

# Simultaneous exhibition of positive and negative cooperativity by purely C-H—O H-bonded (1,3-cyclohexanedione)<sub>n</sub> (n = 2-6) clusters: A density functional theoretical investigation

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## Abstract

Investigation of cooperative effect exhibited by purely C-H—O hydrogen bonded (H-bonded) networks in linear and cyclic clusters of (1,3-cyclohexanedione)<sub>n</sub> (n = 2 to 6) has been carried out using density functional theoretical calculations. Linear clusters were found to show anti-cooperative behavior, while the cyclic clusters showed positive cooperativity. H-bond strengths and binding energies per bimolecular interaction were found to decrease with increasing cluster size for the linear clusters whereas their cyclic counterparts showed opposite trends. The extent of cooperativity has been found to show monotonic behavior for both linear and cyclic clusters and was found to reach an asymptotic limit with increasing cluster size. Natural bond orbital (NBO) analysis and atoms in molecule (AIM) calculations were found to corroborate the obtained results.

## Abstract:

Investigation of cooperative effect exhibited by purely C-H—O hydrogen bonded (H-bonded) networks in linear and cyclic clusters of (1,3-cyclohexanedione)<sub>n</sub> (n = 2 to 6) has been carried out using density functional theoretical calculations. Linear clusters were found to show anti-cooperative behavior, while the cyclic clusters showed positive cooperativity. H-bond strengths and binding energies per bimolecular interaction were found to decrease with increasing cluster size for the linear clusters whereas their cyclic counterparts showed opposite trends. The extent of cooperativity has been found to show monotonic behavior for both linear and cyclic clusters and was found to reach an asymptotic limit with increasing cluster size. Natural bond orbital (NBO) analysis and atoms in molecule (AIM) calculations were found to corroborate the obtained results.

## Introduction:

Hydrogen bond (H-bond) is one of the most extensively studied among various non-covalent interactions. The interest in H-bond is mainly owing to its importance in influencing the structures and activities of various chemical and biological systems, such as proteins, DNA, enzymes etc<sup>1,2,3,4,5,6</sup>. One of the more interesting attributes of H-bond is its role in formation and stabilization of molecular clusters at ambient condition by virtue of a special non-additive property, which is absent in covalent interactions, known as cooperative effect. It plays pivotal roles in various fields like structural stabilization of biological macromolecules, facilitating enzyme reactions and formation of stable supramolecules<sup>7,8,9,10,11,12,13,14</sup>. Depending on the collaborative or antagonistic nature of their mutual behavior, cooperativity could be classified as positive or negative, respectively. Cooperativity between H-bonds was first postulated qualitatively by Frank and Wen<sup>15</sup> as early as in 1957. However, it took almost another 3-4 decades for quantitative estimation employing advanced spectroscopic<sup>16,17,18</sup>, and computational methods<sup>19,20,21,22</sup>. Since then, many research groups have extensively investigated the cooperative nature of H-bonds by studying several H-bonded molecular clusters like of water<sup>18,23,24,25,26</sup> ammonia<sup>27,28,29</sup> 1,3-diones<sup>30</sup> carboxylic acids<sup>31</sup> amides<sup>32,33,34</sup>. It is worth

mentioning here that a large majority of the existing works on cooperativity is focused on the behavior of classical H-bonds. Over the last couple of decades, however, various classes of weak H-bonding interactions have been found to play important roles in dictating structures, and consequently functions, of biological macromolecules<sup>35,36,37</sup>. Cooperative effects imparted by neighboring H-bonds, either classical or weak, on these bonds, and also in the reverse direction, inside the macromolecules are expected to provide appreciable impetus in their extra stabilization. This has prompted several studies on cooperativity involving weak H-bonds, a few of them dealing with negative cooperativity as well<sup>38,39,40,41,42,43,44</sup>. Nevertheless, most of these studies, that include both experimental<sup>45,17,46,47,48</sup> and theoretical<sup>49,50,51,52,53</sup> works, have dealt with how a weak H-bond cooperatively stabilizes (or destabilizes) a classical H-bond in either inter- or intra molecular fashion. On the other hand, not too many studies are available in existing literature on how weak H-bonds cooperatively stabilize themselves in molecular clusters, investigations on C-H—N interactions in HCN<sup>54</sup> and cyanoacetylene<sup>55</sup> clusters and C-H— $\pi$  in ethyne clusters<sup>56</sup> and S-H—S H-bond in H<sub>2</sub>S clusters<sup>57</sup> being a few of them. However, to the best of our knowledge, there exists no work on the negative cooperativity exhibited by one weak H-bond on another.

