Effects of Ionization, Metal Cationization and Protonation on 2′-Deoxyguanosine: Changes on Sugar Puckering and Stability of the N-Glycosidic Bond

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Received: October 24, 2005; In Final Form: December 22, 2005

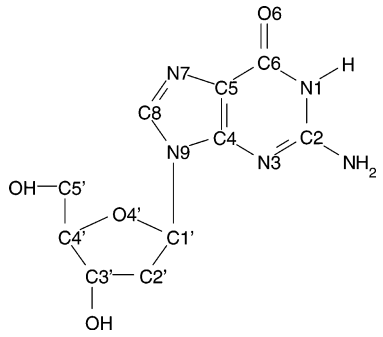
The influence of oxidation, protonation, and metal cationization with Cu^+ and Cu^{2+} on the strength of the N-glycosidic bond in 2′-deoxyguanosine has been studied by means of quantum chemical calculations. In all cases, the N9−C1′ bond distance increases (0.03−0.06 Å) upon introducing positive charge in the guanine moiety, the observed variations being more important for the dicationic systems. Binding energies show that the effect of X^{n+} in guanine hinders the homolytic dissociation, whereas it largely favors the heterolytic process. With respect to the deoxyribose ring, it has been found that metal binding, oxidation, and protonation do not significantly change the values of the phase angle of pseudorotation *P*. However, the glycosyl torsion angle χ varies considerably (from 242.0° to 189.8°) as a consequence of a stabilizing guanine−sugar (H8−O4′) interaction due to the increase of acidity of guanine C8−H8 upon cationization.

1. Introduction

Deoxynucleosides are the building blocks of DNA, and they consist of a nucleobase and a deoxyribose ring linked by the N-glycosidic bond. The cleavage of this bond is a process of great importance for the stability of DNA because it implies the release of a nucleobase, which may lead to the loss of genetic information and, thus, cause mutations in the DNA sequence. Moreover, the cleavage of this bond is involved in the so-called base excision repair (BER) pathways. The enzymes responsible of BER pathways are DNA glycosylases, which recognize damaged bases and excise them from DNA by hydrolyzing the N-glycosidic bond between the nucleobase and the sugar moiety,[1] leading to apurinic or apyrimidinic sites (AP sites). Depurination and depyrimidation can also occur spontaneously or be induced by chemical damage to DNA.[2]

Due to the biological relevance of the N-glycosidic bond, many works have studied the enzymatic processes carried out by glycosylases,[3−8] making special emphasis on the mechanistic aspects, by using kinetic isotopic effects, and on the role of catalytic residues. In addition, in the last 30 years many experimental nonenzymatic studies have analyzed the intrinsic chemical properties of nucleosides glycosidic bond hydrolysis and evaluated the influence of environmental and chemical agents such as pH, metal cations, and alkylating compounds.[9−16] Results show that both protonation and cationic alkylation largely activate purine bases making the leaving group more electron deficient and, thus, better accommodating the increased electron density that develops during the glycosidic bond cleavage. On the other hand, sugar puckering has also been invoked to influence the hydrolysis of N-glycosidc bond.[17] The first principles calculations can help in understanding the fundamental properties of the N-glycosidic bond as well as the changes induced by protonation or metal cation binding. However, theoretical papers on this subject are scarce,[18−21] even though there seems to be an increasing interest in this area.

SCHEME 1: 2′-Deoxyguanosine



Moreover, since oxidative damage to nucleobases is a major pathway for DNA cleavage,[22] it is also interesting to evaluate the effects of oxidation on the N-glycosidic bond stability.

