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A rigid octacationic tetraviologen-based cyclophane, TVBox$^{8+}$, is reported. It possesses a highly electron-deficient rectangular cavity with a length of 23 Å and width of 6.1 Å and is capable of encapsulating either two small π-aromatic guest molecules, such as PhMe and PhCl, simultaneously, or one large molecule, e.g., bis-1,5-dinaphtho[50]crown-14.

The past several decades have witnessed a significant advance in chemistry beyond the molecule that has played in the field of mechanically interlocked molecules (MIMs). CBPQT$^{4+}$ tends to bind strongly small π-electron-rich guest molecules, of which 1,5-dioxy-naphthalene and tetrathiafulvalene derivatives are good examples. Recently, the extended versions of CBPQT$^{4+}$—namely ExBox$^{4+}$ (n = 1 and 2)—have also been prepared, exhibiting the ability to bind a wide spectrum of large polyyclic aromatic hydrocarbons (PAHs) and even two guest molecules simultaneously. An attempt to synthesise ExBox$^{4+}$PF$_6$, however, failed on account of its limited solubility. Instead, a derivative (Fig. 1a), Me$_2$ExBox$^{4+}$, which has 12 methyl groups attached to the central p-phenylene bridges, was prepared but alas it has a sterically encumbered binding pocket as a result of repulsive interactions associated with methyl substituents. In order to avoid the solubility and steric issues, we have identified (Fig. 1b) and synthesised an octacationic tetraviologen-based analogue, namely TVBox$^{8+}$, which shares similar dimensions with ExBox$^{4+}$, yet has a much better solubility as a result of its increased charges.

In pursuit of our interest in the stepwise construction of a nontrivial molecular knot—namely, the Borromean rings—from three independent macrocycles, a ‘ring-in-ring’ complex is a required key intermediate. The octacationic TVBox$^{8+}$, which has a highly electron-deficient binding site spanning the length of ~2 nm, has now been explored for its ability to bind electron-rich crown ethers to form ‘ring-in-ring’ complexes. Within the context of this present investigation, three crown ethers—that is, dibenzo[24]crown-8 (DB24C8), bis-1,5-dinaphtho[38]crown-10 (DN38C10) and bis-1,5-dinaphtho[50]crown-14 (DN50C14)—were all examined and shown to form ‘ring-in-ring’ complexes in solution.

The synthesis (Scheme 1) of TVBox$^{8+}$PF$_6$ begins with a Zincke reaction between the Zincke salt of an excess of 1,4-phenylenediamine, leading to the formation of 4·2PF$_6$, following counterion exchange. Subsequently, 4·2PF$_6$ is treated with an excess of 1,4-bis(bromomethyl)benzene, affording, after counterion exchange, the dibromide DB$^+•$PF$_6$. Finally, the TBAI-catalysed cyclisation between DB$^+•$PF$_6$ and 4·2PF$_6$ yields the desired product TVBox$^{8+}$PF$_6$ in 10% yield, following counterion exchange. The relatively low yield can be attributed to the lack of a template and the lower reactivity of both DB$^+$ and 4$^+$. TVBox$^{8+}$PF$_6$ was fully characterised in solution by $^1$H and $^{13}$C NMR spectroscopies, high-resolution mass spectrometry, and
cyclic voltammetry (CV) as well as in the solid-state single-crystal X-ray diffraction. See the ESI† for the full characterization.

![Scheme 1](image)

**Scheme 1** Synthesis of the octacationic cyclophane TVBox•8PF₆.

**Fig. 2** a) Plan view of the TVBox•8PF₆ solid-state structure illustrating the inner dimensions of the cavity (length = 23 Å, width = 6.1 Å). b) Perspective view of the TVBox•8PF₆ solid-state structure showing the torsional angles (65° and 33°) between adjacent pyridinium rings. c) Plan view of the PhCl⊂TVBox•8PF₆ solid-state superstructure illustrating the distance (3.58 Å) between the Cl atoms of the encapsulated PhCl molecules and para-xylene rings. d) Perspective view of the PhCl⊂TVBox•8PF₆ solid-state superstructure illustrating the torsional angles (13.5° and 19.1°) between adjacent pyridinium rings. The hydrogen atoms, counterions, and solvent molecules are omitted for the sake of clarity.

