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Electron and Geometry Structure of Hydrogen-Bonded Complexes of Guanine with One Molecule Methanol. A DFT Level Study

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Summary. The geometries, harmonic vibrational frequencies, and energies of eight hydrogen-bonded complexes of guanine with one molecule methanol are computed using the DFT (*B3LYP*) method together with the 6-31 + G* basis functions. In the investigation two stable tautomers of guanine (oxo-amino N9H and oxo-amino N7H) were chosen. They were included in a variety of H-bonded complexes with one molecule methanol. In order to investigate the nature of the intermolecular bonds, the bonding energies and thermodynamic properties of the complexes were calculated.

Keywords. *Ab initio* calculations; Guanine; Hydrogen-bonding; Density functional calculations.

Introduction

The nucleobases are *DNA* and *RNA* fragments that play an important biological role in the living world. To understand better their biochemical function, knowledge of their interactions with other organic and inorganic molecules in the living organisms is necessary. It is well known that one very important feature of nucleobases is their ability to constitute intermolecular bridges (hydrogen bonds) between themselves. Moreover, they can also constitute short, *i.e.* strong, H-bridges with other protic molecules. For example, with water molecules nucleobases form heavily hydrated systems [1, 2].

Calculations of the hydrated complexes of guanine, performed using second-order *Møller-Plesset* perturbation theory (*MP*2) [3] and the standard 6-31G* basis set, have shown that the two functional groups (OH and NH_2) and the distance N_1–C_6 (numeration as suggested by IUPAC) are extremely sensitive to

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interactions with water [1]. We suppose that the same effects exhibit also other protic organic molecules (*e.g.* methanol) disposing of H-bondings.

The energies of different monohydrated complexes were recently reported [1], but no attempt has been made to explain the relative stabilities of complexes between guanine and methanol.

According to several reported data from laser spectroscopy measurements [4, 5] three tautomers of free guanine are abundant in the jet experiment: oxo-amino N9H, oxo-amino N7H, and hydroxy-imino N9H. The oxo-amino N9H involved in a dimer with cytosine is the *Watson-Crick G-C* pair, which is known to be more stable than all other possible dimers between these two compounds. In the work of *Nir et al.*, which considers dimers of guanine-guanine (*GG*) (*HF*/6-31G(d,p)), it has been clearly demonstrated that the dioxo-amino-guanine-guanine dimer, with a symmetrical $C{=}O\cdots NH/NH{-}O{=}C$ bonding (it exhibits C_{2V} symmetry) [6], is the most stable one. The major result of that work is the experimental and theoretical estimation of structures, and energetic and thermodynamic properties of the dimers. The most stable *GG* dimer has three nonsymmetrical and two symmetrical H-bonds. The UV-UV and UV-IR spectra do not give an experimental evidence (bands) for keto-enol and enol-enol dimers in the investigated wavelength region [6]. Many other theoretical works revealed that the stability of the *GG* dimer is similar to that of the usual guanine-cytosine base pair and, in fact, considerably more stable than that of the adenine-thymine dimer, usually included in the *DNA* structure [6–9].

Due to its low in vitro oxidation potential (about 0.4 eV) guanine is known to be a more easily oxidized nucleobase [10, 11].

The toxic action of methanol in living organisms is explained by its enzyme oxidation to formaldehyde. Thus, in this investigation we attempted to answer the following questions: (1) In what way does the methanol molecule affect the relative stability of the tautomers of guanine? (2) What are the thermodynamic properties of the complex formations between methanol and guanine? (3) What are the hydrogen bonding energies of the supersystems? We tend to believe that the methanol molecule can replace water molecules from hydrated nucleic acids and in this way could cause damages in their structures.

Recently reported calculations on complexes of guanine were limited only to the canonical tautomeric forms of guanine with water. For example, the theoretical models of hydration of nucleobases have been built by means of molecular dynamics [12, 13], Monte Carlo [14], and other quantum-chemical approaches [15, 16]. These investigations were focused on an estimation of the solvation free energy since this value may be directly compared with experimental data. Unfortunately, there is a lack of information about solvation effects and possible complexes formed between non-water molecules with H-atoms and guanine.

Shishkin et al. have studied theoretically (*B3LYP*/6-31G*) twelve monohydrated complexes of the two ketoforms of guanine [1]. The optimization procedure for supersystems of *Gua*-N9H has been initiated by inclusion of 12 starting geometries that reproduce all possible hydrogen bonds between water and guanine molecules. The optimization converged to five stable monohydrates, which will be examined here. They will be compared to supersystems having the same constitution, but containing methanol. There is spectroscopic evidence for existence of the two ketoforms *Gua*-N9H and *Gua*-N7H as stable forms. Their UV [17] bands are located at $\bar{\nu} = 33910$ and $33269\,\mathrm{cm}^{-1}$ and the band for the hydroxy-imino N9H tautomer at $32864\,\mathrm{cm}^{-1}$.

The purpose of this paper is to throw light upon the geometry and electron structure of several stable H-bonded complexes formed between the two oxo-amino guanine tautomers and the methanol molecule. This investigation would contribute to a clarification of the nature of interactions between methanol and nucleobases.

The calculations here were performed by means of the density functional theory including *Becke*'s three-parameters (*B*3) [18] exchange functional along with the *Lee-Yang-Parr* (*LYP*) non-local correlation functional (*B*3*LYP*) [19] and the $6\text{-}31+\mathrm{G}^*$ basis set. The combinations $B3LYP/6\text{-}31+\mathrm{G}^*$ and $HF/6\text{-}31\mathrm{G}^{**}$ have been proven to produce results in reasonable agreement with the experiment [20, 21, 4] for the supersystems adenine-thymine, guanine-cytosine, and their monomers.

An exclusive recent review of theoretical calculations of electron affinities has shown that the *B*3*LYP* functional has given the smallest average absolute error for 91 different compounds when compared to a number of other functionals [20, 22]. The adiabatic electron affinity of guanine appears most sensitive to diffuse functions [21] as well, which arises from the mixing in the dipole-bound state with the valence state.

