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Hydration energy of Adenine, Guanine, Cytosine and Thymine : Monte Carlo simulation

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ABSTRACT

The hydration of biomolecules is vitally important in molecular biology, so in this paper the solvation energy and radial distribution function of DNA bases have been calculated by the Monte Carlo simulation.The geometries of isolated Adenine, Guanine, Cytosine, and Thymine have been optimized using 6-31+G(d,p) basis function sets. These geometries then will be used in the Monte Carlo calculation of the DNA bases in water.We have used TIP3 model for water and OPLS for nucleic acid bases. The computed solvation energy have Good agreement with the other computational data Radial distribution function of O and N atoms of Adenine, Guanine, Cytosine, and Thymine which have been computed and the results have been compared with other available data observed for these molecules. The Monte Carlo simulation also has been performed by the CHARMM[39, 40] program in the same conditions and the results of two procedures have been compared.

INTRODUCTION

The interaction between the solute and the solvent molecules plays a crucial role in understanding the various molecular processes involved in chemistry and biochemistry. Numerous biological processes involve an ion binding to a nucleic acid or protein and thereby displacing the water hydration. Unfortunately, a biomolecule-water potential energy surface cannot be constructed from accurate ab initio calculations, even with recent growth in computer power, because too many points are required. For example, we have studied the interaction of metal ions with DNA bases in gas phase and different solvent[1,2],but we used Polarized Continuum Model(PCM) for the solution phase ,and we couldn't use all of the solvent molecules in ab initio calculations. Clearly, the construction of a potential energy surface for such large systems, using more elaborate ab initio techniques, is currently not feasible. Thus it is suitable to use computer simulation methods for these systems .

It is well known fact that the thermodynamics of DNA base pairing and base stacking is sensitive to the various environmental conditions[3-7]. One of the principal important determinants of the structure of DNA is water [8, 9, 10]. The ability to accurately calculate solvation energies of molecules using molecular simulation methods is the important developments in computational chemistry. These methods have wide applicability not only in studies of solvation free energies but also in studies of binding free energies and protein and nucleic acid stability. Early works in this area focused on small, non polar molecules[11], but more work has involved investigations of polar molecules[12,13] including systems where polarization effects are thought to be significant[14]. While it is important that these methods reproduce the experimental results, the real aim is to use these theoretical methods in a predictive manner in cases where the experiments cannot be performed.

The nucleic acid bases are an example of a class of molecules Whose solvation free energies are inaccessible experimentally due to problems of low volatility[7]. Because of their hydrophilicity, these

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molecules cannot be detected in the vapor phase in gas/water partition experiments. Knowledge of these free energies would be useful, for example, in understanding the forces involved in protein-nucleic acid interactions and the stability of nucleic acid tertiary structures. In this case, the application of theoretical methods may be our best hope to gain physical insights into the effects of salvation.

This has been recognized for some time, and different theoretical models have been used to compute this solvation energies[16-22].It is discouraging, however, that the various methods sometimes give very different results, bringing in to question the applicability and accuracy of the models themselves.

In this paper we present quantitative results of Monte Carlo calculations of solvation energies of Adenine, Guanine, Cytosine, and Thymine in water. We have used quantum mechanical calculations for isolated solute molecules and then applied Monte Carlo simulation for dilute solutions of DNA bases in water. We have done the Monte Carlo simulation with two procedures. We have written FORTRAN program for the system of DNA bases in water and then calculated the solvation energy and radial distribution functions of systems by the program. Also CHARMM[39, 40] program for Monte Carlo simulation of these DNA bases in water have been used. The conclusions drawn from these calculations are then compared.

