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DFT study of the gas phase proton transfer in guanine assisted by water, methanol, and hydrogen peroxide

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Abstract A computational study of hydrogen-bonded complexes between the oxo-/hydroxo-amino N7/9H tautomers of guanine and water, methanol, and hydrogen peroxide has been performed at the B3LYP/6-31+G(d) level of theory. The mechanisms of the water-, methanol-, and hydrogen peroxide-assisted proton transfers in guanine were studied and compared with the intramolecular proton transfer in guanine in the gas phase. It was found that the assisted proton transfers pass through about three times lower energy barriers than those found for isolated guanine tautomers.

Keywords Density functional methods · Guanine · H-bonding · Proton transfer

Introduction

As exceptional molecular bricks of the living world DNA bases play an important role with their ability to form non-covalent hydrogen bonds responsible for expression and encoding of genetic information [1]. The DNA bases contain transferable hydrogen atoms that determine their existence as several stable tautomers. With respect to the carbonyl/hydroxyl group in the guanine skeleton four tautomeric forms are possible [2]: hydroxo-amino N7H (**A**); oxo-amino N7H (**B**); oxo-amino N9H (**C**), and hydroxo-amino N9H (**D**) (the abbreviations N7H and N9H specify at which nitrogen atom of the imidazole ring the transferrable H atom is attached).

According to a spectroscopic investigation of the tautomers, there is evidence for experimental abundance

of three stable forms—**A**, **B**, and **C** [1, 3–5]. Their observed UV bands are located at 32864, 33269, and 33910 cm^{-1} . Moreover, Mons et al. [1] have given experimental evidence for the existence of the **D**-tautomer as well.

In principle there are two ways to transform an oxo-amino tautomer into a hydroxo-amino one: intramolecular and intermolecular proton transfer, later assisted by protic molecules. It is well known that the first type of proton transfer passes through high-energy barriers, over 200 kJ mol^{-1} [2, 6, 7]. Until now, only water molecules have been taken into account to assist the intermolecular hydrogen transfer in guanine in the gas phase [2]. However, it is interesting to know how other protic molecules, such as, for example, methanol and hydrogen peroxide, support these processes.

The current work is devoted to the comparative study (at the B3LYP/6-31+G(d) level) of the tautomeric transformations assisted by hydrogen peroxide and methanol in the most stable tautomeric forms of guanine. The choice of methanol and hydrogen peroxide is not casual. First, the compounds are a good case for small protic molecules. They are toxic for living organisms and bound to the nucleic acid bases they could eventually cause point mutations in the DNA structure [7]. Although hydrogen peroxide is normally a very strong reagent, and should be far too reactive to induce tautomerization, it is chosen for comparison with methanol and water.

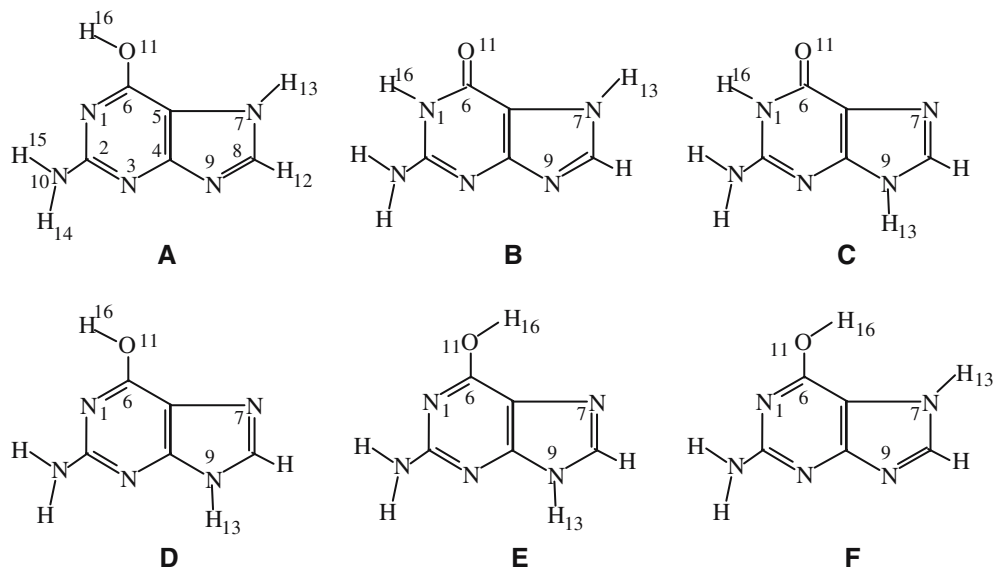
Two conformers of hydroxo-amino tautomers are also involved in this investigation (see Scheme 1 below).

