Theoretical investigation of the complexation, structural, and electronic properties of complexes between oseltamivir drug and cucurbit[n = 6–9]urils

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Abstract
The structural geometries of cucurbit[n]uril CB[n] with n = 6–9 and their complexes with oseltamivir (OST) drug were obtained using the density functional theory computations. The stationary points of the most stable complexes were confirmed using vibrational frequency calculation. The complexation energies and electronic properties of CB[n]/OST complexes were investigated. The calculated results indicate that the intermolecular interactions in all the studied complexes occur via a large number of dipole–dipole interactions, especially hydrogen bonds between oxygen atoms of CB[n] and hydrogen atoms of amine of oseltamivir drug. The negative complexation energies of CB[n]/OST complexes in both gas and water phases indicate that the host–guest complexes are exothermic process and the complexes are more stable than its bare CB[n]. In addition, the CB[7]/OST complex is more stable than that of all studied CB[n]/OST complexes. The frequency calculation results of the most stable complexes for each of CBs indicate that complexations occur via a spontaneous process. The NBO analysis of complexes shows the transferring of partial charge from CB[n]s to oseltamivir which correspond to their MEP contours. The HOMO and the LUMO orbitals are localized on the oseltamivir in CB[n]/OST complexes. After drug complexation, the electronic properties also display that the energy gaps of CB[n] are significantly changed. All of the complexation properties point out that CB[n]s can act as a host for appropriately oseltamivir guest, even in aqueous solution.

Keywords Cucurbit[n]uril · Density functional theory · Influenza virus · Host–guest complex · Oseltamivir

Introduction
In the field of supramolecular chemistry, the design of drug delivery system through the host–guest formation is interesting [1]. One efficiency method is the drug encapsulation with macrocyclic host. Encapsulation method can be utilized in the delivery, solubilization, and stabilization of drug [2, 3]. Moreover, encapsulation can protect the drug from degradation and increase the specific of the drug [4, 5]. Macrocyclic host for drug encapsulation has been widely interested such as cycloexedrinins [6–8] calixarenes [9, 10], crown ethers [11], and cucurbit[n]urils [12–15].

Cucurbit[n]uril (CB[n]) compounds with the molecular formula of \( C_{6n}H_{4n+4}N_4O_2n \) have features of cavities that are suitable for host–guest complex [16]. The cucurbit[n]uril hosts have been synthesized via the condensation between glycoluril and formaldehyde in a strongly acidic solution [17]; the homologs of cucurbit[n]urils (CB[n], n = 5–10) included five to ten glycoluril units acting as hydrophobic cavity are favorable for holding hydrophobic groups/natural molecules. Thus, the host–guest complexes of CB[n]s are produced via noncovalent interactions including ion–dipole interactions and hydrogen bonding interaction [18, 19]. Recently, CB[n] compounds are widely interested for drug delivery applications through host–guest formation because the CB[n] and their derivatives are non–toxic [20]. There are numerous reports focusing on drug delivery of the CB[n] [21–26]. Moreover, the different aspects of the
CB[n] chemistry, such as catalysis [27], material [28], and other potential application in supramolecular [29] have been also reported.

Oseltamivir (OST) has been approved by the Food and Drug Admission (FDA) in 1999 [30]. Oseltamivir is used as an antiviral drug for the treatment of influenza virus. Its action mechanism is correlated to the neuraminidase inhibition of the influenza virus [31]. In the human body, oseltamivir is transformed to oseltamivir acid which is the pharmacologically active metabolite. Oseltamivir acid is also showing indirectly photodegradable [32] and slow degradation in surface waters, but increased degradation in sediment/water systems [33, 34]. Basically, when the hosts transform in the bioenvironment system, their properties could be modified via oxidation, hydrolysis, or reduction phenomena; therefore, it is necessary to control the releasing ability, improve bioavailability, and reduce toxic effects [35].

