Preference prediction for the stable inclusion complex formation between cucurbit [n = 5–7]urils with anticancer drugs based on platinum (II): Computational study

Zabiollah Bolboli Nojini a,⁎, Faezeh Yavari b, Sara Bagherifar b

a Department of Chemistry, Faculty of Science, Shahid Chamran University, Ahvaz, Iran
b Department of Chemistry, Science and Research Branch, Islamic Azad University, Khouzestan, Iran

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ABSTRACT

Host-guest inclusion complex formation of cucurbit [n = 5, 6 and 7]urils (CB[n]) with cisplatin and nedaplatin as anticancer drugs were studied using DFT calculations at the B3PW91/LANL2DZ level of theory. The calculations were carried out just for the 1:1 stoichiometric complexes. Upon encapsulation, the equilibrium geometries, binding energy, structural parameters and electronic structures of formed complexes are investigated. The results show that the CB[7]/cisplatin and CB[6]/nedaplatin complexes are more stable than the other complexes. Also, obtained data show that the cavity of CB[n = 5, 6, and 7] are more favorable to form inclusion complexes of nedaplatin than that of cisplatin. From the NBO calculations, the van der Waals forces and electrostatic interactions are the major factors contributed to the overall stabilities of the complexes.

1. Introduction

Medicinal application of metals can be traced back almost 5000 years [1]. Metal centers, being positively charged, are favored to bind to negatively charged biomolecules; the constituents of proteins and nucleic acids offer excellent ligands for binding to metal ions [2]. The modern medicinal inorganic chemistry was developed by the discovery of cis-diamminedichloroplatinum (II) (Cisplatin). Cisplatin is a potent anticancer drug that has been in clinical use for three decades [3–7]. The accidental discovery of the anti-tumoral properties of cisplatin was discovered by Rosenberg while examining the influence of electric current on bacterial growth [8–10].

A lot of different coordination compounds and the mechanism of cytotoxic action have been discussed with regard to the development of new antitumor agents [2]. Besides cisplatin, several other platinum complexes (carboplatin, oxaliplatin, nedaplatin, and lobaplatin) have been approved for current tumor therapy (Fig. 1) [11]. Nedaplatin is a platinum derivative developed in Japan [12]. Nedaplatin causes much less nephrotoxicity than cisplatin [13], hematologic toxicity including thrombocytopenia and neutropenia is a dose-limiting factor for nedaplatin [14]. A recent in vitro chemosensitivity test suggested that nedaplatin has equivalent or superior antitumor activity to cisplatin in cervical cancer [15]. Pharmacokinetic study has shown that the protein binding ability of nedaplatin is much lower than that of cisplatin [16].

Encapsulation of species of biological interest in macrocyclic compounds have been extensively studied because it can be utilized in the delivery, stabilization, solubilization and controlled release of drugs as well as in analyte sensing [17,18]. Cyclodextrins are the most widely used hosts in these applications [19,20]. This strategy has been extensively explored both for naturally occurring hosts such as cyclodextrins as well as for synthetic molecular receptors such as calixarenes and crown ethers [20].

While cucurbituril (CB[6]) was first discovered in 1905 by Behrend et al. [21], its macrocyclic structure was not determined until 1981 and until 2000, CB[6] was the only cucurbituril to receive any attention as a molecule useful in host–guest chemistry [22]. This changed upon the discovery of different sized cucurbiturils: CB[5], CB[7], CB[8] and the isolation of free CB[10] [23,24]. Their discovery has led to a rapid increase in the interest in, and application of, CB[n] in a variety of fields including: nano machines, chromatography, and drug delivery [25]. Cucurbituril, named for its distinctive pumpkin-like shape, is made from the condensation of glycoluril and formaldehyde in strongly acidic solutions (Fig. 2) [26,27]. There has been increasing recent interest in using cucurbit[n]urils to aid in the delivery of molecules of biological and medicinal interest, through host–guest formation. Cucurbituril and cucurbit[8]uril molecules have been used to form host–guest complexes with mononuclear, dinuclear and trinuclear platinum(II) complexes [28–31]. Urbach and co-workers have used 1:1 host–guest complexes of CB[8] and methylviologen to form ternary complexes with tripeptides with specific recognition of the N-terminus aromatic amino acids such as tryptophan [32,33]. In the case of cucurbit[7]uril (Q[7]), Wheate N. J. et al. has shown utility as drug delivery vehicles for a variety of platinum (II) based complexes [34]. Kim and coworkers have shown that

