Stabilization of Very Rare Tautomers of 1-Methylcytosine by an Excess Electron†

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We characterized valence anionic states of 1-methylcytosine using various electronic structure methods. We found that the most stable valence anion is related to neither the canonical amino-oxo nor a rare imino-oxo tautomer, in which a proton is transferred from the N4 to N3 atom. Instead, it is related to an imino-oxo tautomer, in which the C5 atom is protonated. This anion is characterized by an electron vertical detachment energy (VDE) of 2.12 eV and it is more stable than the anion based on the canonical tautomer by 1.0 kcal/mol. The latter is characterized by a VDE of 0.31 eV. Another unusual low-lying imino-oxo tautomer with a VDE of 3.60 eV has the C6 atom protonated and is 3.6 kcal/mol less stable than the anion of the canonical tautomer. All these anionic states are adiabatically unbound with respect to the canonical amino-oxo neutral, with the instability of 5.8 kcal/mol for the most stable valence anion. The mechanism of formation of anionic tautomers with carbon atoms protonated may involve intermolecular proton transfer or dissociative electron attachment to the canonical neutral tautomer followed by a barrier-free attachment of a hydrogen atom to the C5 or C6 atom. The six-member ring structure of anionic tautomers with carbon atoms protonated is unstable upon an excess electron detachment. Indeed the neutral systems collapse without a barrier to a linear or a bicyclo structure, which might be viewed as lesions to DNA or RNA. Within the PCM hydration model, the anions become adiabatically bound with respect to the corresponding neutrals, and the two most stable tautomers have a carbon atom protonated.

1. Introduction

The nucleic acid bases (NABs) are basic elements of DNA, which is responsible for storing genetic information in cells. Low-energy electrons and hydroxyl radicals are among the most reactive species formed upon interaction of high-energy radiation with living cells. Low-energy electrons might become trapped on nucleic acid bases, and the resulting radical anions might participate in chemical reactions, which can lead to DNA damage.[1,2] Furthermore, the charged nucleic acid bases play a key role in the electron and hole transfer phenomena in DNA.[3−6]

In the past, a large number of theoretical and experimental studies were focused on determination of electron affinity of NABs in the gas and condensed phases. Anions of hydrated NABs are believed to support an excess electron on a valence-type molecular orbital as suggested by experimental[7] as well as theoretical data.[8,9] However, the existence of stable anions of NABs in the gas phase has long been a point of discussion. Early computational studies had predicted negative values of adiabatic electron affinity (AEA).[10] An important development occurred in mid 1990s when Adamowicz and co-workers found stable but loosely bound anionic states supported primarily by large dipole moments of neutral NABs.[11−14] These anionic states were characterized in photoelectron spectroscopy (PES),[15] Rydberg electron transfer,[16] and photodetachment−photoelectron experiments.[17]

Dipole-bound anions are strongly perturbed by other atoms or molecules,[18] and their relevance in condensed phase environments is questionable. In clusters of polar molecules[19] or in polar solvents they are typically replaced by solvated electrons[20] or solvated anions.[21,22] Solvated electrons and valence anionic states are expected to play a role in biochemical processes driven by thermalized excess electrons.[23]

Much less is known about valence anionic states of NABs in the gas phase. Aflatooni et al.[24] characterized temporary anionic states of NABs in electron transmission spectroscopy experiments and reported an electron vertical attachment energy (VAE) of −0.32 eV for cytosine. Huels et al. reported anions of thymine and cytosine with lifetimes exceeding 10 μs, which were obtained by resonant attachment of subionization electrons.[25] Schiedt et al. extrapolated the electron affinity of isolated cytosine from the results obtained for hydrated cytosine with the final prediction being 130 ±120 meV.[17] The extrapolation might be slightly erroneous since a linear extrapolation might be not valid for the first water molecule bound to cytosine.

The most extensive computational study of valence anions of tautomers of cytosine was presented by Ortiz and co-workers.[26] The results obtained at the MP2/6-311++G(2df,-2p) level clearly suggest that none of the known tautomers of cytosine supports an adiabaticaly bound anion. For the canonical amino-oxo tautomer they reported an AEA of −0.382 eV. The values of −0.450 and −0.522 eV were found for two rotamers of the imino-oxo form and −0.853 and −0.549 eV were reported for two rotamers of the amino-hydroxy tautomer. The valence anions of the amino-oxo and imino-oxo tautomers were found to be vertically bound with respect to the neutral with the calculated values of electron vertical detachment energy (VDE) of 0.271, 0.204, and 0.142 eV, respectively. These authors also indicated that a 230 meV peak reported by Schiedt et al. for the anion of cytosine may be related to a valence rather than to

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a dipole-bound state. In another computational study on the anions of cytosine only the amino-oxo and amino-hydroxy tautomers were considered.[27] The results were in agreement with those of ref 26 and the reported value of VDE of the valence anion of the amino-oxo form was 102 meV at the MP4/6-31++G**//MP2/6-31++G** level. In another study, a valence anion of the canonical tautomer of 1-methylcytosine was considered.[28] It was found to be unbound in terms of AEA and VDE. The reported MP2/6-31++G** values of AEA and VDE were −0.677 and −0.025 eV, respectively.

Other computational studies were focused primarily on anionic states of the canonical tautomer, and the DFT method was used with different exchange-correlation functionals.[8,29−31] The values of AEA were either positive or negative depending on the functional and the basis sets used. The most recent study on electron affinities of NABs questioned the previously reported values of the AEA of cytosine.[8] Sevilla and co-workers suggested that inclusion of diffuse functions in the basis set can result in contamination of the valence state with the dipole-bound state. They estimated the AEA of cytosine to be −0.05 eV based on a series of B3LYP calculations with different basis sets.