Materials and methods

All calculations were carried out with the GAUSSIAN 98 program [8] and DFT in the variant B3LYP with the 6-31+G(d) basis set (BSSE is sensitive to diffuse functions [9–11]). It has been shown that the results obtained at the DFT level are in reasonable agreement with the experiment [12–14]. A detailed examination of the

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Scheme 1 Tautomeric forms and OH-conformers of guanine

correlation energy and the DFT functionals has been recorded in the work of Handy et al. [15].

The structures were optimized in the ground state by standard gradient procedures. Frequency calculations were performed to prove that the resulting stationary points are real energy minima. Further, we used the geometry of any two minima and the QST2 algorithm, implemented within GAUSSIAN 98 [8], to find the transition states between these minima. The potential energy surfaces of the proton transfers were derived by SCAN calculations of the area nearest the transition state.

Bonding energies (ΔE_b) and BSSE for each addition complex were estimated according to the equations [16–21]

$$\Delta E_b = E_{SS} - (E'_G + E'_M) \quad \text{and}$$

$$\Delta(\text{BSSE}) = \sum_i^n (E_{m_i} + E'_{m_i}),$$

where E_{SS} is the energy of the supersystem; E'_G (E'_M) is the energy of guanine (methanol/water/hydrogen peroxide) calculated with “ghost” orbitals of the other monomer; E_{m_i} are the energies of the individual monomers frozen in their aggregate geometries, found by single-point calculations.

The energy of the guanine–water (methanol/hydrogen peroxide) interaction (ΔE_{int}) was calculated as the difference between the energies of the complex and isolated molecules of guanine, water, methanol, and hydrogen peroxide ($\text{HOOH} = 118.1^\circ$).

Results and discussions

Structural parameters of tautomers, rotamers, and H-bonded complexes

All tautomers and conformers (of the hydroxo-amino forms), described in the current paper, are given in Scheme 1.

The OH group in the tautomers **A** and **D** deviates slightly from the molecular plane: the deviation of the $\text{C}_5\text{C}_6\text{O}_{11}\text{H}_{16}$ from 180° in **A** and **D** is 0.4° ; the deviation of $\text{C}_5\text{C}_6\text{O}_{11}\text{H}_{16}$ from 0° in **E** and **F** is 0.1 and 1.7° , respectively.

Twelve H-bonded complexes between guanine and water, methanol and hydrogen peroxide, which exhibit intermolecular H-exchange between N_1 and O_{11} , were optimized (Fig. 1). They all lie in energy minima.

The shortest intermolecular H-bonds $\text{N}(1)\dots\text{H}(17)/\text{H}(16)\dots\text{O}(11)$ formed between hydrogen peroxide and guanine monomers, and the shortest H-bonds $\text{O}(18)\dots\text{H}(16)/\text{H}(17)\dots\text{O}(18)$ are computed for the water and methanol complexes. As far as the bonds OH (in compounds **A** and **D**) and N_1H (in compounds **B** and **C**) are concerned, it is clear that all modes of complexation contribute to their elongation. This elongation is larger in the water and methanol-containing complexes.

