

# Atomistic Mechanisms of The Tautomerization of The G·C Base Pairs Through The Proton Transfer: Quantum-Chemical Survey

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## Research Article

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# Abstract

This study is devoted to the investigation of the  $G \cdot C^{*t}_{O_2}(WC) \leftrightarrow G^*_{NH_3} \cdot C^{*t}(WC)$ ,  $G \cdot C^*_{O_2}(WC) \leftrightarrow G^*_{NH_3} \cdot C^*(WC)$  and  $G^* \cdot C^*_{O_2}(WC) \leftrightarrow G^*_{NH_3} \cdot C(w_{WC})_{\downarrow}$  tautomerization reactions occurring through the proton transfer, obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory in gas phase under normal conditions ( $T=298.15$  K). These reactions lead to the formation of the  $G^*_{NH_3} \cdot C^{*t}(WC)$ ,  $G^*_{NH_3} \cdot C^*(WC)$  and  $G^*_{NH_3} \cdot C(w_{WC})_{\downarrow}$  base pairs by the participation of the  $G^*_{NH_3}$  base with  $NH_3$  group. Gibbs free energies of activation for these reactions are 6.43, 11.00 and 1.63 kcal·mol<sup>-1</sup>, respectively. All of these tautomerization reactions are dipole active. Finally, we believe that these non-dissociative processes, which are tightly connected with the tautomeric transformations of the G·C base pairs, play outstanding role in the supporting of the spatial structure of the DNA and RNA molecules with various functional purposes.

## Introduction

In recent years according to the analysis of the literature [1–6], the interest of researchers to the investigation of the prototropic tautomerism significantly increased. It is obviously connected with the fact that this research topic is multidisciplinary and covers wide areas of knowledge such as chemistry, in particular biochemistry, biology, including structural and quantum, molecular and quantum pharmacology, condensed matter physics, crystal physics, electronic technologies, biomolecular technologies etc. [7–12].

It occurs intensive accumulation of the data within the framework of the classical models, describing these processes [13–17], and also it occurs successful searches of both novel atomistic mechanisms of the prototropic tautomerization of the molecular objects [18–21], as well as novel instruments of the penetration into the course of these processes.

Shortly saying, now the mechanisms of the tautomerization of the base pairs, which are accompanied by the significant changing of the geometry of the tautomerizing base pair [22–24], actively enter the arena. It is suggested that exactly these tautomeric transitions are not only responsible for the structural transitions in the nucleic acids, as well as for the supporting of the unique spatial structures of the latest, which are responsible for the certain biological functions.

Aim of this work is to deepen the existing ideas about the quantum mechanisms of the tautomerization of the G·C pairs of nucleotide bases through the proton transfer along the intermolecular neighboring H-bonds as their intrinsic property. We have chosen for its successful realization biologically important G·C base pairs, which monomers are in the basic and rare tautomeric forms.

As a result of the provided quantum-chemical investigations for the first time it was revealed the following regularities.

Tautomerizations of the G·C base pairs are controlled by the transition states, joined by the intermolecular H-bonds and covalent bridges.

In all cases without any exception mechanisms of the tautomerization are step-by-step realized by the proton transfer.

## Computational Methods

**Density functional theory calculations of the geometry and vibrational frequencies.** Equilibrium geometries of the investigated G·C base pairs and transition states (TSs) of their tautomerizations, as well as their harmonic vibrational frequencies have been calculated, using Gaussian'09 program package [25] at the B3LYP/6-311++G(d,p) level of theory [26–30], which approved itself successfully for the calculations of the similar systems and processes and shown acceptable level of accuracy and adequacy of the obtained results [30, 31]. A scaling factor that is equal to 0.9668 has been applied in the present work for the correction of the harmonic frequencies for all complexes [20, 21, 32].

We have confirmed local minima and transition states, localized by Synchronous Transit-guided Quasi-Newton method [33], on the potential energy landscape by the absence or presence, respectively, of one imaginary frequency in the vibrational spectra of the complexes.

All reaction pathways have been reliably confirmed by providing intrinsic reaction coordinate (IRC) calculations [33] from each TS in the forward and reverse directions at the B3LYP/6-311++G(d,p) level of theory.

All calculations have been performed in the continuum with  $\epsilon = 1$ , that adequately reflects the processes occurring in real biological systems without deprivation of the structurally-functional properties of the bases in the composition of the DNA or RNA molecules and satisfactorily models the substantially hydrophobic recognition pocket of the DNA-polymerase machinery as a part of the replisome [34, 35].

**Single point energy calculations.** We continued geometry optimizations with electronic energy calculations as the single point calculations at the MP2/6-311++G(2df,pd) level of theory [36, 37].