Theoretical calculations on model systems can provide fundamental information on the intrinsic properties of these systems, which may be useful to understand more complex situations. The aim of the present work is to evaluate by means of computational studies how the strength of the N-glycosidic bond in 2′-deoxyguanosine (Scheme 1) is influenced by the effect of oxidation and some cationic species such as H^+, Cu^+, and Cu^{2+}. We have chosen this specific nucleoside because, among the four bases that are present in DNA, guanine is the easiest oxidized because of its lowest ionization potential,[23] and it is also the one which preferably interacts with transition metal cations[24,25] both with N7 and O6 of guanine.[26,27] Special attention will be paid to the changes induced on the glycosidic bond orientation (χ) and sugar puckering (P). We expect that this study will provide useful information since these changes may not only influence the hydrolysis mechanism of the N-glycosidic bond but can also affect other properties such as the N9−C1′ chemical shielding tensors, as recently shown.[28]

2. Computational Details

Full geometry optimizations and harmonic vibrational frequencies have been performed using the nonlocal hybrid three-

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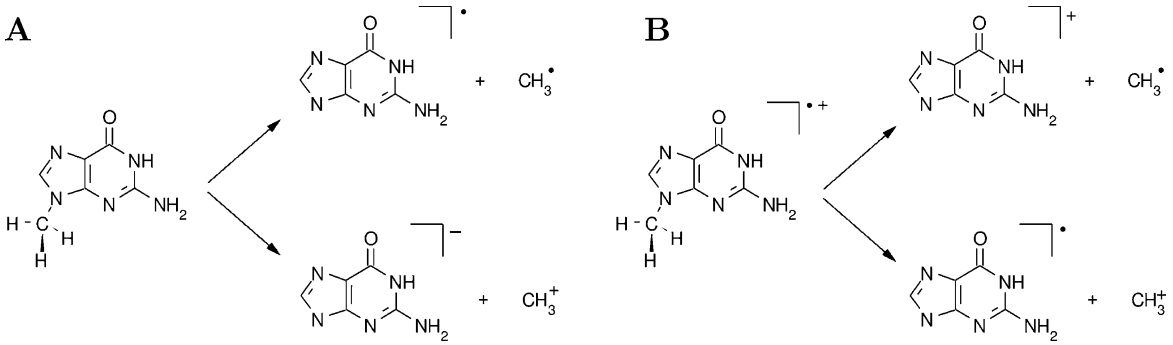
10.1021/jp056089i CCC: $33.50
Published on Web 02/23/2006

SCHEME 2: Homolytic (top) and Heterolytic (bottom) Dissociations of the N9−C_{methyl} Bond in GCH_3 (A) and $GCH_3^{\bullet+}$ (B)



parameter B3LYP density functional approach with the following basis set. For C, N, O, and H we have used the standard 6-31++G(d,p) basis set. The Cu basis set is based on the (14s9p5d) primitive set of Wachters,[29] supplemented with one s, two p, and one d diffuse functions[29,30] as well as one f polarization function,[31] the final contracted basis set being (15s11p6d1f)/[10s7p4d1f]. Hereafter, this basis set will be referred as basis 1. However, to confirm the reliability of B3LYP/basis 1 results, we have also performed single-point calculations, at the B3LYP equilibrium geometries, using the post-Hartree−Fock MP2 and highly correlated CCSD(T) methods for the model 9-methylguanine (GCH_3) system, which differs from 2′-deoxyguanosine in having a methyl group instead of a deoxyribose ring attached to position N9. In the MP2 and CCSD(T) calculations, we have correlated all the electrons except the 1s-like ones of C, N, and O. In addition, to analyze the effect of further enlarging the basis set, we have performed calculations with the 6-311++G(2df,2pd) basis for C, N, O, and H and the (15s11p6d2f1g)/[10s7p4d2f1g] one for Cu^{2+} (basis 2). With this basis, we have only performed single-point calculations at the MP2 level of theory but not at the CCSD(T) one due to its high computational cost.

In all cases, atomic charges and spin densities have been obtained from natural population analysis.[32] All calculations have been performed with the Gaussian 03 package[33] and are spin unrestricted for open shell systems.

Solvent effects were estimated for some of the systems using the CPCM polarizable conductor calculation model[34,35] as implemented in Gaussian03. These calculations were performed with the base B1 at the gas-phase optimized geometries and considering water as solvent.

