

Computer Simulation of Biomolecular Systems. Hydration of DNA Fragments.

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Abstract: Computer study via molecular mechanics and Monte Carlo methods reveals some interesting features of hydration of nucleic acid bases. The calculations of interactions of one water molecule with each of bases allow to find the sites of preferential hydration. The energy of interactions with some sites is changing upon Watson-Crick pair formation. Hydration of all the H-bonded base pairs is less favorable than two individual bases. The energy and structure characteristics are different for various base pairs, and correlates with pair structure and base-base interactions.

Key-Words: - Hydration, Monte Carlo, Computer Simulations, Intermolecular Interactions, Nucleic Acids

1. Introduction

The computer simulation allows studying the problems at the molecular levels, when the application of experimental methods is restricted. The molecular mechanics is one of the empirical methods, widely used to investigate the structure and processes in biological systems at the molecular level. The method uses potential functions, which simulate the interactions between the atoms forming the system.

In 1984, the set of potential functions was suggested for calculation of interactions of nucleic acids with water molecules [1]. Recently, we have refined this set, taking into account new experimental and theoretical data [2].

Calculations performed for the plane interactions between nitrogen bases of DNA using the new potential show the consistency of our model [3].

2 Problem formulation

Water molecules are very important and are mainly responsible for the stabilization of secondary and tertiary structure of DNA. The crystal structure of B-DNA dodecamer d(CGCGAATTCGCG) has shown detailed hydration structure [4]. In the major groove there are 1 to 5 solvent molecules per phosphate oxygen and they form bridges between two or more phosphate oxygens. In addition, monodentate binding of water molecules to keto oxygen and amino groups of purine and pyrimidine was seen. In the minor groove, the water structure is well ordered. Along the central AATT sequence, water molecules bridge thymine O2 and adenine N3, forming a

continuous spine. The antibiotic netropsin, has been crystallized with the same dodecamer. The structure shows that the antibiotic forms hydrogen bonds to adenine N3 and thymine O2 atoms, exactly as in the spine of hydration [5]. The conclusion is made that hydration of fragments of DNA with various base sequences may result in a specific conformation with a certain biological significance. Therefore it is essential to take account of the solvent environment in any atom-based modeling procedure. This paper is dedicated to the study of the structure of hydration shell of the nucleic acids fragments with the new potential.

2.1 Calculation procedure.

Energy minimization was performed to obtain favorable positions of the water molecules around the bases and their pairs. The base positions were fixed while the water molecule migrates until it reaches the local minima. Water molecules are free to rotate around their internal axis. The water-base interactions were modeled by the atom-atom potential function with optimized parameters [1]. Simulation of hydration by the Monte Carlo method (Metropolis sampling) was carried out for 300K. The unit cell contains a base (or base pair) and 400 water molecules. Periodic boundary conditions were imposed. The entropy has not been considered for this simulation. This is justified for the aim, since it has been shown experimentally that the association of the bases and their derivatives in water is determined by enthalpy [6].

3 Hydration of DNA fragments.

3.1 The favorable hydration sites of the individual bases.

Table 1 show the results of calculations of the interaction energy for one water molecule with nucleic acid bases in global minima. The results are compared with experimental values of water-base associations in vacuum [7] and with the values calculated using second generation of Kollman et al potentials [8]. The table suggests, that our results for A and C coincide with experimental data within the error limits.

The differences for G and T are grater up to 0.5 kcal/mol, than experimental errors, but in general we have the best agreement with experimental data of all the potentials available.

Table 1. Comparison of the calculated energy values for global minima of single water-single base interactions with the experimental association enthalpies and with results of calculations with Kollman et al potentials (in kcal/mol).

	Sukhodub [7]	Cornell et al [8]	This work
Ade	-10.6±1.0	-10.0	-10.8
Gua	-14.1±1.0	-12.6	-12.4
Cyt	-11.4±0.8	-11.7	-11.4
Thy	-10.4±0.9	-8.9	-9.0

The favorable sites of base hydration, i.e. the local minima of base-water interaction energy minima, are presented in Fig.1. Most deep minima are formed via two nonlinear hydrogen bonds (e.g. A for guanine). When a minimum is formed by single H bond, this bond is practically linear, and the interaction energy is considerably smaller (e.g. C for adenine).

There are several minima of single base – single water molecule interactions for each base. The most of these minima corresponds to position of water oxygen in base plane. These positions are shown in Fig.1. Most deep minima correspond to formation of two non-linear hydrogen bonds. The interaction energy for minima with single H bond is much smaller by absolute value.

