Does the Hydrated Cytosine Molecule Retain the Canonical Structure? A DFT Study

Oleg V. Shishkin,*,†,‡ Leonid Gorb,‡ and Jerzy Leszczynski‡

Department of Alkali Halide Crystals, Institute for Single Crystals, National Academy of Science of Ukraine, 60 Lenina Ave., Kharkiv 310001, Ukraine, and Computational Center for Molecular Modeling Structure and Interactions, Department of Chemistry, Jackson State University, P.O. Box 17910, 1325 Lynch Street, Jackson, Mississippi 39217

Received: September 1, 1999; In Final Form: February 8, 2000

The molecular geometry of complex of cytosine with 14 water molecules was calculated within the density functional theory using the B3LYP functional. The standard 6-31G(d) basis set has been employed. It was found that the interaction with water molecules forming a locked chain around cytosine results in a significant change of its gas-phase geometry. The structure of the hydrated nucleobase cannot be described by canonical chemical formula, and it is best approximated as a superposition of the oxoamino and zwitterionic hydroxoimino resonance structures. The unique features of the interaction of water with cytosine are also revealed: the formation of three hydrogen bonds with the participation of the oxygen atom of the carbonyl group and the presence of weak C—H···O hydrogen bonds between the water molecules and the hydrophobic part of cytosine.

Introduction

The effects of hydration are known to be vital in DNA and RNA structure and function. Experiments involving sedimentation equilibrium studies,[1] isopiestic measurements,[2] and gravimetric,[3] X-ray diffraction of fiber, infrared,[4] and NMR spectroscopic investigations[5] led to the conclusion that DNA is heavily hydrated. So, it is not surprising that the interaction of nucleic acid bases with water molecules plays a special role in determining the three-dimensional structure of this type of biopolymers.[6] Although the significant efforts of modern experimental techniques are devoted to the investigation of DNA structure and function, in many cases the experiments are still unable to provide direct evidence for the investigated phenomena. Therefore, computational methods are useful and powerful tools which are able to reveal new data especially concerning the detailed mechanism of intermolecular interactions within DNA and its constituents.

The hydration of nucleobases was the subject of numerous theoretical studies[7−9] using various methods: molecular dynamics, Monte Carlo, and quantum-chemical approaches within the continual model of the solvent. These calculations allow to estimate the free energy of solvation, water molecules binding sites, etc. It was also assumed that the molecular structure of DNA bases does not change considerably due to the effects of hydration.

However, recent theoretical studies, which have been performed in the framework of supermolecular approximation allowing us to take into account the interaction between solvent and solute molecules completely at the quantum-mechanical level, lead to controversial results. The calculations of the hydrated complexes of uracil,[10] thymine,[8] cytosine,[8,11] guanine,[12] and adenine[13] performed at the HF and MP2 levels theory give at least two indications that the geometrical parameters of DNA bases could be extremely sensitive to the direct influence of water molecules. First, the elongation of the C═O bonds of guanine up to 0.02 Å during the formation of mono- and dihydrated complexes[14] was found. Second, it has been revealed[11−14] that the geometry of the amino group in cytosine, guanine, and adenine is very sensitive to the interaction with water molecules. The same conclusion has been obtained for the investigation of adenine−uracil, isocytosine−cytosine, and guanine−cytosine base pairs interacting with several water molecules.[15] We also would like to refer to the paper[8] where the geometry of the cytosine·$5H_2O$ complex has been calculated at the Hartree−Fock level. Unfortunately, the influence of water molecules on the geometrical parameters of cytosine has not been discussed there.

The long-term goal of our project is to perform a comprehensive investigation of the stepwise interaction of water molecules with the DNA bases in the framework of supermolecular approximation. For these purposes we have analyzed in part the geometrical and thermodynamic parameters of mono-, di-, and polyhydrated complexes of DNA bases and base pairs.[11−15] A particular issue which we would like to reveal in this paper is how significant are the changes in the geometry and electron density distribution of the cytosine when it is surrounded by water molecules forming a chain around it. Therefore, we used the "static" approach for modeling the hydrated cytosine. Only pure quantum-mechanical optimization of polyhydrated nucleobase allows to analyze reliably possible changes of their molecular structures and electron density distribution. A particular issue which we would like to reveal in this paper is how significant are the changes in the geometry and electron density distribution of the cytosine when it is surrounded by water molecules forming a chain around it. Therefore, we used the "static" approach for modeling the hydrated cytosine. Only pure quantum-mechanical optimization of polyhydrated nucleobase allows to analyze reliably possible changes of their molecular structures and electron density distribution**.** In some sense the proposed model of the solvent influence could represent the influence of the first hydration shell.