In the present research, we present a theoretical study on the possibility of the complexations between oseltamivir and cucurbit[n]uril (CB[n], n = 6, 7, 8, and 9) and investi- gate their energetical and geometrical properties using the density functional theory (DFT) calculations. The charge transfers, energies of the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), and molecular electrostatic potentials (MEP) for the species and complexes have been computed.

**Computational details**

The DFT computations were employed to optimize the structures of CB[n] (n = 6, 7, 8, and 9) and their complexes with oseltamivir. All calculations were carried out with the Becke 3-parameters exchange functionals and LYP correlation functional (B3LYP) theory with the 6–31G(d,p) basis set [36–38]. The complexation has been processed by putting the guest into the cavity of CB[n] hosts. Full geometrical optimizations of the CB[n] and their complexation structures were performed without any geometrical or symmetry constraints in which none of the atoms were fixed. The highest occupied molecular orbital (E\text{HOMO}) and the lowest unoccupied molecular orbital (E\text{LUMO}) energies were computed from the same theoretical level.

All computations were performed with the Gaussian 09 program [39]. Electronic properties of all studied compounds have been computed in the gas phase unless otherwise specified. In the computations of studied compounds in water, the solvent effect under the conductor–like polarizable continuum model (CPCM) [40, 41] was carried out. To understand the stability of the complexes, the complexation energies (E\text{cpx}) were obtained from the energy difference between the energy of host–guest complexes (E\text{H-G}) and energy of the bare CB[n] (E\text{H}) and free oseltamivir guest (E\text{G}) as below:

\begin{equation}
E_{\text{cpx}} = E_{\text{H-G}} - (E_{\text{H}} + E_{\text{G}})
\end{equation}

The natural bond orbital (NBO) analysis implemented in Gaussian 09 program has been used. The partial charge transfers (PCTs) during complexation have been defined as a change in oseltamivir charges during the complexation process using the computed natural bond orbital charges. Finally, the graphics and molecular electrostatic potential (MEP) of studied complexes were generated using the Molekel 4.3 program [42].

**Results and discussion**

**Geometrical structures**

The geometrical structures of cucurbit[n]uril (CB[n], n = 6, 7, 8, and 9) and their complexes with oseltamivir have been computed by full optimization without any constraints using the DFT method. The optimized structures of oseltamivir and bare cucurbit[n]urils are displayed in Figs. 1 and 2, respectively. The optimized structures of the CB[n]s are found to possess as a D\text{n}h symmetrical structure, which is in agreement with the earlier report [43]. The intramolecular depths of the cavity of CB[6], CB[7], CB[8], and CB[9] are 6.23, 6.24, 6.25, and 6.26 Å, respectively. The equatorial widths are extreme and systematical increasing from 7.20 to 11.76 Å with ring size. The computed intermolecular distances between the oxygen portals for CB[6], CB[7], CB[8], and CB[9] are 7.20, 8.77, 10.31, and 11.76 Å, respectively, which are according to the previously calculated values [16].
To investigate the possible geometries of the CB\(_n\)/OST complexes, an oseltamivir was placed inside the cavity of CB\(_n\) with different orientations and allowed to relax. To obtain complete molecular structures of the oseltamivir orientation in the host–guest complexes, we combined the oseltamivir with CB\(_n\) in different orientations before computations. Subsequently, full geometry optimization was carried out. Three types of the possible host–guest inclusion modes of binding motive through ethyl formate (CB\(_n\)/OST–e), acetamide (CB\(_n\)/OST–a), and pentan-3-ol (CB\(_n\)/OST–p) side chains of OST pointing to CB\(_n\) cavities are obtained. The DFT optimized structures of oseltamivir complexes with the CB[6], CB[7], CB[8], and CB[9] are displayed in Figs. 3, 4, 5, and 6, respectively. The optimized geometrical structures for all CB\(_n\)/OST complexes reveal that most of oseltamivir is still positioned inside the cavity of CB[6], CB[7], and CB[8], except for CB[6]/OST–a, CB[6]/OST–p and CB[8]/OST–p complexes, oseltamivir is expelled out of CB\(_n\)s. For the largest cavity host CB[9], only one type of optimized geometries in which OST drug placed at the cavity center of CB[9] is converged and obtained. The computed results also display that the CB\(_n\)s can form stable complexes with oseltamivir through dipole–dipole interactions, especially the hydrogen bonds between the portal oxygen atoms of CB\(_n\) and the amine hydrogen atoms of oseltamivir drug in which the average hydrogen bond distances are found in the range of 1.935 to 2.693 Å. The numbers of hydrogen bonds and average hydrogen bond distances of CB[6], CB[7], CB[8], and

