Theoretical Quantum Chemical Study of Tautomerism and Proton Transfer in 6,8-Dithioguanine

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Ab initio quantum chemical calculations were performed to study the tautomeric rearrangements in the 6,8-dithioguanine. Molecular geometries of all the possible 35 tautomeric structures have been fully optimized without imposing any constraints at the HF/3-21G level. For the seven most favorable structures, full geometry optimizations were performed at the higher level of theory using the 6-31G** basis set. The effects of electron correlation were further accounted for at the second-order Moller−Plesset perturbation theory level with the frozen-core approximation. The proton-transfer reactions were considered between the normal and selected rare tautomeric forms in the gas phase and also for the water assisted proton transfer. It was shown that at all applied levels of theory the standard 6,8-dithioguanine (with protons at the N1, N7, and N9 sites and on its amino group) is the global minimum on the potential energy surface in the gas phase. For the monohydrated complexes of dithioguanine, the complex **1**·H_2O(N1H) is the most stable one and is characterized by the highest interaction energy. The relative stability of monohydrated complexes of normal dithioguanine which interacts with the water through N9H and N7H groups follows stability of **1**·H_2O(N1H). Water-assisted proton-transfer reactions considerably decreases the energy barrier as compared to the ability of gas phase processes to do the same.

Introduction

Water-assisted proton-transfer reactions in nucleic acid bases constitute an important dynamic event in DNA and RNA duplexes.[1,2] Oxidative DNA damage may cause a wide variety of cellular metabolism due to the oxidative modification of DNA bases.[2−4] The NMR experimental studies suggest that ca. 15% of minor "rare" tautomers can be coexist under physiological conditions together with the most predominate 6,8-diketo form of C8-oxidative guanine.[5] The oxygen substitution by sulfur in the oxidative form of purine bases is expected to have drastic effects on the molecular structure, properties, and biological activities of therapeutically important class of nucleic acid derivatives.[6,7] The O6-modified purine bases have an important role in triplex formation due to their ability to reduce the metal ion concentration around the base triplex.[8] Therefore it is significantly important to study such complex phenomena by reliable high level theoretical methods.

Several papers have discussed the tautomerism of nucleic acid bases including the guanine molecule and its sulfur substitution analogues both in the gas phase and in solution.[9−12] Thus, the five most stable tautomers of 6-thioguanine have been investigated at the correlated MP2 and MP4 levels of the theory by Stewart et al. [9] It was shown that the relative stability order of tautomers are quite sensitive to the inclusion of the zero-point energy (ZPE) corrections: at all applied levels of theory (HF, MP2, and MP4 levels) without ZPE corrections, the N1,7(H) tautomer is the most stable one followed by the N9(H) trans (as related to the N1C6 bond of the thioguanine) tautomer. Note that in this case there are two possible tautomers which differ from each other by the position of the proton in the thiol group as compared to the N1C6 bond. Inclusion of the ZPE corrections leads to the reverse stability order though the energy difference is within ca. 1−2 kcal/mol at the highest applied level of the theory. Previously, 6-thioguanine has also been studied at the HF/3-21G*, HF/DZP and MP2/6-311++G(d,p) levels.[10] The larger amino group's nonplanarity has been predicted by MP2 calculations with relatively larger basis sets for 6-thioguanine.[11] Gorb and Leszczynski have reported the intramolecular proton-transfer process in mono- and dihydrated tautomers of guanine by means of an ab initio post Hartree−Fock study.[12] They show that the height of the proton transfer barrier for monohydrated complexes of guanine to be approximately 2 and 3 times lower than the corresponding heights for the tautomeric oxo-hydroxo and hydroxo-oxo reactions, respectively.

The effect of the oxo group in C8-oxidative guanine has been also recently analyzed by means of theoretical methods.[13−15] It was found that the 8-keto-6-enolic form of C8-oxidative guanine is the predominant form over the 6,8-diketo form in the gas phase when applying the higher levels of theory with inclusion of electron correlation.[13] However, this relative stability order changes when one takes into account an aqueous solution where the diketo form become the most stable species. The presence of the 8-oxo group reduces the energy difference between the keto and enolic forms of C8-oxidative guanine as compared to that for normal guanine.[16] Note, however, only the five tautomers which have been expected to be the most important were considered in this paper. Previously, Aida and Nishimura have showed that the diketo form of C8-oxidative guanine is 2.3 kcal/mol more stable than the 8-keto-6-enol tautomer at the HF/3-21G level.[14] The effect of guanine stacking on C8-oxidative guanine in B-DNA have been investigated at the HF

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and DFT levels.[15] To our best knowledge, however, there is no theoretical studies considering its dithioguanine analogues and the intramolecular proton-transfer process.

In the present paper we report ab initio quantum chemical calculations on the tautomeric rearrangements in 6,8-dithioguanine, one of the modified purine base. The water-assisted proton-transfer reactions modeled by explicit involvement of one water molecule were compared with those in the gas phase for the normal and selected rare tautomeric forms. We do not include the electrostatic interaction with a solvent represented by continuum models since they only slightly influence the activation barriers.[17] The intramolecular proton-transfer process in an aqueous solution is mainly controlled through the assistance of a water molecule. On the basis of the results of these calculations, the molecular structures of different tautomers, their relative stability order, the effect of polar solvent on the above phenomena, and proton-transfer reactions will be discussed.

