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Monte Carlo study of three-dimensional organization of water molecules around DNA fragments

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Abstract. Interactions with water molecules are important for the stabilization of three-dimensional structures of nucleic acids and for their functioning. The first hydration shells of macromolecules can be considered as structural parts of nucleic acid. We performed a Monte Carlo study of systems containing a nucleic acid base or base pair with water molecules using improved potential functions. These potential functions enable experimental data on both single base–single water interaction energies and enthalpies of base hydration to be reproduced. Hydration shell structures of base pairs are dependent on the pair geometry. Structural elements of hydration shells can contribute to the pair stability and hence to the probability of mispair formation during nucleic acid biosynthesis. The distribution of water molecules around bases and base pairs is essentially nonhomogeneous.

Keywords: DNA hydration – Monte Carlo – Water bridges – Molecular mechanics – Energy calculations

Introduction

The crucial role of water in DNA helix conformations was demonstrated as early as in 1953 by the first X-ray investigations of DNA fibers [1]. A lot of experimental and theoretical studies suggest that water molecules are structural parts of DNA.

X-ray single crystal analysis of oligonucleotide duplexes enables us to find out the location of water molecules forming bridges between hydrophilic atoms of DNA, and to reveal the full water aggregation, such as the spine of hydration in the minor groove of d(CGCGAATTCGCG) B-DNA dodecamer [2, 3, 4]. However, the accuracy of experimental methods does not allow us to study a detailed picture of water arrangement around the macromolecule in both crystals and solutions, as well as the role of water in the formation and stability of certain conformations. X-ray studies of oligonucleotide duplexes localize only oxygen atoms of water, whereas the positions of hydrogens and the hydrogen-bond network topology remain unknown.

Practically nothing is known about the molecular mechanisms of hydration in DNA replication. The replicative fork is screened from the solvent by DNA polymerase; nevertheless, it does not prevent interactions of single water molecules or aggregates of water molecules with the replicative complex consisting of a DNA template, a primer, incoming nucleoside–triphosphate and DNA polymerase. These interactions could influence the probabilities of errors, namely, promotion of some mispair formation and prevention of other mispairings.

X-ray studies of oligonucleotides with mispairs have shown the presence of water bridges between hydrophilic atoms of bases in the pair, thus stabilizing it (e.g. guanine:thymine mispair [5]) or making it possible to adjust the mispair geometry to the double helix (e.g. for pyrimidine–pyrimidine mispairs, as demonstrated in Ref. [6] for the thymine:cytosine pair). Water molecules can be involved in DNA–protein or DNA–ligand interactions forming bridges between the DNA hydrophilic atoms and those of the protein or ligand [7]. Thus, the hydration characteristics of individual atoms and atomic groups, as well as the total hydration of DNA fragments, are important for DNA functioning. Such characteristics can be obtained by computational molecular mechanics methods.

In 1984 potential functions were proposed for modeling water–water and water–DNA interactions [8]. These functions have been used for studies of hydration of nucleic acid fragments, and enable some interesting

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features of their hydration shells to be revealed [9, 10]. Recently [11, 12], we have improved water–water and water–base potential functions using new experimental data. Some results of the utilization of the refined potential functions for the study of the hydration shells of bases and base pairs are considered in this paper.

Methods of computations

The computations were performed for systems with one DNA base or one hydrogen-bonded base pair. The model molecules of 1-methylpyrymidines and 9-methylpurines were considered to avoid hydrogen bonding for the atoms that participate in glycoside bonds of nucleic acids. The mutual positions of bases in pairs correspond to local base–base interaction energy minima calculated using improved atom–atom potential functions [13]. Standard minimization techniques were used for searching for local minima of single water–single base (or base pair) and *n* water molecules–single base ($n=2$–7) systems.