**Fig. 2** Optimized structures of (a) CB[6], (b) CB[7], (c) CB[8], and (d) CB[9]
CB[9] complexes with OST drug with different inclusion orientations are tabulated in Table 1.

Complexation energies

To comprehend the stability of complexes, the complexation energies ($E_{\text{cpx}}$) of the oseltamivir with CB[n]s were calculated. The complexation energies are obtained from the energy difference between the energy of complex and the energies of the isolated CB[n] as host and free oseltamivir as guest. The complexation energies of the CB[6], CB[7], CB[8], and CB[9] with oseltamivir in gas phase and water solution computed at the B3LYP/6-31G(d,p) theoretical level are tabulated in Table 1. The negative values of complexation energies reveal that the host–guest inclusion complexes are exothermic process and the complexes formed are more stable than isolated molecules. The complexation energies of all complexes formed in gas phase are found to be in the range of $-7.39$ to $-19.83$ kcal/mol. The formation of energy for the CB[7]/OST–e complex has the most energetically favorable value of $-19.83$ kcal/mol among the inclusion complexes. The complexation abilities of CB[n]
to oseltamivir drug in gas phase are in the order: CB[7]/OST–e (−19.83 kcal/mol) ≈ CB[6]/OST–p (−18.69 kcal/mol) ≈ CB[8]/OST–e (−17.75 kcal/mol) > CB[7]/OST–a (−15.13 kcal/mol) ≈ CB[8]/OST–a (−14.62 kcal/mol) ≈ CB[6]/OST–p (−13.63 kcal/mol) ≈ CB[9]/OST (−11.93 kcal/mol) > CB[6]/OST–e (−9.05 kcal/mol) > CB[7]/OST–p (−7.39 kcal/mol).

The vibrational frequency computations have been carried out at 298.15 K and 1 atm. Stationary points of the most stable configurations in gas phase i.e., CB[6]/OST–p, CB[7]/OST–e, and CB[8]/OST–e have been fully characterized by vibrational frequency calculations, which also provided zero-point vibrational energies (ZPVE) [44]. The standard enthalpy (ΔH°) and Gibbs free energy changes (ΔG°) of the reactions at 298.15 K have been derived from the frequency calculations at the B3LYP/6-31G(d,p) theoretical level. The results of frequency calculations display that no imaginary frequencies are observed confirming the CB[6]/OST–p, CB[7]/OST–e, and CB[8]/OST–e configurations are the stationary points. The computed ZPVE correction energy changes of complexations between CBs and OST for CB[6]/OST–p, CB[7]/OST–e, and CB[8]/OST–e complexes are found to be −17.17, −17.62, and −15.89 kcal/mol, respectively. The computed enthalpy changes of complexations for CB[6]/OST–p, CB[7]/OST–e, and CB[8]/OST–e complexes are −15.14, −16.60, and −14.62 kcal/mol, respectively. Whereas the computed free energy changes of complexations for CB[6]/OST–p, CB[7]/OST–e, and CB[8]/OST–e complexes are −5.63, −2.20, and −2.90 kcal/mol, respectively.

