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# Theoretical *Ab initio* and Density Functional Study of the Hydrogen Bonding Nature Between the Pyridine-nitrogenic Base Pair

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**Abstract**

The pyridine interact with two nitrogenic bases (adenine and uracil) so that they may cause a significant point mutation. The results of theoretical *ab initio* study on the hydrogen bonding energies of pyridine with the adenine and uracil are reported. The geometries of the local minima for all suggested cases were optimized with Restricted Hartree-Fock RHF/cc-pVDZ and then density functional B3LYP/cc-pVDZ. The geometrical parameters, relative stability, interaction energies and nature of hydrogen bonding energy are reported. Also, focus on the range of the hydrogen bonding energy and the flexibility of the rotation angle in the P:A¹ base pair have been investigated. Additionally, the influence of the hydrogen bonding energy with the dihedral angle between the two planes of the adenine and the pyridine in the P:A¹ pair are studied. The pyridine with the adenine and uracil may be classified as multi-point mutation. In general, enzymes may have three mechanisms to recorrect the errors in the DNA and the RNA.

*Keywords*: *Ab initio*; Density funtional theory; Mutating; Pyridine ; DNA.


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## 1. Introduction

After accurately describing the structure of DNA, Watson and Crick suggested the effects of spontaneous mutations on DNA [1]. DNA can be damaged by many different sorts of mutagens. These include oxidizing agents, alkylating agents and also high-energy electromagnetic radiation such as ultraviolet light and X-rays. The type of DNA damage produced depends on the type of mutagen. For example, UV light mostly damages DNA by producing thymine dimers, which are cross-links between adjacent pyrimidine bases in a DNA strand [2]. On the other hand, oxidants such as free radicals or hydrogen peroxide produce multiple forms of damage, such as base modifications, particularly of guanosine, as well as double-strand breaks [3]. It has been estimated that in each human cell, about 500 bases suffer oxidation damage per day [4,5]. The most serious damage of these oxidative lesions are the double-strand breaks, as these lesions are difficult to repair and

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can produce point mutations, insertions and deletions from the DNA sequence, as well as chromosomal translocations [6]. The theoretical computations showed that the high electric fields can damage DNA [7-9]. Recently attention has been given to the nitrosamines, which are principal alkaloids that are found in tobacco smoke (they make methylation base pairs) [10]. However, partly due to its influence on hydrogen bonding, methylation is the most pro-mutagenic methyl adducts formed and can both silence gene expression and cause point mutations [11]. Epigenetic methylation occurs at the guanine and cytosine of CpG islands in DNA and is regulated by a methyl transferees and other enzymes [8, 9]. These enzymes interact with DNA by flipping the target base out of the double helix and into its active site [12]. The term base flipping is commonly used to describe the rotation of single base out of the double helix as a result of attractive and repulsive forces imparted by enzyme's active site constituents. The theoretical methods can be used to further investigate and predict the physical and chemical nature of hydrogen bonding interactions. The predictive power of computational biology for DNA has been confirmed in the recent experimental investigation which concluded that amino groups in cytosine and adenine are non-planar [13]. This was postulated and predicted by the molecular quantum calculations over 10 years ago [14]. Theoretical calculations are used to bridge gaps in the understanding of experimental results and used to investigate properties beyond the scope of current crystallographic methods. In many cases, the experimental results are unable to accurately describe the small complex components in nano dimensions and also, the interaction energies that are not easily measured experimentally by the X-ray and NMR experiments [15].

The aim of this theoretical investigation is to use *ab initio* computations to characterize the ability of suggesting the nature of hydrogen bonding between the pyridine and the nitrogen bases to form a pair in the DNA or RNA and then reporting the obtained results.