The energy of interaction of water molecules with the DNA fragment and between themselves was calculated as a sum of pairwise interactions of all atoms constituting the molecules. Each atom–atom interaction consists of a Coulomb term and a Lennard-Jones 6–12 term, commonly used in molecular mechanics calculations (Eq. 1). For descriptions of the interactions of hydrogen atoms capable of forming hydrogen bonds, the 6–12 term is substituted by a 10–12 term (Eq. 2).

$$E_{ij}=\frac{e_i e_j}{r_{ij}}-\frac{A_{ij}}{r_{ij}^{6}}+\frac{B_{ij}}{r_{ij}^{12}}, \tag{1}$$

$$E_{ij}=\frac{e_i e_j}{r_{ij}}-\frac{A_{ij}^{(10)}}{r_{ij}^{10}}+\frac{B_{ij}^{(10)}}{r_{ij}^{12}}. \tag{2}$$

In these equations r_{ij} is the distance between atoms *i* and *j*, and e_i and e_j are charges on atoms *i* and *j* (calculated by the semiempirical methods of quantum chemistry and reproducing the experimentally determined dipole moments of the molecules). The atomic charges have not been changed from our early papers [8, 9, 10, 11, 12]. The coefficients A_{ij}, B_{ij}, $A_{ij}^{(10)}$ and $B_{ij}^{(10)}$ are adjustable parameters, which have been slightly modified recently [11, 12] compared to those of our early studies [8, 9, 10].

We describe here the results of this modification. For directed changes of coefficients A_{ij} and B_{ij} (or $A_{ij}^{(10)}$ and $B_{ij}^{(10)}$) during adjustment, they can be expressed via R_0 (equilibrium distance between two individual neutral atoms) and ϵ (energy value when $r_{ij}=R_0$, i.e. minimal interaction energy between the two atoms). The adjustment of these parameters resulted in better agreement of the results of the calculation with a few sets of experimental data, namely, with O–O, O–H and H–H radial distribution functions and the mean intermolecular interaction energy for pure water, with enthalpies of single water–single base complex formations in vacuum (Sect. 3) and with enthalpies of base hydrations (Sect. 5). The coefficients for water–water and water–base potential functions are listed in Tables 1 and 2, respectively.

Table 1. Parameters of potential functions for calculations of water–water interactions

	$A/A^{(10)}$	B (Å^{12} kcal/mol)	R_0 (Å)	ϵ(kcal/mol)
O···O	366	882,850	4.11	0.038
O···H	7,193[a]	18,360	1.75	4.45
H···H	35	5,914	2.64	0.0516

[a] $A^{(10)}$: Å^{10} kcal/mol

A geometrical criterion is used for determination of hydrogen bonds. The D–H...A configuration is called a hydrogen bond if the A...D distance is less than 3.2 Å and the H...A distance is less than 2.4 Å, where A and D are the acceptor and donor of the hydrogen bond, respectively. Two atoms of a base or base pair are called water-bridged if the same water molecule forms hydrogen bonds with both of them (single-water bridge), if two atoms form a hydrogen bond with two hydrogen-bonded water molecules (two-water bridge) if or each atom forms a hydrogen bond with water molecules hydrogen-bonded with the same third water molecule (three-water bridge).

Average energetic and structural characteristics of hydration shells were calculated from statistically significant sampling of configurations obtained by the Metropolis algorithm. The Monte Carlo procedure is the same as in our earlier papers (NVT ensemble, 300 K [8, 9, 10, 11, 12]). The averaging was carried out over the Markov chains up to 1×10^{6} trials per water molecule. The unit cell contains a base or base pair and 400 water molecules. Periodic boundary conditions and the nearest-image method [14] were imposed. The cutoff value was 8.0 Å, i.e. all the interactions of water molecules with the bases and between the water molecules were taken into account when the distance of any base atom to water oxygen or between water oxygens was less than 8.0 Å. The interactions between bases in neighboring unit cells were ignored.

Single water–single base interaction energy minima. Sites of preferential hydration of bases and base pairs

The mutual positions of bases and water molecules in local energy minima of single base–single water interactions are displayed in Fig. 1. There are several such minima for each base. The deepest minima correspond to the location of the water oxygen in the base plane and to the formation of two nonlinear hydrogen bonds.