Results and Discussion

The investigation was carried out with the $B3LYP/6\text{-}31+\mathrm{G}^*$ combination. As it is well known, theoretical methods based on density functional theory are accurate enough to reproduce geometrical parameters, and spectroscopic and energetic values with an error close to the experimental uncertainty (about $8\text{–}13\,\mathrm{kJ\,mol}^{-1}$) [23]. The main disadvantage of the $B3LYP/6\text{-}31+\mathrm{G}^*$ combination is the extensive computational effort.

Structures and Structural Parameters of the Supersystems

Some internal coordinates (see Table 1) of the optimized monomers of guanine clearly show that the NH_2-group lies out of the molecular plane on which all other atoms are situated. The values of the space angles H(14)N(10)C(2)N(3) and H(15)N(10)C(2)N(1) show that this group is twisted on 11.9 and 36.2°. The bond angle $H_{14}N_{10}H_{15}$ in the N9H and N7H monomers are identical to the data found by *Leszczynski* with another basis set and taking into account the error of the methods (*B*3*LYP*) [24]. The data listed in Table 1 show that the H-bonding to the amino group causes an elongation of the N–H bond involved.

The optimized geometries of all H-bonded complexes studied between methanol and oxo-amino (N9H and N7H) tautomers of guanine are depicted in Fig. 1.

In the *Gua*-N9H-1 supersystem the methanol oxygen O(17) constitutes two intermolecular hydrogen bonds with H(16) and H(15). The hydrogen bond $\mathrm{H(16)\cdots O(17)}$ is 0.167 Å shorter than the $\mathrm{H(15)\cdots O(17)}$ one. On the other hand, the dihedral angles H(15)N(10)C(2)N(1) and H(14)N(10)C(2)N(1) are about 12.8 and 4° smaller than in the related monomer of guanine. Moreover the bond $\mathrm{H(16)\cdots O(17)}$ is 0.059 Å longer and the bond $\mathrm{H(15)\cdots O(17)}$ is 0.154 Å shorter than the same bonds in the water analogue of the *Gua*-N9H-1 supersystem ($MP2/6\text{-}31\mathrm{G}^*$) [1].

Table 1. Selected structural parameters of the two monomers of guanine and all supersystems revealing the behavior of the NH_2 group (all internuclear distances are in Å and all angles are in degree)

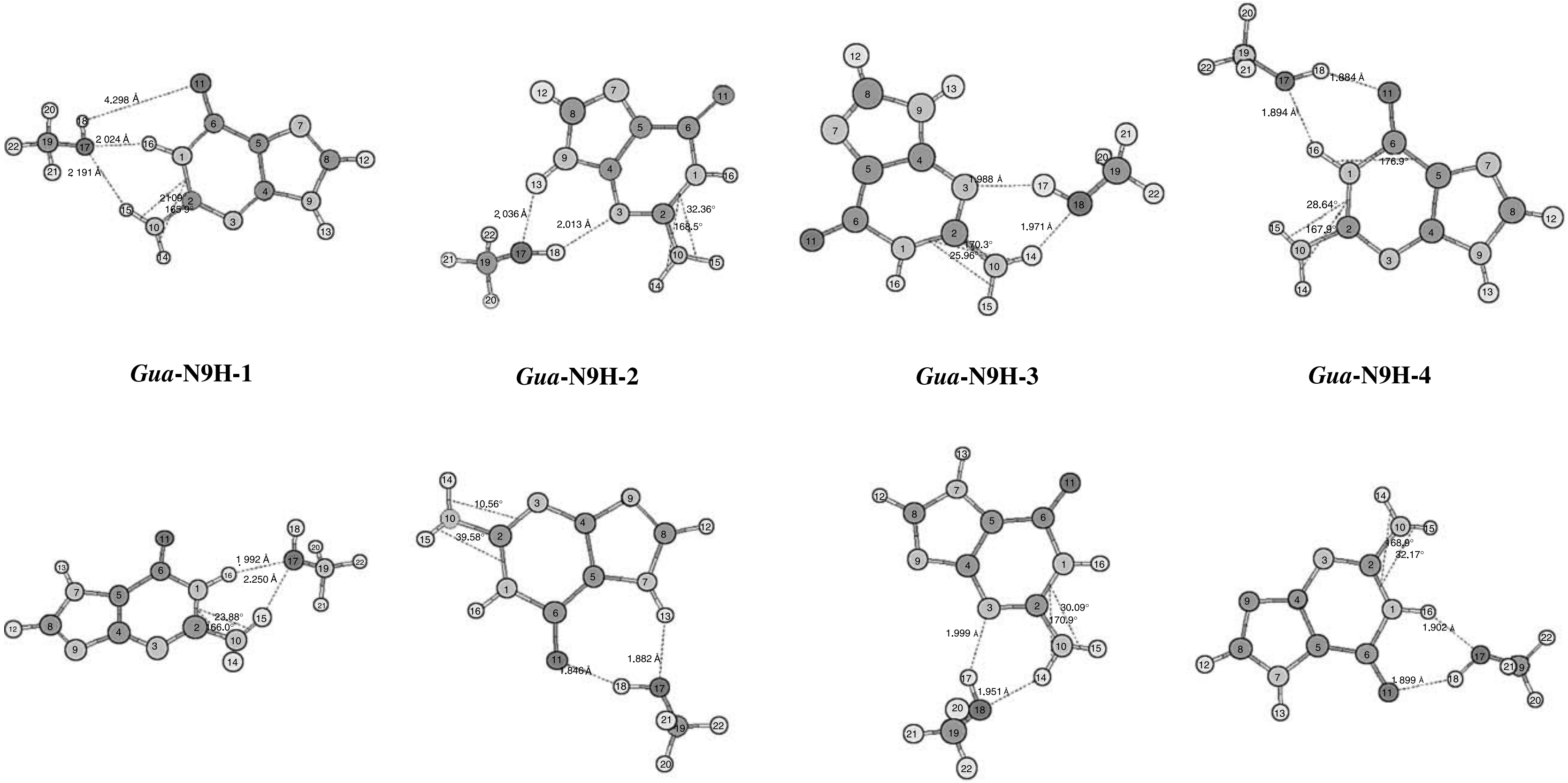
Parameter	Monomers		*Gua*-N9H-*X*				*Gua*-N7H-*X*			
	N9H	N7H	$X=1$	$X=2$	$X=3$	$X=4$	$X=1$	$X=2$	$X=3$	$X=4$
$r(C_2–N_{10})$	1.379	1.383	1.371	1.378	1.366	1.375	1.376	1.384	1.369	1.379
$r(H_{15}–N_{10})$	1.013	1.014	1.014	1.013	1.011	1.012	1.014	1.014	1.012	1.013
$r(H_{14}–N_{10})$	1.013	1.014	1.011	1.013	1.023	1.012	1.012	1.014	1.025	1.013
$\angle(H_{15}N_{10}C_2)$	117.7	117.2	118.2	117.6	118.7	118.1	118.0	117.1	118.3	117.7
$\angle(H_{14}N_{10}C_2)$	113.2	112.2	115.1	113.8	115.2	114.1	114.2	112.0	114.0	113.2
$\angle(H_{15}N_{10}H_{14})$	113.7	113.0	116.9	113.5	116.1	114.7	116.4	112.9	115.6	114.2
$\angle(H_{15}N_{10}C_2N_1)$	33.9	38.5	21.1	32.3	26.0	28.5	23.9	40.0	31.0	32.3
$\angle(H_{14}N_{10}C_2N_3)$	12.6	11.1	16.2	14.1	11.9	14.5	16.3	10.6	11.5	13.7
Parameter	**Monomers**		***GuaW*-N9H-*X***				***GuaW*-N7H-*X***			
	N9H	N7H	$X=1$	$X=2$	$X=3$	$X=4$	$X=1$	$X=2$	$X=3$	$X=4$
$r(C_2–N_{10})$	1.379	1.383	1.371	1.379	1.366	1.375	1.375	1.384	1.369	1.379
$r(H_{15}–N_{10})$	1.013	1.014	1.013	1.013	1.011	1.012	1.013	1.014	1.012	1.013
$r(H_{14}–N_{10})$	1.013	1.014	1.011	1.013	1.021	1.012	1.012	1.014	1.024	1.013
$\angle(H_{15}N_{10}C_2)$	117.7	117.2	118.5	117.5	119.0	118.1	118.5	117.2	118.2	117.7
$\angle(H_{14}N_{10}C_2)$	113.2	112.2	115.1	113.7	115.0	114.2	114.3	112.0	114.2	113.2
$\angle(H_{15}N_{10}H_{14})$	113.7	113.0	116.9	113.4	115.8	114.7	116.5	112.9	115.5	114.2
$\angle(H_{15}N_{10}C_2N_1)$	33.9	38.5	21.1	32.0	21.2	28.7	23.4	39.3	30.7	32.3
$\angle(H_{14}N_{10}C_2N_3)$	12.6	11.1	15.8	14.8	16.6	14.4	15.8	10.7	10.9	13.6

