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ARTICLE

C–H/O interactions of nucleic bases with water molecule. Crystallographic and quantum chemical study.

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The C–H/O interactions of nucleic bases with a water molecule were studied by analyzing data in the Cambridge Structural Database (CSD) and by *ab initio* calculations. The analysis of the C–H/O interactions in the crystal structures from the CSD indicates that nucleic bases–water C–H/O interactions do not show preference for linear contacts. The results of the *ab initio* calculations are in accord with the CSD data and show that the bifurcated C–H/N–H interactions are stronger than linear interactions for all nucleic bases. The bifurcated C–H/N–H interactions are also stronger than the bifurcated C–H/C–H interactions. The strongest interaction is the bifurcated C6–H/N1–H interaction of uracil with energy of -5.46 kcal/mol calculated at the MP2/cc-pVTZ level. All linear C–H/O interactions, except one with adenine, are stronger than -2.0 kcal/mol. The strongest linear interaction is with uracil, -3.59 kcal/mol. The calculated electrostatic potential maps for nucleic base molecules can explain the results we obtained for interaction energies. The results show that C–H/O interactions of nucleic bases with a water molecule are substantially stronger than C–H/O interactions of benzene (-1.28 kcal/mol) and pyridine (-1.97 kcal/mol). The investigation of C–H/O interactions of nucleic bases with water could shed light on the intermolecular interactions of DNA or RNA bases with other molecules.

Introduction

Hydrogen-bonding interactions play a unique role in chemical and biochemical systems.¹ Classical hydrogen bonds represent fundamental stabilizing forces in biomolecules, such as proteins and nucleic acids.² Traditionally, the carbon was not considered as a typical hydrogen bond donor because of its relatively low electronegativity compared with oxygen and nitrogen atoms. However, studies have shown that even carbon atoms are able to form weak hydrogen bonds.^{1,3} Moreover, carbon atoms, with an increased polarization due to the adjacent atoms, can participate in hydrogen bonds as strong as those formed by conventional donors.^{4,5} The C–H/O interactions are now accepted as genuine hydrogen bonds^{6–9} which play a significant role in the stability of biomolecules, biomolecular complexes and crystal structures.^{10–13}

The importance of C–H/O interactions in proteins is evident from the fact that 20–25% of the total number of hydrogen bonds in proteins are C–H/O hydrogen bonds.^{14–20} They are important for β -sheet structures, in interactions with ligands, in stability and specificity of trans-membrane helices, in enzymatic mechanisms.^{14–16,21–23}

The C–H/O interaction energies can vary from very weak, -0.3 kcal/mol, to very strong, over -4 kcal/mol.¹⁴ Recent studies

have revealed a strong C–H/O interaction between fucose and water (-2.55 kcal/mol)¹³ and a very strong interaction in caffeine–theophylline complexes (-4.64 kcal/mol).²⁴ Quantum chemical calculations showed that charged assisted C–H/O interactions can be quite strong, with binding energies up to 20 kcal/mol.²⁵ The interaction energy of C–H/O interactions of aromatic C–H donors depends on the aromatic ring substituents and on the acceptor.^{26–28}

In our previous studies C–H/O interactions of aromatic C–H donors have been investigated.^{29–32} It is interesting to notice that linear C–H/O interactions of aromatic C–H groups are not energetically favored.^{29,30} The studies indicate that aromatic C–H donors do not show strong preference for linear contacts and that the preference depends on the type of the atom or group in *ortho*-position to the interacting C–H group. The acceptor oxygen atom has the possibility for simultaneous C–H/O interactions with atoms or groups in *ortho*-position to the interacting C–H group. The calculated interaction energy for the linear C–H/O interaction between water and benzene is -1.28 kcal/mol, while the interaction energy for the bifurcated C–H/O interaction is -1.38 kcal/mol.²⁹ The interaction energies for the linear C–H/O interactions between water and pyridine *ortho*, *meta*, and *para* C–H groups are -1.24, -1.94 and

-1.97 kcal/mol, whereas the energies for the bifurcated *ortho-meta* and *meta-para* interactions are -1.96 and -2.16 kcal/mol, respectively.³⁰ The results on pyridine show that the simultaneous hydrogen bond with pyridine N atom strengthens the C–H/O interaction by about 20%. The calculations have also showed that two water/benzene C–H/O interactions weaken each other, while O–H/ π and C–H/O strengthen each other.³¹