3. Results and Discussion

3.1. 9-Methylguanine. First, we will present the results corresponding to GCH_3 and $GCH_3^{\bullet+}$ model systems. These calculations will allow us to calibrate the methods used for the 2′-deoxyguanosine larger system and to get a deeper insight on the considered processes. Homolytical dissociation of GCH_3 leads to guanine ($G^{\bullet}$) and methyl ($CH_3^{\bullet}$) radicals, whereas if the cleavage is heterolytic, the obtained products are the guanine anion (G^-) and methyl cation (CH_3^+) (Scheme 2A). The heterolytic cleavage that would produce a guanine cation and a methyl anion is a less favorable process and has not been taken into account.

For analogy, we will refer to homolytic dissociation of $GCH_3^{\bullet+}$ to the one which leads to a guanine cation (G^+) and a methyl radical ($CH_3^{\bullet}$), and heterolytic dissociation to the one producing a guanine radical ($G^{\bullet}$) and a methyl cation (CH_3^+) (Scheme 2B). No constraints have been imposed during the optimization process, and all structures belong to the C_1 symmetry group due to pyramidalization of the amino group. However, deviations from planarity are so small that, for clarity in the discussion, we will refer to σ (a′) and π (a″) molecular orbitals, as in C_S symmetry.

Homolytic dissociation of the N9−C_{methyl} bond, which is a σ bond, would, in principle, lead to an unpaired electron in the σ hybrid orbital (sp^2) of N9. However, results show that the unpaired electron in guanine is a π (a″) type orbital, similar to the HOMO orbital of GCH_3 (Figure 1). On the other hand, population analysis allows us to calculate the number of σ and π electrons before and after the dissociation, the computed numbers for π electrons being 13.9 and 12.9 for GCH_3 and 12.9 and 11.9 for $GCH_3^{\bullet+}$, respectively. Thus, the loss of a π type electron during the cleavage in both systems seems to indicate that the homolytic dissociation involves a crossing between two electronic states, as it is represented in Scheme 3. Calculations at different N9−C_{methyl} bond distances indicate that this crossing takes place close to 2.75 Å.

Table 1 shows the dissociation energy values obtained with different methods and basis. First, it can be noticed that no significant differences exist between the double-ζ and triple-ζ basis sets. On the other hand, all methods provide very similar values for the heterolytic dissociation of the neutral system, the computed differences being less than 1.5 kcal/mol. However,

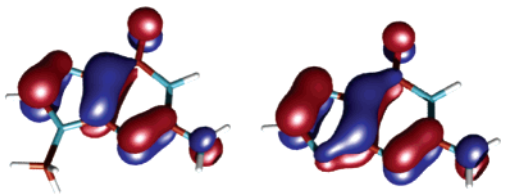


Figure 1. HOMO (left) and SOMO (right) *i* orbitals of GCH_3 and $G^{\bullet}$, respectively.

SCHEME 3: Crossing between Electronic States in the Homolytic Dissociation

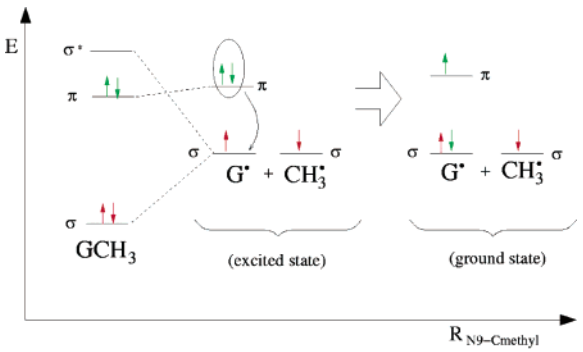


TABLE 1: Dissociation Energies for Homolytic and Heterolytic Cleavages (kcal/mol).

