

Complexation of metal cations (mono-, di- and trivalent) to cucurbiturils: Insights from a DFT/SMD study

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Abstract: Recently, supramolecular complexes based on synthetic macrocyclic host molecules have received much attention due to their broad applications as drug delivery carriers, biological and chemical sensors, light-emitting materials, bioimaging agents, etc. Cucurbit[n]urils are cavitands known for their high affinity for various guest molecules, although some aspects of their coordination chemistry remain enigmatic. They are still not tested as metalloenzyme models and not much is known about their metal-binding properties. Furthermore, there is no systematic study on the key factors controlling the processes of metal coordination to these systems. In the computational study herein, DFT molecular modeling has been employed in order to investigate the interactions of biologically essential mono- (Na^+), di- (Mg^{2+}) and some trivalent (La^{3+} , Lu^{3+}) metal cations to cucurbit[n]urils and evaluate the major determinants shaping the process of recognition. The thermodynamic descriptors (Gibbs energies in the gas phase and in a water medium) of the corresponding complexation reactions have been estimated. The results obtained shed light on the mechanism of host-guest recognition and disclose which factors more specifically affect the metal binding process.

KEYWORDS: METAL SELECTIVITY, THERAPEUTIC EFFECT, CUCURBITURILS, COMPUTATIONAL CHEMISTRY, DFT

1. Introduction

As the list of newly approved pharmaceutical molecules has been declining since the mid-1990s, the urge of developing novel drugs appears even more pressing. With substantial efforts and resources significant progress has been achieved in the development of novel drug delivery technologies resulting in enhanced drug efficacy and specificity, decreased adverse effects, and suppressed unpleasant characteristics of the active substances. Various host systems, such as cyclodextrins,[1] calixarenes,[2] and crown ethers,[3] able to accommodate diverse guest molecules, have been recognized as efficient drug delivery vehicles and subjected to large-scale investigations. Another group of cavitands with unique properties is that of cucurbit[n]urils.[4] They comprise n condensed units formed by glycoluril and formaldehyde fragments (Fig. 1). These are rigid symmetrical macrocycles, which resemble that of a pumpkin (from Latin "*cucurbita*", hence the name). The geometry of the representatives of the CB[n] family with $n = 5-8$, namely cucurbit[5]uril (CB[5]), cucurbit[6]uril (CB[6]), cucurbit[7]uril (CB[7]) and cucurbit[8]uril (CB[8]), are presented in Fig. 1. Additionally, their varying pore size is also noted.

Kim[5] and Day[6] separately have successfully synthesized several members of the cucurbituril family. Notably, this structural diversity allows CB[n]s to act as host molecules for a great amount of guests, thus finding their way to vast areas of scientific and industrial interest such as catalysis, self-assembled monolayers, drug delivery, photo- and electrochemistry.[7] Nonetheless, one main drawback of the cucurbiturils is their insolubility in a water environment. A possible way to circumvent this problem is if they are solvated in aqueous solution of alkali metal salts, in particular sodium sulphate, where the cavitands tend to dissolve much more easily. This effect is attributed to the formation of favorable binding of the metal ions to the host macrocycle groups resulting in stable metal-cucurbituril complex formation.[8] Under specific conditions, e.g. temperature or acidity, metal cations act as a "lid", which can un/block the portal of the cucurbituril, thus specifically releasing the guest-molecule. It can be inferred that metal-CB[n] coordination significantly expands the field of their application, as this process results in the formation of various novel constructs such as molecular capsules, tubular polymers, and molecular "jewelry" – bracelets and necklaces. Therefore, understanding (at the atomic level) the mechanism of cucurbit[n]uril-metal complex formation is of particular interest.

A systematic study delineating the key determinants of the metal cation-cucurbituril recognition is, however, lacking. Herein, we attempt to shed light on the intimate mechanism of the metal binding to cucurbiturils by methodically studying the effect of various factors on the host-guest interactions. The reactions of formation between CB[n]s ($n = 5, 6, 7$ and 8) and a series of

cations: mono- (Na^+), di- (Mg^{2+}) and trivalent (La^{3+} / Lu^{3+}) is studied by employing density functional theory (DFT) calculations in conjunction with polarizable continuum model computations (SMD scheme). The influence of different factors on the thermodynamics of the host-guest interactions is assessed, namely the size of the host cavitand, metal's nature (cation charge, size and inherent chemical properties), as well as the presence/absence of a metal hydration shell.