Minima with single H bond may be formed when the base participates in H bonding by both hydrogen donor (minimum A for cytosine) and hydrogen acceptor group (minima C for adenine, D for cytosine, A and D for thymine). Minima with two H bonds may be of 3 types, namely, when base participates in H bonds by two acceptor groups (minima C for cytosine and A for

guanine), by one donor and one acceptor group (the most of minima), and by two donor groups (minima C for guanine).

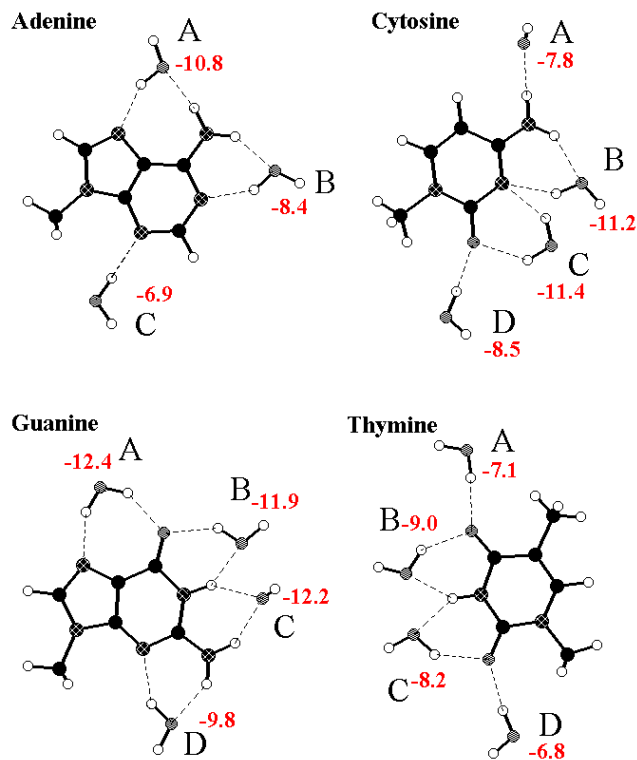


Fig. 1. Positions of water molecules in local interaction energy minima of the nucleic acid bases.

Besides these minima, there are a few minima with water oxygen above (or below) the base plane. These minima are shown in Fig.2. These configurations correspond to formation of one hydrogen bond between water molecule and acceptor group of base. In one minimum water molecule forms two H bonds with two acceptor groups of guanine (minimum B for guanine). The displacement of water oxygen from base plane results in decrease of absolute value of water- base energy for every in-plane minimum. These decrease is the most pronounced, when the base participates in H bond by donor group. In the case of minimum C for guanine, when base acceptor groups form two H bonds with a water molecule, 1A° displacement of water oxygen out of plane results in 3 kcal/mol change of interaction energy. When the base participates by its acceptor groups in one or two H bonds with water molecule, 1A° displacement of water oxygen from base plane results in small changes of the energy in minima (from 0.1 to 1.0 kcal/mol).

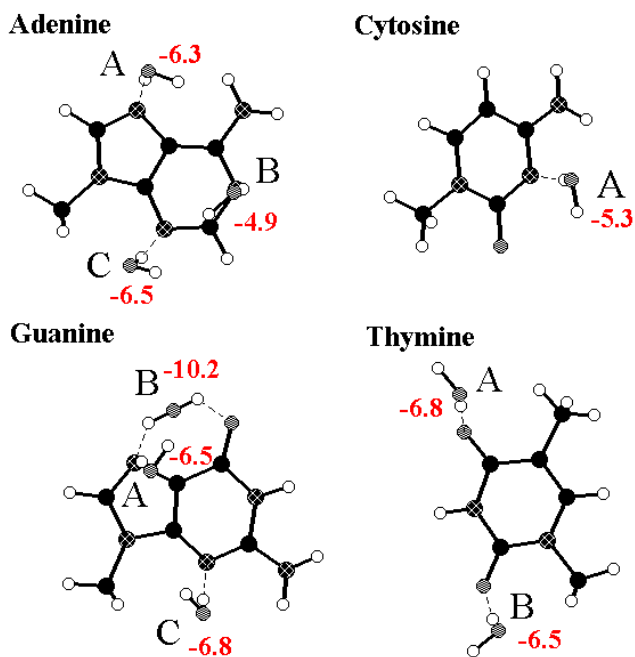


Fig.2. Mutual positions of water and base molecules in local minima of interaction energy, corresponding to out-of-plane location of water oxygen. View along the axes normal to base plane.

