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Renaissance of the Tautomeric Hypothesis of the Spontaneous Point Mutations in DNA: New Ideas and Computational Approaches

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Abstract

In this chapter, we formulate basic physico-chemical principles that define the micro-structural nature of the origin of the spontaneous incorporation and replication point errors—transitions and transversions—arising during DNA biosynthesis. At this point, we relied on the firstly discovered ability of the DNA base mispairs to tautomerize *via* the sequential intrapair proton transfer and highly stable, highly polar, zwitterionic transition states, accompanied by a significant shifting of the base mispairs toward DNA minor or major grooves. These tautomeric transitions are characterized by a change in geometry—from wobble to Watson-Crick and *vice versa*—of the purine·pyrimidine (A·T, G·C, G·T and A·C), purine·purine (A·A, A·G and G·G) and pyrimidine·pyrimidine (C·C, C·T and T·T) DNA base mispairs. Reported results allow us to explain, on one side, the origin of the mutagenic tautomers at the separation of the DNA strands before replication and, on the other side, how DNA base mispairs adapt to enzymatically competent size in the tight recognition pocket of the high-fidelity DNA polymerase.

Keywords: tautomeric hypothesis, spontaneous and induced point mutations in DNA, incorporation and replication point errors, mutagenic tautomerization, pairs of nucleotide bases, enzymatically competent conformation, DNA polymerase, DNA replication, hydrogen bond, van der Waals contact, quantum chemistry, Bader's quantum theory of atoms in molecules (QTAIM)

1. Introduction

High-fidelity DNA replication is a central issue in molecular biology [1]. During DNA replication, spontaneous point mutations [2–4] arise with frequencies $10^{-9} \div 10^{-11}$ [5–8] in functioning of living cells.

Nowadays, it is reliably known that the root cause of the origin of the spontaneous point mutations is the formation in the very tight, slightly deformable base pair recognition pocket of the high-fidelity DNA polymerase in its close state of the “wrong” DNA base pairs (i.e., mismatches) able to acquire in the process of thermal fluctuations the conformation of the correct Watson-Crick DNA base pair (i.e., enzymatically competent conformation), which guarantees their incorporation into the chemical structure of the synthesized DNA double helix [4].

In the literature, two approaches are currently presented, according to physico-chemical principles of the occurrence of the mispairs leading to spontaneous point mutations in DNA. One of them is the “tautomeric hypothesis” suggested by J. Watson and F. Crick [9], which consists in the spontaneous tautomeric transition of the DNA bases from canonical to mutagenic tautomeric forms leading to the formation of the adenine-cytosine ($A \cdot C^*$)/ $A^* \cdot C$ and guanine-thymine ($G^* \cdot T$)/ $G \cdot T^*$ (here and below, mutagenic tautomers are marked with asterisk) Watson-Crick-like mispairs with correct enzymatically competent conformation [10] containing mutagenic tautomers [11–13]. Despite great advances in experimental, in particular X-ray analysis [14, 15], NMR, in particular relaxation dispersion measurements [11–13, 16–18], and theoretical [19–21] investigations, there is no unique approach to the physico-chemical mechanisms enabling DNA bases in the canonical tautomeric form to acquire rare or mutagenic tautomeric form before the dissociation of the Watson-Crick nucleobase pairs into the monomers by the replication machinery in order to produce mispairs resulting in further misincorporations and as a result the spontaneous point mutations at the DNA replication. It is generally accepted in the literature that mutagenic tautomers of the DNA bases can arise *via* the double proton transfer (DPT) along intermolecular H-bonds in the Watson-Crick [22–25] and wobble [26] base pairs, and also in the protein-DNA complexes [27]. However, some authors also consider as the source of the origin of the spontaneous transitions the formation of the ionized DNA base pairs [28].

On contrary, according to second approach, other researchers believe that spontaneous point mutations arise due to the formation of the incorrect base pairs involving only DNA bases in the main, canonical tautomeric form—so-called wobble or shifted A-C and G-T base pairs [29, 30]. However, the mechanisms of their adaptation to the enzymatically competent sizes in the very tight, slightly deformable base pair recognition pocket of the high-fidelity DNA polymerase remain unclear [30, 31].

The common feature of these approaches is the absence of the general physico-chemical theory according the nature of these mispairs causing spontaneous point mutations, and the emergence of each of them is considered as a unique phenomenon. In the literature, there are no attempts or ideas aimed at combining these approaches into a unique, internally noncontradictory conception. Nevertheless, creation of such a microstructural theory is an interdisciplinary challenge with fundamental and applied consequences.

Thus, without clear understanding of basic mechanisms of the origin of spontaneous point mutations [32–34], it is difficult to develop a management strategy of genome instability and produce physico-chemical explanations of evolution [35, 36]; to design highly efficient mutagens—analogs of the nucleotide bases with targeted action for different purposes, in particular, for antiviral and anticancer therapy [37, 38]; to essentially increase precision of DNA-based nanodevices of biomolecular electronics as information carriers [39, 40]; to create synthetic macromolecular structures able to replicate with predetermined accuracy [41] and so on.

Here, we aim to reveal at the microstructural level the molecular grounds of intrinsic DNA mutability without involvement of external agents.

2. Computational methods

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 [42] using B3LYP [43, 44] and MP2 [45] levels of quantum-mechanical (QM) theory combined with a wide variety of basis sets followed by the intrinsic reaction coordinate (IRC) calculations in the forward and reverse directions from each TS using Hessian-based predictor-corrector integration algorithm [46] in vacuum and in the continuum with $\epsilon = 4$, which is characteristic for the active center of the DNA polymerase [47, 48]. Bader's quantum theory of Atoms in Molecules (QTAIM) was applied to analyze the electron density distribution [49]. Physico-chemical parameters have been estimated by the known formulas of physico-chemical kinetics [50].

3. Results and discussion

3.1. Classical mechanisms of DNA base tautomerization *via* DPT along two intermolecular H-bonds in H-bonded complexes

We established from the physico-chemical point of view that the generally accepted mechanism of the DPT along intermolecular H-bonds [22–29] cannot be the source of formation of mutagenic tautomers of DNA bases in the A·T(WC) and G·C(WC) Watson-Crick (so-called Löwdin's mechanism) [51–53] and G·T(w) wobble [54] base pairs, and also in the $m^1\text{T}\cdot\text{CH}_3\text{COOH}$, $m^9\text{A}\cdot\text{CH}_3\text{COOH}$, $m^1\text{C}\cdot\text{CH}_3\text{COOH}$ and $m^9\text{G}\cdot\text{CH}_3\text{COOH}$ complexes by the participation of DNA bases and side chains of the amino acids (m-methyl group) [55].

At this point, the A*·T* Löwdin's base pair is dynamically unstable and has a lifetime that is 6 orders of magnitude less than the characteristic time spent by DNA polymerase on the forced dissociation of the DNA base pairs into the bases ($\sim 10^{-9}$ s [32, 51, 52]). The short-lived G*·C* Löwdin's base pair escapes the DNA polymerase. The other final tautomerized complexes containing mutagenic tautomers of DNA bases are dynamically unstable: the value of the zero-point energy of the corresponding vibrational mode, in which frequency becomes imaginary at the transition state, is higher than the value of the reverse barrier (**Table 1**).