In the past decades, a large number of quantum chemical studies of noncovalent interactions between constituents of DNA and RNA have been performed.^{33–43} The interaction energies between Watson-Crick (W-C) gas-phase-optimized structures of nucleic bases have been calculated. The main attractive forces between nucleic bases are classical hydrogen bonds, however, in the adenine-thymine base pair there is a possibility for an additional C–H/O interaction. A theoretical study reported evidence of enhanced stability in adenine-thymine base pair due to the C–H/O interaction.⁴¹ The C–H/O interaction in adenine-thymine base pair has been confirmed and reconfirmed to be van der Waals interaction.^{42,43}

The C–H/O interactions play a role in interactions of nucleic acids. The C–H/O interactions are involved in the interaction of nucleic acids with proteins;^{44,45} they stabilize the intercalated cytosine-rich DNA quadruplex structure.⁴⁶ The C–H/O interactions in the major groove, together with C–H/N interactions, are responsible for the specific recognition between nucleic acid helices during recombination.⁴⁷ In the crystal structure of RNA hexamer U·U base pair is stabilized by a non-conventional C–H/O bond in addition to a conventional N–H/O hydrogen bond.⁶ Theoretical *ab initio* studies on model systems involving nucleic bases and single water molecules, as well as water clusters, indicate the importance of C–H/O interactions.^{48–50}

In this work, we present the results on C–H/O interactions of a water molecule with adenine, guanine, cytosine, thymine and uracil. The results are based on the analysis of data in the Cambridge Structural Database (CSD) and on quantum chemical calculations. To the best of our knowledge, this is the first CSD study on C–H/O interactions between nucleic bases and water.

Methodology

Data screening

The statistical study is based on the crystal structures archived in the Cambridge Structural Database (CSD) (November 2011 release, version 5.33). Crystal structures involving nucleic base fragments and water molecules were screened for intermolecular contacts (Fig. 1). The CSD search program ConQuest 1.10⁵¹ was used to retrieve structures satisfying the following criteria: a) the crystallographic R factor < 10% b) the error-free coordinates according to the criteria used in the CSD c) the H-atom positions were normalized using the CSD default bond lengths d) no polymer structure e) no powder structures f) not disordered structures g) 3D coordinates determined.

The geometric parameters used for analysis are shown in Fig. 1. The distance between an interacting hydrogen atom of nucleic base and water oxygen atom is *d* (Fig. 1). Angle α is the C–H–O angle.

The structure was considered a hit if the distance between a hydrogen atom of C–H group from nucleic base and an oxygen atom from water was less than 2.9 Å and angle $\alpha \geq 110^\circ$ (Fig. 1).

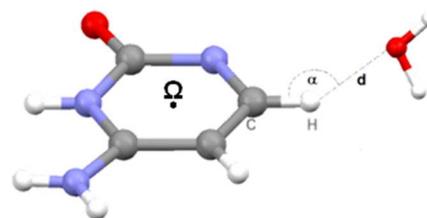


Fig. 1 The geometric parameters and atom labels used for the description of C–H/O interactions.

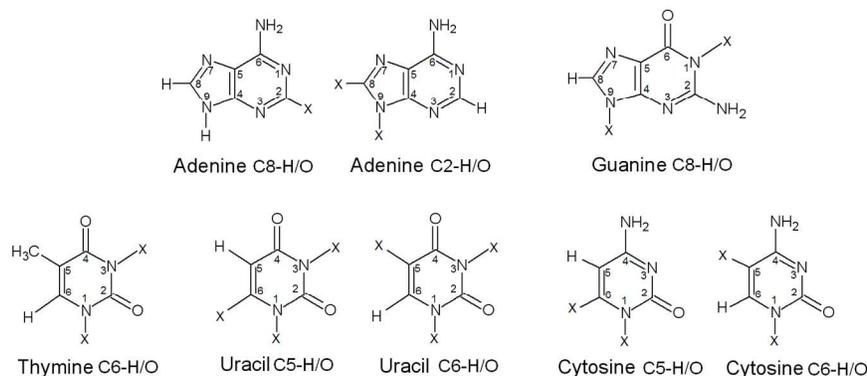


Fig. 2 Nucleic bases fragments used for CSD search. Positions of substituents attached to aromatic rings were labelled with X (X = H or R). H atoms were labelled according to the number of the atom they were attached to.