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

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

where  $E_{\text{el}}$  – electronic energy and  $E_{\text{corr}}$  – thermal correction.

**QTAIM analysis.** Bader's quantum theory of Atoms in Molecules (QTAIM) [38] was applied to analyse the electron density distribution, using program package AIMAll [39].

The presence of the bond critical point (BCP), namely the so-called (3,-1) BCP, and a bond path between the donor and acceptor of the H-bond, as well as the positive value of the Laplacian at this BCP ( $\Delta\rho > 0$ ),

were considered as criteria for the formation of the H-bond [40–43]. Wave functions were obtained at the B3LYP/6-311++G(d,p) level of theory, used for geometry optimisation.

The atomic numbering scheme for the bases is conventional and rare tautomeric forms of the G and C bases are marked by an asterisk (\*) [4].

### Obtained results and their discussion.

In this work investigated tautomerization pathways of the G·C base pairs are presented on Fig. 1 and their discussion is outlined below.

It is interesting to note that  $G\cdot C^{*t}_{O2}(WC)$  base pair (Fig. 1) tautomerizes through the double proton transfer along the  $N1H\cdots N3$  and  $O2H\cdots N2$  H-bonds and *via* the  $TS_{G\cdot C^{*t}_{O2}(WC)\leftrightarrow G^{*}NH_3\cdot C^{*t}(WC)}$ , which are stabilized by the participation of the two intermolecular  $(C)N4H\cdots O6(G)$  and  $(C)O2H\cdots N2(G)$  H-bonds and  $(G)N1-H-N3(C)$  covalent bridge. Eventually, this reaction leads to the formation of the  $G^{*}_{NH_3}\cdot C^{*t}(WC)$  base pair, stabilized by three intermolecular  $N4H\cdots O6$ ,  $N3H\cdots N1$  and  $N2H\cdots O2$  H-bonds. Exactly the proton transfer along the lower  $O2H\cdots N2$  H-bond leads to the formation of the  $NH_3$  group at the G base.

Formed  $G^{*}_{NH_3}\cdot C^{*t}(WC)$  base pair can transform *via* the mutual rotation of the bases around the middle  $N3H\cdots N1$  H-bond, leading to the new reverse  $G^{*}_{NH_3}\cdot C^{*t}(rWC)$  base pair, stabilized by the  $N3H\cdots O6$ ,  $N4H\cdots N1$  and  $N2H\cdots N4$  H-bonds. Transition state of this interconversion  $TS_{G^{*}_{NH_3}\cdot C^{*t}(WC)\leftrightarrow G^{*}_{NH_3}\cdot C^{*t}(rWC)}$  is joined by three  $N4H\cdots N1$ ,  $N3H\cdots N1$ ,  $N2H\cdots N4$  H-bonds and single  $N2\cdots N3$  van der Waals contact.

Another reaction –  $G\cdot C^{*}_{O2}(WC)\leftrightarrow G^{*}_{NH_3}\cdot C^{*}(WC)$  – occurs *via* the transfer of the proton, localized at the  $N1$  nitrogen atom of the G base, to the  $N3$  nitrogen atom of the  $C^{*}_{O2}$  base and of the proton, localized at the  $O2$  oxygen atom of the  $C^{*}_{O2}$  base to the  $N2$  atom of the  $NH_2$  amino group of the G base and finally leads to the  $G^{*}_{NH_3}\cdot C^{*}(WC)$  base pair by the participation of the  $G^{*}_{NH_3}$  base with  $NH_3$  group. Transition state  $TS_{G\cdot C^{*}_{O2}(WC)\leftrightarrow G^{*}_{NH_3}\cdot C^{*}(WC)}$  of this reaction is characterized by the  $(G)O6\cdots N4(C)$  van der Waals contact and two  $(G)N1-H-N3(C)$  and  $(G)N2-H-O2(C)$  covalent bridges.

Formed  $G^{*}_{NH_3}\cdot C^{*}(WC)$  base pair can transform by the mutual rotations of the bases around the middle  $N3H\cdots N1$  H-bond into the reverse  $G\cdot C(rw_{WC})$  base pair:  $G^{*}_{NH_3}\cdot C^{*}(WC)\leftrightarrow G\cdot C(rw_{WC})$ . Transition state  $TS_{G^{*}_{NH_3}\cdot C^{*}(WC)\leftrightarrow G\cdot C(rw_{WC})}$  of this reaction is joined by three intermolecular  $N3H\cdots N1$ ,  $N2H\cdots N4$ ,  $N2H\cdots O2$  H-bonds and  $N2\cdots N3$  van der Waals contact.

