DPT tautomerisation of the wobble guanine-thymine DNA base mispair is not mutagenic: QM and QTAIM arguments

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Abstract

We have shown for the first time, connecting QM methods with QTAIM analysis and using the methodology of the sweeps of the energetical, electron-topological and geometrical parameters, that the tautomerisation of the wobble guanine-thymine (wG·T) DNA base mispair into the wG*·T* base mispair induced by the double proton transfer (DPT), which undergoes a concerted asynchronous pathway, is not mutagenic. The wG·T → wG*·T* DPT tautomerisation does not result in the transition of the G base into its mutagenic tautomeric form G* able to mispair with the T base within the Watson–Crick base pairing scheme. This observation is explained by the so-called quantum protection of the wG·T DNA base mispair from its mutagenic tautomerisation – the dynamical non-stability of the tautomerised wG*·T* base mispair and significantly negative value of the Gibbs free energy of activation for the reverse reaction of the wG·T → wG*·T* DPT tautomerisation.

Keywords: wobble guanine-thymine DNA base mispair; mutagenic tautomer of the guanine; sweeps of the energetical, electron-topological, geometrical, polar and NBO parameters along the IRC; the double proton transfer; cooperativity of the H-bonds; B3LYP and MP2 levels of QM theory; QTAIM analysis

Introduction

The “bottleneck” of the classical Watson–Crick tautomeric hypothesis (Watson & Crick, 1953) linking the origin of the spontaneous point mutations in DNA – transversions and transitions (Friedberg et al., 2006) – with the mutagenic tautomerisation of the nucleotide bases is the physico-chemical mechanism of the latter (Brovarets’, Kolomiets’, & Hovorun, 2012). Despite the gigantic without any exaggeration as experimental (Bebenek, Pedersen, & Kunkel, 2011; Cantara, Murphy, Demirci, & Agris, 2013; Harris et al., 2003; Wang, Hellinga, & Beese, 2011), so theoretical efforts (Brovarets’ & Hovorun, 2013d; Danilov, Anisimov, Kurita, & Hovorun, 2005; Danilov & Kventsel, 1971), it remains unclear so far whether the DNA bases can switch from canonical to mutagenic tautomeric form (herein and after mutagenic tautomeric form of the DNA bases (Brovarets’ & Hovorun, 2013a; Brovarets’, Yurenko, Dubey, & Hovorun, 2012; Kosenkov et al., 2009; Platonov et al., 2005; Samijlenko, Krechkivska, Kosach, & Hovorun, 2004) is marked by an asterisk) in the complementary base-pair recognition pocket of DNA polymerase without intervention into this process of single water molecules (Cerón-Carrasco, Requena, Michaux, Perpète, & Jacquemin, 2009; Cerón-Carrasco et al., 2009, 2011; Fogarasi & Szalay, 2002; Furmanchuk et al., 2011; Gorb & Leszczynski, 1998a, 1998b). Recently, we have shown that the mutagenic tautomerisation of the adenine-thymine (A·T) and guanine-cytosine (G·C) Watson–Crick DNA base pairs via tunnelling is impossible because of the principal circumstances, namely of the quantum protection from this process (Brovarets’ & Hovorun, 2013b, 2013c). The same situation is observed for the DPT tautomerisation of the long A·G (Brovarets’, Zhurakivsky, & Hovorun, 2014c) and short C·T (Brovarets’ & Hovorun, 2013e) Watson–Crick base pairs: in this case, mutagenic tautomers of both purine and pyrimidine bases, respectively, are not produced for similar reasons.

In a recent paper (Padermshoke, Katsumoto, Masaki, & Aida, 2008), a rather simple and persuasive, at first glance, physico-chemical mechanism of the mutagenic tautomerisation of the G base has been proposed. In its authors’ opinion, the transition of the guanine base from the canonical G to the mutagenic G* tautomeric form is carried out by the double proton transfer (DPT) tautomerisation of the wobble wG·T base mispair, which is stabilised by the two antiparallel intermolecular N1H⋯O2 and N3H⋯O6 H-bonds (Scheme 1), with subsequent dissociation of the tautomerised wG*·T* base...
pair into the G* and T* monomers in the rare (which in the first case is mutagenic) tautomeric form. Meanwhile, the dissociation of the tautomerised wG*·T* base pair according to the above scheme can be implemented if and only if it is dynamically stable structure with Gibbs free energy of the reverse barrier of the wG·T → wG*·T* tautomerisation significantly higher than kT. Unfortunately, analysis of such sort is not available in the aforementioned work (Padermshoke et al., 2008).

The main aim of this work – to determine whether the DPT tautomerisation of the wobble wG·T DNA base mispair into the wG*·T* mismatch results in the mutagenic tautomerisation of the G base (Padermshoke et al., 2008). To achieve this goal, we have combined quantum-mechanical (QM) methods with Bader’s Quantum Theory of Atoms in Molecules (QTAIM) analysis and used the methodology of the sweeps of the energetical, electron-topological, geometrical, polar and NBO parameters (Brovarets’ et al., 2013a, 2013b, 2013c, 2014a, 2014b, 2014c), in order to describe the physico-chemical mechanism of this tautomerisation and to establish the main parameters that characterise it.

