Article

Intramolecular Hydrogen Bonding and Cooperative Interactions in Carbohydrates via the Molecular Tailoring Approach

Milind M. Deshmukh, Libero J. Bartolotti, and Shridhar R. Gadre

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Intramolecular Hydrogen Bonding and Cooperative Interactions in Carbohydrates via the Molecular Tailoring Approach

Milind M. Deshmukh,[†] **Libero J. Bartolotti,**[‡] **and Shridhar R. Gadre*,**[†]

Department of Chemistry, University of Pune, Pune 411 007, India, and Department of Chemistry, East Carolina University, Science and Technology Building, Suite 300, Greenville, North Carolina 27858-4353

Received: August 7, 2007

In spite of many theoretical and experimental attempts for understanding intramolecular hydrogen bonding (H-bonding) in carbohydrates, a direct quantification of individual intramolecular H-bond energies and the cooperativity among the H-bonded networks has not been reported in the literature. The present work attempts, for the first time, a direct estimation of individual intramolecular O−H⋯O interaction energies in sugar molecules using the recently developed molecular tailoring approach (MTA). The estimated H-bond energies are in the range of 1.2−4.1 kcal mol^{-1}. It is seen that the OH⋯O equatorial−equatorial interaction energies lie between 1.8 and 2.5 kcal mol^{-1}, with axial−equatorial ones being stronger (2.0−3.5 kcal mol^{-1}). The strongest bonds are nonvicinal axial−axial H-bonds (3.0−4.1 kcal mol^{-1}). This trend in H-bond energies is in agreement with the earlier reports based on the water−water H-bond angle, solvent-accessible surface area (SASA), and ^{1}H NMR analysis. The contribution to the H-bond energy from the cooperativity is also estimated using MTA. This contribution is seen to be typically between 0.1 and 0.6 kcal mol^{-1} when H-bonds are a part of a relatively weak equatorial−equatorial H-bond network and is much higher (0.5−1.1 kcal mol^{-1}) when H-bonds participate in an axial−axial H-bond network.

1. Introduction

Carbohydrates play an important role in many biological processes such as molecular recognition, cell signaling to protein stabilization,[1] and cryoprotection.[2] These recognition processes are mainly attributed to weak interactions such as hydrogen bonding, hydrophobic effects, and van der Waals interactions.[3−5] However, the nature of these interactions is mainly dependent on the topology or stereochemistry of the molecule under consideration, leading to variation in the physical, chemical, and biological properties of these molecules.[2,6] A thorough understanding of the interactions such as H-bonding is thus of utmost importance. The arrangement of hydroxyl groups in carbohydrates leads to a network or chain of H-bonds resulting in a phenomenon called "cooperativity".[7,8] The cooperative H-bond network has been shown to influence the ability of these molecules to interact with other molecules such as pyridine[9] and water.[10] Understanding the cooperative effects would be immensely useful in probing the nature of interactions of these molecules with the protein receptors.

In general, the strength of an intramolecular H-bond is gauged using various indirect experimental observations such as bond lengths, bond angles,[11] and changes in the IR/NMR chemical shifts.[12] Empirical relations based on topographical analysis of the molecular electron density (MED), the molecular electrostatic potential (MESP), and the electron localization function (ELF)[13] have also been employed for this purpose. Recently, a few theoretical methods, namely, ortho−para,[14] cis−trans[15] methods, and the isodesmic reaction approach,[16] have been

explored for a quantitative estimation of intramolecular H-bond energies. However, these methods have not yet been tried out for carbohydrate molecules, probably due to the multitude of such H-bonding interactions present therein.

Apart from these general qualitative and quantitative estimates of H-bond strength, there are attempts[17−23] devoted especially to the study of intramolecular H-bonding in carbohydrate molecules. However, in these studies, the H-bond strength is judged by considering only the corresponding cis(axial−equatorial) and transvicinal (equatorial−equatorial) as well as the syndiaxial (axial hydroxyl groups on the same side of ring) diols having a OH⋯O H-bond. Also, the effect of different substitutents on the strength of these OH⋯O H-bonds is explored. A study by López de la Paz et al.[17] has explored the effect of intramolecular H-bonding on the cooperative assembly of substituted carbohydrates by using ^{1}H NMR spectroscopy. On the basis of coupling constant values in CDCl$_3$, it is suggested[17] that monoalcohols form intramolecular H-bonds with a ring oxygen atom, O(5) (See Figure 1). In contrast, in syndiaxial diols, there exists a stronger H-bond between the OH-(2) and OH(4) groups. From a dimerization study of these alcohols, it was concluded that the intermolecular H-bond formed between the two monosaccharides accounts for 2.5 kcal mol^{-1} in CDCl$_3$. Also, the cooperativity due to the 1,3-syndiaxial interaction in carbohydrates has been examined using ab initio quantum mechanical and density functional treatments.[18] It is concluded from this model study (of substituted glycopyranose) that the interaction between the two 1,3-propanediols is more favored over the *n*-propanol dimer due to the strong cooperative interactions between the inter- and intramolecular H-bonds in 1,3-propanediol dimer.[18,19] In another attempt,[20] Ma, Schaefer, and Allinger, employing density functional theory (DFT) and semiempirical calculations on D-aldohexoses and D-ketohexoses,

Carbohydrates and the MTA

J. Phys. Chem. A, Vol. 112, No. 2, 2008 **313**

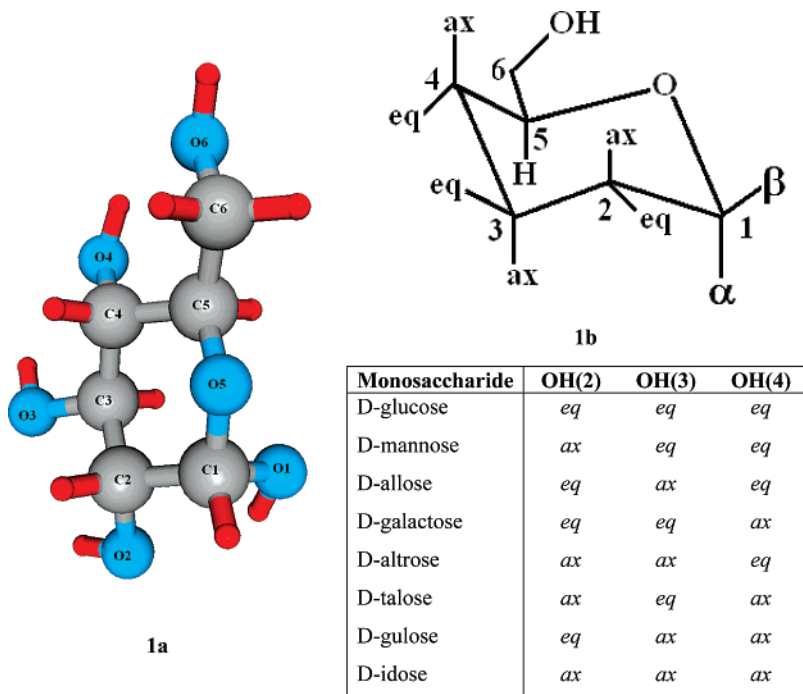| Monosaccharide	OH(2)	OH(3)	OH(4)
D-glucose	*eq*	*eq*	*eq*
D-mannose	*ax*	*eq*	*eq*
D-allose	*eq*	*ax*	*eq*
D-galactose	*eq*	*eq*	*ax*
D-altrose	*ax*	*ax*	*eq*
D-talose	*ax*	*eq*	*ax*
D-gulose	*eq*	*ax*	*ax*
D-idose	*ax*	*ax*	*ax*

Figure 1. (a) Atomic numbering of a sugar molecule. (b) General structure of the aldopyranose sugar. In the table, *ax* represents axial, and *eq* represents equatorial orientations of the hydroxyl group at carbons C2−C4.

showed that the most important factor governing the energetics of these sugars is the intramolecular H-bonding. It was found that the sum of the H-bond energies in the solution phase (upon applying a continuum solvation model) is smaller at the MM3 level than the corresponding value in the gas phase. Also, while comparing the gas-phase B3LYP H-bond energy results (MM3 at B3LYP geometry) with the MM3 results, a discrepancy of 1.5 kcal mol^{-1} was found and attributed to poor representation of electron correlation effects and parametrization at the MM3 level. The individual H-bond energies were not estimated in this work.[20] Thus, it seems worthwhile to embark on a project that directly estimates intramolecular O−H···O interaction energies in sugar molecules at a reliable, correlated level of theory.

