf{TDAC})^{2+}@[\mathbf{1}{\cdot}H_2O{\cdot}MeOH]_2$ and $2(\mathbf{2}){\cdot}3(\mathbf{TDAC})^{2+}{\cdot}2(\mathbf{TDAC})^{+}{\cdot}15(MeOH){\cdot}0.5(H_2O)$ were prepared by mixing 1 : 1 and 1 : 4 molar ratios of **2-MeC2** and **TDAC** in methanol, respectively, followed by slow evaporation at room temperature. The reaction of **2-MeC2** and **TDAC** in a 1 : 1 molar ratio forms a tight neutral hydrogen bonded capsule, $(\mathbf{TDAC})^{2+}@[\mathbf{1}{\cdot}H_2O{\cdot}MeOH]_2$, where the cavity entraps $(\mathbf{TDAC})^{2+}$, as the guest, as shown in Fig. 2. In this dimeric capsule, the capsule halves are held tightly together by hydrogen bonds *via* two methanol $[(O–H)_{host}\cdots(O)_{MeOH}\cdots(H–O)_{host}]$ and two water molecules $[(O–H)_{host}\cdots(O–H)_{water}\cdots(O–H)_{host}]$. The *endo*-cavity $(\mathbf{TDAC})^{2+}$ is encapsulated very tightly *via* additional N–H···O

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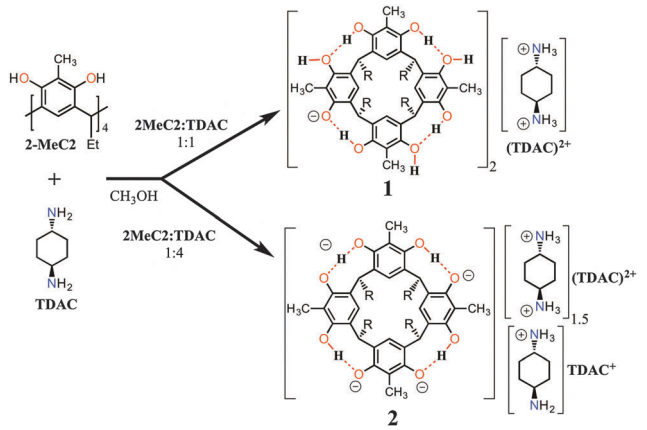

Fig. 1 Synthesis of mono- (**1**) and tetra-anions (**2**) from 2-methylresorcinarene (**2-MeC2**) and *trans*-1,4-diaminocyclohexane (**TDAC**). Nomenclature: **TDAC** = *trans*-1,4-diaminocyclohexane; **(TDAC)$^{+}$** = *trans*-1-ammonium-4-aminocyclohexane; **(TDAC)$^{2+}$** = *trans*-1,4-diammonium-cyclohexane.

and N–H$\cdots\pi$ interactions to the hosting capsule (see ESI,† Fig. S3a). These concerted guest-to-host interactions resulted in an extremely high packing coefficient (PC) of 0.842, *viz.* 84.2%. The volume of **3**, 138.9 Å^3, was obtained using Spartan[14] at MM level, while the cavity volume, 165 Å^3, was calculated using MSroll[15] within X-Seed[16] with a 1.2 Å probe, PC = 138.9 Å^3/165 Å^3 = 0.842.

Contrary to the mono-anion, the tetra-anion **2** is an open inclusion complex, with overall composition of 2(**2**)·3**(TDAC)$^{2+}$**·2**TDAC^{+}**·15(MeOH)·0.5(H_2O), the eight negative charges being counterbalanced with two *endo*-cavity **(TDAC)$^{2+}$**, one *exo*-cavity **(TDAC)$^{2+}$** and two *exo*-cavity **(TDAC)$^{+}$** cations. The deprotonation of the hydroxyl groups in **2-MeC2** can, from very high quality single crystal X-ray diffraction data, be observed from the residual electron density map [in the case of **1**, all H-atoms are clearly visible and this unambiguously confirms that one of the hydroxyl groups does not have a H-atom in it, namely O6 (see ESI,† Fig. S1)]. Another way, which is more reliable with lower quality data (as in case of **2**), is the fact that a normal OH group both accepts and donates H-bonds, while a deprotonated,

