Non-dissociative structural transitions of the Watson-Crick and reverse Watson-Crick A·T DNA base pairs into the Hoogsteen and reverse Hoogsteen forms

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In this study it was theoretically shown that discovered by us recently (Brovarets’ et al., Frontiers in Chemistry, 2018, 6:8; doi: 10.3389/fchem.2018.00008) high-energetical, significantly non-planar (symmetry C₁), short-lived wobbled conformers of the classical Watson-Crick A-T(WC), reverse Watson-Crick A-T(rWC), Hoogsteen A-T(H) and reverse Hoogsteen A-T(rH) DNA base pairs are the intermediates of their pairwise A-T(WC)/A-T(rWC) ↔ A-T(H)/A-T(rH) conformational transformations. These transitions do not require for their realization the energy-consumable anisotropic rotation of the amino group of A around the exocyclic C6-N6 bond. They are controlled by the non-planar transition states with quasi-orthogonal geometry (symmetry C₁) joined by the single intermolecular (T)N3H···N6(A) H-bond (~4 kcal·mol⁻¹). The Gibbs free energies of activation for these non-dissociative, dipole-active conformational transitions consist 7.33 and 7.81 kcal·mol⁻¹, accordingly. Quantum-mechanical (QM) calculations in combination with Bader’s quantum theory of “Atoms in Molecules” (QTAIM) have been performed at the MP2/aug-cc-pVDZ/B3LYP/6-311++G(d,p) level of QM theory in the continuum with ε = 4 under normal conditions.

Spontaneous transition of the DNA base pairs from the Watson-Crick (WC) to Hoogsteen (H) configuration and vice versa is one of the functionally-important physico-chemical properties of DNA. It was shown by NMR methods that Watson-Crick ↔ Hoogsteen breathing in DNA duplex containing A-T rich region occurs via the switching of the Watson-Crick DNA base pair (bp) from the anti- to syn-conformation with the probability ~10⁻² and represents one of the pathways for the reaction of formaldehyde with DNA. Thorough calculations by the method of molecular dynamics indicate that A-T(WC) ↔ A-T(H) transitions of actually bps and anti ↔ syn transitions of the A around the glycosidic bond are closely correlated processes, for which Gibbs free energy of activation is 10–11 kcal·mol⁻¹ under normal conditions.

Based on analysis of the microstructural nature of these transitions, it is quite logical to connect it with the analogical properties of the isolated DNA bps. Comprehensive analysis of the current literature data showed that the nature of these biologically-important processes has not been investigated at all. Currently in the literature there is only one single theoretical work devoted to the study of anti ↔ syn non-dissociative transitions in irregular pairs of nucleotide bases that do not have an exocyclic amino group in its composition.

Recently, we have theoretically revealed novel high-energetic, significantly non-planar (symmetry C₁), short-lived wobbled (w) conformers – A-T(wWC), A-T(wrWC), A-T(wH), A-T(wrH) for each of the four classical A-T(WC) DNA bps – Watson-Crick A-T(WC), reverse Watson-Crick A-T(rWC), Hoogsteen A-T(H) and reverse Hoogsteen A-T(rH). It is known from the literature data, that these bps joined by different H-bonds are formed due to the rotation of the DNA base relative to the other on 180° around: the (A)N1–N3(T) axis for the reverse
It was found that intermolecular contributions to the energy of the N3H···N6 H-bond and decrease of the energy of the intermolecular N6H−TSs of these conformational transitions is significantly increased: this antiparallel (A)N6H/N6H′⋯O4/O2 and (T)N3H···N6 H-bonds (the N6H chemical bond has trans-orientation relative to the N1C6 chemical bond of A). These specific intermolecular contacts involve pyramidalized A amino group, acting simultaneously as an acceptor and a donor of the H-bonding. The transition state (TS) of the dipole-active conformational transformations of the basic, plane-symmetric state of the classical A·T DNA bps into the high-energetic, essentially non-planar wobbled bps and vice versa possess wobble structures (symmetry C2) and are joined by the N6H/N6H′⋯O4/O2 and N3H−N6 H-bonds. The A·T(wHC), A·T(wSC), A·T(wTH) and A·T(wtH) conformers was found to be dynamically stable structures with short lifetime τ = (1.4–3.9) ps. It was assumed that these conformational transformations are directly related to the thermally-driven fluctuational behavior of DNA – pre-melting and breathing.

