Tautomerism and Proton Transfer in 6-Selenoguanine: A Post Hartree−Fock Level ab Initio SCF-MO Investigation

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Tautomerism and proton transfer in 6-selenoguanine (6SeG) have been investigated using high level ab initio calculations. Full geometry optimizations were carried out in the gas phase at the HF and MP2 levels using the 6-31G(d,p) basis set. Furthermore, the single point energies were evaluated using larger basis sets augmented with diffuse and polarization functions. At all applied levels of theory, the N^7 protonated form is shown to be the most stable one in the gas phase and is 3.1 kcal/mol more stable than the N^9 protonated tautomer at the MP2/6-311++G(d,p)//MP2/6-31G(d,p) level. However, aqueous solvation studies using the SCI−PCM continuum models show a different trend for energetic preference for selenoguanines. Estimated free energies of tautomerization in an aqueous medium indicate that the N^9 protonated form is more stable than the N^7 protonated form although the energies of these two tautomers are very close. Our calculations suggest that the Se^6 protonated form of N^9-selenoguanine is the most hydrated one while the selenoic form of N^9-selenoguanine is the least hydrated one. The following stability order may be established for 6-selenoguanine in the gas phase, 6SeG4 > 6SeG3 > 6SeG2 > 6SeG1 > 6SeG5, while in an aqueous solution, a stability order as such is established, 6SeG1 > 6SeG4 > 6SeG3 > 6SeG2 > 6SeG5. The proton transfer from the N^1 to the Se^6 site involves an energy barrier of about 39 kcal/mol for the N^9 protonated tautomer and 46 kcal/mol for the N^7 protonated tautomer at the HF level and 31.8 and 36.6 kcal/mol, respectively, at the MP2/6-311++G(d,p)//HF/DZP level.

Introduction

Proton-transfer reactions in nucleic acid bases constitute an important dynamic event in DNA and RNA duplexes. Owing to their fundamental role in regulating biochemical reactions including protein synthesis and enzymatic activities, structural properties of nucleic acid bases, and a number of their analogues have become attractive targets for various structural studies over the past three decades.[1−3] The importance of their study is reflected by extensive theoretical and experimental investigations in probing their structure and functional properties.[4−11] Modifications of both purine and pyrimidine bases have been studied in depth. For example, incorporation of heavier atoms into DNA bases leads to a therapeutically important class of nucleic acid derivatives.[12,13] The effect of oxygen substitution by sulfur on the molecular structure, properties, and biological activities of pyrimidine-based species has been investigated for a number of compounds. These include the structural studies of thiouracils,[14] selenouracils,[15] thio and selenocytosines,[9] and isocytosine.[10] However, despite their distinct nature, the structural properties of purine modifications are relatively unstudied. One important class of purine modifications includes substitution of the exocyclic oxo group with the S or Se atoms. In the case of guanine, such modifications are known to cause significant alteration of biological activity. Recently, the O^6-modified purine bases have found a potential role in triplex-formation essentially due to their tendency to reduce the metal ion concentration around the base-triplex thereby reducing the possible formation of a tetraplex and favoring the desired triplex formation.[16] 6-thioguanine and 6-mercaptopurine are known to display significant activity against L1210 leukemia cells.[17,18] Complexes of *cis*-diaminoplatinum (II) with selenoguanine, thioguanine, 6-thioxanthine, or 6-mercaptopurine exhibit antitumor activity with very low toxicity. It was shown that the antitumor activity was dependent on the nature of the purine ligand.[17b] This study demonstrates that selenoguanine shows delayed toxicity due to its slow release from the complex, SeG−$Pt(NH_3)_2$. The detailed mechanisms of how such subtle variations could be triggered by single atom substitutions are not known. A detailed molecular understanding of the energetic and geometrial changes in this class of modified guanines would be prerequisite in assessing their demonstrated biological activity. Unlike the case of 6-thioguanine, which has been studied rather widely, detailed information about 6-selenoguanine is scarce. A structural study of 6-selenoguanine is important for several reasons. Previous studies indicate that normal guanine and its sulfur analogue show significant nonplanarity in the exocyclic amino groups.[19] Recent ab initio studies of guanine and thioguanine using large basis sets up to 6-311++G(d,p) at the HF and MP2 levels indicate that nonplanarity of the exocyclic amino groups depends critically on the level and quality of the basis sets employed.[19,20] It is known that the lower level basis sets such as 3-21G(*) forces the amino groups to adopt planar geometries.[21] Larger deviations of the exocyclic amino groups from planar geometries in nucleic acid bases play a significant role in affecting various parameters of DNA both locally and globally through changes in base-pairing, bending, and base stacking.[22,23] A detailed understanding of nonplanarity in both purines and pyrimidines with substitution of oxygen by more heavier atoms such as selenium would be certainly warranted. We have carried out a set of CCSD(T) calculations on the nonplanarity of the amino groups of aniline, aminopyridines, and aminotriazine using large basis sets of AO.[24] The calculations demonstrate that the MP2