Among various weak H-bonds known to us, C-H—O type has been studied very extensively over the past couple of decades, in an earlier work it was shown that C-H—O H-bond could dramatically facilitate the diketo to keto-enol tautomerization process in cyclic 1,3-diketones, the barrier for tautomerization being highly sensitive to both H-bond strength as well as size of the C-H—O H-bonded diketone cluster. 1,3-cyclohexanedione (CHD) has been widely considered to be a prototype for studies focused on cyclic 1,3-diketones<sup>58</sup>. When the diketo form of CHD forms homomeric clusters, then it is bound by only C-H—O type H-bonds. Due to the above reasons, molecular clusters of CHD could prove to be a very suitable system for studying the cooperative nature of C-H—O H-bonds. Besides, CHD provides multiple donors (via eight C-H bonds) and acceptor sites (via two carbonyl groups) which makes possible to monitor chelate effects on cooperative nature. As the change in cluster size would inevitably result in a change in relative orientation between adjacent monomeric moieties, it is expected that interactions between these multiple donor and acceptor sites would undergo mutual alteration.

In this work, we have investigated C-H—O H-bonded molecular clusters (CHD)<sub>n</sub> ( $n = 2$  to  $6$ ) employing density functional theoretical methods. The evolution of geometric and energetic parameters with cluster size has been studied to assess the extent of cooperativity in those clusters. The geometric and energetic trends shown by C-H—O H-bonds have been corroborated with hyper conjugative charge-transfer energies calculated using natural bond orbital (NBO) analysis and electron density values at bond critical points provided by atoms in molecule (AIM) calculations.

## Methodology:

Geometry optimization and normal mode frequency calculation of CHD monomer along with all the studied (CHD)<sub>n</sub> ( $n = 2-6$ ) clusters were performed employing B3LYP functional in conjunction with 6-311++g\*\* basis set. For calculation of binding energies of the clusters, basis set superposition errors (BSSE) were corrected using the single point counterpoise method of Boys and Bernardi<sup>59</sup>. Further, counterpoise corrected single point energies for all the species were calculated at M06-2X/6-311++g\*\* level using the geometries optimized at B3LYP/6-311++g\*\* level. The total binding energy of a cluster comprising of  $n$  monomeric CHDs is defined by equation. (1)

$$E_{\text{stab}} = E_n - nE_1$$

It was found that the binding energy values calculated by B3LYP differ significantly from the same calculated at M06-2X (Table 1). This might be due to the contribution of long-range dispersion interaction which is known to play an important role in stabilizing weak H-bonded complexes. Therefore, geometry optimization, frequency calculation and single point counterpoise correction have been carried out using  $\omega$ B97X-D functional and 6-311++G\*\* basis set. Further, counterpoise corrected single point energy calculation has been performed using M06-2X functional and 6-311++G\*\* basis set for geometries optimized

at  $\omega$ B97X-D/6-311++G\*\* level of theory given in Table 1. Here, the stabilization energy obtained at this level was close to what was predicted by  $\omega$ B97X-D/6-311++G\*\* level of theory. Therefore throughout the manuscript stabilization energy calculated at  $\omega$ B97X-D/6-311++G\*\* level has been used for study the molecular cluster. Natural bond orbital and atoms in molecules calculations have been carried out using  $\omega$ B97X-D functional and 6-311++G\*\* to corroborate with the energetic and geometric findings. All the geometry optimization, normal mode frequency and natural bond orbital (NBO)<sup>60</sup> calculation have been carried out using Gaussian16<sup>61</sup> suite of program where as topological analysis was performed using AIM 2000 software package.<sup>62</sup> Throughout the manuscript, all the binding energy values mentioned are counterpoise corrected values calculated at  $\omega$ B97X-D/6-311++G\*\* level of theory, unless otherwise mentioned.