In this work it was established for the first time that just-mentioned novel conformers A·T(wHC), A·T(wSC), A·T(wTH) and A·T(wtH) control the A·T(wHC)/A·T(wSC), A·T(wTH)/A·T(wtH) conformational transitions. Moreover, in view of the recently discovered conformational transitions for the classical A·T DNA bps - A·T(wHC) ↔ A·T(wSC), A·T(wTH) ↔ A·T(wtH), A·T(H) ↔ A·T(tH) and A·T(T) ↔ A·T(H), they are also intermediates of the biologically-important A·T(WC)/A·T(rWC) ↔ A·T(H)/A·T(rH) conformational transitions.

Energetically favorable mechanism of the conformational pairwise transformation of the intermediates A·T(wHC) ↔ A·T(wSC) and A·T(wTH) ↔ A·T(wtH), and together with them conformational transition of the A·T DNA bps - A·T(WC)/A·T(rWC) ↔ A·T(H)/A·T(rH) does not require for their realization the rotation of the amino group of A around the exocyclic C6N6 bond.

In this case conformational transformations are controlled by the soft, non-planar TSs, stabilized by the participation of the single intermolecular (T)N3H⋯N6(A) H-bond between the imino group of T and pyramidalized amino group of A. The Gibbs free energies of activation for these non-dissociative, dipole-active conformational transitions consist 7.33 and 7.81 kcal mol⁻¹, accordingly.

Two other mechanisms – the A·T(wHC) ↔ A·T(wSC) and A·T(wTH) ↔ A·T(wtH) – are realized via the anisotropic rotation of the amino group of A (together with T interacting with A through two intermolecular antiparallel (A)N6H/N6H′⋯O4/O2(T) and (T)N3H⋯N6(A) H-bonds) around the exocyclic C6N6 bond. In TSs of these conformational transformations the pyramidalization of the amino group of A significantly increases: this causes increase of the energy of the N3H−N6 H-bond and decrease of the energy of the intermolecular N6H/N6H′⋯O4/O2 H-bond. The transitions states of these reactions – TS_39–TS_39, A·T(wHC) ↔ A·T(wSC), A·T(wTH) ↔ A·T(wtH) and TS_39–TS_39, A·T(WC)/A·T(rWC) ↔ A·T(H)/A·T(rH) have close energy in corresponding conformational transformations (14.9 and 15.0 kcal mol⁻¹, accordingly). Thus, these TSs of the mutual conformational transformation of the wobble intermediates - A·T(wHC) ↔ A·T(wSC) and A·T(wTH) ↔ A·T(wtH) of the classical A·T DNA bps - A·T(WC)/A·T(rWC) ↔ A·T(H)/A·T(rH) determine their conformational transformations.

Computational Methods
We have calculated geometries of the basic and high-energetic conformers and transition states (TSs) of their mutual conformational transformations together with their harmonic vibrational frequencies at the B3LYP/6–311++G(d,p) level of theory, using Gaussian09 package, in the continuum with ε = 4, which is typical for the processes in real biological complexes and taking into account the structural and functional characteristics of the bases in the duplex DNA and at the same time satisfactorily reflecting the environment in the essentially hydrophobic base-pair recognition pocket of the high-fidelity DNA-polymerase. Synchronous Transit-guided Quasi-Newton method has been applied for the calculations of the similar tasks and systems. A scaling factor of 0.9668 has been used in order to correct the harmonic frequencies of all bps and TSs of the transitions between them. The local minima or TSs, localized by Synchronous Transit-guided Quasi-Newton method, have been appointed to the complexes on the potential energy landscape containing any or one imaginary frequency.

The Gibbs free energy G for all structures has been received at the MP2/6–311++G(2df,pd) level of theory by the formula:

\[ G = E_\text{el} + E_\text{corr}, \]

where \( E_\text{el} \) – electronic energy, while \( E_\text{corr} \) – thermal correction.

The electronic energies of interaction \( \Delta E_\text{el} \) have been obtained at the MP2/6–311++G(2df,pd) level of theory as a difference between the BSSE-corrected electronic energy of the bp and electronic energies of the isolated bases.

Bader’s quantum theory of Atoms in Molecules (QTAIM) has been applied for the analysis of the electron density distribution by AIMAll program package, using wave functions calculated at the B3LYP/6–311++G(d,p) level of theory. We considered the presence of the (3, −1) bond critical point (BCP), a bond path between the donor and acceptor of the intermolecular contact and positive value of the Laplacian at this BCP \( (\nabla^2 \rho > 0) \) as criteria for the existence of the H-bond or attractive van der Waals contact formation.