The supersystem *Gua*-N9H-2 is formed by two hydrogen bonds: H(13)···O(17) and H(18)···N(3). The first H-bond is 0.38 Å longer than the second one. In the water analogue of the *Gua*-N9H-2 dimer the difference is only 0.04 Å. At the *MP*2/6-31G* level of theory the first H-bond in *GuaW*-N9H-2 is 0.058 Å shorter [1]. Obviously the intermolecular H-bonds are quite sensitive to the theoretical method and basis set used. The data from Table 1 show that the guanine residue is almost planar. Only the space angle H(16)N(1)C(2)N(3) is insignificantly deviated from the planar configuration (4.1°).

Two intermolecular hydrogen bonds between methanol and guanine constitute the supersystem *Gua*-N9H-3: H(17)···N(3) = 1.988 Å and H(14)···O(18) = 1.971 Å, nearly the same as the calculated bond lengths in the water analogue cited in Ref. [1]. These bonds are placed almost in one plane (N(3)H(14)O(18)H(17) = 1.4°) forming a six-membered ring with pseudoaromatic features.

According to a classification of intermolecular bonds in Ref. [1] the hydrogen bonds H(18)···O(11) and H(16)···O(17) in the complex *Gua*-N9H-4 (1.884 and 1.894 Å) are assigned as medium (*Y*···H 1.6–1.9 Å) – Table 1. Proceeding from the assumption "shorter H-bonds – more stable supersystems" one can say that the *Gua*-N9H-4 complex is more stable compared to the *Gua*-N9H-3 one.

Shishkin et al. have discussed in their work [1] that the formation of stronger H-bonds with the participation of the carbonyl group in *GuaW*-N9H-4 and the



Gua-N9H-1

Gua-N9H-2

Gua-N9H-3

Gua-N9H-4

Gua-N7H-1

Gua-N7H-2

Gua-N7H-3

Gua-N7H-4

Fig. 1. Optimized H-bonded complexes between guanine (N9H and N7H forms) and one methanol molecule

amino group in *GuaW*-N9H-3 results from a shortening of the C(2)–N(10) bond and an elongation of the C(6)=O(11) bond. For our theoretical models of the guanine-water supersystems this is also valid.

