Chapter

Where Quantum Biochemistry Meets Structural Bioinformatics: Excited Conformationally-Tautomeric States of the Classical A·T DNA Base Pair

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Abstract

This Chapter summarizes recent quantum-chemical (QM) investigations of the novel conformational and tautomeric states on the potential energy hypersurface of the classical A·T/A·U nucleobase pairs. For the first time, it was observed 28 local minima for each base pair excluding enantiomers - planar, non-planar base pairs and structures with wobble geometry. Considered excited conformationally-tautomeric states of the classical A·T DNA base pair have been revealed in the Nucleic Acid Database by structural bioinformatics. These data shed light on the biological significance of the unusual A·T/A·U nucleobase pairs for the functioning of the nucleic acids at the quantum level.

Keywords: quantum biology, A·T and A·U nucleobase pairs, tautomeric state, conformational state, wobble geometry, quantum-chemical calculation, structural bioinformatics

1. Introduction

Since the discovery of the spatial organization of the DNA molecule by James Watson & Francis Crick [1, 2], it is traditionally believed that canonical Watson-Crick A·T and G·C DNA base pairs are quite conservative structures. These classical DNA base pairs almost do not have tautomeric variability and essential conformational mobility at the dynamical behavior of DNA molecule [2]. Generally, it is suggested that bases in the *anti*-conformation able to form a pair according to the so-called Watson-Crick (WC) scheme joined through the three intermolecular hydrogen (H) bonds [3]. At the same time, many biologists-contemporaries questioned the proposed Watson-Crick conformation, since X-ray resolution does not allow to establish for sure the precise conformation of the base pairs constituting to the DNA double helix. Exactly by this reason Maurice Wilkins – the third author of the discovery of the DNA structure – explained the reason why Rosalind Franklin doubted in modeling the structure of DNA [4]. And even forefathers of the

discovery noted that suggested by them structure "must be regarded as unproved until it has been checked against more exact results" [1]. Also, Linus Pauling opposed Watson-Crick model of the paring of the bases "because of existing uncertainty about the detailed structure of nucleic acid" (personal correspondence to the Nobel Committee for Chemistry and Physics).

After some time, in 1959 Karst Hoogsteen fixed in crystal state a novel structure for the 1-methylthymine. 9-methyladenine base pair [5], which was named afterwards with the same name – Hoogsteen base pair, in which A purine base adopts the *syn*-conformation formed by flipping of its orientation on 180 degree according the T DNA base. Moreover, the distance between the glycosidic atoms C1′–C1′ is shorter for Hoogsteen base pair in comparison with the classical WC base pair.

Altogether, the A·T DNA base pair can acquire four biologically significant classical configurations – Watson-Crick A·T(WC), reverse Watson-Crick A·T(rWC), Hoogsteen A·T(H) and reverse Hoogsteen A·T(rH) [5–26], due to the rotation of one of the bases in the Watson-Crick A·T(WC) base pair according to the other on 180° around:

- the (A)N1–N3(T) axis, leading to the formation of the reverse Watson-Crick A·T(rWC) or so-called Donohue DNA base pair [6], registered in the bioactive parallel-stranded DNA [7–12];

- the (A)C9-N9 axis from the *anti-* to *syn*-conformation, representing Hoogsteen A·T(H) base pair [5] involved into a number of biologically important processes such as recognition, damage induction and replication [11–22];

- the (A)N7–N3(T) axis in the Hoogsteen base pair forming the reverse Hoogsteen A·T(rH) or so-called Haschemeyer–Sobell base pair [23–26].

Discussed DNA base pairs are not static structures in the composition of DNA [27, 28]. Thus, the spontaneous A·T(WC)↔A·T(H) conformational transition has been experimentally registered by the NMR spectroscopy on the DNA regions enriched by the classical A·T nucleobase pairs [22]. Despite numerous theoretical investigations, microstructural nature of these transitions still remains incomprehensible [20, 29].

Recently, in the literature especial attention has been paid to the searching and careful investigation of the novel conformational and tautomeric states of the classical A·T base pair [30–36], since it can expand their functionality. Generally saying, the topic of the prototropic tautomerism has attracted especial attention, in particular in the area of drug design [37], in physics of crystals [38], in the various created databases [39–41], multinuclear magnetic resonance [42], in NMR spectroscopy [43] as well as biologically important molecules [44–46].

This Chapter summarizes previous investigations, in particular performed by quantum-mechanical (QM) modeling [47–53]. Thus, it was established that the planar classical Watson-Crick A·T DNA base pairs – Watson-Crick A·T(WC), reverse Watson-Crick A·T(rWC), Hoogsteen A·T(H) and reverse Hoogsteen A·T(rH) structures possess unique ability to perform conformationally-tautomeric transitions [47–53]. It occurs *via* the non-planar transition states, *through* the structural or conformational rearrangements and intramolecular proton transfer along the intermolecular H-bonds.

These novel excited conformational and tautomeric states occur due to the quantum effects, e.g. amino group pyramidalization because of electron conjugation

of the lone electron pair of nitrogen amino atom with π-electron system of the ring [54–56]. This data enables us to suggest the potential energy surface of the classical A·T base pairs and also to predict pathways of their interconversions. Moreover, this modeling could be used for the understanding and description in details of the physico-chemical mechanisms of the DNA functioning, in particular DNA "breathing", which has significant biological role [27, 28].

