Intramolecular Hydrogen Bond Energy in Polyhydroxy Systems: A Critical Comparison of Molecular Tailoring and Isodesmic Approaches

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The intramolecular hydrogen bond (H-bond) energies in several polyhydroxy systems are estimated using an isodesmic/homodesmic reaction approach as well as a molecular tailoring approach (MTA) [Deshmukh, M. M.; Gadre, S. R.; Bartolotti, L. J. *J. Phys. Chem. A* **2006**, *110*, 12519]. It is shown that the isodesmic/homodesmic reaction approach as advocated in the literature does not give true H-bond energy but 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. The isodesmic H-bond energies are found to be smaller than their MTA energy counterparts typically by the strain energy. The MTA is applied to decitol, a system with more than five different H-bonds for which an application of an appropriate isodesmic reaction is extremely difficult. It has been shown that the MTA method is able to predict not only the H-bond energies but also the trends in conformational energies for three different conformers of decitol studied in the present work.

Introduction

The hydrogen bond (H-bond), being an important contributor[1] to many chemical as well as biological phenomena, has been subjected to detailed theoretical and experimental investigations. The study of the intermolecular H-bond is less intricate than the intramolecular one from the energetic viewpoint. In the literature, some direct as well as indirect attempts for determining the strength of the intramolecular H-bond have been reported. The indirect ways include analysis of the H-bond length,[2] study of the electron density topography[3] at the X−H···Y H-bond, and study of spectral shifts.[4] Very few semidirect or direct ways of theoretically estimating the energy of the H-bond have, however, appeared. Some of these methods are conformational analysis,[5−7] the ortho−para method,[8] and the isodesmic reaction approach.[6,9−10] For instance, in conformational analysis, two conformers of the molecule are chosen in such a way that the H-bond is *present* in one of the conformers and *not present* in the other. The corresponding energy difference is considered as a measure of H-bond energy. Similar to conformational analysis, in the ortho−para method, the H-bond energy is the energetic difference between the ortho conformer in which the intramolecular H-bond is present and the para conformer wherein the H-bond is not seen. In an isodesmic reaction approach, the intramolecular H-bond making/breaking reaction is written in such a way that except for the H-bond, whose energy is to be estimated, the numbers and types of other bonds on either side of the reaction are equal. The H-bond energy is obtained by optimizing the reactants and products, and the energy of the reaction is taken as the H-bond energy. For details of isodesmic reactions see refs 9 and 10. A systematic comparison of the reliability of the above methods is given in refs 5−8.

Recently, we have proposed the use of the molecular tailoring approach (MTA)[11] for the estimation of intramolecular H-bond energy, wherein a molecule is scissored into an appropriately constructed set of fragments. The single point energies of the fragments are then appropriately added and subtracted for the estimation of the H-bond energy. It has been shown that the typical error involved in the calculation is quite small (∼0.5 kcal/mol). In the present work, we employ both the MTA and the isodesmic/homodesmic approach for evaluating the intramolecular H-bond energies in a variety of systems with a view to making a systematic comparison of these two approaches. Further, the cooperative effects in the hydrogen bond interactions in these polyhydroxy compounds are also addressed.

Methodology

All the systems (except decitol; see below for clarification) in the present work are explored at the ab initio MP2 and the density functional theory (DFT) levels viz. B3LYP and MPWB1K employing the 6-311++G(2d,2p) basis set using the Gaussian 03 package of programs.[12] The estimation of intramolecular H-bond energies is carried out employing the MTA and the isodesmic reaction approach. Among the two DFT methods, B3LYP is frequently used for geometry optimization. However, recently it was suggested that MPWB1K is a reliable method for the analysis of weak bonding situations.[13] The intramolecular H-bond energies are also estimated at the MPWB1K level employing 6-31+G(d,p) and 6-311++G(2d,2p) basis sets. The 6-31+G(d,p) basis set is recommended for the use of the MPWB1K functional.[13] However, no such clear preferences of the basis set are mentioned for the other methods; hence calculations are also performed at the 6-311++G(2d,2p) basis set for checking the consistency of the results with other methods. It is expected that, with the use of additional polarization and diffuse functions in the basis set, a more accurate description of the weak bonding interactions, including

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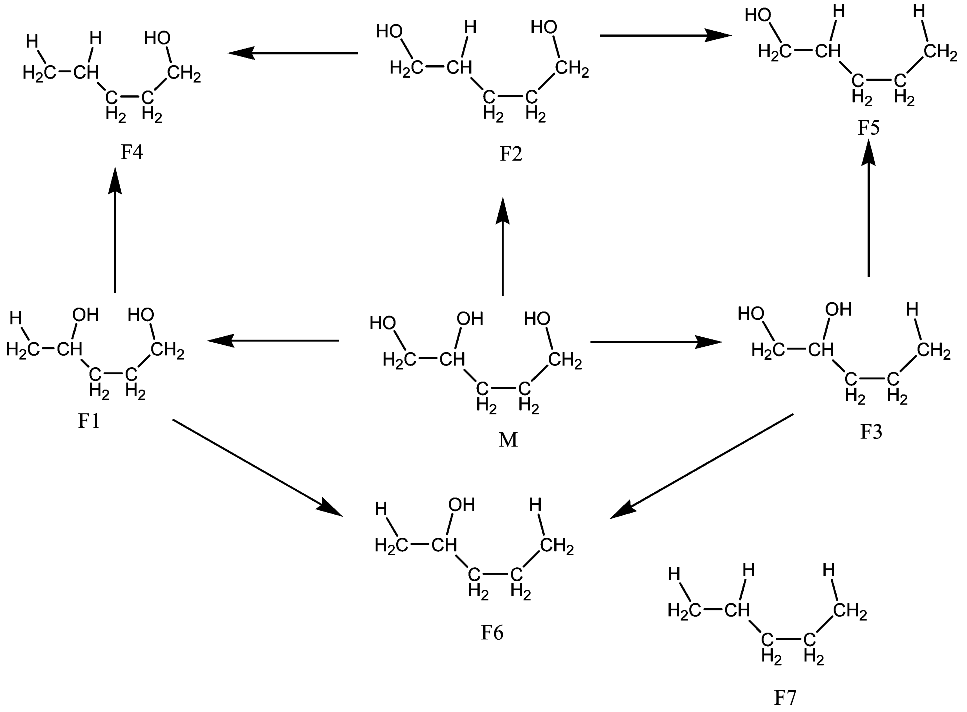


Figure 1. Fragmentation scheme for 1,2,5-pentanetriol (shown as M). See the text for the details of fragmentation. The energies of fragments F1−F7 and M at the MP2(full)/6-311++G(2d,2p) level are −347.543 917, −347.529 407, −347.537 512, −272.411 134, −272.409 820, −272.417 181, −197.292 318, and −422.665 903 au, respectively.

