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Theoretical Evaluation of the Molecular Inclusion Process between Chlordecone and Cyclodextrins: New Method for Mitigating the Basis Set Superposition Error in the Case of Implicit Solvation Model

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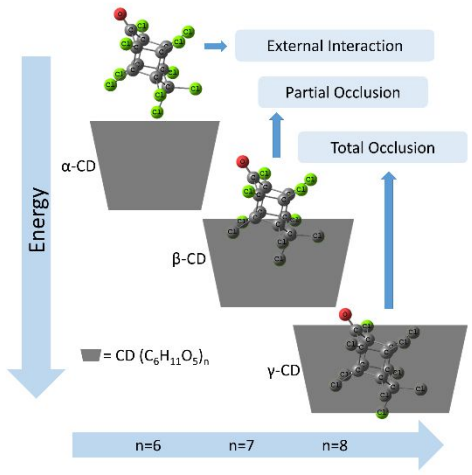
ABSTRACT

The aim of this work is to describe the molecular inclusion of chlordecone with α, β, and γ-cyclodextrin in aqueous solution using quantum mechanics. The guest-host complexes of chlordecone and cyclodextrins are modeled in aqueous solution using the Multiple Minima Hypersurfaces methodology with PM6-D3H4X semiempirical Hamiltonian, the lowest energy minima obtained are re-optimized using the M06-2X density functional and the intermolecular interactions described using Quantum Theory of Atoms In Molecules (QTAIM). The studied complexes are classified according to the degree of inclusion namely: total occlusion, partial occlusion, and external interaction. The more stable complexes are obtained when γ-CD is used as the host molecule. The interactions characterized through QTAIM analysis are all of electrostatic nature, predominantly of dispersive type. In this work, a method based on the counterpoise correction is also discussed, to mitigate the basis set superposition error in density functional theory calculations when using an implicit solvation model.

GRAPHICAL ABSTRACT FIGURE



1. INTRODUCTION

Chlordecone (CLD, $C_{10}Cl_{10}O$, CAS: 143-50-5) is a persistent organic pollutant (POP)[1] used as a pesticide between 1951 and 1993 in meanly, banana producing areas, such as Guadeloupe and Martinique, as a mean to control several plagues, among them the banana root borer, several fly maggots, other larvae, and diverse fungi, mainly in crops. It has also been used in domestic traps for ants and cockroaches.[2] **Figure 1** show a representation of the CLD structure.

CLD presents a high affinity for highly organic soils, as evidenced by its organic carbon adsorption coefficient (log $K_{oc} \approx 4.2$). Moreover, its bioaccumulation and biomagnification alongside the food chain has been evaluated as high due to a high octanol-water partition coefficient (log $K_{ow} \approx 4.5$). This POP does not significantly evaporate nor experiments direct photo-degradation in the atmosphere. The main degradation process for CLD is anaerobic biodegradation which is mostly inefficient in the environment.[2, 3] However, several studies have demonstrated the possibility of using anaerobic bacteria or reduced Vitamin B12 for the dechlorination and degradation of CLD.[4-6]

The presence of CLD in water bodies is expected, given that it was mainly used in agricultural applications. Due to this issue, it is desirable for water purification plants to have systems capable of eliminating CLD. However, CLD, as many similar pollutants, cannot be removed using conventional processes such as coagulation, flocculation, and mechanical filtration.[7-10] For this reason, the search for new technologies for the removal of CLD and other similar POPs, continues to be a recurrent research topic.[11, 12]

For the specific removal of POPs, several methodologies have been evaluated, such as the adsorption onto activated carbons,[9] advanced oxidation processes,[13, 14] and combinations of these and other technologies.[15] The use of molecular inclusion complexes with cyclodextrins has been also experimentally evaluated for removing POPs.[16]

Regarding the formation of guest-host complexes between CLD and cyclodextrins, recent experimental studies support the hypothesis that this method can be efficient enough for the decontamination of water presenting this pollutant,[17] although, the mechanisms of formation of these molecular inclusion complexes have not been yet detailed.

Cyclodextrins (CDs) are homochiral macrocyclic oligosaccharides, they are formed of α-D-(+)-glucopyranose sub-units, linked together by α-(1→4) glycosidic bonds.[18] CDs are obtained by partial degradation of starch with the enzyme cyclodextrin glycosyltransferase.[19, 20] The most common natural occurring cyclodextrins are α, β, and γ-CD with six, seven, and eight glucopyranose units, respectively. Moreover, these three CDs are the most addressed ones in scientific literature.[16] CDs have a truncated cone shape, with a hydrophilic exterior, making them soluble in polar solvents, and a somehow lipophilic cavity,[18] providing them with the ability of encapsulating hydrophobic molecules with specific shapes and properties, hence forming the

known molecular inclusion or guest-host complexes.[21-24] A number of recent review articles have compiled and detailed the characteristics of the CDs, their properties and uses.[25-28]

Within the mathematical modeling methodologies used for the characterization of intermolecular interactions, the ones based on computational chemistry methods are very useful in giving information about the mechanism of interaction, also allow saving in material resources, while optimizing the time of work, as well as workers and environmental safety.

Most of the computational studies addressing CDs involve the formation of guest-host complexes. Variables such as structural parameters, thermodynamic quantities, favorable orientation of association, and selectivity, are the most generally studied.[29] The use of semiempirical Hamiltonians has been important in the determination of the geometrical characteristics of molecular inclusion complexes involving cyclodextrins, mainly as preparative methods for subsequent theoretical and experimental studies.[30-32] Regarding Density Functional Theory (DFT), these methods have been widely used, not only in the determination of geometrical and electronic structure of these complexes,[33, 34] but also in the determination of UV spectra through the study of excited states,[35] and the study of thermodynamic quantities of the molecular inclusion process.[36]

The formation of guest-host complexes between CLD and CDs in aqueous solution has been experimentally studied and discussed by Rana et al.[17] This work demonstrated the possibility of using CDs as removal agents, especially in the modification of adsorbent systems such as activated carbon filters, with the aim of increasing their efficiency. Three naturally occurring CDs: α, β, and γ-CD were evaluated in this study, being α-CD the only that did not show a complexing behavior, and γ-CD the only one able to form a stable molecular inclusion complex with CLD.

The aim of this work is to describe the association process in the formation of molecular inclusion complexes between chlordecone and natural cyclodextrins (CLD@CDs) in aqueous solution, by means of molecular modeling methodologies.