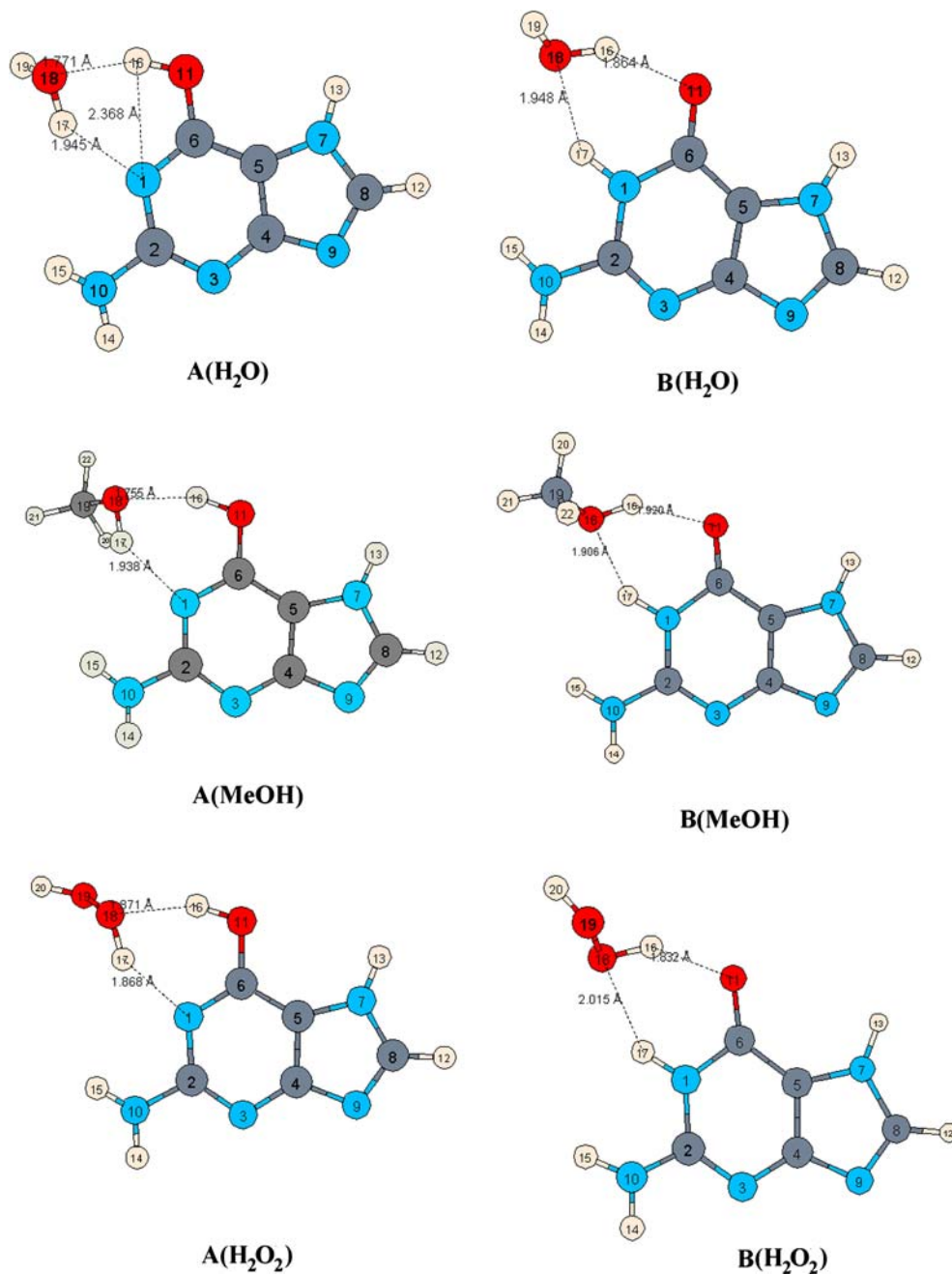
As expected, the influence of H-bonding with water, methanol, and hydrogen peroxide on the bond lengths and angles in guanine is remarkable in the region of the intermolecular H-bonds. It is in full agreement with data in Ref. [22].

Thermodynamic parameters of the internal rotations and complex formations

In Ref. [6], it was shown that structure **B** is the most stable (total energy—542.577446 a.u.). Structures **A**, **C**, and **D** have 24, 3, and 11 kJ mol^{-1} higher energies, respectively, than **B** [6]. We found that structures **E** and **F** have 3 and 35 kJ mol^{-1} higher energies than their rotational analogues, that is, structures **D** and **A**, respectively.

The estimated energy barriers of the forward and reverse rotations $\text{A} \rightleftharpoons \text{F}$ are 44 and 9 kJ mol^{-1} , whereas