## Results and discussion:

In this work, we have investigated the intermolecular C-H...O H-bond formed between two CHD molecules and how they undergo modifications with increasing size of CHD clusters from dimer to hexamer. In order to do so, we have focused on the geometric, energetic and electronic features of the C-H—O H-bonds and subsequently tried to quantify the extent of cooperativity (both positive and negative) exerted by them.

### 3.1. Molecular geometries:

A single CHD unit contains eight hydrogen atoms (four each in axial and equatorial positions) attached to four carbon atoms. So, in a single CHD molecule, there are eight C-H groups available that can potentially act as H-bond donors. However, all the eight atoms don't participate in H-bond formation. During homo dimer formation, only the axial hydrogen atoms (i.e. 2a, 4a and 6a in Figure 1) are known to act as H-bond donor. During the cluster formation if both the axial and equatorial H-atoms will participate, then the resulting geometry will be restricted for further chain propagation. The geometry being restricted will not allow for the formation of higher order clusters. So, only three axial C-H groups participate in H-bonding during cluster formation. The geometries involving the mentioned C-H groups participated in H-bond formation will lead for higher order cluster formation.

The numbering of the donor C-H groups has been done according to their gas phase acidity values. The group having the highest gas phase acidity has been named as donor1. Gas phase acidity of the group 2a was found to be -344.2 kcal mol<sup>-1</sup>, whereas the same for group 4a and 6a were found to have equivalent gas phase acidity value i.e. -367.9 kcal/mol. Therefore the naming follows donor1 for group 2a, donor2 and donor3 for 4a and 6a respectively. Also the naming of the H-bonds present are according to the naming of these groups. H-bond1 (HB1), H-bond2 (HB2) and H-bond3 (HB3) are bonding between C=O group with the hydrogen of donor1, donor2, and donor3 respectively.

#### 3.1.1 Dimer:

It has been shown earlier that three different conformers are possible for CHD homo dimer,<sup>58</sup> out of which dimer3 has all four carbonyl groups H-bonded and dimer1 and dimer2 have one carbonyl group on each monomeric moiety free (Figure S1). The relative orientation of the two free carbonyl groups are cis (designated as C-conformer) and trans (T-conformer) to each other in dimer1 and dimer2, respectively. These free carbonyl groups are key to allow for chain propagation, resulting in higher order cluster formation. This is why dimer3, with all the four carbonyl groups being H-bonded, results in a closed structure and cannot give rise to higher order cluster formation. The energetics of all the conformers are given in Table 1. From the table, it can be found out that dimer3 is most stable among all the possible conformers, while the C and T dimer are energetically very close to each other.

#### 3.1.2 Trimer:

Two distinct possibilities, namely linear and cyclic forms, of cluster formation are possible for trimer. The linear variety can have three different conformers based on the relative orientation of the carbonyl groups in the adjacent monomeric units. Following the same nomenclature discussed in the previous section the conformers present here are named as CC, CT, and TT; the first one represents the relative orientation between first and second monomeric units, while the second letter does the same between second and third.

The geometries of the conformers along with their name are provided in Figure S2. In case of the cyclic trimer, two different conformers are possible, namely trimer1 and trimer2. In trimer1 all three free carboxyl groups are in the same direction, while one is in the opposite direction in trimer2. The geometries of both the conformers are shown in Figure S2.

Binding energies of all the possible trimers are provided in Table 1. The three linear conformers are energetically very close to each other. The binding energies of CC, CT, and TT are -16.1, -16.4 and -16.2 kcal mol<sup>-1</sup>, respectively. Whereas binding energies for cyclic Trimer1 and Trimer2 were found to be -17.9 and -18.3kcal mol<sup>-1</sup>. Therefore, both the cyclic trimers are more stable than their linear counterparts. The difference in binding energies between most stable linear and least stable cyclic cluster being 1.5 kcal mol<sup>-1</sup>.

### 3.1.3 Tetramer:

Similar to its trimeric counterpart, tetramer can also exist in both linear and cyclic forms. Six different linear conformers are possible for tetramer based on the relative orientation of two neighboring monomeric units, and have been named as CCC, CCT, CTC, TCT, CTT, and TTT. Calculations performed at the B3LYP level of theory showed all of the six clusters to be linear (Figure S3). However, when ωb97xd functional was used only two conformers (CTT and TTT) remained linear, while the remaining four were converted to closed form (Figure S4) during optimization. This indicates that consideration of long-range dispersion interaction is a must while working with weakly H-bonded molecular clusters.

