# Molecular Structure and Hydrogen Bonding in Polyhydrated Complexes of Adenine:  A DFT Study

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Molecular structures of complexes of adenine with 12, 13, 14, and 16 water molecules were calculated using the B3LYP/6-31G(d) method. The location of water molecules on one side with respect to the adenine mean plane leads to a significant deformation of the nucleobase geometry. It results in unusual changes to the amino group geometry and a slight increase in the nonplanarity of the purine fragment of the title molecule. The formation of N−H⋯O hydrogen bonds with the participation of an amino group results in a disruption of the relationship between the pyramidality of the nitrogen atom of the amino group and the length of the C−N bond. Because of the specific geometry of the H bonds, a shortening of the C(6)−N(10) bond in the adenine·12H₂O complex does not entail a flattening of the nitrogen atom as compared to that of isolated adenine. Our data reveal the possibility of the formation of unusual hydrogen bonds in polyhydrated complexes of adenine.

## Introduction

It is well known that the hydration of DNA bases plays an important role in the structure and function of biopolymers. Numerous experimental studies using different methods[1−5] have led to the conclusion that DNA bases should be heavily hydrated. In particular, it was demonstrated that interactions of nucleobases with water molecules play a special role in determining the 3D structure of macromolecules.[6−8] Therefore, the hydration of nucleobases was the subject of numerous theoretical studies[9−14] using various methods (molecular dynamics, Monte Carlo, and the quantum chemical approach) within the continuum model of the solvent. These calculations allow the free energy of solvation, the binding sites of water molecules, and so forth to be estimated. It was also assumed that the molecular structure of DNA bases does not change considerably because of the effect of hydration.

However, a recent theoretical investigation of the interaction of nucleobases with water molecules within the supermolecular approximation led to opposite results. The calculations of complexes of uracil,[15,16] thymine,[17,18] cytosine,[17,19] guanine,[20−22] and adenine[22,23] with several water molecules performed at the HF, DFT, and MP2 levels of theory demonstrated that some geometrical parameters of DNA bases are very sensitive to the influence of water. It was found that the elongation of the C= O bonds could reach up to 0.02 Å and that changes to the geometry of the amino group due to the formation of the hydrogen bonds are notable. The same results have been obtained for adenine-uracil, isocytosine-cytosine, and guanine-cytosine base pairs interacting with several water molecules.[24,25]

Our latest study of polyhydrated complexes of uracil and thymine with 11 water molecules[26] and cytosine-14·H₂O[27]

demonstrates the strong influence of the surrounding water on the geometry of the nucleobases. Changes in the structure of DNA bases in these complexes may be explained by the significant contribution of zwitterionic resonance forms to the total geometry of the molecules with the pyrimidine ring having aromatic (uracil, thymine) or 1,4-dihydro (cytosine) character. The presence of C−H⋯O hydrogen bonds and the formation of three H bonds with the participation of the oxygen atom of cytosine, which are never observed in complexes with several water molecules, should also be noted.

In the present paper, we report the results of calculations for 4 polyhydrated complexes of adenine containing 12, 13, 14, and 16 water molecules. A particular issue that we would like to address here is, how significant are the changes in the geometry and electron density distribution of adenine when it is surrounded by water molecules forming a locked chain? This analysis may be performed on the basis of only pure quantum mechanical optimizations of polyhydrated nucleobases. Therefore, we used the "static" approach for modeling hydrated adenine. In some sense, the proposed model of the solvent effect could represent the influence of the first hydration shell.

## Method of Calculation

To build the hydration shell around the adenine molecule, we used the modified scheme of monosolvation that originated in the early works of Pullman.[28−30] A procedure for building a complex of adenine with water molecules is as follows. The structure of all possible monohydrated complexes 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 12 water molecules are arranged around adenine to lock the chain. These calculations were performed at the HF/6-31G(d) level of theory.

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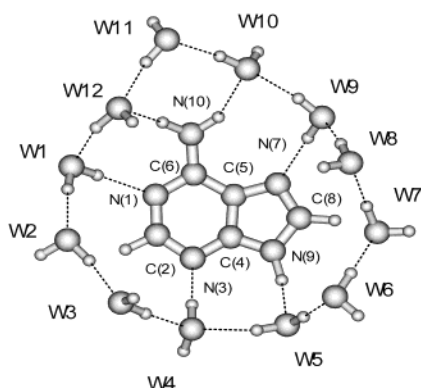[‡] Jackson State University.

