

The Feasibility Of Hydrogen Bonding In Guanine-Adenine (AG) On Subsequent Tautomerization Relevant To Available AG Mispairs: DFT And MP2 Level Of Studies

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Abstract: The structures of stable tautomers of Adenine and Guanine are chosen for analyzing the formation of metastable AG pairing. The metastable structures are optimized using density functional theory (B3LYP) with basis sets 6-31+G(d,p) and 6-31++G(d,p). The structures and energetic of these metastable AG pairs are further analysed to extract information on the available AG mismatches. Moreover the thermodynamics parameters of these AG pairs are used to explain the sensitivity and stability of stable geometries. The geometry of cisA2-cisG3 combination is found energetically favourable and also the structure is very similar to available crystal structure.

Keywords: Mismatches, Crystal structure, DFT, Basis set, Tautomers.

I. INTRODUCTION

The various modes of hydrogen bonding among purine nucleobases can be described in many ways. Several sites of purine nucleobases, A and G can be involved in bonding at different orientations and also interact with surrounding ions and molecules (1-5). Tautomerization pathway on subsequent destabilization of complementary base pairs AT and GC to generate many tautomers of A and G have been shown in several studies, which could be the reason to form metastable AG pairs due to instantaneous interaction between A and G tautomers(5-8). This pathway has been considered as one of the mechanisms of AG pairing and also the driving factors for generating available AG mismatches (Figures 1(a-b)). The hydrogen bonding in these AG mismatches are clearly indicated in Figures 2 (a-b) and both structures obtained from crystallographic database are similar. Some of the dominant tautomers of A and G are shown in Figures 3 and 4. The energetic of these tautomeric forms, and their orientations to form hydrogen bonds together might contribute to generate AG pairs in DNA (Figure 5)(5-14). In such situation pairing of A and G tautomers may take place at any region in the two

strands of DNA or with another strand. Moreover, understanding of the mostly found mismatches could rely on the acid-base characteristics between hydrogen bonding sites and the type of hydrogen bonds between non-complementary base pairs (5-7,15-18). It is also important to calculate the interaction capacity of these mismatches based on the acid-base properties of the interaction sites as well as on the type of hydrogen bonds. The information may be useful for exploring how the AG mismatches occur in DNA sequences.

Understanding the basis of forming mismatches of nucleobases is rather vast, but certain aspects such as detailed mechanisms of forming H-bonds between unstable tautomers species can be looked depending on the basicity of the donor sites of A and G tautomers. It is also known that the exocyclic amino group of G can efficiently form different H-bonds if normal GC base pair is destabilized. Similarly, A tautomers have several sites for bonding with G tautomers (Figures 3 and 4). Moreover energetic of these tautomers can distinctively identify the favorable combinations of A and G. So, the electron donating ability as well as the efficiency of hydrogen bond formation between A and G tautomers are considered to be the model study for understanding the existence of AG

mismatches. Some of the tautomers of A and G may be minor or major, whereas several metastable AG pairs may be formed from any of these tautomers, which is the interest of theoretical chemists.

In many studies on DNA nucleobases and hydrogen bonding DFT (B3LYP) method with medium size basis set have been successfully used (1-9). Moreover, DFT method has been applied in the study of several types of molecules. Hence, this method can be used to study metastable AG mismatches. The method is based on the Kohn-Same (KS) formulation where comparatively large molecules with cubic scaling can be performed in DFT method (18-20). Hence, in the present study we propose to study the formation of several metastable AG pairs with this method and further comparison of the results will be performed with MP2 level of theories.