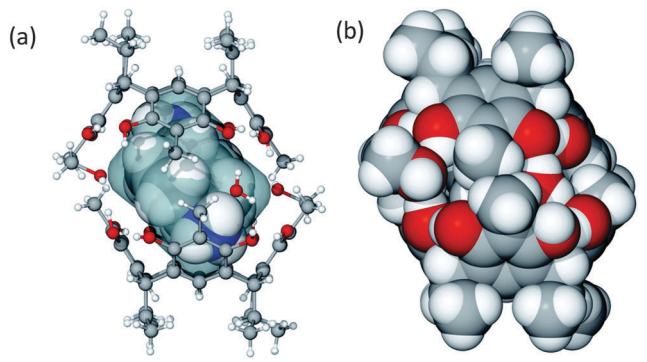

Fig. 2 Dimeric capsule, **(TDAC)$^{2+}$**@[**1**·H_2O·MeOH]$_2$ shown in (a) as ball and stick with the calculated cavity in transparent grey colour and the guest **(TDAC)$^{2+}$** as CPK to illustrate the very tight encapsulation and (b) as the CPK model.

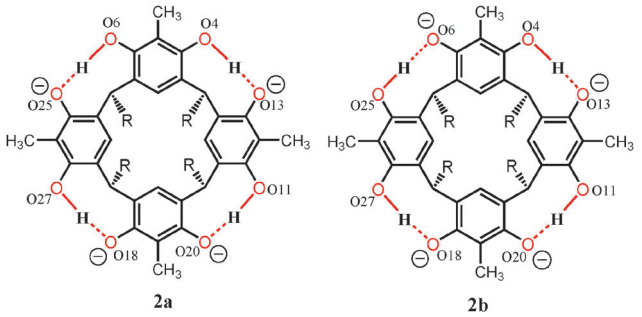

Fig. 3 Chemdraw representation of tetra-anions **2a** and **2b**. The orientation of the resorcinarene core and the oxygen atoms are labelled as in the crystal structure shown in ESI,† Fig. S4.

viz. phenolate, group accepts three H-bonds. In the case of **2**, this is unambiguously verified for the hydroxyl O-atoms O13, O20 and O18 (see ESI,† Fig. S4). While the O-atoms O6 and O25 show a disorder of the hydrogen atoms with a disordered methanol molecule hydrogen bonded to these two O-atoms. Closer inspection reveals that indeed the crystal lattice contains two distinct structural isomers for the tetra-anion **2**, *viz.* **2a** and **2b**, as represented by the 2-D drawings in Fig. 3. The two isomers crystallize so that every second unit cell contains **2a** and **2b** (see ESI,† Fig. S4 for crystal structures), thus manifesting positional 50 : 50 disorder within the same unit cell. However both **2a** and **2b** have the same orientation in the unit cell so that the oxygen atoms O6 (50%) and O25 (50%) accept three hydrogen bonds[13] as shown in Fig. 3.

The following observations were used to ascertain the structure of the mono-anion **1** and the two structural isomers **2a** and **2b** of the tetra-anion:

(1) The hydrogen atom positions were located unambiguously from the electron density map for the protonated –NH_3^+ groups in the **(TDAC)$^{2+}$** and **(TDAC)$^{+}$** cations for both **1** and **2**, as well as the upper rim O–H$\cdots$O$^-$ hydrogen bonds for **1** (see ESI,† Fig. S1 and S2).

(2) Deprotonated, *viz.* the phenolate, oxygen atoms act as triple hydrogen bond acceptors in both **1** and **2**.

(3) The oxygen atoms, O6 and O25, in the two structural isomers **2a** and **2b** were confirmed to act as triple hydrogen bond acceptors at 50 : 50 ratios through careful analysis of the similarly disordered methanol molecules hydrogen bonded to them.

The effect of **TDAC** on the deprotonation of **2-MeC2** in the gas phase was studied through a series of ESI-MS analyses in MeCN/MeOH. Titration experiments showed that the deprotonated charge states of **2-MeC2** increased until four equivalents of **TDAC** were added (Fig. 4a). The mono- and di-deprotonated ions, [**2-MeC2**–H]$^-$ and [**2-MeC2**–2H]$^{2-}$, were clearly observed in the ESI-MS spectra (see ESI,† Fig. S5). Gas phase stability is known to be low for low molecular weight multiply charged ions in conditions where stabilizing solvent interactions are absent.[17] Higher charge density, therefore, usually leads to coulombic explosion of the compound. Gas phase basicities for the multi-deprotonated ions [**2-MeC2**–3H]$^{3-}$ and [**2-MeC2**–4H]$^{4-}$,

