IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 17, Issue 8 Ser. 1 (August 2024), PP 26-31
www.iosrjournals.org

Computational And Theoretical Analysis On The Single Proton Transfer Process In Adenine Base By Using DFT Theory And Thermodynamics

Ahamed M. Sabid[1], Hasan M. Kamrul[2]

Date of Submission: 08-08-2024 Date of Acceptance: 18-08-2024

DNA encodes the genetic information responsible for the development and functioning of living organisms. In a seminal work, Watson and Crick [1] proposed that the structure of DNA is composed by two nucleotide chains organized in double-helix manner around an axis, stabilized by hydrogen bonds formed between the canonical purine and pyrimidine bases: adenine-thymine (AT) and cytosine- guanine (CG). Therefore, the genetic code is stored in the form of hydrogen bonded nucleic acid bases. Nonetheless, it is known, nowadays, that external factors, like the presence of surrounding water molecules, also have a role in the stability and structure of the double helix[2,3]. Alternations in DNA structure, if not repaired, may result in mutations, producing permanent changes in the genetic code, or cell deaths. The sources of stability of the double –stranded helix of nucleic acids have been studied intensively since the structure and biological role of DNA were discovered. The reported studies quoted at least four factors that keep DNA in its unique structure: solvent effects, backbone conformation, stacking of adjacent aromatic purine and pyrimidine bases within each strand, and hydrogen bonding between bases of two strands[4]. While the relative importance of these factors is not definitely known, recent probably play a key role in the formation of spontaneous mutations in DNA. These rare tautomer's have chemical structures, resulting from intra- or intermolecular proton transfer. Many experimental and theoretical investigations have been devoted to the computational study that proved stacking interaction contributes only a little to DNA helix stability[5], and that H-bonding seems to play the dominant role. The hydration of the DNA/RNA bases plays an important role in the biological functions and structure of biopolymers. There are theoretical investigations revealing that the nucleic acid bases could form hydrated complexes with a different number of waters molecules[6-10]. The water molecules can be involved in tautomerizations (intermolecular proton transfers) of bases; thus, they considerably lessen the energy barrier of the proton transfer[11-15]. Although understanding hydrogen bonding interactions between DNA components and other molecules is vital to the understanding of the properties of DNA polymers and the mechanisms of biological processes, it is difficult to identify the role of individual nucleobase interactions from experimental data. For this reason, an abundance of computational studies has appeared in the literature that consider hydrogen bonding involving DNA residues[16-19]. From these computational studies, the structures of hydrogen bonded complexes are isolated, and the relative importance of various interactions are characterized. DNA based system molecules are probably the most important biomolecules because, among other important functions, they store and transfer genetic information. DNA requires about 30% of water by weight to maintain its native conformation in the crystalline state. Of course, the water molecules surrounding DNA can also influence the equilibrium between the canonical form of bases and the possible tautomer, which understands the mechanism of single and double proton transfer reactions in DNA bases[20-22]. It is found that double proton transfer in adenine-thymine or guanine-cytosine base pairs is governed by their structural characteristics, thermodynamic and kinetic factors. Moreover, the chemical environment of DNA (e.g., water molecules and various specific ion configurations) could also induce a considerable influence on the proton transfer reaction. In DNA synthesis process, rare tautomeric forms will increase the probability of mispairing of purines and pyrimidines, and hence may lead to an increase in the chance of point spontaneous mutations. Thereby, proton transfer phenomenon occupies a special place in studies of the structures and properties of DNA bases. The presence of metal ions near bases can strongly affect the electron distribution in the bases and thus also the tautomeric equilibria[23-25]. The intramolecular proton-transfer processes are also observed because of the oxidation of base pair. Metal ions used for the neutralization of the phosphate negative charge play an important role in biological processes by forming noncovalent bonds with nucleic acid bases and in this case, a zwitterionic form of bases can appear[26-28]. Metal ions and water molecules binding with the adenine base facilitates the intramolecular proton transfer. Among the metal ions Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+} are combined with the adenine base at different positions. M^{n+} is expressed as the common metal ions. M^{n+} binds with the adenine base at N_3 and N_7 position. The effects are more pronounced for the divalent cations than for the monovalent ones,

