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Salt Effects on the Apparent Stability of the Cucurbit[7]uril−Methyl Viologen Inclusion Complex

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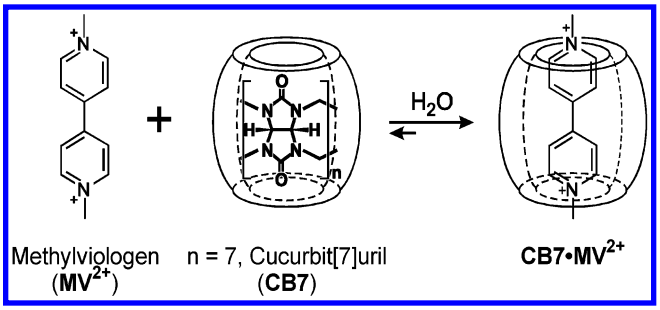
Abstract: The effects of the medium ionic composition on the apparent equilibrium association constant (*K*) for the formation of a 1:1 inclusion complex between the guest methyl viologen ($\mathbf{MV^{2+}}$) and the host cucurbit[7]uril (**CB7**) were studied in aqueous solutions. The *K* values were found to decrease with increasing ionic strength, with more pronounced effects for solutions containing divalent Ca^{2+} ions than for solutions containing monovalent Na^+ ions. The competing ion−dipole interactions between Ca^{2+} or Na^+ and $\mathbf{MV^{2+}}$ ions appear to be responsible for the remarkable modulation of the *K* values observed in this work.

In the past few years the cucurbiturils (CBs) have become a versatile and extremely interesting class of molecular receptors with numerous supramolecular applications.[1] Kim and co-workers are primarily responsible for the recent and very fast expansion on the scope of CB host chemistry.[1a,b] Their report on the preparation and isolation of the higher cucurbiturils[2,3] has led to growing interest on the properties of cucurbit[7]uril (**CB7**) and cucurbit[8]uril (**CB8**).[4] For instance, our group[5] and Kim's[6] reported recently that **CB7** forms very stable 1:1 inclusion complexes with methyl viologen (see structures in Scheme 1) and other simple viologens in aqueous solution. We have recently expanded this work to the investigation of 1:1 inclusion complexes between **CB7** and dendrimer guests containing a single viologen group at their apical positions.[7] During the course of this work, we noticed that the equilibrium association constant (*K*) for the formation of these inclusion complexes seems to be very sensitive to the ionic composition of the solution. These observations combined with the previous finding on the capping of the **CB6** cavity openings with hydrated Na^+ ions[8] clearly pointed to the need for an increased understanding of the effect of electrolytes on the stability of inclusion complexes involving **CB** hosts. From a practical standpoint, some of the experimental techniques (e.g, voltammetry, NMR spectroscopy[9]) utilized in the characterization of CB complexes in solution require the presence of ions, which may be mistakenly perceived as traditional spectator species. Therefore, we set out to investigate the effects of electrolytes on the formation and stability of CB inclusion complexes in a more detailed fashion,[10] taking $\mathbf{CB7{\cdot}MV^{2+}}$ as the model complex. The selection of $\mathbf{MV^{2+}}$ as the model guest for CB binding takes three relevant factors into consideration. First, it is the simplest guest that fits the **CB7** cavity tightly, leading to a highly stable 1:1 dicationic complex. Second, the widespread choice of viologens[5,6,11] as guests for larger CBs will render the results of this work immediately significant. Third, the *K* values can be conveniently and accurately obtained using UV−vis spectroscopy.

SCHEME 1. Formation of a 1:1 Inclusion Complex between Host CB7 and Guest $\mathbf{MV^{2+}}$



The crystallization of an adduct of host **CB6** capped by four sodium ions and ten water molecules,[8] with two sodium ions positioned on each of the openings of the host cavity, is a very relevant precedent for this work. Therefore, we decided to study the effect of sodium ions on the $\mathbf{CB7{\cdot}MV^{2+}}$ binding constant by using variable

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(3) Day and co-workers later reported a wider range of reaction conditions. For details, see: Day, A.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094−8100.