H-bonding, is achieved. All the optimized geometries at different levels have generally been verified to be local minima on the potential energy surface by carrying out frequency calculations. Moreover, for some selected cases, calculations are also performed at the G3MP2 level to obtain accurate energetics. The small systems selected in the present work are 1,2,5-pentanetriol, 1,2,3-propanetriol, and 1,2,3,4-butanetetraol. The calculations are also performed on three different conformers of decitol, wherein at least five different types of H-bonds are present at the MPWB1K and B3LYP levels employing a somewhat more economical 6-31++G(d,p) basis set. It is very difficult to write an appropriate homodesmic reaction for each H-bond in decitol; hence the method is not applied to this case.

The procedure for the estimation of intramolecular H-bond energies employing MTA is illustrated in Figure 1 for a test case of 1,2,5-pentanetriol molecule. Here, three overlapping fragments F1, F2, and F3 are generated from the original molecule (denoted "M" in Figure 1) by replacing an −OH group with a hydrogen atom. Fragments F4, F5, and F6 are obtained by taking the intersection (excluding the dummy atoms) of these basic fragments, i.e., (F1 ∩ F2), (F2 ∩ F3), and (F1 ∩ F3), respectively. The fragment F7 is the common intersection of three fragments F1, F2, and F3, i.e., (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 conformational changes in them are avoided. The total energy of the parent molecule (with the actual energy of E_M) is estimated within MTA 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 actual numerical results for E_e and the estimated H-bond energies are reported in the subsequent section.

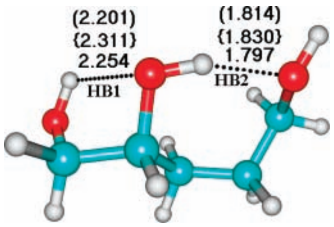


Figure 2. Optimized geometry of 1,2,5-pentanetriol at MP2/6-311++G(2d,2p) level. The values in the curly braces and parentheses are the H-bond lengths at the B3LYP/6-311++G(2d,2p) and MPWB1K/6-311++G(2d,2p) levels, respectively.

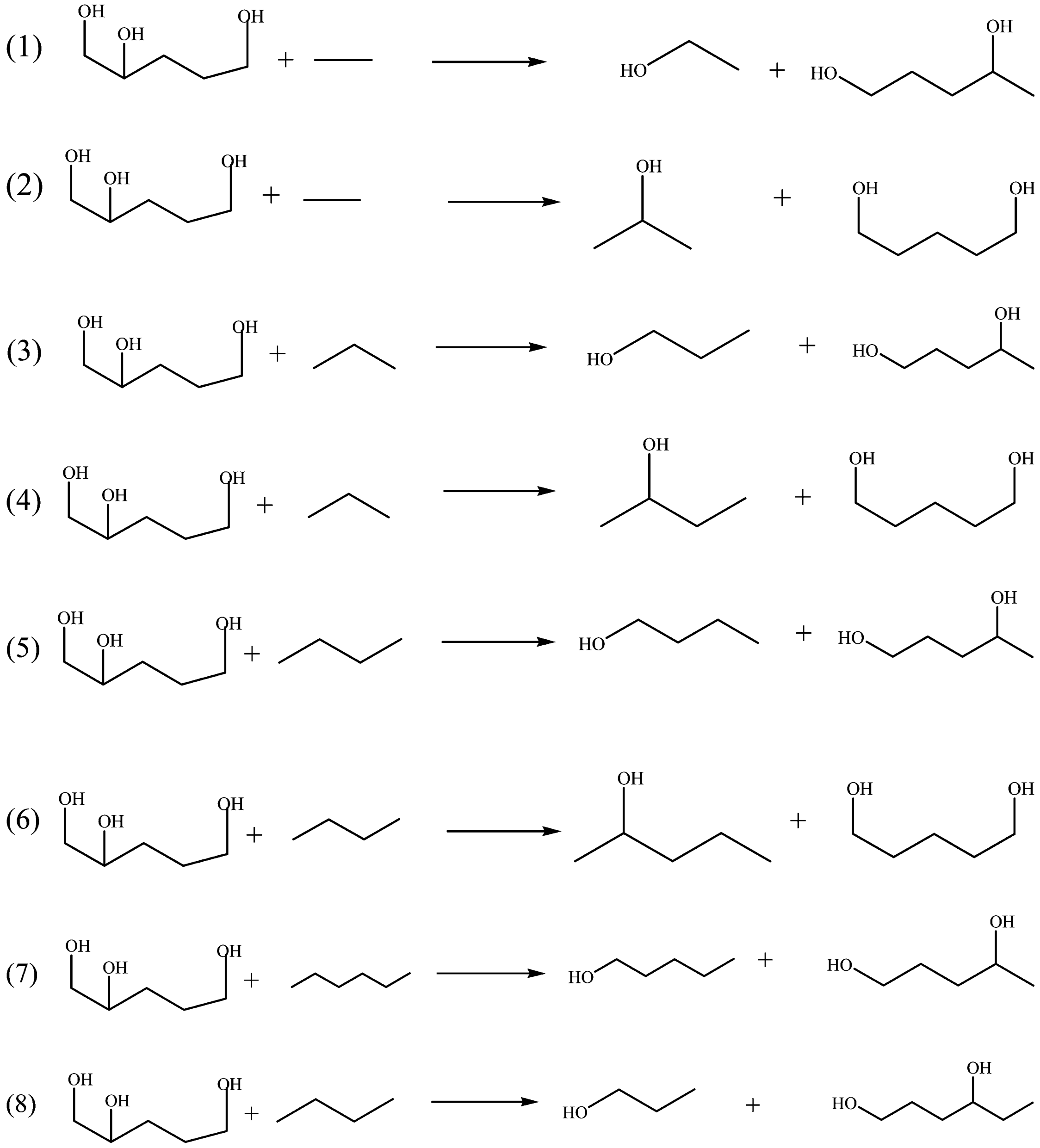
Results and Discussion

1,2,5-Pentanetriol. The optimized geometry of this molecule at the MP2 level is depicted in Figure 2 along with the two H-bond distances of HB1 (2.254 Å) and HB2 (1.797 Å), respectively. The shorter distance, HB2, is expected to be stronger than HB1. A similar observation is made at the B3LYP and MPWB1K levels of theory. For instance, at the B3LYP level, the HB1 and HB2 distances are 2.311 and 1.830 Å, respectively, whereas at the MPWB1K level the corresponding distances are 2.201 and 1.814 Å, respectively (Figure 2). The H-bond lengths are found to be shorter at the MP2 and MPWB1K levels than those at the B3LYP level.

