Remarkable Salt Effect on Stability of Supramolecular Complex between Modified Cueurbit[6]uril and Methylviologen in Aqueous Media

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Remarkable Salt Effect on Stability of Supramolecular Complex between Modified Cucurbit[6]uril and Methylviologen in Aqueous Media

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The supramolecular complex formed by partial inclusion of methylviologen in MeCB6 was described both in solution and in the solid state. The association constant of the complex was determined using ^{1}H NMR and UV−vis spectrophotometric titration. An extraordinary 2000-fold drop in the association constant of the complex was observed when pure water was replaced by 50 mM NaCl solution.

Introduction

Cucurbit[*n*]urils (**CB*n***) are macrocyclic compounds consisting of *n* glycoluril units connected by 2*n* methylene bridges.[1] The shape of the macrocycle resembles a hollow barrel with a hydrophobic interior and partially negative charged rims of carbonyls on both sides of the macrocycle. This structure makes the macrocycles suitable to bind organic guests bearing one or more positive charges in their structures.[2] Synergy of the hydrophobic effect and ion−dipole interactions results in unprecedented strength and selectivity of binding between **CB*n*** and some of the guests in aqueous media. For example, an association constant 3×10^{15} M^{-1} between **CB7** and 1,1′-bis(trimethylammoniummethyl)ferrocene was recently reported, which is comparable to that of the biotin−avidin complex.[3] High selectivity of **CB6** was demonstrated in the case of propanediamine, which binds to this macrocycle 60 000-fold higher compared to butanediamine.[4] On the other hand, poor solubility in common solvents and difficult modification of the surface limit the applications of the **CB*n***. These problems were overcome by Kim's group by the preparation of hydroxylated **CB*n***, which showed good solubility in DMSO and their further derivatization was also demonstrated.[5] There are few other examples of modified **CB** derivatives from **CB5** and **CB6** homologues, where one or more hydrogen atoms at the periphery are substituted by various groups including methyl, phenyl, and cyclohexyl.[6]

The most accessible member of **CB*n*** family, **CB6**, is insoluble in organic solvents and only sparingly soluble in water. Solubility enhancement of **CB6** in aqueous environment was achieved by addition of alkali metal salts.[7] Thus supramolecular interactions of **CB6** with organic molecules are usually studied in aqueous solutions of sodium cation.[8] The association constant value between the macrocycle and the organic guest decreases with increasing cation concentration in the solution, as cations also interact with **CB6** and therefore compete with organic guest.[4,9]

In this paper we describe the formation of a novel inclusion complex between methylviologen and hexamethylated cucurbit[6]uril (**MeCB6**) in solution and in the solid state (Figure 1). We determined the association constant of the complex in pure water and demonstrated an extraordinary 2000-fold decrease of the association constant after the replacement of water by solution of 50 mM NaCl.

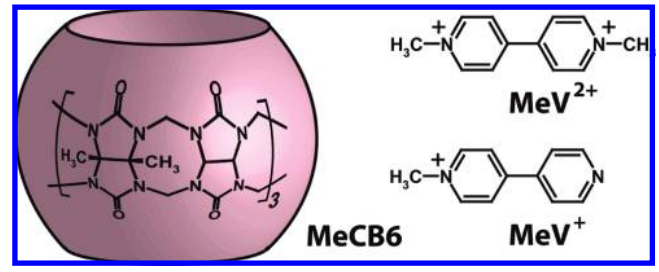

Figure 1. Structure of **MeCB6**, $\mathbf{MeV^{2+}}$, and $\mathbf{MeV^{+}}$.

MeCB6 was first synthesized and characterized using ^{1}H and ^{13}C NMR spectroscopy by Day and co-workers in 2003.[6e] They reported good solubility of this macrocycle in water−acetonitrile (1:1) mixture. Since then, **MeCB6** has been used in two cases only for the preparation of an inclusion complexes in solid state.[6g,6h] We decided to synthesize **MeCB6** and investigate its interactions with $\mathbf{MeV^{2+}}$ for the following reasons: (1) **MeCB6** represents the **CB6** analogue with a similar cavity size, (2) **MeCB6** has good solubility in water, which allows study of its association with the guest in aqueous media without and in the presence of salt, (3) $\mathbf{MeV^{2+}}$ and its derivative have been extensively investigated as suitable guests associating with **CB*n***, including **CB6**.