in addition, because the DNA bases are strongly polar, water also play an important role in their stabilization can dramatically change the relative stabilities of various tautomer. Water molecules bind with the adenine base by hydrogen bonding. Metal ions (M^{n+}) in hydrated condition also bind the adenine bases. All the thermodynamic properties e.g., thermal energies(ΔE), thermal enthalpies(ΔH), thermal free energies(ΔG) and binding energies($\Delta E_{binding}$) of the metal ions and water with adenine base is analyzed. Dipole moments, bond lengths, bond angles, entropies(ΔS) are analyzed. All the calculations are performed using GAUSSIAN09 software. Structures are drawn using GAUSSIAN5.0.8 software. This computational approach is based on density functional theory (DFT) with the B3LYP hybrid exchange correlation functional at the 6-31G (d, p) level. The aim of this work is to analyze the influence of chemical environment, including metal ions and water molecules on the adenine base.

I. Experimental Methods

The methods used cover both static and dynamic situations. In all cases, computer time and other resources (such as memory and disk space) increase rapidly with the size of the system being studied. The system can be one molecule, a group of molecules, or a solid. Computational chemistry methods range from very approximate to highly accurate; the latter are usually feasible for small systems only. Computational chemistry is a new discipline. Its advantages and popularity have paralleled improvements in computing power during the last several decades. It encompasses quantum mechanics, minimization, simulations, conformational analysis, and other computer-based methods for understanding and predicting the behavior of molecular systems. Theoretical chemistry is often considered synonymous with quantum mechanics, but molecular modeling uses all these methods. As with other disciplines in chemistry, computational chemistry uses tools to understand chemical reactions and processes. Scientists use computer software to gain insight into chemical processes. Although computational chemists frequently develop and refine software tools, their primary interest is in applying software tools to enhance knowledge in chemistry. The challenges for computational chemistry are to characterize and predict the structure and stability of chemical systems, to estimate energy differences between different states, and to explain reaction pathways and mechanisms at the atomic level. Meeting these challenges could eliminate time consuming experiments. Software tools for computational chemistry are often based on empirical information. To use these tools, it is needed to understand how the technique is implemented and the nature of the database used to parameterize the methods. This knowledge is used to determine the most appropriate tools for specific investigations and to define the limits of confidence in results. There are three steps for carrying out any quantum mechanical calculation. They are:
Step1: Obtaining an appropriate starting structure.
Step 2: Choice of a calculation method and its associated (set up) options.
Step3: Types of calculation.

Empirical: These calculations are based on database of experimental observations and work best at predicting molecules of the same class or type as those previously well characterized. It is a fast and cheap method. Example: AMBER, OPLS etc.

Semiempirical: Semi-empirical methods are based on the (HF) formalism but make many approximations and obtain some parameters from empirical data. They are very important in computational chemistry for treating large molecules where the full Hartree–Fock method without the approximation is too expensive. The use of empirical parameters appears to allow some inclusion of effects into the methods. Within the framework of Hartree–Fock calculations, some pieces of information (such as two-electron integrals) are sometimes approximated or completely omitted. In order to compensate for this loss, semi-empirical methods are parametrized, that is their results are fitted by a set of parameters, normally in such a way as to produce results that best agree with experimental data, but sometimes to agree with *AB initio* results. Faster and more accurate predictive than semi-empirical. Example ZINDO, AMI, PM3 CNDO etc.

