

Cite this: *Phys. Chem. Chem. Phys.*, 2012, **14**, 7441–7447

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PAPER

Bridging QTAIM with vibrational spectroscopy: the energy of intramolecular hydrogen bonds in DNA-related biomolecules†

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Received 17th January 2012, Accepted 3rd April 2012

DOI: 10.1039/c2cp40176b

Physical properties of over 8000 intramolecular hydrogen bonds (iHBs), including 2901 ones of the types OH...O, OH...N, NH...O and OH...C, in 4244 conformers of the DNA-related molecules (four canonical 2'-deoxyribonucleotides, 1,2-dideoxyribose-5-phosphate, and 2-deoxy-D-ribose in its furanose, pyranose and linear forms) have been investigated using quantum theory of atoms in molecules (QTAIM) and vibrational analysis. It has been found that for all iHBs with positive red-shift of the proton donating group stretching frequency the shift value correlates with ρ^{CP} —the electron charge density at the (3,−1)-type bond critical point. Combining QTAIM and spectroscopic data new relationships for estimation of OH...O, OH...N, NH...O and OH...C iHB enthalpy of formation (kcal mol^{-1}) with RMS error below $0.8 \text{ kcal mol}^{-1}$ have been established: $E_{\text{OH}\cdots\text{O}} = -3.09 + 239 \cdot \rho^{\text{CP}}$, $E_{\text{OH}\cdots\text{N}} = 1.72 + 142 \cdot \rho^{\text{CP}}$, $E_{\text{NH}\cdots\text{O}} = -2.03 + 225 \cdot \rho^{\text{CP}}$, $E_{\text{OH}\cdots\text{C}} = -0.29 + 288 \cdot \rho^{\text{CP}}$, where ρ^{CP} is in $e a_0^{-3}$ (a_0 – the Bohr radius). It has been shown that XH...Y iHBs with red-shift values over 40 cm^{-1} are characterized by the following minimal values of the XHY angle, ρ^{CP} and $\nabla^2 \rho^{\text{CP}}$: 112° , $0.005 e a_0^{-3}$ and $0.016 e a_0^{-5}$, respectively. New relationships have been used to reveal the strongest iHBs in canonical 2'-deoxy- and ribonucleosides and the $\text{O}_5\text{H}\cdots\text{N}_3$ H-bond in ribonucleoside guanosine was found to have the maximum energy ($8.1 \text{ kcal mol}^{-1}$).

Introduction

Hydrogen bonds are believed to be the most universal of non-covalent interactions controlling the spatial structure of biological molecules and their assemblies. Both *inter*- and *intramolecular* hydrogen bonds (H-bonds) play a crucial role in controlling the structure of biological molecules as well as their functions.^{1–5} The most illustrative examples include pairing of nitrogenous base in

the DNA double helix, stabilization of protein secondary structure, DNA–protein complex formation⁶ and various anomalies in physical properties of water.^{7,8} This type of non-covalent interactions is also known to be important in the fields of materials science,^{9,10} solid state chemistry^{11,12} and theory of ionic liquids.¹³ Therefore, despite a century of tremendous research activity in this field,¹⁴ the nature of H-bonds is still being studied vigorously.^{2,15–18}

Various theoretical and experimental techniques are routinely used to probe H-bonds.^{15,16} However, there are just a few ways to estimate H-bond strength quantitatively: use of spectroscopic manifestations of H-bond formation such as red-shift of XH stretching vibration frequency or increase in IR intensity;¹⁹ estimation of complex dissociation energy with modern vibrational predissociation spectroscopy,²⁰ temperature-dependent field ionization mass spectrometry²¹ or calorimetry;^{22–24} investigation of variations in molecules magnetic properties,²⁵ wavefunction-based²⁶ and/or solvation-related^{27,28} descriptors or electron density topology;^{29–31} or theoretical calculation of complex stabilization energy (SE) with *ab initio* techniques.¹⁶ Although experimental methods are quite reliable for simple molecular dimers (like water, ammonia *etc.*), it is not straightforward to use them for investigation of complexation of conformationally flexible molecules, since neither particular conformation of molecules, nor general structure of a complex is known for sure. The same limitations hold true also for small and ‘rigid’ molecules if their large-sized clusters

