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The A·T(rWC)/A·T(H)/A·T(rH) ↔ A·T*(rw_{WC})/A·T*(w_H)/A·T*(rw_H) mutagenic tautomerization via sequential proton transfer: a QM/QTAIM study

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In this study for the first time we have revealed by QM and QTAIM calculations at the MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of QM theory the novel routes of the mutagenic tautomerization of three biologically important A·T DNA base pairs – reverse Watson–Crick A·T(rWC), Hoogsteen A·T(H) and reverse Hoogsteen A·T(rH) – followed by their rebuilding into the wobble (w) A·T*(rw_{WC}), A·T*(w_H) and A·T*(rw_H) base mispairs by the participation of the mutagenic tautomers of the DNA bases (denoted by asterisk) and *vice versa*, thus complementing the physico-chemical property of the canonical A·T(WC) Watson–Crick DNA base pair reported earlier (Brovarets' *et al.*, *RSC Adv.*, 2015, 5, 99594–99605). These non-dissociative tautomeric transformations in the classical A·T(rWC), A·T(H) and A·T(rH) DNA base pairs proceed similarly to the canonical A·T(WC) DNA base pair *via* the intrapair sequential proton transfer with shifting towards major or minor grooves of DNA followed by further double proton transfer along the intermolecular H-bonds and are controlled by the plane symmetric and highly stable transition states – tight ion pairs formed by the A⁺ nucleobase, protonated by the N1/N7 nitrogen atoms, and T[−] nucleobase, deprotonated by the N3H imino group. Comparison of the estimated populations of the tautomerised states (10^{−21} to 10^{−14}) with similar characteristics for the canonical A·T(WC) DNA base pair (10^{−8} to 10^{−7}) leads authors to the conclusion, that only a base pair with WC architecture can be a building block of the DNA macromolecule as a genetic material, which is able for the evolutionary self-development. Among all four classical DNA base pairs, only A·T(WC) DNA base pair can ensure the proper rate of the spontaneous point errors of replication in DNA.

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Introduction

Clarification of the microstructural mechanisms of the mutagenic tautomerization of the DNA base pairs is a classical problem of molecular biophysics, biochemistry and structural biology, which remain topical up to now.^{1–5} Literature analysis shows that the so-called tautomeric hypothesis formulated by Watson and Crick,¹ soon after their discovery of the spatial architecture of DNA – a macromolecule that is the carrier of the genetic information,² represents itself the most vivid theoretical platform for the conduction of these studies. At that time, this hypothesis became a real breakthrough in the understanding of the nature of the origin of the spontaneous point mutations – transitions and transversions⁵ – and also involvement in this biologically important phenomenon of the prototropic tautomerism of the DNA bases.^{6,7}

Advances in technology eventually led to numerous as experimental investigations,^{8–13} in particular X-ray analysis^{8,9} and NMR, in particular relaxation dispersion, measurements,^{10–13} so theoretical examinations^{14–19} of this discovery. However, these results do not clarify the physico-chemical mechanisms of the arising of the rare or mutagenic tautomeric forms of the DNA bases^{20–23} (here and below marked by an asterisk).

It was established for sure that generally accepted mechanism of the double proton transfer (DPT) along intermolecular H-bonds in the Watson–Crick (WC) (so-called Löwdin's mechanism),^{24–29} wobble (w) base pairs,^{30,31} biologically important A·G,³² A·C*,³³ G*.T,³⁴ C·T,³⁵ G·G_{syn}*,³⁶ A*.A_{syn},³⁷ A*.G_{syn}*,³⁸ H·C,^{39,40} H·H^{39,40} and H·A^{39,42} base mispairs and also in the protein–DNA complexes^{26,43,44} can't be considered as the source of the mutagenic tautomers formations due to the dynamical instability of the terminal complexes containing mutagenic tautomers of the DNA bases.^{26–29,31–42,44}

For the first time, we have proposed a novel theoretical approach to the elucidation of the microstructural mechanisms of the incorporation and replication errors arising at the DNA replication due to the intrinsic ability of the purine·pyrimidine (A·T, G·C, G·T and A·C), purine·purine (A·A and G·G) and

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pyrimidine-pyrimidine (C·C and T·T) DNA base mispairs to perform WC ↔ w tautomeric transitions *via* the sequential proton transfer (PT).^{45–53} It was revealed that all these non-dissociative tautomerisations are controlled by the highly stable, highly polar and zwitterionic transition states of the type (protonated base)·(deprotonated base). These interconversions are accompanied by a significant rebuilding of the base mispairs with Watson–Crick architecture into the mismatches wobbled towards minor or major grooves of DNA. Moreover, it was established that these tautomerisation reactions occur non-dissociatively and are accompanied by the consequent replacement of the unique patterns of the intermolecular specific interactions along intrinsic reaction coordinate (IRC).

Thus, in particular, it was found out that the A·T(WC) Watson–Crick DNA base pair exists simultaneously in three other biologically important hypostasis⁴⁵ – short-lived wobble A*·T(w) (population = 5.4×10^{-8}), A·T_{O2}*(w) (9.9×10^{-9}) and A·T*(w) (2.5×10^{-10}) H-bonded mismatches, containing mutagenic tautomers of the nucleotide bases. Their forced separation by the DNA-polymerase machinery into the monomers with necessity generates mutagenic tautomers of the DNA bases, which are long-lived structures causing spontaneous point mutations – transitions and transversions.^{53–55}

Presented approach clarifies the microstructural mechanisms of the mutations induced by the classical mutagens, in particular 2-aminopurine, for which frequencies agree well with the experimental data.^{56–61}

The aim of the current study is to extend the approach launched in our previous work for the canonical DNA base pairs⁴⁵ to the other classical A·T DNA base pairs – reverse Watson–Crick A·T(rWC), Hoogsteen A·T(H) and reverse Hoogsteen A·T(rH).

At this point, the question arises according the urgency of this investigation.

First, the A·T(rWC), A·T(H) and A·T(rH) DNA base pairs have a remarkable biological meaning (see works^{62–79} and the bibliography cited therein). Second, as of today, the mutagenic tautomerization of these biologically important pairs has not even mentioned in the literature. Thirdly, we are interested in the investigation of the evolutionary aspect of the problem, in particular, why *Nature* chose precisely Watson–Crick DNA base pairs for the construction of the genetic material, among which the A·T(WC) DNA base pair is the most evolutionarily distant, since it was the first to appear evolutionary.^{6,80,81}

So, in this regard, we can make an assumption that exactly the A·T(WC) base pair provides necessary frequency of the spontaneous point replication errors in DNA, which lies in the range of 10^{-9} to 10^{-11} per nucleotide, incorporated during one replication cycle.^{82,83}

Such statement of the problem except merely academic value has also practical assignment, *e.g.* for the biomolecular electronics, which are used for the DNA-based carriers of the digital information,^{84,85} since it allows, in principle, to understand how the complementary bases should be modified in order to suppress the tautomeric instability of their pair. This is extremely important for increasing of the accuracy of such molecular devices.⁸⁶

As a result of the systematic quantum-mechanical calculations, we managed to establish the microstructural mechanisms of the mutagenic tautomerisation of the studied A·T DNA base pairs and to reach the conclusion about a unique place of the canonical Watson–Crick A·T(WC) DNA base pair among them. Only this base pair able to provide the necessary rate of the spontaneous point mutations, which, as it is well known, are the source of the genome self-development.^{6,80–83}

Computational methods

Geometries of the investigated DNA base pairs and transition states (TSs) of their mutual tautomeric transformations, as well as their harmonic vibrational frequencies have been calculated at the B3LYP/6-311++G(d,p) level of theory,^{87–91} using Gaussian'09 package⁹² followed by the IRC calculations in the forward and reverse directions from each TS using Hessian-based predictor-corrector integration algorithm.⁹³ Applied level of theory has proved itself successful for the calculations of the similar systems.^{94–96} A scaling factor that is equal to 0.9668 (ref. 97–100) has been applied in the present work for the correction of the harmonic frequencies for all DNA base pairs and TSs of their tautomeric transitions. We have confirmed the local minima and TSs, localized by Synchronous Transit-guided Quasi-Newton method,¹⁰¹ 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 tautomeric transformations.¹⁰² Electronic energy calculations have been performed at the MP2/aug-cc-pVDZ level of theory.^{103,104}

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

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

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

The time $\tau_{99.9\%}$ necessary to reach 99.9% of the equilibrium concentration of the reactant and product in the system of reversible first-order forward (k_f) and reverse (k_r) reactions can be estimated by the formula:¹⁰²

$$\tau_{99.9\%} = \frac{\ln 10^3}{k_f + k_r}. \quad (2)$$

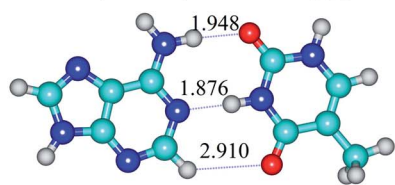
The lifetime τ of the formed mismatches has been calculated using the formula (1)/ k_r , where the values of the reverse k_r and forward k_f rate constants for the tautomerisation reactions were obtained as:¹⁰²

$$k_{f,r} = \Gamma \frac{k_B T}{h} e^{-\frac{\Delta\Delta G_{f,r}}{RT}}, \quad (3)$$

where quantum tunneling effect has been accounted by Wigner's tunneling correction,¹⁰⁵ which has been successfully used for the DPT reactions:^{33–42}

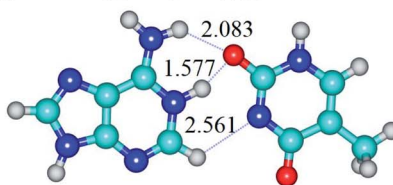
$$\Gamma = 1 + \frac{1}{24} \left(\frac{h\nu_i}{k_B T} \right)^2, \quad (4)$$