⁎ Corresponding author. Fax: + 98 611 3331042.
E-mail addresses: zb_nojini@gmail.com, zb_nojini@scu.ac.ir (Z. B. Nojini).

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inclusion complexes of oxaliplatin with cucurbit[7]uril has moderate cytotoxicity with larger decrease in reactivity towards guanosine and L-methionine respectively [35]. There exist many reports on the theoretical studies of CB[n] [36–38]. Recently Kim and coworkers made a thermo dynamical analysis of macromolecule cyclization from a monomer to hexamer and found that water molecules, formed as one of the products that helps in the stabilization of the macrocycle [39,40]. Gejji and coworkers, made an assessment on the complex formation capability of CB[n] with ferrocene [41].

All the experimental and theoretical methods, when properly utilized in combination with each other, have proved to be extremely powerful in solving the structural, energetic, and dynamic problems associated with the cucurbit[n]uril complexes. To our knowledge, there has been only a few theoretical research work related to that problem. Venkataramanan N. S. et al. using a theoretical method based on first principles, 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 [42].

Fig. 1. Chemical structures of the platinum(II)-based anticancer complexes.

Fig. 2. The general chemical structure of cucurbit[n]uril, where n = 5, 6, 7, 8 or 10.
Density functional theory has been successful in rationalizing popular concepts such as chemical reactivity and selectivity of molecules based on their global and local reactivity indexes. The global index includes electronegativity ($\chi$) [43,44] and hardness ($\eta$) [44,45], while the local index includes the Fukui function ($f(r)$) and $(s(r))$ [46]. As we already know, electronegativity may be considered as the power of an atom in a given molecule to attract electrons to itself [47]. The idea of hardness was given by Pearson in the context of the hard-soft-acid-base (HSAB) [48] principle, which states that “hard likes hard and soft likes soft”. Another hardness-based principle is the maximum hardness principle (MHP) [49], which states that “it seems to be a rule of nature that molecules arrange themselves so as to be as hard as possible” [50]. For a $N$-electron system with potential acting on an electron at $r$ due to the nuclear attraction plus such other external forces as may be present (external potential) $v(r)$ and total energy $E$, electronegativity ($\chi$) [44] and hardness ($\eta$) [49] are defined as the following first-order [51] and second-order [52] derivatives, respectively:

$$\chi = -\frac{\partial E}{\partial N} |_{v(r),T} = -\mu$$

$$\eta = \frac{1}{2} \left( \frac{\partial^2 E}{\partial N^2} |_{v(r),T} \right) = \frac{1}{2} \left( \frac{\partial \mu}{\partial N} |_{v(r),T} \right)$$

where $\mu$ is the electronic chemical potential, defined as the negative of the electronegativity. In addition, the global softness, $S$, of the equilibrium state of an electronic system at temperature $T$, is defined as [53]:

$$S = \frac{1}{2\eta} = \left( \frac{\partial N}{\partial \mu} |_{v(r),T} \right)$$

Recently, Parr and co-workers [54] have introduced an electrophilicity index ($w$), as:

$$w = \left( \frac{\mu^2}{\eta} \right).$$

It was proposed as a measure of the electrophilic power of a molecule.