Tautomeric transition	ΔG^a	ΔE^b	$\Delta\Delta G_{TSy}^c$	$\Delta\Delta E_{TS}^d$	$\Delta\Delta G^e$	$\Delta\Delta E^f$	τ^g
MP2/aug-cc-pVTZ//MP2/6-311++G(d,p)							
A·T \leftrightarrow A*·T* [51–53]	11.95	12.26	10.29	12.40	-1.66	0.14	6.5×10^{-15}
G·C \leftrightarrow G*·C* [52]	9.22	8.22	9.69	13.28	0.47	5.06	1.6×10^{-13}
MP2/cc-pVQZ//MP2/6-311++G(d,p)							
G·T \leftrightarrow G*·T* [54]	11.78	12.12	9.47	12.58	-2.31	0.46	2.1×10^{-15}
MP2/6-311++G(3df,2pd)//M05/6-311++G(2df,pd)							
m ¹ T·CH ₃ COOH \leftrightarrow m ¹ T*·CH ₃ COOH [55]	5.63	6.48	7.24	10.45	1.60	3.97	1.9×10^{-12}
m ⁹ A·CH ₃ COOH \leftrightarrow m ⁹ A*·CH ₃ COOH [55]	8.21	7.23	6.68	8.52	-1.53	1.29	6.1×10^{-15}
m ¹ C·CH ₃ COOH \leftrightarrow m ¹ C*·CH ₃ COOH [55]	3.35	2.91	6.12	7.43	2.77	4.52	1.6×10^{-11}
m ⁹ G·CH ₃ COOH \leftrightarrow m ⁹ G*·CH ₃ COOH [55]	1.93	2.75	2.08	5.96	0.15	3.21	1.0×10^{-13}
MP2/cc-pVQZ//B3LYP/6-311++G(d,p)							
A·A* \leftrightarrow A*·A [65]	0.00	0.00	7.01	10.33	7.01	10.33	1.8×10^{-8}
A·G \leftrightarrow A*·G* [56]	10.07	9.58	9.63	11.46	-0.44	1.88	4.8×10^{-14}
G·G* \leftrightarrow G*·G [66]	0.00	0.00	5.51	8.33	5.51	8.33	8.2×10^{-10}
A·C* \leftrightarrow A*·C [57]	3.99	3.64	8.17	10.53	4.18	6.89	1.1×10^{-10}
G*·T \leftrightarrow G·T* [58]	1.22	1.19	2.63	5.61	2.63	5.61	8.1×10^{-13}
C·C* \leftrightarrow C*·C [64]	0.00	0.00	8.28	10.83	8.28	10.83	1.5×10^{-7}
C·T \leftrightarrow C*·T* [59]	9.15	8.99	9.55	11.38	0.40	2.39	2.1×10^{-13}
T·T* \leftrightarrow T*·T [63]	0.00	0.00	4.64	8.18	4.64	8.18	1.6×10^{-10}
G·G* _{syn} \leftrightarrow G*·G* _{syn} [60]	11.02	11.15	9.07	12.17	-1.96	1.02	4.1×10^{-15}
A*·A _{syn} \leftrightarrow A·A* _{syn} [61]	13.98	14.71	14.15	16.43	0.16	1.72	1.1×10^{-13}
A*·G* _{syn} \leftrightarrow A·G* _{syn} [62]	1.89	2.20	2.42	4.60	0.52	2.40	2.2×10^{-13}

^aThe Gibbs free energy of the product relatively the reactant of the tautomerization reaction (T = 298.15 K).

^bThe electronic energy of the product relatively the reactant of the tautomerization reaction.

^cThe Gibbs free energy barrier for the forward reaction of tautomerization.

^dThe electronic energy barrier for the forward reaction of tautomerization.

^eThe Gibbs free energy barrier for the reverse reaction of tautomerization.

^fThe electronic energy barrier for the reverse reaction of tautomerization.

^gThe lifetime of the product of the tautomerization reaction.

Table 1. Energetic (kcal·mol⁻¹) and kinetic (in s) characteristics of the tautomeric transformations of the canonical Watson-Crick, wobble, model protein-DNA complexes, incorrect long, short and Watson-Crick-like mispairs of nucleotide bases *via* the DPT along the neighboring intermolecular H-bonds in vacuum.

3.2. Can mutagenic tautomers of the DNA bases be formed *via* the DPT in Watson-Crick-like mispairs?

Further, we investigated the physico-chemical mechanisms of the DNA bases tautomerization through the DPT along intermolecular H-bonds of incorrect DNA base pairs.

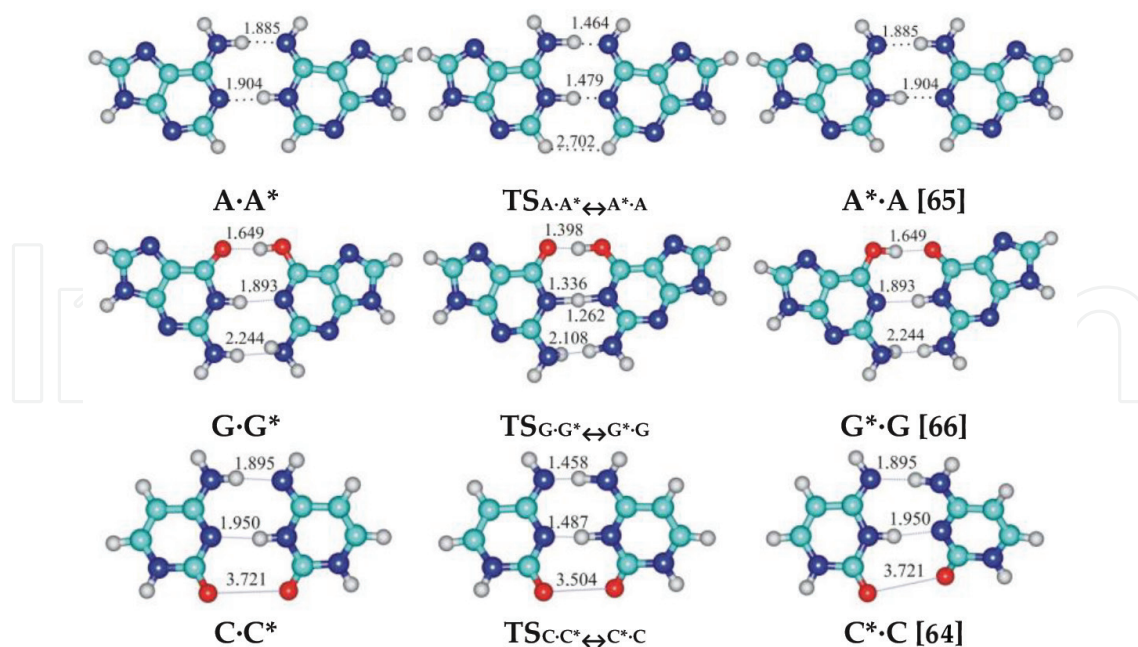


Figure 1. Geometrical structures of the three stationary structures (reagent, transition state and product) describing the progression of the tautomerization *via* DPT along intermolecular H-bonds in some mispairs (B3LYP/6–311++G(d,p) level of theory, $\epsilon = 1$).

It was established that the $A \cdot G \leftrightarrow A^* \cdot G^*$ [56], $A \cdot C^* \leftrightarrow A^* \cdot C$ [57], $G^* \cdot T \leftrightarrow G \cdot T^*$ [58], $C \cdot T \leftrightarrow C^* \cdot T^*$ [59], $G \cdot G^*_{\text{syn}} \leftrightarrow G^* \cdot G^*_{\text{syn}}$ [60], $A^* \cdot A_{\text{syn}} \leftrightarrow A \cdot A^*_{\text{syn}}$ [61] and $A^* \cdot G^*_{\text{syn}} \leftrightarrow A \cdot G^*_{\text{syn}}$ [62] tautomerization processes occur without changing the tautomeric status of the initial DNA base pairs, since the terminal, tautomerized base pairs are dynamically unstable: low-frequency intermolecular vibrations cannot develop during their lifetime (**Figure 1**, **Table 1**). Hence, these transformations do not generate mutagenic tautomers.

During the tautomerization of the dynamically stable short $T \cdot T^*$ [63] and $C \cdot C^*$ [64] mispairs, as well as long $A \cdot A^*$ [65] and $G \cdot G^*$ [66] mispairs, mutagenic tautomers are distributed among the monomers with equal probability. This is important for understanding the consolidation of point mutations in subsequent rounds of DNA replication (**Figure 1**, **Table 1**). Short-lived, low-populated $A^* \cdot C$ and $G \cdot T^*$ mispairs are “providers” of the long-lived enzymatically competent $A \cdot C^*$ [57] and $G^* \cdot T$ base pairs [58], respectively, at the origin of the replication errors in DNA. Moreover, comparisons between calculated distances of intermolecular H-bonds with data from X-ray experiments [14, 15] show that incorrect $A \cdot C$ and $G \cdot T$ base pairs with Watson-Crick geometry occur in the $A \cdot C^*$ and $G^* \cdot T$ tautomeric forms in the active center of the high-fidelity DNA polymerase in its closed state.

Transition from vacuum to continuum with $\epsilon = 4$, characteristics for the hydrophobic interfaces of the protein-DNA complexes, does not significantly influence the course of these tautomerization reactions and does not change the character of the obtained conclusions and generalizations.

Obtained data evidence that tautomeric hypothesis faces significant obstacles that could not be overcome without going beyond the classical framework that mutagenic tautomers of nucleotide bases are generated in the complexes by DPT protons along neighboring intermolecular H-bonds.

3.3. Novel mechanisms of the wobble (w)↔Watson-Crick (WC) tautomeric interconversions in the canonical and incorrect DNA base pairs as a key to understand origins of spontaneous transitions and transversions

For the first time, a novel theoretical approach to elucidate microstructural mechanisms of incorporation and replication point errors arising at the DNA replication was proposed. We show for the first time that pairs of nucleotide bases with Watson-Crick architecture of the H-bonding—classical, long, short, in which one or both bases are in the main or rare tautomeric forms, are in a slow tautomeric equilibrium with the corresponding wobble base pairs in comparison with the time, in which high-fidelity DNA polymerase spends on the incorporation of one nucleotide into the DNA double helix ($\sim 8.3 \times 10^{-4}$ s [67]). In fact, a novel pathway of the chemical reaction was discovered—tautomerization with significant changes of the geometry of the base pair—from Watson-Crick to wobble and *vice versa*.

