Quantum-mechanical survey of the novel conformational and tautomeric transformations of the classical Watson-Crick A·T(WC), reverse Watson-Crick A·T(rWC), Hoogsteen A·T(H) and reverse Hoogsteen A·T(rH) DNA base pairs

Ol'ha O. Brovarets^{1,2,3}, Kostiantyn S. Tsiupa¹, Andrii Dinets³ & Dmytro M. Hovorun^{1,2,5}

1. Department of Molecular and Quantum Biophysics, Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, 3680, UKRAINE, Kyiv, Akademika Zabolotnoho Str., 150, E-mail: o.o.brovarets@gmail.com

2. Department of Molecular Biotechnology and Bioinformatics, Institute of High Technologies, Taras Shevchenko National University of Kyiv, 03022, UKRAINE, Kyiv, Akademika Hlushkova Ave., 2-h

3. Department of Pharmacology, Bogomolets National Medical University, 02000, UKRAINE, Kyiv, Peremohy Ave., 34

4. Department of Surgery #4, Bogomolets National Medical University, 01601, UKRAINE, Kyiv, Tarasa Shevchenko Blvd., 13, E-mail: andrii.dinets@gmail.com

5. Department of Pathophysiology, Bogomolets National Medical University, 02000, UKRAINE, Kyiv, 34 Peremohy Ave., 34, E-mail: d.m.hovorun@imbg.org.ua

Abstract – *This study represents novel and previously unknown conformational and tautomeric transformations of the classical Watson-Crick A·T DNA base pairs – Watson-Crick A·T(WC), reverse Watson-Crick A·T(rWC), Hoogsteen A·T(H) and reverse Hoogsteen A·T(rH), leading to the novel, non-planar conformations or tautomers of these base pairs.*

Keywords – A·T DNA base pairs, Watson-Crick, Reverse Watson-Crick, Hoogsteen, Reverse Hoogsteen, Wobble structure, DNA breathing, DNA pre-melting, Conformational transformation, Tautomeric transition, Transition state, Quantum-chemical calculations, Bader's Quantum Theory of Atoms in Molecules.

Introduction

It is well known from the literature data that the A·T DNA base pair have four classical configurations, which are biologically significant – Watson-Crick A·T(WC), reverse Watson-Crick A·T(rWC), Hoogsteen A·T(H) and reverse Hoogsteen A·T(rH) [1]-[24]. They are stabilized by the participation of three intermolecular H-bonds, one of which is non-canonical C2H/C8H···O4/O2 H-bond [9], and are formed due to the rotation of one of the bases according to the other on 180° around:

- the (A)N1–N3(T) axis, leading to the formation of the reverse Watson-Crick A·T(rWC) or so-called Donohue DNA base pair [1], registered in the bioactive parallel-stranded DNA [2]-[9];

- the (A)C9'–N9 axis from the *anti*- to *syn*-conformation, representing Hoogsteen A·T(H) base pair [10] involved into a number of biologically important processes such as recognition, damage induction, replication [8]-[20];

- the (A)N7–N3(T) axis in the Hoogsteen base pair forming the reverse Hoogsteen A·T(rH) or so-called Haschemeyer–Sobell base pair [21]-[24].

Discussed DNA base pairs are not static structures in the composition of DNA [25], [26]. Thus, the spontaneous A·T(WC)↔A·T(H) conformational transition has been experimentally registered by the NMR method on the DNA regions enriched by the classical A·T nucleobase pairs [20]. Despite numerous theoretical investigations, microstructural nature of these transitions remains incomprehensible [18], [27].

By the methods of the non-empirical quantum chemistry it was investigated only the $A\cdot T(WC) \leftrightarrow A\cdot T(rWC)$ and $A\cdot T(H) \leftrightarrow A\cdot T(rH)$ conformational transitions of the pairs in free state, which occur by turning of the bases relative one to another on the angle of 180° around the central $(T)N3H \cdots N1/N7(A)$ H-bond, which is the strongest in all base pairs [9].

So, in this study for the first time we have theoretically investigated using QM/QTAIM methods the conformational and tautomeric transformations of the classical A·T DNA base pairs [28]-[31]. Transition states (TSs) have quasi-orthogonal geometry and are tight ion pairs (A^+ , protonated by the $N6H_2$ amino group)·(T^- , deprotonated by the $N3H$ group) in the case of the mutagenic tautomerisations, stabilized by the participation of the intermolecular H-bonds.

Computational methods

Geometries of the complexes and transition states (TSs) of their mutual conformational transformations, as well as their harmonic vibrational frequencies have been calculated at the B3LYP/6-311++G(d,p) level of theory [32]-[36], using Gaussian'09 package [37] in free state. Applied level of theory has successfully proved itself for the calculations of the similar systems [38]-[41]. A scaling factor that is equal to 0.9668 [42]-[45] has been applied in the present work for the correction of the harmonic frequencies of all conformers and TSs of their conformational transitions. We have confirmed the local minima and TSs, localized by Synchronous Transit-guided Quasi-Newton method [46], on the potential energy landscape by the absence or presence, respectively, of the imaginary frequency in the vibrational spectra of the complexes. We applied standard TS theory for the estimation of the activation barriers of the conformational transformations [47]. Electronic energy calculations have been performed at the single point at the MP2/aug-cc-pVDZ level of theory [48], [49].

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

$$G = E_{el} + E_{corr}, \quad (1)$$

where E_{el} – electronic energy, while E_{corr} – thermal correction.

Electronic interaction energies ΔE_{int} have been calculated at the MP2/6-311++G(2df,pd) level of theory as the difference between the total energy of the base pair and energies of the monomers and corrected for the basis set superposition error (BSSE) [50],[51] through the counterpoise procedure [52],[53].

Bader's quantum theory of Atoms in Molecules (QTAIM) [54]-[58], using program package AIMAll [59], was applied to analyse the electron density distribution. The presence of the bond critical point (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 criteria for the H-bond formation [60]-[64]. Wave functions were obtained at the level of theory used for geometry optimisation.

The energies of the intermolecular $AH \cdots B$ H-bonds were evaluated by the empirical Iogansen's formula [65]:

$$E_{AH \cdots B} = 0.33 \cdot \sqrt{\Delta\nu - 40}, \quad (2)$$

where $\Delta\nu$ – magnitude of the frequency shift of the stretching mode of the AH H-bonded group involved in the $AH \cdots B$ H-bond relatively the unbound group. The partial deuteration was applied in order to avoid the effect of vibrational resonances [66]-[70].

The atomic numbering scheme for the DNA bases is conventional [71].

Results and their discussion

1. Novel $A\cdot T(rWC) \leftrightarrow A\cdot T(w_{rWC})$, $A\cdot T(rWC) \leftrightarrow A\cdot T(w_{rWC})$, $A\cdot T(H) \leftrightarrow A\cdot T(w_H)$ and $A\cdot T(rH) \leftrightarrow A\cdot T(w_{rH})$ conformational transitions leading to the surprising conformers of the biologically important $A\cdot T$ DNA base pairs [28]

For the first time we have theoretically revealed novel high-energetic, significantly non-planar (symmetry C_1) conformers – $A\cdot T(w_{WC})$, $A\cdot T(w_{rWC})$, $A\cdot T(w_H)$ and $A\cdot T(w_{rH})$ for each of the four biologically important $A\cdot T$ DNA base pairs – $A\cdot T(WC)$, $A\cdot T(rWC)$, $A\cdot T(H)$ and $A\cdot T(rH)$ [28]. These conformers arise *via* the novel $A\cdot T(WC) \leftrightarrow A\cdot T(w_{WC})$, $A\cdot T(rWC) \leftrightarrow A\cdot T(w_{rWC})$, $A\cdot T(H) \leftrightarrow A\cdot T(w_H)$ and $A\cdot T(rH) \leftrightarrow A\cdot T(w_{rH})$ conformational transitions (Fig. 1, Table 1).