Structure and Bonding in Adenine Complexes

*J. Phys. Chem. B, Vol. 107, No. 12, 2003* **2847**



**Figure 1.** Structure of the complex of adenine with 12 water molecules (A12W).
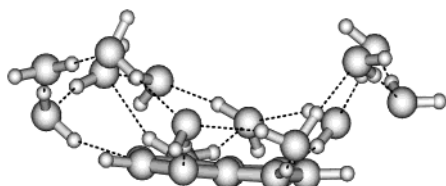


**Figure 2.** Arrangement of the water molecules with respect to the mean plane of adenine in the A12W complex.

**TABLE 1: Geometrical Parameters and Values of the Electron Density ($\rho$) and the Laplacian of the Electron Density ($\nabla^2\rho$) in the Bond (3, $-1$) Critical Points of the Hydrogen Bonds in the Adenine·12H$_2$O Complex (A12W)**

| X···H−Y hydrogen bonds | X···H, Å | X···H−Y, deg | $\rho$, e/au$^3$ | $\nabla^2\rho$, e/au$^5$ |
|---|---|---|---|---|
| Adenine−Water | | | | |
| N(1)···H−O(W1) | 1.923 | 157.2 | 0.033 | 0.091 |
| N(3)···H−O(W4) | 1.733 | 168.4 | 0.049 | 0.126 |
| N(7)···H−O(W9) | 1.904 | 164.1 | 0.034 | 0.092 |
| O(W5)···H−N(9) | 1.695 | 165.0 | 0.051 | 0.141 |
| O(W7)···H−C(8) | 2.344 | 131.1 | 0.013 | 0.044 |
| O(W10)···H−N(10) | 1.970 | 151.5 | 0.028 | 0.079 |
| O(W12)···H−N(10) | 2.051 | 154.6 | 0.024 | 0.067 |
| Water−Water | | | | |
| O(W2)···H−O(W1) | 1.863 | 163.4 | 0.032 | 0.097 |
| O(W3)···H−O(W2) | 1.785 | 170.8 | 0.039 | 0.114 |
| O(W4)···H−O(W3) | 1.807 | 175.3 | 0.038 | 0.108 |
| O(W4)···H−O(W5) | 1.970 | 158.2 | 0.027 | 0.077 |
| O(W6)···H−O(W5) | 1.766 | 171.6 | 0.042 | 0.12 |
| O(W7)···H−O(W6) | 1.755 | 176.8 | 0.042 | 0.122 |
| O(W8)···H−O(W7) | 1.676 | 178.7 | 0.051 | 0.145 |
| O(W9)···H−O(W8) | 1.685 | 172.6 | 0.050 | 0.142 |
| O(W10)···H−O(W9) | 1.907 | 152.9 | 0.029 | 0.09 |
| O(W11)···H−O(W10) | 1.746 | 170.0 | 0.043 | 0.124 |
| O(W12)···H−O(W11) | 1.768 | 167.8 | 0.038 | 0.121 |
| O(W1)···H−O(W12) | 1.648 | 163.7 | 0.055 | 0.153 |

Subsequently, the structure of complexes of adenine with 12 water molecules was fully optimized by analytic gradient techniques using the density functional theory with Becke's three-parameter exchange functional[31] along with the Lee−Yang−Parr nonlocal correlation functional.[32,33] The standard 6-31G(d) basis set was used. Recently, it was demonstrated[34,35] that this method provides reliable enough data concerning the geometry and energetics of hydrated species.

The structure of complexes of adenine with 13, 14, and 16 water molecules was built by the sequential addition of water molecules to the complex with a smaller number of waters starting with the adenine·12H$_2$O complex. Their structure was fully optimized using the B3LYP/6-31G(d) method.

The character of stationary points was checked by Hessian calculations within the harmonic approximation for every complex. No imaginary vibrational frequencies were found.

A topological analysis of the election density distribution has been carried out within Bader's atoms-in-molecules approach[36] using the wave function obtained at the same level of theory.

The interaction energies were corrected for the basis set superposition error (BSSE) using the standard Boys−Bernardi counterpoise correction scheme.[37,38] All calculations were performed using the Gaussian 98 program.[39]

## Results and Discussion

**Structure of the Adenine·12H$_2$O Complex.** The optimized structure of the adenine complex with 12 H$_2$O molecules (A12W) is presented in Figure 1. In the polyhydrated complexes of uracil[26] and cytosine,[27] water molecules are distributed symmetrically with respect to the mean plane of the nucleobase. Significant deviation from this plane was found only for the thymine complex with 13 water molecules. This is cause by the hydrophobic character of the methyl group. Remaining water molecules in this complex are also located near from mean plane of the nucleobase. Contrary to other nucleobases, the hydration shell in the complex under study is essentially nonplanar (Figure 2). All water molecules are displaced to the one side determined by the mean plane of the nucleobase. This probably results from the significantly nonplanar geometry of the amino group of

adenine leading to a deviation of hydrogen-bonded to amino-group water molecules out of the mean plane of the nucleobase.

As can be seen from Figure 1, all water molecules may be divided into two groups. The first group includes H$_2$O molecules that form hydrogen bonds directly with adenine (W1, W4, W5, W7, W9, W10, and W12). The second group involves molecules that play the role of a bridge between the water molecules hydrogen bonded to adenine (molecules W2, W3, W5, W8, and W11).

It is well known[40] that the energy of the hydrogen bonds depends on the Y···H distance and the X − H···Y angle (where X is a hydrogen donor and Y is a hydrogen acceptor). Depending on the Y···H distances, 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).