To expand the scope of cucurbituril and supramolecular chemistry, we have investigated its energetic and geometric properties with the means of DFT calculations. The DFT calculations were performed at the B3PW91/LANL2DZ level of theory. In this paper, we predict the inclusion complex formation between CB[$n=5–7$] with cisplatin and nedaplatin anticancer drugs. The stabilization energy, heat of formation of the complexes, charge transfer, energies of the highest-occupied molecular orbital (HOMO) and lowest-unoccupied molecular orbital (LUMO) for the components and complexes as well as electronic properties and structural parameter i.e. bond lengths were calculated for the different complexes.

2. Computational Method

Computational analysis of host–guest inclusion complex formation of the CB[$n$] with anticancer drugs were carried out, using the DFT calculation at the level of B3PW91/LANL2DZ, and employing the Gaussian 2003 package [55]. The initial geometries of anticancer drugs were optimized with DFT calculations using the Berny analytical gradient algorithm. Full geometry optimization of the CB[$n$] structures were performed without geometrical or symmetry restraints (none of the atoms was fixed). The position of the guest molecules was determined by the $z$ coordinates of the anticancer drugs. The inclusion process were simulated by putting the guest in one end of CB [$n$] cavity and then letting it pass through the CB[$n$] cavity by steps. In every step, single point calculations at the level of B3PW91/LANL2DZ were used to obtain the heat of formation of the host–guest complexes.

The electronic chemical potential ($\mu$) was calculated as half of the energy of the Fermi level ($E_{\text{HOMO}}$) plus the first eigenvalue of the valence band ($E_{\text{LUMO}}$), as follows:

$$\mu = \frac{(E_{\text{HOMO}} + E_{\text{LUMO}})}{2}.$$ (6)

This definition was driven from Eq. (1). The operational definition of hardness ($\eta$) was obtained using a finite difference approximation to the second derivative in Eq. (2), as [56]:

$$\eta = \frac{(I-A)}{2}$$ (7)

where $I$ and $A$ are the ionization potential and electron affinity of the system, respectively. Eq. (7) could be further approximated as follows, using the Koopmans’ theorem [57]:

$$\eta = \frac{(E_{\text{LUMO}} - E_{\text{HOMO}})}{2}.$$ (8)
hard molecules thus have a large HOMO–LUMO gap and soft molecules have a small one [56].

3. Results and discussion

All initial geometries of drugs and CB[n] were optimized in the framework of density functional theory by use of the B3PW91 functional. The optimized geometries of cucurbit[n = 5 to 7]uril, are consistent with the earlier experimental and modeling results [37,58].

Figs. 3 and 4 show that the final optimization geometries of cisplatin, nedaplatin and CB[n].

To determine the geometries of the possible CB[n]/cisplatin and CB[n]/nedaplatin complexes, cisplatin and nedaplatin were placed in one end of the CB[n] cavity and then letting it pass through the CB[n] cavity. The potential energy surface plots (energy of the inclusion complex vs. the z coordinate) of each different complex are shown in Fig. 5.

The structures of all complexes at the minimum energy of complexation (see Fig. 5) were fully optimized using DFT calculations. The final optimization geometry of CB[n]/cisplatin shows that the cisplatin drug penetrates into the cavity of CB[n] by chlorine atoms with 1:1 stoichiometry while the final optimized geometry of the CB[n]/nedaplatin complexes shows that the nedaplatin was expelled out of the cavity (Fig. 6).

A notable feature for the other inclusion complexes was changed in the drug structures. The structural parameters of isolated cisplatin and nedaplatin and of their complexes are summarized in Tables 1 and 2. As can be seen in Tables 1 and 2 the significant changes in bond lengths are observed; this is mainly observed for the bondings that involve the nitrogen atoms bounded to platinum atoms for both cisplatin and nedaplatin during the complexations. The smallest intermolecular distance between CB[n] and drugs to investigate the hydrogen bonding were considered. The final optimization structures of complexes (Fig. 7) show that the nearest distance where found that between the oxygen atom of carbonyl portal groups of cucurbit[n]urils and the amine H atoms of drugs. The amine nitrogen atoms of the nedaplatin lie on the plane of the portal oxygen atoms, with the Pt–N distance in the inclusion complex are reduced from the 2.107 to 2.077 Å. Furthermore, the obtained structural parameters of nedaplatin complexes show that the smallest distance between guest and CB[n] is observed for the CB[7]/nedaplatin complex (about 1.9 Å). In the case of cisplatin as a guest molecule, the nearest distance is obtained for CB[6]/cisplatin (1.95 Å). As a result, the CB[7]/nedaplatin and CB[6]/cisplatin complexes have stronger intermolecular interactions than that of other complexes were formed (see Fig. 7).