It was found that each of these conformers possesses wobble (w) structure and is stabilized by the participation of the two anti-parallel $N6H/N6H'\cdots O4/O2$ and $N3H\cdots N6$ H-bonds (the exocyclic $N6H'$ bond has *trans*-orientation relative to the endocyclic $N1C6$ bond of A). These specific intermolecular contacts involve pyramidalized amino group of the A DNA base, acting simultaneously as an acceptor and a donor of the H-bonding. The transition states (TSs) – $TS_{A\cdot T(WC) \leftrightarrow A\cdot T(w_{WC})}$, $TS_{A\cdot T(rWC) \leftrightarrow A\cdot T(w_{rWC})}$, $TS_{A\cdot T(H) \leftrightarrow A\cdot T(w_H)}$ and $TS_{A\cdot T(rH) \leftrightarrow A\cdot T(w_{rH})}$ – controlling the dipole-active transformations of the conformers from the main state of the classical $A\cdot T$ DNA base pairs into the high-energetic, significantly non-planar state and *vice versa*, have been localized. They also possess wobble structures (symmetry C_1) similarly to the high-energetic conformers and are stabilized by the participation of the $N6H/N6H'\cdots O4/O2$ and $N3H\cdots N6$ H-bonds. It was assumed that these conformational transitions are directly related to the thermally-driven fluctuational behavior – “breathing” of DNA [25].

These reactions are non-dissociative, since they are accompanied by the transformation of the H-bonds and rupture of only some of them. Intermolecular $N6H/N6H'\cdots O4/O2$ H-bonds exist along all intrinsic reaction coordinate opposite the $N3H\cdots N1/N7$ H-bonds, that initially weaken and then rupture with a time delay in order to transform into the $N3H\cdots N6$ H-bond. In other words, in the process of the conformational transformations the $N3H$ group of the T DNA base as proton donor remain for some time free from the intermolecular H-bonding. This comes up with an opinion that discovered conformational transitions could be used for the explanation

Table 1. Energetic and kinetic characteristics of the discovered conformational transitions of the four biologically important A·T DNA base pairs obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) (marked by the asterisk) and MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) (marked by the double asterisk) levels of theory in the continuum with $\epsilon=4$ (see Fig. 1) [28].

Conformational transition	ν_i^a	ΔG^b	ΔE^c	$\Delta\Delta G_{TS}^d$	$\Delta\Delta E_{TS}^e$	$\Delta\Delta G^f$	$\Delta\Delta E^g$	k_f^h	k_r^i	$\tau_{99.9\%}^j$	τ^k
$A\cdot T(WC) \leftrightarrow A\cdot T(w_{WC})$	7.1	5.36	7.32	7.13	7.63	1.77	0.31	$3.64\cdot 10^7$	$3.11\cdot 10^{11}$	$2.22\cdot 10^{-11}$	$3.22\cdot 10^{-12}$
$A\cdot T(rWC) \leftrightarrow A\cdot T(w_{rWC})$	11.4	5.97	7.26	7.26	7.64	1.29	0.38	$2.95\cdot 10^7$	$7.03\cdot 10^{11}$	$9.83\cdot 10^{-12}$	$1.42\cdot 10^{-12}$
$A\cdot T(H) \leftrightarrow A\cdot T(w_H)$	9.4	5.78	7.75	7.67	8.21	1.89	0.45	$1.46\cdot 10^7$	$2.55\cdot 10^{11}$	$2.71\cdot 10^{-11}$	$3.92\cdot 10^{-12}$
$A\cdot T(rH) \leftrightarrow A\cdot T(w_{rH})$	14.6	5.82	7.63	7.44	8.69	1.62	1.07	$2.16\cdot 10^7$	$4.01\cdot 10^{11}$	$1.72\cdot 10^{-11}$	$2.49\cdot 10^{-12}$

^aImaginary frequency at the TS of the conformational transition, cm^{-1} ; ^bThe Gibbs free energy of the product relatively the reactant of the conformational transition (T=298.15 K), $kcal\cdot mol^{-1}$; ^cThe electronic energy of the product relatively the reactant of the conformational transition, $kcal\cdot mol^{-1}$; ^dThe Gibbs free energy barrier for the forward conformational transition, $kcal\cdot mol^{-1}$; ^eThe electronic energy barrier for the forward conformational transition, $kcal\cdot mol^{-1}$; ^fThe Gibbs free energy barrier for the reverse conformational transition, $kcal\cdot mol^{-1}$; ^gThe electronic energy barrier for the reverse conformational transition, $kcal\cdot mol^{-1}$; ^hThe forward rate constant for the conformational transition, s^{-1} ; ⁱThe reverse rate constant for the conformational transition, s^{-1} ; ^jThe time necessary to reach 99.9% of the equilibrium concentration between the reactant and the product of the conformational transition, s; ^kThe lifetime of the product of the conformational transition, s.

of the occurrence of the hydrogen-deuterium exchange in the A·T(WC) DNA base pairs. It is not excluded that revealed by us novel corridor of the spontaneous thermal fluctuations of the A·T DNA base pairs accompanied by the transformation of the base pair from the plane-symmetric geometry into the significantly non-planar wobble conformation could be useful for the explanation of the specificities of the blurriness of the transition at the DNA pre-melting enriched by the A·T DNA base pairs, that could not be explained in details in the framework of the two-states model.

2. Novel A·T(w_{WC})/A·T(w_{rWC})↔A·T(w_H)/A·T(w_{rH}) structural transitions controlling transformations of the Watson-Crick and reverse Watson-Crick A·T DNA base pairs into the Hoogsteen and reverse Hoogsteen forms [29]

For the first time we have theoretically shown that discovered by us [28] high-energetical, significantly non-planar (symmetry C₁), short-lived wobbled conformers of the classical Watson-Crick A·T(WC), reverse Watson-Crick A·T(rWC), Hoogsteen A·T(H) and reverse Hoogsteen A·T(rH) DNA base pairs are the intermediates of their pairwise A·T(WC) / A·T(rWC)↔A·T(H) / A·T(rH) conformational transformations occurring *via* the pathways (see Fig. 2, Table 2) [29]:

$A \cdot T(rWC) (0.00) \leftrightarrow TS_{A \cdot T(rWC) \leftrightarrow A \cdot T(wrWC)_{R,L}} (7.26) \leftrightarrow A \cdot T(wrWC)_{R,L} (5.97) [28] \leftrightarrow TS_{A \cdot T(wrWC)_{R,L} \leftrightarrow A \cdot T(wrH)_{L,R}}^{cys} (15.01) \leftrightarrow A \cdot T(wrH)_{L,R} (5.79) \leftrightarrow TS_{A \cdot T(wrH)_{L,R} \leftrightarrow A \cdot T(rH)} (7.41) \leftrightarrow A \cdot T(rH) (-0.03) [28];$