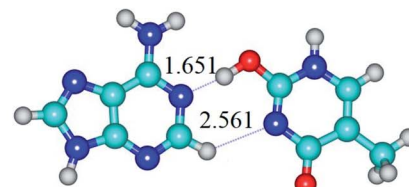
A·T(rWC)

$$(\Delta E_{\text{int}}=-14.71 (0.86) / \Delta G_{\text{int}}=-3.22 / \Delta G=0.00 / \Delta E=0.00)$$



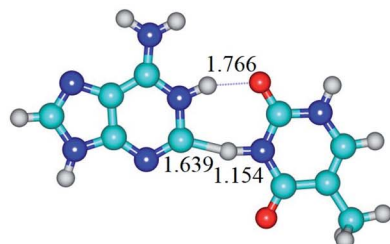
TS^{A+·T-}_{A·T(rWC)→A·T*O2(rwWC)}
($\nu_i=66.5 \text{ i cm}^{-1}$)

$$(\Delta E_{\text{int}}=-120.14 (0.12) / \Delta G_{\text{int}}=-107.21 / \Delta G=32.86 / \Delta E=32.49)$$

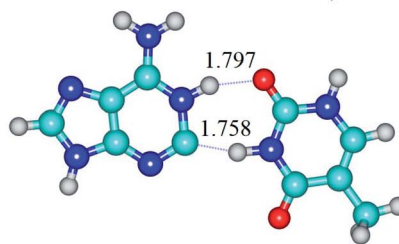


A·T*O₂(rwWC)

$$(\Delta E_{\text{int}}=-15.13 (0.83) / \Delta G_{\text{int}}=-3.41 / \Delta G=27.71 / \Delta E=29.12)$$

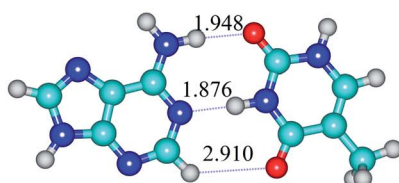
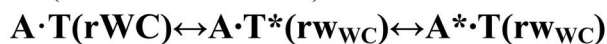


TS_{A·T*O2(rwWC)→A*C2·T(rwWC)}
($\nu_i=137.7 \text{ i cm}^{-1}$)
($\Delta G=55.14 / \Delta E=58.01$)



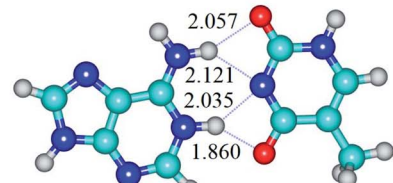
A*C₂·T(rwWC)

$$(\Delta E_{\text{int}}=-26.49 (0.69) / \Delta G_{\text{int}}=-15.79 / \Delta G=56.63 / \Delta E=57.95)$$



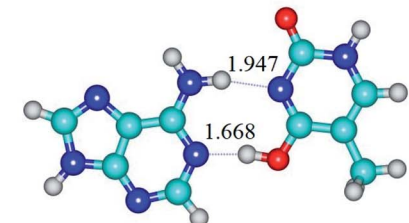
A·T(rWC)

$$(\Delta E_{\text{int}}=-14.71 (0.86) / \Delta G_{\text{int}}=-3.22 / \Delta G=0.00 / \Delta E=0.00)$$



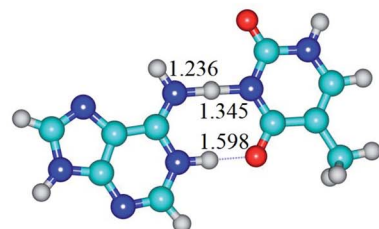
TS^{A+·T-}_{A·T(rWC)→A·T*(rwWC)}
($\nu_i=132.4 \text{ i cm}^{-1}$)

$$(\Delta E_{\text{int}}=-123.77 (0.11) / \Delta G_{\text{int}}=-109.80 / \Delta G=26.84 / \Delta E=25.43)$$

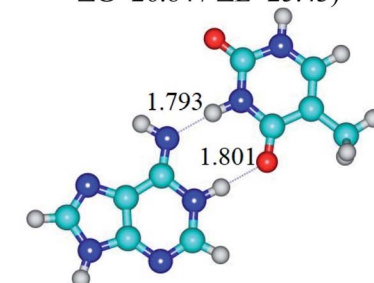


A·T*(rwWC)

$$(\Delta E_{\text{int}}=-19.97 (0.80) / \Delta G_{\text{int}}=-6.28 / \Delta G=18.56 / \Delta E=17.69)$$



TS_{A·T*(rwWC)→A*·T(rwWC)}
($\nu_i=906.3 \text{ i cm}^{-1}$)
($\Delta G=21.56 / \Delta E=22.77$)

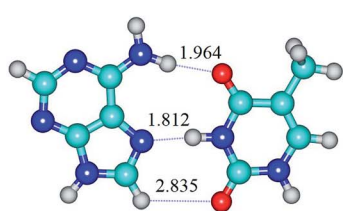


A*·T(rwWC)

$$(\Delta E_{\text{int}}=-18.58 (0.77) / \Delta G_{\text{int}}=-6.44 / \Delta G=20.17 / \Delta E=18.92)$$

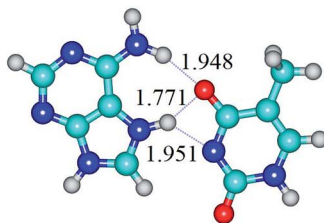
Fig. 1 Geometrical structures of the stationary points on the pathways of the tautomerization of the classical A·T DNA base pairs into the wobble base mispairs via the sequential PT followed by DPT. Electronic ΔE_{int} (contribution of the total energy of the H-bonds) and Gibbs free ΔG_{int} energies of the interaction (MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory, in kcal mol⁻¹), relative Gibbs free energies ΔG and electronic energies ΔE (in kcal mol⁻¹), imaginary frequencies ν_i at the TSs of the tautomeric transitions (MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of theory in the continuum with $\epsilon = 1$ at $T = 298.15$ K) are presented below complexes in brackets. Dotted lines indicate AH...B H-bonds – their lengths H...B are presented in angstroms (for their more detailed physico-chemical characteristics see Table 2); carbon atoms are in light-blue, nitrogen – in dark-blue, hydrogen – in grey and oxygen – in red.



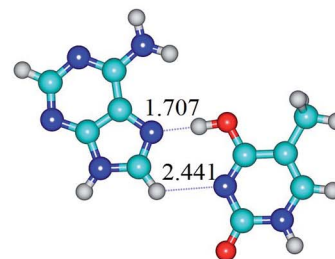


A·T(H)

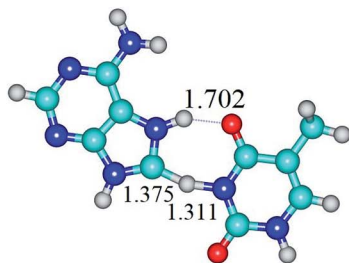
$$(\Delta E_{\text{int}} = -15.93 \text{ (0.78)} / \Delta G_{\text{int}} = -2.71 / \Delta G = 0.00 / \Delta E = 0.00)$$


 $\text{TS}^{\text{A}^+\cdot\text{T}^-}_{\text{A}\cdot\text{T}(\text{H}) \leftrightarrow \text{A}\cdot\text{T}^*(\text{w}_\text{H})}$
 $(\nu_i = 155.3 \text{ i cm}^{-1})$

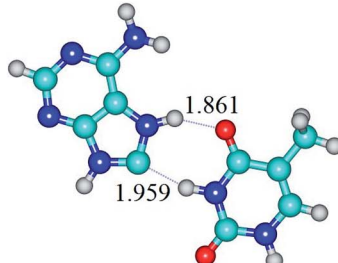
$$(\Delta E_{\text{int}} = -128.62 \text{ (0.10)} / \Delta G_{\text{int}} = -115.33 / \Delta G = 31.91 / \Delta E = 31.69)$$

A·T*(w_H)

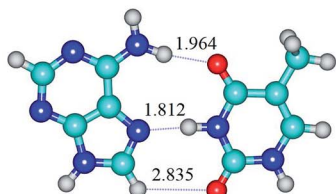
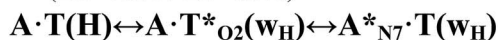
$$(\Delta E_{\text{int}} = -15.95 \text{ (0.69)} / \Delta G_{\text{int}} = -3.64 / \Delta G = 21.92 / \Delta E = 22.94)$$


 $\text{TS}_{\text{A}\cdot\text{T}^*(\text{w}_\text{H}) \leftrightarrow \text{A}^*\text{C}_8\cdot\text{T}(\text{w}_\text{H})}$
 $(\nu_i = 1136.0 \text{ i cm}^{-1})$

$$(\Delta G = 40.91 / \Delta E = 43.75)$$

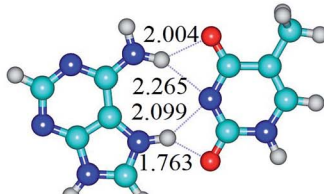
A*_{C8}·T(w_H)

$$(\Delta E_{\text{int}} = -18.34 \text{ (0.72)} / \Delta G_{\text{int}} = -6.67 / \Delta G = 40.87 / \Delta E = 40.92)$$

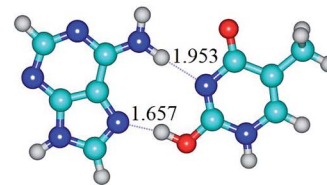


A·T(H)

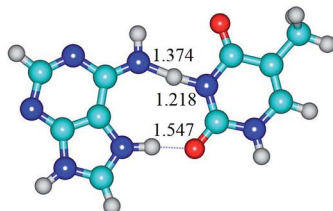
$$(\Delta E_{\text{int}} = -15.93 \text{ (0.78)} / \Delta G_{\text{int}} = -2.71 / \Delta G = 0.00 / \Delta E = 0.00)$$


