Computational Chemistry

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Finding Adiabatically Bound Anions of Guanine through a Combinatorial Computational Approach**

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Anions of nucleic acid bases may be formed by trapping low-energy electrons produced in living cells by high-energy radiation. Recent experiments suggested that single- and double-strand breaks develop in DNA exposed to low-energy electrons.[1] Furthermore, charged nucleobases play a critical role in electron and hole transfer in DNA.[2–4] Anionic states of nucleic acid bases have been intensively studied both experimentally and theoretically. On the basis of calculations, guanine is believed to have the lowest electron affinity among the nucleobases.[5–7] This is consistent with the results of electron spin resonance experiments on γ-irradiated DNA, in which the anion is divided between the pyrimidine but not the purine bases.[8]

Gas-phase experiments on guanine are scarce because this nucleic acid base easily decomposes at elevated temperatures. Burrow and co-workers reported a vertical electron affinity of −0.49 eV for guanine and assigned it to a hydroxy (enol) tautomer.[9] We have recently determined—at the coupled cluster level of theory with single, double, and perturbative triple excitations (CCSD(T))[10]—a negative adiabatic electron affinity (AEA) of −0.49 eV for the canonical tautomer.[11] In contrast to earlier experimental and computational predictions, we demonstrate here that guanine supports anionic tautomers that are adiabatically bound with respect to the neutral canonical tautomer by as much as 8 kcal mol^{-1},[12] as calculated at the CCSD(T) level of theory. These

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tautomers do not result from proton transfer between the electronegative atoms N or O, which were studied in the past for the neutral and anionic species. Instead they result from enamine–imine transformations, that is, a proton is transferred between the N and C atoms. Some of these anionic tautomers do not require a proton transfer from the N9 position (see Figure 1). Thus, they might exist in DNA or RNA, in which N9 is connected to a sugar unit. The new anionic tautomers might affect the structure of DNA and RNA, and might initiate chemical transformations leading to lesions in nucleic acids.[13,14]

The unexpected positive values of AEA for the new imine tautomers were initially counterintuitive, and their discovery was facilitated by two factors. First, we recently demonstrated that the most stable valence anions of pyrimidine bases, such as 1-methylcytosine[13] and uracil,[14] also result from enamine–imine transformations, though a biologically relevant adiabatically bound anion has not been identified so far. Second, a combinatorial computational approach was invoked in the current study to identify the most stable anionic tautomers, without a bias dictated by stereotypes developed from studies on neutral tautomers of nucleic acid bases, that is, a proton being transferred between N or O atoms.[15]

The computational screening of the anionic tautomers of guanine was started from a buckled molecular framework of heavy atoms among which five hydrogen atoms were distributed. We imposed the following constraints: zero or one hydrogen atom on N1, C2, N3, C4, C5, C6, N7, and N9; one or two hydrogen atoms on N2 or C8; zero, one, or two hydrogen atoms on O4 (Figure 1). With these constraints we generated 499 initial structures including the *E* and *Z* tautomers as well as rotamers of imino and hydroxy groups. These structures were divided into three groups: 2N2 (amino tautomers), N2c, and N2t (imino tautomers with a hydrogen atom at N2 arranged *cis* or *trans* with respect to N1). Additionally, each group was divided into two subgroups C8 and 2C8, depending on the number of hydrogen atoms attached to C8. We use the notation G_a^b, where "a" is the group and subgroup and "b" is a string of heavy atoms to which the remaining hydrogen atoms are connected. The anionic species bear a prefix a_{val}.

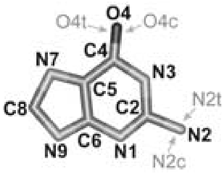

Figure 1. The heavy atoms of guanine; the *cis* and *trans* positions for N2 and O4 are shown.

