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Elementary Molecular Mechanisms of the Spontaneous Point Mutations in DNA: A Novel Quantum-Chemical Insight into the Classical Understanding

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1. Introduction

DNA replication is an amazing biological phenomenon that is essential to the continuation of life (Kornberg & Baker, 1992). Faithful replication of DNA molecules by DNA polymerases is essential for genome integrity and stable transmission of genetic information in all living organisms. Although DNA replicates with immensely high fidelity, upon assembly of millions of nucleotides a DNA polymerase can make mistakes that are a major source of DNA mismatches. The overall accuracy and error spectrum of a DNA polymerase are determined mainly by three parameters: the nucleotide selectivity of its active site, its mismatch extension capacity, and its proofreading ability (Beard & Wilson, 1998, 2003; Joyce & Benkovic, 2004). Yet, natural and exogenous sources of DNA damage result in a variety of DNA modifications, the most common including nucleobase oxidation (Nakabeppu et al., 2007), alkylation (Drabløs et al., 2004) and deamination (Ehrlich et al., 1986; Kow, 2002; Labet et al., 2008).

Depending on the type of mismatch and the biological context of its occurrence, cells must apply appropriate strategies of postreplication repair to avoid mutation (Kunz et al., 2009). However, some replication errors make it past these mechanisms, thus becoming permanent mutations after the next cell division.

Mutations are stable, heritable alterations of the genetic material, namely DNA (Friedberg et al., 2006). They are an important contributor to human aging, metabolic and degenerative disorders, cancer, and cause heritable diseases, at the same time they are the kindling factor for biological evolution of living things. Beyond the individual level, perhaps the most dramatic effect of mutation relates to its role in evolution; indeed, without mutation,

evolution would not be possible. The point mutations caused by the substitution of one nucleotide base for another are divided into *transitions* (replacement of a purine with another purine or replacement of a pyrimidine with another pyrimidine, i.e. purine-pyrimidine mismatches) and *transversions* (replacement of a purine with a pyrimidine or *vice versa*, i.e. purine-purine and pyrimidine-pyrimidine mispairs). Therefore, to maintain a stable genome, it is essential for cells to monitor the state of base pairing in their genomes and to correct mismatches that will occasionally occur.

Spontaneous mutations are generally occurring due to endogenous factors: endogenous chemical lesions generated during normal cell metabolism, errors in normal cellular processes and others.

It has been suggested that there are two major approaches to the origin of mutations arising during DNA replication:

1. *replication errors*, that occur due to mispair formation in the DNA double helix as a result of changing the coding property (for example, tautomeric) of DNA base in the template strand;
2. *incorporation errors*, that occur due to mispair formation in the DNA double helix as a result of changing the coding property (for example, tautomeric) of DNA base in the incoming deoxyribonucleoside triphosphate.

There is a natural – albeit low – error rate that occurs during DNA replication. So, the average frequency of spontaneous errors in DNA replication is in the range of 10^{-8} – 10^{-11} per base pair replicated per one cell division (Drake, 1991; Fersht & Knill-Jones, 1983; Loeb, 2001).

Nowadays the occurrence of the spontaneous point mutations can be explained by several physico-chemical mechanisms.

Today, scientists generally consider that most DNA replication errors are caused by mispairings with “correct” geometry formed either by the protonated or deprotonated bases (i.e., bases with an excess or missing proton, respectively) (Sowers et al., 1986, 1987; Yu et al., 1993), which generation and existence under physiological conditions remains disputable, because it was claimed that the methods used by researchers to determine ionized base pairing involve conditions different from those actually obtained during DNA replication. So, Bebenek et al. (Bebenek et al., 2011) demonstrated that wild-type DNA polymerase λ and its derivative polymerase λ DL misinsert dGTP opposite template Thy at substantially higher efficiencies in reactions performed at pH 9.0 as compared to those at physiological pH (7.0). These pH dependencies of enzymatic catalysis are in agreement with the results of Yu et al. (Yu et al., 1993) and are also consistent with the possible involvement of an ionized base pair. However, in our recent work (Brovarets’ et al., 2010e), it was demonstrated that the ionization mechanism of spontaneous transitions appearance does not imply any advantages in comparison with other mechanisms described in literature. Moreover, we revealed that the protonation/deprotonation of base in any canonical nucleoside significantly perturbs its DNA-like conformations (Brovarets’ et al., 2010e).

It is also generally accepted in the literature that wobble base pairs (Gua·Thy and Ade·Cyt) (Brown et al., 1985; Crick, 1966; Hunter et al., 1986; Kennard, 1985; Padermshoke et al., 2008; Patel et al., 1982a, 1982b, 1984a, 1984b) formed by bases in their canonical tautomeric forms

and positioned in sheared relative to the Watson-Crick configuration represent erroneous occurrences leading to the substitution mutations. The wobble mispairings were observed in X-ray (Brown et al., 1985; Hunter et al., 1986; Kennard, 1985) and NMR (Patel et al., 1982a, 1982b, 1984a, 1984b) model experiments (in the absence of DNA polymerases) on co-crystallization of complementary oligonucleotides containing a single mismatched base pair. But such experimental conditions do not properly reflect those required for enzymatic DNA replication (Kornberg & Baker, 1992). The Gua·Thy and Ade·Cyt mismatches adopt a relatively stable and well-fitting wobble configurations, supporting intrahelical base pair stacking and affecting the DNA helical structure only marginally (Brown et al., 1985; Kunz et al., 2009). By structural considerations, mispairings that cause little distortion to the canonical Watson-Crick geometry are more likely to be tolerated by the polymerase active site and, therefore, to escape proofreading. This fact was demonstrated in structural and biochemical studies of DNA polymerases (Echols & Goodman, 1991; Kool, 2002). However, enzymes, involved in postreplication repair, can easily recognize and correct structural imperfections between such improperly paired nucleotides (Kunz et al., 2009).

Another mechanism of the spontaneously arising point mutations in DNA was originally proposed by James Watson and Francis Crick (Watson & Crick, 1953a, 1953b) and further elaborated by Topal and Fresco (Topal & Fresco, 1976) as the “rare tautomer hypothesis” which suggested that “spontaneous mutation may be due to a base occasionally occurring in one of its less likely tautomeric forms”. Both the purine and pyrimidine bases in DNA exist in different chemical forms, so-called isomers or tautomers, in which the protons occupy different positions in the molecule. Tautomers of DNA bases – Ade, Gua, Thy and Cyt – can cause genetic mutations by pairing incorrectly with wrong complementary bases. Watson and Crick suggested two possible transition mispairs, Gua·Thy and Ade·Cyt, involving the enol form of guanine or thymine and the imino form of adenine or cytosine, respectively – Gua*·Thy, Gua·Thy*, Ade*·Cyt and Ade·Cyt* (herein and after mutagenic tautomeric forms of bases are marked by an asterisk). These mispairs fit well within the dimensions of the DNA double helix to preserve the geometry of a correct canonical base pair in such a way supporting the Watson and Crick’s original idea that spontaneous base substitutions, namely transition mutations, may result from mismatches shaped like correct base pairs, which were experimentally confirmed by Bebenek et al. for DNA polymerase λ (Bebenek et al., 2011) and by Wang et al. for DNA polymerase I (W. Wang et al., 2011). However, it remains out of eyeshot whether these rare (or mutagenic) tautomers are dynamically stable and their lifetimes are long enough to cause mutations or they are short-lived structures unable to yield irreversible errors in DNA and finally induce genomic alterations. The actual lifetime was estimated only for mutagenic tautomer of Cyt, with a value being about 600 years (Zhao et al., 2006). But evidence for these types of tautomeric shifts remains sparse, because the limited sensitivity of the experimental methods prevents an accurate detection of the relative amount of the rare tautomers including mutagenic. Among all rare tautomers, only the imino tautomers of Cyt (Brown et al., 1989b; Dreyfus et al., 1976; Feyer et al., 2010; Szczesniak et al., 1988) and enol tautomers of Gua (Choi & Miller, 2006; Sheina et al., 1987; Plekan et al., 2009; Szczepaniak & Szczesniak, 1987) were experimentally detected. The lack of the experimental data on the rare tautomers of Ade (Brown et al., 1989a) and Thy can be explained by the high value of their relative energy ($\sim 12\div 14$ kcal/mol at 298.15 K) estimated by theoretical investigations (Basu et al., 2005; Brovarets’ & Hovorun, 2010a; Fonseca Guerra et al., 2006; Mejía-Mazariegos & Hernández-Trujillo, 2009; Samijlenko et al., 2000, 2004).

Unusual tautomeric forms of modified bases have been found in damaged DNA duplex, indicating that the transition to such altered forms is indeed feasible (Chatake et al., 1999; Robinson et al., 1998). It is therefore likely that analogues of DNA bases have a propensity to adopt the rare, namely mutagenic tautomeric forms (Brovarets' & Hovorun, 2010b, 2011a).

The molecular nature of formation of mutagenic tautomers is not quite clear yet. Several alternative mechanisms of the rare tautomers formation have been discussed in the literature: i) intramolecular proton transfer in DNA bases (Basu et al., 2005; Brovarets' & Hovorun, 2010a, 2010d, 2011a; Gorb et al., 2005; Zhao et al., 2006), ii) proton transfer in a single base assisted by bulk aqueous solution, by micro-hydration or by a single interacting water molecule (Fogarasi, 2008; Furmanchuk et al., 2011; Gorb & Leszczynski, 1998a, 1998b; H.-S. Kim et al., 2007; Michalkova et al., 2008); iii) Löwdin's mechanism of tautomerisation involving double proton transfer (DPT) along two intermolecular hydrogen (H) bonds of complementary DNA base pairs (Löwdin, 1963, 1965, 1966).