 $\text{TS}^{\text{A}^+\cdot\text{T}^-}_{\text{A}\cdot\text{T}(\text{H}) \leftrightarrow \text{A}\cdot\text{T}^*\text{O}_2(\text{w}_\text{H})}$
 $(\nu_i = 147.1 \text{ i cm}^{-1})$

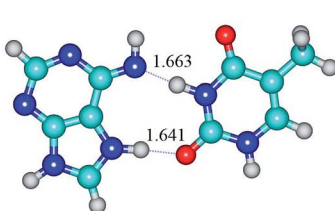
$$(\Delta E_{\text{int}} = -127.70 \text{ (0.11)} / \Delta G_{\text{int}} = -113.81 / \Delta G = 32.46 / \Delta E = 31.46)$$

A·T*_{O2}(w_H)

$$(\Delta E_{\text{int}} = -23.11 \text{ (0.67)} / \Delta G_{\text{int}} = -9.23 / \Delta G = 22.68 / \Delta E = 22.44)$$


 $\text{TS}_{\text{A}\cdot\text{T}^*\text{O}_2(\text{w}_\text{H}) \leftrightarrow \text{A}^*\text{N}_7\cdot\text{T}(\text{w}_\text{H})}$
 $(\nu_i = 797.1 \text{ i cm}^{-1})$

$$(\Delta G = 33.58 / \Delta E = 35.57)$$

A*_{N7}·T(w_H)

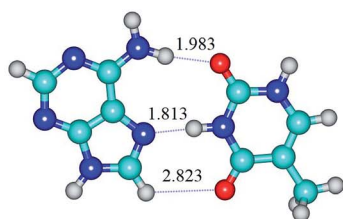
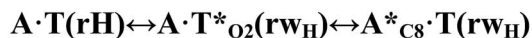
$$(\Delta E_{\text{int}} = -28.49 \text{ (0.67)} / \Delta G_{\text{int}} = -16.50 / \Delta G = 35.55 / \Delta E = 35.40)$$

Fig. 1a (contd.)

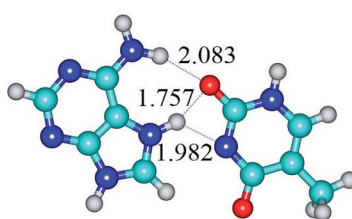
where k_B – Boltzmann's constant, h – Planck's constant, $\Delta\Delta G_{f,r}$ – Gibbs free energy of activation for the tautomerisation reaction in the forward (f) and reverse (r) directions, ν_i – magnitude of the imaginary frequency associated with the vibrational mode at the TSs.

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)^{106,107} through the counterpoise procedure.^{108,109}

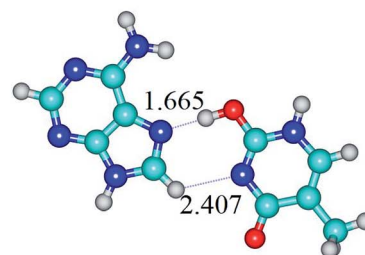


**A·T(rH)**

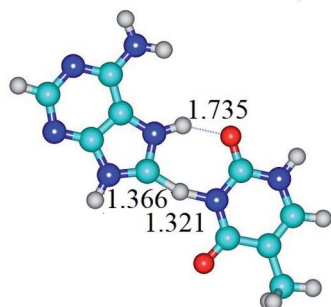
$$(\Delta E_{int} = -15.77 (0.77) / \Delta G_{int} = -2.08 / \Delta G = 0.00 / \Delta E = 0.00)$$

**TS^{A+-T-}_{A·T(rH)↔A·T^{*}O₂(rw_H)}**
($\nu_i = 134.0 \text{ i cm}^{-1}$)

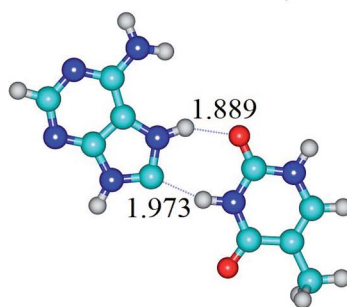
$$(\Delta E_{int} = -127.51 (0.10) / \Delta G_{int} = -114.30 / \Delta G = 33.03 / \Delta E = 32.94)$$

**A·T^{*}O₂(rw_H)**

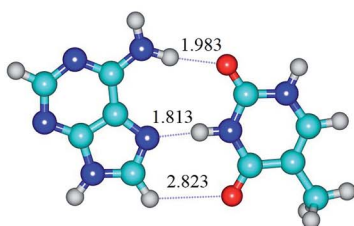
$$(\Delta E_{int} = -17.80 (0.68) / \Delta G_{int} = -5.29 / \Delta G = 25.66 / \Delta E = 26.83)$$

**TS_{A·T^{*}O₂(rw_H)↔A^{*}C₈·T(rw_H)}**
($\nu_i = 1129.2 \text{ i cm}^{-1}$)

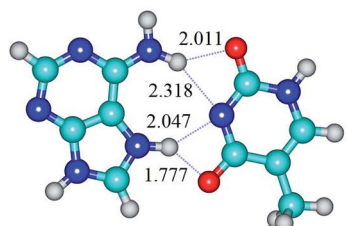
$$(\Delta G = 41.75 / \Delta E = 44.59)$$

**A^{*}C₈·T(rw_H)**

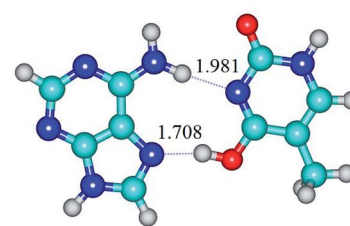
$$(\Delta E_{int} = -17.74 (0.72) / \Delta G_{int} = -5.75 / \Delta G = 41.14 / \Delta E = 41.34)$$

**A·T(rH)**

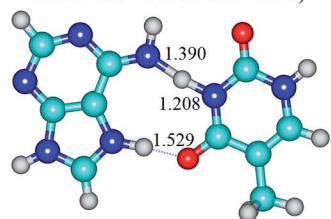
$$(\Delta E_{int} = -15.77 (0.77) / \Delta G_{int} = -2.08 / \Delta G = 0.00 / \Delta E = 0.00)$$

**TS^{A+-T-}_{A·T(rH)↔A·T^{*}(rw_H)}**
($\nu_i = 159.0 \text{ i cm}^{-1}$)

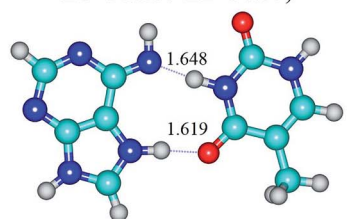
$$(\Delta E_{int} = -128.34 (0.10) / \Delta G_{int} = -114.59 / \Delta G = 31.15 / \Delta E = 30.53)$$

**A·T^{*}(rw_H)**

$$(\Delta E_{int} = -20.61 (0.69) / \Delta G_{int} = -6.66 / \Delta G = 18.99 / \Delta E = 18.42)$$

**TS_{A·T^{*}(rw_H)↔A^{*}N₇·T(rw_H)}**
($\nu_i = 727.4 \text{ i cm}^{-1}$)

$$(\Delta G = 32.35 / \Delta E = 34.15)$$

**A^{*}N₇·T(rw_H)**

$$(\Delta E_{int} = -29.69 (0.67) / \Delta G_{int} = -17.61 / \Delta G = 34.33 / \Delta E = 34.14)$$

Fig. 1b (contd.)

Bader's quantum theory of atoms in molecules (QTAIM),^{110–115} using program package AIMAll,¹¹⁶ 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.^{117,118} Wave functions were obtained at the level of theory used for geometry optimisation.



The energies of the AH...B conventional H-bonds were evaluated by the empirical Iogansen's formula:¹¹⁹

$$E_{\text{AH}\cdots\text{B}} = 0.33\sqrt{\Delta\nu - 40}, \quad (5)$$

where $\Delta\nu$ – magnitude of the frequency shift of the stretching mode of the H-bonded AH group involved into the AH...B H-bond relatively the unbound group. The partial deuteration was applied to minimize the effect of vibrational resonances.^{120–122}

The energies of the weak CH...O/N H-bonds^{123,124} were calculated by the empirical Espinosa–Molins–Lecomte formula^{125,126} based on the electron density distribution at the (3,–1) BCPs of the H-bonds:

$$E_{\text{HB}} = 0.5 V(r), \quad (6)$$

where $V(r)$ – value of a local potential energy at the (3,–1) BCP.

The energies of the NH...O H-bonds in the TSs of the DPT tautomerisations containing loosened covalent bridge have been estimated by the Nikolaienko–Bulavin–Hovorun formula:¹²⁷

$$E_{\text{NH}\cdots\text{O}} = -2.03 + 225\rho, \quad (7)$$

where ρ – the electron density at the (3,–1) BCP of the H-bond.

The atomic numbering scheme for the DNA bases is conventional.¹²⁸

Results and their discussion

In this work based on the results obtained in the pioneering publication,⁴⁵ devoted to the novel WC \leftrightarrow w mutagenic tautomerization of the canonical A·T(WC) and G·C(WC) DNA base

pairs, we have investigated for the first time the microstructural mechanisms of the mutagenic tautomerisation of the three other biologically important A·T DNA base pairs^{62–79} – A·T(rWC)/A·T(H)/A·T(rH) \leftrightarrow A·T*(rw_{WC})/A·T*(w_H)/A·T*(rw_H) – as their intrinsically inherent property (Fig. 1, Tables 1 and 2).