It is concluded from several molecular dynamics (MD) studies that the nature of intramolecular H-bonds in the parent carbohydrate would decide the nature of solvent structuring around it.[21−25] One such attempt by Dashnau et al.[22] is based on MD simulations along with water−water H-bond angle analysis. Solvent-accessible surface area (SASA) and the approximate free energy of solvation has also been used for analyzing the effect of the hydroxyl orientation on solute hydration and solvent structuring around aldohexopyranose sugars. It was concluded that the intramolecular H-bond cooperativity plays a vital role in the structuring of water around the solute molecules. The criterion that the distance between the hydrogen of one hydroxyl group and the oxygen of another or a ring oxygen, O(5) being less than or equal to[22] 2.45 Å, was used by them for defining the presence of a H-bond. It was noticed that there is an increase in H-bond strength with an increase in the number of axial −OH groups. The syndiaxial H-bonds are stronger than vicinal H-bonds. This result is in agreement with the earlier observations in ref 9. Furthermore, the adjacent axial−equatorial H-bonds are seen to be stronger than equatorial−equatorial H-bonds. Because of this stronger intramolecular H-bonding, solute OH groups (when in the axial configuration) do not prefer to bind with the solvent water

molecules. Also, it was suggested by these authors that the orientations of OH(4) and OH(2) groups (see Figure 1 for the atom numbering convention) decide the cooperativity and directionality, which results in the strengthening of the individual H-bond in the network. The OH(4) group forms a H-bond with the OH(6), OH(3), and OH(2), generating a cooperatively bonded H-bond network, and OH(2) is said to provide the directionality for this network. In summary, Dashnau et al.[22] address many useful issues based on qualitative observations such as bond length, water−water angle, and SASA, highlighting the need for more quantitative investigations of the actual energetics of H-bonds.

Despite many theoretical and experimental studies[17−26] dealing with the H-bonds present in carbohydrate molecules, there are no reliable attempts to provide quantitative answers to many questions. For instance, how does one quantify the individual O−H···O interaction energies; how much is the contribution of cooperativity toward such O−H···O interactions; and so on? The answers to these above questions demand a systematic investigation of H-bond energy estimates in carbohydrates. For this purpose, a method recently developed in our laboratory[27a] is employed. Also, an attempt is made to explain the cooperativity phenomenon and quantification of the effect of networking on the individual H-bond strengths. To the best of the authors' knowledge, this is the first quantum chemical attempt to answer the above questions based on the direct individual H-bond energy estimation in carbohydrate molecules at a reliable level of theory.

2. Methodology

At least 10 conformers of each carbohydrate molecule (see Figure 2) with a maximum possibility of H-bond networks were constructed and optimized at the MP2/6-311++G(2d,2p) (frozen core) level of theory using the Gaussian package.[28] The lowest-energy conformers were verified to be local minima on the potential energy surface by carrying out a frequency calculation.
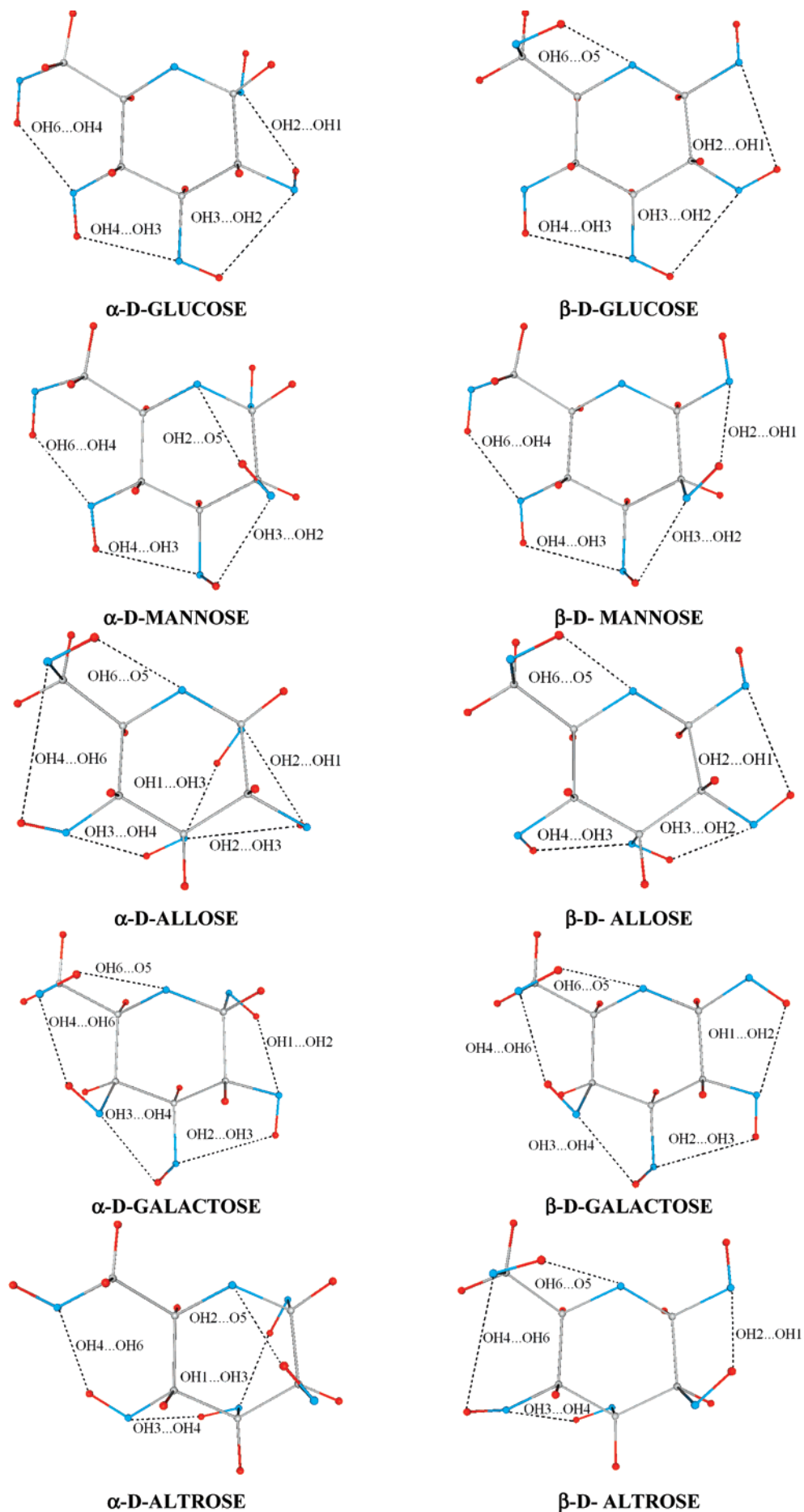
Figure 2. Part 1 of 2.