The energies of the attractive van der Waals contacts in TSs of the conformational transitions have been estimated by the Espinosa-Molins-Lecomte (EML) formula.
where $V(r)$ – value of a local potential energy at the $(3, -1)$ BCP.

The energies of the conventional A-H B-H bonds have been calculated by the logansen's formula:

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

where $\Delta\nu$ – frequency shift of the stretching mode of the H-bonded AH group involved in the A-H B-H bond relatively the unbound group. We applied the partial deuteration in order to avoid the effect of vibrational resonances.

In this study the numerator for the DNA bases is generally accepted.

In this study we have provided investigations at the basic, but sufficient level of the isolated H-bonded pairs of nucleotide bases, that adequately simulates the processes in real biological systems, in particular in the base-pair recognition pocket of the high-fidelity DNA-polymerase. At this, we have relied on the experience received in the previous works on the related topic and systems, in which the negligibly small impact of the stacking and sugar-phosphate backbone on the tautomerisation processes has been shown.

**Results and Their Discussion**

In our previous paper we have succeed to establish in the classical A-T DNA bps with C4 symmetry – Watson-Crick (WC), reverse Watson-Crick A-T (rWC), Hoogsteen A-T (H) and reverse Hoogsteen A-T(rH) DNA bps – novel high-energetic, dynamically-stable, mirror-symmetrical A-T(wrWC), A-T(rH), A-T(wrH), A-T(rWC) conformations. Their distinguished feature independently of the pair, in which they are realized, is significantly non-planar structure (C1 symmetry), caused by the pyramidal structure of the 26N6H2 amino fragment of the A DNA base, in which the amino group acts simultaneously as a donor and an acceptor of the specific intermolecular interaction with T through the two (T)N3H···N6(A) and (A)N6H/N6H′···O4'/O2(T) H-bonds. Each of the four A-T Watson-Crick DNA bps transfers into the aforementioned conformer via two mirror-symmetric pathways through the TS_A·T(WC) ↔ A-T(wrWC)R,L and TS_A·T(H) ↔ A-T(wH)R,L and TS_A·T(rWC) ↔ A-T(wrWC)R,L and TS_A·T(rH) ↔ A-T(rH)R,L (C1 symmetry). At this, the structures, which names differ from each other only by the subscripts R and L, are mirror-symmetrical, that is enantiomers. It is well known that enantiomers have identical scalar physico-chemical characteristics and differ only by the direction of the dipole moment.

Let analyze the biological significance of these non-usual conformers of the classical A-T DNA bps.

In this context it was fixed important result – these conformers are responsible for the two different WC/rWC ↔ H/rH mechanisms of the non-dissociative conformational transformation of the A-T DNA bps (Fig. 1, Tables 1–3).

First of these conformational transformations, which are the most energetically favorable mechanisms, are controlled by the soft TS_A·T(wrWC)L ↔ A-T(wrH)L and TS_A·T(wH)L ↔ A-T(wrH)L (C1 symmetry) with low values of imaginary frequency (7.1 and 16.1 i cm⁻¹, accordingly). Both of them are joined by the one-single intermolecular (T)N3H···N6(A) H-bond (~4 kcal·mol⁻¹) between the imino group of T and pyramidalized amino group of A. In this case, conformational transformations of the A-T DNA bps are realized by the following non-dissociative scenario (each of them – by the mirror-symmetric pathways): A-T(WC) (0.00) ↔ TS_A·T(WC) ↔ A-T(wrWC)R,L (5.36); TS_A·T(WC) ↔ A-T(wH)L (5.35) ↔ TS_A·T(wH)L ↔ A-T(rH) (7.24) ↔ A-T(H) (0.00); A-T(rWC) (0.00) ↔ TS_A·T(rWC) ↔ A-T(wrWC)R,L (5.97) ↔ TS_A·T(wH)L ↔ A-T(wH)L (5.79) ↔ TS_A·T(wrH)L ↔ A-T(rH) (5.44) ↔ A-T(rH) (0.03). Notably, obtained energetic barriers are in good coincidence with the molecular-dynamic data for the A-T(WC) ↔ A-T(H) transition (10-11 kcal·mol⁻¹ under normal conditions).