† National Academy of Science of Ukraine.
‡ Jackson State University.

10.1021/jp993144c CCC: $19.00
Published on Web 05/11/2000

TABLE 1: Total and Interaction Energies for the Most Stable Cytosine−nH$_2$O Complexes (n = 1−14)[a]

n	E_{tot}, au	E_{int}, kcal/mol	n	E_{tot}, au	E_{int}, kcal/mol
1	−471.362 650	12.49	8	−1006.387 500	71.22
2	−547.795 525	22.22	9	−1082.818 721	74.52
3	−624.228 242	34.32	10	−1159.244 385	75.00
4	−700.661 302	44.44	11	−1235.671 195	78.79
5	−777.094 381	54.03	12	−1312.099 771	82.41
6	−853.516 582	60.78	13	−1388.531 323	78.20
7	−929.954 835	62.04	14	−1464.970 970	82.67

[a] Interaction energies are corrected for basis set superposition error.

Method of Calculation

To build the hydration shell around the cytosine molecule we have used the modified scheme of monosolvation which originates in the early works of Pullman.[16]

A procedure for building a complex of cytosine with water molecules is as follows. The structure of all possible monohydrated complexes is fully optimized, and the most stable complex is determined. Then, a second water molecule is added, and the hydrated complex having the lowest energy is found in the same way. Such a procedure is repeated until 14 water molecules are arranged around cytosine to lock the chain. The total energy and interaction energy corrected for the basis set superposition error are listed in Table 1. Small changes or even decrease of the interaction energy in some cases are caused by reorganization of the hydration shell.

It is obvious that the potential surface of the polyhydrated molecules has a number of minima having different orientations of water molecules and close energy values. We assume that a change in orientation should not drastically effect the geometry of cytosine. This is why we did not study the influence of different orientations of water molecules. We also believe that the rotation of any water molecules will destroy the net of hydrogen bonds and will result in a structure that has higher energy than the described complex.

All calculations were carried out using the density functional theory with Becke's three-parameter exchange functional[17] along with the Lee−Yang−Parr nonlocal correlation functional (B3LYP).[18] The standard 6-31G(d) basis set was used. All structures were fully optimized by analytic gradient techniques.

Atomic charges were calculated using the Mulliken and natural bond orbitals (NBO) population analysis.[19] Topological characteristics of electron density distribution were obtained using Bader's "atoms in molecules" approach[20] using a wave function obtained at the same level of theory. All calculations were performed using the Gaussian94 program package.[21]

Results and Discussion

The optimized structure of the cytosine complex with 14 H_2O molecules (**1**) is presented in Figure 1. As can be seen, all water molecules may be divided into three groups. The first group includes H_2O molecules which form hydrogen bonds with cytosine (W1, W3, W8, W11−14). The second group involves molecules W4−W7 which are located around the hydrophobic part of the nucleobase. The remaining H_2O molecules play a role as bridge between the water molecules hydrogen bonded to cytosine (molecules W2, W9, W10).

Unlike the mono- and dihydrates of cytosine[8,11] the hydration shell in complex under study is essentially nonplanar (Figure 2). This especially concerns bridged water, H_2O molecules around the carbonyl group, and the hydrophobic part of cytosine.

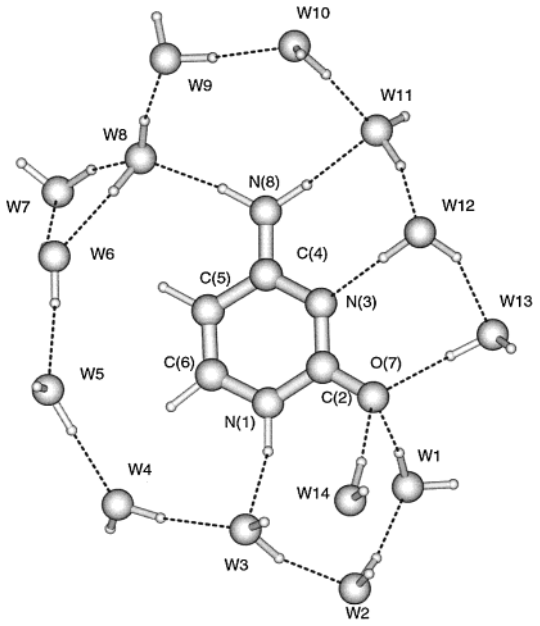


Figure 1. Structure of the complex of cytosine with 14 water molecules.

