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Theoretical Study of the Inclusion Complexation of TCDD with Cucurbit[n]urils

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ABSTRACT

Dioxins are a group of persistent organic pollutants with extreme harm to animals and human beings. There is great significance to develop fast and effective methods enriching (capturing) and detecting dioxins. In this work, molecular dynamics (MD) simulations and quantum chemistry (QM) calculations have been used to study the inclusion complexation of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD), the most toxic dioxin, with cucurbit[*n*]urils (CB*n*, *n*=6, 7, and 8), a group of well-known host complexes applied in the study of host-guest interactions. The inclusions of TCDD with all three CB*n* hosts are found to be energetically favorable processes without remarkable energy barriers. In general, the host and guest form stable 1:1 complexes (TCDD-CB*n*), as indicated by calculated large complexation energies and small deformation energies of the host and guest. Moreover, the 1:2 host-guest complex (2TCDD-CB8) can be formed for CB8 due to its relatively larger cavity. The characteristic infrared (IR) and Raman peaks of TCDD are recognizable in the corresponding spectra of TCDD-CB*n* complexes. Based on the theoretical results, CB*n* are believed to be capable of including TCDD, and the TCDD in the inclusion complexes can be detected using both IR and Raman techniques. The results shown in this work are expected to be informative to the relevant experimental researchers.

Keywords: Cucurbit[n]urils, TCDD, Inclusion complexation, Theoretical study

1. Introduction

Dioxins, the common name for polychlorinated dibenzo-p-dioxin (PCDDs) and polychlorinated dibenzofuran (PCDFs), are a group of notorious persistent organic pollutants (POPs).[1-3] Due to their extremely high carcinogenicity, teratogenicity, and mutagenicity to animals and humans,[4-8] dioxins have attracted enormous attention of scientists,[9] especially the medical and environmental researchers. Monitoring and reducing their presence in the environment is a necessary action for better health protection.[10] The most commonly used analytical technique for the detection of PCDD/Fs is high resolution gas chromatography-high resolution mass spectrometry (HRGC-HRMS).[11, 12] However, this method requires expensive equipment and involves complicated sample preparation.[13] Therefore, developing fast and effective methods enriching (capturing) and detecting PCDD/Fs is of great significance.[14]

Cucurbit[n]urils (CB*n*) are a series of pumpkin-shaped macrocyclic compounds with a polar outside and an apolar cavity. Although the first synthesis of CB*n* appeared as early as 1905,[15] their structures were not elucidated until 1981.[16] In recent years, the family of CB*n* has largely grown to include homologues, derivatives, analogues, and congeners.[17-21] Mock, Buschmann, Kim, and many others have made great effort for the development of the cucurbituril family.[22-26] CB*n* are particularly interesting to chemists because they can act as suitable hosts including appropriately sized guests with high affinity.[27, 28] In the last decades, special attention has been paid to investigating the host-guest interaction between CB*n* and various types of molecules.[29-33] For example, Kim's group[34] recently reported a combined experimental and theoretical study on the host-guest chemistry of CB*n* with α,ω-alkyldiammonium cations to understand the effect of water molecules in the aqueous on the intrinsic characteristics of the host-guest binding.

As far as we know, there is no report available for the inclusion complexation of CB*n* with PCDD/F congeners. In the present work, we try to understand the host-guest interaction between CB*n* (*n*=6, 7, and 8) and PCDD/Fs by performing density functional theory (DFT) calculations and molecular dynamics (MD) simulations. 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD), the most toxic member of the dioxin family, is chosen as a model molecule of PCDD/Fs. We describe its inclusion complexes with CB6, CB7, and CB8 both in gas phase and in aqueous solution. The structures, energetics, and vibrational spectroscopy (IR and Raman spectroscopy) of the inclusion complexes are obtained through DFT calculations, and the dynamics behaviors of the inclusion processes are obtained through MD simulations. Theoretical results are expected to be informative for the future experimental study of the potential complexation of PCDD/Fs with CB*n*, and for the detection of CB*n*-included PCDD/Fs.

2. Computational details

MD simulations: All MD simulations were carried out using GROMACS package (version 4.0.5) with GROMOS96 force field with the simple point charge (SPC) water model in a cubic box with periodic boundary conditions.[35] The force field parameters of CB*n* (*n*=6, 7, and 8) and TCDD were generated by the Automated Topology Builder (ATB) (version 1.2).[36-38] The simulations were performed in the isobaric-isothermal (NPT) ensemble with the pressure of 1 bar and temperature of 298 K controlled by Berendsen thermostat.[39] The long-range electrostatic interactions were treated by the particle mesh Ewald (PME) method[40, 41] with a 1.2 nm cutoff distance, and the short-range van der Waals interactions were modeled using a cut-off distance of 1.4 nm. The systems consist of one host molecule and one or two guest molecules surrounded by water molecules corresponding to a density of about 1.0

g/ml. After the energy minimization using the steepest descent method, the simulation was carried out for 20 ns, which is long enough for the system to reach to equilibrium. Trajectory coordinates were recorded every 500 steps with a time step of 0.001 ps.