Ab initio calculations

Ab initio calculations were performed on model systems involving a nucleic base and a water molecule. The geometries of isolated molecules (adenine, guanine, thymine, uracil, cytosine and water), were optimized using the 6-31G** basis set and the B3LYP method by Gaussian09 series of programs.⁵² These geometries were used for the calculation of C–H/O and N–H/O interaction energies between nucleic bases and a water molecule. The monomer geometries were kept rigid while the distance d (Fig. 1) was changed.

Interaction energies between the nucleic base molecule and water were calculated using the cc-pVTZ basis set and the Møller–Plesset second-order perturbation method (MP2), since in our previous work on benzene/water C–H/O interactions, it was shown that the MP2/cc-pVTZ method is in very good agreement with the CCSD(T)(limit) method. In our previous work the interaction energy of the C–H/O bifurcated interaction between water and benzene was estimated at the CCSD(T) level at the basis set limit, $E_{\text{CCSD(T)}(\text{limit})}$, using Helgaker method of extrapolation.⁵³ The obtained energy was $\Delta E_{\text{CCSD(T)}(\text{limit})} = -1.41$ kcal/mol. The interaction energy calculated at the MP2/cc-pVTZ level was -1.38 kcal/mol, quite close to $E_{\text{CCSD(T)}(\text{limit})}$ value. The basis set superposition error (BSSE) was calculated using the standard Boys–Bernardi counterpoise procedure.⁵⁴

In all calculations on nucleic base/water C–H/O interactions, the water molecule was orthogonal to the plane of the aromatic ring, since it was shown that water/benzene C–H/O interactions of an orthogonal water molecule are stronger than C–H/O interactions of a coplanar water molecule.²⁹ In the bifurcated geometries the oxygen atoms were on the bisector of the C–O–C angle or C–O–N of the aromatic ring of nucleic base molecule. The distance d (Fig. 1) was systematically varied while the monomer geometries were kept rigid.

From wavefunction files electrostatic potential maps were calculated and visualized using the Wavefunction Analysis Program (WFA-SAS).^{55,56}

Results and discussion

Analyses of the data from crystal structures

By searching the Cambridge Structural Database (CSD) with the criteria described in Methodology section, 69 contacts of non-substituted nucleic bases were obtained. Since the number of interactions with non-substituted nucleic bases was quite small, we considered interactions involving non-substituted and substituted nucleic bases (Fig. 2). We obtained 255 contacts with C–H/O interactions between nucleic bases C–H groups and water molecules (Table 1). Geometries of these interactions were analyzed. Since number of interactions of thymine molecule was small, the interactions of this nucleic base were not considered in further analysis.

Most of the nucleic bases found in crystal structures are neutral. In cases where nucleic bases are positively charged (nitrogen atoms are protonated), they form hydrogen bonds between N–H groups and counter anions. In that way, N–H groups are not available for interactions with water molecules and water molecules form C–H/O interaction. (Fig. S1)

In order to study the preference for linear geometries in C–H/O interactions of nucleic bases C–H groups, the distribution of C–H–O angle, angle α , (Fig. 1) was analyzed.

Table 1 Number of structures and contacts with C–H/O interactions between substituted and non-substituted nucleic bases C–H groups and water molecules.

Nucleic base	Number of structures	Number of contacts
Adenine C8–H	23	24
Adenine C2–H	15	18
Guanine C8–H	16	22
Thymine C6–H	9	12
Uracil C5–H	45	51
Uracil C6–H	29	37
Cytosine C5–H	35	42
Cytosine C6–H	43	49
Total	215	255

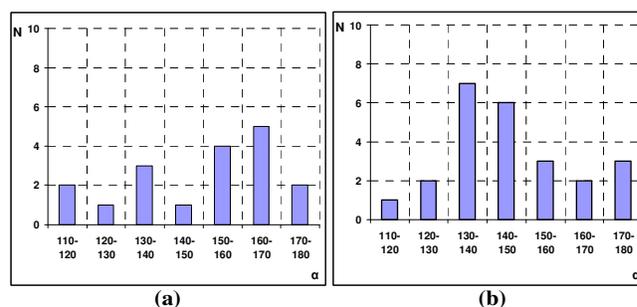


Fig. 3 Distributions of angle α for C–H/O interactions of water molecule with H2 atom of adenine (a) and H8 atom of adenine (b).