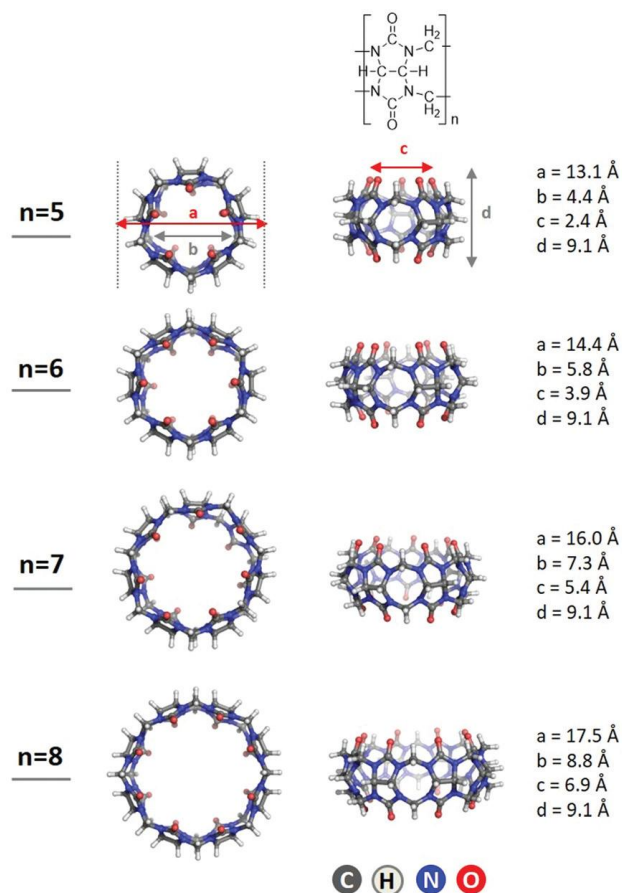


Fig. 1. M062X/6-31G(d,p) optimized molecular structures of CB[n], $n = 5-8$.

Notably, this particular approach has proven quite effective in disclosing the basic determinants of host-guest recognition in other macrocyclic systems.[9], [10]

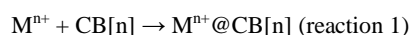
2. Computational Methodology

Models used

Structural data deposited in the Cambridge Crystallographic Data Centre (CCSD) provided the initial geometries of the CB[n] host systems. The necessary constructs were as follows: for CB[5] – LOZNIX (CSD Entry from ref. [11]); for CB[6] – BATWIE (CSD Entry from ref.[12]); for CB[7] – TUHGAG (CSD Entry from ref. [13]), and for CB[8] – BATWEA (CSD Entry from ref. [12]). In all cases, the starting geometry included the metal cation positioned at the center of one of the carbonylated portals of the free CB[n] resulting in the optimization of the 1:1 CB[n]/metal ion complexes.

Reactions Modelled

The aim of the conducted study is to delineate the important factors controlling the complexation between four representatives of the cucurbituril family and various metal cations. Consequently, the reactions were modeled as follows:



The metal species possess different charges, hence M^{n+} stands for Na^+ , Mg^{2+} , La^{3+} , and Lu^{3+} either as bare cations, or modelled with their hydration shell. On the other hand, CB[n] signifies the host-system, where n equals 5 to 8, while the newly formed complex is denoted as $M^{n+}@CB[n]$. The outcome of the reaction is expressed in terms of change in Gibbs free energy. A positive free energy change for reaction 1 implies a thermodynamically unfavorable reaction, whereas a negative value suggests a probable one.