We have discovered novel structural hypostases of the classical A·T(WC) and G·C(WC) Watson-Crick DNA base pairs arising due to their ability to switch into the wobble A*·T↑(w), A·T*_{O2}↑(w), A·T*↓(w) and G·C*↑(w), G*·C↓(w), G·C*↓(w), G*·C↑(w) H-bonded mismatches containing rare tautomers (**Figure 2**) [68]. Estimated populations of the tautomerized states of the A·T(WC) (6.1×10^{-9} – 1.5×10^{-7}) and G·C(WC) (4.2×10^{-11} – 1.4×10^{-9}) base pairs in the continuum with $\epsilon = 4$ correspond to the interface of the protein-nucleic acid interactions. This evidences their involvement in nucleation of spontaneous point replication errors in DNA arising with frequencies $\sim 10^{-11}$ – 10^{-9} errors *per* replicated nucleotide.

We found for the first time the intrinsic ability of the purine-pyrimidine (A·C [69, 70] and G·T [69, 71]), purine-purine (A·A [72], G·G [72] and A·G [73]) and pyrimidine-pyrimidine (C·C [74], T·T [74] and C·T [73]) DNA base mismatches to perform wobble↔Watson-Crick tautomeric transitions *via* the sequential intrapair DPT and subsequent shifting of the bases relative to each other (**Figure 3, Table 2**). These nondissociative tautomerizations *via* the sequential PT are controlled by the highly stable ($\Delta E_{\text{int}} > 100$ kcal·mol⁻¹), highly polar and zwitterionic transition states of the type (protonated base)·(deprotonated base). These interconversions are accompanied by a significant rebuilding of the base mismatches with Watson-Crick architecture into the mismatches wobbled toward both DNA minor and major grooves and *vice versa*.

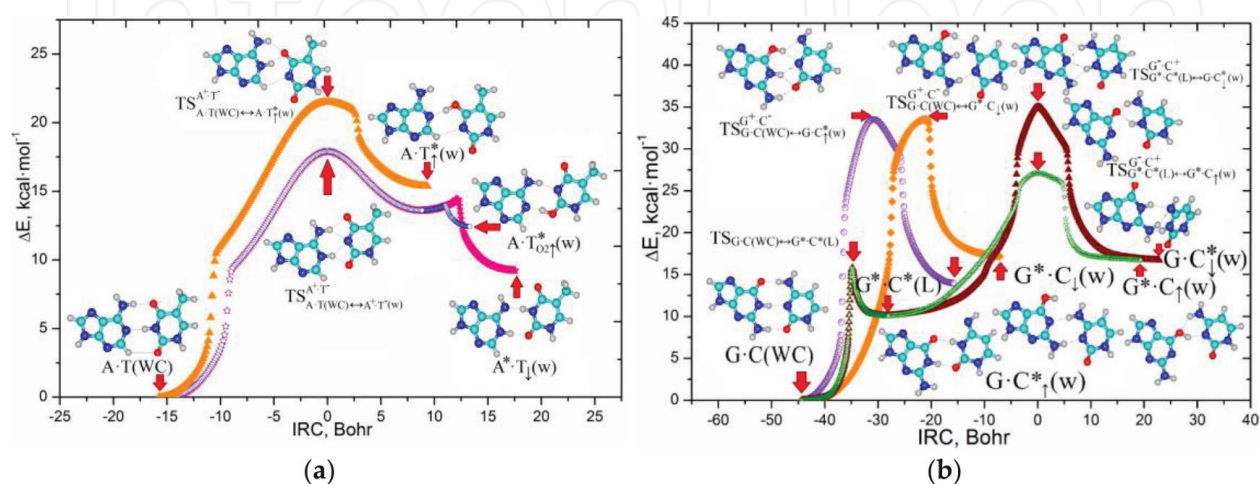


Figure 2. Energetic profiles of the mutagenic tautomerization *via* the wobbling of the (a) A·T(WC) and (b) G·C(WC) DNA base pairs to the H-bonded mismatches containing rare tautomers (B3LYP/6-311++G(d,p) level of theory, $\epsilon = 1$) [68].

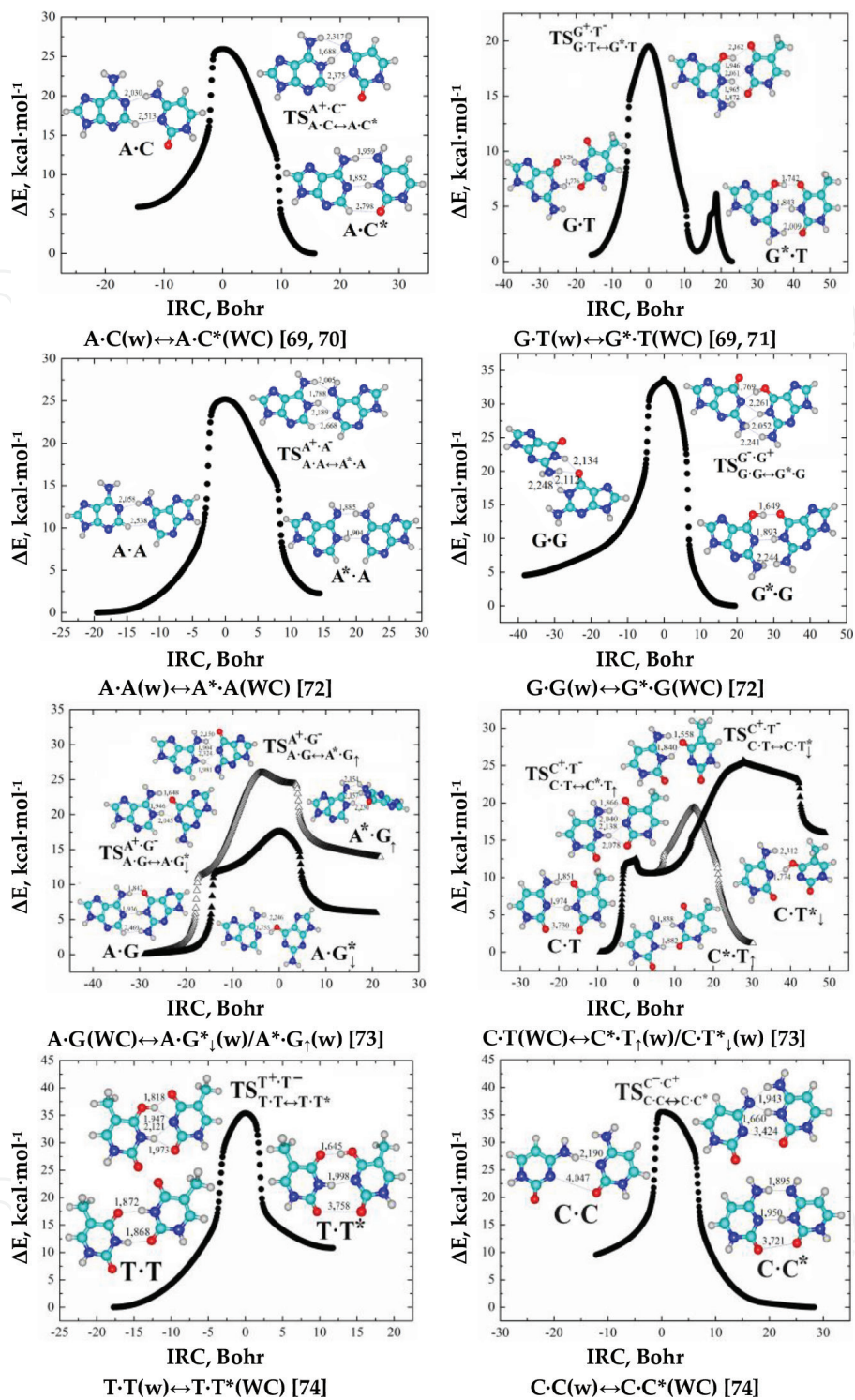


Figure 3. Energetic profiles and stationary structures on the potential energy hypersurface of the biologically important transformations *via* the PT, accompanied by the shifting of the bases relative to each other within a base pair into the sides of the DNA minor or major grooves, leading to the occurrence of the spontaneous transitions and transversions—incorporation and replication errors (B3LYP/6–311+G(d,p) level theory, $\epsilon = 1$).