	Neutral System			
	$GCH_3 \rightarrow G^{\bullet} + CH_3^{\bullet}$		$GCH_3 \rightarrow G^{-} + CH_3^{+}$	
	basis 1	basis 2	basis 1	basis 2
B3LYP	77.4	77.0	236.6	237.6
BHLYP	78.4	77.9	236.7	237.6
MP2	96.1	96.9	236.0	239.2
CCSD(T)	83.6		235.2	
	Radical Cation			
	$GCH_3^{\bullet+} \rightarrow G^{+} + CH_3^{\bullet}$		$GCH_3^{\bullet+} \rightarrow G^{\bullet} + CH_3^{+}$	
	basis 1	basis 2	basis 1	basis 2
B3LYP	86.8	85.5	132.2	132.7
BHLYP	88.3	86.5	130.9	131.3
MP2	75.2	78.6	127.1	129.6
CCSD(T)	81.3		131.3	

for the homolytic cleavage MP2 overestimates the dissociation energy by nearly 12 kcal/mol with respect to CCSD(T), while B3LYP gives a closer value to the CCSD(T) one; the difference being about 6 kcal/mol. It should be mention, however, that in the MP2 calculations the $\hat{S}^2$ expectation value of the reference wave function of $G^{\bullet}$ is 0.868, significantly larger than the 0.75 value corresponding to a pure doublet state. This spin contamination accounts for the overestimation of the dissociation energy found at the MP2 level. The opposite situation occurs for the homolytic dissociation of $GCH_3^{\bullet+}$, for which the MP2 value is about 6 kcal/mol lower than the CCSD(T) one. In this case, this is due to the fact that the $GCH_3^{\bullet+}$ reactant is the species that presents larger spin contamination, the $\hat{S}^2$ expectation value being 0.948. For the heterolytic dissociation, differences between MP2 and CCSD(T) calculations are somewhat smaller because now both the $GCH_3^{\bullet+}$ and reactant and $G^{\bullet}$ product present similar spin contamination. Despite that, also in this case the B3LYP method provides better results than MP2 as compared to the highly correlated CCSD(T) method. This is in agreement with previous studies, which have shown that for certain radical cation systems with significant spin contamination, the Möller−Plesset perturbation expansion converges slowly. Thus, methods such as UMP2 should be taken with caution.[36−38]

Overall, the results show that for both homolytic and heterolytic processes the dissociation energies calculated with B3LYP are much closer to CCSD(T) than the MP2 ones. Moreover, the effect of further enlarging the basis set is small; therefore, the B3LYP method with the small basis set (basis 1) will be used in the following study of our target system.

3.2. 2′-Deoxyguanosine. 3.2.1. Structure. Figure 2 shows the system considered along this study. Note that in order to avoid spurious intramolecular hydrogen bonds, which could lead to different conformers from the one desired, we have taken a slightly modified 2′-deoxyguanosine, in which the hydroxyl group in C3′ has been substituted by OCH_3. From now on, we will refer to this modified system as 2′-deoxyguanosine (dG).

Some considerations regarding to the conformational properties of the system must be kept in mind. First of all, one should consider the puckering of the ribose, which depends on its five endocyclic torsion angles. Even though a great number of conformers are possible depending on the values of these angles, it is known that the furanose ring in nucleosides occurs in two ranges of conformations, usually referred to C(2′)-endo and C(3′)-endo forms[39] (Scheme 4). However, in 2′-deoxyguanosine the lowest energy conformer is C(2′)-endo.[40] Thus, this is the one considered along this study. In addition, all calculations have been performed assuming the anti orientation of the

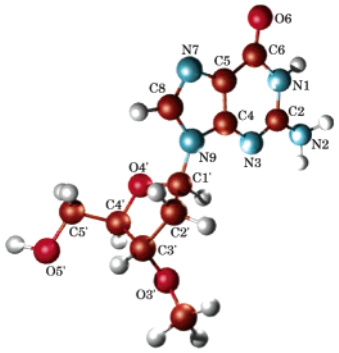


Figure 2. 2′-Deoxyguanosine considered along the study.

