Intramolecular Proton Transfer in Mono- and Dihydrated Tautomers of Guanine: An ab Initio Post Hartree−Fock Study

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Abstract: The results of an ab initio post Hartree−Fock study of the molecular structures, relative stabilities, and mechanisms of intermolecular proton transfer in isolated, mono- and dihydrated guanine complexes are reported. The geometries of the local minima and transition states were optimized without symmetry restrictions by the gradient procedure at the HF and the MP2 levels of theory and were verified by energy second derivative calculations. The standard 6-31G(d) basis set was used. The single point calculations have been performed at the MP4(SDQ)/6-31G(d)//MP2/6-31G(d) and the MP2/6-311++G(d,p)//MP2/6-31G(d) approximations. All values of total energies have been corrected for zero point energy contributions scaled by a factor of 0.9. The post Hartree−Fock ab initio theory predicts the height of the proton transfer barrier for monohydrated guanine complexes to be approximately two times lower for the tautomeric oxo−hydroxo reactions and approximately three times lower for the reverse hydroxo−oxo reactions compared with non-water-assisted processes. The influence of polar media (Onsager's self-consistent reaction field model) slightly changes these values according to the polarity of the tautomers. The influence of the stepwise interaction with one and two water molecules monotonically changes the order of the relative stability of guanine tautomers from the gas phase to the one which corresponds to the experimentally measured relative stabilities in polar solutions. We have found a 2-fold water influence on the NH_2-nonplanarity phenomena: they are the source of nonplanarity for the hydroxo tautomers, and they also decrease the nonplanarity for the oxo tautomers.

1. Introduction

A fundamental understanding of the biological role of the nucleic acid bases is coupled directly with a knowledge of physical and chemical behavior of isolated and/or solvated bases and their hydrogen-bonded pairs. Among the properties of importance is the possible existence of the DNA bases in so-called "rare" tautomeric forms which can increase the probability of mispairing of purines and pyrimidines and hence may lead to an increase in the chance of spontaneous point mutations.[1,2] Therefore, a large number of experimental and theoretical attempts have been undertaken to study the properties of the DNA bases including prototropic tautomer phenomena (for references see refs 3 and 4).

The nucleic acid bases exhibit prototropic tautomerism that can be classified into two types.[5a] One type is connected with a labial hydrogen atom of the substituent (the NH_2− group of adenine and the NH_2− or OH− groups of guanine and cytosine; the OH− group in uracil). The proton may either remain attached to the heterocyclic ring nitrogens or can migrate to the external N or O atoms forming "rare" tautomeric forms (Ade*, Gua*, Ura*, and Cyt*). The second type of prototropic tautomerism of purines is connected with the mobility of the proton attached at the imidazole ring nitrogen. In this case the proton can migrate to another imidazole nitrogen position or to the six-membered- ring nitrogens.

Among a number of physical and chemical factors which are responsible for the tautomeric equilibrium between the "normal" and "rare" forms such as excitation,[6a] chemical modification,[6b] metal stabilization,[6c] electron attachment,[6d] irradiation,[6d] etc., solvation (hydration) occupies one of the most important roles. The solvent can control the dynamics of a proton transfer

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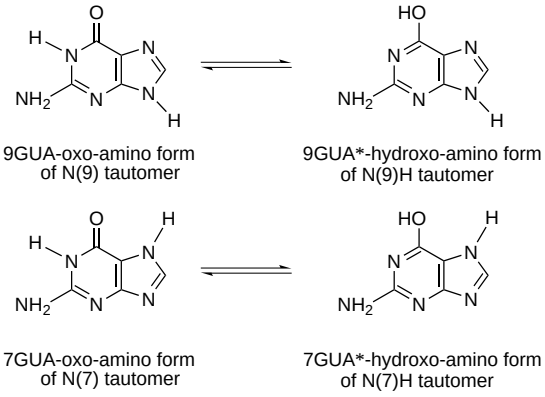
reaction within two distinct types of solute/solvent interactions. First are the specific short-range hydrogen bonding interactions and second the long-range solvent polarization interactions. In the first case an explicit interaction with a limited number of solvent (water) molecules could influence the whole reaction path by lowering the potential energy barrier due to the direct participation in intramolecular proton transfer. This case will be the subject of concern in this paper.

The general phenomena that we will investigate contains a vast number of problems connected with the hydration of DNA bases such as the following: What kind of changes are caused by direct interaction with a few (one and two in our case) water molecules on such characteristics of isolated nucleic bases as geometry, stability of tautomers, and the ability to effect intermolecular proton transfer? And how significant is the influence of the continuum formed by water molecules? Each of these problems is nontrivial. For example, an analysis of geometrical changes is essential to understand the nonplanarity of the amino groups in the DNA bases.[4c,9] The experimental stability of the DNA isolated species in water is well-known—only the amino-oxo forms are observed. However, the questions concerning the relative stability of tautomers hydrated by the selected number of water molecules has risen in response to the possibility of local hydration of the DNA bases in the first solvation shell.[10d,e] Discussions of the relative stability of the bases' tautomers from both theoretical and experimental points of view usually stand on the assumption of thermodynamic control of these transformations. To our knowledge the questions concerning the rate of intramolecular proton transfer and other related details are never discussed in experimental works on DNA bases (there are few papers where an attempt to detect "rare" tautomers in aqueous solutions has been made,[10a−c] but finally these observations did not find support in more precise experiments[11]). However, in the case of prototypic molecules the results of an experimental NMR study of the double proton-transfer phenomena in solvents and in the solid state are available (for references see ref l2).