On the basis of the Watson-Crick's model Löwdin (Löwdin, 1963, 1965, 1966) suggested that spontaneous mutagenesis causing aging and cancer could be induced by tautomerisation of Ade • Thy and Gua • Cyt Watson-Crick base pairs through DPT along neighbouring intermolecular H-bonds joining bases in pairs. Following the pioneering Löwdin's work the DNA base pairs have been extensively studied using a wide range of theoretical approaches, essentially in the gas phase (Cerón-Carrasco et al., 2011a; Cerón-Carrasco & Jacquemin, 2011b; Gorb et al., 2004; Florian et al., 1995; Florian & Leszczynski, 1996; Villani, 2005, 2006, 2010).

After a comprehensive literature review we came to a conclusion that although it is widely accepted that mutations *in vivo* play a very important role in cell functioning, elementary physico-chemical mechanisms of this process remain poorly understood.

The questions of existence of different tautomeric forms of nucleic acid bases and their possible role as mutagenic factors are under intense scrutiny. The understanding of the tautomeric behavior of the purine and pyrimidine bases of the nucleic acids is of fundamental importance not only for quantitative concepts of chemical bonding and physical chemistry, but also for molecular biology and the presumed role of the rare tautomers in mutagenesis.

The structural requirements for tautomeric shifts in the base pairs that may initiate mutations have been formulated in literature (Basu et al., 2005): (i) the bases open out during replication phase in their unusual tautomeric condition and (ii) the unusual tautomers form stable base pairs with isosteric Watson-Crick geometry with their wrong suite. Another group of researchers (Dąbkowska et al., 2005) based on the conclusions earlier reported by Florian et al. (Florian et al., 1994) established that tautomerisation reactions have to fulfill not only thermodynamic but also certain kinetic limits to be relevant to spontaneous DNA mutations. First, the lifetime of the canonical base should be shorter than the reproduction period of a given species. Second, the mutagenic tautomer needs to remain stable during the time period from the occurrence of tautomerisation until the replication process is completed. These conditions impose constraints on barriers for the forward and reverse reactions of DNA bases tautomerisation.

Our purpose in this study is to carefully analyse the molecular mechanisms of spontaneously arising point mutations proposed in literature, to offer truly new ideas for

molecular and structural approaches to the nature of spontaneous DNA mutations caused by prototropic tautomerism of nucleotide bases and to provide a novel quantum-chemical insight into the classical understanding of this biologically important problem.

2. Computational methods

The *ab initio* methods were used to investigate the tautomerisation of the DNA bases and mispairs involving mutagenic tautomers. All quantum-chemical calculations were performed using the Gaussian 03 program package (Frisch et al., 2003).

Geometries and harmonic vibrational frequencies of molecules and complexes were obtained using Becke's three-parameter exchange functional (B3) (Becke, 1993) combined with Lee, Yang, and Parr's (LYP) correlation functional (Lee et al., 1988) implemented in Gaussian 03 that has good performance for calculating barrier heights, thermo-chemical kinetics or intra- and intermolecular H-bonds in the systems recently studied (Brovarets', 2010; Brovarets' & Hovorun, 2010a, 2010b, 2010d, 2010f, 2011a, 2011b; Brovarets' et al., 2010c, 2010e) and 6-311++G(d,p) basis set. The absence of imaginary vibrational frequencies proved that energy-minimized structures perfectly correspond to the local minima of the potential energy landscape.

To consider electronic correlation effects as accurately as possible, we performed single point energy calculations at the MP2/6-311++G(2df,pd) level of theory for the B3LYP/6-311++G(d,p) geometries.

As for the transition states (TS) of tautomerisation of the isolated bases or their complexes, they were located by means of Synchronous Transit-guided Quasi-Newton (STQN) method (Peng & Schlegel, 1993; Peng et al., 1996) using the Berny algorithm and proved to contain one and only one imaginary frequency corresponding to the reaction coordinate. Afterwards the reaction pathway of proton transfer was followed by performing an intrinsic reaction coordinate calculation in order to make sure that transition state really connects the expected reactants and products (Gonzalez & Schlegel, 1989). We applied the standard transition state theory (Atkins, 1998) to estimate barriers for tautomerisation reactions.

The equilibrium constants of tautomerisation were calculated using the standard equation $K = \exp(-\Delta G/RT)$, where ΔG is the relative Gibbs free energy of the reactant or product, T is the absolute temperature, and R is the universal gas constant.

The time $\tau_{99.9\%}$ necessary to reach 99.9% of the equilibrium concentration of the mutagenic tautomer in the system of reversible first-order forward (k_f) and reverse (k_r) reactions (canonical $\leftrightarrow$ mutagenic tautomer transitions) can be estimated from the equation (Atkins, 1998)

$$\tau_{99.9\%} = \frac{\ln 10^3}{k_f + k_r} \quad (1)$$

and the lifetime τ and the half-lifetime $\tau_{1/2}$ of the complexes are given by $1/k$ and $\ln(2)/k$, respectively. We applied the standard transition state theory (Atkins, 1998) in which quantum tunneling effects are accounted by the Wigner's tunnelling correction (Wigner, 1932).

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

that is adequate for proton transfer reactions (Brovarets' & Hovorun, 2010a, 2010b, 2011a; Cerón-Carrasco & Jacquemin, 2011b) to estimate the values of rate constants k_f and k_r

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

where k_B - the Boltzmann's constant, h - the Planck's constant, $\Delta\Delta G_{f,r}$ - the Gibbs free energy of activation for the proton transfer reaction, ν_i - the magnitude of the imaginary frequency associated with the vibrational mode at the transition state that connects reactants and products.

The electronic interaction energies have been computed at the MP2/6-311++G(2df,pd) level of theory for the B3LYP/6-311++G(d,p) geometries. In each case the interaction energy was corrected for the basis set superposition error (BSSE) (Boys & Bernardi, 1970; Gutowski et al., 1986) through the counterpoise procedure (Sordo et al., 1988; Sordo, 2001) implemented in the Gaussian 03 package (Frisch et al., 2003).

The topology of the electron density was analysed using program package AIMAll (AIMAll, 2010) with all the default options. The presence of a bond critical point (BCP), namely the so-called (3,-1) point, and a bond path between hydrogen donor and acceptor, as well as the positive value of the Laplacian at this bond critical point, were considered as the necessary conditions for H-bond formation. Wave functions were obtained at the level of theory used for geometry optimization.

3. DNA bases with amino group: Planar or nonplanar?

The amino group $-NH_2$ in DNA bases, namely, Gua, Cyt and Ade, plays a key role in formation of H-bonds in nucleic acids and in other molecular systems. Thus, the structure of this group is of fundamental importance in the molecular recognition phenomena. The DNA bases were believed to be planar for many years, until the nonplanarity of their amino groups has been predicted in the 1990s (Aamouche et al., 1997; Hobza & Šponer, 1999; Hovorun et al., 1995a, 1995b, 1999; Hovorun & Kondratyuk, 1996; Komarov & Polozov, 1990; Komarov et al., 1992; Šponer & Hobza, 1994; Šponer et al., 2001). Direct experimental results for the nucleic acid bases amino moieties are not available, but indirect experimental evidence does exist. The first indirect experimental evidence was connected with the excellent agreement between the theoretical anharmonic (Bludský et al., 1996) and experimental inversion-torsion (Kydd & Krueger, 1977, 1978; Larsen et al., 1976) vibrational frequencies that provided evidence concerning the nature of the predicted aniline potential energy surface, consistent with a strong nonplanarity of the amino group (Lister et al., 1974; Sinclair & Pratt, 1996; Quack & Stockburger, 1972).

Although a noticeable inertial defect of Ade was observed in a microwave study (Brown et al., 1989a), its source was not directly related to the nonplanarity of this base. Indirect experimental evidence was associated with the vibrational transition moment angles of Ade

reported by Choi et al. (Choi et al., 2008). The mismatched $\text{Gua}_{\text{anti}}\cdot\text{Ade}_{\text{anti}}$ base pair (Privé et al., 1987) is an example exhibiting the strong out-of-plane H-bond character related to the nonplanar guanine amino group.

The internal nonplanarity of the amino group originates from the partial sp^3 hybridization of the amino group nitrogen atom (Govorun et al., 1992; Hovorun et al., 1995a, 1995b, 1999; Hovorun & Kondratyuk, 1996; Gorb & Leszczynski, 1998a, 1998b; Hobza & Šponer, 1999; Šponer & Hobza, 1994).

At least one conclusion that may be drawn from these investigations is that the amines could be much more flexible than previously expected because of the low values of the inversion and rotation barriers of the amino group. The inversion dynamics of the amino group have been investigated by *ab initio* methods with and without inclusion of correlation energy utilizing medium and extended basis sets (Bludský et al., 1996) and the barriers for inversion or internal rotation of the amino group in a quasi-classical approximation have been calculated (Y. Wang et al., 1993).

We present herein a more comprehensive analysis of the $\geq\text{C-NH}_2$ fragment interconversion in DNA bases - its plane inversion and anisotropic internal rotation of the amino group and its influence on the structural relaxation of the molecular ring. Summary of our findings makes it possible to describe a complex mechanism of the amino group motion which includes tunneling (only for rotations) and large amplitude motion above the barrier of planarization. Of particular interest, in this context, is the phenomenon of pyramidalization.

The nitrogenous bases with exocyclic amine fragment $\geq\text{C-NH}_2$ are known to have nonrigid structures (for details see (Bludský et al., 1996; Florian et al., 1995; Hovorun & Kondratyuk, 1996; Hovorun et al., 1999)). Their interconversion, i.e. conformational (without breaking chemical bonds) transitions within a molecule, is accomplished in three topologically and energetically distinct ways - plane inversion of the $\geq\text{C-NH}_2$ fragment and two, clockwise or counterclockwise, rotations of the amino group around exocyclic C-N bond *via* plane symmetrical transition states with substantially pyramidalized amine fragment. It should be mentioned that in the planar transition state (TS_1) of the $\geq\text{C-NH}_2$ fragment inversion the exocyclic C-N bond is shortened and the N-H bonds are elongated as compared to those in the nonplanar equilibrium configuration, the valence angle H-N-H becomes close to 120° . In the plane-symmetric transition states of the amino group rotations TS_2 and TS_3 the C-N bond becomes elongated, the N-H bonds become shortened and the valence angle H-N-H distinctly deviates from 120° , at that the amine fragment $\geq\text{C-NH}_2$ is highly pyramidalized as compared to the equilibrium configuration. All these results clearly demonstrate that the structural nonrigidity of nitrogenous bases is determined by intramolecular quantum-chemical effect - p- π -conjugation of a lone electron pair (LEP) of the nitrogen atom of the amine fragment $\geq\text{C-NH}_2$ with the π -electronic system of the ring (Dolinnaya & Gromova, 1983; Dolinnaya & Gryaznova, 1989).