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and CCSD(T) methods provide nearly identical results as far as the amino group pyramidalization is concerned.

Another important feature of nucleic acid bases is their ability to induce spontaneous mutations in DNA. It has long been speculated that certain minor tautomeric species would play a key role in inducing both transitional and transversional mutations.[25] While there has been no substantial experimental evidence to support such a hypothesis, the matter is still intriguing due in part to the inability of experimental methods clarify such a possibility. As an alternative, high level ab initio methods have emerged as the best techniques to address such crucial structural information. We have studied a number of nucleic acid bases in order to assess the possible role of minor tautomeric forms in inducing spontaneous mutations.[26,27] Guanine is one of the most extensively studied nucleic acid bases and has been shown by various theoretical[8,28] and experimental studies[29] to exist in the N^7 protonated form in a gas phase and in the N^9 protonated form in an aqueous phase. The influence of sulfur in the place of the 6-oxo group has also been studied. Substitution of sulfur for oxygen does not alter the geometrical and energetic parameters of thioguanine.[20] Less known are the structural variations caused by the substitution of oxygen by selenium, the next heavier analogue. Recent theoretical studies of selenoguanine tautomers in a gas phase at the HF and MP2 levels using the DZP basis set indicate that N^7 protonated selenoguanine is the most stable species, whereas the cis form of the 6-selenolic form apprears to be the second most stable tautomer.[20b] However, these studies were done on a limited number of tautomers and included only the single point MP2 energies using the reference HF geometries at the DZP level. Corresponding details about the relative population of selenoguanine tautomers in an aqueous phase are also unknown. While most of these studies lay interest in the relative energies of the isolated tautomers, it should be born in mind that a proton transfer between the most stable tautomers involves the crossing of an energy barrier on the potential energy surface. A knowledge of such information would be crucial in understanding the dynamic role of proton transfer in DNA. The present work, utilizing high level ab initio molecular orbital models, is aimed at understanding the tautomeric preferences of 6SeG in both a polar solvent and in the gaseous phase to gain an insight into the stability of minor tautomers and at attempting to seek the influence of solvent-induced stabilization of minor tautomers and their possible role in tautomerism-induced mutagenesis.

Methods

The ab initio LCAO-MO[30] method was used in the present study. Full geometry optimizations were performed without imposing any symmetry constraints at the HF/6-31G(d,p) and MP2/6-31G(d,p) levels of theory and all optimized geometries at HF/6-31G(d,p) were found to be true minima by analysis of the respective harmonic vibrational frequencies obtained from diagonalization of the force constant matrixes and with the corresponding Hessian eigenvalues being positive. To get more accurate energies using larger basis sets with inclusion of diffused functions and electron correlation effects, we have carried out single point calculations at the MP2/6-311++G-(d,p) level with the HF/6-31G(d,p) and MP2/6-31G(d,p) reference geometries. ZPE corrections were made as the sum of zero-point energies for all normal modes of vibrations scaled by a recommended factor of 0.9 as suggested by Kwiatkowski et al.[31a,b] (For general discussion, see ref 31c.)