II. COMPUTATIONAL DETAILS

B3LYP and DFT methods were used for complete geometry optimization of tautomers and metastable AG pairs(21). Initially the geometries of A and G tautomers are collected from literature, and drawn with Gaussview (22). Complete geometry optimization were performed by using B3LYP with 6-31+G(d,p) and 6-31++G(d,p) basis sets. We performed Moller Plesset second order perturbation theory MP2 calculations utilizing a 6-31G+(d,p) basis set on the optimized geometries. The structures were fully optimized on the respective level with 10^{-8} hartree as SCF convergence in energy. The zero point energy (ZPE) were also calculated using the harmonic frequencies calculated at the B3LYP/6-31+G(d,p) level of theory. The vibrational frequencies were calculated by performing a normal mode analysis on the optimized geometries using analytical gradients of the energy. To calculate the geometries and energies of the various metastable AG pairs, we used B3LYP type of density functional theory (DFT)(18-19). It is based on the generalized gradient approximation and a component of the exact Hartree-Fock (HF) exchange. The ground state gas-phase calculations for AG pairs were chosen after considering 6-31+G(d,p) and 6-31G++G(d,p) basis sets, where p-type polarization functions on H atoms is essential in dealing with hydrogen bonding systems.

III. RESULTS AND DISCUSSIONS

The possible impairing of A and G tautomers to form metastable AG pairs after tautomerization is considered as important pathway for explaining the occurrence of certain AG pairs in DNA(Figures 1(a-b)). As we can see in Figures 5, the hydrogen bonding patterns between A and G tautomers may take place entirely in different ways depending on the conformation of nucleotides involved at the time of pairing, since there are several sites of forming hydrogen bonds. Some of them may produce highly stable pairs due to the presence of strong hydrogen bonds dominating for generation stable AG pair. Moreover, the existence of other types of AG pairs may be due to the pre-reactive hydrogen bonding occurred at a particular orientation. However, it is believed that hydrogen

bonding capacity of various sites are not so different for nucleobases and the chances of forming several hydrogen bonds of various types are possible resulting metastable AG pairs(5-9). In most cases the formation of hydrogen bonds involving terminal oxygen and $-NH_2$ groups of A and G tautomers are found common (Figures 5). The interaction between $-CH$ with terminal oxygen of purine ring is also observed. Hence, the importance of $-C-H\dots O-$ type of H-bond is also highlighted in these AG pairs (Figure). Beyond the understanding of the energetically controlled mechanism of hydrogen bonding by specific site, it would be important to analyse the mode of associations of A and G tautomers at a particular conformation, and further validate the contribution of H-bonds to the stability of metastable AG pairs. As we have seen in Figure 5, the interaction of A and G tautomers can take place in various degrees of orientations, so the theoretical techniques capable of estimating such weak interactions should be properly chosen. Here, DFT (B3LYP) method using 6-31+G(d,p) and 6-31++G(d,p) basis sets has been used to optimize the structures, and the interaction energies of all the tautomer combinations are computed(Tables 1-2). The characteristic of hydrogen bonds are shown in Table 3. Here the harmonic vibrational frequency has been analysed, and ZPE and other thermodynamic contributions for the optimized structures are examined (Table 4). The BSSE corrections are approximately 1 kcal/mole for all the structures for both 6-31+G(d,p) and 6-31++G(d,p) basis sets. To compare the variations of the results of B3LYP, we have performed MP2 calculations with 6-31++G(d,p). The values of B3LYP are quite different from those of MP2 calculations and the variation of energy trend is similar, the method overestimates BSSE (Table 5).

The most significant observation in these metastable AG pairs is the energetic of type of H-bonds. Instantaneous pairing of active A and G tautomers to form metastable AG pairs may be speculated, since slight variations in acidic/basic environment can easily transform to several tautomers of A and G. There are also some rare tautomers of Adenine, which in turn may pair up instantaneously to generate many AG non-canonical pairs. It means that coexistence of A and G tautomers may form several AG pairs shown in Figure 5. Several tautomers of A and G are shown in Figures 3 and 4, and the energy level diagram of these tautomers with respect to normal A and G are also shown in Figures 6 and 7. Small energy differences among tautomers of A can be seen, also the energy gaps of some G tautomers are found very narrow. It is the important reason of prototopic .ie H-migration pathways in G leading to several G tautomers may be easier than A. In order to understand existence of metastable AG pairs, the computed interaction energies with 6-31+G(d,p) and 6-31++G(d,p) can be used, and the values are usually correlated to the nature of bonding between A and G in several AG pairs (Figure). The thermodynamic parameters corresponding to these structures are useful to understand the relative stability of these base pairs. Like other non canonical base pairs, two or three H-bonds are observed in these structures. Although in several structures the number of H-bonds may be numerous, but the interaction distances are fairly large unlike other pairs (Table 3). The types of H-bonds present in these AG combinations are (i) $-N-H\dots O-$ (ii) $-N\dots H-N-$ (iii) $-C-$