Table 2. Coefficients of potential functions for calculations of water–base interactions. O_W and H_W are oxygen and hydrogen atoms of the water molecule, C1 and C2 are aliphatic and aromatic carbons, respectively,N1 is the nitrogen of the amino group, N2 and N3 are pyrrolo and pyridino nitrogens, respectively and O is the carbonyl oxygen. The units are the same as in Table 1

	O_W				H_W			
	A	B	R_0	ϵ	A/A^{10}	B	R_0	ϵ
C1	195	270,670	3.75	0.035	75	40,350	3.20	0.035
C2	240	378,590	3.83	0.038	101	19,510	2.70	0.13
N1	286	605,610	4.02	0.034	80	29,200	3.00	0.055
N2	273	519,360	3.95	0.036	126	24,150	2.70	0.164
N3	348	631,940	3.92	0.048	9,266[a]	27,290	1.88	2.8
O	311	433,080	3.75	0.056	10,667[a]	31,080	1.87	3.4

[a] $A^{(10)}$: Å^{10} kcal/mol

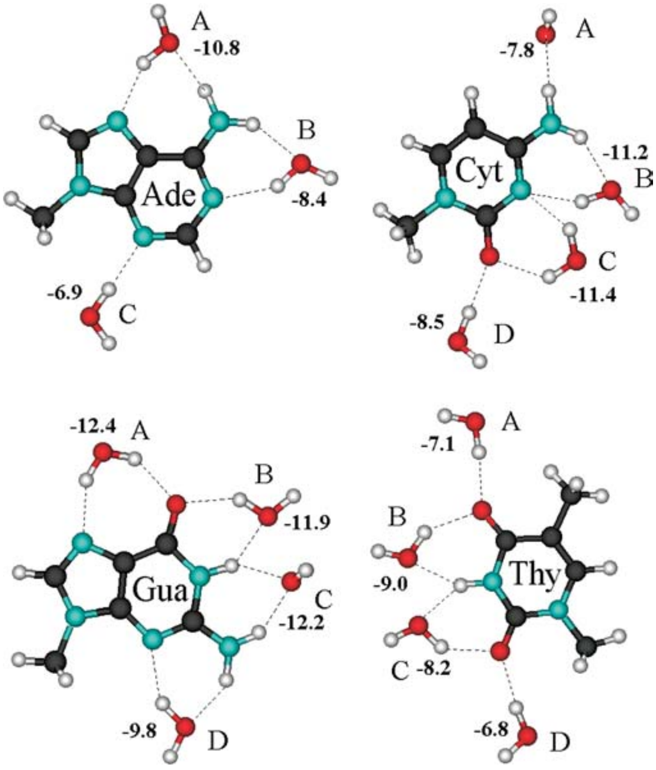

Fig. 1. Mutual positions of DNA bases and water molecules in local energy minima of single base–single water interactions. The values of the water–base interaction energy (kcal/mol) are shown for each minimum. Adenine (*Ade*), cytosine (Cyt), guanine (*Gua*), thymine (*Thy*)

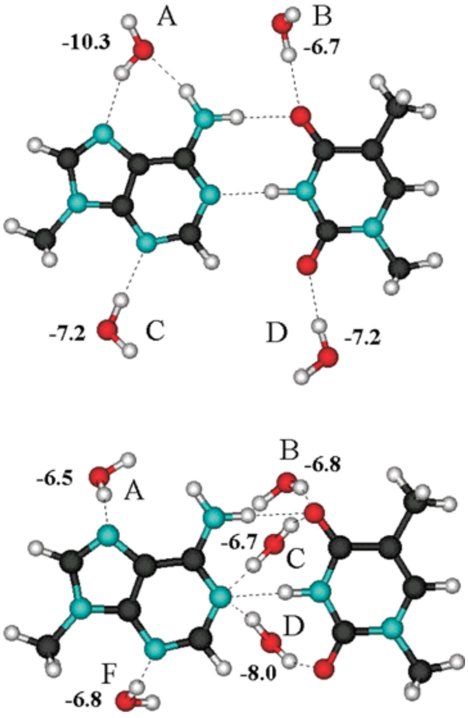

Fig. 2. Positions of water molecules in local energy minima of interactions of a single water molecule with an Ade:Thy base pair. The values of the water–base interaction energy (kcal/mol) are shown for each minimum. Positions are shown corresponding to water oxygen atoms located in (*top*) and above (*bottom*) the base pair plane

Table 3. Comparison of the calculated energy values, *E*, for global minima of single water–single base interactions with the experimental association enthalpies [15]

	E (kcal/mol)	ΔH^{exp} (kcal/mol))
Adenine	−10.8	−10.6 ± 1.0
Guanine	−12.4	−14.1 ± 1.0
Cytosine	−11.4	−11.4 ± 0.8
Thymine	−9.0	−10.4 ± 0.9