Also, obtained data would enable to make new insights into the understanding the DNA and RNA structural biology, which are based on their conformational and tautomeric variety. By the methods of structural bioinformatics it was revealed unusual conformationally-tautomeric states of the A·T DNA base pair in the Nucleic Acid Database, confirming their existence in biological systems. Altogether, further this could be extended to the area of epigenetics and experimental verification.

2. Methods

2.1 Computational methods

Equilibrium geometries of the investigated DNA base pairs, as well as their harmonic vibrational frequencies have been calculated at the B3LYP/6–311++G(d, p) level of theory [54–58], using Gaussian'09 package [59]. Applied level of theory has proved itself successful for the calculations of the similar systems [60–62]. A scaling factor that is equal to 0.9668 has been applied in the present work for the correction of the harmonic frequencies of all complexes [63, 64].

All calculations have been carried out in the continuum with ε = 1, that adequately reflects the processes occurring in real biological systems without deprivation of the structurally functional properties of the bases in the composition of DNA, and in the continuum with ε = 4, which satisfactorily models the substantially hydrophobic recognition pocket of the DNA-polymerase machinery as a part of the replisome [65–70].

Single point energy calculations have been performed at the MP2/6–311++(2df, pd) level of theory [71, 72].

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

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

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

Electronic interaction energies ΔE_{int} have been calculated at the MP2/6–311++G (2df,pd) level of theory as the difference between the total energy of the base pair and energies of the monomers and corrected for the basis set superposition error (BSSE) [73, 74] through the counterpoise procedure [75, 76].

Bader's quantum theory of Atoms in Molecules (QTAIM) [77–82], using program package AIMAll [77], was applied to analyze the electron density distribution. The presence of the bond critical point (BCP), namely the so-called (3,-1) BCP, and a bond path between hydrogen donor and acceptor, as well as the positive value of the Laplacian at this BCP ($\Delta\rho > 0$), were considered as criteria for the H-bond formation [77–82]. Wave functions were obtained at the level of QM theory used for geometry optimization.

The atomic numbering scheme for the DNA bases is conventional [3]. In this study mutagenic or rare tautomeric forms are denoted by the asterisk [83–92].

2.2 Bioinformatical analysis

It was created original author's algorithm in order to reveal the unusual A·T base pairs in the Nucleic Acid Database by Rutgers University [93, 94]. This algorithm is based on the comparison of the calculated structure of the A·T base pairs at the ε = 4 with structure of the analogical base pairs in the Nucleic Acid Database.

3. Obtained results

It was found out novel *tautomerization pathways* for the formation of the *rare tautomers of the A or T DNA bases*:

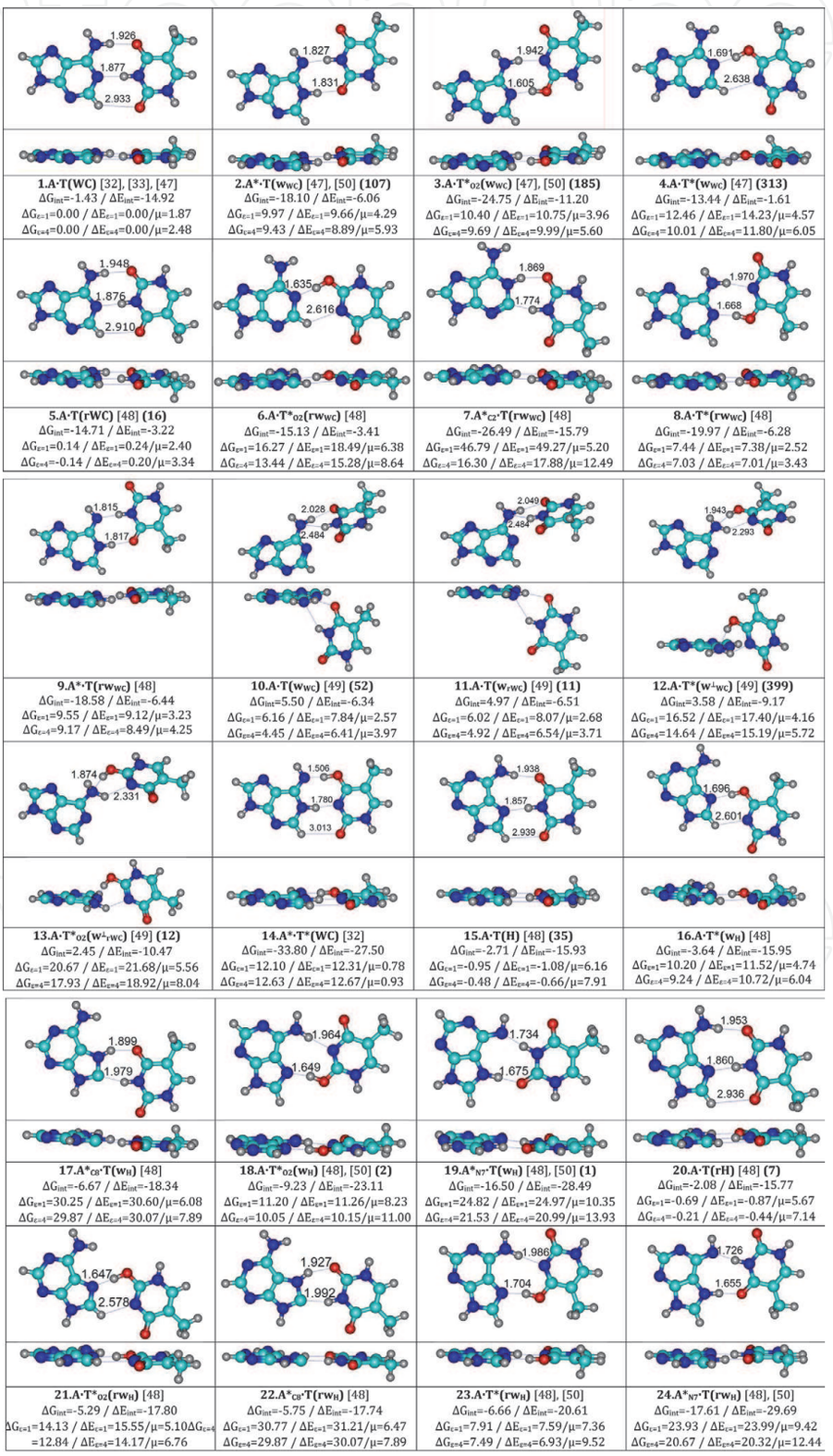
- A·T(WC)↔A*·T(w)/A·T*$_{O2}$(w)/A·T*(w) *via* the sequential proton transfer and shifting of the bases relatively each other [47];
- A·T(rWC)/A·T(H)/A·T(rH)↔A·T*(rw_{WC})/A·T*(w_H)/A·T*(rw_H) mutagenic tautomerization *via* the sequential proton transfer [48];
- A·T(w_{WC})↔A·T*($w^{\perp}_{WC}$), A·T(w_{rWC})↔A·T*$_{O2}$($w^{\perp}_{rWC}$), A·T(w_H)↔A·T*($w^{\perp}_H$), A·T(w_{rH})↔A·T*$_{O2}$($w^{\perp}_{rH}$) reactions of tautomerization [49];
- A·T(WC) / A·T(rWC)↔A*·T(rw_{WC}) / A*·T(w_{WC}), A·T(H) / A·T(rH)↔A*$_{N7}$·T(rw_H) / A*$_{N7}$·T(w_H) reactions *via* sequential proton transfer through the quasi-orthogonal transition states, as well as between the formed base pairs by the participation of the rare tautomers: A*·T(rw_{WC})↔A·T*(rw_{WC}) and A*·T(w_{WC})↔A·T*$_{O2}$(w_{WC}), A*$_{N7}$·T(rw_H)↔A·T*(rw_H) and A*$_{N7}$·T(w_H)↔A·T*$_{O2}$(w_H) through the double proton transfer (DPT) [50].

Also, we found out new pathways of the *conformational transformations* of the *Watson-Crick A·T(WC), reverse Watson-Crick A·T(rWC), Hoogsteen A·T(H) and reverse Hoogsteen A·T(rH) base pairs*:

- A·T(WC)↔A·T(w_{WC}), A·T(rWC)↔A·T(w_{rWC}), A·T(H)↔A·T(w_H) and A·T(rH)↔A·T(w_{rH}) conformational transformations (Gibbs free energies of activation 7.13, 7.26, 7.67 and 7.44 in the continuum with ε = 4) [51], leading to the novel non-planar conformational states – ***A·T(w_{WC}), A·T(w_{rWC}), A·T(w_H)*** and ***A·T(w_{rH})*** (**Figure 1**). This opens up new perspectives for the understanding of the physico-chemical mechanisms of the opening of the base pairs, which precede the melting of DNA molecule and also describe in details the "breathing" of DNA molecule [27];
- A·T(w_{WC})↔A·T(w_H) and A·T(w_{rWC})↔A·T(w_{rH}), which define the conformational transitions - ***A·T(WC)***↔A·T(w_{WC})$_{R,L}$↔A·T(w_H)$_{L,R}$↔***A·T(H)*** and ***A·T(rWC)***↔A·T(w_{rWC})$_{R,L}$↔A·T(w_{rH})$_{L,R}$↔***A·T(rH)***, occurring through the wobble conformers as intermediates [52];
- A·T(w_H)↔A·T(w_{rWC}), A·T(w_{WC})↔A·T(w_{rH}), A·T(w_{WC})↔A·T(w_{rWC}), A·T(w_H)↔A·T(w_{rH}) conformational transitions (Gibbs free energies of activation 3.20, 3.70, 12.04 and 10.69 kcal·mol^{-1} in the continuum with ε = 1 at T = 298.15 K), which define the conformational interconversions: A·T(WC)↔A·T(rWC) / A·T(rH) and A·T(H)↔A·T(rH) / A·T(rWC) [53].

