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Intramolecular Hydrogen Bond Energy and Cooperative Interactions in α-, β-, and γ-Cyclodextrin Conformers

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Accurate estimation of individual intramolecular hydrogen bond (H-bond) energies is an intricate task for multiply H-bonded systems. In such cases, the hydrogen bond strengths could be highly influenced by the cooperative interactions, for example, those between hydroxyl groups in sugars. In this work, we use the recently proposed molecular tailoring approach-based quantification (Deshmukh, Gadre, and Bartolotti, J Phys Chem A 2006, 110, 12519) to the extended systems of cyclodextrins (CDs). Further, the structure and stability of different conformers of α-, β-, and γ-CDs are explained based on the energetics and cooperative contribution to the strength of these H-bonds. The estimated O—H···O H-bond energies in the various CD conformers are found to vary widely from 1.1 to 8.3 kcal mol^{-1}. The calculated energy contributions to cooperativity toward the H-bond strengths fall in the range of 0.25–2.75 kcal mol^{-1}.
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Introduction

Cyclodextrins (CDs) form a family of macrocyclic oligosaccharides consisting of D-glucose units joined to each other by (1–4) linkage. During the degradation of amylase fraction of starch, in the presence of glucosyl transferases, one or several amylose helices are hydrolyzed off and their ends are joined together, thereby producing cyclic oligosaccharides called CDs or cycloamyloses (CAs). As these enzymes are not very specific, a family of macrocycles with different numbers of glucose units is produced.[1,2] The general structure of CD is shown schematically in Figure 1, where *n* denotes the number of glucose units (6, 7, and 8 for α-, β-, and γ-CDs, respectively). All the CDs have a bucket/bowl-like shape and because of this shape and size of these oligosaccharides, they possess a unique ability to act as a molecular container for entrapping a guest molecule in to their cavity. The resulting inclusion complexes are useful in the pharmaceutical industries for a variety of formulations.[3] For a detailed summary of the scientific and technological aspects of CDs, including their synthesis, reactivity, and chemical/biological applications, reference may be made to an entire special issue of *Chemical Reviews*.[4] As may be seen from the Figure 1, there are primary and secondary hydroxyl groups at the top (smaller rim) and bottom (larger rim) of the bowl of CDs, respectively. This leads to the formation of a highly interconnected network of hydrogen bonds (H-bonds) resulting in a phenomenon termed as "cooperativity."[5,6] The cooperative H-bond network has been shown to influence the ability of carbohydrate molecules to interact with other molecules such as pyridine[7] and water.[8] Moreover, such a phenomenon is suggested to be a key to the construction of sophisticated supramolecular assemblies/architectures/materials of the next generation.[9] It is evident from crystal structure data that intramolecular O—H···O and C—H···O interactions favor the macrocyclic conformation and govern interactions with the guest molecule in their cavity.[10] Moreover, binding of a guest is governed by many factors such as cavity dimension, the relative orientation of a guest molecule, and noncovalent interactions such as H-bond between the guest and host.[10] In aqueous solutions, there exists a competition of the intramolecular H-bonds with intermolecular association with water molecules. Such a competition is believed to influence the structure and solubility of various CDs.[11] Understanding such competitive interactions would be immensely useful in probing the nature of interactions of these CDs with the guest molecules.

There are several experimental as well as theoretical attempts reported in the literature for understanding the structure, relative stability of CDs, and the nature of interactions involved.[4,9–24] NMR experiments reveal that the H-bonded interactions of secondary hydroxyl groups provide less flexibility to β-CD than to α-CD or γ-CD, leading partly to the low solubility of the former.[12–15] The empirical force field-based molecular mechanics and molecular dynamics (MD) simulation calculations on these systems are well summarized by Lipkowitz.[16] The chemical shifts in a series of modified CDs functionalized at the primary

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hydroxyl group from density functional calculations show good agreement with the experimental data.[17] Recently, the electronic structure of anhydrous β-CD conformer has been reported[18–20] suggesting the possibility of different geometrical conformers resulting from different patterns of H-bonding.[19] It is suggested that the thermodynamic parameters (e.g., the free energies of CD complexation[20]) and ^{1}H NMR spectra[21] are influenced significantly by solvation effects. The nature of H-bonding in CDs has been a central issue in many articles by Koehler and Saenger.[22] The occurrence of bifurcated (three-center) H-bond as against that of the normal two-center H-bond was also suggested by Koehler et al.[22] based on MD simulation studies. Comparisons between solid state and solution phase H-bonding exist with more three-center H-bonds being found in the latter.[23] Although these theoretical calculations provide useful information, they point to the necessity of a high level *ab initio* investigation. Recently, Pinjari et al.[24] have explored the topography of molecular electrostatic potential (MESP) and molecular electron density (MED) to analyze the intramolecular H-bonding interactions involving both primary as well as secondary hydroxyl groups using the B3LYP/6-31G(d) level of theory. Based on the analysis of MESP topography, it was suggested that the strength of H-bond interactions involving primary hydroxyl groups follows the rank ordering α-CD > β-CD > γ-CD, whereas the interactions involving secondary hydroxyl groups show a reverse trend. It was also shown by these authors that the MED value at bond critical points (BCPs) of some of these interactions correlates well with the corresponding calculated NMR chemical shifts of hydroxyl protons involved in the H-bonding.[24(b)]

There have been many attempts, mostly based on the proton chemical shifts and atoms in molecules analysis, reported toward understanding the strength of hydrogen bonds in the CDs in their different conformers. However, no direct energetic quantification of the strength of the H-bonds has been discussed in the literature. Further, the important issue of the influence on the strength of the H-bonds due to cooperativity has not been addressed, possibly because of the inability of these methods toward such quantification. In this article, we provide a quantification of the strength of H-bonds in CD conformers by estimating intramolecular O—H···O H-bond energy with the help of our recently proposed method based on molecular tailoring approach (MTA).[25–29] To the best of our knowledge, this is the first ever study for a direct quantification of the H-bond energy along with the contribution due to the cooperative interactions within CDs. The recent success in applying the present methodology for estimating the intramolecular H-bond energies in aldopyranose sugars[27] has indeed prompted us to go one step further and attempt to answer questions such as: (a) How strong are the H-bonds in CD when compared with those in free constituent sugars? (b) How does the cooperativity contribution vary among the different hydroxyl groups? (c) Do the estimated H-bond energies and cooperative interactions enable us to distinguish the different conformers of CD? and (d) How do the H-bond energies correlate with proton chemical shifts (δ_H) of hydroxyl protons in CD? This study is aimed at providing answers to these questions.