As a result, we have received convincing evidence that the wG·T → wG*·T* DPT tautomerisation is not mutagenic, since the tautomerised wobble wG*·T* DNA base mispair is dynamically unstable structure and the reverse barrier for the wG·T → wG*·T* tautomerisation on the Gibbs free energy profile is absent at all (ΔG < 0). In other words, the tautomerised wobble wG*·T* base mispair as instantaneous structure with a lifetime 2.14×10−15 s, that is significantly less than the period of the valence vibrations of the NH groups, involved in the intermolecular N1H⋯O2/H⋯N1 and N3H⋯O6/H⋯N3 H-bonds, cannot dissociate into the G* and T* monomers in the rare configuration (Scheme 1). Only wobble wG·T base mispair dissociates into the G and T monomers without changing of their canonical tautomeric status.

Computational methods of investigation
All calculations have been carried out with the Gaussian’09 suite of programs (Frisch et al., 2010). Geometries and harmonic vibrational frequencies of the wG·T and wG*·T* DNA base pairs and the TS_{wG·T ← wG*·T*} of their mutagenic tautomerisation via the DPT were obtained using density functional theory (DFT) (Parr & Yang, 1989) with the Becke’s three-parameter hybrid functional combined with Lee-Yang-Parr correlation functional (B3LYP) (Tirado-Rives & Jorgensen, 2008) and second-order Møller-Plesset perturbation theory (MP2) (Frisch, Head-Gordon, & Pople, 1990) in connection with Pople’s 6-311++G(d,p) basis set in vacuum. DFT and MP2 levels of theory formerly have been successfully applied on similar systems for the exploration of the tautomerisation phenomena and have been verified to give accurate normal mode frequencies, geometries, barrier heights, characteristics of intra- and intermolecular H-bonds (Brovarets’ & Hovorun, 2010b, 2010c, 2010e, 2011b; Brovarets’, Zhurakivsky, & Hovorun, 2010; Danilov et al., 2009; Hovorun, Gorb, & Leszczynski, 1999; Pelmenschikov et al., 2000; Samijlenko, Yurenko, Stepanyugin, & Hovorun, 2011; Shishkin, Pelmenschikov, Hovorun, & Leszczynski, 2000). We subsequently performed single-point energy calculations at the correlated MP2 level of theory (Frisch et al., 1990) with the 6-311++G(2df,pd) and 6-311++G(3df,2pd) Pople’s (Frisch, Pople, & Binkley, 1984; Hariharan & Pople, 1973; Krishnan, Binkley, Seeger, & Pople, 1980) or cc-pVTZ and cc-pVQZ Dunning’s cc-type (Dunning, 1989; Kendall, 1992) basis sets for the geometries optimised at the B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) levels of theory to consider electronic correlation effects as accurately as possible.

The correspondence of the stationary points to the wG*·T → wG*·T* local minima or TS_{wG·T ← wG*·T*}, that has been located by means of synchronous transit-guided quasi-Newton (STQN) method (Peng & Schlegel, 1993; Peng et al., 1996), on the potential energy landscape has been verified by the absence or the presence, respectively, of one and only one imaginary frequency corresponding to the normal mode that identifies the reaction coordinate. Scaling factors (see papers (Palafox, 2000;
Palafox & Rastogi, 2002; Palafox, Iza, & Gil, 2002) about the existing approaches to the definition of this parameter) of .9668 (Brovarets & Hovorun, 2013f; Brovarets’ et al., 2014a) and .9531 (Brovarets’ & Hovorun, 2013b, 2013c, 2013d) have been used in the present work at the B3LYP and MP2 levels of theory, respectively, to correct the harmonic vibrational frequencies of all the studied structures. Since the stationary points and TS were located, the reaction pathway connecting them was established by following the intrinsic reaction coordinate (IRC) in the forward and reverse directions from the TS using the Hessian-based predictor–corrector algorithm (HPC) integration algorithm (Hratchian & Schlegel, 2004, 2005a, 2005b) with tight convergence criteria. We have investigated the evolution of the geometrical, geometrical, polar, electron-topological and NBO characteristics of the base mispair and specific intermolecular contacts stabilising it along the reaction pathway establishing them at each point along the IRC.

The electronic interaction energies $E_{int}$ have been computed at the MP2/6-311++G(2df,pd) level of theory for the geometries optimised at the B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) levels of theory as the difference between the total energy of the base pair and the energies of the isolated monomers. In each case, the interaction energy was corrected for the basis set superposition error (BSSE) (Boys & Bernardi, 1970; Boys, Bernardi, & Rabinovitch, 1980) through the counterpoise procedure (Sordo, 2001; Sordo, Chin, & Sordo, 1988).

The electronic free energy $G$ values for all structures were obtained at room temperature ($T=298.15$ K) in the following way:

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

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

The lifetime $\tau$ of the wG$^*$·T$^*$ base pair was calculated using the formula $1/\kappa_r$, where the value of the reverse $\kappa_r$ rate constant for the wG·T $\rightarrow$ wG$^*$·T$^*$ DPT tautomerisation was evaluated by the formula (Atkins, 1998):

$$\kappa_r = \Gamma \frac{k_B T}{h} e^{-\frac{\Delta G_f}{RT}},$$

where $\Gamma = 1 + \frac{1}{24} \left( \frac{k_B T}{\hbar} \right)^2$ – Wigner’s tunnelling correction (Wigner, 1932) that is adequate for the DPT reactions (Brovarets’ & Hovorun, 2010a, 2010b, 2011a), $k_B$ – Boltzmann’s constant, $T=298.15$ K – absolute temperature, $h$ – Planck’s constant, $\Delta G_f$ – the Gibbs free energy of activation for the DPT reaction in the reverse direction, $R$ – universal gas constant and $v_f$ – the magnitude of the imaginary frequency at the TS$_{wG}$·T$^*$$\rightarrow$wG$^*$·T$^*$. Bader’s QTAIM (Bader, 1990) was applied to analyse in detail the topology of the electron density distribution using program package AIMAll (Keith, 2011) with all the default options. Wave functions were obtained at the level of theory used for geometry optimisation. The presence of a bond critical point (BCP) (Bader, 1990), namely the so-called (3,−1) BCP and a bond path between donor and acceptor, as well as the positive value of the Laplacian at this BCP ($\Delta \rho \geq 0$), were considered as criteria for the H-bond formation (Brovarets’, Yurenko, & Hovorun, 2014; Grabowska, 2013; Grabowski, Alkorta, & Elguero, 2013; Ponomareva, Yurenko, Zhurakivsky, van Mourik, & Hovorun, 2012, 2014; Yurenko, Zhurakivsky, Samijlenko, & Hovorun, 2011).

The energies of the intermolecular H-bonds $E_{HB}$ in the wG·T and wG$^*$·T$^*$ DNA base pairs were evaluated by the empirical Iogansen’s formula (Iogansen, 1999):

$$E_{HB} = 0.33 \cdot \sqrt{\Delta \nu} - 40,$$

where $\Delta \nu$ – the magnitude of the redshift (relative to the free molecule) of the stretching mode of the H-bonded groups. The partial deuteration of the NH, OH and NH$_2$ groups involved in the H-bonding was applied to eliminate the effect of vibrational resonances (Brovarets’ et al., 2013b, 2013c).

The energy of the O6H···N3 H-bond in the TS$_{wG}$·T$^*$$\rightarrow$wG$^*$·T$^*$ was estimated by the Nikolaienko–Bulavin–Hovorun formula (Nikolaienko, Bulavin, & Hovorun, 2012):

$$E_{O6H\cdots N3} = 1.72 + 142 \cdot \rho,$$

where $\rho$ is the electron density at the (3,−1) BCP of the O6H···N3 H-bond.

The energy of the N2H···O2 H-bond in the TS$_{wG}$·T$^*$$\rightarrow$wG$^*$·T$^*$ and the energies of all three intermolecular H-bonds $E_{HB}$ under the investigation of the sweeps (Brovarets’ & Hovorun, 2013f; Brovarets’ et al., 2014a, 2014b) of their energies were evaluated by the empirical Espinosa–Molins–Lecomte (EML) formula (Espinosa, Molins, & Lecomte, 1998; Mata, Alkorta, Espinosa, & Molins, 1998) based on the electron density distribution at the (3,−1) BCPs of the H-bonds:

$$E_{N2H\cdots O2} = 0.5 \cdot V(r),$$

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

The atomic numbering scheme for the nucleobases is conventional (Saenger, 1984).

**Results and their discussion**

All derived results in this work are presented in Tables 1–3 and Figures 1–9 obtained at the MP2/6-311++G(d,p) level of QM theory and in Tables S1–S4 and Figures
Table 1. Electron-topological, structural, vibrational and energetical characteristics of the intermolecular H-bonds revealed in the wG·T, wG*·T* and TSwG·T···wG*·T* and polar characteristics of the latters obtained at the MP2/6-311++G(d,p) level of theory in vacuum.

| Complex            | AH···B H-bond | $\rho^a$ | $\Delta \rho$ | $\langle 100 \nu \rangle^c$ | $d_{A-H}^b$ | $d_{H-B}^b$ | $\angle \text{AH} \cdot \text{B}$ | $\Delta E^b$ | $\mu^\parallel$ | $\mu^\perp$ |
|--------------------|---------------|----------|---------------|-----------------------------|-------------|-------------|----------------------------------|-------------|-------------|-------------|
| wG·T               | N3H···O6      | 0.30     | 0.117         | 5.23                        | 2.860       | 1.828       | 174.2                            | 360.0       | 5.90        | 8.37        |
|                    | N1H···O2      | 0.035    | 0.136         | 6.25                        | 2.801       | 1.776       | 173.4                            | 278.8       | 5.10        |             |
|                    | O6H···N3      | 0.050    | 0.122         | 6.23                        | 2.705       | 1.698       | 177.6                            | 761.5       | 8.86        | 7.55        |
|                    | O2H···N1      | 0.066    | 0.117         | 5.98                        | 2.620       | 1.594       | 174.9                            | 1155.2      | 11.02       |             |
| TSwG·T             | O6H···N3      | 0.077    | 0.104         | 5.32                        | 2.585       | 1.534       | 178.8                            | 12.62*       | 7.84        |             |
|                    | N2H···O2      | 0.009    | 0.041         | 148.49                      | 3.098       | 2.409       | 124.7                            | 2.14*        |             |             |

*The electron density at the (3,−1) BCP of the H-bond, a.u.
*The Laplacian of the electron density at the (3,−1) BCP of the H-bond, a.u.
*The ellipticity at the (3,−1) BCP of the H-bond.
*The distance between the A (H-bond donor) and B (H-bond acceptor) atoms of the AH···B H-bond, Å.
*The distance between the H and B atoms of the AH···B H-bond, Å.
*The elongation of the H-bond donating group AH upon the AH···B H-bonding, Å.
*The redshift of the stretching vibrational mode $\nu$(AH) of the AH H-bonded group, cm$^{-1}$.
*The H-bond angle, degree.
*The redshift of the stretching vibrational mode $\nu$(AH) of the AH H-bonded group, cm$^{-1}$.
*The dipole moment of the complex, D.