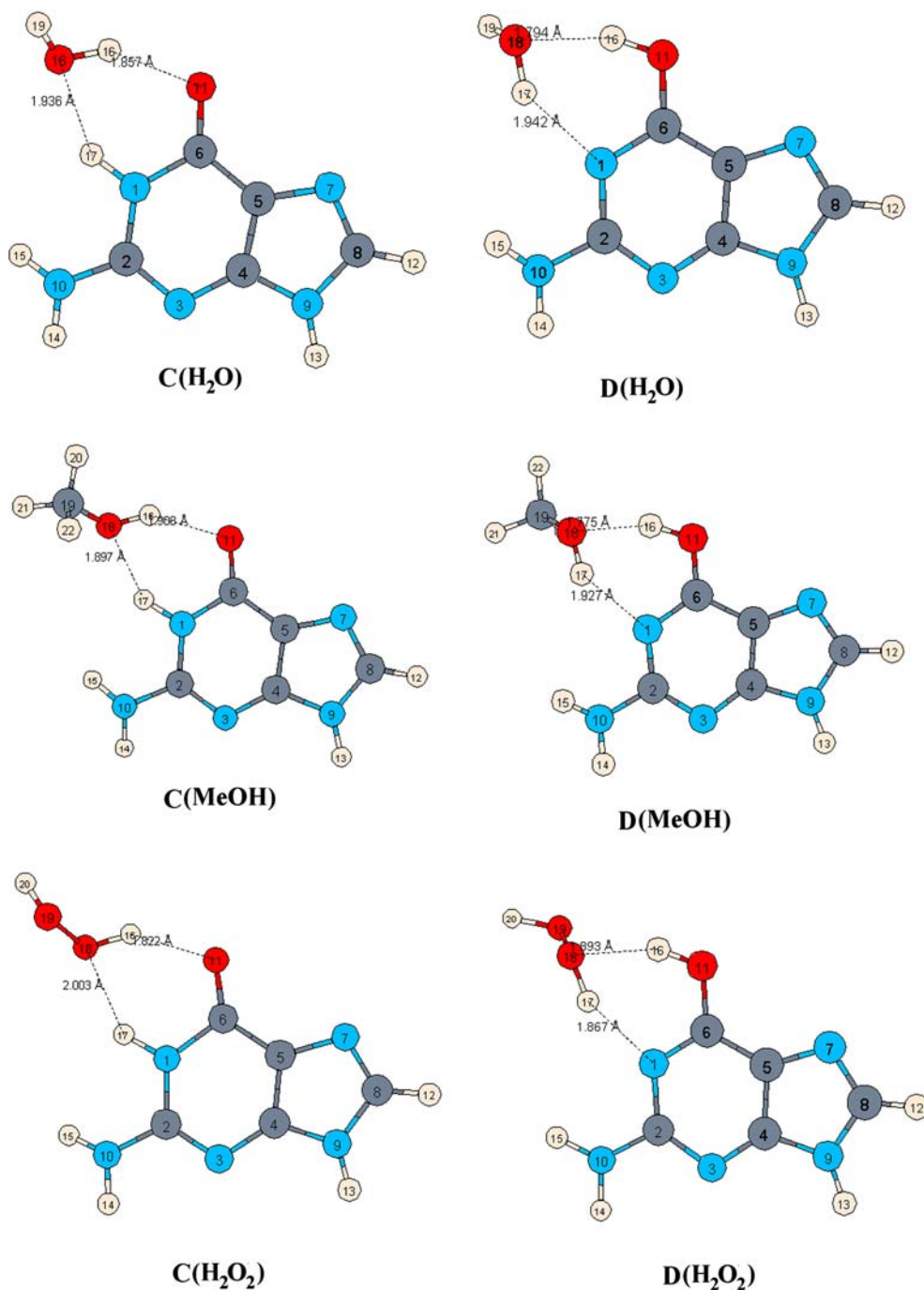
Fig. 1 Optimized structures of the studied H-bonded complexes between guanine and water/methanol/hydrogen peroxide



those of the rotation $\mathbf{D} \rightleftharpoons \mathbf{E}$ in the same directions are 40 and 37 kJ mol⁻¹, respectively. These barriers are fairly small, and could perhaps be overcome under physiological conditions. The forward rotations in both cases are entropically favored [$\Delta S_{298}^0(\mathbf{A} \rightleftharpoons \mathbf{F}$ and $\mathbf{D} \rightleftharpoons \mathbf{E}) = 10$ and 1 J mol⁻¹ K⁻¹], but enthalpically disfavored [$\Delta H_{298}^0(\mathbf{A} \rightleftharpoons \mathbf{F}$ and $\mathbf{D} \rightleftharpoons \mathbf{E}) = 34$ and 3 kJ mol⁻¹]. In general, the rotations are thermodynamically disfavored because the values of the free energy are positive: 31 and 3 kJ mol⁻¹. Both rotations have equilibrium constants $K_p(\mathbf{A} \rightleftharpoons \mathbf{F}) = 3.68 \times 10^{-6}$ and $K_p(\mathbf{D} \rightleftharpoons \mathbf{E}) = 0.298$ with mole fractions of the structures **A**, **D**, **E**, and **F** in the gas phase equal to 0.99(9), 0.77, 0.23, and 3.68×10^{-6} .

Thermochemical calculations were performed for all H-bonded complexes to evaluate the H-bonding effects [bonding energy (ΔE_b), interaction energy (ΔE_{int}), BSSE], and effectiveness of complex formation. The values are listed in Table 1. It is seen that all complex formations are enthalpically favored, but entropically disfavored. Obviously, complex formation is accompanied by significant steric changes of the monomers at 298 K, especially for water, methanol, and hydrogen peroxide. Several complex formations show positive changes of the Gibbs free energy. They are, therefore, disfavored until $|\Delta H| < |T\Delta S|$ or, in other words, they are favored by increasing temperature.

Fig. 1 (Contd.)