The H-bonded complexes between guanine oxo-amino N7H tautomer and methanol are depicted in Fig. 1. The intermolecular hydrogen bonds $H(16)\cdots O(17)$ and $H(15)\cdots O(17)$ in the *Gua*-N7H-1 complex are 0.032 Å shorter and 0.059 Å longer than in the *Gua*-N9H-1 complex. However, in the two supersystems the $H(16)\cdots O(17)$ bonds are shorter, respectively stronger than the $H(15)\cdots O(17)$ bonds. These intermolecular bonds in the *GuaW*-N7H-1 found at the *MP*2 level are $H(16)\cdots O(17) = 1.948$ Å, and $H(15)\cdots O(17) = 2.378$ Å [1]. As we can see from Fig. 2 (below) the first bond (*B*3*LYP*) is 0.088 Å longer and the second 0.139 Å shorter.

The participation of one hydrogen atom from the amino group in the complex formation influences the hybridization of N(10) and, respectively, changes the pyramidal character of the amino group. The dihedral angles H(15)N(10)C(2)N(1) and H(14)N(10)C(2)N(1) are 14.6 and 5.6° smaller compared to the *Gua*-N7H supersystem, *i.e.* the aromatic character of the complex is increased (a detailed discussion will be done below).

The *Gua*-N7H-2 complex is formed by "medium" [1] intermolecular H-bonds $H(18)\cdots O(11) = 1.846$ Å and $H(13)\cdots O(17) = 1.882$ Å. The four atoms forming the intermolecular bonds are placed almost in one plane: $H(13)O(17)H(18)O(11) = 2.7°$. The calculations predicted a nonplanar geometry for the amino group in agreement with previous studies [25, 26].

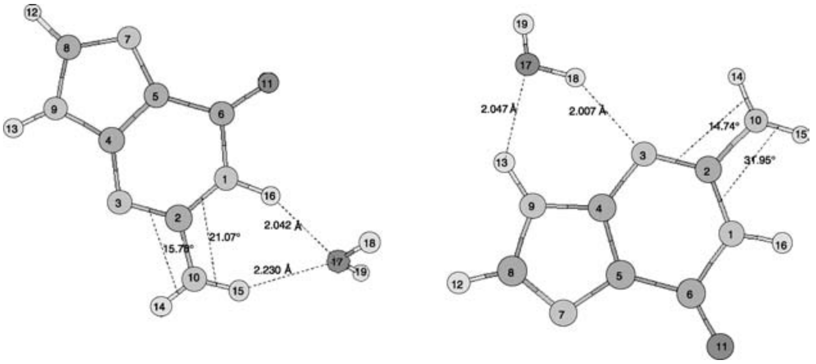
The hydrogen complex *Gua*-N7H-3 is formed by linking one methanol molecule to H(14) and N(3) of the guanine skeleton. As a result two intermolecular hydrogen bonds could be found: $H(14)\cdots O(18) = 1.951$ Å and $H(17)\cdots N(3) = 1.999$ Å, which can be assigned as week bonds ($Y\cdots H > 1.9$ Å) [1]. Nevertheless, these bonds are short enough to contribute to the high stability of the complex.

The complex *Gua*-N7H-4 has shorter intermolecular hydrogen bonds (see Fig. 1, $H(16)\cdots O(17) = 1.902$ Å and $H(18)\cdots O(11) = 1.899$ Å) compared to all N7H supersystems. From the point of view of the intermolecular interactions one can suppose that the *Gua*-N7H-4 complex is the most stable one.

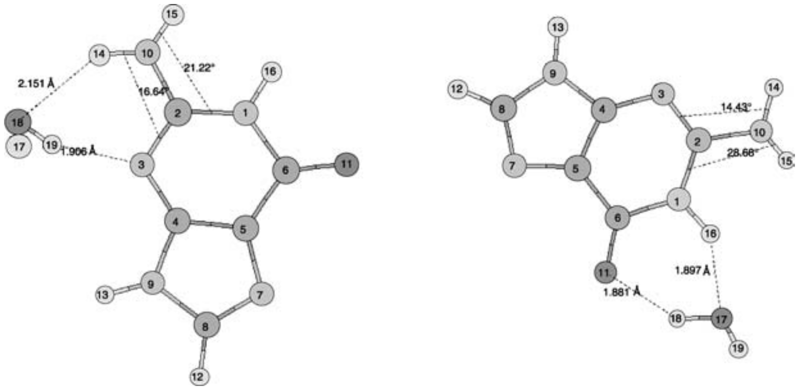
The structures of guanine-water complexes have been discussed in detail in Refs. [1, 27–29]. Therefore these dimers won't be considered here as we have done for the methanol containing complexes. Their structural parameters, energies, and thermodynamic properties found at the $B3LYP/6\text{-}31+G^{*}$ level will be used in the discussion only for comparison. The supersystems that are structural analogues of the complexes in Fig. 1 are depicted in Fig. 2.

One reason for the nonplanarity of the nucleobases is the partial sp^3 hybridization of the amino group [27, 30]. This can be estimated by the deviation of the sum of the angles around the nitrogen atom (ΣAH) from 360° [27]. A comparison between the data on free guanine and its H-bonded complexes with methanol shows that $C–NH_2$ distances are decreased with the rise of the ΣAH values (see Fig. 3 and Table 1).

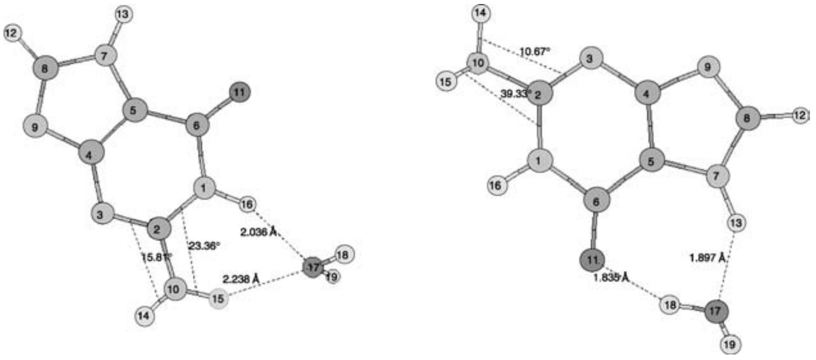
A similar dependence has been reported for guanine-water complexes and free guanine in the work of *Chandra et al.* [27] using the *B*3*LYP* exchange-correlation functional and the $6\text{-}31+G^{**}$ basis functions. The pyramidal character of the amino