Free energy calculations: The free energy change of the inclusion process is calculated using umbrella sampling technique, which is typically used for calculating the free-energy change associated with a change in position coordinates. Using this technique, the system's free energy profiles or potentials of mean force (PMF) were calculated as a function of the host-guest centroid-to-centroid distance (*r*). The values of *r* ranged from -10.0 to 10.0 Å in 1 Å intervals, describing the motion of TCDD through the CB*n* cavity. Umbrella potential with a force constant of 10 kcal/mol/Å^2 was applied for every position. Each biasing MD simulation time was 1ns with same settings to the conventional MD simulations above. The distance data were collected every 1.0 ps. The Weighted Histogram Analysis Method (WHAM)[42, 43] was used to analysis the results.

DFT calculations: The structures and energetics of the inclusion complexes were determined using the Dmol^3 code in Material Studio 4.4 program package.[44] Exchange-correlation energies were treated in the local density approximation (LDA) within the parameterization of Perdew and Wang[45] and the double numerical basis set with polarization function (DND). Solvent effects were estimated with the COSMO solvation model.[46] Vibrational spectroscopy (IR and Raman spectroscopy) of the inclusion complexes were calculated using the B3LYP functional[48], which is most widely used of all the functionals due to its uniformly good performance over a wide range of systems,[49] with the standard 6-31(d, p) basis set, as implemented in the Gaussian 09 package.[50]

3. Results and Discussion

3.1. Optimized geometries

Fig. 1 shows the optimized geometries of isolated TCDD and CB*n* molecules at the B3LYP/6-31G(d,p) level, which has been confirmed to be able to describe TCDD- or CB*n*-containing systems.[51-53] The calculated depth of CB*n* cavities is 6.2 Å, and the diameters of CB6, CB7, and CB8 (the maximum distance between the portal oxygen atoms) are 7.2, 8.3, and 10.5 Å, respectively. The corresponding data in literatures[34, 54] are 6.2, 7.3, 8.2, 10.3 Å. The good agreement between the present work and literature data confirms the reliability of the B3LYP/6-31G(d,p) level for describing CB*n* systems. TCDD is a planar molecule with its dimension in the vertical direction measured to be 5.0 Å, which is smaller than the cavity diameters of all three CB*n* molecules, as indicated by the interatomic distances shown in Fig. 1. This implies the potential possibility of TCDD inclusion by CB*n* (*n*=6, 7, and 8).

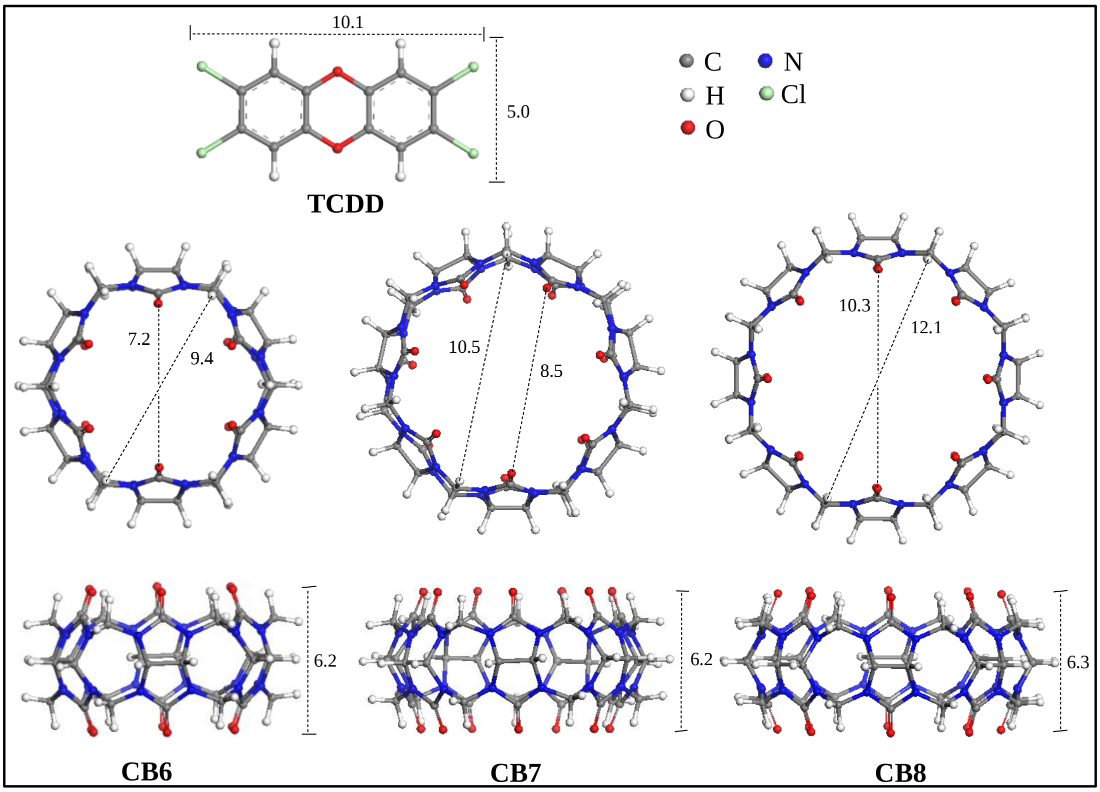

Fig. 1. Geometries of TCDD and CB*n* (*n*=6, 7, and 8), optimized at the B3LYP/6-31G(d,p) level. CB*n* are shown in both top and side views. Distances are in Å.

