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Estimation of the Intramolecular O−H···O═C Hydrogen Bond Energy via the Molecular Tailoring Approach. Part I: Aliphatic Structures

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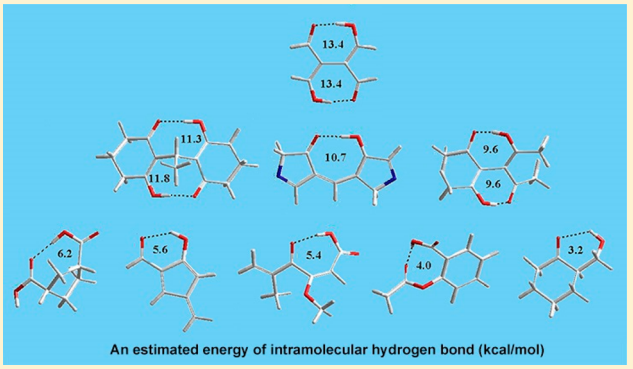
Supporting Information

ABSTRACT: A simple and universal method for the estimation of the intramolecular hydrogen bond (HB) energy (E_{HB}) in hydroxycarbonyl aliphatic compounds is proposed by the application of the molecular tailoring approach (MTA) based on calculations at the second-order Møller−Plesset MP2 level. The calculation of E_{HB} can be realized by the one optimization and three single point calculations of the energy for each compound with carbonyl and hydroxyl groups involved in HB. The intramolecular hydrogen bond energies estimated for 153 structures (of 102 compounds) ranged from 1.4 to 13.7 kcal/mol for systems without resonance-assisted hydrogen bonding (RAHB). To verify the method, we show the correlations of the energy (E_{HB}) in six-, seven-, and eight-membered HB rings in the optimized multifunctional molecules with the usual geometry descriptors of hydrogen bonds. Moreover, topological parameters from the atoms in molecules (AIM) theory and the calculated infrared and proton NMR spectra are correlated. The effects of conjugation and π-electron delocalization, bifurcation, and cooperativity are discussed, along with the correlation between the strength and geometrical parameters of H bonding.



INTRODUCTION

Hydrogen bonding has been one of the most interesting areas of research, primarily due to its crucial role in governing the shapes, properties, and functions of biomolecules. It affects many chemical, physical, and biological systems and processes.[1−3] Thus, methods that allow the prediction of the hydrogen bond strength directly from the molecular structure are particularly helpful in understanding and anticipating the molecular disposition for anticipated interactions.

There are many definitions of the nature, diversity, and range of the strength of hydrogen bonds[4−8] resulting from the covalent three-center four-electron bond and the electrostatic attraction and repulsion interactions between electron-rich groups. *Intramolecular* and *intermolecular* hydrogen bonds can also function as *cooperative* HB, three-center donor (*bifurcated*) HB and three-center acceptor (*anticooperiative*)[2,4,9−11] hydrogen bonds. A special class of intramolecular hydrogen bonds predicted to be very strong because the neutral donor and acceptor atoms are linked by a system of π-conjugated double bonds was defined by Gilli[12,13] as a *resonance-assisted hydrogen bond* (RAHB). The investigations by many authors[8,14,15] have established that RAHB systems by their aromaticity numerical descriptors (aromaticity indices[8]) fulfill (at least partially) the conditions of the aromatic π-electron delocalization; therefore, they can be treated as quasi-aromatic.

The energy of intermolecular interactions is typically investigated through a supermolecular approach in which the interaction enthalpy is evaluated as the difference between the energies of a supermolecular complex and its fragments, but this approach cannot be used to study intramolecular interactions. Direct and indirect attempts for determining the strength of the intramolecular hydrogen bond have been reported in the literature,[12,13,16−19] as extensively studied by a remarkable variety of methods, including X-ray,[12,13,20−22] electron,[23] and neutron diffraction,[21] combustion calorimetry,[24] NMR,[25−27] Raman, and IR[16−20,25,28,29] spectroscopy. Many of these characteristics are correlated with the strength of the hydrogen bond. In addition, it appears that any parameter affecting the electron density of the HB ring will change the hydrogen bond strength.[28] From a spectroscopic perspective, the O−H stretching vibrational mode shifts to the red[17,30] were frequently used for the E_{HB} estimation.

One of the first observations of hydrogen bonding noted that the O···O distance is, with certain exceptions, a reliable indicator of intramolecular HB strength.[31−34] The synthetic parameter Q introduced by Gilli and co-workers[12,13,35] for the description of the RAHB intramolecular H bonds in the enols of β-diketone (π-delocalization of the O═C−C═C−OH

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enolone fragment) can be calculated with considerable accuracy by considering the C−O, C−C, C=C, and C=O crystallographic distances in the HB rings.[18,36] However, correlations between the Q parameter and the H bond energy[37] are not always present; the same is true for the various modified Lippincott−Schroeder models.[9,31]

Hydrogen bonding may be considered a special class of Lewis acid−base interactions.[38,39] Many examples define the role of the hydrogen bond based on the acidity−basicity concept in the properties of interest for drug design. Laurence[38] described in detail the hydrogen bond basicities of functional groups relevant to medicinal chemistry. Recently, the empirical appreciation of the bond strength according to the $pK_a(H_2O)$ equalization principle was used for the prediction of H bond strengths from the acid−base parameters of the interacting partners.[24,39]

The most common approach for the investigation of the energetics of intramolecular H bonds is based on analysis performed by ab initio methods.[22,30,40,41] Generally, the strength of the hydrogen bond is calculated as the difference between the enthalpies of the structures with and without this bond.

Extensive investigations were performed using hybrid density functional theory (DFT) methods,[28,29,37,40−43] neglecting the entropy of conformational changes, at medium and high basis sets and further with higher-level methods, such as the second-order Møller−Plesset (MP2)[44] calculations, providing the best benchmark for comparisons. The Møller−Plesset methods can be considered excellent tools for the study of the HB model; however, the MP2 optimization of large systems can be computationally expensive. It has been demonstrated to be significantly suitable by predicting vibrational frequencies that match outstandingly well with the available experimental data.[18,28,29] The geometry optimizations and frequency predictions were performed with the B3LYP[45,46] and B3P86 hybrid functionals[1] using different[12,33,37,40,43,47−50] basis sets. In terms of the basis sets to be used, the inclusion of polarization and diffuse functions appears to be required to obtain reasonable results, and in that sense, 6-31+G(d) would be the minimum basis set required to study large biological HB systems.[10] Certain[51] theoretical results explicitly show that the zero point vibrational energy (ZPVE) has no significant effect when comparing conformers of the same compound.

The analysis of the natural bond orbitals (NBO), which describe bonding localized orbitals with maximum electron density, developed by Weinhold[52] over the last two decades has become one of the strongest tools available to evaluate intramolecular interactions.[53]

The topological properties of the electron density at bond critical points (BCP) have been evaluated by the analysis of charge densities from diffraction data.[21,40] It appears that characteristics of critical points derived from the Bader[54] theory are especially useful as descriptors of H bonds. The theory of atoms in molecules (AIM), known as the quantum theory of atoms in molecules (QTAIM), implemented in the AIM2000[55] and AIMAll[56] programs, along with ab initio DFT or MP2[45,46,57] calculations with the analysis of the geometrical, energetic, and topological data, enable the description of H bridges by different types of indicators of the H bond strength factor.[28,34−37,40−44,49] The AIM calculations appear to be basis set independent[58] and are very helpful for large systems. Initially, the presence of a BCP between a H atom and an acceptor atom was not considered as a criterion for a bonding interaction and, particularly, for HB.[57] Currently, it is widely accepted that the interatomic interactions, such as hydrogen bonds, can be adequately described and classified by the electron density ρ at the (3,−1) critical points.[10,41−44,50,59−63] In addition, the ring critical points (RCP) found in the intramolecular HB region play a role in the estimation of interaction by reinforcing the binding for intermolecular bifurcated HBs[10] and for compounds with RAHB.[37] Fazli[36] found that the topological characteristics of the RCP are useful for the estimation of the strength of the intramolecular H bond, even in two-ring (chelated intramolecular HB) systems. The electron density and other AIM parameters at the RCP correlate with aromaticity indices and can be used for the estimation of the electron delocalization effect in aromatic and quasiaromatic ring systems.[8,64]

Recently, certain[50,65] calculations of the energy of an intramolecular HB were performed by the *related rotamers method* (RRM) based on the relative energies of related (closed−open) conformers of salicyl and malonic aldehyde derivatives. Although a good linear correlation was found among the calculated HB energy, selected geometrical and topological parameters, and NBO charge transfer energy of the investigated molecule, the authors[50] concluded that the RRM energies overestimate the hydrogen bond energies.

