The significant role of the intermolecular CH⋯O/N hydrogen bonds in governing the biologically important pairs of the DNA and RNA modified bases: a comprehensive theoretical investigation

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This paper is a logical continuation of the theoretical survey of the CH⋯O/N specific contacts in the nucleobase pairs using a wide arsenal of the modern methods, which was initiated in our previous study [J. Biomol. Struct. & Dynam., 2014, 32, 993–1022]. It was established that 34 CH⋯O and 7 CH⋯N interactions, that were detected by quantum-chemical calculations in the 39 biologically important pairs involving modified nucleobases, completely satisfy all geometrical, vibrational, electron-topological, in particular Bader’s and “two-molecule” Koch and Popelier’s, Grunenberg’s compliance constants theory and natural bond orbital criteria indicating that they can be identified as true H-bonds. The geometrical criteria of the H-bond formation are fulfilled for all considered CH⋯O/N H-bonds without any exception. It was shown that the classical rule of the stretching vibration shifts does not work in the ~95% cases of the CH⋯O/N H-bonds. Furthermore, significant increase in the frequency of the out-of-plane deformation modes γ(CH) under the formation of CH⋯O/N H-bonds and corresponding changes of their intensities can be also considered as reliable indicators of the H-bonding. We revealed high linear mutual correlations between the electron density, Laplacian of the electron density, H-bond energy at the (3, −1) bond critical points of the CH⋯O/N H-bonds, and different physico-chemical parameters of the CH⋯O/N H-bonds. We suggested that the electron density ρ and the interaction energy $E^{(2)}_{O/N}$ of the lone orbital pairs are the most reliable descriptors of the H-bonding. The linear dependence of the H-bond energy $E_{CH⋯O/N}$ on the electron density ρ was established: $E_{CH⋯O} = 250.263 \rho + .380/258.255 \rho + .396$ and $E_{CH⋯N} = 196.800 \rho + .172/268.559 \rho + .703$ obtained at the density functional theory (DFT)/Moller–Plesset (MP2) levels of theory, respectively. The studies of the interaction energies show that the contribution of the CH⋯O and CH⋯N H-bonds into the base pairs stability varies from 3.0/4.2 to 35.1/31.2% and from 3.0/4.3 to 44.4/46.5% at the DFT/MP2 levels of theory, accordingly. Energy decomposition analysis performed for all base pairs involving canonical and modified nucleobases defines the electrostatic attraction and Pauli repulsion as dominant stabilizing forces in all complexes. This observation was additionally confirmed by the results of the QTAIM delocalization indexes analysis. The studies reported here advance our understanding of the biological role of the weak CH⋯O/N H-bonds, that dictates the requirements for the structural and dynamical similarity of the canonical and mismatched pairs with Watson–Crick (WC) geometry, which facilitates their enzymatic incorporation into the DNA double helix during DNA replication. Thus, these H-bonds in the base pairs with WC geometry may be also considered as “the last drop” at the transmission of the electronic signal that launches the chemical incorporation of the incoming nucleoside triphosphate into DNA.

Keywords: CH⋯O/N H-bonds; pairs of nucleobases; QTAIM and NBO analyses; Bader’s criteria; “two-molecule” Koch and Popelier’s criteria; Grunenberg’s compliance constants; quantum-chemical methods; energy decomposition analysis; QTAIM delocalization indexes

Introduction

The phenomenon of the hydrogen (H) bonding has nearly hundred-year history (Gilli & Gilli, 2009; Jeffrey, 1997; Pauling, 1960). Today, it is difficult to imagine it without such branches of the natural science as structural organization of nucleic acids and their complexes with proteins, crystal and polymer packing, self-assembly, supramolecular chemistry, solvation, molecular recognition, and protein folding (Frieden, 1975; Kaplan, 2006; Kollman, 1977; Lehn, 1995).

The H-bonding is the main type of the inter- and intramolecular interactions responsible for the functioning of the biopolymers and their complexes in the living cell (Desiraju & Steiner, 1999; Grabowski, 2006; Jeffrey & Saenger, 1991). It is believed that even if the phenomenon of the H-bonding did not exist then there would be...
no life on the Earth, at least in those forms in which it exists today.

Non-covalent interactions, especially the H-bonds, determine the three-dimensional structures (conformations) of the biomolecules (Jones, Barah, Thompson, Scheiner, & Smith, 2012; Suzuki et al., 2014), e.g. peptides (Niaraki, Kondejewski, Wheaton, & Hodges, 2009), proteins and ligands (Gosein, Leung, Krajden, & Miller, 2012), carbohydrates and nucleic acids (Srivastava et al., 2007), lipids, and so on, the proper biological functioning of which is not possible without the formation of different conformations.

The directional character (Arunan et al., 2011) and comparatively low energy of the H-bonds explain their importance in the biologically important processes such as self-assembling and shaping of the biomolecules (Jones et al., 2012; Vibhute & Sureshan, 2014), recognition between them (Couloucher, Pigis, Papavassiliou, & Papavassiliou, 2007), and various biochemical reactions (Nelson & Cox, 2008; Satoh & Manabe, 2013). In biology, besides the conventional H-bonds involving the N and O atoms acting as H-bond acceptors and donors, the non-conventional H-bonds of the CH⋯O/N type (Castellano, 2004; Desiraju & Steiner, 1999; Scheiner, 2000), which includes the C atom as the H-bond donor, have been proved to be widespread, e.g. in proteins (Derewenda, Lee, & Derewenda, 1995; Scheiner, 2005, 2006, 2011), RNA (Auflinger & Westhof, 1997; Brandl, Lindauer, Meyer, & Sühnel, 1999), DNA (Bandyopadhyay & Bhattacharyya, 2006; Berger, Egli, & Rich, 1996; Ghosh & Bansal, 1999), regulatory protein-DNA interfaces (Mandel-Gutfreund, Margalit, Jernigan, & Zhurkin, 1998), DNA-drug complexes (Panigrahi & Desiraju, 2007), and different chemical compounds (Madura et al., 2013; Thomas, Pavan, & Row, 2012; Vibhute & Sureshan, 2014; Yang & Wong, 2013). Notably, that among the wide variety of the H-bonds, that keep living, the weakest of them, the CH⋯O/N H-bonds, are explored the worst. Moreover, the most “white spot” in this sense are nucleic acids, including DNA.

The H-bonds between complementary nucleobases exert a significant influence, to a great extent, on the spatial structure and dynamics of DNA (Neidle, 2008). Many vital processes at the molecular level (e.g. replication, transcription, reparation) are accompanied by the breaking and formation of the H-bonds connecting two complementary DNA strands (Nelson & Cox, 2008). In canonical DNA, the pairs of complementary nucleotide bases (guanine-cytosine and adenine-thymine) are engaged in strong conventional O/N H⋯O/N H-bonds, besides which DNA is netted with the lace of weak H-bonds such as CH⋯O/N H-bonds formed between the two bases, between the bases and the sugar phosphate backbone and between the backbones (Yurenko, Zhurakivsky, Samijlenko, & Hovorun, 2011), as well as of the cross-strand interactions between the non-complementary Watson–Crick (WC) pairs, some of which have been studied experimentally (Berger et al., 1996; Egli & Gessner, 1995; Neidle, 2008; Yoon, Privé, Goodsell, & Dickerson, 1988; Yurenko, Zhurakivsky, et al., 2011) and theoretically (Bandyopadhyay & Bhattacharyya, 2006; Ghosh & Bansal, 1999; Matta, Castillo, & Boyd, 2006). The duplex fragments or three-dimensional secondary structures, that are vitally important for the biological functions of the RNA molecules (Bloomfield, Crothers, & Tinoco, 2000), can be formed in them due to the intra-molecular interactions, although the RNA molecules usually exists as “single strands” in living cells.

In addition to WC base pairing, there are various types of non-canonical base pairs found in crystal structures of different DNA (Neidle, 2008; Saenger, 1984) and RNA macromolecules (Leontis & Westhof, 1998; Saenger, 1984; Strobel, Ortoleva-Donnelly, Ryder, Cate, & Moncoeur, 1998; Wöhnert et al., 1999), which are known to play a crucial role in maintaining the nucleic acid spatial structure and contributing to the diversity of their biological functions (Hermann & Westhof, 1999; Nikolova et al., 2011; Strobel et al., 1998).

This theoretical survey 39 pairs formed with the participation of the modified bases were investigated, among which we can distinguish several classes: the first one includes 5-methylcytosine (5MC), 6-azacytosine (6-azaC), and isocytosine (isoC). 5MC is a common modified base in DNA (Clark, Harrison, Paul, & Frommer, 1994), playing a profound role in the epigenetic regulation of the transcription, development, genome stability (Nabel, Manning, & Kohli, 2012), gene expression, and sustentation of the cellular identity (Jaenisch & Bird, 2003; Jones & Baylin, 2002). Moreover, hypermethylation of DNA, leading in particular to the formation of 5MC, is associated with aging and human diseases including cancer (Jones & Baylin, 2002). 6-azacytosine (Samijlenko et al., 1999a, 1999b) is an analogue of cytosine (C) and, as well as 6-azacytidine (Mishchuk, Potyagaylo, & Hovorun, 2000; Singh & Hodgson, 1974) and 2′-deoxy-6-azacytidine (Yurenko, Zhurakivsky, Ghomi, Samijlenko, & Hovorun, 2007a) nucleosides, exhibit broad-spectrum antiviral activity (Alexeeva et al., 2001). Moreover, chemical modifications in canonical DNA and RNA nucleobases have been widely used in design of antiviral, antitumoral, and fungalid drugs (Herdevijin, 2008). isoC is a pyrimidine base that is an isomer of C base mimicking it while pairing with adenine (A), but is usually considered in combination with isoguanine (isoG) at the studies of the analogues of the normal base pairs in DNA (Dračinský, Jansa, Ahonen, & Buděšínský, 2011; Ivanov, Stepianian, & Adamowicz, 2012; Kwiatkowski & Leszcynski, 1997; Tae, Wu, Xia, Schultz, & Romesberg, 2001).