Notably, each of the discussed tautomerizations is realized precisely through four different topological and energetic pathways. The number of mobile protons (two in each pair) and number of wobbling directions of WC base pairs (two by the number of the grooves in DNA—minor and major) determines the number of tautomerization pathways. Characteristically, in

Tautomeric conversion	ΔG	ΔE	$\Delta\Delta G_{TS}$	$\Delta\Delta E_{TS}$	$\Delta\Delta G$	$\Delta\Delta E$	$\tau_{99.9\%}^a$	N^b
MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p)								
A·T(WC)↔A*·T↑(w) [68]	9.90	9.59	16.72	16.02	6.82	6.43	1.1×10^{-7}	5.4×10^{-8}
A·T(WC)↔A·T* _{o2} ↑(w) [68]	10.91	11.25	16.72	16.02	5.81	4.77	2.0×10^{-8}	9.9×10^{-9}
A·T(WC)↔A·T*↓(w) [68]	13.08	14.84	20.28	20.41	7.20	5.57	2.1×10^{-7}	2.5×10^{-10}
G·C(WC)↔G·C*↑(w) [68]	13.35	14.10	30.47	30.74	17.12	16.64	3.95	1.6×10^{-10}
G·C(WC)↔G*·C↓(w) [68]	15.10	16.49	31.08	31.53	15.98	15.04	0.58	1.3×10^{-11}
G·C(WC)↔G·C*↓(w) [68]	15.08	15.96	30.88	31.41	15.80	15.45	0.42	8.8×10^{-12}
G·C(WC)↔G*·C↑(w) [68]	14.85	17.22	24.87	25.64	10.02	8.42	2.5×10^{-5}	8.4×10^{-12}
MP2/cc-pVQZ//B3LYP/6-311++G(d,p)								
A·C(w)↔A·C*(WC) [69, 70]	4.87	6.77	19.98	18.85	24.84	25.62	4.9×10^2	—
G·T(w)↔G*·T(WC) [69, 71]	-1.69	-2.46	17.04	16.37	18.73	18.83	8.8	—
A·A(w)↔A*·A(WC) [72]	4.18	1.64	26.89	23.59	22.71	21.94	4.4×10^4	—
G·G(w)↔G*·G(WC) [72]	-4.96	-6.75	26.81	26.08	31.77	32.83	5.0×10^7	—
A·G(WC)↔A·G*↓(w) [73]	3.76	6.19	17.01	17.07	13.25	10.88	5.3×10^{-3}	—
A·G(WC)↔A*·G↑(w) [73]	14.29	14.09	25.29	24.39	11.00	10.30	1.2×10^{-4}	—
C·T(WC)↔C*·T↑(w) [73]	0.56	0.55	17.05	17.36	16.48	16.81	6.8×10^{-7}	—
C·T(WC)↔C·T*↓(w) [73]	12.07	14.57	26.64	25.32	14.57	10.75	5.4×10^{-2}	—
T·T(w)↔T·T*(WC) [74]	8.98	8.64	31.06	31.90	22.09	23.26	1.6×10^4	—
C·C(w)↔C·C*(WC) [74]	-8.90	-10.73	25.38	24.32	34.28	35.05	4.4×10^6	—

Note: for designations see **Table 1**.

^aThe time necessary to reach 99.9% of the equilibrium concentration between the reactant and the product of the tautomerization reaction, s.

^bPopulations of the wobble mispairs containing mutagenic tautomers.

Table 2. Energetic and kinetic characteristics of the tautomeric transformations of the classical Watson-Crick or wobble DNA base pairs, which are involved into the processes of the spontaneous point mutagenesis, *via* the DPT accompanied by the substantial changes of their geometry in the continuum with $\epsilon = 1$.

each case mostly, one pathway is most probable at the origin of the spontaneous point mutations (**Figures 2 and 3, Table 2**).

Obtained results are crucial for understanding the microstructural mechanisms of spontaneous transitions and transversions, since they allow us to explain how incorrect purine-pyrimidine, purine-purine and pyrimidine-pyrimidine wobble pairs adapt to the enzymatically competent sizes in the recognition pocket of the high-fidelity DNA polymerase. In particular, established A·C(w) → A·C*(WC) [70] and G·T(w) → G*·T(WC) [71] transformations *via* the sequential PT allow us to interpret the X-ray [14, 15] and molecular dynamics simulations data [19] according the acquisition by the wobble A·C(w)/G·T(w) mispairs of the Watson-Crick geometry by their transformation to the A·C*(WC)/G*·T(WC) Watson-Crick-like base mispairs by the participation of the C* and G* mutagenic tautomers in the recognition pocket of the high-fidelity DNA polymerase. Moreover, we theoretically predicted the G·T(w) → G*·T(WC) transformation for the wobble G·T(w) base mispair, which was confirmed by an NMR experiment of a DNA duplex [16–18].

Mutagenic pressure of the analogues of DNA bases could be explained within the framework of the proposed model of the $w \leftrightarrow WC$ mutagenic tautomerization. In particular, mutagenic action of the analogue of C-6H,8H-3,4-dihydropyrimido[4,5-c] [1, 2]oxazin-7-one [11, 12]—increases the population of the $G \cdot P^* \uparrow$ (4.5×10^{-3}) and $G \cdot P^* \downarrow$ (1.4×10^{-4}) base mispairs by its participation in comparison with the analogical values for the canonical C DNA base. Mutagenic activity of the halogen derivatives of the uracil base is associated with the decreasing of the transformation barriers of the wobble $G \cdot {}^5XU(w)$ ($X = H, CH_3, Br, Cl, F$) mispairs into the $G \cdot {}^5XU^*(WC)$ mispairs with Watson-Crick geometry, thus inducing higher frequency of the transitions. The maximal effect is observed for the 5BrU -calculated frequency of the induced mutations (35 [71]), which is in good accordance with experimental data (from 20 [75] to 29 [76]).

3.4. *Anti* ↔ *syn* conformational transitions of the long purine-purine DNA mismatches

All long purine-purine DNA base mispairs can acquire enzymatically competent conformations— $A^* \cdot A_{syn}(TF)$, $G \cdot A_{syn}$, $A^* \cdot G^*_{syn}$ and $G \cdot G^*_{syn}$ —through the $A^* \cdot A(WC) \leftrightarrow A^* \cdot A_{syn}(TF)$, $G \cdot A(WC) \leftrightarrow G \cdot A_{syn}$, $A^* \cdot G^*(WC) \leftrightarrow A^* \cdot G^*_{syn}$ and $G \cdot G^*(WC) \leftrightarrow G \cdot G^*_{syn}$ conformational transitions [77], eventually guaranteeing their chemical incorporation into the newly synthesized structure of the DNA double helix (TF-Topal-Fresco nucleobase pair [10]; *syn-syn*-orientation of the base according the sugar-phosphate moiety) (**Figure 4**). Characteristic time of these nondissociative conformational transitions ($\sim 10^{-7}$ s) is much less than the period of time the high-fidelity DNA polymerase spends on incorporating one nucleotide into the DNA double helix ($\sim 8.3 \times 10^{-4}$ s [67]). So-called long $A^* \cdot A(WC)$, $G \cdot A(WC)$, $A^* \cdot G^*(WC)$ and $G \cdot G^*(WC)$ DNA base mispairs have been outlined as “node stations” on the way of the formation of the enzymatically competent conformations arising in the recognition pocket of the high-fidelity DNA polymerase at its transition from the open to closed state.

3.5. Physico-chemical scenarios of the origin of the replication and incorporation point errors in DNA

In the framework of such qualitatively new model conceptions, we were able to shed light on the microstructural mechanisms of the occurrence of point mutations—replication and incorporation point errors.

Thus, the spontaneous mutagenic tautomerization of the Watson-Crick pairs of nucleotide bases into the wobble base mispairs, which includes the A^* , T^* , G^* and C^* mutagenic tautomers, has been established to be the source of the generation of the mutagenic tautomers of the DNA bases arising at the separation of DNA strands. At this juncture, *replication errors* would arise in the following way (as an example, we would consider the case, when A^* belongs to the template strand of DNA): $A^* + C \rightarrow A^* \cdot C \rightarrow A \cdot C^*$, $A^* + A \rightarrow A^* \cdot A \rightarrow A^* \cdot A_{syn}$, $A^* + G \rightarrow A^* \cdot G \rightarrow A \cdot G \rightarrow A^* \cdot G^* \rightarrow A^* \cdot G^*_{syn}$. Similar schemes of structural transformations, which occur directly in the recognition pocket of the high-fidelity DNA polymerase, would take place also for three other cases, when G^* , T^* and C^* belong to the template strand of DNA.