The most commonly used method to estimate the energy of the intramolecular HBs is based on the following comparative analysis. For two conformers that essentially differ by the presence of one intramolecular HB, the energy (or the enthalpy) of the bond is estimated as the difference between their energies (*cis−trans method* or *syn-anti method*).[3,5,12,18,29,30,35−37,43,44,49,51] The cis structure is stabilized by the intramolecular H bond, whereas the trans conformer (in which the O−H group rotates around the C−O bond by 180°) is not. Thus, the energy difference ΔE between the cis and trans structures can be expected to be the enthalpy of the intramolecular H bond, which correlates well with the A−H bond proton donating properties, and the measure of its strength based on the bond length change may be used.[41] There are two options to compute the energy of the trans conformer: (1) Energy is obtained by a single point calculation of a structure identical to the cis isomer, except for the 180° rotation of the A−H bond. (2) The energy of the trans conformer is calculated for the optimized structure and includes its full relaxation.[37] Both methods are under discussion[15,26] because the energetic stabilization of the cis conformer includes several extra contributions, such as the balance between attractive and repulsive terms, steric constraints of bulky groups, conjugation, and other interactions, making it difficult to attribute the energy difference only to the H bond. Therefore, the cis−trans energy of the HB only reflects which rotamer is more stable; therefore, it cannot be used to measure the intramolecular hydrogen bond interaction energy, especially for compounds with multiple, cooperative, bifurcated, or anticooperative hydrogen bonds.

The *isodesmic* reactions appear to provide more reasonable results than the cis−trans approach when used to evaluate the intramolecular interaction energy.[48,59,66] In isodesmic reactions,[67] the number and types of bonds are conserved on the reactant and product sides of the reaction. The isodesmic method was used for the estimation of intramolecular HB energies based on the assumption that the total molecular energy can be partitioned into energies of chemically recognizable fragments.[66,68−71] However, the isodesmic reac-

tion approach does not provide the true H bond energy but includes the effect of the energy due to the formation of the ring structure.[49] This method is advocated for systems with one HB but is not recommended for the estimation of the single intramolecular H bond energy in polyhydroxy systems.[69]

Recently, the molecular fragmentation procedure of different order was described by Sánchez-Sanz[63] et al. as an "*intramolecular EDS tool*" to study the electron density shift in intramolecular interaction as a good indication of the strength of this linkage. The author stated that this tool may isolate the interaction zone of electron density from the entire molecule, but when the lost or gain of electron density is small, as in 5-membered HB where no BCP is found, this tool cannot be used.

The other fragmentation method proposed by Nguyen[72] for dicarboxylic acids, where the energy of the intramolecular hydrogen bond was calculated as intermolecular E_{HB} between two molecules of formic acid, after replacing the rest of molecule by the hydrogen atoms added to the both carboxyl fragments.

Since 1994, Gadre[73] introduced the *molecular tailoring approach* (MTA) method of ab initio quality computation of various electron properties (as charge, total energy, electrostatic potential, electron density, total volume, dipole moment) of (large) supermolecules, which involves construction of the density matrix of the supermolecule from block matrices of smaller fragments, each representing a part of supermolecule. This method was primarily drawn for calculation of properties of silicious zeolite clusters[73] and further for various biological systems as alanine polypeptide, albumin binding protein, taxol, γ-cycyclodextrin, polyglycine, α-tocopherol, and other large organic or inorganic crystalline substances.[74−77]

Deshmukh et al.[49,69,78] have proposed application of the MTA method for the systematic fragmentation of the molecule, with accurate results for systems containing multiple O−H···OH intramolecular hydrogen bonds. The energy of these systems was calculated using the fragmentation approach in which the original optimized molecule was cut into three overlapping fragments obtained by replacing the OH group with the cap of hydrogen atom. The authors resigned the use of the calculation of the basis set superposition error (BSSE)[59,79] estimation for these molecules because the use of the triple-ζ quality basis set, such as 6-311++G(2d,2p), is expected to significantly reduce the BSSE correction.[59] By analyzing polyhydroxy molecular systems, Deshmukh[69] found that the molecular tailoring approach yields more reliable H bond energy values than the isodesmic method and can be easily applied to any H-bonded systems with a number of OH···OH interactions. The typical error involved in the molecular tailoring calculation is small (~0.5 kcal/mol for polyalcohols).[69] When the acceptor of H bonding is the carbonyl group, the fragmentation proposed by Deshmukh is not applicable, especially when it is a part of the ring.

To our best knowledge, the MTA method was never used before for the calculation of energies of other types of intramolecular H bonding, and no other universal method of the estimation of E_{HB} was published.

METHODOLOGY

In the present study, 153 structures of 102 saturated and unsaturated aliphatic hydroxy ketones, aldehydes, acids, amides, and esters with intramolecular hydrogen bond(s) forming the six-, seven-, and eight-membered rings were build. Because DFT predicts structural properties in very good agreement with experimental values,[59] we decided to optimize all of the different conformational structures at the DFT B3LYP/6-311++G(d,p) level of theory using the Gaussian 09 program package.[80] All structures were checked by the vibrational analysis at this level and were found to represent true energy minima. The calculated ν_{OH} and $\nu_{C=O}$ frequencies were identified with the GaussView 5.0.9 package. No correction for the zero-point energies was introduced, and no attempts were undertaken to scale the force constants to produce experimental vibrational frequencies. At the same level, the absolute proton shieldings for each structure and TMS (standard tetramethylsilane) were obtained using the gauge-including atomic orbital (GIAO) method.[81,82] The SCF GIAO magnetic isotropic shielding tensors of H-bonded hydrogen atoms were used with the consequent calculation of the chemical shifts δ_H (ppm) by subtraction of the averaged shielding of the TMS hydrogen atoms, calculated with the same method. Table S1 of the Supporting Information contains the systematic names of the compounds examined in this study and our calculated E_{HB}.

The electron correlation was included via the Møller−Plesset treatment of the second order (MP2) in which each structure was finally optimized at MP2(FC)/6-311++G(2d,2p), and its energy was specified at MP2(full)/6-311++G(2d,2p) calculations. The topological properties of the electron density at the bond critical points (BCPs) were characterized using the atoms in molecules methodology (AIM) with the AIM2000[57] and AIMAll[58] program packages for every fully optimized compound on the MP2-derived wave functions. To establish the nature of the hydrogen bonding from the criteria proposed by Koch and Popellier[56] based on the AIM theory, we chose the electron density ρ_{BCP} at the (3,−1) bond critical point, its Laplacian $\nabla^2\rho_{BCP}$ for the BCP between the donor OH hydrogen atom and the O=C oxygen atom of the acceptor, and the electron density ρ_{RCP} at the (3,+1) ring critical point (in the center of the six-, seven- or eight-membered ring of the HB).

Each intramolecular hydrogen bond was described as the length of the O−H covalent bond (d_{OH}), length of the HB as H···O (r_{HB}), angle of the HB as O−H···O (φ_{HB}), distance between both of the oxygen atoms as O···O ($d_{O\cdots O}$), and calculated frequency of O−H and C=O stretching. This information is collected in Table S2 of the Supporting Information, along with the AIM characteristics of the analyzed structures.

For the estimation of the O−H···O=C intramolecular hydrogen bond energy, a systematic fragmentation of each optimized molecule was performed using a modified Deshmukh's[78] methodology, which consists of a comparison of the energies of the fragments of the molecule successively devoid of donor atoms, acceptor atoms, and both groups forming the hydrogen bond. This method enabled the avoidance of contacts between both groups in any of the built structures. Each functional group participating in the intramolecular hydrogen bond was replaced by a hydrogen atom. The valencies of the cut regions (atoms) were satisfied by the addition of the hydrogen atoms at appropriate direction and with a constraint distance of 1.1 Å. It was very important that the hydrogen atom could replace only the sp^3-hybridized atoms of oxygen or carbon and that after this operation any hydrogen atoms remain closer than 2.2 Å (double the van der Waals radius). We propose the new fragmentation of the hydrogen-

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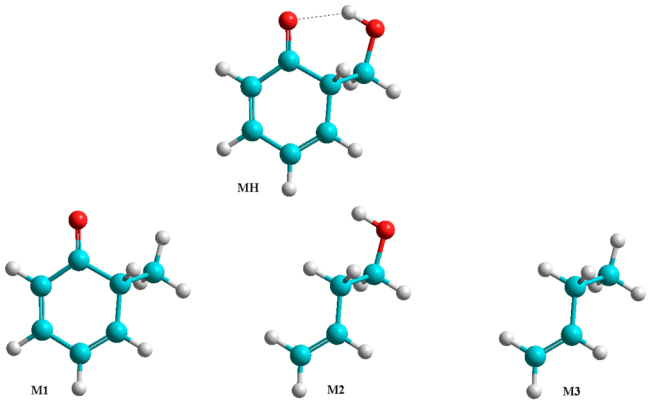
bonded structure in such a manner that the C═O group is removed with the portion of the molecule "behind" C_α, C_β, or C_γ, at the site opposite to the OH group. The energies of these constructed parts (Scheme 1) were calculated, without optimization, at the MP2(full)/6-311++G(2d,2p) level and were used to calculate the strengths of the hydrogen bonds, according to the given equation.