Table 2. Electron-topological and structural parameters of the intermolecular H-bonds revealed in the nine key points and polar characteristics of the latters obtained at the MP2/6-311++G(d,p) level of theory in vacuum along the IRC of the wG·T ↔ wG*·T* tautomerisation via the DPT.

| Complex          | AH···B H-bond/A-H-B covalent bond | $\rho$   | $\Delta \rho$ | $\langle 100 \nu \rangle^c$ | $d_{A-B}^a$ | $d_{H-B}^a$ | $\angle \text{AH} \cdot \text{B}$ | $\Delta E^b$ | $\mu^\parallel$ | $\mu^\perp$ |
|------------------|----------------------------------|----------|---------------|-----------------------------|-------------|-------------|----------------------------------|-------------|-------------|-------------|
| Key point 1 (−11.60 Bohr): wG·T | N3H···O6      | 0.30     | 0.117         | 5.23                        | 2.860       | 1.828       | 174.2                            | 360.0       | 5.90        | 8.37        |
| Key point 2 (−0.96 Bohr): $\Delta \rho_{O6-H} = 0$ | N3H···O6      | 0.122    | 0.000         | 1.97                        | 2.542       | 1.324       | 179.9                            | 126.6       |             |             |
| Key point 3 (−0.80 Bohr): $\rho_{O6-H}^\text{B} \rho_{H-N3}$ | N3-H-O6      | 0.150    | 0.243         | 3.50                        | 2.544       | 1.299       | 179.7                            | 7.02        |             |             |
| Key point 4 (−0.48 Bohr): $\Delta \rho_{H-N3} = 0$ | N1H···O2      | 0.092    | 0.158         | 3.29                        | 2.512       | 1.436       | 173.5                            |             |             |             |
| Key point 5 (−0.16 Bohr): $\Delta \rho_{H-O2} = 0$ | N1H···O2      | 0.010    | 0.040         | 77.18                       | 3.108       | 2.397       | 126.6                            |             |             |             |
| Key points 6 and 7 (−0.00 Bohr): TSwG·T ↔ wG*·T*; $\rho_{H-N3} \rho_{H-O2}$ | N1–H–O2      | 0.163    | −0.285        | 3.28                        | 2.470       | 1.262       | 173.7                            |             |             |             |
| Key point 8 (−0.27 Bohr): $\Delta \rho_{N3-H} = 0$ | O6H···N3      | 0.097    | 0.041         | 147.95                      | 3.100       | 2.406       | 125.0                            |             |             |             |
| Key point 9 (4.81 Bohr): wG*·T* | O6H···N3      | 0.050    | 0.122         | 6.23                        | 2.705       | 1.698       | 177.6                            | 7.55        |             |             |

Note: For footnote definitions see Table 1.

S1–S9 (ESI†) – at the B3LYP/6-311++G(d,p) level of QM theory. In the body of the article, we focus on the discussion of those results received at the MP2/6-311++G(d,p) level of QM theory, while the interested readers can find analogous results obtained at the B3LYP/6-311++G(d,p) level of QM theory in the Electronic Supplementary Information.

With a view to investigate the changes of the energetical, structural, polar, electron-topological and NBO parameters of the wG·T DNA base mispair and intermolecular interactions stabilising it along the IRC of the wG·T ↔ wG*·T* tautomerisation via the DPT, we have performed the calculations of the number of the physico-chemical parameters. These characteristics are the
electronic energy, the first derivative of the electronic energy with respect to the IRC, the dipole moment of the base pair, the distances and the angle of the intermolecular H-bonds, the electron density, the Laplacian of the electron density, the ellipticity and the energy at the (3,−1) BCPs of the intrapair covalent and hydrogen bonds, the NBO charges of the hydrogen atoms involved in the intermolecular interactions, the glycosidic parameters (angles and distance between the glycosidic hydrogens) and dihedral angles of the base mispair and amino group of the G base at each step along the IRC. In such a way, we obtained the scanning (so-called sweeps) of these characteristics that are presented in Figures 2–9 and S2-S9.

Thus, Table 1 includes basic physico-chemical characteristics of the intermolecular H-bonds revealed in the wG·T and wG*·T* base pairs and the TSwG/C1 T → wG*·T* of their tautomerisation via the DPT, indicating that all intermolecular H-bonds satisfy electron-topological, geometrical and vibrational criteria known to date for the canonical H-bonding. Notably, all of these structures have C1 symmetry. Interestingly, the heterocycles of the

Table 3. Energetical and kinetic characteristics of the wG·T ↔ wG*·T* tautomerisation via the DPT obtained at the different levels of QM theory for the geometry calculated at the MP2/6-311++G(d,p) level of QM theory in vacuo.