Theoretical studies demonstrate the existence of three low-energy tautomers of neutral cytosine: the "canonical" amino-oxo, amino-hydroxy, and imino-oxo. The two latter tautmors support various rotamers. Here the name "canonical" indicates that this tautomer is involved in the Watson−Crick pairing with guanine rather than that it is the most stable. The results of highly correlated calculations indicate that the amino-hydroxy tautomer is more stable than the canonical tautomer (amino-oxo) by ca. 1.5 kcal/mol.[32−35] The imino-oxo tautomer was found to be nearly as stable as the canonical tautomer. These computational results confirm the results of spectroscopic studies, which indicate the predominance of the amino-hydroxy tautomer in the gas phase.[36−39]

In DNA or RNA cytosine is connected to a sugar unit through the N1 atom; see Figure 1 for the labels of atoms. Thus, 1-methylcytosine (MC) is often used in gas phase experiments as a mimic of cytosine in DNA or RNA. The methylation of cytosine at N1 not only reduces the number of possible tautomers, e.g., it eliminates the amino-hydroxy tautomer, but also reduces its ability to form intermolecular hydrogen bonds and increases its vapor pressure in comparison with unsubstituted cytosine, hence facilitating gas-phase experiments. The methylation of cytosine increases the relative stability of the amino-oxo relative to the imino-oxo tautomer. The MP2/6-31++G** results of Adamowicz and co-workers[14] and the HF/6-31G* results of Szczesniak et al.[40] suggest that the former is more stable than the latter by 3.27 and 1.00 kcal/mol, respectively. The infrared spectrum of 1-methylcytosine isolated in the Ar matrix suggests that about 6−8% of molecules adopt the imino-oxo tautomeric forms, which coexist in the matrix with the dominating amino-oxo tautomer.[41]

In this report we have identified and characterized the most stable tautomers of MC in valence anionic states. Our hypothesis is that the most stable valence anions of NABs might be related to the tautomers that are very unstable as neutral species. We use a name "very rare tautomers" to discriminate these tautomers from conventional "rare tautomers". In the case of MC, conventional "rare tautomers" are the imino-oxo with the N3 atom protonated or the imino-hydroxy with the O2 atom protonated. On the other hand, "very rare tautomers" that we have in mind result from the enamine-imine transformations, which lead to protonation of the C5 or C6 atoms.

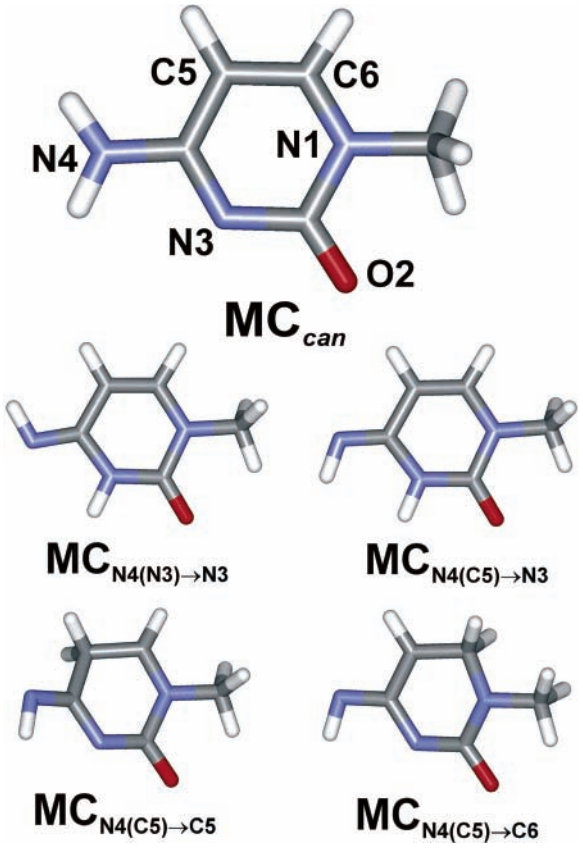

Figure 1. Tautomers of anionic 1-methylcytosine considered at higher than B3LYP levels of theory.

A hint that the tautomerization involving carbon atoms might be advantageous for anionic NABs came from our earlier studies on *intermolecular* proton transfer in complexes involving valence anions of NABs.[22,42−47] Although in these earlier studies we considered primarily proton transfer to the O8 and O7 atoms of uracil or thymine (Thy) and the N3 and O2 atoms of cytosine,[22,42−46] recently we have recognized that the C5 and C6 carbon sites are thermodynamically preferable for intermolecular proton transfer to the anion of a pyrimidinic NAB.[47] Thus, these sites have the largest proton affinity for the canonical tautomers of the anionic bases. Indeed, the results of electron spin resonance investigation of γ-irradiated DNA indicate that the most stable radical $(\mathrm{Thy} + \mathrm{H})^{\bullet}$ is protonated at the C6 position.[48] Here we suggest that not only *intermolecular* proton transfer, which leads leads to $(\mathrm{NAB}+\mathrm{H})^{\bullet}$ species, but also *intramolecular* proton transfer, which leads to new tautomers of NAB^{-}, might favor carbon sites in valence anions of nucleic acid bases.

The concept that higher energy tautomers of the neutral can be stabilized by an excess electron has been explored in the past for amino acids. We have found that a zwitterionic tautomer binds an excess electron more strongly than the canonical tautomer.[49−51] As a consequence, some zwitterionic tautomers solvated by an excess electron might become stable in the gas phase.[50] These theoretical predictions were confirmed in photoelectron spectroscopy experiments.[52] More recent studies concentrated on anionic complexes of glycine hydrated with a few water molecules.[53,54]

Our main finding, which results from coupled cluster calculations with single, double, and perturbative triple excitations with augmented correlation consistent double-ζ basis sets, is that anionic imino-oxo tautomers of MC, which result from the enamine-imine transformations and which have the C5 or C6

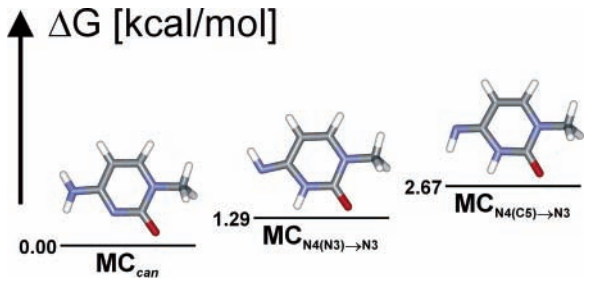

Figure 2. Tautomers of neutral 1-methylcytosine. Relative Gibbs free energy determined at the CCSD(T)/AVDZ level using the MP2/AVDZ geometries and thermodynamic corrections.

atom protonated, are unusually stable. There are strong indications that the valence anion based on the canonical tautomer is not the most stable, both in the gas phase and in water solution. We suggest that the mechanism of formation of anionic tautomers with carbon atoms protonated may involve intermolecular proton transfer or dissociative electron attachment to the canonical neutral tautomer followed by a barrier-free attachment of a hydrogen atom to a carbon atom. The six-member ring structure of very rare tautomers is unstable upon excess electron detachment, and their decompositions might be related to the formation of lesions on cytosine.