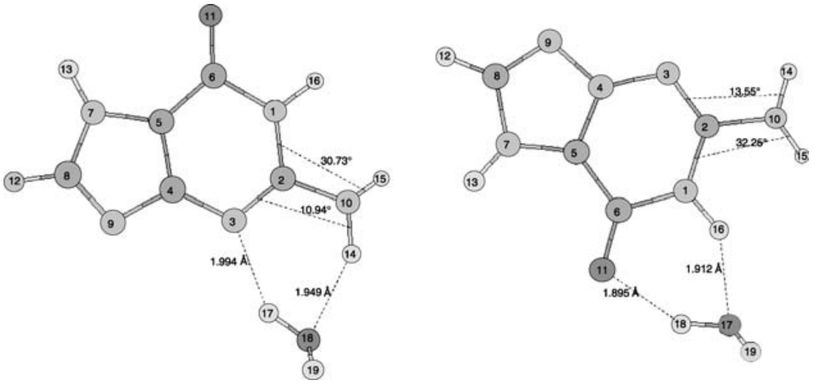
GuaW-**N9H-1** *GuaW*-**N9H-2**



GuaW-**N9H-3** *GuaW*-**N9H-4**



GuaW-**N7H-1** *GuaW*-**N7H-2**



GuaW-**N7H-3** *GuaW*-**N7H-4**

Fig. 2. Optimized H-bonded complexes between guanine (N9H and N7H forms) and one water molecule

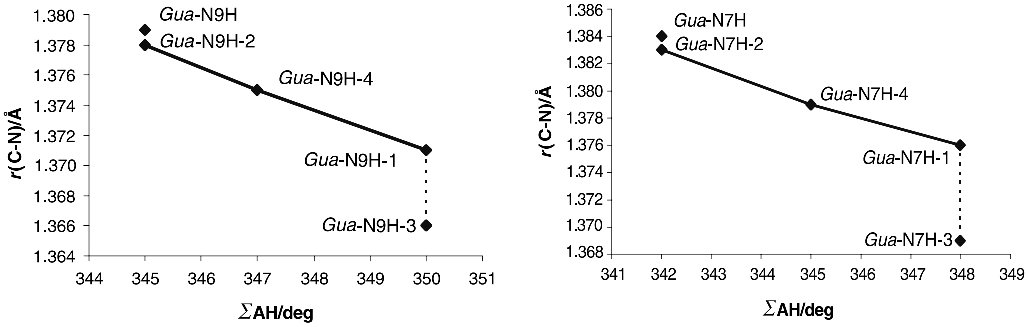


Fig. 3. C–N Distance (in Å) as a function of ΣAH (in deg)

group is larger for the two free guanine oxo-forms – *Gua*-N9H and *Gua*-N7H, in which the C–NH_2 bonds are the longest. The same property exhibits the *Gua*-N7H-2 supersystem. Obviously, the existence of the intermolecular H-bonds between the amino group and methanol or water lowers the pyramidal character of the group (*i.e.* the N(10) atom is almost sp^2 hybridized), which can be seen also from Figs. 1 and 2.

In Table 2 are listed some characteristic molecular harmonic vibrations (not scaled) of the dimers, in which intermolecular vibrations are involved.

It should be mentioned that almost all calculated frequencies ($3 \times 22 - 6 = 60$) for a given supersystem include intermolecular motions with different magnitude. In the supersystems *Gua*-N7H-3 and *Gua*-N7H-4 the vibrations at 3389 and 3337 cm^{-1} involve intermolecular "stretching" vibrations (denoted with ν_i) and other stretching vibrations active mainly in the *Raman* spectrum. Special attention should be paid also to the vibrations below 200 cm^{-1}. They predominantly involve intermolecular "stretchings" mixed with other ring and NH_2 deformations.

As it has been observed previously [17], in the gas phase, the NH_2 asymmetric stretching vibrations in the *Gua*-N9H monomer and *Gua*-N7H monomer are at 3503 and 3490 cm^{-1}, respectively. Values calculated here are larger by 165 cm^{-1}. The 7/9 NH stretchings in the experimental spectra of the same monomers [17] are at 3497 and 3504 cm^{-1}, whereas the calculated ones are at 3640 and 3644 cm^{-1}. The large difference between experimental and theoretical frequencies is due to the computed results, which were not scaled with an appropriate factor. The difference between theoretical and experimental frequencies for the N_1H vibration in the monomers *Gua*-N9H and *Gua*-N7H is 131 and 125 cm^{-1}, respectively. Unfortunately, there are not enough experimental data available for the NH_2 symmetric stretching vibrations in the monomers [17].

Harmonic vibrational frequencies of the two *keto*-guanine tautomers have been calculated also in the S_1 state by means of the ROKS *BLYP*/p.w. method [31]. However, it should be noted that *Nir et al.* [32] have previously stated that vibrational frequencies in the S_1 are on the average 10% larger compared to the ground state. The energies of the normal modes are considerably lower (more than about 100 cm^{-1}) than those in the ground state found by us (*e.g.* $\nu_a NH_2(S_1)$ [31] at 3516 cm^{-1} in the *Gua*-N9H spectrum and at 3512 cm^{-1} in the *Gua*-N7H spectrum). The reason for this discrepancy is presumably that different methods and basis functions have been used in either case.