We found that 2.81% of all screened structures are adiabatically stable at the B3LYP/6-31++G** level of theory, with the range of stability at 0.4–12.2 kcal mol^{-1}. For further studies we selected the following: 1) the most stable valence anion $a_{\mathrm{val}}G^{\mathrm{C2,N3}}_{\mathrm{2N2,C8}}$, which has no hydrogen atom attached to N9; 2) three valence anions that might be biologically relevant because a hydrogen atom is attached to N9 ($a_{\mathrm{val}}G^{\mathrm{N9}}_{\mathrm{2N2,2C8}}$, $a_{\mathrm{val}}G^{\mathrm{N3,N9}}_{\mathrm{N2c,2C8}}$, and $a_{\mathrm{val}}G^{\mathrm{N3,N9}}_{\mathrm{N2t,2C8}}$); and 3) the valence anions $a_{\mathrm{val}}G^{\mathrm{N3,N9}}_{\mathrm{2N2,C8}}$ and $a_{\mathrm{val}}G^{\mathrm{N3,N7}}_{\mathrm{2N2,C8}}$, which are based on the two most stable tautomers of neutral guanine (Figure 2).

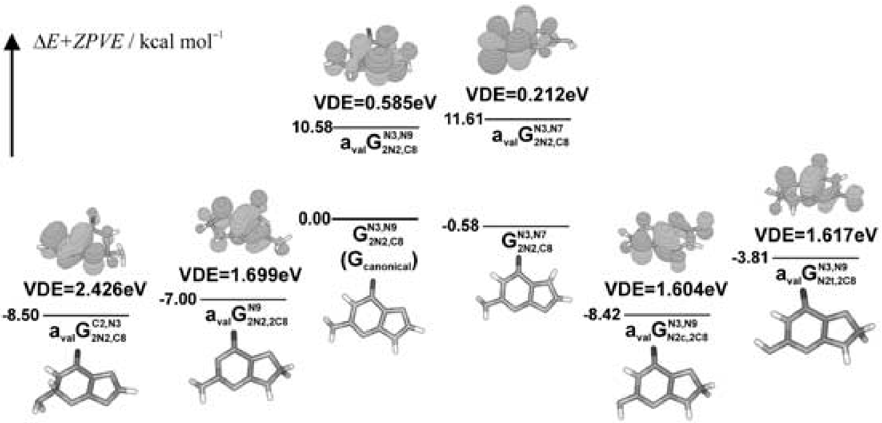

Figure 2. The relative electronic energies of the various tautomers studied, corrected for energies of zero-point vibrations (Δ*E* + ZPVE), as well as the electron vertical detachment energies (VDEs). The adiabatially bound anions are on the left and right sides. In the middle, the two most stable tautomers of the neutral and their accompanying valence anions are shown.

These anionic structures were further optimized, and harmonic frequencies were calculated at the second-order Møller–Plesset level (MP2), and the final energies were then calculated at the CCSD(T) level. The aug-cc-pVDZ basis set[16] was used in the MP2 and CCSD(T) calculations. The effects of hydration were included within the IEF-PCM method with the cavity built up using the United Atom model (UA0).[17] The calculations were performed using Gaussian03[18] NWChem,[19] and Molpro software packages,[20] and the molecular structures and orbitals were drawn with the Molden program.[21]

We found that the four anionic tautomers that result from enamine–imine transformations were adiabatically bound with respect to both the neutral $G^{\mathrm{N3,N9}}_{\mathrm{2N2,C8}}$ canonical tautomer and the most stable neutral tautomer $G^{\mathrm{N3,N7}}_{\mathrm{2N2,C8}}$. These gas-phase results, presented in Figure 2, are based on the CCSD(T) electronic energies and MP2 geometries and harmonic vibrational frequencies. The most stable anion $a_{\mathrm{val}}G^{\mathrm{C2,N3}}_{\mathrm{2N2,C8}}$ is bound with respect to $G^{\mathrm{N3,N9}}_{\mathrm{2N2,C8}}$ by 8.50 kcal mol^{-1}. This anion is characterized by a large vertical detachment energy (VDE) of 2.426 eV. Among the three anionic tautomers that have a hydrogen atom on N9, the anion $a_{\mathrm{val}}G^{\mathrm{N3,N9}}_{\mathrm{N2c,2C8}}$ is 8.42 kcal mol^{-1} more stable than $G^{\mathrm{N3,N9}}_{\mathrm{2N2,C8}}$. This value is much larger than our estimation of uncertainties of the AEAs determined at the CCSD(T)/aug-cc-pVDZ level, which is about 1 kcal mol^{-1}. The two other anions $a_{\mathrm{val}}G^{\mathrm{N9}}_{\mathrm{2N2,2C8}}$and $a_{\mathrm{val}}G^{\mathrm{N3,N9}}_{\mathrm{N2t,2C8}}$ are more stable than $G^{\mathrm{N3,N9}}_{\mathrm{2N2,C8}}$ by 7.00 and 3.81 kcal mol^{-1}, respectively. The values of VDE for the last three anionic tautomers are similar, about 1.6 eV, and still much larger than the VDE values of anions based on the most stable neutral tautomers. We predict that there are many anionic enamine–imine tautomers that are adiabatically bound with respect to neutral guanine.