It was found that the mutagenic tautomerization of each of these classical base pairs is controlled by the two TSs, representing itself tight (electronic energy of the bases interaction ~ 120 – 129 kcal mol^{–1}) ion pairs (A⁺ nucleobase, protonated by the N1/N7 nitrogen atoms)·(T[–] nucleobase, deprotonated by the N3H imino group) with plane symmetric (*C_s* symmetry) quasi-wobble structure. The term “quasi-wobble” means that these structures are no longer rWC/H/rH, but are not yet wobble. Notably, they differ from each other by the shifting direction of the T[–] respectively A⁺ (towards major or minor groove of DNA) and also by the number of the H-bonds, which participate in their stabilization, – three or four, – one or two of them are characterized by the increased ellipticity (Fig. 1, Table 2). The latter points to the dynamic instability of these H-bonds.^{31,97} Thus, the TS_{A·T(rWC) \leftrightarrow A·T*(rw_{WC})}^{A⁺,T[–]}, TS_{A·T(H) \leftrightarrow A·T*(w_H)}^{A⁺,T[–]} and TS_{A·T(rH) \leftrightarrow A·T*(rw_H)}^{A⁺,T[–]} transition states, in which the T[–] deprotonated by the N3H imino group, is shifted towards the minor groove of DNA relatively A⁺, are stabilized by the participation of three H-bonds: (A)N6⁺H...O2[–](T) (2.99), (A)N1⁺H...O2[–](T) (10.16) and (A)C2⁺H...N3[–](T) (1.81 kcal mol^{–1}); (A)N6⁺H'...O4[–](T) (4.76), (A)N7⁺H...O4[–](T) (5.03) and (A)N7⁺H...N3[–](T) (3.27 kcal mol^{–1}); (A)N6⁺H'...O2[–](T) (4.06), (A)N7⁺H...O2[–](T) (5.05) and (A)N7⁺H...N3[–](T) (3.02 kcal mol^{–1}) (their energies are presented in brackets), accordingly (Table 2). At this, in each TS only one H-bond has increased ellipticity (its value is presented in brackets) – (A)C2⁺H...N3[–](T) (18.55); (A)N7⁺H...N3[–](T) (35.39); (A)N7⁺H...N3[–](T) (49.28), respectively (Fig. 1, Table 2).

Table 1 Energetic (in kcal mol^{–1}) and kinetic (in s) characteristics of the tautomerization of the classical A·T DNA base pairs into the wobble base mispairs via the sequential PT followed by DPT 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. 1)

Tautomeric transition	ν_i^a	ΔG^b	ΔE^c	$\Delta\Delta G_{\text{TS}}^d$	$\Delta\Delta E_{\text{TS}}^e$	$\Delta\Delta G^f$	$\Delta\Delta E^g$	$\tau_{99.9\%}^h$	τ^i	P^j
A·T(rWC) \leftrightarrow A·T*(rw _{WC})	66.5	27.71	29.12	32.86	32.49	5.15	3.37	6.62×10^{-9}	9.58×10^{-10}	4.72×10^{-21}
A·T*(rw _{WC}) \leftrightarrow A _{C2} ⁺ ·T(rw _{WC})	137.7	28.92	29.23	27.43	29.29	–1.49	0.06	8.83×10^{-14}	1.28×10^{-14}	2.91×10^{-42}
A·T(rWC) \leftrightarrow A·T*(rw _{WC})	132.4	18.56	17.69	26.84	25.43	8.29	7.74	1.31×10^{-6}	1.90×10^{-7}	2.45×10^{-14}
A·T*(rw _{WC}) \leftrightarrow A [*] ·T(rw _{WC})	906.3	1.61	1.24	3.00	5.08	1.39	3.85	1.08×10^{-11}	1.67×10^{-12}	1.60×10^{-15}
A·T(H) \leftrightarrow A·T*(w _H)	155.3	21.92	22.94	31.91	31.69	9.99	8.75	2.31×10^{-5}	3.35×10^{-6}	8.39×10^{-17}
A·T*(w _H) \leftrightarrow A _{C8} ⁺ ·T(w _H)	1136.0	18.95	17.97	18.99	20.81	0.04	2.84	5.56×10^{-13}	8.04×10^{-14}	1.06×10^{-30}
A·T(H) \leftrightarrow A·T*(rw _H)	147.1	22.68	22.44	32.46	31.63	9.78	9.19	1.62×10^{-5}	2.34×10^{-6}	2.32×10^{-17}
A·T*(rw _H) \leftrightarrow A _{N7} ⁺ ·T(w _H)	797.1	12.87	12.96	10.90	13.14	–1.97	0.18	2.54×10^{-14}	3.68×10^{-15}	8.45×10^{-27}
A·T(rH) \leftrightarrow A·T*(rw _H)	134.0	25.66	26.83	33.03	32.94	7.38	6.11	2.81×10^{-7}	4.07×10^{-8}	1.52×10^{-19}
A·T*(rw _H) \leftrightarrow A _{C8} ⁺ ·T(rw _H)	1129.2	15.49	14.51	16.09	17.76	0.60	3.25	1.43×10^{-12}	2.08×10^{-13}	6.61×10^{-31}
A·T(rH) \leftrightarrow A·T*(rw _H)	159.0	18.99	18.42	31.15	30.53	12.17	12.11	9.13×10^{-4}	1.32×10^{-4}	1.18×10^{-14}
A·T*(rw _H) \leftrightarrow A _{N7} ⁺ ·T(rw _H)	727.4	15.34	15.73	13.36	15.73	–1.98	0.01	3.86×10^{-14}	5.58×10^{-15}	6.65×10^{-26}

^a The imaginary frequency at the TS of the tautomeric transition, cm^{–1}. ^b The Gibbs free energy of the product relatively the reactant of the tautomeric transition ($T = 298.15$ K). ^c The electronic energy of the product relatively the reactant of the tautomeric transition. ^d The Gibbs free energy barrier for the forward tautomeric transition. ^e The electronic energy barrier for the forward tautomeric transition. ^f The Gibbs free energy barrier for the reverse tautomeric transition. ^g The electronic energy barrier for the reverse tautomeric transition. ^h The time necessary to reach 99.9% of the equilibrium concentration between the reactant and the product of the tautomerisation reaction, s. ⁱ The lifetime of the product of the tautomerisation reaction, s. ^j The thermal population of the tautomerised structures, which is situated on the right in the first row of the table.



Table 2 Electron-topological, geometrical and energetic characteristics of the intermolecular H-bonds in the investigated DNA base pairs and TSs of their tautomerization into the wobble base mismatches via the sequential PT followed by DPT obtained at the B3LYP/6-311++G(d,p) level of QM theory ($\epsilon = 1$) (see Fig. 1)

Complex	AH...B H-bond	ρ^a	$\Delta\rho^b$	$100\epsilon^c$	$d_{A...B}^d$	$d_{H...B}^e$	$\angle AH...B^f$	$E_{AH...B}^g$	μ^h
A·T(rWC)	N6H...O2	0.024	0.088	5.26	2.962	1.949	172.9	4.38	2.40
	N3H...N1	0.039	0.093	6.51	2.887	1.843	177.7	7.55	
	C2H...O4	0.004	0.014	3.32	3.696	2.872	132.8	0.77*	
TS _{A·T(rWC) ↔ A·T*(rWC)}	N6 ⁺ H...O2 ⁻	0.017	0.073	8.71	2.910	2.083	136.9	2.99	9.34
	N1 ⁺ H...O2 ⁻	0.067	0.133	1.76	2.614	1.577	159.6	10.16	
	C2 ⁺ H...N3 ⁻	0.011	0.034	18.55	3.207	2.561	117.3	1.81*	
A·T*(rWC)	O2H...N7	0.058	0.100	4.73	2.682	1.665	179.7	10.35	5.10
	C8H...N3	0.013	0.043	2.29	3.131	2.407	123.1	2.21*	
	N1H...O2	0.040	0.125	4.34	2.761	1.766	159.5	6.91**	
TS _{A·T*(rWC) ↔ A*C2·T(rWC)}	N1H...O2	0.037	0.120	4.38	2.787	1.797	159.5	5.77	5.21
	N3H...C2 ⁻	0.061	0.033	103.30	2.840	1.758	164.3	12.53	
	N6 ⁺ H...O2 ⁻	0.020	0.067	12.45	3.026	2.057	155.7	2.86	
TS _{A·T(rWC) ↔ A·T*(rWC)}	N6 ⁺ H...N3 ⁻	0.020	0.069	13.99	2.971	2.121	138.4	2.82	6.11
	N1 ⁺ H...N3 ⁻	0.024	0.081	32.39	2.932	2.035	141.8	2.92	
	N1 ⁺ H...O4 ⁻	0.034	0.098	5.50	2.805	1.860	148.0	4.45	
A·T*(rWC)	N6H...N3	0.030	0.087	7.07	2.682	1.668	170.4	5.76	2.52
	O4H...N1	0.059	0.096	5.10	2.955	1.947	167.0	10.21	
	N1H...O4	0.061	0.142	3.32	2.663	1.598	179.3	11.61**	
TS _{A·T*(rWC) ↔ A*·T(rWC)}	N3H...N6	0.044	0.095	6.22	2.844	1.793	174.7	8.53	3.23
	N1H...O4	0.035	0.117	3.55	2.832	1.801	177.3	5.82	
	N6H...O4	0.023	0.086	3.93	2.972	1.963	170.6	4.18	
A·T(H)	N3H...N7	0.041	0.099	5.75	2.853	1.811	175.9	7.39	6.16
	C8H...O2	0.005	0.016	7.71	3.524	2.835	121.7	0.83*	
	N6 ⁺ H...O4 ⁻	0.022	0.091	1.81	2.936	1.948	161.7	4.76	
TS _{A·T(H) ↔ A·T*(wH)}	N7 ⁺ H...O4 ⁻	0.041	0.112	6.15	2.749	1.771	152.5	5.03	2.09
	N7 ⁺ H...N3 ⁻	0.029	0.097	35.39	2.784	1.951	133.5	3.27	
	O4H...N7	0.052	0.102	4.74	2.717	1.707	178.5	8.99	
A·T*(wH)	C8H...N3	0.012	0.040	2.99	3.149	2.441	121.9	2.08*	4.74
	N7H...O4	0.047	0.133	2.94	2.678	1.702	153.3	8.55**	
	N7H...O4	0.031	0.109	3.24	2.810	1.861	152.7	5.00	
TS _{A·T*(wH) ↔ A*C8·T(wH)}	N3H...C8 ⁻	0.035	0.061	4.38	2.975	1.959	161.6	8.30	6.08
	N6 ⁺ H...O4 ⁻	0.024	0.079	2.31	2.887	2.004	142.4	3.64	
	N6 ⁺ H...N3 ⁻	0.014	0.049	67.29	3.218	2.265	153.9	1.84	
TS _{A·T(H) ↔ A·T*(wH)}	N7 ⁺ H...N3 ⁻	0.021	0.076	382.35	3.022	2.099	144.8	2.36	6.54
	N7 ⁺ H...O2 ⁻	0.042	0.115	3.62	2.688	1.763	143.9	5.72	
	N6H...N3	0.029	0.086	7.38	2.974	1.953	176.4	5.38	
A·T*(wH)	O2H...N7	0.059	0.100	4.48	2.664	1.657	168.0	10.16	8.23
	N7H...O2	0.067	0.152	3.15	2.615	1.547	176.3	12.95**	
	N3H...N6	0.060	0.092	5.58	2.743	1.663	175.7	10.97	
TS _{A·T*(wH) ↔ A*N7·T(wH)}	N7H...O2	0.051	0.145	3.17	2.689	1.641	176.3	8.09	10.35
	N7H...O2	0.029	0.104	3.92	2.829	1.889	151.4	4.61	
	N3H...C8 ⁻	0.034	0.061	4.31	2.984	1.973	160.5	8.12	
TS _{A·T(rH) ↔ A·T*(rH)}	N6 ⁺ H...O2 ⁻	0.023	0.078	1.54	2.902	2.011	143.9	3.51	4.80
	N6 ⁺ H...N3 ⁻	0.013	0.045	127.55	3.263	2.318	152.9	1.65	
	N7 ⁺ H...N3 ⁻	0.023	0.078	82.90	2.987	2.047	146.7	2.64	
A·T*(rH)	N7 ⁺ H...O4 ⁻	0.041	0.113	4.62	2.686	1.776	141.6	5.65	7.36
	N6H...N3	0.027	0.082	7.62	3.000	1.981	175.7	5.09	
	O4H...N7	0.052	0.102	4.48	2.702	1.708	166.4	9.18	



