Ukrainica Bioorganica Acta 2 (2012) 17—24

Ukrainica Bioorganica Acta
www.bioorganica.org.ua

Mutagenic properties of 5-halogen derivatives of uracil: quantum-chemical investigation

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Summary. The mechanisms of the intra- and intermolecular tautomerisation of ^{5}XUra bases (X = H, CH_3, Br, Cl, F) and mispairs involving them and guanine (Gua) or adenine (Ade) have been studied to analyse their implications for the origin of the induced point mutations using quantum-chemical calculations at the MP2/6-311++G(3df,2pd)//B3LYP/6-311++G(d,p) level of theory in the free state. For the first time it has been established that the substitution of the hydrogen atom at the C5 position of Ura for the halogen (Hal = Br, Cl, F) has practically no effect on the main physico-chemical characteristics of intramolecular tautomerisation. The lifetime of the mutagenic tautomers of the 5-halogenuracils exceeds typical time of the DNA replication in the cell (~10^3 s) by 4-13 orders. The absence of intramolecular H-bonds in the canonical and mutagenic tautomeric forms of bases determines their high stability. These results confirm the adequacy of classical «rare tautomeric hypothesis» for substitution mutagenesis originally proposed by Watson and Crick. For the first time the influence of the halogen derivatives of Ura on replication and incorporation errors in DNA has been studied. It was shown that Ura halogenization does not induce replication errors, however causes incorporation errors due to the lowering of the barrier of the Gua·^{5}XUra (X = Hal) wobble base pairs tautomerisation into the Gua*·^{5}XUra base pairs with Watson-Crick geometry in comparison with Gua·Thy base pair.

Keywords: 5-halogen derivatives of Ura, mutagenic properties, induced point mutations, quantum-chemical calculations.

Introduction. 5-bromouracil (^{5}BrUra), 5-chlorouracil (^{5}ClUra) and 5-fluorouracil (^{5}FUra) are halogen derivatives of Ura and classical mutagens, which mutagenic effect on DNA has been studied in detail for decades using molecular biological and genetic methods [1, 2]. Investigation of the mutagenic properties of the 5-halogenuracils is interesting and important due to the several reasons. First of all, Ura is the basic product of the spontaneous damage of DNA by water molecules [3, 4]. Moreover, halogen derivatives of Ura — ^{5}XUra (X = Br, Cl, F) — are classical mutagens and molecular mechanisms of their action have been discussed in the literature for a long time [5, 6].

On the other hand, non-canonical keto or enol tautomeric forms of Ura and its halogen derivatives were supposed to be very unstable and their role in physiological DNA structures was assumed to be negligible. However, despite the fact that the amount of rare tautomeric forms is negligible, an increasing number of data sup-

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ports the importance of non-canonical tautomers in the origin of the mutations and stabilization of certain nucleic acid structures [7, 8].

For the first time the occurrence of spontaneous point mutations in DNA was explained by Watson and Crick [9] and further elaborated by Topal and Fresco [7] within the framework of the «rare tautomeric hypothesis» that consists in the formation of the base pairs involving rare (imino and enol) tautomers of the DNA bases [10, 11].

At the same time, today there are no physical concepts to explain the molecular mechanisms of the mutagenic action of 5-halogenuracils and to properly substantiate them from the quantum-mechanical point of view without internal contradictions. This finding may be explained by the fact, that the mechanisms of the origin of the spontaneous point mutations in DNA have not yet been established.

In this paper we have exhaustively explored the tautomerism of the Ura, Thy and ^{5}XUra (X = Br, Cl, F) bases as the molecular basis for their mutagenic properties. For this purpose, we have studied the mechanisms of the intra- and intermolecular tautomerisation of the aforementioned pyrimidine bases in the free state. High-level quantum-chemical calculations provided a complete picture of the reactivity of the halogen derivatives of Ura and gave new insights into their mutagenicity. Finally, new mechanisms of the replication and incorporation errors in DNA induced by ^{5}XUra compounds, which are based on the mechanisms of the spontaneous point mutations presented in our recent works [12, 13], were proposed.