Eight different isodesmic reactions, with the number of bonds and hybridization type of each atom on either side of the reactions conserved, are designed for evaluating the strength of hydrogen bond HB1. (Several other isodesmic schemes are also possible.) Reaction 8 (see Scheme 1) is a homodesmic reaction, i.e., an isodesmic reaction, which obeys more strict bonding conditions on the reactant and product sides. For instance, in reaction 8, there are two H_3C-CH_2, two H_2C-CH, two H_2C-OH, one $HC-OH$, and three H_2C-CH_2 bonds on either side of reaction.

Within the isodesmic reaction approach, geometries of all the reactants and products are optimized at the appropriate levels

SCHEME 1: Some Isodesmic Reactions for the Estimation of H-Bond Energy E_{HB1} in 1,2,5-Pentanetriol Molecule (See Text for Details)



of theory. The energy changes corresponding to these reactions can be taken as the H-bond energy E_{HB1}, since except HB1, nearly all other types of bonding features are conserved on both sides of the reactions. This means that if the system has multiple hydrogen bonds and one is interested in the H-bond energy of a particular H-bond, the isodesmic reactions are written in such way that all the remaining bonding features including the other H-bonds in the system are retained on the product side of the reaction. This is seen from the reactions given in Scheme 1, and the energies of these reactions would provide a good measure of the desired H-bond energy E_{HB1}. The calculated energies for these eight reactions are reported in Table 1. As seen from Table 1, the estimated values at the MP2 and MPWB1K levels are in the range of 1.84−2.51 kcal/mol, whereas the corresponding B3LYP values are smaller (1.21−1.80 kcal/mol). This is qualitatively consistent with the respective H-bond distances: 2.311 Å at the B3LYP level and 2.201 Å at the MPWB1K level.

The H-bond energy, E_{HB1}, in this molecule is also evaluated using the molecular tailoring approach (MTA)[11] employing a systematic fragmentation scheme for 1,2,5-pentanetriol as already discussed in the previous section (see Figure 1). The MP2(full)/6-311++G(2d, 2p) level approximate total energy of the molecule is evaluated as

$$E_e = E_{F1} + E_{F2} + E_{F3} - E_{F4} - E_{F5} - E_{F6} + E_{F7} \quad (1)$$

According to eq 1, the estimated energy E_e of 1,2,5-pentanetriol is −422.665 02 au, which is in good agreement with the actual energy of the molecule, E_M = −422.665 90 au, showing an error of 0.55 kcal/mol.

The H-bond energy E_{HB1} is given as

$$E_{HB1} = (E_{F1} + E_{F2} - E_{F4}) - E_e \quad (2)$$

Equation 2 can be reduced to eq 3 by substituting the value of E_e from eq 1 in it.

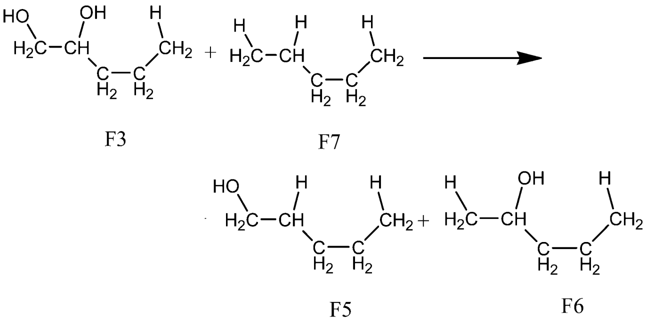
$$E_{HB1} = E_{F5} + E_{F6} - E_{F3} - E_{F7} = 1.78 \text{ kcal/mol} \quad (3)$$

TABLE 1: Estimated H-Bond Energy E_{HB1} (kcal/mol) in 1,2,5-Pentanetriol at Different Levels of Theory Using 6-311++G(2d,2p) Basis Set Applying Both Isodesmic Reaction (Scheme 1) and MTA Methods (See Text for Details)

	isodesmic reaction approach H-bond energy (E_{HB1})			
reaction no.	MP2(full)	MPWB1K	B3LYP	G3MP2
1	1.99	2.10 (2.54)[a]	1.27	1.64
2	2.51	1.94 (2.42)	1.21	1.77
3	2.10	2.25 (2.71)	1.50	1.78
4	2.19	1.94 (2.41)	1.55	1.63
5	2.21	2.41 (2.85)	1.63	1.92
6	2.19	2.05 (2.50)	1.64	1.67
7	2.15	2.34 (2.77)	1.58	1.86
8	1.84	2.23 (2.63)	1.80	1.70
	molecular tailoring approach H-bond energy (E_{HB1})			
	MP2(full)	MPWB1K	B3LYP	G3MP2
	1.78	2.25 (2.73)[a]	1.43	–

[a] The values in parentheses are the estimated H-bond energies at the 6-31+G(d,p) basis set.

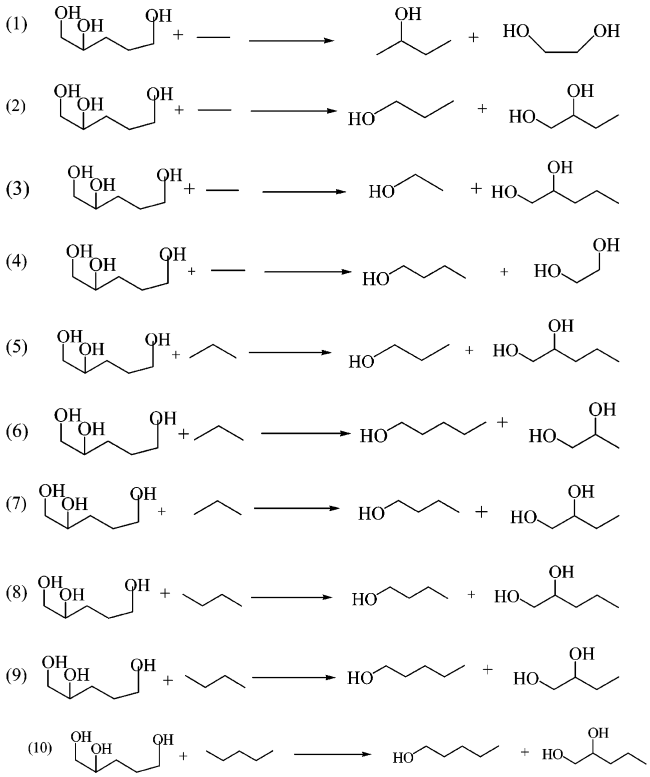
This means that E_{HB1} can be estimated using the chemical reaction given by



