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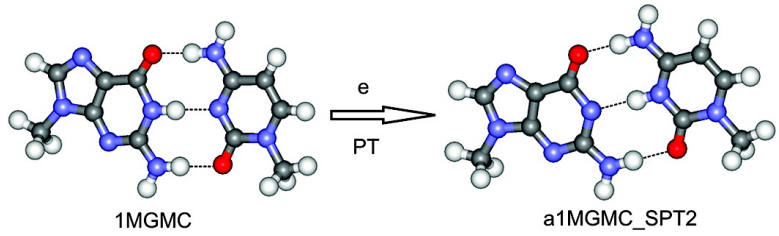

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Valence Anions of 9-Methylguanine−1-Methylcytosine Complexes. Computational and Photoelectron Spectroscopy Studies

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Abstract: The photoelectron spectrum for the radical anion of 9-methylguanine−1-methylcytosine, $MGMC^-$, was recorded for the first time. To interpret the experimental results, B3LYP/6-31++G(d,p) level computational studies were carried out for the neutral and anionic complexes of MGMC/$MGMC^-$ stabilized by three hydrogen bonds and comprising canonical or low-energy tautomeric forms of the methylated nucleobases. The visualization of singly occupied molecular orbitals for the $MGMC^-$ anions indicates that they are valence-bound species since the excess electron is localized on a π^* orbital of cytosine. All but one of the studied anionic complexes are adiabatically stable at the applied B3LYP level of theory. The intensity maximum of the broad band in the photoelectron spectrum was measured at 2.1 eV. This value is very well reproduced by the calculated vertical detachment energy of the calculated global minimum geometry of the $MGMC^-$ anion. This structure is the Watson−Crick base pair anion with proton transferred from the N1 atom of guanine to the N3 site of cytosine. The calculated adiabatic electron affinities span a range of 0.39−0.60 eV. The consequences of electron attachment to the AT or GC base pairs incorporated within DNA are briefly discussed in the context of DNA damage by low-energy electrons.

1. Introduction

Nucleobases, the fundamental building blocks of DNA and RNA, are damaged by the secondary products of water radiolysis. However, low-energy electrons (LEEs) that are one of those secondary products were ignored as possible DNA-damaging factors till 2000 when Sanche et al.[1] demonstrated that LEEs with energies well below the ionization threshold of DNA[2] are capable of inducing single-strand (SSBs) and double-strand (DSBs) breaks to the DNA biopolymer deposited on a tantalum surface.

The first proposals of the DNA breakage mechanism were put forth by the Simons[3] and Sevilla[4] groups and assumed resonance anionic states to be directly responsible for the observed breaks. Although the isolated nucleic acid bases (NABs) do form resonances,[5] it is worth noting that even very weak interactions, such as those caused by the solvation of a nucleobase by a single water molecule, could transform those resonances into the adiabatically bound valence anions.[6,7] Similarly, the importance of intramolecular interactions for the stabilities of NAB anions was pointed out by the theoretical investigation of Schaefer's group.[8] Namely, using a combination of basis sets and functionals calibrated for the prediction of accurate vertical detachment energies and adiabatical stabilities of anionic species, they obtained positive values of adiabatic electron affinities (AEAs) for the 2′-deoxythymidine (dT^-), 2′-deoxycytidine (dC^-), 2′-deoxyadenosine (dA^-), and 2′-deoxyguanosine (dG^-) valence anions of 0.44, 0.33, 0.06, and 0.09 eV, respectively. Their findings were later corroborated by Sevilla et al.,[9] who reported very similar AEA values for dT^- and dC^- of 0.45 and 0.33 eV, respectively, calculated at the B3LYP/6-31+G(d) level. Theoretical vertical detachment energies (VDEs), especially those for dT^- and dC^-, compare well with the experimental values obtained recently in a photoelectron spectroscopy study carried out by the Bowen group.[10] Thus, positive EA values indicate that the presence of the sugar moiety, chemically bound to a nucleic base, stabilizes the valence anions of NABs to such an extent that they become adiabatically stable

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in the gas phase. To this end, it is also worth mentioning that not only nucleosides, but also nucleotides form adiabatically bound valance anions in the gas phase.[11,12] Therefore, although the discrete electron energy dependence of the DNA damage curves obtained by Sanche et al.[1] suggests a contribution of anionic resonances to the formation of SSBs and DSBs, the presence of various inter- and intramolecular interactions, even in the isolated biopolymer, implies that bound rather than metastable states may also play a role in causing damage due to low-energy electrons. Another argument in favor of the involvement of adiabatically bound anions in the rupture of phosphodiester bonds is based on the observation that the efficiency of the DNA single-strand breaks induced by electrons of near 0 eV is similar to that triggered by electrons of 10 eV.[13,14] If anionic resonance states controlled the DNA damage, electrons of nominally zero kinetic energy would not be able to produce a detectable amount of SSBs, since a significant excess of energy is needed to form a metastable resonance.

Proton transfer (PT) reactions, closely related to hydrogen-bonding interactions, may be other important factors stabilizing the valence anions of nucleic acid bases. Indeed, it was shown in a series of experimental and theoretical studies regarding the complexes of nucleobases interacting with organic or inorganic proton donors that electron attachment to these species induces proton transfer, frequently barrier-free, from the proton donor to the anionic base, leading to the strong stabilization of the NABs' valence anions.[15−25]