Scheme 1. MTA Fragmentation Scheme for Intramolecular HB Energy Calculation



$$E_{HB} = E_{M1} + E_{M2} - E_{M3} - E_{MH}$$

In the present study, the energies of several aliphatic hydroxyl ketones, aldehydes, acids, amides, and esters with intramolecular hydrogen bond(s) forming the six-, seven-, and eight-membered rings are discussed; enols with RAHB, structures with a five-membered HB ring, and aromatic (phenolic) systems will be included separately.

To ensure the validity of the tailoring scheme, we used the MTA method for the calculation of the energies of a few *intermolecular* hydrogen bonds, which can be easily verified by the calculation of the energy of simple hydrogen-bonded complexes and their components with a compensation of the basis sets (BSSE) by the counterpoise (CP) correction. The difference in the sum of such calculated energies of both isolated components and the energy of the complex gave $E_{HB/BSSE}$, which was compared with $E_{HB/MTA}$, calculated by our method. Table S3 of the Supporting Information shows that the MTA method provides E_{HB} values with an error below nine percent in relation to the effects of the method universally accepted and applied for the calculation of the energy of the *intermolecular* hydrogen bonds.[10,61,82−84] This result enables the assumption that the molecular tailoring approach is a reliable method for the calculation of the energy of O−H···O═C intramolecular hydrogen bonding in a wide range of compounds. It is worth noting that during the E_{HB} calculation only one optimization of the molecule is needed, and the following single point calculations are not time consuming.

RESULTS

Throughout our study, we define the term E_{HB} as the electronic conformer energy stabilization of the ring system with intramolecular hydrogen bonding with respect to the hypothetical system without such bonding.

Table S1 of the Supporting Information presents the systematic (and trivial when possible) names of the calculated compounds; the estimated energies of hydrogen bond formation are compared as positive values.

In Tables 1−6, the compounds are listed from the simplest representative of the group to the molecules with a more complicated structure, including important naturally occurring compounds with a known biological activity or industrial significance. For example, the active constituent of citrinin **34**[21] and gingerol **39**, acids malonic **24**, malic **25** and **59**, eucomic **38** and **58**, levulinic **52**, succinic **56**, itaconic **57**, glutaric **63**, kainic **64**, adipic **69**, maleic **82**, pulvinic **83**, penicillic acid **88**, and aspirin **66** are given.

The energies of the intramolecular hydrogen bonds calculated with our method are reported as follows: aliphatic β, γ, and δ-hydroxycarbonyl structures (Tables 1−3), chelated aliphatic β, γ, and δ-hydroxycarbonyl structures (Table 4), and aliphatic structures with an enolic hydroxyl group as the proton donor without donor−acceptor electron conjugation (Tables 5−7). Finally, the obtained parameters of the E_{HB} were compared with physicochemical, topological, and geometric properties of the compounds (optimized at the MP2/B3LYP 6-311++(2d,2p) level), and the results are discussed and presented in the form of graphs (Figures 1−6). For each chart, the correlation is calculated, proving the correctness and broad structural capabilities of our method for the estimation of the energy of the intramolecular hydrogen bond.

In Tables 1−7, we compare the energies E_{HB} calculated by the MTA of different classes of intramolecular hydrogen-bonded hydroxycarbonyl functional structures, as regular (i.e., isolated) or cooperative contact. The relative electronic energies of the structures are given for comparison. The conformers of the same compound are marked by an additional letter next to the compound number. When necessary, the chirality, as the configuration descriptor, is given, and the conformation is defined. We checked that the calculated energies for the derivatives of 3-hydroxypropanal **1** met the energy expectations arising from spectral and structural characteristics. The observed differences in the E_{HB} values and the correlations between the energies of the hydrogen bonding within the set of structures of the evaluated compounds can be fully interpreted based on physical organic chemistry[85] confirming the correctness of the method.

Aliphatic β, γ, and δ-Hydroxycarbonyl Structures. The E_{HB} for the 3-hydroxypropanal **1** is estimated as 2.0 kcal/mol, but the energy of these types of simple intramolecular hydrogen bonds for compounds collected in Tables 1−3 range from 1.4 to 6.9 kcal/mol and can be classified as weak H bonding.[7]

The replacement of the hydrogen atom by the methyl group in the model 3-hydroxyaldehyde in pairs **1**−**4** (Table 1), **44b** and **48** (Table 2), and **60** and **61** (Table 3) enhances this bonding by approximately 0.7 kcal/mol by inductively increasing the electron density on the proton acceptor of the carbonyl oxygen. The effect of the resonance of the carbonyl group with the phenyl ring enhances the E_{HB} by approximately 0.8 kcal/mol for **9a** and by 1.0 and 1.4 kcal/mol for **10a** and **10b**, respectively. The strength of the HB also depends on the substituents of the carbon atom of a proton-donating group but does not depend on their number or size, rather on their spatial arrangement in the ring of intramolecular hydrogen bonding. In the 6-membered HB ring (Table 1), the equatorial substituents typically increase the HB energy by approximately 1 kcal/mol, as observed in the examples compared with its axial

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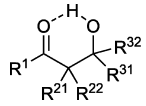
Table 1. MTA Energy of Intramolecular Hydrogen Bond (E_{HB} in kcal/mol) for Aliphatic β-Hydroxy Carbonyl Compounds



	C1[a]	C2[b,c]		C3[c,d]					
no.	R^1	R^{21}	R^{22}	R^{31}	R^{32}	R/S[e]	conform[f]	E_{rel}[g]	$-E_{HB}$
1	H	H	H	H	H	–	-G g	–	**2.0**[h]
2a	H	H	H	Me eq	H	*R*	-G g	0.0	**2.5**
2b	H	H	H	H	Me ax	*S*	-G g	1.3	**1.4**
3	H	H	H	Me eq	Me ax	–	-G g	–	**1.9**
4	Me	H	H	H	H	–	-G g	–	**2.8**[i]
5a	Me	H	H	Me eq	H	*R*	-G g	0.0	**3.2**
5b	Me	H	H	H	Me ax	*R*	G -g	1.2	**2.1**
6a	Me	H	H	Et eq t	H	*R*	-G g	0.0	**3.3**
6b	Me	H	H	Et eq g	H	*R*	-G g	0.6	**3.3**
6c	Me	H	H	Et eq g	H	*R*	-G g	0.6	**3.1**
6d	Me	H	H	H	Et ax t	*R*	G -g	1.2	**2.1**
6d	Me	H	H	H	Et ax g	*S*	-G g	1.4	**2.2**
6f	Me	H	H	H	Et ax -g	*S*	-G g	2.7	**2.3**
7	Me	H	H	H	CH_2CH_2OH ax t	*R*	G -g	–	**2.6**
8a	Me	H	H	Et eq t	Me ax	*R*	-G g	0.0	**2.7**
8b	Me	H	H	Me eq	Et ax g	*S*	-G g	0.2	**2.6**
9a	Ph	H	H	H	H	–	-G g	0.0	**2.8**
9b	H	H	H	Ph eq	H	*R*	G -g	5.5	**2.6**
10a	Ph	H	H	H	Ph ax	*R*	-G g	0.0	**3.0**
10b	Ph	H	H	Ph eq	H	*S*	-G g	2.3	**3.4**
11	Ph	H	H	H	Me eq	*R*	-G g	–	**3.2**
12	Me	H	H	Me eq	Me ax	–	-G g	–	**2.6**
13a	H	OH	H	H	H	*R*	G -g	0.0	**1.9**
13b	H	OH -g	H	H	H	*R*	-G g	2.1	**2.1**
13c	H	OH t	H	H	H	*R*	-G g	2.5	**2.1**
14a	OH trans	H	H	H	H	–	-G g	0.0	**2.3**
14b	OH cis	H	H	H	H	–	-G g	4.9	**2.5**
15	NH_2	H	H	H	H	–	-G g	–	**3.7**
16	CH_2CH_2OH	H	H	H	H	–	-G g	–	**2.5**
17a	OH trans	H	H	Me eq	H	*R*	-G g	0.0	**2.7**
17b	OH cis	H	H	Me eq	H	*R*	-G g	4.9	**3.0**
18	NH_2	H	H	Me eq	H	–	-G g	–	**4.2**
19a	OMe trans	H	H	Me eq	H	*R*	-G g	0.0	**3.1**
19b	OMe cis	H	H	Me eq	H	*R*	-G g	7.2	**3.4**
20	OMe trans	H	H	=O		–	c c	–	**5.8**
21	H	H	H	=O		–	c c	–	**5.5**[j]
22	Me	H	H	=O		–	c c	–	**6.4**
23	F	H	H	=O		–	c c	–	**3.5**[k]
24a	OH trans	H	H	=O		–	-G c	0.0	**5.2**[l]
24b	OH cis	H	H	=O		–	-G c	4.9	**5.9**[m]
25	OH trans	H	H	H	COOH	*R*	-G g	–	**2.8**
26	$-CH{=}CH-CH_2-CH_2-$		H	H	H	*R*	-G g	–	**3.3**[n]
27	H	H	$-CH_2-CH{=}CH-CH_2-$		H	*R R*	-G g	–	**2.2**
28	H		$=CH-C(CH_2)-CH=$			–	c c	–	**5.6**[o]
29	H		$=CH-C(CHNH_2)-CH=$			–	c c	–	**6.8**[p]
30a	H	H	$-(CH_2)_4-$		H	*S S*	G -g	0.0	**2.4**
30b	H	H	$-(CH_2)_4-$		H	*S R*	-G g	0.1	**2.1**
31a	H	H	$-CH{=}CH-CH{=}CH-$		H	*S S*	G -g	0.0	**2.6**
31b	H	H	$-CH{=}CH-CH{=}CH-$		H	*S R*	-G g	1.2	**1.8**
32a	$-CH{=}CH-CH{=}CH-$	H	H	H	*S*	G -g	–	3.5	
32b	$-(CH_2)_4-$		H	H	H	*R*	-G g	–	**3.2**
33a	OH trans	H	C_4H_3S ax	=O		–	-G c	0.0	**5.0**
33b	OH cis	C_4H_3S eq	H	=O		–	-G g	2.8	**5.3**
33c	OH cis	C_4H_3S eq	H	=O		–	-G c	2.4	**5.9**
33d	OH trans	H	C_4H_3S ax	=O		–	-G g	0.2	**4.9**
33e	OH trans	C_4H_3S eq	H	=O		–	-G g	3.4	**4.6**