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† Electronic supplementary information (ESI) available: Fig. S1 presents initial correlations between proton donation group stretching vibration frequency red-shift and electron charge density at the bond critical point; Table S1 contains the structure of the (3*S*,4*R*)-3,4,5-trihydroxypentanal conformer exhibiting a maximum red-shift of the ‘free’ hydroxyl group; details of conformational parameters of canonical ribonucleoside conformers having the strongest H-bonds are given in Table S2. See DOI: 10.1039/c2cp40176b

Table 1 Coefficients of linear regression (3) connecting complex stabilization energy (SE, kcal mol⁻¹) and electron charge density at the bond critical point (ρ^{cp} , e/a_0^3)

Model system (the level of theory in parentheses)	Ref.	Coefficients	
		$A/\text{kcal mol}^{-1} (\text{a.u.})^{-1}$	$\Sigma B/\text{kcal mol}^{-1}$
(HF) _n clusters with $n = 2, \dots, 8$ (DFT B3LYP/6-31++G(d,p))	46	98.0	2.7
HF...HR (R = H, Li, Al, Cl, CCH) complexes under external electric fields parallel to the H...F interaction (MP2/6-311++G (d,p))	41	300	-0.6
Water molecule clusters, (H ₂ O) _n , $n = 2, \dots, 6$ (HF/aug-cc-pVTZ)	7	175	0.3
Water molecule clusters, (H ₂ O) _n , $n = 2, \dots, 20$ (HF/6-31(d, p))	47	263.5	0
Phenol-water clusters (HF/6-31G*)	48	212.6	0
Various canonical and noncanonical DNA base pairs (MP2/6-31G*(0.25))	49	315.6	-2.7
28 different intermolecular H-bonded and van der Waals complexes (MP2/aug-cc-pVDZ)	45	356	-2.2
94 different H-bonded complexes: water clusters, phenol-water clusters, ionic water clusters, DNA base pairs, etc. (various)	15	268	0

are of interest: water clusters (H₂O)_n with $n > 6$ with their structural variability³² can serve as an illustrative example.

Among others, the quantum theory of atoms in molecules (QTAIM) approach²⁹ is, perhaps, the most universal tool to characterize H-bonds^{33,34} since it operates on electron density, an experimentally measurable quantity.³⁵⁻³⁸ However, in its original form QTAIM gives no recipe how to connect electron density-derived properties with H-bond strength. To do it, one may use empirically derived complex parameters (such as Grabowski parameter,^{15,39} for example) or try to estimate H-bond dissociation energy. The latter became possible with the paper of Espinosa *et al.*,⁴⁰ establishing the relationship between the H-bond dissociation energy D_e and the virial density V_{el} in the form of

$$D_e = ca_0^3 V_{\text{el}}(\vec{r}_{\text{cp}}), \quad (1)$$

where a_0 is the Bohr radius and c is the dimensionless proportionality constant, so that ca_0^3 represents a kind of the 'effective volume'. In its original form of (1)⁴⁰ the value $c = 1/2$ has been proposed. Despite being very popular (see, e.g., references in ref. 41), the relationship (1) has several shortcomings. It deals with the virial density, which cannot be measured in experiment directly, so in order to use it in practice one has to employ an additional interrelationship between V_{el} and electron charge density.³⁸ Furthermore, the relationship (1) is based on the data from X-ray diffraction experiments, in which the question of possibility of distinguishing the bonding from simple overlapping of electron clouds of neighboring atoms remains controversial.^{42,43} Moreover, the formula (1) was obtained for XH...O (X = C, N, O) H-bonds assuming that their energy depends univocally and solely on the H...O distance, which is not always true.⁴⁴ Another issue arises from the fact that in the case of non-H...O H-bonds the formula (1) with the $c = 1/2$ coefficient is known to overestimate binding energy. In particular, for H...F bonds the smaller value of c ($c = 0.31$) was obtained as the best fit,⁴¹ making it 'safe' to use (1) for weak interactions only.⁴¹

At the same time, there is another way to extract binding energy from QTAIM analysis results since there is evidence^{7,15,41,45-49} that the electron charge density ρ^{cp} at the BCP (bond critical point, *i.e.*, (3,-1)-type electron charge gradient field critical point lying on the bond path corresponding to the H-bond) can also serve as the measure of H-bond strength. On this ground the following relationships connecting intermolecular complex stabilization energy SE (kcal mol⁻¹) with electron

charge density ρ^{cp} (a.u., 1 a.u. = $e a_0^{-3}$, where e is the elementary charge and a_0 is the Bohr radius) have been proposed:

$$\text{SE} = \sum_i E_i, \quad (2)$$

$$E_i = A\rho_i^{\text{cp}} + B, \quad (3)$$

where summation goes over all bonds connecting molecules and index i enumerates bond critical points on the intermolecular bond paths; A and B coefficient values are summarized in Table 1.