H...N=C, in *cis* or *trans* orientations (iv) –N-H...N=C- type is found in *cisA1-transG5(c)*(Figure 5). So according to these structures the existence of several bonding patterns might be due to the incorporation of A and G in DNA sequences in various possible conformations. Naturally, the type of bonding responsible for AG pairing at that particular orientation is very important. The existence of rare tautomers of Adenine has been discussed in the context of prototropic tautomerization, which on the other hand depends on the acidity/basicity of several sites(5-10). The feasibility of H-atom migration among these respective structures can be understood from these structures and energy level diagrams (Figure 8). It has been indicated that tautomerization of adenine is less feasible compared to guanine. Guanine is the most basic nucleobase and tautomerization processes can occur easily in this nucleobase. In that case guanine tautomers might be more responsible than adenine tautomers in forming metastable AG pairs. The various H-bonds formed between AG are analyzed and the stability of these AG pairs can be understood with respect to these bonds (Table 3). If we consider the structural alignment and conformation of approaching nucleotides of strands of DNA that can bring with A and G closer during pairing may in particular determines what type of metastable pairs can be formed. As we can see that the interaction energies of these AG pairs are not largely different, and formation of any type of bonding are equally possible at a particular conformation. The relative energies of these metastable AG pairs, other thermodynamic properties i.e changes of enthalpy, Gibb's free energy and zero point energies are shown in Table 4. However, all AG pairs are found feasible for pairing forming a H-bonds during association of A and G, since the interaction energies are negative (Table 3 and Tables 1-2). Even the HF/6-31+G(d,p) energies are quite reasonable for predicting metastable AG pairs(Table 6). The existence of –NH-CH-(iv) bonds might be due to structural alignment of these sites during intermolecular interaction of A and G to form other energetically favorable H-bonds ((i), (ii) and (iii) types.

The optimized geometries of AG pairs were found mostly stable with approximately 10-20 kcal differences in the interaction energies. In some cases proton shifting has been observed, it might depend on the sensitivity of proton at the H bonding sites (Figures). The relative energies of these AG pairs are shown in Figure 8, where some are very close energy values, *transA2-transG4* is the most stable pair (Figure 5). From Table 2, we note that AG pairs do not form equivalent H bonds, some has shorter H-bonds, whereas much longer H bonding are also observed (Table 3). It may be one of the reasons for the variation of structures and stability of these AG pairs.

The process of proton transfer once these metastable species are formed might also operate which subsequently transform to available crystal structure AG mismatches. Theoretically it is possible to predict the intermolecular interaction between these unstable species for understanding mispairing pathway through tautomers. Also tautomer preference in A and G association is clearly shown. However the geometries obtained from crystal structures are not the exact form and at the same time what type of tautomer combination is involved cannot be known. The hypothesis of

H-transfer between bases, and bases and surrounding ions and molecules might be relevant in this context. So as far as the stability of these metastable AG pairs computed in the gas phase shows the possibility of AG association through tautomerization pathways.

Metastable AG base pairs	Interaction energies in kcal/mol B3LYP/6-31+G(d,p)	BSSE energies in kcal/mol B3LYP/6-31+G(d,p)
<i>cisA1-1cisG5</i> (a)	-12.270	0.739
<i>cisA1-transG1</i> (b)	-10.568	0.878
<i>cisA1-transG5</i> (c)	-17.147	1.500
<i>cisA2-1cisG4</i> (d)	-12.051	0.778
<i>cisA2-cisG3</i> (e)	-5.572	0.658
<i>cisA2-transG3</i> (f)	-8.036	0.758
<i>cisA2-transG4</i> (g)	-28.149	1.055
<i>transA1-1cisG5</i> (h)	-8.792	0.646
<i>transA1-transG5</i> (i)	-25.057	1.094
<i>transA2-1cisG4</i> (j)	-12.446	0.680
<i>transA2-cisG4</i> (k)	-26.438	0.996
<i>transA2-transG3</i> (l)	-5.059	0.656
<i>transA2-transG4</i> (m)	-29.255	0.983