SCHEME 4: C(3′)-endo (left) and C(2′)-endo (right) Conformations in a Five-Membered Ring

TABLE 2: Endocyclic Torsion Angles $\tau_0 - \tau_4$, Phase Angle of Pseudorotation *P*, and Glycosyl Torsion Angle χ (in deg) for the Different Systems

X	τ_0	τ_1	τ_2	τ_3	τ_4	*P*	χ
ϕ	−28.4	37.0	−31.4	15.8	7.8	149.3	242.0
$\bullet+$	−27.2	38.1	−33.8	19.5	4.5	154.2	202.3
Cu^+	−26.8	37.8	−33.7	19.5	4.2	154.5	195.8
H_{N7}^+	−26.7	38.0	−34.1	20.1	3.7	155.3	190.4
$H_{N7}^+ H_{O6}^+$	−26.2	39.2	−36.2	22.8	1.6	158.4	189.8
Cu^{2+}	−22.2	34.5	−32.8	21.4	0.0	160.8	196.6

glycosyl torsion ($180° \leq \chi \leq 270°$, where $\chi = \phi$(O4′−C1′−N9−C4))[40] (Table 2), since this is the preferred one and also that found in the DNA structure.

Geometrical changes on dG due to oxidation, protonation, and cationization are different for each fragment (i.e., the rings of guanine and the deoxyribose). In the former, variations basically occur on bond distances, whereas in the latter the endocyclic torsion angles are the main modified parameters. We will then discuss separately both kinds of geometrical changes.

Figure 3 shows the optimized structures for the different systems as well as the most relevant bond distances of guanine. Variations with respect to neutral dG upon oxidation, protonation, and metal cationization are due mainly to two factors: (i) the electrostatic effects due to the presence of a positive charge, which produce changes in the σ and in the more polarizable π density, and (ii) the oxidative effects, which mainly induce changes in the π distribution since the orbital from which the electron is withdrawn is of π nature (see the HOMO in Figure 1).

To study both effects separately, two different cases will be discussed in detail: first, we will analyze the interaction of Cu^+ with dG (dG(Cu^+)), which mainly involves electrostatic effects, and second, we will study the radical cation of dG (dG($^{\bullet+}$)), for which oxidative effects are the most important ones.

In the case of dG(Cu^+), the C6−O6 bond becomes longer ($\Delta d = 0.033$ Å) since the presence of the Cu^+ atom polarizes the carbonylic bond in such a way that O6 transfers a certain amount of electron density; consequently, a loss of double bond character is produced. This behavior can be interpreted by means of ressonant structures, as it is shown in Scheme 5. As a result of this lengthening, the contiguous bonds (C6−C5 and C6−N1) become shorter ($\Delta d_{C6-C5} = -0.031$ Å and $\Delta d_{C6-N1} = -0.045$ Å) and C2−N1 becomes longer ($\Delta d_{C2-N1} = 0.023$ Å). It is also noticeably that Cu^+ binding induces a shortening of the