3.2 Local energy minima of the interactions between single water molecule and Watson-Crick base pairs.

Some of hydration sites of individual bases are available for interaction with water in Watson Crick pairs. Fig.3 shows the local minima of interaction energy of A:T and G:C pairs with water molecule located in pair planes. The positions of water molecules in minima A and D of A:T pair coincide with those A and C of separate adenine, while the energy values are smaller by 0.5 and 0.2 kcal/mol respectively. The B minimum corresponds to the A minimum of individual thymine, but has a bit smaller energy. It is interesting, that there is a minimum C with the greater interaction energy (as compared to minimum D of thymine, Fig.1).

There are several energy minima between base pairs and water molecule positioned out of base-pair plane (Fig.4). Some of them correspond to out-of-plane minima for individual bases and differ from them slightly. Other such minima differ more significantly.

The most interesting are minima with water molecule arranged between bases, i.e. C and D minima. Water molecules in these minima form H bonds with both the bases, i.e. these minima correspond to water bridges between acceptor atoms of adenine and thymine. Similar, but not identical, minima are possible of G:C pair with water molecule positioned above the pair plane.

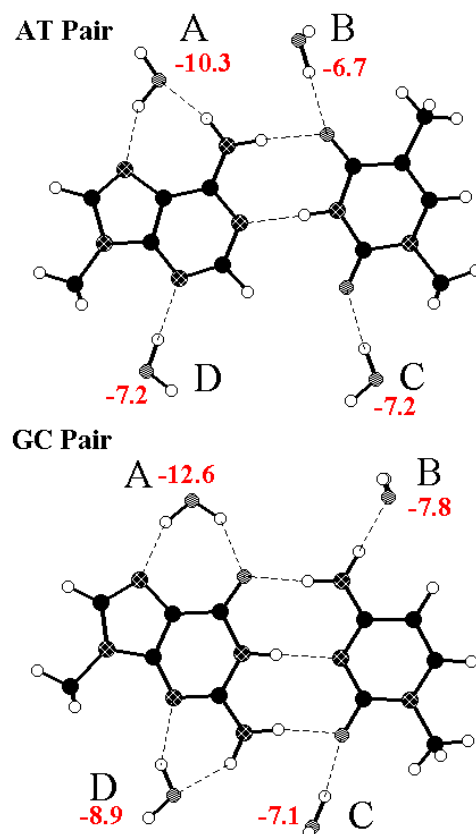


Fig.3. Mutual positions of water and base molecules in local minima of water-base pair interactions. Water oxygens are located in base-pair plane.

3.2 Hydration of various base pairs.

In our earlier paper [9], we calculated the hydration energy of four DNA bases via Monte Carlo simulations. The results of calculations show good agreement of calculated values with experimental values of hydration enthalpy [7]. The results for thymine and adenine (-23.3 and -24.4 kcal/mol) are practically reproduce experimental data (-23.4 and -23.0, respectively). The calculated values for cytosine and guanine (-34.3 and -38.5 kcal/mol) differ from experimental data by only 3.1 and 3.9 kcal/mol.

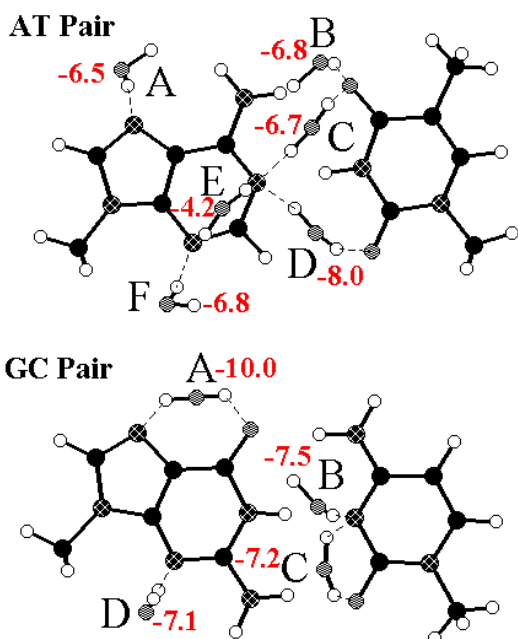


Fig.4. Mutual positions of water and base molecules in local minima of water-base pair interactions. Water oxygens are located out of base-pair plane.