Table 1: Computed Interaction energies and BSSE energies of metastable AG base pairs with B3LYP/6-31+G(d,p)

Mestastable AG base pairs	Interaction energies in kcal/mol B3LYP/6-31++G(d,p)	BSSE energies in kcal/mol B3LYP/6-31++G(d,p)
<i>cisA1-1cisG5</i>	-12.229	0.677
<i>cisA1-transG1</i>	-10.559	0.847
<i>cisA1-transG5</i>	-17.185	1.561
<i>cisA2-1cisG4</i>	-11.837	0.695
<i>cisA2-cisG3</i>	-5.466	0.508
<i>cisA2-transG3</i>	-8.016	0.679
<i>cisA2-transG4</i>	-28.151	1.067
<i>transA1-1cisG5</i>	-8.817	0.680
<i>transA1-transG5</i>	-25.099	1.143
<i>transA2-1cisG4</i>	-12.434	0.671
<i>transA2-cisG4</i>	-26.466	1.062
<i>transA2-transG3</i>	-5.129	0.682
<i>transA2-transG4</i>	-29.276	0.985

Table 2: Computed Interaction energies and BSSE energies of mestable AG mismatch base pairs with B3LYP/6-31++G(d,p)

Metastable AG base pairs	H-bond distance (Å)	Planarity
<i>cisA1-1cisG5</i>	H _u →2.521 H _m →2.093 H _i →2.574	Planar
<i>cisA1-transG1</i>	H _u →2.167	Twisted(51.57°)
<i>cisA1-transG5</i>	H _u →2.260	Twisted(42.76°)
<i>cisA2-1cisG4</i>	H _u →2.577 H _m →1.886 H _i →2.195	Planar
<i>cisA2-cisG3</i>	H _u →2.290 H _i →2.007	Twisted(46.52°)
<i>cisA2-transG3</i>	H _u →2.386 H _m →1.890 H _i →2.384	Planar
<i>cisA2-transG4</i>	H _u →1.719 H _m →1.812 H _i →2.634	Planar
<i>transA1-1cisG5</i>	H _u →2.233 H _i →2.359	Planar
<i>transA1-transG5</i>	H _u →1.454 H _m →1.751 H _i →2.781	Planar
<i>transA2-1cisG4</i>	H _u →1.933 H _i →2.142	Planar
<i>transA2-cisG4</i>	H _u →1.681 H _i →2.047	Twisted(74.90°)
<i>transA2-transG3</i>	H _u →2.128 H _i →2.212	Planar
<i>transA2-transG4</i>	H _u →1.729 H _m →1.777 H _i →2.519	Planar

The values inside the parenthesis () are torsional angle
Table 3: Computed H-bond distances and Planarity of metastable AG base pairs

Metastable AG base pairs	Energies (kcal/mol)	ΔZPE (kcal/mol)
<i>cisA1-1cisG5</i>	-11.105 ^a , 0.393 ^b	-11.192
<i>cisA1-transG1</i>	-7.123 ^a , -1.416 ^b	-9.020
<i>cisA1-transG5</i>	-14.950 ^a , -4.875 ^b	-15.739
<i>cisA2-1cisG4</i>	-10.585 ^a , 0.148 ^b	-11.017
<i>cisA2-cisG3</i>	-4.138 ^a , 5.527 ^b	-4.781
<i>cisA2-transG3</i>	-7.349 ^a , 4.532 ^b	-7.412
<i>cisA2-transG4</i>	-25.962 ^a , -15.057 ^b	-26.407
<i>transA1-1cisG5</i>	-7.881 ^a , 2.938 ^b	-8.066
<i>transA1-transG5</i>	-25.483 ^a , -13.983 ^b	-25.798
<i>transA2-1cisG4</i>	-11.035 ^a , -0.550 ^b	-11.488
<i>transA2-cisG4</i>	-24.489 ^a , -12.240 ^b	-24.290