Methodology

Eight different conformers each of α-, β-, and γ-CD molecules (*cf.* Fig. 2) were constructed and optimized at the B3LYP[30] density functional theory (DFT) level with 6-311++G(d,p) basis set using C_6, C_7, and C_8 symmetry, respectively, by using the Gaussian package.[31] It should be noted that the geometry optimization and all the evaluations of single-point energy are carried out using conventional DFT method, and no usual MTA is used for the purpose of geometry optimization. However, the recently proposed MTA-based approach for estimating intramolecular H-bond energy is used in this work.[25–28] We also present H-bond energies in lowest energy conformers of CDs using MPWB1K functional, as it is recently suggested to be a reliable method for the analysis of weak bonding situations.[32] It is computationally demanding to perform frequency calculation of large molecular systems (ca. 1900 to 2500 basis functions for CDs) even with the current state of art computational resources and methodologies. In view of this, the frequency calculations are not carried out to determine if the stationary points are local minima on the potential energy surface (PES).

It is generally stipulated in the literature that the presence of a (3,–1) MED CP is a signature of the H-bond. However, there is an omnipresent O—H···O interaction energy even in the absence of such a signature. There have been debates whether such a signature is a necessary requirement for naming the O—H···O interaction as a hydrogen bond.[33] The purpose of this work is not to get into the issue of labeling such an O—H···O interaction as a hydrogen bond or not. Thus, for semantic purposes, for those who insist on the existence of a (3, −1) MED CP (henceforth called a BCP) for naming such an interaction as H-bond, the term H-bond energy may be replaced throughout this work by O—H···O interaction energy. The intramolecular H-bond energy as well as the corresponding cooperativity contribution is calculated for these conformers of CDs using our recently proposed MTA-based methodology.[25–28] A critical comparison of the H-bond energy estimated with the MTA and other indirect measures such as the MED value at the BCP, shifts in IR frequency, as well as other approaches for estimating H-bond energy has been reported in our previous studies.[25–28] It has been shown that the H-bond energies estimated with MTA are in good agreement with the other indirect measures of the H-bond[25–28] strength and, hence, a comparative study with other indirect measurements is felt unnecessary in this work. Moreover, a quantitative comparison of proton chemical shifts (δ_H) and our estimated H-bond energies is presented. For details of the basic MTA methodology and our previous work on estimation of intramolecular H-bond energy, please see Refs. [25–29].

Results and Discussion

Geometries of cyclodextrin conformers

The optimized geometries of different conformers of α-CD are shown in Figure 2. These different conformers are generated by allowing the possible combinations of orientation

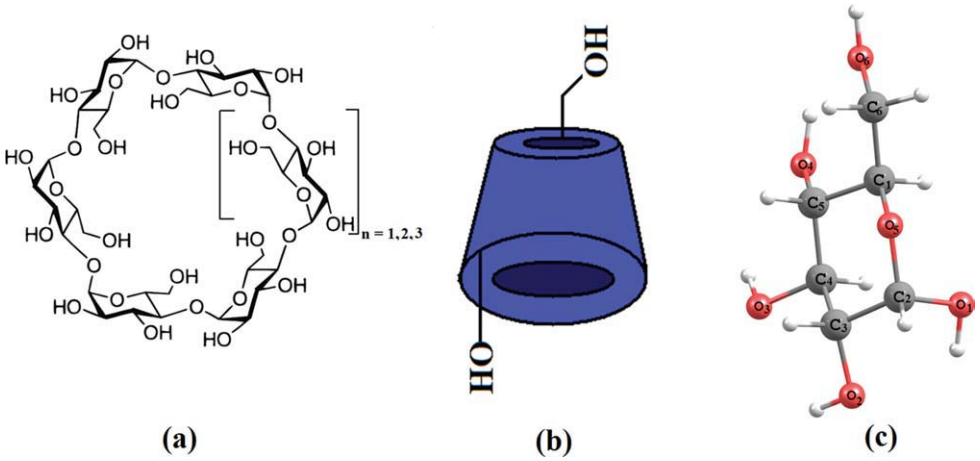

Figure 1. a) A schematic structure of cyclodextrin molecule [n = 1, 2, and 3 for α-, β-, and γ-CD respectively]; b) a cyclodextrin bowl with secondary and primary hydroxyl groups at larger and smaller rim, respectively; c) Atomic numbering in a α-D-glucose.