$A \cdot T(rWC) (0.00) \leftrightarrow TS_{A \cdot T(rWC) \leftrightarrow A \cdot T(wrWC)_{R,L}} (7.26) \leftrightarrow A \cdot T(wrWC)_{R,L} (5.97) [28] \leftrightarrow TS_{A \cdot T(wrWC)_{R,L} \leftrightarrow A \cdot T(wrH)_{L,R}}^{trans} (15.00) \leftrightarrow A \cdot T(wrH)_{L,R} (5.79) \leftrightarrow TS_{A \cdot T(wrH)_{L,R} \leftrightarrow A \cdot T(rH)} (7.41) \leftrightarrow A \cdot T(rH) (-0.03) [28]$ (relative Gibbs free energy is presented after each structure in brackets at the MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of QM theory in the continuum with $\epsilon=4$ under normal conditions).

Table 2. Energetic characteristics (in $kcal \cdot mol^{-1}$) of the discovered conformational transitions of the four biologically important A·T DNA base pairs obtained at the MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of theory in the continuum with $\epsilon=4$ (see Fig. 2) [29].

Conformational transition	v_i^a	ΔG^b	ΔE^c	$\Delta \Delta G_{TS}^d$	$\Delta \Delta E_{TS}^e$	$\Delta \Delta G^f$	$\Delta \Delta E^g$
$A \cdot T(wWC)_{R,L} \leftrightarrow A \cdot T(wH)_{R,L}$	7.7	-0.01	-0.19	1.97	0.08	1.98	0.28
$A \cdot T(wWC)_{R,L} \xleftarrow{cys} A \cdot T(wH)_{L,R}$	250.9	-0.01	-0.19	9.53	9.00	9.54	9.19
$A \cdot T(wrWC)_{R,L} \xleftarrow{trans} A \cdot T(wrH)_{L,R}$	252.7	-0.01	-0.19	9.52	9.15	9.53	9.34
$A \cdot T(wrWC)_{R,L} \leftrightarrow A \cdot T(wrH)_{R,L}$	16.1	-0.18	-0.24	1.84	0.41	2.02	0.64
$A \cdot T(wrWC)_{R,L} \xleftarrow{cys} A \cdot T(wrH)_{L,R}$	252.3	-0.18	-0.24	9.12	8.86	9.30	9.09
$A \cdot T(wrWC)_{R,L} \xleftarrow{trans} A \cdot T(wrH)_{L,R}$	253.7	-0.18	-0.24	9.28	9.24	9.46	9.48

Note: For designations see Table 1.

These transitions are controlled by the non-planar transition states with quasi-orthogonal geometry (symmetry C_1) and are stabilized by the participation of the single intermolecular (T)N3H $\cdots$ N6(A) H-bond (~ 4 $kcal \cdot mol^{-1}$). The Gibbs free energies of activation for these non-dissociative, dipole-active conformational transitions consist 7.33 and 7.81 $kcal \cdot mol^{-1}$, accordingly.

So, it was established that novel conformers $A \cdot T(wWC)$, $A \cdot T(wrWC)$, $A \cdot T(wH)$ and $A \cdot T(wrH)$ control the $A \cdot T(wWC)/A \cdot T(wrWC) \leftrightarrow A \cdot T(wH)/A \cdot T(wrH)$ conformational transformations. Moreover, in view of the recently discovered conformational transitions for the classical A·T DNA base pairs – $A \cdot T(WC) \leftrightarrow A \cdot T(wWC)$, $A \cdot T(rWC) \leftrightarrow A \cdot T(wrWC)$, $A \cdot T(H) \leftrightarrow A \cdot T(wH)$ and $A \cdot T(rH) \leftrightarrow A \cdot T(wrH)$ [25], they are also intermediates of the biologically-important $A \cdot T(WC)/A \cdot T(rWC) \leftrightarrow A \cdot T(H)/A \cdot T(rH)$ conformational transformations.

Two other mechanisms – the $A \cdot T(wWC) \leftrightarrow A \cdot T(wH)$ and $A \cdot T(wrWC) \leftrightarrow A \cdot T(wrH)$ – are realized *via* the anisotropic rotation of the amino group of A (together with T interacting with A through two intermolecular antiparallel (A)N6H/N6H' $\cdots$ O4/O2(T) and (T)N3H $\cdots$ N6(A) H-bonds) around the exocyclic C6N6 bond. In TSs of these conformational transitions the pyramidity of the amino group of A significantly increases: this causes increase of the energy of the N3H $\cdots$ N6 H-bond and decrease of the energy of the intermolecular N6H/N6H' $\cdots$ O4/O2 H-bond. The transitions states of these reactions – $TS_{A \cdot T(wWC) \leftrightarrow A \cdot T(wH)}^{cys}$, $TS_{A \cdot T(wWC) \leftrightarrow A \cdot T(wH)}^{trans}$ and $TS_{A \cdot T(wrWC) \leftrightarrow A \cdot T(wrH)}^{cys}$, $TS_{A \cdot T(wrWC) \leftrightarrow A \cdot T(wrH)}^{trans}$ – have close energy in corresponding conformational transformations (14.9 and 15.0 $kcal \cdot mol^{-1}$, accordingly). Thus, these TSs of the mutual conformational transformation of the wobble intermediates – $A \cdot T(wWC) \leftrightarrow A \cdot T(wH)$ and $A \cdot T(wrWC) \leftrightarrow A \cdot T(wrH)$ of the classical A·T DNA bps – $A \cdot T(WC) / A \cdot T(rWC) \leftrightarrow A \cdot T(H) / A \cdot T(rH)$ – determine their conformational transformations.

3. Unexpected $A \cdot T(w_H) \leftrightarrow A \cdot T(w_{rWC})$, $A \cdot T(w_{WC}) \leftrightarrow A \cdot T(w_{rH})$, $A \cdot T(w_{WC}) \leftrightarrow A \cdot T(w_{rWC})$ and $A \cdot T(w_H) \leftrightarrow A \cdot T(w_{rH})$ conformational transitions, defining the interconversions between the classical A·T DNA base pairs: $A \cdot T(WC) \leftrightarrow A \cdot T(rWC)$ / $A \cdot T(rH)$ and $A \cdot T(H) \leftrightarrow A \cdot T(rH)$ / $A \cdot T(rWC)$ [30]

We have shown for the first time, using QM/QTAIM calculations in the continuum with $\epsilon=1$ under normal conditions, that high-energetic, significantly non-planar (symmetry C_1) conformers of the classical A·T DNA base pairs – $A \cdot T(w_{WC})$, $A \cdot T(w_{rWC})$, $A \cdot T(w_H)$ and $A \cdot T(w_{rH})$ for each of the four biologically important A·T DNA base pairs – $A \cdot T(WC)$, $A \cdot T(rWC)$, $A \cdot T(H)$ and $A \cdot T(rH)$ [28] are intermediates of the non-dissociative $A \cdot T(WC) \leftrightarrow A \cdot T(rWC)$ / $A \cdot T(rH)$ and $A \cdot T(H) \leftrightarrow A \cdot T(rH)$ / $A \cdot T(rWC)$ conformational transitions *via* the essentially non-planar transition states (C_1 symmetry) (Fig. 3, Table 3) [30].