The available theoretical calculations are not conclusive, either. The proton-transfer barrier and the assistance of water molecules have been investigated by the ab initio technique only for such simple prototypic molecules such as formamide,[13] acetamide,[14] and formamidine.[15] According to the most accurate calculations performed for tautomerization of formamide ↔ formamidic acid with the correlation-consistent Dunning's basis set at the MP2 level of theory, the ZPE-uncorrected value of the proton-transfer barrier amounts to 189.1 kJ·mol^{-1}.[16] An intimate involvement of the solvent (a direct water molecule involvement in the proton-transfer transition state) has a crucial role in such transformations, reducing the proton-transfer barrier to the value of 77.4 kJ·mol^{-1}.[13a] Similar results have been obtained for formamidine.[15] The local minima of mono- and dihydrated complexes of pyridone have been calculated at the MP2/6-31+G(d,p) level.[5b] A limited number of geometry optimizations reported in the literature for some DNA bases' monohydrated complexes have been carried out only at the Hartree−Fock level.[5c] We also would like to mention the study where the transition states of water−2-pyridone complexes were located at the HF/3-21G level.[5d] In addition very recently the geometry of a number of monohydrated complexes of cytosine and 9-guanine has been calculated at the MP2/6-31G(d) level, and the electronic spectra of these hydrates have been calculated by using the INDO/S method.[4k]

According to the high-level ab initio calculations (geometry optimization at the MP2 level and the higher order corrections of an energy value up to the MP4(SDTQ) or CCSD(T) level[4e−j]), at least two of the DNA bases (cytosine and guanine) have a number of tautomers with very close internal energies. These calculations are in excellent correspondence with the experimental data on the distribution of isolated tautomers in argon and nitrogen matrixes.[7] It is also known[7a] that guanine is the only nucleic acid base of biological significance for which high concentrations of the "rare" tautomer have been found to occur in the gas phase[8] and in inert gas matrixes.[7a] Among the possible tautomers of guanine, we have chosen for the present study four of the lowest energy forms related by the oxo−hydroxo equilibrium according to the following scheme:



A challenging task of simulating proton transfer over hydrogen bonds in nucleic acid bases has not received proper attention from the computational community. Only one very recent paper[4i] reveals the results of such studies for the gas-phase guanine; however, the evaluated barrier for proton transfer is much higher to be of importance for biological processes.

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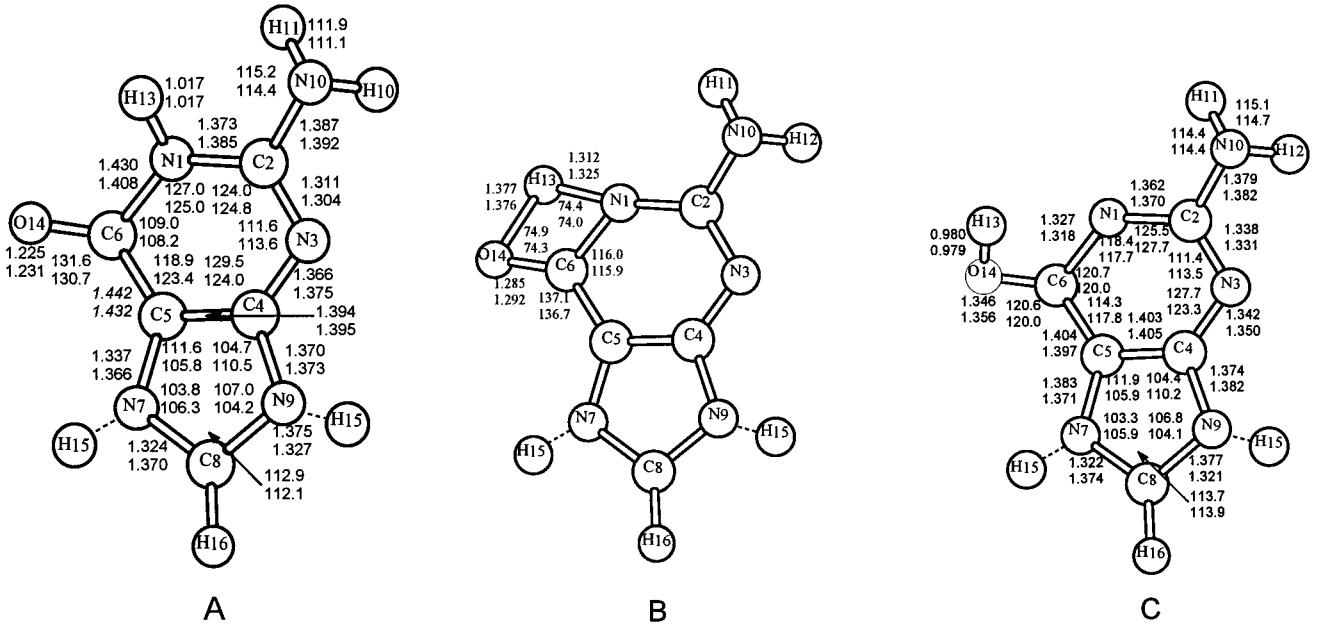

Figure 1. (A) The MP2/6-31G(d) geometry of the oxo-amino-N(9)H (top index, H_{15} connected to N9) and oxo-amino-N(7)H (bottom index, H_{15} connected to N7) guanine. (B) The MP2/6-31G(d) transition state of intramolecular proton transfer from oxo-amino-N(9)H and oxo-amino-N(7)H) guanine to hydroxo-amino-N(9)H and hydroxo-aminoN(7)H guanine. (C) The MP2/6-31G(d) geometry of the hydroxo-amino-N(9)H and hydroxo-amino-N(7)H) guanine.

Our current study devoted to water-assisted proton transfer reveals a quantitative new picture of this phenomena and, contrary to the gas-phase results, proves that this mechanism might depict important subprocess of many biological processes.