The AT and GC base pairs are especially interesting among a pool of various possible complexes of NABs stabilized by hydrogen bonds, since their Watson−Crick configurations are abundant in double-stranded DNA. As indicated by several theoretical[26−29] and experimental[22] reports regarding AT^- and theoretical studies on GC^-,[29−33] the presence of purine bases significantly increases the stabilities of pyrimidine valence anions. Until recently, the electron attachment behavior of the other biologically important base pair, GC, has not been studied experimentally. However, with the advent of a novel ion source,[10] employing a combination of infrared desorption, electron photoemission, and a gas jet expansion, it became possible to introduce both components of this base pair into the gas phase without decomposition. The current study aims, therefore, at the acquisition of experimental and theoretical characteristics for the above-mentioned base pair. To model the GC base pair with its sugar binding positions immobilized by methyl groups, we studied dimers involving 9-methylguanine and 1-methylcytosine (given that both nucleobases are incorporated in DNA via a glycosidic bond to 2′-deoxyribose). In the following we will compare the experimentally measured photoelectron spectroscopy (PES) spectrum of the 9-methylguanine−1-methylcytosine dimer anion, $MGMC^-$, with the computational characteristics of selected configurations of the MGMC anions. This comparison reveals that the Watson−Crick (WC) structure of neutral MGMC, in which electron attachment induces proton transfer from guanine to cytosine, is responsible for the main feature in the recorded PES spectrum of $MGMC^-$. Our combined experimental and theoretical results show that, in the presence of an excess electron, the neutral WC structure of MGMC (being by far more stable than the other possible configurations of the complex) behaves differently compared to the WC methyladenine−methylthymine (MAMT) base pair. The possible biological consequences of this difference will be briefly discussed.

2. Methods

2.1. Experimental Details. The $MGMC^-$ pair anions were generated using a novel pulsed infrared desorption-pulsed visible photoemission anion source which has been described previously.[10,12] Briefly, a slowly moving graphite bar was thinly coated with a mixture of guanine and cytosine powders. An attenuated beam of 1064 nm photons (first harmonic frequency from a pulsed Nd:YAG laser) impinged on the graphite bar desorbed the neutral bases into the gas phase. Nearby, an yttria crystal was irradiated with 532 nm photons from another Nd:YAG laser, producing an intense pulse of electrons. A jet of helium from a pulsed gas valve served to collisionally cool the mixture. The distance between the pulsed valve and the photoemmitter was ∼3 cm. Upon generating the base pair anions, they were extracted into a linear, time-of-flight mass spectrometer (mass resolution ∼600), mass-selected, and photodetached with the third harmonic frequency (355 nm, i.e., 3.49 eV/photon) of a third Nd:YAG laser. The resulting photodetached electrons were then energy analyzed with a magnetic bottle electron

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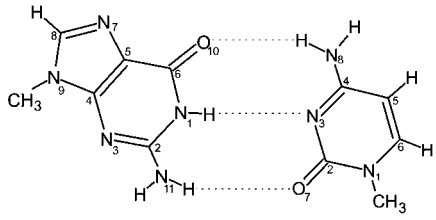

Figure 1. WC structure of the canonical MGMC dimer.

energy analyzer. The EBE maximum of the first peak corresponds to the VDE value.

2.2. Computational Details. In most cases, we have applied the density functional theory method with Becke's three-parameter hybrid functional (B3LYP)[34−36] and the 6-31++G** basis set. All geometries presented here have been fully optimized without geometrical constraints, and the analysis of harmonic frequencies proved that all of them are also geometrically stable (all force constants were positive). The relative energies of neutral and anionic complexes are defined with respect to the energy of the WC configurations (see Figure 1). The stabilization energies, E_{stab}, of neutral complexes are calculated as a difference between the energy of the complex and the sum of the energies of fully optimized isolated monomers.

Two types of anions were identified within the current study. They include complexes which have the same pattern of hydrogen bonding as their parent neutral structures and those which differ from their parent neutral complexes by a single proton transfer. The values of E_{stab} for the anionic dimers without intramolecular proton transfer are obtained by subtracting from the electronic energy of the anionic dimer the sum of the electronic energies of the fully relaxed respective tautomer of neutral methylguanine and the fully relaxed open-shell anion of the appropriate tautomer of methylcytosine. E_{stab} for the remaining anions, where a proton transfer takes place, are calculated as a difference between the energy of the anionic dimer and the sum of the closed-shell deprotonated methylguanine anion and the neutral monohydroradical of cytosine. In addition to the stabilization energies, E_{stab}, we also calculated the stabilization free energies, G_{stab}. The latter is determined by correcting the values of E_{stab} for zero-point vibration terms, thermal contributions to energy, the pV terms, and the entropy terms. These terms were calculated in the rigid rotor−harmonic oscillator approximation for $T = 298$ K and $p = 1$ atm. Vertical detachment energies, direct observables in our PES experiment, were evaluated as differences between the energy of the neutral and anionic complex at the geometry of the fully relaxed anion. A difference in Gibbs free energies of the neutral and the anion at their corresponding fully relaxed structures is denoted AEA_G.

The structures of neutral dimers are denoted *m*MGMC, where MG and MC stand for 9-methylguanine and 1-methylcytosine, respectively, and *m* is a natural number that runs from 1 to 4. The symbols of anions are preceded with a prefix *a*, i.e., *am*MGMC, indicating the *parent* neutral structure, *m*MGMC, to which the anionic structure is related. Additionally, the names of anionic geometries linked to the *m*MGMC structures with a single proton transfer are followed by a suffix SPT*x*, where *x* assumes one of the three values 1, 2, or 3, referring to the actual number of hydrogen bonds in which proton transfer takes place (the hydrogen bonds are numbered from the top to bottom; see Figure 2). For instance, the *a*3MGMC-SPT2 symbol indicates the anion that is related to the 3MGMC structure by proton transfer of the second hydrogen (see Figure 2). All quantum chemical calculations have been carried out with the Gaussian 03[37] code, and the pictures of molecular orbitals were plotted with the Molden package.[38]