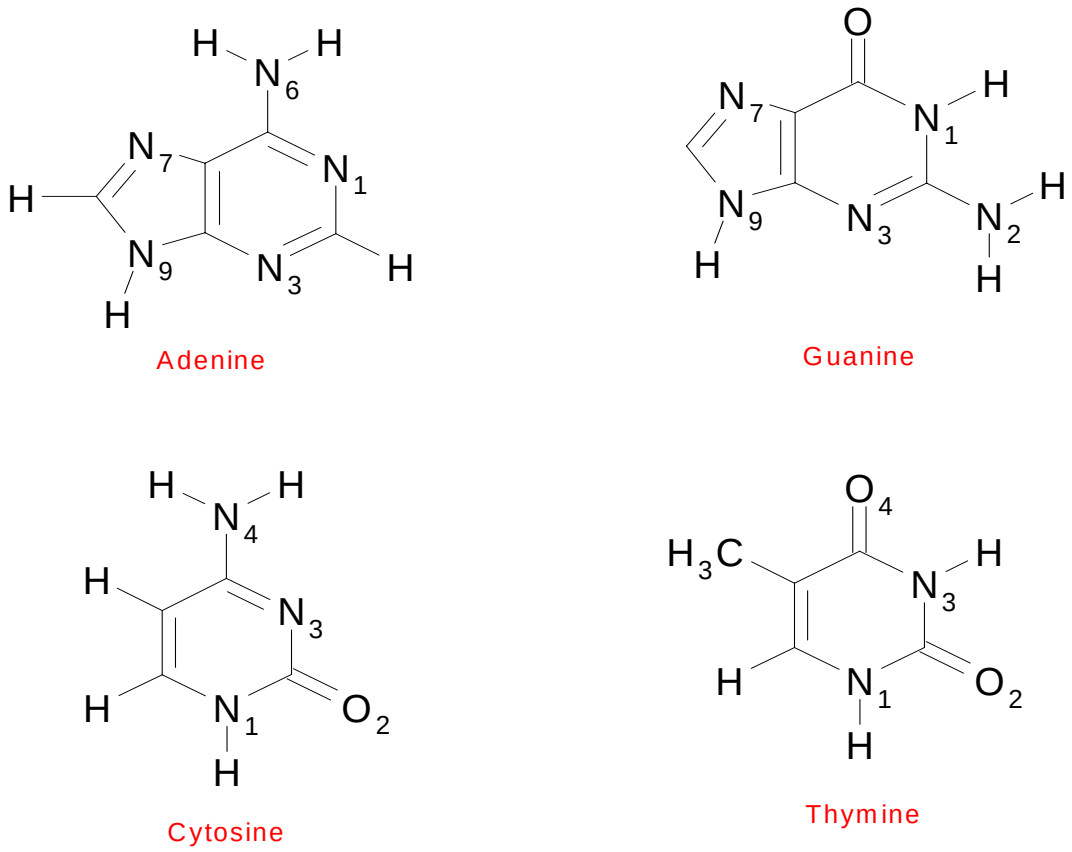


Fig1.DNA bases

METHODS

Geometries . The geometries of the isolated Adenine, Guanine, Cytosine and Thymine have been optimized by ab initio calculations using the standard 6-31+G* basis set[23] in Hartree-Fock level. The calculations have been performed by using the GAUSSIAN 98 suite of program[24]. The respective data are given in table1 and table2. Atomic charges and dipole moments have been used in further calculation. In all subsequent calculations, these geometries were kept constant.

Table 1. Atomic charges for various atoms of DNA bases

adenine		guanine		cytosine		thymine	
atom	**charge**	**atom**	**charge**	**atom**	**charge**	**atom**	**charge**
N3	-0.659	O6	-0.499	C2	0.881	O4	-0.487
C2	0.452	C6	0.602	N1	-0.601	C4	0.586
N1	-0.662	N1	-0.747	C6	0.207	N3	-0.573
C6	0.638	C2	0.841	C5	-0.653	C2	0.666
C5	0.013	N3	-0.654	C4	0.970	N1	-0.475
C4	0.538	C4	0.394	N3	-0.757	C6	-0.059
N9	-0.503	C5	0.051	O2	-0.577	C5	0.055
C8	0.277	N7	-0.498	N4	-1.067	O2	-0.520
N7	-0.522	C8	0.236	H1	0.354	CM	-0.576
N6	-0.844	N9	-0.434	H6	0.129	H3	0.354
H8	0.047	N2	-0.977	H5	0.224	H1	0.351
H2	0.089	H1	0.340	H41	0.442	H6	0.173
H9	0.369	H8	0.091	H42	0.449	HM1	0.177
H61	0.392	H9	0.356			HM2	0.151
H62	0.375	H21	0.420			HM3	0.177
		H22	0.419				