| Level of QM theory | ΔG^a | ΔE^b | ΔΔG^c | ΔΔE^d | ΔΔG^e | ΔΔE^f | τ^g | r^h |
|-------------------|------|------|--------|--------|--------|--------|-----|-----|
| MP2/6-311++G(2df,pd) | 11.39 | 11.73 | 8.88 | 11.98 | −2.51 | .25 | 87.9 | 1.52 × 10⁻¹⁵ |
| MP2/6-311++G(3df,2pd) | 11.99 | 12.33 | 9.61 | 12.71 | −2.38 | .39 | 135.3 | 1.91 × 10⁻¹⁵ |
| MP2/cc-pVTZ | 11.24 | 11.58 | 8.96 | 12.06 | −2.28 | .48 | 168.6 | 2.24 × 10⁻¹⁵ |
| MP2/cc-pVQZ | 11.78 | 12.12 | 9.47 | 12.58 | −2.31 | .46 | 159.5 | 2.14 × 10⁻¹⁵ |

*aThe relative Gibbs free energy of the wG*·T* base pair (ΔG^wG·T−0; T = 298.15 K), kcal·mol⁻¹.
*bThe relative electronic energy of the wG*·T* base pair (ΔE^wG·T−0), kcal·mol⁻¹.
*cThe Gibbs free energy of activation for the forward reaction of the wG·T → wG*·T* tautomerisation via the DPT, kcal·mol⁻¹.
*dThe activation electronic energy for the forward reaction of the wG·T → wG*·T* tautomerisation, kcal·mol⁻¹.
*eThe Gibbs free energy of activation for the reverse reaction of the wG·T → wG*·T* tautomerisation, kcal·mol⁻¹.
*fThe activation electronic energy for the reverse reaction of the wG·T → wG*·T* tautomerisation.
*gThe lifetime of the wG*·T* base mispair, s. The frequency of the vibrational mode in the wG·T* base pair, which becomes imaginary in the TSwG/C1 T → wG·T* DPT tautomerisation, is equal to 2468.7 cm⁻¹ and the zero-point vibrational energy associated with this normal mode is equal to 3.53 kcal·mol⁻¹ or 1234.4 cm⁻¹ (MP2/6-311++G(d,p) level of QM theory).

Figure 1. Geometric structures of the nine key points describing the evolution of the wG·T ↔ wG*·T* tautomerisation via the DPT along the IRC obtained at the MP2/6-311++G(d,p) level of theory in vacuo. Coordinates of the nine key points are presented for each structure. The dotted lines indicate AH⋯B H-bonds, while continuous lines show covalent bonds (their lengths are presented in angstroms). Carbon atoms are in light-blue, nitrogen in dark-blue, hydrogen in grey and oxygen in red.
G and T bases as well as another DNA bases remain almost planar in the base pair, despite the fact that they are flexible molecules (Govorun et al., 1992; Hovorun et al., 1999; Nikolaienko, Bulavin, & Hovorun, 2011). The orientation of the methyl group of the T base relative to the pyrimidine ring does not change during the $wG\cdot T \leftrightarrow wG^*\cdot T^*$ DPT tautomerisation. According to Table 1, the slightly non-planar ($\angle C6N1(G)C2N3(T) = 3.1^\circ$) $wG\cdot T$ base pair is stabilised by the two antiparallel $N3H\cdots O6$ (5.90) and $N1H\cdots O2$ (5.10 kcal/mol$^{-1}$) H-bonds, the non-planar ($\angle C6N1(G)C2N3(T) = 22.3^\circ$) tautomerised $wG^*\cdot T^*$ base pair ($\Delta G = 11.78$ and $\Delta E = 12.12$ kcal/mol$^{-1}$) is stabilised by the two antiparallel canonical $O6H\cdots N3$ (8.86) and $O2H\cdots N1$ (11.02 kcal/mol$^{-1}$) H-bonds, whereas the non-planar ($\angle C6N1(G)C2N3(T) = 14.5^\circ$) TS wG$^\cdot T^\cdot$ (wG$^\cdot T^\cdot$) ($\Delta G = 9.47$ and $\Delta E = 12.58$ kcal/mol$^{-1}$ obtained at the MP2/cc-pVQZ//MP2/6-311++G(d,p) level of QM theory in vacuum) with imaginary frequency $\nu_1 = 772.5 i$ cm$^{-1}$ is stabilised by the N1–H–O2 covalent bridge and the O6H–N3 (12.62) and N2H–O2 (2.14 kcal/mol$^{-1}$) H-bonds (Table 1, Figure 1). The initial wG·T base mispair becomes significantly non-planar during the $wG\cdot T \leftrightarrow wG^*\cdot T^*$ DPT tautomerisation. Notably, the third N2H–O2 H-bond, which is the weakest interaction, is available solely for the TS wG$^\cdot T^\cdot$ wG$^\cdot T^\cdot$. It was established based on the comprehensive analysis of the sweeps of the energies of the intermolecular H-bonds (Figure 4(d)), calculated by the EML formula (Espinosa et al., 1998; Mata et al., 2011), that the N3H–O6 H-bond is cooperative (Brovarets’ & Hovorun, 2013f; Brovarets’ et al., 2013b, 2013c; Mishchuk, Potyagaylo, & Hovorun, 2000) with the N1H–O2 H-bond in the wobble wG·T base pair.

Figure 2. Profiles of: (a) the electronic energy E and (b) the first derivative of the electronic energy with respect to the IRC – dE/dIRC along the IRC of the $wG\cdot T \leftrightarrow wG^*\cdot T^*$ tautomerisation via the DPT obtained at the MP2/6-311++G(d,p) level of theory in vacuo.