Method of Calculation

The ab initio local minimum structures and the transition-state structures have been fully optimized by the analytic gradient techniques using the Gaussian92 and Gaussian94 program packages.[18] The molecular geometries of all the possible 35 tautomeric structures have been fully optimized without imposing any constraints at the HF/3-21G level of the theory. Then the relative energies were verified by single-point calculations at the HF/6-31G**//HF/3-21G level. Further, full geometry optimizations were performed for the seven most favorable structures at the higher level of theory using the standard 6-31G** basis set. The proton-transfer reactions were considered between the normal and selected rare tautomeric forms in the gas phase. In addition, the water-assisted proton-transfer process modeled by explicit involvement of one water molecule was investigated. The effects of electron correlation were accounted for at the second-order Moller−Plesset perturbation theory level with the frozen-core approximation by performing single-point calculations. The interaction energies for the different monohydrated dithioguanine complexes were corrected for the basis set superposition error (BSSE) by using the full Boys−Bernardi counterpoise correction scheme.[19] The intramolecular proton-transfer reaction paths are determined by using the opt = qst2 or qst3 options. Such options correspond to transition structure search codes which require as input the reactant and product structures (for the qst2 option) and the reactant, product, and initial transition structures (for the qst3 option).

Results and Discussion

1. Geometries and Relative Energies. The dithioguanine molecule is characterized by the presence of four labial protons and seven distinct sites to where they can be attached. There is a number of possible attachments of protons leading to 35 tautomers of the dithioguanine molecule. The latter number of tautomers can be estimated using the well-known formulas

$$N = (7!)/(4!)(7 - 4)! \quad (1)$$

where (!) stands for the factorial. All tautomers and their assignments are listed in Table 1 together with the relative energies calculated at the HF/3-21G and HF/6-31G**//HF/3-21G levels of theory. The structure **1** corresponds to the normal 6,8-dithioguanine in which protons are attached to the N1, N2, N9, and N7 sites (Figure 1). Structures **2**−**13** can be obtained from the structure 1 through a single proton transfer process. The other structures correspond to a doubly proton transferred species except for structures **24**, **33**, **34**, and **35** which are obtained through triple proton-transfer reactions. In addition, for the seven most favorable tautomers, full geometry optimizations were performed at the HF/6-31G** level. Table 2 shows the energetic characteristics of these seven tautomers calculated at the HF/6-31G** and MP2/6-31G**//HF/6-31G** levels of the theory. Also similar characteristics for the three transition-state structures for single-proton-transfer reactions are provided together with their dipole moments. Although the details of all optimized geometries for both isolated dithioguanine and their monohydrated complexes are not presented here, they can be obtained upon request from the authors. In the following illustrating figures only the major geometrical parameters which are crucial for further discussion are displayed.

TABLE 1: Relative (ΔE_1 and ΔE_2, kcal/mol) Energies of All Tautomers of Dithioguanine Calculated at the HF/3-21G and HF/6-31G/HF/3-21G Levels of Theory[a]**

structure	N1	N2	N3	N9	S8″	N7	S6″	ΔE_1[b]	ΔE_2[c]
1	x	x		x		x		0	0
2		x		x		x	x	19.2	3.8
3		x	x	x		x		21.5	21.3
4		x		x	x	x		56.2	37.7
5	x		x	x		x		17.2	18.3
6	x			x	x	x		72.0	53.7
7	x			x		x	x	52.9	35.8
8	x	x	x			x		36.4	34.0
9	x	x			x	x		36.9	14.7
10	x	x				x	x	87.3	80.3
11	x	x		x	x			35.9	15.9
12	x	x		x			x	97.1	71.6
13	x	x	x	x				64.8	62.2
14		x	x			x	x	44.5	24.4
15		x			x	x	x	56.6	20.7
16		x	x	x			x	62.8	43.7
17		x		x	x		x	51.1	15.5
18			x	x		x	x	47.5	33.2
19				x	x	x	x	112.7	79.9
20	x		x			x	x	76.5	36.6
21	x				x	x	x	99.4	60.1
22	x		x	x			x	68.9	51.0
23	x			x	x		x	84.6	47.0
24			x	x	x		x	76.6	42.5
25	x	x			x		x	76.0	34.0
26	x	x	x				x	96.2	73.7
27			x	x	x	x		87.3	69.9
28		x	x		x	x		43.1	22.4
29		x	x	x	x			59.3	39.6
30	x		x		x	x		44.5	23.2
31	x		x	x	x			51.7	33.0
32	x	x	x		x			63.5	41.5
33			x		x	x	x	74.8	39.7
34	x		x		x		x	79.8	39.4
35		x	x		x		x	68.2	28.3

[a] The positions of protons are assigned by a mark (x). [b] ΔE_1 relates to the HF/3-21G level. The total energy of the normal dithioguanine amounts to −1253.08868 au at this level of theory. [c] ΔE_2 relates to the HF/6-31G**//HF/3-21G level. The total energy of the normal dithioguanine amounts to −1259.58026 au at this level of theory.