Methods. All calculations were performed using Gaussian'09 suite of programs [14]. All geometries were optimized using the B3LYP/6-311++G(d,p) method [15, 16]. Local minima were verified by establishing that the matrix of second derivatives of the energy (Hessian) has only one positive eigenvalue and were examined for the lack of the imaginary frequencies in their vibrational spectra calculated at the level of theory used for geometry optimization within the framework of the rigid rotor-harmonic oscillator approximation. A scaling factor of 0.9668 has been used in the present work at the B3LYP level of theory to correct the harmonic frequencies of all the studied structures.

Transition states (TSs) were located by means of Synchronous Transit-guided Quasi-Newton (STQN) method [17, 18] using the Berny algorithm and proved to contain one and only one imaginary frequency corresponding to the reaction coordinate.

To consider electronic correlation effects as accurately as possible, we performed single point calculations at the MP2/6-311++G(3df,2pd) level of theory for the B3LYP/6-311++G(d,p) geometries.

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 using BSSE-correction [19].

Rate constants for forward and reverse reactions of tautomerisation were calculated by following equation:

$$k = \Gamma \cdot \frac{k_B T}{h} e^{-\frac{\Delta\Delta G}{RT}},$$

where $\Gamma = 1 + \frac{1}{24}\left(\frac{h\nu_i}{k_B T}\right)^2$ — Wigner's tunneling correction, k_B — Boltzman constant, T=298.15 K — temperature, h — Plank's constant, $\Delta\Delta G$ — Gibbs free energy of activation, R — universal gas constant.

The lifetime τ can be estimated using the expression $\tau = k^{-1}$. The time $\tau_{99.9\%}$ necessary to reach 99.9 % of the equilibrium concentration of the reactant and the product of reversible first-order reaction was estimated by the formula [20]:

$$\tau_{99.9\%} = \frac{ln10^3}{k_f + k_r}.$$

The population of the formed mispairs and rare tautomers can be governed by Boltzmann statistics:

$$K = e^{-\frac{\Delta G}{RT}},$$

where ΔG — the Gibbs free energy of tautomerisation.

An analysis of the electron density distribution was carried out within Bader's «Atoms in Molecules» (AIM) approach using wave functions received at the B3LYP/6-311++G(d,p) level of theory [21]. The AIM analysis has been performed using the AIM2000 program package [22] with all default options.

The energy of the non-canonical intermolecular CH...O/N H-bonds was estimated using the Espinosa-Molins-Lecomte empirical topological formula [23]:

$$E_{HB} = 0.5 \cdot V(r),$$

where V(r) — the value of the local potential energy density in the (3,-1) bond critical point (BCP) of hydrogen bond.

The energy of the canonical H-bonds was calculated using the Iogansen's formula [24]:

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

where Δν — the red-shift of the valence stretching vibrations of the AH H-bonded group.

Results and their discussion. The obtained results are presented in Tables 1-3 and Figures 1, 2.

1. Intramolecular tautomerisation and stability of the mutagenic tautomers of the Thy, Ura and Ura halogen derivatives.

As we can see, the allocation of the halogens ^{5}XUra (X = Br, Cl, F) at the position C5 of Ura does not cause any significant changes in the main physico-chemical characteristics of the intramolecular tautomerisation comparably to the unsubstituted system. So, in the transition state of the ^{5}XUra→^{5}XUra* (X = Br, Cl, F) intramolecular tautomerisation the lengths of the N3H and O4H distended chemical bonds vary no more than for 0.009 and 0.002 Å, respectively, and the angle N3HO4 (formed by the migrating proton) between them — no more than for 0.2°. At the same time, the values of the electron density ρ and the Laplacian of the electron density Δρ at the BCPs of the N3H and O4H bonds are located within quite narrow limits in the TS of the tautomerisation: ρ_{N3H}=0.134÷0.137 a.u., ρ_{O4H}=0.131÷0.132 a.u.; $\Delta\rho_{N3H}$=-0.093÷-0.103 a.u., $\Delta\rho_{O4H}$=-0.023÷-0.026 a.u. The absence of intramolecular H-bonds in the canonical and mutagenic tautomeric forms of bases determines their high stability. These results confirm the adequacy of classical «rare tautomeric hypothesis» for substitution mutagenesis originally proposed by Watson and Crick [9].