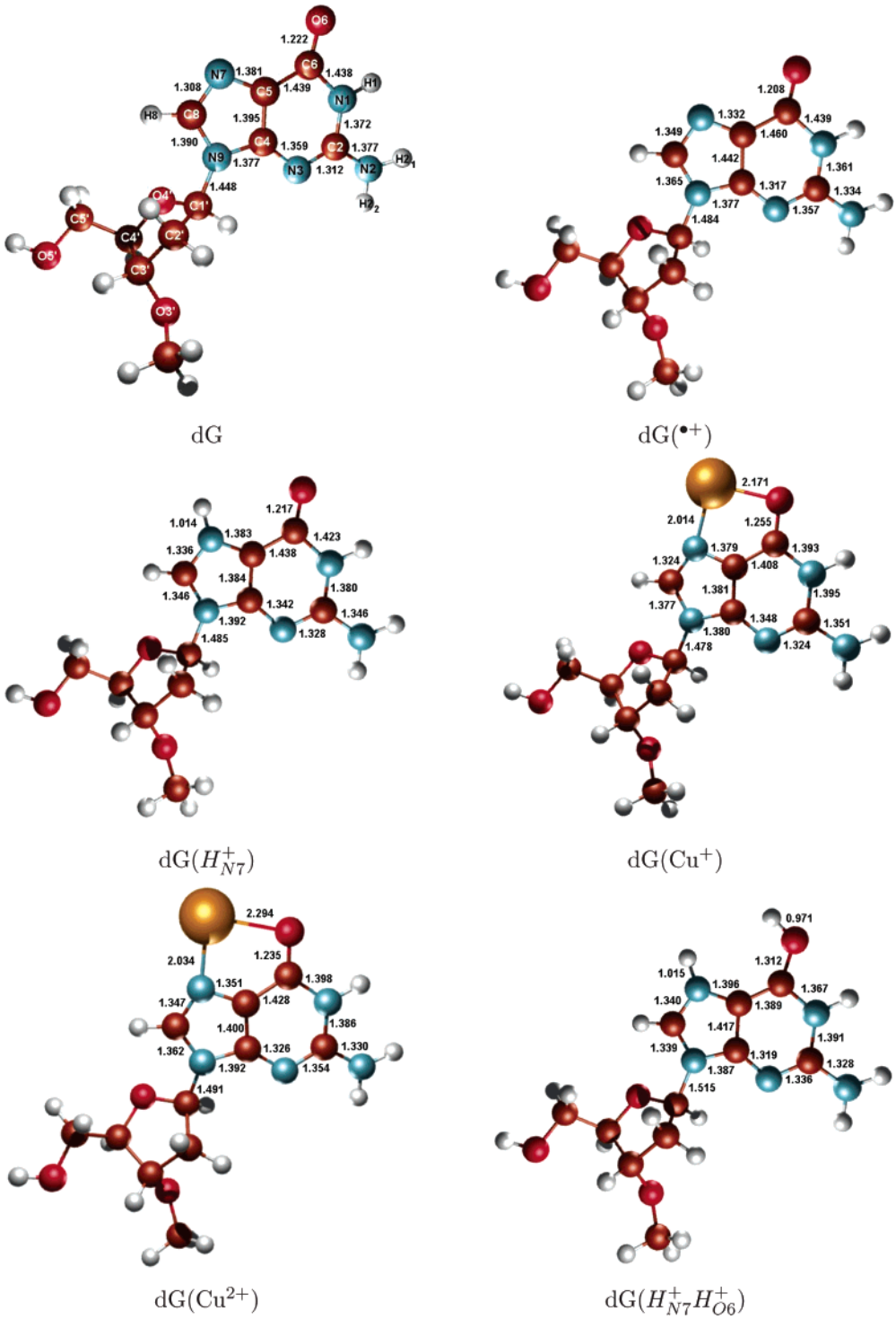


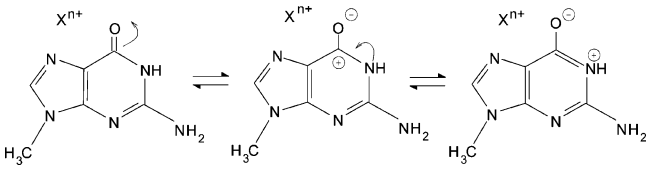
Figure 3. Optimized geometries and their most relevant bond distances (in Å).

C2−N2 bond length of −0.031 Å, which is accompanied by an increase of planarity of the group NH_2. As expected major changes occur on the six-membered ring of guanine, the bond distances of the five-membered rings change by less than 0.015 Å.