Several serious limitations on existing relationships in the form of (2) and (3) should be stressed. First of all, in all the studies mentioned the complex stabilization energy has been assumed to equate the sum of H-bond energies (eqn (2)), which is doubtful (*e.g.*, guanine-cytosine pair of nitrogenous DNA bases is one of the most striking examples of a system, where the stabilization energy markedly exceeds the sum of H-bond energies²⁵). Moreover, the complex stabilization energy itself has been evaluated on the basis of theoretical calculations by means of rather low level computations (except for ref. 45 and 46 and, in part, ref. 7) and was hardly checked experimentally. Second, the regression coefficient values reported by different studies differ substantially (in about 3 times, see Table 1), making it difficult to use regression (3) for practical estimations. The absence of sufficiently large data samplings could also be mentioned. Third, only *intermolecular* H-bonds have been considered. Thus, no reliable data for estimating *intramolecular* H-bonds energy with (3) are available to date.

At the same time, another powerful, but unfairly rarely used in quantum chemistry tool for identification of H-bonds as well as for estimation of their strength is vibrational spectroscopy.¹⁹ Nevertheless, a red-shift of H-bond donor group stretching vibration frequency is, along with QTAIM bond path presence, one of well-accepted criteria for H-bond formation.⁵⁰ Since modern quantum chemical calculations are capable of reproducing experimental vibrational frequencies with the high accuracy (typical RMS deviations of scaled harmonic *vs.* experimentally observed frequencies are less than 40 cm⁻¹⁵¹), calculated vibrational spectra can be considered as a reliable and, which is also important, independent way to evaluate properties of individual H-bonds. In addition, this way is not limited to probing *intermolecular* bonds only.

Therefore, the purpose of the present study is to shed some light on the *intramolecular* H-bond strength evaluation problem

by using large samplings of electron density QTAIM analysis data in conjunction with vibrational spectroscopy data obtained by *ab initio* calculations.

Computational details

The following biologically relevant DNA-related molecules (Fig. 1) have been chosen to obtain (ν_{XH} , E_{HB}) data set: canonical 2'-deoxyribonucleotides (613 conformations of 5'-deoxycytidylic,⁵² 660 conformations of 5'-thymidylic,⁵³ 726 conformations of 5'-deoxyadenylic⁵⁴ and 745 conformations of 5'-deoxyguanylic⁵⁵ acids) and their model structural units: 1,2-dideoxyribose-5-phosphate⁵⁶ (472 conformations), 2-deoxy-D-ribofuranose⁵⁷ (94 conformations of the α -anomer and 107 conformations of the β -anomer), 2-deoxy-D-ribofuranose⁵⁸ (74 conformations of the α -anomer and 83 conformations of the β -anomer) and (3*S*,4*R*)-3,4,5-trihydroxypentanal, the linear (aldehyde) form of 2-deoxy-D-ribose⁵⁹ (670 conformations). Complete conformational families of these molecules have been obtained previously^{52–59} using the DFT B3LYP/6-31G(d,p) level of theory for geometry optimization, calculation of spatial electron density distributions and harmonic frequencies. The scaling factor of 0.961⁶⁰ has been used to scale all harmonic vibrational frequencies, providing their RMS error with respect to experimental values of about 35 cm⁻¹.⁵¹

Large conformational capacity of the molecules under study made it possible to reveal over 8000 intramolecular H-bonds in 4244 conformers in total (see the Results and discussion section for details). Intramolecular H-bonds in each conformer have been detected by means of QTAIM electron density topology analysis using the AimAll software package.⁶¹ The existence of the bond path between two atoms (one and only one of which is hydrogen) containing the (3, -1) critical point was considered as a necessary and sufficient condition to treat the pair of atoms as bonded. Among all H-bonds found in this way only H-bonds of OH...O, OH...N, NH...O and