2. METHODS

2.1. System under Study

The use of symmetric conformers has been used for theoretically describing CDs and their guest-host complexes.[37, 38] For that reason, a model of CDs in solution, based on symmetric conformers was developed[39] and will be used for describing the molecular inclusion process of the possible CLD@CDs complexes, using molecular modeling. **Figure 2** show the structure of the model for α-CD consisting of eight symmetric conformers, making a total of 24 when including the descriptions for β-CD, and γ-CD. Each structure differs from each other in the characteristics and orientation of the intramolecular hydrogen bond patterns.

The system under study consists on the molecular inclusion complexes of CLD (**Figure 1**) with symmetric conformers of α, β, and γ-CD (**Figure 2**). The differences among the conformers of the cyclodextrins and their notation, as well as other aspect regarding thermodynamic and spectroscopic characteristics has been presented and discussed in a previous work.[39] Also, Rana et al.[17] obtained, through isothermal titration calorimetry, a value for the stoichiometry of the binding process between γ-CD and CLD (n) of 0.989 indicating that the host-guest complexes formed, have a 1:1 stoichiometry. Consequently, only inclusion complexes with that stoichiometry were considered in this study.

2.2. General Work Strategy

The general work strategy has been presented and discussed in a previous work.[12] This strategy is composed of three consecutive and dependent approaches. The first one, the Multiple Minima

Hypersurface (MMH) methodology allows the exploration of the configurational space of the CLD@CDs complexes. MMH gives a thermodynamic description of the systems and identifies distinctive structures of local minima to be lately refined using Density Functional Theory (DFT) methods. Geometry and electronic information obtained by means of DFT calculations become the input data for topology analysis of the electron density according to Quantum Theory of Atoms In Molecules (QTAIM).[40, 41]

In this methodological approach all the procedures contribute to a better description of the interactions between CLD and CDs. This allows a better understanding of the phenomena happening during the inclusion process, also, to identify the possible determining factors of this process.

2.3. MMH Calculations

The initial geometries for CLD and the conformers of CDs were generated using the graphical assistant of the program Chemcraft.[42] Then, the structures were optimized using the semiempirical Hamiltonian PM6-D3H4X[43-46] as implemented by the molecular modeling package MOPAC2016.[47] In the absence of halogen atoms, it cannot be distinguished from the PM6-D3H4 Hamiltonian used for the generation of the CDs models.

A given system, such as CLD@CDs guest-host complexes, can be found in different configurations which are close to each other in energy values and will contribute in a similar way to the macroscopic properties of the system. The use of the MMH methodology allows to explore the possible interaction sites of the CLD with the CDs in a random fashion and to calculate the thermodynamic properties of the interacting systems. For each CLD@CD system, 200 non redundant, random configurations were generated from the separate molecular models using the

program GRANADA.[48, 49] The generated supermolecules were taken as input for MOPAC2016 where they were optimized.

The obtained local minima were processed using statistical thermodynamic methods using the program Q3[50] for obtaining the association energy quantities and selecting the most important, non-redundant structures for the description of each system.

After such mathematical treatments, the most populated structures were selected according to a Boltzmann distribution of energy states.

2.4. DFT and QTAIM Analyses

The most stable structures found for the CLD@CDs complexes were further refined using DFT. The hybrid meta-GGA functional M06-2X[51] of the Minnesota family was used with the 6-31G(d,p) Pople's basis set. DFT-D3 dispersive corrections[52] were applied to all DFT calculations, thus, D3 part in M06-2X-D3 method will be omitted hereafter for simplicity and readability. In order to take into account the solvation effects of water the solvation method based on density SMD[53] was used as implicit solvation scheme in DFT calculations. All density functional calculations were performed using the Gaussian09 package.[54] No symmetry restrictions were imposed to geometric or electronic structures during all quantum calculations performed.

In order to describe and classify the interactions present between CLD and each CD conformers in the formation of the CLD@CDs complexes, a QTAIM analysis was made involving several criteria. The first criterion was the detection of a bond critical point (BCP), and bond paths between the BCP and the interacting atoms. The subsequent classification of the detected interactions was made according to the criteria of Nakanishi et al.[55, 56] taking into account several electron density based descriptors at the BCP, such as: the electron density (ρ_c), the Laplacian of the electron density ($\nabla^2\rho_c$), the total energy density (H_c), and the ellipticity of the electron density (ε_c). All

QTAIM calculations were performed using the program Multiwfn 3.3.6[57] from the wave functions generated by M06-2X/6-31G(d,p) calculations.

2.5. BSSE Mitigation using SMD. Modifications to Counterpoise

When performing DFT calculations on systems with a heavy occurrence of non-covalent interactions, the basis set superposition error (BSSE) appears to play a major undesirable role,[58] especially when the association magnitudes are taken into account, overestimating the interactions. When describing the CLD@CDs complexes, the high number of electrons to be described compels to limit the size of the basis set to be used. It is expected that an increase in the extension of the basis set would imply a diminishing of the BSSE, while increasing the calculation time to be unpractical much beyond 6-31G(d,p) basis set.

There are several methods used to mitigate the BSSE.[58] Among them, one of the popular ones is the Counterpoise correction (CP) pioneered by Boys and Bernardi.[59] This method uses the fact that energy is a function of state, and as such, it is possible to describe, separately, two concerted processes like the deformation of the components (A and B) of a system, and their interaction in the final (AB) geometry. In CP the energy of deformation of the components is calculated using the basis set of each component, the interaction energy in the final geometry is then calculated using the basis set of the final complex, as presented in the **System of Equations 1**. Where E_{def} is the deformation energy of the system components and E_{int} is the interaction energy of the components in the final complex geometry. "A" and "B" are the components of the system and "AB" accounts for the final supramolecular system. Energy subscripts indicate the geometry of the system, while superscripts indicate the system from which the basis set is used, being the basis set of "AB" the sum of the basis of "A" and "B", by definition.

$$E_{def} = \left[E^{A}_{AB}(A) + E^{B}_{AB}(B)\right] - \left[E^{A}_{A}(A) + E^{B}_{B}(B)\right]$$

$$E_{int} = E_{AB}^{AB}(AB) - \left[E_{AB}^{AB}(A) + E_{AB}^{AB}(B)\right]$$

$$E_{assoc} = E_{def} + E_{int} \quad (1)$$

This method has been successfully used in many studies, mainly in gas phase systems.[60] However, CP fails when it is applied to those systems that describe the solvent by means of a continuum model. In these cases, the description of the continuum that forms the solvent model becomes incompatible with the mathematical artifices used for mitigating the BSSE. This is due to the inherent dependency of the solvation energy and the solute electron density, as in the SMD model.[53]

So far, no strategy has been published to allow the correction of the BSSE under these calculation conditions, an opportunity that will be exploited in this work.