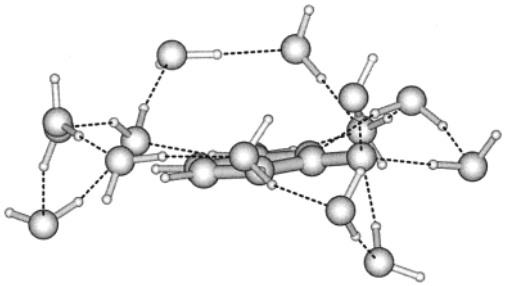


Figure 2. Arrangement of the water molecules with respect to the mean plane of the cytosine.

It is well-known that the energy of the hydrogen bond depends on the Y···H distance and the X−H···Y angle (where X is a hydrogen donor, and Y is a hydrogen-accepting atom). On the basis of the Y···H distance, all hydrogen bonds can be divided into strong (Y···H < 1.6 Å), medium (Y···H = 1.6−1.9 Å), and weak (Y···H > 1.9 Å).[22] According to this criterion the H-bonds in the complex under study should be assigned as medium (see Table 2). The energy of such hydrogen bonds reveal a rather small dependence[23] on the value of the Y···H−X angle in the range of 150°−180°. Therefore, the qualitatively energy of the H-bonds in our case may be estimated based only on the Y···H distances.

An alternative approach to analysis of the hydrogen bonds energy is provided by the topological characteristics of electron density distribution.[20] It was demonstrated that the value of electron density and its Laplacian in the bond critical point (3,−1) correlates well with the bond energy.[20] Therefore, a comparison of H-bonds strength may be carried out based on these magnitudes.

An analysis of the geometrical characteristics of H-bonds and the values of Laplasian of electron density allows us to conclude that, in general, the hydrogen bonds between the water molecules are stronger than between cytosine and water (Table 2). The energy of the former type of H-bonds depends also on the specific site of location of the water molecules. Hydrogen bonds between the water molecules located around the hydrophobic part of cytosine are weaker compared with other sites except for the W12−W13 interaction.

TABLE 2: Geometry of Hydrogen Bonds in Complexes of Cytosine·14H_2O

Y−H···X hydrogen bonds	H···X dist, Å	Y−H···X angle, deg	electron density, e/au^3	Laplacian of electron density, e/au^5
Cytosine−Water Hydrogen Bonds				
O(W1)−H···O(7)	1.818	171.7	0.036	0.107
O(W13)−H···O(7)	1.828	176.7	0.035	0.104
O(W14)−H···O(7)	1.790	172.2	0.038	0.113
N(1)−H···O(W3)	1.787	162.0	0.042	0.118
N(8)−H···O(W8)	1.826	168.3	0.038	0.106
N(8)−H···O(W11)	1.905	173.1	0.032	0.088
O(W12)−H···N(3)	1.900	167.5	0.034	0.094
Water−Water Hydrogen Bonds				
O(W2)−H···O(W1)	1.791	163.5	0.039	0.115
O(W3)−H···O(W2)	1.712	155.4	0.049	0.135
O(W4)−H···O(W3)	1.811	168.2	0.036	0.108
O(W5)−H···O(W4)	1.835	178.5	0.034	0.103
O(W6)−H···O(W5)	1.891	169.1	0.030	0.089
O(W8)−H···O(W6)	1.836	150.3	0.035	0.106
O(W6)−H···O(W7)	1.901	148.0	0.032	0.092
O(W7)−H···O(W8)	1.849	154.2	0.035	0.101
O(W8)−H···O(W9)	1.733	170.0	0.047	0.130
O(W9)−H···O(W10)	1.748	173.3	0.043	0.125
O(W10)−H···O(W11)	1.767	175.0	0.040	0.120
O(W11)−H···O(W12)	1.621	164.3	0.059	0.163
O(W12)-H···O(W13)	1.867	150.8	0.035	0.099
C(5)−H···O(W6)	2.385	152.9	0.013	0.039
C(6)−H···O(W4)	2.401	149.2	0.013	0.038

The characteristics of the hydrogen bonds between cytosine and water depend on the nature of the interacting fragment of the nucleobase. The strongest H-bonds are formed by the CONH fragment of cytosine (Table 2). The amino group and the N(3) atom of the pyrimidine ring form weaker hydrogen bonds. Nevertheless, it should be noted that all cytosine−water hydrogen bonds in the complex under study are considerably stronger compared with the bonds found in mono-, di-, and pentahydrates of cytosine.[8,11] This fact indicates the importance of the cooperative effects within the hydration shell.