Table 2. Dipole Moments of DNA bases

base	μ (D)
adenine	2.55
guanine	6.45
cytosine	6.27
thymine	4.01

Potential energy functions. The key factor in determining the accuracy of computer simulations is the quality of intermolecular potential functions. These functions are obtained either by empirical methods or from quantum-mechanical calculations, the latter method being used in most of the recent simulations of fluids.The intermolecular potential functions are described in detail elsewhere[25-29].

Total potential energy of a chemical system, E_{total} , includes internal potential energy , $E_{internal}$, and external potential energy , $E_{external}$,terms:

$$E_{total} = E_{internal} + E_{external} \quad (1)$$

In our program internal potential function has been disregarded and only external or intermolecular potential function has been considered.The monomers are represented by interaction sites usually located on nuclei. The interaction energy between two molecules, a and b were expressed by pair wise sum of interaction contributions:

$$E_{ab} = \sum_{i}^{ona} \sum_{j}^{onb} E_{ij}^{AB} \quad (2)$$

We have used Transferable Intermolecular Potential functions [25,28](TIP3) for water molecules (solvent) and Optimized Potential For Liquid Simulations [29](OPLS)for Adenine, Guanine, Cytosine, and Thymine in solution. For both models, the pair potential function E_{ij} was represented by Columbic and Lennard-Jones terms between sites centered on nuclei

$$E_{ij}^{AB} = \frac{q_i q_j e^2}{r_{ij}} + \frac{A_{ij}}{r_{ij}^{12}} - \frac{C_{ij}}{r_{ij}^{6}} \quad (3)$$

as indicated in eq1,each type of site has three parameters, a charge in electron, q, and A and C. The TIP3 model uses a total three sites for the electrostatic interactions. The partial positive charges on the hydrogen atoms are exactly balanced by an appropriate negative charge located on the oxygen atom. The TIP3 parameters for water[26] have been included in table 3.

The OPLS model is a modified form of TIPS that has parameters fitted to liquid state properties, and so is more suitable for studies of liquids. The model works well for a variety of alcohols, amines, aliphatic and aromatic hydrocarbons, sulfur compounds, ether, amino acides and nucleic acid bases. It has the form of equation 3 . The Lennard-Jones parameters between pairs of different atoms are obtained from the Lorents-Berthelodt combination rules:

$$A_{ij} = (A_{ii} A_{jj})^{1/2} \quad (4)$$

$$C_{ij} = (C_{ii} C_{jj})^{1/2} \quad (5)$$

$$A_{ii} = 4\varepsilon_i \sigma_i^{12} \quad (6)$$

$$C_{ii} = 4\varepsilon_i \sigma_i^{6} \quad (7)$$

The OPLS Lennard-Jones parameters for nucleic acid bases[29] have been included in table 4. We have used quantum mechanical calculated partial charges that are given in table 1.

Table3. TIP3 Parameters for water

Site	q	$10^{-3}A^2$ KcalÅ^{12}/mol	C^2 KcalÅ^6/mol
O	-0.834	582.0	595.0
H	0.417	0.0	0.0

Table4. OPLS Lennard-Jones Parameters for Nucleic Acid Bases

atom	σ,Å	Є,Kcal/mol
O	2.96	0.210
N	3.25	0.170
C in C=O	3.75	0.105
Other C	3.50	0.080
H on N	0.00	0.000
H on C	2.50	0.050

$$E_{\text{int}ernal} = \sum_{bonds} K_b (b - b_0)^2 + \sum_{UB} K_{UB} (S - S_0)^2 + \sum_{angles} K_\theta (\theta - \theta_0)^2 + \sum_{dihedrals} K_\chi (1 + \cos(n\chi - \delta)) + \sum_{improper} K_{imp} (\varphi - \varphi_0)^2 \quad (8)$$