DFT Calculations

The Gaussian 09 [14] package of programs was employed in order to perform all calculations. The full optimization of each structure in the gas phase was consecutively followed by frequency calculations at the same level of theory, where no negative values were found for the lowest energy configurations. Single point calculations were performed at M062X/6-31+G(d,p) level of theory. Electronic energies obtained at both levels of theory (M062X/6-31G(d,p) and M062X/6-31+G(d,p)/M062X/6-31G(d,p)) were used alongside in the subsequent evaluations. M062X/6-31G(d,p) vibrational frequencies were used to compute the respective thermal energies, E_{th} , including zero-point energy, and entropy, S , yielding the gas-phase Gibbs energy of the molecule/complex at $T = 298.15$ K:

$$G^1 = E_{el} + E_{th} - TS \text{ (eq.1)}$$

The calculations were performed at standard conditions – room temperature (298.15 K) and pressure of 1.0 atm. Changing the temperature and external pressure applied to the system, has negligible effect on the evaluated free energies of the complex formation reactions. Solvation effects were accounted for by employing the SMD (Density-based Solvation Model) method as implemented in the Gaussian 09 suite of programs. Then, a single point calculation in water (dielectric constant of 78) was performed at the same level of theory: M062X/6-31+G(d,p)/M062X/6-31G(d,p). The difference between the gas phase and SMD calculated energies yields the solvation free energy, ΔG_{solv}^{78} , of the respective entity:

$$\Delta G^s = \Delta E_{el}^c + \Delta E_{th}^c - T\Delta S^c \text{ (eq.2)}$$

Solvation free energies of the products and reactants were used to evaluate the free energy of complex formation, ΔG_A , in a water medium:

$$\Delta G^{78} = \Delta G^1 + \Delta G_{solv}^{78} \text{ (products)} - \Delta G_{solv}^{78} \text{ (reactants)} \text{ (eq.3)}$$

The PyMOL molecular graphics system was used to generate the molecular graphics images.[15]

3. Results and Discussion

Effect of cavity size

Complexes between a representative of the metal series, Mg^{2+} and La^{3+} (bare cations), and CB[5], CB[6], CB[7] and CB[8] were optimized and examined (Fig. 2). The thermodynamic data of the reactions of complexation in a gas phase as well as in a water environment are presented in Table 1.

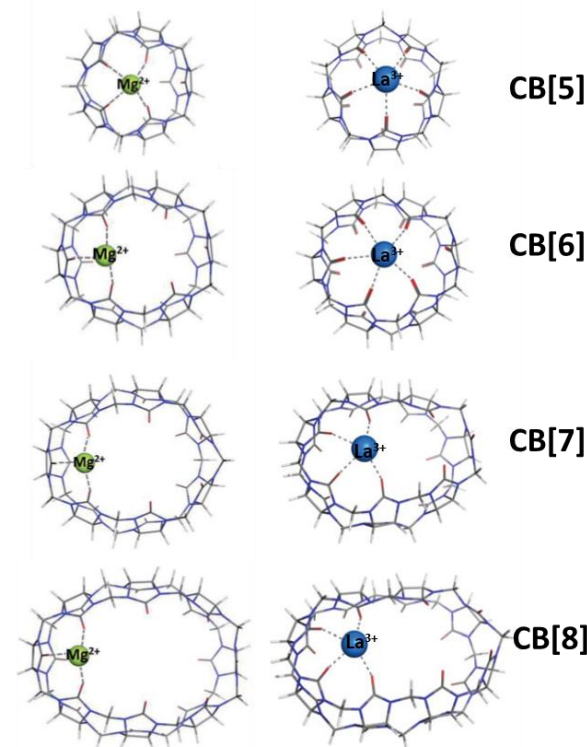


Fig. 2. M062X/6-31G(d,p) optimized geometries of the CB[n], n = 5–8, complexes with bare Mg^{2+} and La^{3+} cations.

Table 1. Gibbs energies for the complex formation in the gas phase (superscript 1), and in a water environment (superscript 78), for the CB[n], n = 5–8, complex formation with bare Mg^{2+} and La^{3+} cations, in kcal mol⁻¹

REACTION	M = Mg		M = La	
	ΔG^1	ΔG^{78}	ΔG^1	ΔG^{78}
$CB[5] + M^{2+/3+} \rightarrow CB[5]@M^{2+/3+}$	-315.6	-48.2	-477.1	32.1
$CB[6] + M^{2+/3+} \rightarrow CB[6]@M^{2+/3+}$	-293.7	-41.7	-449.2	59.0
$CB[7] + M^{2+/3+} \rightarrow CB[7]@M^{2+/3+}$	-285.8	-36.2	-428.0	66.8
$CB[8] + M^{2+/3+} \rightarrow CB[8]@M^{2+/3+}$	-280.9	-33.9	-415.0	74.0