The interaction of water molecules with the hydrophobic part of cytosine is the subject of special interest. During the past decade, the existence of weak C−H···O hydrogen bonds in many crystals[24] and biological structures[25] was established. These bonds are characterized by longer (2.2−2.6 Å) O···H distances for the same range of values of the C−H···O angle as compared with the conventional hydrogen bonds. Such interactions provide additional contribution to the total binding energy. An analysis of the structure of complex under study reveals that the distances between the hydrogen atoms at the C(5)−C(6) double bond of cytosine and the nearest W4 and W6 water molecules and their mutual orientation (Table 2) indicate the existence of weak C−H···O hydrogen bonds.

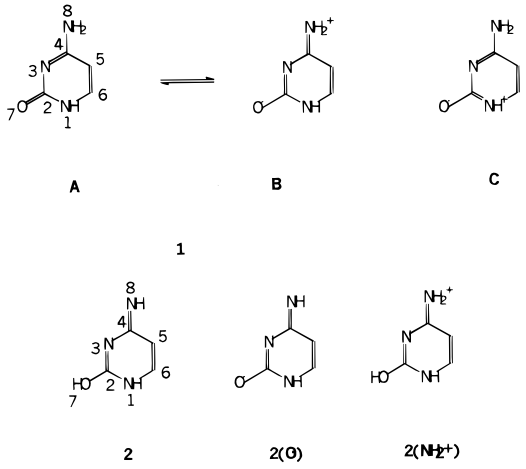
The presence of such bonds may be exactly determined by an analysis of the electron density distribution topology. The existence of the (3,−1) critical point indicates the formation of chemical bond independently of its nature.[20] An analysis of the electron density distribution in the complex under study reveals the presence of such critical points on the C(5)−H···O(W6) and C(6)−H···O(W4) lines. Thus, this confirms the existence of the C−H···O bonds between the hydrophobic part of cytosine and the water molecules. The values of Laplacian of electron density demonstrate that these H-bonds are very weak (Table 2) in agreement with previous consideration.[26]

A comparison of the geometry of isolated and hydrated cytosine demonstrates that the interaction with water molecules significantly influences its molecular structure (Table 3).

TABLE 3: Geometry of Isolated and Hydrated Cytosine

	isolated				hydrated	
	1	**2**	**2**(O^-)	**2**(NH_2^+)	**1**·14H_2O	PCM
Bond Lengths, Å						
N(1)−C(2)	1.430	1.372	1.450	1.361	1.377	1.409
C(2)−N(3)	1.373	1.281	1.337	1.308	1.339	1.364
N(3)−C(4)	1.319	1.412	1.379	1.355	1.358	1.335
C(4)−C(5)	1.441	1.475	1.481	1.435	1.436	1.438
C(5)−C(6)	1.359	1.346	1.350	1.359	1.354	1.359
C(6)−C(1)	1.355	1.387	1.366	1.370	1.365	1.359
C(2)−O(7)	1.220	1.349	1.244	1.318	1.281	1.236
C(4)−N(8)	1.366	1.286	1.313	1.330	1.329	1.347
Bond Angles, deg						
N(1)−C(2)−N(3)	116.0	126.1	118.1	123.6	119.9	117.4
C(2)−N(3)−C(4)	120.3	119.5	122.1	118.3	119.7	120.1
N(3)−C(4)−C(5)	124.2	116.0	118.7	121.2	121.4	123.1
C(4)−C(5)−C(6)	116.0	120.7	119.3	117.4	117.0	116.4
C(5)−C(6)−N(1)	119.9	119.8	119.7	119.8	120.4	120.2
C(6)−N(1)−C(2)	123.5	117.9	122.1	119.6	121.5	122.8
N(1)−C(2)−O(7)	118.5	112.2	114.4	114.0	117.8	118.5
N(3)−C(4)−N(8)	116.9	117.9	119.3	116.9	118.9	117.4
ΣNH_2	353.2			359.9	359.7	358.9
Torsion Angle, deg						
C(6)−N(1)−C(2)−N(3)	0.3	0.0	0.1	0	−2.2	0.6

