Metal directed assembly of ditopic containers and their complexes with alkylammonium salts†

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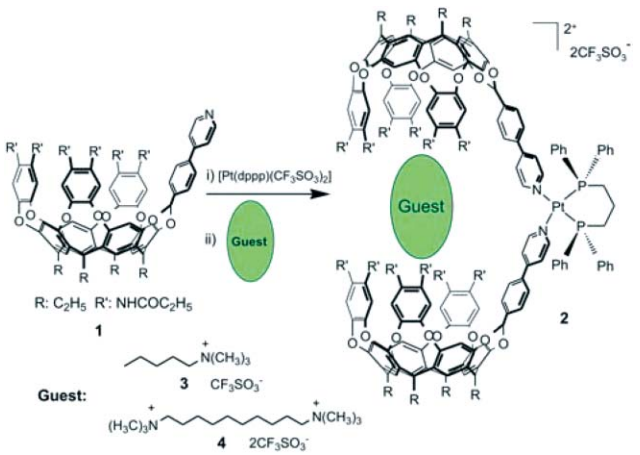
A new self-folding cavitand has been assembled through metal coordination to give a thermodynamically stable ditopic receptor of nanosize dimensions which has been used in the reversible binding of di-alkylammonium and *n*-alkylammonium salts.

Molecule-within-molecule complexes can be formed irreversibly, as in carcerands,[1] or reversibly, as in self-assembled capsules.[2] In between, hemicarcerands with larger portals offer a possibility for the guest to move in and out more or less freely.[3] These supramolecular structures can be formed through covalent bonds[4,5] or through metal–ligand interactions.[6] The advantages of using transition metals in the self-assembly involve the greater directionality offered by metal–ligand coordinative bonds relative to weak electrostatic and π–π stacking interactions or even hydrogen bonds and the higher kinetic stability of the coordinative bonds. Both depend on selection of the appropriate metal precursors and ligands.[7] We report here a new type of cavitand **1** which combines the advantages of a deep vase-like cavity obtained through a network of hydrogen bonds and the presence of a phenylpyridyl group able to coordinate to a square-planar metal complex like $[Pt(dppp)(CF_3SO_3)_2]$. A thermodynamically stable molecular dimer **2** of nanosize dimensions is formed (Scheme 1).



Scheme 1 i) Self-assembly of **2** by mixing **1** and $[Pt(dppp)(CF_3SO_3)_2]$; ii) Inclusion of alkylammonium salts **3**, **4** in molecular dimer **2**.

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The binding of di-alkylammonium salt, decamethonium ditriflate **4**, known to be a nicotinic antagonist at the neuromuscular junction,[8] was analyzed by ^{1}H NMR and ESI-MS to study the cooperative effect of the two concave surfaces relative to the binding of a standard *n*-alkylammonium salt.

The monofunctionalized phenylpyridyl hexaamide cavitand **1** was prepared by reacting hexaamide diol cavitand[5f] with 4-4′-(α,α′-dibromotolyl)pyridine[6] in DMF; this reaction is completely stereoselective due to the size of the phenylpyridyl group which can not be easily accommodated inside the resorcinarene cavity. A crystal structure of cavitand **1** was obtained from CH_2Cl_2/EtOH (Fig. 1), which shows that the amide groups at the upper rim of the cavitand form a seam of six hydrogen bonds which maintain the cavitand in a vase conformation. In the solid state this cavitand is able to include a phthalimide molecule which fills the space of the cavity and shows π–π interactions with the aromatic walls. A water molecule is also present in the cavity and it forms a hydrogen bond with a carbonyl group at the upper rim of the cavitand. The orientation of the phenylpyridyl moiety is "outward", in the correct geometry for the self-assembly of a ditopic receptor.