According to this criterion, the H bonds in the adenine·12H$_2$O complex should be assigned as weak and medium (Table 1). The energy of such hydrogen bonds reveals a rather small dependence on the value of the Y···H−X angle in the range of 150−180°.[41] Therefore, qualitatively, the energy of the H bonds in our case may be estimated only on the basis of the Y···H distances.

Earlier, it was shown[36] that the value of the electron density and the Laplacian of the electron density in the bond critical point (3, −1) correlate well with the bond energy. Therefore, a comparison of the strength of the H bonds may also be carried out on the basis of these descriptors.

An analysis of the geometrical characteristics of H bonds and the values of the Laplacian of the electron density in the bond critical point allows us to conclude that, in general, the hydrogen bonds between the water molecules are stronger than the bonds between adenine and water (Table 1). A similar situation was found for the polyhydrated complex of cytosine.[27] The characteristics of the hydrogen bonds between adenine and water depend on the nature of the interacting fragment of the nucleobase. The N(3) atom and N(9)−H group form the strongest H bonds, and the hydrogen bonds with participating amino groups are the weakest.

The formation of the hydrogen bonds between water and adenine strongly influences the displacement of water molecules

from the mean plane of the nucleobase. Directly bonded W1, W4, W5, W9, and W10 molecules have the smallest displacement. This value for the oxygen atom of water is within 0.91–1.26 Å. Weaker H bonds between W12 and W7 molecules and adenine result in larger displacements (1.96 and 2.05 Å, respectively). The largest deviation is observed for bridged water molecules W3, W6, and W8 (2.86–3.16 Å).

The strength of the H bonds between water molecules also depends on the specific site of the location of the water. In contrast to cytosine,[27] the hydrogen bonds between the water molecules located around the hydrophobic part of adenine are stronger than others (except for the W12–W1 interactions).

In general, all water–water hydrogen-bonding networks can be classified as unidirectional or homodromic (i.e., exhibiting a consequent donor–acceptor arrangement between water molecules). This network is disrupted by the W4 molecule, which forms two hydrogen bonds with neighboring water molecules as a biacceptor. The formation of homodromic networks of hydrogen bonds is associated with the extra stabilization of such networks by many-body nonadditive interactions known as hydrogen bond cooperativity. Taking into account this fact, we can assume that the stronger character of the water–water hydrogen bonds as compared to that of the water–adenine bonds is, in particular, caused by cooperativity effects.

An analysis of the distribution of electron density in the adenine·$12H_2O$ complex reveals the presence of the $(3, -1)$ critical point located on the $C(8)-H\cdots O(W7)$ line. This confirms the existence of $C-H\cdots O$ hydrogen bonds between the hydrophobic part of adenine and water. The value of the Laplacian of the electron density (Table 1) indicates that this H bond is very weak.[42,43]

On the basis of the relatively weak character of adenine–water hydrogen bonds, we can suggest that interactions with nucleobase cannot prevent the exchange of water molecules between the hydration shell and bulk water in aqueous solutions.

A comparison between the geometry of isolated adenine and hydrated adenine demonstrates that the interaction of the nucleobase with water also influences its molecular structure (Table 2). However, changes in the geometrical parameters of the nucleobase in the A12W complex are essentially smaller compared to those of polyhydrated uracil, thymine, and cytosine.[26,27] Only a small deformation of the bonds in the region of the strongest hydrogen bonds between adenine and water is observed. There is some elongation of the $N(3)-C(4)$ ($\Delta l = 0.011$ Å) and $N(1)-C(6)$ bonds ($\Delta l = 0.014$ Å) and a shortening of the $C8-N(9)$ bond ($\Delta l = 0.012$ Å) compared to that of isolated adenine.

The most significant changes in geometry are found for the amino group (Table 2). Unlike polyhydrated cytosine,[27] the interaction of adenine with water results in an increase in the degree of pyramidality of the amino group. Usually, this indicates a shift of the nitrogen atom hybridization to $sp^3$ and should be associated with the elongation of the C–N bond.[42,43] However, we reveal the opposite situation in the adenine·$12H_2O$ complex. Despite the increase in the pyramidality of the amino group, the $C(6)-N(10)$ bond (1.345 Å) is significantly shorter than that of isolated adenine (1.358 Å). This indicates an essential strengthening of the conjugation between the $\pi$ system of the purine bicycle and the lone pair of the nitrogen atom, which is in agreement with previous findings.[42,43] An increase in the values of the electron density at the $C(6)-N(10)$ bond critical point and in the ellipticity of the bond also confirms these changes (Table 3). Therefore, one can assume that an