In the case of the cyclic tetramer, four different conformers are possible based on the relative orientation of the free carbonyl groups; named as tetramer1, tetramer2, tetramer3, and tetramer4 (Figure S4). In tetramer1, all four free carbonyl groups are in the same direction while tetramer2 has two alternate free carbonyl groups on the same side. Tetramer3 has two neighboring free carbonyl groups in the same direction and the remaining two in the opposite direction. For Tetramer4 three free carbonyl groups are in the same direction.

Binding energies of all 10 possible conformers of tetramer are given in Table 1. Out of the 8 cyclic tetramers, tetramer CCC was found to be the most stable with binding energy -29.7 kcal mol<sup>-1</sup>, while tetramer1 was the least stable one with binding energy -25.1 kcal mol<sup>-1</sup>. Therefore, the binding energies of the cyclic tetramers vary by a significant margin (4.6 kcal mol<sup>-1</sup>). On the other hand, the two linear tetramers, which are energetically less stable than all the cyclic conformers are very close to each other; CTT (-24.1 kcal mol<sup>-1</sup>) being only 0.1 kcal mol<sup>-1</sup> more stable than TTT (-24.0 kcal mol<sup>-1</sup>). If the prediction of the B3LYP level of theory is considered, which predicts six linear and four cyclic conformers, the relative energies of the cyclic forms vary by a large amount while the same for linear are pretty close together as can be inferred from in Table 1.

### 3.1.4 Pentamer and Hexamer:

The number of conformers, including both linear and cyclic forms, possible for pentamer and hexamer are appreciably high. Here we would like to reiterate that the goal of this study is not to look for different possible conformers that could exist, but to investigate how the geometric and energetic features of CH—O H-bonds modulate with cluster size and how that modulation influences the cluster formations. For that purpose, we needed to choose a particular type of linear and cyclic conformer each for clusters of various sizes. For linear, we chose all-trans conformer and for cyclic, we chose the ones where all the free carbonyl groups were pointing in the same direction. Binding energy of pentamer (TTTT) and hexamer (TTTTT) was found to be -31.7 and -39.0 kcal mol<sup>-1</sup> respectively, provided in Table 1. The geometries of the two conformers are given in Figure S5. As in the preceding section, we have named the 5-membered and 6-membered cyclic clusters as Pentamer1and Hexamer1. The two are having binding energy -31.9 and -37.9kcal mol<sup>-1</sup> respectively. The energetics have been provided in Table 1, whereas the geometries are being provided in Figure S5.

## 3.2 Cooperative nature of H-bond in CHD clusters:

As there are two distinct types of clusters possible, the discussion on the cooperativity in CHD clusters has been divided into two parts; the first one focusing on linear clusters and the second one centered on cyclic

clusters. As discussed previously, only the all trans linear conformers has been considered for this comparison and the dimer through hexamer are represented as LD, LTr, LTe, LP and LH, respectively. The molecular geometries of the above mentioned linear clusters optimized at  $\omega$ B97X-D/6-311++G\*\* level of theory is shown in Figure 2. Similarly, for cyclic variant only the ones having all free carbonyl pointing in the same direction have been considered for the discussion and they are represented as CD, CTr, CTe, CP and CH in the same order. The molecular geometries of these 5 cyclic clusters optimized at  $\omega$ B97X-D/6-311++G\*\* level of theory is shown in Figure 3.

As multiple H-bonds are involved between two monomers, there doesn't exist any well-defined correlation between H-bond lengths with cluster size that could be used as an indicator for estimating the extent of cooperativity. Therefore, we have used C=O bond length and binding energy to estimate overall cooperative and anti-cooperative nature of cluster. Further, to estimate how strength of one H-bond influences the others, effect of multiple H-bonds formed between two particular monomeric moieties influencing each other with increasing cluster size has also been studied.