Hereupon, some R structures transform into the other R structures, the same concerns L-structures. Saying in other words, pathways of these dipole-active conformational transformations are mirror-symmetric. In fact, the TS_A·T(wH)L ↔ A-T(wH)L and TS_A·T(wrH)L, which pairwise link the A-T(wH)L and A-T(wrH)L, A-T(wrWC)R,L and A-T(wH)L, conformers, are transition states of the WC/rWC ↔ H/rH conformational transformations of the classical A-T DNA bps.

High-energetic mechanism of the WC/rWC ↔ H/rH conformational transitions of the A-T DNA bps is connected with anisotropic rotation of the amino group of A around the exocyclic C6-N6 bond and is controlled by the TS_A·T(wrWC)L ↔ A-T(wH)L, TS_A·T(wH)L ↔ A-T(wrH)L and TS_A·T(wrH)L ↔ A-T(wrH)L, that have non-planar structure (C1 symmetry) and quite high values of the imaginary frequencies (~252 i cm⁻¹). These Ts are joined by the two anti-parallel intermolecular (T)N3H···N6(A) and (A)N6H/N6H′···O4' O2(T) H-bonds; notably, first of them is significantly stronger than the second one. The attractive O2···N7 van der Waals contacts with weak energy (~0.18 kcal·mol⁻¹) also participate in the stabilization of the TS_A·T(wrWC)L ↔ A-T(wH)L and TS_A·T(wrH)L, accordingly.

In this case, the R structures transform into the L-structures and vice versa and WC/rWC ↔ H/rH conformational transitions of the classical A-T DNA bps occur in such a case (each of them through two energetically and topologically non-equivalent ways):

A-T(WC) (0.00) ↔ TS_A·T(WC) ↔ A-T(wrWC)R,L (7.13) ↔ A-T(wH)L (5.36) ↔ TS_A·T(wH)L ↔ A-T(H) (0.44; 11); A-T(WC) (0.00) ↔ TS_A·T(WC) ↔ A-T(wrWC)R,L (7.13) ↔ A-T(wH)L (5.36) ↔ TS_A·T(wH)L ↔ A-T(H) (0.44); A-T(rWC) (0.00) ↔ TS_A·T(rWC) ↔ A-T(wrWC)R,L (7.26) ↔ A-T(wH)L (5.97) ↔ TS_A·T(wH)L ↔ A-T(H) (0.44) ↔ A-T(wrWC)R,L ↔ A-T(rH) (15.01) ↔ A-T(H) (0.03) ↔ A-T(rWC) (0.00) ↔ TS_A·T(rWC) ↔ A-T(wrWC)R,L (7.26) ↔ A-T(wH)L (5.97) ↔ TS_A·T(wH)L ↔ A-T(H) (0.44); A-T(rWC) (0.00) ↔ TS_A·T(rWC) ↔ A-T(wrWC)R,L (7.26) ↔ A-T(wH)L (5.97) ↔ TS_A·T(wH)L ↔ A-T(H) (0.44) ↔ A-T(wrWC)R,L ↔ A-T(H) (0.03) (relative Gibbs free energy is...
Figure 1. Geometrical structures of the stationary points on the reaction pathways of the discovered conformational transitions of the four biologically important A-T DNA bps. Electronic energies of the interaction $\Delta E_{\text{int}}$ (MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory, in kcal mol$^{-1}$), relative Gibbs free energies $\Delta G$ and electronic energies $\Delta E$ (in kcal mol$^{-1}$), imaginary frequencies $\nu$ at the TSs of the conformational transitions (MP2/aug-cc-pVDZ//B3LYP/6-311++G(d,p) level of theory in the continuum with $\varepsilon = 4$ at $T = 298.15$ K) are presented below complexes in brackets. Dotted lines indicate AH···B H-bonds and attractive A···B van der Waals contacts – their lengths are presented in angstroms (for their more detailed physico-chemical characteristics see Table 2); carbon atoms are in light-blue, nitrogen – in dark-blue, hydrogen – in grey and oxygen – in red. Exclusively enantiomers of one type are presented.

Table 1. Energetic characteristics (in kcal mol$^{-1}$) of the discovered conformational transitions of the four biologically important A-T DNA bps obtained at the MP2/aug-cc-pVDZ/B3LYP/6-311++G(d,p) level of theory in the continuum with $\varepsilon = 4$ (see Fig. 1). aImaginary frequency at the TS of the conformational transition, cm$^{-1}$. bThe Gibbs free energy of the product relatively the reactant of the conformational transition (T = 298.15 K). cThe electronic energy of the product relatively the reactant of the conformational transition. dThe Gibbs free energy barrier for the forward conformational transition. eThe electronic energy barrier for the forward conformational transition. fThe Gibbs free energy barrier for the reverse conformational transition. gThe electronic energy barrier for the reverse conformational transition.
It should be noted that the orientation of the methyl group of the T DNA base does not alter in the course of all reactions of conformational transitions. At this, the heterocycles of the DNA bases, capable for the out-of-plane bending\(^{99-101}\), stay planar.