**TABLE 2: Geometry of Isolated Adenine and Adenine in Polyhydrated Complexes with 12 (A12W), 13 (A13W), 14 (A14W), and 16 (A16W) Water Molecules and BSSE-Corrected Adenine–Water Interaction Energies ($E_{BSSE}$)**

| parameter | isolated | A12W | A13W | A14W | A16W |
|---|---|---|---|---|---|
| | | Bond Lengths, Å | | | |
| N(1)–C(2) | 1.343 | 1.336 | 1.338 | 1.334 | 1.336 |
| C(2)–N(3) | 1.337 | 1.335 | 1.335 | 1.336 | 1.333 |
| N(3)–C(4) | 1.339 | 1.350 | 1.347 | 1.349 | 1.348 |
| C(4)–C(5) | 1.400 | 1.400 | 1.403 | 1.397 | 1.394 |
| C(5)–C(6) | 1.411 | 1.415 | 1.409 | 1.418 | 1.420 |
| N(1)–C(6) | 1.345 | 1.359 | 1.353 | 1.361 | 1.362 |
| C(5)–N(7) | 1.386 | 1.385 | 1.384 | 1.388 | 1.388 |
| N(7)–C(8) | 1.310 | 1.320 | 1.319 | 1.324 | 1.323 |
| C(8)–N(9) | 1.381 | 1.369 | 1.370 | 1.364 | 1.366 |
| C(4)–N(9) | 1.378 | 1.368 | 1.367 | 1.371 | 1.374 |
| C(6)–N(10) | 1.358 | 1.345 | 1.365 | 1.338 | 1.328 |
| | | Bond Angles, deg | | | |
| C(2)–N(1)–C(6) | 118.3 | 119.7 | 119.6 | 119.9 | 120.5 |
| N(1)–C(2)–N(3) | 129.0 | 127.9 | 127.6 | 128.0 | 127.7 |
| C(2)–N(3)–C(4) | 111.1 | 112.3 | 112.5 | 112.1 | 111.8 |
| N(3)–C(4)–C(5) | 126.9 | 125.8 | 125.6 | 125.9 | 126.4 |
| C(4)–C(5)–C(6) | 115.8 | 116.8 | 116.6 | 116.9 | 116.8 |
| N(1)–C(6)–C(5) | 118.9 | 117.5 | 118.0 | 117.1 | 116.3 |
| C(4)–C(5)–N(7) | 111.5 | 109.9 | 109.9 | 109.7 | 109.9 |
| C(5)–N(7)–C(8) | 103.9 | 104.3 | 104.2 | 104.3 | 104.5 |
| N(7)–C(8)–N(9) | 113.5 | 113.6 | 113.7 | 113.5 | 113.1 |
| C(4)–N(9)–C(8) | 106.7 | 106.1 | 106.1 | 106.3 | 106.6 |
| C(5)–C(4)–N(9) | 104.4 | 106.1 | 106.0 | 106.2 | 105.9 |
| N(1)–C(6)–N(10) | 118.8 | 118.2 | 118.1 | 118.3 | 118.9 |
| C(5)–C(6)–N(10) | 122.3 | 124.3 | 123.9 | 124.6 | 124.8 |
| C(6)–C(5)–N(7) | 132.7 | 132.9 | 133.0 | 132.9 | 132.9 |
| N(3)–C(4)–N(9) | 128.7 | 128.1 | 128.3 | 127.8 | 127.7 |
| Σ(NH2) (at the N(10)) | 354.9 | 351.4 | 343.1 | 353.7 | 359.6 |
| | | Torsion Angles, deg | | | |
| N(3)–C(4)–C(5)–C(6) | 0.0 | 2.5 | 2.9 | 2.9 | 7.0 |
| C(4)–C(5)–C(6)–N(1) | −0.4 | −3.4 | −4.5 | −4.0 | −8.2 |
| C(5)–C(6)–N(1)–C(2) | 0.5 | 2.6 | 3.6 | 3.1 | 4.8 |
| N(9)–C(4)–C(5)–C(6) | 179.8 | −174.5 | −174.1 | −174.2 | −172.4 |
| C(6)–C(5)–N(7)–C(8) | −179.6 | 172.5 | 172.1 | 172.2 | 170.7 |
| C(4)–C(5)–C(6)–N(10) | 178.2 | 175.4 | 174.4 | 174.5 | 169.9 |
| $E_{BSSE}$, kcal/mol | | −46.77 | −51.42 | −52.98 | −49.51 |

**TABLE 3: Values of the Electron Density ($\rho$), the Laplacian of the Electron Density ($\Delta\rho$), and the Ellipticity ($\epsilon$) in the $(3, -1)$ Bond Critical Point of $C(6)-N(10)$ in Isolated and Hydrated Adenine**

| | $\rho$, e/au$^3$ | $\Delta\rho$, e/au$^5$ | $\epsilon$ |
|---|---|---|---|
| isolated adenine | 0.326 | −1.040 | 0.126 |
| A12W | 0.34 | −1.138 | 0.152 |
| A13W | 0.329 | −1.156 | 0.127 |
| A14W | 0.344 | −1.136 | 0.163 |
| A16W | 0.349 | −1.105 | 0.179 |

increase in the pyramidality of the amino group is forced by the geometry of the hydrogen bonds because of the arrangement of water molecules on one side with respect to the purine fragment. This assumption agrees well with the small values of the transition energy between the planar and pyramidal configurations of the amino group in adenine and related compounds.[44,45] However, our results demonstrate that the degree of pyramidality of the amino group is a very ambiguous indicator of the nitrogen atom hybridization, especially in the condensed phase. In particular, the formation of intermolecular hydrogen bonds may cause significant deviations from the relationship between the degree of pyramidality and the values of the C–N bond lengths. Therefore, for this purpose, it is more reliable to use the characteristics of the C–N bond.