The bonding and interaction energies (ΔE_b , ΔE_{int}) are highest for the complex **C(H₂O)**. Another addition complexes with values for these energies about/over 50 kJ mol⁻¹ are **C(H₂O₂)** and **C(MeOH)**. The values from Table 1 show that the most unstable should be the addition complex **D(H₂O₂)**. However, it contains two not very long H-bonds. Obviously, the length of the H-bonds and ΔE_b and ΔH_{298}^0 cannot be used alone to determine the stability of the addition complexes. As a more accurate criterion, ΔG_{298}^0 and ΔE_b values should be used. They show that the addition systems **C(H₂O)**, **C(H₂O₂)**, and **C(MeOH)** must be the most stable,

despite the long H-bond calculated in the **C(H₂O₂)** addition complex (Fig. 1).

The BSSEs are comparatively small as they are (at this theoretical level) 8–18% of the H-bonding energies.

Vibrational modes of tautomers/rotamers and addition complexes

Intermolecular harmonic vibrations (ν_{int}) in the addition complexes were calculated at lower wave numbers with very low IR intensities (see Table 2).

Table 1 Energies (in a.u.), interaction energies (in kJ mol⁻¹), and thermodynamic properties of the addition complexes and complex formations (in kJ mol⁻¹), all in the gas phase

System	E	E_0	ΔE_b	ΔE_{int}	ΔBSSE	ΔH_{298}^0	ΔG_{298}^0	$T\Delta S_{298}^0$
A(H₂O)	-619.009464	-618.867482	-46	-48	7	-40	3	-43
B(H₂O)	-619.019056	-618.877187	-48	-50	4	-42	-1	-41
C(H₂O)	-619.018984	-618.877214	-51	-52	5	-45	-4	-41
D(H₂O)	-619.012645	-618.870524	-42	-44	7	-36	6	-42
A(MeOH)	-658.311749	-658.140910	-46	-47	6	-40	3	-43
B(MeOH)	-658.320723	-658.149954	-47	-47	4	-40	1	-41
C(MeOH)	-658.320578	-658.149870	-49	-50	4	-43	-1	-42
D(MeOH)	-658.314899	-658.143913	-42	-44	4	-36	-7	-29
A(H₂O₂)	-694.113254	-693.987695	-42	-45	7	-38	3	-41
B(H₂O₂)	-694.143408	-693.997650	-47	-48	5	-41	-2	-39
C(H₂O₂)	-694.143443	-693.997753	-50	-51	5	-44	-4	-40
D(H₂O₂)	-694.136470	-693.990803	-39	-41	7	-34	6	-40

Table 2 Frequencies (in cm⁻¹)/IR intensities (in km mol⁻¹) of the intermolecular vibrations in the addition complexes

Tautomeric form A			Tautomeric form D			Ass.
A(H₂O)	A(MeOH)	A(H₂O₂)	D(H₂O)	D(MeOH)	D(H₂O₂)	
3464/945	3477/955	3431/1264	3474/997	3476/1030	3458/1133	vOH ^a , vOH
3288/559	3237/826	3306/393	3325/468	3278/719	3319/484	vOH
885/168	887/115	879/192	887/155	887/118	873/175	ρH_{17} , ρH_{16}
794/234	791/84	788/14	796/69	797/78	793/11	ρH_{17} , ρH_{16}
790/45	785/175	766/108	790/213	788/174	763/119	ρH_{16}
365/47	373/46	367/22	360/76	375/45	367/19	ν_{int}
195/1	193/3	192/2	192/0	187/2	189/2	ν_{int}
132/24	185/2	146/17	128/14	–	142/11	ν_{int}
Tautomeric form B			Tautomeric form C			Ass.
B(H₂O)	B(MeOH)	B(H₂O₂)	C(H₂O)	C(MeOH)	C(H₂O₂)	
3484/681	3525/602	3435/807	3471/740	3513/649	3427/790	vOH ^a , $\nu\text{N}_1\text{H}$
3392/210	3349/476	3379/212	3387/182	3342/469	3362/270	$\nu\text{N}_1\text{H}$
1761/626	1755/848	1751/866	1775/613	1770/805	1764/848	$\nu\text{C}=\text{O}$
726/181	726/50	778/79	730/193	729/85	782/100	ρH_{16}
722/115	719/109	764/43	723/105	720/102	–	ρH_{16}
711/5	711/37	709/2	688/3	689/8	688/6	γH_{17}
182/4	189/3	116/2	184/1	196/1	197/0	ν_{int}
126/7	157/4	135/3	127/13	158/3	135/6	ν_{int}

^a OH group in the molecule of water, methanol, or hydrogen peroxide

Table 3 Energies of the transition states (E_{TS} , in a.u.), energy barriers, and thermodynamic parameters of the water-, methanol-, hydrogen peroxide-assisted proton transfers (in kJ mol⁻¹)