2. Methods

We use the following notation for the neutral and anionic tautomers. The canonical amino-oxo tautomer is named "MC-$_{can}$". The names of the remaining tautomers and rotamers of MC reflect these intramolecular proton transfers that lead from MC_{can} to the tautomer/rotamer at hand. For example, an imino-oxo rotamer with N4 deprotonated from the N3 side and the N3 atom protonated is called "$MC_{N4(N3)\rightarrow N3}$"; see Figure 1. In addition, prefixes "a_{val}" and "na_{val}" are used to distinguish properties of the valence anion and the neutral, respectively, determined at the minimum energy geometry of the anion. Sevilla et al. addressed a problem,[8] which set of atomic orbitals should be used in calculations of valence anions of nucleic acid bases, which are characterized by negative values of vertical electron affinity, but which support dipole-bound anionic states. In this study we deal only with these regions of the potential energy surface, in which the valence anion is vertically bound with respect to the neutral. Then, we perform calculations with standard basis sets that contain basis functions with small exponents. The diffuse functions contribute to the proper description of the anionic charge distribution but do not lead to a collapse to the dipole-bound state, which is usually less strongly bound than the valence anionic state. It is known that "buckling" of the ring of a nucleic acid base might increase the electronic stability of the anion, because the excess electron occupies a π^* orbital.[42] Thus, our B3LYP/6-31++G**(5d) energy minimizations for the anionic tautomers of MC were initiated from "buckled" structures.

Fourteen neutral and anionic tautomers and rotamers were initially considered at the density functional level of theory with a B3LYP exchange-correlation functional[55−57] and 6-31++G**-(5d) basis set;[58] see Table S-1 and Figure S-1. The most important forms are displayed in Figures 1−4. The five anionic tautomers/rotamers preselected at the B3LYP/6-31++G** level span a narrow range of 7 kcal/mol in terms of energy corrected for zero-point vibrations ($\Delta E + \Delta E_{vib} = \Delta E_{ZPVE}$); see Table S-1 and Figure 1. They were further optimized at the second-order Møller−Plesset (MP2) level with the augmented, correlation-consistent, polarization, double-ζ (AVDZ) basis set.[59]

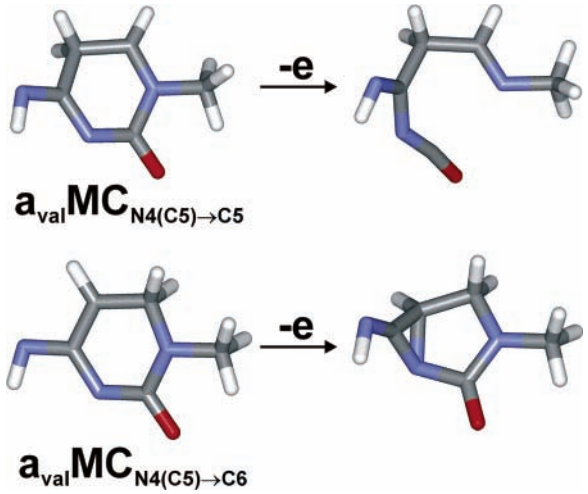

Figure 3. Electron detachment leads to a decomposition of the six-member ring structure of anionic tautomers with carbon atoms protonated.

A typical spin contamination was small with the value of S^2 smaller than 0.77 at the UHF level, with an exception of the $MC_{N4(C5)\rightarrow C6}$ tautomer, for which the UHF value of S^2 was 0.86. The spin contamination was even smaller at the B3LYP/6-31++G** level.

Final single-point calculations were performed at the coupled cluster level of theory with single, double, and noniterative triple excitations[60] (CCSD(T)/AVDZ) at the optimal MP2 geometries. The open-shell CCSD(T) calculations were carried out at the R/UCCSD(T) level. In this approach, a restricted open shell Hartree−Fock calculation was initially performed to generate the set of molecular orbitals and the spin constraint was relaxed in the coupled cluster calculation.[61−63] The 1s orbitals of carbon, nitrogen, and oxygen atoms were excluded from the MP2 and coupled-cluster treatments.

The relative energies of the anion with respect to the neutral were first corrected for the energies of zero-point vibrations to derive the values of AEA. Next, thermal corrections as well as the entropy terms, calculated at either the B3LYP or MP2 levels for $T = 298$ K and $p = 1$ atm in the harmonic oscillator-rigid rotor approximation, were included to derive the relative stability in terms of Gibbs free energy.

The effects of solvation were studied by performing single point calculations at the optimal B3LYP/6-31++G**(5d) gas-phase geometries within the polarized continuum model (PCM).[64−66] In this approach a solute occupies a cavity within the solvent. A charge distribution of the molecule will polarize the medium, and the electric field applied by the solvent's distribution of charge will in turn interact with the charge distribution of the molecule. For water, $\epsilon = 78.4$ and $\epsilon_{opt} = 1.8$. We apply the same value of dielectric constant ($\epsilon = 78$) for the neutral and the anion when calculating the values of AEA. The values of VDE and VAE were calculated with $\epsilon = 78$ for the initial state and $\epsilon = 2$ for the final state. In this approach only electronic polarization of the solvent is taken into account for the final state, whereas orientational polarization is neglected. This approach relies on the assumption that the solvent geometry remains essentially fixed on the time scale of the electron detachment or attachment.[67]

The DFT and MP2 geometry optimizations were performed with Gaussian98,[58] the MP2 frequency calculations with NWChem,[68] and the CCSD(T) calculations with the MOLPRO[69] package. The codes were run on Intel/P4Xeon workstations, SGI Altix server, and a cluster of dual Intel Itanium2 nodes with