Our calculations also have been performed with the simulation program CHARMM[43, 44], in which an empirical energy function that contains terms of both internal and external interactions was used. The internal energy function has the form

Where K_b , K_{UB}, K_θ, K_χ and K_{imp} are the bond, Urey-Bradley, angle, dihedral angle, and improper dihedral angle force constants, respectively; b, S, θ, χ, and φ are bond length, Urey-Bradley 1,3-distance, bond angle, dihedral angle, and improper torsion angle, respectively, with the subscript zero representing the equilibrium values for the individual terms.

Monte Carlo procedure. Monte Carlo statistical mechanical simulations were carried out in standard manner using Metropolis sampling technique[21] in canonical (T,V,N) ensemble. All calculations were performed in a cubic box at experimental density of water, 1 g/cm^3 . The edges of the box were 22×22×22 Å, which corresponds to 352 H_2O molecules of pure solvent. A spherical cut off for the potential at an OO separation of half the length of an edge of the cube were used. One molecule was picked and displaced randomly on each move. An acceptance rate of 50% for new configurations was achieved by using ranges of ± 0.12 Å for the translations and ± 15º for the rotation about a randomly chosen axis. Periodic boundary conditions were employed in computation of initial configuration's energy, in cut off, in translations and rotations, and computation the energy of each produced configurations. The system was thoroughly equilibrated by using several hundred thousand configurations.The energy of a configuration was obtained from the pair wise sum of the dimerization energies for each monomer as usual.

Each run consisted of 10^6 attempted moves. Initial steps (roughly 5×10^5) were disregarded for equilibrium. Every calculation was extended to include as many configurations as were necessary to reduce the statistical error to the level at witch calculated energy differences have quantitative significance.In the CHARMM calculations we used Adenine residue in a cubic box image of water. The edge of the cubic box is 22 Å like befor. The translation and the rotation and the number of steps have been considered the same as previous work.

RESULTS AND DISCUSSION

Solvation energies. In this research, we have analyzed the solvation of the DNA bases, Adenine, Guanine, Thymine and Cytosine in the presence of water. We have used very dilute solution of DNA bases, so one molecule of Adenine, Guanine, Cytosine, and Thymine has merged in water and then average energies calculated from Monte Carlo simulations. The resultant configuration of the MC simulation of Adenine and cytosine in water has been shown in Figure 2. This gives a qualitative idea of the formation of the solvation shell around the selected DNA bases. The total energy of the bases (including van der Waals and Coulombs interaction) in water has been calculated. The average energy (E_{total}) calculated from Monte Carlo simulations, as well as the energies of solute-solvent (E_{soln}) and solvent-solvent (E_{solv}) components, have been given in table 5. This table also includes the number of solvent molecules, N, the total number of MC steps, NSTEP, and the actual number of configurations, $NSTEP_{av}$, used in calculating ensemble averages for every run.

Calculated energy values, as well as various structural parameters, can be further used to analyze solvation energies of the nucleic acid bases. The process of solvation of the solute molecule, Base, in water is :

Base (g) ↔ Base (aq) (9)

The ΔE_{tot} term can be presented as the sum of the energy contributions from solute-solvent (ΔE_{soln}), solvent-solvent (ΔE_{solv}), and intramolecular (ΔE_{int}) interactions:

$$\Delta E_{tot} = \Delta E_{soln} + \Delta E_{solv} + \Delta E_{int} \quad (10)$$

Since the positions of atoms in the solute molecule have been kept fixed, ΔE_{int} remains constant through the Monte Carlo process.The results shown in the last column of Table 5 indicate that the solvation energy of DNA bases in water are in the following order: E_{total}*(Guanine)* > E_{total} *(Thymine)* > E_{total} *(Cytosine)* > E_{total} *(Adenine)*

It is known that polar molecules are soluble in polar solvent and non-polar molecules dissolve readily in non-polar solvent system. As it is seen in table 2, guanine and cytosine are very polar bases . Thymine has smaller dipole moment and adenine is even less polar. As a result, we expect that guanine has the most solvation energy and adenine has the smallest amount. In our calculations, as well we observe the less polar DNA bases exhibit less solubility in the water.