The present work proposes, for the first time, a modification to the Counterpoise method for the mitigation of the BSSE when using SMD implicit solvation model. This approach is based in a general idea of calculating the interaction energy in gas phase, while seizing the property of the energy of state to artificially desolvating and resolvating the calculated system. **Scheme 1** shows the scheme of the original idea based on a thermodynamic cycle, considering that energy changes are independent of path transited by the system.

As previously explained, the concerted processes of deformation and interaction present in the association of the components of the "AB" system, can be treated independently, according to the energy property of being a state function. As such, the arbitrary and fictitious de-solvation and re-solvation of the systems do not affect the determination of the interaction energy, where the BSSE cannot be corrected from E_3, but it can be easily corrected from E_6.

Equation 2 shows the calculation problem for correcting E_0.

$$E_0 = E_1 + E_2 + E_3 \quad (2)$$

where E_1 and E_2 are the deformation energies of the components "A" and "B", respectively, while E_3 is the formation energy of the "AB" complex, that cannot be corrected using Counterpoise and can be easily calculated using **Equation 3** following the scheme of the **Scheme 1**.

$$E_3 = -E_4 - E_5 + E_6 + E_7 \qquad (3)$$

where E_4, E_5, and E_7 are the solvation energies of "A", "B", and "AB", respectively. The interaction energy in the gas phase E_6 can be corrected using CP, and the association energy can be finally written according to **Equation 4**.

$$E_0 = E_1 + E_2 - E_4 - E_5 + E_6^{CP} + E_7 \qquad (4)$$

where the superscript "CP" on E_6 indicates that the interaction energy is corrected using Counterpoise.

System of Equations 5 show the problem simplification, as reducing the complexity of the scheme presented in **Scheme 1**. Hence, a new expression is obtained for the association energy (E_0) according to **Equation 6** and the scheme of **Scheme 2**.

$$E_1 = E_{AB}^{A}(A_{(aq)}) - E_{A}^{A}(A_{(aq)})$$

$$E_2 = E_{AB}^{B}(B_{(aq)}) - E_{B}^{B}(B_{(aq)})$$

$$-E_4 = E_{AB}^{A}(A_{(g)}) - E_{AB}^{A}(A_{(aq)})$$

$$-E_5 = E_{AB}^{B}(B_{(g)}) - E_{AB}^{B}(B_{(aq)})$$

$$E_6^{CP} = E_{AB}^{AB}(AB_{(g)}) - \left[E_{AB}^{AB}(A_{(g)}) + E_{AB}^{AB}(B_{(g)})\right]$$

$$E_7 = E_{AB}^{AB}(AB_{(aq)}) - E_{AB}^{AB}(AB_{(g)}) \qquad (5)$$

This calculation scheme allows to mitigate the BSSE of a supramolecular system considering the solvent effects on the energy with a minimum computational expense. All geometries used in the gas phase calculations correspond exactly with those theoretically obtained in solution, for that

reason, no further optimizations of the geometries are needed, allowing the CP correction with single point energy calculations.

$$E_0 = \left[E_{AB}^{A}(A_{(g)}) - E_{A}^{A}(A_{(aq)})\right] + \\ + \left[E_{AB}^{B}(B_{(g)}) - E_{B}^{B}(B_{(aq)})\right] + E_{AB}^{AB}(AB_{(aq)}) + \\ - \left[E_{AB}^{AB}(A_{(g)}) + E_{AB}^{AB}(B_{(g)})\right] \quad (6)$$

3. RESULTS AND DISCUSSION

3.1. MMH Calculations. Formation of the CLD@CD Inclusion Complexes

A total of 24 systems were studied corresponding to the interactions between the CLD and each of the eight conformers of the three studied CDs. For each system, 200 non-redundant random configurations were optimized. They will be called hereafter CLD/CDs before verifying a guest-host complexation, in which case the notation will take the form of CLD@CDs. **Chart 1** shows the mean association energies (ΔE_{ASSOC}) for CLD/CDs systems. Numerical values of these data are reported in **Table S1** of the electronic supporting material.

As it can be observed in **Chart 1**, the interaction strength, directly related to the decrease in the association energy, is much stronger for the complexes involving γ-CD. When comparing the behavior of the CDs conformers, it can be observed for the conformers of type **A**, the association energies were similar for α and β-CD, while for γ-CD, the association strength was systematically higher in these conformers. For the conformers of types **B** and **C** the stability of the systems grows with the increase of the cavity size of the CD, as it can be inferred from the monotonous diminishing of ΔE_{ASSOC}. Conformers of the types **B3** and **C4** presented the most favorable behavior regarding the molecular association for MMH studies using PM6-D3H4X as calculation method.

Resulting from the MMH/PM6-D3H4X calculations, several types of distinctive interactions were obtained according to the inclusion degree of the CLD in the CD cavity. The comparison of

these inclusion degrees is shown in **Figure 3**, where these were classified as: external interaction without occlusion, partial occlusion, and total occlusion.

Table 1 shows the distribution of the inclusion degrees for the systems CLD/CDs according to the percentage of population from the Boltzmann energy distribution. The sampling was made based on a 99 % of the sum of populations.

The external interaction results the most stable one when the cavity size or conformation is not the adequate for the inclusion phenomenon to occur. This type of interaction was observed when the host molecule was the α-CD, or in the cases where the cavity was obstructed at one of the sides as those of type **A** conformers in α-CD and some cases the β-CD. As such, the partial occlusion was observed for the CDs with a more adequate cavity, but not wide enough for hosting the whole CLD. This phenomenon was observed mainly for CLD@β-CD systems and in some cases of the **A** type conformers of the γ-CD. Finally, the total occlusion phenomenon was exclusively observed for the CLD@γ-CD complexes, highlighting the types **B** and **C** of the γ-CD host molecule with a totally occluded CLD.

During the bibliographic study performed for the preparation of this work, no referenced studies were found explicitly indicating the different inclusion degrees of molecules into CDs. Some studies detected a single inclusion degree of a molecule among several CDs, like in the case of a work by Shanmugam *et al*.,[31] where stable partial occlusions were reported for three S-triazine derivatives into α and β-CD, calculated using the PM3 method. Maia *et* al.,[36] showed the formation of guest-host complexes between norfloxacin and β-CD in two opposite orientations, both structures presented partial occlusion, however, only one of them resulted stable in aqueous solution when calculated with the DFT functional B97D. Such study demonstrated that the inclusion degree, although important in the complex stability, is not a definitive criterion, with the

interaction types stablished between the interacting atoms and moieties being also important. Another study performed by Biernacka *et al*.[34] depicted the partial occlusion of alendronate@β-CD by means of DFT B3LYP. The formed complex was positively detected using mass spectrometry, demonstrating the complex formation and stability.