As we can see, the reaction is a homodesmic reaction with the restriction that all the molecular systems are fragment structures taken from the parent molecule. Since the fragments are not optimized within MTA, the structural position of atoms is also conserved in the reaction. In other words, the estimated energy (cf. Table 1) is expected to provide a good measure of the H-bond energy, E_{HB1}. As we can see from Table 1, the estimated H-bond energies at the different levels of theory are consistent with the H-bond distances (see Figure 2). Among the four different methods, the G3MP2 level value is the most accurate, and at this level, irrespective of the reaction chosen, the E_{HB1} value using the isodesmic reaction approach is found to be ~1.70 kcal/mol. The MTA method at the MP2 level gives nearly the same answer (1.78 kcal/mol) for the E_{HB1} value. At the MPWB1K level, this value is slightly higher (2.25 kcal/mol), while at the B3LYP level, the MTA value is slightly smaller (1.43 kcal/mol). It is not possible to estimate the single point G3MP2 value for the MTA fragments; hence G3MP2 cannot be used for MTA H-bond energy estimates. It is known that the B3LYP method performs poorly for weak bonding situations[14] and the small value of E_{HB1} verifies that. In general, it can be concluded that the MTA value obtained for this case (of HB1) is in good agreement with the E_{HB1} values obtained from the isodesmic reaction approach.

Also, as seen from Table 1, the estimated intramolecular H-bond energies by both MTA and the isodesmic reaction approach at the MPWB1K level employing the 6-31+G(d,p) basis set are higher than the corresponding values at the 6-311++G(2d,2p) basis set. Though there is a numerical difference in the values of the H-bond energies, the rank ordering at both basis sets is identical, suggesting that even though the use of the 6-31+G(d,p) basis set is recommended[13] for the MPWB1K level, the calculations employing the 6-311++G(2d,2p) basis set are consistent with the other levels and basis sets studied in the present work.

SCHEME 2: Some Possible Isodesmic Reactions for the Estimation of H-Bond Energy E_{HB2} for 1,2,5-Pentanetriol Molecule



Ten isodesmic reactions were similarly designed for estimating E_{HB2} in 1,2,5-pentanetriol and are shown in Scheme 2. Except for HB2, most of the other bonding features are conserved on both sides of the reaction, and therefore the energy of the reaction would yield E_{HB2}. Reaction 8 in Scheme 2 is a homodesmic one, following more strict conditions as discussed for homodesmic reactions for HB1. The calculated H-bond energies for these isodesmic reactions at different levels are reported in Table 2. As seen from Table 2, the calculated energies using the isodesmic reactions presented in Scheme 2 are consistent with the HB2 bond distance at different levels of theory. The shortest distance is found at the MP2 level having the strongest H-bond, and the longest distance is found at the B3LYP level having the weakest H-bond among these three different levels of theory. The E_{HB2} H-bond energies lie between 1.68 and 3.42 kcal/mol at all these levels of theory.

The H-bond energy E_{HB2} is also estimated by the MTA method using the same set of fragments as shown in Figure 1. Here eq 4 yields E_{HB2}.

$$E_{HB2} = (E_{F2} + E_{F3} - E_{F5}) - E_e \tag{4}$$

Equation 4 is reduced to eq 5 with an appropriate substitution of E_e.

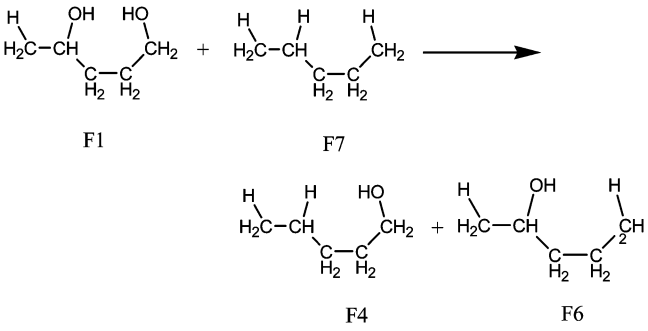
$$E_{HB2} = E_{F4} + E_{F6} - E_{F1} - E_{F7} \tag{5}$$

TABLE 2: Estimated H-Bond Energy E_{HB2} (kcal/mol) in 1,2,5-Pentanetriol at Different Levels of Theory Using 6-311++G(2d,2p) Basis Set Applying Both Isodesmic Reaction (Scheme 2) and MTA Methods

	isodesmic reaction approach H-bond energy (E_{HB2})			
reaction no.	MP2(full)	MPWB1K	B3LYP	G3MP2
1	3.14	2.22 (3.08)[a]	1.97	2.04
2	2.88	1.98 (2.90)	1.82	1.96
3	3.42	2.03 (2.73)	1.89	2.21
4	3.40	2.13 (2.97)	1.68	2.22
5	2.99	2.13 (3.07)	2.05	2.10
6	3.17	2.14 (2.99)	1.76	2.08
7	3.36	2.19 (2.91)	2.09	2.24
8	3.11	2.28 (3.21)	2.18	2.24
9	3.30	2.19 (3.12)	2.10	2.20
10	3.04	2.22 (3.13)	2.13	2.17
	molecular tailoring approach H-bond energy (E_{HB2})			
	MP2(full)	MPWB1K	B3LYP	G3MP2
	4.97	4.50 (5.37)[a]	4.69	−

[a] The values in parentheses are the estimated H-bond energies at the 6-31+G(d,p) basis set.

Equation 5 may be described by the following reaction:



This is again a homodesmic reaction wherein only the fragments of the parent molecules are employed for estimating the H-bond energy. The estimated H-bond energy E_{HB2} is 4.97 kcal/mol at the MP2(full) level. The H-bond energies at the B3LYP and MPWB1K levels are 4.69 and 4.50 kcal/mol. Thus the MTA-based hydrogen bond energies at all three different levels of theory are consistent with one another.