Each of the four A·T DNA base pairs transfers into the aforementioned conformer *via* two mirror-symmetric pathways through the soft $TS_{A \cdot T(WC) \leftrightarrow A \cdot T(w_{WC})_{R,L}}$, $TS_{A \cdot T(rWC) \leftrightarrow A \cdot T(w_{rWC})_{R,L}}$, $TS_{A \cdot T(H) \leftrightarrow A \cdot T(w_H)_{R,L}}$ and $TS_{A \cdot T(rH) \leftrightarrow A \cdot T(w_{rH})_{R,L}}$ (C_1 symmetry) with low values of the imaginary frequencies. At this, the structures, which names differ from each other only by the subscripts R and L, are mirror-symmetrical, that is enantiomers, which have identical scalar physico-chemical characteristics and differ only by the direction of the dipole moment.

At this, the $A\cdot T(H) \leftrightarrow A\cdot T(rWC)$ and $A\cdot T(WC) \leftrightarrow A\cdot T(rH)$ conformational transformations are controlled by the TSs stabilized by the participation of the intermolecular (T)N3H $\cdots$ N6(A) H-bond (~ 3.70 kcal $\cdot$ mol $^{-1}$) between the imino group N3H of T and pyramidilized amino group N6H $_2$ of A. Gibbs free energies of activation for these processes consist 12.22 and 11.11 kcal $\cdot$ mol $^{-1}$, accordingly.

Table 3. Energetic characteristics (in kcal $\cdot$ mol $^{-1}$) of the discovered conformational transitions of the four biologically important A-T DNA base pairs obtained at the MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of QM theory in the continuum with $\epsilon=1$ under normal conditions (see Fig. 3) [30].

Conformational transition	v_i^a	ΔG^b	ΔE^c	$\Delta\Delta G_{TS}^d$	$\Delta\Delta E_{TS}^e$	$\Delta\Delta G^f$	$\Delta\Delta E^g$
$A\cdot T(w_H)_{R,L} \leftrightarrow A\cdot T(w_{rWC})_{R,L}$	19.9	-1.17	-0.74	3.20	2.30	4.37	3.04
$A\cdot T(w_{WC})_{R,L} \leftrightarrow A\cdot T(w_{rH})_{R,L}$	21.9	0.65	0.65	4.08	3.34	3.42	2.69
$A\cdot T(w_{WC})_{R,L} \leftrightarrow A\cdot T(w_{rWC})_{L,R}$	274.7	-0.10	0.26	12.04	11.18	12.15	10.92
$A\cdot T(w_H)_{R,L} \leftrightarrow A\cdot T(w_{rH})_{L,R}$	270.8	-0.41	-0.35	10.69	9.35	11.10	9.70

Note: For designations see Table 1.

Conformational transformations of the A-T DNA base pairs are realized by the following non-dissociative scenario (each of them – by the mirror-symmetric pathways):

- $A\cdot T(H)$ (0.00) $\leftrightarrow$ $TS_{A\cdot T(H) \leftrightarrow A\cdot T(w_H)_{R,L}}$ (9.15) $\leftrightarrow$ $A\cdot T(w_H)_{R,L}$ (9.02) $\leftrightarrow$ $TS_{A\cdot T(w_H)_{R,L} \leftrightarrow A\cdot T(w_{rWC})_{R,L}}$ (12.22) $\leftrightarrow$ $A\cdot T(w_{rWC})_{R,L}$ (7.85) $\leftrightarrow$ $TS_{A\cdot T(w_{rWC})_{R,L} \leftrightarrow A\cdot T(rWC)_{R,L}}$ (9.40) $\leftrightarrow$ $A\cdot T(rWC)$ (1.08 kcal $\cdot$ mol $^{-1}$);

- $A\cdot T(WC)$ (0.00) $\leftrightarrow$ $TS_{A\cdot T(WC) \leftrightarrow A\cdot T(w_{WC})_{R,L}}$ (7.28) $\leftrightarrow$ $A\cdot T(w_{WC})_{R,L}$ (7.03) $\leftrightarrow$ $TS_{A\cdot T(w_{WC})_{R,L} \leftrightarrow A\cdot T(w_{rH})_{R,L}}$ (11.11) $\leftrightarrow$ $A\cdot T(w_{rH})_{R,L}$ (7.68) $\leftrightarrow$ $TS_{A\cdot T(w_{rH})_{R,L} \leftrightarrow A\cdot T(rH)_{R,L}}$ (9.67) $\leftrightarrow$ $A\cdot T(rH)$ (-0.65 kcal $\cdot$ mol $^{-1}$);

- $A\cdot T(WC)$ (0.00) $\leftrightarrow$ $TS_{A\cdot T(WC) \leftrightarrow A\cdot T(w_{WC})_{R,L}}$ (7.28) $\leftrightarrow$ $A\cdot T(w_{WC})_{R,L}$ (7.03) $\leftrightarrow$ $TS_{A\cdot T(w_{WC})_{R,L} \leftrightarrow A\cdot T(w_{rWC})_{L,R}}$ (19.07) $\leftrightarrow$ $A\cdot T(w_{rWC})_{L,R}$ (6.92) $\leftrightarrow$ $TS_{A\cdot T(w_{rWC})_{L,R} \leftrightarrow A\cdot T(rWC)_{L,R}}$ (8.47) $\leftrightarrow$ $A\cdot T(rWC)$ (0.16 kcal $\cdot$ mol $^{-1}$);

- $A\cdot T(H)$ (0.00) $\leftrightarrow$ $TS_{A\cdot T(H) \leftrightarrow A\cdot T(w_H)_{R,L}}$ (9.15) $\leftrightarrow$ $A\cdot T(w_H)_{R,L}$ (9.02) $\leftrightarrow$ $TS_{A\cdot T(w_H)_{R,L} \leftrightarrow A\cdot T(w_{rH})_{L,R}}$ (19.71) $\leftrightarrow$ $A\cdot T(w_{rH})_{L,R}$ (8.61) $\leftrightarrow$ $TS_{A\cdot T(w_{rH})_{L,R} \leftrightarrow A\cdot T(rH)_{L,R}}$ (10.60) $\leftrightarrow$ $A\cdot T(rH)$ (0.27 kcal $\cdot$ mol $^{-1}$) (after each structure in brackets relative Gibbs free energy is presented obtained at the MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of QM theory in the continuum with $\epsilon=1$ under normal conditions).

TSs, which control $A\cdot T(WC) \leftrightarrow A\cdot T(rWC)$ and $A\cdot T(H) \leftrightarrow A\cdot T(rH)$ conformational transitions are stabilized by the participation of the intermolecular (T)N3H $\cdots$ N6(A) H-bond (5.82 kcal $\cdot$ mol $^{-1}$) and bifurcating intermolecular (T)N3H $\cdots$ N6(A) (5.00) and (T)N3H $\cdots$ N7(A) (0.61 kcal $\cdot$ mol $^{-1}$) H-bonds, accordingly. Notably, in these two TSs amino group N6H $_2$ of A is significantly pyramidilized; Gibbs free energies of activation for these reactions are 19.07 and 19.71 kcal $\cdot$ mol $^{-1}$, accordingly.