2. Computational Methods

The ab initio LCAO-MO method[17] was used for the study of the interaction of guanine tautomers with water molecules. The calculations were carried out with the Gaussian-92 program.[18] The standard 6-31G-(d) basis set was used. All the geometries of local minima were optimized without symmetry restrictions (C_1 symmetry was assumed) by the gradient procedure[19] initially at the HF level and subsequently at the second order of closed shell restricted Möller−Plesset perturbation theory.[20] The initial geometries of the transition state structures were established on the basis of the geometrical parameters of the oxo and hydroxo complexes with water molecules and were completely optimized by the gradient procedure by using OPT = TS in the Gaussian-92 program. The local minima and transition states were verified by establishing that the matrixes of the energy second derivatives (Hessians) (at the HF/6-31G(d) level) have zero and one negative eigenvalue, respectively. The single point calculations were performed at the MP4(SDQ)/6-31G(d)//MP2/6-31G(d) level of theory and at the MP2/6-311++G(d,p)//MP2/6-31G(d) level. The total energies have been corrected for the HF/6-31G(d) zero-point energies scaled by a factor of 0.9.

To estimate the effect of the polar medium on the relative stability of guanine tautomers and their mono- and dihydrated complexes, we applied the Onsager reaction field model[21] as implemented in the Gaussian-92 program. In this model the solvent is viewed as a continuous dielectric medium, of uniform dielectric permittivity ϵ. The solute occupies a spherical cavity within the solvent. We have used the relative permittivity $\epsilon = 80.0$ and the cavity radius obtained from the calculation of the volume (option VOLUME of the Gaussian-92 program) of a given molecule. The MP2 single point energy calculated in this way ($MP2_{solv}$) was also corrected for the scaled zero point energy. To estimate the influence of the polar medium at the MP4 level, the energy difference between MP2 and $MP2_{solv}$ has been added to the MP4(SDQ) results for all isolated molecules and complexes ($MP4_{solv}$).

The entropy values have been evaluated from the 6-31G(d) optimized geometries for the gas phase and in solvent. The Gibbs free energy has been estimated at 298.3 K with use of the standard expression $\Delta G = \Delta H - T\Delta S$.

3. Results and Discussion

Before discussing the obtained results, we would like to justify our choice of the considered mono- and dihydrated complexes of guanine tautomers. Because the main goal of this study is an evaluation of water-assisted proton transfer, we are only interested in the cyclic forms of these complexes. In such systems the water molecules are specifically located in positions appropriate for direct assistance of the proton-transfer process modifying the reaction path. In addition, both experimental and theoretical data support the existence of structures similar to those of the water−guanine complexes calculated by us: (i) according to the X-ray data of guanidine monohydrate,[23a] the water molecule is located in the vicinity of the carbonyl oxygen; (ii) according to the calculations of formamide, and acetamide−water complexes,[13,14] the >C═O··H_2O··HN< bifurcated structure is really the global minimum; (iii) very recently it has been concluded from the studies of the rotationally resolved fluorescence excitation spectrum[23c] that the mono- and dihydrated complexes of pyridone have the same geometrical structure as assumed for the 9(7)GUA·H_2O and the 9(7)GUA·$2H_2O$ species in this study.

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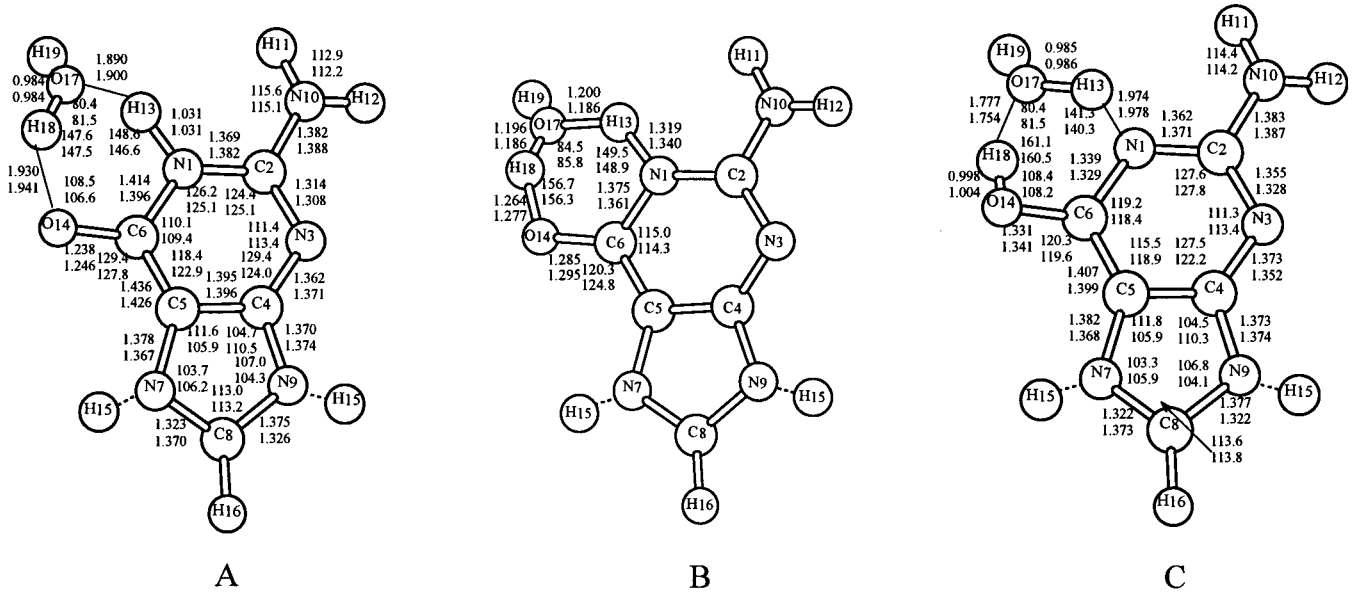

Figure 2. (A) The MP2/6-31G(d) geometry of the monohydrated oxo-amino-N(9)H (top index, H_{15} connected to N9) and oxo-amino-N(7)H (bottom index, H_{15} connected to N7) guanine. (B) The MP2/6-31G(d) transition state of intramolecular proton transfer from monohydrated oxo-amino-N(9)H and oxo-amino-N(7)H guanine to monohydrated hydroxo-amino-N(9)H and hydroxo-amino-N(7)H guanine. (C) The MP2/6-31G(d) geometry of the monohydrated hydroxo-amino-N(9)H and hydroxo-amino-N(7)H guanine.