(clockwise and counterclockwise) between the primary and secondary hydroxyl groups. Such orientational conformers for α-, β-, and γ-CD[19,24] have recently been explored in the literature. We hope to explain the stability of these conformers by estimating the corresponding H-bond energies. These conformers are labeled as A, B, and C depending on the interaction of primary hydroxyl groups (see Fig. 2). For instance, in conformer A, the primary hydroxyl forms an H-bond with the adjacent primary hydroxyl group; such an interaction is labeled as $O_6H\cdots O_6'$. Here, the prime indicates that the interaction is between hydroxyl groups on the neighboring/adjacent pyranose rings. Four different conformers *viz*. A1, A2, A3, and A4 can be obtained by allowing the combination of orientation of hydroxyl groups in top (primary hydroxyl groups) and bottom rim (secondary hydroxyl groups) of CDs. Here, label 1 refers to conformers wherein the hydroxyl protons are oriented counterclockwise in the top rim and clockwise in the bottom, respectively. The conformer which has reverse orientations in top and bottom rims is designated as label 2. The labels 3 and 4 denote the hydroxyl groups oriented in top and bottom rims to be either both clockwise or both counterclockwise, respectively. The conformers wherein the primary hydroxyl groups form a hydrogen bond ($O_6H\cdots O_5'$) with the O_5' atom of the adjacent pyranose ring (cf. Fig. 1 for atomic numbering) are labeled as B. Thus, only two conformers *viz*. B2 and B3 are possible with the secondary hydroxyl groups oriented with

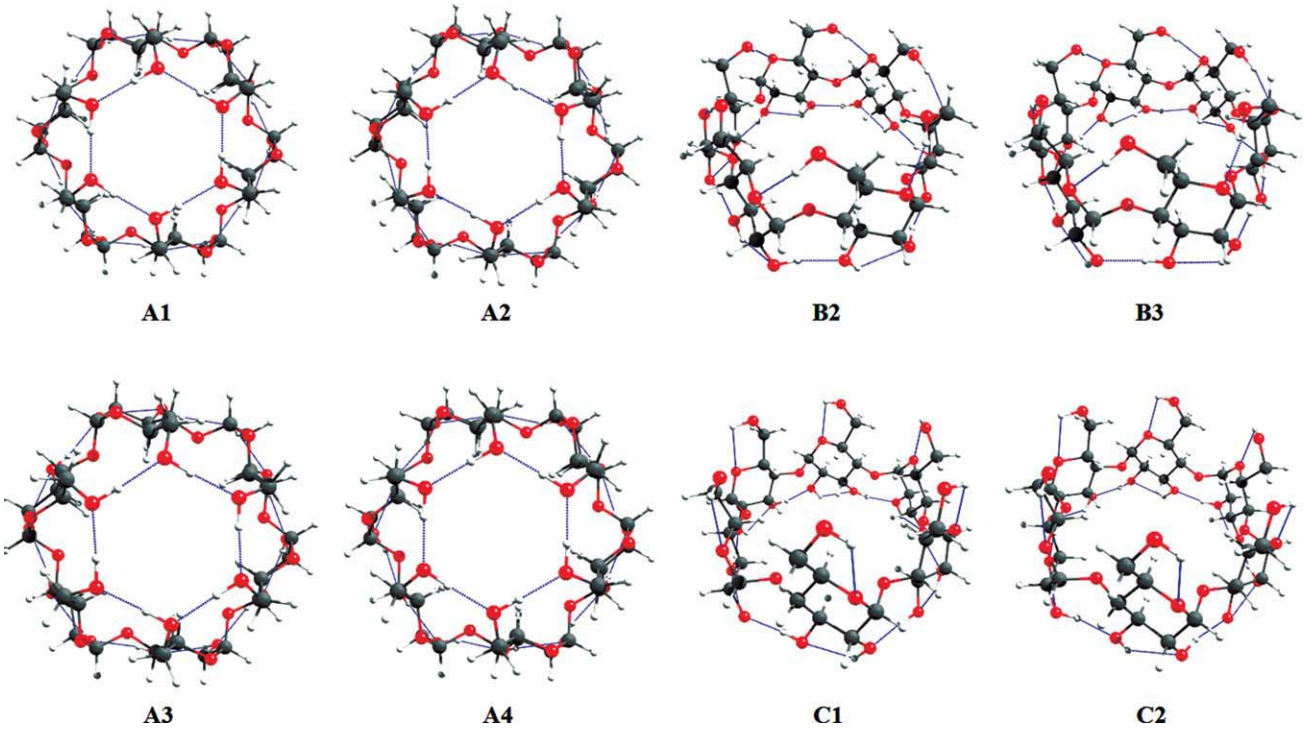

Figure 2. B3LYP/6-311++G(d,p) optimized geometries of different conformers of α-cyclodextrin.

Table 1. Absolute (in a.u.) and relative energies (in kcal mol^{-1}) of different conformers of **α-**, **β-** and γ-CD at B3LYP/6-311++G(d,p) level of theory. See text for details and Figure 2 for geometries.

	A1	A2	A3	A4	B2	B3	C1	C4
α-CD	−3665.696241	−3665.693742	−3665.697340	−3665.692952	−3665.659333	−3665.662782	−3665.669745	−3665.665880
	0	1.57	−0.69	2.06	23.16	21.00	16.63	19.05
β-CD	−4276.644884	−4276.639414	−4276.643571	−4276.640912	−4276.608026	−4276.611431	−4276.618019	−4276.614835
	0	3.43	0.82	2.49	23.13	21.00	16.86	18.86
γ-CD	−4887.585299	−4887.576226	−4887.581523	−4887.580332	−4887.551025	−4887.553128	−4887.561766	−4887.558108
	0	5.69	2.37	3.12	21.51	20.19	14.77	17.06

counterclockwise and clockwise, respectively. The conformers of type C involve interaction of the primary hydroxyl groups with the oxygen O_5 of the same pyranose ring ($O_6H\cdots O_5$), leading to the formation of two different isomers *viz*. C1 and C2. In all these conformers (A, B, and C), the secondary hydroxyl groups are involved in two types of hydrogen bonds. One type of hydrogen bond that results from interaction between the vicinal hydroxyl groups of same pyranose ring is termed as $O_2H\cdots O_3$. The other type is a consequence of the interaction between the secondary hydroxyl groups on the adjacent pyranose ring and is designated as $O_3H\cdots O_2'$. For the sake of simplicity, we have adopted the current notation, which differs from the one used earlier in the literature (based on the atomic numbering as shown for aldopyranose[24] in Fig. 1).