An analysis of Tables 1 and 2 show that at all applied levels, 6,8-dithioguanine (structure **1**) is the global minimum on the potential energy surface (PES) in the gas phase. Structure **2** obtained through proton transfer from the N1−H group to the S6 site is the second most stable one within the higher level of theory, while the HF/3-21G level predicts structure **5** to be the second most favorable tautomer formed via rearrangement of the amino-group's proton to the N3 site. Note also that the relative stability of the normal tautomer is highly overestimated

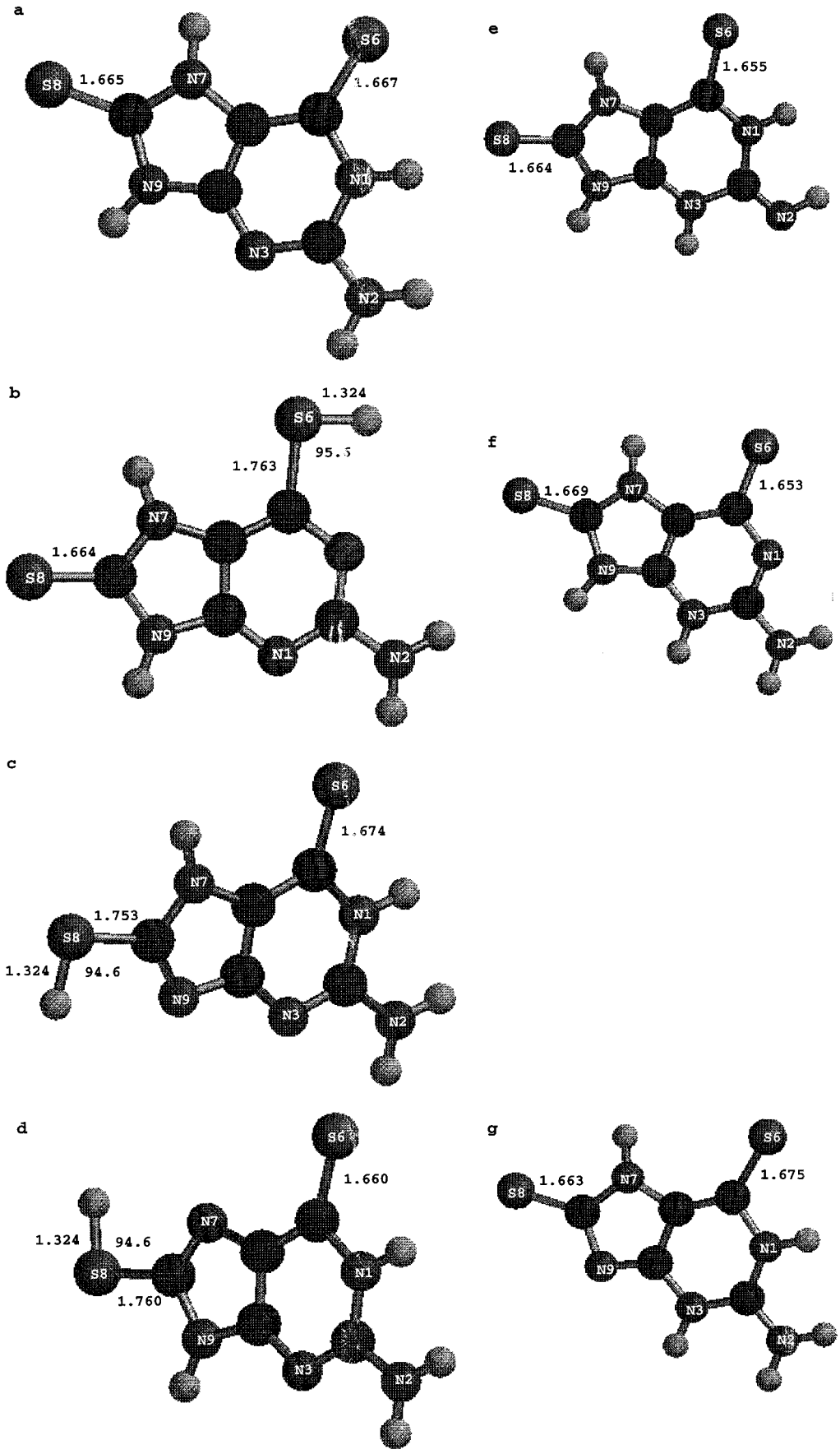

Figure 1. Seven tautomers of dithioguanine as computed at the HF/6-31G** level of theory: (a) structure **1**, (b) structure **2**, (c) structure **9**, (d) structure **11**, (e) structure **5**, (f) structure **3**, and (g) structure **8** (see Table 2). Bond lengths in angstroms, bond angles in degrees.

within the lower HF/3-21G level as is well-known.[13,20] Moreover, the latter level leads to a somewhat different stability order of the tautomers compared to higher levels of theory. Inclusion of electron correlation through the MP2 single-point calculations