To understand the stability of complexes, the binding energy of the cisplatin and nedaplatin with CB[5], CB[6] and CB[7] as the hosts at the B3PW91 level of theory are calculated. The binding energy of complexes (∆E) is obtained from the energy difference between the resulting complexes with the lowest HF (heat of formation) energy and energy of the isolated cucurbit[n]urils as host and cisplatin and nedaplatin as guests, which defined as below:

$$\Delta E = E_{\text{complex}} - (E_{\text{CB}[n]} + E_{\text{drug}})$$. (5)

Negative interaction energies obtained from the DFT calculations indicate that complexation of guests into the CB[n] cavities is highly favored.

First, the effect of the cavity of CB[n] on the stability of the complexation was considered. The fit of the entire or at least a part of the guest molecule in the CB[n] host cavity determines the stability of the inclusion complex. The most complexation energies reported in Table 3 have negative values which mean that the formed complexes are stable. The value of binding energy for the CB[5]/cisplatin complex (30.12 kcal/mol) in the inclusion process indicates that the inclusion complex process is endothermic and the formed complex is not stable. From these results, it concludes that the cavity of CB[5] is not a good candidate to accept cisplatin as a guest molecule. The key features in the complexation are summarized in Table 3. With the change in the host molecule from CB[5] to CB[n = 6,7], the stability of the formed complexes is increased. In other words, the formed complex between CB[6] and cisplatin is stable than CB[5]/cisplatin. When the host molecule is CB[7], the formed complex has the
most stability (−28.24 kcal/mol). As a result, the stability of the form complexes is increased with increasing cavity of CB[n]. In other words, our results predict that the CB[7] as host molecule adopts the guest molecule inside the cavity in order to increase the stability of the complexes. Obtained data are in well agreement with the results of the inclusion complex formation between CB[n] and oxaliplatin [42]. Venkataramanan N. S. et al. [42] using a theoretical method based on first principles show that the formation energy increases with the increase in the size of CB[n] and the energetically favored complex was CB[7]/oxaliplatin.

Second, the effect of the guest molecule on the inclusion complex formation is investigated. As reported in Table 3, all the complexation energies are negative which means that the formed complexes are stable and the inclusion processes are exothermic. The results of complexation energies of the CB[n]/nedaplatin show that the CB[n] cavities are more favorable to form a CB[n]/nedaplatin complexes and the CB[6]/nedaplatin is more stable than the others. Comparing the results of the complexation processes of cisplatin and nedaplatin reveals that complexes of nedaplatin and CB[n=5–7] are more favorable than that of via cisplatin with CB[n=5–7]. As it could be observed in Table 3, the CB[6]/nedaplatin is the most stable than the other complexes.