Carbohydrates and the MTA

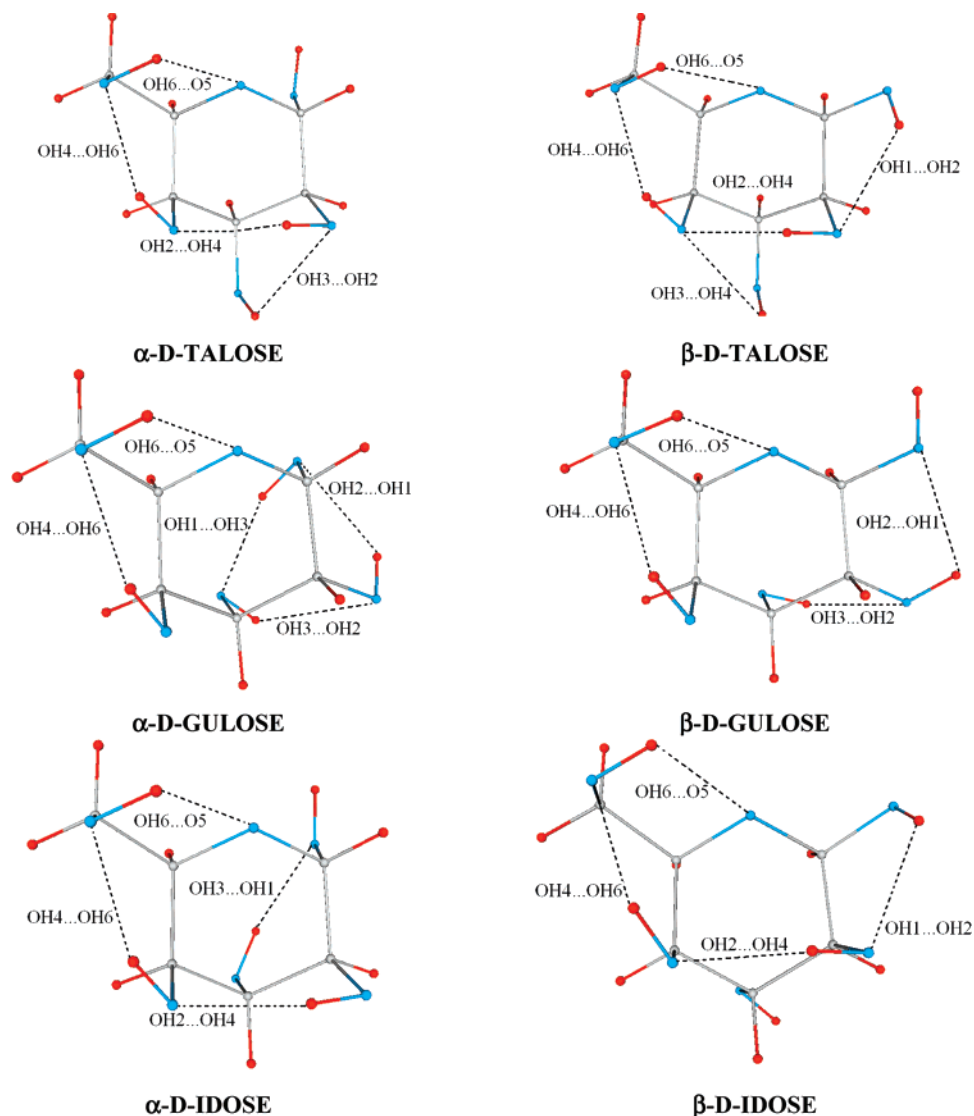*J. Phys. Chem. A, Vol. 112, No. 2, 2008* **315**

Figure 2. Part 2 of 2. MP2/6-311++G(2d,2p) level optimized geometries of sugar molecules. See text for details.

The corresponding O−H stretching frequencies were also evaluated from these calculations. The lowest-energy structures are shown in Figure 2. Further, the molecular electron density (MED), $\rho(\mathbf{r})$, topography is mapped[29] for these molecules. It is generally stipulated in the literature that the presence of a (3,−1) MED critical point (CP) is a signature of a hydrogen 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 H-bond.[30] The purpose of the present work is not to get into the issue of labeling such an O−H···O interaction as a hydrogen bond. In view of this, for those who insist on the existence of a (3,−1) $\rho(\mathbf{r})$ CP (henceforth called a bond critical point, BCP) for calling such an interaction a H-bond, the term H-bond energy may be replaced throughout the present work by O−H···O interaction energy for semantic purposes.