## 2. Experimental

### 2.1. *Computational details*

First geometries for all suggested cases were optimized by the Restricted Hartree-Fock (RHF) method with basis set cc-pVDZ and then optimized by the Density Functional B3LYP method to include correlation corrections with basis set cc-pVDZ [16, 17]. This functional, defined, by Becke, contains an exchange functional that consists of: 20% Hartree-Fock Exchange, 8% Slater Exchange, 72% Becke-88 Exchange plus a correlation functional that consists of: 19% VWN#5 Correlation, 81% LYP Correlation. This unusual combination was empirically determined by comparing with the results of very accurate calculations [18]. Some previous calculations [8-10] suggested that the results of B3LYP are in good agreement with experiment. All geometries were performed using the Gaussian98 [19].

## 3. Results and Discussions

To examine the ability of interaction between the pyridine with the any one from the nitrogenic bases set (adenine, thymine, guanine, cytosine and uracil), initially, we

suggested that each pyridine forms pair with the adenine base as the single P:A base pair and then with the thymine base as the single P:T base pair, etc. At least there will be five suggested pairs; P:A, P:T, P:G, P:C and P:U respectively. According to probability of the pyridine to make hydrogen bonds with any one of these five nitrogenic bases, the pyridine may forms two approaches with the adenine, two approaches with the thymine and two approaches with the uracil (see Fig. 1). The hydrogen bonding (HB) energy between the pyridine and any one of these five nitrogenic bases is caluclated from:

$$HB = E_{\text{Pyridine:Nitrogenic base pair}} - (E_{\text{Nitrogenic base}} + E_{\text{Pyridine}})$$

where $E_{\text{Pyridine:Nitrogenic base pair}}$ is the total energy of the suggested pair, $E_{\text{Nitrogenic base}}$ is the total energy of the nitrogenic base (adenine/ thymine/ guanine/ cytosine or uracil) alone and $E_{\text{Pyridine}}$ is the total energy of the pyridine only. The hydrogen bonding energies for all the suggested pairs are collected in Table 1. The results of the DFT calculations (B3LYP/cc-pVDZ) show the ability of the pyridine to make three pairs with some nitrogenic bases as P:A¹, P:A² and P:U[1], respectively. On the other hand, the results of the restricted Hartree-Fock calculations (RHF/cc-pVDZ) show that all pairs can occur. From the comparison between the results of the total energy for the DFT and the RHF calculations, we may note that $HB^{B3LYP} > HB^{RHF}$. From Table 1 we can note that the pyridine can forms two approaches with the adenine as the two single base pairs P:A¹ and P:A² respectively. But the P:A¹ base pair has the hydrogen bonding energy higher than the P:A² pair. While the stability of the P:A¹ base pair is lower than the P:A[2] base pair and the relative change between them was equal to 7.62 kcal/mol. For that, the probability to form the P:A² base pair is more than the P:A¹ base pair. The enzymes may face difficulty to flipp the pyridine from the P:A² base pair out of double helix than from the case of the P:A¹ base pair. Also the pyridine and uracil showed stable form as the single P:U¹ base pair. The hydrogen bonding energy of the P:U¹ base pair is the highest in comparison with the P:A¹ and P:A¹, so, enzymes are facing difficulty to flipp the pyridine from among them.

Table 1. The hydrogen binding energy (HB) for all suggested base pairs using B3LYP/ cc-pVDZ and RHF/ cc-pVDZ level.

| Pair | $E^{HB}_{B3LYP}$ (kcal/mol) | $E^{HB}_{HF}$ (kcal/mol) |
|---|---|---|
| P:A¹ | -12.262 | -5.702 |
| P:A² | -4.643 | -2.100 |
| P:T¹ | … | -7.692 |
| P:T² | … | -7.762 |
| P:G | … | -9.231 |
| P:C | … | -7.115 |
| P:U[1] | -14.628 | -7.955 |
| P:U² | … | -7.971 |