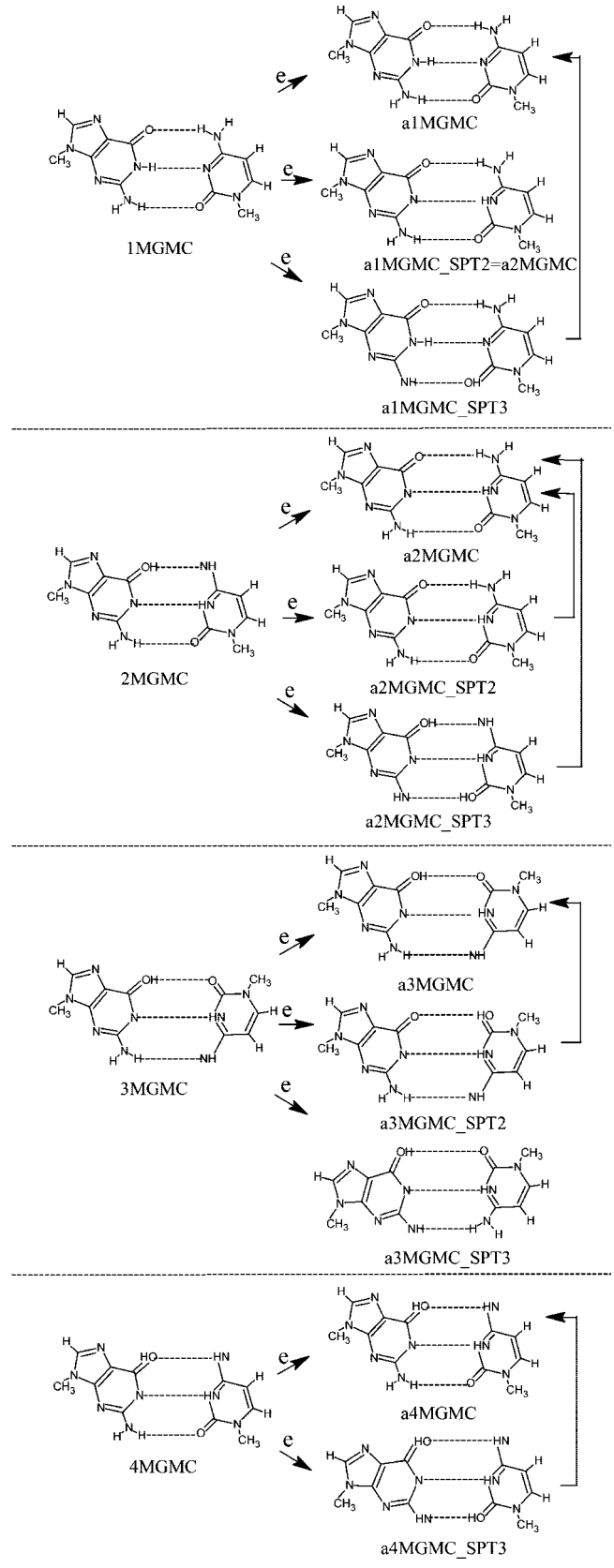

Figure 2. Relationships between the neutral and anionic MGMC dimers.

3. Results

3.1. Photoelectron Spectrum. The photoelectron spectrum of $MGMC^-$ anions recorded with 3.49 eV photons is shown in

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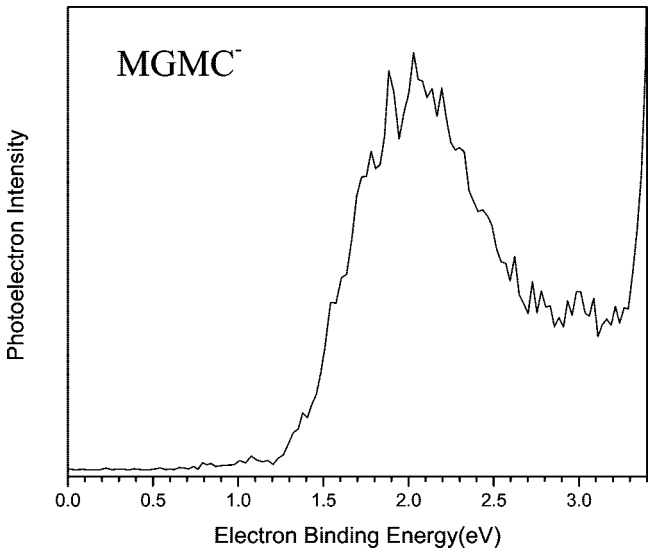

Figure 3. Photoelectron spectrum of the 9-methylguanine−1-methylcytosine anion recorded with 3.49 eV photons.

Table 1. Values of the Stabilization Energy (E_{stab}) and Stabilization Free Energy (G_{stab}) and Their Relative Values (ΔE and ΔG) with Respect to the Watson−Crick Pair, Dipole Moments of the Complexes (μ_{AB}) and Sums of the Dipole Moments of Individual Monomers ($\mu_A + \mu_B$), and the Mean Values of the Deprotonation Energies (⟨DPE⟩) and Proton Affinities (⟨PA⟩) for the Neutral Methylguanine−Methylcytosine Complexes Calculated at the B3LYP/6-31++G** Level[a]

structure	E_{stab}	ΔE	G_{stab}	ΔG	μ_{AB}	$\mu_A + \mu_B$	⟨DPE⟩	⟨PA⟩
1MGMC (WC)	−26.0	0.0	−12.7	0.0	6.31	13.67	339.9	224.4
2MGMC	−18.9	10.14	−5.8	10.0	6.60	8.83	347.3	215.6
3MGMC	−16.9	12.13	−3.5	12.1	6.33	8.83	347.3	215.6
4MGMC	−12.8	18.64	0.7	18.9	3.93	4.30	357.1	201.8

[a] Energies are given in kilocalories per mole and dipole moments in debyes.

Figure 3. In principle, both guanine and cytosine should support dipole-bound states since the dipole moments of the canonical forms of guanine and cytosine are 6.55 and 6.39 D, respectively, at the MP2/aug-cc-pVDZ level.[39] The MGMC pair is also thought to exhibit a large enough dipole moment to support the dipole-bound anion. (See Table 1 for the dipole moments of various MGMC pair conformers (μ_{AB}) and sums of dipole moments of individual monomers ($\mu_A + \mu_B$)). Since the PES spectrum shown in Figure 3 consists of a broad peak with the maximum EBE value (VDE) at 2.1 eV, the observed species is not dipole bound but is instead a valence anion. Thus, in our experiment the valence anion is the more favored structure.