Results and Discussion

First we decided to investigate the interactions between $\mathbf{MeV^{2+}}$ and **MeCB6** in the solid state. We were able to obtain good quality single crystals by slow evaporation of aqueous solution of the host and guest in 1:1 ratio. X-ray crystallography revealed the binding mode between $\mathbf{MeV^{2+}}$ and **MeCB6** in the solid state (Figure 2). In this complex one pyridinium ring together with the attached methyl group of the guest is located inside the macrocycle while the second identical part of the guest remains outside the cavity. The driving forces for such a location of the guest are many short-distance C−H---O hydrogen bonds

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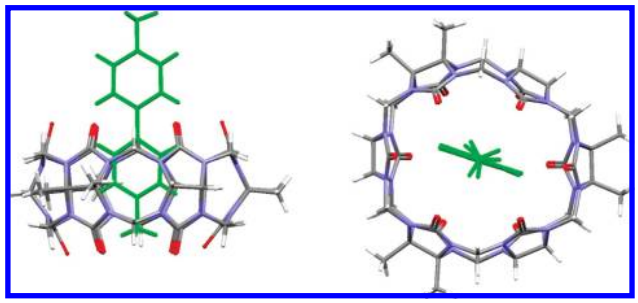

Figure 2. Wireframe representations of the crystal structure of **MeV**$^{2+}$**−MeCB6** complex.

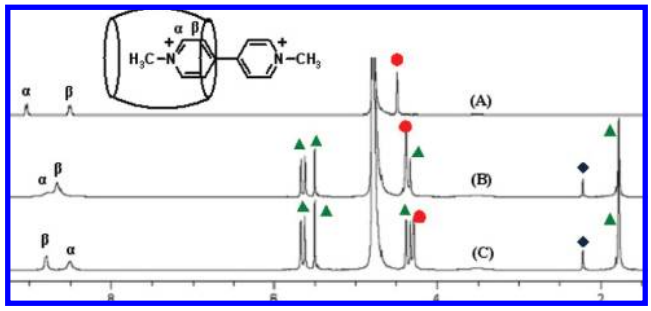

Figure 3. ^{1}H NMR spectra (300 MHz, D_2O) of **MeV**$^{2+}$ in the absence (A) and in the presence of 0.5 equiv (B) and 1 equiv (C) of **MeCB6**. Signals of methyl protons of **MeV**$^{2+}$ (red ●), **MeCB6** (green ▲), and acetone (blue ◆).

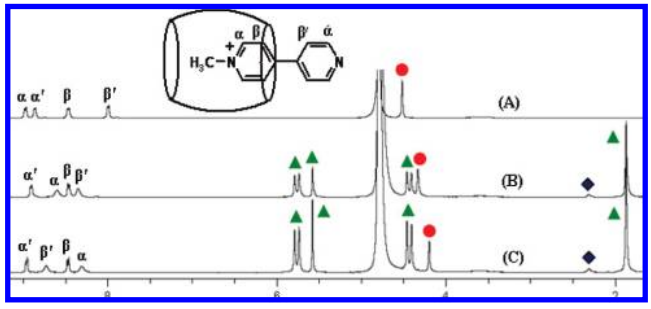

Figure 4. ^{1}H NMR spectra (300 MHz, D_2O) of **MeV**$^{+}$ in the absence (A) and in the presence of 0.5 equiv (B) and 1 equiv (C) of **MeCB6**. Signals of **MeV**$^{+}$methyl protons (red ●), **MeCB6** (green ▲), and acetone (blue ◆).

between methyl protons of the guest and carbonyls on portals of the macrocycle which fully overcome ion-dipole interactions.

^{1}H NMR spectroscopy was used to monitor the interactions between **MeCB6** and **MeV**$^{2+}$ in D_2O (Figure 3). After addition of 1 equiv of **MeCB6** into **MeV**$^{2+}$ solution, the α protons and methyl protons of the guest experienced an upfield shift of 0.53 and 0.2 ppm, respectively, while the β protons shift ca. 0.29 ppm downfield. The complexation between **MeV**$^{2+}$ and **MeCB6** is fast on the ^{1}H NMR time scale. Therefore the binding mode of the complex is difficult to predict from ^{1}H NMR spectra as α, β, and methyl protons on both sides of symmetrical guest appear as average signals.

We decided to find out more about the binding mode by replacing **MeV**$^{2+}$ with **MeV**$^{+}$. In the ^{1}H NMR spectra of **MeV**$^{+}$ the aromatic protons on both aromatic rings are well separated allowing us to obtain more information about the location of the guest upon the interaction with **MeCB6** (Figure 4). Gradual addition of **MeCB6** into solution of the guest results in upfield shift of the aromatic α protons (0.67 ppm) and methyl protons (0.32 ppm). Protons α′ and β' move 0.10 and 0.74 ppm downfield, while the β protons do not experience any shift.