3.1 Pyramidalization of the amine fragment of the Ade

So, we demonstrated that Ade ($\text{N1C6N6H}=0.013^\circ$; $\text{C5C6N6H}=-0.014^\circ$) is an effectively planar molecule (effective symmetry C_s) (Hovorun et al., 1995a, 1995b, 1999; Hovorun & Kondratyuk, 1996). Its interconversion is accomplished *via* two plane-symmetric transition states with Gibbs free energy of 14.34 and 14.57 kcal/mol and also through the planar transition state with

the activation energy of 0.12 kcal/mol¹ (Table 1). MP2 complete basis set limit method with the aug-cc-pVTZ → aug-cc-pVQZ (aTZ → aQZ) extrapolation scheme has predicted very small planarization barrier of the Ade amino group, 0.015 kcal/mol (Zierkiewicz et al., 2008), which is in very good agreement with the MP2-predicted planarization barrier of 0.020 kcal/mol reported by Wang and Schaefer III (S. Wang & Schaefer III, 2006). Similar results were calculated using coupled cluster CCSD(T) complete basis set method – 0.125 kcal/mol (Zierkiewicz et al., 2008). Thus, the literature review highlights that the amino group in isolated Ade, in the gas phase, is very flexible with a small degree of nonplanarity.

Base	Plane inversion (TS ₁)				Rotation (TS ₂)				Rotation (TS ₃)			
	$\Delta\Delta G$	$\Delta\Delta E$		v, cm ⁻¹	$\Delta\Delta G$	$\Delta\Delta E$		v, cm ⁻¹	$\Delta\Delta G$	$\Delta\Delta E$		v, cm ⁻¹
		kcal/ mol	cm ⁻¹			kcal/ mol	cm ⁻¹			kcal/ mol	cm ⁻¹	
Ade	-0.06*	0.12* 0.02#	42.3* 7.0#	309.4*	14.34	13.30 4652.7	539.5	14.57	13.51 4727.3	539.5		
Gua	0.37	0.91 0.74#	318.6 258.9#	542.6	9.14	9.48 3316.4	327.9	5.40	5.35 1872.1	327.9		
Cyt	0.06	0.08 0.03#	28.9 10.5#	212.2	11.9	11.74 4105.3	524.6	15.85	16.11 5633.7	524.6		

* - values obtained at the MP2/6-311++G(2df,pd)//B3LYP/cc-pVDZ level of theory (Brovarets' & Hovorun, 2010b);
- values obtained at the MP2/aug-cc-pVQZ level of theory (S. Wang & Schaefer III, 2006);
TS₂ - transition state of the amino group rotation toward the N1 atom for Ade, Gua or the N3 atom for Cyt;
TS₃ - transition state of the amino group rotation toward the N7 atom for Ade, the N3 atom for Gua or the C5-H group for Cyt

Table 1. Relative values of Gibbs free energy ($\Delta\Delta G$) (T=298.15 K) and electronic energy ($\Delta\Delta E$) (in kcal/mol) for the Ade, Gua, and Cyt transition states of amino group interconversion (plane inversion TS₁ and anisotropic rotations TS₂, TS₃) and corresponding vibrational modes (in cm⁻¹) obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory in vacuum

We obtained that the deviations from the main geometric parameters of ≥C6-N6H₂ amine fragment of Ade are the following: the length of the C6-H6 bond is increased by 0.072 and 0.074 Å, the lengths of the N6-H are decreased on average by 0.011 Å, and the valence angle H-N6-H is decreased from 120.4° up to 105.8° and 105.9° at the transition states TS₂ and TS₃, respectively, as compared to those in the nonplanar equilibrium configuration of Ade (Brovarets' and Hovorun, 2010b). In the planar transition state TS₁ of the ≥C6-N6H₂ fragment inversion the exocyclic C6-N6 bond is shortened by 0.005 Å, the N6-H bonds are elongated by 0.002 Å as compared to those in the nonplanar equilibrium configuration, and the valence angle H-N6-H becomes close to 120° and is equal to 120.9° comparatively with the equilibrium state (118.7°).

3.2 Pyramidalization of the amine fragment of the Gua

It is commonly thought that exactly due to the presence of the neighbouring N1-H group, the pyramidalization of the amino group in guanine is higher than in canonical cytosine and

¹ The result obtained at the MP2/6-311++G(2df,pd)//B3LYP/cc-pVDZ level of theory.

adenine, which have no proton at the nitrogen atom located in the neighbourhood of the amino group. In guanine, one of the amino group hydrogen atoms oriented toward the N1-H bond is more bent down than the second amino group hydrogen atom oriented opposite to this bond. The amine fragment $\geq\text{C2-N2H}_2$ ($\text{N1C2N2H}=-31.1^\circ$; $\text{N3C2N2H}=12.2^\circ$) of Gua can not be considered to be pyramidalized even at $T=0$ K, since the zero-point vibrational energy associated with competent normal mode (542.6 cm^{-1}), which frequency becomes imaginary (371.1 i cm^{-1}) in the transition state of plane inversion, is higher than the planarization electronic energy barrier (0.91 kcal/mol or 318.6 cm^{-1}).

The Gibbs free energies of activation of Gua interconversion *via* the plane-symmetric transition states TS_2 and TS_3 of the amino group rotation (5.40 and 9.14 kcal/mol) from its *trans*- and *cis*-orientation relative to the N1-C2 bond differ markedly from each other. Such a difference in Gibbs free energies of activation can be explained by the fact that the transition state TS_2 is stabilized by electrostatic interactions of the LEP of the N2 atom with the hydrogen atom of the N1-H group and the amino group hydrogen atoms with the LEP of the N3 atom, while in the transition state TS_3 these electrostatic interactions are displaced by repulsion of LEP of the N2 and N3 atom and the amino group hydrogen atoms from the N1-H group hydrogen atom that leads to destabilization of this transition state (Brovarets' and Hovorun, 2010b).

In the Gua* mutagenic tautomer ($\Delta G=0.13\text{ kcal/mol}$) which can mispair with Thy (Dąbkowska et al., 2005; Danilov et al., 2005; Mejía-Mazariegos & Hernández-Trujillo, 2009) the hydroxyl group O6-H is *cis*-oriented relatively to the N1-C6 bond. The barrier of planar inversion for Gua* is significantly lower than that for Gua (Brovarets' & Hovorun, 2010b).

3.3 Pyramidalization of the amine fragment of the Cyt

We also demonstrated that Cyt is a structurally nonrigid molecule. Its interconversion occurs through three topologically and energetically distinct ways - plane inversion of the amine fragment $\geq\text{C4-N4H}_2$ ($\text{N3C4N4H}=7.2^\circ$; $\text{C5C4N4H}=-11.7^\circ$) *via* the transition state TS_1 and two anisotropic (clockwise and counterclockwise) rotations of the amino group around the exocyclic C4-N4 bond *via* the transition states TS_2 and TS_3 , respectively. The planarization barrier of Cyt amino group is not large enough (28.9 cm^{-1}) (Table 1) to allow the arrangement at least one vibrational level ($n=0$) of competent mode (212.1 cm^{-1}), which frequency becomes imaginary (154.6 i cm^{-1}) in the transition state TS_1 of planarization of the Cyt amino group. The calculated low planarization barrier of Cyt leads to large amplitude anharmonic vibration of the amino group of Cyt over the barrier (Brovarets' and Hovorun, 2011a).

The Gibbs free energy of activation for rotation of the amino group about the C4-N4 bond when the LEP of the N4 atom is oriented to the hydrogen atom of the C5-H group ($\text{N3C4N4H}_1=56.6^\circ$; $\text{N3C4N4H}_2=-56.5^\circ$; $\text{HN4H}=104.8^\circ$) is found to be notably lower (11.85 kcal/mol) than in the case when the LEP of the N4 atom is oriented to the N3 atom ($\text{N3C4N4H}_1=120.6^\circ$; $\text{N3C4N4H}_2=-120.6^\circ$; $\text{HN4H}=107.4^\circ$) - 15.85 kcal/mol . This can be explained by the fact that the attractive interactions in the first case (the LEP of the N4 atom with the C5-H and amino protons with the LEP of the N3 atom) are replaced by repulsive ones (between the LEPs of the N4 and N3 atoms and between the amino protons and the hydrogen atom of the C5-H group).

So, extremely low planarization barrier implies that Ade, Cyt and Gua require very little energy to conform the structure of the amino group for formation of the complementary H-bonds with other molecules. This fact is very important for base pairing in nucleic acids or other polymers containing Ade, Gua and Cyt residues.