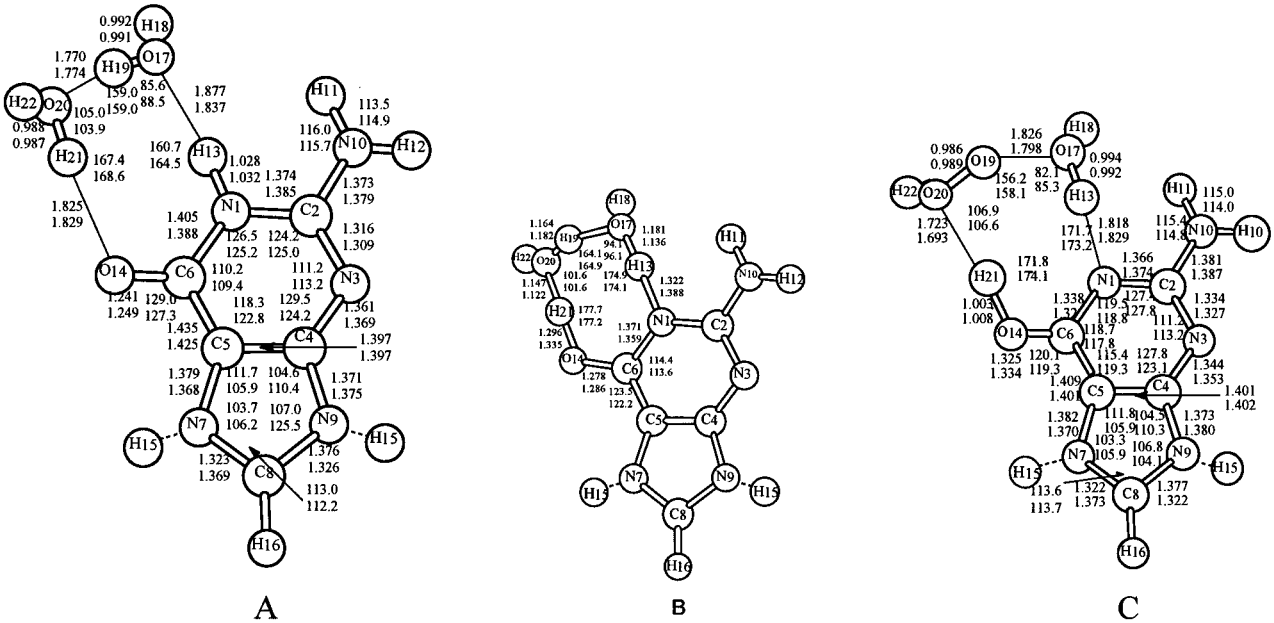

Figure 3. (A) The MP2/6-31G(d) geometry of the dihydrated oxo-amino-N(9)H (top index, H_{15} connected to N9) and oxo-amino-N(7)H (bottom index, H_{15} connected to N7) guanine. (B) The MP2/6-31G(d) transition state of intramolecular proton tranfer from dihydrated oxo-amino-N(9)H and oxo-amino-N(7)H guanine to dihydrated hydroxo-amino-N(9)H to hydroxo-amino-N(7)H guanine. (C) The MP2/6-31G(d) geometry of the dihydrated hydroxo-amino-N(9)H and hydroxo-amino-N(7)H guanine.

3.1. Geometry of Local Minima. The geometrical parameters of the considered forms of 7(9)GUA and 7(9)GUA*, their mono- and dyhydrated complexes, and the corresponding transition states are presented in Figures 1−3. To date the calculations of the geometrical parameters of the guanine tautomers at a correlated level have been reported by a number of groups.[4f−i,22] However, a brief discussion of the geometrical structure of guanine tautomers is only presented in two papers.[4f,i] The usual explanation for a short discussion is the lack of appropriate experimental reference data because the structural parameters for the molecule of interest are known only for the crystallographic structures of guanine monohydrate. In Figure 4 the calculated molecular parameters and X-ray geometry of the monohydrate of 9GUA and 9-ethylguanine[23] are presented to conclude a close correspondence between these and our MP2 calculated data. However, due to the differences in the physical meaning of the geometrical parameters derived from the crystallographic data and from the MO calculations considering the crystal bulk influence and the limitations of the MP2 approach, we did not perform a statistical analysis for the correspondence between our data of 9GUA·H_2O (Figure 2) and the experimental X-ray data of the 9GUA-monohydrate.[23a]

As expected, the influence of the interaction with one and/or two water molecules on the bond distances and bond angles of guanine tautomers manifests itself mainly in the region of intermolecular hydrogen bonding. All other structural param-

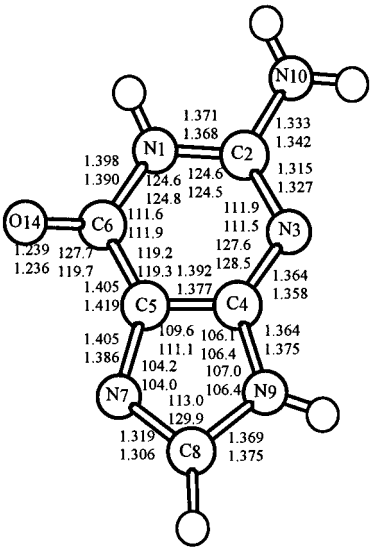

Figure 4. X-ray geometry[23] of the oxo-amino-N(9)H guanine monohydrate (top index) and 9-ethylguanine (bottom index).

Table 1. The Distances (Å) between Heavy Atoms of Hydrogen Bonded Systems in Monoydrated Guanine Forms Calculated at the MP2/6-31G(d) Level

complex	R_{N1O17}	R_{O14O17}
9GUA·H_2O	2.822	2.811
9GUA*·H_2O	2.810	2.740
9TS·H_2O	2.431	2.410
7GUA·H_2O	2.818	2.820
7GUA*·H_2O	2.808	2.718
7TS·H_2O	2.434	2.411

eters of the heterocyclic rings are virtually the same (except for the N_1-C_6 "single" bond of the 9(7)GUA tautomers, which also undergoes the influence of hydrogen bonding) and depend only on the chemical structure of the tautomers.