All ab initio calculations were carried out using the GAUSSIAN 92 and GAUSSIAN 94 packages.[32] The aqueous solvation

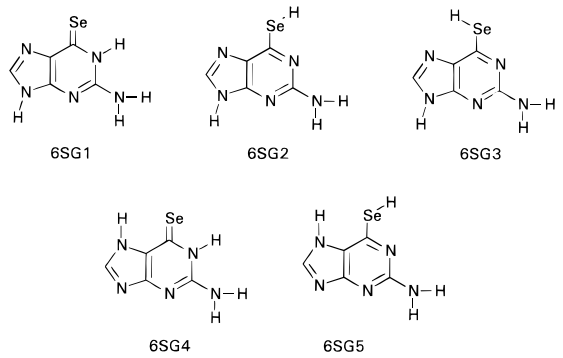

Figure 1. Structures of studied 6-selenoguanine tautomers.

effects were studied using the SCI−PCM self-consistent isodensity polarizable continuum model as developed by Tomasi et al. and incorporated into Gaussian 94.[33] The absolute free energies of hydration were obtained as the difference between the total solute and solvent energies estimated at the both HF and MP2/6-31G(d,p) levels. Full geometry optimization of the tautomers using the SCI−PCM model at either the HF or MP2/6-31G(d,p) levels is extremely computationally intensive. Therefore, we restricted our study of deriving free energies of hydration by using single-point energies obtained from the corresponding gas phase HF and MP2/6-31G(d,p) geometries. We used a relative permittivity constant of 80.0 to model an aqueous medium and a default 0.001 e isodensity surface. The free energy of tautomerization in an aqueous solution were subsequently determined from the gas phase free energies ($\Delta g^{gas}_{A\rightarrow B}$) and free energies of hydration ($\Delta\Delta G^{hyd}_{A\rightarrow B}$) according to eq 1. Since the entropic terms approximately cancel out in structurally similar systems, we consider the gas phase energies obtained at the HF level (corrected with ZPE) to be equal to the rather more rigorously obtained free energy terms.

$$\Delta G^{aq}_{A\rightarrow B} = \Delta G^{gas}_{A\rightarrow B} + \Delta G^{hyd}_{B} - \Delta G^{hyd}_{A} = \Delta G^{gas}_{A\rightarrow B} + \Delta\Delta G^{hyd}_{A\rightarrow B} \cdots \quad (1)$$

Results and Discussion

In all purine bases, there are two labile protons at the N^1 and N^9 sites. Migration of either of these protons to other nucleophilic sites leads to a number of possible tautomeric structures and some of them are biologically significant. Taking the que from our previous studies on guanine and thioguanine, we considered five most significant tautomers of 6-selenoguanine which were found to be the most stable in the present study are shown in Figure 1. Three are in the selenolic form and the others in the selenoic forms. The 6-selenolic forms are considered in both cis and trans forms with respect to the N^1 site.

The geometrial parameters of various tautomers studied in the present work are shown in Figures 2−5. The values shown are the computed bond lengths and bond angles at both HF and MP2 levels. One should be able to draw two important observations from these molecular parameters. The electron correlated geometries at the MP2 level are consistently different from those derived from the HF level. The MP2 bond lengths are systematically larger (about 0.01 Å) than those derived from the HF calculations suggesting that the MP2 geometries are rather slightly more expanded than those of the HF geometries. However, we do not find appreciable differences in bond angles between the HF and MP2 geometries. The exocyclic amino groups in all tautomers show significant deviations from the base plane. The largest amino group pyramidalization is noticed