Interactions of adenine with water molecules also result in some out-of-plane deformations of the purine bicycle (Table 2). Maximal changes are observed for the $C(4)-C(5)-C(6)-$

Structure and Bonding in Adenine Complexes

*J. Phys. Chem. B, Vol. 107, No. 12, 2003* **2849**

N(1) and C(6)−C(5)−C(7)−C(8) torsion angles (−3.4° and 172.5°, respectively).

Recently, it was revealed[46,47] that the pyrimidine ring in adenine is nonrigid. The transition of the purine bicycle to a nonplanar conformation with a C(4)−C(5)−C(6)−N(1) torsion angle of ±20° requires less than 2.6 kcal/mol. Taking into account these data, one can assume that the location of water molecules on one side with respect to the adenine mean plane induces the out-of-plane deformation of adenine. In this case, the high conformational nonrigidity of the purine bicycle provides the easiest route to the relaxation of the nucleobase geometry in order to maximize the interaction with water molecules.

Taking into account the location of water molecules on one side with respect to the adenine mean plane, one can suggest that such a polyhydrated complex should exists in two symmetrical conformations with the arrangement of water above and under the purine bicycle. The transition between these two isomers requires an inversion of the amino group and a change in the direction of the purine fragment's out-of-plane deformation. Additionally, some reorganization of the hydration shell should occur in the transition state. We expect that the energy of transition between two symmetrical isomers of A12W should be about 5−10 kcal/mol. Therefore, such a flipping of the adenine polyhydrated complex is impossible in the gas phase but may be induced by interactions with bulk water in aqueous solution.

**Modeling of the −N(H₂)···HOH Interactions.** A recent analysis of the character of interactions between amino groups in DNA and olygonucleotides[48] led to the conclusion that the nitrogen atom of the amino group may form an additional hydrogen bond with water molecules, where it acts as an acceptor of the proton. This assumption is also confirmed by the experimental data concerning the structure of the monohydrate of *N,N′*-dimethyl-5,6-diaminouracil[49,50] and aniline.[51]

An investigation of monohydrate complexes of cytosine,[17,19] guanine,[20−22] and adenine[22,23] did not reveal the existence of structures containing the N···H−O bond with the participation of an amino group. The existence of such a bond is probably caused by the presence of a binding site for several waters within the nucleobase. However, the question concerning the ability of the amino group in cytosine, guanine, and adenine to form N···H−O bonds is still unclear.

The complex between adenine and 12H₂O is a very convenient starting model for investigations of such a possibility. In this case, all water-binding sites within the nucleobase are locked. Therefore, an additional water molecule can interact with adenine the other way.

The results of the calculations concerning the geometry of a complex of adenine with 13 water molecules (A13W) demonstrate that an additional water is located near the amino group (Figure 3). An analysis of the electron density distribution reveals the presence of the (3, −1) bond critical point that indicates the existence of the N(10)···H−O(W13) weak hydrogen bond (Table 4).

The results of the calculations demonstrate that, in general, the nitrogen of the amino group in adenine is able to act as a proton acceptor in hydrogen bonds. Recently, the same conclusion was made for the amino group in rare tautomers of guanine[52] and amino derivatives of uracil.[53] Therefore, we performed additional calculations for adenine monohydrate to locate the complex containing the N(10)···H−O hydrogen bond. However, it was found that such a complex does not correspond to local minimum on the potential energy surface. Similar results
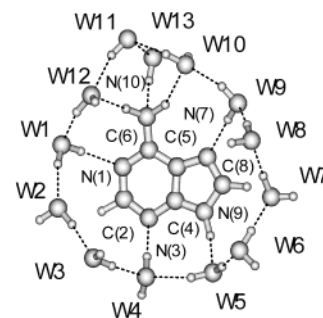


**Figure 3.** Structure of the complex of adenine with 13 water molecules (A13W).

**TABLE 4: Geometry and Values of the Electron Density (ρ) and the Laplacian of the Electron Density (∇²ρ) in the Bond (3, −1) Critical Points of the Hydrogen Bonds in the Adenine·13H₂O Complex (A13W)**