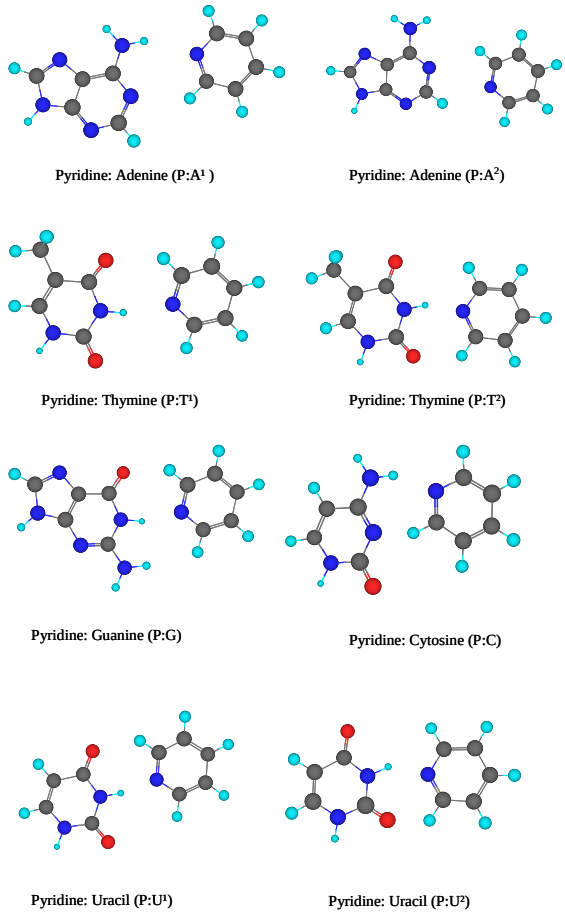


Fig. 1. The suggested base pairs between pyridine and five nitrogen bases (adenine, thymine, guanine, cytosine and uracil). The colors red, blue, gray and cyan are due to oxygen, nitrogen, carbon and hydrogen atom, respectively.

The hydrogen bond length $R_1$ of the P:A¹ and P:A² pairs shows small difference between these two approaches, while the length of the hydrogen bond $R_2$ of the P:A¹ base pair is shorter than the $R_1$ of the P:A² base pair in quantity equal to 0.419Å. The recognized point, that the values of the hydrogen bond lengths of the P:A² and the P:A¹ pairs are closer than the hydrogen bonding lengths of the A:T base pair as reported by other worker [9]. To examine the nature of the hydrogen bonding range between the pyridine and any one from nitrogenic bases we calculated the hydrogen bonding (HB) energy as a function of the hydrogen bonding length between the pyridine and the adenine in the P:A¹ base pair using B3LYP/ cc-pVDZ, as shown in Fig. 2. Whereas the distance between the pyridine and the adenine in the P:A¹ base pair increases from the optimized

distance, or the equilibrium point. Hydrogen bonding energy, between the pyridine and the adenine, shows rapid decrease to 50% as the distance between them increases to ~1 Aº from the optimized distance. Then, slowly decreases in the HB until it almost disappears. The energy equal to 0.55eV, in the visible region is enough to disperse the hydrogen bonding in the P:A¹ base pair.

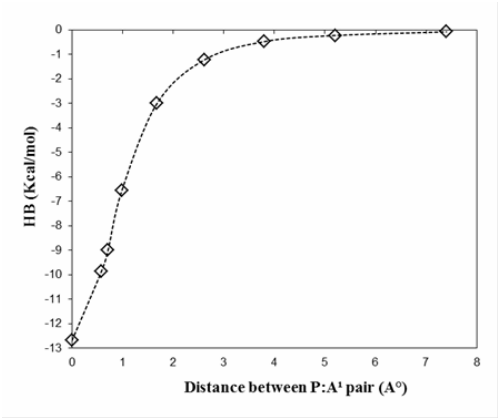


Fig. 2. The hydrogen binding (HB) energy as a function of the distance between the pyridine and the adenine in the P:A¹ pair at B3LYP/ cc-pVDZ level.