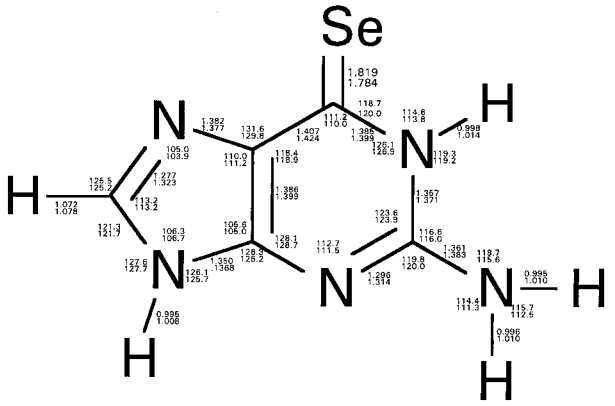

Figure 2. Bond angles and lengths for 6SeG1, calculated at HF/6-31G(d,p) (upper values) and MP2/6-31G(d,p) (lower values).

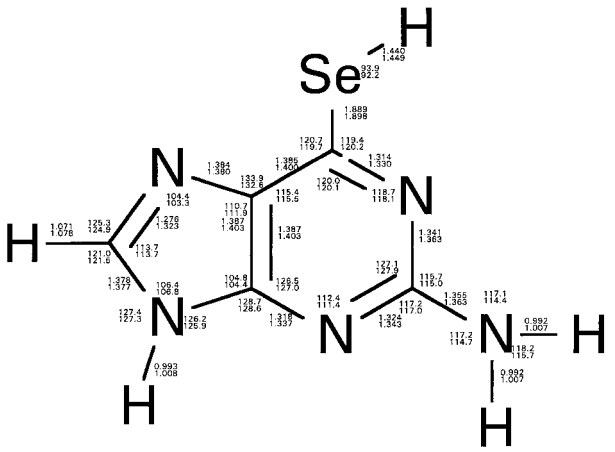

Figure 3. Bond angles and lengths for 6SeG2, calculated at HF/6-31G(d,p) (upper values) and MP2/6-31G(d,p) (lower values).

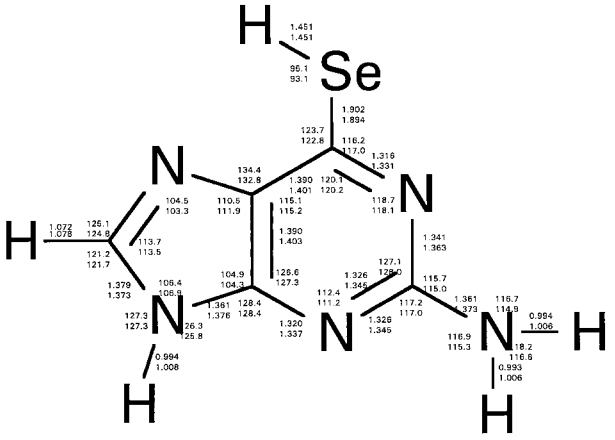

Figure 4. Bond angles and lengths for 6SeG3, calculated at HF/6-31G(d,p) (upper values) and MP2/6-31G(d,p) (lower values).

in the case of 6SeG4 (N^7 protonated tautomer) which is estimated at the HF level to be 30° while 6SeG2 shows minimum deviation. In general, all selenone tautomers show larger deviations than the selenolic tautomers. Here too, electron correlation plays a significant role in stabilizing amino group pyramidalization. All MP2 geometries show systematically larger deviations from nonplanarity than the corresponding HF geometries.[22−29] We refer to the "nonplanarity" of the amino group as to the dihedral angle made between the planes of N−H bond of exocyclic amino group and the plane of the ring (see Figure 1). At the HF and MP2 levels, these deviations, in degrees, correspond to 6SeG1 (−27.5°, −41.0°), 6SeG2 (15.7°, 22.9°), 6SeG3 (16.5°, 21.0°), 6SeG4 (30.0°, 47.4°), and 6SeG5 (19.7°, 25.6°), respectively. The largest influence of electron correlation is seen in the case of 6SeG4 (47.4°).