One of the essential characteristics affecting the possibility of interaction of host–guest complexes inside the cavitant is the distribution of effective charges on the atoms. Tables 4 and 5 indicate that the partial charge of the Pt, Cl, O and N atoms of drugs significantly changed during the complexation. Charge distribution computed by the natural bond orbital (NBO) approach reveals that the charges of the O(3), N(1) and N(2) atoms of the cisplatin and nedaplatin in complexes are more negative than those in isolated components while the Pt atoms are more positive than those in the isolated drugs. This means that when the guest molecule interacts with CB[n], its charge distribution changes. So, when cisplatin and nedaplatin molecules penetrate into the CB[n] cavities, there is a charge-transfer from drugs to CB[n] that occurs and producing a common chemical potential. In this case, CB[n] serves as weak Lewis acids. The atomic numbering schemes of drugs are shown in Fig. 3. The results of the HOMO and LUMO energies of the complexes are summarized in Table 3. The partial charge transfer will occur by a contribution from the mixing of the filled orbital of one component molecule with the vacant orbital of another. The most important terms in this kind of interaction are contributed from the partial charge transfer between the HOMO of one component and the LUMO of another. The HOMO–LUMO (H–L) energy gap is large in magnitude for these complexes and corresponds to 3.1–4.8 eV. According to the difference between the frontier orbital energies when the energy gap is higher, the system behaves like a very stable molecule. In addition, the high HOMO energy indicates that the molecule can undergo an electrophilic attack with a large probability. The typical structures of the HOMO and LUMO are shown in Fig. 8a and 8b. These figures show that the HOMO orbital localized on the drugs and the LUMO orbital are observed on the CB[n].

The global indices of reactivity in the context of DFT are presented in Table 6. The value of hardness, softness, electrophilicity and
electronic chemical potential for complexes are differing from the individual CB[n] and drug molecules. When drug molecule and CB[n] are brought together, electrons will flow from that of lower $\chi$ to that of higher $\chi$. On the other hand, electron is being transferred to the lower electronic chemical potential, until the electronic chemical potentials become equal\textsuperscript{55}. The difference in electronegativity drives the electron transfer, and the sum of the hardness parameters acts as a resistance. The electronic chemical potential and the hardness are molecular and not orbital properties. As a result, the electrons will

![Figure 6](image_url)

**Fig. 6.** Optimized structures at each energy minimum obtained from DFT calculations for the (a) bird’s-eye-view of CB[7]/cisplatin, (b) bird’s-eye-view of CB[7]/nedaplatin, (c) side view of CB[7]/cisplatin and (d) side view of CB[7]/nedaplatin complexes.

### Table 1
The significant bond lengths ($\text{Å}$) of optimized complexes of cisplatin with CB[n]urils calculated by B3PW91/LANL2DZ method.

<table>
<thead>
<tr>
<th>Bond lengths</th>
<th>Cisplatin</th>
<th>CB[5]/cisplatin</th>
<th>CB[6]/cisplatin</th>
<th>CB[7]/cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt – O(1)</td>
<td>2.393</td>
<td>2.394</td>
<td>2.35</td>
<td>2.422</td>
</tr>
<tr>
<td>Pt – O(2)</td>
<td>2.392</td>
<td>2.395</td>
<td>2.408</td>
<td>2.420</td>
</tr>
<tr>
<td>Pt – N(1)</td>
<td>2.090</td>
<td>2.063</td>
<td>2.077</td>
<td>2.069</td>
</tr>
<tr>
<td>Pt – N(2)</td>
<td>2.091</td>
<td>2.069</td>
<td>2.073</td>
<td>2.070</td>
</tr>
<tr>
<td>N(1) – H(1)</td>
<td>1.033</td>
<td>1.040</td>
<td>1.029</td>
<td>1.027</td>
</tr>
<tr>
<td>N(1) – H(2)</td>
<td>1.021</td>
<td>1.021</td>
<td>1.025</td>
<td>1.028</td>
</tr>
<tr>
<td>N(1) – H(3)</td>
<td>1.021</td>
<td>1.022</td>
<td>1.025</td>
<td>1.021</td>
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<tr>
<td>N(2) – H(4)</td>
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<td>1.020</td>
<td>1.021</td>
<td>1.029</td>
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<tr>
<td>N(2) – H(5)</td>
<td>1.033</td>
<td>1.028</td>
<td>1.032</td>
<td>1.021</td>
</tr>
<tr>
<td>N(2) – H(6)</td>
<td>1.021</td>
<td>1.038</td>
<td>1.021</td>
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</tbody>
</table>

### Table 2
The significant bond lengths ($\text{Å}$) of optimized complexes of nedaplatin with CB[n]urils calculated by B3PW91/LANL2DZ method.