OH...C types have been selected for further analysis since others, 'nonconventional' (*i.e.*, CH...X) bonds, are difficult to handle with spectroscopic methods.⁶²

Normal vibrations responsible for a given XH proton donating group stretching have been identified by analytical calculation of the derivative $c_j^{\text{XH}} = \partial l_{\text{XH}} / \partial x_j$ of the XH bond length l_{XH} with respect to the j -th normal coordinate x_j and comparing it with the fixed threshold value ($c_{\text{th}} = 0.92$).⁶⁴

H-bond formation enthalpy (referred to simply as 'H-bond energy' hereinafter) has been estimated with Iogansen's relationship^{19,63}

$$E_{\text{HB}} [\text{kcal mol}^{-1}] = 0.33 \sqrt{\Delta\nu [\text{cm}^{-1}] - 40}, \quad (4)$$

where $\Delta\nu = \nu_{\text{XH}}^{\text{free}} - \nu_{\text{XH}}^{\text{bonded}}$ represents the red-shift value of the ν_{XH} frequency caused by H-bond formation with XH group being the proton donor. To obtain the value of $\nu_{\text{XH}}^{\text{free}}$ each molecule as well as each XH group within it have been analyzed independently; $\nu_{\text{XH}}^{\text{free}}$ has been calculated as the simple average of stretching vibration frequencies for XH groups such that: (i) their H atom does not participate in any XH...Y bonding (*i.e.*, no QTAIM bond path ends on it except for the one corresponding to the XH covalent bond), and (ii) unique normal vibration exists with $c_j^{\text{XH}} > c_{\text{th}}$. The RMS deviation of $\nu_{\text{XH}}^{\text{free}}$ obtained in this way falls within the (6.0–28.0) cm⁻¹ range which is lower than both scaled harmonic frequencies error (about 35 cm⁻¹)⁵¹ and the 'lowest possible' red-shift value allowed by (4) (*i.e.*, 40 cm⁻¹). For NH...Y bonds vibrational spectra obtained after non-H-bonded H-atom deuteration have been used to split degeneracy of vibrations of the dGMP -NH₂ group being the proton donor in all NH...O bonds analyzed. In this case the scaled average $\nu_{\text{XH}}^{\text{free}}$ value was 3505 cm⁻¹ with RMS deviation of only 1.7 cm⁻¹.

Using H-bonds energy obtained by (4) linear regression coefficients in eqn (3) have been determined by a standard least-squares fitting procedure for each of four H-bond types independently. XH...Y bonds where the XH group participates