### Cooperativity in linear clusters:

In case of the linear clusters, binding energies of LD, LTr, LTe, LP and LH were found to be -8.8, -16.2, -24.0, -31.7, and -39.0 kcal mol<sup>-1</sup>, respectively, given in Table 2. Also binding energy per interaction was calculated by dividing the total binding energy by the number of bonded carbonyls. It was found that binding energy per interaction decreases gradually from LD (-4.4 kcal mol<sup>-1</sup>) to LTr (-4.1 kcal mol<sup>-1</sup>), LTe (-4.0 kcal mol<sup>-1</sup>), LP (-4.0 kcal mol<sup>-1</sup>) and LH (-3.9 kcal mol<sup>-1</sup>) as can be seen from Figure 4. Therefore, the linear clusters show overall anti-cooperative behavior as binding energy per interaction decreases monotonically with increase in cluster size.

The above values clearly show that, on average, H-bonding interaction becomes weaker with increasing size in linear clusters. However, it would be more interesting to see how the interaction energy of a particular cluster gets modified upon addition of one or more monomeric units to the cluster. For example, the existing 4 H-bonds in LD get affected when another CHD molecule gets attached to form LTr. Now if the binding energy of LD is calculated in its conformation inside LTr, this will provide the exact change in binding energy LD experiences when a CHD molecule is added to it. Now, when two CHD molecules are added to LD, there are two possibilities, both of them could be added to the same side or to either sides. When binding energy LD is calculated in similar manner for LTr, it will give us an idea of how addition of two monomeric moieties influence the interaction in LD. Similar calculations have been carried out for LD within LP and LH, for LTr within LTe, LP and LH, for LTe within LP and LH and finally for LP within LH. For easier comparison the obtained results have been normalized by considering binding energies per interaction as defined above (Table 3) and plotted as bar diagram (Figure 5). It was found that the binding energy of a certain size of cluster decreases monotonically with increasing addition of CHD monomer to that cluster and finally reaches an asymptotic limit near the upper limit. For example, the value for LD (4.4 kcal mol<sup>-1</sup>) reduces to 4.3 kcal mol<sup>-1</sup> in LTr and 4.1 kcal mol<sup>-1</sup> in LTe and remains at the same value in LH. The other clusters also show similar trends. This result unambiguously shows that addition of one or more CHD molecules to an existing linear cluster results in weakening of the existing H-bonds originally holding the cluster. This is a clear manifestation of anti-cooperative behavior of C-H—O H-bonds in linear CHD clusters.

The anti-cooperative behavior is also evident from the C=O bond length of the H-bonded carbonyl groups. C=O bond length of H-bonded carbonyl group is known to be sensitive to H-bond strength; stronger H-bond results in longer C=O bond<sup>63,64</sup> Average C=O bond length of H-bonded carbonyl groups for the LD, LTr, LTe, LP and LH were found to be 1.2104, 1.2095, 1.2094, 1.2093 and 1.2093 Å, respectively (Figure 4). Thus, it is evident that the decrease in average C=O bond length with increasing cluster size is due to the weakening of H-bonds as a result of anti-cooperative effect. Therefore, both binding energy per interaction and average C=O bond length show that C-H—O H-bond is anti-cooperative in the linear clusters.

In linear clusters, every H-bonded carbonyl group forms two H-bonds, i.e. HB1 and HB2 as defined beforehand. Consequently, it would be interesting to see how each of these two types of H-bonds individually modulate

and also how they influence each other, both as a function of cluster size. For this purpose we have plotted the H-bond length of both HB1 and HB2 against the number of H-bonded carbonyl groups, as each carbonyl group forms one each of HB1 and HB2 (Figure 6). The numbering of H-bonded carbonyl groups in Figure 2 is done from one end of the cluster to the other end. As two carbonyl groups remain free in every cluster, irrespective of its size, the total number of H-bonded carbonyl groups would be  $2N-2$  for a cluster formed by  $N$  CHD molecules. It is evident from Figure 6 that neither HB1 nor HB2 show any monotonic variation in their length with cluster size. Nevertheless, there are systematic modulations of HB1 and HB2, both individual as well as mutual, in each of the clusters. In each of the clusters, the two terminal HB1s are the shortest and shows a zigzag pattern as one moves from one end to the other. HB2 also shows a similar zigzag pattern, but in completely opposite manner, i.e. it increases when HB1 decreases and vice versa. Therefore, it could be said that these two types of H-bonds show an anti-cooperative behavior between themselves; strengthening of one is always accompanied by weakening of the other.