The intramolecular hydrogen bond energies are calculated for these molecules using the molecular tailoring approach (MTA)[27a] recently developed in our laboratory. The fragmentation procedure is illustrated for a test sugar molecule having two H-bonds, HB1 and HB2, as shown in Figure 3 (only two H-bonds are shown for illustrative purposes). Here, the original sugar molecule (denoted as M in Figure 3) is "cut" into three overlapping fragments F1, F2, and F3, which are obtained by replacing a −OH group with a hydrogen atom. The added H-atom is placed at the standard C−H distance (1.0 Å) along the direction of the C−O bond in the parent molecule. The scissored −OH regions are shown by dotted circles on the original molecule in Figure 3. Fragments F4, F5, and F6 are obtained by taking the intersection (a common structure of the respective fragments apart from added dummy H-atoms) of these basic fragments, that is, (F1 ∩ F2), (F2 ∩ F3), and (F1 ∩ F3), respectively. The fragment F7 is the intersection of three fragments F1, F2, and F3, that is, (F1 ∩ F2 ∩ F3). A single point energy evaluation is carried out on all seven fragments obtained by the above fragmentation procedure at the appropriate level of theory. The fragments are not optimized so that conformational changes in them are avoided (for the further details on why fragments are not optimized, see ref 31). The total energy of the sugar molecule (actual energy, E_M) is estimated as $E_e = E_{F1} + E_{F2} + E_{F3} - E_{F4} - E_{F5} - E_{F6} + E_{F7}$. The H-bond energies, E_{HB1} and E_{HB2}, in this molecule are calculated as $E_{HB1} = (E_{F1} + E_{F2} - E_{F4}) - E_e$ and $E_{HB2} = (E_{F2} + E_{F3} - E_{F5}) - E_e$, respectively. The error in the estimation of the total molecular energy ($\Delta E = E_e - E_M$) has been shown to be very small (typically 0.5 kcal mol^{-1}) for the case of triols studied earlier,[27a] leading to the expectation that the error in
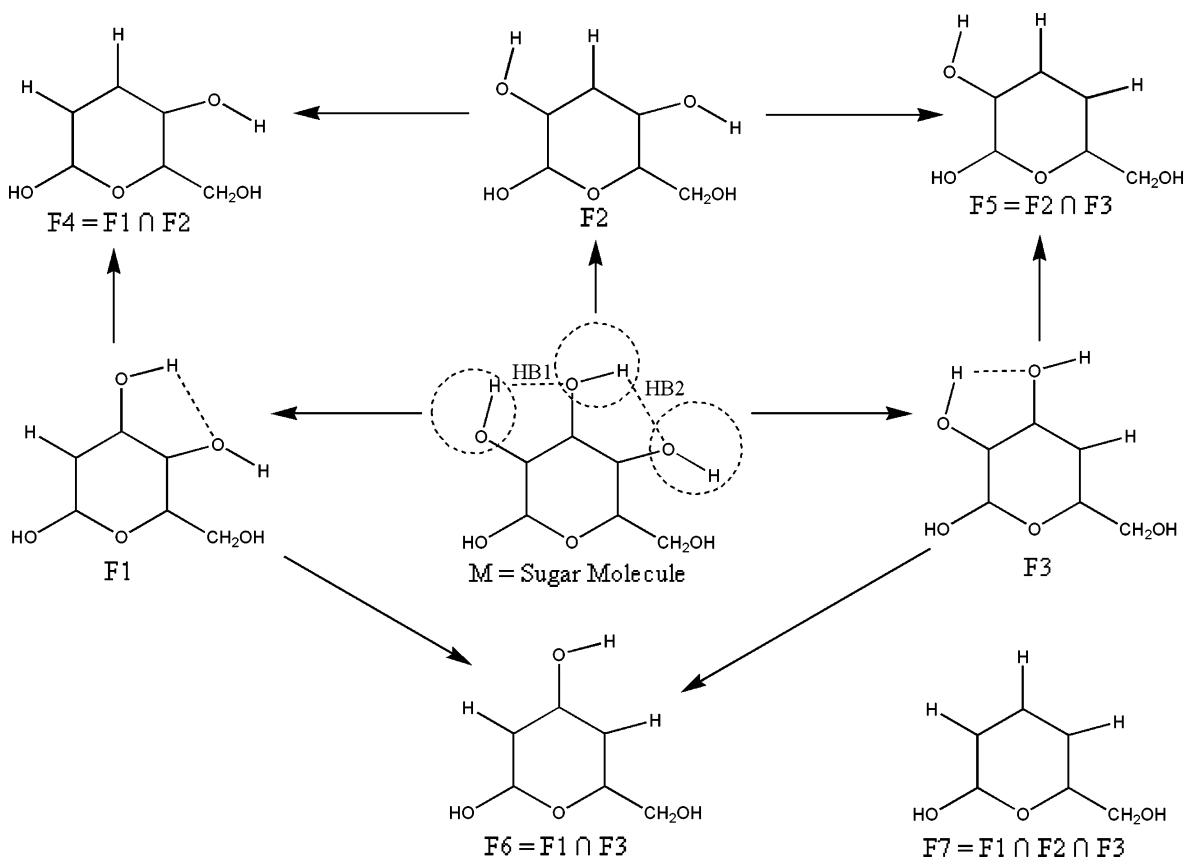
Figure 3. A schematic fragmentation scheme for a prototype sugar molecule (shown as M). See text for details of fragmentation and H-bond energy estimates. Also see ref 27a for further details.

the estimated H-bond energies would be also small. We expect the error in the estimated molecular energies for these cyclic systems to be even smaller due to the rigid structure therein. The intramolecular hydrogen bond energies of all of the chosen molecules are estimated by following this procedure along with the benchmark estimation of the respective molecular energies. The results are presented in the subsequent section. The intramolecular O−H⋯O interaction energy when a ring oxygen atom acts as a proton acceptor is also estimated by considering the appropriate fragments. See supplementary figure for more details.

Recently, we have critically compared[31] the H-bond energies estimated using MTA[27a] with those obtained using the isodesmic reaction approach, as advocated in the contemporary literature. It has been shown that the isodesmic reaction approach does not give the true H-bond energy but also includes the effect of strain energy due to the formation of a ring structure. Such a ring strain is duly accounted for in the MTA method. Moreover, the use of the isodesmic reaction approach is difficult for systems having an interlinked H-bond network (such as 1,2,3-propanetriol). Also, it is very difficult to come up with a single isodesmic reaction pertaining to a single H-bond in a system wherein a multitude of H-bonds are present. To the contrary, we could apply[31] MTA to decitol, a system having at least five different H-bonds. This has prompted us to investigate more intricate systems, such as sugar molecules, incorporating a network of H-bonds.

3. Results and Discussion

A. Geometries of Sugars. The optimized geometries of different sugars selected in the present work are shown in Figure 2. It is seen that in sugars from glucose to allose, wherein most

of the −OH groups are in an equatorial position, the orientations of −OH groups are in an counterclockwise direction, that is, it forms a network of OH(6) → OH(4) → OH(3) → OH(2) → OH(1) H-bonds. However, as the number of −OH groups in the axial position increases upon going from D-galactose to D-idose (Figure 2), the orientation of −OH changes to the clockwise direction, that is, it forms the OH(1) → OH(2) → OH(3) → OH(4) → OH(6) H-bond network. Also, instead of a OH(2) → OH(3) → OH(4) → OH(6) H-bond network, it prefers the formation of a OH(2) → OH(4) → OH(6) H-bond network where the OH(2) and OH(4) groups are in axial positions. This is in agreement with the previous reports of Schaefer[20] and Dashnau et al.[22] The corresponding OH⋯O H-bond lengths are reported in Table 1 (see Supporting Information data for O−H⋯O angles). Let us take the example of OH(1)⋯OH(2), from Table 1. This indicates that the hydrogen atom in OH(1) is interacting with the oxygen atom in OH(2) or vice a versa. The exact nature of such an interaction is clear from Figure 2. As seen from Table 1, most of the OH⋯O bond lengths fall in the range of 1.9−2.5 Å. Also, when both of the −OH groups are in the equatorial position, the vicinal OH⋯O bond lengths lie between 2.2 and 2.5 Å. However, as the number of −OH groups in the axial position increases, the OH⋯O bond lengths are between 1.9 and 2.3 Å. This indicates that the OH⋯O bond gets strengthened when −OH groups are in the axial position. The unscaled MP2/6-311++G(2d,2p) level O−H stretching frequencies are reported in Table 2. As seen from this table, the unscaled O−H frequency values lie between 3624 and 3881 cm⁻¹. In sugars having equatorial −OH groups forming a OH⋯O H-bond, the corresponding O−H stretching frequency is of the order of 3800 cm⁻¹, as that in glucose and mannose. However, with an increasing number of axial−equatorial

Carbohydrates and the MTA

J. Phys. Chem. A, Vol. 112, No. 2, 2008 **317**

TABLE 1: Intramolecular OH⋯O Hydrogen Bond Lengths (in Å) in Various Sugar Molecules Optimized at the MP2/6-311++G(2d,2p) Level; See Text and Figure 2 for Details

molecules	OH1⋯OH2	OH2⋯OH3	OH3⋯OH4	OH4⋯OH6	OH6⋯O5	OH1⋯OH3	OH2⋯O5	OH2⋯OH4
α-D-glucose	2.22	2.49	2.36	2.04				
β-D-glucose	2.49	2.45	2.41		2.32			
α-D-mannose		2.28	2.39	2.04			2.42	
β-D-mannose	2.22	2.21	2.39	2.03				
α-D-allose	2.49	2.52	2.27	3.29	2.40	1.91		
β-D-allose	2.41	2.29	2.16		2.31			
α-D-galactose	2.19	2.41	2.21	1.91	2.35			
β-D-galactose	2.30	2.45	2.17	1.89	2.32			
α-D-altrose			2.11	1.94		1.89	2.31	
β-D-altrose	2.20		2.27	3.26	2.39			
α-D-talose		2.39	2.57	1.91	2.37			1.90
β-D-talose	2.16	2.87	2.53	1.91	2.37			1.90
α-D-gulose	2.21	2.55		1.91	2.34	1.96		
β-D-gulose	2.42	2.25		1.93	2.31			
α-D-idose				1.90	2.36	1.99		1.91
β-D-idose	2.16			1.89	2.33			1.93