Large nanoscale molecular containers obtained through covalent bonds generally exist as C-shaped and S-shaped diastereoisomers.[9] They are generally separated through chromatographic techniques and characterized using 2D NMR spectrometry. In contrast, metal connected ditopic cavitand complexes can be obtained in quantitative yield following the typical cage self-assembly protocol.[10] The ditopic structure **2** was obtained by mixing cavitand **1** with $[Pt(dppp)(CF_3SO_3)_2]$ (2 : 1 molar ratio) at room temperature in acetone. The exclusive formation of the desired *cis* ditopic complex was dictated by the presence of the bidentate dppp ligand. The self-assembly of **2** was monitored by ^{1}H NMR (Fig. 2). Addition of $[Pt(dppp)(CF_3SO_3)_2]$ (0.5 equivalents) to a solution of cavitand **1** in acetone-d_6 (4 : 1 ratio) gave as the

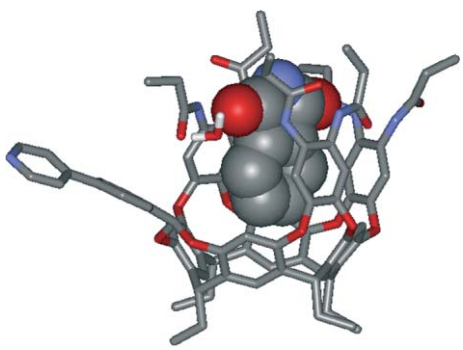

Fig. 1 X-ray crystal of cavitand **1** crystallized from CH_2Cl_2/EtOH.

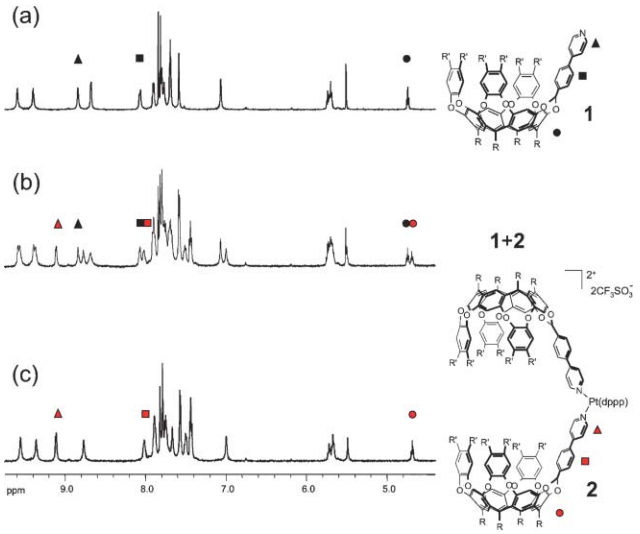

Fig. 2 Self-assembly of molecular dimer **2** in acetone-d_6: (a) Free cavitand **1**; (b) Cavitand **1** + [Pt(dppp)$(CF_3SO_3)_2$] 4 : 1; (c) Cavitand **1** + [Pt(dppp)$(CF_3SO_3)_2$] 2 : 1.

only species present in solution the free cavitand and the ditopic complex. No evidence of partially complexed products could be detected. After the addition of another 0.5 equivalents of the metal complex (2 : 1 cavitand/metal complex final ratio), only the ditopic receptor **2** was present in solution. The first coordination of cavitand **1** on the Pt center facilitates the entrance of the second cavitand molecule, driving the reaction to the thermodynamically favored final product which is obtained in quantitative yield. Further evidence of the formation of **2** was obtained by ESI-MS, which recorded prominent peaks at $[(MH)^+ - CF_3SO_3]^{2+} = 1793$ and $[M - 2CF_3SO_3]^{2+} = 1718$.

Large nanoscale host molecules rarely show kinetically stable complexes,[9,11] since the large holes in their structures permit fast entry and exit of solvents and most guests. The corresponding NMR chemical shift changes describe an average of the guest's many environments. Alkylammonium salts **3** and **4** have been used in host–guest complexation experiments with cavitand **1**. These guests form kinetically stable 1 : 1 inclusion complexes on the NMR timescale in acetone-d_6 at low temperatures (273 K, 253 K; see ESI†). The electron-rich aromatic surfaces of the host provide cation–π attractions with the partially positive hydrogens on the surface of the guests. ESI-MS clearly shows that in both cases only one guest molecule is contained in the gas phase in cavitand **1** (prominent peak at [**3@1**-$CF_3SO_3]^+$; [**4@1**-$CF_3SO_3]^+$, Table 1).

The affinity of **3** and **4** for this kind of cavity is relatively low; the presence of the phenylpyridyl group interrupts the network of hydrogen bonds and changes the shape of the cavity to something more elliptical than spherical (see structure of cavitand **1**, Fig. 1). As a result the guests move rapidly in and out from the cavity at room temperature.