3.2. The MD simulations

To better understand the interaction of TCDD and CB*n*, we carried out MD simulations for the 1:1 complex systems of CB*n* and TCDD in the water solvent. In the initial structures for MD simulations, the distance between centroids of TCDD and CB*n* was set to ~14Å. As an representative example, Fig. 2 shows the initial basic unit cell structure of the CB7 system that contains one TCDD, one CB7, and 3409 water molecules corresponding to a concentration of 1g/ml. Fig. 3 collects average geometries of TCDD-CB*n* complex obtained from the MD trajectories. Clearly, in these average structures, TCDD has been embedded in the hydrophobic cavities of CB*n* forming 1:1 inclusion complexes. Furthermore, we also studied the host-guest complexes in 1:2 stoichiometry. However, only CB8 can form stable 1:2 complex with TCDD. As shown in Fig.3, two TCDD molecules are partially included in the cavity of CB8.

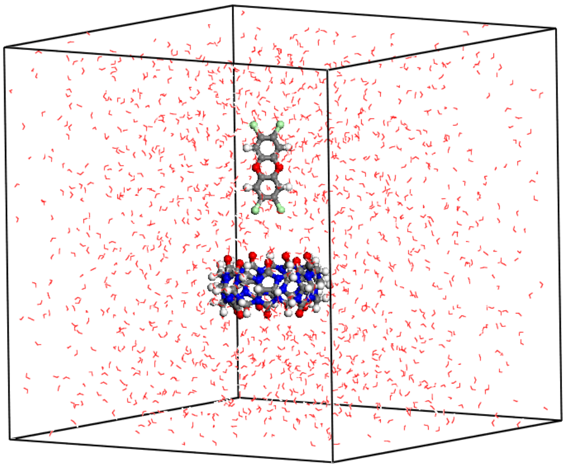

Fig. 2. The initial basic unit cell of CB7 system, it contains one TCDD, one CB7, and 3409 water

molecules in a 23.5×23.5×23.5 Å^3 cubic box.

To observe the formation process of the inclusion complex, we collect several snapshots of the CB7 system in Fig. 4, where only six water molecules inside the cavity are shown for clarity. Similar results for the CB6 and CB8 systems are not given for simplification. Rotational motion of TCDD was observed as it approached CB7. It is found that when the simulation was carried out to 3225 ps, one aromatic ring of TCDD entered the cavity of CB7. The complete inclusion of TCDD by CB7 was found at about 3251 ps. It is observed that six water molecules inside the cavity are successively extruded out as TCDD moves into the cavity. Similar results are also found for CB6 and CB8 systems, where initial two and eight waters inside the cavities are extruded out of the cavities upon the TCDD complexation, respectively. The hydrophobic interaction between CB*n* and TCDD is the key factor that prompts water releasing from the cavity[34, 55-57] and hence results in guest binding in aqueous solution.[58] Fig. 5 shows the trajectories of the host-guest interaction energies (ΔE) and centroid-to-centroid distances (d) with the simulation time. It is found that ΔE and d no longer fluctuate sharply after 3251 ps, implying that the stable TCDD-CB7 inclusion complex has been formed and the guest is not easy to escape from the cavity of the host. It indicates that CB*n* are high-affinity receptors to TCDD and thus the resulting inclusion complexes are expected to be stable for a long time at room temperature, which is crucial for the detection of dioxin using routine analysis techniques.

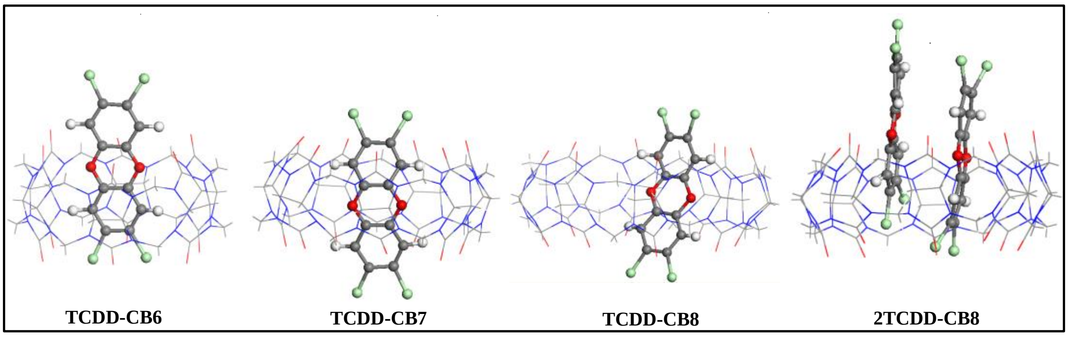

Fig. 3. Average geometries of the inclusion complexes of TCDD and CB*n* obtained from the MD trajectory files. The water molecules were not shown for clarity.

