Molecular Principles of the Spontaneous Mutagenesis in DNA

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Abstract – Reported results are crucial for understanding of the microstructural mechanisms of the spontaneous transitions and transversions, since they allow us to explain, from the one side, the origin of the mutagenic tautomers at the separation of the DNA strands before its replication and, from the other side, in what way occurs the adaptation of the incorrect purine/pyrimidine, purine-purine and pyrimidine-pyrimidine wobble pairs to the enzymatically competent sizes in the recognition pocket of the high-fidelity DNA-polymerase.

Key words – spontaneous point mutagenesis, incorporation and replication errors, tautomerisation, pairs of nucleotide bases, enzymatically-competent conformation, hydrogen bond, quantum chemistry.

I. Introduction

High-fidelity DNA replication is the central issues of the molecular biology [1]. At present time, it was established the important biological role of the spontaneous point mutations [2-4], arising with frequencies \(10^{-7}-10^{-13}\) during DNA replication [5-8], in the functioning of the living cell.

Nowadays, it is reliably known that the root cause of the origin of the spontaneous point mutations is the formation in the recognition pocket of the high-fidelity DNA-polymerase in its close state the wrong DNA base pairs (i.e. mismatches) able to adapt the conformation of the correct Watson-Crick DNA base pair (i.e. enzymatically-competent conformation) that guarantees their incorporation into the chemical structure of the synthesized DNA double helix [4].

In the literature it is currently presented two approaches according physico-chemical principles of the occurrence of the mismatches leading to spontaneous point mutations in DNA. One of them is the “tautonomic hypothesis” suggested by J. Watson and F. Crick [9] that consists in the spontaneous tautomeric transition of the DNA bases from the canonical to mutagenic tautomeric form leading from the formation of the adenine-cytosine* (A*C*)/A*C and guanine*-thymine (G*T)/G*T* (here and below mutagenic tautomers are marked with asterisk) Watson-Crick-like mismatches with correct enzymatically-competent conformation [10] containing mutagenic tautomers [11-13]. Despite great advances in experimental, in particular X-ray analysis [14, 15] and NMR relaxation dispersion measurements [16], and theoretical [17, 18] investigations, there are no unique approach to the physico-chemical mechanisms enabling DNA bases in the canonical tautomeric form to acquire rare or mutagenic tautomeric form before the dissociation of the Watson-Crick nucleobase pairs into the monomers by the replication machinery in order to produce mismatches resulting in further misincorporations and as a result – the spontaneous point mutations at the DNA replication. It is generally accepted in the literature that mutagenic tautomers of the DNA bases can arise via the double proton transfer (DPT) along intermolecular H-bonds in the Watson-Crick [19–22] and wobble [23] base pairs, and also in the protein-DNA complexes [24].

On contrary, other researchers believe that spontaneous point mutations arise due to the formation of the incorrect base pairs involving only DNA bases in the main, canonical tautomeric form – so-called wobble or shifted A-C and G-T base pairs [25]. However, it remains unclear the mechanisms of their adaptation to the enzymatically-competent sizes in the very tight, slightly deformable base pair recognition pocket of the high-fidelity DNA-polymerase [26, 27].

The common feature of these two approaches is the absence of the general physico-chemical conception according the nature of these mismatches causing spontaneous point mutations and the emergence of each of them is considered as a unique phenomenon. In the literature it is not represented attempts or ideas aimed at combining these approaches into the unique, internally non-contradictory conception. Nevertheless, creation of such theory is extremely actual interdisciplinary challenge called to solve urgent needs of the fundamental and applied character.

Thus, without the clear understanding of the basic mechanisms of the origin of the spontaneous point mutations, it is impossible to advance in the development of the management strategy of the genome instability and in the explanation of the physico-chemical grounds of evolution [28, 29]; at the design of the highly-efficient mutagens – analogs of the nucleotide bases with targeted action for different purposes, in particular, for anti-viral and anti-cancer therapy [30, 31]; for essential increase in precision of the DNA-based nanodevices of biomolecular electronics as information carriers [32, 33]; creation of synthetic macromolecular structures able to replicate with a predetermined accuracy [34] and so on.

In our study we have pursued the goal to reveal at the microstructural level the molecular grounds of the intrinsic DNA mutability without involvement of the external agents.