Good quality single crystals of TVBox•8PF₆ were obtained by slow vapour diffusion of iPrO into a MeCN solution. The solid-state structure (Fig. 2a, b) reveals that the octacationic cyclophane possesses C₂ symmetry with a two-fold rotation axis running orthogonally through the center of the cavity. With a length of 23 Å and a width of 6.1 Å, it shares a similar geometry to that of Me₃ExBox⁺, and can accommodate multiple small guest molecules or potentially one guest molecule with large extended aromatic surfaces. The two torsional angles between the adjacent pyridinium units are ~33° and ~65°, respectively, which are larger than the average¹⁰ torsional angle (~20°) present in CBPQT⁺, and are a consequence presumably of minimizing the steric repulsion arising from the pyridinium and central p-phenylene groups.

![Fig. 3](image)

**Fig. 3** Comparison of cyclic voltammograms (DMF, 0.1 M TBAPF₆, 200 mV·s⁻¹) of solutions of a) DB⁺⁺ (1 mM) and b) TVBox⁺⁺ (0.5 mM).

The redox properties of DB⁺⁺ and TVBox⁺⁺ were investigated (Fig. 3) by CV. The first reduction wave of DB⁺⁺ is a two-electron process occurring (Fig. 3a) at a peak potential of ~190 mV, in which one electron is transferred to each bipyridinium unit to yield the diradical dication DB⁺⁺, an observation which indicates that the two bipyridinium units behave independently in spite of the existence of the p-phenylene bridge. The second two-electron reduction occurs in two separate processes with peak potentials of ~500 and ~620 mV, corresponding to the reduction of the two remaining bipyridinium radical cations. The separation suggests that the redox units of the whole molecule begin to couple electronically with each other after the first reduction process, as observed for many organic mixed-valence compounds. The CV of TVBox⁺⁺ shows (Fig. 3b) almost identical reduction processes, indicating that the two bis-(bipyridinium) units which constitute the walls of the box are not communicating in the first two-electron reduction, once again because of the nonplanarity of the p-phenylene bridges. The nature of the second two-electron process, however, suggests the onset of coupling between the bipyridinium radical cations through the p-phenylene bridges.

In the light of the fact that ExBox⁺⁺ can accommodate two aromatic molecules, the encapsulation of two aromatic guest molecules was also explored in the case of TVBox⁺⁺. It was found that two molecules of either PhMe or PhCl can be encapsulated, as evidenced by the solid-state superstructures obtained by performing X-ray crystallography on a single crystal following slow vapour diffusion of iPrO into the solution of TVBox⁺⁺ in MeCN containing 50 equiv of PhMe or PhCl. The solid-state superstructure (Fig. 2c, d) of PhCl⊂TVBox⁺⁺ demonstrates that two PhCl molecules are located at each end of the cavity, leaving its center unoccupied. The significantly decreased torsional angles (13.5° and 19.1°) and the short contacts (3.57 Å)
between Cl atoms and the centroid of the p-xylene units demonstrate that the encapsulated PhCl molecules are stabilised cooperatively as a result of both aromatic π–π stacking and [Cl⋯−π] interactions.\(^{19}\) In addition, two more PhCl molecules are lined up in an aromatic π–π stacking motif alongside each viologen subunit of TVBox\(^8^+\). In the case (Fig. S15) of PhMe, the encapsulated molecules are stabilised cooperatively as a result of both aromatic π–π stacking and [C–H⋯π] interactions.

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Fig. 4 Partial \(^1\)H NMR spectra (500 MHz, CD\(_3\)CN) of a) TVBox\(^8^+\)PF\(_6^−\), b) DN50C14 and 1:1 molar mixture of DN50C14 and TVBox\(^8^+\)PF\(_6^−\) at c) 298, d) 293, e) 283, f) 273 and g) 263 K. The cross denotes CHCl\(_3\).