The second subset contains mutagenic bases, which result either from natural deamination, in particular of the
guanine with the formation of xanthine (X) (Platonov, Samijlenko, Sudakov, Kondratyuk, & Hovorun, 2005), and oxidation of A and G with the formation of 8-oxoadenine (8oxoA) and 8-oxoguanine (8oxoG) (Kamiya et al., 1995; Shibutani, Takeshita, & Grollman, 1991; van Loon, Markkanen, & Hübscher, 2010), respectively, that are highly mutagenic in mammalian cells. 8oxoG and 8oxoA modified bases, formed as a result of the DNA lesion by the free radicals forms of the oxygen, are especially deleterious due to their ability to functionally mimic thymine (T) in the syn-conformation and to give rise to the formation of the very stable Hoogsteen (H) base pairs with adenine (A·8oxoG<sub>syn</sub> and A·8oxoA<sub>syn</sub>) in addition to the formation of the very stable Hoogsteen (H) base pairs with adenine (A·8oxoG<sub>syn</sub> and A·8oxoA<sub>syn</sub>) in addition to the formation of the very stable Hoogsteen (H) base pairs with adenine (A·8oxoG<sub>syn</sub> and A·8oxoA<sub>syn</sub>). Thus, among these modified bases, A·8oxoG<sub>syn</sub> and A·8oxoA<sub>syn</sub> are the most mutagenic.

The third class of the modified bases consists of the analogues of the nucleobases lacking the N3 or O2 conformation of the CH<sub>O/N</sub> H-bonds and concomitant changes of their intensities have been established to be the reliable indicators of the H-bonding. We revealed 8-azaA has attracted much attention in the literature due to its antifungal, antiviral, and anticancer activities in biological systems (Seela & Mersmann, 1992; Seela, Münster, Lüchner, & Rosemeyer, 1998; Seela & Röling, 1992). It was established in the course of the numerous studies (Grein et al., 1994; Seela & Röling, 1992) that 7-deazaP significantly affects the stability of the DNA duplex. It is noteworthy that recent NASA meteorite studies (Callahan et al., 2011) revealed some DNA and RNA nucleobases, among which there are adenine, guanine, xanthine, hypoxanthine, and purine capable to form canonical base pairs, which may have been formed extraterrestrially in outer space.

In our previous work (Brovarets’, Yurenko, & Hovorun, 2013), we have gained insight into the physico-chemical nature and energetic of the non-conventional CH⋯O/N H-bonds in the 36 biologically important pairs involving natural nucleobases in the canonical and rare tautomeric forms by using quantum-chemical methods. As a result, we succeeded for the first time in the establishment that all CH⋯O/N contacts completely satisfy all known criteria of the classical H-bonding, in particular geometrical, electron-topological (Bader’s and “two-molecule” Koch and Popelier’s), natural bond orbital (NBO), Grunenberg’s compliance constants, and vibrational. Moreover, significant increase in the frequency of the out-of-plane deformation modes γ(CH) under the formation of the CH⋯O/N H-bonds and concomitant changes of their intensities have been established to be the reliable indicators of the H-bonding. We revealed high linear mutual correlations between the H-bond energy, estimated by the Espinosa–Molins–Lecomte (EML) method (Espinosa, Molins, & Lecomte, 1998; Mata, Alkorta, Espinosa, & Molins, 2011; Matta et al., 2006), and different physico-chemical parameters of the CH⋯O/N H-bonds. The electron density ρ at the (3, −1) CH⋯O/N H-bond critical points (BCP) and the stabilization energy Ḣ<sup>2</sup> related to the delocalization trend of electrons from donor to acceptor orbitals were suggested to be the most reliable descriptors of the H-bonding.

These results can be applied at the identification of the CH⋯O/N H-bonds in the other biologically important base pairs: they can be considered as true H-bonds with great probability, if their basic physico-chemical parameters, especially the ρ and NBO parameters, do not
extend beyond the range for the similar characteristics presented in the paper (Brovarets’ et al., 2013).

We supposed that unconventional CH⋯O/N H-bond plays the role of the third “fulcrum,” ensuring structural and dynamical similarity of the isomorphic base pairs of different origin, incorporating well into the structure of the DNA double helix, with themselves and with the A:T WC and G:C WC canonical base pairs. Furthermore, the CH⋯O/N H-bonds play a crucial role in the stabilization of those base pairs, stabilized solely by the weak CH⋯O/N contacts.

This paper is a logical continuation of the previous one (Brovarets’ et al., 2013). It aims to extend the approaches grounded earlier by us to the wider range of the biologically important objects, namely to the H-bonded pairs of the modified bases. In this context, we have carefully reviewed the available literature to identify the H-linked pairs involving modified bases, which are potential applicants for the presence in them intermolecular CH⋯O/N H-bonds. Then we have investigated them in the way it was done in the work (Brovarets’ et al., 2013), using the whole arsenal of powerful state-of-art quantum chemical techniques including Bader’s QTAIM theory (Bader, 1990), “two-molecule” Koch and Popelier’s criteria (Koch & Popelier, 1995), compliance constants theory (Brandhorst & Grunenberg, 2008, 2010; Grunenberg & Barone, 2013; Grunenberg, Barone, & Spinello, 2014), NBO (Weinhold & Landis, 2005), geometrical (Brovarets’ & Hovorun, 2014a, 2014b), vibrational (Brovarets’, Zhurakivsky, & Hovorun, 2014a, 2014b, 2014c), electron-topological (Brovarets’ & Hovorun, 2014c; Brovarets’, Zhurakivsky, & Hovorun, 2014d; Yurenko, Zhurakivsky, Samijlenko, Ghomi, & Hovorun, 2007; Yurenko, Zhurakivsky, Ghomi, Samijlenko, & Hovorun, 2007b, 2008), energy decomposition, and delocalization (te Velde et al., 2001) comprehensive analyzes to reveal the electronic nature of the CH⋯O/N interactions in the pairs involving modified bases, to provide the first accurate estimation of the CH⋯O/N H-bonds energies, as well as their contribution to the overall base pair stability, and to characterize them from the physico-chemical point of view. In all considered base pairs the sugar-phosphate residues at the N1 and N9 positions of the pyrimidine and purine bases, respectively, have been replaced by the hydrogen atoms.

Similarly to our previous work, we have used the same configurations of the pairs involving modified bases in the canonical and rare tautomeric forms (Brovarets’, 2013a, 2013b; Brovarets’ & Hovorun, 2013a; Brovarets’, Zhurakivsky, & Hovorun, 2013a; Furmanchuk et al., 2011; Jacquemin, Züñiga, Requena, & Cérón-Carrasco, 2014; Kosenkov et al., 2009; Lin, Wang, Wu, Gao, & Schaefer, 2014; Samijlenko, Krechkivska, Kosach, & Hovorun, 2004; Samijlenko, Yurenko, Stepanyugin, & Hovorun, 2011). The choice of the base pairs set with potential CH⋯O/N contacts seems to be quite logical, since it gives insight into the effect of the chemical modifications of the bases on the structure and stability of the CH⋯O/N interactions.

As a result, we have identified 39 base pairs, in which 41 CH⋯O/N contacts, that are true H-bonds, have been totally fixed. It turned out that the vast majority of these base pairs possess the closest relationship to such important biological problem as understanding of the mechanisms of the high fidelity of the DNA biosynthesis and physico-chemical nature of the errors that occur at this. Based on the obtained results, we have managed to supplement the previously formulated hypothesis about the role of the CH⋯O/N H-bonds in both canonical and irregular base pairs, that are synthesized by the DNA-polymerase, as the “last drop” at the transmission of the electrical signal that in the base-pair recognition center base pairs have geometrical and electrical structure suitable for the synthesis into actually the active center of the DNA-polymerase.

Computational methods

All calculations have been carried out with the Gaussian’09 suite of programs (Frisch et al., 2010). Geometries and harmonic vibrational frequencies of the base pairs were obtained using B3LYP variant (Tirado-Rives & Jorgensen, 2008) of density functional theory (DFT), which includes Becke’s three-parameter exchange functional (B3) (Parr & Yang, 1989) combined with Lee, Yang and Parr’s (LYP) correlation functional (Lee, Yang, & Parr, 1988) and second-order Möller–Plesset (MP2) method (Frisch, Head-Gordon, & Pople, 1990) in connection with 6–31G(d,p) Pople’s basis set (Frisch, Pople, & Binkley, 1984; Hariharan & Pople, 1973; Krishnan, Binkley, Seeger, & Pople, 1980) of valence double-ζ quality augmented with polarization functions (hereinafter in this Article referred to as “DFT” and “MP2”, respectively) used earlier by Koch and Popelier (1995). Scaling factors of .9580 and .9531 (Brovarets’ & Hovorun, 2013d, 2013e, 2014d, 2014e) have been used in the present work at the DFT and MP2 levels of theory, respectively, to correct the harmonic frequencies of all the studied base pairs. The correspondence of the stationary points to minima on the potential energy landscape has been checked by the absence of imaginary frequency in the vibrational spectra (Brovarets’ & Hovorun, 2011a; Brovarets’, Yurenko, Dubey, & Hovorun, 2012; Brovarets’, Zhurakivsky, & Hovorun, 2013b, 2013c; Shishkin, Pelemenshikov, Hovorun, & Leszczynski, 2000). DFT and MP2 levels of theory have recommended itself well in previous studies of the similar objects (Brovarets’ et al., 2013; El-Sayed, Tamara Molina, Alvarez-Ros, & Alcolea Palafoux, 2014; Lozynski, Rusinska-Roszak, & Mack, 1998; Matta, 2010; Palafoux, 2014).
To completely include electronic correlation effects at the calculations of the electronic energy, we followed the geometry optimizations with single point energy calculations in vacuum at the MP2 level of theory using 6–311++G(2df,pd) Pople's basis set (Frisch et al., 1984; Hariharan & Pople, 1973; Krishnan et al., 1980) of valence triple-$\zeta$ quality augmented with polarization and diffuse functions.