TABLE 2: Total (E_{tot}, au) and Relative (ΔE, kcal/mol) Energies and Dipole Moments (D, debye) of the Most Favorable Seven Tautomers of Dithioguanine and the Three Transition-State Structures for a Single-Proton-Transfer Reactions in the Gas Phase Calculated at the HF/6-31G and MP2/6-31G**//HF/6-31G** Levels of Theory[a]**

structure	N1	N2	N3	N9	S8″	N7	S6″	$-E_{tot}$	ΔE	D
1	x	x		x		x		1259.584 46	0	10.0
								1261.275 21	0	
2		x		x		x	x	1259.578 61	3.7	6.1
								1261.271 19	2.5	
9	x	x			x	x		1259.564 26	12.7	3.6
								1261.258 95	10.2	
11	x	x		x	x			1259.559 33	15.8	7.8
								1261.255 01	12.7	
5	x		x	x		x		1259.555 74	18.0	5.7
								1261.248 87	16.5	
3		x	x	x		x		1259.550 18	21.5	11.7
								1261.244 37	19.4	
8	x	x	x			x		1259.530 00	34.2	16.5
								1261.224 86	31.6	
TS1[b]	xx	x		x		x	xx	1259.515 77	43.1 (39.4)	7.0
								1261.224 93	31.6 (29.0)	
TS2[b]	x	x		xx	xx	x		1259.495 41	55.9 (43.2)	6.2
								1261.208 07	42.1 (31.9)	
TS3[b]	x	xx	xx	x		x		1259.480 47	65.3 (47.2)	7.7
								1261.192 27	52.0 (35.5)	

[a] The positions of protons are assigned by a mark (x). The second set of values corresponds to MP2/6-31G**//HF/6-31G** level. [b] The activation energy barrier is calculated as an energy difference for the forward(reverse) proton-transfer reactions. The mark (xx) stand for the position of the proton in the transition-state structure.

leads to the further decrease in the relative energy differences as compared to the main structure **1** by ca. 1−3 kcal/mol (see Table 2).

As is mentioned in the Introduction, five tautomers of C8-oxidative guanine were considered in ref 13. Two of these tautomers, i.e., the structures denoted as 8OG4 and 8OG5 (Figure 1 from the ref 13, differs only in the orientation of the O6H-group as compared to the N7 site of dioxoguanine), are expected to be important in base mispairing and inducing mutations. For dithioguanine these tautomers correspond to structure **17** (Table 1). Although structure **17** has a relative energy of 51 kcal/mol at the HF/3-21G level, we further optimized its geometry at the higher levels of theory. It was found that this tautomer lies 15.4 and 11.2 kcal/mol higher in energy than structure **1** at the HF/6-31G** and MP2/6-31G**// HF/6-31G** levels of theory, respectively. On the basis of these data and taking into account that such a form can be obtained through a double proton-transfer reaction from 6,8-dithoguanine, its complexes with one water molecule were not considered further.

The relative stability order of the tautomers of dithioguanine are somewhat opposite to the analogous dioxoguanine tautomers. The 8-keto-6-enolic form of dioxoguanine was found to be the most stable tautomer in the gas phase,[13] while structure **1** is the most favorable one in the case of dithioguanine. This can be expected if one considers the distinct bond dissociation energies in the well-characterized substances. Thus, the instability of structure **2** as compared to that of structure **1** (Table 2) can be explained by the bond energy difference between the S−H and N−H bonds, respectively in the H_2S and NH_3 molecules: the average N−H bond energy in NH_3 is ca. 16 kcal/mol higher than the S−H bond in H_2S.[21] The preferability of the 8-keto-6-enolic form of dioxoguanine[13] is due to the fact that the average N−H bond energy in NH_3 is ca. 12 kcal/mol lower than the O−H bond in H_2O.[21] Similar trends were also predicted for isocytosine where the enol form is the most stable one as compared to the keto form.[22]

The seven lowest energy gas phase structures are shown in Figure 1. As can be expected, the replacement of the oxo-group by the thio-group leads to the differences in the five- and six-membered rings' geometries due to the larger ionic radii for sulfur as compared to oxygen. Such a difference in the ionic radii directly affects the polarity of the C−X bond where X = O or S and the geometry of the next-neighbor five- and six-membered rings. Thus the relative increasing of the C−S bond length as compared to the C−O bond length is effectively compensated by strengthening and decreasing both the N1−C6 and C5−C6 bonds in the six-membered ring and N7−C8 and C8−N9 bonds in the five-membered ring (ca. 0.03−0.05 Å) of dithioguanine. Therefore, we will not discuss all these changes in purine rings and, instead, let us only compare the main characteristics related to the S-containing fragments. An analysis of the C−S bond lengths and the C−S−H bond angles in these tautomers of dithioguanine shows that they are marginally longer and larger than the similar parameters of the well-characterized thioformaldehide, thioformamide, and dihydrogen sulfur molecules.[21] Thus, the C═S double bond is ca. 0.05 Å longer in these tautomers of dithioguanine while the C−S−H angle is larger by ca. 2−3° as compared to the above molecules. Furthermore, the changes are very small when one compares the above properties with the similar characteristics of the monosubstituted thioguanine analogues: the differences in the C−S bond lengths and the C−S−H bond angles are within ca. 0.005 Å and 0.2°.[9]