Fig. 3. Discovered new pathways of the $A \cdot T(w_H)_{R,L} \leftrightarrow A \cdot T(w_{rWC})_{R,L}$, $A \cdot T(w_{WC})_{R,L} \leftrightarrow A \cdot T(w_{rH})_{R,L}$, $A \cdot T(w_{WC})_{R,L} \leftrightarrow A \cdot T(w_{rWC})_{L,R}$ and $A \cdot T(w_H)_{R,L} \leftrightarrow A \cdot T(w_{rH})_{L,R}$ conformational transitions of the four biologically important A·T DNA base pairs in the continuum with $\epsilon=1$ at $T=298.15 \text{ K}$ (see Table 3). ΔG_{int} – Gibbs free energy of the interaction (MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory, in $\text{kcal} \cdot \text{mol}^{-1}$) [30]. For more designations see Fig. 1.

4. Novel routes of the mutagenic tautomerization of the T nucleobase in the classical A·T DNA base pairs: $A \cdot T(w_{WC}) \leftrightarrow A \cdot T^*(w_{WC}^\perp)$; $A \cdot T(w_{rWC}) \leftrightarrow A \cdot T^*_{O2}(w_{rWC}^\perp)$; $A \cdot T(w_H) \leftrightarrow A \cdot T^*(w_H^\perp)$; $A \cdot T(w_{rH}) \leftrightarrow A \cdot T^*_{O2}(w_{rH}^\perp)$ [31]

For the first time, we have theoretically demonstrated that novel highly-energetic conformers of the classical A·T DNA base pairs – Watson-Crick ($A \cdot T(w_{WC})$), reverse Watson-Crick ($A \cdot T(w_{rWC})$), Hoogsteen ($A \cdot T(w_H)$) and reverse Hoogsteen ($A \cdot T(w_{rH})$) – act as intermediates of the intrapair mutagenic tautomerization of the T nucleobase owing to the novel tautomerisation pathways: $A \cdot T(w_{WC}) \leftrightarrow A \cdot T^*(w_{WC}^\perp)$; $A \cdot T(w_{rWC}) \leftrightarrow A \cdot T^*_{O2}(w_{rWC}^\perp)$;

Table 4. Energetic characteristics (in $\text{kcal} \cdot \text{mol}^{-1}$) of the discovered mutagenic tautomerizations of T in the classical A·T DNA base pairs via the DPT and conformational transformations of their products obtained at the MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of QM theory in the continuum with $\epsilon=1$ at $T=298.15 \text{ K}$ (see Fig. 4) [31].

Tautomeric / conformational transition	ν_i^a	ΔG^b	ΔE^c	$\Delta \Delta G_{TS}^d$	$\Delta \Delta E_{TS}^e$	$\Delta \Delta G^f$	$\Delta \Delta E^g$
$A \cdot T(w_{WC})_{R,L} \leftrightarrow A \cdot T^*(w_{WC}^\perp)_{L,R}$	945.3	10.44	9.64	20.76	22.14	10.32	12.49
$A \cdot T(w_{rWC})_{R,L} \leftrightarrow A \cdot T^*_{O2}(w_{rWC}^\perp)_{L,R}$	749.4	14.69	13.66	23.06	23.66	8.37	10.00
$A \cdot T(w_H)_{R,L} \leftrightarrow A \cdot T^*(w_H^\perp)_{L,R}$	906.9	9.20	8.53	19.00	20.23	9.80	11.70
$A \cdot T(w_{rH})_{R,L} \leftrightarrow A \cdot T^*_{O2}(w_{rH}^\perp)_{L,R}$	704.8	13.75	13.22	21.48	22.41	7.72	9.20

Note: For designations see Table 1.

$A \cdot T(w_H) \leftrightarrow A \cdot T^*(w_H^\perp)$; $A \cdot T(w_{rH}) \leftrightarrow A \cdot T^*_{O_2}(w_{rH}^\perp)$ (Fig. 4, Table 4) [31]. Thus, it was theoretically shown using QM/QTAIM methods, that the transition of these pairs into the substantially non-planar, high-energy conformers [28] provokes intrapair mutagenic tautomerization of T – transition from the canonical, diketo into the rare, enol tautomeric forms T^* and $T^*_{O_2}$ [72]-[75].

TSs of these mutagenic tautomerisations are tight ion pairs (A^+ , protonated by the $N6H_2$ amino group)·(T^- , deprotonated by the $N3H$ group) with quasi-orthogonal geometry, which are stabilized by the participation of the strong $(A)N6^+H \cdots O4^-/O2^-(T)$ and $(A)N6^+H \cdots N3^-(T)$ H-bonds. Discovered reaction of the mutagenic tautomerization proceeds through the stepwise mechanism of the PT along the H-bonds: primarily proton moves from the imino group $N3H$ of T to the $N6H_2$ amino group of A and then proton transfers from the protonated $N6^+H_3$ amino

group of A to the oxygen atom $O4/O2$ of T, leading to the products – $A \cdot T^*(w_{WC}^\perp)$, $A \cdot T^*_{O_2}(w_{rWC}^\perp)$, $A \cdot T^*(w_H^\perp)$ and $A \cdot T^*_{O_2}(w_{rH}^\perp)$, which are substantially non-planar, conformationally-labile complexes. These complexes are stabilized by the participation of the $(A)N6H/N6H^+ \cdots N3(T)$ and $(T)O2H/O4H \cdots N6(A)$ H-bonds, for which the pyramidalized amino group of A DNA base acts as their donor and acceptor. The free Gibbs energy of the activation of the mutagenic tautomerizations lies in the range of 27.79 – 29.83 kcal·mol⁻¹ at $T=298.15$ K.

Moreover, for the first time we have investigated in details conformationally-tautomeric properties of the classical A·T DNA base pairs. Also it was shown that the formed $A \cdot T^*(w_{WC}^\perp)$, $A \cdot T^*(w_H^\perp)$, $A \cdot T^*_{O_2}(w_{rWC}^\perp)$ and $A \cdot T^*_{O_2}(w_{rH}^\perp)$ complexes can conformationally interconvert

according to the pathways $A \cdot T^*(w_{WC}^\perp) \leftrightarrow A \cdot T^*(w_H^\perp)$ and $A \cdot T^*_{O2}(w_{rWC}^\perp) \leftrightarrow A \cdot T^*_{O2}(w_{rH}^\perp)$ through three different TSs.

Conclusion

In this paper the instructions for preparing of the Camera Ready Paper for including in the Proceedings of International Joint Forum LEA'2018 & YSTCMT'2018 is given. We have uncovered for the first time at the at the MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of QM theory novel mechanisms of the conformational and tautomeric transitions of the classical A·T DNA base pairs and their wobble conformers:

- The $A \cdot T(WC) \leftrightarrow A \cdot T(w_{WC})$, $A \cdot T(rWC) \leftrightarrow A \cdot T(w_{rWC})$, $A \cdot T(H) \leftrightarrow A \cdot T(w_H)$ and $A \cdot T(rH) \leftrightarrow A \cdot T(w_{rH})$ conformational transformations (Gibbs free energies of activation 7.13, 7.26, 7.67 and 7.44 in the continuum with $\epsilon=4$) [28] open new perspectives for the understanding of the physico-chemical mechanisms of the opening of the base pairs preceding DNA melting and also to describe in details the breathing of DNA.