All calculated Gibbs energies for the magnesium cation stay firmly on negative ground, which corresponds to readily formed $CB[n]@Mg^{2+}$ complexes. The results obtained show a clear trend: smaller cavitands favor metal complexation in larger extent than their bulkier homologs ($\Delta G^{78} = -48.2$ and -41.7 kcal mol⁻¹ for the CB[5] and CB[6], respectively, vs. -36.2 and -33.9 kcal mol⁻¹ for the CB[7] and CB[8], accordingly). A few factors contribute to this outcome, namely the number of bonds in the complex along with additional interaction with the distanced C=O groups. The hydrogen bonds between the metal cation and the smaller CB[5/6] are due mainly to the smaller radius of the cavity and close proximity of the oxygen-containing residues to the guest metal. As the size of the host molecule increases, the Gibbs energies decrease in absolute

value (but still remain negative) as a result of the fewer bonds formed.

All calculated ΔG^1 for bare La^{3+} cation are negative, whereas ΔG^{78} are positive, which corresponds to a thermodynamically unfavorable complex formation for La^{3+} in a water environment. Still, the results obtained show the same trend: smaller CB[n]s favor metal complexation in greater extent than the larger homologs. There is a sharp jump in the $\Delta G^1/\Delta G^{78}$ values between CB[5] and CB[6] complexes.

Effect of cation properties

In order to assess the effect of the cation properties on the thermodynamics of the complex formation, complexes between all four cations studied (Na^+ , Mg^{2+} , La^{3+} , and Lu^{3+}) and CB[7] (as a representative of the CB[n] hosts) have been modelled and the corresponding Gibbs energies of formation in aqueous solution, ΔG^{78} in kcal mol^{-1} , calculated. The corresponding data is presented in Table 2 along with the ionic radii in their tetra- and hexacoordinated complexes in Å. [9], [10]

Table 2. Metal cationic radii for their tetra- and hexacoordinated complexes (in Å) and Gibbs energies for the $\text{CB}[7]@M^{n+}$ complex formation, in kcal mol^{-1} in a water environment (superscript 78).

Metal ion	Ionic radius in tetra-/hexa-coordinated complexes in Å	ΔG^{78} in kcal mol^{-1} for the formation of $M^{n+}@CB[7]$
Na^+	0.99/ 1.02	- 17.1
Mg^{2+}	0.57 0.72	- 36.2
La^{3+}	1.03/ 1.22	66.8
Lu^{3+}	0.86/ 1.03	7.0

The results indicate a clear tendency: as the ionic radius decreases (Table 2), the Gibbs energy decreases as well, i.e. the host system prefers to bind smaller cations. The reactions of complex formation in a water medium are characterized with the lowest ΔG^{78} ($-36.2 \text{ kcal mol}^{-1}$) for the smallest Mg^{2+} whereas those for the bulkier Lu^{3+} and La^{3+} are even positive: 7.0 and $66.8 \text{ kcal mol}^{-1}$, respectively, indicating a thermodynamically unfavorable reaction.

Effect of cation hydration shell

The presence of a hydration shell affects significantly the structure and characteristics of a complex, especially in the cases of highly charged species. By applying a hybrid explicit/implicit solvation model, we assessed the importance of the metal hydration: the first hydration shell around the studied cations has been treated explicitly and the resulting metal/ H_2O clusters and CB[6/7]-hydrated metal cations complexes have been surrounded by a dielectric continuum ($\epsilon = 78$). The optimized structures of the studied $M^{n+}@CB[6/7]$ complexes as well as the obtained thermodynamic data are given in Fig. 3.