The six monohydrated complexes of dithioguanine are shown in Figure 2. They can be divided into two classes. The first set corresponds to the complexes solvated through their N1−H (Figure 2a), or N9−H (Figure 2b), or N7−H groups (Figure 2c), while the second set of higher energy structures can be viewed as the monohydrated complexes formed through the proton-transfer reactions from the distinct N−H groups to the distinct S sites (Figure 2d−f). Table 3 shows the energetic characteristics of these monohydrated complexes of dithioguanine calculated at the HF/6-31G** and MP2/6-31G**//HF/6-31G** levels of the theory, respectively. Also similar properties of the three transition state structures for single proton-transfer reactions together with their dipole moments are displayed in Table 3.

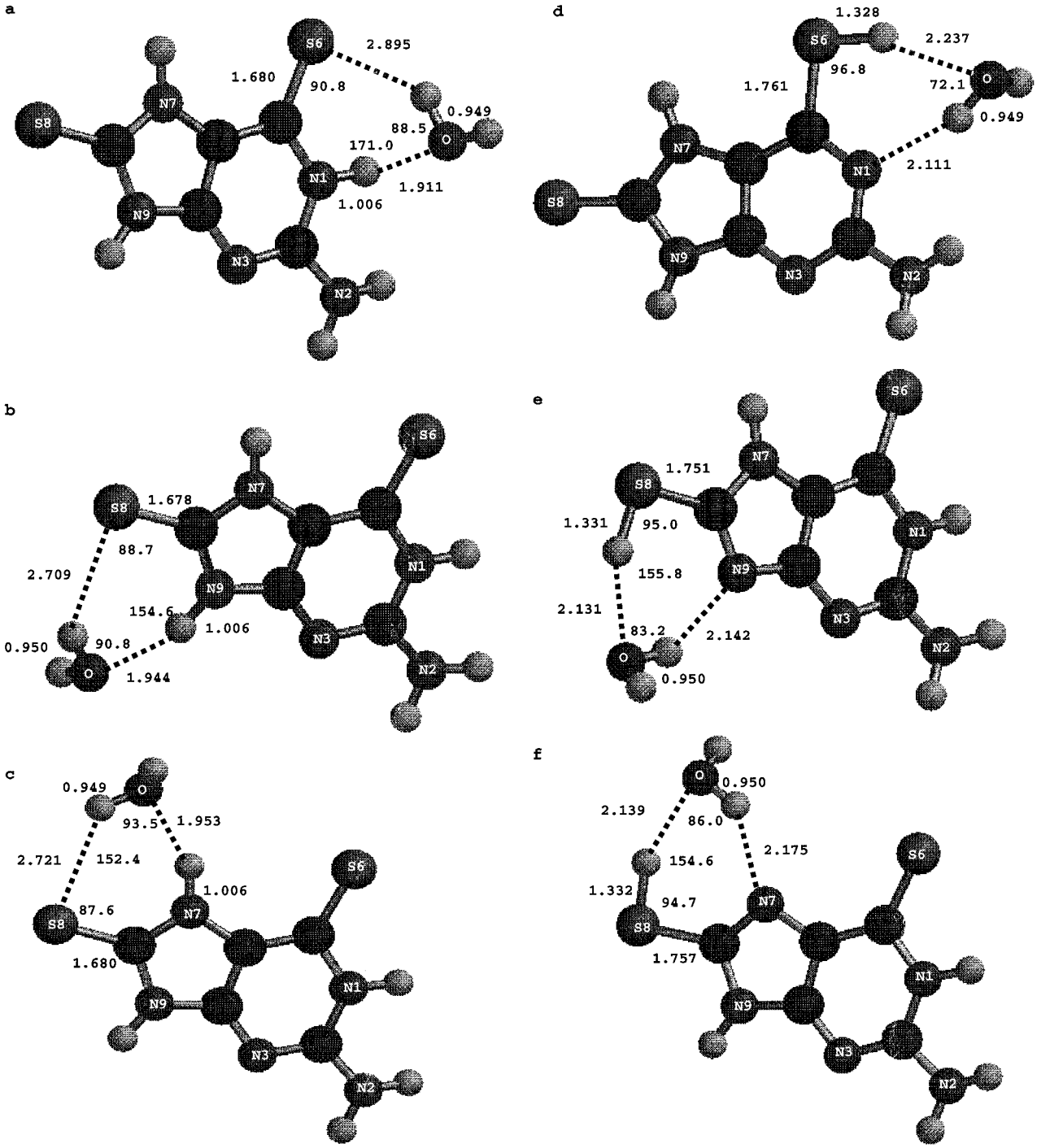

Figure 2. The most important six monohydrated complexes of dithioguanine as computed at the HF/6-31G** level of theory: (a) **1**·H_2O(N1H), (b) **1**·H_2O(N9H), (c) **1**·H_2O(N7H), (d) **2**·H_2O(S6H), (e) **9**·H_2O(S8H), and (f) **11**·H_2O(S8H) (see Table 4). Bond lengths in angstroms, bond angles in degrees.