- The $A \cdot T(WC) \leftrightarrow A \cdot T(H)$ and $A \cdot T(rWC) \leftrightarrow A \cdot T(rH)$ structural transitions (Gibbs free energies of activation 1.97 / 9.53 / 9.52 and 1.84 / 9.12 / 9.28 kcal·mol⁻¹ in the continuum with $\epsilon=4$) act as intermediates of the pairwise $A \cdot T(WC) / A \cdot T(rWC) \leftrightarrow A \cdot T(H) / A \cdot T(rH)$ conformational transformations [29].

- The $A \cdot T(w_H) \leftrightarrow A \cdot T(w_{rWC})$, $A \cdot T(w_{WC}) \leftrightarrow A \cdot T(w_{rH})$, $A \cdot T(w_{WC}) \leftrightarrow A \cdot T(w_{rWC})$ and $A \cdot T(w_H) \leftrightarrow A \cdot T(w_{rH})$ conformational transitions (Gibbs free energies of activation 3.20, 3.70, 12.04 and 10.69 kcal·mol⁻¹ in the continuum with $\epsilon=1$ at T=298.15 K) define the interconversions between the classical A·T DNA base pairs: $A \cdot T(WC) \leftrightarrow A \cdot T(rWC) / A \cdot T(rH)$ and $A \cdot T(H) \leftrightarrow A \cdot T(rH) / A \cdot T(rWC)$ [30].

- The $A \cdot T(w_{WC}) \leftrightarrow A \cdot T^*(w_{WC}^\perp)$, $A \cdot T(w_{rWC}) \leftrightarrow A \cdot T^*_{O2}(w_{rWC}^\perp)$, $A \cdot T(w_H) \leftrightarrow A \cdot T^*(w_H^\perp)$, $A \cdot T(w_{rH}) \leftrightarrow A \cdot T^*_{O2}(w_{rH}^\perp)$ tautomeric transitions proceed through the stepwise proton transfer *via* the TSs as tight $A^+ \cdot T^-$ ion pairs (Gibbs free energy of activation 20.76, 23.06, 19.00 and 21.48 kcal·mol⁻¹ in the continuum with $\epsilon=1$ at T=298.15 K), thus creating the substantially non-planar, conformationally-labile complexes – $A \cdot T^*(w_{WC}^\perp)$, $A \cdot T^*_{O2}(w_{rWC}^\perp)$, $A \cdot T^*(w_H^\perp)$ and $A \cdot T^*_{O2}(w_{rH}^\perp)$ [31].

Acknowledgments

The authors gratefully appreciate technical support and computational facilities of joint computer cluster of SSI “Institute for Single Crystals” of the National Academy of Sciences of Ukraine (NASU) and Institute for Scintillation Materials of the NASU incorporated into Ukrainian National Grid. This work was partially supported by the Grant of the President of Ukraine to support the research of young scientists from the State Fund for Fundamental Research of Ukraine of the Ministry of the Education and Science of Ukraine given to DrSci Ol’ha O. Brovarets’.

References

- [1] Donohue, J., & Trueblood K.N. Base pairing in DNA. *J. Mol. Biol.*, 1960, 2, 363–371.
- [2] Tchurikov, N.A., Chernov, B.K., Golova, Y.B., & Nechipurenko, Y.D. Parallel DNA: Generation of a duplex between two *Drosophila* sequences *in vitro*. *FEBS Lett.*, 1989, 257, 415–418.
- [3] Cubero, E., Luque, F.J., & Orozco, M. Theoretical studies of d(A:T)-based parallel-stranded DNA duplexes. *J. Am. Chem. Soc.*, 2001, 123, 12018–12025.
- [4] Parvathy, V. R., Bhaumik, S. R., Chary, K. V., Govil, G., Liu, K., Howard, F. B., & Miles, H. T. NMR structure of a parallel-stranded DNA duplex at atomic resolution. *Nucleic Acids Res.*, 2002, 30, 1500–1511.
- [5] Poltev, V. I., Anisimov, V. M., Sanchez, C., Deriabina, A., Gonzalez, E., Garcia, D., Rivas, N., & Polteva, N. A. Analysis of the conformational features of Watson–Crick duplex fragments by molecular mechanics and quantum mechanics methods. *Biophysics*, 2016, 61, 217–226.
- [6] Ye, M. Y., Zhu, R. T., Li, X., Zhou, X. S., Yin, Z. Z., Li, Q., & Shao, Y. Adaptively recognizing parallel-stranded duplex structure for fluorescent DNA polarity analysis. *Anal. Chem.*, 2017, 89, 8604–8608.
- [7] Szabat, M., & Kierzek, R. Parallel-stranded DNA and RNA duplexes: structural features and potential applications. *FEBS J.*, 2017, 284, 3986–3998.
- [8] Brovarets' O.O. Under what conditions does G·C Watson-Crick DNA base pair acquire all four configurations characteristic for A·T Watson-Crick DNA base pair? *Ukr. Biochem. J.*, 2013, 85, 98–103.
- [9] Brovarets' O.O. Structural and energetic properties of the four configurations of the A·T and G·C DNA base pairs. *Ukr. Biochem. J.*, 2013, 85, 104–110.
- [10] Hoogsteen, K. The crystal and molecular structure of a hydrogenbonded complex between 1-methylthymine and 9-methyladenine. *Acta Cryst.*, 1963, 16, 907–916.
- [11] Abrescia, N.G., Thompson, A., Huynh-Dinh, T., & Subirana, J.A. Crystal structure of an antiparallel DNA fragment with Hoogsteen base pairing. *Proc. Natl. Acad. Sci. USA*, 2002, 99, 2806–2811.
- [12] Abrescia, N.G., Gonzalez, C., Gouyette, C., & Subirana, J.A. X-ray and NMR studies of the DNA oligomer d(ATATAT): Hoogsteen base pairing in duplex DNA. *Biochemistry*, 2004, 43, 4092–4100.
- [13] Pous, J., Urpi, L., Subirana, J.A., Gouyette, C., Navaza, J., & Campos, J.L. Stabilization by extra-helical thymines of a DNA duplex with Hoogsteen base pairs. *J. Am. Chem. Soc.*, 2008, 130, 6755–6760.
- [14] Campos, L., Valls, N., Urpí, L., Gouyette, C., Sanmartín, T., Richter, M., Alechaga, E., Santaolalla, A., Baldini, R., Creixell, M., Ciurans, R., Skokan, P., Pous, J., & Subirana, J.A. Overview of the structure of allAT oligonucleotides: organization in helices and packing interactions. *Biophys. J.*, 2006, 91, 892–903.
- [15] Nikolova, E.N., Zhou, H., Gottardo F.L., Alvey, H. S., Kimsey, I. J., & Al-Hashimi, H. M. A historical account of Hoogsteen base-pairs in duplex DNA. *Biopolymers*, 2014, 99, 955–968.
- [16] Alvey, H.S., Gottardo, F.L., Nikolova, E.N., & Al-Hashimi, H.M. Widespread transient Hoogsteen base-pairs in canonical duplex DNA with variable energetics. *Nature Comm.*, 2014, 5, 4786–4794.