The most interesting case represents the last transformation –  $G^{*}\cdot C^{*}_{O2}(WC)\leftrightarrow G^{*}_{NH_3}\cdot C(w_{WC})_J$ , since proton transfer within the  $G^{*}\cdot C^{*}_{O2}(WC)$  base pair leads not only to the changing of its tautomeric status, but also to its geometrical rearrangement. This reaction occurs through the proton transfer along the upper  $O6H\cdots N4$  and lower  $O2H\cdots N2$  H-bonds from the  $O2$  atom of the  $G^{*}$  base to the  $N4$  atom of the  $C^{*}_{O2}$  base and from the  $O2$  atom of the  $C^{*}_{O2}$  base to the  $N2$  atom of the  $G^{*}$  base, respectively. Finally, C base

shifts down accordingly the  $G^*_{\text{NH}_3}$  base, forming the  $G^*_{\text{NH}_3}\cdot\text{C}(\text{w}_{\text{WC}})\downarrow$  base pair by the participation of the G base with  $\text{NH}_3$  group.

Altogether it was revealed four G·C base pairs, involving  $G^*_{\text{NH}_3}$  base with  $\text{NH}_3$  group –  $G^*_{\text{NH}_3}\cdot\text{C}^{\text{t}}(\text{WC})$ ,  $G^*_{\text{NH}_3}\cdot\text{C}^{\text{t}}(\text{rWC})$ ,  $G^*_{\text{NH}_3}\cdot\text{C}^*(\text{WC})$  and  $G^*_{\text{NH}_3}\cdot\text{C}(\text{w}_{\text{WC}})\downarrow$  (Fig. 1).

In general, considered here G·C base pairs form the following order in terms of their relative Gibbs free  $\Delta G$  and electronic  $\Delta E$  energies (in  $\text{kcal}\cdot\text{mol}^{-1}$ ):  $G\cdot\text{C}(\text{rw}_{\text{WC}})$  (0.00 and 0.00) <  $G^*_{\text{NH}_3}\cdot\text{C}(\text{w}_{\text{WC}})\downarrow$  (16.08 and 14.54) <  $G\cdot\text{C}^{\text{t}}_{\text{O}_2}(\text{WC})$  (19.43 and 17.53) <  $G^*\cdot\text{C}^*_{\text{O}_2}(\text{WC})$  (19.44 and 17.56) <  $G^*_{\text{NH}_3}\cdot\text{C}^{\text{t}}(\text{WC})$  (24.60 and 22.32) <  $G^*_{\text{NH}_3}\cdot\text{C}^*(\text{WC})$  (31.67 and 30.17) <  $G^*_{\text{NH}_3}\cdot\text{C}^{\text{t}}(\text{rWC})$  (32.97 and 31.80).

Notably, that difference in Gibbs free and electronic energies between the classical  $G\cdot\text{C}(\text{WC})$  and reverse  $G\cdot\text{C}(\text{rw}_{\text{WC}})$  base pairs consists 11.53 and 13.09  $\text{kcal}\cdot\text{mol}^{-1}$ , respectively, while the  $G\cdot\text{C}^{\text{t}}_{\text{O}_2}(\text{WC})$  and  $G\cdot\text{C}^*_{\text{O}_2}(\text{WC})$  base pairs are iso-energetical (19.43 and 19.44  $\text{kcal}\cdot\text{mol}^{-1}$ , respectively).

## Conclusions

This paper reports for the first time novel tautomerization mechanisms for the G·C base pairs, leading to the base pairs by the participation of the  $G^*_{\text{NH}_3}$  base with  $\text{NH}_3$  group:  $G\cdot\text{C}^{\text{t}}_{\text{O}_2}(\text{WC})\leftrightarrow G^*_{\text{NH}_3}\cdot\text{C}^{\text{t}}(\text{WC})$ ,  $G\cdot\text{C}^*_{\text{O}_2}(\text{WC})\leftrightarrow G^*_{\text{NH}_3}\cdot\text{C}^*(\text{WC})$  and  $G^*\cdot\text{C}^*_{\text{O}_2}(\text{WC})\leftrightarrow G^*_{\text{NH}_3}\cdot\text{C}(\text{w}_{\text{WC}})\downarrow$ .

Gibbs free energies of activation for these reactions are 6.43, 11.00 and 1.63  $\text{kcal}\cdot\text{mol}^{-1}$ , respectively, obtained at the MP2/6-311 ++ G(2df,pd)//B3LYP/6-311 ++ G(d,p) level of theory in gas phase under normal conditions ( $T = 298.15 \text{ K}$ ).