The absolute and relative energies of α-, β-, and γ-CD conformers are reported at B3LYP/6-311++G(d,p) level of theory in Table 1. The relative energies of the conformers are obtained by subtracting the absolute energies from that of the conformer A1 of the corresponding α-, β-, and γ-CD. It is seen from Table 1, the conformers of type A are most stable when compared with those of type C which are, in turn, more stable than conformers of type B. This may be due to a stronger interaction between primary hydroxyl groups of conformers A when compared with those in the conformer B and C. The present rank-ordering of conformers is different from the one reported previously which predicted the higher stability of B over C.[24] Among the different types of conformers of CDs, the lowest energy ones are A1, B3, and C1 except for α-CD, wherein the conformer A3 is found to be lower in energy by 0.7 kcal mol^{-1} than the A1.

The corresponding H-bond distances and angles in different conformers of α-, β-, and γ-CD are reported in Tables 2 and 3, respectively. The OH···O distances are seen to be the shortest for the H-bonds formed by interaction between the adjacent primary hydroxyl groups, that is, $O_6H\cdots O_6'$. The next shorter H-bonds are the ones formed by the secondary hydroxyl groups of the adjacent pyranose ring, that is, $O_3H\cdots O_2'$. The OH···O distances between the H-bonds formed by secondary hydroxyl groups on the same pyranose ring, that is, $O_2H\cdots O_3$ are the largest ones. This suggests that the strength of hydrogen bond would follow the order $O_6H\cdots O_6' > O_3H\cdots O_2' > O_2H\cdots O_3$. Moreover, the $O_3H\cdots O_2'$ distances are shorter in C than those in B or A in all the CD conformers. For instance, in the lowest energy conformers A3, B3, and C1, the corresponding $O_3H\cdots O_2'$ distances are 2.23, 1.91, and 1.90 Å, respectively, in α-CD.

With increase in the size of CDs, the $O_3H\cdots O_2'$ and $O_2H\cdots O_3$ distances seem to become shorter. Significant differences are seen between these distances in conformers of type A when compared with those of types B or C. To the contrary, the $O_6H\cdots O_6'$ distances become longer as one goes from α-CD to γ-CD. Thus, the H-bond distances for primary hydroxyl groups

Table 2. The O—H···O intramolecular hydrogen bond distances (Å) in different optimized conformers of **α-**, **β-**, and γ-CD at B3LYP/6-311++G(d,p) level of theory.

	H-bond	A1	A2	A3	A4	B2	B3	C1	C4
α-CD	$O_2H\cdots O_3$	2.45 (2.37)[a]	2.46	2.45	2.46	2.36	2.34	2.33	2.44
	$O_3H\cdots O_2'$	2.20 (2.12)	2.27	2.23	2.22	1.90	1.91	1.90	1.89
	$O_6H\cdots O_6'$	1.82 (1.81)	1.85	1.85	1.82				
	$O_6H\cdots O_5'$					1.97	1.99		
	$O_6H\cdots O_5$							2.42	2.44
β-CD	$O_2H\cdots O_3$	2.46 (2.38)	2.46	2.46	2.46	2.33	2.25	2.31	2.33
	$O_3H\cdots O_2'$	2.15 (2.06)	2.20	2.18	2.17	1.88	1.88	1.87	1.88
	$O_6H\cdots O_6'$	1.86 (1.84)	1.90	1.90	1.86				
	$O_6H\cdots O_5'$					1.95	1.93		
	$O_6H\cdots O_5$							2.41	2.43
γ-CD	$O_2H\cdots O_3$	2.47 (2.39)	2.46	2.47	2.46	2.30	2.29	2.30	2.31
	$O_3H\cdots O_2'$	2.13 (2.08)	2.17	2.14	2.15	1.85	1.86	1.86	1.86
	$O_6H\cdots O_6'$	1.93 (1.88)	1.97	1.97	1.93				
	$O_6H\cdots O_5'$					1.95	1.95		
	$O_6H\cdots O_5$							2.40	2.42

[a] The O—H···O hydrogen bond distance in CD conformers optimized at MPWB1K/6-311++G(d,p) level of theory.

Table 3. The O—H···O intramolecular hydrogen bond angles (degree) in different optimized conformers of α-, β-, and γ-CD at B3LYP/6-311++G(d,p) level of theory.

	H-bond	A1	A2	A3	A4	B2	B3	C1	C4
α-CD	$O_2H\cdots O_3$	106.1 (107.3)[a]	107.9	106.0	107.8	110.1	108.5	108.8	110.3
	$O_3H\cdots O'_2$	165.1 (165.9)[a]	161.3	164.8	162.1	167.1	167.5	168.1	167.4
	$O_6H\cdots O'_6$	174.5 (173.5)[a]	174.1	174.4	174.1				
	$O_6H\cdots O'_5$					161.7	161.1		
	$O_6H\cdots O_5$							103.4	103.0
β-CD	$O_2H\cdots O_3$	105.8 (107.0)[a]	107.7	105.7	107.7	110.9	109.1	109.3	110.6
	$O_3H\cdots O'_2$	164.3 (164.8)[a]	160.3	164.1	160.7	166.1	166.4	166.8	165.8
	$O_6H\cdots O'_6$	173.1 (171.4)[a]	171.0	171.1	172.9				
	$O_6H\cdots O'_5$					164.6	163.8		
	$O_6H\cdots O_5$							103.2	102.8
γ-CD	$O_2H\cdots O_3$	105.5 (106.8)[a]	107.6	105.5	107.5	111.5	109.4	109.3	111.0
	$O_3H\cdots O'_2$	163.2 (162.9)[a]	159.3	163.3	159.6	165.3	165.3	165.5	164.9
	$O_6H\cdots O'_6$	170.2 (168.1)[a]	168.1	168.1	169.9				
	$O_6H\cdots O'_5$					166.6	166.0		
	$O_6H\cdots O_5$							103.3	102.9

[a] The O—H···O hydrogen bond angles in CD conformers optimized at MPWB1K/6-311++G(d,p) level of theory.