Table 2 (Contd.)

Complex	AH...B H-bond	ρ^a	$\Delta\rho^b$	100 ϵ^c	$d_{A...B}^d$	$d_{H...B}^e$	$\angle AH...B^f$	$E_{AH...B}^g$	μ^h
$TS_{A\cdot T^*(r_{WH})} \leftrightarrow A^*N7\cdot T(r_{WH})$	N7H...O4	0.070	0.151	2.34	2.603	1.529	175.7	13.76**	8.37
$A_{N7}^*\cdot T(r_{WH})$	N3H...N6	0.062	0.090	5.55	2.731	1.648	174.5	11.26	9.42
	N7H...O4	0.055	0.147	2.33	2.671	1.619	175.8	8.61	

^a The electron density at the (3,−1) BCP of the H-bond, a.u. ^b The Laplacian of the electron density at the (3,−1) BCP of the H-bond, a.u. ^c The ellipticity at the (3,−1) BCP of the H-bond. ^d The distance between the A and B atoms of the of the AH...B H-bond, Å. ^e The distance between the H and B atoms of the AH...B H-bond, Å. ^f The H-bond angle, degree. ^g Energy of the H-bond, calculated by Iogansen's,¹¹⁹ Espinose–Molins–Lecomte^{125,126} (marked with an asterisk) or Nikolaienko–Bulavin–Hovorun¹²⁷ (marked with double asterisk) formulas, kcal mol^{−1}. ^h The dipole moment of the complex, D.

Three other TSSs – $TS_{A\cdot T^*(r_{WC})}^{A^+\cdot T^-}$ and $TS_{A\cdot T^*(r_{WH})}^{A^+\cdot T^-}$ in which the T[−] deprotonated by the N3H imino group, is shifted towards major groove of DNA relatively A⁺, are joined by the participation of the four H-bonds: (A)N6⁺H...O2[−](T) (2.86), (A)N6⁺H...N3[−](T) (2.82), (A)N1⁺H...N3[−](T) (2.92) and (A)N1⁺H...O4[−](T) (4.45 kcal mol^{−1}); N6⁺H...O4[−] (3.64), N6⁺H...N3[−] (1.84), N7⁺H...N3[−] (2.36) and N7⁺H...O2[−] (5.72 kcal mol^{−1}); N6⁺H...O2[−] (3.51), N6⁺H...N3[−] (1.65), N7⁺H...N3[−] (2.64) and N7⁺H...O4[−] (5.65 kcal mol^{−1}). Two H-bonds have increased ellipticity for each of these TSSs – (A)N6⁺H...N3[−](T) (13.99) and (A)N1⁺H...N3[−](T) (32.39); N6⁺H...N3[−] (67.29) and N7⁺H...N3[−] (382.35); N6⁺H...N3[−] (127.55) and N7⁺H...N3[−] (82.90), accordingly (Fig. 1, Table 2).

Values of the Gibbs free energies of activation of the processes of the dipole-active tautomerization of the investigated A·T DNA base pairs are quite high and lie within the range 27–33 kcal mol^{−1} under normal conditions (Fig. 1, Table 1).

The A·T_{O2}^{*}(r_{WC}), A·T*(r_{WC}), A·T*(r_{WH}), A·T_{O2}^{*}(r_{WH}), A·T_{O2}^{*}(r_{WH}) and A·T*(r_{WH}) base mispairs, which are the products of the mutagenic tautomerization of classical A·T DNA base pairs, represent themselves wobble structures with plane symmetric architecture (C_s symmetry), stabilized by two anti-parallel intermolecular H-bonds. They are noticeably more stable than the starting A·T(r_{WC}), A·T(H) and A·T(r_H) DNA base pairs and have quite high relative energies, lying in the range 19–28 kcal mol^{−1}, and hence – insignificant population ($\leq 1.2 \times 10^{-14}$ under normal conditions). It is interesting to note, that these wobble base mispairs are figuratively speaking “terminal stations” on the way of the mutagenic tautomerization of the investigated DNA base pairs, since they do not tautomerise further (Fig. 1, Tables 1 and 2).

Really, the A_{N7}^{*}·T(r_{WH}) and A_{N7}^{*}·T(r_{WH}) complexes, which are formed from the A·T_{O2}^{*}(r_{WH}) and A·T*(r_{WH}) base pairs *via* the DPT, respectively, return without any barrier into the initial pairs due to the asynchronous DPT along the intermolecular H-bonds *via* the $TS_{A\cdot T^*(r_{WH})}^{A^+\cdot T^-}$ and $TS_{A\cdot T^*(r_{WH})}^{A^+\cdot T^-} \leftrightarrow A^*N7\cdot T(r_{WH})$, accordingly. The same situation also takes place for the complex by the participation of the ylidic form^{20,39,129} of A – A_{C2}^{*}·T(r_{WC}). Two other A_{C8}^{*}·T(r_{WH}) and A_{C8}^{*}·T(r_{WH}) complexes involving ylidic forms of the A DNA base, which are formed from the A·T*(r_{WH}) and A·T_{O2}^{*}(r_{WH}) by the asynchronous DPT along the intermolecular H-bonds, one of which (A)C8H...

N3(T) H-bond is non-canonical,^{123,124} are short-lived (~0.1 ps), dynamically-unstable systems. Low-frequency intermolecular normal vibrations, lying in the range 20–83 cm^{−1}, could not develop during their lifetimes. From the other side, the lifetime of the A^{*}·T(r_{WC}) complex (1.7 ps), which is formed from the A·T*(r_{WC}) pair by the asynchronous DPT along the intermolecular H-bonds, is significantly less than the time (10^{−9} s)^{27,28}, spent by the DNA-polymerase for the forced dissociation of the complementary pairs of the DNA bases into the monomers. As a result, this complex “slips out of its hands” and canonical tautomeric status of the A DNA base does not change (Table 1).

Base pairs remain plane symmetric structures during the entire PT and DPT tautomerization processes along the IRC. The methyl group of the T DNA base does not change its orientation during these tautomerization processes *via* the PT and DPT. Moreover, the heterocycles of the A and T DNA bases remain planar, despite their ability for the out-of-plane bending^{130–133} (Fig. 1).

Interestingly, that the total energy of the intermolecular H-bonds only partially contributes to the electron energy of the monomers interactions among all without any exceptions H-bonded structures investigated in this work (see Fig. 1). In particular, in the TSSs of mutagenic tautomerization, which are ion pairs, contribution of the H-bonds into the energy of their stabilization consist only 10–12% in comparison with the background of strong electrostatic (Coulomb) interactions. In other complexes it is much higher – from 67 to 86% (Fig. 1). These regularities agree well with the previously reported data for the other H-bonded pairs of nucleotide bases.^{31–42}

Conclusions

So, revealed microstructural mechanisms of the mutagenic tautomerization of the A·T DNA base pairs provide the generation of the mutagenic tautomers of only one among two DNA bases, in particular T DNA base, within the pair of bases. However, this generation is much more slower in comparison with the classical A·T(WC) DNA base pair and does not provide adequate population of the mutagenic tautomers (10^{−9} to 10^{−11}).

Finally, these results lead us to a conclusion, which is very interesting from an evolutionary point of view:^{6,80,81} among all classical pairs of the DNA bases only the Watson–Crick A·T(WC)



DNA base pair can pretend on the role of the building block of the genetic material – DNA macromolecule with antiparallel strands, able for the self-development during large time intervals.