So, on the potential energy surface of the classical A·T/A·U base pair it was received ***28 various conformationally-tautomeric states*** (**Figure 1**, **Table 1**):

- *Planar structures (C_s point symmetry) with wobble geometry:* WC & rWC – 2.A*·T(w_{WC}), 3.A·T*$_{O2}$(w_{WC}), 4.A·T*(w_{WC}), 6.A·T*$_{O2}$(rw_{WC}), 7.A*$_{C2}$·T(rw_{WC}), 8. A·T*(rw_{WC}), 9.A*·T(rw_{WC}) and H & rH – 16.A·T*(w_H), 17.A*$_{C8}$·T(w_H), 18. A·T*$_{O2}$(w_H), 19.A*$_{N7}$·T(w_H), 21.A·T*$_{O2}$(rw_H), 22.A*$_{C8}$·T(rw_H), 23.A·T*(rw_H), 24.A*$_{N7}$·T(rw_H);



1.A·T(WC) [32], [33], [47]
ΔG_{int}=-1.43 / ΔE_{int}=-14.92
$\Delta G_{E=1}$=0.00 / $\Delta E_{E=1}$=0.00/μ=1.87
$\Delta G_{E=4}$=0.00 / $\Delta E_{E=4}$=0.00/μ=2.48

2.A*·T(w_{WC}) [47], [50] **(107)**
ΔG_{int}=-18.10 / ΔE_{int}=-6.06
$\Delta G_{E=1}$=9.97 / $\Delta E_{E=1}$=9.66/μ=4.29
$\Delta G_{E=4}$=9.43 / $\Delta E_{E=4}$=8.89/μ=5.93

3.A·T*$_{O2}$(w_{WC}) [47], [50] **(185)**
ΔG_{int}=-24.75 / ΔE_{int}=-11.20
$\Delta G_{E=1}$=10.40 / $\Delta E_{E=1}$=10.75/μ=3.96
$\Delta G_{E=4}$=9.69 / $\Delta E_{E=4}$=9.99/μ=5.60

4.A·T*(w_{WC}) [47] **(313)**
ΔG_{int}=-13.44 / ΔE_{int}=-1.61
$\Delta G_{E=1}$=12.46 / $\Delta E_{E=1}$=14.23/μ=4.57
$\Delta G_{E=4}$=10.01 / $\Delta E_{E=4}$=11.80/μ=6.05

5.A·T(rWC) [48] **(16)**
ΔG_{int}=-14.71 / ΔE_{int}=-3.22
$\Delta G_{E=1}$=0.14 / $\Delta E_{E=1}$=0.24/μ=2.40
$\Delta G_{E=4}$=-0.14 / $\Delta E_{E=4}$=0.20/μ=3.34

6.A·T*$_{O2}$(rw_{WC}) [48]
ΔG_{int}=-15.13 / ΔE_{int}=-3.41
$\Delta G_{E=1}$=16.27 / $\Delta E_{E=1}$=18.49/μ=6.38
$\Delta G_{E=4}$=13.44 / $\Delta E_{E=4}$=15.28/μ=8.64

7.A*$_{C2}$·T(rw_{WC}) [48]
ΔG_{int}=-26.49 / ΔE_{int}=-15.79
$\Delta G_{E=1}$=46.79 / $\Delta E_{E=1}$=49.27/μ=5.20
$\Delta G_{E=4}$=16.30 / $\Delta E_{E=4}$=17.88/μ=12.49

8.A·T*(rw_{WC}) [48]
ΔG_{int}=-19.97 / ΔE_{int}=-6.28
$\Delta G_{E=1}$=7.44 / $\Delta E_{E=1}$=7.38/μ=2.52
$\Delta G_{E=4}$=7.03 / $\Delta E_{E=4}$=7.01/μ=3.43

9.A*·T(rw_{WC}) [48]
ΔG_{int}=-18.58 / ΔE_{int}=-6.44
$\Delta G_{E=1}$=9.55 / $\Delta E_{E=1}$=9.12/μ=3.23
$\Delta G_{E=4}$=9.17 / $\Delta E_{E=4}$=8.49/μ=4.25

10.A·T(w_{WC}) [49] **(52)**
ΔG_{int}=5.50 / ΔE_{int}=-6.34
$\Delta G_{E=1}$=6.16 / $\Delta E_{E=1}$=7.84/μ=2.57
$\Delta G_{E=4}$=4.45 / $\Delta E_{E=4}$=6.41/μ=3.97

11.A·T(w_{rWC}) [49] **(11)**
ΔG_{int}=4.97 / ΔE_{int}=-6.51
$\Delta G_{E=1}$=6.02 / $\Delta E_{E=1}$=8.07/μ=2.68
$\Delta G_{E=4}$=4.92 / $\Delta E_{E=4}$=6.54/μ=3.71

12.A·T*(w^{i}_{WC}) [49] **(399)**
ΔG_{int}=3.58 / ΔE_{int}=-9.17
$\Delta G_{E=1}$=16.52 / $\Delta E_{E=1}$=17.40/μ=4.16
$\Delta G_{E=4}$=14.64 / $\Delta E_{E=4}$=15.19/μ=5.72

13.A·T*$_{O2}$(w^{i}_{rWC}) [49] **(12)**
ΔG_{int}=2.45 / ΔE_{int}=-10.47
$\Delta G_{E=1}$=20.67 / $\Delta E_{E=1}$=21.68/μ=5.56
$\Delta G_{E=4}$=17.93 / $\Delta E_{E=4}$=18.92/μ=8.04