($O_6H\cdots O'_6$) show opposite rank ordering when compared with those in secondary hydroxyl groups ($O_3H\cdots O'_2$ and $O_2H\cdots O_3$). These observations are in agreement with their literature counterparts.[24] Apart from these, two other types of interactions, *viz*. $O_6H\cdots O'_5$ and $O_6H\cdots O_5$, are seen in conformer B and C, respectively. In conformer B, O_6H forms a hydrogen bond with the ring oxygen O_5 of neighboring pyranose ring, whereas in conformer C, it forms the H-bond with the ring oxygen (O_5) of the same pyranose ring. As can be inferred from Table 2, the former ($O_6H\cdots O'_5$) is seen to be shorter than the later one ($O_6H\cdots O_5$). Among the conformers of type A, the $O_6H\cdots O'_6$ distances are found to be similar between the conformers A1 and A4 and A3 and A2, whereas the $O_3H\cdots O'_2$ and $O_2H\cdots O_3$ distances are similar between the pairs of conformers A1 and A3 and A2 and A4. This may be attributed to the orientational effect of hydroxyl groups. In conformers A1 and A4, the primary hydroxyl groups are oriented in counterclockwise direction. To the contrary, the primary hydroxyl groups are oriented in clockwise direction in the conformers A2 and A3. The secondary hydroxyl groups in conformers A1 and A3 are oriented in the clockwise direction, whereas they are oriented in counterclockwise direction in A2 and A4 conformers. These OH···O distance-based observations are in general agreement with the corresponding OH···O angle-based ones reported in Table 3, *viz*. the deviation of OH···O angles from linearity implies weakening of these interactions.

We now present a comparison between these geometrical parameters obtained using the better basis set and the symmetry restriction on geometry optimization, used in this work with the ones reported by Pinjari et al.[24] at smaller basis set [6-31G(d)] and use of no symmetry constrains. These geometrical parameters presented by us and Pinjari et al.[24] are calculated using B3LYP functional. In general, it is found that the better basis set results in slight longer H-bond distances and the smaller O—H···O bond angles. Although this may be attributed to use of better basis set and symmetry constraints used in this work, it should be noted that the trends in H-bond strengths as discussed above are similar between the two approaches. Also the present result about basis set effects is in agreement with our previous study[26] using MPWB1K functional, 6-31+G(d,p), and 6-311++G(2d,2p) basis sets.

Thus, the geometrical orientational effects are well reflected in the respective H-bond distances and angles in these conformers. However, these geometrical parameters are qualitative tools for explaining the strength of these weak interactions and may not be necessarily quantitative. Estimating the intramolecular H-bond energies in these conformers of CDs offers a direct quantitative measure of the interactions.

Intramolecular hydrogen bond energy in cyclodextrin conformers

Table 4 reports the intramolecular OH···O H-bond energies in α-, β-, and γ-CD conformers estimated at the B3LYP/6-311++G(d,p) level using the MTA-based approach. As can be seen from this table, the estimated H-bond energies lie in the wide range of 1.1–8.3 kcal mol^{-1}, with the typical error in this estimation being[27] less than 0.1 kcal mol^{-1}. Remarkably, strong H-bonds (6.7–8.3 kcal mol^{-1}) are noticed between inter primary hydroxyl groups (O_6H). The weakest (1.1–1.3 kcal mol^{-1}) are those involving the H-bond of the type $O_6H\cdots O_5$. Among the two types of H-bonds formed by secondary hydroxyl groups, $O_3H\cdots O'_2$ H-bonds are stronger than the $O_2H\cdots O_3$ ones. For instance, the $O_3H\cdots O'_2$ H-bond energies are in the range of 3.3–5.5 kcal mol^{-1} in contrast to the values of 1.9–3.2 kcal mol^{-1} for $O_2H\cdots O_3$ H-bonds. The estimated H-bond energies for all the vicinal interactions in D-gluocse[27] lie in the range of 1.8–2.3 kcal mol^{-1}. To the contrary, $O_2H\cdots O_3$ H-bond energy in all the CD conformers varies from 1.9 to 3.2 kcal mol^{-1}. The higher values of vicinal interactions in CDs may be attributed to more extended cooperative network of H-bonds in these conformers. Such an estimation of cooperative contribution in these H-bonds is discussed in the following section. The general rank ordering of the energetics

Table 4. The O—H···O intramolecular hydrogen bond energies (kcal mol^{-1}) in different optimized conformers of **α-**, **β-**, and **γ-CD** at B3LYP/6-311++G(d,p) level of theory.

