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Self-assembly of a ternary architecture driven by cooperative Hg^{2+} ion binding between cucurbit[7]uril and crown ether macrocyclic hosts[†]

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A novel supramolecular assembly comprising CB[7], styrylpyridinium dye (1) and Hg^{2+} forms in aqueous solution based on the hydrophobic effect and metal–ligand and ion–dipole interactions. The binding of Hg^{2+} to 1·CB[7] displays positive cooperativity relative to 1 itself.

Nature relies on an intricate network of covalent reactions and non-covalent interactions to produce higher order structure and function. Among the processes driven by non-covalent interactions (*e.g.* hydrogen bonds, electrostatic interactions, hydrophobic effect) within natural systems those that display high cooperativity are particularly prized.¹ Systems that display high cooperativity often display all-or-nothing assembly processes which can be used as the basis of molecular switches or machines.² Accordingly, much work has been directed toward understanding the fundamentals of cooperative systems and their utilization to create complex functional systems.

We, and others, have been studying the synthesis and recognition properties of a class of molecular containers known as cucurbit[*n*]urils (CB[*n*], Scheme 1).³ CB[*n*] are pumpkin-shaped macrocycles comprising *n* glycoluril units connected by 2n CH₂-groups which feature two identical ureidyl carbonyl portals.² CB[*n*] compounds undergo high affinity, highly selective interactions in water with cationic species (*e.g.* metal cations and ammonium ions) at their portals and with hydrophobic species by inclusion in the inner cavity.³ Accordingly, CB[*n*] compounds have been used as building blocks for the creation of functional molecular systems like supramolecular polymers, sensing ensembles, molecular machines, and drug delivery systems.⁴

In most CB[n]-based systems, the presence of metal ions reduces the binding affinity of host toward guest due to competitive binding of metal ion at the ureidyl C=O portal of CB[n] resulting in dissociation of the host-guest complex.⁵



Scheme 1 Chemical structure of CB[7], styrylpyridinium dye 1 and competitive ligand 2.

Notable cases where addition of metal ion to CB[n] host-guest assemblies results in a distinct three component assembly include Mohanty's thioflavin T-CB[7] and Pang's squaraine dye CB[8] systems.⁶ We have been working toward marrying the recognition properties of the CB[n] family with the outstanding optical properties of styrylpyridinium dyes with an eye toward creating stimuli (e.g. photochemical or metal ion) responsive molecular machines.7 We choose styryl dyes for these studies because of their intense absorption in an analytically favorable region of the UV/Vis spectrum and the wide application for optical detection in biological systems.⁸ Recently, we reported host-guest complex formation of CB[7] with crown ether derived cationic styryl and bis(styryl) dyes possessing pyridinium moiety.⁷ In this paper, we exploit the combined ability of electrostatically negative ureidyl C=O portal of $CB[n]^{3,9}$ and the dithia-dioxa-monoaza crown ether moiety of styryl dye 19 to bind to Hg^{2+} ions to create a three component system that displays positive cooperativity.

To achieve this goal the *N*-methyl 4-styrylpyridinium dye derivatized with dithia-dioxa-monoaza 15-crown-5 residue (1) was synthesized according to the reported method.⁹ The binding properties of 1 with CB[7] or Hg²⁺ ions were investigated in aqueous solution by UV-Vis and NMR spectroscopy. The UV-Vis spectrum of 1 in water (Fig. 1) is characterized by a very intense long wavelength absorption band (LAB) centered at 456 nm ($\varepsilon = 2.81 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). This band is assigned to an efficient intramolecular charge transfer (ICT) process from the donor nitrogen atom of the crown ether moiety to the acceptor

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Fig. 1 UV-Vis spectra recorded (black lines) for a mixture of CB[7] (100 μ M) and **1** (20 μ M) upon addition of Hg(ClO₄)₂ (0–240 μ M). The bold lines correspond to the spectra of: (1) free **1**, (2) CB[7]·**1**, (3) **1**·Hg²⁺, and (4) CB[7]·Hg²⁺·**1**.