In the present work it can be observed that both, the thermodynamic results based on ΔE_{ASSOC} and the geometries for the different inclusion degrees, indicate that the formation of the molecular inclusion complexes is highly disfavored for α-CD. For the cases of the other CDs, the complex stability should be higher for the γ-CD than for the β-CD. The experimental study of Rana *et al*.[17] demonstrated experimentally the formation of guest-host complexes between CLD and the β and γ-CD, being unable to verify the inclusion for α-CD. Moreover, an important weight of the research is devoted to the characterization of the CLD@γ-CD complex as it was the most stable one.

The theoretical results obtained in the present work by MMH calculations corroborate the experimental studies, also indicating that the complexes presenting partial occlusion, mainly for β-CD, can also be stable, although total occlusion is highly favored. These results could be considered as non-conclusive, since they were obtained from the application of a semiempirical methods at a relative low "theoretical level". However, MMH can serve as a guidance with the aim of identifying the models to be used for a more reliable theoretical consideration, meaning higher level calculations and topological descriptions of electron properties.

3.2. Refinement of the Representative Structures using DFT

Re-optimization of the geometries and wave functions obtained by MMH/PM6-D3H4X followed, by using the M06-2X/6-31G(d,p) DFT level of theory. A total of 12 structures obtained by MMH were refined, corresponding to the lowest energy minima of the systems CLD/CDs (or CLD@CDs where the occlusion was verified). The CDs present in these structures correspond to

conformers classified as types B and C, as they were selected as the most probable to occur in aqueous solution[39] and were theoretically determined by MMH to be the hosts that lead to the most stable complexes with CLD.

Figure 4 show the four molecular inclusion complexes corresponding to the systems CLD@γ-CD, the ones obtained by MMH/PM6-D3H4X and their re-optimizations according to M06-2X/6-31G(d,p). The eight remaining complexes, four for each, the α and the β-CD, are presented in **Figures S1** and **S2** of the electronic supporting material.

In general, from the structures presented in **Figure 4**, small variations can be observed in the geometries calculated with DFT when comparing to those semi-empirical as direct result of MMH. In that matter, for the molecular inclusion process, the complexes of CLD@γ-CD obtained by both methods can be visually considered to be almost identical regarding the CLD orientation and the inclusion deepness of the CLD into the γ-CD conformers of types B and C. In these cases, the guest-host complexes can be considered as total occlusion complexes.

In a previous study following a similar calculation methodology[12], the differences between the structures calculated by PM7 semiempirical Hamiltonian and those calculated using DFT (CAM-B3LYP) resulted to have some geometrical differences, evidencing differences in the geometrical description of the studied complexes by means of these two approximated methods. In the present work, the small differences found in the geometries under different theoretical levels demonstrate a better articulation of the methods used, and therefore justifying the concatenation of these methods according to the general work strategy.

The considerations presented for the results depicted in **Figure 4** correspond in the same manner with the obtained results for the conformers of types B and C for α and β-CD (**Figures S1** and **S2**, supporting information), where a partial occlusion is defined in these CDs that have a narrower

cavity. In that matter, the increase of the inclusion degree is proportional to the size of the CD involved, in correspondence with the findings of Rana et al.[17], where the CLD did not form a guest-host complex with α-CD, but it did with β and γ-CD, this last complex (CLD@γ-CD) being formed more rapidly and consistently.

With the aim of achieving a better description of the thermodynamic properties of the molecular inclusion complexes CLD@CDs, the mitigation of the BSSE was made using the modifications to the CP correction developed in the present work according to **Equation 6**, for the correction of the BSSE when an implicit solvation model is used. Hereafter, the method will be called just Counterpoise, or CP for the sake of clarity. The results for the punctual association energies ($\Delta E_{ASSOC,i}$) are presented in **Table 2** as calculated by DFT.

The values of association energy obtained using M06-2X/6-31G(d,p) for the punctual structures ($\Delta E_{ASSOC,i}$) presented in **Table 2** follow the same trend that the ΔE_{ASSOC} values obtained by means of MMH/PM6-D3H4X, again demonstrating the articulation of the two methods of this calculation strategy. Also, the energy values generally correspond to the inclusion degree of the described complexes, being the best association obtained for the complexes CLD@γ-CD in which the total occlusion of the CLD was observed. The percentage of BSSE mitigation, as determined by CP, oscillates between 9.5 % and 53.8 % based on the uncorrected value of $\Delta E_{ASSOC,i}$. Apart from a 9.5 % obtained of the complex CLD@B3-β-CD, it was found that, the stronger the interaction, the lower the BSSE correction. As such, in the complexes with C type conformers, a diminishing of the BSSE percentage is observed while the CD's cavity broadens.

A study performed in 2004 by Hugas et al.,[61] describes systems with non-covalent di-hydrogen bonds by means of both the hybrid density functional B3LYP and the ab initio MP2 perturbative method. When using the 6-31G++(d,p) Pople's basis set, up to a 50 % of the interaction energy

was corrected as BSSE for these systems. Another study by Lopes et al.[62] depicted the guest-host complex of sertraline@β-CD. Several methods were used, including M06-2X, and basis set used ranged between 6-31G(d,p) and 6-311++G(2df,p), detecting a BSSE between 20 % and 58 % of the calculated interaction energy. These values were very different to those obtained for the water dimer with the same methods, evidencing the sensitivity of the BSSE regarding the geometry and the system's nature. BSSE values obtained in the previous work correspond to the percentages determined in the present study.

3.3. QTAIM analysis

To perform a qualitative and quantitative description of the intermolecular interactions present in the molecular inclusion complexes CLD@CDs, a topological study was performed regarding some magnitudes related with the electron density. With this aim, a QTAIM study was made for the 12 guest-host complexes CLD/CDs modeled at M06-2X/6-31G(d,p) from which geometries and wave functions were taken.

Figure 5 shows the pictorial representation of the bond critical points and the bond paths for the guest-host complex CLD@C1-γ-CD. The different types of interactions identified are denoted and colored.

The bond paths detected describe the intra and intermolecular interactions according to QTAIM theory. The identified intermolecular interactions depicted in **Figure 5** form a dense network between the CLD and the CD. It is to be expected that this number of interactions lead to the formation of strong complexes, despite all being non-covalent. It can also be observed that the interaction types present in the complexes were mainly of dispersive character (vdW), even though, it can be observed several interactions that can be classified as halogen bonds (XB) due to the anisotropy of the electron density of the chlorine atoms of the CLD.

The bond paths presented in **Figure 5** are mainly straight, with some exceptions for very weak dispersive interactions, in which the electron density topology is poorly emphasized, and it is affected by the surrounding density, showing a bond path with a slight curvature.