14.A*·T*(WC) [32]
ΔG_{int}=-33.80 / ΔE_{int}=-27.50
$\Delta G_{E=1}$=12.10 / $\Delta E_{E=1}$=12.31/μ=0.78
$\Delta G_{E=4}$=12.63 / $\Delta E_{E=4}$=12.67/μ=0.93

15.A·T(H) [48] **(35)**
ΔG_{int}=-2.71 / ΔE_{int}=-15.93
$\Delta G_{E=1}$=-0.95 / $\Delta E_{E=1}$=-1.08/μ=6.16
$\Delta G_{E=4}$=-0.48 / $\Delta E_{E=4}$=-0.66/μ=7.91

16.A·T*(w_H) [48]
ΔG_{int}=-3.64 / ΔE_{int}=-15.95
$\Delta G_{E=1}$=10.20 / $\Delta E_{E=1}$=11.52/μ=4.74
$\Delta G_{E=4}$=9.24 / $\Delta E_{E=4}$=10.72/μ=6.04

17.A*$_{C8}$·T(w_H) [48]
ΔG_{int}=-6.67 / ΔE_{int}=-18.34
$\Delta G_{E=1}$=30.25 / $\Delta E_{E=1}$=30.60/μ=6.08
$\Delta G_{E=4}$=29.87 / $\Delta E_{E=4}$=30.07/μ=7.89

18.A·T*$_{O2}$(w_H) [48], [50] **(2)**
ΔG_{int}=-9.23 / ΔE_{int}=-23.11
$\Delta G_{E=1}$=11.20 / $\Delta E_{E=1}$=11.26/μ=8.23
$\Delta G_{E=4}$=10.05 / $\Delta E_{E=4}$=10.15/μ=11.00

19.A*$_{N7}$·T(w_H) [48], [50] **(1)**
ΔG_{int}=-16.50 / ΔE_{int}=-28.49
$\Delta G_{E=1}$=24.82 / $\Delta E_{E=1}$=24.97/μ=10.35
$\Delta G_{E=4}$=21.53 / $\Delta E_{E=4}$=20.99/μ=13.93

20.A·T(rH) [48] **(7)**
ΔG_{int}=-2.08 / ΔE_{int}=-15.77
$\Delta G_{E=1}$=-0.69 / $\Delta E_{E=1}$=-0.87/μ=5.67
$\Delta G_{E=4}$=-0.21 / $\Delta E_{E=4}$=-0.44/μ=7.14

21.A·T*$_{O2}$(rw_H) [48]
ΔG_{int}=-5.29 / ΔE_{int}=-17.80
$\Delta G_{E=1}$=14.13 / $\Delta E_{E=1}$=15.55/μ=5.10$\Delta G_{E=4}$ =12.84 / $\Delta E_{E=4}$=14.17/μ=6.76

22.A*$_{C8}$·T(rw_H) [48]
ΔG_{int}=-5.75 / ΔE_{int}=-17.74
$\Delta G_{E=1}$=30.77 / $\Delta E_{E=1}$=31.21/μ=6.47
$\Delta G_{E=4}$=29.87 / $\Delta E_{E=4}$=30.07/μ=7.89

23.A·T*(rw_H) [48], [50]
ΔG_{int}=-6.66 / ΔE_{int}=-20.61
$\Delta G_{E=1}$=7.91 / $\Delta E_{E=1}$=7.59/μ=7.36
$\Delta G_{E=4}$=7.49 / $\Delta E_{E=4}$=6.93/μ=9.52

24.A*$_{N7}$·T(rw_H) [48], [50]
ΔG_{int}=-17.61 / ΔE_{int}=-29.69
$\Delta G_{E=1}$=23.93 / $\Delta E_{E=1}$=23.99/μ=9.42
$\Delta G_{E=4}$=20.67 / $\Delta E_{E=4}$=20.32/μ=12.44

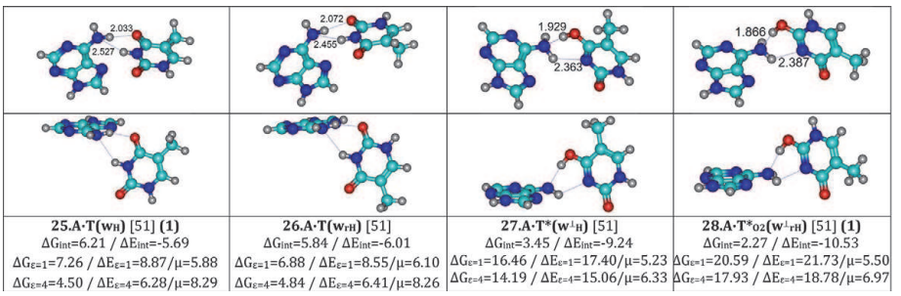


Figure 1.
Unusual A·T base pairs formed through the newly discovered conformationally-tautomeric transformations at the MP2/6–311++G(2df,pd)//B3LYP/6–311++G(d,p) level of QM theory. Graphs of the A·T base pairs are presented for the data in the continuum with ε = 4. ***Definitions:*** *ΔG relative Gibbs free and ΔE electronic energies (in kcal·mol^{-1}) in vacuum, ε = 1 (upper row) and also in the continuum with ε = 4 (lower row); ΔE_{int} electronic and ΔG_{int} Gibbs free energies of the interaction in free state (MP2/6–311++G(2df,pd)//B3LYP/6–311++G(d,p) level of QM theory, in kcal·mol^{-1}). Intermolecular AH…B H-bonds are designated by dotted lines, their lengths H…B are presented in angstroms. Number of the unusual A·T base pairs, which have been identified in the Nucleic Acid Database [62, 63] by structural bioinformatics, is presented in brackets in bold.*