SCHEME 1



The formation of hydrogen bonds with participation of the amino group results in a planar geometry of this moiety in agreement with previous considerations.[11,12] This also strongly enhances the conjugation between the lone pair of the nitrogen atom and the π-system of the pyrimidine ring. As a result, the C(4)−N(8) bond in the hydrated molecule is essentially shorter compared with isolated cytosine (Table 3), and its length (1.329 Å) is closer to the mean value of the C═N double bond[27] (1.281 Å) than to the single one (1.416 Å) (Scheme 1).The most drastic changes in geometry were found for the carbonyl group and the pyrimidine ring. Interaction with water molecules causes significant elongation of the C(2)−O(7) bond up to 1.281 Å. This value is typical for a single C−O^- bond (mean value for carboxylate anions[27] is 1.255 Å). Therefore, this bond may be considered as a single C−O^- bond rather than a double bond. The existence of the carbonyl group in the enolic form also is confirmed by changes in the bond lengths within the pyrimidine ring. The N(1)−C(2) and C(2)−N(3) bonds are essentially shorter, and the N(3)−C(4) bond is longer compared with the respective values for the isolated cytosine molecule (Table 3). The concerted changes of the C(2)−N(3) and N(3)−C(4) bond lengths should be noted. In isolated cytosine, the double N(3)−C(4) bond is essentially shorter than the single C(2)−N(3) bond. An opposite trend was found for the hydrated nucleobase. The

TABLE 4: Bond Order and Ellipticity in Isolated and Hydrated Cytosine

	bond ellipticity		bond order[a]	
bond	isolated	**1**·14H_2O	isolated	**1**·14H_2O
N(1)−C(2)	0.102	0.155	0.888	1.052
C(2)−N(3)	0.122	0.188	1.150	1.297
N(3)−C(4)	0.149	0.090	1.484	1.226
C(4)−C(5)	0.170	0.159	1.132	1.166
C(5)−C(6)	0.348	0.322	1.675	1.691
C(6)−N(1)	0.077	0.031	1.076	1.041
C(2)−O(7)	0.154	0.091	1.771	1.255
C(4)−N(8)	0.105	0.157	1.081	1.244

[a] Bond orders were calculated at the HF/6-31G* level of theory for the B3LYP/6-31G* optimized geometry using the GAMESS program[28] because of the failure of such calculations by the Gaussian94 package.

C(2)−N(3) bond is shorter than N(3)−C(4), and its bond length (1.339 Å) is closer to the mean value for the double C═N bond (1.329 Å) in heterocycles. Also the N(3)−C(4) bond length (1.358 Å) is closer to the average value[27] for the single C−N bond (1.376 Å). Therefore, we can assume that the molecular structure of cytosine surrounded by 14 water molecules may be represented as a superposition of two resonant structures **A** and **B**.

This assumption is also confirmed by a comparison of the values of bond orders and bond ellipticity (which reflects the contribution of the π-component into the total bonding) for isolated and hydrated cytosine (Table 4). The C(2)−N(3) and N(3)−C(4) bonds in the complex under study have essential double and single character, respectively, in contrast to isolated cytosine. A considerable decrease of the C(2)−O(7) bond order and an increase of the C(4)−N(8) bond order also support the significant contribution of resonance structure **B** into the total structure of hydrated cytosine.

The shortening of the N(1)−C(2) bond to 1.377 Å compared to isolated cytosine (1.430 Å) and the increase of its bond order and ellipticity due to interaction with water molecules (Table 3) may result from either contribution of resonance form **C** into the total structure of hydrated cytosine or change of conjugation between the N(1)−C(2) bond and the rest of the molecule as depicted by resonance structure **B**. For an analysis of the latest assumption, we can use the similarity between the resonance structure B and one of the rare tautomers of cytosine **2**. The geometry of the neutral tautomer **2** differs significantly from hydrated cytosine (Table 3). However, taking into account the zwitterionic character of structure **B**, we compared the geometry of hydrated cytosine and two isolated ionic forms of compound **2** (Table 3). The results of the calculations demonstrate that the values of the bond lengths in the complex under study are intermediate between the corresponding values for **2**(O^-) and **2**(NH_2^+). Moreover, this effect is observed in all cases. Therefore, we can conclude that a shortening of the N(1)−C(2) bond results from a change of the conjugation character within the pyrimidine ring in hydrated cytosine. Therefore, contribution of the resonant structure **C** with the double N(1)−C(2) bond should be ruled out.