3.4 Planarity or nonplanarity of DNA bases

The thorough analysis of our results and also interpretation of the data reported in literature (Bludský et al., 1996; Hobza & Šponer, 1999; Hovorun et al., 1995a, 1995b, 1999; Hovorun & Kondratyuk, 1996; Larsen et al., 1976; Lister et al., 1974; Šponer & Hobza, 1994; S. Wang & Schaefer III, 2006; Zierkiewicz et al., 2008) allow us to offer the following conclusions. The nucleobases with amino group are effectively planar structures with effective symmetry C_s . This is due to the fact that zero-point vibrational level of inverse out-of-plane vibration of their $\geq C-NH_2$ amine fragment is located above the barrier of its plane inversion, and the maximum of the quadrate of the ψ -function for this vibration coincides with the barrier of the inversion (Fig. 1). In other words, the above-mentioned inversion oscillator has an essentially quantum behavior and can not be appropriately described in the framework of classical mechanics. “Equilibrium”, “static” characteristics of the $\geq C-NH_2$ amine fragment, namely the valence and dihedral angles, which are commonly interpreted by investigators as geometric parameters of equilibrium “nonplanarity” of amine fragment of Ade, Cyt and Gua, should be considered rather as dynamic characteristics of vibration mode of amine fragment inversion and no more than this.

At the same time, the two other nucleobases, Ura and Thy, are undoubtedly planar structures with point symmetry C_s (S. Wang & Schaefer III, 2006): the maximum of the quadrate of the ψ -function for low-frequency out-of-plane vibrations of pyrimidine ring coincides with the minimum of the potential energy that meets the planar structure (Fig. 1).

Fig. 1. Qualitative representation of potential energy profile (red line) of the amino group planarization in the case of Ade, Cyt and Gua (a) and out-of-plane ring deformation in the case of Ura and Thy (b) and quadrate of the ψ -function (blue line) for corresponding zero-point vibrational levels

All canonical DNA bases are rather “soft” structures taking into account nonplanar out-of-plane deformation. Therefore, their static, equilibrium nonplanarity, which is observed, particularly in crystal state and in isolated nucleosides (Yurenko et al., 2007a, 2007b, 2007c, 2008, 2009; Zhurakivsky & Hovorun, 2006, 2007a, 2007b) or nucleotides (Nikolaienko et al.,

2011a, 2011b, 2011c), is induced by anisotropic forces of crystal packaging and intramolecular interactions within nucleosides or nucleotides, respectively.

The amine fragment $\geq\text{C-NH}_2$ of DNA bases indeed determines their structural nonrigidity, which is in turn conditioned by quantum intramolecular effect, namely p- π -conjugation of a LEP of amino nitrogen atom with π -electron system of the ring. This specific phenomenon of conjugation is purely quantum and has no classical analogue.

Exactly the structural nonrigidity of the polar amine fragment in DNA bases is a reason to adequately explain a static nonplanarity of amine fragment induced by an external electrical field which deforms it so that the projection of the induced dipole moment on the field direction is maximal and coincides with vector of field strength (Brauer et al., 2011; Choi et al., 2005, 2008; Dong & Miller, 2002).

4. Mutagenic tautomers of DNA bases and possible molecular mechanisms of their formation

4.1 Mutagenic tautomers of DNA bases

For structural chemists, rare tautomers of DNA bases are of special interest because they exert strong mutational pressures on the genome (Friedberg et al., 2006; Harris et al., 2003; Kwiatkowski & Pullman, 1975). That's why the tautomerism of DNA bases and their biologically active modifications (Kondratyuk et al., 2000; Samijlenko et al., 2001) have been the subject of a great number of theoretical and experimental investigations due to their biochemical significance.

Numerous experimental and theoretical efforts have been directed towards the elucidation of qualitative and quantitative aspects of Cyt tautomerism, the data obtained up until about 1974 have been reviewed by Kwiatkowski and Pullman (Kwiatkowski & Pullman, 1975). In the solid phase, Cyt exists in a single keto-amino tautomeric state. However, experiments performed in the gas phase and in low-temperature inert matrices clearly demonstrated that Cyt exists as a mixture of several tautomeric forms (Bazsó et al., 2011; Brown et al., 1989b; Choi et al., 2005; Dong & Miller, 2002; Feyer et al., 2009; Govorun et al., 1992; Kostko et al., 2010; Lapinski et al., 2010; Min et al., 2009; Nir et al., 2001a, 2002a, 2002b; Nowak et al., 1989a; Radchenko et al., 1984; Szczesniak et al., 1988). Still, there are three matrix-isolation infrared spectroscopic studies on Cyt tautomerisation (Nowak et al., 1989a, 1989b; Radchenko et al., 1984; Szczesniak et al., 1988). Three tautomers of Cyt have been identified by molecular beam microwave spectroscopy with an estimated abundance of 1:1:0.25 for keto:amino-enol:keto-imino tautomers (Brown et al., 1989b). Several groups have explored the ultrafast excited-state dynamics of Cyt in molecular beams (Canuel et al., 2005; Kang et al., 2002; Kosma et al., 2009; Ullrich et al., 2004). As have been pointed out elsewhere (Fogarasi, 2002; Kosma et al., 2009; Ullrich, 2004), one ambiguity in these experiments is the coexistence of two or more tautomeric forms of Cyt in the gas phase.

The first experimental observation of amino-keto and amino-enol tautomeric forms of Gua has been performed on isolated species in cold inert gas matrix by ground state infrared spectroscopy (Sheina et al., 1987; Szczepaniak & Szczesniak, 1987). By using UV-UV, IR-UV hole burning (Nir et al., 2001b, 2002b) and resonance-enhanced multiphoton ionization (REMPI) (Nir et al., 1999, 2002b) spectroscopy, de Vries and co-workers found spectral

features that they assigned to the N9H keto, N7H keto, and N9H enol (*cis*- or *trans*-) forms. However, the most intense band assigned to the N9H enol was later attributed by Mons and co-workers (Chin et al., 2004; Mons et al., 2002) to a higher-energy form of the N7H enol tautomer. Furthermore, they observed the fourth band, which they assigned to the N9H *cis*-enol form. Choi and Miller studied Gua molecules embedded in He droplets (Choi & Miller, 2006) and assigned the IR spectroscopic data to a mixture of the four more stable tautomeric forms: N7H keto, N9H keto, and N9H *cis*- and *trans*-enol. Mons et al. (Mons et al., 2006) later reported a new interpretation of the resonant two-photon ionization (R2PI) spectra. The authors suggested the occurrence of a fast nonradiative relaxation of the excited states of the N7H keto, N9H keto, and N9H *trans*-enol tautomeric forms that prevents the observation of these species in the R2PI spectra. The consistency between the experimental data obtained by molecular-beam Fourier-transform microwave (MB-FTMW) spectroscopy and theoretical calculations enabled Alonso and his collaborators to unequivocally identify the four most stable tautomers of guanine in the gas phase (Alonso et al., 2009). Recently also different tautomers of Gua were detected using vacuum ultraviolet (VUV) photoionization (Zhou et al., 2009). Theoretical calculations (Chen & Li, 2006; Elshakre, 2005; Hanus et al., 2003; Marian, 2007; Trygubenko et al., 2002) predict the existence of four low-energy tautomers with stabilities in the range 0–400 cm⁻¹, whereby the keto tautomers with a hydrogen atom at the N7 or N9 atoms are the most stable.

Besides its role as a nucleic acid building block, Ade and its derivatives are of interest in various other biochemical processes. For example, it is the main component of the energy-storing molecule adenosine triphosphate. Its high photostability under UV irradiation is an intriguing property that has been suggested to be essential for the preservation of genetic information (Crespo-Hernández et al., 2004).

Furthermore, the various tautomeric forms of Ade have been under substantial scrutiny (Hanus et al., 2004; Kwiatkowski & Leszczynski, 1992; Laxer et al., 2001; Mishra et al., 2000; Nowak et al., 1989b, 1991, 1994a, 1994b, 1996; Plützer et al., 2001; Plützer & Kleinermanns, 2002; Salter & Chaban, 2002), because of their proposed role in mutagenic and carcinogenic processes (Danilov et al., 2005; Harris et al., 2003; Topal & Fresco, 1976). Some of the first IR spectra of Ade recorded in low-temperature inert gas matrices in the 400 to 4000 cm⁻¹ range date back to 1985 (Stepanian et al., 1985). This study was extended by comparing the experimental spectra with calculated IR frequencies at different levels of theory (Brovarets' & Hovorun, 2011b; Nowak et al., 1989b, 1991, 1994a, 1994b, 1996). It was concluded that the absorption of Ade was due to its 9H tautomer. Ade in the gas phase has been studied by UV photoelectron (Lin et al., 1980), microwave (Brown et al., 1989a), IR (Colarusso et al., 1997), jet-cooled REMPI (N.J. Kim et al., 2000; Lühns et al., 2001; Nir et al., 2001a, 2002b), IR-UV ion-dip (Nir et al., 2001a, 2002b; Plützer & Kleinermanns, 2002; Plützer et al., 2001; Van Zundert et al., 2011) and IR multiple-photon dissociation (IRMPD) spectroscopic investigations (Van Zundert et al., 2011). In all of these studies, it was suggested that the 9H amino tautomer of Ade is the dominant contributor to the spectra. The experimental results agree closely with calculations at different levels of theory and consistently show the 9H amino tautomer to be the most stable one (Brovarets' & Hovorun, 2011b; Hanus et al., 2004; Fonseca Guerra et al., 2006; Kwiatkowski & Leszczynski, 1992; Norinder, 1987; Nowak et al., 1989b, 1991, 1994a, 1994b, 1996; Sabio et al., 1990; Saha et al., 2006; Sygula & Buda, 1983; Wiorkiewicz-Kuczera & Karplus, 1990).

The existence of other Ade tautomers was evidenced by experimental studies (García-Terán et al., 2006; Gu & Leszczynski, 1999; Lührs et al., 2001; Stepanyugin et al., 2002a; Sukhanov et al., 2003), often in the presence of a metal (Samijlenko et al., 2004; Vrkic et al., 2004). It was also found that the Ade imino tautomer is more stabilized under the influence of charged platinum (Burda et al., 2000) or mercury (Zamora et al., 1997) cations.