In order to estimate the contribution of the CH⋯O/N interactions into the base-pairing energies, we have computed the electronic interaction energies in vacuum $E_{\text{int}}$ at the MP2/6–311++G(2df,pd) level of theory for the geometries optimized at the DFT and MP2 levels of theory as the energy difference between the base pair and the isolated monomers. The interaction energies of all base pairs have been corrected for the basis set superposition error (BSSE) (Boys & Bernardi, 1970; Gutowski, Van Lenthe, Verbeek, Van Duijneveldt, & Chalasinski, 1986) using the counterpoise (CP) correction procedure (Sordo, 2001; Sordo, Chin, & Sordo, 1988).

In order to perform energy decomposition analysis (EDA) of the interaction energies ($\Delta E_{\text{int}}$) between two moieties in the pairs involving natural and modified bases in DNA and RNA we have re-optimized them by means of ADF program (ADF2012.01; te Velde et al., 2001) using the B3LYP exchange-correlation functional augmented by Grimme’s D3 empirical dispersion correction (Grimme, Antony, Ehrlich, & Krieg, 2010) in combination with polarized triple-$\zeta$ basis set of Slater-type orbitals (TZP). The resulting optimized structures were subject to EDA at the same level of theory into electrostatic interaction ($\Delta V_{\text{elstat}}$), Pauli repulsion ($\Delta E_{\text{Pauli}}$), attractive orbital interactions ($\Delta E_{\text{oi}}$) (accounting for charge transfer and polarization), and dispersion energy ($\Delta E_{\text{disp}}$) terms:

$$\Delta E_{\text{int}} = \Delta V_{\text{elstat}} + \Delta E_{\text{Pauli}} + \Delta E_{\text{oi}} + \Delta E_{\text{disp}}.$$  

The Gibbs free energy $G$ for all structures were obtained in the following way:

$$G = E_{\text{el}} + E_{\text{corr}},$$

where $E_{\text{el}}$ – the electronic energy, $E_{\text{corr}}$ – the thermal correction.

To confirm the presence of the intermolecular CH⋯O/N H-bonds, Bader’s quantum theory “Atoms in molecules” (QTAIM) was applied to calculate the charge density $\rho(r)$, its second derivative – Laplacian of the charge density $\Delta \rho(r)$ and the delocalization index (DI) (Ponomareva, Yurenko, Zhurakivsky, van Mourik, & Hovorun, 2012, 2014; Yurenko, Zhurakivsky, Samijlenko, & Hovorun, 2011). A topological analysis of the electron density has been carried out using AIM-All program package (Keith, 2010) with all the default options. Wave functions were obtained at the level of theory used for geometry optimization. The presence of a BCP, namely the so-called (3, −1) BCP and a bond path between hydrogen donor and acceptor, as well as the positive value of the Laplacian at this BCP ($\Delta \rho > 0$), were considered as indicators of the H-bond formation (Brovarets et al., 2013; Ponomareva et al., 2012, 2014; Yurenko, Zhurakivsky, et al., 2011).

Moreover, additional Koch and Popelier’s criteria (1995), including changes of atomic properties (positive charge increase $\Delta q$, dipolar polarization decrease $\Delta M$, reduction in atomic volume $\Delta V$ and energetic destabilization $\Delta E$), and mutual penetration of hydrogen and acceptor atoms (the sum $\Delta r_{\text{H}} + \Delta r_{\text{O/N}}$ of variations in atomic radii of the H donor and O/N acceptor atoms) were applied to test each of the CH⋯O/N H-bonds in the biologically important pairs involving modified nucleobases. Furthermore, the CH⋯O/N contacts were verified by geometric (the sum of van der Waals radii (Bondi, 1964; Kaplan, 2006) of the H and O/N atoms should be greater than the distance between them; the $<\text{CH}⋯\text{O/N}$ angle should be obtuse; changes of the CH covalent bond) and vibrational criteria (shifts in the frequencies of the stretching and out-of-plane vibrational modes and corresponding ratio of the intensities).

The energies of the CH⋯O/N H-bonds were evaluated by the empirical EML formula (Espinosa et al., 1998; Mata et al., 2011), which was first successfully applied for the estimation of the individual energetic contributions of the separate H-bonds in the two WC DNA base pairs (Matta et al., 2006), based on the electron density distribution at the (3, −1) BCPs of the H-bonds:

$$E_{\text{HB}} = 0.5 \cdots V(r),$$

where $V(r)$ is the value of a local potential energy (virial field) at the (3, −1) BCPs.

The partial deuteration was applied to minimize the effect of vibrational resonances (Brovarets’ & Hovorun, 2010a, 2010b, 2011b; Brovarets’, Zhurakivsky, & Hovorun, 2010). The atomic numbering scheme for the purine and pyrimidine bases is conventional (Brovarets’ & Hovorun, 2010c, 2010d, 2010e). All results obtained in this article at the DFT and MP2 levels of theory are presented through slash (DFT/MP2).

Moreover, relative H-bond strengths were estimated by means of Grunenberg’s compliance constants formalism (Brandhorst & Grunenberg, 2008, 2010; Grunenberg & Barone, 2013; Grunenberg et al., 2014). In contrast to force constants, the numerical values of compliance constants do not depend on the coordinate system. The physical meaning of compliance constants is deduced from their definition as partial second derivative of the potential energy due to an external force:

$$C_{ij} = \partial^2 E / \partial f_i \partial f_j.$$
In other words, compliance constants measure the displacement of an internal coordinate resulting from a unit force acting on it. As follows from this definition, a lower numerical value of compliance constant represents a stronger bond. The compliance constants were calculated using Compliance 3.0.2 program (Brandhorst & Grunenberg, 2008, 2010; Grunenberg & Barone, 2013; Grunenberg et al., 2014).

To study the charge transfer property in the interacting orbitals of the H-bonds, we have resorted to the NBO analysis (Weinhold & Landis, 2005), which interprets the electronic wave function in terms of a set of occupied Lewis and a set of unoccupied non-Lewis localized orbitals. The second-order Fock matrix analysis was carried out to evaluate interaction between donor (i) and acceptor (j) bonds. The result of such interaction is a migration of the electron density from the idealized Lewis structure into an empty non-Lewis orbital $\sigma_i^*$. For each donor (i) and acceptor (j) bonds, the stabilization energy is:

$$E^{(2)} = \Delta E_{ij} = q_i F(i,j)^2 \varepsilon_{ij} - \varepsilon_i,$$

where $q_i$ is the donor orbital occupancy, $\varepsilon_{ij}$ and $\varepsilon_i$ are the diagonal elements, and $F(i,j)$ is the off diagonal element of NBO Fock matrix.

By fixing the glycosidic angles and the distance between the protons localized at the glycosidic nitrogen, the P·T WC, P·U WC, and 7-dezaP·U base pairs were energy-minimized by the DFT and MP2 methods to visualize their physico-chemical characteristics. These base pairs are denoted by the “r” subscript.

**Obtained results and their discussion**

In this paper we have systematically investigated the CH⋯O/N H-bonds in the purine–purine or purine–pyrimidine base pairs involving modified nucleobases by applying a powerful arsenal of the methods (Grunenberg’s compliance constants theory; NBO formalism; QTAIM, geometrical, and vibrational analyses) used in our previous paper on this topic (Brovarets’ et al., 2013), supplementing it with the calculations of the EDA and AIM DI (Figures 1–12, Tables 1–9, and S1–S14). Altogether, we have revealed 41 CH⋯O/N H-bonds, among which there are 34 CH⋯O and 7 CH⋯N interactions in the 39 biologically important base pairs. The majority of base pairs (30 base pairs) examined in this study are planar structures (C, symmetry), while the others of them (11 base pairs) are non-planar structures (C1 symmetry), selected dihedral angles for which are presented in Table S3. Notably, the heterocycles of the bases in the canonical and rare tautomeric states remain almost planar in the base pairs, although they are flexible molecules (Govorun et al., 1992; Nikolaenko et al., 2011; Shishkin et al., 2000).

Computational results provided in this work (Table 1) revealed that the base mispairs containing 5BrUra in the WC, reverse Watson–Crick (rWC), Hoogsteen (H), and reverse Hoogsteen (rH) configurations possess the same order of stability as in the case of the pairs formed by the canonical bases (Brovarets’ et al., 2013): A·6-azaC, H<A·5MC < A·isoC; A·isoC < A·isoC* rWC < A·isoC* rH < 8-aza-9-deazaA·C* < 8-aza-9-deazaA·C < 8-aza-9-deazaA·C in contrast to the base pairs involving 6-azaC: A·6-azaC* < A·6-azaC < A·6-azaC* < A·6-azaC.

**Geometrical parameters of the base mispairs and the CH⋯O/N H-bonds in them**

The values of the $\alpha_1$ angle subtended at the glycosidic nitrogen of the purine base of the purine–purine or purine–pyrimidine base pairs (23.5÷59.0/24.5÷57.2° and 49.7÷74.7/49.4÷74.3°), the $\alpha_2$ angle subtended at the glycosidic nitrogen atom of the other purine or pyrimidine base of the aforementioned pairs (27.5÷70.0/28.2÷68.8° and 46.4÷53.2/47.3÷53.7°), and the H distance between the protons localized at the glycosidic nitrogens (7.353÷12.289/7.415 ÷ 12.241 Å for the CH⋯O H-bonds and 10.007÷10.240/9.896÷10.216 Å for the CH⋯N H-bonds) obtained at the DFT/MP2 levels of theory, respectively, slightly differ from each other.