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Table 1. continued

	C1[a]	C2[b,c]		C3[c,d]					
no.	R^1	R^{21}	R^{22}	R^{31}	R^{32}	R/S[e]	conform[f]	E_{rel}[g]	$-E_{HB}$
34[q]	$C_{10}H_{12}O_2$				=O	–	c c	–	**12.5**
35[r]	$C_{11}H_7O$				=O	–	c c	–	**11.2**
36[s]	$C_{13}H_9O$				=O	–	c c	–	**9.4**
37a	H	=CH−OH s-cis			=O	–	c c	0.0	**9.3**
37b	H	=CH−OH s-trans			=O	–	c c	14.8	**6.9**
38[t]	OH trans	H	H	COOH eq	$-CH_2-C_6H_4(OH)-$	*R*	G -g	0.0	**2.4**
39[u]	$C_9H_{11}O_2$	H	H	H	C_5H_{11} eq	*S*	G -G	–	**3.3**
40[v]	−CH=CH−CO−CH=			H	H	–	-G g	–	**2.8**
41a[w]	−CH=C−CH_2(OH)-CO−CH=			H	H	–	G -g/-G g	0.0	**2.8**
41b[x]	−CH=CH−CO−C(CH_2OH)=			H	H	–	G -g/G -g	1.8	**3.0**
42[y]	$-C_6H_4-CH_2-C(OH)=$				=O	–	–	–	**6.4**
43[z]	Me	tBu			Me	–	–	–	**13.7**

[a]Conformation cis and trans of acids and esters marked by H−O−C3−C2 or C−O−C3−C2 torsional angle 0° and 180°, respectively. [b]Conformation defined by H−O−C2−C1 dihedral angle. [c]Eq means substituent approximately equatorial to the plane of HB ring; ax means substituent axial to the HB ring. [d]Conformation of ethyl group defined by C2−C3−C1′−C2′ dihedral angle. [e]Chirality at C3. [f]Conformations defined by O3−C3−C2−C1 dihedral (capitals) and by H3−O3−C3−C2 dihedral (lower case) angles; c means dihedral close to 0°. [g]Electronic energy relative to the most stable conformer (kcal/mol). [h]Ref 26, 7.53 kcal/mol; ref 86, 1.4 kcal/mol. [i]Ref 9, 0.63 kcal/mol. [j]Ref 87, 3.28, 10.14, 9.35, 12.02 kcal/mol. [k]Ref 87, 2.45, 8.08, 7.78, 9.62 kcal/mol. [l]Ref 87, 2.10, 7.09, 5.58, 8.43 kcal/mol; ref 72, 6.2 kcal/mol. [m]Ref 87, 3.45, 10.52, 9.74, 12.32 kcal/mol; ref 72, 6.16 kcal/mol. [n]Ref 65, 1.32 kcal/mol. [o]Ref 14, 7.07 kcal/mol. [p]Ref 14, 8.71 kcal/mol. [q]Citrinin [(3*R*,4*S*)-8-hydroxy-3,4,5-trimethyl-6-oxo-4,6-dihydro-3H-isochromene-7-carboxylic acid]. [r](*Z*)-2-carboxy-3-hydroxyphenalen-1-on. [s](*Z*)-7-hydroxy-5-oxo-5H-dibenzo[a,c]-[7]annulene-6-carboxylic acid. [t](*R*)-eucomic acid, compare with conformer **58** in Table 2. [u]Gingerol [(*S*)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone]. [v]2-(Hydroxymethyl)benzoquinone. [w]2,5-Di(hydroxymethyl)benzoquinone. [x]2,3-Di(hydroxymethyl)benzoquinone. [y](*Z*)-2-carboxy-3-hydroxyind-2-en-1-one. [z](*Z*)-3-*tert*-butyl-4-hydroxypent-3-en-2-one; ref 19, 22.55; ref 88, 22.11 kcal/mol.

counterpart, **2a** and **2b** and **5a** and **5b**, whereas for 7-membered rings (**45a** and **45b** or **49a** and **49b** Table 2), this difference vanishes. In conformers of 1,3-dicarboxycyclopentane enols **67a** and **67b**, the E_{HB} values resemble those for glutaric acid **63a** and **63b**; however, for cyclohexanes **68a** and **68b**, these values are a fraction because of the syn-1,3-diaxial[89] repulsions at the ax−ax conformers forming the intramolecular 8-membered HB. The smallest energy of the intramolecular hydrogen bond of only 1.4 kcal/mol was calculated for (*S*)-3-hydroxybutanal **2b** in which the methyl group is situated perpendicularly to the HB ring.

When the proton donor is an alcoholic group and the acceptor is a carboxylic group, the HB with its carbonyl oxygen is stronger for acids than for esters by approximately 0.4 kcal/mol, as observed in pairs with a 6-membered HB (**17a**−**19a**, **17b**−**19b**) and with a 7-membered HB (**53a**−**54a**, (**53b**−**54b**). However, replacement of the aldehyde hydrogen atom in 3-oxopropanoic acid **21** by the fluorine atom (acid fluoride **23**), as expected, decreases the energy of intramolecular hydrogen bonding by as much as 2.0 kcal/mol, resulting from the C−F bond polarization.

The H bonding is much stronger for carboxylic acids in which the carboxyl group is the proton donor (i.e., 4.6−5.9 kcal/mol in 6- and 7-membered rings, for example, **24** and **33** in Table 1, **56**−**59** in Table 2, and about 6 kcal/mol in 8-membered rings **63**, **64**, **66**, and **69** in Table 3). This strengthening is a natural consequence of the enhanced acidity of the hydroxyl group of these molecules.

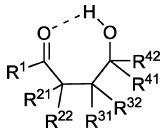
For dicarboxylic acids, it can be observed that the cis hydroxyl group[90] in a carboxylic proton acceptor slightly increases the energy of hydrogen bonding by 0.2−0.7 kcal/mol (i.e., pairs **24a** and **24b**, **33b**−**33e** (Table 1), **56a** and **56b** (Table 2), and **63a** and **63b**, **64a** and **64b**, **67a** and **67b**, and **68a** and **68b** (Table 3)). However, *the stability* of the cis conformer itself diminishes considerably (0.6 to approximately 7 kcal/mol).

The increasing E_{HB} value from 2.1 kcal/mol for (*R*)-4-hydroxyhexan-2-one **6d** to 2.7 kcal/mol for its dihydroxy derivative **7** (Table 1) indicates the effect of cooperativity of the additional intramolecular HB of the two alcoholic groups. The structure known as citrinin **34**[21] allows the coexistence of two different patterns of six-membered intramolecular hydrogen bonds such that the carboxyl group is bonded with the enolic group so that the hydrogen bonding can be recognized as cooperative[11] rather than as chelated; therefore, its strength of 12.5 kcal/mol is not surprising. In the *double closed* structure **37a** (up to 9.3 kcal/mol) and in the *one-closed* structure **37b** (up to 6.9 kcal/mol), an increasing of the HB energy is caused by the hydroxyvinyl substituent at C2. The additional, cooperating HB acts in **37a** as the element "pushing" the donor and the acceptor together. The conformer **37b**, which is extremely unstable toward the **37a** structure, does not contain the extra bonding of the RAHB type, similar to the pair of substituted fulvenes **28** and **29** in which the increasing E_{HB} value can be explained by the effect of the interaction with extra π-electrons.[14]

The same trend can be observed for β-hydroxyacids and esters in which the proton donating group is alcoholic in its trans and cis pairs, respectively (**14a** and **14b**, **17a** and **17b**, **19a** and **19b** (Table 1) and **47a** and **47b** (Table 2)); herein, the energy increase is considerably smaller (0.3 kcal/mol). It can be assumed that although the repulsion of the oxygen atoms of the donor and acceptor in intramolecular hydrogen bonding is a reason for the low stability of the cis conformers of acids and esters the greater electron density of the acceptor increases the carbonyl basicity, consequently strengthening the HB.