CDs	H-bond	A1	A2	A3	A4	B2	B3	C1	C4
α-CD	$O_2H\cdots O_3$	1.95 (2.02)[a]	2.38	1.90	2.22	2.78	2.56	2.27	2.48
	$O_3H\cdots O'_2$	4.21 (4.45)	3.38	4.02	3.43	4.99	5.45	5.25	4.69
	$O_6H\cdots O'_6$	7.78 (7.06)	8.32	8.10	7.81				
	$O_6H\cdots O'_5$					3.08	3.01		
	$O_6H\cdots O_5$							1.28	1.25
	Total	13.94	14.08	14.02	13.46	10.85	11.02	8.80	8.42
β-CD	$O_2H\cdots O_3$	1.99 (2.33)	2.38	1.99	2.29	3.11	2.58	2.31	2.60
	$O_3H\cdots O'_2$	4.38 (4.68)	3.58	4.27	3.65	5.17	5.37	5.19	4.64
	$O_6H\cdots O'_6$	7.46 (7.11)	7.77	7.84	7.32				
	$O_6H\cdots O'_5$					3.29	3.05		
	$O_6H\cdots O_5$							1.28	1.14
	Total	13.83	13.73	14.10	13.26	11.57	11.00	8.78	8.38
γ-CD	$O_2H\cdots O_3$	1.95 (2.58)	2.26	1.87	2.48	3.24	2.89	2.11	2.62
	$O_3H\cdots O'_2$	4.32 (4.63)	3.56	4.25	3.81	5.05	5.47	4.85	4.54
	$O_6H\cdots O'_6$	6.85 (6.58)	6.90	7.10	6.70				
	$O_6H\cdots O'_5$					3.06	3.06		
	$O_6H\cdots O_5$							1.16	1.20
	Total	13.12	12.71	13.22	12.99	11.35	11.42	8.12	8.36

[a] Values in the parentheses are estimated using MPWB1K/6-311++G(d,p) level of theory.

among these types of H-bonds in CDs follows $O_6H\cdots O'_6 > O_3H\cdots O'_2 > O_2H\cdots O_3$. Among the conformers of type B and C, the H-bond energetics follows: $O_3H\cdots O'_2 > O_6H\cdots O'_5 > O_2H\cdots O_3 > O_6H\cdots O_5$. This general rank ordering of H-bond energies is in qualitative agreement with that based on the corresponding H-bond distances as discussed earlier

With the increase in size of CD, as one goes from α- to γ-CD, in general, the $O_6H\cdots O'_6$ H-bond energy seems to decrease. For example, the $O_6H\cdots O'_6$ H-bond energy in the lowest energy conformers A1, changes from 7.8 to 6.8 kcal mol^{-1} in α-, β-, and γ-CD, respectively. In general, one may expect higher strength of H-bonds in γ-CD than those in α- or β-CD due to more extended network of H-bonds (larger cooperativity). However, it should be noted that due to increase in the size of CD, there is an increase in $O_6H\cdots O'_6$ separation as one goes from α- to γ-CD (Table 2). In contrast to $O_6H\cdots O'_6$ bond, the H-bond energies in the larger rim of the CDs, that is, $O_3H\cdots O'_2$ and $O_2H\cdots O_3$, the H-bond energies show, in general, only a small increase with the size of CD.

In Table 4, the H-bond energies calculated with MPWB1K functional are also presented in the parenthesis for lowest energy conformers (A1) in all three CDs. In general, the H-bond energies calculated with MPWB1K functional are numerically somewhat different than those obtained using B3LYP functional, although the rank ordering is similar. This result is consistent with the geometrical parameters in Tables 2 and 3 and with our previous finding for some polyhydroxy compounds.[26]

As discussed in the previous section, the orientational effects of the hydroxyl groups in the CD conformers are also well reflected in the estimated H-bond energies as well. The $O_6H\cdots O'_6$ H-bond energies are found to be similar between the conformers A1 and A4 and A3 and A2. For instance, the estimated $O_6H\cdots O'_6$ H-bond energies in conformers A1 and A4 are 7.78 and 7.81, 7.46 and 7.32, and 6.85 and 6.70 in α-, β-, and γ-CD, in contrast to higher values, that is, 8.32 and 8.10, 7.77 and 7.84, and 6.90 and 7.10 in A2 and A3 conformers, respectively. The $O_3H\cdots O'_2$ and $O_2H\cdots O_3$ H-bond energies are found to be similar between the pairs of conformers A1 and A3 and A2 and A4. Moreover, the higher values of H-bond energies are found in the conformers wherein the hydroxyl groups are oriented in the clockwise manner. These results, based on H-bond energies, are in agreement with the previous reports based on H-bond distances and MED value at BCP.

We now present a quantitative comparison between the estimated H-bond energy and the proton chemical shifts of corresponding protons involved in H-bond calculated at the present basis set and level of theory. The proton involved in H-bond is deshielded and hence expected to exhibit downshift in NMR spectra. Thus, the strength of H-bond can be correlated to chemical shift (δ_H) value. In Figure 3, chemical shift values of the protons involved in $O_2H\cdots O_3$ and $O_3H\cdots O'_2$ are plotted against the corresponding H-bond energies. The correlation coefficient values (R^2) of 0.60 and 0.91 suggest a reasonable linear relation between the two quantities. A plot of δ_H value of primary hydroxyl protons with the corresponding H-bond energy values is also shown in Figure 3, bringing out a strong linear relation ($R^2 = 0.98$) between the variables involved. Further, this correlation plot clearly brings out the difference in the various H-bonds, $O_6H\cdots O_5$, $O_6H\cdots O'_5$, and $O_6H\cdots O'_6$ formed by primary hydroxyl groups denoted as I, II, and III, respectively. Thus, the estimated H-bond energy values can be correlated well with δ_H value in the NMR spectra. A similar correlation plots between the proton chemical shift (δ_H) and corresponding hydrogen bond distances were presented by Pinjari et al.[24] This suggests that with the present MTA-based approach provides reliable estimates of intramolecular hydrogen bond energy in the CD conformers.