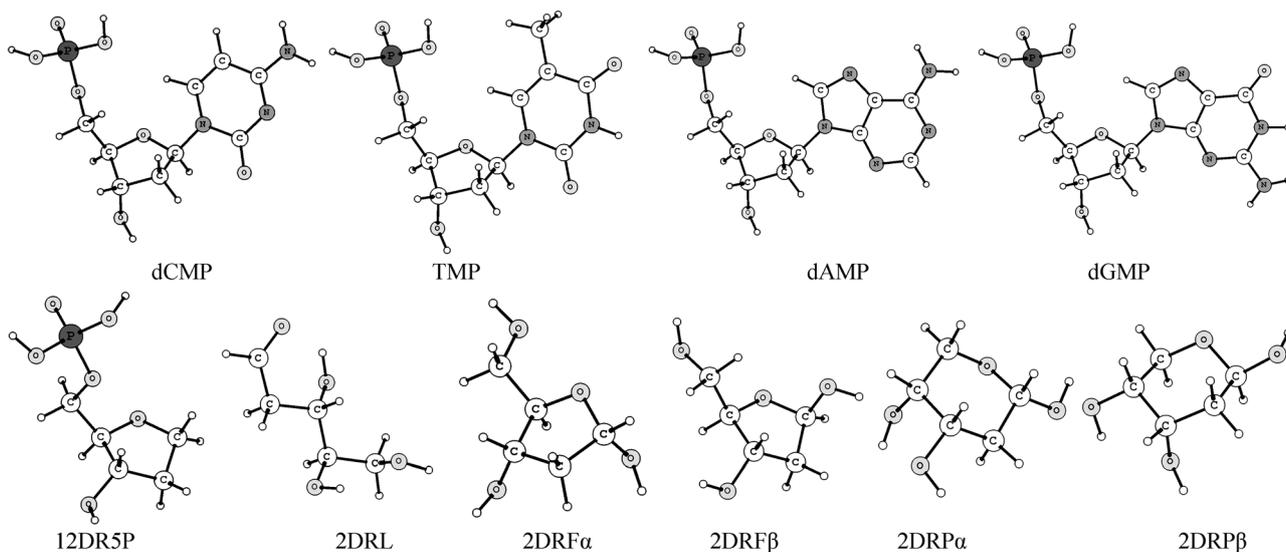


Fig. 1 Biomolecules under study: canonical 2'-deoxyribonucleotides (5'-deoxycytidylic (dCMP), 5'-thymidylic (TMP), 5'-deoxyadenylic (dAMP) and 5'-deoxyguanylic (dGMP) acids), 1,2-dideoxyribose-5-phosphate (12DR5P), 2-deoxy-D-ribose in linear (2DRL), furanose (α -2DRF α) and β -2DRF β) anomers) and pyranose (α -2DRP α) and β -2DRP β) anomers) forms.

in more than one H-bond simultaneously (bifurcating H-bond) have been excluded (8 H-bonds in total).

Results and discussion

In total as many as 2901 conventional H-bonds (2331 OH...O, 297 OH...N, 184 NH...O and 89 OH...C) have been identified in 4424 conformations on the basis of QTAIM electron charge density analysis. Among them, there are 2796 conventional H-bonds having well-established normal vibration corresponding to proton donor group stretching. All but 4 H-bonds are characterized by a red-shift, while only 88% (2457 bonds) have had its value of 40 cm⁻¹ or above—the reasonable threshold value in the sense that this minimal shift value is needed by eqn (4). H-bonds with $\Delta\nu_{\text{XH}} \geq 40 \text{ cm}^{-1}$ will be referred to as ‘well-red-shifted H-bonds’ hereinafter. Next, bifurcating H-bonds (*i.e.*, with more than one proton acceptor bonded to a given proton donor) have been excluded so that the final data sampling contained 2449 H-bonds.

It should be mentioned, however, that 127 OH-groups have been detected (about 4% as compared to a total number of conventional H-bonds) with red-shift values over 40 cm⁻¹, but for which no bonding path indicating the presence of H-bonds has been found with QTAIM. The maximum red-shift value for such ‘free’ OH group was found to be 78 cm⁻¹ and found in the 2DRL molecule (the structure of the corresponding conformer is available, see the ESI†).

Table 2 contains the total number of bonds of each type as well as minimum and maximum values of their geometrical parameters and physical properties of bond critical points. Fig. 2 outlines the distribution of H-bonds geometrical properties in the ‘distance–angle’ frame.

It is noteworthy that no H-bonds with the XHY angle below 112° were found among well-red-shifted conventional H-bonds. This agrees well with a generally accepted lower threshold of 110°.¹⁸ Another important finding is that no well-red-shifted H-bond has its ρ^{cp} value below 0.005 $e a_0^{-3}$ and $\nabla^2 \rho^{\text{cp}}$ below 0.016 $e a_0^{-5}$ (see Table 2), which is also in good agreement with the values recommended by Koch and

Table 2 Ranges of geometrical parameters and bond critical point physical properties for well-red-shifted hydrogen bonds^a

H-bond	No. of bonds	Geometry ^b		Bond critical point properties ^c					
		$L_{\text{XY}}/\text{Å}$	$\angle \text{XHY}/^\circ$	$\rho^{\text{cp}}, 10^{-2} \text{ a.u.}$	$\nabla^2 \rho^{\text{cp}}, 10^{-2} \text{ a.u.}$	min	max		
OH...O	1949	2.581	3.089	112.7	177.5	1.18	4.96	4.14	15.8
OH...N	269	2.589	3.173	122.0	178.3	0.88	7.64	3.27	11.7
NH...O	150	2.828	3.489	129.7	178.4	0.61	3.58	2.39	10.2
OH...C	81	3.125	3.780	129.3	179.0	0.49	1.49	1.64	3.80

^a ‘Well-red-shifted’ are hydrogen bonds with the donor group stretching vibration frequency red-shift value of 40 cm⁻¹ or above. ^b L_{XY} denotes the distance between the nuclei of ‘heavy’ atoms X and Y and $\angle \text{XHY}$ is the angle between lines X–H and H–Y. ^c ρ^{cp} and $\nabla^2 \rho^{\text{cp}}$ are electron charge density and its laplacian values calculated at the bond critical point; one atomic unit (a.u.) corresponds to e/a_0^3 for electron density and to e/a_0^5 for its laplacian, e is elementary charge, $a_0 \approx 0.529 \text{ Å}$ is the Bohr radius.