The distributions of angle α for C–H/O interactions of two hydrogen atoms of adenine are shown in Fig. 3. The most pronounced peak for the distribution of angle α for H8 atom is between 130° and 140° , while C–H/O interactions with H2 atom of adenine have a strong tendency to be linear with the peak between 160° – 170° . As mentioned before, in the search we also considered adenine fragments with substituents at position X9, adjacent to H8 atom. The data indicate that the hydrogen atom and substituent in adjacent position influence the linearity of C–H/O interaction of H8, because of the possibility for simultaneous interaction of the water molecule. The H2 atom does not have adjacent hydrogen or substituent and has a greater tendency to be linear C–H/O interactions (Fig. 3). The example of the structure with the substituted adenine is shown in Fig. 8a.

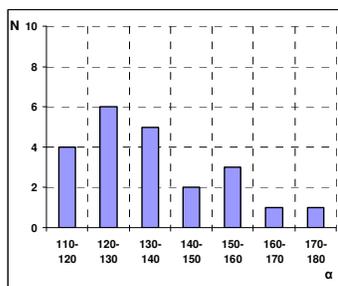


Fig. 4 Distributions of angle α for C–H/O interactions of water molecule with H8 atom of guanine.

For guanine, the distribution of angle α for C–H/O interactions with the interacting hydrogen atom gives peak between 120–130° (Fig. 4). The interacting hydrogen atom of guanine, like H8 atom of adenine, has H9 or substituent on the neighboring N9 atom, which influences geometry of C–H/O interactions. The example of the structure with the substituted guanine is shown in Fig. 7b.

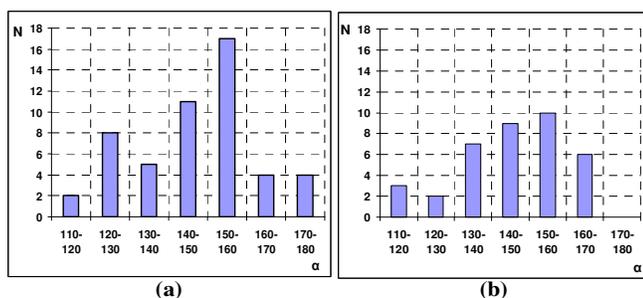


Fig. 5 Distributions of angle α for C–H/O interactions of water molecule with H5 atom (a) and H6 atom of uracil (b).

The distributions of angle α for both hydrogen atoms of uracil, H5 and H6 show peaks between 150 and 160° (Fig. 5). In the uracil atom H6 has two neighboring H atoms or substituents which can also interact with water, while H5 atom has one neighboring H atom or substituent and one neighboring oxygen atom from carbonyl group.

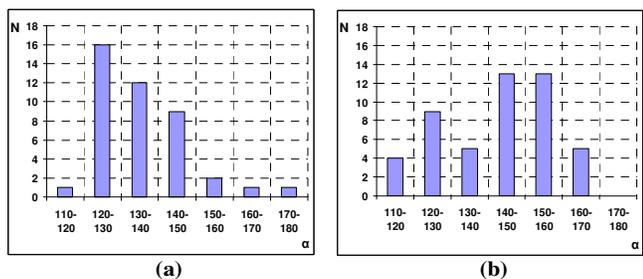


Fig. 6 Distributions of angle α for C–H/O interactions of C–H fragment with water molecule for H5 atom of cytosine (a) and H6 atom of cytosine (b).

The distributions of angle α for C–H/O interactions of two hydrogens of cytosine (Fig. 6) show that the distribution for H5 atom has peak between 120 and 130°, while for H6 atom the majority of C–H/O interactions have angle α values between 140 and 160°. Similar as in the case of uracil, H6 atom of

cytosine has two neighboring H atoms or substituents that can also interact with oxygen atom from water and the distributions are very similar (Fig. 5b and 6b). Cytosine H5 atom has one neighboring H atom (H6) or substituent. Unlike uracil H5 atom, which has neighboring carbonyl group, H5 atom of cytosine has neighboring NH₂ group. It causes the difference in angle α for H5 atom of uracil and cytosine (Fig. 5a and 6a).