- [17] Acosta-Reyes, F.J., Alechaga, E., Subirana, J.A., & Campos, J.L. Structure of the DNA duplex d(ATTAAT)₂ with Hoogsteen hydrogen bonds. *PLoS One*, 2015, 10, e0120241.
- [18] Yang, C., Kim, E., & Pak, Y. Free energy landscape and transition pathways from Watson–Crick to Hoogsteen base pairing in free duplex DNA. *Nucleic Acids Res.*, 2015, 43, 7769–7778.
- [19] Zhou H. *Occurrence and function of Hoogsteen base pairs in nucleic acids*. PhD Thesis: Department of Biochemistry, Duke University, 2016.
- [20] Sathyamoorthy, B., Shi, H., Zhou, H., Xue, Y., Rangadurai, A., Merriman, D.K., Al-Hashimi, H.M. Insights into Watson–Crick/Hoogsteen breathing dynamics and damage repair from the solution structure and dynamic ensemble of DNA duplexes containing m1A. *Nucleic Acids Res.*, 2017, 45, 5586–5601.
- [21] Haschemeyer, A.E.V., & Sobell, H.M. The crystal structure of an intermolecular nucleoside complex: Adenosine and 5-bromouridine. *Proc. Natl Acad. Sci. USA*, 1963, 50, 872–877.
- [22] Sühnel, J. Beyond nucleic acid base pairs: From triads to heptads. *Biopolymers*, 2002, 61, 32–51.
- [23] Zagryadskaya, E.I., Doyon, F.R., & Steinberg, S.V. Importance of the reverse Hoogsteen base pair 54–58 for tRNA function. *Nucleic Acids Res.*, 2003, 31, 3946–3953.
- [24] Liu, K., Miles, H. T., Frazier, J. & Sasisekharan, V. A novel DNA duplex. A parallel-stranded DNA helix with Hoogsteen base pairing. *Biochemistry*, 1993, 32, 11802–11809.
- [25] von Hippel, P., Johnson, N.P., & Marcus, A.H. Fifty years of DNA “breathing”: reflections on old and new approaches. *Biopolymers*, 2013, 99, 923–953.
- [26] Frank-Kamenetskii, M., & Prakash, S. Fluctuations in the DNA double helix: a critical review. *Phys. Life Rev.*, 2014.
- [27] Chakraborty, D., & Wales, D.J. Energy landscape and pathways for transitions between Watson-Crick and Hoogsteen base pairing in DNA. *J. Phys. Chem. Lett.*, 2018, 9, 229–241.
- [28] Brovarets', O.O., Tsiupa, K.S., & Hovorun, D.M. Surprising conformers of the biologically important A·T DNA base pairs: QM/QTAIM proofs. *Front. Chem.* 2018, 6:8, doi: 10.3389/fchem.2018.00008.
- [29] Brovarets', O. O., Tsiupa, K. S., & Hovorun, D. M. Non-dissociative structural transitions of the Watson-Crick and reverse Watson-Crick A·T DNA base pairs into the Hoogsteen and reverse Hoogsteen forms. *Sci. Repts.* 2018, 8, 10371.
- [30] Brovarets', O. O., Tsiupa, K. S., & Hovorun, D. M. Unexpected A·T(WC)↔A·T(rWC)/A·T(rH) and A·T(H)↔A·T(rH)/A·T(rWC) conformational transitions between the classical A·T DNA base pairs: A QM/QTAIM comprehensive study. *Int. J. Quantum. Chem.* 2018, 118, e25674.
- [31] Brovarets' O.O., Tsiupa K.S., Dinets A., Hovorun D.M. Unexpected routes of the mutagenic tautomerization of the T nucleobase in the classical A·T DNA base pairs: A QM/QTAIM comprehensive view. *Front. Chem.*, 2018, 6:532; doi: 10.3389/fchem.2018.00532.
- [32] Tirado-Rives, J., & Jorgensen, W.L. Performance of B3LYP Density Functional Methods for a large set of organic molecules. *J. Chem. Theory Comput.*, 2008, 4, 297–306.
- [33] Parr, R.G., & Yang, W. *Density-functional theory of atoms and molecules*. Oxford: Oxford University Press, 1989.
- [34] Lee, C., Yang, W., & Parr, R.G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B.*, 1988, 37, 785–789.
- [35] Hariharan, P.C., & Pople, J.A. The influence of polarization functions on molecular orbital hydrogenation energies. *Theor. Chim. Acta*, 1973, 28, 213–222.

- [36] Krishnan, R., Binkley, J.S., Seeger, R., & Pople, J.A. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. *J. Chem. Phys.*, 1980, 72, 650–654.
- [37] Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., & Cheeseman, J.R., ... Pople, J.A. (2010). *GAUSSIAN 09* (Revision B.01). Wallingford CT: Gaussian Inc.
- [38] Matta, C.F. How dependent are molecular and atomic properties on the electronic structure method? Comparison of Hartree-Fock, DFT, and MP2 on a biologically relevant set of molecules. *J. Comput. Chem.*, 2010, 31, 1297–1311.
- [39] Brovarets', O. O., & Hovorun, D. M. Quantum-chemical investigation of tautomerization ways of Watson-Crick DNA base pair guanine-cytosine. *Ukr. Biochem. J.*, 2010, 82, 55-60.
- [40] Brovarets', O. O., & Hovorun, D. M. Quantum-chemical investigation of the elementary molecular mechanisms of pyrimidine-purine transversions. *Ukr. Biochem. J.*, 2010, 82, 57-67.
- [41] Brovarets', O.O., & Hovorun, D.M. How the long G·G* Watson-Crick DNA base mispair comprising keto and enol tautomers of the guanine tautomerises? The results of the QM/QTAIM investigation. *Phys. Chem. Chem. Phys.*, 2014, 6, 15886-15899.
- [42] Brovarets', O. O., & Hovorun, D. M. The nature of the transition mismatches with Watson-Crick architecture: the G*·T or G·T* DNA base mispair or both? A QM/QTAIM perspective for the biological problem. *J. Biomol. Struct. & Dynam.*, 2015, 33, 925-945.
- [43] Brovarets', O.O., Zhurakivsky, R.O., & Hovorun, D.M. DPT tautomerisation of the wobble guanine-thymine DNA base mispair is not mutagenic: QM and QTAIM arguments. *J. Biomol. Struct. & Dynam.*, 2015, 33, 674-689.
- [44] Palafox, M.A. Molecular structure differences between the antiviral nucleoside analogue 5-iodo-2'-deoxyuridine and the natural nucleoside 2'-deoxythymidine using MP2 and DFT methods: conformational analysis, crystal simulations, DNA pairs and possible behavior. *J. Biomol. Struct. & Dynam.*, 2014, 32, 831–851.
- [45] El-Sayed, A.A., Tamara Molina, A., Alvarez-Ros, M.C., & Palafox, M.A. Conformational analysis of the anti-HIV Nikavir prodrug: comparisons with AZT and thymidine, and establishment of structure-activity relationships/tendencies in other 6'-derivatives. *J. Biomol. Struct. & Dynam.*, 2015, 33, 723–748.
- [46] Peng, C., Ayala, P.Y., Schlegel, H.B., & Frisch, M.J. Using redundant internal coordinates to optimize equilibrium geometries and transition states. *J. Comput. Chem.*, 1996, 17, 49–56.
- [47] Atkins, P.W. *Physical chemistry*. Oxford: Oxford University Press, 1998.
- [48] Frisch, M.J., Head-Gordon, M., & Pople, J.A. Semi-direct algorithms for the MP2 energy and gradient. *Chem. Phys. Lett.*, 1990, 166, 281-289.
- [49] Kendall, R.A., Dunning, Jr., T.H., & Harrison, R.J. Electron affinities of the first-row atoms revisited. Systematic basis sets and wave functions. *J. Chem. Phys.*, 1992, 96, 6796–6806.
- [50] Boys, S.F., & Bernardi, F. The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors. *Mol. Phys.*, 1970, 19, 553–566.
- [51] Gutowski, M., Van Lenthe, J.H., Verbeek, J., Van Duijneveldt, F.B., & Chalasinski, G. The basis set superposition error in correlated electronic structure calculations. *Chem. Phys. Lett.*, 1986, 124, 370–375.
- [52] Sordo, J.A., Chin, S., & Sordo, T.L. On the counterpoise correction for the basis set superposition error in large systems. *Theor. Chim. Acta*, 1988, 74, 101–110.