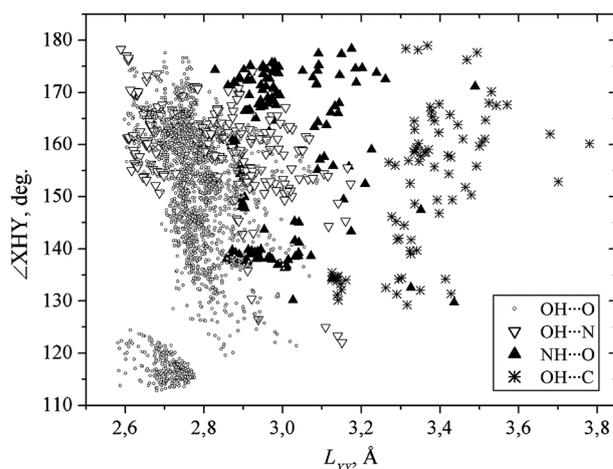


Fig. 2 Geometrical parameters distribution of well-red-shifted intramolecular hydrogen bonds (XH...Y) found in biomolecules under study.

Popelier criteria^{65,66} and molecular crystal analysis by Munshi and Guru Row.⁶⁷

As can be seen from Fig. 2 and Table 2, all the OH...C H-bonds investigated are slightly ‘longer’ than the others: the average value of O–C distance is 3.36 Å with standard deviation (SD) of 0.13 Å while corresponding X–Y distances for other H-bond types are 2.99 Å (SD = 0.12 Å) for NH...O, 2.77 Å (SD = 0.08 Å) for OH...O and 2.82 Å (SD = 0.14 Å) for OH...N. For OH...Y bonds there is a clear trend for the

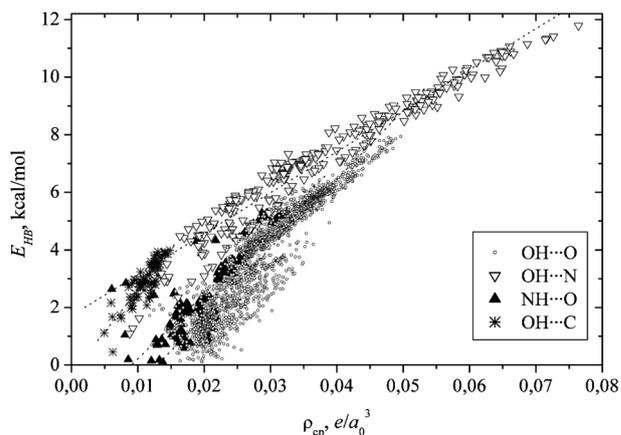


Fig. 3 Hydrogen bond energy (E_{HB}) plotted vs. electron charge density (ρ^{cp}) in the bond critical point for well-red-shifted intramolecular hydrogen bonds found in biomolecules under study.

Table 3 Linear fit parameter values for linear relation $E_{\text{HB}} = A\rho^{\text{cp}} + B$ between the HB energy E_{HB} (kcal mol⁻¹) and the electron charge density value ρ^{cp} (e/a_0^3) at the bond critical point^a

H-bond	$A/\text{kcal mol}^{-1} (e a_0^{-3})^{-1}$	$B/\text{kcal mol}^{-1}$	Correlation coefficient, R	Standard deviation, $\sigma_E/\text{kcal mol}^{-1}$
OH...O	239 ± 2.2	-3.09 ± 0.07	0.93	0.69
OH...N	142 ± 2.1	1.72 ± 0.08	0.97	0.50
NH...O	225 ± 12	-2.03 ± 0.25	0.85	0.76
OH...C	288 ± 19	-0.29 ± 0.22	0.86	0.35

^a Estimates for the parameter standard deviations are given after ‘±’ sign.