The resemblance of the geometrical dimensions, namely the glycosidic with the deviation of the $-7=1.6÷9=1.5\text{°}$ for the $\alpha_1$ and $-2.9=2.5÷2.4=3.2\text{°}$ for the $\alpha_2$ angles, and $-1.22÷1.11÷1.19÷1.16\text{ Å}$ for the H distance between the glycosidic hydrogens of the A·5BrU WC, A·5MC*, A·5MC, A·isoC*, A·isoC* rWC, A·isoC, A·isoC* rWC, and 8azaA·T base mispairs with respect to the canonical A·T WC base pair, evidence that they would excellently accommodate within the DNA double helix (Table S1 in the present work and Table S1 in the work (Brovarets’ et al., 2013)).

We also considered the glycosidic parameters of the biologically important pairs containing modified bases in
Figure 1. Geometries of the 39 base pairs, involving modified DNA and RNA bases, optimized at the MP2/6-31G (d,p) level of theory in vacuum. The atom labeling is conventional (Jeffrey & Saenger, 1991). Black dashed lines designate the conventional H-bonds (NH···O, OH···O NH···N, and OH···N), whereas red dotted lines indicate the weak CH···O H-bonds and red dashed lines indicate the CH···N H-bonds.
order to make their comparison with the corresponding characteristics for the pairs involving canonical bases. Finally, we have revealed that the A·5BrU H, A·5BrU rH, A·5BrU WC, A·5BrU rWC, A·5MC*, A·5MC, A isoC*, A·isoC, and A·isoC base pairs in different configurations containing the 5BrU, 5MC, and isoC bases perfectly match analogous pairs formed by the canonical bases (Tables: Table S1 in the present work and Table S1 in the work (Brovarets’ et al., 2013)).

By examining the $d_{H \cdots O/N}$ distances between the C and O/N atoms involved in the CH⋯O/N H-bonds, that span the range 3.140÷3.818/3.322÷3.529 Å obtained at the MP2 level of theory, respectively, we have obtained that they fall within the interval for the weak H-bonds established both experimentally (Desiraju & Steiner, 1999) and theoretically (Ponomareva et al., 2012, 2014; Yurenko, Zhurakivsky, et al., 2011; Yurenko, Zhurakivsky, Samijlenko, et al., 2007; Yurenko, Zhurakivsky, Ghomi, et al., 2007, 2008; Yurenko, Zhurakivsky, Samijlenko, et al., 2011) (Tables 2 and S4). The angles of the H-bonding are obtuse – 123.9÷142.0/126.0÷142.4° – upon the formation of the CH⋯O/N H-bonds, respectively (for more details, refer to Tables 2 and S4).

The geometric criteria of the bonding, developed for the classical H-bonds, are not fulfilled for all considered CH⋯O/N interactions, since their $d_{H \cdots O/N}$ distances are less than the sum of corresponding Bondi’s (1964) van der Waals radii (2.720/2.750, respectively) in the case of the A·5BrU WC, P·T rWC, P·U H, P·U rWC, A·isoC*, rWC, A·6-azaC, 8-aza-9-deazaA·U, A·X, A·8oxoA syn, A·8oxoG syn, 8oxoA·T, and 8-azaA·T base mispairs, which is also confirmed by the negative values of the $\Delta d_{H \cdots O/N}$ distances (Table 2 and S4). At this the CH H-bond donating group insignificantly (by less than .001 Å) elongates, as well as contracts upon the formation of the CH⋯O/N H-bond.

Electron-topological parameters and Koch and Popelier’s criteria of the H-bonding

In order to clarify, if the observed CH⋯O/N H-bonds meet the criteria of the H-bonding, we have employed the AIM-based empirical criteria for identifying the AH⋯B interactions as true H-bonds (Koch & Popelier, 1995). As a result, we established that the eight criteria formulated by Koch and Popelier are fulfilled without any exception.

Firstly, we have indicated the H-bonding-like interaction in all considered base pairs by the bond path between the H and O/N atoms involved in the CH⋯O/N H-bonding along with the (3, −1) BCP on this path (Criterion 1). Then we have established that the electron density $\rho$ at the (3, −1) H-bonding-like CP spans the range .002÷.014/.003÷.013 a.u. and .006÷.013/.007÷.013 a.u. for the CH⋯O and CH⋯N H-bonds, respectively (Tables 3 and S5) and therefore it can be considered as a typical feature of the true H-bond (Criterion 2) (Brovarets’ et al., 2013).
density $\Delta \rho$ at the (3, −1) BCPs of the suggested H-bonds are positive and its values are typical for closed-shell interactions, locating in the range .009÷.045/.011÷.043 a.u. and .020÷.034/.022÷.039 a.u. for the CH⋯O and CH⋯N H-bonds, accordingly (Criterion 3) (Tables 3 and S5). The 4th criterion claims that the mutual penetration of the H hydrogen and O/N acceptor atoms, estimated by the formulas $\Delta r(H) = r(H)^{\circ} - r(H)$ and $\Delta r(O/N) = r(O/N)^{\circ} - r(O/N)$, respectively, are positive for all CH⋯O/N H-bonds studied here (Tables 4 and S6). Our results indicating the loss of charge on the hydrogen atom ($\Delta q(H) = q(H) - q(H)^{\circ} < 0$) upon the CH⋯O/N H-bonding are in agreement with the 5th criterion of Koch and Popelier. Criteria 6–8 postulated by Koch and Popelier are also satisfied, since the energetic destabilization $\Delta E(H) = E(H) - E(H)^{\circ} > 0$ (Criterion 6), the reducing of the dipolar polarization of the acidic hydrogen atom involved in the CH⋯O/N H-bonding $\Delta M(H) = |M(H)| - |M(H)^{\circ}| < 0$ (Criterion 7) and the decreasing of the hydrogen atom’s volume $\Delta V(H) = V(H) - V(H)^{\circ} < 0$ (Criterion 8) are observed upon the complexation (Tables 4 and S6). All these data agree well with previous literature expectations (Brovarets’ et al., 2013; Ponomareva et al., 2012, 2014; Yurenko, Zhurakivsky, Samijlenko, et al., 2011).

**QTAIM DI observed for the CH⋯O/N H-bonds**

The DI measures the degree of the electron sharing, i.e. the covalency between two atoms. The comparison of
the DI values with corresponding $E_{\text{CH}$--\text{O}}$ H-bond energies calculated by means of EML formula at the MP2/6–31G(d,p) level of theory (Table 3 and S5) suggests an excellent correlation between these two quantities with correlation coefficient of .972. The graphical representation of the correlation is shown in Figure 5. The linear regression can be described by the formula $E_{\text{CH}$--\text{O}} = 77.581 \cdot $DI$ - .1684 (rmsd = .16 kcal/mol).

It should be noted that the DI values for the CH--O/N contacts in the DNA and RNA base pairs are noticeably smaller than in the case of the strong O/N H--O/N H-bonds (Badri, Bouzková, Foroutan-Nejad, & Marek, 2014). This fact suggests that the CH--O/N H-bonds are mainly stabilized by electrostatic forces. However, our data point to an important role of a covalent component in controlling and tuning H-bond strengths: H-bonds get stronger at the increasing of the degree of the electron sharing between hydrogen and the acceptor (oxygen/nitrogen) atoms.

**Energies of the intermolecular interactions in the pairs containing modified bases**

As shown in Table 10, the A·5BrU H, A·5BrU rH, A·5BrU WC, A·5BrU rWC, 2AP·T rWC, 2AP·T WC, 2AP·C*, A·5MC*, A·5MC*, A·isoC*, A·isoC* rWC, A·isoC, A·isoC* rWC, A·6-azaC*, A·6-azaC, 8-aza-9-deazaA·C*, 8-aza-9-deazaA*·C, 8-aza-9-deazaA·U, A·X, A·8oxoA*syn, A·8oxoA*syn, 8oxoA·T, 3-deazaA·T, and 8-azaA·T base pairs are the most stable complexes among all examined due to considerably larger binding energies. The studies of the interaction energies show that the contribution of the CH--O/N H-bonds energies into the BSSE-corrected electronic interaction energies (the ratio of the energy of the single CH--O/N H-bond to the electronic energy of the interaction between two bases within the pair -- $E_{\text{CH}$--\text{O/N}}/|E_{\text{int}}|$) spans the range from 3.0/4.2 and 3.0/4.3 to 35.1/31.2 (CH--O) and 44.4/46.5% (CH--N) (Tables 8 and S10 (see Supplemental...
Notably, among all considered pairs involving modified bases we did not reveal a base pair stabilized solely by the CH⋯O/N H-bonds, only those coexisting with the classical H-bonds (Figure 1). The C8H⋯O4, C8H⋯O2, C6H⋯O4, C6H⋯O2, C6H⋯O4, C8H⋯O2, C2H⋯N3, C2H⋯N3, C2H⋯N3, C2H⋯N3, and C6H⋯O4 H-bonds make the highest contributions into the stabilization energies of the P·T rH (35.1/31.2), P·T H (33.6/29.1), P·T WC (26.1/23.9), P·U rH (33.9/31.0), P·U H (30.5/27.6), P·U WC (25.9/34.7), 2AP·T rH (30.7/28.4), 2AP·T H (27.0/24.8), A·5MC (38.7/40.4), A·isoC (34.2/37.7), A·6-azaC (30.9/33.0), 8-aza-9-deazaA·C (44.4/46.5), and 7-dezaP·U (25.6/23.9%) base pairs, even exceeding the total contribution ($E_{\text{CH⋯O}} + E_{\text{CH⋯N}}$)/|Δ$E_{\text{int}}$| = 17.8/19.5 and 19.2/17.7% of the two separate CH⋯O H-bonds in the P·T WC and P·U WC base pairs, respectively (Tables 8 and S10).