The H-bond energy values E_{HB2} calculated using the isodesmic reactions are much smaller (typically by about 40−50% smaller) than those estimated using the MTA method. On the contrary, the E_{HB1} isodesmic values are mostly in good agreement with the respective MTA energies. The reason for such a discrepancy is clear if one looks carefully at the isodesmic reactions in Schemes 1 and 2. As seen from Scheme 1, most of the chain or ring part due to the 2−4-type of H-bond present in the parent molecule is retained on the product sides of the reactions, enabling the conservation of the strain effect on both the reactant and the product sides. However, ring strain due to the H-bond (HB1) whose energy has to be estimated is not preserved on the product side. Therefore, the estimated E_{HB1} is not just the pure H-bond energy, but it also includes the ring strain in the parent molecule due to a 1,2-type vicinal H-bond. However, such a stain effect from a 1,2-vicinal H-bond is very small compared to the ring strain in a 2−4-type H-bond, meaning that the estimated H-bond energies E_{HB1} are close to those obtained from the MTA energy. Similarly, in the case of reactions presented in Scheme 2 for E_{HB2}, the strain effect due to the 2−4-type H-bond is not preserved while the 1,2-type H-bond is preserved on the product side. Therefore, the molecules on the product side are more relaxed, losing most of their ring strain due to loss of the 2−4 H-bond. Hence, the finer effects of the bonding situation are not mimicked properly on either side of the reaction, resulting in poor estimates of H-bond energies of E_{HB2}. On the contrary, in the MTA method, the positioning of atoms is the same on either side of the reaction, resulting in cancellation of ring strain, giving true estimates of H-bond energies. In other words, the isodesmic reactions, as advocated in the literature, do not yield the true H-bond energies. In fact, this can be considered as the main drawback of the isodesmic approach for estimating the hydrogen bond strengths in multiply hydrogen bonded systems.

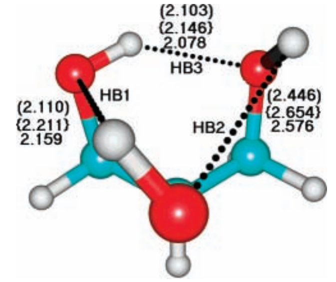


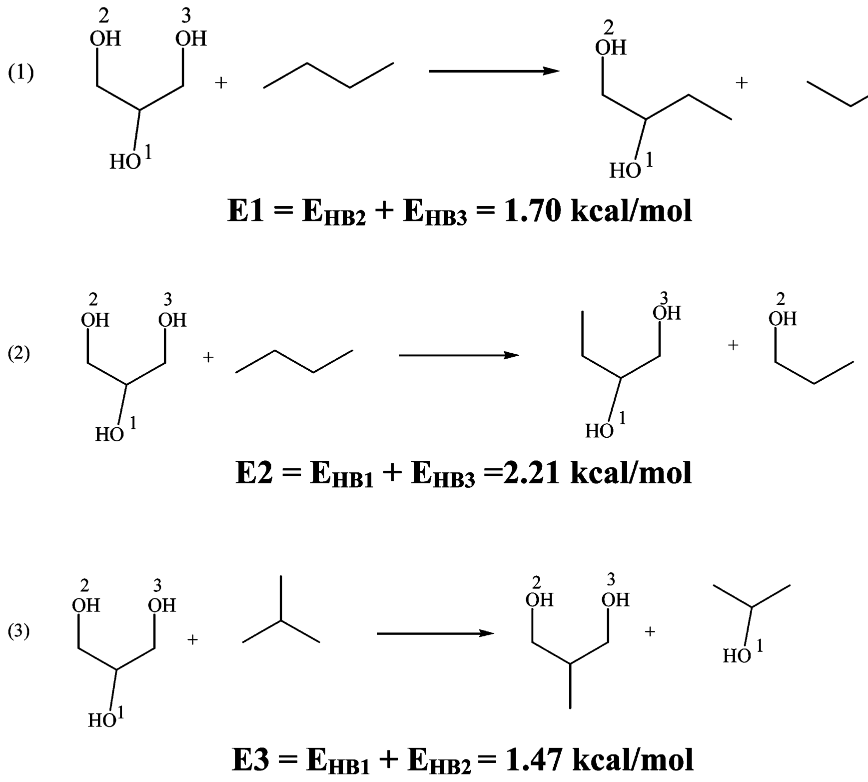
Figure 3. Optimized geometry of 1,2,3-propanetriol at MP2/6-311++G(2d,2p) level. The values in the curly braces and parentheses are the H-bond lengths at the B3LYP/6-311++G(2d,2p) and MPWB1K/6-311++G(2d,2p) levels, respectively.

1,2,3-Propanetriol. The optimized geometry of this molecule at the MP2 level is shown in Figure 3, displaying three H-bonds, viz., HB1, HB2, and HB3. HB3 is the shortest among them, and it is expected to be stronger than the other two H-bonds. On the basis of bond length data, the next stronger H-bond should be HB1. In general, the H-bond lengths obtained at the MPWB1K level are shorter than those at the MP2 and B3LYP levels (HB3 is an exception).

To quantify the H-bond strengths, three homodesmic reactions are selected (Scheme 3). It may be noted that, among the three reactions in Scheme 3, none gives the strength of a particular H-bond. For instance, in reaction 1, the H-bond between OH1 and OH2 is present in the product side and, therefore, the energy of the reaction is $E_{\mathrm{HB2}} + E_{\mathrm{HB3}}$. Similarly, reactions 2 and 3 give $E_{\mathrm{HB1}} + E_{\mathrm{HB3}}$ and $E_{\mathrm{HB1}} + E_{\mathrm{HB2}}$, respectively.