Incorporation errors would occur according to the following scenario: in the recognition pocket of the high-fidelity DNA polymerase, it would form the appropriate wobble base mispair

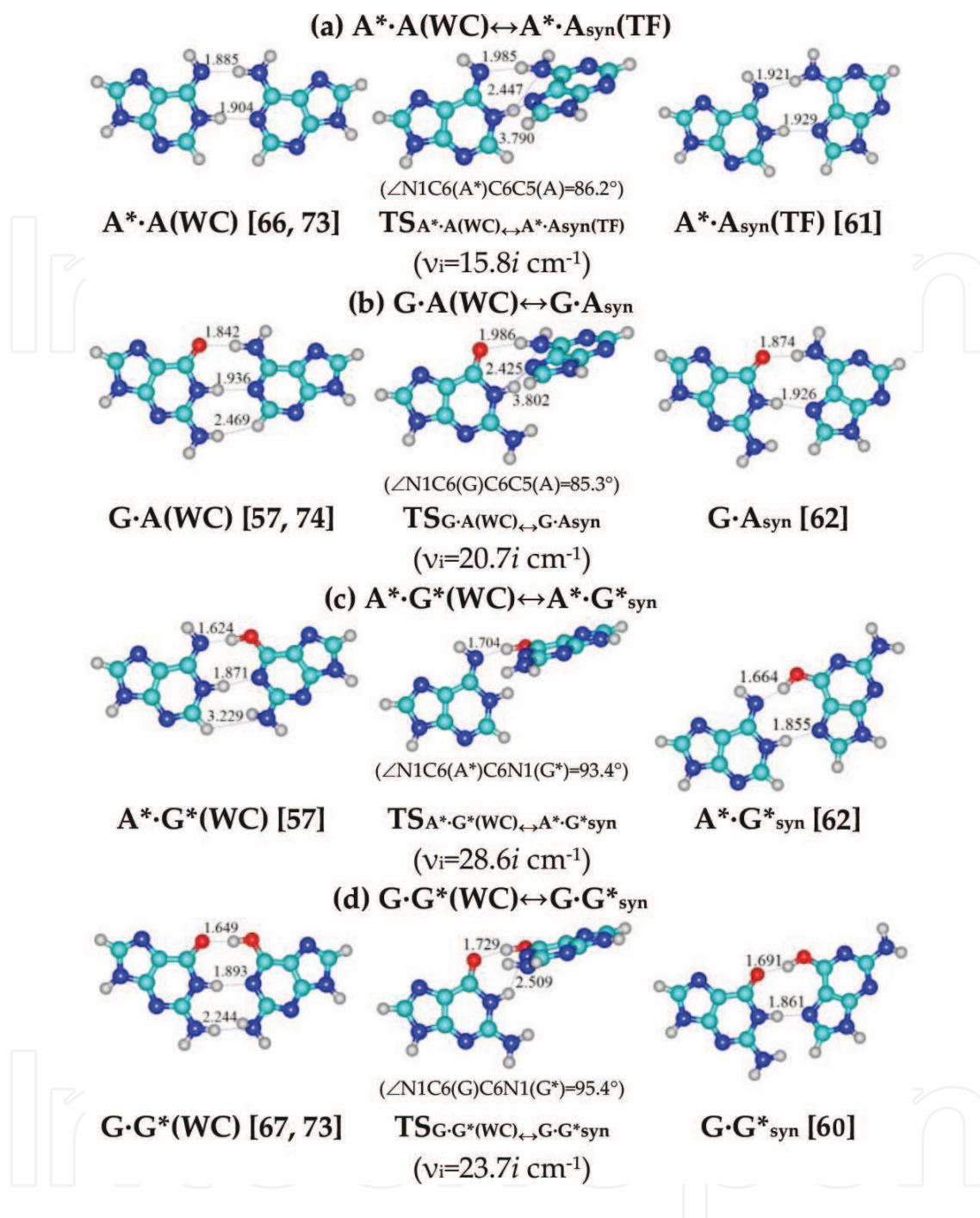


Figure 4. Structures corresponding to the stationary points on the reaction pathways of the (a) $A^* \cdot A(WC) \leftrightarrow A^* \cdot A_{syn}(TF)$, (b) $G \cdot A(WC) \leftrightarrow G \cdot A_{syn}$, (c) $A^* \cdot G^*(WC) \leftrightarrow A^* \cdot G^*_{syn}$ and (d) $G \cdot G^*(WC) \leftrightarrow G \cdot G^*_{syn}$ *anti*↔*syn* conversions through the large-scale adjustments of the bases relative to each other, obtained at the B3LYP/6-311++G(d,p) level of theory, $\epsilon = 1$ [77].

tautomerizing into the pair with Watson-Crick architecture of the binding. For the case, when A belongs to the template strand of DNA: $A + C \rightarrow A \cdot C \rightarrow A \cdot C^*$, $A + A \rightarrow A \cdot A \rightarrow A^* \cdot A \rightarrow A^* \cdot A_{syn}$, $A + G \rightarrow A \cdot G \rightarrow A^* \cdot G^* \rightarrow A^* \cdot G^*_{syn}$.

Both processes have two common features—they involve the same pairs, which play the role of intermediates on the path of formation of enzymatically competent conformations of some incorrect pairs, as well as the same set of terminal incorrect pairs, able to acquire the enzymatically competent conformations during the process of thermal fluctuations.

Finally, it becomes clear why spontaneous point errors occur quite rarely. This, in particular, is due to the fact that the mechanisms of their occurrence are kinetically controllable, with the time $\tau_{99.9\%}$, which is necessary to reach 99.9% of the equilibrium concentration of the reactant and product, significantly greater than the time that the DNA polymerase spends incorporating one nucleotide into the DNA double helix that is synthesized ($\sim 8.3 \times 10^{-4}$ s [67]).

Based on our own theoretical data, which have been successfully confirmed by experimental data [16–18], one can make an assumption, why the DNA-repair enzymes, “sharpened” precisely for the wobble base mispairs, do not provide 100% accuracy. The reason consists in the ability of this pair to transform into a pair with Watson-Crick geometry, which, figuratively speaking, is a “hiding place” from the enzyme, because it is not recognized by it, thus restricting the ultimate accuracy of the repair process.

So, obtained data, in principle, enable to understand the mechanism of elimination from the genome of mutagenic tautomers, whose lifetime exceeds by orders of magnitude the time of cellular DNA replication.

Again, established ability of the wobble pair to be formed from the Watson-Crick-like pair involving mutagenic tautomer of the DNA bases enables DNA-repair complex to reveal and eliminate them from the genome during several cycles of DNA replication.

3.6. Profiles of the physico-chemical parameters along the IRC of tautomerizations *via* DPT and PT

We developed original methodology tracking the evolution of all physico-chemical parameters along the entire reaction pathways: in particular, the electronic energy, the first derivative of the electronic energy by the IRC-dE/dIRC, the dipole moment of the base pair, the distances and the angle of the intermolecular specific contacts (H-bonds or van der Waals contacts), electron density, the Laplacian of the electron density, ellipticity and the energy at the (3,-1) bond critical points of the intrapair specific contacts, the NBO charges of the hydrogen atoms involved in the tautomerization, the glycosidic angles and the distance between the glycosidic hydrogens. This works not only in the stationary structures such as reagent, product and transition state of the tautomerizations *via* the DPT and $w \leftrightarrow WC$ tautomeric reactions *via* the PT [51–74, 78].

Additionally, for the first time, we have introduced the conception of the key points (KPs) based on the electron-topological characteristics of the intermolecular bonds, namely the value of the electron density and its Laplacian at the corresponding (3,-1) bond critical points. This approach allows us to comprehensively describe the mechanism of the tautomerization process. Thus, depending on the symmetry and nature of the system, maximum number of KPs could reach 9 and minimal—5, when KPs are degenerated (see **Figures 5** and **6** for illustration on the example of the $2AP \cdot T(WC) \leftrightarrow 2AP \cdot T^*(w)$).

Arrangement of the extrema of the derivative of the energy by IRC—dE/dIRC—coincides with the second and penultimate KPs, where mutual transformations of the H-bond into a covalent bond and *vice versa* occur. These data allow us to separate the pathway of the tautomerization reaction into the zones of reagent, transition state and product of the reaction. In general, these key points could be considered as “fingerprints” of the tautomerization process *via* DPT or PT.