- *Non-planar structures (C_1 point symmetry):* WC & rWC – 10.A·T(w_{WC}), 11.A·T(w_{rWC}), 12.A·T*($w^{\perp}{}_{WC}$), 13.A·T*$_{O2}$($w^{\perp}{}_{rWC}$); and H & rH – 25.A·T(w_H), 26.A·T(w_{rH}), 27.A·T*($w^{\perp}{}_{H}$), 28.A·T*$_{O2}$($w^{\perp}{}_{rH}$).

Notably, that Gibbs free and electronic energies of the A·T/A·U base pairs are in the wide range of values, which insignificantly decrease at the transition from the continuum with ε = 1 to the continuum with ε = 4, while dipole moment increases at this (**Table 1**).

We have carefully scanned all 28 unusual conformationally-tautomeric states of the A·T DNA base pairs in the Nucleic Acid Database by Rutgers University using original author's methodology for structural bioinformatics analysis. It was identified most part of the theoretically investigated by us excited conformationally-tautomeric states of the classical A·T DNA base pair (**Figure 1**, **Table 1**).

4. Discussion of the obtained results

Let us start the discussion and more detailed analysis of the obtained results from the consideration of the traditional area of the biological applications of the prototropic tautomerism of the DNA bases [54], as well as their role in the origin of the spontaneous point mutations – transitions and transversions at the DNA biosynthesis – so-called replication errors [58–63]. This physico-chemical model should satisfy strict conditions. Saying shortly, in order to point on the most important things, from one side – barriers of the mutagenic tautomerization of the base pairs should not be quite high in view of the quite rigid kinetic requirements for the incorporation into the double strand of DNA by the DNA-polymerase during the one act of replication ($\sim 10^{-4}$ s) [54]. At this, the lifetime of the tautomerized states of the pairs should exceed characteristic time of the inertial DNA-polymerase machinery ($\sim 10^{-9}$ s). Only at this condition the inertial replicational DNA-polymerase machinery would successfully dissociate tautomerized base pairs into the monomers, in particular into the rare tautomeric forms.

From the other side, these barriers should be quite high in order to overcome resistance of the stacking interactions and sugar-phosphate backbone of DNA on the way of the incorporation of the tautomerizing base pair into the double structure of DNA [54].