Figure 4. The relationship between the shift $\Delta v = \nu_0 - \nu$ of the stretching vibrational mode of the H-bonded CH group and the change in the length $\Delta d_{\text{CH}} = d_{\text{CH}} - d_{\text{CH}0}$ of the donating group CH upon the CH⋯O (upper row) and CH⋯N (lower row) H-bondings in the biologically important pairs including modified nucleobases at the DFT and MP2 levels of QM theory.

Figure 5. The relation between the $E_{\text{CH⋯O}}$ energy calculated by the EML formula (Espinosa et al., 1998; Mata et al., 2011) and the DI of the CH⋯O/N H-bonds obtained in the biologically important pairs involving modified nucleobases at the MP2 level of QM theory.
Quantitative EDA of the CH⋯O/N H-bonds in the pairs containing canonical and modified nucleobases

EDA was performed for all base pairs with modified nucleobases (Tables 9 and S11). For the purpose of comparison, the same procedure was done for the natural DNA and RNA base pairs investigated in our previous paper (Brovarets’ et al., 2013).

EDA indicates that there are two main contributions into the interaction energy of the CH⋯O/N H-bonds examined in the framework of the Kohn–Sham molecular orbital model using a quantitative EDA: electrostatic interaction $\Delta V_{\text{elstat}}$ and Pauli-repulsive orbital interaction $\Delta E_{\text{Pauli}}$ (comprising the destabilizing interactions between occupied orbitals and responsible for the steric repulsion) that are of the same order of magnitude (Tables 9 and S11). Notably, the latter one exceeds the electrostatic attraction in many cases that causes its partial compensation. Moreover, we found that the orbital interactions $\Delta E_{\text{ori}}$ accounting for the charge transfer and polarization upon the H-bond formation, do not negligibly contribute into the H-bond energy, but are of the same order of magnitude as the electrostatic interaction. It is evident that exceptionally electrostatic interaction $\Delta V_{\text{elstat}}$ is unable to ensure the bonding interaction, since only together with the orbital $\Delta E_{\text{ori}}$ and dispersion $\Delta E_{\text{disp}}$ summands it can provide non-repulsive interaction, corresponding to the negative value of the $\Delta E_{\text{int}}$, thereby disproving the generally accepted view that hydrogen bonding in DNA base pairs is predominantly electrostatic by their nature. Interestingly, in the present work we find out that total attractive CH⋯O/N interactions are provided for 45.0÷138.6% by orbital interaction, for

Figure 6. The dependencies of the $E_{\text{CH⋯O}}$ (upper row) or $E_{\text{CH⋯N}}$ (lower row) energies on the electron density $\rho$ at the $(3, -1)$ BCPs of the CH⋯O/N H-bonds revealed in the biologically important pairs involving canonical and modified nucleobases at the DFT and MP2 levels of QM theory.
84.3±221.0% by Pauli repulsion, for 108.4±180.6% by electrostatic part, and for 9.3±41.7% by dispersion component (Tables 9 and S11).

Generally, the results of EDA lead us to the following conclusions:

1) In contrast to the popular notion that the H-bonding is mainly electrostatic interaction, the results given in Table S11 show an important contribution of the attractive orbital interaction term $\Delta E_{oi}$ (accounting polarization and charge transfer effects) to the total formation energies of the H-bonded nucleic acid base pairs. Although the electrostatic term $\Delta V_{elstat}$ makes the greatest contribution to the total interaction energy between the base pairs, its magnitude (absolute value) is comparable with positive values of the Pauli repulsion component $\Delta E_{Pauli}$. In many cases, a single electrostatic term is even unable to compensate the destabilizing Pauli repulsion part. Therefore, the orbital interaction $\Delta E_{oi}$ is crucial for stability of the H-bonded base pairs and determines, to a great extent, the total interaction energy of the complexes. For instance, the values of the $\Delta E_{oi}$ are close to the values of the total energy of formation $\Delta E_{int}$ in many cases. These results also suggest that the H-bonding in DNA base pairs may benefit from some degree of covalency (Grabowski, 2011a), although orbital interaction part $\Delta E_{oi}$ accounts not only for charge transfer from one base to another (measure of covalency), but also for charge redistribution (polarization) within individual base monomers.

2) Base pairs with very strong H-bonds (e.g. A*-T*) are characterized by the highest interaction energies $\Delta E_{int}$ ($\sim$40 kcal/mol) with the
great contribution of the orbital term $\Delta E_{oi}$. This fact indicates that the H-bonds in such base pairs possess a strong covalent character (Grabowski, 2011a).

(3) The ratio of the dispersion contribution $\Delta E_{disp}$ to the total interaction energy ranges from ~10% to ~30%. It is noteworthy that the greatest input of the $\Delta E_{disp}$ term to the total interaction energy $\Delta E_{int}$ is observed in the case of the most weakly associated base pairs with $\Delta E_{int} < -10$ kcal/mol.

(4) EDA did not reveal fundamental differences in the nature of the base pairing for the complexes involving natural and modified nucleobases. For instance, absolute values of the formation energies for the pairs involving $^5$BrU are only slightly higher as compared to the corresponding values for pairs with canonical U. The presence of a substituent (bromine atom in this case) does not substantially affect the balance between four main components ($\Delta V_{elstat}$, $\Delta E_{Pauli}$, $\Delta E_{oi}$, and $\Delta E_{disp}$) of the interaction energy.

(5) Among all studied base pairs, the U·U₃ base pair deserves a special attention since it is shaped by only two weak CH···O H-bonds and does not contain conventional H-bonds of the O/NH···O/N type. The electrostatic component $\Delta V_{elstat}$ is perceptibly higher than $\Delta E_{oi}$ for this base pair. However, they are still of the same order of magnitude. This leads us to conclusion that there is no fundamental difference in the nature of the weak and conventional H-bonds in DNA and RNA base pairs. Although for the U·U₃ base pair...
containing only CH⋯O H-bonds the electrostatic part dominates over the orbital component, the latter still contributes significantly to the interaction energy $\Delta E_{\text{int}}$. Therefore, weak CH⋯O interactions can be definitely considered as true H-bonds, and not electrostatic (or van der Waals) contacts. It should be also noted that our data agree with the results by other authors (Gu et al., 1999; Joseph & Jemmis, 2007), which demonstrated that strong (e.g. O/N H⋯O/N) and weak (e.g. CH⋯O/N) H-bonds are governed by the same interplay of fundamental physical forces.

**The natural bond orbital analysis of the CH⋯O/N H-bonds**

NBO analysis (Weinhold & Landis, 2005) of the CH⋯O/N H-bonding interactions demonstrates a substantial charge transfer lone pairs (LP) – bonding orbital (BD*) from one (in the case of the nitrogen atom) or several (in the case of the oxygen atom) Lewis electron LP of the O/N acceptor atoms to the anti-BD* of the CH donor group, that can be expressed through the BD* orbital populations, ranging from .015 to .026 e for the CH⋯O and from .024 to .030 e for the CH⋯N H-bonds (Tables 7 and S9).

The values of the $E^{(2)}$ energy of the interaction between the LP of the O/N acceptor atoms and the antibonding orbital BD* of the CH donor group (.09±3.34 for the CH⋯O and .91±3.13 kcal/mol for the CH⋯N H-bonds) slightly exceed the values of the $E_{\text{CH⋯O/N}}$ energies (.29±3.23/.43±3.07 for the CH⋯O and 1.04±2.34/1.25±2.71 kcal/mol for the CH⋯N H-bonds) calculated by the EML formula (Espinosa et al., 1998; Mata et al., 2011) (Tables 3 and 7). However, these values can be considered as equivalent in view of the high correlation coefficient between them (.992 for the CH⋯O H-bonds in the pairs containing modified bases) (Table S12).

The calculation of the partial charges on the donor C, hydrogen H, and acceptor O/N atoms ($q_C$, $q_H$, and $q_{O/N}$, respectively) involved in the CH⋯O/N H-bonding revealed that carbon donor atom possesses positive charge, while the oxygen/nitrogen atom – negative (Table S9).

According to the statements of the NBO theory (Weinhold & Landis, 2005), the intermolecular donor–acceptor interaction arises on the condition that the electron density from the lone pair LP of the H-bond acceptor delocalizes into the unfilled BD* antibonding orbital of the H-bond donor. The LP–BD* orbital overlap is characteristic for the H-bonding interaction. Generally, the formation of the H-bond leads to the increasing of the occupancy of the antibonding orbital and further weakening and elongation of the C-H group, which leads to the red-shifting of the $\nu_{\text{CH}}$ stretching frequency.

**Vibrational analysis of the CH group involved in the CH⋯O/N H-bonding**

In contrast to the presented above considerable NBO charge transfer from the lone pair LP to the BD* antibonding orbital under the formation of the non-canonical CH⋯O/N H-bonds, the values of the shifts of the stretching vibrational mode of the H-bonded CH group...
Δν(CH) = ν(CH) − ν0(CH) were established to be negative with the order of a several cm$^{-1}$ to a several tens of cm$^{-1}$ or, in other words, they are blue-shifted, except the CH stretching frequency for the C8H···O4 H-bond in the P·T rH and P·U rH base pairs that was found to be red-shifted (Tables 5 and S7). These data are in a good accordance with the shortening of the proton donating CH group upon the CH···O/N H-bonding (Table 2). At this, the intensity of the stretching vibration increases under the formation of the CH···O/N H-bond only on several occasions, especially noticeably for the C8H···O4 H-bond in the P·T rH base pair, C8H···O2 H-bond in the P·T H base pair, C8H···O4 H-bond in the P·U H base pair, C8H···O2 H-bond in the P·U H base pair, C8H···O4 H-bond in the 2AP·T rH base pair, and C8H···O2 H-bond in the 2AP·T H base pair, decreasing for all other (Tables 5 and S7).