The same situation is observed also for the orientation and values of the dipole moments of the bases that change during tautomerisation: in all cases, except Ura, the values of the dipole moments increase in the following order — mutagenic tautomer of the base, canonical tautomer of the base, transition state of the intramolecular tautomerisation, while for the Ura base the order is reverse (Figure 1).

Ura halogenization does not significantly influence on the energetic and kinetic parameters

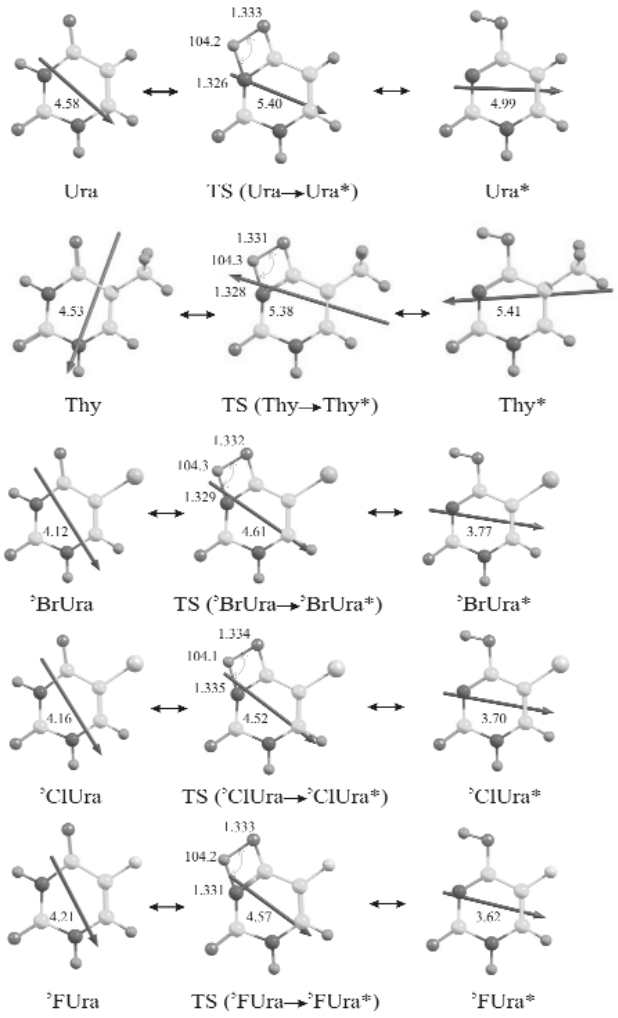

Figure 1. Intramolecular tautomerisation of the Thy, Ura and Ura halogen derivatives: geometric (the lengths of the chemical bonds formed by migrating proton are provided in Angstroms and valence angles between them are given in degrees) and electrical (dipole moments are depicted by arrows and their absolute values are presented in Debye near them) representations.

of the ^{5}XUra→^{5}XUra* (X = Br, Cl, F) intramolecular tautomerisation. As a result, both equilibrium constant of the ^{5}XUra→^{5}XUra* tautomeric equilibrium and the lifetime of the mutagenic tautomers are the values of the same order: ~10^{-9} and ~10^{15} s, respectively (Table 1).

So, the results obtained in this paper dispel the myth of the instability (the short lifetime) of the mutagenic tautomers of Ura and Thy nucleotide bases and Ura halogen derivatives, circulated in biological literature. Furthermore, our findings evidence in favor of the Watson and Crick's tautomeric hypothesis, since the lifetime of the mutagenic tautomers exceeds by several

Table 1

Basic thermodynamic and kinetic characteristics of the intramolecular tautomerisation of Ura and Thy bases and their halogen derivatives obtained at the MP2/6-311++G(3df,2pd)//B3LYP/6-311++G(d,p) level of theory (see Figure 1)