So, obtained by us results launch the conception of the “mechanics” of the non-dissociative WC/rWC ↔ H/rH conformational transformations of the classical A-T DNA bps.

### Table 2. Electron-topological, geometrical and energetic characteristics of the intermolecular specific contacts in the investigated conformers of the A-T DNA bps and TSs of their conformational transformations obtained at the B3LYP/6-311++G(d,p) level of theory (\(\varepsilon = 4\)) (see Fig. 1). aThe electron density at the (3, -1) BCP of the specific contact, a.u. bThe Laplacian of the electron density at the (3, -1) BCP of the specific contact, a.u. cThe ellipticity at the (3, -1) BCP of the specific contact. dThe distance between the A and B atoms of the specific contact, Å. eThe distance between the H and B atoms of the AH···B H-bond, Å. fThe H-bond angle, degree. gEnergy of the AH···B H-bond or attractive A···B van der Waals (vdW) contact, calculated by logansen's or Espinose-Molins-Lecomte (marked with an asterisk) formulas, kcal·mol\(^{-1}\). The dipole moment of the complex, D.

| Complex | AH···B H-bond/ A···B vdW contact | \(\rho^a\) | \(\Delta \rho^b\) | 100-\(\varepsilon^c\) | \(d_{A-H^d}\) | \(d_{H-B^e}\) | \(\angle AH-B^f\) | \(E_{AH-B}^g/\mu^h\) |
|---------|----------------------------------|-----------|-----------|-------------|-----------|-----------|-------------|----------------|
| A-T(w\(_{WC}\))_{3,1} & N6H···O4 | 0.022 | 0.076 | 2.10 | 2.988 | 2.028 | 156.2 | 4.11 | 3.97 |
| N3H·N6 | 0.010 | 0.030 | 31.69 | 3.337 | 2.484 | 141.1 | 1.75 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & N6H·N6 | 0.019 | 0.055 | 3.09 | 3.184 | 2.161 | 180.0 | 4.02 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & N3H·N6 | 0.026 | 0.076 | 3.24 | 2.976 | 2.019 | 153.3 | 5.52 |
| O2·N7 | 0.001 | 0.005 | 83.95 | 4.095 | — | — | 0.17* |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & N6H·N4 | 0.011 | 0.037 | 18.97 | 3.134 | 2.397 | 128.3 | 1.29 |
| N3H·N6 | 0.029 | 0.081 | 2.33 | 2.953 | 1.978 | 156.4 | 5.88 |
| A-T(w\(_{WC}\))_{3,1} & N6H·N4 | 0.021 | 0.075 | 2.64 | 2.983 | 2.033 | 154.4 | 4.01 |
| N3H·N6 | 0.009 | 0.028 | 34.33 | 3.370 | 2.527 | 140.1 | 1.55 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & N6H·N4 | 0.020 | 0.072 | 1.98 | 3.000 | 2.049 | 154.6 | 3.85 |
| N3H·N6 | 0.010 | 0.030 | 26.08 | 3.332 | 2.484 | 140.6 | 1.81 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & N6H·N2 | 0.011 | 0.036 | 19.20 | 3.143 | 2.406 | 128.4 | 1.05 |
| N3H·N6 | 0.027 | 0.076 | 2.09 | 2.979 | 2.017 | 154.4 | 5.54 |
| O4·N7 | 0.001 | 0.005 | 83.95 | 4.093 | — | — | 0.17* |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & N6H·N2 | 0.011 | 0.036 | 17.71 | 3.137 | 2.393 | 129.0 | 1.21 |
| N3H·N6 | 0.028 | 0.079 | 2.26 | 2.962 | 1.995 | 155.0 | 5.74 |
| O4·N7 | 0.001 | 0.005 | 83.95 | 4.093 | — | — | 0.17* |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & N6H·N2 | 0.020 | 0.069 | 2.88 | 2.998 | 2.072 | 150.5 | 3.71 |
| N3H·N6 | 0.010 | 0.032 | 21.42 | 3.308 | 2.455 | 141.1 | 1.55 |