Table 4 Geometrical and physical properties of the strongest intramolecular H-bonds of each type found among all possible conformations of canonical 2'-deoxy- and ribonucleosides^{71–73}

H-bond ^a (nucleoside ^b)	Conformational attributes: $\chi/P/\beta/\gamma/\varepsilon^c$ (ref. and the conformer number within it)	Geometry ^d			BCP properties		Bond energy ^e / kcal mol ⁻¹
		$L_{XY}/\text{\AA}$	$L_{H\dots Y}/\text{\AA}$	$\angle XHY/^\circ$	ρ^{CP} 10 ⁻² a.u.	$\nabla^2\rho^{\text{CP}}$ 10 ⁻² a.u.	
O ₂ H⋯O ₂ (rC)	<i>anti</i> /C _{2'} <i>endo</i> /g ⁺ /g ⁺ /t (ref. 72 and 16)	2.664	1.739	154.9	4.1	12.3	6.7
O ₃ H⋯N ₃ (rG)	<i>syn</i> /C _{2'} <i>endo</i> /g ⁺ /g ⁺ /g ⁺ (ref. 73 and 6)	2.753	1.770	172.8	4.5	10.6	8.1
N ₂ H⋯O _{5'} (rG)	<i>syn</i> /C _{2'} <i>exo</i> /g ⁻ /g ⁻ /g ⁺ (ref. 73 and 118)	3.243	2.296	154.6	1.2	3.7	0.7
O ₃ H⋯C ₈ (rG)	<i>anti</i> /C _{4'} <i>endo</i> /g ⁺ /g ⁺ /t (ref. 73 and 75)	3.302	2.456	146.0	1.0	3.6	2.6

^a Conventional atom names used (see ref. 74). ^b rC = cytidine, rG = guanosine. ^c Details of conformer structures can be found in ESI. ^d $L_{H\dots Y}$ denotes the distance between the hydrogen atom and proton acceptor atom nuclei, while L_{XY} is the distance between proton donor (X) and proton acceptor (Y) atoms nuclei. ^e Hydrogen bond energies have been estimated with eqn (3) using regression coefficients from Table 3.

average O–Y distance; the bigger the van-der-Waals radii⁶⁸ of Y (1.71 Å for C, 1.50 Å for N and 1.29 Å for O), the bigger this distance is.

Fig. 3 displays correlation between the electron charge density at the bond critical point ρ^{CP} and H-bond energies E_{HB} (and hence the red-shift values) obtained by eqn (4) along with the corresponding linear regressions (shown with dotted lines). Peculiar properties of OH⋯C H-bonds can also be seen here since their maximum energy is just $E_{\text{HB}}^{\text{max}} = 4.0$ kcal mol⁻¹, which is small as compared to others ($E_{\text{HB}}^{\text{max}} = 5.6$ kcal mol⁻¹ for NH⋯O, 7.9 kcal mol⁻¹ for OH⋯O and 11.8 kcal mol⁻¹ for OH⋯N). Relatively large spread of points in the low H-bond energy region is due to the fact that in this region the values of $\Delta\nu$ are close to the typical RMS deviation of scaled harmonic frequencies obtained *ab initio* with respect to experimental ones (about 35 cm⁻¹⁵¹). Table 3 outlines linear regression (3) parameters for each of four H-bond types separately.

First of all we should note that regression coefficients differ substantially (up to twice: A from 142 to 288, B from -3.1 to 1.7) depending on the bond type. This makes it clear why the linear regression coefficient values reported for intermolecular H-bonded complexes previously (see Table 1) differ so much. As an additional justification we have performed linear approximation of the whole (ρ^{CP} , E_{HB}) dataset making no distinction by the bond type. This resulted in coefficient values $A = 200 \pm 2.2$ and $B = -1.70 \pm 0.07$ with correlation coefficient $R = 0.88$ and standard deviation $\sigma_E = 1.0$ kcal mol⁻¹ much higher than those for individual bonds (see Table 3).