| X···H−Y hydrogen bonds | X···H, Å | X···H−Y, deg | ρ, e/au³ | ∇²ρ, e/au⁵ |
|---|---|---|---|---|
| Adenine−Water | | | | |
| N(1)···H−O(W1) | 1.940 | 157.3 | 0.032 | 0.088 |
| N(3)···H−O(W4) | 1.753 | 167.6 | 0.047 | 0.122 |
| O(W5)···H−N(9) | 1.683 | 165.1 | 0.052 | 0.144 |
| O(W7)···H−C(8) | 2.320 | 131.3 | 0.014 | 0.046 |
| N(7)···H−O(W9) | 1.925 | 164.6 | 0.032 | 0.089 |
| O(W12)···H−N(10) | 1.911 | 170.0 | 0.032 | 0.087 |
| O(W10)···H−N(10) | 1.954 | 150.8 | 0.03 | 0.082 |
| N(10)···H−O(W13) | 2.031 | 146.8 | 0.026 | 0.071 |
| Water−Water | | | | |
| O(W2)···H−O(W1) | 1.885 | 158.3 | 0.03 | 0.093 |
| O(W3)···H−O(W2) | 1.782 | 172.0 | 0.04 | 0.115 |
| O(W4)···H−O(W3) | 1.811 | 175.3 | 0.038 | 0.107 |
| O(W4)···H−O(W5) | 1.971 | 158.1 | 0.027 | 0.076 |
| O(W6)···H−O(W5) | 1.762 | 171.5 | 0.043 | 0.121 |
| O(W7)···H−O(W6) | 1.753 | 176.4 | 0.043 | 0.123 |
| O(W8)···H−O(W7) | 1.671 | 177.7 | 0.052 | 0.147 |
| O(W9)···H−O(W8) | 1.677 | 171.9 | 0.051 | 0.145 |
| O(W10)···H−O(W9) | 1.902 | 153.3 | 0.029 | 0.091 |
| O(W11)···H−O(W10) | 1.790 | 155.4 | 0.041 | 0.114 |
| O(W12)···H−O(W11) | 1.894 | 161.5 | 0.029 | 0.091 |
| O(W1)···H−O(W12) | 1.669 | 163.4 | 0.052 | 0.147 |
| O(W11)···H−O(W13) | 1.977 | 146.1 | 0.026 | 0.078 |

were obtained for guanine monohydrates, where the formation of such complexes was observed only for rare tautomers but not for canonical oxo-amino tautomer.

The appearance of an additional water molecule results in a significant increase in the pyramidality of the amino group, which is accompanied by a considerable elongation of the C(6)−N(10) bond (Table 2). This indicates a shift in the N(10) atom hybridization toward sp³ and a decrease in the conjugation between the amino group and the π system of the purine fragment. As a result, an essential decrease in the ellipticity of the C−N bond is observed (Table 3). The remaining geometrical parameters of adenine are almost unchanged in A13W, in contrast to those in A12W. A further increase in the nonplanarity of the purine bicycle should be noted (Table 2).

The formation of the N(10)···H−O(W13) hydrogen bonds results in a shortening of the N(10)−H···O bonds (Table 2). This indicates that pyramidalization of the amino group in complex A13W is additionally stabilized by a strengthening of the N−H···O hydrogen bonds formed by this substituent.

**Modeling of O−H···π Interactions.** During the past decade, there have been extensive discussions concerning the existence and properties of hydrogen-bonded complexes where the π system is an acceptor of a proton. There are numerous reports about compounds whose properties have been explained on the basis of the presence of H···π bonds.[54,55] It is thought that these
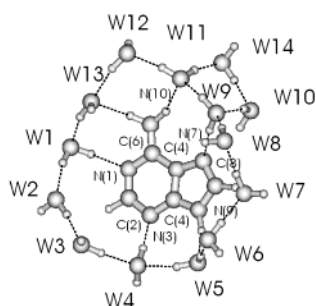
**Figure 4.** Structure of the complex of adenine with 14 water molecules (A14W).
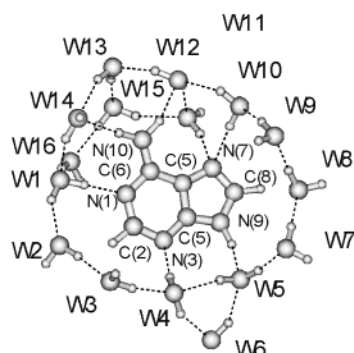


**Figure 5.** Structure of the complex of adenine with 16 water molecules (A16W).

interactions are important to the preferential formation of some stereoisomers in coordination compounds and that they can play a central role in defining the crystal structure of some noninclusion crystals of $\pi$-containing molecules.[55,56] Spectroscopic studies of benzene dimers have revealed the presence of this type of H bond.[57]

The existence of O−H$\cdots\pi$ hydrogen bonds was also recognized. A recent UV and IR−UV ion-dip spectroscopy study of aryl alcohol demonstrated the presence of intra- and intermolecular $\pi$-type hydrogen bonding.[58,59]

An attempt at modeling the formation of O−H$\cdots\pi$ hydrogen bonds led to a study of the structure of complexes of adenine with 14 water molecules (A14W). The appearance of an additional water molecule results in the formation of two hydrogen bonds with the participation of the N(7) atom (Figure 4). These H bonds have significantly different geometrical parameters, values of the electron density, and Laplacian of the electron density at the bond critical points (Table 5). They are located almost symmetrically with respect to the adenine mean plane (the values of the C(4)−C(5)−N(7)$\cdots$H torsion angle are 132.4 and −136.5° for HO(W10) and HO(W9), respectively). Taking into account the geometrical characteristics of these H bonds, one can suppose that both are formed mainly by the lone pair of the nitrogen atom. The contribution of the $p_z$ AO of the nitrogen atom to interactions with water molecules is fairly small. Differences in the geometrical characteristics of these H bonds are probably caused by differences in the interactions with neighboring water molecules. The water−water hydrogen bonds with the participation of the W9 and W10 molecules are essentially stronger than the adenine−water bonds mentioned above (Table 5). Therefore, the orientation of the neighboring water molecules should strongly influence the geometrical characteristics of the N(7)$\cdots$H−O(W9) and N(7)$\cdots$H−O(W10) bonds.