It is evident that the rule of the stretching vibration shifts, which has been traditionally considered as spectroscopic signature of the H-bond formation (Buckingham et al., 2008; Hermansson, 2002; Joseph & Jemmis, 2007; Matsuura et al., 2003; Scheiner & Kar, 2002; Zhou & Qiu, 2009; Zundel, 2000), does not work in the ~95% cases of the non-canonical CH···O/N H-bonds.

However, as it was reported earlier (Brovarets’ et al., 2013; Brovarets, Kolomiets’, & Hovorun, 2012; Desiraju & Steiner, 1999; Dong et al., 2007; Grabowski, 2001, 2004, 2011b; Scheiner et al., 2001; Szatylowicz & Sadlej-Sosnowska, 2010) the spectroscopic criteria concerning stretching vibration shifts for the formation...
of the weak H-bonds surrounded by the considerably stronger classical H-bonds cannot be applied rigorously, since the latters can affect them, disturbing their vibrational characteristics, namely stretching frequencies and intensities. In this case, the rule based on the out-of-plane vibration $\gamma(CH)$ is more appropriate: the frequency of the out-of-plane vibration of the CH group under the formation of the CH⋯O/N H-bond should increase and the corresponding intensity should vary (Schuster et al., 1976).

Thus, for all 41 CH⋯O/N H-bonds the frequency of the out-of-plane deformation vibrations $\gamma(CH)$ of the CH groups increases at the formation of the CH⋯O/N H-bonds: $\Delta \gamma(CH) = \gamma(CH) - \gamma_0(CH)$ spans the range from 13.0 to 62.5 / from 14.6 to 52.7 cm$^{-1}$ for the CH⋯O and from 30.5 to 60.2 / from 18.6 to 61.8 cm$^{-1}$ for the CH⋯N H-bonds, at this ratio of the intensities of these vibrations $I/\gamma_0$ changes from .6 to 10.7 / from .7 to 2.1 for the CH⋯O and from .9 to 1.6 / from .8 to 1.7 for the CH⋯N H-bonds (Tables 5 and S7). So, this rule is satisfied for all H-bonds without any exception. These observations evidence that the blue-shift of the CH stretching frequency does not exclude that the CH⋯O/N interaction is true H-bond. It should be mentioned that spectroscopic data obtained at the DFT level of theory are in line with the MP2 results.

The relative strengths of the CH⋯O/N interactions by means of Grunenberg’s compliance constants

The analysis of the values of the compliance constants $C_l$ calculated for the individual CH⋯O/N interactions points out that in the majority they are quite weak and soft H-bonds, falling into the range 11.156÷42.077/
10.127±41.251 for the CH⋯O and 10.799±15.828/10.127±13.605 Å/mDyn for the CH⋯N H-bonds with the exception of the maximum values observed for the C6H⋯O2(413.612/287.719)/C2H⋯O4(306.648/223.596) and C6H⋯O2(178.011/426.360)/C2H⋯O4(119.717/453.129 Å/mDyn) H-bonds in the P·T rWC and P·U rWC base mispairs, respectively (Tables 6 and S8), corresponding to the weakest interactions and consistent with our previous findings obtained for the CH⋯O/N H-bonds in the pairs involving canonical bases (Brovarets et al., 2013), albeit exceed several times the data for the O/NH···O/N conventional H-bonds accumulated in the literature (Brandhorst & Grunenberg, 2008, 2010; Grunenberg & Barone, 2013; Grunenberg et al., 2014; Ponomareva, Yurenko, Zhuraviksky, van Mourik, & Hovorun, 2012, 2014). In general, the values of the compliance constants $C_{ij}$ reconstitute well the energetic characteristics of the CH⋯O/N H-bonds, demonstrating their applicability for the estimation of the strength of the non-covalent interactions in the base pairs.

Linear correlations between the geometrical, electronic, topological, energetic, vibrational, compliance constants, NBO parameters, and delocalization indexes

As evidence the data presented in Tables S13 and S14, the energy $E_{CH⋯O/N}$ estimated for the CH⋯O/N H-bonds in the biologically important base pairs involving canonical and modified nucleobases by the EML formula (Espinosa et al., 1998; Matta et al., 2006; Mata et al., 2011), demonstrates the strongest positive correlations with the following variables: $\rho$ (.985/996 and .921/989), $\Delta \rho$ (.976/982 and .896/946), $\Delta d_{H⋯O}$ (.966/971 and .940/983) for the CH⋯O and CH⋯N H-bonds, respectively. Interestingly, the $\Delta d_{H⋯O}$ and $d_{C⋯O/N}$ values anticorrelate or, in other words, they have negative or inverse correlation (Tables S13 and S14). However, we did not consider and analyze the correlation coefficients separately for the pairs formed by the modified bases involving the CH⋯N H-bonds, since there are only 7 units, and also for those corresponding to the pairs with the fixed glycosidic parameters. Thereafter, in order to
Table 1. The relative Gibbs free energies at room temperature ($\Delta G$) and relative electronic energies ($\Delta E$) (in kcal/mol) of the studied pairs involving modified bases, obtained at the MP2/6-311+G(2df,pd) level of theory for the geometries calculated at the DFT and MP2 levels of theory in vacuum.

| Base pairs | $\Delta G$ (DFT) | $\Delta G$ (MP2) | $\Delta E$ (DFT) | $\Delta E$ (MP2) |
|------------|------------------|------------------|------------------|------------------|
| A·5BrU H   | 0.00             | 0.00             | 0.00             | 0.00             |
| A·5BrU rH  | 0.10             | 0.30             | 0.14             | 0.14             |
| A·5BrU WC  | 0.73             | 0.92             | 0.89             | 0.89             |
| A·5BrU rWC | 1.03             | 1.32             | 1.23             | 1.23             |
| P·T rH     | 0.00             | 0.00             | 0.00             | 0.00             |
| P·T WC     | 0.13             | 0.43             | 0.34             | 0.35             |
| P·T WCf    | 0.83             | 0.96             | 1.16             | 1.19             |
| P·U WC     | 0.92             | 1.16             | 1.23             | 1.23             |
| P·U WCf    | 1.17             | 1.55             | 1.32             | 1.39             |
| 2AP·T rWC  | 0.00             | 0.00             | 0.00             | 0.00             |
| 2AP·T WC   | 1.61             | 1.61             | 2.17             | 2.03             |
| 2AP·T rH   | 2.71             | 1.94             | 3.17             | 3.06             |
| A·5MC*     | 4.30             | 4.05             | 3.96             | 3.95             |
| A·5MC      | 5.06             | 6.13             | 7.28             | 7.28             |
| A·isoC*    | 0.00             | 0.00             | 0.00             | 0.00             |
| A·isoC* rWC| 0.36             | 0.38             | 0.39             | 0.37             |
| A·isoC     | 5.67             | 6.34             | 5.69             | 5.73             |
| A·isoC f   | 7.48             | 8.05             | 9.04             | 9.12             |
| A·isoC* rWC| 12.03            | 12.37            | 12.11            | 12.04            |
| A·6-azaC*  | 3.84             | 4.69             | 5.80             | 5.73             |
| A·6-azaC   | 4.34             | 4.44             | 3.96             | 3.97             |
| 8-aza-9-deazaA·C* | 3.84 | 4.69 | 5.80 | 5.73 |
| 8-aza-9-deazaA·C | 1.43 | .10 | .94 | .72 |
| 7-deazaP·U | 0.00             | 0.00             | 0.00             | 0.00             |
| 7-deazaP·Uf | 0.51             | −1.00            | 0.20             | 0.27             |

Table 2. Minimal, maximal, and average values of the geometrical parameters of the CH···O/N H-bonds in the biologically important pairs containing modified nucleobases, obtained at the DFT and MP2 levels of theory in vacuum (see also Figure 1).

| H-bonds | Parameters | $d_{C-O/N}$ a | $d_{H-O/N}$ b | $\angle{CH-O/N}$ c | $\Delta d_{CH}$ d | $\Delta d_{H-O/N}$ e |
|---------|------------|----------------|----------------|-------------------|-----------------|---------------------|
| CH···O  | Min. value | 3.117          | 2.281          | 122.2             | −0.00092        | −0.00033            |
|         | Max. value | 3.888          | 3.198          | 139.9             | 0.01111         | 0.01199             |
|         | Avg. value | 3.489          | 3.266          | 132.3             | −0.00002        | 0.00026             |
| CH···N  | Min. value | 3.381          | 2.442          | 126.8             | −0.00041        | −0.00062            |
|         | Max. value | 3.596          | 3.281          | 144.5             | 0.00044         | 0.00057             |
|         | Avg. value | 3.464          | 3.407          | 138.3             | 0.00006         | 0.00003             |

aThe distance between the C and O/N atoms involved in the CH···O/N H-bond, Å.
bThe distance between the H and O/N atoms involved in the CH···O/N H-bond, Å.
cThe CH···O/N H-bond angle, degree.
dContraction (negative value) or elongation (positive value) of the donating CH group upon the CH···O/N H-bonding, Å.
eThe difference between the sum of the Bondi’s van der Waals radii (Bondi, 1964) of the H and O/N atoms (2.720/2.750 Å, respectively) and the $d_{H-O/N}$ distances, accordingly, Å.
Table 3. Minimal, maximal, and average values of the electron-topological and energetic characteristics of the intermolecular CH···O/N H-bonds in the investigated base pairs, obtained at the DFT and MP2 levels of theory in vacuum.