A comparison of calculated values of the water–base interaction energy in global minima with experimental values of the association enthalpy [15] is presented in Table 3. This table demonstrates good agreement between the two sets of data for adenine and cytosine; the agreement for guanine and thymine is somewhat worse, but better agreement for these data would result in disagreement between the calculated hydration energy and the experimental enthalpies of hydration (Sect. 5). The interaction energies in the minima with a single linear hydrogen bond are lower in absolute value. Minima with single hydrogen bonds may be formed when the base participates in hydrogen bonding by both a hydrogen donor (minimum A for cytosine) and a hydrogen acceptor groups (minimum C for adenine, minimum D for cytosine, minima A and D for thymine). Minima with two hydrogen bonds may be of three types, namely, when the base participates in hydrogen bonds using two acceptor groups (minimum C for cytosine and A for guanine), by one donor and one acceptor group (most of the minima), and by two donor groups (minimum C for guanine).

In addition to these minima, there are a few less profound local minima with water oxygen above (or below) the base plane (numerical data not shown).

Studies of single water–single base interactions enable the sites of preferential hydration of bases to be revealed. Some hydration sites of individual bases are available for interaction with water in Watson–Crick base pairs and there are local minima of single water–base pair interaction energies, close to those for individual bases. For interactions of single water molecules with base pairs, there are also energy minima, corresponding to formation of hydrogen bonds with both bases. Such minima are presented in Figs. 2 and 3 for the adenine:thymine and guanine:cytosine base pairs, respectively.

Interaction of bases with a few water molecules

The deepest minima of single water–single base interactions correspond to single-water bridge formation between two hydrophilic atoms of bases or base pairs. The energies of the global minima have been compared with experimental data, but the mutual positions of base

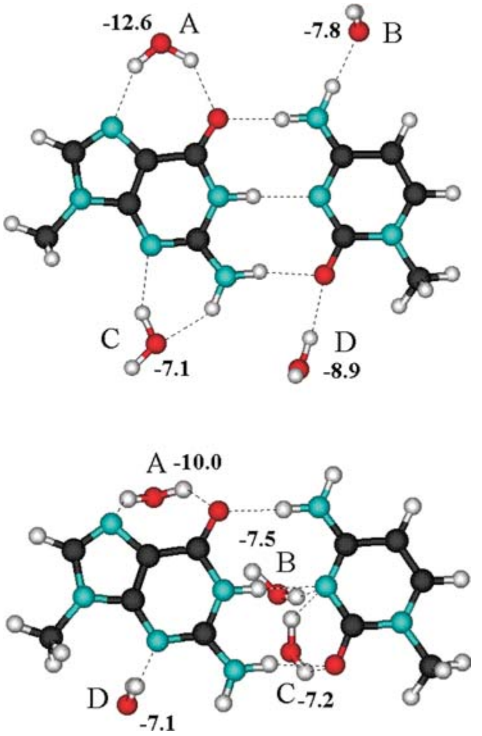

Fig. 3. Positions of water molecules in local energy minima of interactions of a single water molecule with a Gua:Cyt base pair. The values of the water–base interaction energy (kcal/mol) are shown for each minimum. Positions are shown corresponding to water oxygen atoms located in (*top*) and above (*bottom*) the base pair plane

and water cannot be compared directly with experimental data. Nevertheless, these positions are nearly the same for different potential functions and for accurate quantum mechanics studies [16].

Recently, quantum mechanics ab initio studies have been published for interactions of a few water molecules with pyrimidine bases [17, 18]. The data can be compared with our computations. Some water molecules in such complexes form both water–base and water–water hydrogen bonds. Other molecules can form water–water hydrogen bonds only; thus three-water and n-water bridges can be studied and compared with those in systems with many water molecules (considered in the next part of this paper). We started the systematic study of local minima for systems containing a base and n water molecules.

The results for guanine interactions with n water molecules ($n = 2$–7) are presented here (Figs. 4, 5). These results demonstrate that water–water hydrogen-bonds can be formed in deep minima for all the systems, starting from those containing two water molecules. Starting from four water molecules, some deep minima involve water molecules which do not form hydrogen bonds with the base, but all such water molecules (the calculations for $n \leq 7$) in deep minima form hydrogen bonds with other water molecules hydrogen-bonded to the base.