An analysis of the structural parameters in hydrogen bonded systems A−H···B (where A and B are heavy atoms which are involved in hydrogen bonding) is crucial for an understanding of the reasons for the lowering of the proton-transfer barrier.[24] According to the classification of nearly linear hydrogen bonds [24b] (angle AHB is > 165°), the very low values of the proton-transfer barriers take place when the A−B distance is <2.5 Å (A and B are oxygens and/or nitrogens). The decreasing of the AHB angle usually leads to a reduction in the hydrogen bond energy. In the case of an A−B distance between 2.8 and 3.0 Å, the value of the proton-transfer barrier is rather high. An analysis of the data collected in Tables 1 and 2 together with the structural data presented in Figure 1−3 allows us to make some conclusions. First, based on the calculated geometrical parameters of mono- and dihydrated guanine tautomers, the hydrogen bonds predicted for these systems are rather weak. Second, the addition of a second water molecule makes noticeable changes in the geometrical structure of hydrogen bonded complexes. All of them became much more linear compared to the monohydrated complexes; the distance between $O_{14}-O_{20}$ of the dihydrated complexes is much shorter than the corresponding distance between $O_{14}-O_{17}$ of the monohydrated complexes, and also the distance between $O_{17}-O_{20}$ is much

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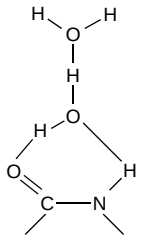
Table 2. The Distances (Å) between Heavy Atoms of Hydrogen Bonded Systems in Dihydrated Guanine Forms Calculated at the MP2/6-31G(d) Level

complex	R_{N1O17}	R_{O17O20}[a]	R_{O14O20}
9GUA·$2H_2O$	2.868	2.719	2.794
9GUA*·H_2O	2.805	2.757	2.720
9TS·$2H_2O$	2.501	2.443	2.413
7GUA·$2H_2O$	2.845	2.752	2.804
7GUA*·H_2O	2.817	2.740	2.697
7TS·$2H_2O$	2.521	2.409	2.456

[a] The O−O distance in $(H_2O)_2$ is 2.915 Å at the MP2/6-31G(d) level of theory.

shorter than the interatomic distance in a free water dimer (see data in Tables 1 and 2). In addition the N_1-O_{17} interatomic distance becomes longer in all dihydrated complexes except 9GUA*·$2H_2O$. All observed tendencies for the 9(7)GUA·H_2O and 9(7)GUA·$2H_2O$ complexes are also in very good correspondence with the available experimental[23c] and calculated[5b] data of the mono- and dyhydrated complexes of pyridone. Thus, one might expect that the participation of two water molecules in a proton-transfer reaction between the N_1 and O_{14} atoms of a guanine molecule should be more favorable than the participation of only one water. On the other hand, we should take into account that the interaction of guanine tautomers with one water molecule forms around the target proton the well-known six-membered ring which is, as usual, more stable than the eight-membered ring formed in dihydrated tautomers. Consequently, only direct evaluation of the proton-transfer barrier can distinguish whether the reaction involving one or two water molecules is more favorable.

Finally we need to mention that an attempt to optimize the dihydrated guanine complex of the following structure



has not been successful due to the conversion of this structure during geometry optimization to the 9(7)GUA·$2H_2O$ complex presented in Figure 3.

The *ab initio* calculations[9a−g] predict the nonplanar geometry of the amino groups of the isolated DNA bases. There are two structural sources of nonplanarity for the DNA bases: (i) a partial sp^3 hybridization of the amino group and (ii) the interaction of the amino group hydrogen atoms with the closest atoms belonging to the rest of the DNA base. Because both of these factors are the result of a delicate balance of intramolecular forces and are sensitive to the chemical structure,[4e] even indirect interaction with a water molecule should produce noticeable changes in these parameters. The simplest way to analyze the partial sp^3 hybridization of the amino group (we will call it the nonplanarity of the first type) is to discuss the sum of the CNH and HNH angles of the amino group[9g] ($\sum$AH in Table 3). In this case the degree of nonplanarity could be estimated as the deviation of $\sum$AH from 360° (δ in the Table 3).

To analyze the nonplanarity of the second type, it is also convenient instead of $\angle H_{11}N_{10}C_2N_3$ to introduce the angle $\varphi = 180° - \angle H_{11}N_{10}C_2N_3$. In this case it should be clear that the difference between φ and $\angle H_{11}N_{10}C_2N_3$ (let us call it Δ in

Table 3. Selected Values of Torsion Angles of 9- and 7-Guanine Tautomers[a] Calculated at the MP2/6-31G(d) Level

	molecules											
parameter	9GUA	9GUA*	9GUA·H_2O	9GUA*·H_2O	9GUA·$2H_2O$	9GUA*$2H_2O$	7GUA	7GUA*	7GUA·H_2O	7GUA*·H_2O	7GUA·$2H_2O$	7GUA*$2H_2O$
$\sum$AH[b]	337.9	343.7	340.2	341.5	345.4	343.9	335.2	342.4	337.9	339.9	343.0	341.2
δ[c]	22.1	16.3	19.8	18.5	14.6	16.1	24.8	17.6	22.1	20.1	17.0	18.8
$\angle H_{11}N_{10}C_2N_3$	140.2	158.1	146.3	153.3	156.7	155.6	133.4	155.6	141.3	150.4	152.8	151.0
$\angle H_{12}N_{10}C_2N_3$	11.8	22.4	15.2	20.5	18.8	19.8	8.3	21.5	12.8	19.4	18.1	18.6
φ[d]	39.8	21.9	33.7	26.7	23.3	24.5	46.1	24.4	38.7	29.6	27.2	29.0
Δ[e]	28.0	−0.5	18.5	6.2	4.9	4.7	37.8	2.9	25.9	10.2	9.1	10.4

[a] The calculated distortion of the atoms of heterocycles from planarity is nonsignificant (±1−2°) and completely corresponds to the data of ref 4f. [b] $\sum AH = \angle H_{11}N_{10}C_2 + \angle C_2N_{10}H_{12} + \angle H_{12}N_{10}H_{11}$. [c] $\delta = 360 - \sum AH$. [d] $\varphi = 180.0 - \angle H_{11}N_{10}C_2N_3$. [e] $\Delta = \varphi - \angle H_{12}N_{10}C_2N_3$.