TABLE 2: Unscaled H−O Stretching Frequency (cm^{-1}) Obtained for Various Sugar Molecules Employing the MP2/6-311++G(2d,2p) Level of Theory; See Text and Figure 2 for Details

molecules	O(1)-H	O(2)-H	O(3)-H	O(4)-H	O(6)-H
α-D-glucose	3855	3808	3831	3824	3807
β-D-glucose	3827	3814	3807	3804	3812
α-D-mannose	3819	3782	3762	3785	3775
β-D-mannose	3816	3792	3772	3788	3776
α-D-allose	3693	3812	3788	3845	3812
β-D-allose	3826	3806	3798	3778	3811
α-D-galactose	3792	3817	3795	3697	3824
β-D-galactose	3794	3798	3762	3657	3784
α-D-altrose	3694	3816	3769	3754	3880
β-D-altrose	3854	3820	3827	3881	3835
α-D-talose	3854	3708	3824	3680	3823
β-D-talose	3737	3652	3804	3629	3791
α-D-gulose	3701	3806	3837	3707	3823
β-D-gulose	3827	3812	3791	3695	3789
α-D-idose	3845	3712	3792	3676	3823
β-D-idose	3779	3660	3836	3624	3786

TABLE 3: Molecular Electron Density, $\rho(r)$ Value (in au) at the (3,−1) Bond Critical Point (BCP) at the H-bond[a] in Sugar Molecules at the MP2/6-311++G(2d,2p) Level of Theory

molecules	OH4⋯OH6	OH1⋯OH3	OH2⋯OH4
α-D-glucose	0.02048	−	−
β-D-glucose	−[b]	−	−
α-D-mannose	0.02031	−	−
β-D-mannose	0.02068	−	−
α-D-allose	−	0.02875	−
β-D-allose	−	−	−
α-D-galactose	0.02967	−	−
β-D-galactose	0.03069	−	−
α-D-altrose	0.02981	0.03015	−
β-D-altrose	−	−	−
α-D-talose	0.02981	−	0.03015
β-D-talose	0.03018	−	0.03028
α-D-gulose	0.02951	0.02772	−
β-D-gulose	0.02874		
α-D-idose	0.03051	0.02903	0.02282
β-D-idose	0.03105	−	0.02820

[a] There are no BCPs for the other O−H⋯O bonds. [b] Dash indicates the absence of BCP for tabulated interactions.

H-bonds, the frequency shifts to a lower wavenumber (typically of the order of 3700 cm^{-1}). Also, when axial−axial H-bonds are present, larger red shifts in the O−H stretching frequency up to 3624 cm^{-1} are seen. Such a red shift is generally considered in the literature as the manifestation of a hydrogen bond (or O−H⋯O interaction), although there are debates regarding red- and blue-shifting hydrogen bonds.

Thus, it is seen from the H-bond lengths and O−H stretching frequencies that stronger OH⋯O bonds are formed when there are more axial−axial OH⋯O interactions. Moreover, the axial−equatorial O−H⋯O interactions are generally stronger than the equatorial−equatorial ones. This gas-phase observation is in accordance with the water−water H-bond angle, solvent-accessible surface area (SASA) analysis of Dashnau and co-workers,[22] and ^{1}H NMR analysis of López de la Paz et al.,[9,17] wherein it was suggested that the syndiaxial H-bonds are stronger and more stable in solution than the vicinal ones. Additionally the cisvicinal (axial−equatorial or equatorial−axial) H-bonds are stronger than the equatorial−equatorial vicinal bonds. The details of the energetics of the OH⋯O H-bonds are presented in the next section, wherein the recently developed MTA[27a] method for the estimation of the H-bond energy is employed.

The presence of the (3,−1) $\rho(r)$ BCP at the O−H⋯O bond is generally considered by many researchers as the manifestation of a hydrogen bond.[13] However, such a (3,−1) BCP at the O−H⋯O bond is seen to be conspicuous by its absence in most of the polyols having O−H⋯O interactions between vicinal −OH groups.[13,15] Recently, Klein[13g] has shown the presence of such a (3,−1) BCP in some strained cyclic vicinal diols. Of course, such examples are exceptions rather than a rule. Going further from our own earlier observations[13e] in this regard, it is clear that an O−H⋯O interaction undeniably exists even in the absence of such a (3,−1) BCP. It is a subjective opinion whether such an interaction is to be called a hydrogen bond. In the present work, such O−H⋯O interactions are called H-bonds even in the absence of a (3,−1) BCP. In Table 3, the MED value at the (3, −1) BCPs are reported. It is seen from this table that the BCPs are found only for the nonvicinal OH⋯O bonds. In the sugar molecules, wherein the nonvicinal H-bonds are a part of the H-bond network, we note in passing the following. For the case of an equatorial−equatorial or axial−equatorial H-bond network (e.g., D-glucose to D-allose), the ρ-(r) values at the (3,−1) BCP are smaller (∼0.020 au) than those involved in an axial−axial H-bond network (∼0.031 au). This indicates that upon moving from α-D-glucose to β-D-idose, the electron density becomes more localized at the OH⋯O bonds, leading to stronger H-bonds when they are a part of an axial−axial H-bond network. This is in agreement with the H-bond length and O−H stretching frequency trends discussed earlier. However, the presence or absence of a BCP is not an indicator of the presence or absence of an O−H⋯O interaction. It is certainly not the central theme of the present study and is a subject of recent debate[30] requiring further detailed investigations.

B. Intramolecular Hydrogen Bond Energies in Sugars. The total- and H-bond energies of the sugar molecules at the MP2-(full)/6-311++G(2d,2p) level are estimated[27a] using the MTA

TABLE 4: Error ($E_e - E_M$) in Molecular Energy by the MTA for Various Sugar Molecules at the MP2(full)/ 6-311++G(2d,2p) Level of Theory; See Text and Figure 2 for Details

molecules	estimated energy (au)	actual energy (au)	error (kcal mol^{-1})
α-D-glucose	−686.06490	−686.06491	0.00320
β-D-glucose	−686.06335	−686.06335	0.00130
α-D-mannose	−686.06334	−686.06338	0.01883
β-D-mannose	−686.06248	−686.06248	0.00088
α-D-allose	−686.06521	−686.06521	0.00050
β-D-allose	−686.06498	−686.06498	0.00163
α-D-galactose	−686.06704	−686.06704	0.00013
β-D-galactose	−686.06220	−686.06220	0.00201
α-D-altrose	−686.06546	−686.06546	0.00251
β-D-altrose	−686.06213	−686.06213	0.00016
α-D-talose	−686.06799	−686.06799	0.00188
β-D-talose	−686.06827	−686.06827	0.00107
α-D-gulose	−686.06568	−686.06568	0.00815
β-D-gulose	−686.06525	−686.06525	0.00320
α-D-idose	−686.06678	−686.06678	0.00300
β-D-idose	−686.06707	−686.06710	0.01839

and are reported in Tables 4 and 5, respectively. As seen From Table 4, the estimated energy of the molecules is in very good agreement with the actual one, the error in the estimation being very small (0.001−0.02 kcal mol^{-1}). The estimated H-bond energies are reported in Table 5 and are seen to lie in the range of 1.2−4.1 kcal mol^{-1}. Some values are below 1.2 kcal mol^{-1}, indicating that the corresponding O−H···O interactions are weaker. The OH···O bond lengths for such weak bonds are indeed larger. The energy of OH···O(5), that is, an intramolecular H-bond with the ring oxygen, is also estimated using the MTA. The estimated OH(6)···O(5) and OH(2)···O(5) H-bond energies are in the range of 1.2−1.9 and 2.6−2.7 kcal mol^{-1}, respectively. As seen from Table 5, the estimated energies of equatorial−equatorial OH···O bonds lie in the range of 1.8−2.5 kcal mol^{-1}. This is predominantly seen in the case of D-glucose molecule, wherein the H-bond energies are seen to be between 1.8 and 2.3 kcal mol^{-1}.

