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REVIEW ARTICLE

Theoretical insights into the formation, structure, and electronic properties of anticancer oxaliplatin drug and cucurbit[*n*]urils n = 5 to 8

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Abstract Geometries, formation and electronic properties of cucurbit[n]uril-oxaliplatin n = 5–8, host-guest complexes are investigated with DFT calculations. The formation of inclusion complexes of CB[n]-oxaliplatin are facile in CB[n] n = 6–8. In the complex, the cyclohexyl group is found to be deep inside the cavity, with the formation of a hydrogen bonding between the portal oxygen atoms and the amine nitrogen of the oxaliplatin guest. NBO analysis shows the transfer of charge from the metal center to the CB[7] unit and the existence of hydrogen bonding between the oxygen portal and amine nitrogen. The HOMO orbital is localized on the carboxylate group and the LUMO orbital are localized on the cucurbituril unit in CB[7]-oxaliplatin complex. The strength of the interaction determined here reflects the ability of CB[n] to act as a host for suitably oxaliplatin guests, even in aqueous solution.

Keywords Cucurbit[n]urils · DFT · Cancer drugs · Oxaliplatin · Inclusion complex

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Introduction

After the discovery of the anticancer activity of cisplatin, a great deal of attention was drawn to platinum compounds of both Pt(II) and Pt(IV) [1]. Toward the end of 1980s, a second generation of cisplatin analogues appeared of which carboplatin and oxaliplatin were proven to be one of the most useful drugs [2, 3]. They exhibit similar activity to cisplatin due to their similarity in their structures [4], however, they all are susceptible to the development of drug resistance, and display severe dose-limiting toxicities [5]. Hence in recent years, attention has been focused towards the creation of controlled and targeted drug delivery vehicles [6]. One promising method was the encapsulation of the drug with a macrocyclic host which protects the drugs from degradation by using steric hindrance. Moreover, encapsulation increases the specificity of the drugs [7, 8].

Cucurbituril is a family of homologues which are most favored cavitands for host-guest complex formation. Effective chemical and physical properties of these complexes with organic molecules and cations as molecular switches and catalysts have been well demonstrated [9–16]. Cucurbituril homologues, cucurbit[*n*]uril (CB[*n*], n = 5, 6, 7, 8 and 10) contains five to ten glycoluril units, provides a hydrophobic cavity assessable though two identical carbonyl-fringed portals [17, 18]. Recently, CB[*n*] has shown utility as drug delivery vehicles for a variety of platinum(II)—based complexes [19]. Kim and coworkers have shown that inclusion complexes of oxaliplatin with cucurbit[7]uril has moderate cytotoxicity with larger decrease in reactivity towards guanosine and L-methionine respectively. They have calculated the association constant measured in TRIS buffer to be 2.3×10^5 M^{-1} for the guest oxaliplatin to bind to CB[7]. Their NMR studies for the

inclusion complex shows that there is an exchange of the guest oxaliplatin inside and outside the CB[7] cage despite the high binding constant for the Pt guest molecule [20].

There exist many reports on the theoretical studies of CB[*n*]. Nau and coworkers made a MM+ force field optimization on the CB[6] molecule and reported a less symmetric collapsed structure which presumably allows for some additional dispersion interactions between the walls without a significant increase in strain energy [21]. Later Pichierri made a DFT study on CB[n] n = 5–10, and indicate that the macrocycle's do possess D*nh* symmetry [22]. Zielesny and coworkers, made DFT investigation on the geometries, electronic and NMR-shielding properties of CB[n] $n = 5$ to 8, and reported that the molecules are highly symmetrical with a distinct geometric flexibility and a characteristic partial charge distribution [23]. Very recently Kim and coworkers made a thermodynamical analysis of macromolecule cyclization from a monomer to hexamer and fond that water molecules, formed as one of the products helps in the stabilization of the macrocycle [24, 25]. Gejji and coworkers, made an assessment on the complex formation capability of CB[n] with ferrocene [26]. The present work is to predict the formation, structure and stability of oxaliplatin inside the CB[n] with $n = 5$ to 8, and to understand the nature of interaction that stabilizes the guest oxaliplatin inside the cucurbituril molecule by using the density functional theory in detail.