Table 4. Relative Stability (kJ·mol^{-1}) and Dipole Moments (D) of Guanine Tautomers and Their Mono- and Dihydrated Forms

species	MP4(SDTQ)/6-31G(d,p)//MP2/6-31G(d,p)[a]	MP4(SDQ)/6-31G(d)//MP2/6-31G(d)	MP4(SDQ)/6-31G(d)//MP2/6-31G((d) (in solvent)[b]	MP2/6-311++G(d,p)//MP2/6-31G(d)	MP2/6-311++G(df,pd)//MP2/6-31G(d,p)[a]	MP2/6-31G(d)//MP2/6-31G(d)	MP2/6-31G(d)//MP2/6-31G(d) (in solvent)[b]	μ[c]	μ_{solv}[b,c]
9GUA	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.0 (5.9)[c]	7.5 (6.6)[d]
9GUA*	7.8	13.6	26.2	1.2	−4.3	9.5	22.1	3.3	3.8
7GUA	−0. 4	1.6	18.5	1.8	−0.8	−0.2	13.3	1.6 (2.0)[c]	2.3 (2.6)[d]
7GUA*	21.2	28.7	36.2	13.1	9.0	22.4	30.0	4.4	5.3
9GUA·H_2O		0.0	0.0	0.0		0.0	0.0	5.7 (5.0)[c]	5.9 (5.7)[d]
9GUA*·H_2O		19.7	21.7	9.5		15.1	17.2	4.3	4.9
7GUA·H_2O		−4.1	−11.0	0.5		−2.3	−9.3	1.6 (2.6)[c]	2.7 (3.7)[d]
7GUA*·H_2O		15.6	10.6	17.6		12.8	7.8	3.1	3.8
9GUA·$2H_2O$		0.0	0.0	0.0		0.0	0.0	4.9 (4.1)[c]	5.1 (4.5)[d]
9GUA*0·$2H_2O$		28.7	30.7	19.5		23.6	25.4	3.9	4.4
7GUA·$2H_2O$		6.8	9.3	2.7		4.8	7.3	2.8 (4.4)[c]	4.1 (6.0)[d]
7GUA*0·$2H_2O$		34.3	41.3	26.1		31.8	33.5	3.4	4.2

[a] ZPE not included, referred from ref 4i. [b] Using the Onsager model, $\epsilon = 80.0$. [c] Evaluated from MP2-optimized geometry using HF density. [d] Dipole moment of the corresponding transition state.

Table 3) is the simplest estimation of the interaction of the H_{11} amino group hydrogen atom with the closest H_{13} atom of the guanine tautomers.

Let us start the analysis of the nonplanarity of the calculated guanine tautomers with a consideration of the first type of nonplanarity. Because $\sum$AH (Table 3) practically does not change for the same type (oxo/hydroxo) of tautomers and differs significantly from the value of 360° (see parameter δ in Table 3), we should conclude that neither a change in the chemical structure of the guanine tautomers nor the interactions with two water molecules are able to change significantly the partial sp^3 hybridization of the amino group. This is not the case for nonplanarity of the second type. First of all one can clearly see that the source of this type of nonplanarity in the isolated tautomers is the repulsion between the H_{11} atom of the amino group and the H_{13} atom attached to the ring because the value of Δ approaches near zero degrees for both hydroxo tautomers when the H_{13} atom is not connected to the N_1 atom. The influence of the water molecules is 2-fold. They are the source of the second type of nonplanarity for the hydroxo tautomers, and they also reduce this type of nonplanarity for the oxo type of tautomers. Hence, we can conclude that this kind of nonplanarity is extremely sensitive to the chemical nature of the tautomers. Also the interactions of the amino group hydrogens with atoms of the six member rings are virtually the same for both oxo- and hydroxo- tautomers.

3.2. Relative Stability. The calculated data of the relative stability and Gibbs free energy of isolated mono- and dihydrated guanine tautomers are collected in Tables 4 and 5. The entropy contributions are rather negligible, so the data collected in Tables 4 and 5 imply the same order of stability, and we will discuss them together. According to the results of matrix isolation IR studies of guanine tautomers[7b,8,26] the 7GUA molecule is probably the most stable one among the lowest energy forms 7GUA, 9GUA, and 9GUA*. This conclusion is supported by our data obtained at the MP2/6-31G(d)//MP2/6-31G(d) level and by the calculations performed at the MP2/6-311++G(d,p)//HF/6-31G(d,p) level.[4h] However, a precise experimental evaluation of the relative stability of the hydrated guanine complexes still does not exist. That is why we will concentrate our discussion mainly on the qualitative aspects of this problem.