The negative values of complexation free energy changes indicate that the complexations are occurred via a spontaneous process. In which the negative values of complexation energies and enthalpy changes imply that the complexations are exothermic process and the formed complexes are stable in gas phase which corresponding to the previous report [45]. The complexation energies of all complexes formed in water solution are found to be in the range of −4.70 to −10.04 kcal/mol. This means that complexations are also found to be exothermic process and the complexes formed are also stable in water solution as same as in the gas phase.

### Electronic properties

Upon the complexation of oseltamivir drug with CB[n]s, the effect of oseltamivir drug on electronic behavior of CB[n]s was investigated to describe the change of their electronic structures. For more understanding the chemical activity of CB[n]s to oseltamivir, the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), and energy gap (E_{gap}) were calculated.

![Optimized structures of CB[9]/OST complex, bird-eye view (left) and side view (right)](image_url)
The electronic properties of the CB[n]s compared with their complexes with oseltamivir could be used to evaluate the chemical activity of CB[n]s and their complexes. The calculated HOMO and LUMO energies and energy gaps of CB[n]s and their complexes with oseltamivir drug are listed in Table 2. The results show that the energy gaps of CB[6], CB[7], CB[8], and CB[9] are 7.228, 7.237, 7.224, and 7.207 eV, respectively; these results are found to be consistent with the previous reports [16, 25]. For the CB[n]/OST complexes, the energy gaps of CB[6]/OST, CB[7]/OST, and CB[8]/OST complexes are calculated to be in the range of 4.355–5.133, 4.527–4.944, and 4.662–5.024 eV, respectively. While the energy gap of a CB[9]/OST complex is found to be 4.759 eV. The decrease in energy gaps of CBs after complexation with oseltamivir drug may be due to their chemical activity of CB[n]s and their complexes. The results point out that all of CB[n]s are changed in their electrical conductivities due to oseltamivir complexation.

In addition, the quantum molecular descriptions such as chemical electronic potential (μ), electronegativity (χ), chemical hardness (η), electrophilicity (ω), and chemical softness (S) of the CB[n] and their complexation with oseltamivir molecule have been analyzed (Table 2), which were calculated from HOMO and LUMO energy levels (Eqs. (2)–(6)). The μ, χ, η, ω, and S could be considered the first and the second partial derivatives of electronic energy (E) with respect to the number of electrons (N) at a fixed external potential (α(ν)) [46]. According to the Janak’s approximation [47], analytical and operational definitions of the quantum molecular descriptions were given as follows:

| Type       | \(E_{\text{HOMO}}\) (eV) | \(E_{\text{LUMO}}\) (eV) | \(E_{\text{gap}}\) (eV) | \(\mu\) (eV) | \(\chi\) (eV) | \(\eta\) (eV) | \(\omega\) (eV) | \(S\) (eV) |
|------------|--------------------------|--------------------------|--------------------------|-------------|-------------|-------------|-------------|-------------|
| OST        | −6.248                   | −1.354                   | 4.894                    | 3.801       | 3.801       | 2.447       | 2.953       | 0.204       |
|            | (−6.504)                 | (−1.279)                 | (5.225)                  | (3.891)     | (2.612)     | (2.898)     | (0.191)     |             |
| CB[6]      | −6.424                   | 0.803                    | 7.228                    | −2.811      | 3.614       | 1.093       | 0.138       |             |
|            | (−6.694)                 | (0.626)                  | (7.320)                  | (−3.034)    | (3.660)     | (1.258)     | (0.137)     |             |
| CB[7]      | −6.507                   | 0.730                    | 7.237                    | −2.888      | 3.619       | 1.153       | 0.138       |             |
|            | (−6.749)                 | (0.599)                  | (7.347)                  | (−3.075)    | (3.674)     | (1.287)     | (0.136)     |             |
| CB[8]      | −6.574                   | 0.649                    | 7.224                    | −2.963      | 3.612       | 1.215       | 0.138       |             |
|            | (−6.803)                 | (0.571)                  | (7.374)                  | (−3.116)    | (3.687)     | (1.316)     | (0.136)     |             |
| CB[9]      | −6.632                   | 0.576                    | 7.207                    | −3.028      | 3.604       | 1.272       | 0.139       |             |
|            | (−6.857)                 | (0.544)                  | (7.402)                  | (−3.157)    | (3.701)     | (1.346)     | (0.135)     |             |
| CB[6]/OST–e| −5.244                   | −0.111                   | 5.133                    | −2.677      | 2.566       | 1.396       | 0.195       |             |
|            | (−6.232)                 | (−0.844)                 | (5.388)                  | (−3.538)    | (2.694)     | (2.323)     | (0.186)     |             |
| CB[6]/OST–a| −4.848                   | −0.493                   | 4.355                    | −2.670      | 2.178       | 1.637       | 0.230       |             |
|            | (−6.095)                 | (−1.197)                 | (4.898)                  | (−3.646)    | (2.449)     | (2.715)     | (0.204)     |             |
| CB[6]/OST–p| −5.555                   | −0.527                   | 4.928                    | −2.991      | 2.464       | 1.815       | 0.203       |             |
|            | (−6.395)                 | (−1.143)                 | (5.252)                  | (−3.769)    | (2.626)     | (2.705)     | (0.190)     |             |
| CB[7]/OST–e| −4.843                   | 0.073                    | 4.917                    | −2.385      | 2.458       | 1.157       | 0.203       |             |
|            | (−6.095)                 | (−0.952)                 | (5.143)                  | (−3.524)    | (2.572)     | (2.415)     | (0.194)     |             |
| CB[7]/OST–a| −4.841                   | −0.314                   | 4.527                    | −2.577      | 2.263       | 1.467       | 0.221       |             |
|            | (−6.095)                 | (−1.225)                 | (4.871)                  | (−3.660)    | (2.435)     | (2.750)     | (0.205)     |             |
| CB[7]/OST–p| −5.167                   | −0.223                   | 4.944                    | −2.695      | 2.472       | 1.469       | 0.202       |             |
|            | (−6.313)                 | (−1.007)                 | (5.306)                  | (−3.660)    | (2.653)     | (2.524)     | (0.188)     |             |
| CB[8]/OST–e| −4.679                   | 0.085                    | 4.765                    | −2.297      | 2.382       | 1.107       | 0.210       |             |
|            | (−6.041)                 | (−1.170)                 | (4.871)                  | (−3.606)    | (2.435)     | (2.669)     | (0.205)     |             |
| CB[8]/OST–a| −4.913                   | −0.252                   | 4.662                    | −2.583      | 2.331       | 1.431       | 0.215       |             |
|            | (−6.259)                 | (−1.225)                 | (5.034)                  | (−3.742)    | (2.517)     | (2.781)     | (0.199)     |             |
| CB[8]/OST–p| −5.291                   | −0.267                   | 5.024                    | −2.779      | 2.512       | 1.537       | 0.199       |             |
|            | (−6.340)                 | (−1.116)                 | (5.225)                  | (−3.728)    | (2.612)     | (2.660)     | (0.191)     |             |
| CB[9]/OST  | −7.487                   | −0.028                   | 4.759                    | −2.408      | 2.379       | 1.218       | 0.210       |             |
|            | (−6.313)                 | (−1.143)                 | (5.170)                  | (−3.728)    | (2.585)     | (2.688)     | (0.193)     |             |
\[
\mu = \left( \frac{\partial E}{\partial N} \right)_{v(i)} = \frac{E_{\text{LUMO}} + E_{\text{HOMO}}}{2} \tag{2}
\]

\[
x = -\mu \tag{3}
\]

\[
\eta \cdot \eta = \frac{1}{2} \left( \frac{\partial^2 E}{\partial N^2} \right)_{v(i)} = \frac{E_{\text{LUMO}} - E_{\text{HOMO}}}{2} \tag{4}
\]

\[
\omega = \frac{\mu^2}{2\eta} \tag{5}
\]

\[
S = \frac{1}{2\eta} \tag{6}
\]