In order to reduce the guest exchange rate and form inclusion complexes with a higher kinetic stability we decided to test the binding performance of molecular dimer **2**. In this case the preorganization of the two cavities obtained by metal-directed self-assembly reduces the exchange rate in the case of di-alkylammonium **4** compared to *n*-alkylammonium **3**. In the self-assembled dimer **2** the two trimethylammonium "knobs" of **4** are

Table 1 Data of alkylammonium salts included in cavitand **1** and dimer **2**

Guest	Host	K_a[a] (253 K)	ΔG°/ Kcal mol^{-1}	ESI-MS X: $CF_3SO_3^-$
3	**1**	20 M^{-1}	−1.5	[**3@1**-X]$^+$ = 1491
4	**1**	15 M^{-1}	−1.4	[**4@1**-X]$^+$ = 1821
				[**4@1**-2X]$^{2+}$ = 836
3	**2**	2100 M^{-2}	−3.8	[(2***3@2**)-2X]$^{2+}$ = 1997
				[(2***3@2**)-3X]$^{3+}$ = 1281
4	**2**	95 M^{-1}	−2.3	[**4@2**-2X]$^{2+}$ = 1996
				[**4@2**-3X]$^{3+}$ = 1281

[a] Hosts **1** or **2** at 2 mM were mixed with guests **3** or **4** at ~30 mM concentration in acetone-d_6. The relative binding affinities were determined by direct integration of the corresponding $N(CH_3)_3$ peaks of the encapsulated and free guests.

simultaneously coordinated in the cavities: ESI-MS shows prominent peaks in the gas phase consistent with 1 : 1 inclusion complex **4@2** (Table 1).

^{1}H NMR studies of complex **4@2** show inclusion signals already at 300 K; at 273 K two different $N(CH_3)_3$ peaks can be clearly seen. This slight difference in the chemical shifts may be due to the different arrangement of hydrogen bonds at the upper rim of the cavitands; they can be either clockwise or anti-clockwise (Fig. 3).

As already mentioned inclusion of *n*-alkylammonium molecules **3** in molecular dimer **2** (2***3@2**) yields a complex with lower kinetic stability: to follow the complexation by NMR the experiment has to be performed at 253 K where the two cavities of **2** are simultaneously occupied by two trimethylammonium "knobs" and no evidence of inclusion of a single guest molecule **3** could be

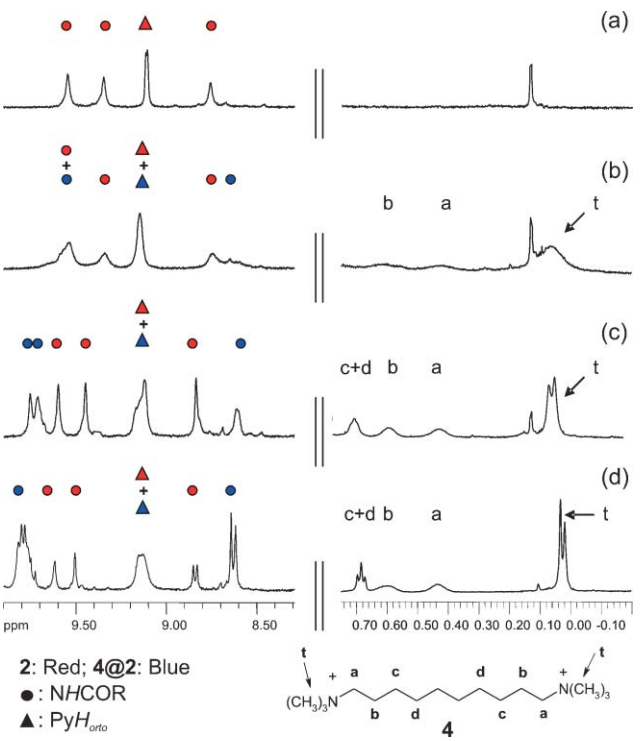

Fig. 3 Downfield and upfield regions of the ^{1}H NMR (600 MHz, acetone-d_6): (a) Molecular dimer **2**, 300 K; (b) **4@2**, 300 K; (c) **4@2**, 273 K; (d) **4@2**, 253 K. At [**2**] = 2 mM; [**4**] = 35 mM.

detected (see ESI†). Further evidence of the formation of 2 : 1 inclusion complex (2***3**@**2**) was obtained by ESI-MS (Table 1).