Tautomerization	E_{TS}	IF ^a /intensity	ΔH_{298}^0	ΔG_{298}^0	$T\Delta S_{298}^0$	ΔE		$\Delta E_0 = \Delta EZP\Delta E$	
						Forward	Reverse	Forward	Reverse
A\rightleftharpoonsB^b	-542.511153	-1904/717	-22	-23	1	150	174	137	159
C\rightleftharpoonsD^b	-542.515082	-1897/738	8	9	-1	161	152	147	139
A(H₂O)\rightleftharpoonsB(H₂O)	-618.989641	-1616/338	-25	-27	2	52	77	35	60
C(H₂O)\rightleftharpoonsD(H₂O)	-618.991450	-1603/334	17	18	-1	72	56	56	38
A(MeOH)\rightleftharpoonsB(MeOH)	-658.292751	-1519/280	-23	-25	2	50	73	32	56
C(MeOH)\rightleftharpoonsD(MeOH)	-658.294257	-1573/307	15	17	-2	69	54	51	35
A(H₂O₂)\rightleftharpoonsB(H₂O₂)	-694.117005	-1177/606	-26	-27	1	43	69	26	52
C(H₂O₂)\rightleftharpoonsD(H₂O₂)	-694.119717	-1087/475	18	19	-1	62	44	46	28

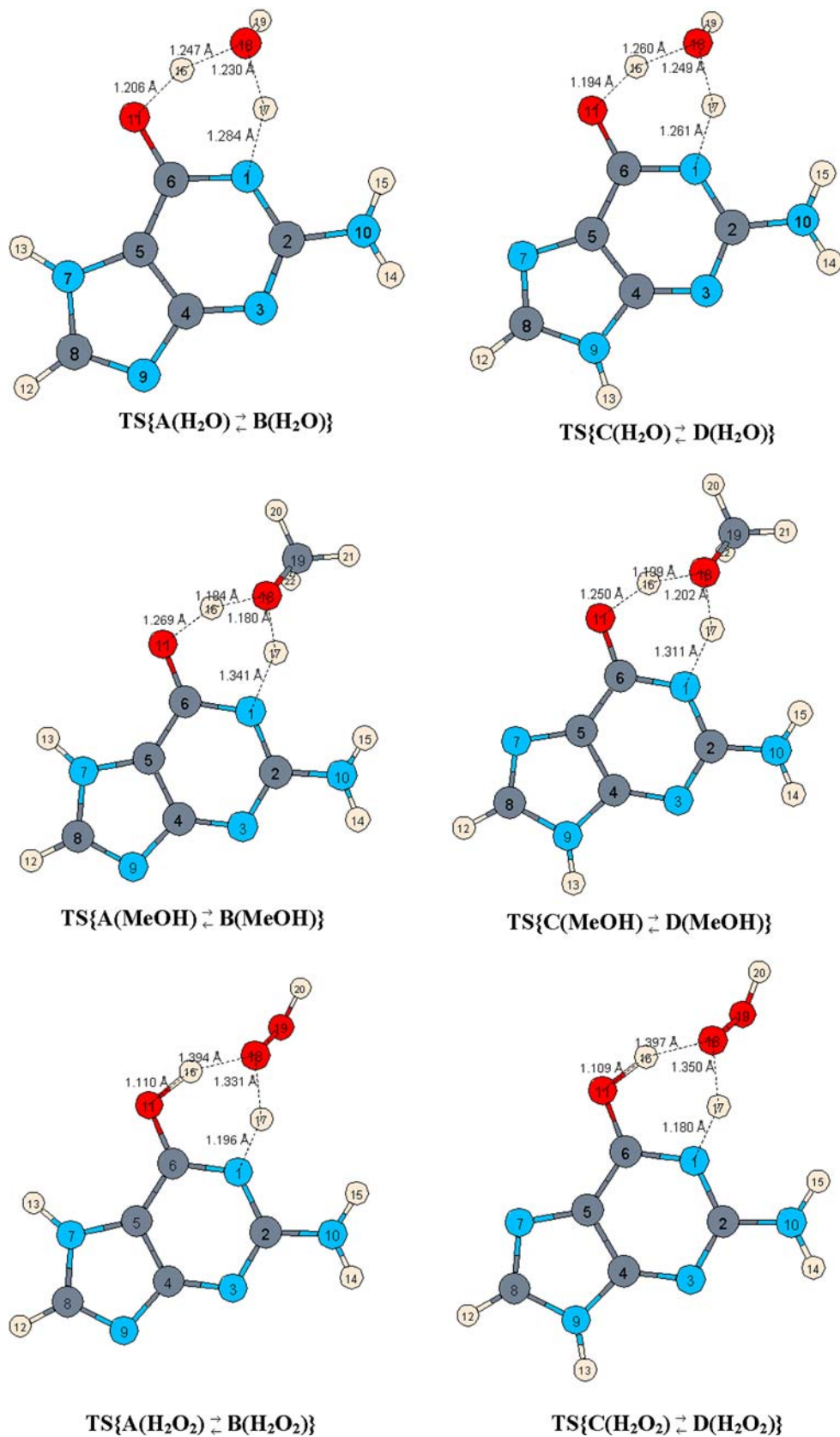
^a Imaginary frequency (in cm⁻¹)/Intensity (in km mol⁻¹) calculated in each transition state's vibration spectrum