Tautomerisation	ΔG	K	ΔΔG	k	τ	$\tau_{99.9\%}$	$-i\cdot\nu_i$	Γ
Ura→Ura*	10.90	$1.02\cdot10^{-8}$	39.17	$4.91\cdot10^{-16}$	$2.04\cdot10^{15}$	$1.91\cdot10^{8}$	1900.1	4.24
Ura*→Ura			28.27	$4.83\cdot10^{-8}$	$2.07\cdot10^{7}$			
Thy→Thy*	11.72	$2.54\cdot10^{-9}$	39.49	$2.84\cdot10^{-16}$	$3.52\cdot10^{15}$	$8.24\cdot10^{7}$	1903.1	4.25
Thy*→Thy			27.78	$1.12\cdot10^{-7}$	$8.95\cdot10^{6}$			
^{5}BrUra→^{5}BrUra*	11.54	$3.44\cdot10^{-9}$	39.93	$1.37\cdot10^{-16}$	$7.31\cdot10^{15}$	$2.32\cdot10^{8}$	1911.3	4.28
^{5}BrUra*→^{5}BrUra			28.39	$3.98\cdot10^{-8}$	$2.51\cdot10^{7}$			
^{5}ClUra→^{5}ClUra*	11.55	$3.37\cdot10^{-9}$	40.11	$1.01\cdot10^{-16}$	$9.92\cdot10^{15}$	$3.08\cdot10^{8}$	1911.7	4.28
^{5}ClUra*→^{5}ClUra			28.56	$2.99\cdot10^{-8}$	$3.34\cdot10^{7}$			
^{5}FUra→^{5}FUra*	11.82	$2.15\cdot10^{-9}$	40.78	$3.23\cdot10^{-17}$	$3.09\cdot10^{16}$	$6.13\cdot10^{8}$	1911.1	4.28
^{5}FUra*→^{5}FUra			28.97	$1.50\cdot10^{-8}$	$6.65\cdot10^{7}$			

Notes: ΔG — the relative Gibbs free energy of the tautomer, kcal/mol; K — the equilibrium constant; ΔΔG — the activation Gibbs free energy of the tautomerisation (T=298.15 K), kcal/mol; k — rate constant, s^{-1}; τ — the lifetime of the mutagenic or canonical tautomer of the base, s; $\tau_{99.9\%}$ — the time necessary to reach 99.9 % of the equilibrium concentration of the canonical and mutagenic tautomer, s; $-i\cdot\nu_i$ — imaginary frequency, cm^{-1}; Γ — Wigner's tunneling correction.

orders the time of the DNA replication in the cell (~10^3 s).

2. Do the 5-halogenuracils induce the replication errors in DNA?

The results are shown in Figure 2A and Table 2. Substitution of the hydrogen atom at the C5 position of Ura doesn't change the character of the tautomerisation: similarly to the Ade·Thy canonical base pair, it occurs through the two transition states which are the Ade^{+}·^{5}XUra^{-} ion-pair-like structures joined by H-bonds. Their structures are similar to the structure of the Ade·Thy base pair (Figure 2A). The Ade*·^{5}XUra and Ade·^{5}XUra* base pairs formed through the tautomerisation of the Ade·^{5}XUra base pairs (X = Br, Cl, F) are dynamically stable because in all cases the value of the reverse barrier of tautomerisation exceeds the corresponding zero-point energies of vibrational modes, which thermal excitation induces these transitions.

It should be especially emphasized that the time of the thermalization processes (establishment of the thermodynamic equilibrium) of the Ade·Thy base pair tautomerisation into the Ade*·Thy and Ade·Thy* base pairs is much smaller than the time of the elementary act of the enzymatic incorporation of one nucleotide during the biosynthesis of DNA (10^{-3} s [25]). This means that in this case the mutagenic effect will be determined by the occupancy of the wobble tautomerised Ade*·^{5}XUra and Ade·^{5}XUra* base pairs (X = Br, Cl, F) base pairs. This conclusion coincides with the molecular biological experiments indicating that the Ade·^{5}XUra base pairs (X = Br, Cl, F) are not mutagenic and extended [5].

Obtained by us computational results strongly suggest that Ura halogen derivatives do not induce DNA replication errors.