Thus the combination of the three reactions and simple arithmetic would yield the values of E_{HB1}, E_{HB2}, and E_{HB3}. Although the reactions in Scheme 3 are easy to model, the situation becomes increasingly complicated when more H-bonds are interconnected in a molecule. Even for 1,2,3-propanetriol, one cannot write just a single reaction pertaining to a particular H-bond because the removal of one particular −OH group will remove at least two H-bonds. As for the previous cases, the calculated H-bond energies at different levels of theory are given in Table 3 and are consistent with the H-bond distances. Although this is the expected trend, the H-bond energy values are significantly smaller than the related values obtained in the case of 1,2,5-pentanetriol. For instance, the vicinal H-bond of length 2.201 Å (HB1) obtained in the case of 1,2,5-pentanetriol at the MPWB1K level is found to be much higher in energy ($E_{\mathrm{HB1}} = 2.23$ kcal/mol) than the very similar vicinal H-bond of length 2.110 Å obtained at the same level of theory in the case of 1,2,3-pentanetriol ($E_{\mathrm{HB1}} = 1.34$ kcal/mol). Therefore, it is felt that combining several reactions to obtain the H-bond strength may decrease the accuracy of the final result. Another reason is the larger strain effect in 1,2,3-pentanetriol compared

SCHEME 3: Best Possible Homodesmic Reactions for Estimating the H-Bond Energies in 1,2,3-Propanetriol Molecule at the MP2(full)/6-311++G(2d,2p) Level of Theory



$E1 = E_{HB2} + E_{HB3} = 1.70$ kcal/mol

$E2 = E_{HB1} + E_{HB3} = 2.21$ kcal/mol

$E3 = E_{HB1} + E_{HB2} = 1.47$ kcal/mol

TABLE 3: Estimated H-Bond Energies (kcal/mol) in 1,2,3-Propanetriol at Different Levels of Theory Using 6-311++G(2d,2p) Basis Set Applying Both Isodesmic Reaction (Scheme 3) and MTA Methods (See Text for Details)

H-bond energy	MP2(full)	MPWB1K	B3LYP	G3MP2
Isodesmic Reaction Approach H-Bond Energies				
E_{HB1}	0.99	1.34 (1.44)[a]	0.81	0.65
E_{HB2}	0.48	1.21 (1.21)	0.65	0.36
E_{HB3}	1.22	1.41 (1.67)	0.99	0.81
Molecular Tailoring Approach H-Bond Energies				
E_{HB1}	1.90	2.33 (2.73)[a]	1.49	–
E_{HB2}	1.63	2.03 (2.26)	1.16	
E_{HB3}	2.47	2.55 (3.17)	2.24	

[a] The values in parentheses are the estimated H-bond energies at the 6-31+G(d,p) basis set.

to 1,2,5-pentanetriol because of the interconnected nature of the H-bonds in the former and this strain effect is not properly accounted for in the product side of the reactions presented in Scheme 3.

The H-bond energies in 1,2,3-propanetriol using the MTA method are given in Table 3. The gratifying point is that the estimated MTA values are consistent with the corresponding H-bond lengths (Figure 3). The values obtained at the MPWB1K level are higher compared to those obtained at other levels, while the lowest H-bond energies are obtained at the B3LYP level. It may be noted that the previously discussed discrepancy in the H-bond energy of HB1 in 1,2,3-pentanetriol and 1,2,5-pentanetriol is not seen in the MTA, suggesting that the energetic trends of various H-bonds are well explained by this method.

1,2,3,4-Butanetetraol. In this molecule, two different kinds of H-bonds are present, viz. vicinal HB1 and HB2 and nonvicinal HB3 and HB4 (Figure 4). Two homodesmic reactions shown in Scheme 4 are written in such a way that the first will give the total energy of the two nonvicinal H-bonds and the second will give the total energy of the two vicinal H-bonds. Since the optimized structure is symmetric with respect to the H-bond distribution, the energy of individual H-bonds is equal to half of the energy of the reaction. The calculated H-bond energies at different levels of theory are given in Table 4. As expected from the H-bond distances, the nonvicinal H-bonds are found to be stronger than the vicinal H-bonds ($E_{HB1} = E_{HB2} = 1.59$ kcal/mol and $E_{HB3} = E_{HB4} = 2.50$ kcal/mol at the MP2 level of theory). The energy values estimated at the G3MP2 level of theory are smaller compared to the ones obtained from other levels. The H-bond energies obtained using the MTA are also given in Table 4. The values at the MP2 level of theory are 2.76 kcal/mol for both HB1 and HB2 and 3.59 kcal/mol for both HB3 and HB4. The estimated MTA energies are larger than the corresponding homodesmic energies. The discrepancy in the homodesmic and MTA values may be due to the inherent problems that are associated with the homodesmic reaction approach.

Thus, a careful study of all the above test cases, viz. 1,2,5-pentanetriol, 1,2,3-propanetriol, and 1,2,3,4-butanetetraol, brings us to the conclusion that the isodesmic/homodesmic reaction approach as popularly practiced today is not a good method

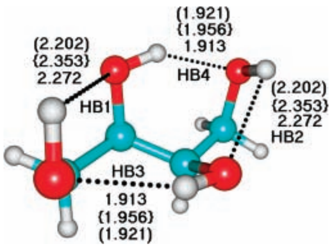
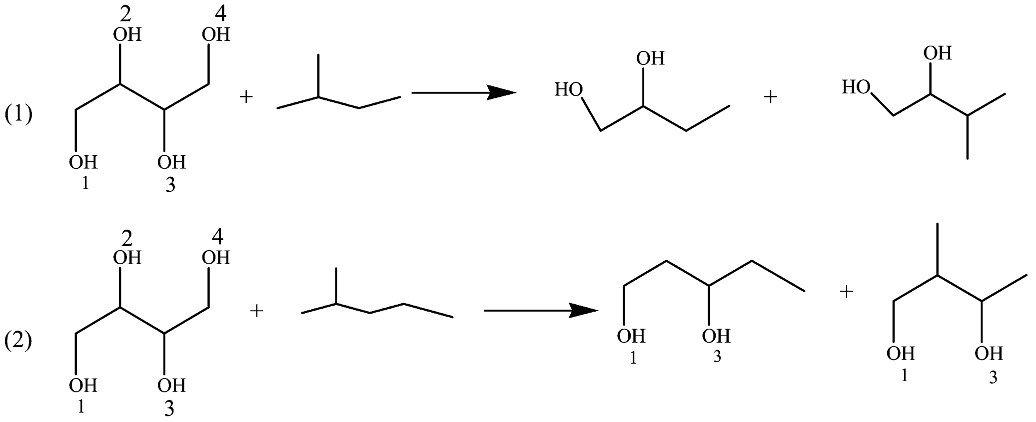


Figure 4. Optimized geometry of 1,2,3,4-butanetetraol at MP2/6-311++G(2d,2p) level. The values in the curly braces and parentheses are the H-bond lengths at the B3LYP and MPWB1K1 levels (with identical basis set), respectively.