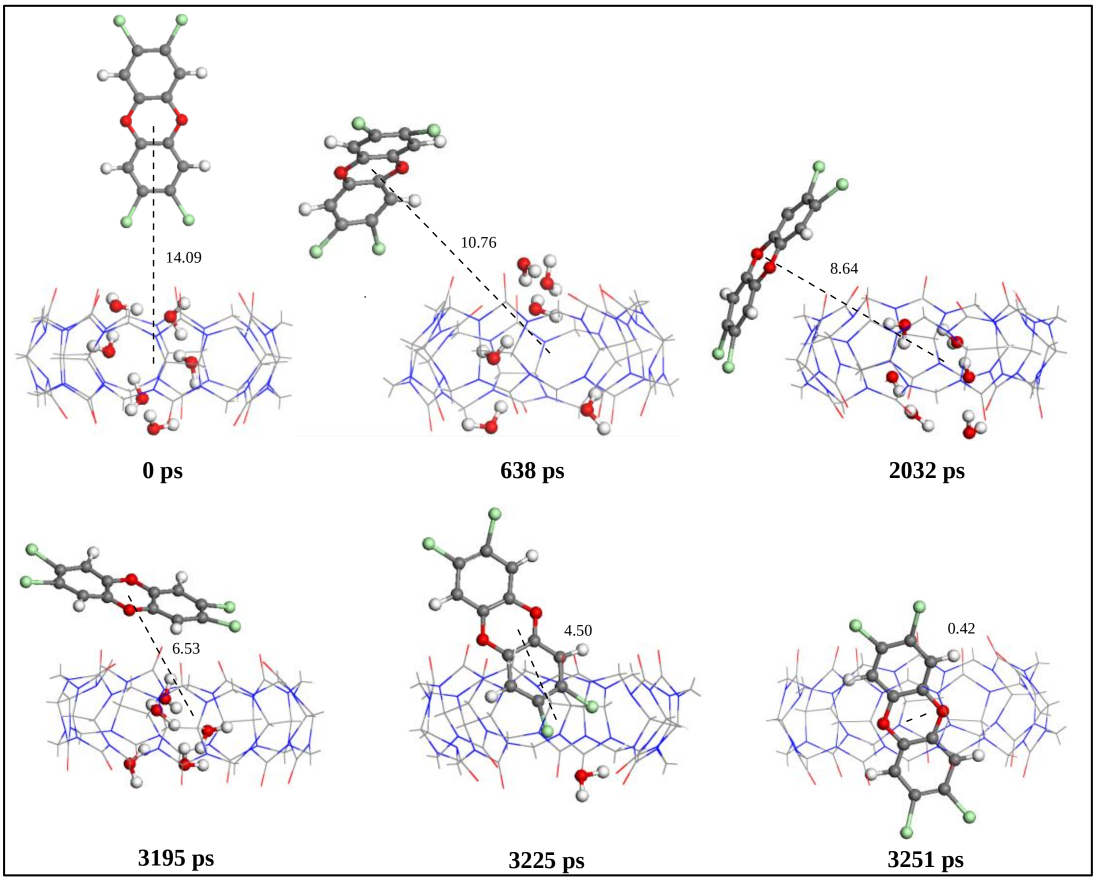

Fig. 4. Snapshots showing the formation process of TCDD-CB7 complex, obtained from the MD trajectory. Only the water molecules inside the cavity are shown for clarity. The distance between centroids of TCDD and CB*n* are given in Å.