Now, we continue to study the hydration of more complex fragments of nucleic acids. We have performed the simulation of 28 pairs of bases with two or three inter-base hydrogen bonds.

Hydration characteristics of some of them are shown in the Table 2.

Table 2. Hydration characteristics of some H-bonded base pairs.

	E_t	E_{pur}	E_{pyr}	E_{ww}	ΔE
AT1	-3815.5	-36.2	-34.0	-3745.3	-34.3
AT2	-3814.5	-35.7	-32.8	-3746.0	-33.3
AT3	-3818.3	-44.4	-32.6	-3741.3	-35.8
AT4	-3814.9	-36.4	-32.4	-3746.1	-33.7
GC1	-3829.6	-50.0	-41.8	-3737.8	-48.4
GC2	-3834.0	-53.8	-46.8	-3733.5	-52.8
GC3	-3836.7	-57.2	-46.8	-3732.8	-55.5
GT1	-3827.8	-59.2	-30.6	-3738.0	-46.6
GT2	-3828.3	-62.2	-32.8	-3733.2	-47.1
AC1	-3826.4	-35.6	-50.7	-3740.0	-45.2
AC2	-3825.6	-35.3	-49.5	-3740.7	-44.4

Note: see text for explanations.

The table includes the total energy of the system (base pair with 400 water molecules in a proper unit cell with periodic boundary conditions, E_t ; E_{pur} , water-purine (A or G) interaction energy; E_{pyr} , water-pyrimidine energy; E_{ww} , water-water interactions, and ΔE , hydration energy, calculated as a difference between total energy of the system considered and of pure water under same conditions (3782.5 kcal/mol).

The results show, that hydration energy of each pair is smaller by absolute value, than the sum of hydration energies of the bases of a pair. This is because a part of space around H-bonded hydrophilic atoms becomes inaccessible upon pair formation.

The difference between hydration energy of each pair and hydration energy of two bases of the pair is greater than the energy of base-base interaction in this pair. Thus, the formation of all the pairs is unfavorable in water solution, and such pairs do not practically form in accord with experimental data.

Simulation results suggest that hydration of Watson-Crick (GC1) pair is less favorable than two other GC pairs. It is a result of formation of three H bonds in pair GC1 in contrast to two H bonds in GC2 and GC3 (as well as in all other pair considered). More favorably hydrated pairs GC2 and GC3 have less favorable energies of base-base interactions. The same is true for a set of AT pair. Watson-Crick pair, AT1, is more favorably hydrated than Hoogsteen pair AT2, the latter being more favorable from viewpoint of base-base interactions.

Besides energy characteristics of base pair hydrations, it is interesting to consider hydration patterns of various pairs. X-ray studies of crystals of DNA fragments allow localizing some water molecules in vicinity of hydrophilic atoms.

These data are summarized in paper [10]. There is a correlation between calculated "hydration indices", i.e. average number of water molecules H-bonded with the atom and experimental data. Other interesting characteristics of hydration pattern of base pairs (and of DNA fragment in general) are the probabilities of "water-bridge" formation between hydrophilic atoms of two bases of pairs. Such bridges may contain one, two, three or more water molecules.

Table3 shows that the probabilities of one water bridges between bases in some pairs. These probabilities can be rather great and water bridging can contribute to a formation of such pairs in nucleic acids.

Table 3. The probabilities (P) of one-water bridge formations between hydrophilic atoms of bases in pairs.

Par	Enlace-H	P
TT1	O2(1)..O2(2)	34%
	O4(1)..O4(2)	29%
TT2	O4(1)..O2(2)	25%
TT3	O4(1)..O2(2)	35%
GT1	H21G..O4T	50%
	O6G..O2T	28%
GT2	H21G..O2T6	45%
AC1	H62A..O2C	25%
GC2	O6G..O2C	20%
	H22G..H41C	26%
CT1	O2C..O2T	14%
CT2	O2C..O4T*	63%
GG2	O6(1)..H21(2)	37%
GG4	O6(1)..O6(2)	40%

Note: the number in brackets determines base number (for pairs of equivalent bases).