- [53] Sordo, J.A. On the use of the Boys–Bernardi function counterpoise procedure to correct barrier heights for basis set superposition error. *J. Mol. Struct.*, 2001, 537, 245–251.
- [54] Bader, R.F.W. *Atoms in molecules: A quantum theory*. Oxford: Oxford University Press, 1990.
- [55] Matta, C.F., & Hernández-Trujillo, J. Bonding in polycyclic aromatic hydrocarbons in terms of the electron density and of electron delocalization. *J. Phys. Chem. A*, 2003, 107, 7496–7504.
- [56] Matta, C.F., Castillo, N., & Boyd, R.J. Atomic contributions to bond dissociation energies in aliphatic hydrocarbons. *J. Chem. Phys.*, 2006, 125, 20, 204103.
- [57] Matta, C.F. Modeling biophysical and biological properties from the characteristics of the molecular electron density, electron localization and delocalization matrices, and the electrostatic potential. *J. Comput. Chem.*, 2014, 35, 1165–1198.
- [58] Lecomte, C., Espinosa, E., & Matta, C.F. On atom–atom ‘short contact’ bonding interactions in crystals, *IUCrJ*, 2015, 2, 161–163.
- [59] Keith, T.A. (2010). *AIMAll* (Version 10.07.01). Retrieved from aim.tkgristmill.com.
- [60] Matta, C.F., Castillo, N., & Boyd, R.J. Extended weak bonding interactions in DNA: π -stacking (base-base), base-backbone, and backbone-backbone interactions. *J. Phys. Chem. B*, 2006, 110, 563–578.
- [61] Brovarets', O.O., Zhurakivsky, R.O., & Hovorun, D.M. Is the DPT tautomerisation of the long A·G Watson-Crick DNA base mispair a source of the adenine and guanine mutagenic tautomers? A QM and QTAIM response to the biologically important question. *J. Comput. Chem.*, 2014, 35, 451–466.
- [62] Brovarets', O.O., & Hovorun, D.M. DPT tautomerisation of the G·A_{syn} and A*·G*_{syn} DNA mismatches: A QM/QTAIM combined atomistic investigation. *Phys. Chem. Chem. Phys.*, 2014, 16, 9074–9085.
- [63] Brovarets', O. O., & Hovorun, D. M. Tautomeric transition between wobble A·C DNA base mispair and Watson-Crick-like A·C* mismatch: microstructural mechanism and biological significance. *Phys. Chem. Chem. Phys.*, 2015, 17, 15103–15110.
- [64] Matta, C.F., & Boyd, R.J. *The Quantum Theory of Atoms in Molecules: from solid state to DNA and drug design*. Wiley-VCH Verlag GmbH & Co. KGaA, 2007.
- [65] Iogansen, A.V. Direct proportionality of the hydrogen bonding energy and the intensification of the stretching $\nu(\text{XH})$ vibration in infrared spectra. *Spectrochim. Acta Part A: Mol. Biomol. Spectrosc.*, 1999, 55, 1585–1612.
- [66] Brovarets', O.O., Zhurakivsky, R.O., & Hovorun, D.M. The physico-chemical mechanism of the tautomerisation *via* the DPT of the long Hyp*·Hyp Watson-Crick base pair containing rare tautomer: a QM and QTAIM detailed look. *Chem. Phys. Lett.*, 2013, 578, 126–132.
- [67] Brovarets', O.O., & Hovorun, D.M. Does the G·G*_{syn} DNA mismatch containing canonical and rare tautomers of the guanine tautomerise through the DPT? A QM/QTAIM microstructural study. *Mol. Phys.*, 2014, 112, 3033–3046.
- [68] Brovarets', O. O.; Voiteshenko, I. S.; Pérez-Sánchez, H. E.; Hovorun, D. M. A QM/QTAIM research under the magnifying glass of the DPT tautomerisation of the wobble mispairs involving 2-aminopurine. *New J. Chem.*, 2017, 41, 7232–7243.
- [69] Brovarets', O. O.; Voiteshenko, I. S.; Hovorun, D. M. Physico-chemical profiles of the wobble↔Watson-Crick G*·2AP(w)↔G·2AP(WC) and A·2AP(w)↔A*·2AP(WC) tautomerisations: a QM/QTAIM comprehensive survey. *Phys. Chem. Chem. Phys.*, 2017, 20, 623–636.

- [70] Brovarets', O.O., & Hovorun, D.M. A novel conception for spontaneous transversions caused by homo-pyrimidine DNA mismatches: a QM/QTAIM highlight. *Phys. Chem. Chem. Phys.*, 2015, 17, 21381-21388.
- [71] Saenger, W. *Principles of nucleic acid structure*. New York: Springer, 1984.
- [72] Brovarets', O. O., & Hovorun, D. M. New structural hypostases of the A·T and G·C Watson-Crick DNA base pairs caused by their mutagenic tautomerisation in a wobble manner: a QM/QTAIM prediction. *RSC Adv.*, 2015, 5, 99594-99605.
- [73] Brovarets' O. O., & Hovorun D. M. How many tautomerisation pathways connect Watson-Crick-like G*·T DNA base mispair and wobble mismatches? *J. Biomol. Struct. & Dynam.*, 2015, 33, 2297-2315.
- [74] Brovarets', O.O., Zhurakivsky, R.O., & Hovorun, D.M. DPT tautomerisation of the wobble guanine·thymine DNA base mispair is not mutagenic: QM and QTAIM arguments. *J. Biomol. Struct. & Dynam.*, 2015, 33, 674-689.
- [75] Brovarets', O.O., Zhurakivsky, R.O., & Hovorun, D.M. Structural, energetic and tautomeric properties of the T·T*/T*·T DNA mismatch involving mutagenic tautomer of thymine: a QM and QTAIM insight. *Chem. Phys. Lett.*, 2014, 592, 247-255.