II. Computational methods

All geometric, energetic and vibration calculations of the considered base mismatches and transition states (TSs) of their conversion have been performed by Gaussian’09 package [35] using B3LYP [36, 37] and MP2 [38] levels of quantum-mechanical (QM) theory combined with a wide variety of basis sets followed by the intrinsic reaction coordinate (IRC) calculations in the forward and reverse directions from each TS using Hessian-based predictor-corrector integration algorithm [39]. Bader’s quantum theory of Atoms in Molecules (QTAIM) was applied to analyse the electron density distribution [40]. Physico-chemical parameters have been estimated by the known formulas of the physico-chemical kinetics [41].
III. Obtained results and their discussion

For the first time it was outlined a complete set of the 12 incorrect DNA base mispairs causing spontaneous point incorporation and replication errors (B3LYP/6-311+G(d,p) level of theory, ε=1). Here and below dotted lines indicate NH→B H-bonds and continuous – loosened A-H-B covalent bridges (their lengths are presented in Å; carbon atoms are in light-blue, nitrogen – in dark-blue, hydrogen – in grey and oxygen – in red along the ICR) along entire internal reaction coordinate, not only in the stationary structures such as reagent, product and transition state on the reaction pathways of the tautomeric transformations.

Additionally, based on the electron-topological characteristics of the neighboring intermolecular bonds, along which protons migrate, namely the value of the electron density and its Laplacian in the corresponding critical points, for the first time we have introduced the conception of the key points (their maximum number reaches 9), which comprehensively describe the mechanism of tautomeration. In this case 3 key points correspond to the two abovementioned local minima (the first and the last, ninth – reagent and product, respectively) and transition state of the tautomeration. Other 6 key points include 2 key points, in which migrating proton is localized midway between the electronegative atoms and are characterized by the loosened covalent bonds, and also 4 key points, in which H-bonds begin to acquire the features of the covalent bond and vice versa, that is where the Laplacian of the electron density passes through zero.

TABLE 1

<table>
<thead>
<tr>
<th>Mispairs</th>
<th>Geometrical parameters</th>
<th>Energetical parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R(HN base-H)Å, qHÅ, qÅ</td>
<td>ΔE int/ΔE int, ΔG</td>
</tr>
<tr>
<td>A-C</td>
<td>10.235</td>
<td>53.42, 41.2</td>
</tr>
<tr>
<td>G*T</td>
<td>10.399</td>
<td>51.38, 35.0</td>
</tr>
<tr>
<td>A*G</td>
<td>10.411</td>
<td>50.33, 37.5</td>
</tr>
<tr>
<td>G*C</td>
<td>10.425</td>
<td>48.73, 35.1</td>
</tr>
<tr>
<td>A*G</td>
<td>9.996</td>
<td>55.53, 58.2</td>
</tr>
<tr>
<td>G*T</td>
<td>10.291</td>
<td>51.51, 51.1</td>
</tr>
<tr>
<td>T*G</td>
<td>10.202</td>
<td>50.56, 52.3</td>
</tr>
<tr>
<td>C*C</td>
<td>8.086</td>
<td>60.39, 59.5</td>
</tr>
<tr>
<td>C*T</td>
<td>8.215</td>
<td>59.37, 57.0</td>
</tr>
<tr>
<td>T*G</td>
<td>8.385</td>
<td>53.56, 58.1</td>
</tr>
<tr>
<td>A*G</td>
<td>10.130</td>
<td>54.34, 54.8</td>
</tr>
<tr>
<td>G*C</td>
<td>10.209</td>
<td>52.91, 55.3</td>
</tr>
</tbody>
</table>

Note: The distance between the glycosidic protons at the N1/N9 atoms, Å; The glycosidic angle for the base situated on the left within the base pair, º; The glycosidic angle for the base situated on the right within the base pair, º; The electronic energy of deformation, necessary to apply to the mismatch to acquire the sizes of the A*T and G*C Watson-Crick DNA base pairs, kcal/mol; The electronic energy of interaction, kcal/mol; The contribution of the total energy of the intermolecular H-bonds to the electronic energy of interaction, %; The Gibbs free energy of interaction (T=298.15 K), kcal/mol.