In order to corroborate the above findings, we carried out NBO analysis to examine the delocalization energies associated with the charge transfer from lone pairs of acceptor oxygen atom to the anti-bonding orbital of donor C-H bond. Besides, AIM analysis was performed to estimate electron density and its Laplacian at the bond critical points for HB1 and HB2. When these obtained values given in Table S1 were plotted against H-bond lengths (Figure S6), delocalization energy along with electron density and its Laplacian for both HB1 and HB2 were found to decrease monotonically with diminishing strength (i.e. lengthening) of both H-bonds.

### 3.2.2 Cooperativity in Cyclic clusters

Similar to its linear counterpart, the number of possible cyclic conformers also increases with cluster size. Therefore, it becomes imperative to choose one particular type of conformer for all the sizes, from dimer to hexamer, to study the evolution of H-bonds with increasing cluster size. We chose cyclic clusters 1, the ones with all free carbonyl groups pointing in the same direction, for the study of H-bond cooperativity. Total binding energies of CD, CTr, CTe, CP and CH were found to be -8.8, -17.9, -25.1, -31.9 and -37.9 kcal mol<sup>-1</sup>, respectively, and binding energy per interaction were -4.4, -6.0, -6.3, -6.4 and -6.3 kcal mol<sup>-1</sup>, in the same order (Table 2 and Figure 4). Here, binding energy per interaction increases monotonically with increasing cluster size up to pentamer, and then decreases marginally for hexamer. This steady increment clearly indicates that cyclic clusters enjoy cooperative stabilization and the effect gets saturated when the cluster size reaches pentamer. It may be noted here that the binding energy per interaction for linear clusters was also found to reach saturation point at pentamer.

The above values clearly show that, on average, H-bonding interaction becomes stronger with increasing size of cyclic cluster. Therefore, if one or more CHD molecules are removed from a particular cluster keeping the remaining part as it was in the cluster, the binding energy per interaction would decrease steadily with successive removal of monomeric units. For example, when one CHD molecule is removed from CH, the resulting structure would have lesser binding energy per interaction than the cluster itself. Removal of another monomer would lower the value further and so on till two monomeric units remain. Similar procedure has been followed for CP, CTe and CTr as well. The obtained values have been tabulated (Table 3) for quantitative analysis and a bar diagram has been constructed (Figure 7) for easier qualitative assessment. As monomeric units are removed from CH, the binding energy per interaction decreases from 6.3 kcal mol<sup>-1</sup> successively to 6.0, 5.6, 5.2 and 4.5 kcal mol<sup>-1</sup>. Similar trends are observed for CP, CTe and CTr as well. The above findings clearly show that upon addition of each CHD molecule, the binding energy per interaction increases steadily for all the cyclic clusters. Therefore, it could easily be inferred that the cyclic clusters enjoy cooperative stabilization.

The above discussions clearly indicate that the H-bonding interactions become stronger, and consequently H-bond accepting capability of the bound carbonyl groups increase, with the size of cyclic clusters. This increment should result in consistent increase in C=O bond length of H-bonded carbonyl groups. It was found that the C=O bond length in monomer, CD, CTr, CTe, CP and CH are 1.2041, 1.2104, 1.2130, 1.2134, 1.2134, and 1.2135 Å respectively (Table 4 and Figure 4). The lengthening of H-bonded C=O bonds

with cluster size is clear evidence of positive cooperativity in cyclic clusters and the findings are in accordance with the energetic aspect discussed above.