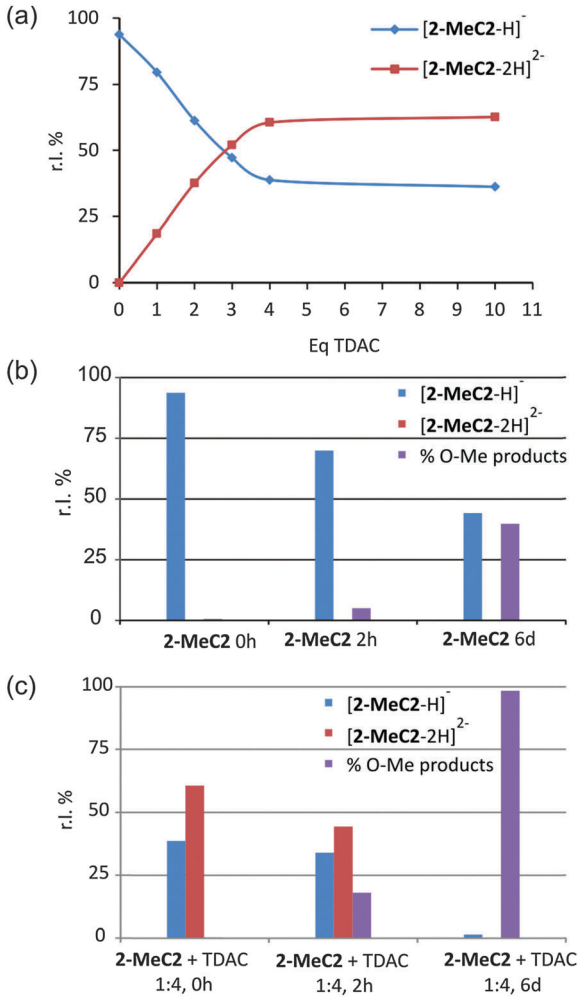

Fig. 4 (a) Relative intensities (r.i.%) of deprotonated ions observed in (−)ESI-MS spectra as a function of added **TDAC** equivalents. Relative intensities (r.i.%) of the deprotonated ions observed in (−)ESI-MS spectra in aged samples; (b) **2-MeC2** in MeCN : MeOH (25 : 1 v/v) and (c) **2-MeC2** and **TDAC** 1 : 4 in MeCN : MeOH (25 : 1 v/v).

are assumed to be relatively high. Hence, the tri- and tetra-deprotonated ions can easily abstract a proton from methanol, which originates from the MeCN : MeOH (25 : 1 v/v) mixture used in the ESI-MS experiments due to too low solubility of **TDAC** in aprotic solvents. The stabilizing interactions between the deprotonated OH groups of the **2-MeC2** and **TDAC** molecules (which were present in the solid state structures) were not observed in gas phase measurements. However, interaction of the deprotonated ions with solvent molecules was clearly observed in time-dependent ESI-MS experiments, in which the samples of **2-MeC2** and **2-MeC2** + **TDAC** (1 : 4) were aged (Fig. 4b and c). The interaction of **2-MeC2** with methanol or acetonitrile resulted in mono- and di-*O*-methylation products and methanol adducts (see ESI,† Scheme S1). The characterization of the *O*-methylation products was verified by collision induced dissociation (CID) experiments (see ESI,† Fig. S6).

In conclusion, we have utilized a simple organic diamine, *trans*-1,4-diaminocyclohexane, **TDAC**, to deprotonate the 2-methyl-resorcinarene and were able to isolate the mono- and tetra-anions. The mono-anion **1** forms, with the help of two water molecules and two methanol molecules, an unprecedented fully closed and charge-neutral hydrogen bonded dimeric capsule which has an extremely high packing coefficient PC of 84.2% for the *trans*-1,4-diammoniumcyclohexane as the guest. The X-ray crystal structure of **2** not only proves the existence of the tetra-anion in solid state, but reveals two structural isomers of it. The isomers, which occur in the same crystal lattice with a position of 50% occupancy each, show the same deprotonation pattern for the three hydroxyl groups and the difference between **2a** and **2b** occurring with the deprotonation of the fourth hydroxyl group at one "corner" of the resorcinarene skeleton in such a way that it does not affect the overall conformation of the tetra-anion, being C_{4v} for both isomers.

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