Intramolecular hydrogen bond cooperativity in cyclodextrin conformers

The effect of intramolecular H-bond cooperativity on the strength of the individual H-bonds is assessed by isolating the

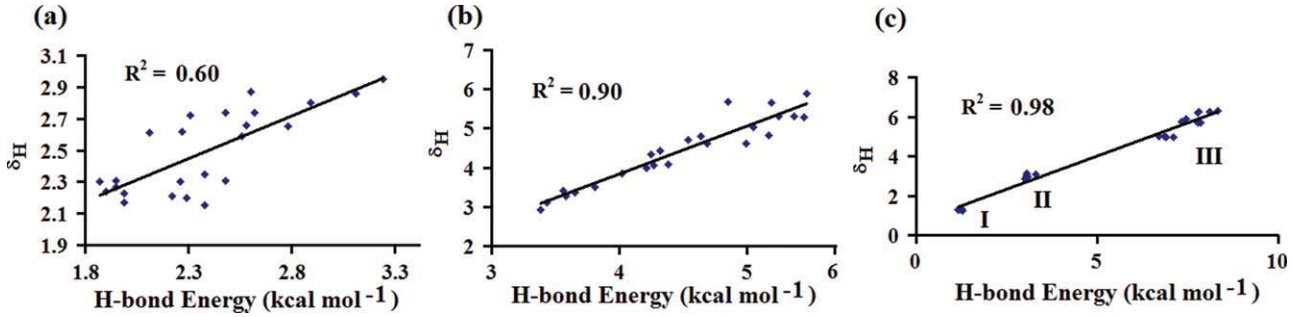

Figure 3. The hydrogen bond energy in CD conformers plotted against the δ_H of proton involved in the corresponding hydrogen bond calculated at B3LYP/6-311++G(d,p) level of theory. The plot for hydrogen involved in a) $O_2H\cdots O_3$, b) $O_3H\cdots O_2'$, and c) O_6H proton for all the conformers A, B, and C, respectively.

corresponding OH···O interactions from the H-bond network. Here, a systematic replacement of one or more —OH groups with the hydrogen atom(s) is done such that the OH···O bond whose energy is to be estimated is no longer a part of the H-bond network. The difference between the H-bond energies in the presence and in the absence of cooperative network of H-bonds is used as the measure of the cooperative contribution toward the strength of a particular H-bond. For further details regarding the estimate of cooperative interaction energy, see our previous work on aldopyranose sugars.[27]

Table 5 presents the intramolecular OH···O H-bond energies in the absence of cooperative network in α-, β-, and γ-CD conformers. Here, the cooperative interaction energies are calculated only for the $O_6H\cdots O_6'$, $O_3H\cdots O_2'$, and $O_2H\cdots O_3$ interactions which form the larger network of H-bonds than the other interactions. The $O_6H\cdots O_5'$ and $O_6H\cdots O_5$ interactions do not form continuous network of H-bonds when compared with other types that are involved in the conformers of type A, and, hence, the cooperative contributions are not evaluated in these cases. The H-bond energy values presented in Table 5, corresponding to the $O_6H\cdots O_5'$ and $O_6H\cdots O_5$ interactions, are identical to those presented in Table 4. The reason for presenting these values in the Table 5 is to evaluate the total of all the H-bond energies in the particular conformers of CDs. As can be noticed from Tables 4 and 5, the cooperative contribution toward the individual H-bond strength varies from 0.25 to 2.75 kcal mol^{-1}. The contribution of cooperativity toward the $O_6H\cdots O_6'$ H-bonds formed between the primary hydroxyl groups is larger (1.32–2.74 kcal mol^{-1}) than the sum of the individual contribution of cooperativity toward $O_3H\cdots O_2'$ (0.3–1.0 kcal mol^{-1}) and $O_2H\cdots O_3$ (0.25–1.10 kcal mol^{-1}) H-bonds formed by the secondary hydroxyl groups. Moreover, the $O_3H\cdots O_2'$ H-bonds seem to be more strengthened due to cooperativity than the vicinal $O_2H\cdots O_3$ ones. With the increase in the size of CDs, the cooperativity contribution to the $O_6H\cdots O_6'$ H-bonds is seen to decrease. This is in agreement with the conjecture made in the estimated H-bond energy values in the presence of cooperative network. In contrast to the $O_6H\cdots O_6'$ H-bond, the contribution due to cooperativity toward the H-bonds in the larger rim of CDs (e.g., $O_3H\cdots O_2'$ and $O_2H\cdots O_3$), is in general seen to be slightly enhanced with the increase in size of CDs. This result is more prevalent in the conformers B and C when compared with that in A. Thus, the cooperative contribution is found to be higher in the

Table 5. The O—H···O intramolecular hydrogen bond energies (in kcal mol^{-1}) in the absence of a cooperative H-bond network in different optimized conformers of α-, β-, and γ-CD at B3LYP/6-311++G(d,p) level of theory.

CDs	H-bond	A1	A2	A3	A4	B2	B3	C1	C4
α-CD	$O_2H\cdots O_3$	1.58	1.94	1.52	1.98	2.21	1.83	1.80	2.23
	$O_3H\cdots O_2'$	3.74	3.11	3.66	3.13	4.26	4.51	4.56	4.24
	$O_6H\cdots O_6'$	5.10	5.71	5.61	5.07				
	$O_6H\cdots O_5'$ [a]					3.08	3.01		
	$O_6H\cdots O_5$ [a]							1.28	1.25
	Total	10.42	10.76	10.79	10.18	9.55	9.35	7.64	7.72
β-CD	$O_2H\cdots O_3$	1.53	1.88	1.58	1.65	2.36	1.82	1.77	2.31
	$O_3H\cdots O_2'$	3.96	3.15	3.85	3.32	4.20	4.41	4.47	4.20
	$O_6H\cdots O_6'$	5.20	5.63	5.64	5.16				
	$O_6H\cdots O_5'$ [a]					3.29	3.05		
	$O_6H\cdots O_5$ [a]							1.28	1.14
	Total	10.69	10.66	11.07	10.13	9.85	9.28	7.52	7.65
γ-CD	$O_2H\cdots O_3$	1.61	1.95	1.48	1.99	2.34	1.79	1.72	2.36
	$O_3H\cdots O_2'$	3.82	3.20	3.85	3.20	4.22	4.45	4.43	4.19
	$O_6H\cdots O_6'$	5.25	5.57	5.77	5.18				
	$O_6H\cdots O_5'$ [a]					3.06	3.06		
	$O_6H\cdots O_5$ [a]							1.16	1.20
	Total	10.68	10.72	11.10	10.37	9.62	9.30	7.31	7.75

[a] The values presented in the above table are identical to those reported in Table 4.