It is generally believed that Thy exists in the canonical diketo form in the gas phase as well as in the aqueous solution (Kwiatkowski & Pullman, 1975), but there is experimental evidence of small amounts of its rare tautomeric forms in the gas phase (Fujii et al., 1986; Tsuchiya et al., 1988) and in the solution (Hauswirth & Daniels, 1971; Katritzky & Waring, 1962; Morsy et al., 1999; Samijlenko et al., 2010; Suwaiyan et al., 1995). Also laser ablation in combination with MB-FTMW spectroscopy spectroscopy has been used to establish unambiguously the presence of the diketo form of thymine in the gas phase and to obtain its structure (López et al., 2007). In some theoretical reports, there is also a substantial emphasis on the energetic and structural characteristics of the stable isolated tautomers of Thy (Basu et al., 2005; Fan et al., 2010; Mejía-Mazariegos & Hernández-Trujillo, 2009), indicating that the diketo is the most stable isomer both in the gas phase and in solution.

4.2 Intramolecular tautomerisation of the DNA bases

In this section the intramolecular tautomerisation of nucleotide bases as a factor in spontaneous mutagenesis is considered using quantum-chemical calculation methods. In particular, the forward and reverse barrier heights for proton transfer reactions in isolated DNA bases have been estimated and analysed.

The mutagenic tautomers of all DNA bases are depicted in Figure 2, while Table 2 shows their relative Gibbs free energies and kinetic parameters of the tautomerisation. As seen from Table 2 the mutagenic tautomers both of Cyt and Gua are energetically close to their

Conversion	$\Delta\Delta G_{TS}$, kcal/mol	k, s ⁻¹	τ , s	$\tau_{1/2}$, s	$\tau_{99.9\%}$, s	ΔG , kcal/mol	K
Ade→Ade*	45.58	9.67 ·10 ⁻²¹	1.03 ·10 ²⁰	7.17 ·10 ¹⁹	5.14 ·10 ¹⁰	14.00	5.4 ·10 ⁻¹¹
Ade*→Ade	31.58	1.79 ·10 ⁻¹⁰	5.59 ·10 ⁹	3.87 ·10 ⁹			
Thy→Thy*	39.09	5.60 ·10 ⁻¹⁶	1.79 ·10 ¹⁵	1.24 ·10 ¹⁵	4.73 ·10 ⁷	11.64	2.88·10 ⁻⁹
Thy*→Thy	27.45	1.95 ·10 ⁻⁷	5.14 ·10 ⁶	3.56 ·10 ⁶			
Cyt→Cyt*	38.47	1.61 ·10 ⁻¹⁵	6.22 ·10 ¹⁴	4.31 ·10 ¹⁴	1.35 ·10 ¹⁴	2.21	2.88·10 ⁻⁹
Cyt*→Cyt	36.27	6.68 ·10 ⁻¹⁴	1.50 ·10 ¹³	1.04 ·10 ¹³			
Gua→Gua*	32.17	6.50 ·10 ⁻¹¹	1.54 ·10 ¹⁰	1.07 ·10 ¹⁰	6.28 ·10 ¹⁰	0.13	7.98·10 ⁻¹
Gua*→Gua	32.04	8.15 ·10 ⁻¹¹	1.23 ·10 ¹⁰	8.50 ·10 ⁹			

$\Delta\Delta G_{TS}$ – the Gibbs free energy of activation for tautomerisation (T=298.15 K); k - the rate constant; τ – the lifetime; $\tau_{1/2}$ – the half-lifetime;; $\tau_{99.9\%}$ – the time necessary to reach 99.9% of the equilibrium concentration of rare tautomer in the system; ΔG – the relative Gibbs free energy of the tautomerized base (T=298.15 K); K – the equilibrium constant of tautomerisation

Table 2. Basic thermodynamic and kinetic characteristics of intramolecular tautomerisation of DNA bases obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory in vacuum #

canonical tautomers that is in a complete agreement with the experimental data on Cyt and Gua tautomers (Nir et al., 1999, 2001a, 2001b, 2002a, 2002b) and their Gibbs free energy differences are only 2.21 and 0.13 kcal/mol, relatively. The considerably greater differences in energy of 14 and 12 kcal/mol were found for the mutagenic tautomers of Ade and Thy, respectively. This finding can explain why the mutagenic tautomers of Ade and Thy can not be detected experimentally.

Fig. 2. Intramolecular tautomerisation of the DNA bases. The dotted line indicates intramolecular H-bond N1H...O6 in TS₄, while continuous lines show covalent bonds. Relative Gibbs free energy is presented near each structure in kcal/mol (T=298.15 K, in vacuum)

The intramolecular proton transfer schemes for isolated DNA bases are displayed in Figure 2. The MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) reaction barriers for the forward tautomerisation are 45.58 (Ade), 39.09 (Thy), 38.47 (Cyt) and 32.17 kcal/mol (Gua) and these values tightly correlate with the literature data (Basu et al., 2005; Brovarets' & Hovorun, 2010a, 2010f; Danilov et al., 2005; Fan et al., 2010; Fogarasi & Szalay, 2002; Fogarasi, 2008; Fonseca Guerra et al., 2006; Gorb & Leszczynski, 1998a, 1998b; Gorb et al., 2001; Gu & Leszczynski, 1999; Hanus et al., 2003, 2004; Kosenkov et al., 2009; Mejía-Mazariegos & Hernández-Trujillo, 2009; Saha et al., 2006). Very large kinetic barriers for intramolecular tautomerisation of all isolated DNA bases (above 32 kcal/mol) indicate that such tautomerisation will be very slow and this process may not occur readily in the isolated molecule. So, in such a way it is not possible to attain the equilibrium concentrations within biologically important period of time, namely during the replication of one base pair (*ca.* 10^{-4} s), as the value of $\tau_{99.9\%}$ amounts to more than 10^7 s. However, mutagenic tautomers, once formed, will be stable with a lifetime that by 3–10 orders exceeds the typical time of DNA replication in the cell ($\sim 10^3$ s). This fact confirms that the postulate, on which the Watson-Crick tautomeric hypothesis of spontaneous transitions grounds, is adequate (Brovarets' & Hovorun, 2010a). It should be noted that equilibrium constants of Ade ($5.4 \cdot 10^{-11}$) and Thy ($2.88 \cdot 10^{-9}$) tautomerisation fall within the range of measured mutation frequency, but for the Cyt ($2.4 \cdot 10^{-2}$) and Gua ($8.0 \cdot 10^{-1}$) - remain above this value.

Of course, DNA bases are not isolated in living systems. In cellular DNA, the transition from canonical to mutagenic tautomers of nucleotide bases could be facilitated by the interactions with surrounding molecules. Also as suggested by Rodgers (Yang & Rodgers, 2004), bimolecular (intermolecular) tautomerisation may be much more feasible than monomolecular (intramolecular) tautomerisation.

4.3 The Löwdin's mechanism of the spontaneous point mutations

As seen from the literature survey, the possible tautomerisation of Gua·Cyt and Ade·Thy Watson-Crick base pairs occurs by Löwdin's mechanism (Fig. 3) through proton transfer along two neighbouring intermolecular H-bonds (Löwdin, 1963, 1965, 1966). However, the models exploring Löwdin's mechanism (Cerón-Carrasco et al., 2011; Cerón-Carrasco & Jacquemin, 2011; Florian et al., 1994, 1995; Florian & Leszczynski, 1996; Gorb et al., 2004; Villani, 2005, 2006, 2010) neglect the fact that electronic energy of reverse barriers of Gua·Cyt and Ade·Thy tautomerisation must exceed zero-point energy of vibrations causing this tautomerisation to provide dynamic stability (Gribov & Mushtakova, 1999) of the formed (Löwdin's) Gua*·Cyt* and Ade*·Thy* mispairs, accordingly. In addition, this barrier must exceed a dissociation energy of the formed mispair to allow such complex easily dissociate into mutagenic tautomers during DNA replication. The results of our calculations definitely demonstrated that the zero-point energy 1475.9 and 1674.6 cm⁻¹ (Table 7) for Gua*·Cyt* and Ade*·Thy* base pairs, accordingly, of corresponding vibrational modes which frequencies become imaginary in the transition states of Gua·Cyt and Ade·Thy base pairs tautomerisation lies above (1800.8 cm⁻¹) and under (37.7 cm⁻¹) the value of the reverse barrier, accordingly (Table 3, 7). This means that Ade*·Thy* mispair is

Fig. 3. Interconversion of Ade·Thy↔Ade*·Thy* and Gua·Cyt↔Gua*·Cyt* base pairs resulting from the mutagenic tautomerisation of DNA bases. Relative Gibbs free (T=298.15 K, in vacuum) and electronic (in brackets) energies are obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory and reported near each structure in kcal/mol. The dotted lines indicate H-bonds AH...B (their lengths H...B are presented in angstroms), while continuous lines show covalent bonds

dynamically unstable, moreover, the value of its reverse barrier (in terms of Gibbs free energy) is negative (-1.01 kcal/mol) indicating that Ade*.Thy* minimum completely disappears from the Gibbs free energy surface. Therefore, Ade*.Thy* mispair really doesn't exist (Fig. 3). By comparing the values of zero-point energy (Table 3, 7) and the reverse barrier (Tables 3, 7) of the Gua·Cyt↔Gua*.Cyt* tautomerisation, we came to the conclusion that Gua*.Cyt* mispair is metastable.