In the series of saturated simple six-membered HB bonding hydroxyketones, we found that for three hydroxymethylbenzoquinones (2-(hydroxymethyl) **35**, 2,5-di(hydroxymethyl) **36a**, and 2,3-di(hydroxymethyl) **36b**), the HB energies are approximately 3 kcal/mol and do not indicate any interaction

Table 2. MTA Energy of Intramolecular Hydrogen Bond (E_{HB} in kcal/mol) for Aliphatic γ-Hydroxy Carbonyl Compounds



	C1[a]	C2–C3		C4[b]					
no.	R^1	R^{21}=R^{22}	R^{31}=R^{32}	R^{41}	R^{42}	R/S[c]	conform[d]	E_{rel}[e]	$-E_{HB}$
44a	H	H	H	H	H	–	-G -g	0.0	**2.7**
44b	H	H	H	H	H	–	-G g	0.8	**3.3**
45a	H	H	H	Me eq	H	*S*	G -g	0.0	**3.1**
45b	H	H	H	H	Me ax	*R*	G -g	0.5	**3.3**
46	H	H	H	Me eq	Me ax	–	-G g	–	**3.1**
47a	H	H		–CH=CH–CH=CH–		–	c g	0.0	**4.6**
47b	H	=CH–CH=CH–CH=		H	H	–	-G g	2.4	**4.1**
48	Me	H	H	H	H	–	-G g	–	**4.0**
49a	Me	H	H	Me eq	H	*R*	-G g	0.0	**3.8**
49b	Me	H	H	H	Me ax	*S*	-G g	0.5	**3.9**
50	Me	H	H	Me eq	Me ax	–	-G g	–	**3.8**
51	Me	=CH–CH=CH–CH=		H	H	–	-G g	–	**4.7**
52[f]	Me	H	H	=O		–	-G c	–	**5.9**
53a	OH trans	H	H	H	H	–	-G g	0.0	**3.3**
53b	OH cis	H	H	H	H	–	-G g	5.1	**3.4**
53c	OH cis	H	H	H	H	–	-G -g	3.9	**2.7**
54a	OMe trans	H	H	H	H	–	-G g	0.0	**3.9**
54b	OMe cis	H	H	H	H	–	-G g	7.8	**3.7**
55[g]	C_3H_6OH	H	H	H	H	–	-G g	–	**4.1**
56a[h]	OH trans	H	H	=O		–	-G c	0.0	**5.1**
56b[h]	OH cis	H	H	=O		–	-G c	5.0	**5.4**
57a[i]	OH trans	$=CH_2$	H	=O		–	-G c	0.0	**5.5**
57b[i]	OH trans	H	$=CH_2$	=O		–	-G -g	2.3	**5.8**
58[j]	OH trans	H	[j]	=O		*R*	c -g	1.5	**5.9**
59[k]	OH trans	H	[k]	=O		*S*	-G c	–	**6.3**

[a]Conformation cis and trans of acids defined by H–O–C1–C2 torsional angle 0° and 180°, respectively. [b]Eq means substituent equatorial to the plane of HB ring; ax means substituent axial to the HB ring. [c]Chirality at C4. [d]Conformations defined by O4–C4–C3–C2 torsional angle (capitals) and by H4–O4–C4–C3 torsional angle (lower case); c means angle close 0°. [e]Energy relative to the most stable conformer. [f]Levulinic acid. [g]1,7-Dihydroxyheptan-4-one. [h]Succinic acid; ref 72, 3.2, 5.1; ref87, 2.60, 8.58, 6.45, 9.69 kcal/mol. [i]Itaconic acid. [j]R^{31} –OH, R^{32} -C_7H_7O, (*R*)-eucomic acid, compare with conformer **38** in Table 1. [k]Malic acid, R^{31} –OH

with the quinone system. Each of the two HBs in the same molecule have the same strength as the isolated HB.

Our estimated energies of intramolecular hydrogen bonding for dicarboxylic acids: glutaric **63a** and **63b** (5.9 and 6.0 kcal/mol), adipic acid **69a** and **69b** (5.3 kcal/mol), and succinic acid **56a** and **56b** (5.2 and 5.9 kcal/mol) are in accordance with these given by Nguyen's[72] fragmentation method (6.6 and 6.9 kcal/mol), with the exception of **56a** (3.2 kcal/mol).

Chelated Aliphatic β, γ, and δ-Hydroxycarbonyl Structures. In Table 4, the data on the dihydroxyketones are summarized, each with two hydrogen bonds directed to the same carbonyl group, known as chelated or anticooperative HBs.[3] When we compare these results with the single hydrogen bonding in the same configuration and conformation, we may expect a decreased[36] E_{HB} from 0.2 to 0.6 kcal/mol because of the divisibility of the donor–oxygen lone pair electrons (compare **2a–71b**, **5a–72a**, **12–73a**, and **40** with **74** or **75** (Tables 1 and 4).

Although there is limited information in the literature on the energies of HBs for the compounds examined in this study, generally they do not agree with our results. The energy calculated herein for 3-hydroxypropanal (**1**, E_{HB} = 2.0 kcal/mol) is nearly four times overestimated (7.53 kcal/mol)[26] or underestimated (1.4 kcal/mol)[86] in studies based on the NMR spectra analysis. Our HB energy value for 4-hydroxybutan-2-one (**4**, 2.8 kcal/mol) is four times greater than the value calculated based on the $d_{O\cdots O}$ distance and the φ_{HB} angle of O–H···O bonding (0.63 kcal/mol[9]). The similar discrepancy is found for chelated 1,5-dihydroxypentan-3-one **71** with an E_{HB} of 0.48 kcal/mol.[9] The method[65] using the substitution of the OH group by the methyl group yielded for 2-hydroxymethyl-cyclohex-5-en-1-one **26** a result (1.32 kcal/mol) much closer to ours (3.3 kcal/mol) but was still over two times lower. Our MTA calculated energies of HBs in fulvenes **28** and **29** (5.6 and 6.8 kcal/mol) prove the effect of the aromaticity of the system (7.07 and 8.71 kcal/mol,[14] respectively). The other results compared in Tables 1–4 are from a study by Fuster[87] in which the author calculated the energies of the intramolecular HB based on the $d_{O\cdots O}$ distance and the calculated electron density. The equations used in this study[87] for the hydroxyacids **21–24b** (Table 1) and **56a** (Table 2) give results that understate and others that overstate the E_{HB} calculated by the MTA method.

Aliphatic Structures with an Enolic Hydroxyl Group as the Proton Donor without Donor–Acceptor Conjugation. The unsaturated hydroxyaldehydes, ketones, acids,

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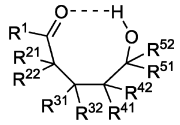
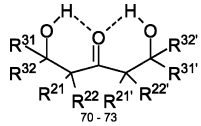
Table 3. MTA Energy of Intramolecular Hydrogen Bond (E_{HB} in kcal/mol) for Aliphatic δ-Hydroxy Carbonyl Compounds

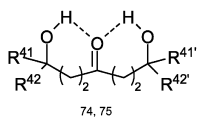


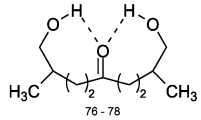
	C1[a]	C2–C3	C4		C5					
no.	R^1	R^{21}=R^{22}	R^{31}=R^{32}	R^{41}=R^{42}	R^{51}	R^{52}	R/S[b]	conform[c]	E_{rel}[d]	$-E_{HB}$
60	H	H	H	H	H	H	–	-G -g	–	**3.1**
61	Me	H	H	H	H	H	–	-G -g	–	**3.8**
62	Me	H	=CH–CH=CH–CH=		H	H	–	-G -g	–	**4.1**
63a[e]	OH trans	H	H	H	=O		–	G c	0.0	**5.9**
63b[e]	OH cis	H	H	H	=O		–	G c	5.0	**6.0**
64a[f]	OH trans	H	–CH[C(CH_3)=CH_2]–C_3H_5–CH_2–NH–		=O		all *S*	-G c	0.0	**6.2**
64b[f]	OH cis	H	–CH[C(CH_3)=CH_2]–C_3H_5–CH_2–NH–		=O		all *S*	G c	6.9	**6.5**
64c[f]	OH cis	H	–CH[(C=CH_2)(CH_3)]–C_3H_5–CH_2–NH–		=O		all *S*	G c	7.1	**6.4**
65	Me	instead of C2C3C4C5 is –O–CH=CH–CO–						–	–	**4.4**
66[g]	Me	instead of C2C3C4C5 is –O–C_4H_4-ortho-CO–						–	–	**4.4**
67a	OH trans	H[h]	$–CH_2–CH_2–$ ax–eq		H	=O	1*S* 3*R*	–G c	0.0	**6.0**
67b	OH cis	H[h]	$–CH_2–CH_2–$ ax–eq		H	=O	1*S* 3*R*	–G c	5.0	**6.2**
68a	OH trans	H[i]	$–CH_2–CH_2–CH_2–$ ax–ax		H	=O	1*S* 3*R*	c -g	0.0	**3.7**
68b	OH cis	H[i]	$–CH_2–CH_2–CH_2–$ ax–ax		H	=O	1*S* 3*R*	c -g	5.3	**4.3**
69a[j]	OH trans	$–(CH_2)_4–$			=O			G c	0.0	**5.3**
69b[j]	OH cis	$–(CH_2)_4–$			=O			G c	5.3	**5.3**

[a]Conformation cis and trans of acids defined by H–O–C1–C2 torsional angle 0° and 180°, respectively. [b]Chirality at C5. [c]Conformations defined by O5–C5–C4–C3 torsional angle (capitals) and by H5–O5–C5–C4 torsional angle (lower case); c means angle close to 0°. [d]Energy relative to the most stable conformer (kcal/mol). [e]Glutaric acid; ref 72, 6.6, 5.4 kcal/mol. [f]Kainic acid. [g]Aspirin. [h]Instead of H22 and H42 is $–CH_2–CH_2–$, ax–eq means axial–equatorial substitution in cyclopentanedicarboxylic acid. [i]Instead of H22 and H42 is $–CH_2–CH_2–CH_2–$; ax–ax means diaxial substitution in cyclohexanedicarboxylic acid in chair conformation. [j]Adipic acid; 9-membered ring; ref 72, 6.9, 5.8 kcal/mol.