The quantitative description of the bond critical points corresponding the interactions described by means of QTAIM for **Figure 5** is presented in **Table 3**. This topology analysis allows to classify the intermolecular interactions using magnitudes related to the electron density at the BCP according to criteria published by Nakanishi et al.[55, 56] **Tables S2-S12** of the electronic supporting material show the results of the topological analysis of the electron density for the rest of the structures refined by means of DFT calculations.

In **Table 3**, even though the interaction identity (the atoms involved) and its distance (d) of a given interaction, are both indicative of weak bonding, the functions related to the electron density are the ones that allow to rigorously classify the nature of these bindings. These magnitudes (ρ_C, $\nabla^2 \rho_C$, and H_C) finally prove mainly dispersive interactions (vdW), with the occurrence of some interactions evidencing a slight charge transfer at the BCP, such as the weak halogen bonds (XB, interactions 19 and 23 of **Table 3**) and some hydrogen bonds (HB) also with very low strength (**Tables S2-S12**, supporting information).

It is also worth mentioning the very low ellipticity (ε) values of the vdW interactions 2, 11, 13, and others from **Table 3**, which are lower than 0.05, indicating a high directionality for these interactions that could be uncommon for these weak interactions in systems as complexes as the present study. On the other hand, interactions such as the numbered 1, 8, 16, and others, also from **Table 3**, present ε values higher than 1.00 that indicate non-directional interactions, the influence of more than two atoms in the topology of an interaction, and a higher anisotropy of the electron density around the BCP.

It is noteworthy the high number of interactions detected, indicating the formation of complexes with high stability in spite of being bonded by weak interactions. A previous study[12] also described the interactions of CLD, this time with an activated carbon model, using QTAIM. Such study reported a much lesser number of interactions; however, these were found to be in a much wider range, from vdW to covalent bonds, conferring a high stability to supramolecular systems. Another work by Attoui-Yahia et al.[63] described, using QTAIM, the interactions present in the complex pyridoxine@β-CD, while a research by Sifaoui et al.[64] described the formation of guest-host complexes between aromatic compounds and β-CD in an anhydrous environment. Both studies, depicted interactions mainly of dispersive nature. However, the presence of hydrogen bonds of moderate strength provided stability to the complexes. The weakness of the interactions observed in the present work, joined to the impossibility of the CLD of forming hydrogen bonds with the oxygen atoms of the CD, allow to reach the conclusion that the high stability of the CLD@CDs complexes is fundamentally given by the great number of interactions, equilibrating little strength of each separate interaction.

4. CONCLUSIONS

Guest-host complexes between chlordecone and cyclodextrins were characterized using a calculation strategy based in the articulation of three different calculation methodologies:

First, the Multiple Minima Hypersurface methodology using the semiempirical Hamiltonian PM6-D3H4X for the identification of local minima of interaction and the estimations of mean association energies. Next, the DFT scheme M06-2X/6-31G(d,p) for refinement of the MMH output geometries and wave functions of lowest energy minima. Finally, a QTAIM analysis was performed for identifying and classifying the intermolecular interaction present in the CLD@CDs complexes.

All the supramolecular complexes were found to be thermodynamically stable and were classified according to the inclusion degree in complexes with total occlusion of the CLD into the CD, with partial occlusion, and with no occlusion (external interaction of the pollutant with the host molecule).

The intermolecular interactions, determined by means of Quantum Chemical Topology using QTAIM, were classified as electrostatic with manly dispersive characteristics.

The Counterpoise correction method was modified for the mitigation of the basis set superposition error with application in a system where the SMD implicit solvation method is used. The used thermodynamic cycle was consistent in all calculations performed and its application lead to a computational cost similar to the original Counterpoise method.

FIGURES

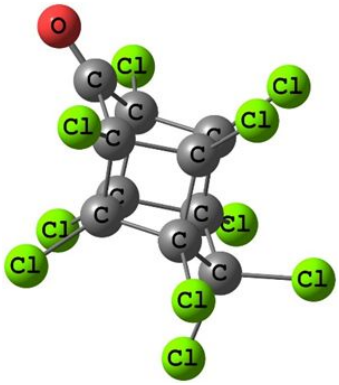


Figure 1. Representation of the model corresponding the chlordecone molecule.