The quantum molecular descriptions can be used to describe the electron transfer between donor and acceptor molecules and supplies data about the structural stability and reactivity of complexes. The increasing of chemical potential and chemical hardness results in the decrease electronegativity, electrophilicity, and chemical softness which induce the increasing of the stability and decreasing of the reactivity. The global indices of stability and reactivity in both gas and water phases are listed in Table 2. All of values of hardness, chemical potential, electronegativity, electrophilicity, and chemical softness for complexes are modified from the individual CB[n]s and oseltamivir molecule.

Due to the chemical softness values of CB[n]/OST complexes being found higher than the bare CB[n]s, thus, the reactivity of CB[n]/OST complexes is higher than the bare CB[n]s. Inspections of calculated data display that the electronic chemical potential values of all complexes are in the range of $-2.991$ to $-2.297$ eV, the electronegativity values are in the range of 2.297 to 2.991 eV, and the chemical hardness values are in range of 2.178 to 2.566 eV. The electronegativity values are found in range of 2.323 to 2.781 eV and the chemical softness values are in range of 0.186 to 0.205 eV. Suggesting that, when oseltamivir forms complexes with CB[n], the electronic chemical potential and chemical hardness values of complexes are decreased while the values of the electronegativity, electrophilicity, and softness will be increased. Thus, the results confirm that, after oseltamivir complexes with CB[n], the stability of the CB[n]/OST complexes is lower than the bare CB[n]s, while the chemical reactivity of the CB[n]/OST complexes is higher than the bare CB[n]s. The results confirm that CB[n]s are changed in their electrical conductivity due to oseltamivir complexation.

In summarize here, it is also found that the values of the energy gaps, electronegativity, chemical hardness, and electrophilicity of bare CB[n]s and CB[n]/OST complexes in the gas phase are lower than in the water phase. In the other hand, the values of electronic chemical potential and softness of bare CB[n]s and CB[n]/OST complexes in the gas phase are higher than in the water phase.

One of the essential characteristics disturbing the possible complexation interaction between the host and guest is partial charge transfer. The transferring of electrons has been determined by natural bond orbital analysis before and after oseltamivir complexations with cucurbiturils. The PCT was defined as $Q_{\text{CB[n]/OST}} - Q_{\text{OST}}$, where the $Q_{\text{CB[n]/OST}}$ is the total charge of oseltamivir complexation with CB[n], and the $Q_{\text{OST}}$ is the charge of isolated oseltamivir. Considering the PCT of oseltamivir complexation, the positive value of PCT represents the electron transfer from oseltamivir molecule to CB[n]; negative value of PCT means the opposite procedure. The computed PCTs of CB[n]/OST complexes are found in the range of $-0.022$ to $-0.042$ e. The computed PCT results confirm that the charge transfer takes place from the CB[n]s to the oseltamivir. This means that, when the CB[n] molecules interacted with oseltamivir, their charge distributions are modified.

The orbital distributions have been performed to analyze electronic property modification of CB[n]s corresponding to the complexation with oseltamivir drug. The HOMO and the LUMO distributions of the CB[6], CB[7], CB[8], and CB[9] and their complexes with oseltamivir are plotted and displayed in Figs. 7 and 8. For the bare CB[n]s, all of the HOMO and the LUMO orbitals display charge delocalization on the CB[n]s, while all of the HOMO and the LUMO orbitals of CB[n]/OST complexes are delocalized on oseltamivir drug. This means that, after the bare CB[n]s complexed with oseltamivir drug, their HOMO and the
LUMO orbitals are clearly redistributed or changed. These approve the significant modifications in the electronic structures of CB[$n$]s by oseltamivir drug complexation.