Some changes in the characteristics of the other H bonds are also observed in the A14W complex (Table 5). There is some

**TABLE 5: Geometrical Parameters and Values of the Electron Density ($\rho$) and the Laplacian of the Electron Density ($\nabla^2\rho$) in the Bond (3, −1) Critical Points of the Hydrogen Bonds in the Adenine·14H$_2$O Complex (A14W)**

| X$\cdots$H−Y hydrogen bonds | X$\cdots$H, Å | X$\cdots$H−Y, deg | $\rho$, e/au$^3$ | $\nabla^2\rho$, e/au$^5$ |
|---|---|---|---|---|
| Adenine−Water | | | | |
| N(1)$\cdots$H−O(W1) | 1.926 | 157.7 | 0.033 | 0.091 |
| N(3)$\cdots$H−O(W4) | 1.734 | 168.0 | 0.049 | 0.126 |
| O(W5)$\cdots$H−N(9) | 1.685 | 164.8 | 0.052 | 0.144 |
| O(W7)$\cdots$H−C(8) | 2.371 | 130.4 | 0.013 | 0.043 |
| N(7)$\cdots$H−O(W9) | 1.871 | 169.9 | 0.036 | 0.098 |
| N(7)$\cdots$H−O(W10) | 2.474 | 136.7 | 0.011 | 0.034 |
| O(W11)$\cdots$H−N(10) | 1.883 | 157.4 | 0.035 | 0.094 |
| O(W13)$\cdots$H−N(10) | 2.014 | 156.8 | 0.026 | 0.072 |
| Water−Water | | | | |
| O(W2)$\cdots$H−O(W1) | 1.878 | 161.7 | 0.031 | 0.094 |
| O(W3)$\cdots$H−O(W2) | 1.793 | 170.9 | 0.039 | 0.112 |
| O(W4)$\cdots$H−O(W3) | 1.814 | 175.8 | 0.038 | 0.106 |
| O(W4)$\cdots$H−O(W5) | 1.959 | 158.7 | 0.028 | 0.078 |
| O(W6)$\cdots$H−O(W5) | 1.771 | 171.3 | 0.042 | 0.119 |
| O(W7)$\cdots$H−O(W6) | 1.766 | 177.0 | 0.041 | 0.119 |
| O(W8)$\cdots$H−O(W7) | 1.676 | 177.8 | 0.051 | 0.145 |
| O(W9)$\cdots$H−O(W8) | 1.737 | 167.4 | 0.043 | 0.129 |
| O(W9)$\cdots$H−O(W10) | 1.864 | 154.5 | 0.035 | 0.098 |
| O(W11)$\cdots$H−O(W9) | 1.765 | 153.0 | 0.04 | 0.124 |
| O(W10)$\cdots$H−O(W14) | 1.742 | 166.3 | 0.045 | 0.127 |
| O(W14)$\cdots$H−O(W11) | 1.731 | 166.7 | 0.045 | 0.13 |
| O(W12)$\cdots$H−O(W11) | 1.799 | 166.0 | 0.039 | 0.111 |

weakening of the C(8)−H$\cdots$O bonds and some strengthening of the N(9)−H$\cdots$O(W5) and O(W12)$\cdots$H−O(W14) bonds.

The most notable changes are found for the amino group. The addition of a water molecule results in the disappearance of the N$\cdots$H−O bond. This causes a significant decrease in the degree of pyramidality of the N(10) atom (Table 2). Therefore, an increase in the conjugation between the amino group and the $\pi$ system of the purine bicycle confirmed by a shortening of the C(6)−N(10) bond (Table 2) and an increase of its ellipticity is observed (Table 3).

To analyze the possibility of the formation of an O−H$\cdots\pi$ hydrogen bond with the participation of the other nitrogen atoms of the purine fragment, we have investigated the molecular structure of the complex of adenine with 16 water molecules. The equilibrium geometry of A14W was used as the initial geometry of the adenine·16H$_2$O complex (A16W), and two molecules of water were added above the N(1) and N(3) atoms. The results of the calculations also demonstrate that the equilibrium geometry of A16W does not contain O−H$\cdots\pi$ hydrogen bonds. The addition of two water molecules results in a significant reorganization of the solvation shell. This leads to considerable changes in the hydrogen bonds pattern and characteristics (Table 6). In particular, an increase in the number of bridged water molecules causes a weakening in the interaction between water and adenine. This results in a considerable decrease in the energy of the adenine−water interaction.