Ab initio: *Ab initio* quantum chemistry methods are computational chemistry methods based on quantum chemistry. The term *ab initio* was first used in quantum chemistry by Robert Parr and coworkers, including David Craig in a semi-empirical study on the excited states of benzene [1-2]. In the Hartree–Fock (HF) and the configuration interaction(CI) method formalism of *Ab initio* method, the Schrödinger equation was treated as a "simple" eigenvalue equation of the electronic molecular Hamiltonian, with a discrete set of solutions .*Ab initio* electronic structure methods have the advantage that they can be made to converge to the exact solution, when all approximations are sufficiently small in magnitude and when the finite set of basic functions tends toward the limit of a complete set. In this case, configuration interaction, where all possible configurations are included (called "Full CI"), tends to the exact non-relativistic solution of the electronic equation. One needs to consider the computational cost of *ab initio* methods when determining whether they are appropriate for the problem at hand. When compared to much less accurate approaches, such as molecular mechanics (MM), *ab*

initio methods often take larger amounts of computer time, memory, and disk space, though, with modern advances in computer science and technology such considerations are becoming less of an issue. The HF method scales nominally as N^4, N being a relative measure of the system size, not the number of basic functions. For example, if we double the number of electrons and the number of basic functions (double the system size), the calculation will take 16 (2^4) times as long per iteration. However, in practice it can scale closer to N^3 as the program can identify zero and extremely small integrals and neglect them. Correlated calculations scale less favorably, though their accuracy is usually greater, which is the trade off one needs to consider: Second–order many–body perturbation theory (MBPT(2)), or when the HF reference is used, Møller–Plesset perturbation theory (MP2) scales as N^4 or N^5, depending on how it is implemented, MP3 scales as N^6 and coupled cluster with singles and doubles (CCSD) scales iteratively as N^6, MP4 scales as N^7 and CCSD(T) and CR-CC(2,3) scale iteratively as N^6, with one noniterative step which scales as N^7. Density functional theory (DFT) methods using functionals which include Hartree–Fock exchange scale in a similar manner to Hartree–Fock but with a larger proportionality term and are thus more expensive than an equivalent Hartree–Fock calculation. DFT methods that do not include Hartree–Fock exchange can scale better than Hartree–Fock.

II. Results And Discussions

Adenine-metal ions complexes are analyzed. A (1) means N_7 coordination and A (2) means N_3 coordination. The same is true for the other tables. Among the metal ions Zn^{2+} has the least binding energies both at N_7 and N_3 coordination. So, adenine-Zn^{2+} complex is the most stable complex.

Table 01: Optimized energies of metal ions

Metal ions (M^{n+})	Optimized energies (a.u)
Na^+	-162.0812
K^+	-599.7249
Mg^{2+}	-199.2273
Ca^{2+}	-676.8668
Zn^{2+}	-1778.1070

Table 02: Binding energy calculation of reactant adenine base with metal ions (M^{n+}) at the B3LYP/6-31G (d, p)

Complexes	$\Delta E_{binding}$ a.u(atomic unit)	$\Delta E_{binding}$ Kcal/mol
Na^+-A (1)	-0.0649	-40.76
K^+-A (1)	-0.0419	-26.32
Mg^{2+}-A (1)	-0.2774	-174.05
Ca^{2+}-A (1)	-0.1730	-108.56
Zn^{2+}-A (1)	-0.3689	-231.43
Na^+-A (2)	-0.3436	-215.55
K^+-A (2)	-0.1750	-109.81
Mg^{2+}-A (2)	-0.2305	-144.63
Ca^{2+}-A (2)	-0.1388	-87.11
Zn^{2+}-A (2)	-0.3261	-204.61

Among the metal ions Zn^{2+} has the least binding energies both at N_7 and N_3 coordination. So, adenine-Zn^{2+} complex is the most stable complex.

Table 03: Analysis of the thermal enthalpies and thermal energies when metal ions are added to the N_7 position of the reactant adenine base at B3LYP/6-31G (d, p)

Metal ions-Adenine	Thermal Energies(ΔE) a. u	Thermal Enthalpies(ΔH) a. u
Na^+-Adenine	-629.4775	-629.3534
K^+-Adenine	-1067.0983	-1066.9743
Mg^{2+}-Adenine	-666.8361	-666.7115
Ca^{2+}-Adenine	-1144.3731	-1144.2470
Zn^{2+}-Adenine	-2245.8073	-2245.6829

Here adenine-zinc ion complex has the least thermal energies(ΔE) and thermal enthalpies(ΔH).