Conversion	$\Delta\Delta G_{TS}$, kcal/mol	k, s ⁻¹	τ , s	$\tau_{1/2}$, s	$\tau_{99.9\%}$, s	ΔG , kcal/mol	K
Ade·Thy→Ade*.Thy*	11.05	5.49 ·10 ⁴	1.82 ·10 ⁻⁵	1.26 ·10 ⁻⁵	2.37 ·10 ⁻¹³	12.07	1.41 ·10 ⁻⁹
Ade*.Thy*→Ade·Thy	-1.01	3.88 ·10 ¹³	2.57 ·10 ⁻¹⁴	1.78 ·10 ⁻¹⁴			
Gua·Cyt→Gua*.Cyt*	9.70	9.02 ·10 ⁵	1.11 ·10 ⁻⁶	7.68 ·10 ⁻⁷	9.61 ·10 ⁻¹²	8.22	9.42 ·10 ⁻⁷
Gua*.Cyt*→Gua·Cyt	1.49	9.58 ·10 ¹¹	1.04 ·10 ⁻¹²	7.24 ·10 ⁻¹³			
Ade·Cyt*→Ade*.Cyt	7.76	2.26 ·10 ⁷	4.42 ·10 ⁻⁸	3.06 ·10 ⁻⁸	4.63 ·10 ⁻¹⁰	4.01	1.14 ·10 ⁻³
Ade*.Cyt→Ade·Cyt*	3.75	1.99 ·10 ¹⁰	5.03 ·10 ⁻¹¹	3.49 ·10 ⁻¹¹			
Gua·Thy*→Gua*.Thy	2.33	2.74 ·10 ¹¹	3.65 ·10 ⁻¹²	2.53 ·10 ⁻¹²	4.18 ·10 ⁻¹²	1.16	1.42 ·10 ⁻¹
Gua*.Thy→Gua·Thy*	1.17	1.93 ·10 ¹²	5.18 ·10 ⁻¹³	3.59 ·10 ⁻¹³			

see designations in Table 2

Table 3. Basic thermodynamic and kinetic characteristics of tautomerisation of Watson-Crick DNA base pairs obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory in vacuum #

Comparatively with the reverse barriers heights of tautomerisation of the Gua*.Cyt* and Ade*.Thy* mispairs (5.15 and 0.11 kcal/mol, respectively) the values of their interaction energies (22.94 and 33.80 kcal/mol , respectively) are high enough for mispairs dissociation into mutagenic tautomers (Table 6).

Although the equilibrium constants of tautomerisation of the Gua*.Cyt* (9.42 ·10⁻⁷) and Ade* ·Thy* (1.41 ·10⁻⁹) (Table 3) mispairs involving mutagenic tautomers fall within the range of the mutation frequency (Drake, 1991), their lifetimes (1.04 ·10⁻¹² s and 2.57 ·10⁻¹⁴ s , accordingly, see Table 3) are negligible comparably with the time of one base pair dissociation during the enzymatic DNA replication (10⁻⁹ s) to cause spontaneous mutations. So, Löwdin's mispairs "escape from the hands" of replication apparatus.

These data indicate that Löwdin's mechanism is not sufficient to explain the mutagenic tautomers formation within Ade ·Thy and Gua ·Cyt base pairs of DNA.

4.4 Tautomerisation of the DNA bases facilitated by an isolated water molecule

It has been established quite some time ago that there is a shell of tightly bound water molecules at the surface of DNA with properties significantly different from those of bulk water and it seems that DNA interaction with water largely determines its conformation, stability, and ligand binding properties (J.H. Wang, 1955; Tunis & Hearst, 1968; Falk et al., 1970; Kubinec and Wemmer, 1992). The pure rotational spectra of the binary adducts of Ura and Thy with water were first observed by laser ablation molecular beam Fourier transform

microwave spectroscopy (López et al., 2010). Investigation of the structure of the adducts from the rotational constants of the different isotopologues shows that the observed conformers of bases correspond to the most stable forms in which water closes a cycle with the nucleic acid bases through H-bonds (López et al., 2010).

In this work we for the first time present a complete study of the proton transfer kinetic of intramolecular water-assisted tautomerisation mechanism for all DNA bases (Fig. 4) by computing the rate constants with the conventional transition state theory (Atkins, 1998), including the Wigner's tunnelling correction (Wigner, 1932).

Fig. 4. Water-assisted tautomerisation of the DNA bases. The dotted lines indicate H-bonds AH...B (their lengths H...B are presented in angstroms), while continuous lines show covalent bonds. Relative Gibbs free energies (T=298.15 K, in vacuum) are obtained at the MP2/6-311++G(2df,pd)/B3LYP/6-311++G(d,p) level of theory and reported near each structure in kcal/mol

We found that the interaction of the canonical tautomers of the DNA bases with a water molecule at the Watson-Crick edge changes the gas-phase stability: the relative Gibbs free energies of the Ade and Thy decrease, while those of the Cyt and Gua – increase (Table 4). So, it means that in the case of complexes with water, the order of stability of Ade and Thy mutagenic tautomers remains the same as for isolated bases; moreover, they are stabilized in these complexes. On the contrary, the order of stability of Cyt and Gua mutagenic tautomers

changes in their complexes with water. So, equilibrium constants of tautomerisation for the Ade·H₂O and Thy·H₂O complexes ($4.89 \cdot 10^{-8}$ and $3.39 \cdot 10^{-7}$, respectively) fall into the mutationally significant range, while for the Cyt·H₂O and Gua·H₂O complexes ($4.16 \cdot 10^{-3}$ and $2.16 \cdot 10^{-2}$, respectively) these values are considerably higher (Table 4).

For comparison, computation results reported by Gorb and Leszczynski (Gorb & Leszczynski, 1998a, 1998b) are of a special interest. As part of their comprehensive study of water-mediated proton transfer between canonical and mutagenic tautomers of Cyt and Gua, the authors have shown that the interaction with water changes the order of relative energies of cytosine tautomers.

Conversion	$\Delta\Delta G_{TS}$, kcal/mol	k, s ⁻¹	τ , s	$\tau_{1/2}$, s	$\tau_{99.9\%}$, s	ΔG , kcal/mol	K
Ade·H ₂ O→Ade*·H ₂ O	18.53	$3.80 \cdot 10^{-1}$	2.63	1.82	$1.19 \cdot 10^{-6}$	9.97	$4.89 \cdot 10^{-8}$
Ade*·H ₂ O→Ade·H ₂ O	8.56	$7.77 \cdot 10^6$	$1.29 \cdot 10^{-7}$	$8.92 \cdot 10^{-8}$			
Thy·H ₂ O→Thy*·H ₂ O	15.51	$8.12 \cdot 10^1$	$1.23 \cdot 10^{-2}$	$8.54 \cdot 10^{-3}$	$3.84 \cdot 10^{-8}$	8.82	$3.39 \cdot 10^{-7}$
Thy*·H ₂ O→Thy·H ₂ O	6.69	$2.40 \cdot 10^8$	$4.17 \cdot 10^{-9}$	$2.89 \cdot 10^{-9}$			
Cyt·H ₂ O→Cyt*·H ₂ O	15.00	$1.80 \cdot 10^2$	$5.57 \cdot 10^{-3}$	$3.86 \cdot 10^{-3}$	$2.13 \cdot 10^{-4}$	3.25	$4.16 \cdot 10^{-3}$
Cyt*·H ₂ O→Cyt·H ₂ O	11.75	$4.32 \cdot 10^4$	$2.32 \cdot 10^{-5}$	$1.61 \cdot 10^{-5}$			
Gua·H ₂ O→Gua*·H ₂ O	11.63	$5.78 \cdot 10^4$	$1.73 \cdot 10^{-5}$	$1.20 \cdot 10^{-5}$	$3.37 \cdot 10^{-6}$	2.27	$2.16 \cdot 10^{-2}$
Gua*·H ₂ O→Gua·H ₂ O	9.36	$2.68 \cdot 10^6$	$3.74 \cdot 10^{-7}$	$2.59 \cdot 10^{-7}$			

see designations in Table 2

Table 4. Basic thermodynamic and kinetic characteristics of water-assisted tautomerisation of DNA bases obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory in vacuum #

It should be noted that in the works devoted to the water-assisted tautomerisation (Fogarasi & Szalay, 2002; Furmanchuk et al., 2011; Gu & Leszczynski, 1999; H.-S. Kim et al., 2007; López et al., 2010; Michalkova et al., 2008; Sobolewski & Adamowicz, 1995) the authors did not justify their choice of the Watson-Crick edges of nucleotide bases (Watson & Crick, 1953a, 1953b) for interaction with a water molecule. This can be explained by the absence of the experimental or theoretical data on hydration of the isolated DNA bases. Up to date, the reported data include only the analysis of hydration of DNA bases in crystal structures of oligonucleotides of A- (Schneider et al., 1992), B- (Schneider et al., 1992, 1993; Schneider & Berman, 1995) and Z-forms of DNA (Schneider et al., 1992, 1993) and wide angle neutron scattering study of an A-DNA fiber (Langan et al., 1992). These studies revealed that sites of the preferred hydration of base pairs are localized in the major groove of DNA. Later on Fogarasi et al. (Fogarasi & Szalay, 2002) have demonstrated that the preferable position for water binding to Cyt is the O=C2-N1-H (H-O-C2=N1 in the enol form) moiety.

The energy barriers for water-assisted tautomerisation are greatly reduced (by 21-27 kcal/mol) as compared with the corresponding ones in the gas phase. Therefore, the explicit water molecules could accelerate by several orders the tautomerisation process from canonical to mutagenic tautomer. Such significant reduction in the internal tautomerisation barriers could be explained by the formation of the H-bonds between the water molecule and nucleic acid bases, which stabilize the transition state.