Firstly, the population of the tautomerised base pairs involving Ura halogen derivatives is less than the corresponding value for the Ade·Thy Watson-Crick base pair, except Ade*·^{5}FUra base pair ($9.35\cdot10^{-8}$) (Table 2).

Second, the lifetime of these base pairs is shorter than the time required for the replication machinery to forcibly dissociate a base pair into the monomers during DNA replication (10^{-9} s [26]) (Table 2). As a result, the tautomerised base pairs, figuratively speaking, «escape from the hands of the replicational machinery» and can not successfully dissociate into the pair of the isolated bases, one of which is in the mutagenic tautomeric form.

3. Mechanism of the incorporational errors induced by 5-halogenuracils.

For the first time the universal molecular mechanism of the mutagenic effect of the Ura halogen derivatives was established and based on the fact that barrier of the Gua·^{5}XUra→Gua*·^{5}XUra reaction is lower than of the Gua·Thy→Gua*·Thy reaction, which

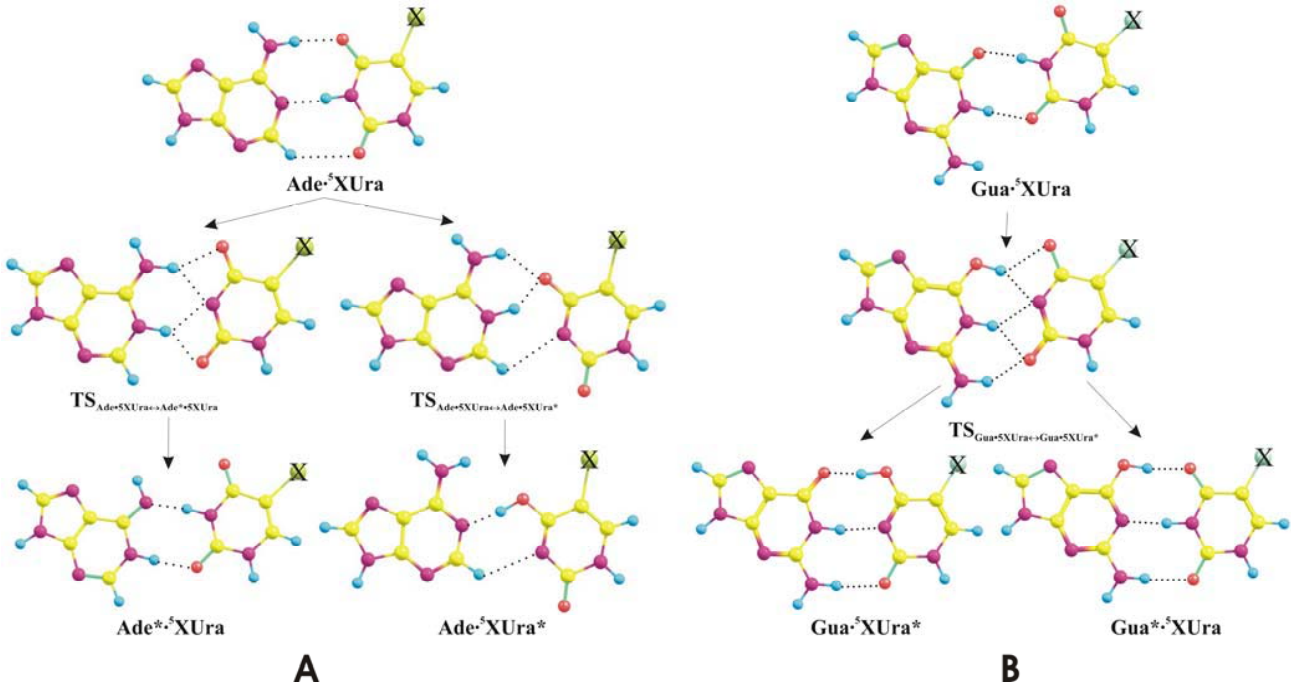

Figure 2. Geometrical structures of the studied base pairs involving ^{5}XUra halogen derivatives (X = Br, Cl, F) and transitions states of their appropriate conversions for A — replication errors and B — incorporation errors. H-bonds are designated as dotted lines.

induces spontaneous transitions (Figure 2B, Table 3).