Unlike linear clusters, where every H-bonded carbonyl group form two H-bonds, namely HB1 and HB2, number of H-bond donors attached to a single carbonyl group increases with size of cyclic clusters. It was found that one carbonyl group is attached to two C-H donors in only CD, while it is bound to three C-H donors in CTe, CTr, CP and CH forming HB3 (as defined earlier) beside HB1 and HB2. Therefore, it would be interesting to investigate how HB1 and HB2 affects each other as the size of the cluster changes and also how formation HB3 in the higher clusters affects the existing HB1 and HB2. For this purpose, all the individual H-bond lengths in cyclic clusters have been given in Table 4 and a plot against cluster size (Figure 8) has been constructed to easily analyze the trend they show. The length of HB1 in CD, CTr, CTe, CP and CH are 2.506, 2.328, 2.332, 2.332-2.345 and 2.338 Å, respectively. Similarly, HB2 bond lengths are 2.633, 2.412, 2.421, 2.412-2.446 and 2.429 Å, in the same order as above. It is evident from the above values that both HB1 and HB2 becomes shorter (and therefore stronger) while moving from CD to CTr. However, they both become longer from CTe onwards. This lengthening of both HB1 and HB2 must have some connection to the behavior of HB3. The length of HB3 in CTr, CTe, CP, and CH are 2.902, 2.664, 2.568-2.582 and 2.562 Å, respectively. The above values show that there is a significant shortening, and hence strengthening, of HB3 upon going from CTr to CTe. As discussed above, HB1 and HB2 also become longer while moving from CTr to CTe. In fact, HB3 shows monotonic shortening with increasing cluster size all the way up to CH and both HB1 and HB2 behave in completely opposite manner. Therefore, for cyclic clusters, strengthening of HB3 is accompanied by concomitant weakening of HB1 and HB2, i.e. they clearly show anti-cooperative nature towards each other. Nevertheless, the three H-bonds show an overall cooperative interaction as a whole as the overall binding energy of the three H-bonds increases with increasing size of the cluster as evident from both binding energy per interaction and C=O bond length of H-bonded carbonyl groups. This behavior is in stark contrast to what was observed for the linear clusters. In those cases, the mutual anti-cooperativity existing between HB1 and HB2 showed overall anti-cooperative destabilization of higher clusters.

Finally, NBO and AIM analyses were conducted for the H-bonds in cyclic clusters in similar manner to what has been done for the same in their linear counterparts. Hyperconjugative charge transfer energies along with electron densities and their Laplacians at bond critical points were calculated (Table S2) and plotted against H-bond lengths (Figure S7). The plots clearly show a direct relationship of all the above mentioned three parameters with H-Bond length and corroborate the above findings.

## 4 Summary

Cooperativity exhibited by purely C-H—O H-bonded networks in linear and cyclic clusters of (1,3-cyclohexanedione)<sub>n</sub> (n=2 to 6) has been systematically studied using density functional theoretical calculations. As linear cluster having cis conformers tend to undergo cyclization after tetramer, only the all-trans conformers were chosen for this purpose. In case of their cyclic counterparts, trans conformers were found to get puckered. Therefore, only the all-cis conformers were considered for cyclic clusters. It was found that the linear clusters show anti-cooperative behavior, with H-bond strengths and binding energies per bimolecular interaction decreasing monotonically with increasing cluster size. On the other hand, their cyclic counterparts were found to show positive cooperativity; both H-bond strengths and binding energies per bimolecular interaction systematically increasing with increasing cluster size. All the studied linear clusters were found to have two C-H donor groups H-bonded to each carbonyl oxygen, while in the cyclic clusters, a third C-H group participates in H-bonding in trimer and higher clusters. The extent of cooperativity has been found to show monotonic behavior for both linear and cyclic clusters and was found to reach an asymptotic limit with increasing cluster size. Natural bond orbital (NBO) analysis and atoms in molecule (AIM) calculations were found to corroborate the obtained results.

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**Figure 1** Molecular geometry of CHD monomer optimized at  $\omega$ B97X-D/6-311++G\*\* level with numbering and position of different donor sites

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**Figure 2** Molecular structure of the all trans linear clusters optimized at  $\omega$ B97X-D/6-311++G\*\* level of theory.

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**Figure 3** Molecular structure of the all cis cyclic clusters optimized at  $\omega$ B97X-D/6-311++G\*\* level of theory.