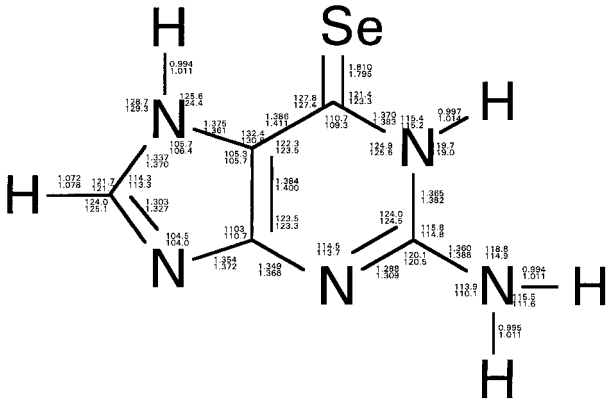

Figure 5. Bond angles and lengths for 6SeG4, calculated at HF/6-31G(d,p) (upper values) and MP2/6-31G(d,p) (lower values).

The total electronic energies are estimated at several levels of theory and are tabulated in Table 1. The relative energies of the tautomers are included in Table 2. The N^7 protonated form of selenoguanine turns out to be the most stable one at both HF and MP2 levels of theory while the stability pattern of the rest of the tautomers depends critically on the level and quality of the basis sets employed. When the Dunnings' DZP basis set is used, the N^9 protonated tautomer (6SeG1) emerges as the second most stable tautomer at both the HF and MP2 levels. However, as the basis set quality is improved to 6-31G(d,p) with inclusion of the polarization functions on both hydrogen and non-hydrogen atoms, the stability order changes with the *trans*-6-selenolic form (6SeG3) turning out to be the second most stable form. The energy difference between the two most stable tautomers 6SeG4 and 6SeG3 is estimated to be 1.9 kcal/mol in the gas phase at the MP2/6-311++G(2d,2p)//MP2/6-31G(d,p) level. The energy difference between the cis- and trans-rotomers of the 6-selenolic form of selenoguanine is only 1.0 kcal/mol at the same basis set (6SeG2 and 6SeG3 in Figure 1). As can be seen in Table 2, the ZPE contributions play a crucial role by not only changing the relative energies but also by altering the relative order of the tautomers. Inclusion of ZPE corrections makes both cis- and trans-enolic forms of 6-selenoguanine (6SeG3) to be the most stable species over the other tautomers. The cis-enolic form (6Se3) is more stable than the trans form and the N^7 protonated tautomer by 0.9 and 1.3 kcal/mol.

Comparison of the energetic trends followed by various selenoguanine tautomers with normal guanine in the gas phase deserves some attention. Our recent ab initio studies[34a] on the relative energies of guanine tautomers reveal that both the keto and enolic forms are energetically very close, and the relative stability of the keto and enolic forms would depend critically on the level of the basis set employed. While at MP2/6-311++G(df,pd)//MP2/6-31G(d,p) level the enolic form is stabilized by about 1.0 kcal/mol over the keto form (N^9 protonated); the enolic form is destabilized by about 1.9 kcal/mol when the MP4(SDTQ)/6-31G(d,p)//HF/6-31G(d,p) basis set is employed. Considering the fact that the keto and enolic forms are well stabilized within 2 kcal/mol depending on the basis set, it is reasonable to believe that keto and enolic forms of guanine are equally populated in the gas phase. In contrast, the presence of selenium at guanine would show a significant effect on the stabilization of the selenolic form as shown in Table 2. It is interesting to observe that the relative stability