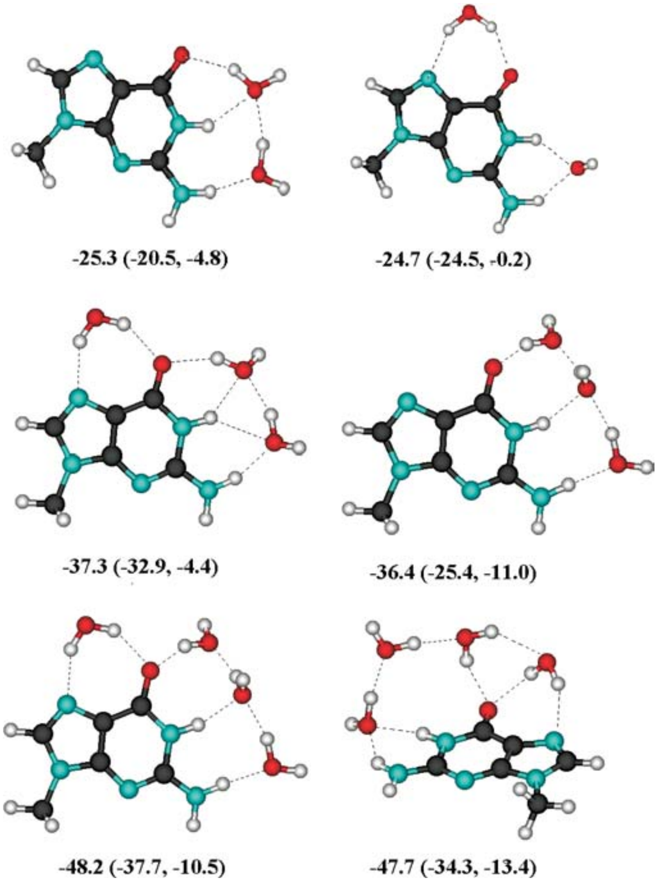

Fig. 4. Positions of water molecules in local energy minima of interactions of two (*top*), three (*middle*) and four (*bottom*) water molecule with Gua. The total interaction energies and water-base and base–base contributions are given in *parentheses* (kcal/mol). The base plane in *bottom right* structure is somewhat inclined for clarity

Hydration patterns of base pairs

Using refined potential functions, Monte Carlo simulations were performed for each of the DNA bases and for various base pairs with hydrogen bonds. We will not discuss here the hydration characteristics of individual bases. They do not differ much from those obtained with previous versions of the potentials [9, 10, 11]. The main distinctive feature of new potential functions is the better agreement of calculated hydration energies with experimental values of hydration enthalpies (Table 4).

Although the calculated hydration energies for guanine and cytosine differ from experimental values (see Ref. [11] for notes about them), the differences are the least compared to calculations with other potential functions. The results for base pairs show that the hydration energy of each pair is lower in absolute value than the sum of the hydration energies of the bases of a pair. This is because part of the space around hydrogen-bonded hydrophilic atoms becomes inaccessible on base pair formation. The difference between the hydration energy of a pair and the sum of the hydration energies of