A·T pair	$\Delta G_{\varepsilon=1}$ [a]	$\Delta E_{\varepsilon=1}$ [b]	$\mu_{\varepsilon=1}$ [c]	$\Delta G_{\varepsilon=4}$ [a]	$\Delta E_{\varepsilon=4}$ [b]	$\mu_{\varepsilon=4}$ [c]	A·U pair	$\Delta G_{\varepsilon=1}$ [a]	$\Delta E_{\varepsilon=1}$ [b]	$\mu_{\varepsilon=1}$ [c]	$\Delta G_{\varepsilon=4}$ [a]	$\Delta E_{\varepsilon=4}$ [b]	$\mu_{\varepsilon=4}$ [c]
1. A·T(WC) [47]	0.00	0.00	1.87	0.00	0.00	2.48	**1. A·U(WC)**	0.00	0.00	1.69	0.00	0.00	2.25
2. A^*·T(w_{WC}) [47]	9.97	9.66	4.29	9.43	8.89	5.93	**2. A^*·U(w_{WC})**	10.35	9.92	4.83	9.67	9.04	6.52
3. A·T^*_{O2}(w_{WC}) [47]	10.40	10.75	3.96	9.69	9.99	5.60	**3. A·U^*_{O2}(w_{WC})**	10.96	11.33	4.59	10.15	10.41	6.32
4. A·T^*(w_{WC}) [47]	12.46	14.23	4.57	10.01	11.80	6.05	**4. A·U^*(w_{WC})**	11.82	13.53	4.09	9.57	11.38	5.42
5. A·T(rWC) [48]	0.14	0.24	2.40	−0.14	0.20	3.34	**5. A·U(rWC)**	0.34	0.42	2.78	0.26	0.28	3.77
6. A·T^*_{O2}(rw_{WC}) [48]	16.27	18.49	6.38	13.44	15.28	8.64	**6. A·U^*_{O2}(rw_{WC})**	16.95	19.02	6.98	10.15	10.41	6.32
7. A^*_{C2}·T(rw_{WC}) [48]	46.79	49.27	5.20	16.30	17.88	12.49	**7. A^*_{C2}·U(rw_{WC})**	46.71	49.42	5.85	16.66	17.76	13.23
8. A·T^*(rw_{WC}) [48]	7.44	7.38	2.52	7.03	7.01	3.43	**8. A·U^*(rw_{WC})**	6.99	6.94	1.97	17.73	17.25	1.97
9. A^*·T(rw_{WC}) [48]	9.55	9.12	3.23	9.17	8.49	4.25	**9. A^*·U(rw_{WC})**	9.55	9.05	2.69	20.29	19.36	2.69
10. A·T(w_{WC}) [49]	6.16	7.84	2.57	4.45	6.41	3.97	**10. A·U(w_{WC})**	6.12	8.15	2.50	5.06	6.39	4.10
11. A·T(w_{rWC}) [49]	6.02	8.07	2.68	4.92	6.54	3.71	**11. A·U(w_{rWC})**	6.25	8.18	2.63	5.31	6.52	3.50
12. A·T^*($w^{\perp}_{WC}$) [49]	16.52	17.40	4.16	14.64	15.19	5.71	**12. A·U^*($w^{\perp}_{WC}$)**	16.02	16.86	3.67	14.24	14.87	5.20
13. A·T^*_{O2}($w^{\perp}_{rWC}$) [49]	20.67	21.68	5.56	17.93	18.92	8.04	**13. A·U^*_{O2}($w^{\perp}_{rWC}$)**	21.38	22.32	6.21	18.58	19.40	8.85
14. A^*·T^*(WC) [50]	12.10	12.31	0.78	12.63	12.67	0.93	**14. A^*·U^*(WC)**	11.96	12.04	0.73	12.42	12.45	0.83
15. A·T(H) [48]	−0.95	−1.08	6.16	−0.48	−0.66	7.91	**15. A·U(H)**	−0.59	−0.96	6.34	−0.18	−0.57	8.12
16. A·T^*(w_H) [48]	10.20	11.52	4.74	9.24	10.72	6.04	**16. A·U^*(w_H)**	9.32	10.97	4.45	9.19	10.34	5.67
17. A^*_{C8}·T(w_H) [48]	30.25	30.60	6.08	29.87	30.07	7.89	**17. A^*_{C8}·U(w_H)**	30.17	30.50	5.80	29.91	30.06	7.52
18. A·T^*_{O2}(w_H) [48]	11.20	11.26	8.23	10.05	10.15	11.00	**18. A·U^*_{O2}(w_H)**	11.91	11.91	8.65	10.23	10.62	11.46
19. A^*_{N7}·T(w_H) [48]	24.82	24.97	10.35	21.53	20.99	13.93	**19. A^*_{N7}·U(w_H)**	25.32	25.39	10.79	21.66	21.25	14.40
20. A·T(rH) [48]	−0.69	−0.87	5.67	−0.21	−0.44	7.14	**20. A·U(rH)**	−0.40	−0.74	5.38	−0.19	−0.38	6.79
21. A·T^*_{O2}(rw_H) [48]	14.13	15.55	5.10	12.84	14.17	6.76	**21. A·U^*_{O2}(rw_H)**	14.82	16.10	5.40	13.25	14.52	7.11
22. A^*_{C8}·T(rw_H) [48]	30.77	31.21	6.47	29.87	30.07	7.89	**22. A^*_{C8}·U(rw_H)**	31.18	31.49	6.68	30.62	30.66	8.88

A·T pair	$\Delta G_{\varepsilon=1}$ [a]	$\Delta E_{\varepsilon=1}$ [b]	$\mu_{\varepsilon=1}$ [c]	$\Delta G_{\varepsilon=4}$ [a]	$\Delta E_{\varepsilon=4}$ [b]	$\mu_{\varepsilon=4}$ [c]	A·U pair	$\Delta G_{\varepsilon=1}$ [a]	$\Delta E_{\varepsilon=1}$ [b]	$\mu_{\varepsilon=1}$ [c]	$\Delta G_{\varepsilon=4}$ [a]	$\Delta E_{\varepsilon=4}$ [b]	$\mu_{\varepsilon=4}$ [c]
23. A·T*(rw_H) [48]	7.91	7.59	7.36	7.49	6.93	9.52	**23. A·U*(rw_H)**	7.48	7.11	6.88	6.81	6.62	8.91
24. A^*_{N7}·T(rw_H) [48]	23.93	23.99	9.42	20.67	20.32	12.44	**24. A^*_{N7}·U(rw_H)**	23.69	23.83	8.91	20.77	20.26	11.75
25. A·T(w_H) [49]	7.26	8.87	5.88	4.50	6.28	8.29	**25. A·U(w_H)**	7.35	8.12	5.12	4.75	6.47	7.92
26. A·T(w_{rH}) [49]	6.88	8.55	6.10	4.84	6.41	8.26	**26. A·U(w_{rH})**	6.88	8.53	6.02	4.84	6.54	8.21
27. A·T*($w^{\perp}_H$) [49]	16.46	17.40	5.23	14.19	15.06	6.33	**27. A·U*($w^{\perp}_H$)**	16.00	16.90	4.83	14.01	14.68	5.97
28. A·T*$_{O2}$($w^{\perp}_{rH}$) [49]	20.59	21.73	5.50	17.93	18.78	6.97	**28. A·U*$_{O2}$($w^{\perp}_{rH}$)**	21.28	22.36	5.88	18.19	19.25	7.25