An analysis of the data presented in Table 3 shows that the monohydrated complex **1**·H_2O(N1H) (Figure 2a) is the most stable one at both applied levels of theory. The water molecule acts as a proton donor to and a proton acceptor from the dithioguanine molecule, and such interactions result in the formation of a ring-like structure. One of the H bonds is between the H atom of the N1−H group of dithioguanine and the O atom of the water molecule while the second relatively weaker H bond is placed between the H atom of the water molecule and the S6 site of dithioguanine. This can be expected since the proton acceptor ability of the S6 site is much smaller than that of the O6 site of C8-oxidative or normal guanine.[12,13]

The second and third most stable structures are dithioguanine complexes hydrated with the water through the N9−H and N7−H groups, i.e., **1**·H_2O(N9H) and **1**·H_2O(N7H) complexes. These ringlike structures lie only 1.9 (1.3) and 3.4 (2.4) kcal/mol higher in energy then the complex **1**·H_2O(N1H) at the HF/6-31G** (MP2/6-31G**//HF/6-31G**) levels of theory, respectively. Both H bonds are relatively shorter than those of the **1**·H_2O(N1H) complex and strongly deviate from the linearity. Probably this is due to the fact that the five-member ring is able to effectively withdraw the electron density from the H atoms of the N9−H or N7−H groups as compared to the influence of the six-membered ring on the H atom of the N1−H

TABLE 3: Total (E_{tot}, au), Relative (ΔE, kcal/mol), and Interaction (E_{int}, kcal/mol) Energies and Dipole Moments (D, debye) of Dithioguanine with a Water Molecule and Transition-State Structures for a Water-Assisted Single-Proton-Transfer Reactions Calculated at the HF/6-31G and MP2/6-31G**//HF/6-31G** Levels of Theory[a]**

structure	N1	N2	N3	N9	S8″	N7	S6″	$-E_{tot}$	ΔE	$-E_{int}$	D
1·H_2O	xw	x		x		x	w	1335.627 64	0	10.6	9.5
(N1H)								1337.518 15	0	11.2	
1·H_2O	x	x		xw	w	x		1335.624 69	1.9	8.9	8.5
(N9H)								1337.516 01	1.3	9.9	
1·H_2O	x	x		x	w	xw		1335.622 28	3.4	7.6	8.4
(N7H)								1337.514 36	2.4	9.1	
2·H_2O	w	x		x		x	xw	1335.611 98	9.8	4.2	5.2
(S6H)								1337.506 39	7.4	5.6	
9·H_2O	x	x		w	xw	x		1335.602 02	16.1	6.6	4.8
(S8H)								1337.498 93	12.1	8.1	
11·H_2O	x	x		x	xw	w		1335.598 28	18.4	7.7	7.9
(S8H)								1337.495 80		9.0	
TS1w	xw	x		x		x	xw	1335.580 41	29.6(19.8)[b]		9.9
(N1H)								1337.489 39	18.1(10.7)[b]		
TS1w	x	x		xw	xw	x		1335.575 24	31.0(16.8)[b]		8.0
(N9H)								1337.484 70	19.7(8.9)[b]		
TS1w	x	x		x	xw	xw		1335.572 24	31.4(16.3)[b]		5.3
(N7H)								1337.483 05	19.7(8.0)[b]		

[a] The positions of protons are assigned by a mark (x). The mark (w) stand for a water molecule which has H bonds with distinct active sites of dithioguanine marked as (xw). The second set of the numbers correspond to the MP2/6-31G**//HF/6-31G** level. [b] The activation energy barrier is calculated as an energy difference for the forward(reverse) proton-transfer reactions.

group. Therefore, the acidity of the N9−H and N7−H groups are much higher than that of the N1−H group.

The structures shown in Figure 2d−f correspond to the monohydrated complexes of dithioguanine in the thiol forms. They can be obtained through single proton-transfer reactions from the N1−H, or N9−H, or N7−H groups. The relative stability order of these three complexes correlates well with the initial three structures of the parent tautomer (Table 3), and it can be described as follows:

$$\mathbf{1}\cdot H_2O(\text{N1H}) > \mathbf{1}\cdot H_2O(\text{N9H}) > \mathbf{1}\cdot H_2O(\text{N7H}) > \mathbf{2}\cdot H_2O(\text{S6H}) > \mathbf{9}\cdot H_2O(\text{S8H}) > \mathbf{11}\cdot H_2O(\text{S8H})$$

This relative stability order is somewhat opposite to that of the analogous monohydrated complexes of dioxoguanine.[23] In the case of dioxoguanine, the monohydrated complex of 6,8-dioxoguanine is the most stable one followed by the 6-hydroxo-8-oxo, 6-oxo-8-hydroxo, and 6,8-dihydroxo monohydrated forms.[23] In the case of dithioguanine, the most favorable monohydrated **2**·H_2O(S6H) complex in which it is in the 6-thiol-8-thione rare tautomeric form is only fourth in its relative stability (see also Table 3). The reason for this is that the parent 6-hydroxo tautomer of dioxoguanine[13] is more strongly stabilized than the 6-thiol form of dithioguanine, as is explained above. A full comparison is not possible since only four monohydrated complexes of dioxoguanine have been considered.