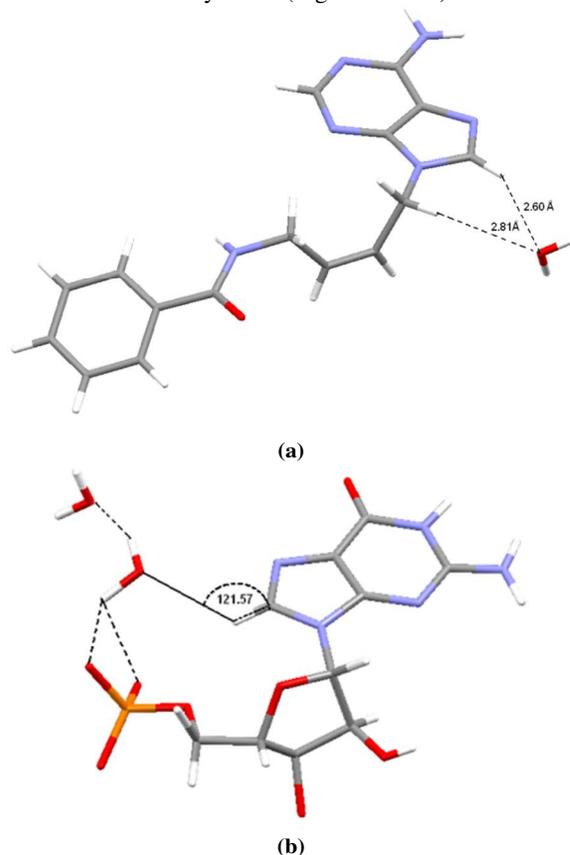


Fig. 7 Example of C–H/O interactions in crystal structures OJUTET⁵⁷ (a) and GUANPH⁵⁸ (b). In crystal structure OJUTET water molecule forms C–H/O interaction with C–H fragment of adenine, and with hydrogen atom of substituent in *ortho*-position to interacting hydrogen atom. In crystal structure GUANPH water molecule forms C–H/O interaction with C–H fragment of guanine, with substituent on neighboring N atom, and with other water molecule.

Calculations

To study preference for linear C–H/O interactions between nucleic base molecules and water, calculations of interaction energies for linear interactions and bifurcated interactions (not linear) were performed.

To estimate the interaction energies calculations were performed on the model systems: adenine-water, guanine-water, cytosine-water and uracil-water. Two different geometries of C–H/O interactions were considered: linear and bifurcated (where possible). We considered two types of bifurcated interactions, C–H/C–H and C–H/N–H. The calculated interaction energies for linear and bifurcated interactions at MP2/cc-pVTZ level are shown in Table 2.

Table 2 Calculated ^a interaction energies and distances of C–H/O interactions in adenine-water, guanine-water, cytosine-water, uracil-water and thymine-water model systems.

Model system	Geometry	Distance (Å)	ΔE (kcal/mol)
Adenine-water	Linear C8–H	2.3	-2.67
	Linear C2–H	2.5	-0.60
	Bifurcated (C8–H, N9–H)	2.5	-4.71
Guanine-water	Linear C8–H	2.3	-2.38
	Bifurcated (C8–H, N9–H)	2.6	-4.31
Thymine-water	Linear C6–H	2.3	-3.47
	Bifurcated (C6–H, N1–H)	2.5	-5.24
Uracil-water	Linear C5–H	2.3	-1.95
	Linear C6–H	2.3	-3.59
	Bifurcated (C5–H, C6–H)	2.7	-3.00
	Bifurcated (C6–H, N1–H)	2.5	-5.46
Cytosine-water	Linear C5–H	2.4	-2.92
	Linear C6–H	2.3	-3.09
	Bifurcated (C5–H, C6–H)	2.7	-2.78
	Bifurcated (C5–H, C6–NH ₂)	2.4	-4.81
	Bifurcated (C6–H, N1–H)	2.5	-4.61

^a MP2/cc-pVTZ level

The data show that the bifurcated C–H/N–H interactions are the strongest for all nucleic base – water model systems; they are stronger than bifurcated C–H/C–H interactions and linear interactions. The strongest is bifurcated C6–H/N1–H interaction of uracil – water model system with the energy of -5.46 kcal/mol. The other bifurcated C–H/N–H interactions are also quite strong; in all cases the energies are stronger than -4.0 kcal/mol.