[a] *Relative Gibbs free energy of the base pair (T = 298.15 K), kcal·mol^{-1}.*
[b] *Relative electronic energy of the base pair, kcal·mol^{-1}.*
[c] *Dipole moment of the base pair, Debay.*

Table 1.
Energetic and polar characteristics of the conformers and tautomers of the A·T/A·U nucleobase pairs obtained at the MP2/6–311++G(2df,pd) // B3LYP/6–311++G(d,p) level of QM/PCM theory in the isolated state (ε = 1) and in the continuum with ε = 4 under normal conditions (see ***Figure 1****).*

Nowadays, just one single model satisfies these strict conditions [47]. According to this model (**Figure 1**), mutagenic tautomerization of the bases in the A·T(WC) base pair is controlled by the transition states, which represent itself tight ion pairs $A^{+}\cdot T^{-}$, and is realized through the step-by-step proton transfer along the intermolecular H-bonds and is assisted by the lateral changing of the configuration of the pair – its transition from the Watson-Crick configuration to the wobble or shifted [47]. In fact, complementary A base plays a role of catalysator of the intramolecular mutagenic tautomerization of the T base within the A·T(WC) base pair. Below it would be outlined experimental confirmations that wobble structures of the A·T base pair, containing mutagenic tautomeric forms of the T base, are real objects of the structural biology. This fact, in our opinion, experimentally confirms reality of the tautomeric mechanisms of the origin of the replication errors [47].

We have demonstrated for the first time, that others three biologically important configurations of the A·T base pair – A·T(rWC), A·T(H) and A·T(rH) [47] – tautomerises by the abovementioned and described mechanism of the tautomerization, forming wobble pairs by the participation of the mutagenic tautomers (**Figure 1**). Moreover, we have arrived to the conclusion by the comparison of their energetical characteristics, that *Nature* quite consciously choose evolutionary the most remote A·T(WC) base pair for the building of the carrier of the genetic information in the form of the right-handed DNA [47].

In this regard, it arises quite logical question – "Whether *Nature* uses prototropic tautomerization of the DNA bases beyond the borders of classical tautomeric hypothesis?" Let us say – for the supporting of the unusual DNA structures. Principle of economy of thinking (*Entia non sunt multiplicanda praeter necessitate*), which is quite often applied by the living nature, enables in principle, affirmatively answer on the quite interesting question. Below we would provide number of examples of the application in the structural biology of all without exception wobble configurations of the A·T pair by the participation of the mutagenic tautomers.

Biological role of the prototropic tautomerism of the DNA bases is not limited by the presented here examples. It is quite more complex and wider. Let us attract readers' attention to the one more so-called unusual role of the tautomeric-conformational transformations in the DNA structural transitions. However, their mechanism of action could be explained only at the macroscopical level.

In the work [61] at the example of the hypoxanthine dimer it was revealed novel way of the conformationally-tautomeric transformations of the structures, which are joined by the neighboring antiparallel H-bonds, through the quasi-orthogonal transition state with the changing of the mutual orientation of the dimmers on 180 degree. Conformationally-tautomeric transitions of such a nature have been fixed in all without exception four configurations of the classical A·T DNA base pair [53]. Combining these data with previous, concerning the WC/H↔w_{WC}/w_{H} conformationally-tautomeric transitions [50], we have obtained joined picture of the WC/H↔rWC/rH at the quantum level:

- A·T(WC)↔A·T*(rw_{WC})↔A·T(rWC)↔A·T*$_{O2}$(w_{WC})↔A·T(WC);

- A·T(H)↔A·T*(rw_{H})↔A·T(rH)↔A·T*$_{O2}$(w_{H})↔A·T(H),

as well as experimental confirmation (see below) of the existence of these structures in real macromolecular biosystems.

Bioinformatical analysis. This data convincingly evidence on the real occurrence of these base pairs in the real biological systems [93, 94] and thus – on their biological importance. This situation remains for a long time the hidden side of the classical A·T DNA base pair. However, it became successfully resolved in the current work.

5. Conclusions

Concluding, we can state that it was received the most complete up to now quantum map of the biologically-important conformationally-tautomeric transitions of the classical A·T/A·U nucleobase pair, which enable to classify it as a ***quantum choreography with all further going consequences***. But it is not a pursuit of a new term, but rather an attempt to realize the molecular logic of the quantum evolution at its initial stages, when it was formed its behavior, which is evolutionary programmed in its electronic structure.

For the first time, it was shown for the classical A·T DNA base pair that prototropic tautomerism of the DNA bases is responsible both for the origin, as well as for the supporting of the unusual local structures in the constitution of DNA and in complexes with proteins and small biomolecules. Moreover, prototropic tautomerism of the classical A·T DNA base pair significantly expands its conformational possibilities and its impact on the biological importance.

It is connected with the fact that presented mechanisms of the tautomerization are assisted by the significant changing of the geometry of the tautomerizing base pair. This means that they are conformationally-tautomeric transitions by their essence.

This conclusion is confirmed by the structural bioinformatics. Thus, it was identified hundredth of the structures containing tautomers of the DNA bases. This fact points that all described exited conformationally-tautomeric states of the A·T and A·U nucleobase pairs, corresponding to local minima, are real structures.

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