How do these O−H···O interaction energy estimates vary upon the use of a variety of correlated methods employing a good-quality basis set? Table 6 present benchmark results of molecular and H-bond energies for the four different H-bonds in α-D-glucose (see Figure 2 and Table 1 for bond lengths) at different size-consistent correlated levels of theory. Here, a MP2-(frozen core)/6-311++G(2d,2p)-optimized geometry is used for performing the H-bond estimates at other levels of theory mentioned in Table 6. Looking at this table, it is amply clear that, within themselves, the molecular energies as well as the estimated H-bond energies are remarkably consistent. For example, the average O−H···O interaction energy for the bond with a H-bond length of 2.039 Å is 2.70 kcal/mol. The interaction energy obtained by all of the methods is seen to be within ±0.1 kcal/mol of this value. Considering this consistency, we believe that at any accurate correlated size-consistent theory with a good-quality basis set, the estimated H-bond energy will not differ much from the value reported in Table 6.

Upon moving from mannose to altrose (Table 5), stronger OH···O equatorial−axial (equatorial OH as a proton donor and axial OH as a proton acceptor) or axial−equatorial (axial OH as a proton donor and equatorial OH as a proton acceptor) H-bonds are seen. The typical energy of such a OH···O H-bond is in the range of 1.7−3.5 kcal mol^{-1}. It can also be seen in general that the axial−equatorial H-bonds are stronger than their equatorial−axial counterparts if both the bonds are present in the same molecule. For instance, in β-D-mannose, the axial−equatorial OH(2)···OH(1) H-bond has the energy value of 2.7 kcal mol^{-1}. The corresponding equatorial−axial OH(3)···OH(2)

interaction energy is 1.8 kcal mol^{-1}. The typical energy of an equatorial−axial H-bond lies between 1.8 and 2.5 kcal mol^{-1}, whereas the axial−equatorial H-bond energy is in the range of 2.0−3.5 kcal mol^{-1}. Going further from talose to idose in Table 5, a network of stronger axial−axial OH···O H-bonds is seen to emerge (cf. Figure 2). The estimated H-bond energy for these axial−axial H-bonds varies from 3.0 to 4.1 kcal mol^{-1}, which is the strongest among the other equatorial−equatorial and axial−equatorial H-bonds. Also, the OH(4)···OH(6) H-bond becomes stronger as we go through Table 5. The OH(4)···OH(6) intramolecular H-bond energy varies from 2.7 to 3.8 kcal mol^{-1}. The increase in the OH(4)···OH(6) H-bond energies from D-glucose to D-idose is probably due to better networking of the OH(4)···OH(6) H-bond with the other axial−axial and axial−equatorial H-bonds.

The estimated H-bond energies (vicinal as well as nonvicinal) in all sugar molecules examined here are higher than the corresponding values estimated previously for alkanetriols using MTA.[27a] The typical estimated H-bond energy value for alkanetriols is about 2.0 and 3.0 kcal mol^{-1} for the vicinal and nonvicinal (1−3 type) bonds, respectively. The higher values (2.0−3.5 kcal mol^{-1} for vicinal and 3.0−4.1 kcal mol^{-1} for axial−axial nonvicinal) in the sugar molecules may be due to the cooperative networking of H-bonds. Also, the error in the estimation of total energy in these cyclic sugar molecules is much smaller (0.001−0.02 kcal mol^{-1}) than the corresponding errors in open-chain alkanetriols (0.4−0.6 kcal mol^{-1}) studied before.[27a] As mentioned before, this may be attributed to the rigid structure in these cyclic systems such that when a −OH group is replaced by a hydrogen atom, the other nonbonding interactions are not effected much. This may be due to loss in directionality of interactions between added H-atoms and other atoms in molecules, as compared to those in open-chain systems. It may be pointed out that the sum of H-bond energy values in the sugar molecules estimated using the MTA are in qualitative agreement with the MM3 values of Schaefer et al. (reference 20). However, as expected, there is no quantitative agreement, which could be attributed to poor representation of electron correlation and the effect of parametrization within the MM3 method, as pointed out by Schaefer and co-workers.

In general, it can be seen that the strength of an individual H-bond is enhanced in the presence of other cooperative interactions. For instance, in α-D-idose, though there are more axial−axial hydrogen bonds present, the corresponding H-bond energy values are found to be larger in the case of β-D-idose. This is due to the better cooperative H-bonding network in β-anomer. Similarly, upon comparing the OH(3)···OH(4) and OH(2)···OH(3) interaction energy values in the anomers of D-glucose, it may be noticed that the H-bond energy values are larger in α-D-glucose compared to those in its β-counterpart. Such a bond cooperativity effect is discussed and quantified in the following section.

C. Intramolecular Hydrogen Bond Cooperativity. The effect of intramolecular H-bond cooperativity on the strength of the individual H-bonds may be assessed by estimating the corresponding OH···O interaction energy in the absence of a 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. For instance, in α-D-glucose (cf. Figure 2), when the OH(3) group is replaced by a hydrogen atom, OH(2)···OH(1) and OH(6)···OH(4) bonds are no longer "connected" with the other H-bonds, and the network is broken. Hence, in this situation, the estimates of the H-bond energies

Carbohydrates and the MTA

J. Phys. Chem. A, Vol. 112, No. 2, 2008 **319**

TABLE 5: O−H⋯O Interaction Energies (in kcal/mol) Obtained by the MTA for Various Sugar Molecules at the MP2(full)/6-311++G(2d,2p) Level of Theory; For the Convention of Labeling of Hydrogen Bonds and Other Details, See Text and Figure 2

molecules	OH1⋯OH2	OH2⋯OH3	OH3⋯OH4	OH4⋯OH6	OH6⋯O5	OH1⋯OH3	OH2⋯O5	OH2⋯⋯OH4
α-D-glucose	2.31 (1a2e)[a]	2.07 (2e3e)	1.87 (3e4e)	2.75 (4e)				
β-D-glucose	2.12 (1e2e)	1.79 (2e3e)	1.87 (3e4e)		1.30			
α-D-mannose		2.40 (2a3e)	2.37 (3e4e)	2.75 (4e)			2.64(2a)	
β-D-mannose	2.67 (1e2a)	1.75 (2a3e)	2.47 (3e4e)	2.79 (4e)				
α-D-allose	0.38 (1a2e)	0.87 (2e3a)	2.20(3a4e)	0.87 (4e)	1.67	3.44 (1a3a)		
β-D-allose	2.31 (1e2e)	2.37 (2e3a)	1.83 (3a4e)	−	1.23			
α-D-galactose	3.28 (1a2e)	2.34 (2e3e)	2.00 (3e4a)	3.57 (4a)	1.85			
β-D-galactose	2.32 (1e2e)	2.30 (2e3e)	2.20 (3e4a)	3.70 (4a)	2.00			
α-D-altrose			3.62 (3a4e)	3.66 (4e)		4.11 (1a3a)	2.65(2a)	
β-D-altrose	2.18 (1e2a)		1.86 (3a4e)	1.14 (4e)	1.42			
α-D-talose		0.65 (2a3e)	0.64(3e4a)	3.50 (4a)	1.53			3.07 (2a4a)
β-D-talose	3.53 (1e2a)	0.24 (2a3e)	0.83 (3e4a)	3.74 (4a)	1.79			3.63 (2a4a)
α-D-gulose	2.49 (1a2e)	2.46 (2e3a)		3.27 (4a)	1.60	3.51 (1a3a)		
β-D-gulose	2.13 (1e2e)	2.26 (2e3a)		3.15 (4a)	1.48	-		
α-D-idose				3.50 (4a)	1.39	2.92 (1a3a)		3.70 (2a4a)
β-D-idose	3.41 (1e2a)			3.79 (4a)	1.77			4.06 (2a4a)