We have made for the first time significant conclusion that the processes of the tautomerisation of the Gua·^{5}XUra wobble base pairs (X = Hal) into the Gua*·^{5}XUra base pairs with Watson-Crick geometry are slower (0.11÷5.43 s) than the process of the incorporation of a nucleotide by DNA-polymerase (10^{-3} s [25]). This means that the mechanism of incorporation errors is kinetic, i.e., it is determined by the barrier of the Gua·^{5}XUra→Gua*·^{5}XUra tautomerisation.

Electronic ΔE_{int} and Gibbs free ΔG_{int} energies of interaction of the bases in the Gua·^{5}XUra wobble mispairs containing halogens are almost the same as in the Gua·Thy mispair (see Table 3). H-bonds stabilizing these mispairs can be characterized in the same way. It means that these mispairs can be formed with the same probability. The same conclusions can be reached at the comparison of the corresponding characteristics of the Gua*·^{5}XUra and Gua·^{5}XUra* mispairs with that for the Gua*·Thy and Gua·Thy* mispairs, respectively.

Conclusions. We established that classical tautomeric hypothesis of Watson and Crick [9] may be applied for Thy, Ura bases and Ura halogen derivatives.

The mechanisms of the intra- and intermolecular tautomerisation of ^{5}XUra bases (X = H, CH3, Br, Cl, F) and mispairs involving them and guanine (Gua) or adenine (Ade) have been studied to analyse their implications for the origin of the induced point mutations using quantum-mechanical calculations at the MP2/6-311++G(3df,2pd)//B3LYP/6-311++G(d,p) level of theory in the free state. For the first time it has been established that the substitution of the hydrogen atom at the C5 position of Ura for the halogen (Hal = Br, Cl, F) has practically no effect on the main physico-chemical characteristics of intramolecular tautomerisation. The lifetime of the mutagenic tautomers of the 5-halogenuracils exceeds typical time of the DNA replication in the cell (~10^{3} s) by 4-13 orders.

The absence of intramolecular H-bonds in the canonical and mutagenic tautomeric forms of bases determines their high stability. These results confirm the adequacy of classical «rare tautomeric hypothesis» for substitution mutagenesis originally proposed by Watson and Crick. For the first time the influence of the halogen derivatives of Ura on replication and incorporation errors in DNA has been studied. It was

Table 2

Energetic characteristics (in kcal/mol under standard conditions) of the base pairs involving Ade, Thy and ^{5}XUra (X = Br, Cl, F) and TSs of their mutual tautomeric conversion (see also Figure 2A)