The number of the first shell water molecules for the biologically essential Na^+ and Mg^{2+} is six, while the number of the first shell water molecules determined for La^{3+} and Lu^{3+} cations varies depending on the environment and experimental/theoretical approach used. It is accepted that lighter lanthanoid ions (La–Eu) are predominantly ninefold-coordinated while the higher species (Gd–Lu) are mostly eightfold-coordinated. Whereas the formation of $\text{CB}[6]@La^{3+}$ starting from the bare La^{3+} cation appears thermodynamically unfavorable (59 kcal mol^{-1}), the formation of $\text{CB}[6]@La(\text{H}_2\text{O})_9^{3+}$ is a thermodynamically favorable process ($-11.7 \text{ kcal mol}^{-1}$) (Fig. 3). The calculations reveal that a more adequate result can be achieved when the first hydration shell around the studied cations is taken into account and modelled explicitly, i.e. a hybrid explicit/implicit solvation model is applied for the free/complexed metal cation. The results clearly show the hydration

shell should be modelled as the obtained theoretical data now well falls in line with the experimental observations. The previous tendencies concerning the effect of the cation properties are still valid: among the metal cations, the greatest preference is toward the smallest cation, e.g. Mg^{2+} .

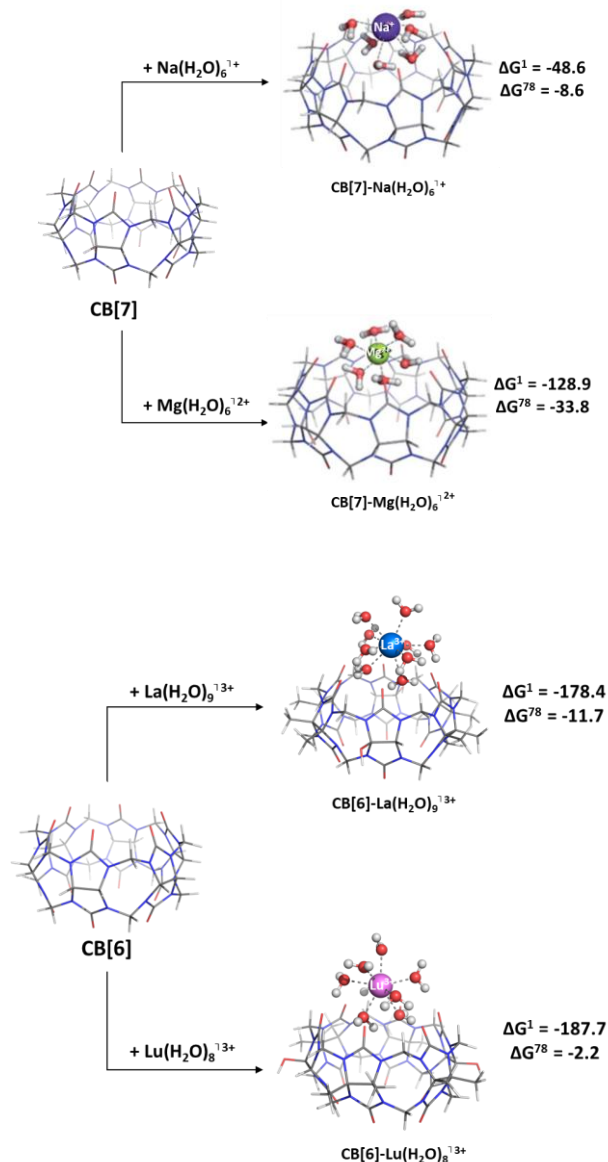


Fig. 3. M062X/6-31G(d,p) optimized structures of $\text{CB}[6/7]-M^{n+}$ complexes in the gas phase. Calculated Gibbs energies for complex formation in the gas phase, ΔG^1 , and in aqueous medium, ΔG^{78} , for the $\text{CB}[6/7]-M^{n+}$ complex formation, in kcal mol^{-1} .

4. Conclusion

A systematic study of biologically essential (mono- and divalent) metal cations (Na^+ , Mg^{2+}) and trivalent La^{3+} and Lu^{3+} binding thermodynamics to cucurbit[5–8]urils has been performed using density functional theory computations combined with solvation model based on density (SMD) calculations. The effects of the cavity size of the host molecule, as well as the specific metal's physicochemical characteristics such as radius, charge, charge accepting abilities and water hydration shell have been assessed by modelling the corresponding interaction between the host cavitand and the incoming metal species. The results obtained indicate a well-defined preference towards small and highly charged metals at atomic level. Governing factors of high importance have been outlined and have showed, consequently, the future perspectives in the coordination/ host-guest binding.

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