The reorganization of the hydration shell also entails changes in the nucleobase geometry. This especially concerns the amino group. An almost complete flattening of the amino group is observed (Table 2). This causes a strengthening of the conjugation between the substituent and the $\pi$ system of purine and manifests itself through the considerable shortening of the C(6)−N(10) bond and an increase in bond ellipticity (Tables 2 and 3). Despite this, the purine bicycle is the most nonplanar among all of the complexes under consideration. The value of the C(4)−C(5)−C(6)−N(1) torsion angle is −8.2°. The amino group significantly deviates from the mean plane of the purine fragment. The C(4)−C(5)−C(6)−N(10) torsion angle is 169.9°.

Structure and Bonding in Adenine Complexes

*J. Phys. Chem. B, Vol. 107, No. 12, 2003* **2851**

**TABLE 6: Geometrical Parameters and Values of the Electron Density ($\rho$) and the Laplacian of the Electron Density ($\nabla^2\rho$) in the Bond (3, −1) Critical Points of the Hydrogen Bonds in the Adenine·16H$_2$O Complex (A16W)**

| X···H−Y hydrogen bonds | X···H, Å | X···H−Y, deg | $\rho$, e/au$^3$ | $\nabla^2\rho$, e/au$^5$ |
|---|---|---|---|---|
| Adenine−Water | | | | |
| N(1)···H−O(W1) | 1.746 | 175.3 | 0.049 | 0.126 |
| N(3)···H−O(W4) | 1.811 | 162.5 | 0.041 | 0.113 |
| O(W5)···H−N(9) | 1.801 | 156.0 | 0.04 | 0.112 |
| O(W8)···H−C(8) | 2.403 | 124.4 | 0.012 | 0.042 |
| N(7)···H−O(W10) | 1.951 | 174.6 | 0.03 | 0.084 |
| N(7)···H−O(W11) | 2.047 | 160.5 | 0.024 | 0.068 |
| O(W14)···H−N(10) | 1.909 | 173.5 | 0.032 | 0.087 |
| O(W12)···H−N(10) | 1.843 | 162.0 | 0.038 | 0.102 |
| Water−Water | | | | |
| O(W2)···H−O(W1) | 1.985 | 148.8 | 0.024 | 0.075 |
| O(W3)···H−O(W2) | 1.821 | 172.0 | 0.036 | 0.104 |
| O(W4)···H−O(W3) | 1.828 | 169.9 | 0.036 | 0.102 |
| O(W4)···H−O(W5) | 1.955 | 148.7 | 0.029 | 0.08 |
| O(W6)···H−O(W4) | 1.863 | 151.8 | 0.035 | 0.098 |
| O(W5)···H−O(W6) | 1.889 | 149.4 | 0.032 | 0.094 |
| O(W7)···H−O(W5) | 1.712 | 169.1 | 0.047 | 0.135 |
| O(W8)···H−O(W7) | 1.747 | 176.6 | 0.043 | 0.124 |
| O(W9)···H−O(W8) | 1.678 | 175.4 | 0.051 | 0.144 |
| O(W10)···H−O(W9) | 1.693 | 167.9 | 0.048 | 0.142 |
| O(W12)···H−O(W11) | 1.928 | 148.3 | 0.030 | 0.087 |
| O(W11)···H−O(W15) | 2.090 | 160.2 | 0.020 | 0.06 |
| O(W13)···H−O(W12) | 1.740 | 160.7 | 0.045 | 0.126 |
| O(W14)···H−O(W13) | 2.055 | 159.2 | 0.021 | 0.065 |
| O(W1)···H−O(W14) | 1.771 | 156.4 | 0.040 | 0.121 |
| O(W15)···H−O(W13) | 1.766 | 166.7 | 0.042 | 0.12 |
| O(W16)···H−O(W15) | 1.858 | 177.3 | 0.033 | 0.095 |
| O(W1)···H−O(W16) | 1.853 | 161.5 | 0.034 | 0.099 |

## Conclusions

In the contrast to earlier data, the results of a computational study of polyhydrated adenine complexes demonstrate that interactions of adenine with water may cause significant deformations of the nucleobase geometry. The location of water molecules on one side with respect to the adenine mean plane leads to considerable nonplanarity of the purine fragment and unusual changes in the amino group geometry. The formation of N−H···O hydrogen bonds with the participation of this substituent results in a disruption of the relationship between the pyramidality of the amino group and the length of the C−N bond. Because of the specific geometry of the H bonds, a shortening of the C(6)−N(10) bond in the adenine·12H$_2$O complex does not entail a flattening of the nitrogen atom as compared to isolated adenine.

Our data reveal the possibility of the formation of unusual hydrogen bonds in polyhydrated complexes of adenine. The saturation of water binding sites within nucleobase creates possibilities for the formation of nonstandard hydrogen bonds. Among them are the C−H···O and N(H$_2$)···H−O bonds. In particular, the ability of the amino group to form N···H−O bonds where the nitrogen atom acts as a proton acceptor has been demonstrated. This indicates that the character of the interactions between adenine and water is much more complex, as concluded earlier. An unsymmetrical arrangement of 12−16 water molecules around adenine allows us to assume that the cavity around the nucleobase in adenine aqueous solution should be unsymmetrical. We can also assume that this number of water molecules cannot cover both faces of adenine because of the nonplanar geometry of the nucleobase.

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