[a] The numbers in the parentheses represent the positioning of the −OH group (i.e., the carbon number to which the −OH group is attached; see Figure 1); "a" and "e" represents the axial and equatorial orientation of the −OH group, respectively.

TABLE 6: O−H⋯O Interaction Energies (in kcal/mol) in α-D-Glucose at Different Levels of Theory Employing the MP2(full)/6-311++G(2d,2p) Geometry; See Text and Figure 2 for Details

H-bond length (Å)	hydrogen bond energy			
	MP2 $\Delta E^a = -0.0030$	MP2 (full) $\Delta E = -0.0030$	MP3 $\Delta E = -0.0030$	CCSD $\Delta E = -0.0029$
2.22	2.28	2.31	2.21	2.18
2.49	2.04	2.06	1.99	1.98
2.36	1.84	1.87	1.88	1.83
2.04	2.71	2.75	2.72	2.61

[a] Error in the molecular energy in kcal/mol.

TABLE 7: O−H⋯O Interaction Energies (in kcal/mol) in the Absence of a Cooperative H-bond Network in Some Selected Sugars at the MP2(full)/6-311++G(2d,2p) Level of Theory; See Text and Figure 2 for Details

molecules	OH1⋯OH2	OH2⋯OH3	OH3⋯OH4	OH⋯OH6	OH6⋯O5	OH2⋯OH4
α-D-glucose	2.18 (0.009)[a]	1.59 (0.031)	1.31 (0.039)	2.55 (0.009)	−	−
β-D-mannose	2.38 (0.004)	1.29 (0.030)	1.95 (0.200)	2.58 (0.004)	−	−
α-D-galactose	3.01 (0.050)	1.97 (0.047)	1.46 (−0.020)	2.66 (0.070)	1.35 (0.050)	−
β-D-galactose	1.95 (0.051)	1.88 (0.019)	1.55 (0.074)	2.70 (0.063)	1.25 (0.051)	−
β-D-talose	2.95 (0.074)	−[b]	−[b]	2.60 (0.224)	1.26 (0.074)	2.68 (0.016)
β-D-idose	2.87 (0.077)	−	−	2.63 (0.175)	1.23 (0.077)	3.15 (−0.061)

[a] The values in the parentheses are the corresponding error estimates in evaluating the total energy of the molecule. [b] These values are small in the presence of the H-bond network and hence are not estimated in that case.

of the OH(2)⋯OH(1) and OH(6)⋯OH(4) bonds are expected to be close to the H-bond energy in the absence of a cooperative network of H-bonds. Similarly, the OH(3)⋯OH(2) and OH-(4)⋯OH(3) H-bond energies in the absence of cooperativity are estimated by replacing OH(1), OH(4) (both of them at a time) and OH(2), OH(4) (both of them at a time) with hydrogen atoms, respectively. Such a difference between the estimated H-bond energy in the presence and absence of the cooperative network of H-bonds gives an idea of the enhancement of a particular H-bond strength due to the cooperativity. The intramolecular H-bond energies in the absence of cooperativity in some sugar molecules are reported in Table 7 along with the estimated error in the total energy of the molecule (i.e., the molecule after replacement of appropriate −OH groups with H atoms). As seen from Tables 5 and 7, when the H-bond is part of a network of weak H-bonds (equatorial−equatorial and axial−equatorial), as in the case of α-D-glucose and β-D-mannose, the strength of the individual H-bond is enhanced by 0.1−0.6 kcal mol⁻¹ due to cooperativity. It may be remembered that these are theoretical estimates for a given level of theory and basis set with some error bars associated with them. However, we expect these energies to be quite reliable even when better correlated calculations are done (cf. Table 6), although we have not carried out such calculations for estimating

cooperativity effects. From the earlier estimates of consistency of the O−H⋯O interaction energies at various levels of correlated theories, we expect that the cooperativity values are consistent to within ±0.2 kcal/mol. As one goes to the network of stronger H-bonds (especially that involving more axial−axial H-bonds), as in case of β-D-talose and β-D-idose, the strength of the individual H-bond increases by 0.5−1.2 kcal mol⁻¹. The strengths of nonvicinal H-bonds, namely, OH(2)⋯OH(4) and OH(6)⋯OH(4), are enhanced to a larger extent, namely, by 0.6−1.2 kcal mol⁻¹, due to cooperativity. How large is the effect of cooperativity on the sum of intramolecular hydrogen bond energies in the sugar molecules under study? The sum of the H-bond energies in the presence of the H-bond network for the molecules of α-D-glucose, β-D-mannose, α-D-galactose, β-D-galactose, β-D-talose, and β-D-idose is 9.0, 9.7, 13.2, 12.5, 13.8, and 12.8, respectively. However, the corresponding sums of H-bond energies in the absence of a H-bond network are 7.6, 8.2, 10.5, 9.3, 9.4, and 9.9, respectively. Thus, in general, it is seen that strong hydrogen bonds become even stronger, but the strength of a weak hydrogen bond is only marginally enhanced by a cooperative network of H-bonds. Also as seen from the Table 7, in general, the error in molecular energy estimates (for a structure wherein the network of H-bonds is broken) while estimating the H-bond strengths is less that 10% of the total

Deshmukh et al.

enhancement in the H-bond energy due to cooperativity. An exception is for the OH(4)···OH(6) H-bond in β-D-talose and β-D-idose (typically 0.2 kcal/mol). This may be attributed to involvement of the open-chain structure as seen earlier in the case of alkanetriols.[27a] Thus, considering the error in the estimation of the total energy in the absence of a cooperative network of H-bonds, the estimated cooperative H-bond energies seem to be quite reliable, especially if these are greater than 0.5 kcal/mol.

4. Concluding Remarks

In this work, we have applied the recently developed molecular tailoring approach for the estimation of intramolecular H-bond energies in a variety of sugar molecules. To the best of our knowledge, this is the first-ever attempt toward such quantification in carbohydrate chemistry. It is seen that the error in the estimation of the total molecular energy of these sugars is very small, leading to the expectation that the estimation of intramolecular H-bond energies is quite reliable. We would like to benchmark our estimates with those given by some other reliable nonempirical methods. However, such estimates are conspicuous by their absence from the literature.