The thermodynamic data relative to inclusion complexes **4@2** and (2***3**@**2**) show a different trend (Table 1). The ΔG° of the former is lower because the longer guest **4** has to modify its conformation to adapt to the shape of **2**. The two shorter guests **3** are included in the cavities independently each other and they do not have to modify their conformations (see ESI†).

In order to investigate if the intramolecular process that takes place between guest **4** and dimer **2** shows a cooperative effect over the intermolecular one that occurs between guest **3** and dimer **2**, the effective molarity (EM) was evaluated, which is defined as the ratio K_{intra}/K_{inter}.[12] When the concentration of binding sites is lower than the EM, the intramolecular binding is favored over the intermolecular one, whereas the opposite occurs when the concentration of binding sites is greater than the EM. Therefore, an intramolecular process could display positive or negative cooperativity depending on the concentration. In our case the binding constant for the inclusion complex (2***3**@**2**) can be obtained from the independent contribution of two intermolecular interactions and can be written as $K_{a(2*\mathbf{3}@\mathbf{2})} = K_{inter}$.[2] In the other case $K_{a(\mathbf{4}@\mathbf{2})}$ is obtained from an intermolecular process and an intramolecular one, it can be written as $K_{a(\mathbf{4}@\mathbf{2})} = 2K_{intra}K_{inter}$ (see ESI†). From these data we calculate that EM = $K_{a(\mathbf{4}@\mathbf{2})}/2K_{a(2*\mathbf{3}@\mathbf{2})} = 2.2$ mM. Thus if [**2**] $\leqslant$ 1.1 mM the inclusion of **4** takes place with a positive cooperative effect gained from the preorganization of the self-assembled structure.

In conclusion, the self-assembled container reported here represents a new species of molecular host, distinct from the covalently sealed carcerands and the reversibly formed hydrogen-bonded capsules. It is formed by metal-directed self-assembly in quantitative yield, has nanoscale dimensions and is able to reversibly bind di-alkylammonium salt **4**. The formation of the inclusion complex **4@2** is slow on the NMR time scale and takes place with cooperative effect if performed at host concentration lower than 1.1 mM. The application of this host as a sensor for chemical analysis or as a reaction chamber is underway.‡

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Notes and references

‡ Crystal data of **1**: $C_{93}H_{94}N_8O_{18}$, $M = 1611.76$, Temperature: 183(2) K, Wavelength: 0.71073 Å, Monoclinic, space group: $P2_1/n$ (No. 14, C_{2h}^5), $a = 11.284(2)$ Å, $b = 26.028(5)$ Å, $c = 28.804(6)$ Å, $\alpha = 90^{\circ}$, $\beta = 92.98(3)^{\circ}$, $\gamma = 90^{\circ}$, Volume: 8448(3) Å^3, Z: 4, Density: 1.267 Mg m^{-3}, Absorption coefficient: 0.089 mm^{-1}, $F(000)$: 3408, Crystal size: 0.32 × 0.15 × 0.04 mm, θ range for data collection: 1.06 to 22.50°, Limiting indices $-12 \leqslant h \leqslant 12$, $-26 \leqslant k \leqslant 28$, $-31 \leqslant l \leqslant 31$, Reflections collected: 49055, Independent reflections: 11037 ($R_{int} = 0.1450$), Completeness to $\theta = 25.00^{\circ}$: 99.9%, Absorption correction: Empirical, Max. and min. transmission: 0.9965 and 0.9722, Refinement method: Full-matrix least-squares on F^2, Data/restraints/parameters: 11037/5/1050, Goodness-of-fit on F^2: 1.131, Final R indices $I > 2\sigma(I)$: $R1 = 0.1293$, $wR2 = 0.3080$, R indices (all data): $R1 = 0.1956$, $wR2 = 0.3467$, Extinction coefficient: 0.0074(6), Largest diff. peak and hole: 0.980 and −0.612 e Å^{-3}. CCDC 278172 & 278173. See http://dx.doi.org/10.1039/b509189f for crystallographic data in CIF or other electronic format.

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