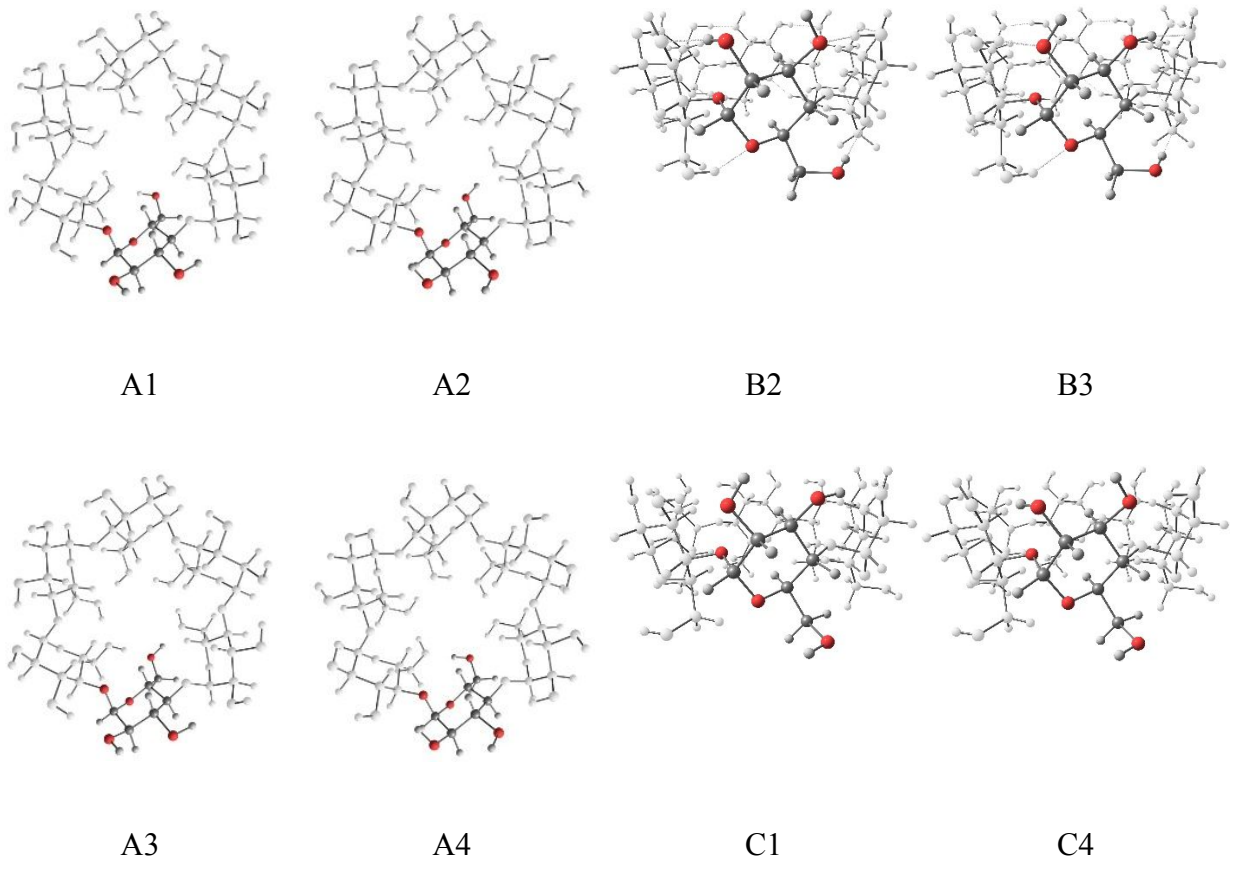


Figure 2. Theoretical model based on symmetric conformers of cyclodextrin generated using PM6-D3H4 semiempirical Hamiltonian. Only α-CD is presented and one glucopyranose unit is detailed for clarity. Reproduced with permission from Springer Nature.[39]

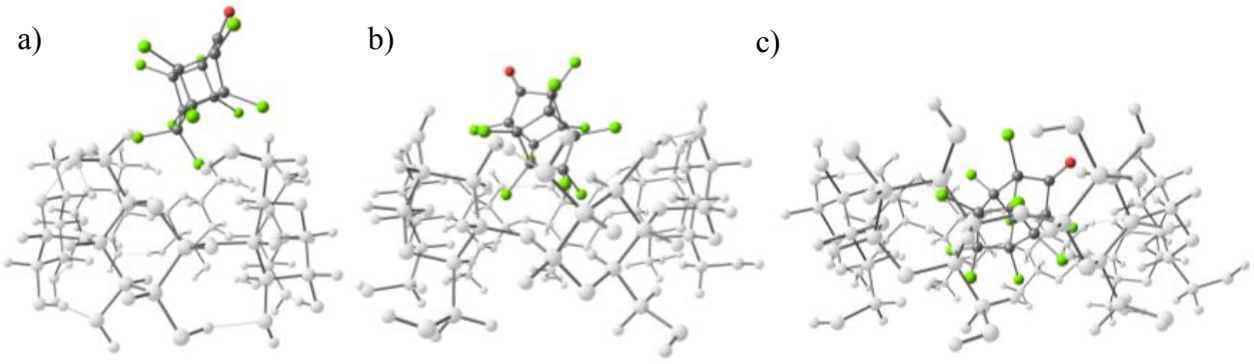
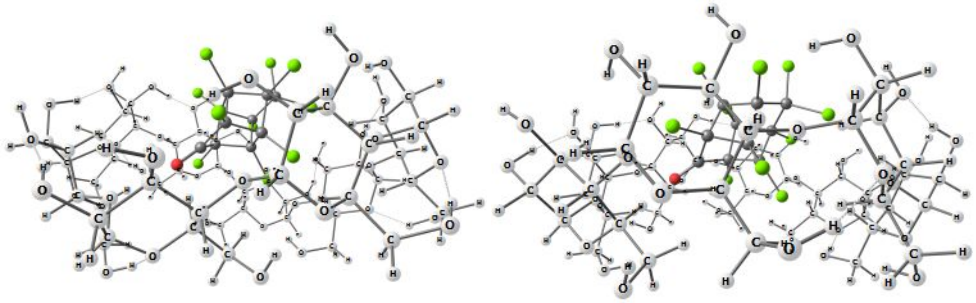


Figure 3. Inclusion degrees observed in the interactions calculated using MMH/PM6-D3H4X: a) external interaction without occlusion (CLD/B2-α-CD), b) partial occlusion (CLD@C1-β-CD), c) total occlusion (CLD@C4-γ-CD).

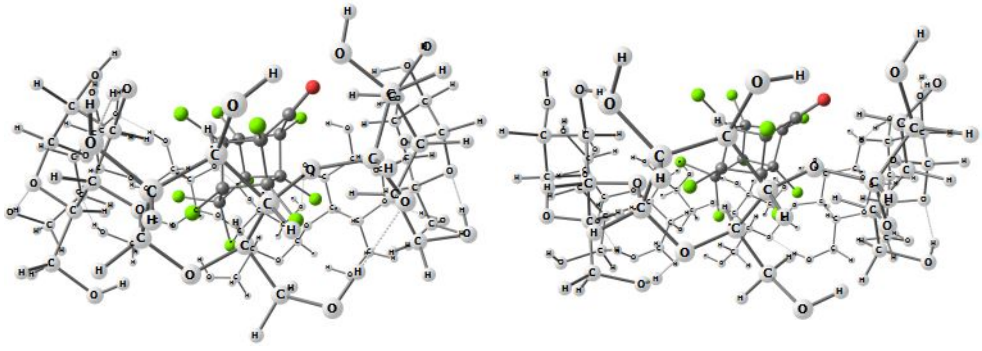
CLD@B2-γ-CD

(86.0 %)



CLD@B3-γ-CD

(58.9 %)