Encouraged by these findings, we surmised that π-electron-rich crown ethers could potentially enter the cavity to form ‘ring-in-ring’ complexes by virtue of cooperative aromatic π–π stacking, [C–H⋯π] interactions and possibly also [C–H⋯O] interactions between the bipyridinium units and polyether loops. Three crown ethers—namely, DB24C8, DN38C10 and DN50C14 bearing π-electron-rich aromatic units with different lengths of polyether loops were investigated by \(^1\)H NMR spectroscopy in CD\(_3\)CN. Fig. 4c shows \(^1\)H NMR spectra recorded at 298 K for a 1:1 molar ratio of TVBox\(^8^+\)PF\(_6^−\) and DN50C14, along with spectra (Fig. 4a, b) of the free components. The resonances for the aromatic protons in DN50C14 are moved upfield and signals corresponding to TVBox\(^8^+\) are also shifted and broadened. The \(^1\)H–\(^1\)H NOESY NMR spectrum (Fig. S12) of the complex reveals that the DNP rings of DN50C14 are located at the ends of the cavity and the polyether loops are folded and are directed top and bottom of the long sides of TVBox\(^8^+\). All these observations indicate the complexation of DN50C14 by TVBox\(^8^+\) in line with previous studies.\(^{15a,16}\) The variable temperature (VT) \(^1\)H NMR spectra (Fig. 4c-g) were also recorded on the same 1:1 molar mixture. As the sample was cooled, significant upfield shifting and broadening of the aromatic signals of DN50C14, in particular for H\(_{28}\), occurs, illustrating that the complex becomes more stable at lower temperatures. Furthermore, since the upfield shifts originate from the mutual shielding effect of aromatic rings, those protons that are shifted most of all overlap to a greater extent with aromatic rings in the host. On the basis of these observations, it can be concluded that the 1,5-dioxynaphthalene (DNP) units of DN50C14 adopt a perpendicular orientation inside the cavity of TVBox\(^8^+\) with H\(_{28}\) pointing towards the p-xylene plane as in the energy minimized structure (Fig. 5). This co-conformation is also evidenced by the observation that the shifts of protons H\(_2\) and H\(_3\) on TVBox\(^8^+\) are greater than those of other signals arising from the host. All these observations support the formation of a ‘ring-in-ring’ complex, in which the crown ether resides inside of the cavity. Similar changes in chemical shifts are also observed (Fig. S7 and S9) for the equimolar mixtures involving the other two crown ethers and TVBox\(^8^+\), implying that both DB24C8 and DN38C10 form similar ‘ring-in-ring’ complexes with TVBox\(^8^+\) in solution.

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Fig. 5 Plan a) and side-on b) views of stick representations of the energy minimized structure of DN50C14\(^8^+\)TVBox\(^8^+\) by MM3.

The binding ratios between crown ethers and TVBox\(^8^+\) were determined by Job plots (Fig. S5), revealing a 1:1 binding ratio for all three crown ethers, confirming the formation of ‘ring-in-ring’ complexes. Subsequently, \(^1\)H NMR titrations were performed (Fig. S10) to determine the binding constants between each crown ether and TVBox\(^8^+\). The titration of DN50C14 into a solution of TVBox\(^8^+\) resulted in continuous changes in the chemical shifts of the host proton resonances. By employing the software program Dynafit\(^{17}\) with a 1:1 binding model, the binding constant between DN50C14 and TVBox\(^8^+\) was determined to be 1430 M\(^{-1}\). The same experimental approach was applied (Fig. S6 and S8) to the other two crown ethers and the results are summarised in Table 1. Given the fact that DN38C10 fits \(^{18}\) perfectly inside ExBox\(^8^+\) and that TVBox\(^8^+\) is 4 Å longer than ExBox\(^8^+\), it is obvious that DN38C10 is not large enough to occupy the cavity of TVBox\(^8^+\) fully with maximum interactions, an outcome which leads to its lower binding affinity. The larger crown loop of DN50C14 allows its two DNP units to position themselves close enough to both electron-deficient portions inside TVBox\(^8^+\), thus maximising both π–π stacking and [C–H⋯π] interactions. As a result, DN50C14 enjoys the highest binding affinity of all. By contrast, the even shorter DB24C8 can barely interact with both electron-deficient portions of the host simultaneously, resulting in the lowest binding affinity.

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**Table 1 Thermodynamic parameters for three ‘ring-in-ring’ complexes**

| Guest | \(K_b \times 10^9 \text{(M}^{-1}\) | \(|AG| \text{ (kcal*mol}^{-1}\) |
|-------|------------------------|------------------|
| DB24C6 | 0.59 ± 0.03 | −3.78 ± 0.06 |
| DN38C10 | 0.63 ± 0.03 | −3.82 ± 0.06 |
| DN50C14 | 1.43 ± 0.07 | −4.30 ± 0.06 |

The binding constant was determined by \(^1\)H NMR titration at room temperature.

We have described the synthesis and characterisation of a novel rigid octacationic cyclophane, TVBox\(^8^+\). This tetraviologen-based cyclophane possesses a ~2 nm long highly electron-deficient box-shaped binding pocket, which is capable of encapsulating either two π-aromatic guest molecules, such as PhMe and PhCl, concurrently, or a single aromatic crown ether with varying polyether loop lengths. The binding affinity between TVBox\(^8^+\) and DN50C14 in MeCN is as high as ~1400 M\(^{-1}\), meaning that this 1:1 complex can, in principle, be used as a building block for the construction of molecular Borromean rings in a stepwise manner.
Notes and references