SCHEME 4: Best Possible Homodesmic Reactions for the Estimation of H-Bond Energies in 1,2,3,4-Butanetetraol Molecule



$$E_1 = E_{HB3} + E_{HB4} \qquad E_{HB3} = E_{HB4} = E_1/2$$

$$E_2 = E_{HB1} + E_{HB2} \qquad E_{HB1} = E_{HB2} = E_2/2$$

TABLE 4: Estimated H-Bond Energies (kcal/mol) in 1,2,3,4-Butanetetraol at Different Levels of Theories Using 6-311++G(2d,2p) Basis Set Applying Both Isodesmic Reaction (Scheme 4) and MTA Methods

H-bond	MP2(full)	MPWB1K	B3LYP	G3MP2
	Isodesmic Reaction Approach H-Bond Energies			
E_{HB1}	1.59	2.16 (2.27)[a]	1.60	1.27
E_{HB2}	1.59	2.16 (2.27)	1.60	1.27
E_{HB3}	2.50	2.44 (2.86)	1.98	1.86
E_{HB4}	2.50	2.44 (2.86)	1.98	1.86
	Molecular Tailoring Approach H-Bond Energies			
E_{HB1}	2.76	3.32 (3.72)[a]	2.22	–
E_{HB2}	2.76	3.32 (3.72)	2.22	
E_{HB3}	3.59	3.57 (4.08)	3.27	
E_{HB4}	3.59	3.57 (4.08)	3.27	

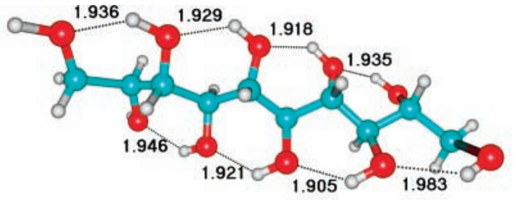
[a] The values in parentheses are the estimated H-bond energies at the 6-31+G(d,p) basis set.

for the estimation of H-bond energy for multiply H-bonded intramolecular systems. On the other hand, the H-bond energy values obtained using MTA are more convincing with respect to the respective H-bond lengths. Moreover, the MTA method is very simple and avoids the cumbersome job of designing appropriate isodesmic reactions for complicated multiply H-bonded systems.

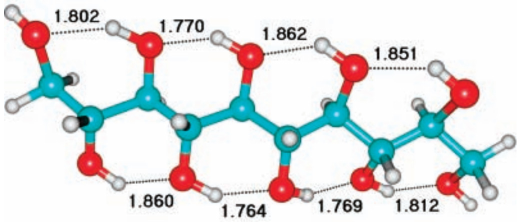
Decitol. To illustrate the utility of the MTA approach to a more complicated problem, a larger test molecule, viz. decitol, was chosen. It is nearly impossible to come up with a simple isodesmic scheme for estimating the H-bond energies in this molecule. Although several conformations are possible for this molecule, for illustrative purposes, we restrict our calculations to only three different conformations. Further, owing to the large size of the system, optimization and subsequent computation are done at the more affordable B3LYP and MPWB1K levels employing the 6-31++G(d,p) basis set.

The MPWB1K/6-31++G(d,p) level optimized geometries of the three conformations are shown in Figure 5, along with all the H-bond lengths. Frequency runs have not been carried out for these conformers. In conformer 1, all the O−H···O bonds are arranged in the same direction, while in conformers 2 and 3 the O−H···O bonds above and below the molecular backbone are pointing in opposite directions. In conformer 3, two extra vicinal O−H···O bonds are present. The order of stability in terms of total energy is conformer 3 > conformer 2 > conformer 1. In all the conformers, the H-bonds in the middle region of the molecule are shorter than those in the terminal regions, suggesting higher strength for the former compared to the latter. The MTA-based H-bond energies along with the respective H-bond distances are tabulated in Table 5 for all the conformers.

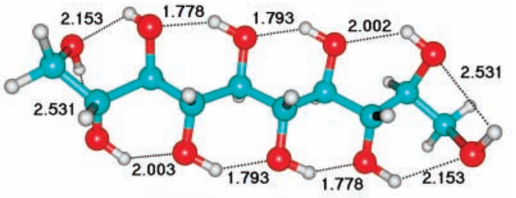
From Table 5, it can be seen that the MPWB1K level H-bond energies lie between 2.34 and 5.84 kcal/mol. As discussed before, the terminal H-bonds are seen to be weaker than the middle H-bonds, in accordance with the H-bond distances (cf. Table 5). This is predominantly seen in all three conformers. In conformer 3, obviously the vicinal H-bonds are the weakest (2.34 kcal/mol) as they show the largest H-bond length of 2.531 Å, justifying the above statement. However, in general, no particular trend is seen between the estimated H-bond energies and the respective H-bond lengths. In Table 5, the H-bond energies for three different conformers of decitol at



Decitol –Conformer-1



Decitol –Conformer-2



Decitol –Conformer-3

Figure 5. Optimized geometries of three different conformers of decitol at MPWB1K/6-31++G(d,p) level. H-bond distances are in angstroms. See the text and Table 5 for the details.

TABLE 5: Estimated H-Bond Energies (kcal/mol) in Decitol Conformers (cf. Figure 5) at Different Levels of Theories Using 6-31++G(d,p) Basis Set Applying MTA, and Respective H-Bond Distances (in angstroms)

B3LYP		MPWB1K	
H-bond distance	E_{HB} using MTA	H-bond distance	E_{HB} using MTA
Conformer 1; $E_M = -1146.075\ 78$ au[a] ($E_M = -1146.599\ 90$ au)[b]			
1.928	3.89	1.935	4.05
1.888	4.48	1.918	4.78
1.895	4.61	1.929	5.06
1.909	4.05	1.936	4.54
1.991	3.79	1.946	4.87
1.885	4.44	1.921	5.02
1.888	4.53	1.905	4.78
1.925	4.14	1.983	4.36
Conformer 2; $E_M = -1146.078\ 95$ au[a] ($E_M = -1146.606\ 29$ au)[b]			
1.834	4.59	1.851	4.51
1.739	4.82	1.862	5.79
1.739	5.17	1.770	5.15
1.806	4.42	1.802	4.49
1.804	4.46	1.860	4.95
1.745	5.35	1.764	5.52
1.740	5.22	1.769	5.84
1.826	4.52	1.812	4.17
Conformer 3; $E_M = -1146.088\ 31$ au[a] ($E_M = -1146.610\ 53$ au)[b]			
2.692	1.65	2.531	2.34
2.021	4.68	2.003	5.23
1.788	5.05	1.793	5.19
1.780	5.07	1.778	4.99
2.176	4.08	2.153	4.70
2.692	1.65	2.531	2.34
2.021	4.68	2.003	5.23
1.788	5.05	1.793	5.19
1.780	5.07	1.778	4.99
2.176	4.08	2.153	4.70

[a] Absolute energies of the conformers at the MPWB1K level. [b] Absolute energies of the conformers at the B3LYP level.

the B3LYP level are also reported. The H-bond energies at the B3LYP level are seen to be in general smaller than the corresponding values at the MPWB1K level.