In the valence anion of $MGMC^-$, the excess electron might have been localized on the methylcytosine moiety due to the relative electron affinities of the two moieties. If the studied anion pair had been comprised of the canonical MC^- anion solvated by methylguanine, the VDE value would be expected to be around 1.0 eV on the basis of our prior experiences.[25] Thus, it is unlikely that this is the case in the current study.

Very recently, photoelectron spectra for all five nucleobases have been measured by Bowen using a laser vaporization ion source.[40] These spectra were ascribed to the very rare tautomeric anions in which the acidic N−H hydrogens are transferred to the ring carbon atoms. For cytosine the maximum high-energy feature was measured at 2.3 eV. A comparison of the PES spectra of thymine and uracil rare tautomer anions reveals that methylation shifts the spectrum of the valence anions of T^- by approximately 0.1 eV in the direction of lower binding energies.[22] Thus, the VDE of the rare tautomer of MC^- might be expected to be ∼2.2 eV. If the $MGMC^-$ was a rare tautomer of MC^- solvated by an MG molecule, then its VDE of the resulting dimer anion would be expected to be at least 2.6 eV, due to the expected solvation shift of MG interacting with the rare tautomer of MC^-. Given the fact that we measured the VDE of $MGMC^-$ to be ∼2.1 eV, this is a rather unlikely possibility. This is supported by the realization that rare tautomers were formed due to laser vaporization, while in the present study the much gentler IR desorption source was utilized.

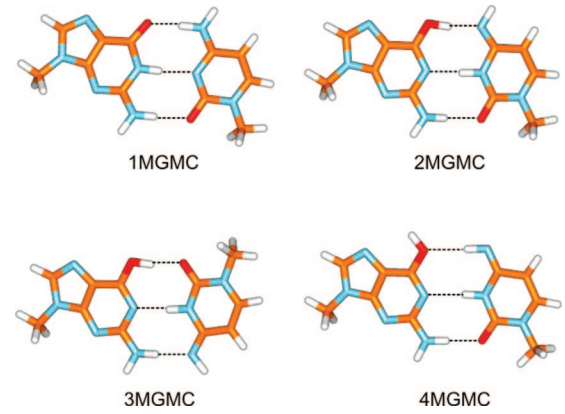

Figure 4. Optimized structures of the neutral complexes of 9-methylguanine−1-methylcytosine.

After exclusion of the aforementioned possibilities, the actual position of the PES feature implies a proton transfer triggered by electron attachment from guanine to the cytosine valence anion. In the following, we will provide computational evidence that the anionic $MGMC^-$ dimer of Watson−Crick configuration, in which proton transfer occurs in the middle hydrogen bond, is responsible for the observed PES spectrum.

3.2. Computational Results. 3.2.1. Neutral Complexes. Both guanine and cytosine possess several low-energy tautomers.[41] Hence, to interpret the PES spectrum, one should consider various arrangements of neutral MGMC dimers involving those highly stable tautomeric forms of cytosine and guanine. In Figure 4 the structures of the MGMC complexes optimized at the B3LYP/6-31++G** level are displayed. Additionally, their energetic characteristics such as the stabilization and relative energies are gathered in Table 1. We limited our conformational search to those complexes that are stabilized by three hydrogen bonds. Moreover, we considered only the tautomers of individual bases which are well represented in the gas phase,[41] which means the canonical and 4-imino forms of cytosine and the canonical and 9*H*-hydroxy tautomers of guanine. Thus, our structural search resulted in the geometries presented in Figure 4 which overlap with the low-energy dimer structures identified also by the Hobza group for the neutral GC[42] and MGMC[43]

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Table 2. Values of the Stabilization Energy (E_{stab}) and Stabilization Free Energy (G_{stab}) and Their Relative Values (ΔE and ΔG) with Respect to the Most Stable Anionic Complex (a1MGMC_SPT2) and Electron Vertical Detachement Energy (VDE) and Adiabatic Electron Affinity (AEA) for the Methylguanine−Methylcytosine Complexes Calculated at the B3LYP/6-31++G** Level[a]

structure	E_{stab}	ΔE	G_{stab}	ΔG	AEA	VDE
a1MGMC	−37.0	0.0	−24.6	0.0	0.54	1.01
a3MGMC	−31.1	13.4	−21.1	14.3	0.45	0.91
a1MGMC_SPT2	−28.8	−2.9	−15.7	−1.3	0.60	1.93 (2.12)[b]
a3MGMC_SPT3	−31.6	14.1	−17.9	15.7	0.39	1.91
a4MGMC	−13.8	30.6	−2.5	29.8	0.07	−0.05

[a] ΔE, ΔG, E_{stab}, and G_{stab} are given in kilocalories per mole and VDE and AEA in electronvolts. [b] Value calculated at the B3LYP/6-31++G**//MP2/6-31++G** level.

base pairs. Altogether four neutral configurations stabilized by three hydrogen bonds have been considered within the current study (see Table 1 and Figure 4).

The data presented in Table 1 show that the relative stabilities of particular complexes differ by as much as 18.9 kcal/mol. On the other hand, their stabilization energies span a somewhat smaller range of −26.0 to −12.8 kcal/mol (see Table 1). As indicated in Figure 2 various tautomeric forms of individual bases are involved in the studied dimers. However, these forms vary in electronic energy by only 0.3 and 0.5 kcal/mol at the QCISD(T)/TZV(2df,2pd) level for cytosine and guanine tautomers, respectively.[41] Hence, the main factor determining the stability of the dimers is the strength of the hydrogen bonds that link the two nucleobases. It is well-known that the energy of a hydrogen bond depends on the proton affinity (PA) and deprotonation energy (DPE) of the respective proton donor and acceptor sites.[44] Accordingly, in the last two columns of Table 1 we present for each dimer the arithmetic mean of the PAs (⟨PA⟩) and DPEs (⟨DPE⟩) of the molecular centers involved in the respective hydrogen bonds. The strongest stabilization should occur for the system which is characterized by the lowest value of ⟨DPE⟩ and the highest value of ⟨PA⟩. Indeed, one can observe this trend for data gathered in Table 1. In particular, ⟨PA⟩ amounts to the highest value of 224.4 kcal/mol and ⟨DPE⟩ to the lowest value of 339.9 kcal/mol for the most stable Watson−Crick configuration (see Table 1). Accordingly, for the least stable structure, 4MGMC, the highest ⟨DPE⟩ of 357.1 kcal/mol and the lowest ⟨PA⟩ of 201.8 kcal/mol were calculated (see Table 1).