^b From Ref. [6]

A comparison of the C=O characteristic frequencies of monomers **B** and **C** and their complexes shows that the complexation process is accompanied by lowering of

the vibrational energy of the C=O bond. In other words, the bands of the C=O vibration in the complexes are shifted downward as compared to the guanine

Fig. 2 Transition states of the water-/methanol-/hydrogen-peroxide-assisted tautomerizations of guanine



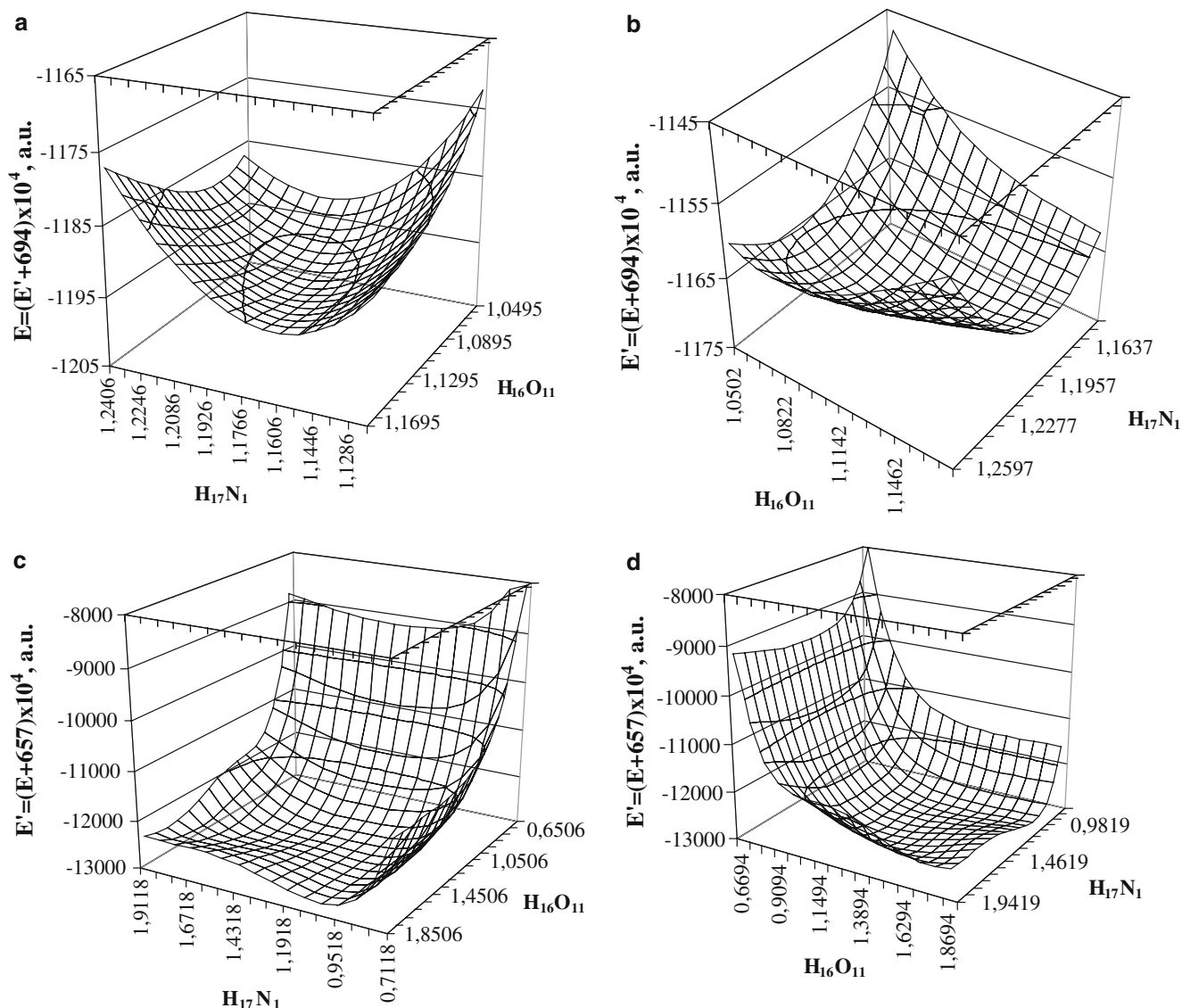


Fig. 3 Potential energy surfaces of the tautomerizations. **a** $C(H_2O_2) \rightleftharpoons D(H_2O_2)$; **b** $A(H_2O_2) \rightleftharpoons B(H_2O_2)$; **c** $C(MeOH) \rightleftharpoons D(MeOH)$; **d** $A(MeOH) \rightleftharpoons B(MeOH)$