The MTA-based H-bond energy values can be used for interpreting the energetic preference of one conformer over another. For instance, in conformer 1, the sum of all the H-bond energies is 37.46 kcal/mol and the corresponding sums for conformer 2 and conformer 3 are 40.42 and 44.90 kcal/mol. The individual energy values of conformers 1−3 at MPWB1K/6-31++G(d,p) are −1146.075 78, −1146.078 95, and −1146.088 31 au, respectively. Thus conformer 3 is more stable by 7.86 and 5.87 kcal/mol compared to conformer 1 and conformer 2, respectively. This is qualitatively in accordance with the energetic difference between the corresponding sums of the H-bond energy. Also, the energetic difference between conformer 1 and conformer 2 is 1.99 kcal/mol, which is in fair agreement with the corresponding difference in the sums of H-bond energies (2.96 kcal/mol). Thus not only the strength of H-bond energies but also the energetic differences between the different conformers of decitol is also qualitatively explained by the molecular tailoring approach.

Cooperative Interaction Energy. Cooperative effect of H-bond interaction is operative in a system when the nature of one H-bond is influenced by the presence of another H-bond. This effect is inherent in all the multiply H-bonded systems containing intramolecular hydrogen bonds. For instance, in the case of 1,2,5-pentanetriol, the replacement of OH at the fifth position by H has led to the elongation of the HB1 bond length from a value of 2.254 to 2.282 Å (Figure 6a). Similarly, in the same molecule substituting OH at the first position with H, the HB2 bond length is changed to a value of 1.839 from 1.797 Å (Figure 6b). Even if we remove the HB1 H-bond in 1,2,5-pentanetriol by simple rotation of the C1−C2 bond such that the O1−C1−C2−O2 dihedral angle is 180° (Figure 6c), the HB2 bond shows a weakening of its strength as it shows an elongation by a small amount of 0.033 Å (MP2 result). This means that the interconnected nature of the H-bond arrangements is indeed helping the system to achieve higher stability. However, this is attained at the cost of some amount of ring strain in the system.

It was earlier noted that the estimated H-bond energies using the isodesmic approach are always less than the corresponding value obtained by MTA. This is predominantly seen from the example of 1,2,5-pentanetriol wherein the E_{HB1} calculated using the isodesmic approach (1.70 kcal/mol at the MP2 level) is close to the MTA value (1.78 kcal/mol at the MP2 level). However, the E_{HB2} isodesmic value (3.11 kcal/mol at the MP2 level) is much less than the MTA value (4.95 kcal/mol at the MP2 level). This discrepancy arises because the ring strain effect cannot be properly accounted for on the product side of an isodesmic reaction scheme due to the loss of one or more H-bond interactions. In other words, the isodesmic/homodesmic approach to the evaluation of H-bond strength is seen to suffer from the serious defect of not incorporating the cooperative effect. Compared to the isodesmic approach, the strain effect is nearly conserved in the MTA method as it uses the fragments derived from the parent molecule to complete the homodesmic reaction scheme. Therefore, the difference between the isodesmic H-bond energy and the corresponding MTA H-bond energy can be considered as a good measure of the strain energy that a molecule experiences due to the cooperative interactions arising from the interconnected H-bonds. According to this argument, the strain effect is causing an energetic destabilization of 0.08 kcal/mol in the 1,2-vicinal H-bond (HB1) and 1.84 kcal/mol for the 2−5 H-bond (HB2) in 1,2,5-pentanetriol.

Concluding Remarks

In the present study, the intramolecular H-bond energies in various polyhydroxy systems are estimated using the isodesmic reaction approach (as advocated in the literature) and the molecular tailoring approach at various levels of theory employing the 6-311++G(2d,2p) basis set. On the basis of energetics of the H-bond, a systematic comparison of the isodesmic reaction and molecular tailoring approaches is carried out. It has been shown that the use of the isodesmic reaction approach does not give a true representation of H-bond energies but

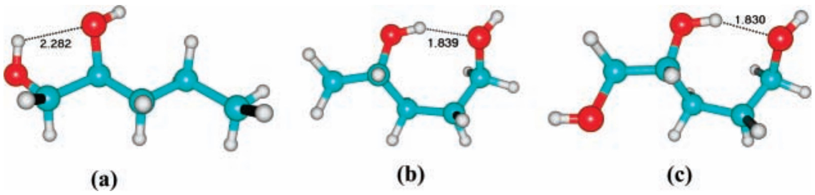


Figure 6. Optimized geometry of (a) 1,2-pentanediol, (b) 1,4-pentanediol, and (c) conformation of 1,2,5-pentanetriol at MP2/6-311++G(2d,2p) level of theory.

incorporates the inherent ring strain in the system due to formation/breaking of intramolecular H-bonds. This strain is more predominant when there is a formation of network of H-bonds in more complicated systems. On the contrary, the H-bond energies estimated using the MTA are free from such strain. The H-bond energies estimated using both the isodesmic/homodesmic reaction approach and MTA are consistent with the respective H-bond distances. It is difficult to write a single isodesmic/homodesmic reaction pertaining to a particular H-bond in a system in which there is an interlinked network of H-bonds, e.g., 1,2,3-propanetriol. Instead, energies of different homodesmic reactions are added and subtracted to obtain the H-bond energies in 1,2,3-propanetriol. It is nearly impossible to write the isodesmic/homodesmic reaction for an individual H-bond in multiply intramolecular H-bonded systems such as decitol. The H-bond energies obtained using MTA are able to explain not only the H-bond strength of individual H-bonds but also the energetic trends in the various conformers of decitol based on the difference in sums of H-bond energies in these conformers.

In conclusion, the isodesmic reaction approach as advocated in the literature is not recommended for estimating the intramolecular H-bond energy in polyhydroxy systems. The molecular tailoring approach yields more reliable H-bond energy values and can be easily applied to any complicated H-bonded systems with large numbers of OH···OH interactions. In fact, the methodology developed in this work could be exploited for any system containing intramolecular H-bonds. This offers several interesting possibilities for exploring intramolecular interactions in large biomolecules.

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Supporting Information Available: Geometric parameters. This material is available free of charge via the Internet at http://pubs.acs.org.

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