<table>
<thead>
<tr>
<th>Bond lengths</th>
<th>Nedaplatin</th>
<th>CB[5]/nedaplatin</th>
<th>CB[6]/nedaplatin</th>
<th>CB[7]/nedaplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt – O(1)</td>
<td>1.987</td>
<td>2.008</td>
<td>2.009</td>
<td>2.004</td>
</tr>
<tr>
<td>Pt – O(2)</td>
<td>1.997</td>
<td>2.018</td>
<td>2.021</td>
<td>2.017</td>
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<tr>
<td>Pt – N(1)</td>
<td>2.107</td>
<td>2.077</td>
<td>2.084</td>
<td>2.093</td>
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<tr>
<td>Pt – N(2)</td>
<td>2.09</td>
<td>2.067</td>
<td>2.065</td>
<td>2.073</td>
</tr>
<tr>
<td>N(1) – H(1)</td>
<td>1.028</td>
<td>1.023</td>
<td>1.024</td>
<td>1.025</td>
</tr>
<tr>
<td>N(1) – H(2)</td>
<td>1.02</td>
<td>1.024</td>
<td>1.024</td>
<td>1.021</td>
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<tr>
<td>N(1) – H(3)</td>
<td>1.02</td>
<td>1.024</td>
<td>1.024</td>
<td>1.026</td>
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<tr>
<td>N(1) – H(4)</td>
<td>1.03</td>
<td>1.024</td>
<td>1.025</td>
<td>1.026</td>
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<td>N(1) – H(5)</td>
<td>1.02</td>
<td>1.023</td>
<td>1.024</td>
<td>1.021</td>
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<tr>
<td>N(1) – H(6)</td>
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<td>1.026</td>
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<tr>
<td>C(1) – O(3)</td>
<td>1.364</td>
<td>1.349</td>
<td>1.347</td>
<td>1.351</td>
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<tr>
<td>C(2) – O(2)</td>
<td>1.451</td>
<td>1.444</td>
<td>1.444</td>
<td>1.446</td>
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<tr>
<td>C(1) – C(2)</td>
<td>1.544</td>
<td>1.544</td>
<td>1.544</td>
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<tr>
<td>C(1) – O(1)</td>
<td>1.242</td>
<td>1.252</td>
<td>1.252</td>
<td>1.250</td>
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<td>C(2) – H(7)</td>
<td>1.099</td>
<td>1.102</td>
<td>1.102</td>
<td>1.100</td>
</tr>
<tr>
<td>C(2) – H(8)</td>
<td>1.099</td>
<td>1.102</td>
<td>1.102</td>
<td>1.102</td>
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</table>
flow from a definite occupied orbital in drugs and will go into a definite empty orbital in CB[n]. Also, results show that when the drug molecules penetrate to the cavity of the CB[n], the hardness of the complexes were decreased, which means that the stability of the complexes are lower than pristine CB[n].

4. Conclusion

In this paper we report a QM density functional calculation of the inclusion complex formation between CB[n] and two anticancer drugs, cisplatin and nedaplatin. To summarize, the following conclusions can be made. Molecular modeling calculations, predict that the cisplatin penetrates into the CB[n] cavity by the chlorine atoms with 1:1 stoichiometry while the optimized geometry of the nedaplatin complexes show that nedaplatin was expelled out of the cavity. Also, the analysis of the binding energy indicates that the complexes of CB[n]/nedaplatin are more favorable than that of the CB[n]/cisplatin and the final optimized geometries of the complexes show that the hydrogen bonding between the portal oxygen atoms of CB[n] and the amine group of the cisplatin and nedaplatin as guest molecules occurred. The NBO calculations show that the inclusion complexes accompanied with charge transfer from the drugs to the CB[n] and also, significant changed in the gap energy of the CB[n] occurred when the drug molecule penetrates to the cavity of CB[n]. The strength of the interaction determined here reflects the van der Waals forces and electrostatic interactions are the major factors contributed to the overall stabilities of the complexations in vacuo.