Calculation and methodology

All calculations on cucurbituril and their inclusion complexes were made with GAUSSIAN G03 package [27]. All the structures were optimized using the Becke hybrid B3LYP functional. H, C, O, and N atoms were described with 6-31+G(d) pople's basis set. For a description of the Pt atom the quasi-relativistic Stuttgart-Dresden pseudopotentials (MWB-60) were utilized. Frequency calculations were done to verify that the geometries were minima on the potential energy surface. Energies were computed at the MP2 level of theory at the same basis set, on the optimized geometry. The binding energy (ΔBE) of the complexes was determined from the difference in the total energy of the complex and the sum of the total energies of the corresponding isolated cucurbituril and oxaliplatin. Finally NBO analyses for the complexes are done at the same basis set as implemented in Gaussian G03 program package [28].

Results and discussion

Geometry

The optimized geometries of cucurbit[*n*]uril $n = 5$ to 8, are consistent with the earlier experimental and modeling results [12, 29]. The optimized structures of the cucurbit[n]urils are found to posses a D_{nh} symmetry and are shown in supporting information as Fig. S1. The structural parameters for them were provided in Table 1. The depth of the cavity is about 6.27 Å is all the cucurbiturils, but their equatorial widths, vary systematically from 5.51 to 10.33 Å with ring size as shown in Table 1. The calculated intermolecular distance between the oxygen portals for CB[5], CB[6], CB[7], and CB[8] are 5.51, 7.27, 8.21, 10.33 respectively which are in agreement with the previous reported values [18]. The calculated HOMO-LUMO band gap values are in close to the previous reported values [22]. The portals guarding the entry to all CB[*n*] are approximately 2 Å narrower than the cavity itself which results in constrictive binding that produces significant steric barriers to guest association and dissociation.

In order to know the ground spin state of oxaliplatin, its structures were optimized in singlet and triplet spin state. Though oxaliplatin can exist in different conformers, the trans-*l* isomer was found to be low energy geometry [30]. Thus we have considered only the trans- isomer for our further studies. The ground spin state of the oxaliplatin was found to be singlet and the triplet is 225 kJ/mol higher in energy. The optimized geometry and geometrical parameters for the oxaliplatin are provided in the supporting information Table S1. From the table it is evident that the calculated bond parameters have a close agreement with the experimental values. This result provides us enough confident in the present computational methods.

Table 1 Selected geometrical parameters for optimized geometries (in Å) and the calculated HOMO–LUMO band gap (in eV) for CB[*n*]

CB[*n*]	Diameter of oxygen portal a[a]	Intramolecular depth of cavity b[b]	HOMO	LUMO	HOMO–LUMO energy gap (eV)
5	5.51	6.29	−6.69	−0.680	7.37
6	7.27	6.27	−6.77	−0.789	7.55
7	8.21	6.27	−6.83	−0.897	7.72
8	10.33	6.27	−6.91	−0.897	7.81

[a, b] See Fig. 1

To determine the geometries of the possible cucurbit[*n*]uril–oxaliplatin complexes, oxaliplatin was placed inside the cavity of CB[*n*] and allowed to relax. Since the previous X-ray crystal structure of CB[7]–oxaliplatin complex has a geometry in which cyclohexane was present inside the cavity of CB[7], we have restricted our further studies to this position. The optimized geometries for the inclusion complexes are shown in Fig. 1. Our optimized geometry of the inclusion complex of cucurbit[7]uril-oxaliplatin, resembles the corresponding experimental data obtained from single crystal X-ray analysis [20].

The optimized geometry for the cucurbit[5]uril-oxaliplatin complex, shows that oxaliplatin was expelled out of the cavity. A notable feature for the other inclusion complexes was the structural change in the CB[*n*] structure. The intramolecular distance between the oxygen portals are enlarged in one direction and are reduced in the perpendicular distance. This shows that cucurbiturils are flexible hosts and could accommodate large guests. The amine nitrogen atoms of the oxaliplatin guest lie on the plane of the portal oxygen atoms, with the possible existence of a hydrogen bonding, while the Pt–N distance in the inclusion complex are reduced from the 2.11 to 2.09 Å.

Energetics

To understand the formation and stability of the inclusion complex we have calculated the formation energy and other thermodynamic parameters for the CB[6], C[7] and CB[8] with oxaliplatin as the host at the B3LYP level of theory and the results are provided in Table 2. We have defined the binding energy (ΔBE) as the energy gained