### Table 3. Selected geometrical parameters, characterizing the non-planarity of the discovered conformers with wobble geometry of the four biologically important A-T DNA bps and TSs of their conformational interconversions, obtained at the B3LYP/6-311++G(d,p) level of theory in the continuum with \(\varepsilon = 4\). Note: Signs of the dihedral angles are presented exclusively for one type of enantiomers.

| Complex/Base | Dihedral angle, degree |
|--------------|-----------------------|
|              | C5G6N6H* | N1G6N6H | HN9P9N1H |
| A-T(w\(_{WC}\))_{3,1} & C5G6N6H* | -13.8 | 14.9 | -44.4 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & C5G6N6H* | -22.8 | 22.1 | -5.0 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & C5G6N6H* | -123.8 | 60.4 | -49.1 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & C5G6N6H* | 57.3 | 120.3 | -57.1 |
| A-T(w\(_{WC}\))_{3,1} & C5G6N6H* | -16.8 | 12.9 | 25.0 |
| A-T(w\(_{WC}\))_{3,1} & C5G6N6H* | -14.2 | 15.4 | 99.4 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & C5G6N6H* | -23.4 | 20.8 | -130.3 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & C5G6N6H* | 124.0 | 60.3 | 63.9 |
| TS\(_{A-T(w_{WC})\rightarrow A-T(w_{RLL})}\) & C5G6N6H* | 57.4 | 120.8 | -75.6 |
| A-T(w\(_{WC}\))_{3,1} & C5G6N6H* | -18.2 | 14.0 | -88.0 |
| A & C5G6N6H* | -7.2 | 6.6 | — |
| A\(_{419}\) & C5G6N6H* | 57.9 | 122.1 | — |
| A\(_{420}\) & C5G6N6H* | 122.5 | 57.5 | — |
Of course, in the composition of DNA these conformational transitions represent a self-consistent transformation of the bps, the anti ↔ syn transition of A around the glycosidic bond ($\Delta \Delta G_{TS} = 3.4$ kcal·mol$^{-1}$ at $\chi_{TS} = 121^\circ$ for BI-conformer of the isolated 2'-deoxyadenosine$^{185}$) and reorganization of stacking and hydration$^{19}$. Simple comparison of the energetics, determining these processes, clearly indicates that the first two of them plays a leading role. This fact gives hope that obtained in this paper data are closely related to the nature of the A-T(WC) ↔ A-T(H) thermal fluctuation process, which occurs in DNA$^{1-7}$. This conclusion can be verified, applying the newest methods of ab initio dynamics for the short fragments of DNA.

Conclusions

By applying developed by us novel ideas according the high-energetic conformers of the classical A-T DNA bps$^{11}$, we offered novel non-dissociative mechanisms of the A-T(WC) ↔ A-T(H) and A-T(rWC) ↔ A-T(rH) conformational transitions, that do not require for their realization energy-consuming anisotropic rotation of the amino group of the A DNA base around the C6-N6 exocyclic bond. Figuratively speaking, at the transformation of the A base from the anti- to syn-conformation leading to the formation of the Hoogsteen A-T(H) and reverse Hoogsteen A-T(rH) bps, it dynamically relies as on the support on the T DNA base through the pyramidilized amino group of A, interacting with it in the TS region by one single (T)NH···N6(A) H-bond.

In the light of the obtained by us results, it could be suggested that the A-T(WC) ↔ A-T(H) conformational transition in DNA duplex, which was registered experimentally$^{1-7}$, most likely occurs by the non-dissociative mechanism: A, rotating from the anti- to syn-configuration, interacts with T via the intermolecular H-bonds along the entire process of the conformational transformation.

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Author Contributions
D.M.H. proposed the idea of the study, formulated the task and suggested possible pathways of the non-dissociative structural transitions of the Watson-Crick and reverse Watson-Crick A·T DNA base pairs into the Hoogsteen and reverse Hoogsteen forms and partly wrote the text of the manuscript. O.O.B. localized the pathways of the investigated interconversions, prepared numerical data for Tables and graphical materials for Figures, performed QM/QTAIM calculations and partly wrote the text of the manuscript. K.S.T. performed QM/QTAIM calculations, participated in the preparation of the text of the manuscript. All authors were involved in the proofreading of the final version of the manuscript.

Additional Information
Competing Interests: The authors declare no competing interests.

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