The considerable contribution of the resonance structure **B** into the total structure of hydrated cytosine is also confirmed by the unusual character of the hydrogen bonds formed by the oxygen atom of the carbonyl group. It was found that the O(8) atom forms three H-bonds (Figure 1). Two of them do not lie in the mean plane of cytosine (Figures 1 and 2). It should be stressed that the orientation of these hydrogen bonds approximately corresponds to the arrangement of three lone pairs of the O^- atom.

TABLE 5: Atomic Charges Derived from Mulliken and Natural Bond Orbitals Population Analysis

	Mulliken charges		NBO charges	
atom	isolated	**1**·14H_2O	isolated	**1**·14H_2O
N(1)	−0.61	−0.64	−0.62	−0.62
C(2)	0.69	0.77	0.79	0.82
N(3)	−0.56	−0.63	−0.59	−0.65
C(4)	0.52	0.56	0.45	0.47
C(5)	−0.22	−0.21	−0.40	−0.36
C(6)	0.13	0.08	0.06	0.06
O(7)	−0.52	−0.67	−0.62	−0.80
N(8)	−0.76	−0.84	−0.81	−0.78
H(1)	0.34	0.38	0.44	0.46
H(8A)	0.35	0.38	0.42	0.43
H(8B)	0.33	0.41	0.41	0.44

Additional evidence for the existence of a carbonyl group in the enolic form is provided by the predicted value of the C−O stretching vibration frequency in the complex under study. This value related to such a mode in hydrated cytosine (1620 cm^{-1}) is essentially lower compared with the isolated molecule (1820 cm^{-1}). The frequency of this normal vibration strongly depends on the C−O bond order. Therefore, a considerable decrease in this value confirms the mainly single character of the carbonyl bond in hydrated cytosine.

Interestingly, the deformation of the bond lengths within the pyrimidine ring caused by interactions with water molecules results in some changes of endocyclic bond angles (Table 3) which are much closer to 120° than in isolated cytosine.

Taking into account the considerable contribution of zwitterionic form **B** into the total structure of hydrated cytosine, we can assume essential redistribution of the electron density in cytosine due to the interaction with water molecules. However, the results of the calculations reveal that the changes in the atomic charges are rather small (Table 5) except for the oxygen atom. The existence of the carbonyl group in the enolic form causes a considerable increase in negative charge on this atom.

Comparison of the geometry of the cytosine complex under study and the results of calculation using polarized continuum model (PCM)[29] (Table 3) demonstrates that application of the latter model of solvent predicts a similar trend of nucleobase structure deformation. However, changes of the geometrical parameters predicted by PCM approach are rather small and they do not allow to make definite conclusion about possible deformation of the cytosine due to the hydration.

The results of our calculations do not contradict the experimental and theoretical data (ref 9 and references therein) concerning relative stability of cytosine tautomers in water solution. The predicted deformation of the geometry of nucleobase occurs within oxoamino tautomer of cytosine which is the most stable in the water. Contribution of the zwitterionic resonant form into the total structure of molecules cannot be observed directly by experimental methods. However, deformation of cytosine due to hydration may be responsible for discrepancy between spectroscopic data for gas phase and solution.

Conclusions

In conclusion, our study reveals that the interaction of cytosine with water molecules results in significant changes in its intramolecular geometry. We believe that the method applied to modeling of the water chain surrounding cytosine provides good representation for the first solvation shell of this molecule. Therefore, we conclude that based on our results the structure

of cytosine in water cannot be described by convential chemical formula. It could be represented as a superposition of the two resonant structures: one of them corresponds to the conventional chemical formula and the second one has zwitterionic character. Significant contribution of the enolic form into the structure of the carbonyl group in the cytosine·$14H_2O$ complex results in an unusual pattern of hydrogen bonds formed by the oxygen atom of this group. Spatial orientation of these H-bonds approximately corresponds to the arrangement of three lone pairs of the O^- atom.

An analysis of the topological characteristics of the electron density distribution in the cytosine·$14H_2O$ complex using a wave function obtained at the B3LYP/6-31G(d) level of theory reveals the presence of weak C—H···O hydrogen bonds between the hydrophobic part of cytosine and water. Thus, our calculations provide strong support for the findings from molecular dynamics simulation[30a−c] and analysis of the distribution of water around the nucleobases derived from X-ray diffraction data for DNA and oligonucleotides[30d] related to the existence of such bonds in hydrated DNA.