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**Figure 4** Cluster size vs C=O bond length and binding energy per interaction of the linear and cyclic clusters calculated at  $\omega$ B97X-D /6-311++G\*\* level of theory

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**Figure 5** Binding energy per interaction of various cluster fragments for linear clusters calculated at  $\omega$ B97X-D /6-311++G\*\* level of theory

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**Figure 6** H-bond lengths of HB1 and HB2 in the linear clusters calculated at  $\omega$ B97X-D /6-311++G\*\* level of theory

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**Figure 7** Binding energy per interaction of various cluster fragments for cyclic clusters calculated at  $\omega$ B97X-D /6-311++G\*\* level of theory

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**Figure 8** H-bond lengths of HB1, HB2 and HB3 in the cyclic clusters calculated at  $\omega$ B97X-D /6-311++G\*\* level of theory

**Table 1:** BSSE corrected binding energies of linear and cyclic clusters at B3LYP and M06-2X level from geometries optimized at B3LYP/6-311++G\*\* level of theory, and  $\omega$ B97X-D/6-311++G\*\* level of theory.

BSSE corrected binding energy (kcal/mol)	BSSE corrected binding energy (kcal/mol)	BSSE corrected binding energy (kcal/mol)
Dimer	Dimer	Dimer
Linear	B3LYP	B3LYP
	B3LYP	M062-X
C	-3.9	-7.5
T	-4.1	-7.6
Trimer	Trimer	Trimer
CC	-7.1	-13.6
CT	-7.3	-13.8
TT	-5.2	-10.8
Tetramer	Tetramer	Tetramer
CCC	-10.3	-20.1
CCT	-10.5	-20.3
CTC	-10.5	-20.3
TCT	-10.6	-20.1
CTT	-10.6	-19.7
TTT	-10.6	-19.8
Pentamer	Pentamer	Pentamer
TTTT	-13.8	-26.2
Hexamer	Hexamer	Hexamer
TTTTT	-16.9	-32.7

**Table 2:** BSSE corrected binding energies ([?E] and [?E/n\*of linear and cyclic clusters at  $\omega$ B97X-D/6-311++G\*\* level of theory. [?E/n\*= BSSE corrected binding energies divided by the number of interactions

Cluster size	Linear	Linear	Cluster size	Cyclic	Cyclic
	[?E (kcalmol <sup>-1</sup> )	[?E/n* (kcalmol <sup>-1</sup> )		[?E (kcalmol <sup>-1</sup> )	[?E/n* (kcalmol <sup>-1</sup> )
LD	-8.8	-4.4	CD	-8.8	-4.4
LTr	-16.2	-4.1	CTr	-17.9	-6.0
LTe	-24.0	-4.0	CTe	-25.1	-6.3
LP	-31.7	-4.0	CP	-31.9	-6.4
LH	-39.0	-3.9	CH	-37.9	-6.3

**Table 3:** Binding energy per interaction of various cluster fragments for cyclic and linear cluster calculated at  $\omega$ B97X-D /6-311++G\*\* level of theory

Cluster size	Binding energy per interaction (kcal mol <sup>-1</sup> ) cyclic cluster1	Binding energy per interaction (kcal mol <sup>-1</sup> ) cyclic cluster2
	2	3
LD	-4.4	
LTr	-5.1	-6.0
LTe	-4.7	-5.7
LP	-4.5	-5.3
LH	-4.5	-5.2

**Table 4:** Binding energies, H-bond length and angle, C=O bond length and C=O—C angle in (CHD)<sub>n</sub> clusters (n = 2-6) calculated using ωB97X-D/6-311++G\*\* level of theory

Unit	[?] E (kcal mol <sup>-1</sup> )	[?] E/n* (kcal mol <sup>-1</sup> )	HB1	HB1	HB2	HB2	HB3	HB3	C=O bond length (Å)
	ωB97X- D	ωB97X- D	Length (Å)	Angle (degree)	Length (Å)	Angle (degree)	Length (Å)	Angle (degree)	
Monomer	0	0	-	-	-	-	-	-	1.2041
CD	-8.8	-4.4	2.506	129.3	2.633	125.1		111.5	1.2104
CTr	-17.9	-6.0	2.329	139.1	2.412	136.9	2.902	128.7	1.2130
CTe	-25.1	-6.3	2.322	139.3	2.421	137.2	2.664	132.9	1.2134
CP	-31.9	-6.4	2.332-	138.7	2.411-	136.9	2.568-	134.5	1.2134
			2.345		2.436		2.582		
CH	-37.9	-6.3	2.338	139.3	2.429	137.3	2.562	134.2	1.2135