<i>transA2-transG3</i>	-5.028 ^a , 8.176 ^b	-4.634
<i>transA2-transG4</i>	-27.607 ^a , -15.294 ^b	-27.443

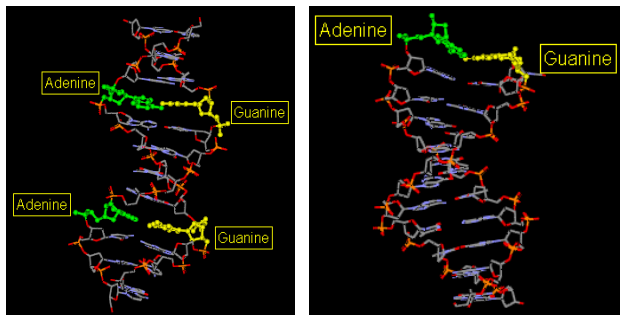
a → change of enthalpy(ΔH), *b* → change of free energy(ΔG)
Table 4: Computed ΔH, ΔG and ΔZPE of metastable AG mismatch base pairs with B3LYP/6-31+G(d,p) methods of calculations

AG base pairs	Interaction energies in kcal/mol MP2/6-31+G(d,p)	BSSE energies in kcal/mol MP2/6-31+G(d,p)
<i>cisA1-1cisG5</i>	-16.218	2.816
<i>cisA1-transG1</i>	-16.562	3.975
<i>cisA1-transG5</i>	-23.968	5.924
<i>cisA2-1cisG4</i>	-16.314	3.311
<i>cisA2-cisG3</i>	-10.443	3.243
<i>cisA2-transG3</i>	-12.229	3.246
<i>cisA2-transG4</i>	-32.964	4.440
<i>transA1-1cisG5</i>	-12.006	2.516
<i>transA1-transG5</i>	-27.731	4.902
<i>transA2-1cisG4</i>	-16.455	3.204
<i>transA2-cisG4</i>	-30.598	4.237
<i>transA2-transG3</i>	-8.690	2.707
<i>transA2-transG4</i>	-33.261	4.431

Table 5: Computed interaction energies and BSSE energies of metastable AG base pairs with MP2/6-31+G(d,p)

Metastable AG base pairs	Interaction energies in kcal/mol HF/6-31+G(d,p)
<i>cisA1-1cisG5</i>	-13.150
<i>cisA1-transG1</i>	-9.238
<i>cisA1-transG5</i>	-14.523
<i>cisA2-1cisG4</i>	-10.046
<i>cisA2-cisG3</i>	-3.870
<i>cisA2-transG3</i>	-5.895
<i>cisA2-transG4</i>	-23.819
<i>transA1-1cisG5</i>	-9.500
<i>transA1-transG5</i>	-18.401
<i>transA2-1cisG4</i>	-10.839
<i>transA2-cisG4</i>	-23.726
<i>transA2-transG3</i>	-3.736
<i>transA2-transG4</i>	-25.464

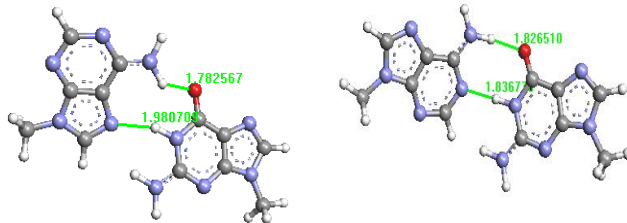
Table 6: Computed interaction energies of metastable AG base pairs with HF/6-31+G(d,p)



a: 1DNM

b: 1NKO

Figure 1: AG mismatches in Crystal structures (pdb files)