Bifurcated C–H/C–H interactions exist only in cytosine – water and uracil – water model systems (Table 2). It is interesting to note that these bifurcated C–H/C–H interactions are weaker than linear C–H/O interactions between the same nucleic base and water molecule. The energy of bifurcated C5–H/C6–H interaction between uracil and water is -3.00 kcal/mol, while energies of linear interactions are -1.95 and -3.59 kcal/mol; the energy of bifurcated C5–H/C6–H interaction between cytosine and water is -2.78 kcal/mol, while energies of linear interactions are -2.92 and -3.09 kcal/mol. This is in contrast with previous results for benzene-water and pyridine-water systems. Namely, the bifurcated C–H/C–H interaction in benzene – water model system (-1.38 kcal/mol) was stronger than linear (-1.28 kcal/mol). It is similar to pyridine – water model system, where bifurcated C–H/C–H interaction between *meta* and *para* C–H groups of pyridine (-2.16 kcal/mol) was stronger than linear interaction of C–H group in *para* position (-1.97 kcal/mol).^{29,30} It is worth noting that bifurcated C–H/C–H interactions of uracil – water and cytosine – water model systems, in spite of being weaker than linear interactions, are stronger (Table 2) than bifurcated C–H/O interactions of water with benzene and pyridine (-1.38 and -2.16 kcal/mol respectively).^{29,30}

All calculated linear C–H/O interactions in nucleic base – water model systems are stronger than -2.0 kcal/mol, with the exception of one adenine-water interaction of -0.60 kcal/mol. Some of the linear C–H/O

interactions are quite strong; the interactions of thymine and uracil with a water molecule are about -3.5 kcal/mol. Similar to bifurcated interactions, linear C–H/O interactions between nucleic bases and water are substantially stronger than previously calculated linear C–H/O interactions of benzene and pyridine with water. Namely, the calculated linear C–H/O interactions of benzene and pyridine with a water molecule are -1.28 and -1.97 kcal/mol, respectively.^{29,30} These data show that heteroatoms in nucleic base molecules could reduce the electron density of C–H bond, making it a good proton donor; thus a stronger C–H/O interaction could form.

To understand calculated energies of C–H/O interactions and the unexpected results which show linear interactions are stronger than bifurcated C–H/C–H interactions, we calculated electrostatic potential maps for nucleic base molecules (Fig. 8). The calculated electrostatic potentials are in accord with the calculated interaction energies. For example, the weakest interaction is the interaction between adenine C2–H fragment and water (Table 2). Electrostatic potential map shows that this region is the least positive of all interacting C–H fragments. Adenine and guanine have similar energies for linear C8–H/O interactions and for C8–H/N9–H bifurcated interactions (Table 2), and they have very similar electrostatic potentials in that region (Fig. 8). Also, stronger bifurcated C8–H/N9–H interactions in both molecules are a consequence of more positive potential between C8 and N9 atoms. The calculated electrostatic potential map for thymine molecule shows that the region between C6–H and N1–H fragments has more positive potential than the area around C6–H, which is in agreement with the calculated energies for linear and bifurcated interactions (-3.47 and -5.24 kcal/mol, respectively).

Table 3 Calculated^a interaction energies and distances of N–H/O interactions in adenine-water, guanine-water, cytosine-water, uracil-water and thymine-water model systems.

Model system	Interaction	Distance (Å)	ΔE (kcal/mol)
Adenine-water	N9–H/O	1.9	-6.21
Guanine-water	N9–H/O	1.9	-5.98
	N1–H/O	2.0	-5.55
	C2–NH ₂ /O	2.0	-6.05
Thymine-water	N3–H/O	2.0	-4.22
	N1–H/O	2.0	-5.84
Uracil-water	N3–H/O	2.0	-4.39
	N1–H/O	1.9	-6.06
Cytosine-water	N1–H/O	1.9	-4.71
	C4–NH ₂ /O	2.0	-5.45

^a MP2/cc-pVTZ level.

The electrostatic potential maps for cytosine and uracil show that the strongest interactions occur in the regions of molecules with the most positive potential. The weaker linear C–H/O interaction of uracil involves C5 hydrogen, which is situated in the part of molecule with the less positive potential, while stronger C–H/O interaction involves C6–H situated in the region with more positive potential (Fig. 8). The bifurcated interaction involving C5 and C6 hydrogen atoms is stronger than C5–H/O, and less strong than C6–H/O interaction (Table 2), in accord with the potential (Fig. 8).