Conflicts of interest

There are no conflicts to declare.

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References

- 1 J. D. Watson and F. H. C. Crick, The Structure of DNA, *Cold Spring Harbor Symp. Quant. Biol.*, 1953, **18**, 123–131.
- 2 J. D. Watson and F. H. C. Crick, Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid, *Nature*, 1953, **171**, 737–738.
- 3 P.-O. Löwdin, Proton tunneling in DNA and its biological implications, *Rev. Mod. Phys.*, 1963, **35**, 724–732.
- 4 P.-O. Löwdin, Quantum genetics and the aperiodic solid: Some aspects on the biological problems of heredity, mutations, aging, and tumors in view of the quantum theory of the DNA molecule, in *Advances in Quantum Chemistry*, ed. P.-O. Löwdin, Academic Press, New York, USA, London, UK, 1966, vol. 2, pp. 213–360.
- 5 M. D. Topal and J. R. Fresco, Complementary base pairing and the origin of substitution mutations, *Nature*, 1976, **263**, 285–289.
- 6 B. Pullman and A. Pullman, Electronic delocalization and biochemical evolution, *Nature*, 1962, **196**, 1137–1142.
- 7 B. Pullman, and A. Pullman, *Quantum biochemistry*, Interscience Publishers, New York, NY, 1963.
- 8 K. Bebenek, L. C. Pedersen and T. A. Kunkel, Replication infidelity via a mismatch with Watson–Crick geometry, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 1862–1867.
- 9 W. Wang, H. W. Hellinga and L. S. Beese, Structural evidence for the rare tautomer hypothesis of spontaneous mutagenesis, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 17644–17648.

- 10 A. N. Nedderman, M. J. Stone, P. K. T. Lin, D. M. Brown and D. H. Williams, Base pairing of cytosine analogues with adenine and guanine in oligonucleotide duplexes: evidence for exchange between Watson-Crick and wobble base pairs using ¹H NMR spectroscopy, *J. Chem. Soc., Chem. Commun.*, 1991, 1357–1359.
- 11 A. N. Nedderman, M. J. Stone, D. H. Williams, P. K. Y. Lin and D. M. Brown, Molecular basis for methoxyamine-initiated mutagenesis: ¹H nuclear magnetic resonance studies of oligonucleotide duplexes containing base-modified cytosine residues, *J. Mol. Biol.*, 1993, **230**, 1068–1076.
- 12 I. J. Kimsey, K. Petzold, B. Sathyamoorthy, Z. W. Stein and H. M. Al-Hashimi, Visualizing transient Watson-Crick-like mispairs in DNA and RNA duplexes, *Nature*, 2015, **519**, 315–320.
- 13 E. S. Szymanski, I. J. Kimsey and H. M. Al-Hashimi, Direct NMR evidence that transient tautomeric and anionic states in dG·dT form Watson-Crick-like base pairs, *J. Am. Chem. Soc.*, 2017, **139**, 4326–4329.
- 14 J. Florian, V. Hroudá and P. Hobza, Proton transfer in the adenine-thymine base pair, *J. Am. Chem. Soc.*, 1994, **116**, 1457–1460.
- 15 L. Gorb, Y. Podolyan, P. Dziekonski, W. A. Sokalski and J. Leszczynski, Double-proton transfer in adenine–thymine and guanine–cytosine base pairs. A post-Hartree-Fock *ab initio* study, *J. Am. Chem. Soc.*, 2004, **126**, 10119–10129.
- 16 J. Bertran, L. Blancafort, M. Noguera, and M. Sodupe, Proton transfer in DNA base pairs, in *Computational studies of RNA and DNA*, ed. J. Šponer and F. Lankaš, Springer, Dordrecht, 2006, pp. 411–432.
- 17 J. P. Cerón-Carrasco, A. Requena, C. Michaux, E. A. Perpète and D. Jacquemin, Effects of hydration on the proton transfer mechanism in the adenine-thymine base pair, *J. Phys. Chem. A*, 2009, **113**, 7892–7898.
- 18 J. P. Cerón-Carrasco and D. Jacquemin, Electric field induced DNA damage: an open door for selective mutations, *Chem. Commun.*, 2013, **49**, 7578–7580.
- 19 S. N. Maximoff, Sh. C. L. Kamerlin and J. D. N. A. Florián, Polymerase λ active site favors a mutagenic mispair between the enol form of deoxyguanosine triphosphate substrate and the keto form of thymidine template: a free energy perturbation study, *J. Phys. Chem. B*, 2017, **121**, 7813–7822.
- 20 I. V. Kondratyuk, S. P. Samijlenko, I. M. Kolomiets' and D. M. Hovorun, Prototropic molecular-zwitterionic tautomerism of xanthine and hypoxanthine, *J. Mol. Struct.*, 2000, **523**, 109–118.
- 21 S. P. Samijlenko, O. M. Krechkivska, D. A. Kosach and D. M. Hovorun, Transitions to high tautomeric states can be induced in adenine by interactions with carboxylate and sodium ions: DFT calculation data, *J. Mol. Struct.*, 2004, **708**, 97–104.
- 22 V. I. Danilov, V. M. Anisimov, N. Kurita and D. Hovorun, MP2 and DFT studies of the DNA rare base pairs: the molecular mechanism of the spontaneous substitution



- mutations conditioned by tautomerism of bases, *Chem. Phys. Lett.*, 2005, **412**, 285–293.
- 23 M. O. Platonov, S. P. Samijlenko, O. O. Sudakov, I. V. Kondratyuk and D. M. Hovorun, To what extent can methyl derivatives be regarded as stabilized tautomers of xanthine?, *Spectrochim. Acta, Part A*, 2005, **62**, 112–114.
- 24 P.-O. Löwdin, Isotope effect in tunneling and its influence on mutation rates, *Mutat. Res. Fundam. Mol. Mech. Mutagen.*, 1965, **2**, 218–221.
- 25 V. I. Danilov and G. F. Kventsel, *Electronic representations in the point mutation theory*, Naukova Dumka, Kyiv, 1971.
- 26 O. O. Brovarets', I. M. Kolomiets' and D. M. Hovorun. Elementary molecular mechanisms of the spontaneous point mutations in DNA: A novel quantum-chemical insight into the classical understanding, in *Quantum chemistry – molecules for innovations*, ed. Tomofumi Tada, InTech Open Access, Rijeka, Croatia, 2012.
- 27 O. O. Brovarets' and D. M. Hovorun, Can tautomerisation of the A·T Watson-Crick base pair *via* double proton transfer provoke point mutations during DNA replication? A comprehensive QM and QTAIM analysis, *J. Biomol. Struct. Dyn.*, 2014, **32**, 127–154.
- 28 O. O. Brovarets' and D. M. Hovorun, Why the tautomerization of the G·C Watson-Crick base pair *via* the DPT does not cause point mutations during DNA replication? QM and QTAIM comprehensive analysis, *J. Biomol. Struct. Dyn.*, 2014, **32**, 1474–1499.
- 29 O. O. Brovarets' and D. M. Hovorun, Proton tunneling in the A·T Watson-Crick DNA base pair: myth or reality?, *J. Biomol. Struct. Dyn.*, 2015, **12**, 2716–2720.
- 30 A. Padermshoke, Y. Katsumoto, R. Masaki and M. Aida, Thermally induced double proton transfer in GG and wobble GT base pairs: a possible origin of the mutagenic guanine, *Chem. Phys. Lett.*, 2008, **457**, 232–236.
- 31 O. O. Brovarets', R. O. Zhurakivsky and D. M. Hovorun, DPT tautomerisation of the wobble guanine·thymine DNA base mispair is not mutagenic: QM and QTAIM arguments, *J. Biomol. Struct. Dyn.*, 2015, **33**, 674–689.
- 32 O. O. Brovarets', R. O. Zhurakivsky and D. M. Hovorun, 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.
- 33 O. O. Brovarets' and D. M. Hovorun, The physicochemical essence of the purine·pyrimidine transition mismatches with Watson-Crick geometry in DNA: A·C* *versa* A*·C. A QM and QTAIM atomistic understanding, *J. Biomol. Struct. Dyn.*, 2015, **33**, 28–55.
- 34 O. O. Brovarets' and D. M. Hovorun, 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. Dyn.*, 2015, **33**, 925–945.
- 35 O. O. Brovarets' and D. M. Hovorun, Atomistic understanding of the C·T mismatched DNA base pair tautomerization *via* the DPT: QM and QTAIM computational approaches, *J. Comput. Chem.*, 2013, **34**, 2577–2590.
- 36 O. O. Brovarets' and D. M. Hovorun, 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.
- 37 O. O. Brovarets', R. O. Zhurakivsky and D. M. Hovorun, Does the tautomeric status of the adenine bases change upon the dissociation of the A*·A_{syn} Topal-Fresco DNA mismatch? A combined QM and QTAIM atomistic insight, *Phys. Chem. Chem. Phys.*, 2014, **16**, 3715–3725.
- 38 O. O. Brovarets' and D. M. Hovorun, 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.
- 39 O. O. Brovarets' and D. M. Hovorun, Prototropic tautomerism and basic molecular principles of hypoxanthine mutagenicity: An exhaustive quantum-chemical analysis, *J. Biomol. Struct. Dyn.*, 2013, **31**, 913–936.
- 40 O. O. Brovarets', R. O. Zhurakivsky and D. M. Hovorun, The physico-chemical "anatomy" of the tautomerisation through the DPT of the biologically important pairs of hypoxanthine with DNA bases: QM and QTAIM perspectives, *J. Mol. Model.*, 2013, **19**, 4119–4137.
- 41 O. O. Brovarets', R. O. Zhurakivsky and D. M. Hovorun, 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.
- 42 O. O. Brovarets', R. O. Zhurakivsky and D. M. Hovorun, A QM/QTAIM microstructural analysis of the tautomerisation *via* the DPT of the hypoxanthine·adenine nucleobase pair, *Mol. Phys.*, 2014, **112**, 2005–2016.
- 43 P. Strazewski and C. Tamm, Replication experiments with nucleotide base analogues, *Angew. Chem., Int. Ed.*, 1990, **29**, 36–57.
- 44 O. O. Brovarets', Y. P. Yurenko, I. Y. Dubey and D. M. Hovorun, Can DNA-binding proteins of replisome tautomerize nucleotide bases? *Ab initio* model study, *J. Biomol. Struct. Dyn.*, 2012, **29**, 1101–1109.
- 45 O. O. Brovarets' and D. M. Hovorun, 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.
- 46 O. O. Brovarets' and D. M. Hovorun, Wobble↔Watson-Crick tautomeric transitions in the homo-purine DNA mismatches: a key to the intimate mechanisms of the spontaneous transversions, *J. Biomol. Struct. Dyn.*, 2015, **33**, 2710–2715.
- 47 O. O. Brovarets' and D. M. Hovorun, Novel physico-chemical mechanism of the mutagenic tautomerisation of the Watson-Crick-like A·G and C·T DNA base mispairs: a quantum-chemical picture, *RSC Adv.*, 2015, **5**, 66318–66333.
- 48 O. O. Brovarets' and D. M. Hovorun, A novel conception for spontaneous transversions caused by homo-pyrimidine