Table 4. MTA Energy of Intramolecular Hydrogen Bond (E_{HB} in kcal/mol) for Chelated β-, γ-, and δ Dihydroxy Ketones


70 - 73


74, 75


76 - 78

	C2		C3[a]		C4[a]			C2′		C3′[a]		C4′[a]				
no.	R^{21}	R^{22}	R^{31}	R^{32}	R^{41}	R^{42}	conform[b] (config)	$R^{21'}$	$R^{22'}$	$R^{31'}$	$R^{32'}$	$R^{41'}$	$R^{42'}$	conform[b] (config)	E_{rel}[c]	$-E_{HB}$
70[d]	H	H	H	H	–	–	-G g	–	–	H	H	–	–	c c	–	**2.0**[d]
71a	H	H	H	H	–	–	-G g	H	H	H	H	–	–	-G g	0.0	**2.3**[e]
71b	H	H	H	H	–	–	-G g	H	H	H	H	–	–	G -g	0.2	**2.2**
72a	H	H	Me eq	H	–	–	-G g (*R*)	H	H	Me eq	H	–	–	G -g (*S*)	0.0	**2.6**
72b	H	H	Me eq	H	–	–	G -g (*S*)	H	H	Me eq	H	–	–	G -g (*S*)	0.3	**2.8**
73a	H	H	Me	Me	–	–	-G g	H	H	Me	Me	–	–	G -g	0.0	**2.0**
73b	H	H	Me	Me	–	–	-G g	H	H	Me	Me	–	–	-G g	0.5	**2.2**
74[f]	C_3H_2O		H	H	–	–	-G g	C_3H_2O		H	H	–	–	-G g	–	**2.6**
75[g]	$C_5H_6O_3$		H	H	–	–	-G g	$C_5H_6O_3$		H	H	–	–	-G g	–	**2.6**
76	H	H	H	H	H	H	G g	H	H	H	H	H	H	G g	–	**3.2**
77	H	H	H	H	Me	Me	G g	H	H	H	H	Me	Me	G g	–	**3.3**
78	H	H	H	H	Me eq	H	-G -g (*S*)	H	H	H	H	Me eq	H	-G -g (*S*)	–	**2.9**

[a]Eq means substituent equatorial to the plane of HB ring; ax means substituent axial to the HB plane. [b]Conformations defined by O3–C3–C2–C1 torsional angle (capitals) and by H3–O3–C3–C2 torsional angle (lower case); c means angle about 0°. [c]Energy relative to the most stable conformer (kcal/mol). [d]1,4-Dihydroxybutan-2-one; E_{HB} given for six-membered ring. [e]Ref 9, 0.48 kcal/mol. [f]2,6-Di(hydroxymethyl)benzoquinone. [g]2,3,5,6-Tetra(hydroxymethyl)benzoquinone.

dicarboxylic acids, and amides listed in Table 5 form the seven-membered hydrogen bonds containing double C=C bonds conjugated with the exo enolic or carboxylic acceptor. In the model 4-oxo-2-butenoic acid **79**, also in 4-hydroxypenta-2,4-dienal **80** and in maleic acid **82a**, the HB energy of 6.6, 5.8, and 6.4 kcal/mol, respectively, is similar to that calculated for six-membered saturated dicarboxylic structures, such as the malonic acid conformers **24a** (5.2 kcal/mol) and **24b** (5.9)

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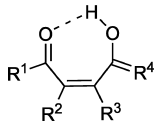
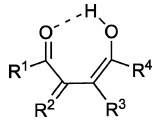
Table 5. MTA Energy of Intramolecular Hydrogen Bond (E_{HB} in kcal/mol) for Aliphatic γ-Hydroxy-αβ, γδ-Diunsaturated Carbonyl Compounds



no.	R[1a]	R[2]	R[3]	R[4]	E_{rel}[b]	$-E_{HB}$
79	H	H	H	=O	–	**6.6**
80	H	H	H	$=CH_2$	–	**5.8**
81a	OH trans	H	H	$=CH_2$	0.0	**5.3**
81b	OH cis	H	H	$=CH_2$	5.4	**5.7**
82a[c]	OH trans	H	H	=O	0.0	**6.4**
82b[c]	OH cis	H	H	=O	5.7	**7.0**
83a[d]	OH trans	Ph	–O–CO–CPh–		0.0	**9.2**
83b[d]	OH cis	Ph	–O–CO–CPh–		0.6	**10.6**
84a	OH trans	H	–O–CO–CH–		0.0	**9.2**
84b	OH cis	H	–O–CO–CH–		5.1	**10.1**
85a	OH trans	Ph	H	=CHPh	0.0	**6.3**
85b	OH cis	Ph	H	=CHPh	1.6	**7.1**
86a	NH(Me) trans	H	H	=O	0.0	**9.6**
86b	NH(Me) cis	H	H	=O	3.5	**9.9**
87	NH_2	H	H	=O	–	**9.0**
88a[e]	$CMe=CH_2$ s-cis	OMe cis	H	=O	0.0	**4.8**
88b[e]	$CMe=CH_2$ s-trans	OMe cis	H	=O	1.6	**5.4**

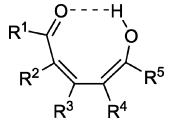
[a]Conformation s-cis and s-trans defined by H–O–C1–C2 or C–N–C1-C2 torsional angle. [b]Relative to the most stable conformer (kcal/mol). [c]Maleic acid. [d]Pulvinic acid. [e]Penicilic acid.

Table 6. MTA Energy of Intramolecular Hydrogen Bond (E_{HB} in kcal/mol) for Aliphatic α-Alkilidene-γ-Hydroxy-βγ-Unsaturated Carbonyl Compounds



no.	R[1]	R[2]	R[3]	R[4]	$-E_{HB}$
89	H	H H	H	H	**6.3**
90	H	$=CH_2$	H	H	**8.1**
91	Me	H H	H	Me	**6.1**
92	Me	$=CH_2$	H	Me	**8.2**
93	H	=CH(OH)	CHO	H	**13.4**
94	Me	=CMe(OH)	CMeO	Me	**9.6**

Table 7. MTA Energy of Intramolecular Hydrogen Bond (E_{HB} in kcal/mol) for Aliphatic δ-Hydroxy-αβ, γδ-Diunsaturated Carbonyl Compounds



no.	R[1]	R[2]	R[3]	R[4]	R[5]	$-E_{HB}$
95	H	H	H	H	H	**12.3**
96	H	H	[a]	H	H	**12.1**
97	Me	Me	H	Me	Me	**11.5**
98	$-CH_2-CH=CH-$		H	$-CH=CH-CH_2-$		**11.5**
99	–CH(Me)-CH=C(Me)–		H	–CH(Me)–CH=C(Me)-		**11.8**
100	$-CH_2-N=CH-$		H	$-CH=N-CH_2-$		**10.7**
101	–CH(Me)–N=C(Me)–		H	–CH(Me)-N=C(Me)-		**12.1**
102a	$-CH_2-CH_2-CH_2-C(OH)=$		H, Me	$-CO-CH_2-CH_2-CH_2-$		**11.3**
102b	$-CH_2-CH_2-CH_2-C(OH)=$		H, Me	$-CO-CH_2-CH_2-CH_2-$		**11.8**

[a]N instead of C3-R[3]. [b]C2–C3 is exceptionally saturated C–C bond.

from Table 1. These types of rings are not quasiaromatic because they lack full π-electron conjugation.