TABLE 1: Estimated Energies of Various Tautomers of 6-Selenoguanine (all Values in hartree)

method	6SeG1	6SeG2	6SeG3	6SeG4	6SeG5
HF/DZP	−2862.344 102	−2862.342 309	−2862.343 569	−2862.349 828	−2862.331 799
MP2/DZP	−2863.897 252	−2863.894 783	−2863.896 169	−2863.902 391	−2863.885 969
HF/6-31G(d,p)	−2862.110 566	−2862.112 707	−2862.113 479	−2862.115 684	−2862.102 056
MP2/6-31G(d,p)	−2863.680 163	−2863.681 096	−2863.681 825	−2863.685 443	−2863.672 377
MP2/6-311++G(d,p)[b]	−2866.091 924	−2866.092 330	−2866.093 859	−2866.096 863	−2866.084 130
SCI−PCM[a]	−2862.144 487	−2862.128 966	−2862.129 222	−2862.143 512	−2862.122 658
SCI−PCM[b]	−2862.135 816	−2862.123 209	−2862.123 336	−2862.135 098	−2862.117 345
ZPE	0.123 367	0.118 463	0.118 522	0.123 634	0.117 837

[a] At HF/6-31G(d,p) geometry. [b] At MP2/6-31G(d,p) geometry.

TABLE 2: Relative Gas Phase Energies of Various Tautomers of 6-Selenoguanine with Respect to 6SeG1 (in kcal/mol)

method	6SeG1	6SeG2	6SeG3	6SeG4	6SeG5
HF/DZP	0.00	1.13	0.33	−3.59	7.72
MP2/DZP	0.00	1.55	0.68	−3.23	7.08
HF/6-31G(d,p)//HF/6-31G(d,p)	0.00	−1.34	−1.83	−3.21	5.34
MP2/6-31G(d,p)//MP2/6-31G(d,p)	0.00	−0.59	−1.04	−3.31	4.89
MP2/6-311++G(d,p)[a]	0.00	−0.26	−1.21	−3.09	5.13
MP2/6-311++G(d,p)[a] + ZPE	0.00	−3.34	−4.25	−2.92	1.66

[a] At MP2/6-31G(d,p) geometry.

of selenoguanine tautomers follows a different trend from that of guanine. As can be seen from Table 2 and discussed above, at all high levels of theory, the enolic forms are clearly dominant over the keto form in both N^9 and N^7 protonated selenoguanines. This goes to indicate that the presence of selenium would stabilize the enolic forms more than that of oxygen.

The energy barriers involved in the proton transfer are crucial in understanding the kinetic feasibility for such a transition. We have estimated the potential barrier for a proton transfer from the N^1 site to the Se^6 site in both the N^7 and N^9 protonated selenoguanines at the HF and MP2 levels using the DZP basis set. The transition state is located in both the N^7 and N^9 protonated selenoguanines and are characterized by a hydrogen on the reaction path of proton transfer with a distance of 1.745 and 1.761 Å distance from the Se^6 site, respectively, and 1.395 and 1.369 Å from the N^1 atom. The potential energy estimated at the HF level indicates that the proton transfer is more facile in the case of the N^9 protonated tautomer than that of the N^7 protonated form. It is estimated that a proton transfer from the N^1 to the Se^6 site involves an energy barrier of 39.1 and 45.8 kcal/mol for the N^9 and N^7 protonated selenoguanines. To estimate the effect of electron correlation on these energies, we have also estimated the energy barriers at the MP2/6-311++G-(d,p) level using the HF/DZP reference geometries. With this basis set, the energy barriers for proton transfer are decreased to 31.8 and 36.6 kcal/mol for the N^7 and N^9 protonated tautomers. It is interesting to compare these energy barriers with our recent studies on the corresponding proton transfer kinetics in the case of normal guanine.[34] We estimate an energy barrier of about 37.8 and 40.4 kcal/mol for the N^1 to O^6 proton transfer in the case of the N^7 and N^9 protonated guanine tautomers at the MP2/6-311++G(d,p) level using the MP2/6-31G(d,p) reference geometry. A schematic representation of the transition state structures for the N^1 to Se^6 proton transfer for the N^7 and N^9 protonated selenoguanines are shown in Figure 6a and b. These results indicate that selenium substitution for oxygen facilitates the proton transfer process from the N^1 to the Se^6 site with respect to guanine. Also, it is interesting to see that the energy barriers for the N^7 and N^9 protonated forms are reversed in the case of selenoguanine when compared with those of guanine.[34]