Selected structural and energetic characteristics of the incorrect DNA base pairs, responsible for the origin of the spontaneous transitions and transversions (MP2/6-311++G(d,f,p)/B3LYP/6-311++G(d,p) level of theory, ε=1).

Arrangement of the extremums of the derivative of the energy by the IRC, which coincide with the second and penultimate key points, allows to separate the pathway of...
the tautomerisation reaction to the areas of reagent, transition state and product of the reaction. This set of these key points could be considered as "fingerprints" of the tautomerisation process via the DPT.

**TABLE 2**
Energetic and kinetic characteristics of the tautomeric transformations of the incorrect long, short and Watson-Crick-like pairs of nucleotide bases via the DPT along the neighboring intermolecular H-bonds (MP2/cc-pVQZ/B3LYP/6-311++G(d,p) level of theory, ε=1)

<table>
<thead>
<tr>
<th>Tautomeric transition</th>
<th>∆G</th>
<th>∆E</th>
<th>∆AG13</th>
<th>∆E13</th>
<th>∆AG</th>
<th>∆E</th>
<th>τ</th>
</tr>
</thead>
</table>
| A·A*→A*·A            | 0.00| 0.00| 10.33 | 7.01 | 10.33| 1.82| 10-10-
| A·G→A*·G*            | 10.079.58 | 9.63 | 11.46 | 0.44 | 1.88 | 4.83| 10-10-
| G·G*→G·G              | 0.00 | 0.00 | 5.51 | 8.33 | 5.51 | 8.33 | 8.22| 10-10-
| A·C*→A*·C            | 3.99 | 3.64 | 8.17 | 10.53 | 4.18 | 6.89 | 1.08| 10-10-
| G·T→G·T*             | 1.22 | 1.19 | 2.63 | 5.61 | 2.63 | 5.61 | 8.13| 10-10-
| C·C*↔C·C*            | 0.00 | 0.00 | 8.28 | 10.83 | 8.28 | 10.83 | 8.13| 10-10-
| C·T→C*·T*            | 9.15 | 8.99 | 9.55 | 11.38 | 0.40 | 2.39 | 2.13| 10-10-
| T·T*↔T·T             | 0.00 | 0.00 | 4.64 | 8.18 | 4.64 | 8.18 | 8.18| 10-10-
| G·G*↔G·G*            | 11.02 | 11.15 | 9.07 | 12.17 | 1.96 | 1.02 | 4.10| 10-10-
| A·A*↔A*·A*           | 13.98 | 14.71 | 14.15 | 16.43 | 0.16 | 1.72 | 1.12| 10-10-
| A·G*↔A*·G*           | 8.15  | 2.20 | 2.42 | 4.60 | 0.52 | 2.40 | 2.17| 10-10-

Note: "The Gibbs free energy of the product relatively the reactant of the tautomerisation reaction (T=298.15 K), kcal·mol⁻¹; 1" The electronic energy of the product relatively the reactant of the tautomerisation reaction, kcal·mol⁻¹; 2" The Gibbs free energy barrier for the forward reaction of tautomerisation, kcal·mol⁻¹; 3" The electronic energy barrier for the forward reaction of tautomerisation, kcal·mol⁻¹; 4" The free energy barrier for the reverse reaction of tautomerisation, kcal·mol⁻¹; 5" The electronic energy barrier for the reverse reaction of tautomerisation, kcal·mol⁻¹; 6" The lifetime of the product of the tautomerisation reaction, s.

![Fig. 2. Geometrical structures of the 3 stationary structures (initial, transition state and terminal) describing the progression of the tautomerisation via the DPT along the intermolecular H-bonds in some mispairs (B3LYP/6-311++G(d,p) level of theory, ε=1) (A: A*, T: T*)](image)

This methodology enables to make an objective conclusion about the character of tautomeration (concerted, synchronous or asynchronous), quantitatively estimate the cooperativity of the specific intermolecular interactions (H-bonds and attractive van der Waals contacts) and trace how these interactions are grouped into the patterns and how they consistently substitute each other along the IRC of tautomerisation.