Oxidation removes a π electron from the aromatic system of guanine. Thus, for dG(•+), the most important variations on bond distances, as compared to the neutral system, are related to the nodal properties of the HOMO of dG. That is, those bonds that imply centers with a bonding contribution in the HOMO orbital increase (e.g., $\Delta d_{C2-N3} = 0.045$ Å, $\Delta d_{C4-C5} = 0.047$ Å, and $\Delta d_{N7-C8} = 0.041$ Å), whereas those in which the HOMO is antibonding undergo shortening (e.g., $\Delta d_{N3-C4} = -0.042$ Å, $\Delta d_{C5-N7} = -0.049$ Å, and $\Delta d_{C6-O6} = -0.014$ Å). It should also be pointed out that alterations on the π electron density may induce modifications on the σ electron density polarizing it. So, it is not easy to totally separate the geometrical changes due to each effect. In fact, except the two cases dG(Cu^+) and dG(•+) discussed above, all the other systems undergo variations that are a consequence of both electrostatic and oxidative effects simultaneously.

The interaction of dG with Cu^{2+} in dG(Cu^{2+}) is an interesting case in which the metal cation oxidizes the system, leading to a formal Cu^+ atom and a radical cation on the guanine rings.

SCHEME 5: Ressonant Structures Involving the Carbonylic Bond



There are some evidences that confirm this fact: first, the spin density on the Cu atom is not 1, as we would expect for a d^9 species but is 0.01 instead, which corresponds to Cu^+; second, considering that the more positive the cation is and, thus, the smaller is its radius, we would expect a shorter distance for $Cu^{2+}-O6$ than for Cu^+-O6. However, the opposite case is observed ($d_{Cu^{2+}-O6} = 2.294$ Å and $d_{Cu^+-O6} = 2.171$ Å) because of the repulsion between the radical cation on guanine and the formal Cu^+.[41,42] In fact, variations on bond distances in dG-(Cu^{2+}) follow the same tendencies as in dG($^{\bullet+}$) as a consequence of the oxidative effects, with the exception of the carbonylic bond, which becomes longer ($\Delta d_{C6-O6} = 0.013$ Å) due to the electrostatic interaction between the metal cation and the O6 atom. The protonated (dG(H_{N7}^+)) and diprotonated (dG-(H_{N7}^+ H_{O6}^+)) systems are special cases, because actually the proton bonding is covalent, and the charge is delocalized all over the ring.

Regardless of the specific changes occurring in each particular case, some general trends are found among all the positively charged systems. First, the C2−N2 bond shortens because the electron-donating N2 atom tends to compensate the electron deficiency on the rings. As a consequence of the higher conjugation of the π electrons in N2 over the aromatic system, the degree of pyramidalization of the amino group decreases as compared to the neutral system dG. We can measure this degree of pyramidalization by means of the $H2_1-H2_2-N2-C2$ dihedral angle, which would be 180° for a completely planar amino group. For the dG neutral system, the computed value $\phi = 140°$ indicates significant pyramidalization, while for the charged systems the value approaches 180: $\phi(dG(Cu^+)) = 168°$, $\phi(dG(H_{N7}^+)) = 175°$, $\phi(dG(^{\bullet+})$, $dG(Cu^{2+})$, $dG(H_{N7}^+H_{O6}^+)) = 179°$.

Second, and most important, in all cases the N9−C1′ bond distance increases upon cationization, the observed variations correlating to the positive amount of charge X^{n+} introduced in the system. Thus, these results seem to indicate that the presence of positive charge in guanine generated either through oxidation, protonation, or metal cationization weakens the N-glycosidic bond.

With respect to the deoxyribose ring, the geometrical parameters that undergo some changes are the τ_0, τ_1, τ_2, τ_3, and τ_4 angles, which correspond to endocyclic torsion angles about O4′−C1′(τ_0), about C1′−C2′(τ_1), about C2′−C3′(τ_2), and so on in a clockwise manner. Depending on the relationship between these angles, a great number of conformations are possible for a given five-membered ring. The concept of pseudorotation *P* (eq 1) as described in ref 39 has been used to establish the conformation in our systems. According to this definition, values of *P* between 0° and 36° correspond to C(3′)-endo conformations, while those between 144° and 180° correspond to C(2′)-endo (note that in cases where τ_2 is negative one should add 180° to the calculated value of *P*):

$$\tan P = \frac{(\tau_4 + \tau_1) - (\tau_3 + \tau_0)}{2\tau_2(\sin 36 + \sin 72)} \qquad (1)$$