In our calculations which have been used CHARMM program, we placed an Adenine residue in water and then optimized the system by the program. It has used the functions and the parameters[41] that are implemented in CHARMM.

The E_{total} With 98035 NSTEP is -35.2383 K cal/mol by CHARMM That has been averaged over 46169 configurations. With 1000000 configurations the E_{total} has been -35.3429, over 373399 configuration average.

Table 5. Summary of Monte Carlo runs

solute	N	NSTEP	$NSTEP_{av}$	E_{soln}	E_{solv}	E_{total}
Adenine	345	10^6	5×10^6	-2.7328	-36.5154	-39.2482
Guanine	342	10^6	5×10^6	-3.1648	-44.8275	-47.9923
Cytosine	343	10^6	5×10^6	-3.2786	-37.3000	-40.5786
Thymine	342	10^6	5×10^6	-3.4148	-37.2160	-40.6308

-E_{soln}, E_{solv}, E_{total} are in kcal/mol

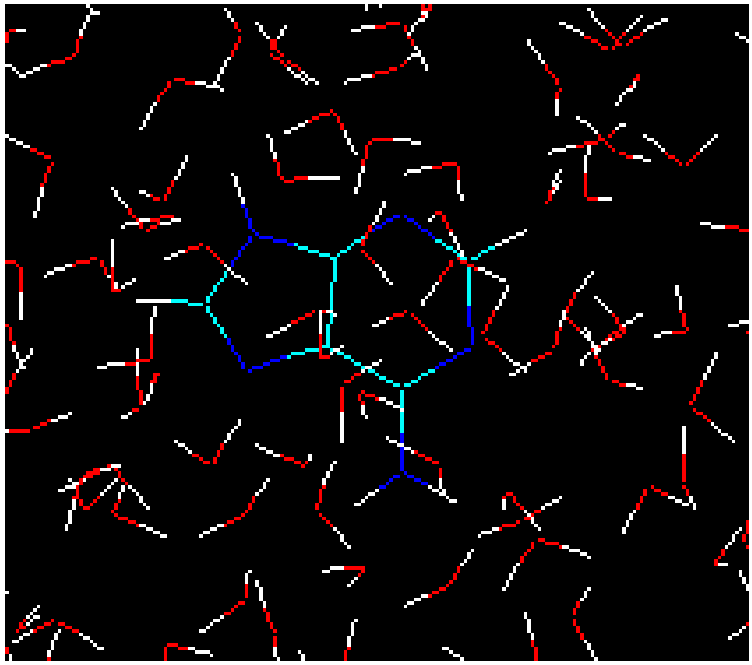


Fig 2. Final configuration of Adenine-water

Table 6. Computed solvation free energies

Method	Adenine	Guanine	Cytosine	Thymine	Ref.
MonteCarlo (OPLS,TIP3)	-39.284	-47.9923	-40.5786	-40.6308	This work
CHARMM	-35.3429	-	-	-	This work
AMBER/FEP	-12.6	-19.6	-12.7	-7.5	33
QM/MM	-5.1	-13.5	-16.3	-8.5	35
SCRF(AM1)	-11.3	-18.1	-14.4	-8.6	36
SCRF(6-31G*)	-6.5	-16.1	-13.0	-8.9	37