- DNA mismatches: a QM/QTAIM highlight, *Phys. Chem. Chem. Phys.*, 2015, **17**, 21381–21388.
- 49 O. O. Brovarets' and D. M. Hovorun, Physicochemical mechanism of the wobble DNA base pairs Gua·Thy and Ade·Cyt transition into the mismatched base pairs Gua*·Thy and Ade·Cyt* formed by the mutagenic tautomers, *Ukr. Bioorg. Acta*, 2009, **8**, 12–18.
- 50 O. O. Brovarets' and D. M. Hovorun, 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.
- 51 O. O. Brovarets' and D. M. Hovorun, By how many tautomerisation routes the Watson-Crick-like A·C* DNA base mispair is linked with the wobble mismatches? A QM/QTAIM vision from a biological point of view, *Struct. Chem.*, 2016, **27**, 119–131.
- 52 O. O. Brovarets' and D. M. Hovorun, How many tautomerisation pathways connect Watson-Crick-like G*·T DNA base mispair and wobble mismatches?, *J. Biomol. Struct. Dyn.*, 2015, **33**, 2297–2315.
- 53 O. O. Brovarets', Microstructural mechanisms of the origin of the spontaneous point mutations, DrSci Thesis, Taras Shevchenko National University of Kyiv, Kyiv, Ukraine, 2015.
- 54 O. O. Brovarets' and D. M. Hovorun, Stability of mutagenic tautomers of uracil and its halogen derivatives: the results of quantum-mechanical investigation, *Biopolym. Cell*, 2010, **26**, 295–298.
- 55 O. O. Brovarets' and D. M. Hovorun, Intramolecular tautomerization and the conformational variability of some classical mutagens – cytosine derivatives: Quantum chemical study, *Biopolym. Cell*, 2011, **27**, 221–230.
- 56 O. O. Brovarets', H. E. Pérez-Sánchez and D. M. Hovorun, Structural grounds for the 2-aminopurine mutagenicity: A novel insight into the old problem of the replication errors, *RSC Adv.*, 2016, **6**, 99546–99557.
- 57 O. O. Brovarets' and H. E. Pérez-Sánchez, Whether 2-aminopurine induces incorporation errors at the DNA replication? A quantum-mechanical answer on the actual biological issue, *J. Biomol. Struct. Dyn.*, 2017, **35**, 3398–3411.
- 58 O. O. Brovarets' and H. E. Pérez-Sánchez, Whether the amino-imino tautomerism of 2-aminopurine is involved into its mutagenicity? Results of a thorough QM investigation, *RSC Adv.*, 2016, **110**, 108255–108264.
- 59 O. O. Brovarets', I. Voiteshenko, H. E. Pérez-Sánchez and D. M. Hovorun, A QM/QTAIM detailed look at the Watson-Crick ↔ wobble tautomeric transformations of the 2-aminopurine·pyrimidine mispairs, *J. Biomol. Struct. Dyn.*, 2017, DOI: 10.1080/07391102.2017.1331864.
- 60 O. O. Brovarets', I. S. Voiteshenko, H. E. Pérez-Sánchez and D. M. Hovorun, 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.
- 61 O. O. Brovarets', I. S. Voiteshenko and D. M. Hovorun, 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.*, 2018, **20**, 623–636.
- 62 N. A. Tchurikov, B. K. Chernov, Y. B. Golova and Y. D. Nechipurenko, Parallel DNA: Generation of a duplex between two Drosophila sequences in vitro, *FEBS Lett.*, 1989, **257**, 415–418.
- 63 E. Cubero, F. J. Luque and M. Orozco, Theoretical studies of d(A·T)-based parallel-stranded DNA duplexes, *J. Am. Chem. Soc.*, 2001, **123**, 12018–12025.
- 64 V. R. Parvathy, S. R. Bhaumik, K. V. Chary, G. Govil, K. Liu, F. B. Howard and H. T. Miles, NMR structure of a parallel-stranded DNA duplex at atomic resolution, *Nucleic Acids Res.*, 2002, **30**, 1500–1511.
- 65 V. I. Poltev, V. M. Anisimov, C. Sanchez, A. Deriabina, E. Gonzalez, D. Garcia, N. Rivas and N. A. Polteva, Analysis of the conformational features of Watson-Crick duplex fragments by molecular mechanics and quantum mechanics methods, *Biophysics*, 2016, **61**, 217–226.
- 66 M. Y. Ye, R. T. Zhu, X. Li, X. S. Zhou, Z. Z. Yin, Q. Li and Y. Shao, Adaptively recognizing parallel-stranded duplex structure for fluorescent DNA polarity analysis, *Anal. Chem.*, 2017, **89**, 8604–8608.
- 67 M. Szabat and R. Kierzek, Parallel-stranded DNA and RNA duplexes: structural features and potential applications, *FEBS J.*, 2017, **284**, 3986–3998.
- 68 O. O. Brovarets', 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.
- 69 O. O. Brovarets', 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.
- 70 K. Hoogsteen, The crystal and molecular structure of a hydrogen-bonded complex between 1-methylthymine and 9-methyladenine, *Acta Crystallogr.*, 1963, **16**, 907–916.
- 71 N. G. Abrescia, A. Thompson, T. Huynh-Dinh and J. A. Subirana, Crystal structure of an antiparallel DNA fragment with Hoogsteen base pairing, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 2806–2811.
- 72 N. G. Abrescia, C. Gonzalez, C. Gouyette and J. A. Subirana, X-ray and NMR studies of the DNA oligomer d(ATATAT): Hoogsteen base pairing in duplex DNA, *Biochemistry*, 2004, **43**, 4092–4100.
- 73 J. Pous, L. Urpi, J. A. Subirana, C. Gouyette, J. Navaza and J. L. Campos, Stabilization by extra-helical thymines of a DNA duplex with Hoogsteen base pairs, *J. Am. Chem. Soc.*, 2008, **130**, 6755–6760.
- 74 L. Campos, N. Valls, L. Urpi, C. Gouyette, T. Sanmartín, M. Richter, E. Alechaga, A. Santaolalla, R. Baldini, M. Creixell, R. Ciurans, P. Skokan, J. Pous and J. A. Subirana, Overview of the structure of all AT oligonucleotides: organization in helices and packing interactions, *Biophys. J.*, 2006, **91**, 892–903.
- 75 E. N. Nikolova, H. Zhou, F. L. Gottardo, H. S. Alvey, I. J. Kimsey and H. M. Al-Hashimi, A historical account of