Table 3
The calculated electronic energy (E kcal/mol), binding energy (ΔE kcal/mol), HOMO (eV), LUMO (eV) and Gap energy (eV) of the complexes and its components.

<table>
<thead>
<tr>
<th>Type</th>
<th>E</th>
<th>ΔE</th>
<th>HOMO</th>
<th>LUMO</th>
<th>Gap energy</th>
</tr>
</thead>
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<tr>
<td>Cisplatin</td>
<td>−164,627.25</td>
<td>-</td>
<td>−6.313</td>
<td>−1.796</td>
<td>4.517</td>
</tr>
<tr>
<td>Nedaplatin</td>
<td>−335,894.81</td>
<td>-</td>
<td>−5.388</td>
<td>−0.517</td>
<td>4.871</td>
</tr>
<tr>
<td>CB[5]</td>
<td>−1,886,972.14</td>
<td>-</td>
<td>−6.44</td>
<td>0.381</td>
<td>7.021</td>
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<tr>
<td>CB[6]</td>
<td>−2,264,376.74</td>
<td>-</td>
<td>−6.694</td>
<td>0.462</td>
<td>7.156</td>
</tr>
<tr>
<td>CB[7]</td>
<td>−2,641,774.43</td>
<td>-</td>
<td>−6.748</td>
<td>0.462</td>
<td>7.21</td>
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<tr>
<td>CB[5]/cisplatin</td>
<td>−2,051,569.27</td>
<td>30.12</td>
<td>−5.113</td>
<td>−0.435</td>
<td>4.678</td>
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<tr>
<td>CB[6]/cisplatin</td>
<td>−2,429,004.61</td>
<td>−0.627</td>
<td>−5.116</td>
<td>−0.218</td>
<td>4.898</td>
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<tr>
<td>CB[7]/cisplatin</td>
<td>−2,806,429.92</td>
<td>−28.24</td>
<td>−4.707</td>
<td>−0.008</td>
<td>4.715</td>
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<td>CB[5]/nedaplatin</td>
<td>−2,222,897.7</td>
<td>−30.74</td>
<td>−3.537</td>
<td>−0.354</td>
<td>3.183</td>
</tr>
<tr>
<td>CB[6]/nedaplatin</td>
<td>−2,600,302.92</td>
<td>−31.38</td>
<td>−3.755</td>
<td>−0.082</td>
<td>3.673</td>
</tr>
<tr>
<td>CB[7]/nedaplatin</td>
<td>−2,977,695.6</td>
<td>−26.35</td>
<td>−3.839</td>
<td>−0.027</td>
<td>3.812</td>
</tr>
</tbody>
</table>

Table 4
The calculated NBO charges (esu) of the cisplatin and inclusion complex of CB[n]/cisplatin.

<table>
<thead>
<tr>
<th>Atom no.</th>
<th>Cisplatin</th>
<th>CB[5]/cisplatin</th>
<th>CB[6]/cisplatin</th>
<th>CB[7]/cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt</td>
<td>0.574</td>
<td>0.579</td>
<td>0.545</td>
<td>0.613</td>
</tr>
<tr>
<td>Cl(1)</td>
<td>−1.075</td>
<td>−1.055</td>
<td>−1.055</td>
<td>−1.055</td>
</tr>
<tr>
<td>Cl(2)</td>
<td>0.104</td>
<td>−1.056</td>
<td>−1.065</td>
<td>−1.056</td>
</tr>
<tr>
<td>N(1)</td>
<td>−0.51</td>
<td>−0.532</td>
<td>−0.492</td>
<td>−0.581</td>
</tr>
<tr>
<td>N(2)</td>
<td>−0.51</td>
<td>−0.531</td>
<td>−0.543</td>
<td>−0.581</td>
</tr>
<tr>
<td>H(1)</td>
<td>0.477</td>
<td>0.443</td>
<td>0.431</td>
<td>0.417</td>
</tr>
</tbody>
</table>

Table 5
The calculated NBO charges (esu) of the nedaplatin and inclusion complex CB[n]/nedaplatin.