| H-bonds | Parameters | \( \rho^a \) | \( \Delta \rho^b \) | 100-e^c | DI^d | \( E_{\text{CH-ON}}^e \) |
|---------|------------|-------------|-------------|--------|------|-----------------|
|         | DFT MP2    | DFT MP2     | DFT MP2     | DFT MP2 | DFT MP2 |
| CH···O  | Min. value | .002 .002   | .009 .011   | 1.6    | .4    | .0116 .29 .43   |
|         | Max. value | .014 .013   | .045 .043   | 78.6   | 37.2  | .0466 3.23 3.07 |
|         | Avg. value | .007 .008   | .024 .027   | 11.1   | 8.5   | .0288 1.42 1.59 |
| CH···N  | Min. value | .006 .007   | .020 .022   | .7     | .3    | .0306 1.04 1.25 |
|         | Max. value | .013 .013   | .034 .039   | 2.9    | 2.3   | .0542 2.34 2.71 |
|         | Avg. value | .010 .011   | .028 .032   | 1.6    | 1.1   | .0455 1.80 2.14 |

^aThe electron density at the (3, -1) BCP, a.u.
^bThe Laplacian of the electron density at the (3, -1) BCP, a.u.
^cThe ellipticity at the (3, -1) BCP.
^dThe DI at the (3, -1) BCP.
^eThe energy of the CH···O/N H-bonds estimated by the Espinosa–Molins–Lecomte formula (Brovarets' et al., 2013; Espinosa et al., 1998; Mata et al., 2011), kcal/mol.

Table 4. Minimal, maximal, and average values of the changes of the atomic properties of the C, H, O, and N atoms involved in the intermolecular CH···O/N H-bonds in the biologically important pairs with the participation of the modified nucleosides. Geometries and wave functions were calculated at the MP2/6-31G(d,p) level of theory in vacuum.

| H-bonds | Parameters | \( q^{(H)}^a \) | \( \Delta q^{(H)} | M^{(H)} | \) | \( \Delta | M^{(H)} | | \) | \( \Delta V^{(H)}^c \) | \( \Delta | E^{(H)} | r^{(H)}^e \) | \( \Delta r^{(O/N)}^f \) |
|---------|------------|----------------|----------------|--------|--------|-----------------|-----------------|-----------------|-----------------|
|         | DFT MP2    | DFT MP2        | DFT MP2        | DFT MP2 | DFT MP2 |
| CH···O  | Min. value | .059 .005     | .093 .001     | 38.4   | .9     | .001 1.74 2.68  |
|         | Max. value | .166 .400     | .147 .035     | 46.1   | 8.8    | .036 2.45 3.40  |
|         | Avg. value | .102 .054     | .126 .014     | 42.5   | 5.0    | .013 2.01 2.97  |
| CH···N  | Min. value | .094 .025     | .098 .002     | 37.6   | 3.9    | .003 1.74 2.82  |
|         | Max. value | .138 .119     | .155 .022     | 43.3   | 9.6    | .053 2.06 3.16  |
|         | Avg. value | .125 .072     | .128 .013     | 40.5   | 7.1    | .059 1.87 2.96  |

^aThe charge of the hydrogen atom.
^bThe dipolar polarization of the hydrogen atom.
^cThe volume of the hydrogen atom.
^dThe energy of the hydrogen atom.
^eThe radius of the hydrogen atom upon the H-bonding.
^fThe radius of the O/N acceptor atoms upon the H-bonding.
All changes of values are indicated with respect to free monomers (bases). All units are given in atomic units (a.u.).

Table 5. Minimal, maximal, and average values of the vibrational characteristics of the CH···O/N H-bonds in the biologically important pairs involving modified nucleobases, obtained at the DFT and MP2 levels of theory in vacuum.

| H-bonds | Parameters | \( \Delta \nu(CH)^a \) | \( I/I_0^b \) | \( \Delta \gamma(CH)^c \) | \( I/I_0^d \) |
|---------|------------|-----------------|--------|-----------------|--------|
|         | DFT MP2    | DFT MP2         | DFT MP2 | DFT MP2         | DFT MP2 |
| CH···O  | Min. value | -19.8 -15.2     | .03    | .01              | 13.0   |
|         | Max. value | 1.6 4.2         | 90.4   | 79.3            | 62.5   |
|         | Avg. value | -10.2 -6.8      | 10.5   | 10.4            | 36.0   |
| CH···N  | Min. value | -16.8 -17.9     | .1     | .1              | 30.5   |
|         | Max. value | -6.6 -2.1       | 1.2    | 1.1             | 60.2   |
|         | Avg. value | -10.5 -10.4     | .7     | .7              | 49.6   |

^aThe red-shift (positive value) or the blue-shift (negative value) \( \Delta \nu(CH) = \nu(CH) - \nu(CH)_{\text{base}} \) of the stretching vibrational mode of the H-bonded CH group, cm\(^{-1}\).
^bThe ratio of the intensity of the \( \nu(CH) \) stretching vibrational mode of the H-bonded CH group in the base pair \( I \) to the corresponding mode of the non-bonded CH group in the monomer \( I_0 \).
^cThe shift \( \Delta \gamma(CH) = \gamma(CH) - \gamma(CH)_{\text{base}} \) of the out-of-plane vibrational mode of the H-bonded CH group, cm\(^{-1}\).
^dThe ratio of the intensity of the \( \nu(CH) \) out-of-plane vibrational mode of the H-bonded CH group in the base pair \( I \) to the corresponding mode of the non-bonded CH group in the monomer \( I_0 \).
investigate these observations in more details we have graphically re
lected their correlations, further fitting them by the analytical formulas (Figures 2–12). Thus, we have revealed that the energy \( E_{\text{CH}} \) of the CH···O/N H-bonds, calculated by the EML method (Espinosa et al., 1998; Mata et al., 2011), rapidly decreases with the growing of the electron density \( \rho \) at the \((3, -1)\) H-bonding-like critical point, which is usually treated as a typical feature of the H-bond (Brovarets’ et al., 2013). By combining the data-sets for the pairs containing canonical and modified bases and by the linear interpolation of the relationship between the \( E_{\text{CH}} \) and \( \rho \), we have established that the minimal CH···O/N H-bond energy \( E_{\text{CH}} \) of the CH···O/N H-bonds (Figure 6). This relationship enables us to specify the minimal possible value of the \( \rho \) corresponding to the minimal CH···O/N H-bond energy \( E_{\text{CH}} \min = .1 \) kcal/mol (Kaplan, 2006) in these structures: \( \rho_{\text{CH}} \min = .0019/.0019 \text{ a.u.} \) and \( \rho_{\text{CH}} \min = .0019/.0025 \text{ a.u.} \). These

| Table 6. Minimal, maximal, and average values of the Grunenberg’s compliance constants \( (C_{ij} \text{ in Å/mDyn}) \) for the CH···O/N H-bonds in the biologically important pairs including modified nucleobases, obtained at the DFT and MP2 levels of theory in vacuum. |
|---|---|---|---|
| H-bonds | Parameters | DFT | MP2 |
| CH···O | Min. value | 11.156 | 10.127 |
| Max. value | 413.612 | 453.129 |
| Avg. value | 46.387 | 57.547 |
| CH···N | Min. value | 10.799 | 10.127 |
| Max. value | 15.828 | 13.605 |
| Avg. value | 14.185 | 12.327 |

| Table 7. Minimal, maximal, and average values of the NBO parameters of the donor–acceptor interactions corresponding to the CH···O/N H-bonds in the biologically important pairs containing modified nucleobases, obtained at the DFT level of theory in vacuum. |
|---|---|---|---|---|---|
| H-bonds | Parameters | \( E^{(2)a} \) | Occupancy of LPb | Energy of LPc | Occupancy of BD*d | Energy of BD*e |
| CH···O | Min. value | .09 | 1.827 | \(-.687\) | .015 | .475 | .034 | .235 | \(-.668\) |
| Max. value | 3.34 | 1.977 | .236 | .026 | .512 | .491 | .268 | .583 |
| Avg. value | 1.23 | 1.910 | \(-.435\) | .024 | .493 | .215 | .250 | .633 |
| CH···N | Min. value | .91 | 1.883 | \(-.362\) | .024 | .490 | .092 | .240 | .787 |
| Max. value | 3.13 | 1.930 | \(-.306\) | .030 | .528 | .289 | .262 | .595 |
| Avg. value | 2.07 | 1.902 | \(-.334\) | .027 | .513 | .239 | .255 | .685 |

aThe interaction energy of the listed orbital pairs, kcal/mol. bOccupancy of the orbital corresponding to a lone electron pair (LP), e. cEnergy of the LP orbital, a.u. dOccupancy of the BD* antibonding orbital, e. eEnergy of the BD* antibonding orbital, a.u. fg The NBO partial charges of the donor (C), hydrogen (H), and acceptor (O/N) atoms involved in the CH···O/N H-bonds, respectively, e.

| Table 8. Minimal, maximal, and average values of the energetic characteristics of the intermolecular CH···O/N H-bonds in the studied base pairs involving modified nucleobases, obtained at the DFT and MP2 levels of theory in vacuum. |
|---|---|---|---|---|---|
| H-bonds | Parameters | \( -\Delta E_{\text{int}} \)b | \( E_{\text{CH}} \)/\( -\Delta E_{\text{int}} \), % | \( E_{\text{CH}} \)/\( -\Delta E_{\text{int}} \), % |
| CH···O | Min. value | 7.85 | 8.38 | 3.0 | 4.2 |
| Max. value | 25.33 | 23.05 | 35.1 | 31.2 |
| Avg. value | 13.10 | 13.00 | 13.1 | 13.8 |
| CH···N | Min. value | 4.95 | 5.66 | 3.0 | 4.3 |
| Max. value | 34.34 | 29.34 | 44.4 | 46.5 |
| Avg. value | 12.20 | 11.77 | 24.4 | 26.7 |

bThe BSSE-corrected electronic interaction energy, kcal/mol. cThe energy of the CH···O/N H-bonds estimated by the Espinosa–Molins–Lecomte formula (Brovarets’ et al., 2013; Espinosa et al., 1998; Mata et al., 2011), kcal/mol.
values can be considered as reliable, since they are derived based on the wide database of the CH···O/N H-bonds in the biologically important pairs of the canonical and modified nucleobases.