monomers. The same effect has been reported by Chandra et al. [23] for several guanine–water complexes. The opposite effect has been observed for the in plane δNH_2 modes, the rocking and torsion vibrations of the NH_2 group being coupled with other modes [24].

Proton transfer

The gas phase intramolecular hydrogen transfer in the tautomeric forms of guanine has been well studied at different theoretical levels [2, 6, 7, 24]. The results obtained show that all transformations pass through high-energy barriers ($150\text{--}251\text{ kJ mol}^{-1}$ [6], see Table 3). The data from Table 3 reveal that the water-/methanol-/hydrogen peroxide-assisted tautomerizations have approximately 100 kJ mol^{-1} lower energy barriers in the

gas phase. Moreover, the molecule of hydrogen peroxide causes the lowest reduction of the energy barrier. For example, the energy barriers in the H_2O_2 -proton transfers are $7\text{--}10\text{ kJ mol}^{-1}$ (forward) and $4\text{--}12\text{ kJ mol}^{-1}$ (reverse) lower compared to the energy barrier heights in the MeOH- and H_2O -proton transfers, respectively. In addition, it can be said that methanol facilitates the H-exchange to a greater extent than water.

The transition states (Fig. 2) of the assisted tautomerizations were calculated, each with one parallel mode (see Table 3, E_{TS} —the energy of a certain transition state), whose form describes the real pathway of the intermolecular H-exchange.

The transition states of the H_2O_2 -assisted tautomerizations look rather strange. It is seen that, in these structures, the bonds $O(11)\text{--}H(16)$ are not completely broken. In other words, the saddle points of the

transition states are closer to the minima (on the energy hypersurface) of the complexes containing the hydroxoguanine tautomers. It is a reactant-like (so-called “early”) transition state [25].

A general feature of all $C \rightleftharpoons D$ tautomerizations is that they are thermodynamically (ΔG_{298}^0) and enthalpically (ΔH_{298}^0) disfavored with a small negative entropy factor as compared to the $A \rightleftharpoons B$ conversions.

Since the H_2O -assisted transfer is discussed in Ref. [24], we performed SCAN calculations only of the $MeOH$ - and H_2O_2 -assisted proton reactions.

All PESs (Fig. 3) describe the two-dimensional energy change along the internal coordinates $H_{17}N_1$ and $H_{16}O_{11}$ in the area nearest the saddle point of the transition state. The PESs are set up by 256 points in all directions beginning at the transition state. The PESs of the H_2O_2 -assisted proton transfers were set up with a gradient of 0.008 Å, whereas those of the $MeOH$ -assisted transformations with a gradient of 0.08 Å. In this way, the PESs visualize the reaction pathways better. There are clearly salient slits, along which the proton transfers proceed.

Concluding remarks

High-level quantum chemistry calculations were used to explore the intermolecular proton transfer exchange in four tautomers of guanine and their H-bonded complexes with water, methanol, and hydrogen peroxide. The analyses of the energies, geometry and electron structures, thermodynamic parameters, and vibrational modes are summarized in the following conclusions:

1. The analysis of the equilibrium constants for the internal rotations $A \rightleftharpoons F$ and $D \rightleftharpoons E$ showed that the amount of rotamer **F** in the gas phase at 298 K should be low, whereas rotamers **D** and **E** should have significant concentrations under the same conditions.
2. The most stable H-bonded complexes are formed between the **C** tautomer of guanine and a molecule of water, methanol, and hydrogen peroxide. The high stability of these systems results from the high absolute values of the bonding energy and the short-intermolecular H-bonds.
3. Complexation between oxo-guanine tautomers and $H_2O/MeOH/H_2O_2$, leads to a shift of the characteristic $C=O$ vibration downward, which is in full agreement with the investigations of Chandra et al. [23] for water complexes of guanine.
4. The proton transfers in guanine assisted by water, methanol, and hydrogen peroxide have about 100 kJ mol^{-1} lower energy barriers than intramolecular proton transfer in guanine itself. The largest

energy decrease is caused by hydrogen peroxide with $4\text{--}12 \text{ kJ mol}^{-1}$ lower energy barriers than those of $MeOH$ - and H_2O -assisted proton transfers, respectively.

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