In the pulvinic acids **83a** and **83b**, the HB energy grows to approximately 10 kcal/mol and does not change upon the removal of both phenyl substituents (**84a** and **84b**) but decreases upon removal of the rigid lactic fragment of the compound (**81a**, **81b**, **85a**, and **85b**). The electronic influence of replacing OH with the NH_2 group in the donor for maleic acid **82a** to its monoamide **87** (ΔE_{HB} = 2.6 kcal/mol) is greater than in the saturated 6-membered systems (**14a–15**) with the strengthening of E_{HB} by 1.4 kcal/mol, in **17a–18** by 1.5 kcal/mol. Interestingly, the isopropenyl substitution of the donor in penicillic acid **88a**, which introduces further conjugation with the carbonyl group and the efflux of π-electrons, decreases the E_{HB} and makes the HB ring nonplanar.

Compounds **90** and **92** in Table 6 are seven-membered intramolecular hydrogen bonded with an additional exo double bond conjugated with the enolic bond. These compounds have a medium strength (approximately 8 kcal/mol), which is greater by approximately 2 kcal/mol than that for the enolic structures **89** and **91** in which the enolic group is isolated off the carbonyl and strictly related to conformers **64a**, **64b**, and **64c** of the (saturated) kainic acid in Table 3.

When the clamp between the C2 and C3 atoms is formed by the competitive hydrogen bonded ring, as in compound **93** (E_{HB}= 13.4 kcal/mol, Table 6), the delocalization of the conjugated π-electrons is difficult to obtain in the entire molecule, and the resonance is also most likely in two trans linear O=C–C=C systems. The energy of the intramolecular HB slightly diminishes (to 9.6 kcal/mol) when both π–π

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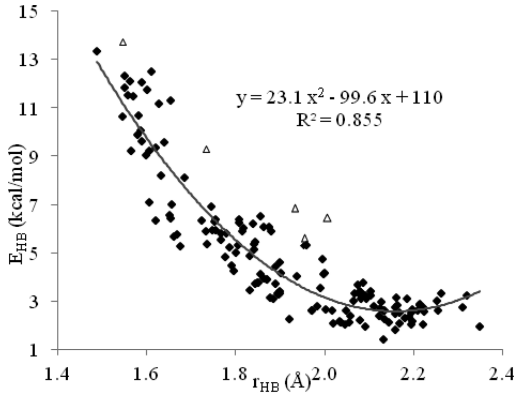

Figure 1. MTA intramolecular hydrogen bond energy as a function of hydrogen bond length H···O; the exceptional structures are marked as triangles.

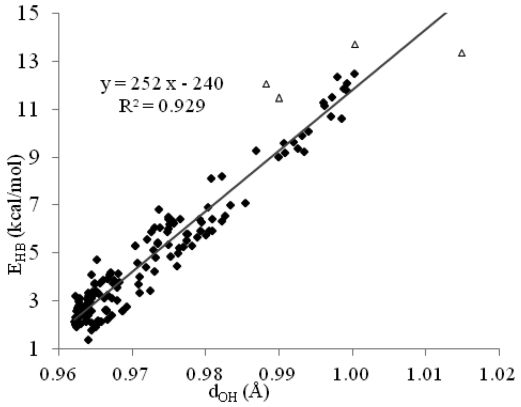

Figure 2. MTA intramolecular hydrogen bond energy as a function of the length of covalent bond O−H; the exceptional structures are marked as triangles.

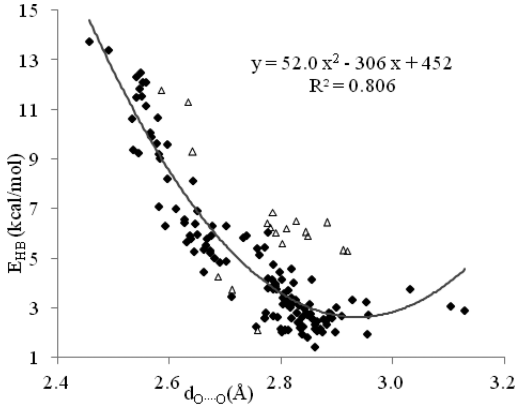

Figure 3. MTA intramolecular hydrogen bond energy as a function of oxygen atoms distance O···O; the exceptional structures are marked as triangles.

resonances are excluded, as observed in the nonplanar structure **94**, because of the steric hindrance of the four extra methyl groups.

Table 7 describes the eight-membered hydrogen bonded structures from 5-hydroxypenta-2,4-dienal **95** to four different derivatives of the rubazoic acid with two (**100** and **101**) or four atoms of nitrogen (**98** and **99**) replaced by carbon atoms. The relatively lower HB energy ranging from 10.7 to 12.1 kcal/mol is most likely due to the long conjugated chain of eight π-

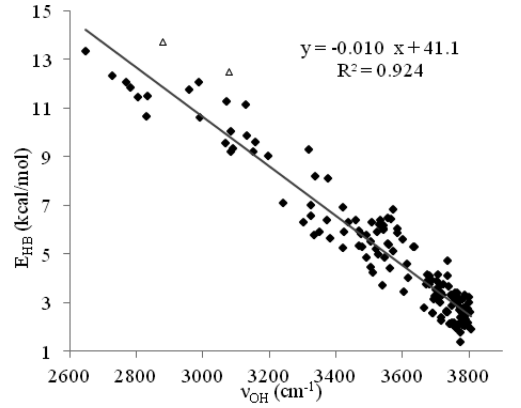

Figure 4. MTA intramolecular hydrogen bond energy as a function of $\nu_{(O-H)}$ frequency; the exceptional structures are marked as triangles.

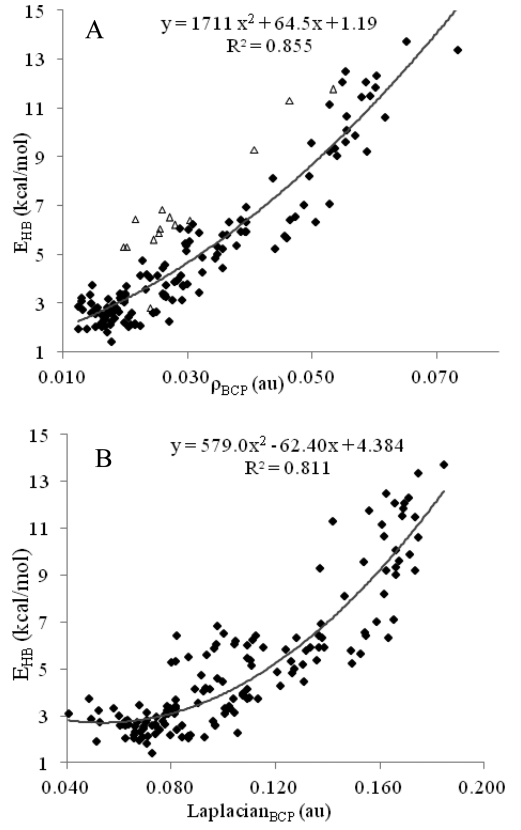

Figure 5. MTA intramolecular hydrogen bond energy as a function of HB topological parameters, electron density in BCP (A), and Laplacian in BCP (B); the exceptional structures are marked as triangles.

electrons, which is without the quasiaromatic character typical for RAHB systems.[14] The nonplanar enolic form of 2,2′-ethylenebis(1,3-cyclohexanedione) dienol comprises the two intramolecular conjugated hydrogen bonds **102a** and **102b** with an $E_{HB} \approx 11.5$ kcal/mol, much less than for RAHB systems (unpublished results).

DISCUSSION

The energies of intramolecular hydrogen bonds calculated by the MTA method shown in Tables 1−7 were correlated with geometrical, spectral, and topological calculated properties of the investigated structures. We found fair correlations between

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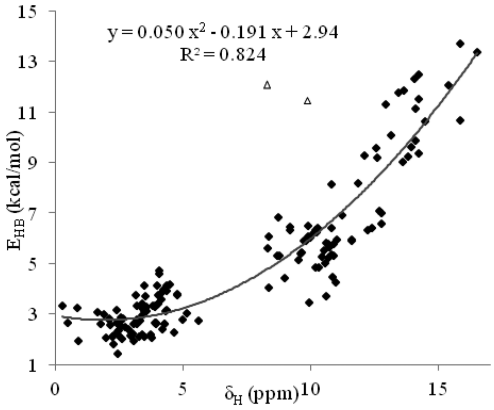

Figure 6. MTA intramolecular hydrogen bond energy as a function of chemical shift of H-bonded proton; the exceptional structures are marked as triangles.

the geometrical and topological parameters derived from MP2(FC)/6-311++G(2d,2p) wave functions with the energy of the intermolecular hydrogen bond calculated and found that certain correlations can be described by the linear or quadratic equation. The O−H (d_{OH}) and O···O ($d_{O\cdots O}$) distances used as the parameters to characterize the HB strength are correlative but are not sufficient to quantify the HB interactions.