The chemical reactivities of molecules can be also associated with their electrostatic potentials, and therefore, the molecular electrostatic potentials (MEP) are extensively used to identify electrophilic and nucleophilic areas of molecules in electrostatic interactions. In order to identify the MEP contours of the bare CB[$n$]s (Fig. 9) and the most stable CB[7]/OST–e complex (Fig. 10), the MEP surfaces are defined based on electron density and represented by a RGB color model, in which red regions are more negative charge and blue regions are more positive charge. Based on Fig. 9, it is seen that the negative charges are localized over the portal oxygen atoms on CB[$n$]s. Based on Fig. 10, after the CB[7] complexed with oseltamivir drug, the red regions of portal oxygen atoms on CB[7] are decreased. Imply that the charge transfer takes place from the CB[7] to the oseltamivir drug which corresponds to the PCT values approving the host–guest, oseltamivir-CB[$n$] complex interaction.

Fig. 7 Plots of the LUMO (top) and the HOMO (bottom) orbitals of (a) CB[6], (b) CB[6]/OST–e, (c) CB[6]/OST–a, (d) CB[6]/OST–p, (e) CB[7], (f) CB[7]/OST–e, (g) CB[7]/OST–a, and (h) CB[7]/OST–p

LUMO orbitals are clearly redistributed or changed. These approve the significant modifications in the electronic structures of CB[$n$]s by oseltamivir drug complexation.
Fig. 8 Plots of the LUMO (top) and the HOMO (bottom) orbitals of (a) CB[8], (b) CB[8]/OST–e, (c) CB[8]/OST–a, (d) CB[8]/OST–p, (e) CB[9], and (f) CB[9]/OST.
Fig. 9 Computed molecular electrostatic potentials on the molecular surfaces of (a) CB[6], (b) CB[7], (c) CB[8], and (d) CB[9]. Blue regions are more positive charges and red regions are more negative charge.
Conclusions

The DFT B3LYP/6–31G(d,p) optimized structures of cucurbit[n]urils \( n = 6–9 \) are found to possess a \( D_{nh} \) symmetry. The formation of host–guest complexes of CB\( [n] \)–OST is proper in CB\( [n] \) cavity, except for CB\( [6] \)/OST–a, CB\( [6] \)/OST–p, and CB\( [8] \)/OST–p complexes; oseltamivir drug is expelled out of the cavity. The intermolecular interactions in all CB\( [n] \)/OST complexes occur via a large number of dipole–dipole interactions, especially the hydrogen bonds between the portal oxygen atoms of CB\( [n] \) and the hydrogen atoms of amine group of oseltamivir drug. The negative complexation energy values of CB\( [n] \)/OST complexes in both gas and water phases indicate that the host–guest complexes are exothermic process and the complexes are more stable than bare CB\( [n] \). In addition, the CB\( [7] \)/OST complex is more stable than that of all studied CB\( [n] \)/OST complexes. The frequency calculation results of the most stable complexes for each of CBs indicate that complexations occur via a spontaneous process. The NBO calculations and MEP plots indicate that the host–guest complexes attend with charge transfer from the CB\( [n] \) host to the oseltamivir guest. In addition, after oseltamivir drug complexation, the HOMO and LUMO orbitals and the energy gaps of CB\( [n] \) are also clearly modified. All of the calculated complexation properties point out here that CB\( [n] \) can act as a host for appropriately oseltamivir guest, even in aqueous solution.

Author contribution  W. Rakrai and B. Wanno contributed to the study conception and design. The DFT calculations were performed by W. Rakrai, C. Tabtimsai, and B. Wanno. The data analysis and the first draft of the manuscript were made by W. Rakrai and B. Wanno. Revising the manuscript critically for important intellectual content on subsequent versions of the manuscript has been done by W. Rakrai, C. Kaewtong, and B. Wanno. All the authors read and approved the final manuscript.

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Declarations

Ethics approval  The ethical standards have been met.

Consent for publication  All co-authors have seen and approved the manuscript.

Conflict of interest  The authors declare no competing interests.
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