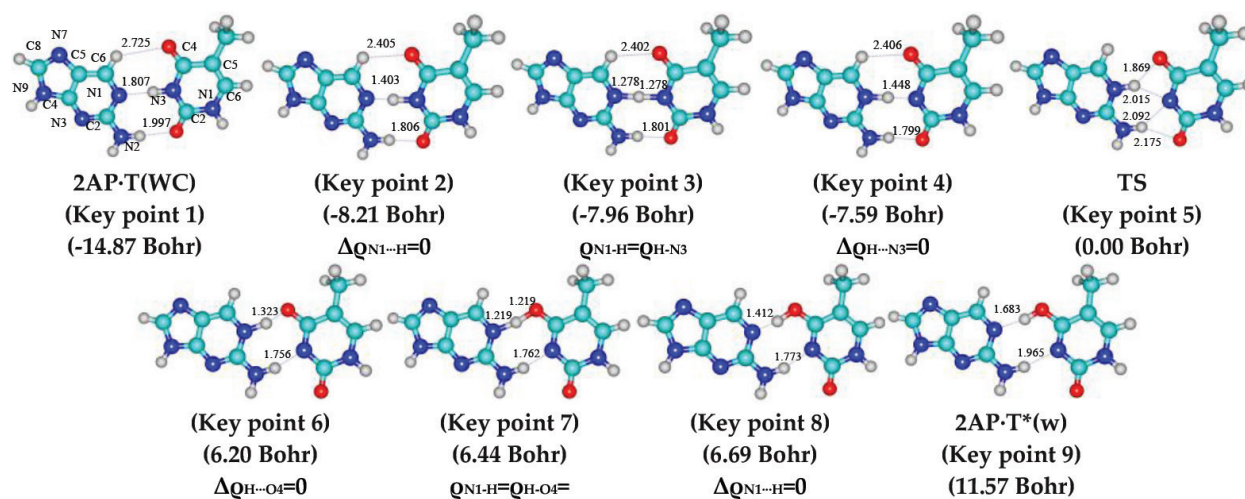


Figure 5. Geometric structures of the nine key points with their IRC coordinated describing the evolution of the 2AP·T(WC)↔2AP·T*(w) tautomerization *via* the single PT and sequential shifting of the bases relative to each other within the base pair into the minor groove side of the DNA helix along the IRC obtained at the B3LYP/6-311++G(d,p) level of theory, $\epsilon = 1$ [79] tautomerization). At this point, three KPs correspond to the two abovementioned local minima (the first and the last KPs—reagent and product, respectively) and transition state of the tautomerization. Other KPs include two KPs, for which migrating proton is localized midway between the electronegative atoms involved in the specific contact and are characterized by the loosened A-H-B covalent bridge, and also four key points, in which the H-bonds begin to acquire the features of the covalent bond and *vice versa*, that is where the Laplacian of the electron density passes through zero: $\Delta Q = 0$.

This methodology enables to make an objective conclusion about the character of tautomerization (concerted, synchronous or asynchronous), quantitatively estimate the cooperativity of the specific intermolecular interactions (namely, H-bonds, in particular nonclassical CH...O/N or dihydrogen AH...HB H-bonds, loosened A-H-B covalent bridges and attractive A...B van der Waals contacts), sequentially changing each other along the IRC of the tautomerization, and trace how these interactions are grouped into the patterns (from 9 to 15) and how they successively substitute each other along the IRC of tautomerization.

3.7. Complete set of incorrect DNA base pairs responsible for the origin of spontaneous transitions and transversions in DNA

For the first time, we outline a complete set of the 12 incorrect DNA base pairs representing a primary cause of spontaneous point mutations and determining both incorporation and replication errors: A·C*/C*·A, G*·T/T·G*, G·A_{syn'} A*·G*_{syn'} A*·A_{syn'} G·G*_{syn'} C·T/T·C, C*·C/C·C* and T*·T/T·T* (three of these mismatches—G·A_{syn'}, C·T and T·C—consist exclusively of the canonical tautomers of the DNA bases) (**Figure 7**). Precisely, these mismatches, which quite easily in the process of the thermal fluctuations acquire enzymatically competent conformations and do not cause steric constraints in the recognition pocket of the high-fidelity replication DNA polymerase (**Table 3**), should be experimentally observed in the closed conformation of the latter.

3.8. Key microstructural mechanisms of the 2-aminopurine (2AP) mutagenicity

Based on the mechanisms of the spontaneous point mutations [33, 34, 51–66, 68–74, 78], we established physico-chemical mechanisms of the mutagenic action of the classical mutagen

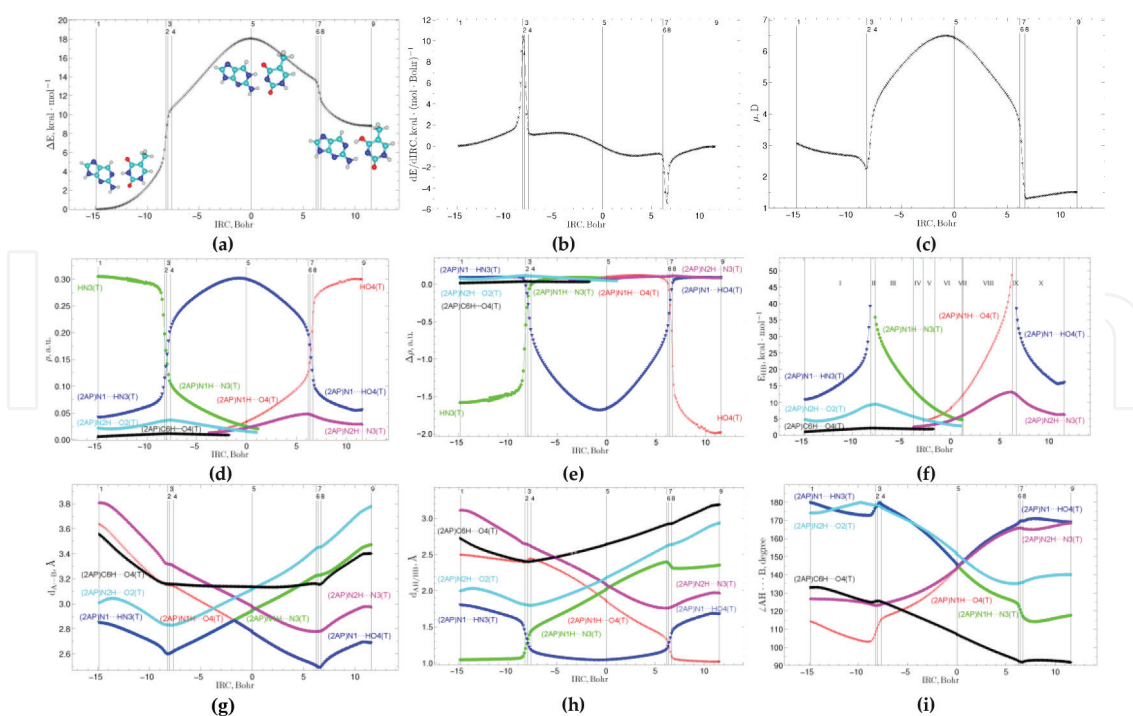


Figure 6. Profiles of: (a) the relative electronic energy ΔE , (b) the first derivative of the electronic energy with respect to the IRC ($dE/dIRC$), (c) the dipole moment μ , (d) the electron density ρ , (e) the Laplacian of the electron density $\Delta\rho$, (f) the energy of the intermolecular H-bonds E_{HB} estimated by the EML formula [79] at the (3,-1) BCPs, (g) the distance d_{A-B} between the electronegative A and B atoms, (h) the distance $d_{AH/HB}$ between the hydrogen and electronegative A or B atoms and (i) the angle $\angle AH \cdots B$ of the covalent and hydrogen bonds along the IRC of the $2AP:T(WC) \leftrightarrow 2AP:T^*(w)$ tautomerization obtained at the B3LYP/6-311++G(d,p) level of theory, $\epsilon = 1$.

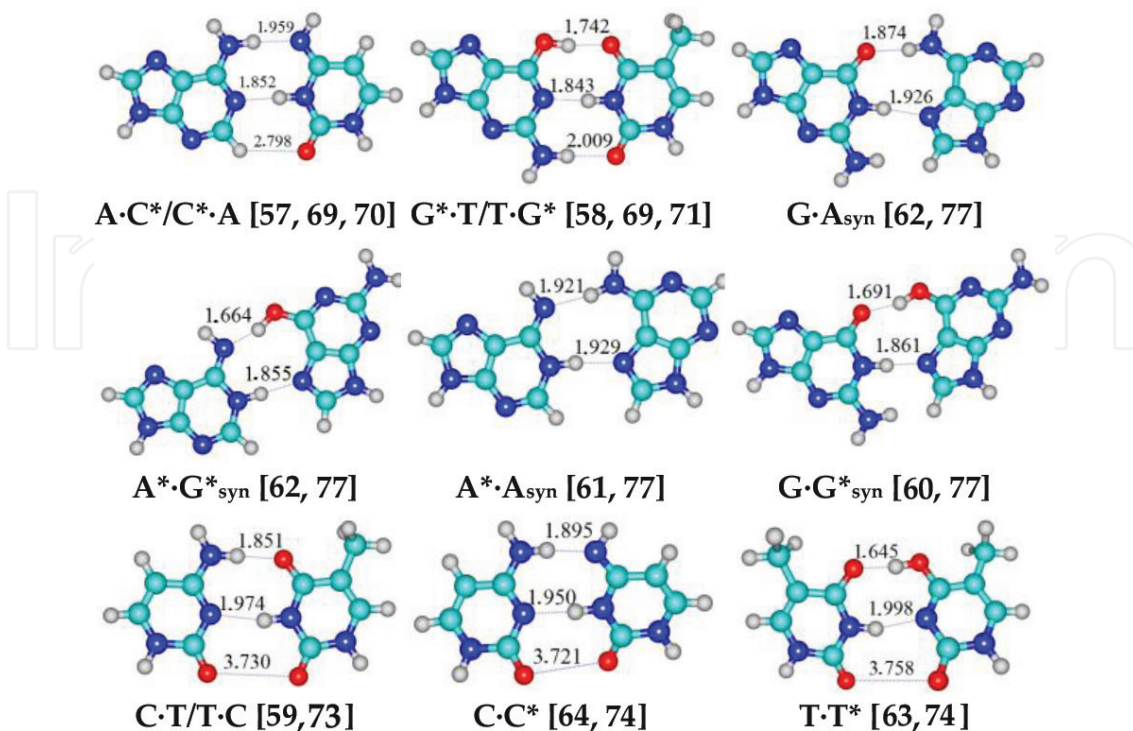


Figure 7. Geometrical structures of the 12 incorrect DNA base mismatches causing spontaneous point incorporation and replication errors (B3LYP/6-311++G(d,p) level of theory, $\epsilon = 1$).