Our estimated H-bond energies at the MP2(full)/6-311++G-(2d, 2p) level of theory are mostly in the range of 1.2−4.1 kcal mol^{-1}. For the case of equatorial−equatorial H-bonds, the energy is generally in the range of 1.7−2.5 kcal mol^{-1}. Moreover, the axial−equatorial H-bonds are stronger (2.0−3.5 kcal mol^{-1}) than their equatorial−equatorial counterparts. The strongest bonds are nonvicinal axial−axial H-bonds (3.0−4.1 kcal mol^{-1}) seen generally between OH(1)···OH(3), OH-(2)···OH(4), and OH(4)···OH(6) groups. Thus, the general ordering of these H-bonds strength is axial−axial > axial−equatorial > equatorial−equatorial. This ordering of H-bonds is in agreement with the water−water H-bond angle, solvent-accessible surface area (SASA) analysis of Dashnau and co-workers,[26] ^{1}H NMR analysis of López de la Paz et al.,[9,17] and OH···O H-bond length and O−H stretching frequency analysis presented in this work. Also in the present study, an attempt is made to estimate the energetic contribution toward the intramolecular H-bond cooperativity. It has been found that the energetic contribution toward cooperativity for vicinal (equatorial−equatorial or axial−equatorial) OH···O interactions is less than 0.6 kcal mol^{-1}. On the other hand, the strength of nonvicinal H-bonds is relatively much more enhanced (up to about 1 kcal mol^{-1}).

In summary, the present MTA method is not only able to provide energies of intramolecular H-bonds but also offers estimates of the systematic energetic contribution of each H-bond toward the cooperative networking. We hope that such estimated H-bond energies are useful for providing some insights into the physicochemical properties of the sugar molecules.

Supporting Information Available: Table of intramolecular O−H···H H-bond angles. Figure for estimate of H-bond energy when ring oxygen acts as a proton acceptor. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Varki, A. *Glycobiology* **1993**, *3*, 97.
(2) Harding, M. M.; Anderberg, P. I.; Haymet, A. D. J. *Eur. J. Biochem.* **2003**, *270*, 1381.
(3) Rini, J. M. *Annu. Rev. Biophys. Biomol. Struct.* **1995**, *24*, 551.
(4) Lis, H.; Shanon, N. *Chem. Rev.* **1998**, *98*, 637.
(5) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2978.
(6) Woods, R. J.; Szarek, W. A.; Smith, V. H., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 4732.
(7) Frank, H. S.; Wen, W. Y. *Discuss. Faraday Soc.* **1957**, *24*, 133.
(8) Huyskens, P. L. *J. Am. Chem. Soc.* **1977**, *99*, 2578.
(9) López de la Paz, M.; Ellis, G.; Perez, M.; Perkins J.; Jimenez-Barbero, J.; Vicent, C. *Eur. J. Org. Chem.* **2002**, 840.
(10) Hunter, C. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5310.
(11) (a) Jeffery, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997. (b) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond*; Oxford University Press: Oxford, U.K., 1999.
(12) (a) Bellamy, L. J. *Advances in Infrared Group Frequencies*; Methuen: London, 1968; p 241. (b) Glasel, J. A. In *Water: A Comprehensive Treatise*; Frank, F., Ed; Plenum Press: New York, 1982; Vol. 1, Chapter 6, p 223. (c) Hobza, P.; Havlas, Z. *Chem. Rev.* **2000**, *100*, 4253.
(13) (a) Bader, R. F. W. *Atoms in Molecules−A Quantum Theory*; Oxford University Press: Oxford, U.K., 1990. (b) Fuster, F.; Silvi, B. *Theor. Chem. Acc.* **2000**, *104*, 13 and references therein. (c) Espinosa, E.; Alkorta, I.; Elguero, J.; Molins, E. *J. Chem. Phys.* **2002**, *117*, 5529 and references therein. (d) Klein, R. A. *J. Comput. Chem.* **2003**, *24*, 1120 and references therein. (e) Deshmukh, M. M.; Sastry, N. V.; Gadre, S. R. *J. Chem. Phys.* **2004**, *121*, 12402. (f) Grabowski, S. J.; Sokalski, W. A.; Leszczyński, J. *J. Phys. Chem. B* **2006**, *110*, 6444. (g) Klein, R. A. *Chem. Phys. Lett.* **2006**, *429*, 633.
(14) Estacio, S. G.; Cabral do Counta, P.; Costa Cabral, B. J.; Minas Da Piedade, M. E.; Martinho Simoes, J. A. *J. Phys. Chem. A* **2004**, *108*, 10834 and references therein.
(15) Rozas, I.; Alkorta, I.; Elguero, J. *J. Phys. Chem. A* **2001**, *105*, 10462 and references therein.
(16) Roy, D.; Sunoj, R. B. *J. Phys. Chem. A* **2006**, *110*, 5942 and references therein.
(17) López de la Paz, M; Jimenez-Barbero, J.; Vicent, C. *Chem. Commun.* **1998**, 465.
(18) Luque, F. J; López, M.; López de la Paz, M; Vicent, C.; Orozco, M. *J. Phys. Chem. A* **1998**, *102*, 6690.
(19) Muñoz, E. M.; López de la Paz, M.; Jimenez-Barbero, J.; Ellis, G.; Perez, M.; Vicent, C. *Chem.−Eur. J.* **2002**, *8*, 1908.
(20) Ma, B.; Schaefer, H. F., III; Allinger, N. L. *J. Am. Chem. Soc.* **1998**, *120*, 3411.
(21) Lui, Q.; Brady, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 12276.
(22) Dashnau, J. L.; Sharp, K. A.; Vanderkooi, J. M. *J. Phys. Chem. B* **2005**, *109*, 24152.
(23) Galema, S. A.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1990**, *112*, 9665.
(24) Galema, S. A.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Org. Chem.* **1992**, *57*, 1995.
(25) Tait, M. J.; Suggett, A.; Franks, F.; Ablett, S.; Quickenden, P. A. *J. Solution Chem.* **1972**, *1*, 131 and references therein.
(26) (a) Klein, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 13931. (b) Klein, R. A. *Chem. Phys. Lett.* **2006**, *433*, 165.
(27) (a) Deshmukh, M. M.; Gadre, S. R.; Bartolotti, L. J. *J. Phys. Chem. A* **2006**, *110*, 12519. For the details of MTA, see the original works on the method: (b) Ganesh, V.; Dongare, R. K.; Balanarayan, P.; Gadre, S. R. *J. Chem. Phys.* **2006**, *125*, 104109. (c) Gadre, S. R.; Ganesh, V. *J. Theor. Comput. Chem.* **2006**, *5*, 835. (d) Gadre, S. R.; Shirsat, R. N.; Limaye, A. C. *J. Phys. Chem.* **1994**, *98*, 9165. (e) Deev, V.; Collins, M. A. *J. Chem. Phys.* **2005**, *122*, 154102.
(28) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui,

Carbohydrates and the MTA

J. Phys. Chem. A, Vol. 112, No. 2, 2008 **321**

Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(29) *Program UNIPROP, the molecular property calculation package*; developed by Theoretical Chemistry Group, Department of Chemistry, University of Pune, Pune, India; see: (a) Bapat, S. V.; Shirsat, R. N.; Gadre, S. R. *Chem. Phys. Lett.* **1992**, *200*, 373. (b) Balanarayan, P.; Gadre, S. R. *J. Chem. Phys.* **2003**, *119*, 5037.

(30) See, for example, IUPAC Discussion Meeting on Hydrogen Bonding and Other Molecular Interactions Website. http://ipc.iisc.ernet.in/~arunan/Bangalore_iupac_meet2.html and references therein.

(31) Deshmukh, M. M.; Suresh, C. H.; Gadre, S. R. *J. Phys. Chem.* **2007**, *111*, 6472.