The free energy differences between two states 1 and 2, of a system may be derived from classical statistical mechanics[32] allowing us to express this function as,

$$A_2 - A_1 = -RT \ln < \exp[-(E_2 - E_1)/RT] > \quad (9)$$

$(E_2 - E_1)$ is the potential energy differences(ΔA) between states 1 and 2of the system. R is molar gas constant, T is absolute temperature, and the symbol < > indicates an ensemble average. Since the isothermal-isobaric ensemble has been used, Gibbs free energies has the same expression. The computed free energies are presented in table 6. the table has also the result of other authors and other methods as well as semiempirical[36], ab initio[37], combined quantum mechanical and molecular mechanical methods(QM/MM)[35],and AMBER[33]. It should be noted that except our work and QM/MM method, the values are for methylated DNA bases. Methylation decreases the hydration free energy of the bases[34].

The results of our work show that Guanine is the most stable DNA base in water. The other methods also give this conclusion. Of course their results are different numerically, but the approach of data is the same. The differences are due to many reasons. The use of force field by the methods is different. We use only intermolecular potential function that has Columbic and Lennard-Jones terms, and don't consider internal coordinate, while in AMBER and CHARMM force field total potential energy is the sum of the bond stretching, angle bending torsional terms plus Columbic and Lennard-Jones terms. The goal of each simulation procedure is simplicity of the system together with quality of results. We have given the similar results by the simpler force field. For monomers (solute and solvent molecules) the geometries during the simulations were kept fixed so intramolecular vibrational effects have not been considered. This simplicity is correct for small molecules and reduces the time consuming of calculations. The results of our CHARMM computations confirm this conclusion. In SCRF and other quantum mechanical procedures, the solvent is viewed as a continuous medium of uniform dielectric constants.

Radial Distribution Functions (RDFS). Radial distribution functions between water molecules and each site of the solute molecule are important in hydrogen bonding and interaction of that site with the ions. So we have computed radial distribution functions between water molecules and N1,N3,N7, and N6 atoms of Adenine, N1, N3, N7, and O6 atoms of Guanine, N3, N4, and O2 atoms of Cytosine, and N1, N3, O2, and O4 atoms of Thymine. We have computed rdfs under 4 Å, since the R bigger than 4 Å is related to hydrogen bonding of water molecules with each other. The results have been reported in table 7. Under 4 Å, there are two coordination layer of water molecules around each site. ρ_1 is the first coordination layer that has located at the distance r_1 and ρ_2 is the second coordination layer that has located at the distance r_2. Figure 3 and 4 show RDFS for some sites of DNA bases. All of the rdfs diagrams have two peak that related to the first and second solvent shells. As it has been shown, the first peak of the all sites and bases has occurred on 1.2 Å and is a sharp peak.N6 and N7 in Adenine,O6 in Guanine, N4 in Cytosine , and N3 in Thymine have the highest first peak . For all of the DNA bases, the second coordination shell has been occurred in about 3 Å. Table 6 reveals that the highest second peak for Adenine and Guanine is related to the N7 centered in 3.30 Å and 3.00 Å respectively. For Cytosine and Thymine the highest second bond can be assigned to water molecules around N3 and N1 and have located in 3.15 Å and 3.3 Å respectively. These results reveal that N7and N6 in Adenine and Guanine, N3 in Cytosine and N3 and O4 in Thymine are the most hydrophilic atoms in each bases. It means that these sites are the most active atoms in these molecules, and have the potential to take part in the hydrogen bonding or interaction with cations. These results are in good agreement with the experimental data since the watson grick model for hydrogen boding between the bases proposed the interaction of the N6 and N7 of Adenine and O4 and N3 of Thymine. Figure 5 shows these hydrogen bonding and confirms our results.