For cytosine, C–H/C–H bifurcated interaction is weaker than both C–H/O linear interactions (Table 2), which is in accordance with smallest positive potential between C5–H and C6–H (Fig. 8).

As can be anticipated, electrostatic potentials are the most positive in N–H regions (Fig. 8), indicating strong hydrogen bonds with water molecule. The calculated energies of N–H/O bonds presented in Table 3 show that N–H/O bonds are indeed the strongest hydrogen bonds of nucleic bases. However, it is interesting to observe that some of the bifurcated C–H/N–H interactions (Table 2) are stronger than some N–H/O interactions (Table 3).

Although nucleic base-water N–H/O interactions are very strong, N–H groups in DNA and RNA are involved in other interactions. Namely, hydrogen atoms of C6–NH₂ group of adenine, N1–H and C2–NH₂ groups of guanine, N3–H group of thymine, N3–H group of uracil, and C4–NH₂ group of cytosine are involved in hydrogen bonds between bases, forming base pairs. Moreover, hydrogen atoms N9–H of adenine and guanine and N1–H of thymine, uracil, and cytosine are substituted with sugars. Hence, in recognition between DNA and RNA with proteins (and other molecules), C–H groups play very important role.

The results of the calculations are in agreement with the observed angle α in the crystal structures, and with explanation based on possibility for bifurcated interactions. Namely, we assumed that smaller tendency for linear interaction is a

consequence of possibility for bifurcated interaction. The calculations supported that assumption. Namely, all C–H hydrogen atoms except H2 of adenine form bifurcated interactions that are stronger than linear C–H/O bonds. It is in agreement with the observed values of angle α in crystal structures (Figs. 3-6), which is significantly less than 180° indicating that interactions are not linear. The most linear C–H–O angle was observed for H2 of adenine, where bifurcated interactions are not possible (Fig. 2, Table 2).

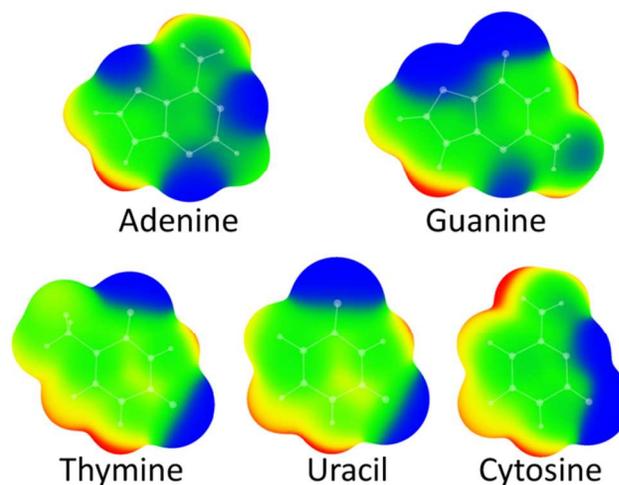


Fig. 8 Computed MP2/cc-pVTZ electrostatic potential on the 0.001 au surface of: a) adenine b) guanine c) thymine d) uracil e) cytosine. Color ranges, in kcal/mol, are: red, greater than 31.31; yellow, from 10.17 to 31.31; green, from -10.92 to 10.17; blue, more negative than -10.92. In all nucleic bases hydrogen atoms from C–H fragments have positive potentials.

Conclusions

The analysis of the distribution of C–H–O angle in the crystal structures from the Cambridge Structural Database and *ab initio* calculation on model systems are in agreement, indicating no preference for linear C–H/O interactions between nucleic bases and water.

The calculated energies show that heteroatoms in nucleic base molecules have a strong influence, enhancing substantially C–H/O interactions. Namely, the heteroatoms in nucleic base molecules reduce the electron density of C–H bond, making it a good proton donor. As a consequence, the C–H/O interactions between nucleic bases and water are substantially stronger than previously calculated C–H/O interactions of benzene (-1.28 kcal/mol) and pyridine (-1.97 kcal/mol) with water.

The investigation of C–H/O interactions of nucleic bases with water could shed light on the intermolecular interactions of DNA or RNA bases with other molecules.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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C–H/O interactions of nucleic bases with water molecule. Crystallographic and quantum chemical study.

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The C–H/O interactions of nucleic bases are substantially stronger than C–H/O interactions of benzene and pyridine. These results can be very important for molecular recognition of DNA and RNA.