Inspection of data gathered in Table 1 indicates that the WC configuration is by far the most stable form. Employing the relative values of free energy, one can calculate that in the equilibrated mixture of gaseous guanine and cytosine the molar ratio of the second most stable complex, 2MGMC, to the WC dimer is equal to 4.6×10^{-8} at 298 K; thus, the mixture should be completely dominated by the WC base pair. This finding is in contrast to the other important base pair, MAMT, for which two configurations are almost isoenergetic in the gas phase, namely, the biologically relevant Watson−Crick base pair and the Hoogsteen configuration.[22]

3.2.2. Valence Anions. All neutral dimers described in the previous section form adiabatically stable valence anions (see Table 2). Due to differences in the electron affinities of the involved nucleobases the excess electron always attaches to a π^* orbital localized on the cytosine moiety (see Figure 5). Even

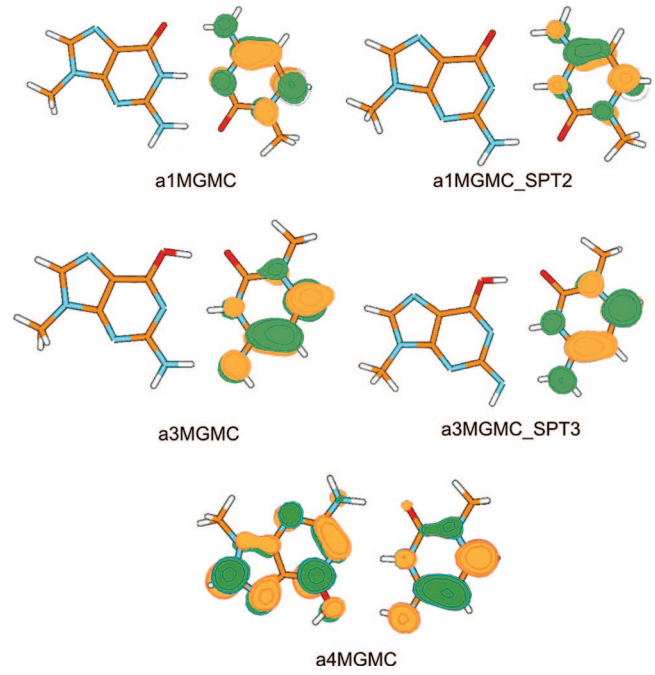

Figure 5. Unpaired electron orbitals plotted with a contour line spacing of 0.03 bohr$^{-3/2}$ for the four most stable anions of the MGMC pair.

though the isolated guanine and cytosine form π-shaped resonances in the gas phase,[5] interactions existing in the MGMC complexes apparently render their valence anions thermodynamically stable.

The attachment of an excess electron to a nucleobase pair may lead to a structure having the same pattern of hydrogen bonds as the neutral complex or to proton transfer from guanine to cytosine (see Figure 5). A driving force for the latter process is the stabilization of the excess electron on a π^* orbital of the anionic cytosine. This reaction has been observed in the past for a number of nucleobase complexes stabilized by hydrogen bonds.[15−24] Figure 2 provides a schematic representation of possible proton transfer reactions occurring after electron attachment to the considered dimers. The geometry optimizations starting from the eleven anionic structures depicted in Figure 2 led to only five stable geometries which are presented in Figure 5 (some optimizations converged to the same anionic structures, which is pointed out by the arrows in Figure 2). The stability of the anionic dimers compared to their neutral counterparts is larger by 9.90−14.20 and 9.90−17.60 kcal/mol in terms of energy and free energy, respectively (cf. Tables 1 and 2; the energetic characteristics for the *a*4MGMC anion were discarded when the stability range was calculated since this anion represents a resonance rather than the VB state (note a negative value of its VDE, Table 2)). First, the excess negative charge makes the PAs of the respective cytosine sites larger. For instance, the PA for the canonical MC anion increases by 104−117 kcal/mol with respect to the neutral tautomer (cf. Tables S1 and S2, Supporting Information). Moreover, the 1-methylcytosine anion is much more polarizable than the neutral molecule.

Two structures are more stable than the remaining anions by at least 14 kcal/mol (a1MGMC and a1MGMC_SPT2; see Table 2). Both geometries originate from electron attachment to the neutral WC complex, and they are linked to one another via a proton transfer between N1(G) and N3(C). The proton-transferred structure is more stable than the WC form by 2.9

(43) Rejek, J.; Hobza, P. *J. Phys. Chem. B* **2007**, *111*, 641–645.
(44) Dąbkowska, I.; Rak, J.; Gutowski, M. *J. Phys. Chem. A* **2002**, *106*, 7423–7433.

and 1.3 kcal/mol, while the kinetic barrier that separates these two geometries amounts to 0.12 and 0.10 kcal/mol in terms of energy and free energy, respectively. The calculated values of the relative free energy indicate that in the equilibrated gaseous mixture of anionic complexes only two anions could be presented in detectable amounts (see Table 2) and enable a molar ratio of these anions, [a1MGMC]:[a1MGMC_SPT2], to be calculated. At 298 K it is equal to 0.093, which means that the mixture is dominated by the proton-transferred form. The B3LYP vertical detachment energy estimated for this anion is 1.93 eV. Recently, we traced a small underestimation of VDEs observed in some systems to possible inaccuracies in molecular geometries predicted at the B3LYP level.[23] To correct for this flaw of the DFT model, we carried out an additional MP2 optimization for the most stable anionic structure. The resulting MP2-corrected geometry yields a VDE of 2.12 eV. This computational value remains in excellent agreement with our experimental results. Indeed, the maximum of the PES feature is observed at ~2.1 eV (see Figure 2). This good correspondence between experimental and computational data confirms thus that injection of electrons to the gas-phase mixture of equimolar amounts of MG and MC leads primarily to the formation of adiabatically stable π^* valence anions in which the closed-shell anion of deprotonated (at the N1 position; for atom numbers see Figure 1) 9-methylguanine interacts with the monohydro-radical of 1-methylcytosine (the MC open-shell anion protonated at the N3 center; for atom numbers see Figure 1).