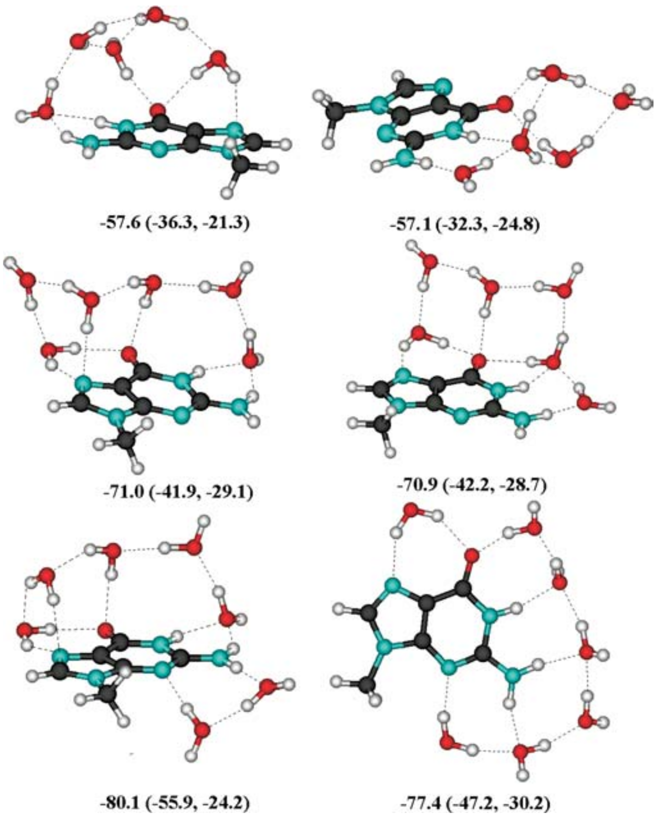

Fig. 5. Positions of water molecules in local energy minima of Gua interactions with five (*top*), six (*middle*) and seven (*bottom*) water molecules. The total interaction energies and water–base and base–base contributions are given in parentheses (kcal/mol). The base planes in some structures are somewhat inclined for clarity

Table 4. Comparison of the calculated hydration energies of DNA bases with experimental enthalpies of hydration. All the energy-values are expressed in kilo calories per mole.E_T is the total average energy of the system,containing the base and 400 water molecules, E_{WB} and E_{WW} are water–base and water–water contributions, ΔE is the calculated hydration energy, $\Delta E = E_T - E_W$, where $E_W = 3{,}781.2$, is the energy of a system consisting of 400 water molecules (without a base molecule), ΔH^{exp} is the experimentally estimated enthalpy of hydration obtained as the difference between the heat of sublimation and the heat of dissolution [19, 20] and H is the mean number of water–base hydrogen bonds

Base	E_T	E_{WB}	E_{WW}	ΔE	ΔH^{exp}	H
Adenine	−3805.6	−45.1	−3760.5	−24.4	−23.0	6.1
Guanine	−3819.7	−71.2	−3748.5	−38.5	−36.5	8.7
Cytosine	−3815.5	−61.0	−3754.5	−34.3	−29.5	6.4
Thymine	−3804.5	−42.5	−3762.1	−23.3	−23.4	5.3

the two bases of the pair is greater in absolute value than the energy of the base–base interactions in this pair. Thus, formation of all the base pairs with hydrogen bonds is unfavorable in aqueous solution, and such pairs practically should not be formed in accordance with the experimental data.

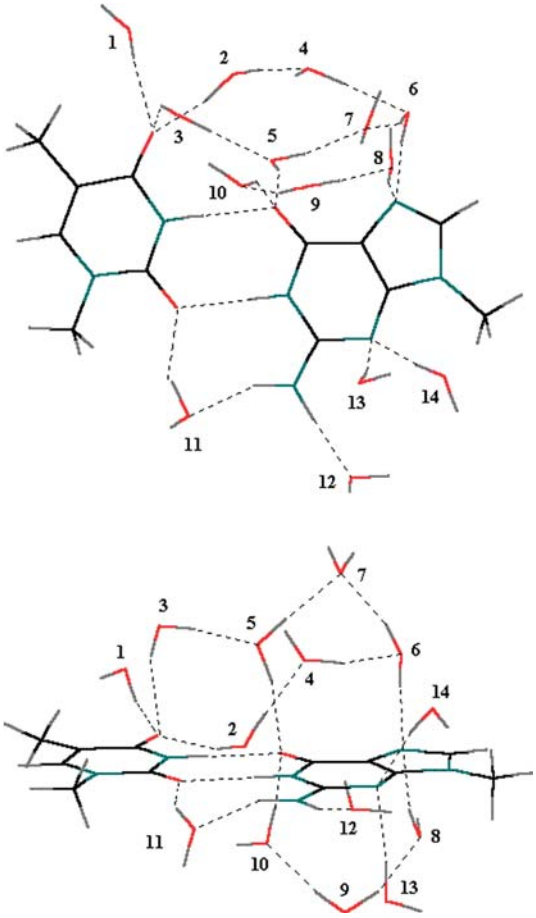

Fig. 6. Arrangement of water molecules around the Gua:Thy mispair. Water molecules forming hydrogen bonds with the bases and those forming two-water and three-water bridges between two hydrophilic atoms of the bases are shown. Two projections are displayed for clarity

In addition to the energy characteristics of base pair hydration, we considered patterns of hydration shells of various base pairs. The most interesting feature of the hydration patterns of DNA fragments is a set of water bridges forming between hydrophilic atoms of the bases. We calculated the probabilities of such bridges at room temperature. It appears that each pair (and more complex DNA fragments) can be characterized by a set of single-water, two-water and three-water bridges. We also considered the so-called frozen structures, i.e. water structures around base pairs corresponding to local minima of interaction energies in the system, containing the DNA base pair and 400 water molecules. An example of such frozen structures is shown in Fig. 6 for the guanine:thymine wobble pair.