Withing the framework of this approach we have investigated for the first time the microstructural mechanisms of the tautomerisation of the base pairs involved into the origin of the spontaneous point mutations. It was established that for the A·G→A*·G* [48], A·C*→A*·C [[49]], G·T→G·T* [50], C·T→C·T* [51], G·G*↔G·G* [52], A·A* ↔A·A* [53] and A·G*↔G·A* [54] tautomerisation processes final, tautomerised base pairs are dynamically unstable: low-frequency intermolecular vibrations can’t develop during their lifetime (Fig. 2, Table 2). At the tautomerisation of the dynamically stable short T·T* [55] and C·C* [56] mispairs, as well as long A·A* [57] and G·G* [58] mispairs mutagenic tautomers are distributed among the monomers with equal probability, that is important for understanding of the consolidation of the point mutations in the subsequent rounds of DNA replication (Fig. 2, Table 2). It was established that short-lived, low-populated A*·C and G·T* mispairs are "providers" of the long-lived enzymatically-competent A·C* [49] and G·T* base pairs [50], respectively, at the origin of the replication errors in DNA.

**TABLE 3**
Energetic and kinetic characteristics of the tautomeric transformations of the classical Watson-Crick (WC) or wobble (w) DNA base pairs, that are involved into the processes of the spontaneous point mutagenesis, via the DPT accompanied by the substantial changes of their geometry (MP2/cc-pVQZ/B3LYP/6-311++G(d,p) level of theory, ε=1)

<table>
<thead>
<tr>
<th>Tautomeric conversion</th>
<th>∆G</th>
<th>∆E</th>
<th>∆AG13</th>
<th>∆E13</th>
<th>∆AG</th>
<th>∆E</th>
<th>τ99,9%</th>
</tr>
</thead>
</table>
| A·T(wC)→A*·T(d)        | 9.90| 9.59| 16.72 | 16.02| 6.82| 6.43| 1.10| 10-10-
| A·T(wC)→A*·T*(w)      | 13.08| 14.84| 20.28 | 20.41| 7.20| 5.57| 2.09| 10-10-
| G·G(wC)→G·G*(w)      | 12.08 | 12.55 | 31.35 | 31.73 | 19.27 | 19.18 | 148.66 | 1.69| 10-10-
| G·G(wC)→G·G*(w)      | 14.14 | 14.50 | 32.50 | 32.40 | 18.36 | 17.00 | 32.45 | 1.69| 10-10-
| A·C(wC)→A·C*(WC)      | 4.87 | 6.77 | 19.98 | 18.85 | 24.84 | 25.62 | 4.94| 10-10-
| G·T(wC)→G·T*(WC)      | -1.69 | -2.46 | 17.04 | 16.37 | 18.73 | 18.83 | 8.83 | 1.69| 10-10-
| A·A*(wC)→A·A*(wC)     | 4.18 | 1.64 | 26.89 | 23.59 | 22.71 | 21.94 | 4.39| 10-10-
| G·G*(wC)→G·G*(wC)     | -4.96 | -6.75 | 26.81 | 26.08 | 31.77 | 32.83 | 5.03| 10-10-
| A·G(wC)→A·G*(wC)     | 3.76  | 6.19  | 17.01 | 17.07 | 13.25 | 10.88 | 5.31| 10-10-
| A·G(wC)→A·G*(wC)     | 14.29 | 14.09 | 25.29 | 24.39 | 11.00 | 10.30 | 1.21| 10-10-
| C·T(wC)→C*·T(w)      | 0.56 | 0.55 | 17.05 | 17.36 | 16.48 | 16.61 | 8.76 | 1.69| 10-10-
| C·T(wC)→C*·T*(w)     | 12.07 | 14.57 | 26.54 | 25.32 | 14.57 | 10.75 | 5.38| 10-10-
| T·T(wC)→T·T*(w)      | 8.98 | 8.64 | 31.06 | 31.90 | 22.09 | 23.26 | 1.65| 10-10-
| C·C(wC)→C·C*(wC)     | -8.90 | -10.73 | 25.38 | 24.32 | 34.28 | 35.05 | 4.35| 10-10-

Note: for designations refer to Table 2. The time necessary to reach 99.9% of the equilibrium concentration between the reactant and the product of the tautomerisation reaction, s.