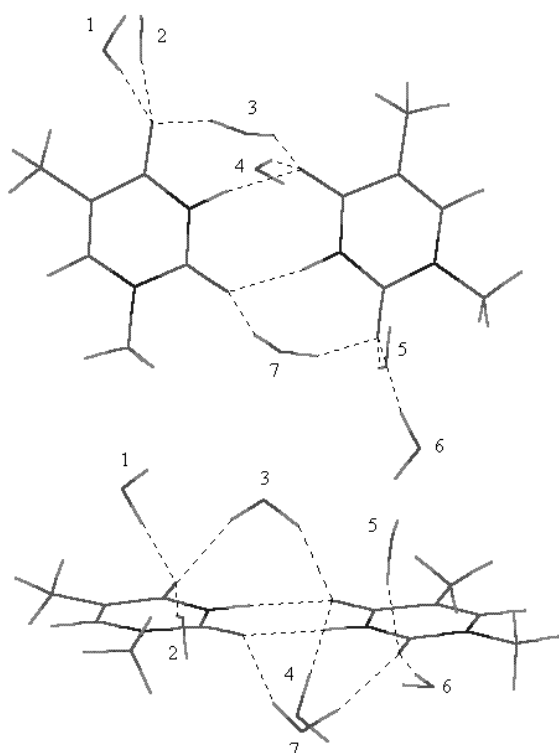


Fig.5 Configuration of hydration shells of TT1 base pairs. The water molecules displayed are those H-bonded to the bases and forming water bridges between hydrophilic atoms. Dashed lines stand for hydrogen bonds.

Fig. 5 shows the arrangement of water molecules around two base pairs. The water structure was “frozen” by lowering temperature to 5K. Only water molecules H-bonded to bases or forming the water bridges are displayed. Rather different hydration patterns can be seen for different base pairs.

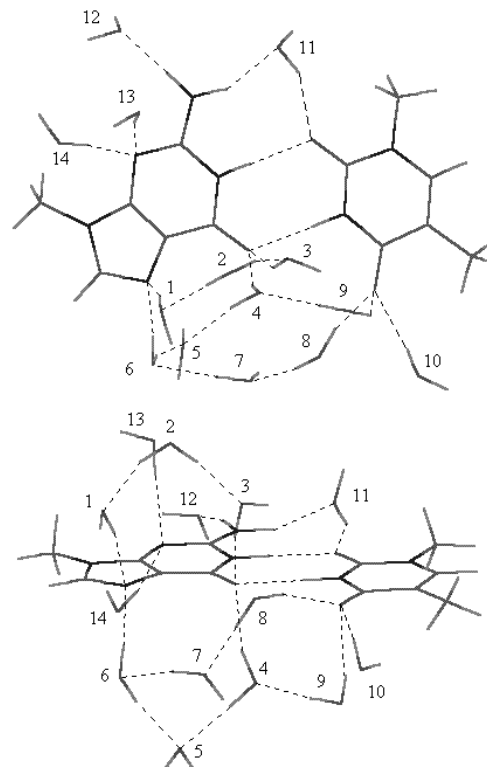


Fig.6 Configuration of hydration shells of GT2 base pairs.

3.4 Biological implications

Interactions of invariantly arranged atomic groups of Watson-Crick pairs with the polymerase fragments (“recognition site” of the enzyme) was theoretically suggested as the mechanism of high DNA biosynthesis accuracy [11]. The most suitable sites of such interactions are atoms N3 of purines and O2 of pyrimidines. Positions of these atoms in the DNA duplex are practically the same for all Watson-Crick pairs (AT1 y GC1) and differ from all the mismatches. Thus, the minor groove atomic groups of base pairs are screened by the enzyme from interactions with water. The only parts of bases, which can be involved in interactions with water surroundings during biosynthesis, are major groove edges of base pairs. Thus, the most important for biosynthesis fidelity hydration characteristics are those of major groove hydrophilic atoms.

As it was mentioned before, hydration characteristics of the major groove are nearly the same for all the Watson-Crick pairs, so the formation of mispair changes hydration characteristics of the major groove atoms. These changes contribute to the probability of such mispair formation.

Water molecules between hydrophilic atoms of the base pairs not only can obstruct the recognition but also can stabilize a mispair.

4. Conclusion

The minima of water-base interaction energy correspond to the sites of preferential hydration of nucleic acid bases. Water molecules in such minima are located in base planes. The formation of Watson-Crick pair results in considerable changes of position and energy of some of these minima. Monte Carlo simulations of various base pairs show the differences in hydration patterns for different pairs. The most interesting features of the hydration patterns are the probabilities of water bridges between atoms of two bases.

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