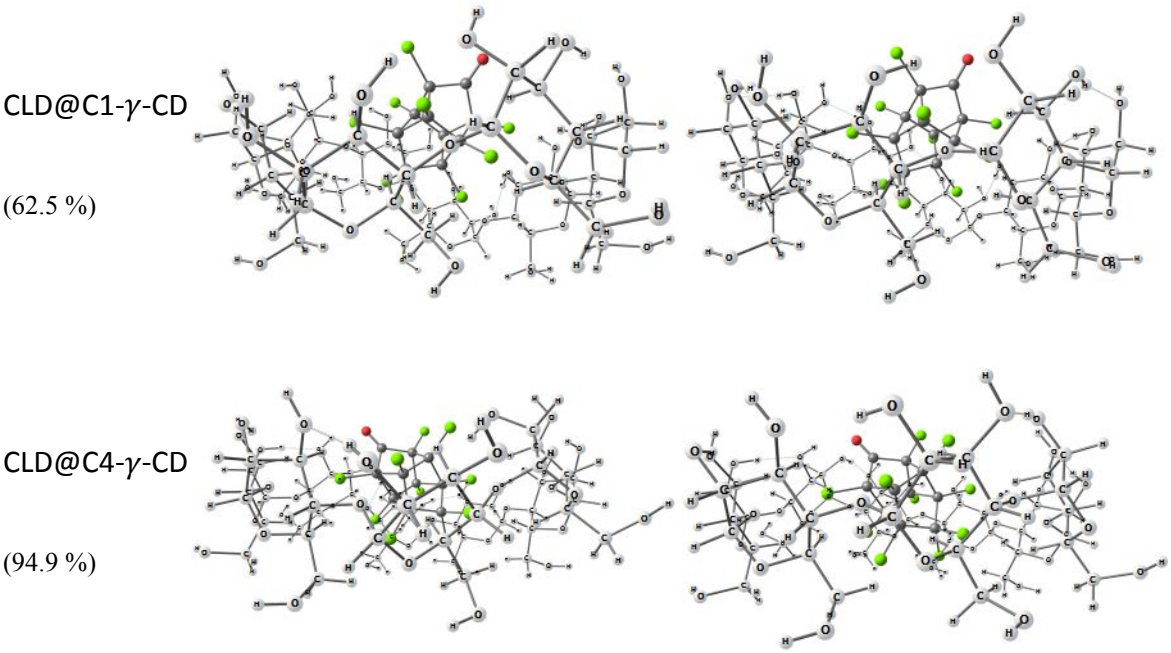


Figure 4. Distinctive structures for the complexes CLD@γ-CD. The CLD is shown in colors, while the γ-CD structures are presented in gray. For every couple of structures it is shown, to the left: the lowest energy minimum structure obtained by means of MMH/PM6-D3H4X, to the right: the refined structure obtained from M06-2X/6-31G(d,p) calculations. The population according to the Boltzmann energy distribution is shown in parentheses for the structures obtained from MMH calculations.

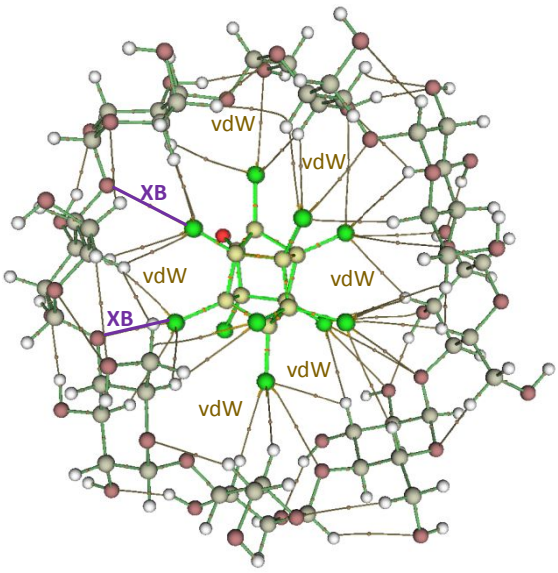
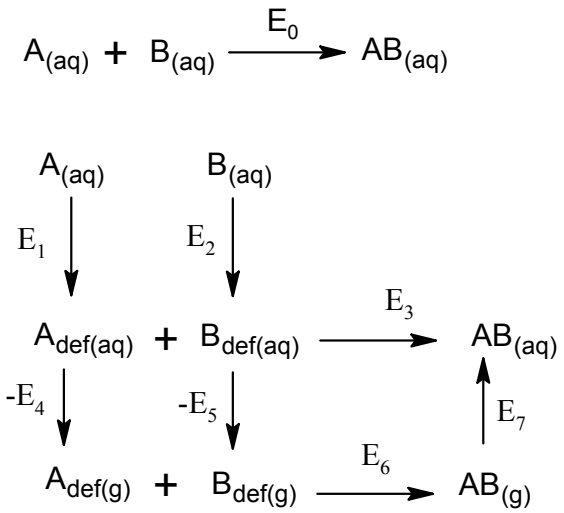
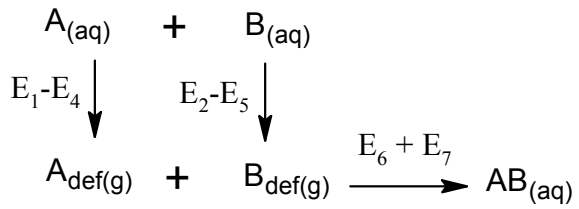


Figure 5. Intermolecular interactions for the guest-host complex CLD@C1-γ-CD as determined using QTAIM from the geometry and wave function given by M06-2X/6-31G(d,p) calculation. Two types of interactions were identified: van der Waals interactions (vdW, colored in mustard) and halogen bonds (XB, colored violet).

SCHEMES



Scheme 1. General scheme of the thermodynamic cycle generated for the calculation of the association energy (E0). E1 and E2 are the deformation energies of the components of the system separated to the infinity. E4, E5, and E7 account the solvation energies of the two components and the supermolecule, respectively. E3 is the interaction energy of the components in aqueous solution (aq) and E6 account for the same in gas phase (g). The subscript "def" indicates deformation.



Scheme 2. Final scheme of the simplified thermodynamic cycle for the calculation of the association energy (E0). E1 and E2 are the deformation energies of the system components separated to the infinity. E6 is the interaction energy in the complex. These energies are calculated in conjunction with E4, E5, and E7 that are the solvation energies of the components and the supermolecule, respectively. The subscript "def" accounts for deformation.

CHARTS

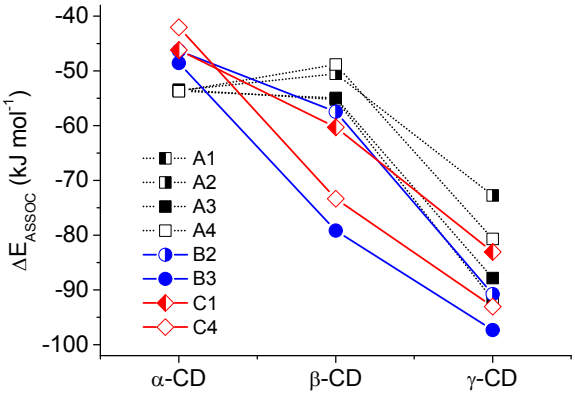


Chart 1. Mean association energies (ΔE_{ASSOC}) for the supramolecular systems CLD/CDs calculated by means of MMH with the method PM6-D3H4X.