pyridinium ring. Addition of CB[7] to a solution of 1 results in a moderate bathochromic shift ($\Delta \lambda_{max} = 26 \text{ nm}$) of the LAB, which is diagnostic for inclusion of 1 in a less polar environment (Fig. 1). The spectrophotometric titration data fits well to a 1:1 CB[7].7 binding model which allowed us to determine the association constant for the CB[7]·1 complex (log $K = 5.36 \pm 0.02$). Separately, we added Hg^{2+} to a solution of **1** in water and observed that the intensity of the absorption maximum of free 1 at 456 nm gradually decreased along with the formation of a new band centered at 346 nm (Fig. 1). The coordination of the Hg^{2+} ion to styryl dye 1 decreases the electron-donating ability of the crown ether residue which in turn makes the ICT process unfavorable which results in a large blue shift ($\Delta \lambda_{max} = 110 \text{ nm}$) of the LAB. The highly effective complexation of Hg^{2+} by **1** is achieved due to formation of strong $Hg^{2+} \cdots S$ interactions in the dithiadioxa-monoaza crown terminus of 1.9 It was not possible to extract a value of K_a for the interaction between 1 and Hg²⁺ from this titration because the lack of well defined isosbestic points (Fig. S8) suggests that the interaction model is complex most likely due to Hg^{2+} hydrolysis in water.

Next, we examined the behaviour of the ternary system comprising 1, CB[7], and Hg^{2+} ion in aqueous solution. For this purpose, we measured the UV/Vis spectral changes of a solution of 1 (20 μ M) and CB[7] (100 μ M, corresponding to >95% complexation of 1) as the concentration of Hg^{2+} ions was increased (Fig. 1). In sharp contrast to our related earlier work⁷ – which showed competitive binding at the ureidyl C=O portals of CB[7] and therefore complex dissociation upon addition of metal ions $(Mg^{2+}, Ba^{2+}, Zn^{2+}, Cu^{2+})$ – the addition of an excess of Hg^{2+} ions (up to 10 eq.) in the form of $Hg(ClO_4)_2$ does not lead to the appearance of the absorption spectra characteristic of the individual components or the binary complexes 1·Hg²⁺ and CB[7]-Hg²⁺. We conclude that the addition of Hg²⁺ does not cause dissociation of CB[7]·1 complex. On the contrary, the addition of Hg^{2+} ions to solutions containing 1 and CB[7] results in a new absorption band centred at 361 nm, which is ascribed to the formation of the CB[7] $Hg^{2+} \cdot 1$ ternary complex. This band is red-shifted by 15 nm relative to the absorption of the 1·Hg²⁺ complex and substantially blue-shifted by 95 and 121 nm with respect to the absorption of free dye 1 and the CB[7]·1 complex, respectively (Fig. 1).

In order to confirm the cooperative character of the ternary complex $CB[7] \cdot Hg^{2+} \cdot 1$ formation (Scheme 2) we measured the relative stability constants of CB[7] Hg^{2+} 1 and 1 Hg^{2+} complexes by competitive spectrophotometric titration with crown ether 2 as competitor (ESI[†]). In both cases, increasing the concentration of competitor 2 results in the displacement of Hg^{2+} ions from the cavity of 1 and formation of the 2·Hg²⁺ complex (Fig. 2). The displacement of Hg^{2+} ion from the ternary CB[7]·Hg²⁺·1 complex requires a much larger excess of competitor than the displacement of the same amount of Hg^{2+} ions from the binary $1 \cdot Hg^{2+}$ complex. The competitive titration data showed that the ratio of the ternary complex stability constant $(CB[7] \cdot Hg^{2+} \cdot 1)$ to the binary complex stability constant $K_{\rm B}/K_{\rm A}$ is equal to 25, that is, ${\rm Hg}^{2+}$ affinity for CB[7]·1 is about 25 times greater than the Hg^{2+} affinity for free 1. We attribute the dramatic increase in the binding of CB[7]·1 toward Hg^{2+} relative to free 1 to the formation of $C = O \cdots Hg^{2+}$ coordination interactions between CB[7] and Hg^{2+} in the CB[7]·Hg^{2+}·1 complex. All the available evidence establishes that the CB[7]·Hg²⁺·1 ternary complex forms with positive cooperativity.

To provide evidence of the three dimensional geometry of the CB[7]·Hg²⁺·1 complex we performed ¹H NMR spectroscopy measurements of the various components and the complexes (Fig. 3). The ¹H NMR assignments were established by a combination of 2D NMR techniques including COSY and ROESY (ESI†). The ¹H NMR spectra recorded for free 1 and the CB[7]·1 in D₂O (Fig. 3b) show that the signals for the



Scheme 2 Schematic representation of the geometry of CB[7]·1 and CB[7]· Hg^{2+} ·1, and an MMFF minimized geometry of the ternary complex CB[7]· Hg^{2+} ·1.