For the first time it was proposed novel theoretical approach to the elucidation of the microstructural mechanisms of the incorporation and replication errors arising at the DNA replication. It was discovered for the first time the intrinsic ability of the purine-pyrimidine (A·T [59], G·C [59], G·T [60], [61] and A·C [60], [62]).
Fig. 3. Energetic profiles and stationary structures on the potential energy hypersurface of the biologically important transformations via the DPT, accompanied by the shifting of the bases relative to each other within a base pair into the minor or major DNA groove sides, leading to the occurrence of the spontaneous transitions and transversions – incorporation and replication errors (B3LYP/6-311++G(d,p) level theory, ε=1).
Fig. 4. Reaction pathways of the biologically important tautomerasions and conformational transitions of the investigated structures containing canonical DNA bases and 2-aminopurine (2AP) base in the main and rare tautomeric forms leading to incorporation and replication errors caused by the rare tautomer of the 2AP (B3LYP/6-311++G(d,p) level of theory, ε=1). The base, belonging to the template strand of DNA, is situated on the left, while the base of the incoming nucleotide – on the right.

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ENERGETIC AND KINETIC CHARACTERISTICS OF THE BIOLOGICALLY IMPORTANT TAUTOMERISATIONS AND CONFORMATIONAL TRANSITIONS OF THE INVESTIGATED STRUCTURES CONTAINING CANONICAL DNA BASES AND 2-AMINOPURINE BASE IN THE MAIN OR TWO TAUTOMERIC FORMS LEADING TO INCORPORATION AND REPLACEMENT ERRORS CAUSED BY THE RARE TAUTOMER OF THE 2AP (MP2/aug-cc-pVDZ//B3LYP/6-311+G(d,p) LEVEL OF THEORY, ε=1)