Table 04: Analysis of the thermal free energies and thermal entropies when metal ions are added to the N_7 position of the reactant adenine base at B3LYP/6-31G (d, p)

Metal ions-Adenine	Thermal free energies(ΔG) a. u	Thermal enthalpies(ΔS) Cal/Mol-Kelvin
Na^+-Adenine	-629.3544	33.15
K^+-Adenine	-1067.0196	31.65
Mg^{2+}-Adenine	-666.7536	31.52
Ca^{2+}-Adenine	-1144.2908	32.28
Zn^{2+}-Adenine	-2245.7257	32.88

Table 05: Analysis of the dipole moments (DM) when metal ions are added to the N_7 position of the reactant adenine base at B3LYP/6-31G (d, P)

Metal ions-Adenine	Dipole Moments (Debye)
Na^+-Adenine	16.2950
K^+-Adenine	17.5105
Mg^{2+}-Adenine	35.3540
Ca^{2+}-Adenine	33.5650
Zn^{2+}-Adenine	26.4756

Table 06: Analysis of the thermal free energies and thermal entropies when metal ions are added to the N_3 position of the reactant adenine base at B3LYP/6-31G (d, p)

Metal ions-Adenine	Thermal free energies(ΔG) a. u	Thermal enthalpies(ΔS) Cal/Mol-Kelvin
Na^+-Adenine	-629.3582	33.35
K^+-Adenine	-1067.1577	32.78
Mg^{2+}-Adenine	-666.7100	33.43
Ca^{2+}-Adenine	-1144.2590	33.67
Zn^{2+}-Adenine	-2245.6874	34.68

Table 07: Analysis of the thermal enthalpies and thermal energies when metal ions are added to the N_3 position of the reactant adenine base at B3LYP/6-31G (d, p)

Metal ions-Adenine	Thermal energies(ΔE) a. u	Thermal enthalpies(ΔH) a. u
Na^+-Adenine	-629.3544	-629.3124
K^+-Adenine	-1067.1091	-1067.1082
Mg^{2+}-Adenine	-666.6667	-666.6658
Ca^{2+}-Adenine	-1144.2146	-1144.2136
Zn^{2+}-Adenine	-2245.6423	-2245.6414

Table 08: Analysis of the dipole moments (DM) when metal ions are added to the N_3 position of the reactant adenine base at B3LYP/6-31G (d, P)

Metal ions-Adenine	Dipole Moments (Debye)
Na^+-Adenine	14.5033
K^+-Adenine	13.7368
Mg^{2+}-Adenine	20.1422
Ca^{2+}-Adenine	14.5037
Zn^{2+}-Adenine	4.5633

Zinc ion reacts more spontaneously with adenine base as it has the least ΔG, ΔE, ΔS and ΔH. As adenine is a polar compound it can easily bind with the water molecule at different positions. Water has a very significant influence on the adenine base.

Table 09: Analysis of reactant adenine-water complexes at N_3 position

Complex	ΔE a. u	ΔH a. u	ΔG a. u	ΔS a. u	Dipole moment (Debye)
Adenine-Water complex	-543.6498	-543.6041	-543.6050	36.75	3.8861

Table 10: Analysis of reactant adenine-water complexes at N_7 position

Complex	ΔE a. u	ΔH a. u	ΔG a. u	ΔS a. u	Dipole moment (Debye)
Adenine-Water complex	-543.6012	-543.6003	-543.6463	37.08	5.4230

GAUSSIAN 5.8.0 software has been used to draw all the structure.