The calculations performed at *BLYP*/p.w., *BLYP*/6-31++G**, *B3LYP*/6-31++G**, and *MP*2/6-31G** [31, 33] level revealed that the keto-*Gua*-N7H

Table 2. Vibrational frequencies (cm^{-1}), in which the intermolecular motions are included

Gua-N9H forms

Gua-N9H-1		*Gua*-N9H-2		*Gua*-N9H-3		*Gua*-N9H-4	
Freq.	Ass.	Freq.	Ass.	Freq.	Ass.	Freq.	Ass.
3552	$\nu_s NH_2$	3477	νN_9H_{13}	3534	νOH	3331	νN_1H
(0.853)[a]	(17-15)[b]	(0.896)	(17-13)	(1.110)	(17-3)	(1.102)	(17-16)
3480	νN_1H	1635	νN_3C_2	3418	$\nu_s NH_2$	1768	νCO
(1.214)	(17-16)	(0.159)	(18-3)	(1.088)	(18-14)	(0.464)	(17-16)
165	$\nu_i + \gamma$	167	$\nu_i + \tau CH_3$	173	γ	169	$\nu_i + \gamma$
(0.378)	(17-16)	(0.151)	(16-3)	(0.248)	(18-14)	(0.263)	(18-11)
(0.288)	(17-15)	(0.436)	(17-13)				
159	ν_i	163	$\nu_i + \gamma$	167	ν_i	166	ν_i
(0.393)	(17-16)	(0.396)	(17-13)	(0.479)	(17-3)	(0.664)	(17-16)
(0.530)	(17-15)			(0.341)	(18-14)	(0.497)	(18-11)
144	τCH_3	159	ν_i	161	ν_i	88	ν_i
(0.340)	(17-16)	(0.626)	(16-3)	(0.410)	(17-3)	(0.105)	(17-16)
(0.307)	(17-15)	(0.346)	(17-13)	(0.516)	(18-14)	(0.229)	(18-11)
67	$\tau CH_3 + \gamma$	62	γ	59	γ	68	γ
(0.300)	(17-16)	(0.195)	(16-3)	(0.167)	(17-3)	(0.121)	(17-16)
(0.167)	(17-15)	(0.197)	(17-13)	(0.136)	(18-14)	(0.110)	(18-11)

Gua-N7H forms

Gua-N7H-1		*Gua*-N7H-2		*Gua*-N7H-3		*Gua*-N7H-4	
Freq.	Ass.	Freq.	Ass.	Freq.	Ass.	Freq.	Ass.
3553	$\nu_s NH_2$	3360	νN_7H	3528	νOH	3337	ν_i
(0.885)	(17-15)	(1.076)	(17-13)	(1.066)	(17-3)	(1.079)	(17-16)
3463	νN_1H	1577	ρH_{13}	3389	ν_i	1754	νCO
(1.246)	(17-16)	(0.619)	(17-13)	(1.108)	(18-14)	(0.483)	(17-16)
160	$\nu_i + \gamma$	162	ν_i	165	ν_i	168	ν_i
(0.395)	(17-16)	(0.487)	(17-13)	(0.686)	(18-14)	(0.169)	(18-11)
(0.514)	(17-15)	(0.246)	(18-11)	(0.634)	(17-3)	(0.474)	(17-16)
158	$\nu_i + \gamma$	159	$\nu_i + \gamma$	157	$\nu_i + \gamma$	165	$\gamma + \nu_i$
(0.354)	(17-16)	(0.350)	(17-13)	(0.241)	(18-14)	(0.580)	(18-11)
(0.282)	(17-15)	(0.473)	(18-11)	(0.197)	(17-3)	(0.473)	(17-16)
150	ν_i	153	$\nu_i + \gamma$	77	$\nu_i + \gamma$	86	ν_i
(0.358)	(17-16)	(0.222)	(17-13)	(0.214)	(17-3)	(0.224)	(18-11)
(0.260)	(17-15)	(0.096)	(18-11)			(0.110)	(17-16)
64	γ	94	$\nu_i + \gamma$	61	γ	68	γ
(0.128)	(17-16)	(0.125)	(17-13)	(0.131)	(18-14)	(0.110)	(18-11)
(0.332)	(17-15)	(0.229)	(18-11)	(0.164)	(17-3)	(0.122)	(17-16)

[a] Deviation [Å] of the [b] atoms involved in the hydrogen bond; $\nu_i \cdots$ intermolecular "stretching" vibration

monomer is the most stable one. The energy difference between *Gua*-N9H and *Gua*-N7H has been found to be only 2.4 kJ mol^{-1} (*B3LYP*/6-31++G**) [31]. In our case it is about 0.2 kJ mol^{-1} larger.

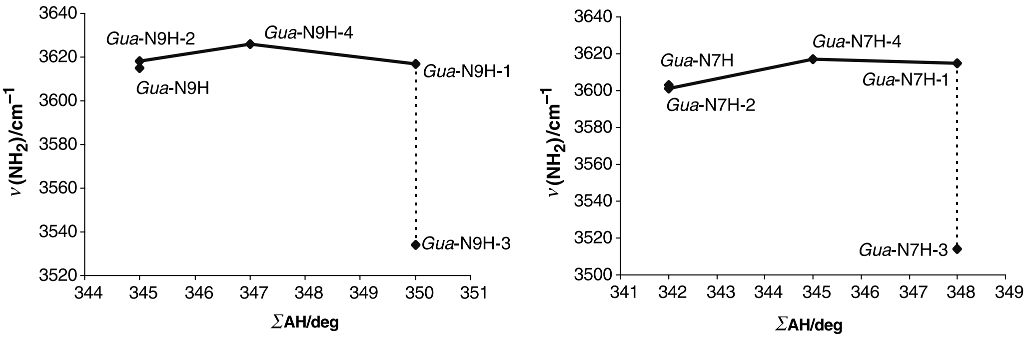


Fig. 4. Mean values of the $\nu_{as}(NH_2)$ and $\nu_s(NH_2)$ (in cm^{-1}) as a function of ΣAH (in deg) for the supersystems *Gua*-N7H and methanol

As became clear above the pyramidal behavior of the amino group has also a marked influence on the NH_2 stretching frequencies [27]. For supersystems *Gua*-N9H-2, *Gua*-N9H-4, *Gua*-N7H-2, *Gua*-N7H-4 in which the amino group is not involved in the complex formation, the average of the vibrations $\nu_{as}(NH_2)$ and $\nu_s(NH_2)$ was correlated to ΣAH in Fig. 4, as it has been done for guanine-water complexes [27] (the frequencies are not scaled with any factor).