Mispairs	Geometrical parameters			Energetic parameters				
	$R(H_{N1/N9} - H_{N1/N9})^a$	α_1^b	α_2^c	ΔE_{def}^d		$-\Delta E_{int}^e$	$\Sigma E_{HB} / \Delta E_{int} ^f$	$-\Delta G_{int}^g$
A·C*	9.996	55.3	58.2	0.10	0.29	15.73	91.8	2.27
A*·C	10.059	55.3	57.2	0.29	0.53	23.50	65.9	10.76
G*·T	10.291	51.5	51.1	0.14	0.40	19.79	87.7	7.09
G·T*	10.202	50.6	52.2	0.45	0.90	33.40	61.3	20.66
G·A _{syn}	10.399	51.6	38.5	3.00	3.61	17.00	65.9	2.80
A*·G _{syn}	10.411	50.3	37.5	3.18	3.72	23.00	72.6	11.47
A*·A _{syn}	10.322	53.9	41.2	2.18	2.72	16.73	74.8	3.83
G·G _{syn} *	10.425	48.7	36.1	4.04	4.66	19.82	69.5	7.28
C·T	8.215	59.7	57.0	8.67	8.87	13.86	85.4	1.54
C·C*	8.086	60.3	59.5	8.57	8.76	14.75	91.2	2.34
T·T*	8.385	53.6	58.1	10.97	10.91	16.67	84.0	4.69
A·T	10.130	54.3	54.8	0.00	0.25	14.92	86.9	1.43
G·C	10.209	52.9	55.3	0.11	0.00	29.28	60.8	15.97

^aThe distance between the glycosidic protons at the N1/N9 atoms, Å.

^bThe glycosidic angles for the bases situated on the left and right within the base pair, respectively, degree.

^cThe glycosidic angles for the bases situated on the left and right within the base pair, respectively, degree.

^dThe electronic energy of deformation, necessary to apply to the mismatch to acquire the sizes of the A·T (in the left column) and G·C (in the right column) Watson-Crick DNA base pairs.

^eThe electronic energy of interaction.

^fThe contribution of the total energy of the intermolecular H-bonds to the electronic energy of interaction, %.

^gThe Gibbs free energy of interaction (T = 298.15 K).

Table 3. Selected structural and energetic (in kcal·mol⁻¹) characteristics of the canonical and noncanonical DNA base pairs, responsible for the origin of the spontaneous transitions and transversions (MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory, $\epsilon = 1$).

2AP—high-energy structural isomer of A nucleotide base [75–77, 80–82]. In the literature, a great amount of experimental and theoretical phenomenological data on 2AP has been collected [83–87] without proper justification and substantiation.

We have found for the first time that the microstructural mechanism of the mutagenic action of 2AP, causing induced *replication errors*, generates with higher probability the mutagenic tautomer T* according to the 2AP·T(WC) → 2AP·T*(w) tautomeric reaction, than for the Watson-Crick A·T(WC) DNA base pair according to the A·T(WC) → A·T*(w) tautomerization reaction [68, 88]. At this point, the ratio of probabilities determining *replication errors* consists $P_{2AP·T} / P_{A·T} = 1.8 \cdot 10^3$. The mutagenic effect is achieved due to the greater stability of the 2AP·T*(w) complex by the participation of 2AP ($\Delta E_{int} = -20.95$ and $\Delta G_{int} = -9.18$ kcal·mol⁻¹) in comparison with the analogical A·T*(w) base mispair by the participation of A ($\Delta E_{int} = -13.44$ and $\Delta G_{int} = -1.61$ kcal·mol⁻¹) (Figure 8a, Table 4) [68, 88].

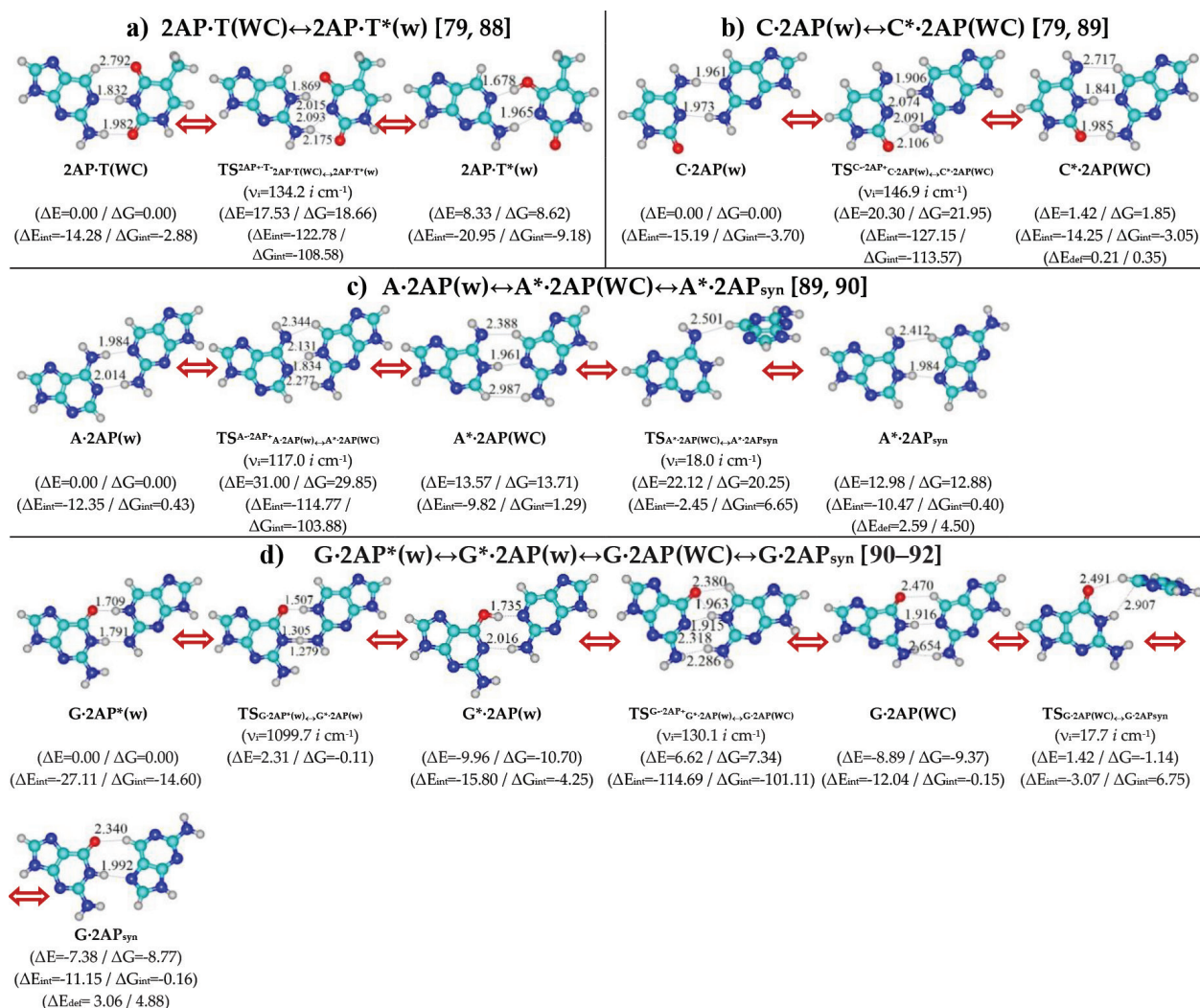


Figure 8. Reaction pathways of the biologically important tautomerizations and conformational transitions of the structures containing canonical DNA bases and 2AP in the main and rare tautomeric forms leading to the replication (a) and incorporation (b, c, d) errors—transitions and transversions. Relative electronic ΔE and Gibbs free ΔG energies, electronic ΔE_{int} and Gibbs free ΔG_{int} energies of interaction, the deformation energies $\Delta E_{\text{def}}(\text{A}\cdot\text{T})/\Delta E_{\text{def}}(\text{G}\cdot\text{C})$ necessary to apply to the mismatch to acquire the sizes of the A·T(WC)/G·C(WC) Watson-Crick DNA base pairs (in kcal·mol⁻¹), imaginary frequencies ν_i (cm⁻¹) at the TSs of the interconversions are presented below them in brackets (MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of theory in vacuum at T = 298.15 K). The base, belonging to the template strand of DNA, is situated on the left, while the base of the incoming nucleotide—on the right.

