Wobble↔Watson-Crick tautomeric transitions in the homo-purine DNA mismatches: a key to the intimate mechanisms of the spontaneous transversions

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The intrinsic capability of the homo-purine DNA base mispairs to perform wobble↔Watson–Crick/Topal–Fresco tautomeric transitions via the sequential intrapair double proton transfer was discovered for the first time using QM (MP2/DFT) and QTAIM methodologies that are crucial for understanding the microstructural mechanisms of the spontaneous transversions.

Keywords: DNA biosynthesis; incorporation error; spontaneous transversion; Watson–Crick-like mispair; homo-purine mismatch; tautomeric transition; MP2 and B3LYP; QTAIM

Clarification of the incorrect DNA base pairs representing a primary cause of the spontaneous point mutations, and the way of their enzymatically competent conformation acquisition in the hydrophobic pocket of the high-fidelity replication DNA-polymerase in its closed conformation is central issue in the theory of these biologically important processes (Friedberg et al., 2006; von Borstel, 1994; Watson & Crick, 1953).

It was found out due to the recent advances in experimental and computational techniques that the root cause of the spontaneous point transitions is the formation of the enzymatically competent Watson–Crick (WC)-like G·T(WC) (Bebenek, Pedersen, & Kunkel, 2011) and A·C*(WC) (Wang, Hellinga, & Beese, 2011) DNA base pairs (here and below mutagenic tautomers (Furmanchuk, Isayev, Gorb, Shishkin, Hovorun, & Leszczyński, 2011; Samijlenko, Yureno, Stepanyugin, & Hovorun, 2012) are marked by the asterisks) in the recognition pocket of the high-fidelity DNA-polymerase in its closed conformational state. Moreover, it has been theoretically confirmed that these base pairs are formed by the DPT tautomerisation of the wobble (w) G·T(w) (Brovarets & Hovorun, 2015b) and A·C(w) (Brovarets & Hovorun, 2015e) mismatches without direct involvement of the endogenous water molecules. Furthermore, theoretical predictions for the G·T(w)↔G·T(WC) tautomerisation process have been completely confirmed experimentally (Kimsey, Petzold, Sathyamoorthy, Stein, & Al-Hashimi, 2015).

At the same time, progress in understanding of the microstructural mechanisms of the spontaneous transversions is constrained by the lack of experimental data on the enzymatically competent conformation of the incorrect purine-purine and pyrimidine-pyrimidine DNA base pairs in the recognition pocket of the high-fidelity DNA-polymerase in its closed conformational state at the site of incorporation (Brovarets & Hovorun, 2010, 2015a, 2015d). Such state of affairs actualizes theoretical, in particular model, quantum-chemical investigations.

Currently, atomic mechanisms of the spontaneous purine–purine transversions – replication errors – is more or less understandable. It is a widespread assumption that they are generated by the one and the same scenario: initially, the long A*·A(WC) (Brovarets’, Zhurakivsky, & Hovorun, 2013) and G·G*(WC) (Brovarets’ & Hovorun, 2014b) Watson–Crick DNA base pairs (on the left is the base that belongs to the template strand) are formed in the recognition pocket of the high-fidelity DNA-polymerase, thereafter these mispairs acquire enzymatically competent conformation, as a result of the rapid A*·A(WC)→A*·A syn(TF) and G·G*(WC)→G·G syn anti→syn conformational transitions (Brovarets’ & Hovorun, 2015c), respectively. In its turn, the A*·A syn(TF) (Brovarets’, Zhurakivsky, & Hovorun, 2014; Topal & Fresco, 1976) and G·G syn Brovarets’ & Hovorun, 2014a base pairs, especially first of them – Topal–Fresco (TF) base pair, quite easily acquire characteristic geometrical dimensions of the classical A·T(WC) and G·C(WC) Watson–Crick DNA base pairs during thermal fluctuations (Brovarets’ & Hovorun, 2014a), that eventually guarantees their chemical incorporation into the structure of the DNA double helix that is synthesized.

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The aim of our study was to establish the most probable process of the origin of the spontaneous purine–purine transversions – incorporation errors.