- Hoogsteen base-pairs in duplex DNA, *Biopolymers*, 2014, **99**, 955–968.
- 76 H. S. Alvey, F. L. Gottardo, E. N. Nikolova and H. M. Al-Hashimi, Widespread transient Hoogsteen base-pairs in canonical duplex DNA with variable energetics, *Nat. Commun.*, 2014, **5**, 4786–4794.
- 77 F. J. Acosta-Reyes, E. Alechaga, J. A. Subirana and J. L. Campos, Structure of the DNA duplex d(ATTAAT)₂ with Hoogsteen hydrogen bonds, *PLoS One*, 2015, **10**, e0120241.
- 78 C. Yang, E. Kim and Y. Pak, Free energy landscape and transition pathways from Watson–Crick to Hoogsteen base pairing in free duplex DNA, *Nucleic Acids Res.*, 2015, **43**, 7769–7778.
- 79 H. Zhou, Occurrence and function of Hoogsteen base pairs in nucleic acids, PhD Thesis, Department of Biochemistry, Duke University, Durham, North Carolina, USA, 2016.
- 80 S. Kaur, P. Sharma and S. D. Wetmore, Structural and electronic properties of barbituric acid and melamine-containing ribonucleosides as plausible components of prebiotic RNA: implications for prebiotic self-assembly, *Phys. Chem. Chem. Phys.*, 2017, **19**, 30762–30771.
- 81 A. Rich, On the problems of evolution and biochemical information transfer, in *Horizons in Biochemistry*, ed. M. Kasha and B. Pullman, Academic Press, New York, USA, 1962, pp. 103–126.
- 82 J. W. Drake, B. Charlesworth, D. Charlesworth and J. F. Crow, Rates of spontaneous mutation, *Genetics*, 1998, **148**, 1667–1686.
- 83 M. Lynch, Rate, molecular spectrum, and consequences of human mutation, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 961–968.
- 84 E. Del Grosso, A.-M. Dallaire, A. Vallée-Bélisle and F. Ricci, Enzyme-operated DNA-based nanodevices, *Nano Lett.*, 2015, **15**, 8407–8411.
- 85 T. Liedl, T. L. Sobey and F. C. Simmel, DNA-based nanodevices, *Nanotoday*, 2007, **2**, 36–41.
- 86 M. Piccolino, Biological machines: from mills to molecules, *Nat. Rev. Mol. Cell Biol.*, 2000, **1**, 149–153.
- 87 J. Tirado-Rives and W. L. Jorgensen, Performance of B3LYP Density Functional Methods for a large set of organic molecules, *J. Chem. Theory Comput.*, 2008, **4**, 297–306.
- 88 R. G. Parr, and W. Yang, *Density-functional theory of atoms and molecules*, Oxford University Press, Oxford, 1989.
- 89 C. Lee, W. Yang and R. G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, **37**, 785–789.
- 90 P. C. Hariharan and J. A. Pople, The influence of polarization functions on molecular orbital hydrogenation energies, *Theor. Chim. Acta*, 1973, **28**, 213–222.
- 91 R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions, *J. Chem. Phys.*, 1980, **72**, 650–654.
- 92 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman and J. A. Pople, *GAUSSIAN 09 (Revision B.01)*, Gaussian Inc, Wallingford CT, 2010.
- 93 H. P. Hratchian, and H. B. Schlegel, Finding minima, transition states, and following reaction pathways on *ab initio* potential energy surfaces, in *Theory and applications of computational chemistry: The first 40 years*, ed. C. E. Dykstra, G. Frenking, K. S. Kim and G. Scuseria, Elsevier, Amsterdam, 2005, pp. 195–249.
- 94 C. F. Matta, 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.
- 95 O. O. Brovarets' and D. M. Hovorun, Quantum-chemical investigation of tautomerization ways of Watson-Crick DNA base pair guanine-cytosine, *Ukr. Biochem. J.*, 2010, **82**, 55–60.
- 96 O. O. Brovarets' and D. M. Hovorun, Quantum-chemical investigation of the elementary molecular mechanisms of pyrimidine·purine transversions, *Ukr. Biochem. J.*, 2010, **82**, 57–67.
- 97 O. O. Brovarets', R. O. Zhurakivsky and D. M. Hovorun, Is there adequate ionization mechanism of the spontaneous transitions? Quantum-chemical investigation, *Biopolym. Cell*, 2010, **26**, 398–405.
- 98 O. O. Brovarets' and D. M. Hovorun, DPT tautomerization of the long A·A* Watson-Crick base pair formed by the amino and imino tautomers of adenine: combined QM and QTAIM investigation, *J. Mol. Model.*, 2013, **19**, 4223–4237.
- 99 O. O. Brovarets' and D. M. Hovorun, How does the long G·G* Watson-Crick DNA base mispair comprising keto and enol tautomers of the guanine tautomerise? The results of a QM/QTAIM investigation, *Phys. Chem. Chem. Phys.*, 2014, **16**, 15886–15899.
- 100 M. A. Palafox, 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. Dyn.*, 2014, **32**, 831–851.
- 101 A. A. El-Sayed, A. Tamara Molina, M. C. Alvarez-Ros and M. A. Palafox, 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. Dyn.*, 2015, **33**, 723–748.
- 102 C. Peng, P. Y. Ayala, H. B. Schlegel and M. J. Frisch, Using redundant internal coordinates to optimize equilibrium geometries and transition states, *J. Comput. Chem.*, 1996, **17**, 49–56.
- 103 P. W. Atkins, *Physical chemistry*, Oxford University Press, Oxford, 1998.
- 104 M. J. Frisch, M. Head-Gordon and J. A. Pople, Semi-direct algorithms for the MP2 energy and gradient, *Chem. Phys. Lett.*, 1990, **166**, 281–289.
- 105 R. A. Kendall, T. H. Dunning Jr and R. J. Harrison, Electron affinities of the first-row atoms revisited. Systematic basis



- sets and wave functions, *J. Chem. Phys.*, 1992, **96**, 6796–6806.
- 106 E. Wigner, Über das Überschreiten von Potentialschwellen bei chemischen Reaktionen [Crossing of potential thresholds in chemical reactions], *Zeitschrift für Physikalische Chemie*, 1932, **B19**, 203–216.
- 107 S. F. Boys and F. Bernardi, The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors, *Mol. Phys.*, 1970, **19**, 553–566.
- 108 M. Gutowski, J. H. Van Lenthe, J. Verbeek, F. B. Van Duijneveldt and G. Caahalasinski, The basis set superposition error in correlated electronic structure calculations, *Chem. Phys. Lett.*, 1986, **124**, 370–375.
- 109 J. A. Sordo, S. Chin and T. L. Sordo, On the counterpoise correction for the basis set superposition error in large systems, *Theor. Chim. Acta*, 1988, **74**, 101–110.
- 110 J. A. Sordo, 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.
- 111 R. F. W. Bader, *Atoms in molecules: A quantum theory*, Oxford University Press, Oxford, UK, 1990.
- 112 C. F. Matta and J. Hernández-Trujillo, Bonding in polycyclic aromatic hydrocarbons in terms of the electron density and of electron delocalization, *J. Phys. Chem. A*, 2003, **107**, 7496–7504.
- 113 C. F. Matta, N. Castillo and R. J. Boyd, Atomic contributions to bond dissociation energies in aliphatic hydrocarbons, *J. Chem. Phys.*, 2006, **125**(20), 204103.
- 114 I. Cukrowski and C. F. Matta, Hydrogen–hydrogen bonding: A stabilizing interaction in strained chelating rings of metal complexes in aqueous phase, *Chem. Phys. Lett.*, 2010, **499**, 66–69.
- 115 C. F. Matta, 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.
- 116 C. Lecomte, E. Espinosa and C. F. Matta, On atom–atom ‘short contact’ bonding interactions in crystals, *IUCrJ*, 2015, **2**, 161–163.
- 117 T. A. Keith, *AIMAll (Version 10.07.01)*, retrieved from aim.tkgristmill.com, 2010.
- 118 C. F. Matta, N. Castillo and R. J. Boyd, Extended weak bonding interactions in DNA: π -stacking (base–base), base–backbone, and backbone–backbone interactions, *J. Phys. Chem. B*, 2006, **110**, 563–578.
- 119 C. F. Matta, R. J. Boyd, *The Quantum Theory of Atoms in Molecules: from solid state to DNA and drug design*, Wiley-VCH Verlag GmbH & Co. KGaA, 2007.
- 120 A. V. Iogansen, Direct proportionality of the hydrogen bonding energy and the intensification of the stretching $\nu(\text{XH})$ vibration in infrared spectra, *Spectrochim. Acta, Part A*, 1999, **55**, 1585–1612.
- 121 O. O. Brovarets' and D. M. Hovorun, IR vibrational spectra of H-bonded complexes of adenine, 2-aminopurine and 2-aminopurine⁺ with cytosine and thymine: quantum-chemical study, *Opt. Spectrosc.*, 2010, **111**, 750–757.
- 122 O. O. Brovarets', R. O. Zhurakivsky and D. M. Hovorun, 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.
- 123 O. O. Brovarets' and D. M. Hovorun, Atomistic nature of the DPT tautomerisation of the biologically important C·C* DNA base mispair containing amino and imino tautomers of cytosine: a QM and QTAIM approach, *Phys. Chem. Chem. Phys.*, 2013, **15**, 20091–20104.
- 124 O. O. Brovarets', Y. P. Yurenko and D. M. Hovorun, Intermolecular CH···O/N H-bonds in the biologically important pairs of natural nucleobases: A thorough quantum-chemical study, *J. Biomol. Struct. Dyn.*, 2013, **32**, 993–1022.
- 125 O. O. Brovarets', Y. P. Yurenko and D. M. Hovorun, 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, *J. Biomol. Struct. Dyn.*, 2015, **33**, 1624–1652.
- 126 E. Espinosa, E. Molins and C. Lecomte, Hydrogen bond strengths revealed by topological analyses of experimentally observed electron densities, *Chem. Phys. Lett.*, 1998, **285**, 170–173.
- 127 I. Mata, I. Alkorta, E. Espinosa and E. Molins, Relationships between interaction energy, intermolecular distance and electron density properties in hydrogen bonded complexes under external electric fields, *Chem. Phys. Lett.*, 2011, **507**, 185–189.
- 128 T. Y. Nikolaienko, L. A. Bulavin and D. M. Hovorun, Bridging QTAIM with vibrational spectroscopy: The energy of intramolecular hydrogen bonds in DNA-related biomolecules, *Phys. Chem. Chem. Phys.*, 2012, **14**, 7441–7447.
- 129 W. Saenger, *Principles of nucleic acid structure*, Springer, New York, 1984.
- 130 D. M. Govorun and I. V. Kondratyuk, The quantum mechanical calculations evidence molecular-zwitterionic features of prototropic tautomerism of canonical nucleotide bases. 2. Purines, *Biopolym. Cell*, 1996, **12**, 49–52.
- 131 D. M. Govorun, V. D. Danchuk, Y. R. Mishchuk, I. V. Kondratyuk, N. F. Radomsky and N. V. Zheltovsky, AM1 calculation of the nucleic acid bases structure and vibrational spectra, *J. Mol. Struct.*, 1992, **267**, 99–103.
- 132 T. Y. Nikolaienko, L. A. Bulavin and D. M. Hovorun, How flexible are DNA constituents? The quantum-mechanical study, *J. Biomol. Struct. Dyn.*, 2011, **29**, 563–575.
- 133 D. M. Hovorun, L. Gorb and J. Leszczynski, From the nonplanarity of the amino group to the structural nonrigidity of the molecule: a post-Hartree-Fock *ab initio* study of 2-aminoimidazole, *Int. J. Quantum Chem.*, 1999, **75**, 245–253.