The time necessary to reach 99.9% of the equilibrium concentration of mutagenic tautomer in the system ($\tau_{99.9\%}$) for these barriers falls within the range $3.84 \cdot 10^{-8} \div 2.13 \cdot 10^{-4}$ s, which is by orders smaller, except Cyt, than the time of an elementary act of one base pair replication (*ca.* $4 \cdot 10^{-4}$ s). The barriers for the reverse reactions lead to a half-lifetime of about 10^{-9} s, and tunneling effects will further facilitate the reverse process. So, complexes “mutagenic tautomer-water” produced in the DPT process represent unstable intermediates, which quickly converted back into the complexes “canonical tautomer-water” in the time scale of the nucleotide-water interaction. However, if the dissociation of the water from the tautomerized complex occurs, the mutagenic tautomer would be a long-lived species, as the barrier for the reverse conversion to canonical tautomer is more than *ca.* 27 kcal/mol (see Table 2). It should be noted that electronic energy of the dissociation of the Ade*·H₂O and Thy*·H₂O complexes (Table 5) are lower than the corresponding reverse barriers. So, it can mean that these complexes more probably decay to the mutagenic tautomers and water molecule. To the contrary, in the case of Gua and Cyt – the Gua*·H₂O and Cyt*·H₂O transition to the complexes involving canonical tautomers will be more probable than the decay of the tautomerized complexes. Following the electronic energies of the interaction between bases and molecules of water, we could conclude that transition to the complexes containing mutagenic tautomers of Ade and Thy isn’t preferential as they have larger electronic energies of the interaction that complicates their dissociation into mutagenic tautomers (Table 5). Interaction energy of the DNA bases with water is less than the energy of interaction with the complementary bases. So, the nucleotide bases competing with water for binding will displace water to the periphery of the interaction interface.

Complex	-ΔE _{int}	ΔΔE	ΔΔG
Ade·H ₂ O	9.60	-	-
Ade*·H ₂ O	12.72	11.56	8.56
Thy·H ₂ O	8.74	-	-
Thy*·H ₂ O	12.48	9.55	6.69
Cyt·H ₂ O	11.26	-	-
Cyt*·H ₂ O	10.16	14.93	11.75
Gua·H ₂ O	11.52	-	-
Gua*·H ₂ O	9.72	12.40	9.36

ΔE_{int} – the counterpoise-corrected electronic energy of interaction; ΔΔE – the reverse barrier (difference in electronic energy) of tautomerisation; ΔΔG – the reverse barrier (difference in Gibbs free energy) of tautomerisation

Table 5. Electronic and Gibbs free energies (in kcal/mol) (T= 298.15 K) of complexes of DNA bases with water molecule obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory in vacuum#

4.5 Tautomerisation of the DNA bases in dimers

Theoretical and experimental studies also explored agents other than water, which can enhance the stability of rare tautomers of DNA bases in the gas phase. Of particular interest were their interactions with amino acids (Fan et al., 2010; Samijlenko et al., 2001, 2004;

Stepanyugin et al., 2002a, 2002b) and protons or alkali metal cations (Lippert et al., 1986; Lippert & Gupta, 2009; Samijlenko et al., 2010; Šponer et al., 2001), as the extra positive charge could stabilize the structure of rare tautomers through an intramolecular salt bridge. Moreover, the coordination of metal ions to nucleobases is known to lead frequently to the stabilization of rare tautomeric forms (Burda et al., 2000; Lippert et al., 1986; Lippert & Gupta, 2009; Samijlenko et al., 2010), with numerous examples reported for various nucleobases (Lippert & Gupta, 2009; Lippert et al., 1986; Schoellhorn et al., 1989; Renn et al., 1991; Zamora et al., 1997). In these metal-stabilized rare tautomers, the metal is located at a position that is usually occupied by a proton, forcing the proton to move to another position and thereby generating the rare tautomer.

Yang and Rodgers (Yang & Rodgers, 2004) were probably the first to bring up the important question that a possible way of tautomerisation may be through dimerization.

In the literature, there are available papers devoted to the investigation of the tautomerisation of DNA bases by the different chemical compounds, e.g. glycine-assisted tautomerisation of Ura (Dąbkowska et al., 2005) and tautomerisation of Thy by methanol (Fan et al., 2010). However, it was established that such interactions result in the reducing of the internal barrier of tautomerisation and thermodynamic equilibrium could be easily attained at room temperature, the dynamical stability of the tautomerized in such a way complexes remained out of authors' eyeshot.

Providing *ab initio* quantum-chemical study of hydrogen-bonded complexes of acetic acid with canonical and mutagenic tautomers of DNA bases methylated at the glycosidic nitrogen atoms *in vacuo* and continuum with a low dielectric constant we established that all tautomerized complexes are dynamically unstable because their electronic energy barriers for the reverse tautomerisation reaction do not exceed zero-point energy of corresponding vibrational modes, frequencies of which become imaginary in the transition states of tautomerisation (Brovarets' et al., 2010c; Brovarets' et al., 2012) (Fig. 5).

Fig. 5. Qualitative representation of potential energy profile of the $X \leftrightarrow X^*$ conversion. X and X^* - complexes containing DNA base in canonical and mutagenic tautomeric forms, respectively

A potential pathway for the generation of the mutagenic amino-enol form of guanine is reported by Padermshoke et al. (Padermshoke et al., 2008), who investigated DPT reactions in three guanine-guanine dimers, a guanine-thymine wobble base pair, and a model

compound 4(3H)-pyrimidinone dimer using *ab initio* MO calculations and liquid-phase IR spectroscopy. The calculations suggest that the DPT processes in these dimers are energetically accessible and temperature-dependent IR measurements of the model compound reveal that slight thermal energy can induce the DPT reaction, and hence the enol tautomer can appear.

5. Mispairs involving mutagenic tautomers of DNA bases

The mutagenic tautomers of DNA bases can form six possible purine-pyrimidine base pairs - Ade·Cyt*, Ade*·Cyt, Gua*·Thy, Gua·Thy*, Ade*·Thy* and Gua*·Cyt* - thereby demonstrating the electronic and geometrical complementarity.

In a DNA double helix, Gua forms an H-bonded pair with Cyt. Meanwhile, the mutagenic enol form of Gua (Gua*) can pair with Thy (Brovarets' & Hovorun, 2010d; Danilov et al., 2005; Mejía-Mazariegos & Hernández-Trujillo, 2009) instead of Cyt. Similarly, the mutagenic imino form of Cyt (Cyt*) pairs with Ade (Danilov et al., 2005; Fonseca Guerra et al., 2006) instead of Gua. Then, during replication, when the two strands separate the Thy and Ade bases of the anomalous Gua*·Thy and Ade·Cyt* base pairs would combine with Ade and Thy instead of Cyt and Gua, respectively. Thus, the scheme postulated in (Watson & Crick, 1953a, 1953b) leads to a spontaneous transition Gua·Cyt→Ade·Thy in the subsequent rounds of replication if not repaired appropriately (Kunz et al., 2009). In DNA, the canonical form of Ade combines with the canonical form of Thy; however, the Ade* mutagenic imino tautomer combines with Cyt rather than with Thy, while the mutagenic enol form of Thy* forms a pair with Gua instead of Ade. After the strand separation, the counter-base pairs Gua·Cyt and Cyt·Gua instead of Ade·Thy and Thy·Ade are formed, respectively. As a result this leads to a spontaneous Ade·Thy→Gua·Cyt transition.

To gain more insight into the nature of the formed tautomeric base pairs, we have analysed their hydrogen-bonding mechanism and geometrical features to compare them with the same characteristics obtained for the natural Watson-Crick base pairs.

As shown by Kool et al. in the experiments on DNA replication (Guckian et al., 2000; Kool et al., 2000; Morales & Kool, 2000; Kool, 2002), an incoming nucleotide must be able to form, with its partner in the template, a base pair which sterically resembles the natural Watson-Crick base pair (Ade·Thy or Gua·Cyt). In addition, it was recently shown that the ability of the incoming base to form H-bonds with the template base is also of great importance (Bebenek et al., 2011; W. Wang et al., 2011). Bebenek et al. (Bebenek et al., 2011) have shown that a human DNA polymerase λ poised to misinsert dGTP opposite a template Thy can form a mismatch with Watson-Crick-like geometry and Wang et al. (W. Wang et al., 2011) observed that the Ade·Cyt mismatch can mimic the shape of cognate base pairs at the site of incorporation.

According to the geometric selection mechanism of bases as a principal determinant of DNA replication fidelity (Echols & Goodman, 1991; Goodman, 1997; Sloane et al., 1988), the geometrical and electrostatic properties of the polymerase active site are likely to have a profound influence on nucleotide-insertion specificities. This influence would strongly favor the insertion of the base pairs having an optimal geometry, in which the distance between C1 atoms of paired nucleotides and the N9-C1(Pur)-C1(Pyr) and N1-C1(Pyr)-C1(Pur) angles characterizing the nucleotide pair in double helix are most closely approximated to

those of the Watson–Crick base pairs. These values for the irregular base pair as distinguished from the Watson–Crick base pairs reflect the distortion of double helix conformation and can be factor taking into account the recognition of the structural invariants of the sugar-phosphate backbone by the polymerase.

Detailed study of the geometric characteristics for the optimized mutagenic and Watson–Crick base pairs leads to the following results. The distance between the bonds joining the bases to the deoxyribose groups in the Gua^{*}·Thy and Gua·Thy^{*} mutagenic base pairs is close to the corresponding canonical distance in the Gua·Cyt base pair, and the corresponding distance in the Ade^{*}·Cyt and Ade·Cyt^{*} base pairs is close to that in the Ade·Thy base pair. Moreover, in each pair of stereoisomers (Gua^{*}·Thy, Gua·Thy^{*} and Ade^{*}·Cyt, Ade·Cyt^{*}), the N9–C1–C1 and N1–C1–C1 glycosidic angles are close to the corresponding value in one of the Watson–Crick canonical base pairs. Analogous conclusions were made earlier by Topal and Fresco (Topal & Fresco, 1976) and Danilov et al. (Danilov et al., 2005), who studied each of the above-mentioned mutagenic base pairs by model building and by *ab initio* methods, respectively, and showed that these pairs are sterically compatible with the Watson–Crick base pairs.