Key idea of this work consists in the fact that, in this case, the A*·A(WC) and G·G*(WC) base pairs – intermediates on the way of the formation of the enzymatically competent conformations of the incorrect purine-purine pairs – arise as a result of the DPT tautomomerisation of the corresponding A·A(w) and G·G(w) mismatches, that is the limiting stage of the origin of the point mutations of this type.

All geometric, energetic, and vibrational calculations of the considered base mispairs and transition states (TSs) of their conversion have been performed by Gaussian’09 package (Frisch et al., 2010) using B3LYP (Tirado-Rives & Jorgensen, 2008) and MP2 (Frisch, Head-Gordon, & Pople, 1990) levels of theory combined with a wide variety of basis sets. Bader’s quantum theory of Atoms in Molecules was applied to analyze the electron density distribution (Bader, 1986; Lecomte, Espinosa, & Matta, 2015; Matta, 2014) (for more details see Supplementary Material).

In the current work, we have found out for the first time that A*·A(WC) (Brovarets’ et al., 2013) and G·G* (WC) (Brovarets’ & Hovorun, 2014b) mispairs are connected by the intrapair tautomeric transition through the successive DPT with the A·A(w) and G·G(w) mismatches, respectively. Our quantum-chemical simulations have shown that these conversions, which are crucial for understanding the nature of the purine–purine transversions, are carried out through the non-dissociative mechanism via the highly stable, highly polar, and zwiterionic TSs that are electroneutral tight ion pairs such as protonated base–deprotonated base. Consequently, it has been elucidated that the A·A(w)↔A*·A(WC) tautomeric transition is much faster ($\tau_{99.9\%} = 4.39 \times 10^4$ s), than the G·G(w)↔G·G*(WC) transition ($\tau_{99.9\%} = 5.03 \times 10^7$ s). Dynamical behavior of these mispairs correlates well with the experimental data, showing significantly higher frequency for the AA, than for the GG spontaneous transversions (Huang, Arnheim, & Goodman, 1992; Perrino & Loeb, 1989), and also significantly lower frequencies of these transversions in comparison with the spontaneous transitions (Lee, Popodi, Tang, & Foster, 2012; Lynch, 2010).

We have shown here for the first time that wrong pairs involving A base (electronic structure of the A base allows formation of only three pairs – A·A(w), A·A_syn(w), and A·A_syn(TF), which glycosidic bonds are in the syn-orientation relatively to each other (DeCarlo, Gowda, Suo, & Spratt, 2008; Kretulskie & Spratt, 2006), can switch via the sequential DPT either directly into the A*·A_syn(TF) mispair, or into the A*·A(WC) mismatch (Figure 1 and Table 1). All these processes are controlled by the highly stable, highly polar, and zwiterionic TSs, representing itself electroneutral tight ion pairs (Supplementary Figures S1, S2 and Supplementary Tables S1, S2, S6). Strong electrostatic interaction between the protonated and deprotonated bases in the TSs of the tautomomerization reaction (>100 kcal mol$^{-1}$ (Supplementary Table S7)) is a characteristic peculiarity of these reactions (Brovarets’ & Hovorun, 2015a, 2015b, 2015d, 2015e). All three A·A(w)↔A*·A(WC), A·A_syn(w)↔A*·A_syn(TF), and A·A_syn(w)↔A*·A_syn(TF) tautomomerization processes proceeding via the sequential DPT occur by the non-dissociative mechanism (Supplementary Figures S1, S2 and S7) – pairs, which tautomere, considerably change their geometry from wobble to Watson–Crick and vice versa without breakage. In particular, the fastest A·A(w)↔A*·A (WC) tautomomerization process ($\tau_{99.9\%} = 4.39 \times 10^4$ s) is accompanied by the 10 patterns of the intermolecular interactions, which include as AH⋯B H-bonds, so loosened A–H–B covalent bridges (Supplementary Figure S3 and Supplementary Table S3). We give preference exactly to this tautomomerization reaction involving A·A(w) mispair, that was observed in the double-stranded DNA under physiological conditions.