TABLES

Table 1. Distribution of the occlusion degrees for each conformer of α, β, and γ-CD in the complexes CLD@CDs.[a]

CD	Conformer	TO (%)	PO (%)	NO (%)
α-CD	A1	0.0	8.9	**90.3**[b]
	A2	0.0	14.2	**85.3**
	A3	0.0	9.1	**90.0**
	A4	0.0	9.6	**89.5**
	B2	0.0	1.6	**97.5**
	B3	0.0	0.0	**99.1**
	C1	0.0	**54.3**	44.7
	C4	0.0	9.8	**89.4**
β-CD	A1	0.0	**97.7**	1.6
	A2	0.0	**50.2**	49.1
	A3	0.0	39.1	**60.1**
	A4	0.0	47.9	**51.4**
	B2	0.0	**99.1**	0.0
	B3	0.0	**95.9**	3.5
	C1	0.0	**99.7**	0.0
	C4	0.0	**99.5**	0.0
γ-CD	A1	0.0	**99.1**	0.0
	A2	0.0	**99.3**	0.0
	A3	0.0	**99.3**	0.0
	A4	0.0	**99.5**	0.0

B2	**99.4**	0.0	0.0
B3	**86.0**	6.5	6.6
C1	**92.9**	5.7	0.6
C4	**98.0**	1.1	0.0

[a] Total occlusion (TO), partial occlusion (PO), external interaction with no occlusion (NO). The percentages are based in the minima summing over 99 % of the total population based in a Boltzmann energy distribution. [b] Values in bold represent the inclusion degree with the higher population according to a Boltzmann energy distribution.

Table 2. Punctual association energies ($\Delta E_{ASSOC,\,i}$) calculated using M06-2X/6-31G(d,p) for the lowest energy minima of the CLD/CDs complexes. Uncorrected and Counterpoise corrected values are compared.

Conformer	Occlusion[a]	$\Delta E_{ASOC,i}$[b] (kJ mol^{-1})	$\Delta E_{ASOC,i}^{CP}$[c] (kJ mol^{-1})	BSSE (%)
B2-α-CD	NO	-57.12	-33.85	40.7 %
B2-β-CD	PO	-81.44	-41.67	48.8 %
B2-γ-CD	TO	-91.00	-46.28	49.1 %
B3-α-CD	NO	-90.36	-54.85	39.3 %
B3-β-CD	PO	-84.80	-76.71	9.5 %
B3-γ-CD	TO	-112.37	-77.78	30.8 %
C1-α-CD	PO	-72.99	-33.75	53.8 %
C1-β-CD	PO	-107.37	-64.51	39.9 %
C1-γ-CD	TO	-124.76	-84.58	32.2 %
C4-α-CD	PO	-94.38	-45.43	51.9 %
C4-β-CD	PO	-101.39	-59.61	41.2 %
C4-γ-CD	TO	-111.54	-70.27	37.0 %
C1-γ-CD[d]	TO	-129.10	-86.59	32.9 %

[a] Total (TO), partial (PO), no occlusion (NO).

[b] Calculated according: $\Delta E_{ASSOC,i} = E(CLD@CD) - (E(CLD) + E(CD))$

[c] Corrected using Counterpoise according to the methodology presented in this work.

[d] Modeled in gas phase.

Table 3. Nature of interatomic interactions in the complex CLD@C1-γ-CD.[a]

Interactio	Atoms[b]	d (Å)	ρ_C	$\nabla^2\rho_C$	H_C	ε	Type[c]
1	Cl···H	3,54	0,002	0,006	0,0004	1,49	vdW
2	Cl···H	3,04	0,005	0,017	0,0009	0,04	vdW
3	Cl···H	2,87	0,005	0,021	0,0013	0,06	vdW
4	Cl···O	3,67	0,003	0,013	0,0008	0,25	vdW
5	Cl···H	3,51	0,002	0,006	0,0004	0,21	vdW
6	Cl···O	3,31	0,007	0,027	0,0012	0,27	vdW
7	Cl···H	2,99	0,006	0,022	0,0012	0,24	vdW
8	Cl···O	3,76	0,003	0,013	0,0008	2,92	vdW
9	Cl···O	3,27	0,007	0,027	0,0011	0,16	vdW
10	Cl···H	2,84	0,008	0,027	0,0013	0,04	vdW
11	Cl···H	2,76	0,009	0,032	0,0015	0,03	vdW
12	Cl···O	3,25	0,007	0,028	0,0012	0,12	vdW
13	Cl···H	2,93	0,006	0,021	0,0012	0,02	vdW
14	Cl···H	2,63	0,009	0,035	0,0016	0,04	vdW
15	Cl···H	3,02	0,005	0,018	0,0011	0,05	vdW
16	Cl···H	3,25	0,004	0,015	0,0009	1,14	vdW
17	Cl···H	2,99	0,006	0,020	0,0011	0,04	vdW
18	Cl···H	2,93	0,006	0,021	0,0013	0,13	vdW
19	Cl···O	3,01	0,011	0,043	0,0011	0,02	XB
20	Cl···H	2,85	0,007	0,025	0,0012	0,08	vdW
21	Cl···H	2,92	0,006	0,022	0,0013	0,10	vdW
22	Cl···H	2,82	0,008	0,028	0,0014	0,09	vdW
23	Cl···O	2,95	0,012	0,047	0,0011	0,05	XB
24	Cl···H	2,87	0,006	0,022	0,0013	0,08	vdW
25	Cl···H	2,68	0,010	0,034	0,0014	0,04	vdW
26	Cl···H	3,19	0,004	0,013	0,0007	0,79	vdW
27	Cl···O	3,31	0,006	0,024	0,0011	0,15	vdW
28	Cl···H	2,73	0,010	0,034	0,0015	0,06	vdW
29	Cl···H	3,10	0,004	0,014	0,0009	0,44	vdW
30	Cl···H	2,65	0,011	0,038	0,0016	0,05	vdW
31	Cl···O	3,07	0,010	0,037	0,0011	0,05	vdW
32	Cl···H	2,71	0,009	0,031	0,0014	0,06	vdW
33	Cl···O	4,00	0,002	0,008	0,0005	1,12	vdW
34	Cl···H	3,12	0,004	0,013	0,0008	0,10	vdW
35	Cl···O	3,67	0,002	0,006	0,0004	1,49	vdW
36	Cl···O	3,29	0,006	0,025	0,0011	0,07	vdW
37	Cl···H	2,79	0,009	0,029	0,0014	0,02	vdW

[a] Interatomic distances (d), electron densities (ρ_C), Laplacian of the electron density ($\nabla^2\rho_C$), total energy density (H_C), and ellipticity of the electron density (ε) at the BCPs for the complex CLD@C1-γ-CD. Unless otherwise noted, all values are reported in atomic units. [b] To the left, the atom corresponding to the CLD is identified, to the right, the one corresponding to the CD. [c] The types of interactions classified were: dispersive (vdW) and halogen bonds (XB).

ASSOCIATED CONTENT

Supporting Information.

Mean association values, figures for distinctive structures, QTAIM descriptions of the interactions.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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GRAPHICAL ABSTRACT/TOC FIGURE