Finally, according to the molecular mechanism of recognition of the complementary base pairs of nucleic acids by DNA polymerase (Li & Waksman, 2001), the key role in the selection of the correct substrate is the interactions of the certain amino acid residues in the recognition site of DNA polymerase with the invariant arrangement of the N3 purine and O2 pyrimidine atoms (Beard & Wilson, 1998, 2003; Poltev et al., 1998). These hydrogen-bonding interactions may provide a means of detecting misincorporation at this position. Our data show that the structural invariants of the mutagenic nucleotide pairs are very close to those of the correct nucleotide pairs. In other words, the mutual position of the atoms and atomic groups is practically the same both for the correct and the irregular pairs, so that the DNA polymerase (more exactly its recognizing site) can play the role of additional matrix under the inclusion of the nucleotides. Therefore, we conclude that the formation of the DNA mutagenic base pairs satisfies the geometric constraints of the standard double helical DNA. If these mutagenic base pairs would be incorporated into a standard Watson–Crick double helix, the helix would not likely experience significant distortion and its stability would not be greatly deteriorated.

The comparison of the formation energies of the canonical and mutagenic base pairs (Table 6) shows that the Löwdin's Ade^{*}·Thy^{*} base pair, which electronic formation energy is -33.80 kcal/mol, is the most stable among all the studied base pairs. At the same time, the formation of the Gua^{*}·Thy and Ade^{*}·Cyt mispairs is more favorable than that of the Ade·Thy canonical base pair, Gua·Thy^{*} and Ade·Cyt^{*} mispairs which have -14.92; -33.39 and -23.50 kcal/mol formation energy, respectively (Table 6). From the other point of view, it may evidence that dissociation of the Gua^{*}·Thy and Ade^{*}·Cyt mispairs will be complicated during the strand separation. These data therefore confirm that Ade·Cyt^{*} and Gua^{*}·Thy mispairs are suitable candidates for the spontaneous point mutations arising in DNA (Fig. 6). The Ade^{*}·Cyt and Gua·Thy^{*} lifetimes ($3.49 \cdot 10^{-11}$ s and $3.59 \cdot 10^{-13}$ s, accordingly) are too short comparably with the time of one base pair dissociation during the enzymatic DNA replication (10^{-9} s). This means that these mispairs will "slip away" from replication machinery: they transfer to Ade·Cyt^{*} and Gua^{*}·Thy accordingly (Fig. 6). In this way Ade^{*}·Cyt and Gua·Thy^{*} mispairs act as intermediates in this reaction.

Base pair	$-\Delta E_{\text{int}}$	$\Delta\Delta E$	$\Delta\Delta G$
Ade·Thy	14.92	-	-
Ade*·Thy*	33.80	0.11	-1.01
Gua·Cyt	29.28	-	-
Gua*·Cyt*	22.94	5.15	1.49
Ade·Cyt*	15.73	-	-
Ade*·Cyt	23.50	6.44	3.75
Gua·Thy*	33.39	-	-
Gua*·Thy	19.82	4.16	1.17

see designations in Table 5

Table 6. Electronic and Gibbs free energies (in kcal/mol) (T=298.15 K) of base pairs obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory in vacuum#

Fig. 6. Interconversion of Ade·Cyt*↔Ade*·Cyt and Gua*·Thy↔Gua·Thy* mispairs involving mutagenic tautomers of DNA bases. Relative Gibbs free energies (T=298.15 K, in vacuum) are obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory and reported near each structure in kcal/mol. The dotted lines indicate H-bonds AH...B (their lengths H...B are presented in angstroms), while continuous lines show covalent bonds

The obtained Gibbs free energies of interaction indicate that Gua*·Thy and Ade·Cyt* are more favorable than Gua·Thy* and Ade*·Cyt. It was established that the Ade*·Cyt and Gua*·Cyt* base pairs are metastable and easily (i.e., without facing significant barrier) „slip“ into the energetically more favorable Ade·Cyt* and Gua·Cyt base pairs, respectively. The comparison of reverse electronic barriers of interconversion with the zero-point energies of competent vibrational modes (Table 7) of the tautomerized complexes allows concluding that Ade*·Thy* and Gua·Thy* complexes are dynamically unstable their electronic barriers of the reverse transition are noticeably lower than zero-point energy of corresponding vibrational modes.

Tautomerisation reaction	ΔE , kcal/mol	$\Delta\Delta E_{TS}$, kcal/mol	$\Delta\Delta E$		ν , cm ⁻¹
			kcal/mol	cm ⁻¹	
Gua·Cyt↔Gua [*] ·Cyt [*]	7.87	13.02	5.15	1800.8	2951.8
Ade·Thy↔Ade [*] ·Thy [*]	12.26	12.37	0.11	37.7	3349.2
Ade·Cyt [*] ↔Ade [*] ·Cyt	3.67	10.11	6.44	2253.5	3024.9
Gua [*] · Thy↔Gua · Thy [*]	1.13	5.29	4.16	1455.4	3155.7

ΔE – the relative electronic energy of the tautomerized complex; $\Delta\Delta E_{TS}$ – the activation barrier of tautomerisation in terms of electronic energy; $\Delta\Delta E = \Delta\Delta E_{TS} - \Delta E$ – the reverse barrier of tautomerisation in terms of electronic energy; ν – the frequency of the vibrational mode of the tautomerized complex which becomes imaginary in the transition state of tautomerisation

Table 7. Energetic characteristics of DNA bases tautomerisation in studied base pairs obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory in vacuum#

6. Conclusions

In this study, we made an attempt to answer some actual questions related to physico-chemical nature of spontaneous point mutations in DNA induced by prototropic tautomerism of its bases.

It was shown that the lifetime of mutagenic tautomers of all four canonical DNA bases exceeds by many orders not only the time required for replication machinery to enzymatically incorporate one incoming nucleotide into structure of DNA double helix (~4·10⁻⁴ s), and even a typical time of DNA replication in cell (~10³ s). The high stability of mutagenic tautomers of DNA bases is mainly determined by the absence of intramolecular H-bonds in their canonical and mutagenic forms.

This finding substantially supports the tautomeric hypothesis of the origin of spontaneous point mutations, for instance replication errors, removing all doubts on instability of mutagenic tautomers of isolated DNA bases, which are sometimes expressed by biologists.

Notwithstanding a tremendous heuristic and methodological role of the classical Löwdin’s mechanism of the origin of spontaneous point mutations during DNA replication, it was demonstrated that this mechanism probably has substantial limitations. From the physico-chemical point of view, the advantage of Löwdin’s mechanism lies in the fact that the tautomerisation of base pairs does not disturb standard Watson-Crick base-pairing geometry. Its main disadvantage is the instability of Ade^{*}·Thy^{*} base pair and metastability of Gua^{*} · Cyt^{*} base pair. The lifetime of tautomerized (Löwdin’s) Ade^{*}·Thy^{*} and Gua^{*}·Cyt^{*} base pairs is less by orders than a characteristic time required for replication machinery to separate any Watson-Crick base pair (~10⁻⁹ s). Figuratively speaking, the Löwdin’s base pairs “slip away” from replication apparatus: they transform to canonical base pairs and then dissociate without losing their canonical coding properties, as they haven’t enough time to dissociate to mutagenic tautomers. These facts put the possibility of such mispairs involving mutagenic tautomers formation under a doubt, not to mention their complicated dissociation into mutagenic tautomers.

In this context, a topic of current importance is the search of novel physico-chemical mechanisms of tautomerisation of DNA bases in Watson-Crick base pairs: the pioneering, but encouraging steps have been already made in this direction (Brovarets', 2010; Cerón-Carrasco et al., 2009a, 2009b, 2011; Cerón-Carrasco & Jacquemin, 2011; Kryachko & Sabin, 2003).

It was found that a specific interaction of a single water molecule with the site of mutagenic tautomerisation in each of four canonical DNA bases could transform to into mutagenic tautomeric form in a definite time notably less than $\sim 4 \cdot 10^{-4}$ s. The most vulnerable point of this model of origin of replication error in DNA is a complete lack of experimental and especially theoretical support for a probability of the penetration of water molecules at a replication fork per one Watson-Crick base pair. Most likely such a probability is very low, since a compact, essentially hydrophobic organization of replisome (Marians, 2008; Pomerantz & O'Donnell, 2007) is supposed to minimize this probability.

In this work it was found that among all purine-pyrimidine base pairs with Watson-Crick geometry involving one base in mutagenic tautomeric form - Ade Cyt*, Gua* Thy, Ade* Cyt and Gua Thy*, Gua Thy* mispair is dynamically unstable and Ade* Cyt mispair has very small lifetime ($< 10^{-9}$ s) and therefore plays an intermediate role in DNA replication cycle, "sliding down" to the Ade Cyt* mispair. This fact substantially alters the Löwdin's scheme (Löwdin, 1963, 1965, 1966) of replication point errors fixation arising due to the prototropic tautomerism of DNA bases, which treats all four base pairs Ade Cyt*, Ade* Cyt, Gua* Thy and Gua Thy* as stable structures.

In our opinion, the results reported here not only provide more evidence in support of Watson and Crick classical tautomeric hypothesis of point mutations, but also fill it with concrete physico-chemical content.

By combining the data from the literature with our findings, we concluded that the tautomeric mechanism of the origin of mutations in DNA should satisfy the following thermodynamic and kinetic criteria:

- the time needed to reach tautomerisation equilibrium in the complex $\tau_{99,9\%}$ should be considerably less than a specific time of one elementary DNA replication event (several ms);
- the tautomerized complex should be dynamically stable and moreover should have the lifetime significantly exceeding a specific time required for a replication machinery to forcibly dissociate a Watson-Crick base pair into monomers (several ns);
- a dissociation energy of the tautomerized complex should not exceed a dissociation energy of the complex with canonical tautomer participation;
- a thermodynamic population (equilibrium constant of tautomerisation) of the pair with a mutagenic tautomer participation relative to the basic tautomeric state should be within the range of 10^{-8} - 10^{-11} , that agrees fully with biological experimental data.

Finishing our conclusions, we hope that this theoretical study gives valuable and thorough information on the chemically intriguing and biologically relevant questions of the DNA bases tautomerism. Our results presented here are believed to provide a new insight into the molecular nature of spontaneous point mutations in DNA and also be a promising and perspective tool for experimentalists working in the field of DNA mutagenesis.

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