We have shown for the first time that 2AP very effectively produces induced *incorporation errors* by binding with C DNA base and forming the wobble C·2AP(w) mispair, which is tautomerized *via* the C·2AP(w) → C*·2AP(WC) tautomeric reaction into the Watson-Crick-like C*·2AP(WC) base mispair, which quite easily in the process of the thermal fluctuations acquires enzymatically competent conformation (estimated ratio of probabilities $P_{\text{C}\cdot\text{2AP}}/P_{\text{C}\cdot\text{A}} = 1.92 \cdot 10^4$) (Figure 8b, Table 4) [89].

By estimating the probability ratio $P_{\text{A}\cdot\text{2AP}}/P_{\text{A}\cdot\text{A}} = 40.5$, we conclude that 2AP in the case of the A·2AP(w) → A*·2AP(WC) → A*·2AP_{syn} structural transformations (Figure 8c, Table 4) causes transversion, when a pyrimidine base (in this case T) is substituted by a purine, in particular—A [89].

Tautomerization/ Conformational transition	v_i	ΔG	ΔE	$\Delta\Delta G_{TS}$	$\Delta\Delta E_{TS}$	$\Delta\Delta G$	$\Delta\Delta E$	$\tau_{99,9\%}$	τ
a) 2AP·T(WC)↔2AP·T*(w) [79, 88]	134.2	8.62	8.33	18.66	17.53	10.04	9.21	$2.53 \cdot 10^{-5}$	3.7×10^{-6}
A·T(WC)↔A·T*(w) [51, 53, 68]	99.7	13.08	14.84	20.28	20.41	7.20	5.57	$2.09 \cdot 10^{-7}$	3.0×10^{-8}
b) C·2AP(w)↔C*·2AP(WC) [79, 89]	146.9	1.85	1.42	21.95	20.30	20.11	18.88	$5.87 \cdot 10^2$	8.9×10^1
C·A(w)↔C*·A(WC) [57, 70]	588.5	-6.07	-7.20	19.51	17.61	25.58	24.81	$1.74 \cdot 10^2$	7.1×10^5
c) A·2AP(w)↔A*·2AP(WC) [89, 90]	117.0	13.71	13.57	29.85	31.00	16.14	17.43	0.76	0.1
A*·2AP(WC)↔A*·2AP _{syn} [89]	18.0	-0.83	-0.59	6.54	8.55	7.37	9.14	$5.59 \cdot 10^{-8}$	4.1×10^{-8}
A·A(w)↔A·A*(WC) [72]	152.4	3.63	1.09	25.86	22.56	22.24	21.47	$2.22 \cdot 10^4$	3.2×10^3
A·A*(WC)↔A*·A(WC) [65]	497.5	0.00	0.00	6.39	9.71	6.39	9.71	$2.28 \cdot 10^{-8}$	6.4×10^{-9}
A*·A(WC)↔A*·A _{syn} (TF) [61, 77]	15.8	0.56	1.23	8.09	8.09	7.53	6.85	$2.66 \cdot 10^{-7}$	5.3×10^{-8}
d) G·2AP*(w)↔G*·2AP(w) [91, 92]	1099.7	-10.70	-9.96	-0.11	2.31	10.59	12.26	$4.39 \cdot 10^{-13}$	4.5×10^{-6}
G*·2AP(w)↔G·2AP(WC) [90, 91]	130.1	1.33	1.07	18.04	16.58	16.70	15.51	1.77	0.3
G·2AP(WC)↔G·2AP _{syn} [91]	17.7	0.60	1.51	8.23	10.31	7.63	8.80	$3.22 \cdot 10^{-7}$	6.4×10^{-8}
G·A*(w)↔G·A(WC) [73]	126.8	-6.93	-6.73	16.98	16.32	23.92	23.05	3.14	5.5×10^4
G·A(WC)↔G·A _{syn} [56, 62, 77]	20.7	0.76	0.58	8.39	8.89	7.64	8.31	$3.47 \cdot 10^{-7}$	6.4×10^{-8}

Note: see **Tables 1** and **2**.

Table 4. Energetic and kinetic characteristics of the biologically important tautomerizations and conformational transitions of the structures containing canonical DNA bases and 2AP in the main or rare tautomeric forms leading to replication and incorporation errors—transitions and transversions (MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of theory, $\epsilon = 1$).

We prove for the first time that 2AP* as a base of the incoming nucleotide may produce also another transversion, when 2AP* mutagenic tautomer pairs with G base and formed G·2AP*(w) mispair converts according to the route of the sequential tautomeric and conformational transformations—G·2AP*(w) → G*·2AP(w) → G·2AP(WC) → G·2AP_{syn} (**Figure 8d**, **Table 4**) [91]. Estimated ratio of probabilities $P_{G \cdot 2AP^*} / P_{G \cdot A^*} = 1.90 \cdot 10^7$ points that this route of the tautomericly conformational transformations is mutagenic, generating appropriate transversions, when pyrimidine bases (in this case C) are replaced by the analogue of the purine base—2AP. This also causes low-probable transitions and transversions, since in the next rounds of the DNA replication, 2AP pairs not only with T, but also with the C and A DNA bases [91].

Our theoretical data are in good agreement with existing experimental results [80, 81, 83, 84] and also allow a unified physico-chemical interpretation of them.

By analyzing profiles of the physico-chemical characteristics for the tautomerization reactions *via* the DPT and PT involving 2AP, which are integral parts of the biologically important tautomericly conformational transformations, we have established that 2AP·T(WC)↔2AP·T*(w) [79], 2AP·C*(WC)↔2AP·C(w) [79], G*·2AP(w)↔G·2AP(WC) [90] and A·2AP(w)↔A*·2AP(WC) [90] tautomerization pathways proceed through the stepwise concerted mechanism *via* the sequential intrapair PT between the bases followed by the shifting of the 2AP relatively the T/C*/G*/A bases, accordingly, while the T·2AP*(w)↔T*·2AP(w) and G·2AP*(w)↔G*·2AP(w) [92] DPT tautomerization reactions proceed through the asynchronous concerted mechanism.

4. Conclusions

Reported results are crucial for understanding the microstructural mechanisms of the spontaneous transitions and transversions, since they allow us to explain, on one side, the origin of the mutagenic tautomers at the separation of the DNA strands before DNA replication and, on the other side, how incorrect purine·pyrimidine, purine·purine and pyrimidine·pyrimidine wobble mispairs adapt to enzymatically competent sizes in the recognition pocket of the high-fidelity DNA polymerase.

Obtained results allow us to explain biological experiments available in the literature, which still remain without proper theoretical justification:

- Numerical estimations of the frequencies of the mispair occurrence satisfactorily explain experimental data: $(10^{-3} \div 10^{-4})$ G·T/T·G >> A·C/C·A >> C·T/T·C > A·A > G·A/A·G >> G·G \approx C·C (10^{-6}) [93].
- Established $A \cdot C(w) \leftrightarrow A \cdot C^*(WC)$ and $G \cdot T(w) \leftrightarrow G^* \cdot T(WC)$ wobble(w) \leftrightarrow Watson-Crick(WC) transformations *via* the sequential PT allow us to explain the way of the acquisition by the A·C(w)/G·T(w) wobble mispairs of the Watson-Crick geometry in the active center of the high-fidelity DNA polymerase or DNA duplex and also to interpret X-ray [14, 15] and NMR [16–18] experiments.
- Presented approach allows us to clarify the microstructural mechanisms of the mutations induced by the classical mutagens, in particular 2-aminopurine, for which induced frequencies agree well with the experimental data.
- Ionization mechanism cannot entirely explain the nature of the spontaneous transitions [94].

These data clarify the nature of genome variability and reveals new facets of the Watson-Crick hypothesis of the spontaneous point mutagenesis arising during DNA replication and significantly expands the possibilities for rational design of chemical mutagens with targeted action, which could be interesting for synthetic biology and biotechnology.

Finally, authors believe that these principles could be extended without any constrains to the processes determining the protein synthesis.

In view of the prominent role, that play parallel and antiparallel Hoogsteen pairings in DNA:RNA helices, as it was reliably established by Prof. Seligmann [95, 96] for mitochondrial genomes, it is important to explore in future mutagenic tautomerization of these classical base pairs by the quantum-chemical methods.

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Conflict of interest

There are no conflicts to declare.

Dedication

This chapter is dedicated to 100th anniversary of the National Academy of Sciences of Ukraine.

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