(a) 1DNM

(b) 1NKO

Figure 2: The structures of mismatch AG from crystal structure DNA

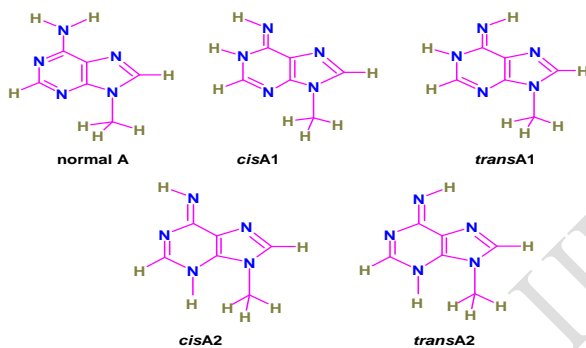


Figure 3: Tautomers of adenine

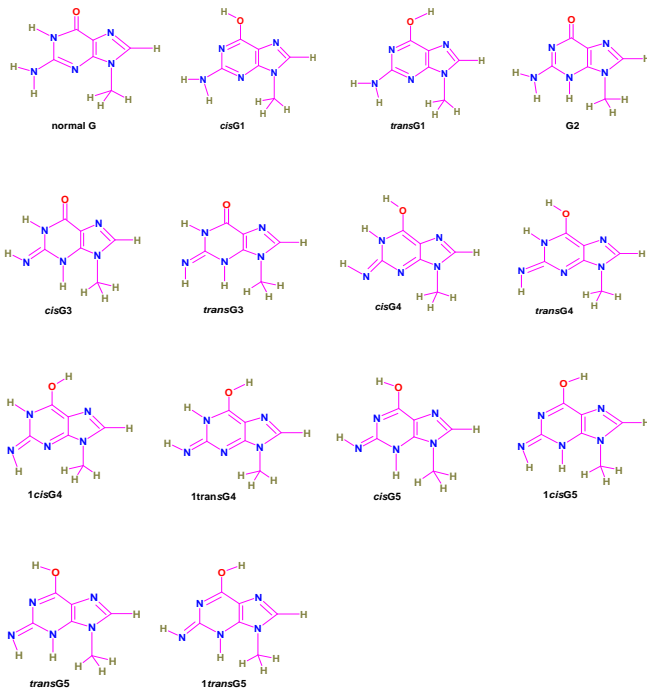
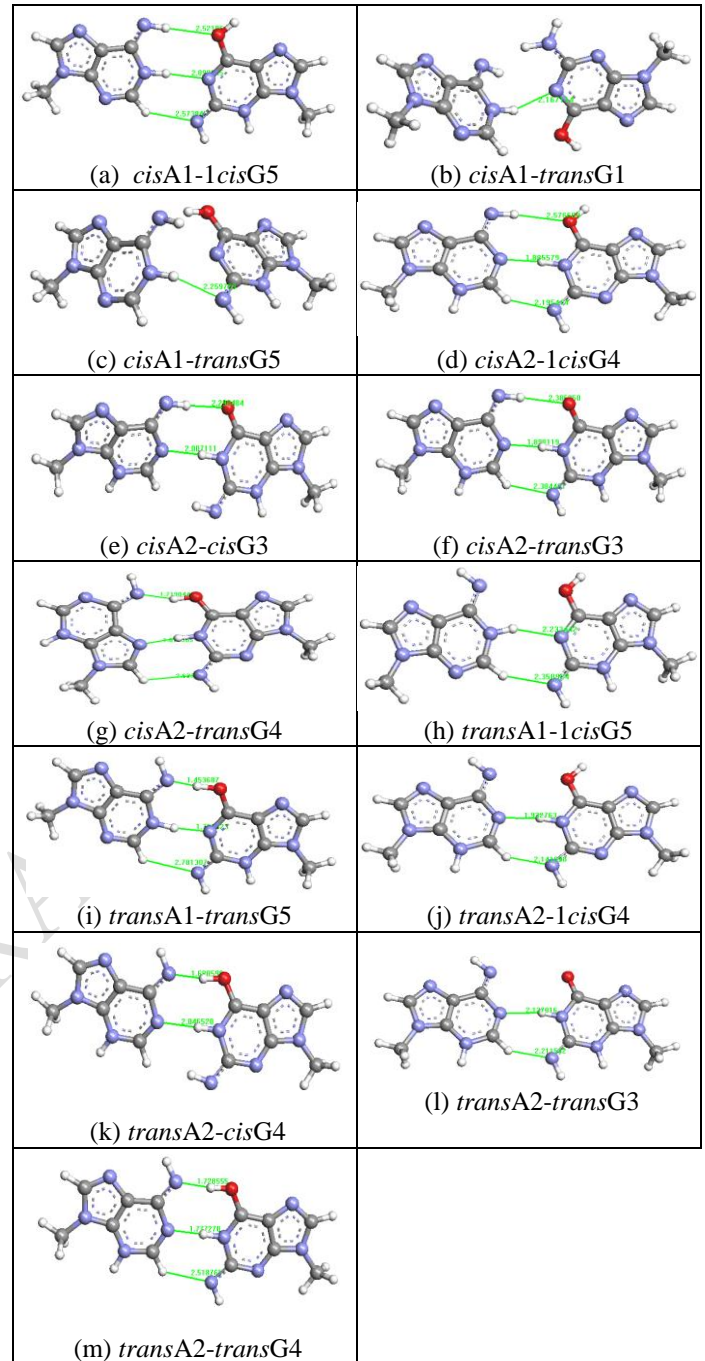