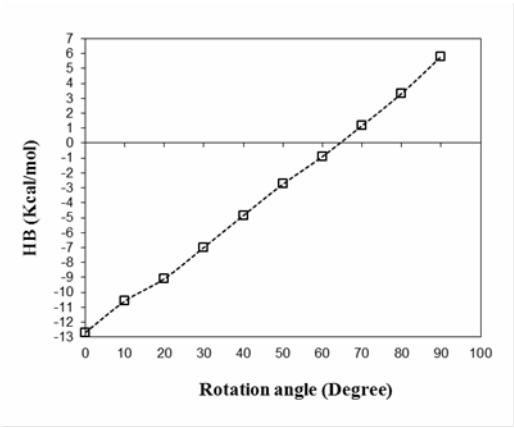


Fig. 3. The hydrogen bonding (HB) energy as a function of the rotation angle, between the adenine and the pyridine of the P:A¹ pair at B3LYP/ cc-pVDZ level.

To explore more about enzymes potential with DNA for flipping the target base, pyridine out of the double helix we rotates the pyridine about the axis that connects it with the adenine in the P:A¹ pair. The results of rotation, with step 10°, between the pyridine and adenine in the P:A¹ base pair are shown in Fig. 3. We noted that the hydrogen binding (HB) energy between the pyridine and adenine in the P:A¹ base pair decreases to 50% at the rotation angle equal to ~33° and drops to zero at ~64°. While beyond the rotation

angle 64° the hydrogen attractive force exchanges to the repulsive force. The maximum repulsion appears at angle of rotation that equal to 90°. We may expect that the enzyme will rotate the pyridine in the P:A¹ base pair with angle equal to ~33° to flipp it out of the double helix. Finally, we examined the effect of the dihedral angle between the plane of the pyridine and the plane of the adenine in the P:A¹ base pair. The ability of the dihedral angle to break the hydrogen bonding between the pyridine and the adenine in the P:A¹ pair is shown in Fig. 4. The dihedral from the angle equal to 20° to 30° shows rapid decreases in the hydrogen binding (HB) energy and it drops to 50% approximately. According to the steric effect, which may occurs with surround molecules in DNA or RNA, the dihedral angle in the limit 25°±5° may not give interesting geometry steric effect. Hence, the dihedral of the pyridine plane towards the adenine plane may happen due to the enzymes potential with DNA for flipping the pyridine out of the double helix.

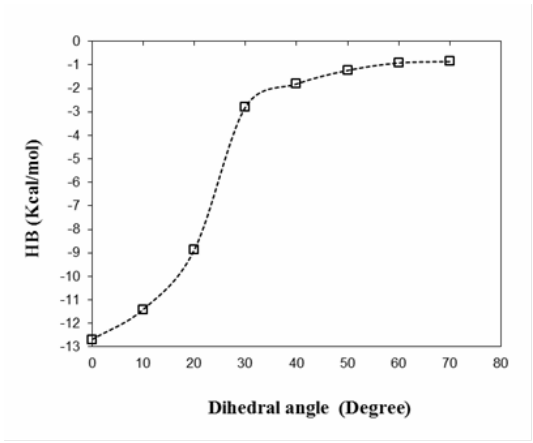


Fig. 4. The hydrogen bonding (HB) energy as a function of the dihedral angle between the two planes of the adenine and the pyridine of the P:A¹ pair at B3LYP/ cc-pVDZ level.

## 4. Conclusion

The results of our calculations show that the pyridine with two nitrogenic bases have significant pairs compared to the Watson-Crick hydrogen-bonding pattern. The comparison between the DFT and RHF levels in calculating the hydrogen bonding energies shows that RHF gives error and the role of the electron correlation is very important in these computations. The results can be summarized as follows:

a. Based on our data, the pyridine can form significant base pairs with the adenine and the uracil in DNA and RNA and lead to point mutations.
b. The range of the hydrogen bonding distance is about ~1Aº for the P:A¹ base pair and the energy of the visible region is enough to disperse this mutation. Aº
c. The enzymes potential with DNA or RNA for flipping the target base out of the double helix may be active at angle of rotation equal to ~33°.

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