A knowledge of the relative stability of such local hydrated species might be useful not only for studies of the DNA bases carried out in nonpolar solvents[25] but also to provide a general picture of the DNA interactions especially taking into account the suggestion that the hydration of the DNA bases in the first solvation shell might be very local.[10d,e] While for the isolated

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Table 5. Gibbs Free Energy (kJ·mol^{-1}) of Guanine Tautomers and Their Mono- and Dihydrated Forms

species	MP4(SDQ)/6-31G(d)// MP2/6-31G(d)	MP4(SDQ)/6-31G(d)// MP2/6-31G(d) (in solvent)[a]	MP2/6-31++G(d,p)// MP2/6-31G(d)	MP2/6-31G(d)//MP2/ 6-31G(d)	MP2/6-31G(d)// MP2/6-31G(d) (in solvent)[a]
9GUA	0.0	0.0	0.0	0.0	0.0
9GUA*	14.2	26.6	1.8	10.1	22.5
7GUA	1.4	18.3	1.6	−0.4	13.1
7GUA*	28.8	36.3	13.2	22.5	30.1
9GUA.H_2O	0.0	0.0	0.0	0.0	0.0
9GUA*.H_2O	20.4	23.1	10.2	16.8	18.6
7GUA.H_2O	−3.6	−10.4	1.0	1.8	−8.7
7GUA*.H_2O	16.1	11.9	18.1	13.3	9.1
9GUA.2H_2O	0.0	0.0	0.0	0.0	0.0
9GUA*0·2H_2O	30.4	32.7	21.2	25.3	27.0
7GUA.2H_2O	6.4	9.8	2.5	4.6	7.8
7GUA*0·2H_2O	35.5	43.0	27.3	33.0	35.2

[a] Using the Onsager model, $\epsilon = 80.0$.

tautomers of guanine the relative stability increases in the following way

$$7GUA \approx 9GUA \approx 9GUA^* \gg 7GUA^* \quad (1)$$

the stability in water solution (continuum solvent model) follows a different pattern

$$9GUA \gg 7GUA \gg 9GUA^* \gg 7GUA^* \quad (2)$$

Relationships 1 and 2 correspond well to the available experimental data for the species in the gas phase[7,8,26] and in a polar medium.[27] The tendency to stabilize the 7GUA tautomer remains for the guanine monohydrates. According to the data presented in Table 4, the following stability pattern is established for the complexes of guanine with one water molecule:

$$7GUA{\cdot}H_2O \approx 9GUA{\cdot}H_2O \gg 9GUA^*{\cdot}H_2O \gg 7GUA^*{\cdot}H_2O \quad (3)$$

The electrostatic contribution to the interaction with polar solvents makes the absolute preference of the 7GUA·H_2O complex:

$$7GUA{\cdot}H_2O > 9GUA{\cdot}H_2O \gg 9GUA^*{\cdot}H_2O \gg 7GUA^*{\cdot}H_2O \quad (4)$$

We would like to make the following comments on relationships 3 and 4. Because solvation of the DNA bases in the first solvation sphere is very local[10d,e] the model that takes into account a small number of water molecules which are surrounded in a dielectric continuum seems to be one of the possible approximations which account for these phenomena. The results obtained in this way are considerably different compared to the data of the pure Onsager model (2). The described peculiarity of monohydrated complexes is changed for the dihydrated isolated species which display the quite usual tendency to approach the stability of fully hydrated complexes (2):

$$9GUA{\cdot}2H_2O > 7GUA{\cdot}2H_2O \gg 9GUA^*{\cdot}2H_2O \gg 7GUA^*{\cdot}2H_2O \quad (5)$$

3.3. Proton Transfer. The picture of prototropic transformations in the nucleic acid base tautomers will never be complete without a knowledge of inter- and intramolecular proton transfer kinetics. The most general data describing the kinetics of proton transfer are the set of temperature dependent rate constants. As mentioned earlier, these data for nucleic acid bases are not yet available from either experimental or theoretical studies. Nevertheless, very recently the theoretical calculations of prototypic molecules (isolated and monohydrated complexes of formamidine and formamide[28]) have been carried out at the correlated ab initio and DFT levels to evaluate the thermal rate constants by using a canonical variational transition state theory[29] with multidimensional semiclassical tunneling corrections.[29] To calculate the rate constants at this level of approximation, at least 40 points on the path of proton transfer should be available. Such calculations are not feasible for such a big system as guanine with use of the available computational facilities; so we will discuss only the calculated values of the proton transfer barriers which are directly coupled with the values of the rate constants. We will also use the published values of the thermal rate constants[28] as the reference points in our discussion.

Let us define the forward reaction as the proton transfer from the oxo to the hydroxo form of the guanine and hydrated guanine complexes, and the reverse is the reaction in the opposite direction. The calculated values of the proton transfer barriers in 7- and 9-guanine and in their hydrated complexes are collected in Tables 6 and 7. Due to the high sensitivity of the barrier height at the correlated levels of computation (for example, for water assisted proton transfer in formamide the calculated barrier height is as follows:[28b] 108.3 (QCISD), 100.8 (DFT/BH&H-LYP), 94.1 (MP2), 81.6 (DFT/B3-LYP), and 69.0 (DFT/B-LYP) kJ·mol^{-1}) the observed difference between the MP4 and the MP2 results is not surprising for us. First of all, one can see a dramatic decrease in the barrier heights (to compare with the gas-phase data) when at least one water molecule participates directly in the proton transfer reactions. The values of the proton transfer barriers are decreasing approximately 2-fold for the forward reactions and approximately 3-fold for the reverse reactions. Also there are differences between the barrier heights in mono- and dihydrated guanine complexes. However, generally the values of the proton

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Table 6. Zero-Point Corrected[a] Barrier Heights for Proton Transfer for 9-Guanine (kJ·mol^{-1})

process	MP4(SDQ)/6-31G (d)// MP2/6-31G(d)	MP2/6-31G(d)// MP2/6-31G(d)	MP4(SDQ)/6-31G(d)// MP2/6-31G(d) (in solvent)	MP2/6-31G(d)// MP2/6-31G(d) (in solvent)
forward reaction				
9GUA → 9TS	164.0	148.5	166.9	150.6
9GUA·H_2O → 9TS·H_2O	76.1	58.1	74.5	56.5
9GUA·2H_2O → 9TS·2H_2O	95.4	71.9.	98.3	73.2
reverse reaction				
9GUA* → TS	150.2	128.4	141.0	128.4
9GUA*·H_2O → 9TS·H_2O	56.9	42.7	53.1	39.3
9GUA*·2H_2O → 9TS·2H_2O	66.5	48.5	65.7	47.7

[a] ZPE evaluated at the HF/6-31G(d) level.