We have revealed the unique phenomena of the studied system which could be described only within the supermolecular approach. It is a strong indication that in order to obtain reliable data related to the hydrated system such an approach should be applied during calculations of solvation free energy and other properties of nucleobases and other constituents of nucleic acids.

Acknowledgment. This study was supported by NSF Grants 9805465 and 9706268, and ONR Grant N00014-98-1-0592. The Mississippi Center for Supercomputing Research is acknowledged for a generous allotment of computer time.

References and Notes

(1) (a) Wolf, B.; Hanlon, S. *Biochemistry* **1975**, *14*, 1661. (b) Cohen, G.; Eisenberg, H. *Biopolymers* **1968**, *6*, 1077. (c) Hearst, J. E.; Vinograd, J. *Proc. Natl. Acad. Sci. U.S.A.* **1961**, *47*, 825.

(2) Hearst, J. *Biopolymers* **1965**, *3*, 57.

(3) Falk, M.; Hartman, K. A.; Lord, R. C. *J. Am. Chem. Soc.* **1962**, *84*, 3843.

(4) (a) Falk, M.; Hartman, K. A.; Lord, R. C. *J. Am. Chem. Soc.* **1963**, *85*, 387. (b) Falk, M.; Hartman, K. A.; Lord, R. C. *J. Am. Chem. Soc.* **1963**, *85*, 391. (c) Falk, M.; Poole, A. G.; Goymour, C. G. *Can. J. Chem.* **1970**, *48*, 1536.

(5) (a) Brandes, R.; Rupprecht, A.; Kearns, D. R. *J. Biophys.* **1989**, *56*, 683. (b) Diverdi, J. A.; Opella, S. J. *J. Mol. Biol.* **1981**, *149*, 307. (c) Shindo, H.; Hiyama, Y.; Roy, S.; Cohen, J. S.; Torchia, D. A. *Bull. Chem. Soc. Jpn* **1980**, *60*, 1631.

(6) (a) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1988. (b) Poltev, V. I.; Teplukhin, A. V.; Malenkov, G. G. *Int. J. Quantum Chem.* **1992**, *42*, 1499.

(7) (a) Sponer, J.; Hobza, P.; Leszczynski, J. In *Computational Chemistry: Reviews of Current Trends*; Leszczynski, J., Ed.; World Scientific Publisher: Singapore, 1996. (b) Kwiatkowski, J. S.; Person, W. B. In *Theoretical Biochemistry and Molecular Biophysics*; Beveridge, D. L., Lavery L., Eds.; Adenine Press: Giderland, NY, 1990; Vol.1. (c) Hobza, P.; Sandorfy, C. *J. Am. Chem. Soc.* **1987**, *109*, 1302. (d) Miller, J. L.; Kollman, P. A. *J. Phys. Chem.* **1996**, *100*, 8587. (e) Cullis, P. M.; Wolfenden, R. *Biochemistry* **1981**, *20*, 3024. (f) Pohorille, A.; Burt, S. K.; MacElroy, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 402. (g) Subramanian, V.; Sivanesan, D.; Ramasami, T. *Chem. Phys. Lett.* **1998**, *290*, 189. (h) Pullman, A.; Perahia, D. *Theor. Chim. Acta* **1978**, *48*, 29. (i) Del Bene, J. E. *J. Comput. Chem.* **1983**, *4*, 226. (j) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810. (k) Smets, J.; Adamowicz, L.; Maes, G. *J. Mol. Struct.* **1994**, *322*, 113. (l) Orozco, M.; Colominas, C.; Luque, F. J. *Chem. Phys.* **1996**, *209*, 19.

(8) (a) Aleman, C. *Chem. Phys. Lett.* **1999**, *302*, 461. (b) Aleman, C. *Chem. Phys.* **1999**, *244*, 151.

(9) (a) Cramer, C. J.; Truhlar, D. G. *Chem. Phys. Lett.* **1992**, *198*, 74. (b) Paglieri, L.; Corongiu, G.; Estin, D. A. *Int. J. Quantum Chem.* **1995**, *56*, 615. (c) Orozco, M.; Cubero, E.; Barril, X.; Colominas, C.; Luque, F. J. In *Computational Molecular Biology*; Leszczynski, J., Ed.; Elsevier: Amsterdam, 1999. (d) Colominas, C.; Luque, F. J.; Orozco, M. *J. Am. Chem. Soc.* **1996**, *118*, 6811.