Figure 3. Profile of the dipole moment $\mu$ along the IRC of the $wG\cdot T \leftrightarrow wG^*\cdot T^*$ tautomerisation via the DPT obtained at the MP2/6-311++G(d,p) level of theory in vacuo.
while the O6H···N3 H-bond is also cooperative with the O2H···N1 H-bond in the wG*·T* base pair (dEO6H···N3/dEO2H···N1 = .13 at the IRC = 4.81 Bohr), mutually reinforcing each other.

We have established by analysing the electronic ΔE_int and Gibbbs free ΔG_int energies of interaction that the wG·T (ΔE_int = −16.71 and ΔG_int = −5.06 kcal·mol⁻¹) and wG*·T* (ΔE_int = −24.20 and ΔG_int = −10.57 kcal·mol⁻¹) base pairs are thermodynamically stable structures, since their Gibbs free energies of interaction, obtained at the MP2/6-311++G(d,p) level of theory in vacuum, are less than zero, differing greatly from each other. Notably, the electronic and Gibbs free energies of interaction increase for the tautomerised wG*·T* base mispair comparably with the starting wG·T base mispair. Furthermore, these energies of interaction are less than those for the G·C Watson–Crick base pair (ΔE_int = −27.87 and ΔG_int = −14.17 kcal·mol⁻¹), obtained at the MP2/6-311++G(2df,pd)/MP2/6-311++G(d,p) level of theory in vacuum (Brovarets’ & Hovorun, 2013c). It is important to note that the intermolecular H-bonds make a major contribution into the stabilisation of the wG·T (|ΔE_int| = 65.8%) and wG*·T* (|ΔE_int| = 82.2%) base pairs, that cannot be considered as a unique physico-chemical characteristic exceptionally of these base pairs, since it was also observed for the other H-bonded base pairs (Brovarets’ & Hovorun, 2013b, 2013c, 2013e; Brovarets et al.,2014c).

The pro file of the electronic energy E along the IRC of the wG·T ↔ wG*·T* tautomerisation via the DPT contains plateau in the product region and the graph of the first derivative of the electronic energy with respect to the IRC – several extrema, two of which are located in the vicinity of the key points 2 and 8 (Figure 2). The profile of the dipole moment μ, that alters within the broad range of values 6.72–7.35 D, is characterised by the sharp peak (7.35 D) in the vicinity of the key point 4 (IRC = −.37 Bohr) (Figure 3).

It draws attention to the fact that the values of the electron density ρ, the Laplacian of the electron density Δρ at the (3,−1) BCPs of the intermolecular bonds and the distances d_AH/HA between the hydrogen and
electronegative A or B atoms of the AH⋯B H-bonds vary within a wide range of values along the IRC of the wG·T ↔ wG*·T* tautomerisation via the DPT: .033–.318 a.u., −2.098–.180 a.u. and 1.007–1.824 Å, respectively, demonstrating at this high similarity of their profiles to each other (Figures 4(a), 4(b) and 5(b)). Dependencies of the geometrical and electron-topological characteristics at the (3,−1) BCPs of the chemical bonds intersect exactly at the key points 3 and 6/7, forming a χ-like graphs for the loosened N3H⋯O6 and N1H⋯O2 covalent bridges, respectively. An interesting change of the values of the ellipticity ε at the (3,−1) BCPs of the intermolecular covalent and hydrogen bonds along the IRC of the wG·T ↔ wG*·T* DPT tautomerisation (Figure 4(c)). Notably, the profile of the ellipticity ε at the (3,−1) BCP of the third N2H⋯O2 H-bond is U-like, slightly depends on the IRC within the range of values from −3.80 to −.37 Bohr and then sharply increases, varying at this within a wide range from .70 to 13.21 (Figure 6(c)). The above observations are in a good agreement with the results obtained in our recent works (Brovarets’ & Hovorun, 2013f; Brovarets’ et al., 2013a, 2013b, 2013c, 2014a).

It should be noted that the N3H⋯O6 and N1H⋯O2 H-bonds observed in the wG·T base mispair exist within the key points 1–2 and 1–5 inclusively, reaching their maxima at the key points 2 and 5, respectively. The O6H⋯N3 and O2H⋯N1 H-bonds revealed in the wG*·T* base mispair exist within the key points 4–9 and 8–9 inclusively, reaching their maxima at the key points 4 and 8, respectively (Figures 1 and 4(d)). Notably, on the profiles of the energies of the H-bonds $E_{HB}$ are shown only those of them corresponding to the value $\Delta\rho \geq 0$ (Figure 4(b)). It is noteworthy that the N3H⋯O6 and O2H⋯N1 H-bonds are available exclusively at the reactant and product regions, respectively, while the N1H⋯O2 and O6H⋯N3 H-bonds except the reactant and product regions are available also at the TS region, i.e. they actually assist the chemical reaction (Figures 1 and 4(d)). It is interesting to note that the energetic profile of the N1H⋯O2 H-bond intersects with those of the O6H⋯N3 H-bond exactly at the key point 4, that means the equalisation of the energies of these H-bonds (Figure 4(d)).
Interestingly, the $\text{wG} \leftrightarrow \text{wG}^\ast \cdot \text{T}^\ast$ DPT tautomerisation is assisted by the third N2H···O2 H-bond due to the rearrangement of the H-bonded network at the IRC = −4.28 Bohr that terminates almost after TS$_{\text{wG} \leftrightarrow \text{wG}^\ast}$ at the IRC = .27 Bohr (the key point 8). Profiles of the energetical, electron-topological and geometrical characteristics of the third low-energy N2H···O2 H-bond are represented in Figures 6 and 7.