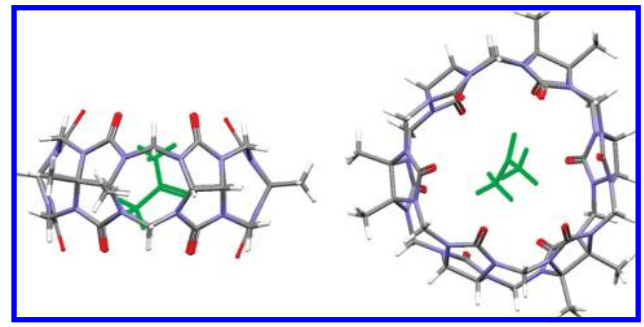

Figure 5. Wireframe representations of the crystal structure of acetone−**MeCB6** complex.

This pattern of complexation-induced shifts is consistent with an inclusion complex where the pyridinium ring of **MeV**$^{+}$ guest is engulfed in the host cavity, while the pyridyl ring is located outside the macrocycle. The lack of shift of the β protons indicates that these protons are placed in the edge of the host cavity where the influence of the host shielding and deshielding regions are compensated. On the basis of the obtained data, we predict that binding mode of the **MeV**$^{2+}$**−MeCB6** complex is similar to that of the **MeV**$^{+}$**−MeCB6** complex and also corresponds to the complex appearance in the solid state.

It is important to note that during the ^{1}H NMR titration of **MeV**$^{2+}$ solution with **MeCB6** a new signal at 2.22 ppm appeared in the spectrum. The observed chemical shift is similar to that of acetone. Very broad signal of acetone at 1.23 ppm was detected by ^{1}H NMR in stock solutions of the host (See SI). We assume that acetone is encapsulated inside **MeCB6**. Acetone motion within the cavity is slowed down and very broad signal is observed due to its coalescence. When **MeV**$^{2+}$ is added to the host solution, acetone is pushed out from the macrocycle, which results in the appearance of the free acetone peak in the ^{1}H NMR spectra. The presence of acetone in **MeCB6** can be explained by the use of diffusing acetone vapor to the solution of crude material during the purification of **MeCB6**. Furthermore, we were able to obtain a single crystal of **MeCB6** suitable for X-ray diffraction (Figure 5). The crystal structure revealed encapsulation of one acetone molecule inside the macrocycle which is in agreement with the ^{1}H NMR experiments. We were unable to remove the acetone from **MeCB6** cavity even after drying at 100 °C for 24 h.

Fast exchange of free and bound guest in the host cavity observed by ^{1}H NMR spectroscopy allows us to determine association constant of the **MeV**$^{2+}$**−MeCB6** complex following chemical shift of α protons of the guest as a function of increasing concentration of the host in D_2O solution. Experimental points can be well fitted to a 1:1 binding model to afford the association constant of $(1.2 \pm 0.2) \times 10^5$ M^{-1}.[10] The high value of the association constant is very surprising, as the association constant between **CB6** and **MeV**$^{2+}$ in the 0.2 M NaCl solution was reported to be 21 M^{-1}.[11] What is the reason for these extraordinary differences between association constants of both complexes? Is it the variation in structure of the host or does the presence of NaCl have an impact on such a drop of association constant? To answer these questions, we used ^{1}H NMR spectroscopy to determine the association constant of the **MeCB6**−**MeV**$^{2+}$ complex in the presence of 0.2 M NaCl. We obtained association constant of (60 ± 25) M^{-1}, which is in good agreement with value determined for the **CB6**−**MeV**$^{2+}$ complex.[11] From the

TABLE 1: Values of Association Constants of the MeV^{2+}−MeCB6 Complex (K_{MeCB6}) and the MeV^{2+}−CB7 Complex (K_{CB7}) in the Presence of Increasing NaCl Concentration Determined by UV−vis Spectrophotometric Titration except for *c*[a]

NaCl/mM	K_{MeCB6}/M^{-1}	K_{CB7}/M^{-1}
0	$(1.23 \pm 0.15) \times 10^5$[c]	nd[d]
0	$(2.05 \pm 0.21) \times 10^5$	$(1.68 \pm 0.30) \times 10^6$
0.1	$(1.97 \pm 0.13) \times 10^5$	nd[d]
0.2	$(1.03 \pm 0.06) \times 10^5$	nd[d]
0.4	$(6.85 \pm 0.43) \times 10^4$	nd[d]
0.5	$(7.17 \pm 0.45) \times 10^4$	nd[d]
0.8	$(3.15 \pm 0.28) \times 10^4$	nd[d]
1	$(2.84 \pm 0.31) \times 10^4$	nd[d]
2	$(2.47 \pm 0.21) \times 10^4$	nd[d]
3	$(1.17 \pm 0.12) \times 10^4$	nd[d]
5	$(3.76 \pm 0.35) \times 10^3$	nd[d]
10	$(2.15 \pm 0.20) \times 10^3$	$(8.3 \pm 1.8) \times 10^5$
20	$(7.6 \pm 1.4) \times 10^2$	nd[d]
30	$(3.02 \pm 0.55) \times 10^2$	nd[d]
40	$(1.25 \pm 0.63) \times 10^2$	nd[d]
50	$(1.00 \pm 0.67) \times 10^2$	$(3.45 \pm 0.52) \times 10^5$
100	nb[b]	$(1.49 \pm 0.16) \times 10^5$
200	$(6.0 \pm 2.5) \times 10^1$[c]	$(9.4 \pm 1.0) \times 10^4$