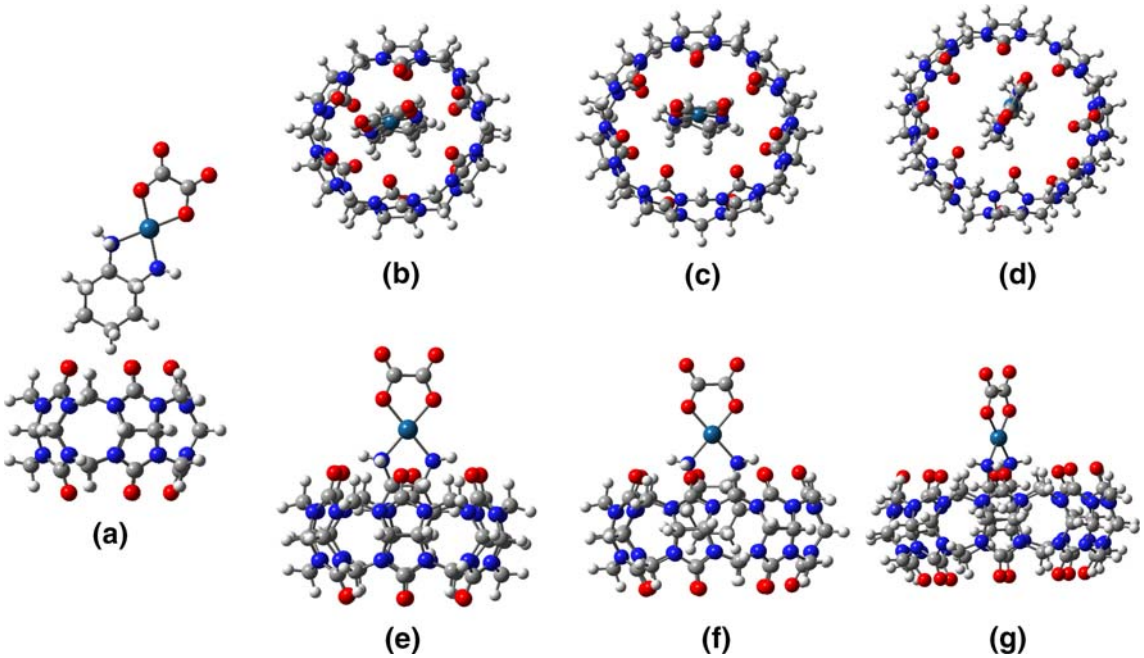


Fig. 1 Optimized structures of **a** CB[5]-oxaliplatin **b** birds eye-view of CB[6]-oxaliplatin **c** birds eye-view of CB[7]-oxaliplatin **d** birds eye-view of CB[8]-oxaliplatin **e** side view of CB[6]-oxaliplatin **f** CB[7]-oxaliplatin **g** CB[8]-oxaliplatin complexes

Table 2 Electronic energy (E), BSSE corrected energy (E_{BSSE}) and binding energy (ΔBE) (in hartrees) of oxaliplatin-CB[*n*] complexes and its components

Subsistent	E	E_{BSSE}	Binding energy ΔBE	
			ΔBE	ΔBE_{BSSE}
Oxaliplatin	−842.944105	–	–	–
CB[6]	−3,610.602111	–	–	–
CB[7]	−4,212.377044	–	–	–
CB[8]	−4,814.146712	–	–	–
CB[6]-oxaliplatin	−4,452.235212	−4,452.21365759	1.31	1.33
CB[7]-oxaliplatin	−5,053.148537	−5,053.13218920	2.17	2.18
CB[8]-oxaliplatin	−5,655.336159	−5,655.32939559	1.75	1.76

during the formation of inclusion complex from its isolated constituents cucurbit[n]uril and oxaliplatin. The positive values of ΔBE indicate that there is an energy gain during the formation of the inclusion complex. The electronic energy (E), basis set superposition corrected (BSSE) (E_{BSSE}) (in hartrees) are reported in Table 2, along with the formation energy of the inclusion complex. The ΔBE data in the gas phase predict that the complex formation is favored in a CB[n], n = 6,7 and 8. The use of MP2 energy was found to increase the formation energy value for these complexes. The computed formation energies are found to be in the range of 1.33–2.18 hartrees. The formation of energy for the cucurbit[7]uril–oxaliplatin complex has the energetically most favorable value of 2.18 hartrees among the inclusion complex. It should be pointed out here that the experimental association constant calculated for the guest oxaliplatin inside the CB[7] molecule is also huge and found to be 2.5×10^5 M^{-1}. The crystal structure of CB[7]-oxaliplatin has been obtained by Kim et. al at high temperature in a sealed glass tube followed by slow cooling. Hence further studies have been carried out for the cucurbit[7]uril–oxaliplatin complex.