Table 6. ^{1}H NMR chemical shifts in different **α-**, **β-**, and γ-CD conformers calculated at B3LYP/6-311++G(d,p) level of theory.

CDs	H-bond	A1	A2	A3	A4	B2	B3	C1	C4
α-CD	$O_2H\cdots O_3$	2.27	2.15	2.24	2.21	2.65	2.59	2.62	2.74
	$O_3H\cdots O'_2$	4.00	2.92	3.86	3.11	4.61	5.29	5.30	4.61
	$O_6H\cdots O'_6$	6.21	6.30	6.23	6.25				
	$O_6H\cdots O'_5$					2.95	2.86		
	$O_6H\cdots O_5$							1.24	1.32
β-CD	$O_2H\cdots O_3$	2.17	2.35	2.23	2.20	2.86	2.66	2.72	2.87
	$O_3H\cdots O'_2$	4.08	3.27	4.05	3.37	4.82	5.30	5.66	4.79
	$O_6H\cdots O'_6$	5.87	5.70	5.72	5.75				
	$O_6H\cdots O'_5$					3.06	3.02		
	$O_6H\cdots O_5$							1.24	1.30
γ-CD	$O_2H\cdots O_3$	2.31	2.30	2.30	2.31	2.95	2.80	2.61	2.74
	$O_3H\cdots O'_2$	4.43	3.42	4.34	3.50	5.04	5.89	5.67	4.70
	$O_6H\cdots O'_6$	4.99	4.97	4.97	4.99				
	$O_6H\cdots O'_5$					3.13	3.01		
	$O_6H\cdots O_5$							1.31	1.29

stronger H-bonds formed between the primary hydroxyl groups when compared with their counterparts in the larger rim. With the increase in size of CDs, the cooperative contribution is seen to decrease for H-bonds formed by primary hydroxyl groups. A reverse trend is noticed for H-bonds formed by secondary hydroxyl groups. The cooperative contribution in simple glucopyranose is around 0.1–1.1 kcal mol^{-1}, much smaller than the one in CDs. The higher H-bond strength in CDs due to much larger cooperative contribution (0.25–2.75 kcal mol^{-1} per hydrogen bond) could be one of the possible reasons for the much lower aqueous solubility of the natural CDs than that of comparable acyclic polysaccharides.[34] In the end, we wish to correlate the effect of cooperativity on the sum of intramolecular H-bond energy in the particular conformers. Here, for instance, the higher contribution seems to stabilize the conformers of type A (∼2.0–3.5 kcal mol^{-1}) over those of types B (∼1.3–2.1 kcal mol^{-1}) or C (∼0.7–1.3 kcal mol^{-1}).

Conclusions

The recently proposed MTA-based method[25–29] has been applied for estimating the intramolecular H-bond energies in the CD conformers, representing a first-ever direct attempt toward this goal. The estimated intramolecular H-bond energies vary widely from 1.1 to 8.3 kcal mol^{-1} suggesting that indeed stronger H-bonds are seen in CDs. The H-bond energy falls in the range of 6.7–8.3 kcal mol^{-1} for the $O_6H\cdots O'_6$ H-bonds which are as strong as the sum of the two types of H-bonds formed by secondary hydroxyl groups (3.3–5.5 kcal mol^{-1} for $O_3H\cdots O'_2$ and 1.9–2.8 kcal mol^{-1} for $O_2H\cdots O_3$). The energies of H-bonds in CDs follow the rank ordering: $O_6H\cdots O'_6 > O_3H\cdots O'_2 > O_6H\cdots O'_5 > O_2H\cdots O_3 > O_6H\cdots O_5$. In general, the estimated H-bond energies in the $O_6H\cdots O'_6$ H-bonds follow the rank ordering as α-CD > β-CD > γ-CD. The reverse trend is seen in the H-bonds formed by secondary hydroxyl groups. The energetic contribution of cooperativity toward the H-bond strengths in CDs is also quantified for the first time. The contribution of cooperativity toward the $O_6H\cdots O'_6$ H-bonds formed between the primary hydroxyl groups is found to be larger (1.32–2.74 kcal mol^{-1}) than the sum of the individual contributions of cooperativity toward $O_3H\cdots O'_2$ (0.3–1.0 kcal mol^{-1}) and $O_2H\cdots O_3$ (0.25–1.10 kcal mol^{-1}) ones formed by the secondary hydroxyl groups. On going from α-CD to γ-CD, the cooperativity contribution is seen to increase in the case of H-bonds formed due to interactions between primary hydroxyl groups. The reverse trend is seen in the H-bonds formed by secondary hydroxyl groups.

In summary, the present MTA-based method is not only able to provide energies of intramolecular H-bonds and the respective cooperative contributions in these CD conformers but is also able to explain the stability of these conformers. We hope that such estimated H-bond energies would be useful for providing insights into the physicochemical properties of CDs toward the host-guest chemistry. For instance, a partial reason for unusually low aqueous solubility of β-CD (18.5 mg/ml) when compared with α-CD (145 mg/ml) or γ-CD (232 mg/ml),[34] may lie in the intramolecular H-bond strengths and the respective competitive intermolecular interactions with solvent molecules. We believe that the results of this work would be beneficial for such detailed investigations, which would be taken up in future studies.

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