Figure 1 presents the quadratic correlation between the H···O (r_{HB}) distance of the intramolecular H bond and the HB energy (E_{HB}). A few points in figure (triangles) require the following comment. The HB for 6-membered structures **28**, **29**, and **43** from Table 1 show an irregularity to the equation because their HB energy is determined by the effect of the peculiar fulvene substitution, which acts as the strong reinforcement of the HB by the polarization of the exocyclic double bond[85] or by the cooperation with the hydroxyvinyl C2 substituent in the *double closed* structure **37a.** For these structures, the HB energy does not well correlate with the HB distance; the hydrogen bond is much stronger than can be estimated from its length. For the 2-*tert*-butyl substituted pentanedione enolic form **43**, the energy of the intramolecular HB highly increases because of the a conjugated π-electrons of the enolic group. Despite the short bond,[19,88] because of nonplanarity of the bonded ring, this structure does meet any of the conditions qualifying it for RAHB.

The elongation of the O−H bond of the O···H−O system is one of the *signatures of H bonding.* There is a very good linear correlation (Figure 2) between the calculated HB energy and the O−H covalent bond length (d_{OH}). The planar structure **93** (triangle, Figure 2, Table 6) shows an E_{HB} value lower than expected from the O−H bond elongation because of anticooperation with another HB in the same molecule (see above). Nonplanar structures **96** and **97** (triangles, Figure 2, Table 7) have 8-membered HB with rings rich in π-electrons (the resonance of enol and carbonyl groups but not in the RAHB fashion), increasing the E_{HB} above that expected from the d_{OH} function. The same is valid for the nonplanar 6-membered **43** structure.

The O···O distance ($d_{O\cdots O}$), often used for the estimation of the strength of the intramolecular hydrogen bond, can be applied to the comparison of the energy of the closed groups of compounds[20,33] in quadratic dependence. Figure 3 reveals that this parameter is insufficient for certain planar six-membered fulvenes **28**, **29**, and **42** (triangles, Table 1) and for compounds with nonplanar HB exo stiffened rings as hydroxycyclohexane carbaldehyde **30b** and greater than six, such as glutaric **63a** and **63b**, kainic **64a**, **64b**, and **64c**, adipic acids **69a** and **69b**, dicarboxycyclopentanes **67a** and **67b**, and dicarboxycyclohexanes **68a** and **68b** (Table 3), and **102a** and **102b** (Table 7). Interestingly, the HB energy calculated for the nonplanar hydrogen bonded six-membered ring with the steric repulsion of alkyl groups nonplanar structure **43** is highly correlated with its ($d_{O\cdots O}$) parameter.

The ν_{OH} frequency was obtained from the IR spectra of the analyzed compounds calculated at the B3LYP/6-311++G(d,p) level of theory. A few structures showed two bands for the symmetric and asymmetric vibrations; in such cases, the arbitrary higher frequency was considered because it was typically more intense. The linear correlation of the E_{HB} and the ν_{OH} is good (Figure 4). Only for the nonplanar HB exo stiffened structures **34** and **43** the calculated E_{HB} is higher than expected from the $\nu_{(O-H)}$ frequency.

Over the last two decades, the theoretical analysis of electron density topology (AIM theory) has been the most widely used method for the investigation of hydrogen bond systems by the electron density at the bond critical point ρ_{BCP} and its Laplacian $\nabla^2\rho_{BCP}$ value extended by electron density at the ring critical point ρ_{RCP}, which are occasionally treated as universal descriptors of the hydrogen bond strength.[83]

The energy of over 100 intramolecular hydrogen bonds presented in this study is correlated with the electron density at the bond critical points ρ_{BCP} (Figure 5A) in quadratic relations for the analyzed hydroxycarbonyl compounds. As mentioned previously, structures **28**, **29**, and **42** (Table 1, triangles, Figure 5A) with a fulvene electron-rich substitution show hydrogen bonds stronger than indicated by the ρ_{BCP} value, which is the natural consequence of the polarization of the exocyclic double bond. In most cases of the structures of acids (**25**, **37a**, **42**, **63a**, **63b**, **64a**, **64b**, **64c**, **69a**, and **69b**, the electron-rich carboxyl group is the reason for the stronger hydrogen bonds than that determined by its critical point densities.

The E_{HB} for saturated compounds changes proportionally to the Laplacian $\nabla^2\rho_{BCP}$ value at the H····O bond critical point (Figure 5B) (with exceptions described above for ρ_{BCP}), with a quadratic trend.

The absolute shieldings σ (isotropic tensors) calculated at the B3LYP/6-311++G(d,p) level of theory for a proton engaged in the intramolecular hydrogen bonding were transformed into chemical shifts δ_H. The correlation between the E_{HB} and δ_H is quadratic, with the R^2 coefficient = 0.824. Only the 8-membered 5-hydroxy-3-azapentadienal **96** and hydroxydimethylheptadienone **97** (Table 7) display a HB energy of approximately 6 kcal/mol greater than expected from the chemical shift (triangles, Figure 6). Both of the compounds are eight π-electrons conjugated and belong to the group named by Gilli as R_5-RAHB and are not planar. The other parameters analyzed herein for these two compounds do not fit the RAHB group.

The angle of the intramolecular hydrogen bond, strongly dependent initially on the membering of the HB ring formed, generally cannot serve as an evaluator of the HB energy. The calculated E_{HB} does not correlate with the frequency of the C=O vibrations (Table S2, Supporting Information). The dependence between the energy of the intramolecular HB and the electron density ρ_{RCP} at the ring critical point is unspecified for compounds with simple various substituents and sizes of the bonded rings.

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Figures 1−6 show that the energies of the intramolecular hydrogen bonds depend on a variety of topological, geometrical, and spectral parameters of the bonded molecules and can be described, respectively, by the linear or quadratic equations. This finding entitles us to treat the resonance-assistant hydrogen bond as a special category of intramolecular hydrogen bonding and will be described in the next article.

The observed correlations verify the application of the presented MTA method for the calculation of the intramolecular hydrogen bond energy and show that it can be successfully used for the great structural diversity of compounds because of its sensitivity to configuration and subtle conformation features.

CONCLUSIONS

A novel method proposed for the estimation of intramolecular hydrogen bond energy is based on fragmentation strategies. This new simple computational method uses a density functional theory (for preliminary optimization) and an *ab initio* procedure during final optimizations and single point energy calculations. The correctness of our modification of the MTA method was verified using a number of representative *intermolecular* interactions. The presented fragmentation method was tested on over 100 hydroxycarbonyl compounds wherein only three single point energies of tailored fragments are required for the estimation of one intramolecular hydrogen bond energy. The estimated intramolecular hydrogen bond energies range from −1.4 to −13.7 kcal/mol and show a qualitative rank ordering with the O−H···O corresponding lengths, distance $d_{(O\cdots O)}$, stretching frequencies ν_{OH}, NMR chemical shift δ_H, and electron density topological parameters ρ_{BCP} and $\nabla^2\rho_{BCP}$ at a (3,−1) value. Moreover, it appears that for this group of compounds the energy of intramolecular hydrogen bonding is not bound with the electron density in the hydrogen-bonded ring critical point.

The values of the hydrogen bond energy calculated by the present MTA-modified method are not always in agreement with those reported in the literature, although they are generally consistent with the parameters typically used to describe the problem. Our model is able to convincingly interpret the fine changing of structural fragments as a cause of the weakening/strengthening of the intramolecular hydrogen bond by electron-donating/withdrawing substituents or conjugated extra hydrogen bonds accepted by the carbonyl. The hydrogen bond strength for all of the compounds depends on the spatial arrangement of the bonds, steric accessibility of the donor−acceptor environment, and cooperativity/anticooperativity with other HB bonds. Importantly, even the subtle structural and stereoelectronic effects are well reflected by the hydrogen bond relative energies. Moreover, we show that when the molecules become more complex or the number of intramolecular hydrogen bonds increases (including the cooperative H bond phenomenon) the presented exhaustive stereoelectronic effects interpretation may still be accessible.

The H bond as an intrinsic feature of the ground-state structure of many molecules may affect their shape and properties. The calculated values of E_{HB} can be a good and intelligible explanation for the number of interactions and the structural and conformational H-bonding phenomenon in a given compound. To the best of our knowledge, this is the first study of a direct computational assessment of the H bond energy of intramolecular H bonds with the carbonyl group.

Currently, we recognize that the method, being quite general, can be applied also to the RAHB and to the aromatic systems and generally to intramolecular hydrogen bonded systems, including N−H···O and O−H···N in amides and peptides. The five-membered structures of the O−H···O═C intramolecular hydrogen bond are essentially dependent on the ring molecular strains and special steric interactions; therefore, they will be described separately.

ASSOCIATED CONTENT

Supporting Information

Table S1: Systematic names of examined compounds and calculated energy of the hydrogen bonds. Table S2: MTA energy of intramolecular hydrogen bonding E_{HB}, length of the HB as H···O (r_{HB}), angle of the HB as O−H···O (φ_{HB}), length of the O−H bond (d_{OH}), distance between the oxygen atoms as O···O ($d_{O\cdots O}$), frequency of O−H and C═O stretching, electron density in the bond critical point (ρ_{BCP}) and its Laplacian, electron density in the ring critical point (ρ_{RCP}), and H NMR chemical shifts calculated for structures 1−102b. Table S3: Energy of intermolecular hydrogen bond in dimers, calculated with BSSE and by MTA method. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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

Notes

The authors declare no competing financial interest.

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