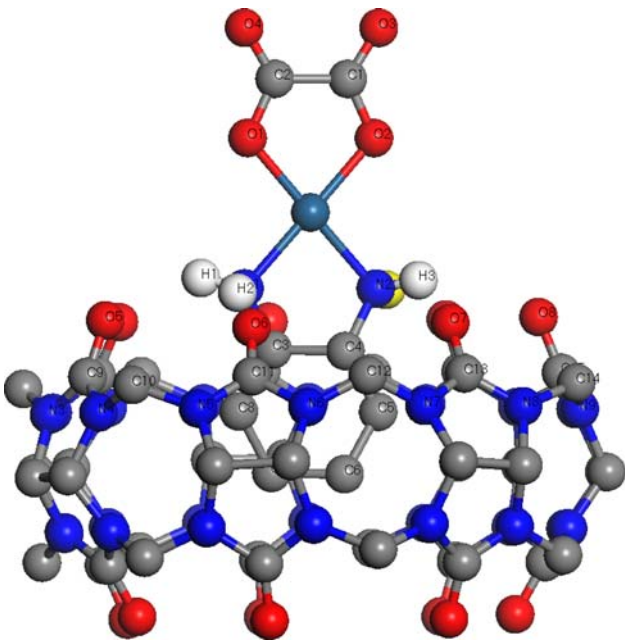
Table 3 The calculated Mulliken charges and NBO charges (in parentheses) of the inclusion complex, CB[7] and oxaliplatin

Atom No.[a]	Oxaliplatin	CB[7]	CB[7]—oxaliplatin
Pt1	0.262 (0.678)		0.159 (0.691)
O1, O2	−0.544 (−0.715)		0.539 (−0.721)
O3, O4	−0.401 (−0.533)		0.448 (−0.578)
N1	−0.787 (−0.863)		−0.825 (−0.863)
N2	−0.787 (−0.863)		−0.818 (−0.859)
H1	0.386 (0.456)		0.428 (0.469)
H3	0.400 (0.455)		0.425 (0.461)
C1	0.511 (0.655)		0.506 (0.657)
C2	0.511 (0.655)		0.510 (0.654)
C3	0.027 (−0.087)		0.021 (−0.090)
C4	−0.259 (−0.493)		0.031 (−0.087)
C5	−0.253 (−0.476)		0.269 (−0.483)
C6	−0.253 (−0.479)		0.255 (−0.474)
C7	−0.259 (−0.493)		0.255 (−0.474)
C8	0.027 (−0.087)		0.274 (−0.484)
C9		0.608 (0.857)	0.771(0.803)
C10		−0.426 (−0.067)	0.039 (−0.098)
C11		0.545 (0.849)	0.770 (0.808)
C12		−0.507 (−0.067)	0.250 (0.149)
C13		0.664 (0.849)	0.761 (0.806)
C14		−0.678 (−0.067	0.037 (−0.098)
C15		0.545 (0.859)	0.771 (0.805)
N3		0.142 (−0.545)	−0.550 (−0.502)
N4		0.244 (−0.546)	−0.553 (−0.508)
N5		0.243 (−0.545)	−0.544 (−0.497)
N6		0.158 (−0.546)	−0.564 (−0.502)
N7		0.258 (−0.545)	−0.564 (−0.501)
N8		0.126 (−0.545)	−0.549 (−0.508)
O5		−0.447 (0.608)	−0.432 (−0.611)
O6		−0.447 (0.608)	−0.444 (−0.627)
O7		−0.447 (0.608)	−0.423 (−0.610)
O8		−0.447 (0.608)	−0.431 (−0.610)

[a] See Scheme 1 for the numbering of atoms

Charge and electronic properties

Table 3 provides the calculated Mulliken partial atomic charges and the Natural Bond Orbital (NBO) charges for the free CB[7], oxaliplatin and CB[7]-oxaliplatin inclusion complex. The numbering patterns are provided in the Scheme 1. Since the Mulliken charges are consider being dependent on the basis set and functional, NBO charges are used in our further discussion. The charge on the metal atom in free state is 0.678, upon complex formation, the charge increases to 0.691, which indicates the change in electron density from the metal center to the ligands has occurred. To see how the change in electron density occurs, we compare the charge on free ligand and the complex, in which the imido carbonyl and the nitrogen atoms gains charge. Simultaneously, electron density is transferred from the cyclohexyl group of the oxaliplatin to the CB[7] unit. Further, the charge on hydrogen atoms on the amine



Scheme 1 Structure and numbering scheme of CB[7]—oxaliplatin inclusion complex. Hydrogen atoms are omitted from the CB[7] and on cyclohexdiamine molecule for clarity