Complexes	ΔG	K	$\sum E_{HB}$	-ΔE_{int}	$-\frac{\sum E_{HB}}{E_{int}}$, %	-ΔG_{int}	τ	$\tau_{99.9\%}$
Ade·Thy	0.00		13.03	13.20	98.8	0.30		
Ade*·Thy	9.78	$6.70\cdot10^{-8}$	13.80	16.59	83.2	4.56	$3.96\cdot10^{-8}$	$3.65\cdot10^{-7}$
Ade·Thy*	10.74	$1.32\cdot10^{-8}$	10.83	11.75	92.2	0.07	$2.67\cdot10^{-6}$	$2.46\cdot10^{-5}$
$TS_{Ade\cdot Thy\leftrightarrow Ade^*\cdot Thy}$	17.14		13.17	119.98	11.0	88.84		
$TS_{Ade\cdot Thy\leftrightarrow Ade\cdot Thy^*}$	20.59		14.83	118.36	12.5	88.06		
Ade·^{5}BrUra	0.00		13.43	13.86	96.9	0.42		
Ade*·^{5}BrUra	9.92	$5.32\cdot10^{-8}$	14.21	17.32	82.0	5.32	$8.09\cdot10^{-10}$	$7.45\cdot10^{-9}$
Ade·^{5}BrUra*	11.87	$1.96\cdot10^{-9}$	11.57	13.71	84.4	1.86	$2.75\cdot10^{-9}$	$2.54\cdot10^{-8}$
$TS_{Ade\cdot 5BrUra\leftrightarrow Ade^*\cdot 5BrUra}$	14.97		12.61	114.02	11.1	100.00		
$TS_{Ade\cdot 5BrUra\leftrightarrow Ade\cdot 5BrUra^*}$	17.65		14.09	112.98	12.5	99.96		
Ade·^{5}ClUra	0.00		13.35	13.85	96.4	0.48		
Ade*·^{5}ClUra	9.95	$5.07\cdot10^{-8}$	14.22	17.37	81.9	5.36	$8.65\cdot10^{-10}$	$7.97\cdot10^{-9}$
Ade·^{5}ClUra*	12.10	$1.32\cdot10^{-9}$	11.70	13.77	85.0	1.74	$3.16\cdot10^{-9}$	$2.91\cdot10^{-8}$
$TS_{Ade\cdot 5ClUra\leftrightarrow Ade^*\cdot 5ClUra}$	15.04		12.61	114.49	11.0	100.49		
$TS_{Ade\cdot 5ClUra\leftrightarrow Ade\cdot 5ClUra^*}$	17.96		14.09	113.34	12.4	100.16		
Ade·^{5}FUra	0.00		13.33	13.88	96.1	0.43		
Ade*·^{5}FUra	9.58	$9.35\cdot10^{-8}$	14.33	17.63	81.3	5.63	$9.89\cdot10^{-10}$	$9.11\cdot10^{-9}$
Ade·^{5}FUra*	12.04	$1.46\cdot10^{-9}$	11.77	13.95	84.4	2.01	$3.77\cdot10^{-9}$	$3.47\cdot10^{-8}$
$TS_{Ade\cdot 5FUra\leftrightarrow Ade^*\cdot 5FUra}$	14.76		12.56	115.30	10.9	101.14		
$TS_{Ade\cdot 5FUra\leftrightarrow Ade\cdot 5FUra^*}$	18.01		14.11	113.85	12.4	100.57		

Notes: ΔG — the relative Gibbs free energy of the base pairs or TSs obtained at the MP2/6-311++G(3df,2pd)//B3LYP/6-311++G(d,p) level of theory, kcal/mol; K — the equilibrium constant; ΣE_{HB} — the total energy of the intermolecular H-bonds, kcal/mol; -ΔE_{int} — the BSSE-corrected electronic interaction energy obtained at the MP2/6-311++G(2df,pd) level of theory, kcal/mol; -ΔG_{int} — the Gibbs free energy of interaction obtained at the MP2/6-311++G(2df,pd) level of theory, kcal/mol; τ — the lifetime of the mispair containing mutagenic tautomer of the base, s; $\tau_{99.9\%}$ — the time necessary to reach 99.9 % of the equilibrium concentration of the base pair with Watson-Crick geometry and mispair containing mutagenic tautomer, s.

shown that Ura halogenization does not induce replication errors, however causes incorporation errors due to the lowering of the barrier of the Gua·^{5}XUra (X = Hal) wobble base pairs tautomerisation into the Gua*·^{5}XUra base pairs with Watson-Crick geometry in comparison with Gua·Thy base pair.

So, taking aforementioned results into consideration we can conclude that incorporation error is the main and the sole mechanism of the mutations induced by the halogen derivatives.

Acknowledgments. This work was partly supported by the State Fund for Fundamental Research of Ukraine within the Ukrainian-Russian (project № F40.4/039) and Ukrainian-Slovenian research bilateral projects for 2011-2012 years. Author was supported by the Grant of the President of Ukraine to support scientific research of young scientists for 2012 year from the State Fund for Fundamental Research of Ukraine (project № GP/F44/086) and by the Grant of the President of Ukraine for talented youth for 2012 year from the Ministry of Education and Science, Youth and Sports of Ukraine. Author thanks Bogolyubov Institute for Theoretical Physics of the National Academy of Sciences of Ukraine for providing calculation resources and software. This work was performed using computational facilities of joint computer cluster of SSI «Institute for Single Crystals» of the National Academy of Sciences of Ukraine and Institute for Scintillation Materials of the National Academy of Sciences of Ukraine incorporated into Ukrainian National Grid.

Надійшла в редакцію 30.11.2012 р.