4. Discussion

Previously five computational studies concerning the valence anions of the GC base pair have been published.[29] Adamowicz et al. studied the WC and reverse WC GC base pair valence anion at the UHF and MP2 levels.[31] Due to large spin contamination of the reference UHF wave function, they predicted adiabatic electron affinities for both geometries to be negative. At the same time Sevilla et al. demonstrated that at the B3LYP/6-31+G(d) level the VB anion of Watson−Crick GC is adiabatically stable, and they estimated the positive zero-point-energy-corrected AEA of 0.49 eV.[32] Moreover, this group demonstrated that a geometry in which a proton is transferred from N1(G) to N3(C) is more stable than the regular WC configuration by ca. 3 kcal/mol. One year later the Schaefer group, using their bracketing technique, calculated the most accurate AEA for WC GC, which amounts to 0.6 eV.[33] Finally, Kumar et al. characterized the WC GC anion employing the SCC-DFTB-D method together with various functionals.[29] For all levels of theory they predicted a positive AEA; however, their values span a broad range from 0.28 to 1.15 eV. Our study expands the data on the GC system to include the methylated GC pair, which is a more realistic model for the DNA environment. Furthermore, to reproduce the experimental PES spectrum, we scrutinized both the tautomer and the conformational space accessible to bases and base pairs, respectively. While the studies published in the past were devoted to one or two conformations of the unsubstituted GC involving canonical bases,[29−33] we focused on a comprehensive search including various tautomers of individual methylated bases and arrangements of base pairs. We, therefore, believe that our studies comprise all relevant gas-phase, anionic geometries. The fact that we accurately reproduced the position of the main feature in the experimental PES spectrum further validates our geometries.

The combination of our computational data and results of the photoelectron spectroscopy experiment for the $MGMC^-$ anions leads to two main conclusions. First, when MC and MG interact, the resulting neutral complex is able to form a stable valence anion (AEA = 0.60 eV; see Table 2), whereas the isolated MC cannot. This finding is in line with the positive EA of GC anions reported in the literature.[29−33] Moreover, the very low activation barrier for proton transfer from guanine to cytosine predicted for the Watson−Crick MGMC VB anion renders a1MGMC_SPT2 a dominant species in the gas phase.

One could consider these two conclusions in a somewhat broader perspective linking them to the mechanism of DNA damage by low-energy electrons. First, an excess electron attaching itself to cytosine should be easily stabilized when it interacts with a guanine molecule in double-stranded DNA, rendering the cytosine valence anion thermodynamically stable. While in DNA, nucleobases interact not only with complementary bases but also with sugar residues, phosphates, the protein backbone, amino acid side chains, metal cations, and the surrounding water. Therefore, an excess electron should be easily trapped by the GC base pair, forming adiabatically stable anions. After formation of a thermodynamically stable anion, the GC base pair has sufficient time for thermalization and subsequent chemical reactions, such as proton transfer.

As we noted above, the proton-transferred anion, a1MGMC_SPT2, is more stable than the regular base pair and it is separated from a1MGMC by a tiny activation barrier which, however, will be quickly overcome at the ambient temperature. Here one can ask whether this PT process may actually proceed in DNA if an excess electron can be efficiently transferred from the π^* orbital of cytosine to the σ^* orbital of the phosphate. Indeed, the maximum rate calculated for the through-bond electron transfer (ET) for the nucleotide of cytosine amounts to as much as 10^{10} s^{-1}.[3] However, the rate of N1(G) → N3(C) PT in the Watson-Crick MGMC anion is equal to 8×10^{12} s^{-1} for the calculated barrier of 0.10 kcal/mol (see above). Hence, the proton transfer within the MGMC anion should easily compete with the through-bond ET from the π^* resonance of cytosine.

The above-mentioned arguments suggest that the attachment of excess electron to GC incorporated in double-stranded DNA should lead to the most stable proton-transferred configuration. This is in contrast to the behavior of the AT base pair in DNA. Namely, the presence of an electron in the close vicinity to AT built into double-stranded DNA will result in the formation of a thermodynamically stable valence-bound (VB) anion, having the same hydrogen bond pattern as its parent AT base pair. A proton transfer within this species is forbidden due to energetic reasons. This anion may first be protonated at the C6 position and then can abstract a hydrogen from its own or neighboring sugar, which will produce a derivative of 5,6-dihydrothymine and ultimately lead to a single-strand break. It was demonstrated experimentally that thymine anion incorporated into DNA is easily protonated at the C6 atom.[45] Similarly, a high yield of 5,6-dihydrothymine was confirmed experimentally in the reaction of electrons with thymine bound in DNA.[46] Finally, many experimental studies demonstrate that a single-strand break is generated in DNA whenever one of the deoxyribose hydrogen atoms is abstracted.[47]

(45) Becker, D.; Sevilla, M. D. The chemical consequences of radiation damage to DNA. In *Advances in Radiation Biology*; Lett, J. T., Sinclair, W. K., Eds.; Academic Press: San Diego, CA, 1993; pp 121−180.
(46) Falcone, J. M.; Becker, D.; Sevilla, M. D.; Swarts, S. G. *Radiat. Phys. Chem.* **2005**, *72*, 257–264.
(47) Pogozelski, W. K.; Tullius, T. D. *Chem. Rev.* **1998**, *98*, 1089–1107.