Finally, it might be interesting to verify regressions obtained in this work for *intermolecular* complexes. Since the number of OH⋯O bonds analyzed is the highest it seems to be reasonable to use this case for testing. According to data in Table 3 the corresponding linear regression would be

$$E_{\text{OH}\dots\text{O}} [\text{kcal mol}^{-1}] = -3.09 + 239 \cdot \rho^{\text{CP}} [\text{a.u.}], \quad (5)$$

For instance, in the case of water dimer optimized at the DFT B3LYP/6-31G(d,p) level of theory the BSSE-correction accounted ρ^{CP} value at the OH⋯O H-bond critical point is 0.026 a.u. hence (5) gives $E_{\text{HB}} = 3.1$ kcal mol⁻¹, which is in excellent agreement with the stabilizing enthalpy (3.2 ± 0.1 kcal mol⁻¹) with thermal corrections at 373 K obtained theoretically⁶⁹ and with the experimental binding enthalpy of 3.15 ± 0.03 kcal mol⁻¹.²⁰ In contrast to our results, Espinosa–Molins–Lecomte's eqn (1) gives 6.25 kcal mol⁻¹ (the virial density at the bond critical point is $V_{\text{el}} = 0.020$ a.u.) if $c = 1/2$ is taken. Considering

thermal correction to be $3k_{\text{B}}T \approx 1.75$ kcal mol⁻¹ this gives the enthalpy of $\Delta H^{\text{EML}} = 4.50$ kcal mol⁻¹ being about 30% higher than its real value, while with $c = 0.31$ $\Delta H^{\text{EML}} = 2.12$ kcal mol⁻¹, about 30% lower than the real value.

We believe that the discrepancies between real bond energies and energies calculated by means of the Espinosa–Molins–Lecomte equation originate from the fact that the latter has been parametrized using H-bonds data for the substance in crystalline state effectively strengthening H-bonds.⁷⁰

The H-bond energy expressions obtained in the present paper have also been applied to find the strongest intramolecular H-bonds in all possible conformations of canonical 2'-deoxy- and ribonucleosides,^{71–73} the elementary DNA units.⁷⁴ Table 4 lists geometrical parameters and physical properties of the strongest H-bonds of each type revealed. It may be concluded that OH⋯O and OH⋯N H-bonds have the maximum energy (6.7 and 8.1 kcal mol⁻¹ respectively) and hence have the strongest impact on stabilization of the molecules conformations.

Conclusions

Intramolecular H-bonds in 4244 conformers of the DNA-related molecules have been investigated using DFT calculations, Bader's quantum theory of atoms in molecules and vibrational analysis.

It has been established that in 88% of 2901 XH⋯Y bonds (OH⋯O, OH⋯N, NH⋯O and OH⋯C) detected by the presence of the bond path connecting the hydrogen atom with the Y atom, the XH stretching vibration red-shift value exceeds 40 cm⁻¹. At the same time, red-shifts over 40 cm⁻¹ in OH groups without such a bond path have been found in only 4% of cases. This implies that the presence of the bond path connecting H and Y atoms can, in most cases, be considered as a necessary and sufficient criterion for H-bond detection.

All conventional H-bonds with red-shift over 40 cm⁻¹ have their XHY angle above 112°, electron charge density value at the bond critical point (ρ^{CP}) above 0.005 $e a_0^{-3}$ and $\nabla^2\rho^{\text{CP}}$ above 0.016 $e a_0^{-5}$.

Using well-established spectroscopic relationship connecting H-bond enthalpy of formation (E_{HB}) and the red-shift value, linear relationships between E_{HB} (kcal mol⁻¹) and bond critical point electron charge density (ρ^{CP} , e/a_0^3) have been established: $E_{\text{HB}} = -3.09 + 239 \cdot \rho^{\text{CP}}$ (OH⋯O), $E_{\text{HB}} = 1.72 + 142 \cdot \rho^{\text{CP}}$ (OH⋯N), $E_{\text{HB}} = -2.03 + 225 \cdot \rho^{\text{CP}}$ (NH⋯O), $E_{\text{HB}} = -0.29 + 288 \cdot \rho^{\text{CP}}$ (OH⋯C). These relationships have been

used to reveal the strongest intramolecular H-bonds in canonical 2'-deoxy- and ribonucleosides and the $O_5H \cdots N_3$ H-bond in ribonucleoside guanosine was found to have the maximum energy (8.1 kcal mol⁻¹).

Acknowledgements

The authors highly appreciate the access to high-performance computational resources and software provided by the Boholubov Institute for Theoretical Physics of National Academy of Sciences of Ukraine. We also encourage the kind help of Dr Yevgen P. Yurenko in article preparation and Dr Roman O. Zhurakivsky for nucleoside database processing.

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