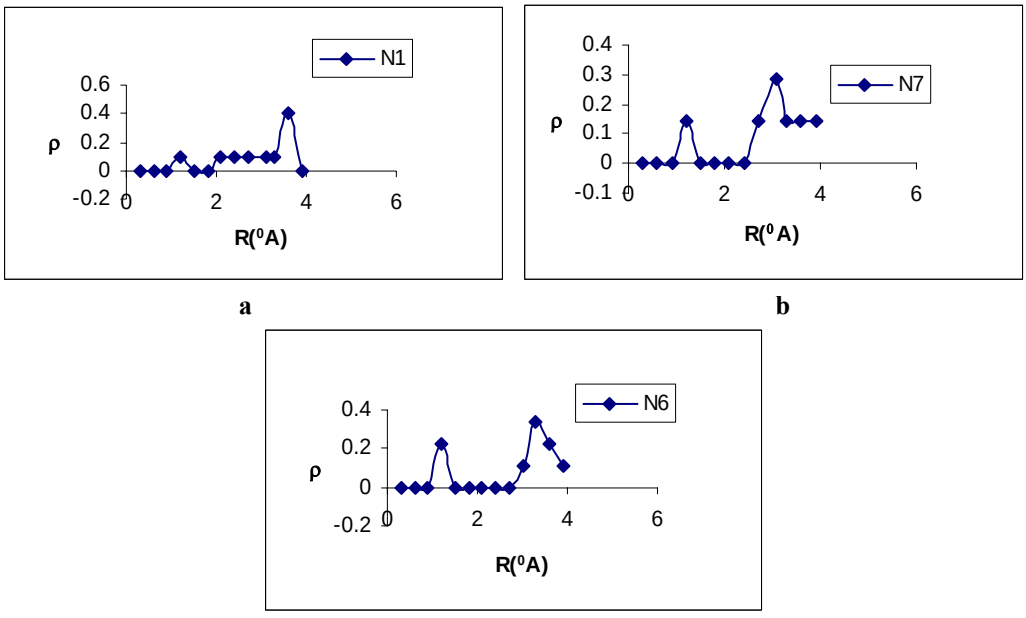
The proton affinity of the O and N atoms of the DNA bases have been computed by Chandra & Et al and the results are given in Table 8. Their results show that N7 in guanine and adenine, N3 in cytosine and O4 in thymine are the most active sites in these bases that are conformity our results. Also the experimental results show that the best site for protonation of Adenine and Guanine is N7, for Cytosine is N3 and for Thymine is N1 or N3 [38] .

Table7. RDFS between different sites of DNA bases and water

Site	r_1 (Å)	ρ_1	r_2 (Å)	ρ_2
Adenine				
N7	1.20	0.1429	3.30	0.8573
N1	1.20	0.1000	2.85	0.9000
N3	1.20	0.1111	3.15	0.8888
N6	1.20	0.2222	3.45	0.7777
Guanine				
N7	1.20	0.0909	3.00	1.0908
N1	1.20	0.1111	3.15	0.8888
N3	1.20	0.1111	3.00	0.8888
O6	1.20	0.1667	3.00	0.8334
Cytosine				
N3	1.20	0.1000	3.15	0.9000
N4	1.20	0.2000	2.70	0.8000
O2	1.20	0.1250	2.90	0.8750
Thymine				
N1	1.20	0.0833	3.30	0.9166
N3	1.20	0.1429	2.85	0.8572
O2	1.20	0.1250	2.85	0.7500
O4	1.20	0.125	3.00	0.8750

Table 8. B3LYP/6-31+G(d,p) Proton Affinities(kJmol^{-1}) of Adenine,Guanine,Cytosine, and Thymine[42]

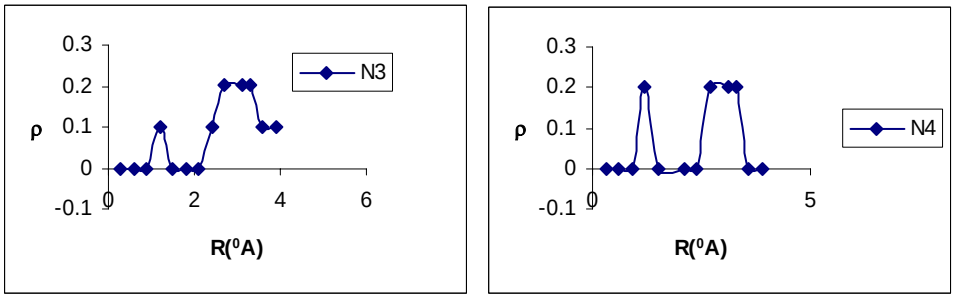
nucleobase	PA(B)		
Adenine	N3: 937.6	N7: 909.6	N1: 943.8
Guanine	N3: 887.4	N7: 960.1	O6: 900.8
Cytosine	N3: 955.5	O2: 921.7	
thymine	O4: 854.4	O2: 830.2	