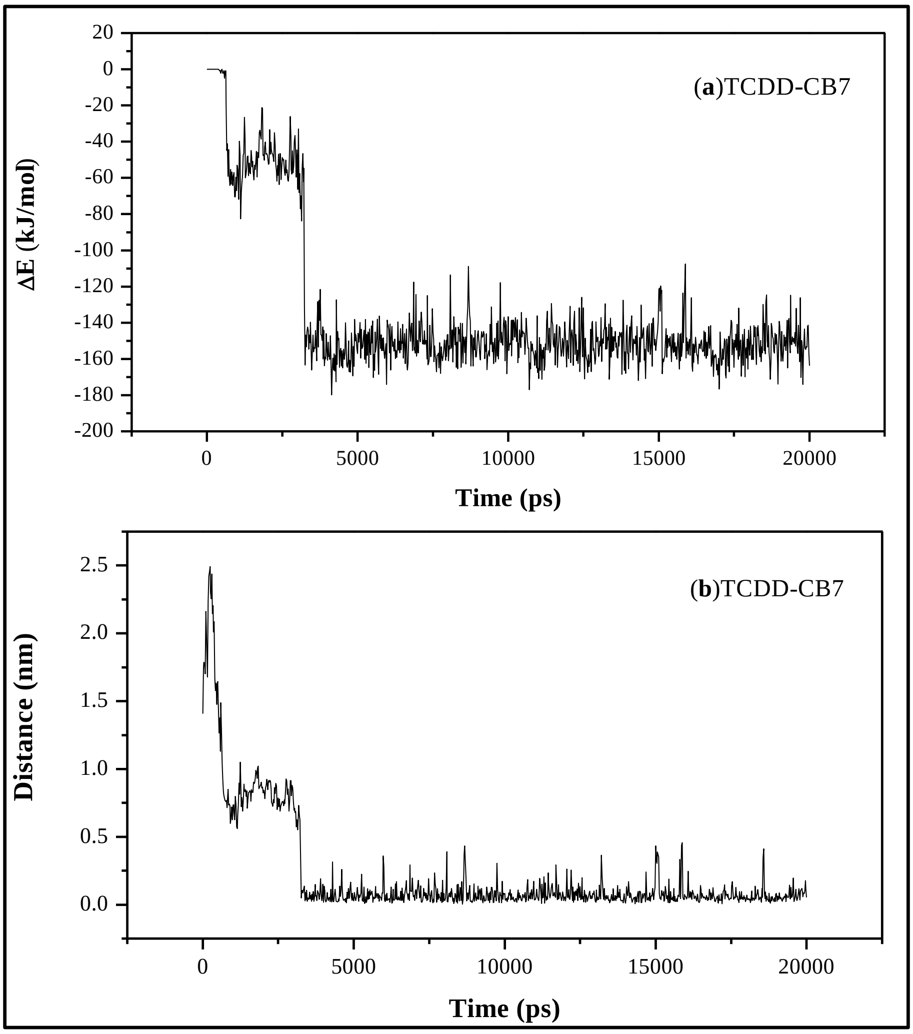

Fig. 5. (a) The host-guest interaction energies (ΔE) versus the simulation time and (b) the distances between centroids of CB7 and TCDD versus the simulation time.

3.3. Umbrella sampling (PMF calculations)

Fig. 6 shows the calculated Potentials of Mean Force (PMF) of three systems studied, i.e. the free energy profiles along the host-guest centroid-to-centroid distance (*r*). It is found that three systems show similar energetic characteristics with the reaction coordinate. Similar PMF profiles were also gained for the inclusion of methyl viologen by CB*n* from the work of El-Barghouthi et al.[59] In general, the free energy decreases when TCDD enters the CB*n*, and shows the lowest value in the vicinity of *r*=0. The minima in Fig. 6 correspond to stable inclusion complexes of TCDD with

CB*n*. The increase of the free energies with *r* can be understood as follows: the cavity of CB*n* provides a hydrophobic environment which stabilizes TCDD by van der Waals interactions, so a destabilization takes place when TCDD escapes from the hydrophobic cavity. As shown in Fig. 6, the free energy profiles monotonously change with increasing absolute value of *r* from -10.0 to 0.0 Å. In other words, there is no remarkable barrier when TCDD moves into the cavity of CB*n*. However, minor barriers exit as TCDD moves out of the cavity of CB*n*. The inclusion complexes are most stable when *r* is closer to zero. The PMF results well agree with results of the average geometries of the inclusion complexes of TCDD and CB*n* obtained from the MD simulations. As shown in Table 1, the free energy changes (ΔG) of the complexation processes of TCDD-CB*n* (*n*=6, 7, 8) are calculated to be -18.6, -19.2, -17.4 kJ/mol, respectively.

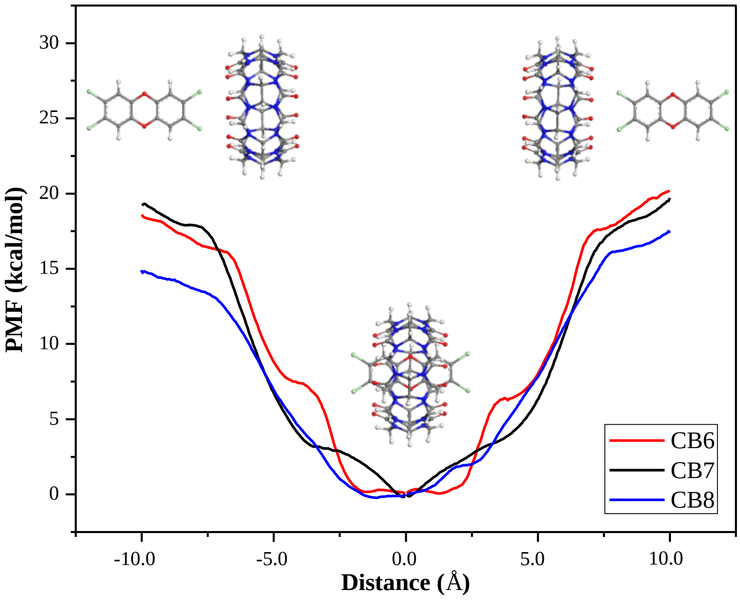

Fig. 6. PMF profiles for inclusions of TCDD with CB*n* (*n*=6, 7, and 8).