The effect of an aqueous environment on the stability of the new anionic tautomers was tested within the PCM model (Table 1). The new imine tautomers are again more stable than anions based on the two most stable tautomers of the neutral molecule. Additionally, the three imine tautomers with a hydrogen atom attached to N9 are more stable than $a_{val}G^{C2,N3}_{2N2,C8}$. Thus the tautomers with a hydrogen atom attached to N9 might dominate in aqueous solution. These tautomers might be susceptible to further transformations, and lesions in the DNA might develop. For instance, the $a_{val}G^{N9}_{2N2,2C8}$ and $a_{val}G^{N3,N9}_{N2c,2C8}$ tautomers cannot maintain Watson–Crick-type hydrogen bonding with cytosine.

Table 1: Adiabatic electron affinities (AEAs) and electron vertical detachment energies (VDEs) for the tautomers of hydrated guanine characterized within the PCM model.

Tautomer	AEA [eV][a]	VDE [eV][b]
$G^{N3,N9}_{2N2,C8}$	1.329	3.381
$G^{N3,N7}_{2N2,C8}$	1.496	2.643
$G^{N9}_{2N2,2C8}$	2.211	4.625
$G^{N3,N9}_{N2c,2C8}$	2.026	4.424
$G^{N3,N9}_{N2t,2C8}$	1.953	4.566
$G^{C2,N3}_{2N2,C8}$	1.861	5.350

[a] $\varepsilon = 78$. [b] $\varepsilon = 78$ and 2 for the initial and final states, respectively.

We suggest two formation pathways for the new anionic tautomers. First, they might be formed through intermolecular proton transfer, with acidic and basic sites interacting with $a_{val}G^{N3,N9}_{2N2,C8}$. Second, dissociative electron attachment[22,23] to $G^{N3,N9}_{2N2,C8}$ [Eq. (1)]—where $(G^{N3,N9}_{2N2,C8})^{*-}$ denotes a scattering

$$G^{N3,N9}_{2N2,C8} + e \rightarrow (G^{N3,N9}_{2N2,C8})^{*-} \rightarrow (G^{N3,N9}_{N2c,C8})^{-} + H^{\cdot} \qquad (1)$$

state for an excess electron and $(G^{N3,N9}_{N2c,C8})^{-}$ denotes a deprotonated guanine in the ground electronic state—can be followed by attachment of a hydrogen atom to C8 [Eq. (2)].

$$(G^{N3,N9}_{N2c,C8})^{-} + H^{\cdot} \rightarrow (G^{N3,N9}_{N2c,2C8})^{-} \qquad (2)$$

We have found that this step is barrier-free.

In summary, guanine supports many adiabatically bound valence anions, which result from enamine–imine transformations of the most stable neutral tautomers. These stable anionic tautomers were found using combinatorial computational prescreening at the B3LYP level of theory followed by CCSD(T)/aug-cc-pVDZ calculations. The new anionic tautomers might be formed by dissociative electron attachment followed by attachment of a hydrogen atom to a carbon atom. These tautomers may affect the structure and properties of DNA and RNA exposed to low-energy electrons. Chemical transformations of DNA triggered by the new anionic tautomers will be explored in our future studies.

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