a **b**

c

Fig 3. Computed radial distributions between water and a-N1, b-N7, c-N6 atoms of Adenine



a **b**

Fig 4. Computed radial distributions between water and a-N3 b-N4 atoms of Cytosine

Errors estimating. A simulation can generate an enormous amount of data that should be properly analyzed to extract relevant properties and to check that the calculation has behaved properly. The three most important factors that determine the accuracy of Monte Carlo calculations are the quality of intermolecular potentials, the sample-size effect, and statistical fluctuations of calculated ensemble averages. The first was briefly discussed. The second factor arises because locating a limit number of molecules in a box followed by subsequent application of periodic boundary conditions introduces an error into the molecular correlations. For a given system, this effect decrease in the sample size. In most cases of interest we don't know how to choose the size of the system in order to minimize an effect of periodic boundary conditions. The most straightforward test is to perform a series of calculations in which the sample size is systematically increased until calculated values remain unchanged.

The statistical errors are often reported as standard deviations. The errors have been reported in table 9. STDEV is the standard deviation of the calculated average in the simulation of finite number of steps. As it has been shown in table 10, the simulation error is between 2-4%.

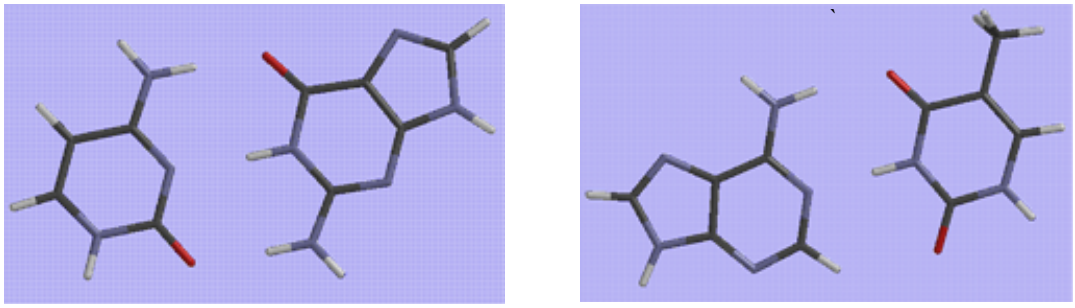
CONCLUSION

In this research study, we calculated solvation free energy for the nucleic acid bases. These energies are unattainable experimentally because of the lack of volatility of the bases. Our computation shows that Guanine is the most stable DNA base in water. Adenine has the minimum value of the solvation free energy and Guanine has the maximum valueof the solvation free energy. Our work is comparable with CHARMM and other computational methods.

We have also computed radial distribution function between the active sites in the DNA bases and water molecules . Our computation have been shown that N7and N6 in Adenine and Guanine, N3 in Cytosine and N3 and O4 in Thymine are the most active sites for the interaction of these bases with Hydrogen of water and with other positive sites. These results determine the best site of hydrogen bonding between DNA bases that are compatiable with Watson Crick model.

Table 9. Simulation errors

Base	<E>	STDEV	Relative error
Adenine	-39.248	1.1629	0.029
Guanine	-47.9923	0.9859	0.024
Cytosine	-40.5786	1.2632	0.026
Thymine	-40.6308	1.6646	0.041



(a) **(b)**

Fig. 5. Structures of H-bonded NA base pairs **a)** guanine-cytosine **b)** adenine-thymine

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