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(7) Ong, W.; Kaifer, A. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2164−2167.

(8) Jeon, Y.-M.; Kim, J.; Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 9790−9791.

(9) **CB6**, as well as a commercial sample of **CB8** from Sigma-Aldrich, is essentially water-insoluble, and a considerable amount of acid is needed to prepare millimolar solutions for NMR work. Such strongly acidic conditions may not be practical for the simple analyses of CB complexes in aqueous media by ^{1}H NMR. On the other hand, ionic additives are easier to handle and can be conveniently combined with buffered solutions.

(10) The effect of acids on the stability of **CB6** complexes and the interaction of transition metal cations with **CB5** and **CB6** has been previously described. For details, see, respectively: (a) Neugebauer, R.; Knoche, W. *J. Chem. Soc., Perkin Trans. 2* **1998**, 529−534. (b) Buschmann, H.-J.; Cleve, E.; Jansen, K.; Schollmeyer, E. *Anal. Chim. Acta* **2001**, 157−163.

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TABLE 1. Thermodynamic Data for Formation of 1:1 the Inclusion Complex[a] between Methyl Viologen[b] and CB7 in Aqueous Solution Containing 0.030 M Tris Buffer (pH = 7.2) and Variable Salt Concentrations at 25 °C

added salt	concn, M	K, M^{-1}	$\Delta G°$, kcal/mol
none		2.24×10^5	−7.3
NaCl	0.010	1.67×10^5	−7.1
NaCl	0.050	1.03×10^5	−6.8
NaCl	0.10	6.81×10^4	−6.6
NaCl	0.20	2.49×10^4	−6.0
$CaCl_2$	0.010	1.34×10^5	−7.0
$CaCl_2$	0.050	4.53×10^4	−6.3
$CaCl_2$	0.10	1.63×10^4	−5.7
$CaCl_2$	0.20	5.60×10^3	−5.1

[a] The molar absorptivity coefficients for the complex were also measured in each case; the values were in the range $1.12-1.36 \times 10^4$ M^{-1} cm^{-1}. [b] The methyl viologen concentration was kept constant at 30 μM throughout the measurements.

concentrations of NaCl. In addition to this, we also selected $CaCl_2$ to compare the relative effects of divalent and monovalent cations of similar sizes. Here, we report the results of this investigation, which should have important implications to any equilibrium association data involving CB hosts.

All of the binding isotherms obtained in the absence and in the presence of variable concentrations of NaCl show the expected shape (see Supporting Information). In all cases the absorbance data could be fitted very well to the equations describing 1:1 complex formation.[12] Variations in the nature or concentration of the electrolyte do not seem to affect the stoichiometry of the methyl viologen−**CB7** complex. Similar results were also obtained with $CaCl_2$ (data not shown), and the results are collectively summarized in Table 1. From the tabulated data, we can conclude that the binding constant values are strongly affected by the concentration and nature of the electrolyte. Two very clear trends are visible in the data. First, the binding constant values decrease with increasing electrolyte concentration. Second, at similar cation concentrations, calcium ion causes a more pronounced depression on the K value than sodium ion. The observed salt effects on the binding constants are considerable. The range of binding constants measured extends from a highest value of 2.24×10^5 L/mol (in the presence of 0.030 M Tris buffer, pH = 7.2) to a lowest value of 5.6×10^3 L/mol (upon addition of 0.2 M $CaCl_2$). In other words, the relatively moderate salt concentrations used in this work are enough to cause a depression of more than 1 order of magnitude in the apparent equilibrium association constant for the **CB7**·$\mathbf{MV^{2+}}$ complex.