Water bridges between the bases, which stabilize this pair, can be seen. Some of them, namely, a single-water bridge (molecule 11) and two-water bridge (molecules 4, 9), are identical to those observed in an X-ray study of an oligonucleotide duplex with this mispair [5].

Another interesting characteristic of the DNA fragment is the distribution of water molecules around various atomic groups. We calculated the probability of the location of water oxygen in various elementary cells of a space around base pairs. It appears that this probability in some positions near to hydrophilic atoms is

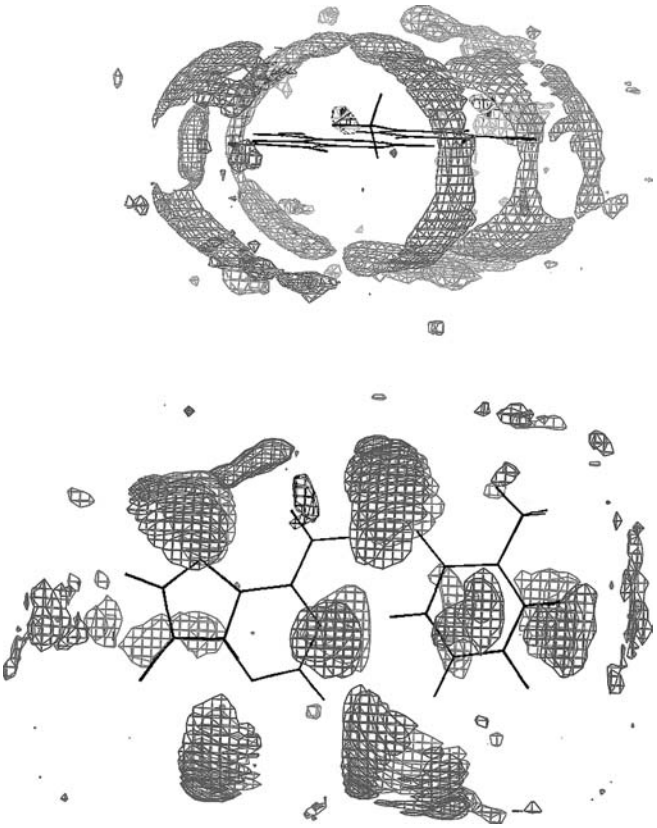

Fig. 7. Distribution of water molecules around an Ade:Thy base pair. Positions of water oxygens are shown when the probabilities of these locations are 2.5 times or higher than in pure water. The *darker contours* correspond to more distant positions from the observer. Two projections are shown for clarity

several times higher than in bulk water. The regions of higher probabilities of the water location occur specifically around each base pair. An example of the distribution of the regions with the probability of water molecule locations 2.5 times and higher than in bulk water around an adenine:thymine pair is shown in Fig. 7. Besides regions of "high water density" around hydrophilic atoms, corresponding to water molecules hydrogen-bonded to them, such regions exist at positions which can be referred to molecules forming bridges between hydrogen-bonded water molecules. Other, less extended, regions can be observed near hydrophobic groups of bases.

Conclusions

1. Refined potential functions for molecular mechanics simulation of DNA fragment hydration enable us to reproduce satisfactorily a few sets of experimental data and to reveal interesting features of the hydration shells of base pairs.
2. Three-dimensional organization of water molecules around some mispairs contributes to their stability, and hence to an increase in the probability of these mispair formations during DNA biosynthesis. This contribution can be quantitatively characterized by the probabilities of water bridging between atoms of the two bases.
3. The distribution of water molecules around bases and base pairs is essentially nonhomogeneous. The regions of high water density exist around hydrophilic atoms and in positions corresponding to water bridges between such atoms.

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