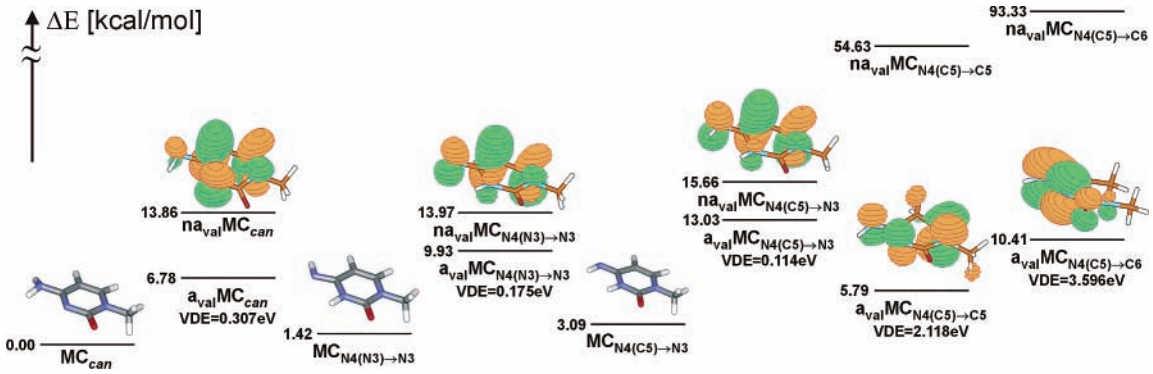

Figure 4. Valence-type anionic states of 1-methylcytosine. Singly occupied orbitals plotted with a spacing of 0.03 $b^{-3/2}$.

TABLE 1: Relative Energies (kcal/mol) of Tautomers of Neutral 1-Methylcytosine Determined at the B3LYP, MP2, and CCSD(T) Levels

	B3LYP				MP2				CCSD(T)				ref 14	ref 40
tautomer	ΔE	ΔE_{ZPVE}	ΔH	ΔG	ΔE	ΔE_{ZPVE}	ΔH	ΔG	ΔE	ΔE_{ZPVE}	ΔH	ΔG	ΔE	ΔE
MC_{can}	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0
$MC_{N4(N3)\rightarrow N3}$	2.53	3.04	2.89	2.55	2.34	2.58	2.55	2.22	1.42	1.66	1.62	1.29	3.27	1.00
$MC_{N4(C5)\rightarrow N3}$	4.34	4.76	4.60	4.46	4.09	4.13	4.13	3.67	3.09	3.12	3.13	2.67		2.77

Quadrics interconnect. Molden was used for visualization of singly occupied molecular orbitals.[70]

3. Results

3.1. Tautomers of Neutral 1-Methylcytosine. The cannonical tautomer MC_{can} is the most stable at every level of theory in terms of energy, enthalpy, and Gibbs free energy (Tables S-1 and 1, and Figure 2). The calculated values of electronic energies, energies of zero-point vibrations, and thermal contributions to Gibbs free energy from enthalpy and entropy are collected in Table S-2. At the CCSD(T)/AVDZ//MP2/AVDZ level the imino-oxo $MC_{N4(N3)\rightarrow N3}$ tautomer is only 1.4 and 1.3 kcal/mol less stable than MC_{can} in terms of energy and Gibbs free energy, respectively. The imino-oxo rotamer $MC_{N4(C5)\rightarrow N3}$ is less stable than MC_{can} by 3.1 kcal/mol in terms of energy. These results are consistent with the infrared spectrum of 1-methylcytosine isolated in the Ar matrix.[41] It was concluded that about 6−8% of molecules adopt imino-oxo tautomeric forms, which coexist in the matrix with the dominating amino-oxo tautomer.

A difference in the stability between the amino-oxo and the $MC_{N4(N3)\rightarrow N3}$ tautomer of more than 1 kcal/mol is a consequence of methylation of cytosine. Indeed, the past computational results for cytosine[33,34] indicate that the amino-oxo and $MC_{N4(N3)\rightarrow N3}$ have a very similar energy. MC is the simplest model of cytosine connected to a sugar in DNA or RNA. The higher stability of MC_{can} in comparison with rare tautomers might be important for informational fidelity of nucleic acids. Any coexistence of rare tautomers may lead to mismatches of base pairs in comparison to the Watson−Crick scheme and in consequence to a point mutation.

Lower level methods, such as MP2 and B3LYP, predict correctly the relative ordering of the tautomers as well as the quantitative energy difference between $MC_{N4(N3)\rightarrow N3}$ and $MC_{N4(C5)\rightarrow N3}$. The stability of the amino-oxo tautomer with respect to both rotamers $MC_{N4(x)\rightarrow N3}$ (x = N3 or C5) is overestimated by ca. 1 kcal/mol at both the MP2 and B3LYP levels. A similar overestimation of stability of the amino-oxo form of cytosine by DFT methods was reported before.[33,34] Suprisingly, the HF/6-31G* results reported by Szczesniak et al.[40] are in excellent agreement with our CCSD(T)/AVDZ results; see Table 1.

In agreement with previous calculations,[14] the largest dipole moments of 6.0 and 4.9 D were found for the MC_{can} and $MC_{N4(N3)\rightarrow N3}$ tautomers. Thus, these tautomers can support dipole-bound anions in addition to valence anions.[18,28] A dipole moment of 2.9 D for $MC_{N4(C5)\rightarrow N3}$ is too small to support a dipole-bound state with an electron binding energy exceeding 1 meV.

The neutral $MC_{N4(C5)\rightarrow C5}$ and $MC_{N4(C5)\rightarrow C6}$ do not support minima for six-member ring structures. The B3LYP and MP2 geometry optimizations result in a linear or a bicyclo structure for $MC_{N4(C5)\rightarrow C5}$ and $MC_{N4(C5)\rightarrow C6}$, respectively; see Figure 3. This finding might be important for DNA or RNA damage induced by excess electrons. If the $a_{val}MC_{N4(C5)\rightarrow C5}$ and $a_{val}MC_{N4(C5)\rightarrow C6}$ structures were populated, then the electron detachment might lead to a destruction of the six-member ring of MC; see also section 4.

3.2. Valence Anions. Our preliminary B3LYP/6-31++G** (5d) searches for vertically bound valence anions of 1-methylcytosine in the gas phase ended up with positive results for 10 isomers; see Table S-1. Five most stable structures, $a_{val}MC_{can}$, $a_{val}MC_{N4(N3)\rightarrow N3}$, $a_{val}MC_{N4(C5)\rightarrow N3}$, $a_{val}MC_{N4(C5)\rightarrow C5}$, and $a_{val}MC_{N4(C5)\rightarrow C6}$, have been considered at higher levels of theory. The structures were reoptimized at the MP2/AVDZ level, and final energies were calculated at the CCSD(T) level; see Table 2 and Figure 4. The anions remain vertically bound at the MP2 level, which makes the converged structures reliable, and they maintain their electronic vertical stability at the CCSD(T) level. The calculated values of electronic energies, energies of zero-point vibrations, and thermal contributions to Gibbs free energy from enthalpy and entropy are collected in Table S-2.