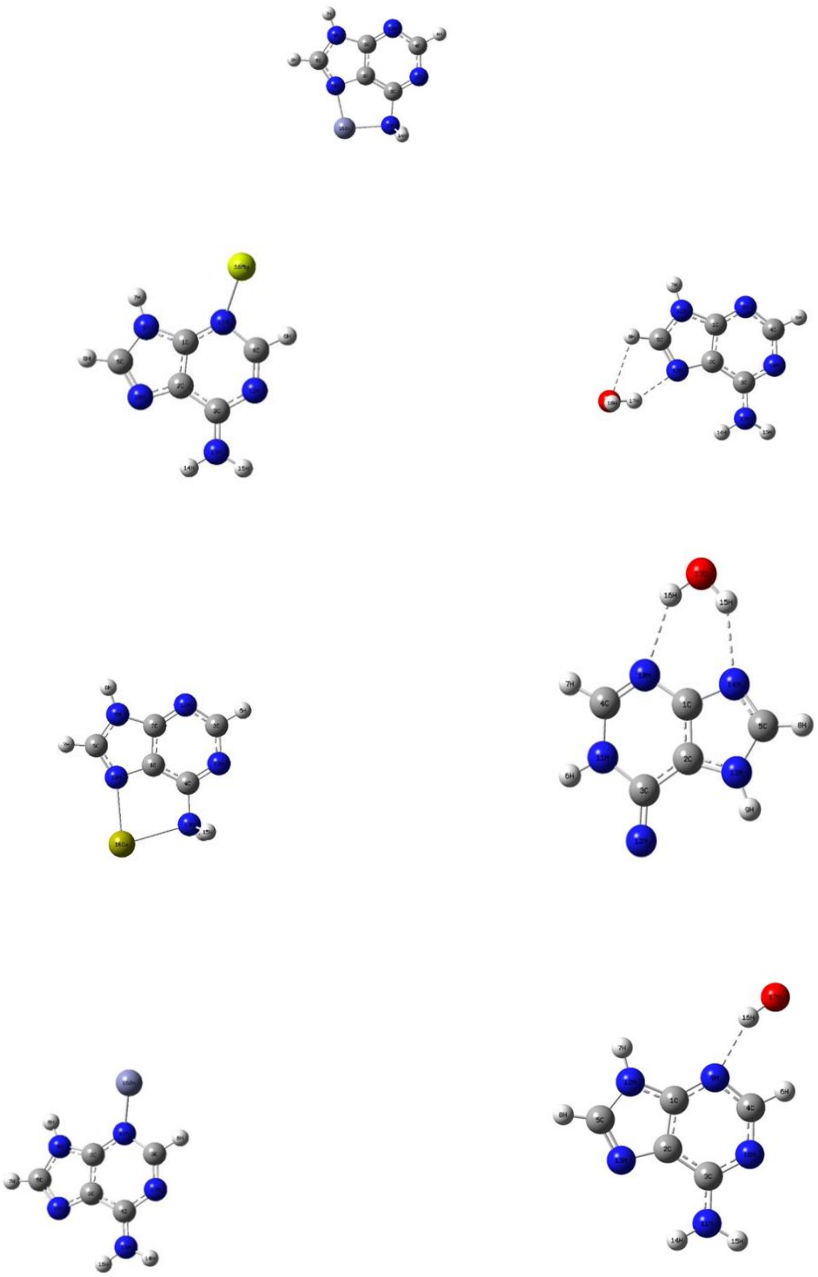

Figure 01: Adenine with different metal ions and water complex at N_3 and N_7 position

III. Conclusions:

Metal ions can bind to DNA directly or indirectly through hydrogen bonding of the coordinating water molecules surrounding the metal ions. Metal binding to the adenine base usually disrupts hydrogen bonding and destabilizes the double helix. The binding of metals to DNA and RNA also influences indirectly the sugar conformation. As a result of this change in sugar puckering the two helical conformations of A-DNA and B-DNA or RNA are characterized by the orientation of the bases with respect to the axis of the double helix. This may be the reason why some metal ions influence DNA synthesis and the replication process. Trace and ultra trace metal ions control essential biological processes of living cells and without their catalytic presence many biological reactions would not take place. The appearance of several diseases may be related to metal ion depletion. For instance, deficiency of Mg^{2+} and Ca^{2+} causes anemia, cardiovascular diseases, or osteoporosis. The monovalent cations (Na^{+}, K^{+}) do not react tightly with the DNA base adenine. The results show that Zn^{2+} can significantly bind the adenine base. Thus, we can determine which essential elements bind more significantly with the adenine base. Two preferred binding positions including N_3 and N_7 have been considered for metal ions (M^{n+}= Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, Zn^{2+} or hydrated Na^{+} ions). One water molecule also has been bonded to both the adenine base and its tautomer at different positions. Among the metal ions Zn^{2+} has the least binding energies at N_7 position both for the adenine base and its tautomer. Zinc is a d block element as well as an essential element for the living organism. Excess zinc can be harmful for organisms. The results show that it forms the most stable complex. Water can also bind with adenine as it is a polar compound. Among them A_{12} has the least binding energy (-14.89 Kcal/mol). These water molecules and metal ions facilitate the proton transfer in adenine base which can play a very important role during the catalytic incorporation of new nucleotides into the growing DNA stand before pair. Hydrated metal ions have greater influence on the adenine base. The analysis of thermodynamic parameters (ΔG, ΔH, ΔS) also shows the effect of metal ions on adenine base.