In all cases without any exception tautomeric transitions are dipole active with minimum realized at the starting  $G\cdot\text{C}^{\text{t}}_{\text{O}_2}(\text{WC})$  (9.98 D),  $G\cdot\text{C}^*_{\text{O}_2}(\text{WC})$  (7.91 D) and  $G^*\cdot\text{C}^*_{\text{O}_2}(\text{WC})$  (6.91 D) base pairs.

## Declarations

Funding: Not applicable.

Conflicts of interest/Competing interests: Not applicable.

Availability of data and material: Not applicable.

Code availability: Gaussian'09 program package – gaussian.com; AIMAll program package – <http://aim.tkgristmill.com/>.

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manuscript. DH – idea formulation, preparing, and proofreading of the draft of the manuscript. All authors contributed to the article and approved the submitted version.

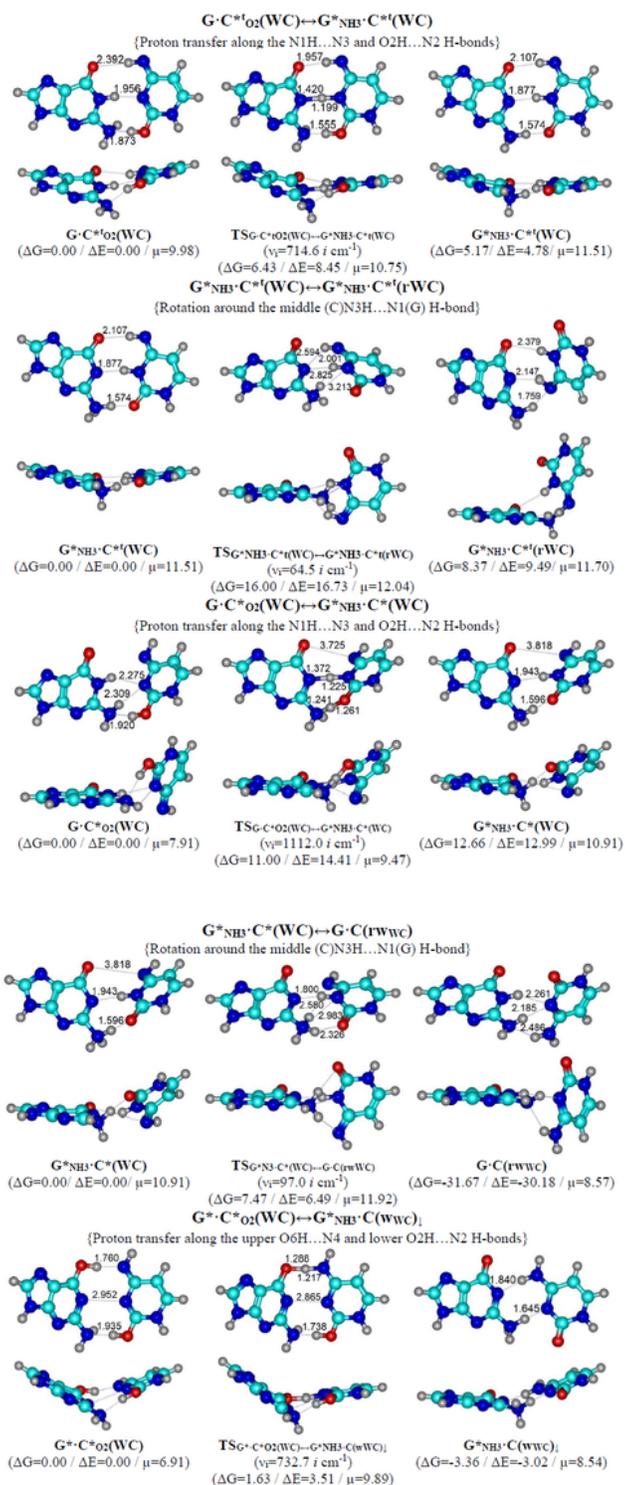
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## Figures



**Figure 1**

Tautomeric and conformational transformations of the G·C base pairs through the proton transfer and mutual rotations of the bases, obtained at the MP2/6-311++G(2df,pd)//B3LYP/6-311++G(d,p) level of theory in gas phase under normal conditions (ΔG – relative Gibbs free energy (T=298.15 K), kcal·mol<sup>-1</sup>; ΔE – electronic energy, kcal·mol<sup>-1</sup>; ν<sub>i</sub> – imaginary frequency at the TS; μ – dipole moment of the complex, D). Intermolecular AH...B H-bonds and A...B van der Waals contacts are designated by the dotted

lines, their lengths H...B and A...B are presented in Angstroms. Symbol "↓" means displacement of the base on the right down relatively the base on the left.