Our main finding is that the most stable valence anion is $a_{val}MC_{N4(C5)\rightarrow C5}$, which is unrelated to any low-lying tautomer of neutral MC. The anion is characterized by an electron vertical detachment energy of 2118 meV. The anion $a_{val}MC_{N4(C5)\rightarrow C5}$ is more stable by 1.0 kcal/mol than the anion $a_{val}MC_{can}$. The latter is characterized by a VDE of only 307 meV. Another low-lying anionic tautomer with a carbon atom protonated, $a_{val}MC_{N4(C5)\rightarrow C6}$, is 3.6 kcal/mol less stable than $a_{val}MC_{can}$ and its VDE amounts 3596 meV. The two conventional imino-oxo tautomers with N3 protonated, $MC_{N4(N3)\rightarrow N3}$ and $MC_{N4(C5)\rightarrow N3}$, also support vertically bound valence anionic states with VDEs of 175 and 114 meV, respectively. They are, however, less stable than the anion

TABLE 2: Adiabatic Electron Affinities (AEA) and Electron Vertical Detachment Energies (VDE) in meV, Determined at the MP2, CCSD, and CCSD(T) Levels with the AVDZ Basis Set

	MP2			CCSD		CCSD(T)	
valence anions	AEA − ΔE_o^{vib}	AEA	VDE	AEA	VDE	AEA	VDE
$a_{val}MC_{can}$	−382[a]	−280[a]	239	−214[a]	366	−192[a]	307
$a_{val}MC_{N4(N3)\rightarrow N3}$	−394[a]	−285[a]	165	−299[a]	216	−261[a]	175
$a_{val}MC_{N4(C5)\rightarrow N3}$	−451[a]	−343[a]	114	−368[a]	144	−323[a]	114
$a_{val}MC_{N4(C5)\rightarrow C5}$	−413[b]	−311[b]	2131	−156[b]	2248	−149[b]	2118
$a_{val}MC_{N4(C5)\rightarrow C6}$	−567[b]	−474[b]	3827	−342[b]	3779	−358[b]	3596

[a] Calculated with respect to the corresponding neutral. [b] Calculated with respect to the neutral MC_{can}.

TABLE 3: Effects of Hydration on the Stability of Anions of 1-Methylcytosine[a]

	VAE[b]	AEA[c,d]	$AEA_{MC_{can}}$[c,e]	VDE[b]
MC_{can}	−0.07	1.96	1.96	2.75
$MC_{N4(N3)\rightarrow N3}$	0.10	2.11	1.91	3.10
$MC_{N4(C5)\rightarrow N3}$	−0.01	1.85	1.60	2.89
$MC_{N4(C5)\rightarrow C5}$	*f*	*f*	1.98	4.83
$MC_{N4(C5)\rightarrow C6}$	*f*	*f*	2.01	6.29

[a] The electron vertical attachment energy (VAE), adiabatic electron affinity (AEA), and electron vertical detachment energy (VDE) were studied at the B3LYP/6-31++G**(5d) level within the PCM model using the optimal gas-phase geometries of the neutral and anionic species. [b] $\epsilon = 78$ and 2 for the initial and final state, respectively. [c] $\epsilon = 78$ for the initial and final state. [d] AEA calculated with respect to the corresponding neutral. [e] $AEA_{MC_{can}}$ calculated with respect to the neutral MC_{can}. [f] The six-member ring structure is unstable for the neutral.

of the canonical tautomer by 3.2 and 6.3 kcal/mol, respectively. The relative stability is similar in terms of Gibbs free energy. With respect to $a_{val}MC_{can}$, $a_{val}MC_{N4(C5)\rightarrow C5}$ is more stable by 1.1 kcal/mol whereas $a_{val}MC_{N4(N3)\rightarrow N3}$, $a_{val}MC_{N4(C5)\rightarrow C6}$, and $a_{val}MC_{N4(C5)\rightarrow N3}$ are less stable by 3.2, 4.0, and 6.1 kcal/mol, respectively.

For the three most important anionic tautomers, $a_{val}MC_{can}$, $a_{val}MC_{N4(C5)\rightarrow C5}$, and $a_{val}MC_{N4(C5)\rightarrow C6}$, differences in the AEA values determined at the CCSD and CCSD(T) levels do not exceed 22 meV. The discrepancies between the MP2 and CCSD(T) values are much larger and exceed 160 meV. Thus, higher than second-order electron correlation effects are important for the stability of valence anions. The convergence of correlated methods is faster for the anions of conventional rare tautomers than for the tautomers with carbon atoms protonated.

All anions are adiabatically unbound with respect to the corresponding neutrals with the CCSD(T) values of AEA of −192, −261, and −323 meV for MC_{can}, $MC_{N4(N3)\rightarrow N3}$, and $MC_{N4(C5)\rightarrow N3}$, respectively (see Table 2). The neutrals $MC_{N4(C5)\rightarrow C5}$ and $MC_{N4(C5)\rightarrow C6}$ do not support minima for six-member ring structures, see Figure 3, and the values of AEA reported in Table 2 of −149 and −358 meV, respectively, were calculated with respect to the neutral MC_{can}. The values of AEA for these tautomers would be positive if they were calculated with respect to the fully relaxed structures of the neutrals presented in Figure 3.