The compression of the geometrical sizes of the wG·T base mispair in the course of the wG·T ↔ wG$^\ast$·T$^\ast$ DPT tautomerisation arises primarily due to the reduction of the distance between the G and T bases within the base pair that is reflected by the slight variations of the distances $d_{O6 \cdots N3}/d_{N1 \cdots O2}$ between the electronegative O and N atoms of the intermolecular H-bonds (2.470–2.856 Å), of the angles of the H-bonding (172.0–179.9°), of the R(H–H) distance between the glycosidic protons (9.541–9.898 Å) and of the $\alpha_1$ ($\angle \text{N1H} \text{(T)H(G)}$) (67.3–70.0°) and $\alpha_2$ ($\angle \text{N9H} \text{(G)H(T)}$) (42.0–42.9°) glycosidic angles (Figures 5(a), 5(c) and 9). Notably, the $d_{O6 \cdots N3}/d_{N1 \cdots O2}/d_{N2 \cdots O2}$ and the R(H-H) distances notably decrease during the wG·T ↔ wG$^\ast$·T$^\ast$ DPT tautomerisation, indicating the reduction of the distance between the bases (Figures 5(a) and 9(a)). The $\angle \text{N1C2N2H} \text{(G)}$ dihedral angle, reflecting the non-planarity of the amino group of the G base (Hovorun et al., 1999) relative to its plane, lies within the range from 33.9° (IRC = −.80 Bohr) to 42.6° (IRC = −11.60 Bohr).

Graphs of the NBO charges of the hydrogen atoms involved in the N3H···O6/O6HI···N3 and N1H···O2/O2HII···N1 intermolecular interactions non-monotonically increase, whereas of those included in the third N2H···O2 H-bond – decrease without crossings along the IRC of the wG·T ↔ wG$^\ast$·T$^\ast$ tautomerisation via the DPT (Figure 8).

By analysing the spans of the $\chi$-like crossings on the $d_{\text{N3H} \cdots \text{O6}}, d_{\text{N1H} \cdots \text{O2}}, \rho$ and $\Delta \rho$ profiles of the intermolecular H-bonds along the IRC of the wG·T ↔ wG$^\ast$·T$^\ast$ tautomerisation via the DPT (Figures 4(a), 4(b) and 5(b)), it was established that the wG·T ↔ wG$^\ast$·T$^\ast$ tautomerisation proceeds through the asynchronous concerted mechanism. Moreover, based on the changes of the electron density and geometry of the intermolecular H-bonds along the IRC, the nine key points, that characterise the
Figure 7. Profiles of: (a) the distance $d_{N2-O2}$ between the N2 and O2 atoms of the N2H⋯O2 H-bond; (b) the distances $d_{N2H}$ and $d_{H⋯O2}$ of the N2H⋯O2 H-bond and (c) the angle $\angle N2H⋯O2$ of the N2H⋯O2 H-bond along the IRC of the wG·T ↔ wG*·T* tautomerisation via the DPT obtained at the MP2/6-311++G(d,p) level of theory in vacuo.

Figure 8. Profiles of the NBO charges of the hydrogen atoms involved in the N3H⋯O6/O6H⋯N3, N1H⋯O2/O2H⋯N1 and N2H⋯O2 H-bonds along the IRC of the wG·T ↔ wG*·T* tautomerisation via the DPT obtained at the MP2/6-311++G(d,p) level of theory in vacuo.
The established nine key points allow us to provide a separation of the pathway of the \( \text{wG} \cdot \text{T} \leftrightarrow \text{wG}^* \cdot \text{T}^* \) DPT tautomerisation into three distinct regions: the reactant, TS and product regions, separated by the key points 2 and 8, in which the extrema of the first derivative of the electron energy with respect to the IRC (or reaction force (Politzer et al., 2013)) are reached (Figures 1 and 2).

It was established that the reactant region, where structural changes such as bond stretching, angle bending and mutual adjustment of the bases within the \( \text{wG} \cdot \text{T} \) base pair, requiring 9.83 kcal mol\(^{-1}\) that constitutes 71.0% of the TS\( \text{wG} \cdot \text{T} \rightarrow \text{wG}^* \cdot \text{T}^* \) electronic energy relatively to the \( \text{wG} \cdot \text{T} \) base pair, take place to acquire such mutual deformation and orientation, that eventually lead to the DPT reaction, is located between the key points 1 (−11.60 Bohr) and 2 (−9.60 Bohr). The TS region, where the G and T bases lose their chemical individuality, structurally and electronically rearranging with the inter-molecular covalent bond breakages and formations, and where the DPT reaction actually occurs, is limited by the key points 2 (−9.60 Bohr) and 8 (−.27 Bohr). The product region, where the structural relaxation of the reaction complex starts to reach the final \( \text{wG}^* \cdot \text{T}^* \) base mispair, is located between the key points 8 (−.27 Bohr) and 9 (4.81 Bohr), releasing comparably small amount of the electronic energy (1.13 kcal mol\(^{-1}\)), that represents 8.2% of the TS\( \text{wG} \cdot \text{T} \rightarrow \text{wG}^* \cdot \text{T}^* \) electronic energy relatively to the \( \text{wG} \cdot \text{T} \) base pair. Observed data evidence that the substantial amount of energy is spent at the rebuilding and reorganisation of the G and T bases within the \( \text{wG} \cdot \text{T} \) base pair actually before the initiation of the chemical reaction, that is almost nine times larger than the energy used at the relaxation of the key point 8 to the final \( \text{wG}^* \cdot \text{T}^* \) base mispair.