Figure 1. Structures of the stationary points of the (a) A·A (w)↔A*·A(WC), (b) A·A_syn(w)↔A*·A_syn(TF) and (c) A·A_syn(w)↔A*·A_syn(TF) conversions via the sequential DPT obtained at the B3LYP/6-311++G(d,p) level of theory. Dotted lines indicate AH⋯B H-bonds (their lengths H⋯B are presented in angstroms); carbon atoms are in light-blue, nitrogen – in dark-blue and hydrogen – in gray; $\nu_i$ – value of the imaginary frequency.
Table 1. Energetic (in kcal·mol⁻¹) and kinetic (in s) characteristics of the considered tautomerizations via the sequential DPT obtained at the MP2/cc-pVQZ/B3LYP/6-311++G(d,p) level of theory (see also Figures 1 and 2).

| Transitions                      | ΔG°   | ΔE°   | ΔΔG_TS° | ΔΔE_TS° | ΔΔG^d  | ΔΔE^d  | τ_99.9%<sup>8</sup> |
|----------------------------------|-------|-------|---------|---------|---------|---------|---------------------|
| A·A(w)→A·A*(WC)                 | 4.18  | 1.64  | 26.89   | 23.59   | 22.71   | 21.94   | 4.39 × 10⁴        |
| A·A_syn(TF)→A·A*·A_syn(TF)       | 4.35  | 3.02  | 29.39   | 25.99   | 25.04   | 22.97   | 2.23 × 10⁴        |
| A·A_syn(TF)→A·A*·A_syn(TF)       | 5.82  | 4.79  | 31.34   | 28.47   | 25.53   | 23.68   | 5.75 × 10⁵        |
| G·G*(WC)→G·G*(w)                | 5.00  | 7.14  | 13.94   | 15.17   | 8.94    | 8.03    | 3.98 × 10⁻⁶       |
| G·G*·G*·G*(WC)→G·G*(w)          | 4.96  | 6.75  | 31.77   | 32.83   | 26.81   | 26.08   | 5.03 × 10⁷        |

<sup>a</sup>The Gibbs free energy of the product relatively the reactant of the tautomerization reaction (T = 298.15 K).
<sup>b</sup>The electronic energy of the product relatively the reactant of the tautomerization reaction.
<sup>c</sup>The Gibbs free energy barrier for the forward reaction of tautomerization.
<sup>d</sup>The electronic energy barrier for the forward reaction of tautomerization.
<sup>e</sup>The Gibbs free energy barrier for the reverse reaction of tautomerization.
<sup>f</sup>The electronic energy barrier for the reverse reaction of tautomerization.
<sup>g</sup>The time necessary to reach 99.9% of the equilibrium concentration between the reactant and the product of the tautomerization reaction.

(Rossetti et al., 2015) in view of its biological role in the occurrence of the spontaneous point mutations (see discussion below).

In the free state, the planar A·A(w) mispair stabilised by two antiparallel N6H⋯N1 (4.88) and C2H⋯N1 (1.52 kcal·mol⁻¹) H-bonds (Supplementary Table S1) has pseudo-twofold symmetry. These symmetrical states of the A·A(w) mismatch are linked with each other by the tautomeric transition (Supplementary Figure S8), that must be experimentally observed also in the DNA double helix (however, in this case the pseudo-twofold symmetry, strictly speaking, is disturbed (Rossetti et al., 2015)).

We have elucidated for the first time (Figure 2 and Table 1, Supplementary Figures S4, S5 and Supplementary Tables S1, S4) that the G·G*(WC) mispair (Brovarets’ & Hovorun, 2014b) simultaneously takes part in two different tautomerization processes through the consistent DPT – slow G·G*(w)→G·G*(WC) (τ_99.9% = 5.03 × 10⁷ s) and fast G·G*(w)→G·G*·G*(w) (τ_99.9% = 3.98 × 10⁻⁶ s) reactions. Both of these biologically important processes (see discussion below) are governed by the highly stable, highly polar, and zwitterionic TSs (Supplementary Tables S1, S6 and S7), stabilised by the participation of the maximally five different intermolecular H-bonds, in addition to the strong electrostatic interactions. These tautomerization pathways are realised by the non-dissociative mechanism (Supplementary Figure S9), and are controlled by the 10 and 12 patterns of the specific intermolecular interactions, respectively, successively replacing each other along the IRC during the tautomerization of the pairs (Supplementary Figure S6 and Supplementary Table S5).