The effect of hydration was studied at the B3LYP/6-31++G**(5d) level within the PCM model using the optimal gas phase geometries; see Table 3. Within this model, all five isomers are adiabatically bound with respect to the neutral MC_{can}. The relative stability of the anions is different than that in the gas phase. The tautomer $a_{val}MC_{N4(C5)\rightarrow C6}$ becomes the most stable with a VDE of 6.29 eV. The second most stable anion $a_{val}MC_{N4(C5)\rightarrow C5}$ is less stable by 0.7 kcal/mol and is characterized by a VDE of 4.83 eV. The anion of the canonical tautomer comes third and very close in stability to $a_{val}MC_{N4(C5)\rightarrow C5}$ with a VDE of 2.75 eV. The orientational

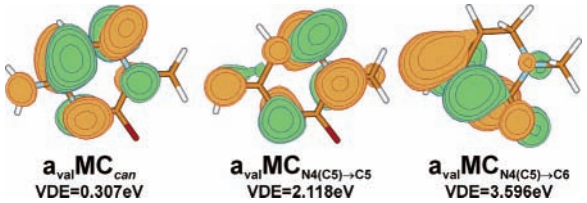

Figure 5. Singly occupied orbitals of $a_{val}MC_{can}$, $a_{val}MC_{N4(C5)\rightarrow C5}$, and $a_{val}MC_{N4(C5)\rightarrow C6}$ plotted with a spacing of 0.03 $b^{-3/2}$.

polarization of the solvent is critical as the values of VAE are negative or close to zero. Even though the $a_{val}MC_{N4(C5)\rightarrow C6}$ and $a_{val}MC_{N4(C5)\rightarrow C5}$ tautomers are the most stable within the PCM hydration model, their thermodynamic dominance should be viewed only as a possibility, because accuracy of the PCM model for charged species is not sufficient to make a more definite prediction.

Many anionic tautomers of 1-methylcytosine are electronically vertically bound in the gas phase. The vertical electronic stability is accompanied by serious geometrical relaxations with respect to the structure of the corresponding neutrals. The nonplanarity of the neutral MC_{can} is limited to the $N4H_2$ group and both $MC_{N4(X)\rightarrow N3}$ (X = C5 or N3) isomers have a symmetry plane. A serious buckling of the ring develops in consequence of localization of a π^* electron in the C4−C5−C6 region. These geometrical distortions involve both hydrogens and heavy atoms. As measures of nonplanarity we use deviations from 0° of dihedral angles N1C6C5C4 and N3C2N1C6. They are, respectively, −12° and −14° in $a_{val}MC_{can}$, −46° and −6° in $a_{val}MC_{N4(C5)\rightarrow C5}$, and 32° and 33° in $a_{val}MC_{N4(C5)\rightarrow C6}$. Thus, it is not surprising that the energy of the neutral is much higher at the optimal anionic geometry than at its minimum energy structure. Indeed, the energy of the corresponding neutral at the anionic geometry is larger by 13.9, 54.6, and 93.3 kcal/mol than the energy of the fully optimized MC_{can}. The corresponding values of VDE are only 7.1, 48.8, and 82.9 kcal/mol, which render the anionic states adiabatically unbound. Strong distortions of molecular frameworks are characteristic for valence anionic states. The buckling of the ring is still significant but smaller in the PCM hydration model.

The unpaired electron in $a_{val}MC_{can}$ is localized primarily in the C4−C5−C6 region; see Figure 5. It is then not surprising that the C5 and C6 sites have a significant proton affinity and the tautomers resulting from proton transfers from N4H to C5 or C6 might be quite stable. The unpaired electron in the $a_{val}MC_{N4(C5)\rightarrow C5}$ and $a_{val}MC_{N4(C5)\rightarrow C6}$ tautomers has, however, a different distribution than that in $a_{val}MC_{can}$; see Figure 5. These distributions and relative stabilities of the resulting anionic tautomers can be naturally determined in the course of quantum chemical electronic structure calculations.

What might be formation pathways for the $a_{val}MC_{N4(C5)\rightarrow C5}$ and $a_{val}MC_{N4(C5)\rightarrow C6}$ anions? We calculated barriers for the unimolecular proton transfer from $a_{val}MC_{can}$ to $a_{val}MC_{N4(C5)\rightarrow C5}$ and from $a_{val}MC_{N4(C5)\rightarrow C5}$ to $a_{val}MC_{N4(C5)\rightarrow C6}$, and the results

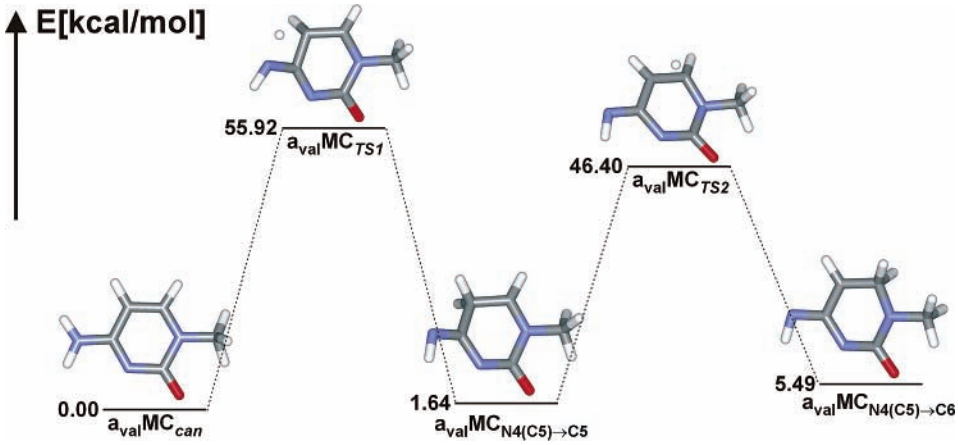

Figure 6. Transitions states for the $a_{val}MC_{can} \rightarrow a_{val}MC_{N4(C5)\rightarrow C5}$ and $a_{val}MC_{N4(C5)\rightarrow C5} \rightarrow a_{val}MC_{N4(C5)\rightarrow C6}$ tautomerizations determined at the B3LYP/6-31++G** level.