To understand the influence of aqueous solvation on tautomeric energies, we have estimated the free energies of hydration

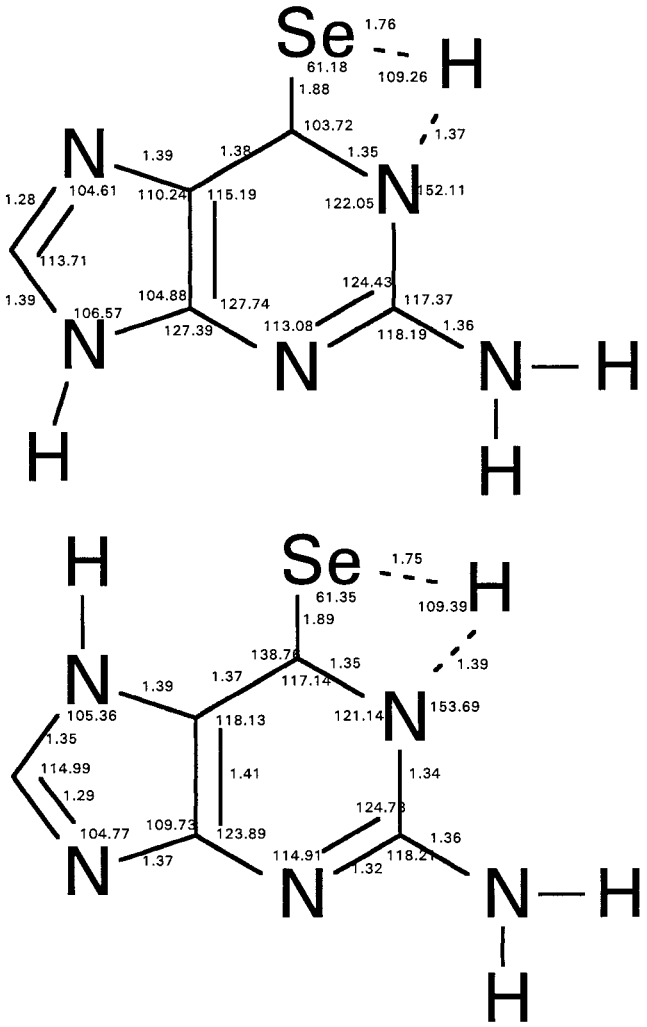

Figure 6. Transition state structures of proton transfer from the N^1 to the Se^6 site, calculated at HF/DZP for (a) N^9 protonated selenoguanine and (b) N^7 protonated selenoguanine.

by the polarized continuum model SCI−PCM. We have evaluated the free energies of hydration using the single point energies obtained at the HF level using both HF/6-31G(d,p) and MP2/6-31G(d,p) reference geometries. The computed results are tabulated in Table 3. When the MP2/6-31G(d,p) reference

TABLE 3: Relative Free Energies of Hydration Estimated by Continuum Models with Respect to 6SeG1 (in kcal/mol) and Dipole Moments of 6-Selenoguanine Tautomers

method	6SeG1	6SeG2	6SeG3	6SeG4	6SG5
SCI−PCM[a]	0.00	11.08	11.41	3.82	8.36
SCI−PCM[b]	0.00	9.26	9.66	3.66	6.25
dipole moments					
HF/6-31G(d,p)	8.70	3.49	3.86	2.24	3.73
MP2/6-31G(d,p)	8.31	3.51	4.05	1.91	4.18
MP2/6-311++G(d,p)[b]	8.38	3.45	4.01	1.23	4.29

[a] At HF/6-31G(d,p) geometry. [b] At MP2/6-31G(d,p) geometry.