Table 3

Energetic characteristics (in kcal/mol under standard conditions) of the base pairs involving Gua, Thy and ^{5}XUra (X = Br, Cl, F) and TSs of their mutual tautomeric conversion (see also Figure 2B)

Complexes	ΔG	$\sum E_{HB}$	-ΔE_{int}	$-\frac{\sum E_{HB}}{E_{int}}$, %	-ΔG_{int}	τ	$\tau_{99.9\%}$
Gua·Thy	0.00	11.43	15.33	74.5	3.46		
Gua·Thy*	-0.22	20.57	32.23	63.8	19.38	1.44	5.43
Gua*·Thy	-1.39	17.99	17.94	100.3	5.29		
$TS_{Gua\cdot Thy \leftrightarrow Gua\cdot Thy*}$	17.45	18.15	132.92	13.7	116.59		
Gua·^{5}BrUra	0.00	11.90	15.32	77.6	3.48		
Gua·^{5}BrUra*	0.0002	20.65	31.99	64.6	19.43	$2.78\cdot10^{-2}$	0.13
Gua*·^{5}BrUra	-0.94	17.46	17.42	100.2	4.65		
$TS_{Gua\cdot 5BrUra \leftrightarrow Gua\cdot 5BrUra*}$	15.33	17.31	126.06	13.7	109.85		
Gua·^{5}ClUra	0.00	11.57	15.38	75.2	3.50		
Gua·^{5}ClUra*	-0.08	20.72	32.09	64.6	19.57	$3.22\cdot10^{-2}$	0.14
Gua*·^{5}ClUra	-0.88	17.10	17.40	98.3	4.57		
$TS_{Gua\cdot 5ClUra \leftrightarrow Gua\cdot 5ClUra*}$	15.34	17.36	126.56	13.7	110.35		
Gua·^{5}FUra	0.00	11.64	15.65	74.4	3.79		
Gua·^{5}FUra*	0.30	20.84	32.36	64.4	19.78	$1.99\cdot10^{-2}$	0.11
Gua*·^{5}FUra	-0.55	17.21	17.44	98.7	4.66		
$TS_{Gua\cdot 5FUra \leftrightarrow Gua\cdot 5FUra*}$	15.43	17.35	127.46	13.6	111.06		

Notes: see Table 2.

Мутагенні властивості 5-галогенпохідних урацилу: квантово-хімічне дослідження

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Резюме. Використовуючи квантово-хімічні розрахунки на рівні теорії MP2/6-311++G(3df,2pd)//B3LYP/6-311++G(d,p) у вільному стані, вивчено механізми внутрішньо- та міжмолекулярної таутомеризації основ ^{5}XUra (X = H, CH_3, Br, Cl, F) та неправильних пар за їхньою участю, а також гуаніну (Gua) та аденіну (Ade) з метою дослідження природи індукованих ними точкових мутацій. Вперше встановлено, що заміщення атома водню в положенні C5 Ura на галоген (Hal = Br, F, Cl) майже не впливає на основні фізико-хімічні характеристики внутрішньомолекулярної таутомеризації. Час життя мутагенних таутомерів 5-галогенурацилів на 4-13 порядків перевищує характерний час реплікації ДНК в клітині (~10^3 сек). Висока стабільність канонічної та мутагенної таутомерних форм основ зумовлена відсутністю в них внутрішньомолекулярних H-зв'язків. Ці результати підтверджують адекватність класичної «гіпотези рідкісних таутомерів», уперше запропонованої Вотсоном і Криком для пояснення спонтанних мутацій заміщення. Уперше вивчено вплив галогенпохідних Ura на частоту помилок реплікації та включення, які виникають при синтезі ДНК. Показано, що галогенізація Ura не індукує помилок реплікації, проте спричиняє помилки включення за рахунок зниження бар'єру таутомеризації воблівських пар основ Gua·^{5}XUra (X = Hal) у пари основ із вотсон-криківською геометрією Gua*·5XUra порівняно із парою основ Gua·Thy.

Ключові слова: 5-галогенпохідні Ura, мутагенні властивості, індуковані точкові мутації, квантово-хімічні розрахунки.

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