TABLE 4: Relative Electronic Energies (ΔE), Energies Corrected for Zero-Point Vibrations (ΔE_{ZPVE}), Enthalpies (ΔH), and Gibbs Free Energies (ΔG) for Stationary Points of the Proton Transfer Reactions $a_{val}MC_{can} \rightarrow a_{val}MC_{N4(C5)\rightarrow C5}$ and $a_{val}MC_{N4(C5)\rightarrow C5} \rightarrow a_{val}MC_{N4(C5)\rightarrow C6}$ Calculated at the B3LYP/6-31++G(5d) Level[a]**

	ΔE	ΔE_{ZPVE}	ΔH	ΔG	ΔE_{ZPVE}^{hydr}	ΔG^{hydr}
$a_{val}MC_{can}$	0.00	0.00	0.00	0.00	0.00	0.00
$a_{val}MC_{TS1}$	55.92	52.17	51.98	52.30	60.09	59.86
$a_{val}MC_{N4(C5)\rightarrow C5}$	1.64	2.52	2.21	2.60	−0.49	−0.39
$a_{val}MC_{TS2}$	46.40	44.17	43.73	44.48	42.19	42.22
$a_{val}MC_{N4(C5)\rightarrow C6}$	5.49	5.94	5.56	6.20	−1.11	−0.71

[a] See Figure 6 for visualization of the corresponding transition states, TS1 and TS2. The PCM model used to simulate hydration effects (ΔE_{ZPVE}^{hydr} and ΔG^{hydr}).

are summarized in Table 4 and Figure 6. In both cases the barriers exceed 40 kcal/mol. The time $\tau_{99.9\%}$ necessary to reach 99.9% of the equilibrium concentration[71] of $a_{val}MC_{N4(C5)\rightarrow C5(6)}$ in the system of reversible first-order forward and reverse reactions was found to be 6.6×10^{27} and 1.1×10^{18} s for the first and second reaction, respectively. Thus the unimolecular tautomerizations are not probable at standard conditions. Formation of the anionic tautomers with carbon atoms protonated might proceed through intermolecular proton transfers, with acidic and basic sites interacting with $a_{val}MC_{can}$. These pathways have typically lower energy barriers then intramolecular tautomerizations,[72,73] but this mechanism is beyond the scope of this project. Here we point out that dissociative electron attachment to MC_{can} follwed by a barrier-free attachment of a hydrogen atom to a carbon atom of the deprotonated MC_{can} might be an efficient pathway to the $a_{val}MC_{N4(C5)\rightarrow C5}$ and $a_{val}MC_{N4(C5)\rightarrow C6}$ tautomers. Indeed, it was demonstrated in the experiments of Illenberger et al.[74] and Märk et al.[75] that nitrogen sites of NABs are the most susceptible to dehydrogenation in the course of dissociative electron attachment

$$(NAB)_{N-H,C} + e \rightarrow (NAB)_{N-H,C}{}^{*-} \rightarrow (NAB-H)_{N,C}{}^{-} + H^{\bullet}$$

where $(NAB)_{N-H,C}$ denotes an intact NAB with a hydrogen atom attached to a nitrogen atom, $(NAB)_{N-H,C}{}^{*-}$ denotes a scattering state for an excess electron, and $(NAB-H)^{-}{}_{N,C}$ denotes a deprotonated NAB in the ground electronic state. In these experiments, the kinetic energies of excess electrons are typically in the 1−2 eV range. We have found that the hydrogen atom attachment to a carbon atom of $(NAB-H)_{N,C}{}^{-}$

$$(NAB-H)_{N,C}{}^{-} + H^{\bullet} \rightarrow (NAB)_{N,C-H}{}^{-}$$

is barrier-free in the case of the C5 or C6 position of MC deprotonated at the N4 position. As a consequence, the $a_{val}MC_{N4(C5)\rightarrow C5}$ and $a_{val}MC_{N4(C5)\rightarrow C6}$ anions might be formed.

4. Discussion

We performed the most accurate so far calculations for valence anions of various tautomers of 1-methylcytosine. The consistency of theoretical predictions at the MP2, CCSD, and CCSD(T), see Table 2, strengthens our conclusion that the considered isomers of 1-methylcytosine support vertically bound anions; see Table 2. Moreover, the anionic tautomers resulting from enamine-imine transformations are very stable, with $a_{val}MC_{N4(C5)\rightarrow C5}$ being more stable than $a_{val}MC_{can}$ by 1.0 kcal/mol in terms of ΔE_{ZPVE} at the CCSD(T)/AVDZ level of theory. These anions are, however, adiabatically unbound in the gas phase with respect to the neutral MC_{can}.

A difference in stability by 1 kcal/mol is marginal from the perspective of accuracy of current electronic structure methods, though very relevant for the distribution of various tautomers at standard conditions. For example, this difference is smaller than the accuracy of current exchange-correlation functionals, which routinely overestimate electron binding energies in valence anions[42−46] and do not predict a correct ordering of tautomers of nucleic acid bases.[33,34] The current results, however, were obtained at the CCSD(T)/AVDZ level of theory and we can judge their accuracy on the basis of previous experiences of our and other groups. The results for uracil, for which more experimental information is available than for MC, allow us to conclude that the relative energies of neutral tautomers are accurate to within 1 kcal/mol at the CCSD(T)/AVDZ level of theory.[76] The calculations for anionic dimer of formic acid, in which an excess electron is bound in a similar fashion as in valence anionic states of nucleic acid bases, allow us to conclude that the CCSD(T)/AVDZ electron binding energies are also converged to within 1 kcal/mol.[77] It is very plausible that in the gas phase the $a_{val}MC_{N4(C5)\rightarrow C5}$ anion is indeed more stable than the $a_{val}MC_{can}$ anion.

The relative stability of various anionic tautomers in water solution is more dubious. We admit that an explicit treatment of water molecules in highly correlated calculations would make the problem computationally prohibitive. At the same time we recognize that the first few water molecules might engage is specific binding with the anion of MC that is not included in a continuum model, such as PCM. Thus the PCM results presented in Table 3 should be viewed cautiously. We used the PCM solvation model to provide a preliminary insight into the stability

upon hydration. These and the gas phase results are consistent: the tautomers with a proton transferred to a carbon atom are the most stable. Moreover, these tautomers are characterized by significantly larger values of VDE than the canonical and conventional rare tautomers. We would welcome experimental verification of our predictions, both in the gas phase and in condensed phases.

The highest stability of the anionic tautomers with a carbon atom protonated implies that excess electrons might affect the structure of DNA and RNA by favoring these very rare tautomers of nucleic acid bases. An important feature of the $a_{val}MC_{N4(C5)\rightarrow C5}$ and $a_{val}MC_{N4(C5)\rightarrow C6}$ anionic tautomers of MC is that the six-member ring structure is unstable for the neutral species. The six-member ring collapses without a barrier to a linear and a bicyclo structure, respectively; see Figure 3, which might be viewed as lesions to DNA or RNA. The transformed forms of neutral MC could affect the fidelity of replication, transcription, and translation.