The above-described path for SSB formation, based on the stable AT valence anion, is an alternative to the generally accepted resonance mechanism of LEE-induced DNA damage. Moreover, one should realize that there is no experimental data on the actual kinetics of the damage process and the main evidence supporting the resonance mechanism is the shape of the DNA damage curve. If activation barriers associated with the cleavage of the stable anionic nucleotides were relatively low (less than 20−23 kcal/mol; then the cleavage of the phosphate bonds could be completed within the time frame of electrophoresis), the yield of SSBs as a function of the electron energy should have the shape reflecting the resonance cross-section since then the electron attachment efficiency would decide the yield of strand break formation. This would explain the observed features in the DNA damage quantum yield versus incident electron energy, which in the 0−3 eV electron energy range corresponds to the position of π^* resonance states of the isolated nucleobases.[13,14] Thus, one can assume that the primary role of the resonance states is to allow for energy transfer between the impinging electron and the neutral target. Therefore, anionic resonance states may be viewed as doorways to bound valence anionic states. The latter could be involved in chemical transformations, such as DNA strand breaks, while the former are required to absorb excess electrons into the DNA environment.[25]

The reaction sequence described above for the AT valence anion in DNA, i.e., formation of a stable T^- anion, followed by its protonation, hydrogen atom transfer from its own or neighboring sugar, and finally a strand break, would be impossible for the GC anion. Indeed, electron attachment to GC incorporated into DNA would lead, almost without a kinetic barrier, to a structure in which the cytosine anion is protonated at the N3 atom and solvated by the deprotonated guanine anion at N1. Abstraction of a hydrogen atom from the sugar moiety by the [C + (N3H)] radical, however, faces a very high thermodynamic barrier that amounts to at least 22.7 kcal/mol in terms of free energy at the B3LYP/6-31++G** level.[48] A possible DNA cleavage will, therefore, be prohibited at the stage of proton transfer induced by electron attachment to the GC base pair.

Finally, we conclude that the potential consequences of electron attachment to the two complementary nucleobase pairs incorporated into double-stranded DNA are very different. While the formation of the AT anion should lead to a single-strand break, the attachment of an excess electron to the GC base pair will result in a stable species in which a proton is transferred from guanine to the cytosine VB anion.

5. Summary

A combined experimental and computational study on the electron attachment process to MGMC complexes reveals that adiabatically stable valence anions are formed in the gas phase. The measured VDE of 2.1 eV is very well reproduced by the calculated value for the most stable anionic structures of $(MGMC)^{\bullet -}$ anions.

The B3LYP/6-31++G(d,p) level calculations were carried out for complexes comprising canonical as well as low-energy tautomeric forms of the methylated nucleobases. In all cases, an excess electron localizes on the π^* orbital of cytosine and the geometrical relaxation of the neutral structure is coupled to a small buckling of the cytosine ring. All but one of the scrutinized anionic complexes are vertically stable at the B3LYP level. The calculated adiabatic electron affinities span a range from 0.39 to 0.60 eV.

Two types of $MGMC^-$ anions were characterized in the current study. Among them are those having a hydrogen bond pattern identical to that of the parent neutral complexes and those in which electron attachment triggers proton transfer from guanine to cytosine. The driving force for the PT process is to stabilize an excess charge localized on the cytosine molecule. Due to proton transfer, the VDE moves to a higher energy region. As a consequence, the VDEs for anions lacking PT span a range from 0.91 to 1.01 eV, while for those where PT takes place a range of 1.91−1.93 eV is predicted.

The consequences of electron attachment to the AT or GC base pairs incorporated into double-stranded DNA are quite different. In the former case, the stable valence-bound anion in which an excess electron is localized on thymine may undergo protonation at the C6 site and transform in a sequence of processes leading to a single-strand break. In contrast, electron attachment to GC leads to a swift proton transfer between guanine and cytosine which should stop the reaction sequence that for the AT anion produces a strand break. Thus, in the presence of an excess electron, the $(AT)_n$ double-stranded DNA sequences should behave differently compared to the $(GC)_n$ double-stranded DNA sequences.

Acknowledgment. This work was supported by the (i) Polish State Committee for Scientific Research (KBN), Grant No. KBN/N N204 023135, and Scientific and Technological International Cooperation Joint Project (MNiSW), Grant No. dec.127/02/E-335/S/2008 (J.R.), (ii) ONR Grant No. N00034-03-1-0116 and NSF CREST Grant No. HRD-0318519 (J.L.), and (iii) the National Science Foundation under Grant No. CHE-0809258 (K.H.B.). The calculations were performed at the Academic Computer Center in Gdańsk (TASK) and the Mississippi Center for Supercomputing Research.

Supporting Information Available: Proton affinities of the N/O atoms and deprotonation energies of the NH/OH bonds for selected sites of neutral 9-methylguanine and 1-methylcytosine as well as anionic 1-methylcytosine. This material is available free of charge via the Internet at http://pubs.acs.org.

JA808313E

(48) Storoniak, P.; Kobyłecka, M.; Rak, J. Thermodynamics of hydrogen transfer within the neutral radicals of nucleotides. A proposal of DNA strand break formation induced by an excess electron. Presented at the XVII-th International Conference, Horizons in Hydrogen Bond Research, Saint Petersburg, Russia, Sept 2−8, 2007.