Table 1. Free energy changes (ΔG) of the formation processes of TCDD-CB*n* (*n*=6, 7, and 8) at 298.15 K.

Complexes	TCDD-CB6	TCDD-CB7	TCDD-CB8
ΔG (kJ/mol)	-18.6	-19.2	-17.4

3.4. Complexation energies and deformation energies

From the results above, it is clear that CB*n* (*n*=6, 7 and 8) are capable of catching TCDD into their hydrophobic cavities. To value the stability of the inclusion complexes, we calculated the complexation energies (ΔE_C) of the inclusion complexes, which is defined as follows:

$$\Delta E_C = E_{CBn} + E_{TCDD} - E_{TCDD\text{-}CBn} \qquad (1)$$

where E_{CBn}, E_{TCDD}, and $E_{TCDD\text{-}CBn}$ stand for the energies of CB*n*, TCDD, and the inclusion complex, respectively. The larger ΔE_C value implies the more thermodynamically favorable inclusion complex. On the other hand, to inspect the deformations of the host and guest induced by the inclusion complexation, we also calculated deformation energies (ΔE_D) of the host and guest molecules using the following relationship:

$$\Delta E_D = E_{SP\text{-}OPT} - E_{OPT} \qquad (2)$$

where $E_{SP\text{-}OPT}$ is the single point energy of CB*n* or TCDD at the geometry in optimized inclusion complex, and E_{OPT} is the energy of CB*n* or TCDD at respective optimized geometry. ΔE_D is also an important index indicating the driving force leading to the inclusion complex. A smaller ΔE_D value may mean an energetically more favorable inclusion process.

Table 2 shows the theoretical ΔE_C and ΔE_D values from the Dmol^3 calculations both in gas phase and in aqueous solution. Here the solvent effect is treated using the

COSMO solvation model, one of implicit solvent models, which represent a standard tool in theoretical chemistry and have become popular for many applications in molecular simulations due to their ability to pre-average solvent behavior.[60] Applications to mimic host-guest interactions have also been envisaged in recent years.[61-62] However, it should be kept in mind that implicit solvent models can become questionable in some cases, such as systems with strong solvent-solute interactions and strong solvent coordination of ionic species.[63] The present CB*n*-TCDD systems involve only nonspecific interactions between the solvent and solute, which are expected to be able to be described by implicit solvent models. In Table 2, it is noted that ΔE_{C} values both in gas phase and in aqueous solution are generally large enough, confirming that CB*n* (n=6, 7, and 8) can form stable inclusion complexes with TCDD. On the other hand, the calculated ΔE_{C} values in aqueous solution are remarkably smaller than the corresponding those in gas phase, indicating that the presence of aqueous solvent destabilizes the inclusion complexes. This may be due to the much stronger hydrogen bonding and dipole interactions between water molecules than the water-CB*n* interactions, which reduces the host-guest interaction and destabilizes the inclusion complexes. Furthermore, from the calculated ΔE_{C} values in aqueous solution, TCDD-CB6 is much less stable than TCDD-CB7 and TCDD-CB8, which can be attributed to the limited cavity dimension of CB6. This is consistent with the calculated much larger ΔE_{D} value of CB6 in aqueous solution than CB7 and CB8 (19.2 vs 2.4/4.7 kcal/mol). It is also found from Table 2 that the ΔE_{D} values of TCDD in all three situations are smaller than 1.0 kcal/mol, implying an energetically favorable conformation adaptation for TCDD in the CB*n* cavities.

In additional, we also calculated the contribution of the basis set superposition error (BSSE) to the complexation energy by using the counterpoise method, as implemented in Gaussian 09. The values in parentheses in Table 2 correspond to the BSSE-corrected complexation energies. Clearly, both before and after BSSE correction, CB7 possesses the highest complexation energy, implying that CB7 may be the best host for the complexation of TCDD.

Table 2. Calculated complexation energies (ΔE_C) and the deformation energies (ΔE_D) of the host and guest molecules in gas phase and aqueous solution.[a]

Complexes	TCDD-CB6	TCDD-CB7	TCDD-CB8
ΔE_C	29.5 (12.6) [9.9]	34.2 (23.6) [21.3]	25.9 (21.2) [22.1]
ΔE_D (CB*n*)	11.7 [19.2]	2.7 [2.4]	3.5 [4.7]
ΔE_D (TCDD)	0.6 [0.8]	0.7 [0.7]	0.1 [0.2]

[a] Energies are in kcal/mol, the BSSE-corrected complexation energies are given in parentheses and the values in square brackets correspond to the results in the aqueous solution.