There is an open question how the anionic tautomers resulting from the enamine-imine transformations would act in condense phases. Thermodynamically, they are probably the most stable valence anions, and therefore they are expected to dominate the distribution of various tautomers. It is known, however, that the environment plays an important role in formation of anionic species. For instance, distributions of anions between the cytosine and thymine moieties is different is single-stranded and double-stranded DNA, which was interpreted in terms of intrastrand and interstrand transfer of holes and electrons in the former and latter, respectively.[48] There are also significant differences in the distribution of counterions between single-stranded and double-stranded DNA as well as RNA, which may affect the relative stability of various anionic tautomers of NABs embedded in RNA or DNA.[78] Finally, the anionic tautomers with carbon atoms protonated might engage in chemical reactions with the environment. We have not explored these reactions yet, but they may provide doorways to the formation of lesions in DNA. If true, this would make the anionic tautomers transient but biologically relevant. To conclude, the new anionic tautomers might contribute to the chemistry of RNA and DNA exposed to low-energy electrons. This problem will be at the center of our future studies.

5. Summary

It is well established that cytosine in the gas phase does not support a bound valence anionic state at the geometry of the neutral[24] and that the anion of canonical tautomer is adiabatically unbound with respect to the neutral.[26] One might expect only a smaller electron affinity in 1-methylcytosine due to an electron donating effect of the methyl group. A question that we addressed in this study was whether other tautomers, in particular those with carbon atoms protonated, would display a larger electron affinity than the canonical tautomer.

We prescreened 14 tautomers/rotamers of anionic 1-methylcytosine at the B3LYP/6-31++G** level. The five most stable anionic isomers were further studied at the second-order Møller−Plesset/AVDZ level and final energies were determined at the coupled cluster level to theory with single, double, and perturbative triple excitations. Our main findings are as follows:

1. The canonical (amino-oxo) tautomer of neutral MC is the most stable in terms of energy, enthalpy, and Gibbs free energy. The imino-oxo $MC_{N4(N3)\rightarrow N3}$ tautomer is only 1.4 and 1.3 kcal/mol less stable in terms of energy and Gibbs free energy, respectively.

2. Amino-oxo and imino-oxo tautomers support vertically bound valence anionic states. The most stable valence anion is $a_{val}MC_{N4(C5)\rightarrow C5}$, which is an imino-oxo tautomer with a hydrogen atom transferred from $N4H_2$ to C5. It is characterized by a VDE of 2.12 eV. This structure is unrelated to any of the most stable tautomers of neutral MC. The anion $a_{val}MC_{N4(C5)\rightarrow C5}$ is more stable by 1.0 kcal/mol than the anion $a_{val}MC_{can}$. The latter is characterized by a VDE of only 0.31 eV.

3. Another low-lying anionic tautomer with a carbon atom protonated, $a_{val}MC_{N4(C5)\rightarrow C6}$, is 3.6 kcal/mol less stable than $a_{val}MC_{can}$ and its VDE amounts to 3.60 eV.

4. The two conventional imino-oxo tautomers with N3 protonated: $MC_{N4(N3)\rightarrow N3}$ and $MC_{N4(C5)\rightarrow N3}$ also support vertically bound valence anionic states with VDEs of 0.18 and 0.11 eV, respectively. They are, however, less stable than the anion of the canonical tautomer by 3.2 and 6.3 kcal/mol, respectively.

5. All valence anions are adiabatically unbound in the gas phase with respect to the neutral MC_{can}.

6. Within the PCM model of hydration, all five valence anions become adiabatically bound. The tautomer $a_{val}MC_{N4(C5)\rightarrow C6}$ becomes the most stable with a VDE of 6.29 eV. The second most stable anion $a_{val}MC_{N4(C5)\rightarrow C5}$ is less stable by 0.7 kcal/mol and is characterized by a VDE of 4.83 eV. The anion of the canonical tautomer comes third and very close in stability to $a_{val}MC_{N4(C5)\rightarrow C5}$ with a VDE of 2.75 eV.

7. An important feature of the N4→C5 and N4→C6 tautomers of MC is that the six-member ring structure is unstable for the neutral species. It collapses without a barrier to a linear and a bicyclo structure, respectively. These transformed forms might be viewed as lesions to MC. They could further modify the structure of DNA and RNA and may affect the fidelity of replication, transcription, and translation.

8. The barriers for unimolecular proton transfer from $a_{val}MC_{can}$ to $a_{val}MC_{N4(C5)\rightarrow C5}$ and from $a_{val}MC_{N4(C5)\rightarrow C5}$ to $a_{val}MC_{N4(C5)\rightarrow C6}$ exceed 40 kcal/mol. Thus unimolecular tautomerizations are not probable at standard conditions. Formation of the "very rare" anionic tautomers might proceed through intermolecular proton transfers, with acidic and basic sites interacting with $a_{val}MC_{can}$. Another possibility is a two-step process, with the dissociative electron attachment to MC_{can} followed by a barrier-free attachment of a hydrogen atom to a carbon atom of the deprotonated MC_{can}.

Our recent results for uracil,[76] guanine,[79] and tymine[80] indicate that valence anions of other nucleic acid bases also favor tautomers resulting from the enamine-imine transformations. In the case of guanine, uracil, and thymine we found adiabatically bound valence anionic states, which have been pursued for years by many experimental and computational groups. For instance, guanine, which is believed to have the *smallest* electron affinity among nucleic acid bases, has tautomers that are adiabatically stable by ca. 8 kcal/mol. This adiabatic stability is much larger than inherent uncertainties of the CCSD(T)/AVDZ calculations that we performed.

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AC06-76RLO 1830. NWChem Version 4.6, as developed and distributed by Pacific Northwest National Laboratory, P.O. Box 999, Richland, WA 99352 USA, and funded by the U.S. Department of Energy, was used to obtain some of these results.

Supporting Information Available: Structures and relative stability of 14 tautomers/rotamers of neutral and anionic 1-methylcytosine considered in this study at the B3LYP/6-31++G** level, energies and thermodynamic corrections for the most stable neutral and anionic tautomers of 1-methylocytosine, the energies calculated at the CCSD(T)//MP2 level with the AVDZ basis set, the thermal corrections calculated at the MP2 level for $T = 298$ K and $p = 1$ atm, complete refs 23, 58, 68, and 69. This material is available free of charge via the Internet at http://pubs.acs.org.

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