<table>
<thead>
<tr>
<th>Atom no.</th>
<th>Nedaplatin</th>
<th>CB[5]/nedaplatin</th>
<th>CB[6]/nedaplatin</th>
<th>CB[7]/nedaplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt</td>
<td>0.769</td>
<td>0.771</td>
<td>0.764</td>
<td>0.776</td>
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<tr>
<td>O(1)</td>
<td>−0.631</td>
<td>−0.675</td>
<td>−0.678</td>
<td>−0.675</td>
</tr>
<tr>
<td>O(2)</td>
<td>−0.841</td>
<td>−0.865</td>
<td>−0.867</td>
<td>−0.861</td>
</tr>
<tr>
<td>O(3)</td>
<td>−0.791</td>
<td>−0.781</td>
<td>−0.791</td>
<td>−0.784</td>
</tr>
<tr>
<td>N(1)</td>
<td>−1.086</td>
<td>−1.067</td>
<td>−1.073</td>
<td>−1.077</td>
</tr>
<tr>
<td>N(2)</td>
<td>−1.078</td>
<td>−1.065</td>
<td>−1.065</td>
<td>−1.063</td>
</tr>
<tr>
<td>C(1)</td>
<td>0.794</td>
<td>0.79</td>
<td>0.791</td>
<td>0.796</td>
</tr>
<tr>
<td>C(2)</td>
<td>−0.169</td>
<td>−0.167</td>
<td>−0.17</td>
<td>−0.171</td>
</tr>
</tbody>
</table>

Fig. 7. The nearest distance where found that between the oxygen atom of carbonyl portal groups of cucurbit[n]urils and the H atoms of amine group of drugs: (a) CB[6]/cisplatin and (b) CB[7]/nedaplatin.
Fig. 8. Typically contour plots of (a) HOMO of the CB[5]/nedaplatin, (b) LUMO of the CB[5]/nedaplatin, (c) HOMO of the CB[7]/cisplatin and (d) LUMO of the CB[7]/cisplatin.

Table 6

<table>
<thead>
<tr>
<th>Type</th>
<th>μ (eV)</th>
<th>ξ (eV)</th>
<th>η (eV)</th>
<th>ω (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>−4.054</td>
<td>4.054</td>
<td>2.258</td>
<td>3.639</td>
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<tr>
<td>Nedaplatin</td>
<td>−2.939</td>
<td>2.939</td>
<td>2.422</td>
<td>1.783</td>
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<tr>
<td>CB[5]/cisplatin</td>
<td>−2.774</td>
<td>2.774</td>
<td>2.339</td>
<td>1.644</td>
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<tr>
<td>CB[6]/cisplatin</td>
<td>−2.667</td>
<td>2.667</td>
<td>2.45</td>
<td>1.452</td>
</tr>
<tr>
<td>CB[7]/cisplatin</td>
<td>−2.357</td>
<td>2.357</td>
<td>2.349</td>
<td>1.182</td>
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<tr>
<td>CB[5]/nedaplatin</td>
<td>−1.946</td>
<td>1.946</td>
<td>1.592</td>
<td>1.189</td>
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<tr>
<td>CB[6]/nedaplatin</td>
<td>−1.919</td>
<td>1.919</td>
<td>1.837</td>
<td>1.062</td>
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<tr>
<td>CB[7]/nedaplatin</td>
<td>−1.932</td>
<td>1.932</td>
<td>1.903</td>
<td>0.981</td>
</tr>
</tbody>
</table>

References