3.5. IR and Raman spectra

Experimentally, host-guest inclusion complexes in aqueous solution are generally characterized using nuclear magnetic resonance (NMR) spectroscopy, ultraviolet-visible absorption spectroscopy, and fluorescence emission.[64] In contrast, there are only a few studies that analyzed them by means of vibrational techniques, such as infrared and Raman spectra, which is not sensible to the generally weak non-covalent interaction between the host and guest. However, the usefulness of vibrational techniques in host-guest inclusion complex systems has been acknowledged in recent years.[65-67] Here, to confirm whether IR and Raman techniques are suitable for the detection of TCDD within TCDD-CB*n* inclusion complexes, and also to provide spectral information for inclusion complexes, we calculated the IR and Raman spectra of TCDD, CB*n*, and TCDD-CB*n* complexes at the B3LYP/6-31G(d,p) level. The relevant results are gathered in Figs. 7 and 8. The blue, red and black lines stand for the spectra of TCDD, CB*n*, and TCDD-CB*n*, respectively. As shown in figures, both IR and Raman spectra of TCDD-CB*n* include almost all main characteristic bands of free TCDD and CB*n*, which means the intrinsic properties of the host and guest have no obvious change after the formation of the complexes. In other words, the TCDD-CB*n* inclusion complexes still keep the properties of the isolated TCDD and CB*n*, which is essentially important for routine analysis. Though some characteristic bands of TCDD are in the range of the absorption bands of CB*n* molecules, some other characteristic absorption bands of TCDD in the IR and Raman spectra of inclusion complexes can still be distinguished easily. As shown in Fig. 7, the IR characteristic peak of isolated TCDD molecule at 1518 cm^{-1}, which corresponds to in-plane scissoring vibration of C-H bonds on benzene rings, is still recognizable in TCDD-CB*n* complexes. However, it is shifted to 1511 cm^{-1} in TCDD-CB6, and 1502 cm^{-1} in TCDD-CB7, and 1513 cm^{-1} in TCDD-CB8. In the Raman spectra (Fig. 8), the isolated TCDD molecule shows a characteristic single peak at 1268 cm^{-1}, which corresponds to the benzene ring skeleton vibration, and a double-peak in the region of 1628-1647 cm^{-1}, which correspond to asymmetric and symmetric in-plane scissoring vibrations of C-H bond on benzene rings, respectively. Though the three peaks also have slight shift of wavenumber in TCDD-CB*n* inclusion complexes, the characteristics are clearly recognizable in TCDD-CB*n* complexes. Thus our calculations prove that both IR and Raman spectra can deliver the specific structural information of TCDD in TCDD-CB*n* inclusion complexes. These results indicate that the two common analytical techniques (IR and Raman) are suitable for detection of TCDD included by CB*n*.

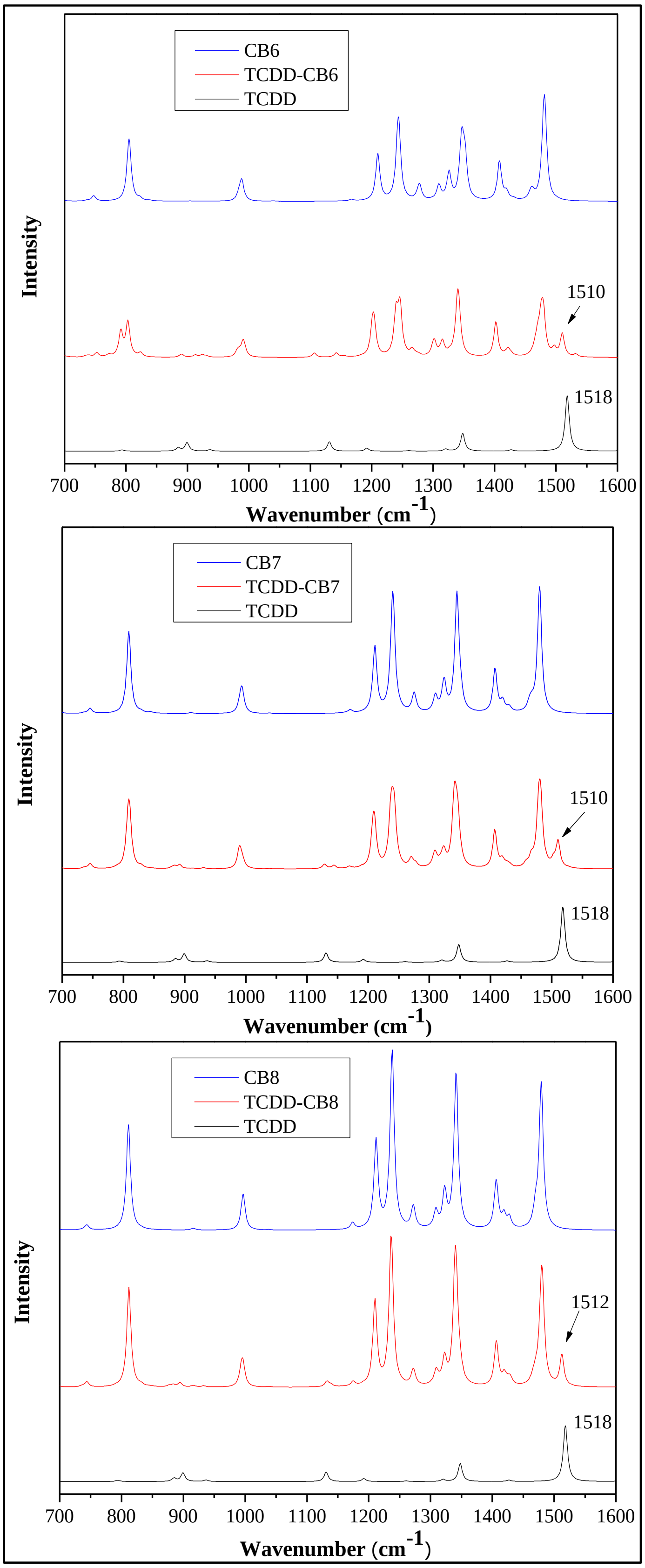

Fig. 7. Calculated IR spectra TCDD and CB*n* molecules as well as TCDD-CB*n* complexes at the B3LYP/6-31G(d,p) level.