Table 7. Zero-Point Corrected[a] and Barrier Heights for Proton Transfer for 7-Guanine (kJ·mol^{-1})

process	MP4(SDQ)/6-31G(d)// MP2/6-31G(d)	MP2/6-31G(d)// MP2/6-31G(d)	MP4(SDQ)/6-31G(d)// MP2/6-31G(d) (in solvent)	MP2/6-31G(d)// MP2/6-31G(d) (in solvent)
forward reaction				
7GUA → 7TS	176.5	161.0	174.3	162.3
7GUA·H_2O → 7TS·H_2O	81.3	62.2	79.6	60.7
7GUA·2H_2O → 7TS·2H_2O	94.7	71.3	89.3	65.9
reverse reaction				
7GUA* → 7TS	149.3	138.5	156.4	145.6
7GUA*·H_2O → 7TS·H_2O	54.4	40.6	54.8	41.4
7GUA*0·2H_2O → 7TS·2H_2O	61.9	48.5	57.3	39.7

[a] ZPE evaluated at the HF/6-31G(d) level.

transfer barrier of two hydrated complexes are slightly higher in both directions compared to the mohohydrated species.

The influence of a polar surrounding, included in the framework of the Onsager continuum model, is not so noticeable; nevertheless, due to the opposite change of the dipole moments in pairs 9GUA ↔ 9GUA* and 7GUA ↔ 7GUA* and their corresponding hydrated species, the important change still exists. The 9GUA ↔ 9GUA* reaction is followed by a decrease of the dipole moment value in the forward direction, but the 7GUA ↔ 7GUA* reaction manifests the opposite tendency. As a result, the barrier heights in a polar medium are slightly larger for forward reactions in the 9GUA species and slightly smaller for reverse reactions in the 9GUA* complexes. For the 7GUA and 7GUA* species this trend is reversed (see Tables 6 and 7).

According to the published results[28b] a noticeable influence of tunneling in contributing to the barrier height in the formamide water complex exists even at 300 K, so we cannot use our values to estimate the rate constants. Nevertheless, some comparisons using the data obtained in refs 28a and 28b could be made. The available value of the calculated thermal rate constant for the proton-transfer barrier in formamidine (gas-phase, non-water-assisted reaction) amounts to 8.37×10^{-14} s^{-1} (300 K) with a corresponding zero-point energy corrected barrier height of 189.1 kJ·mol^{-1}. The calculated value of rate constant for forward water molecule assisted reactions in formamide−water complexes is 4.6×10^{-4} s^{-1} (300 K), and the corresponding value of the proton transfer barrier is 90.8 kJ·mol^{-1}. The calculated value of the rate constant for the reverse reaction is 1.0×10^{5} (300 K) with a barrier height of 46.0 kJ·mol^{-1}.

Because these values have been obtained for the same reaction of prototypic molecules, we believe that the following assumptions concerning gas-phase and water-assisted proton transfer in 9- and 7-guanine molecules are justified. Comparing our values of the proton transfer barriers with those listed below, we expect that the calculated non-water-assisted gas-phase rate constants for both forward and reverse reactions will be significantly different compared to the calculated value for formamidine, but they will never reach the values which characterize any appreciable rate at room temperature. In other words, the value of the proton transfer barrier for non-water-assisted reactions (see Tables 6 and 7) is too large in both directions to be reached with any really observable rate at room temperature. In contrast, the value of water-assisted barriers could produce much higher interconversion rates that should be observable at least in the reverse direction. We expect that a profound preference for the reverse reaction will occur at any temperature of biological importance.

Finally we would like to return to the discussion of the geometrical parameters for the transition states specie (Figures 1−3, Tables 1 and 2). The most prominent difference between the geometries of the local minima and the transition states is demonstrated in a decrease in the interatomic distances between heavy atoms involved in the hydrogen bond which are remarkably shorter in all hydrated transition states (Tables 1 and 2). Except for R_{N1O17} in 9- and 7TS·2H_2O, they certainly reached the threshold of 2.5 Å that divides the strong and the weak hydrogen bonds. Thus, the hydrogen bonds which could be classified as rather weak in minimum energy forms of guanine become considerably stronger for the related transition state forms. As mentioned earlier[24a,b] this kind of change is common for biological molecules and is associated with the possibility of a decrease in the value of the proton transfer barrier. Such a conclusion also has been confirmed by recent studies.[24d,e]

4. Conclusions

In this paper we have reported the results of a comprehensive post Hartree−Fock investigation of the structural parameters, stabilities, and intermolecular proton transfer phenomena in mono- and dihydrated tautomers of guanine. The principal conclusions from this study are the following:

1. The structural parameters of the oxo N(9)H guanine monohydrated molecule calculated at the MP2/6-31G* level are in very good correspondence with X-ray experimental data for N(9)H guanine monohydrate. The calculated trends of the change of structural parameters of mono- and dihydrated oxo

forms of 9- and 7- guanines are in line with the conclusions based on the microwave spectrum of mono- and dihydrated species of pyridone.

2. The unique role of water molecules in controlling the nonplanarity of the NH_2- group has been found. The influence of water molecules is 2-fold. They are the source of nonplanarity for the hydroxo forms of guanine and they also decrease the nonplanarity for the oxo tautomers.

3. We have found that the interaction of guanine tautomers with one and two water molecules monotonically changes the order of gas-phase stability (7GUA $\approx$ 9GUA $\approx$ 9GUA* $\gg$ 7GUA) into the order that corresponds to the stability of the guanine tautomers in a polar solvent: (9GUA$\gg$ 7GUA $\gg$ 9GUA* $\gg$ 7GUA*).

4. An analysis of the barrier heights of forward and reverse reactions of intramolecular proton transfer of isolated mono- and dihydrated guanine species has been performed. We expect that the value of the rate constant in isolated guanine tautomers will be characterized by a nonappreciable rate in both directions at room temperature. The situation should be completely different in mono- and dihydrated guanine complexes where we expect quite sizable rate constants in the direction yielding the oxo-type of guanine tautomers.

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