<table>
<thead>
<tr>
<th>Tautomerisation / Conformational transition</th>
<th>ν(E)</th>
<th>ΔG</th>
<th>ΔE</th>
<th>ΔAGTS</th>
<th>ΔEETS</th>
<th>ΔAG</th>
<th>ΔE</th>
<th>τpp,s</th>
<th>τ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2AP-TCW-&gt;2AP-T*(w)</td>
<td>134.2</td>
<td>8.62</td>
<td>8.33</td>
<td>18.66</td>
<td>17.53</td>
<td>10.04</td>
<td>9.21</td>
<td>2.53·10⁻³</td>
<td>3.66·10⁻⁴</td>
</tr>
<tr>
<td>A-TCW-&gt;A-T*(w)</td>
<td>99.7</td>
<td>13.08</td>
<td>14.84</td>
<td>20.28</td>
<td>20.41</td>
<td>7.20</td>
<td>5.57</td>
<td>2.09·10⁻⁴</td>
<td>3.03·10⁻⁴</td>
</tr>
<tr>
<td>C-2AP(w)-&gt;C*-2AP(WC)</td>
<td>146.9</td>
<td>1.85</td>
<td>1.42</td>
<td>21.95</td>
<td>20.30</td>
<td>20.11</td>
<td>18.88</td>
<td>5.87·10⁻²</td>
<td>8.88·10⁻¹</td>
</tr>
<tr>
<td>C-A(w)-&gt;C*-A(WC)</td>
<td>588.5</td>
<td>-6.07</td>
<td>-7.20</td>
<td>19.51</td>
<td>17.61</td>
<td>25.58</td>
<td>24.81</td>
<td>1.74·10⁻²</td>
<td>7.13·10⁻³</td>
</tr>
<tr>
<td>A-2AP(w)-&gt;A*-2AP(WC)</td>
<td>117.0</td>
<td>13.71</td>
<td>13.57</td>
<td>29.85</td>
<td>31.00</td>
<td>16.14</td>
<td>17.43</td>
<td>0.76</td>
<td>0.11</td>
</tr>
<tr>
<td>A*-2AP(WC)-&gt;A*-2AP_syn</td>
<td>18.0</td>
<td>-0.83</td>
<td>-0.59</td>
<td>6.54</td>
<td>8.55</td>
<td>7.37</td>
<td>9.14</td>
<td>5.59·10⁻⁴</td>
<td>4.07·10⁻⁴</td>
</tr>
<tr>
<td>A-A(w)-&gt;A-A*(WC)</td>
<td>152.4</td>
<td>3.63</td>
<td>1.09</td>
<td>25.86</td>
<td>22.56</td>
<td>22.24</td>
<td>21.47</td>
<td>2.22·10⁻⁴</td>
<td>3.22·10⁻³</td>
</tr>
<tr>
<td>A-A*(WC)-&gt;A-A*syn</td>
<td>497.5</td>
<td>0.00</td>
<td>0.00</td>
<td>6.39</td>
<td>9.71</td>
<td>6.39</td>
<td>9.71</td>
<td>2.28·10⁻⁸</td>
<td>6.42·10⁻⁹</td>
</tr>
<tr>
<td>A*-A(WC)-&gt;A*-Asyn(TF)</td>
<td>15.8</td>
<td>0.56</td>
<td>1.23</td>
<td>8.09</td>
<td>8.09</td>
<td>7.53</td>
<td>6.85</td>
<td>2.66·10⁻⁷</td>
<td>5.33·10⁻⁸</td>
</tr>
<tr>
<td>G-2AP(w)-&gt;G*-2AP(w)</td>
<td>1099.7</td>
<td>-10.70</td>
<td>-9.96</td>
<td>-0.11</td>
<td>2.31</td>
<td>10.59</td>
<td>12.26</td>
<td>4.39·10⁻³</td>
<td>4.52·10⁻⁴</td>
</tr>
<tr>
<td>G*-2AP(w)-&gt;G-2AP(WC)</td>
<td>130.1</td>
<td>1.33</td>
<td>1.07</td>
<td>18.04</td>
<td>16.58</td>
<td>16.70</td>
<td>15.51</td>
<td>1.77</td>
<td>0.28</td>
</tr>
<tr>
<td>G-2AP(WC)-&gt;G-2AP_syn</td>
<td>17.7</td>
<td>0.60</td>
<td>1.51</td>
<td>8.23</td>
<td>10.31</td>
<td>7.63</td>
<td>8.80</td>
<td>3.22·10⁻⁷</td>
<td>6.35·10⁻⁸</td>
</tr>
<tr>
<td>G-A*(w)-&gt;G-A(WC)</td>
<td>126.8</td>
<td>-6.93</td>
<td>-6.73</td>
<td>16.98</td>
<td>16.32</td>
<td>23.92</td>
<td>23.05</td>
<td>3.14</td>
<td>5.54·10⁻⁴</td>
</tr>
<tr>
<td>G-A(WC)-&gt;G-Asyn</td>
<td>20.7</td>
<td>0.76</td>
<td>0.58</td>
<td>8.39</td>
<td>8.89</td>
<td>7.64</td>
<td>8.31</td>
<td>3.47·10⁻⁴</td>
<td>6.42·10⁻⁴</td>
</tr>
<tr>
<td>C-2AP*(w)-&gt;C-2AP(W)</td>
<td>314.8</td>
<td>-26.99</td>
<td>-28.84</td>
<td>14.39</td>
<td>13.17</td>
<td>41.37</td>
<td>42.01</td>
<td>3.65·10⁻²</td>
<td>3.29·10⁻¹</td>
</tr>
</tbody>
</table>

Note: for designations refer to Table 2. *Imaginary frequency at the TSs of the interconversions, cm⁻¹.*

Conclusions

Obtained results allow us to explain the number of biological experiments available in the literature, but remained yet without proper theoretical justification:

- Obtained numerical estimations of the frequencies of the mispairs occurrence satisfactorily explain experimental data: (10⁻⁵–10⁻³) G·T/T·G >> A/C·A >> C/T·T>C>A>A > G·A/G·A >> G·G ≈ C·C (10⁻⁶) [69].

- Established A-C(w)->A-C*(WC) and G-T(w)->G*-T(WC) wobble(w)->Watson-Crick(WC) transformations via the sequential DPT allow us to explain the way of the acquisition by the A-C(w)/G-T(w) wobble mispairs of the Watson-Crick geometry in the active center of the high-fidelity DNA-polymerase or DNA duplex and to interpret X-ray [14, 15] and NMR [16] experiments.

- Presented approach allows us to clarify microstructural mechanisms of the mutations induced by the classical mutagens, in particular 2-aminopurine, for which induced frequencies agree well with the experimental data.

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