(10) (a) Broo, A.; Holmen, A. *J. Phys. Chem. A* **1997**, *101*, 3589. (b) van Mourik, T.; Price, S. L.; Clary, D. C. *J. Phys. Chem. A* **1999**, *103*, 1611.

(11) Gorb, L.; Leszczynski, J. *Int. J. Quantum Chem.* **1998**, *70*, 855.

(12) Gorb, L.; Leszczynski, J. *Int. J. Quantum Chem.* **1997**, *65*, 759.

(13) Gu, J.; Leszczynski, J. *J. Phys. Chem. A* **1999**, *103*, 2744.

(14) Gorb, L.; Leszczynski, J. *J. Am. Chem. Soc.* **1990**, *112*, 5024.

(15) (a) Zhanpeisov, N. U.; Sponer, J.; Leszczynski, J. *J. Phys. Chem. A* **1998**, *102*, 10374. (b) Zhanpeisov, N. U.; Leszczynski, J. *J. Phys. Chem. A* **1998**, *102*, 6167.

(16) (a) Pullman, A. In *Quantum Theory of Chemical Reactions;* Daudel, R., Ed.; Reidel: Amsterdam, 1980; Vol. 11. (b) Pullman, A. In *The New World of Quantum Chemistry, Proceeding of the Second International Congress of Quantum Chemistry*; Pullman, B., Parr, R., Eds.; Reidel: Amsterdam, 1976; p 149. (c) Simkin, B. Ya.; Sheyhet, I. I. *Quantum-Chemical and Statictical Theory of Solutions. Computational Methods and Their Application*; Khimiya: Moscow, 1989 (in Russian).

(17) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(18) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200.

(19) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(20) (a) Bader, R. W. F. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: Oxford, UK, 1990. (b) Spackman, M. A. *Chem. Phys. Lett.* **1999**, *301*, 425.

(21) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Rob, M. A.; Replogle, E. S.; Comperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Fox, D. J.; Defrecs, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *GAUSSIAN 94*; Gaussian, Inc.: Pittsburgh, PA, 1994.

(22) Cleland, W. W.; Kreevoy, M. M. *Science* **1994**, 264.

(23) (a) Addalsteinsson, H.; Maulitz, A. H.; Bruice, T. C.; *J. Am. Chem. Soc.* **1996**, *118*, 7689. (b) Gresh, N.; Leboeuf, M.; Salahub, D. In *Modeling the Hydrogen Bond*; Smith, D. A., Ed.; American Chemical Society: Washington, DC, 1994.

(24) (a) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290. (b) Steiner, T. *J. Chem. Soc., Chem. Commun.* **1994**, 2341. (c) Borbulevych, O. Ya.; Shishkin, O. V.; Khrustalev, V. N.; Gol'ding, I. R.; Gololobov, Yu. G. *Russ. Chem. Bull.* **1998**, *47*, 1935.

(25) Wahl, M. C.; Sundaralingham, M. *Trends Biochem. Sci.* **1997**, *97*, 22.

(26) (a) Luisi, B.; Orozco, M.; Sponer, J.; Luque, F. J.; Shakked, Z. *J. Mol. Biol.* **1998**, *279*, 1123. (b) Cubero, E.; Orozco, M.; Hobza, P.; Luque, F. J. *J. Phys. Chem. A* **1999**, *103*, 6394.

(27) *Structure Correlation*; Burgi, H.-B., Dunitz, J. D., Eds.; VCH: Weinheim, Germany, 1994; Vol. 2.

(28) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windees, T. L.; Dupois, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(29) (a) Barrone, V.; Cossi, M.; Tomassi, J. *J. Comput. Chem.* **1998**, *19*, 404. Cossi, M.; Barrone, V.; Tomassi, J. *Chem. Phys. Lett.* **1998**, *286*, 253.

(30) (a) Steiner, T.; Saenger, W. *J. Am. Chem. Soc.* **1993**, *115*, 4540. (b) Steiner, T. *Acta Crystallogr.* **1995**, *D51*, 93. (c) Auffinger, P.; Louise-May, S.; Westhof, E. *Faraday Discuss.* **1996**, *103*, 151. (d) Schneider, B.; Cohen, D. M.; Schleifer, L.; Srinivasan, A. R.; Olson, W. K.; Berman, H. M. *Biophys. J.* **1993**, *65*, 2291.