Based on the data collected in Table 3, it can be seen that the tautomerised \( \text{wG}^* \cdot \text{T}^* \) base pair is dynamically
unstable structure (Brovarets’, Yurenko, et al., 2012), since the zero-point energy (3.53 kcal·mol⁻¹ or 1234.4 cm⁻¹) obtained at the MP2/6-311++G(d,p) level of QM theory of the corresponding vibrational mode, which frequency becomes imaginary at the TS_wG ↔ wG*·T base mispair. It has been shown that the intermolecular N3H···O6 (5.90)/O6H···N3 (8.86) and N1H···O2 (5.10)/O2H···N1 (11.02 kcal·mol⁻¹) H-bonds are cooperative, mutually reinforcing each other both in the wG·T/wG*·T° base mispairs, respectively. The total energy of the H-bonds in each base pair is noticeably smaller than the electronic energy of interaction between the G/G° and T/T° bases in the wG·T/wG*·T° base mispairs. The wG·T↔wG*·T° tautomerisation is assisted by the third N2H···O2 H-bond (1.64–2.22 kcal·mol⁻¹) from −4.28 to −2.7 Bohr.

Finally, we have arrived at the methodological deduction that B3LYP level of QM theory can be recommended for the description of the tautomerisation phenomena of the H-bonded nucleobase pairs (Danilov et al., 2009; Brovarets’ & Hovorun, 2010c, 2010d, 2010e), since it represents itself a reasonable compromise between accuracy and computational cost, allows to reach the same conclusions obtained at MP2 level of QM theory and therefore can be considered as the shortest way to MP2 results (Matta, 2010; Lozynski et al., 1998).

**Supplementary information**

Electron-topological, structural, vibrational and energetical characteristics of the intermolecular H-bonds revealed in the wG·T, wG*·T and TS_wG ↔ wG*·T° and polar characteristics of the latters obtained at the B3LYP/6-311++G(d,p) level of QM theory in vacuum; electron-topological and structural characteristics of the intermolecular H-bonds revealed in the nine key points and polar characteristics of the latters obtained at the B3LYP/6-311++G(d,p) level of QM theory in vacuum; energetical and kinetic characteristics of the wG·T ↔ wG*·T° tautomerisation via the DPT obtained at the different levels of QM theory for the geometry calculated at the B3LYP/6-311++G(d,p) level of QM theory in vacuum; electronic and Gibbs free energies of bases interactions within the wG·T and wG*·T° base mispairs obtained at the MP2/6-311++G(2df,pd)/B3LYP/6-311++G(d,p) level of QM theory in vacuum; sweeps of the electronic energy, the first derivative of the electronic energy with respect to the IRC, the dipole moment of the base pair, the distances and the angle of the intermolecular H-bonds, the electron density, the Laplacian of the electron density, the ellipticity and the energy at the (3,−1) BCPs of the intrapair H-bonds, the NBO charges of the hydrogen atoms involved in the intermolecular interactions.

**Concluding remarks**

It has been proved for the first time that the wG·T↔wG*·T° tautomerisation via the concerted asynchronous DPT does not generate mutagenic tautomer of the G base, because the tautomerised wobble DNA base mispair is dynamically unstable structure with extremely short lifetime (2.14×10⁻¹⁵ s) and is characterised by the significant negative value of the Gibbs free energy of the reverse barrier for the wG·T → wG*·T° tautomerisation (−2.31 kcal·mol⁻¹).

So, fundamentally important from the biological point of view issue of the intimate physico-chemical mechanisms of the mutagenic tautomerisation of the DNA bases in substantially hydrophobic base pair recognition pocket of DNA polymerase (see reference (Brovarets’, Yurenko, et al., 2012) and literature presented there) remains open. It can be regarded as a challenge for theory and experiment (Danilov & Kventsel, 1971).

It has been shown that the intermolecular N3H···O6 (5.90)/O6H···N3 (8.86) and N1H···O2 (5.10)/O2H···N1 (11.02 kcal·mol⁻¹) H-bonds are cooperative, mutually reinforcing each other both in the wG·T/wG*·T° base mispairs, respectively. The total energy of the H-bonds in each base pair is noticeably smaller than the electronic energy of interaction between the G/G° and T/T° bases in the wG·T/wG*·T° base mispairs. The wG·T↔wG*·T° tautomerisation is assisted by the third N2H···O2 H-bond (1.64–2.22 kcal·mol⁻¹) from −4.28 to −2.7 Bohr.

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and the glycosidic parameters (angles and distance between the glycosidic hydrogens) of the base mispair along the IRC of the wG·T ↔ wG··T· tautomerisation via the DPT obtained at the B3LYP/6-311++G(d,p) level of QM theory in vacuum. This material is available free of charge via the Internet at http://dx.doi.org/10.1080/07391102.2014.897259.

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