2. Proton-Transfer Transition State. The predicted transition state species were verified by establishing the matrixes of the energy second derivatives which contain only one negative eigenvalue. Tables 2 and 3 contain the energetic characteristics of the transition state forms considered in this study for the gas phase and for water-assisted proton-transfer reactions. These transition-state structures have been depicted in Figures 3 and 4, respectively, for the gas phase and for monohydrated complexes. Note that previously the water-assisted proton-transfer reactions have been investigated by ab initio methods only for some simple prototypic molecules such as acetamide,[24] formamide,[25] formamidine,[26] and also for mono- and dihydrated complexes of guanine.[12]

An analysis of the data presented in Tables 2 and 3 shows that the proton transfer is characterized by a high energy barrier in the gas phase. Although the inclusion of the electron correlation effects substantially decreases the height of the barriers (by ca. 10−13 kcal/mol), the value of the gas-phase proton-transfer barrier is still too large for this process to be observed at room temperature, even for reverse reactions. This is consistent with the aforementioned theoretical studies.[12,21−23] As can be expected, the water-assisted proton-transfer reactions might be feasible due to the further substantial decrease of the height of the barrier. Thus, such barriers amount to only ca. 10 kcal/mol for all three reverse reactions at the correlated MP2/6-31G**//HF/6-31G** level of theory (see Table 3). That justifies the possibility that the reverse water-assisted proton-transfer reactions might occur with a profound preference at any temperature of biological importance. This might be due to the relatively much higher interconversion rates for the reverse water-assisted proton-transfer reactions as compared to those for the gas-phase reactions.

It is worth noting that the dipole moment for the transition state forms of dithioguanine somewhat correlates with the proton-transfer reactions in the gas phase. Their values are smaller than that of **1** and larger than those tautomers in the thiol forms; that is, it decreases for the thione−thiol tranformations and increases for the thiol-thione transformations (see Table 2). One also can find that the dipole moment for the transition state structure is less than half the sum of the dipole moments of the initial thione and thiol forms of dithioguanine. However, there are no such correlations for the monohydrated dithioguanine complexes (Table 3).

3. Interaction Energies. In line with our previous studies,[27,28] the BSSE corrected interaction energies were calculated as the energy differences between the monohydrated complex and the sum of isolated monomers. Note also that we have used the standard Boys−Bernardi counterpoise correction scheme,[18] whereas additional nonincluded corrections for BSSE take into account geometry reorganization when going from isolated subsystems to the monohydrated complex. The **1**·H_2O(N1H) complex has the relatively highest interaction energy among the considered structures at both HF/6-31G** and MP2/6-

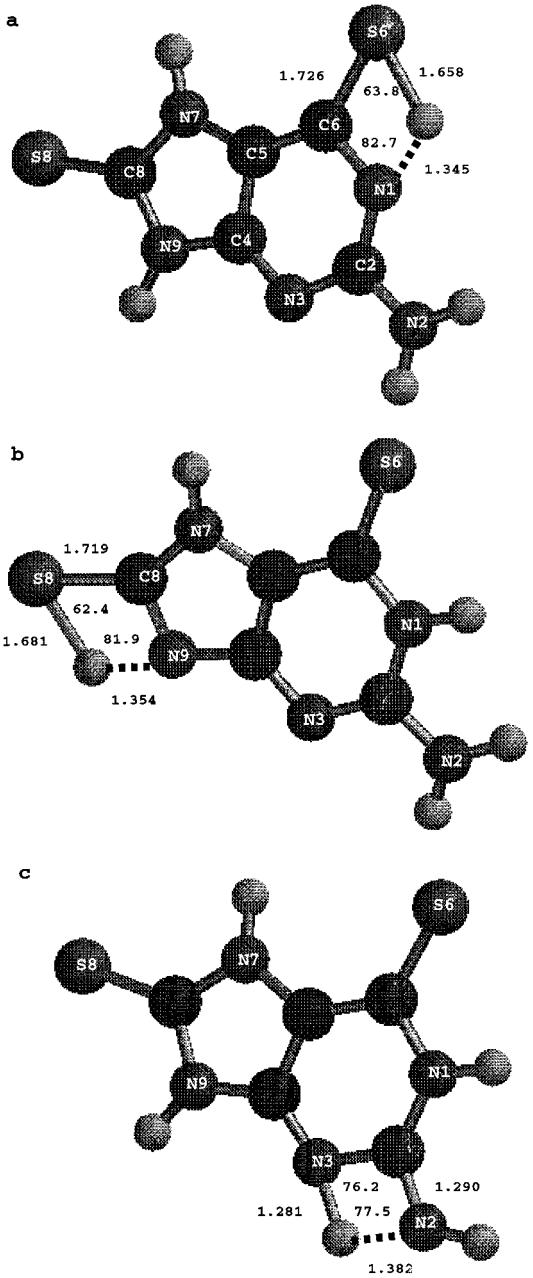

Figure 3. Three proton-transfer transition-state structures in the gas phase as computed at the HF/6-31G** level of theory: (a) from the N1−H group to the S6 site, (b) from the N9−H group to the S8 site, and (c) from the N2−H group to the N3 site of dithioguanine. Bond lengths in angstroms, bond angles in degrees.