The binding constant value (2.24×10^5 L/mol) determined by us in aqueous solution containing only 0.030 M Tris buffer (pH 7.2) is very close to the value (2.0×10^5 L/mol) measured calorimetrically by Kim and coworkers in a similar medium[6] (0.05 M Tris buffer, pH 7.0). Also, we have previously reported a K value of 1.03×10^5 L/mol,[5] which was obtained spectrophotometrically in aqueous solution containing 0.2 M NaCl (no Tris buffer). These K values and the data in Table 1 clearly suggest that Na^+, Ca^{2+}, and the protonated form of Tris can all compete to some extent for the host with the methyl viologen dication. Any association equilibrium between two charged partners is indeed expected to exhibit thermodynamic parameters that will strongly depend on the ion strength of the medium. However, the uncharged nature of the cucurbituril host leads us to rationalize the observed electrolyte-induced depressions of the binding constant as resulting from cation competition for the host binding sites. This hypothesis is in agreement with the observed formation of adducts between the **CB6** host and sodium ions.[8] In these crystalline adducts two sodium ions and five water molecules form a cap on each of the two openings of the cucurbituril cavity. It is reasonable to assume that solvated sodium and calcium ions can give rise to similar interactions with the slightly larger openings of the **CB7** cavity. The solvated cations at the cavity openings would act as lids, hindering the insertion of the methyl viologen dication into the **CB7** cavity and, thus, decreasing the apparent stability of the resulting inclusion complex. In this model, stronger ion−dipole interactions would be expected from divalent calcium ions than from monovalent sodium ions, in agreement with the experimental observation that $CaCl_2$ causes more pronounced effects than NaCl. On the other hand, contributions from chloride ions cannot be entirely disregarded.[13]

Host−guest interactions, as any other chemical equilibria, are indeed subject to medium effects. However, the salt effects reported here are very pronounced and very different from reported salt effects on the formation of cyclodextrin inclusion complexes,[14] for instance. Ion pairing effects are often very relevant in nonaqueous host−guest chemistry,[15] but the salt effects on CB binding reported here take place in aqueous solution, where ion pairing is less important.

In conclusion, we have convincingly shown that electrolyte salts tend to depress the apparent binding constant observed for the formation of a 1:1 inclusion complex between the guest $\mathbf{MV^{2+}}$ and the host **CB7**. Considerable effects on the K values were observed from rather moderate salt concentrations ($c \leq 0.2$ M). These strong salt effects should be present, in principle, in any association equilibria involving cucurbituril hosts and must be taken into account when comparing thermodynamic (as well as kinetic) data from media containing different electrolytes.

Experimental Section

Methyl viologen was obtained as its dichloride salt, and its concentration in solution was accurately determined using its molar absorptivity coefficient (20 500 M^{-1} cm^{-1} at 257 nm). Host **CB7** was prepared as reported by the groups of Kim[2] and Day.[3] All other chemicals were of the best grade commercially available. The equilibrium association constants between methyl viologen and **CB7** were determined by measuring the absorbance at 257 nm of solutions containing a fixed concentration of methyl

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(13) We used Cl^- as the only counterion (for both Na^+ and Ca^{2+}) to avoid possible effects from the nature of the anion, but it has been suggested that Cl^- also binds with CBs (see ref 3 for details).

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(15) Böhmer, V.; Dalla Cort, A.; Mandolini, L. *J. Org. Chem.* **2001**, *66*, 1900−1902.

viologen and variable concentrations of **CB7** (in the 0−0.15 mM range).[5] In a typical experiment using a 1.0-cm cuvette, a 30 μM solution of guest $\mathbf{MV^{2+}}$ (2.50 mL) was titrated with a 0.82 mM solution of **CB7** (also containing 30 μM $\mathbf{MV^{2+}}$) until the total volume reached 3.00 mL. The absorbance values were fitted by regression analysis to the equations describing the binding isotherm of a 1:1 association equilibrium.[12] Optimization of the fitting allowed the determination of the parameters K and ϵ_{comp}.

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Supporting Information Available: Plot of binding isotherms at variable NaCl concentrations. This material is available free of charge via the Internet at http://pubs.acs.org.

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