Unfortunately, in the case of guanine-methanol supersystems the linear dependence is disturbed due to the considerable deviation of the points for *Gua*-N9H-3 and *Gua*-N7H-3. We supposed that the reason for this is the fairly short $HN–H\cdots OH(CH_3)$ distance in the supersystems *Gua*-N9H-3 and *Gua*-N7H-3. In these forms the NH_2 symmetric stretchings are to a certain extent influenced by the intermolecular H-bonds: they are significantly shifted towards smaller frequencies.

Table 3. Standard enthalpy (ΔH^o_{298}), entropy ($T\Delta S^o_{298}$), and free energy (ΔG^o_{298}) changes for the formation processes of the complexes (computed at the *B3LYP*/6-31 + G* level) ($kJ\,mol^{-1}$)

Complexes	ΔH^o_{298}	$T\Delta S^o_{298}$	ΔG^o_{298}
Gua-N9H-1	−32.2	−35.8	3.6
Gua-N9H-2	−31.2	−39.9	8.7
Gua-N9H-3	−31.0	−40.1	9.1
Gua-N9H-4	−43.8	42.0	−1.8
Gua-N7H-1	−31.0	−35.6	4.6
Gua-N7H-2	−48.4	−54.6	−6.2
Gua-N7H-3	−37.7	−40.4	2.7
Gua-N7H-4	−41.5	−41.7	0.2
GuaW-N9H-1	−31.6	−35.0	3.4
GuaW-N9H-2	−32.4	−40.0	7.6
GuaW-N9H-3	−23.5	−37.8	14.3
GuaW-N9H-4	−44.5	−41.6	−2.9
GuaW-N7H-1	−30.3	−35.0	4.7
GuaW-N7H-2	−49.4	−41.9	−7.5
GuaW-N7H-3	−38.3	−40.4	2.1
GuaW-N7H-4	−42.2	−41.5	−0.7

Thermodynamic Properties of the Complex Formations

The thermodynamic parameters of all hydrogen-bonded systems were calculated in order to explain their formations in the gas phase (see Table 3).

The values of standard enthalpies show that all complex formations are energetically favored (and in addition exothermic). The absolute value of the entropy factor $T\Delta S^o_{298}$ (the negative value of this factor shows that the complex formation process is attended with an enhancing of the system's order) is higher than the absolute value of ΔH^o_{298}. Thus, the *Gibbs* free energy at standard conditions for a large number of complex formations is positive. The values of ΔG^o_{298} are in the interval $-42\,\mathrm{kJ\,mol^{-1}} - +42\,\mathrm{kJ\,mol^{-1}}$, however, and it remains questionable whether the complex formations are thermodynamically favored or not. The low absolute values of ΔG^o_{298} for dimers indicate that the aggregation occurs although it is not entropically favored.

Complex formations of supersystems with short intermolecular H-bonds have negative ΔG^o_{298}. *Shishkin et al.* have found at the *MP*2 level that all complex formations of the water containing supersystems have positive free energy at standard conditions and at 0 K [1], because they used only data for the thermal *Gibbs* free energy as obtained directly by the computations. Moreover their values have been related to the supersystem having the lowest absolute free energy [1].

Hydrogen-Bonding Energies and Energy Properties of the Supersystems

Calculated energies, hydrogen-bonding energies and other energetic characteristics of the supersystems guanine-methanol are presented in Table 4, and those of the supersystems guanine-water in Table 5.

The results in Table 4 show that the absolute value of the bonding energy (ΔE_b) is over $45\,\mathrm{kJ\,mol^{-1}}$ for three systems: *Gua*-N7H-2, *Gua*-N9H-4, and *Gua*-N7H-4.

Table 4. Guanine–methanol interaction energies, their components and energies of the complexes ($\mathrm{kJ\,mol^{-1}}$)

Complex	Δ(BSSE)	ΔE_b	ΔE_{int}	ΔE	E_{SS}	E_{m_i}		E'	
						guanine	methanol	guanine	methanol
Gua-N9H-1	4.6	−38	−40	−42	18.9	3.5	0[c]	3.3	~0
Gua-N9H-2	4.4	−36	−39	−40	19.9	2.5	0.1	2.6	0[e]
Gua-N9H-3	4.6	−35	−38	−40	20.5	2.7	0.2	2.6	0.1
Gua-N9H-4	4.1	−50	−51	−54	7.2	3.2	0.5	3.2	0.8
Gua-N7H-1	8.0	−37	−38	−45	17.8	1.0	3.7	0.8	0.3
Gua-N7H-2	4.7	−54	−56	−59	0[a]	0.8	0.5	0.8	0.2
Gua-N7H-3	4.6	−42	−45	−47	11.0	0[b]	0.2	0[d]	0.1
Gua-N7H-4	4.1	−47	−49	−52	7.0	0.4	0.4	0.4	0.7

The absolute energy ([a] 658.323911 hartrees) of supersystem *Gua*-N7H-2 was taken as conventional zero; the single-point energies ([b] 542.576904 hartrees and [c] 115.725037 hartrees) and the "attraction" energies ([d] 542.577305 hartrees and [e] 115.726326 hartrees) of guanine and methanol in supersystems corresponding to *Gua*-N7H-3, *Gua*-N9H-1 and *Gua*-N7H-3, *Gua*-N9H-2 were taken as conventional zeros as well

Table 5. Guanine–water interaction energies, their components and energies of complexes (kJ mol^{-1})