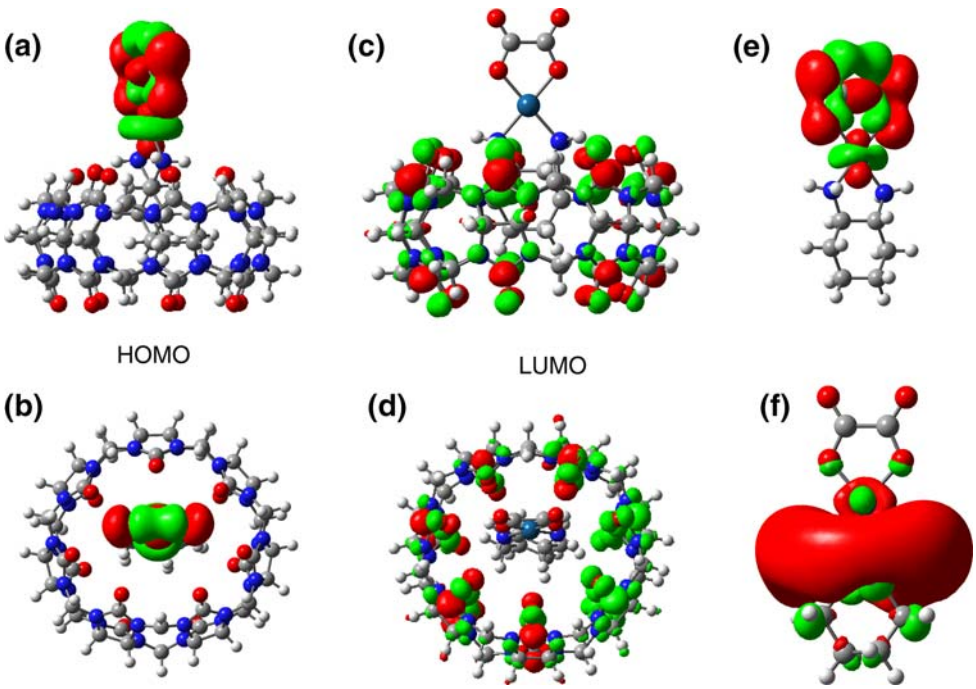


Fig. 2 **a** HOMO of CB[7]-oxaliplatin (side view) **b** birds eye view of HOMO orbital of CB[7]-oxaliplatin **c** side view of LUMO orbital of CB[7]-oxaliplatin **d** birds eye view of LUMO orbital of CB[7]-oxaliplatin **e** HOMO orbital of oxaliplatin **f** LUMO orbital of oxaliplatin

group of oxaliplatin is increases significantly. These observations indicate the involvement of hydrogen bonding between the carbonyl oxygen and the amine hydrogen atoms during the formation of the complex.

The highest occupied molecular orbital (HOMO) of CB[7]-oxaliplatin complex and the lowest unoccupied molecular orbital (LUMO) are shown in Fig. 2. The HOMO orbital is localized on the carboxylate group and the LUMO orbital are localized on the cucurbituril unit in the CB[7]-oxaliplatin complex. For the oxaliplatin, the HOMO orbital are observed on the carboxylate group and the LUMO orbital are observed on the cyclohexyl ligand. This was further conformed by the electron densities with mapped electrostatic potential for the complex (see supporting Information Fig. S2). These findings indicate an intense electronic interaction between cucurbit[7]uril and oxaliplatin which account for the very high formation energy during the complex formation.

Conclusion

In conclusion, DFT analysis of cucurbit[n]urils n = 5–8 are found to posses a D_{nh} symmetry with a large cavity. The formation of inclusion complexes of CB[n]-oxaliplatin are facile in CB[n] n = 6–8, while for the cucurbit[5]uril, the oxaliplatin is expelled out of the cavity. In the complexes, the cyclohexyl group is found to be deep inside the cavity, with the formation of a hydrogen bonding between the portal oxygen atoms and the amine nitrogen of the oxaliplatin guest. The formation energy increases with the increase in the size of CB[n] and the energetically favored complex was CB[7]–oxaliplatin. NBO analysis shows the transfer of charge from the metal center to the CB[7] unit and the existence of hydrogen bonding between the oxygen portal and amine nitrogen. The HOMO orbital is localized on the carboxylate group and the LUMO orbital are localized on the cucurbituril unit in the CB[7]-oxaliplatin complex. The strength of the interaction determined here reflects the ability of cucurbit[n]urils to act as a host for suitably oxaliplatin guests, even in aqueous solution.

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