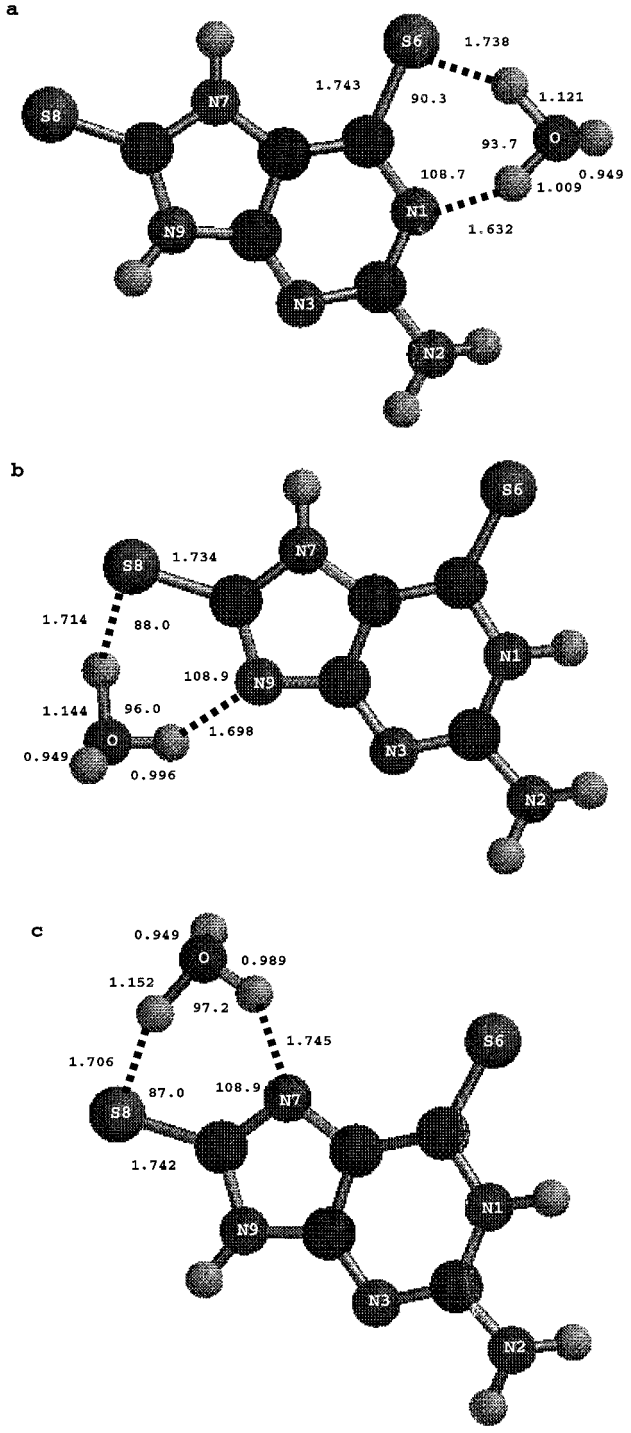

Figure 4. Three proton-transfer transition-state structures for the monohydrated dithioguanine complexes: (a) from the N1−H group to the S6 site, (b) from the N9−H group to the S8 site, and (c) from the N7−H group to the S8 site. Bond lengths in angstroms, bond angles in degrees.

31G**/HF/6-31G** levels of theory. As usual,[27,28] the interaction energy values increase by ca. 1−1.5 kcal/mol at the correlated MP2 level compared with the HF level of theory.

Conclusions

Ab initio quantum chemical calculations show that at all applied levels (i.e., HF/3-21G, HF/6-31G**//HF/3-21G, HF/6-31G**, and MP2/6-31G**//HF/6-31G** levels) 6,8-dithioguanine (structure **1**) is the global minimum on the PES in the gas phase followed by structure **2** obtained through the proton transfer from the N1−H group to the S6 site. This is somewhat opposite to the analogous dioxoguanine tautomers for which the 8-keto-6-enolic form is found to be the most stable tautomer in the gas phase.[13] For the monohydrated complexes of dithioguanine, the **1**·H_2O(N1H) complex is the most stable one on the PES and has the highest interaction energy. In this complex, hydration takes place through the N1−H group and the S6 site. The relative stability order of all monohydrated complexes may be described as follows:

1·H_2O(N1H) > **1**·H_2O(N9H) > **1**·H_2O(N7H) > **2**·H_2O(S6H) > **9**·H_2O(S8H) > **11**·H_2O(S8H)

The height of the proton transfer barriers are too large for this processes to be observed at room temperature for the gas

phase while they substantially decrease when one considers the monohydrated complexes of dithioguanine: it can be expected that the reverse proton-transfer reactions might occur with a profound preference at any temperature of biological importance.

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