References

[1] Watson, J.; Crick, F. Nature 1953, 171, 964.
[2] Rueda, M.; Kalko, S.; Luque, F. Orzoco, M. J.Am.Chem.Soc.2003, 125, 8007.
[3] Rueda, M.; Kalko, S.; Luque, F. Orzoco, M. J.Am.Chem.Soc.2006, 128, 3608.
[4] Rein, R. (1978) In Intermolecular Interactions: From Diatomics To Biopolymers, Pullman, B., Ed., John Wiley & Sons, New York, Pp. 307-362.
[5] Forner, W., Otto, P. & Ladik, J. (1984) Chem.Phys.86, 49-56.
[6] Hobza, P. & Sanfordy, C. (1987) J.Am.Chem.Soc.109, 1302-1307.
[7] Lowdin, P. Rev. Mod. Phys . 1963, 35, 724-732.
[8] Lowdin, P. Electronic Aspects Of Biochemistry ; Academic Press: New York, 1964.
[9] Grebneva, H.J.Mol.Struct.2003, 645, 133-143.
[10] Florián, J.; Hrouda, V.; Hobza, P.J.Am. Chem Soc .1994, 116, 1457-1460.
[11] Florián, J.; Leszcynski, J. J. Am. Chem. Soc. 1996, 118, 3010-3017.
[12] Marañón, J.; Fontani, A.; Grigera, J.J. Theor. Biol. 1999, 201,93-206.
[13] Guallar, V.; Douhal, A.; Moreno, M.; Lluch, J. J. Phys. Chem. A 1999, 103, 6205-6256.
[14] Li, X.; Cai, Z.; Sevilla, M.J. Phys. Chem. B 2001, 105, 10115-10123.
[15] Kryachko, E.; Sabin, J. Intl. J. Quantum Chem. 2003, 91, 695-710.
[16] Sobolewski, A.; Domcke, W. Phys. Chem. Chem. Phys. 2004, 6, 2763-2771
[17] Herrera, B.; Toro-Labbe, A. J. Chem. Phys. 2004, 121, 7096-7102.
[18] Danilov, V.; Anisimov, V.; Kurita, N.; Hovorun, D. Chem. Phys. Lett.2005, 412, 285-293.
[19] Shimizu, N.; Kawano, S.; Tachikawa, M.J. Mol. Struct. 2005, 243-248.
[20] Villani, G. Chem. Phys. 2005, 316, 1-8.
[21] Villani, G. Chem. Phys. 2006, 324, 438-446
[22] Gu J, Leszczynski J. J. Phys. Chem A. 1999, 103, 2744-2750.
[23] Shish Mourik T, Price Sl, Clary Dc J. Phys. Chem A. 1999, 103, 1611-1618.
[24] Kin Ov, Sukhanov Os, Gorb L, Leszczynski J. Phys. Chem Chem Phys. 2002, 4, 5359-5364.
[25] Van Mourik T, Price Sl, Clary Dc J. Phys. Chem A. 1999, 103, 1611-1618.
[26] Van Mourik T, Price Sl, Clary Dc J. Phys. Chem A. 2001, 3, 2886-2892.
[27] Gorb L, Leszczynski J. J.Am. Chem Soc. 1998, 112, 5024-5032.
[28] Leszczynski J. J.Am. Chem Soc. 1998, 102, 2357-236