Figure 10 shows linear relationships between the $E_{CH\cdots O/N}$ energy and the $\Delta\nu(\text{CH})$ frequency shift of the out-of-plane vibrational mode of the CH group involved in the CH···O/N H-bonds, which can be reflected by the formulas: $E_{CH\cdots O} = .05\Delta\nu - .38/0.5\Delta\nu - 1.11$ (rmsd = .60/50 kcal/mol) and $E_{CH\cdots N} = .03\Delta\nu + 45/0.3\Delta\nu + 1.05$ (rmsd = .31/27 kcal/mol), respectively. These formulas mean that the larger is the $\Delta\nu(\text{CH})$ frequency shift, the stronger is the CH···O/N H-bonds. At this, the minimal value of the $\Delta\nu$ ($E_{\text{CH}\cdots O} = .1$ kcal/mol) is a non-zero value equal to 7.6/2.2 cm$^{-1}$ for the CH···O H-bonds. This fact can be explained by the induced increasing of the frequency of the CH group out-of-plane vibration by the far reaching electrostatic interactions (i.e. neighboring H-bonds) even without the formation of the H-bonding. Thus, the out-of-plane frequencies of the non-bonded CH group involved in the C2H···O2 H-bond in the P·T WC$_T$ (995.2/969.8), P·U WC$_T$ (995.4/969.0), and 7-deazaP·U$_T$ (984.4/965.6 cm$^{-1}$) base pairs with the frozen glycosidic parameters increase comparably with those in the P (968.2/944.2) and 7-deazaP (963.5/937.4 cm$^{-1}$) isolated monomers; at this, the values of the $\Delta\nu$ (26.0/24.5, 26.2/23.8, and 20.0/27.1 cm$^{-1}$) in these base pairs with the fixed glycosidic parameters exceed more than twice the aforementioned threshold $\Delta\nu$(C2H)$_{\text{min}}$ (7.6/2.2 cm$^{-1}$) and the values for the non-bonded CH group (9.3/6.7, 9.2/6.5, and 7.2/5.6 cm$^{-1}$) in the P·T, P·U, and 7-deazaP·U base pairs, respectively.

The vibrational characteristics, namely the shift of the stretching vibrational mode $\Delta\nu$(CH) of the H-bonded CH group, presented in the Figure 12 definitely depends on the geometrical parameters of the CH group, in particular on the change of the length $\Delta d_{CH}$ of the H-bonded CH group. This tendency can be expressed by the relationship: $\Delta\nu = 14287.559\cdot \Delta d_{CH} - 9.905/15545.187\cdot \Delta d_{CH} - 10.460$ (rmsd = 2.22/1.83 cm$^{-1}$) for the CH···O H-bonds and $\Delta\nu = 15039.376\cdot \Delta d_{CH} - 9.893/15411.897\cdot \Delta d_{CH} - 8.538$ (rmsd = 2.88/3.52 cm$^{-1}$) for the CH···N H-bonds. It is evident from the $\Delta\nu(\Delta d_{CH})$ dependency that the shifts of the stretching frequencies are mostly blue-shifted in the case of the CH···O/N H-bonds. Interestingly, we suggested that the function $\Delta\nu(\Delta d_{CH})$ does not go through the origin of coordinates due to the influence of the neighboring H-bonds on the length and the stretching frequency of the C2H unbonded group (Brovarets’ et al., 2012).

We also established good relations between $E_{CH\cdots O/N}$ and $\Delta\rho$, $E_{CH\cdots O/N}$ and $E^{(2)}$, $E_{CH\cdots O/N}$ and $\Delta d_{H\cdots O/N}$, $\rho$ and $\Delta\rho$ values (Figures 7–9, and 11). Notably, the fitting coefficients for the $E_{CH\cdots O/N}$ ($\rho$), $E_{CH\cdots O/N}$ ($\Delta\rho$), and $\Delta\nu(\Delta d_{CH})$ correlations do not significantly differ from those obtained separately for the pairs involving the canonical or modified nucleobases (see Figures 2–4, 6, 10, and 12 in the present study and Figures 2–4 in the work (Brovarets’ et al., 2013)). It can be predicted from the Figure 9 that the $E_{CH\cdots O/N}$ energy, calculated by the EML formula (Matta et al., 2011) and the $E^{(2)}$ stabilization energy, associated with the LP–BD* donor–acceptor interaction, correlate good (.955 for the CH···O and .860 for the CH···N H-bonds in the pairs containing canonical and modified nucleobases (Tables S13 and S14)), since they both reflect the degree of the H-bonds strength and their relationship can be described by the formula: $E_{CH\cdots O} = .594E^{(2)} - .608$ (rmsd = 1.41) and $E_{CH\cdots N} = .336E^{(2)} - 1.128$ (rmsd = 3.09 kcal/mol) (Figure 9).

The principal point of interest in this study is to determine the physico-chemical features of the CH···O/N H-bonds. Thus, taking into account the observations above we can conclude that the $E_{CH\cdots O/N}$ depends on the two main factors: $\rho$ and $E^{(2)}$. So, we can confirm once again our previous assumption (Brovarets’ et al., 2013) that the electron density $\rho$ and the interaction energy of the orbital pairs $E^{(2)}$ are reliable descriptors of the CH···O/N H-bonding.
Concluding remarks

For the first time, 41 intermolecular CH···O/N H-bonds in the 39 biologically significant pairs containing modified bases were identified and comprehensively characterized. A large arsenal of modern state-of-art quantum-chemical techniques including Bader’s QTAIM theory (Bader, 1990), Koch and Popelier’s criteria (Koch & Popelier, 1995), NBO analysis (Weinhold & Landis, 2005), compliance constants theory (Brandhorst & Grunenberg, 2008, 2010; Grunenberg et al., 2014; Grunenberg & Barone, 2013), vibrational, geometrical, and energy decomposition analyzes were used to reveal the electronic nature of the CH···O/N interactions in the considered base pairs, to estimate their strengths, as well as contribution to the overall base pair stability, and to describe their physico-chemical features.

In particular, it was shown that the frequencies of the out-of-plane deformation modes γ(CH) increase by 13.0÷62.5 / 14.6÷52.7 cm⁻¹ for the CH···O and by 30.5÷60.2 / 18.6÷61.8 cm⁻¹ for the CH···N H-bonds obtained at the DFT/MP2 levels of theory, respectively, and concomitant changes of their intensities can be considered as reliable indicators of the H-bonding.

The thorough analysis of the physico-chemical characteristics of the non-conventional CH···O/N H-bonds leads us to some qualitative considerations about possible biological significance of these interactions.

On the one hand, these interactions play the role of the third “support point” from the minor or major groove side, i.e. guarantee structural and dynamical similarity of the canonical and mismatched pairs with WC geometry, which facilitates their enzymatic incorporation into the DNA double helix during DNA replication. First of all, this fact concerns the A³BrU WC, 2AP·T WC, 2AP·C*, A³MC*, A多媒体MC, A·isoC*, A·isoG*, A·6-azaC*, A·6-azaG, 8-aza-9-deazaA·C*, 8-aza-9-deazaA·C*, 8-aza-9-deazaA·U, A·8oxoGsyn, 8oxoA·T, 3-deazaA-T, and 8-azaA·T base pairs and helps to shed light on their role in the origin of the point mutations in DNA.

On the other hand, rather weak non-conventional CH···O/N H-bonds in the base pairs with WC geometry may be also considered as “the last straw” or “missing link” at the formation of the electronic signal, which launches chemical process of the incorporation of the incoming nucleoside triphosphate into DNA. In this context the P·T WC, P·U WC, and 7-deazaP·U pairs serve as a good example, since their adaptation to the WC geometry is accompanied by the formation of the third CH···O H-bond from the side of the minor groove.

Moreover, the data obtained for the 79 CH···O/N H-bonds in the 75 pairs involving canonical and modified nucleobases were combined and analysed in conjunction. Together, these observations have been established to be consistent with previous calculations provided separately for the pairs formed by the canonical and modified nucleobases and did not reveal key differences in the physico-chemical properties of the CH···O and CH···N H-bonds.

Therefore, we have demonstrated in this work that the phenomenon of the CH···O/N H-bonding in nucleic acids may have greater variety of biological roles that it was previously thought.

Supporting Information

Selected glycosidic parameters, dihedral angles, energetic characteristics of the biologically important pairs involving modified nucleobases, EDA of the interaction energies for the studied pairs of the DNA and RNA natural and modified bases; geometrical, electron-topological, energetic, vibrational, and atomic properties, NBO analysis and compliance constants for the intermolecular CH···O/N H-bonds. Matrices of the linear correlation coefficients of the physico-chemical parameters that describe the CH···O/N H-bonds in the pairs involving canonical and modified nucleobases obtained at the DFT and MP2 methods. This material is available free of charge via the Internet at http://tandfonline.com/toc/tbsd.

Supplementary material

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