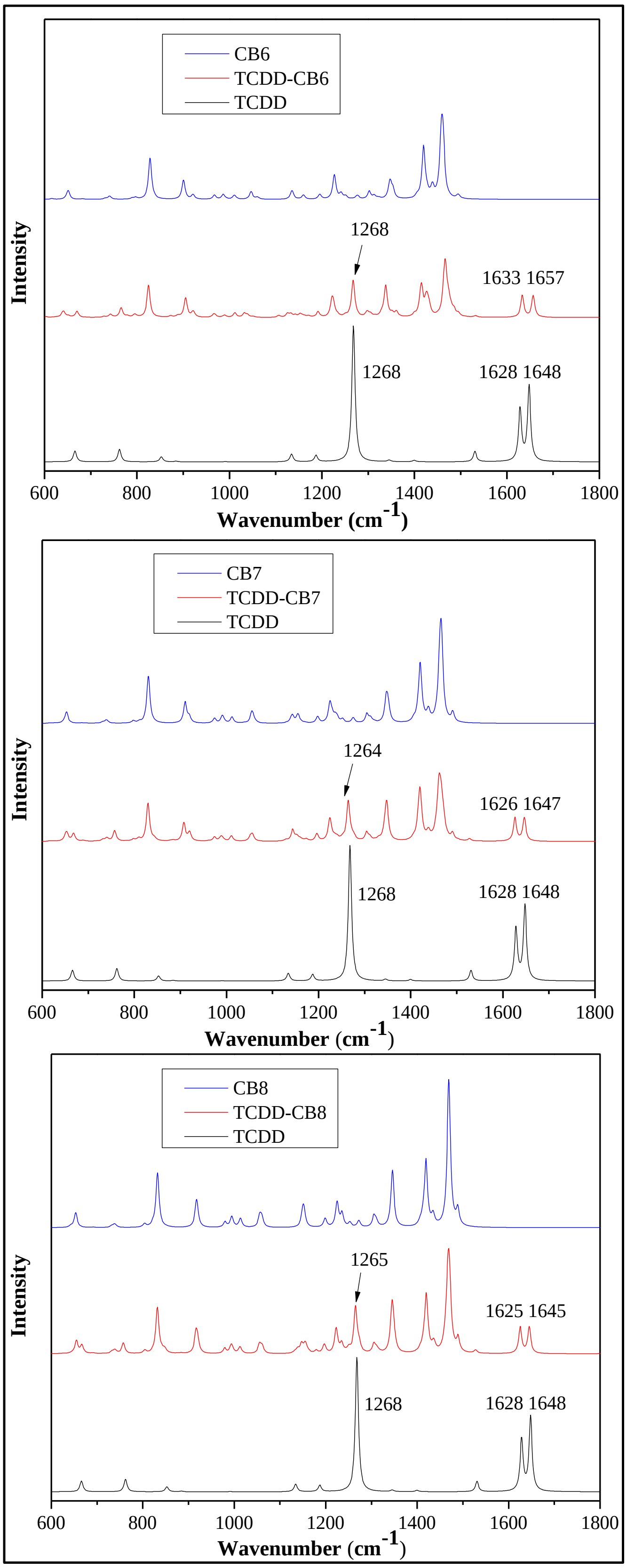

Fig. 8. Calculated Raman spectra for TCDD and CB*n* molecules as well as TCDD-CB*n* complexes at the B3LYP/6-31G(d,p) level.

4. Conclusions

MD simulations and QM calculations were carried out to understand the inclusion complexation of TCDD with CB*n* (*n*=6, 7, and 8). All three CB*n* can form stable 1:1 inclusion complexes with TCDD both in gas phase and in water solution. The 1:2 host-guest complex is only formed for CB8 with TCDD. The stability of the host-guest complexes has been indicated by the calculated large complexation energies of the inclusion complexes and small deformation energies of the host and guest molecules. The theoretical results indicate that CB*n* can act as suitable host to accommodate TCDD guest. The MD simulations have given a clear picture of the formation process of inclusion complexes. The characteristic IR and Raman peaks of TCDD can be recognized from the corresponding spectra of TCDD-CB*n* complexes. IR and Raman techniques are suitable for detecting of TCDD in TCDD-CB*n* inclusion complexes. This work may be especially informative to scientists who are devoting themselves to developing fast and effective methods for dioxin detection.

Acknowledgements

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