TABLE 4: Free Energies of Tautomerization of Various Tautomers with Respect to 6SeG1 (kcal/mol)

method[a]	6SeG1	6SeG2	6SeG3	6SeG4	6SeG5
MP2/6-311++G(d,p)	0.00	8.99	8.45	0.56	11.38
MP2/6-311++G(d,p)+ZPE	0.00	5.92	5.41	0.74	7.91

[a] At MP2/6-31G(d,p) reference geometry.

geometry is used, the free energies of hydration are systematically lower than that of the corresponding energies evaluated with the HF/6-31G(d,p) geometry. However, both geometries yield qualitatively similar trends for the 6-selenoguanine tautomers. The trans-rotomer of the 6-selenolic form (6SeG3) is predicted to be the most hydrated species with a $\Delta\Delta G_{hyd}$ value of 9.7 which is very close in energy to the corresponding syn-rotomer (6SeG2) (only 0.4 kcal/mol less). The selenone tautomer 6SeG1 is estimated to be the least hydrated species. Finally, we evaluated the free energies of tautomerization by combining the gas phase free energies with the hydration free energies according to eq 1 (Table 4). It should be noted that aqueous solvation has a profound influence on the relative population of various selenoguanine tautomers. From the data shown in Table 4, it is clear that due to their greater solvation free energies aqueous solvation greatly destabilizes several tautomers that seem to be dominant in the gas phase. This effect is more pronounced in the case of the selenolic forms 6SeG2 and 6SeG3 which are the most predominant forms in the gas phase. Upon solvation, these tautomers turned out to be less populated than the corresponding selenone tautomers. Our best estimation of the free energy of tautomerization using gas phase energies evaluated at the MP2/6-311++G(2d,2p)//MP2/6-31G-(d,p) level including ZPE corrections indicates that the selenone-selenol tautomeric transition between 6SeG1 and 6SeG2 involves a free energy difference of about 5.4 kcal/mol. It is interesting to observe the relative population of the N^9 and N^7 protonated tautomers. While the latter is about 3 kcal/mol more stable than the former in a gas phase, aqueous solvation results in an energy difference between the forms of only 0.7 kcal/mol with N^9 being dominant. Thus in an aqueous phase, the following order of stability has been established for the 6-selenoguanines: 6SeG1 > 6SeG4 > 6SeG3 > 6SeG2 > 6SeG5.

Conclusions

High level post Hartree−Fock ab initio calculations of the energies and structural properties of the 6-selenoguanines were performed for both gas phase species and tautomers in an aqueous solution. The significant influence of selenium on the structural properties of the most important nucleic acid base guanine has been clearly shown in the present study. Some important conclusions from the present work may be delineated as follows.

In the gas phase, the 6-selenolic form of selenoguanine is the most stable form with an energy difference of 4.3 kcal/mol when compared with the 6-selenone form. Zero-point energy corrections play a critical role in stabilizing the various tautomers considered in the present study. Four of the major tautomers lie within a 5 kcal/mol energy difference which indicates that usage of highly accurate basis sets is clearly prerequisite for a proper evaluation of the relative population of various tautomeric forms. In the gas phase the following order of stability has been established: 6SeG3 > 6SeG2 > 6SeG4 > 6SeG1 > 6SeG5.

The estimated energy barriers for proton transfer from the N^1 to Se^6 site indicate that such a transition for the N^9 protonated tautomer is more facile than that of the N^7 protonated forms. We estimate an energy barrier of about 39.1 kcal/mol for the N^9 protonated selenoguanine and about 45.8 kcal/mol for the N^7 protonated species at the HF/DZP level and 31.8 and 36.6 kcal/mol at MP2/6-311++G(d,p)//HF/DZP. The estimated free energies of hydration by the SCI−PCM model suggest that the selenolic forms are better hydrated than the selenone forms. The syn rotamer of 6-selenolicguanine is the most hydrated one with the corresponding anti rotomer form being very close in energy (about 0.4 kcal/mol). In an aqueous solution, the selenone form of selenoguanine is predicted to be the most stable one with the N^7 protonated form being energetically very close to the N^9 protonated tautomer. It may be expected that both N^9−H and N^7−H tautomers could coexist in significant population in an aqueous phase.

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References and Notes

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