Addition/Correction

Valence Anions of 9-Methylguanine#1-Methylcytosine Complexes. Computational and Photoelectron Spectroscopy Studies

Anna Szyperska, Janusz Rak, Jerzy Leszczynski, Xiang Li, Yeon Jae Ko, Haopeng Wang, and Kit H. Bowen

J. Am. Chem. Soc., **2009**, 131 (18), 6641-6641• DOI: 10.1021/ja9020638 • Publication Date (Web): 20 April 2009

J|A|C|S
ADDITIONS & CORRECTIONS

Residue-Specific pK_a Determination of Lysine and Arginine Side Chains by Indirect ^{15}N and ^{13}C NMR Spectroscopy: Application to *apo* Calmodulin [*J. Am. Chem. Soc.* **2007,** *129,* 15805–15813]. Ingemar André, Sara Linse, and Frans A. A. Mulder*

Page 15807. A typographical mistake was found in eq 1. The correct form of the Henderson−Hasselbalch equation for deprotonation should read

$$\delta_{obs} = \frac{(\delta_{HA} + \delta_{A^-}\, 10^{(pH-pK_a)})}{(1 + 10^{(pH-pK_a)})} \qquad (1)$$

where δ_{obs} is the observed chemical shift and δ_{HA} and δ_{A^-} are the chemical shifts of the protonated and unprotonated forms, respectively.

Importantly, all data were analyzed with this correct form of eq 1, and in no way does this correction change the results or conclusions presented in the original paper. We thank Mr. Jelle Slager for bringing this mistake to our attention.

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10.1021/ja902385j
Published on Web 04/21/2009

Ligand Controlled Highly Regio- and Enantioselective Synthesis of α-Acyloxyketones by Palladium-Catalyzed Allylic Alkylation of 1,2-Enediol Carbonates [*J. Am. Chem. Soc.* **2008,** *130,* 11852–11853]. Barry M. Trost,* Jiayi Xu, and Thomas Schmidt

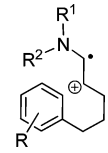
Page 11853. In Table 2, entries 11 and 12, the stereochemical assignments of the cyclohexenyl ring of compound **20** and the cycloheptenyl ring of compound **22** should be *S*, not *R*. This assignment is based on the empirical model we proposed (Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545), which has been supported by extensive experimental data.

JA902816Z

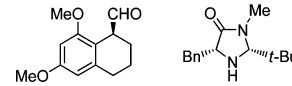
10.1021/ja902816z
Published on Web 04/21/2009

Enantioselective Intramolecular Friedel−Crafts-Type α-Arylation of Aldehydes [*J. Am. Chem. Soc.* **2009,** *131,* 2086–2087]. K. C. Nicolaou,* Rüdiger Reingruber, David Sarlah, and Stefan Bräse

Page 2086. The intermediate in eq 1 should be a cation radical as follows:

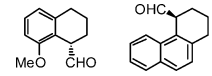


The structures **1b** and **A** in Table 1 should be as follows:

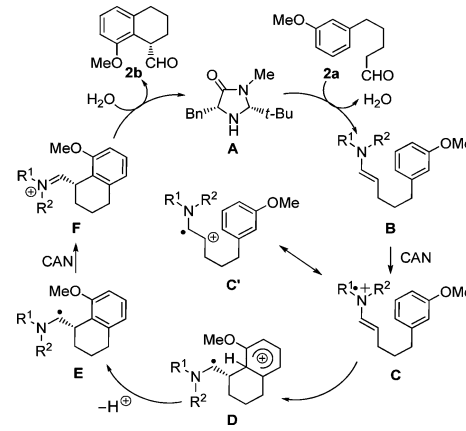


The intramolecular attack from the aromatic nucleus occurs from the *Re* face of the enamine when using (2*R*,5*R*)-**A**.

Page 2087. The structures of the products in Table 2, entries 3 and 10, should be as follows:



Correspondingly, Scheme 1 should be corrected as follows:



We deeply regret these oversights and errors. A corrected Supporting Information file that reflects these changes is available. These corrections have no implications on the main discoveries and conclusions described in the paper.

Supporting Information Available: Experimental procedures and compound characterization (corrected). This material is available free of charge via the Internet at http://pubs.acs.org.

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10.1021/ja902385j CCC: $40.75

Valence Anions of 9-Methylguanine−1-Methylcytosine Complexes. Computational and Photoelectron Spectroscopy Studies [*J. Am. Chem. Soc.* **2009,** *131,* 2663–2669]. Anna Szyperska, Janusz Rak,* Jerzy Leszczynski,* Xiang Li, Yeon Jae Ko, Haopeng Wang, and Kit H. Bowen*

Page 2668. In the last paragraph of section 3.2.2, the activation barrier for the proton transfer process from the N1 atom of methylguanine to the N3 atom of methylcytosine should be corrected as written below:

The kinetic barrier that separates a1MGMC and a1MGMC_SPT2 structures is 2.78 and 2.39 kcal/mol in terms of energy and free energy, respectively.

The conclusion remains the same.

Page 2663−2664. An important reference was inadvertently omitted from the Introduction. Schaefer and co-workers[1] used the B3LYP/DZP++ theoretical approach to study the 2′-deoxyguanosine-2′-deoxycytidine (dG:dC) nucleoside pair. Their research revealed that electron attachment to the dC moiety in the dG:dC pair is able to trigger proton transfer from N1(dG) to N3(dC), forming the more stable anionic complex $d(G\text{-}H)^-$:$d(C+H)^\bullet$, and the energy barrier for this reaction is 2.4 kcal/mol, which is in good agreement with data presented in our article.

Literature Cited

(1) Gu, J.; Xie, Y.; Schaefer, H. F., III *J. Chem. Phys.* **2007**, *127*, 155107/1–155107/6.

JA9020638

10.1021/ja9020638
Published on Web 04/20/2009

Jacobsen's Catalyst for Hydrolytic Kinetic Resolution: Structure Elucidation of Paramagnetic Co(III) Salen Complexes in Solution via Combined NMR and Quantum Chemical Studies [*J. Am. Chem. Soc.* **2009,** *131,* 4172–4173]. Sebastian Kemper, Peter Hrobárik, Martin Kaupp,* and Nils E. Schlörer*

Page 4173. Footnote *a* of Scheme 2 should read "S-epoxide" instead of "R-epoxide".

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10.1021/ja902706f
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