Complex	Δ(BSSE)	ΔE_b	ΔE_{int}	ΔE	E_{SS}	E_{m_i}		E'	
						guanine	water	guanine	water
GuaW-N9H-1	5.9	−35	−39	−41	21.0	3.2	0[c]	3.1	0[e]
GuaW-N9H-2	5.0	−37	−40	−42	19.7	2.5	0.5	2.5	1.3
GuaW-N9H-3	5.4	−29	−31	−34	28.8	3.4	0.9	3.4	1.3
GuaW-N9H-4	4.8	−51	−52	−55	7.4	3.1	1.0	3.1	2.1
GuaW-N7H-1	5.9	−34	−37	−39	19.8	0.8	∼0	0.6	∼0
GuaW-N7H-2	5.5	−54	−58	−60	0[a]	0.6	1.0	0.6	1.3
GuaW-N7H-3	5.2	−43	−46	−48	11.4	0[b]	0.7	0[d]	1.4
GuaW-N7H-4	4.8	−48	−50	−53	7.3	0.3	1.2	0.5	2.0

The absolute energy ([a] 619.021830 hartrees) of supersystem *GuaW*-N7H-2 was taken as conventional zero; the single-point energies ([b] 542.576920 hartrees and [c] 76.422570 hartrees) and the "attraction" energies ([d] 542.577210 hartrees and [e] 76.424480 hartrees) of guanine and water in supersystems corresponding to *GuaW*-N7H-3, *GuaW*-N9H-1 and *GuaW*-N7H-3, *GuaW*-N9H-1 were taken as conventional zeros as well

Moreover, ΔG^o_{298} of formation (Table 3) is negative for the first two complexes. In the guanine-methanol supersystems the stability decreases according to the following order: *Gua*-N7H-2 > *Gua*-N9H-4 > *Gua*-N7H-4 > *Gua*-N7H-3 > *Gua*-N9H-1 > *Gua*-N7H-1 > *Gua*-N9H-2 > *Gua*-N9H-3.

The most stable guanine-water complexes are analogues to the most stable guanine-methanol ones (*GuaW*-N7H-2, *GuaW*-N9H-4, and *GuaW*-N7H-4). In the remaining supersystems the stability decreases in the following order: *GuaW*-N7H-3 > *GuaW*-N9H-2 > *GuaW*-N9H-1 > *GuaW*-N7H-1 > *GuaW*-N9H-3.

BSSEs are comparatively low for all supersystems. That's why the bonding energies and the bonding energies without BSSE (ΔE) differ not much (see Tables 4 and 5). Only for the *Gua*-N7H-1 supersystem BSSE was calculated to be about two times higher than in all other cases.

In general, the complex formations between water, methanol, and the nucleobase guanine are competitive reactions. Small amounts of methanol in the living organisms can reversibly replace water molecules from the hydrated *DNA* bases (mostly guanine). We suppose that such a process can cause damages in the *DNA* structure especially during the splitting of the double helix, when the nucleobases are in contact with the surrounding liquid medium.

Conclusions

The study of all stable dimers of the oxo-amino N9H and oxo-amino N7H tautomers of guanine and methanol was performed at the $B3LYP/6\text{-}31+\mathrm{G}^*$ level of theory. It was found that: 1) The nonplanarity of the complexes of guanine with methanol can be estimated by the deviation of the sum of the angles around the nitrogen atom (ΣAH) from 360° which determines the pyramidal character of the amino group. In this aspect, it was demonstrated that the existence of an intermolecular H-bond between the amino group and the methanol or water drastically lowers the pyramidal character of this group and the N(10) atom becomes almost sp^2 hybridized; 2) All complex formations are exothermic but only two (*M*eOH) and three (H_2O), respectively, of them have negative standard free energy changes. These are the processes leading to the formation of the most stable complexes with the shortest intermolecular H-bonds; 3) The values of the bonding energies of the supersystems guanine-methanol in the gas phase are very close to those of the guanine-water complexes. Therefore the complex formations between guanine and methanol as well as guanine and water are competitive and can occur simultaneously.

Methods

The structures and harmonic frequencies of all monomers and dimers (complexes) were found at the $B3LYP/6\text{-}31+G^*$ level using the *Gaussian* 98 package [33]. In studying a certain dimer *GM* (guanine-methanol) the energy was computed together with the optimized structure. Then the energy was calculated leaving out the electrons and nuclei of one of the monomers (for example *G*). The difference between this energy and the energy of the other monomer *M*, alone, with not nearby functions, is taken to be "attraction" of *M* for the functions of *G*. In the same way was calculated the "attraction" of *G* for the functions of *M* [35]. Subtracting these two estimates of the artificial attraction from the directly computed bond strengths was suggested as a more realistic value for the bond strength [35]. Therefore the bonding energy ΔE_b for each supersystem (complex) was estimated according to the Eq. (1) [36, 37], where E_{SS} is the energy of the supersystem and E'_G and E'_M are energies of the monomers (guanine and methanol) calculated as described above (with 'ghost' orbitals of the other monomer).

$$\Delta E_b = E_{SS} - (E'_G + E'_M) \tag{1}$$

The BSSE was evaluated using the counterpoise method [36, 38–41] as given in Eq. (2), where E_{m_i} are the energies of the individual monomers frozen in their aggregate geometries (single-point) [42].

$$\Delta(\text{BSSE}) = \sum_i^n (E_{m_i} - E'_{m_i}) \tag{2}$$

The energy of the guanine–methanol (water) interaction (ΔE_{int}), was calculated as the difference between the energies of the complex and isolated guanine and methanol molecules. The difference between the energies of the complex and the deformed configurations of guanine and methanol in the complex (ΔE) was found by single-point calculations of the monomers in their configurations like in the corresponding supersystem.

The use of diffuse functions for the calculations is desirable since basis set superposition errors (BSSE) are known to decrease with basis set size and are reduced by the inclusion of diffuse functions [20, 43, 44]. The diffuse functions allow orbitals to occupy a larger region of space. Therefore basis sets with diffuse functions are important for systems where electrons are relatively far from the atomic nucleus [45] like in our hydrogen-bonded systems which have a lot of lone electron pairs.

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