Figure 4: Tautomers of guanine



Figures 5(a-m): Structures of metastable AG base pairs

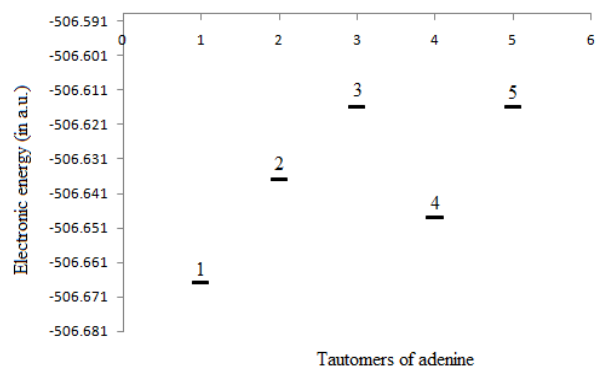


Figure 6: Variation of energies of A tautomers with respect to A.

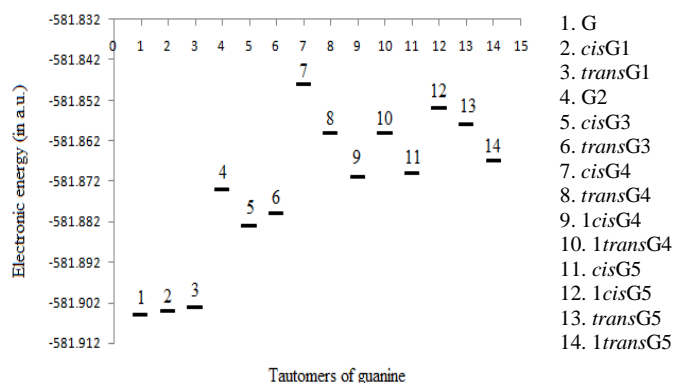


Figure 7: Variation of energies of G tautomers with respect to G.

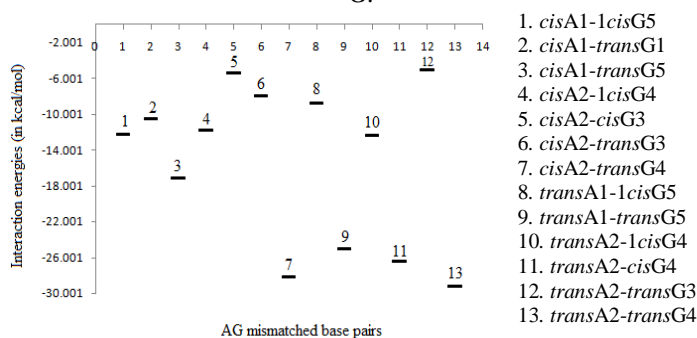


Figure 8: Comparison of interaction energies of metastable AG base pairs

IV. CONCLUSION

The geometries and energies computed with B3LYP and MP2 calculations can reasonably predict the formation of several metastable AG mismatches. The results of two basis sets 6-31+G(d,p) and 6-31++G(d,p) used in B3LYP can predict the favorable association of metastable AG mismatches and most are found at close energy levels. The *cisA2-cisG3* combination is one of the energetically favorable combination and structurally similar to crystal structure. The most favorable combination is *transA2-transG4*.

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