In the free state, we firstly reported in this work that the G·G*(w) and G·G*·G*(w) mismatches possess pseudo-twofold symmetry. Calculations show that symmetrical states of these pairs are interconverted by the tautomeric transitions (Supplementary Figures S10 and S11) that should be also realized for them in the DNA duplex.

Characteristic peculiarity of the structures involved in the tautomerization of the irregular G·G homo-pairs, except planar G·G*(w) pair is their essential non-planarity (Supplementary Figures S4, S12, S13 and Supplementary Table S8). In order to verify whether this is hindrance or not for their incorporation into the DNA double helix (Jissy & Datta, 2014), we have examined in detail the structural non-rigidity of these complexes with quantum geometry, in particular energetic and kinetic properties of the conformational interconversions of their mirror-symmetric enantiomers (Supplementary Figures S12, S13 and Supplementary Table S8).

It turned out that all these conformational transformations are carried out through the plane-symmetric transition states, furthermore, their energetic and kinetic characteristics evidence in favor of the more or less successful adaptation of the structures depicted in Supplementary Figure S4 into the DNA double helix.

Figure 2. Structures of the stationary points of the (a) G·G*(WC)→G·G*·G*(w) and (b) G·G*(WC)→G·G*(w) conversions via the sequential DPT obtained at the B3LYP/6-311++G(d,p) level of theory. For designations see Figure 1; oxygen atoms are in red.
Finally, we would like to note that the revealed routes of the G*·G*(w) ↔ G·G*ₙ₂·G(w) and G·G*ₙ₂·G(w) ↔ G*·G*ₙ₁₃(w) tautomerizations do not realize: for them $\Delta \Delta G < 0$ and short-lived G*ₙ₂·G(w) and G*·G*ₙ₁₃(w) complexes are dynamically unstable (Supplementary Figures S14, S15 and Supplementary Table S9).

Biological significance of our results concerns fundamental mechanisms of the spontaneous transversions, namely incorporation errors. There are all grounds to believe that spontaneous point AA incorporation errors arise in accordance with the following microstructural scenario. This process begins with the formation of the incorrect A·A(w) homo-pair in the significantly hydrophobic (Brovarets’, Yurenko, Dubey, & Hovorun, 2012; Yang et al., 2014) recognition pocket of the high-fidelity DNA-polymerase. The acquisition process of this mispair of the enzymatically competent conformation, which guarantees its chemical incorporation into the structure of the DNA double helix that is synthesized, includes two stages – a slow (limitative) and fast (final). The kinetically controlled A·A(w) → A*·A(WC) tautomeration process via the sequential DPT is the limitative stage; the next fast stage – anti→syn conformational conversion of the A*·A(WC) base pair into the well-known A*·Aₛₚₚ(TF) pair (Brovarets’ & Hovorun, 2015c; Brovarets’ et al., 2014; Topal & Fresco, 1976), which quite easily acquires standard Watson–Crick sizes in the process of thermal fluctuations (Brovarets’ & Hovorun, 2014a).

Spontaneous point GG incorporation errors are formed by a similar scheme, which represents a chain of the following successive events: formation of the G·G(w) base mispair in the recognition pocket of the high-fidelity DNA-polymerase → kinetically controlled tautomeration of the G·G(w) base mispair into the G·G*(WC) mismatch through the sequential DPT → fast anti→syn conformational conversion of the G·G*(WC) pair into the G·G*ₛₛₚₚ(w) mismatch (Brovarets’ & Hovorun, 2014a, 2015c) → acquisition by the latter of the enzymatically competent Watson–Crick sizes during thermal fluctuations (Brovarets’ & Hovorun, 2014a). The slowness of these two scenarios in comparison with the time $\Delta t_{pd} \approx 8.3 \times 10^{-4}$ s (Kimizialtin, Nguyen, Johnson, & Elber, 2012), that DNA-polymerase spends for the incorporation of the single correct incoming nucleotide into the structure of the DNA double helix that is synthesized, determines the low frequencies of the AA and GG incorporation errors as thermodynamically non-equilibrium processes.