Fig. 2 Absorbance values recorded for the $1 \cdot \text{Hg}^{2+}$ and $\text{CB}[7] \cdot \text{Hg}^{2+} \cdot 1$ complexes at 480 nm as a function of the concentration in competitor 2 in H₂O ([1] = 2.0×10^{-5} M; [CB[7]] = 1.0×10^{-4} M; [Hg²⁺] = 1.0×10^{-4} M, [2] = $0 - 3.2 \times 10^{-4}$ M).



Fig. 3 ¹H NMR spectra (600 MHz, D_2O) for: (a) **1** and Hg^{2+} (1.6 eq.), (b) **1** and CB[7] (1.1 eq.), and (c) **1**, CB[7] (1 eq.) and Hg^{2+} (1.3 eq.).

pyridinium (H2, H6, H3, H5), ethylene (H7, H8), and aromatic (H10, H14) ring protons are significantly upfield shifted in the CB[7]·1 complex whereas the aromatic ring (H11, H13) protons and CH₂-groups (H_a-H_e) are downfield shifted. The direction and magnitude of these shifts allowed us to deduce the geometry of the complex based on the fact that the CB[7] cavity constitutes a shielding region whereas the region just outside the portals constitutes a deshielding region.¹⁰ We propose that the vinyl-pyridinium unit of 1 is located inside the hydrophobic cavity of CB[7] whereas the crown ether residue is outside the CB[7] cavity in the CB[7]·1 complex (Scheme 2).

The binding interactions between 1 and Hg²⁺ ions also can be conveniently monitored by ¹H NMR spectroscopy. Upon addition of 1.6 eq. of Hg(ClO₄)₂ to an aqueous solution of 1, the resonances for the most protons demonstrate downfield shifts, compared to chemical shifts in the absence of Hg²⁺, due to the complexation induced decrease in electron density on CH₂-groups adjacent to the N, S, and O-atoms of crown ether 1 (ESI[†]). The most noticeable effect was observed for the H10, H14 and H11, H13 protons of aromatic ring ($\Delta \delta = 0.24$ and 0.74 ppm, respectively) and the H8 ethylene proton ($\Delta \delta = 0.27$ ppm). It should be noted that the resonances for the dithia–dioxa–monoaza crown moiety are significantly broadened (Fig. 3a). This pattern of complexation-induced chemical shifts can be attributed to the coordination of Hg²⁺ inside the crown ether ring of 1.

The pattern of changes in the ¹H NMR spectrum recorded for solutions containing ternary complex $CB[7] \cdot Hg^{2+} \cdot 1$ (Fig. 3c) are similar to those observed for its binary constituents (e.g. CB[7]·1 and $1 \cdot \text{Hg}^{2+}$). For example, the resonances for the vinylpyridinium unit of 1 are upfield shifted by 0.32-0.57 ppm relative to free 1 which is due to the shielding effect of the CB[7] cavity. At the same time the resonances of the dithiadioxa-monoaza crown moiety (Ha-Hc) undergo downfield shifts by 0.13–0.57 ppm and become distinctly separated. This pattern of complexation induced shifts indicates that the $CB[7] \cdot Hg^{2+} \cdot 1$ complex assumes the geometry shown in Scheme 2. In this well-organized ternary complex, the components are arranged in such a way that the Hg²⁺ ion is complexed by two macrocycles, namely the cavity of crown ether and the one of the oxygen portals of CB[7]. Simultaneously, the remote portal of CB[7] interacts with the pyridinium unit of 1 by ion-dipole interactions.

Unfortunately, we were unable to obtain single crystals of the CB[7]·Hg²⁺·1 complex that were suitable for X-ray analysis. Nevertheless, the MMFF minimized geometry of the CB[7]·Hg²⁺·1 complex (Scheme 2) is completely congruent with the proposed structure.

In summary, we have demonstrated that mixtures of 1, CB[7], and Hg²⁺ form ternary complex CB[7]·Hg²⁺·1 in a process that displays substantial positive cooperativity. The Hg²⁺ ion simultaneously coordinates to the ureidyl C=O portals of CB[7] and the crown ether moiety of 1. Because the geometry of the binary CB[7] \cdot 1 binary and ternary CB[7] \cdot Hg²⁺ \cdot 1 complexes are similar, the addition of metal ion does not involve a substantial shuttling motion of the components. It is straightforward, however, to imagine that lengthening of the linker between the styrylpyridinium and crown ether moieties would result in complexes that would undergo shuttling processes in response to the addition of metal ions. As such, we believe that CB[7] styrylpyridinium derived systems hold promise as components of more complex molecular machines and sensing systems that function in biologically relevant aqueous media.

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