[a] The standard deviation of the fit is given for each measurement. [b] *K* not obtained by UV−vis spectroscopy. [c] Determined by ^1H NMR titration. [d] Not measured.

obtained results it is clear that the value of association constant for the **MeCB6**−$\mathbf{MeV^{2+}}$ complex (and probably also for the **CB6**−$\mathbf{MeV^{2+}}$ complex) is dramatically influenced by the presence of sodium cation and not by the chemical modification of the host.

We decided to study the influence of sodium cation on the complexation between **MeCB6**−$\mathbf{MeV^{2+}}$ in detail. The spectrophotometric titration of the guest by the macrocycles was performed at constant salt concentrations. The UV−vis absorption spectra were processed by global and target factoral analysis. This allowed for association constants of the complex as well as the absorption spectra of each species, e.g., guest, host, and complex (see Supporting Information). The model for the 1:1 complex was found to fit well to the measured spectra. As it is clearly demonstrated in Table 1, the association constants of $\mathbf{MeV^{2+}}$−**MeCB6** in aqueous solution are significantly influenced by the amount of NaCl present in solution. The association constant of the complex in pure water was found to be $(2.05 \pm 0.21) \times 10^5$ M^{-1}, which is in good agreement with the value obtained from ^1H NMR measurements. The value of the association constant continuously decreases with the addition of sodium chloride. The last measurable value of the association constant $(1.00 \pm 0.67) \times 10^2$ M^{-1} was obtained in the presence of 50 mM NaCl, which is more than 2000-fold lower compared to the association constant of the complex determined in pure water.

Previously, Kaifer et al. reported the impact of NaCl concentration on the values of the association constant of the $\mathbf{MeV^{2+}}$−**CB7** complex.[12] Due to better solubility of **CB7** they were able to determine several association constants of the $\mathbf{MeV^{2+}}$−**CB7** complex in aqueous solution containing 0.030 M Tris buffer (pH 7.2) and variable salt concentrations. Our values of association constants for the $\mathbf{MeV^{2+}}$−**CB7** complex similarly decrease with increasing NaCl concentration. However, obtained values are 10-fold higher than was previously published, probably due to the absence of the buffer. Association constant values of the $\mathbf{MeV^{2+}}$−**CB7** complex show about a 5-fold decrease when pure water was replaced by 50 mM NaCl solution. This is in large contrast to the more than 2000-fold decrease measured for the $\mathbf{MeV^{2+}}$−**MeCB6** complex. In other words, in pure water $\mathbf{MeV^{2+}}$ is bound by **CB7** 8-fold stronger compared to **MeCB6**, while in the presence of 50 mM NaCl solution the affinity of $\mathbf{MeV^{2+}}$ toward **CB7** is more than 3400 higher compared to **MeCB6**. The reason for this remarkable difference is probably due to the different affinity and binding mode of Na^+ toward **MeCB6** compared to **CB7**, as well as the different location of $\mathbf{MeV^{2+}}$ in the cavity of both macrocycles. We are currently undertaking detailed additional work to justify our assumptions.

Conclusions

In summary, we report the formation of a new supramolecular complex between $\mathbf{MeV^{2+}}$ and **MeCB6** in solution and solid state. Both ^1H NMR and UV−vis spectroscopy measurements suggested similar values of $(1.2 \pm 0.2) \times 10^5$ M^{-1} and $(2.05 \pm 0.21) \times 10^5$ M^{-1} for association constants in water, respectively. The high value of the association constant in water dramatically decreases with the addition of NaCl. We also demonstrated that the stability of $\mathbf{MeV^{2+}}$−**CB7** complex is significantly less sensitive to the presence of NaCl compared to the $\mathbf{MeV^{2+}}$−**MeCB6** complex.

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Supporting Information Available: Experimental section and crystal structure details, ^1H and ^{13}C NMR spectra of **MeCB6**, MALDI-TOF MS of **MeCB6** and $\mathbf{MeV^{2+}}$−**MeCB6**, electronic absorption spectra of **MeCB6**, $\mathbf{MeV^{2+}}$−**MeCB6**, $\mathbf{MeV^{2+}}$, **CB7**, and **CB7**−$\mathbf{MeV^{2+}}$, ^1H NMR titration curve for $\mathbf{MeV^{2+}}$−**MeCB6**, and X-ray crystallographic files (CIF) for $\mathbf{MeV^{2+}}$−**MeCB6** and acetone−**MeCB6** complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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