In the first approximation, frequencies of these spontaneous transversions would be determined by the probability of the acquisition by the wobble pairs of the Watson–Crick-like geometry (Brovarets’ & Hovorun, 2015b, 2015e). It could be easily estimated (Podolyan, Gorb, & Leszczynski, 2003), taking into account that $k_f = 1.38 \times 10^{-7}/k_r = 1.57 \times 10^{-4}$ s⁻¹ for the A·A (w) → A*·A(WC) tautomeration, $k_f = 3.15 \times 10^{-11}/k_r = 1.37 \times 10^{-7}$ s⁻¹ for the G·G(w) → G·G*(WC) tautomeration, and the time for the incorporation of the wrong incoming nucleotide $(8.3 \times 10^{-3}$ s) exceeds approximately by the order (Kimizialtin et al., 2012; Sun, Cukier, & Bu, 2007) the similar value for the correct pairing (Kimizialtin et al., 2012): $2.6 \times 10^{-9}$ and $2.6 \times 10^{-13}$, respectively. Despite the maximum simplicity of this model, it satisfactorily explains experimental data, namely – significantly higher frequency for the AA, than for the GG spontaneous transversions (Huang et al., 1992; Kunkel & Alexander, 1986; Perrino & Loeb, 1989), and also significantly lower frequencies of these transversions in comparison with the spontaneous transitions (Lee et al., 2012; Lynch, 2010).

It could be assumed that the biological significance of the very rapid $(k_f = 3.98 \times 10^{-6}$ s) G·G* (WC) ↔ G·G*(w) tautomeric transformation touches the process of the recognition of the irregular G·G*(WC) pair by the reparation systems (Cho, Han, & Ban, 2008; Dohet, Wagner, & Radman, 1985; Joseph, Duppatla, & Rao, 2005), “sharened” exactly for the wobble configuration of the incorrect pairs. It is not excluded that these mismatch repair proteins induce transition of the G·G*(WC) pair from the Watson–Crick-like to wobble G·G*ₚₚ(w) configuration, which they recognize and remove from the genome (Aleman, de Silva, Patrick, Musier-Forsyth, & Rueda, 2014; Tsai, 2014; Xia, Wang, & Konigsberg, 2013).

By summing up, we arrive to the biologically important conclusion that the A*·Aₛₚₚ(TF) and G·G*ₛₛₚₚ mispairs are responsible for the occurrence of both spontaneous point incorporation and replication errors, since in both cases the acquisition processes of the enzymatically competent conformation pass through the joint intermediates – the A*·A(WC) and G·G*(WC) mismatches, which, figuratively speaking, play the role of the “node stations” in both these processes.

We have revealed for the first time the w→WC/TF tautomeric transitions of the A·A and G·G homo-pairs and determined their energetic and kinetic characteristics. These findings are principal for the understanding of the microstructural mechanisms of the spontaneous purine-purine transversions and lay down foundations for the searching and recognizing the incorrect base pairs by the mismatch repair proteins in order to maintain genome integrity.

We believe that consideration of the influence of the microstructural environment of the hydrophobic recognition pocket of the high-fidelity replication DNA-polymerase on the energetics and kinetics of the A·A (w) → A*·A(WC) and G·G(w) → G·G*(WC) tautomeric transformations, and also experimental fixation of the incorrect A*·Aₛₚₚ(TF) and G·G*ₛₛₚₚ mispairs in the
hydrophobic recognition pocket of the high-fidelity replicative DNA-polymerase in its closed conformation (Bebenek et al., 2011; Wang et al., 2011) would be the most important and promising lines of this work development.

Notably, this theoretical study provides a stimulus for setting up the new biologically important experiments and application of the modified DNA purine bases that exert mutagenic effect in synthetic biology (Ryadnov,Brunsveld, & Suga, 2014).

**Supplementary material**

The supplementary material for this paper is available online at: http://dx.doi.org/10.1080/07391102.2015.1077737: (i) Computational details; (ii) Structures of the investigated complexes; (iii) Energetic and kinetic characteristics of the mispairs tautomerisation; (iv) Physico-chemical parameters of the intermolecular H-bonds; and (v) Profiles of the energetic and geometric parameters of the tautomerisation.

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