TABLE 3: Dissociation Energy Values (kcal/mol)

X	D_e (homolytic)	D_e (heterolytic)
ϕ	70.9	144.0
H_{N7}^+	82.0	44.3
$\bullet+$	83.1	42.5
Cu^+	84.7	58.0
Cu^{2+}	106.3	−29.2
H_{N7}^+ H_{O6}^+	114.6	−36.2

It can be shown from Table 2 that the values of *P* become higher as the positive charge increases in the system. However, in all cases the five-membered ring remains in the most stable conformation, C(2′)-endo, since the corresponding *P* values still lye within the $144° \le P \le 180°$ range. The main variations in endocyclic torsion angles are those corresponding to C2′−C3′−C4′−O4′ (τ_3, from 15.8° to 22.8°) and C3′−C4′−O4′−C1′ (τ_4, from 7.8° to 0.0°), which increase and decrease, respectively, as the positive charge increases.

Particularly striking is the change of the glycosyl torsion angle χ upon introducing positive charge in the system, the computed value decreases from 242.0° in the neutral system to 189.8° in dG($H_{N7}^+H_{O6}^+$). This variation implies a significant change in orientation between the guanine and the deoxiribose in the charged systems, which allows a stronger interaction between the H8 and O4′ atoms. In fact, the shortening of the distance H8−O4′ (from 3.008 Å in dG to 2.347 Å in dG($H_{N7}^+H_{O6}^+$)) as well as the increase of positive charge on H8 (0.226 and 0.318 in dG and dG($H_{N7}^+H_{O6}^+$), respectively) seem to indicate that oxidation, protonation, and cationization enhance the acidic character of the H8−C8 bond, thereby, promoting the formation of a weak hydrogen bond interaction.

3.2.2. Binding Energies. Dissociation energies for the two kind of processes studied are listed in Table 3. It can be observed that homolytic dissociation becomes more difficult upon introducing positive charge in guanine, the changes being more pronounced for dications. For monopositive systems, the dissociation energy increases about 11−14 kcal/mol whereas for the dipositive ones changes can be as large as 45 kcal/mol. This is due to the fact that the presence of X^{n+} polarizes the electron pair of the N-glycosidic bond toward N9 and, consequently, hinders the homolytic cleavage.

In contrast, heterolytic dissociation is highly favored by the introduction of positive charge in guanine, the dissociation energy deacreasing as much as 180 kcal/mol. As expected, the presence of X^{n+} in guanine allows a better accommodation of the negative charge produced during the heterolytic cleavage, and indeed for dicationic systems the process is so favored that dissociation energies have negative values. This results are in good agreement with the trends observed for N-glycosidic bond distances, which showed that the larger the positive charge in guanine is, the more polarized is the N9−C1′ bond and the larger the lengthening of the bond distance.

These binding energies are obviously significantly modified when the environment effects are taken into account. As expected, major effects are observed for the heterolytic dissociation of the neutral system, which decreases about 96 kcal/mol when including solvation with the continuum CPCM model. In contrast, the homolytic dissociation energy of 2′-deoxyguanosine changes only about 5 kcal/mol. As a consequence, after including solvent effects, the heterolytic dissociation becomes the most favorable process.

For the charged systems, dGH_{N7}^+ and $dG^{\bullet+}$, variations on the heterolytic dissociation energies are much smaller since bond cleavage does not produce a creation of charges but a transfer of a positive charge. For both dGH_{N7}^+ and $dG^{\bullet+}$ systems, the

heterolytic dissociation energy decreases around 15 kcal/mol. Such decrease is due to the fact that the charge is more localized in the sugar than in the 2′-deoxyguanosine. Homolytic dissociation follows the same trend, the dissociation energy decreasing also about 16 kcal/mol due to the smaller cavity of the charged system in the products. Since both processes, homolytic and heterolytic dissociations, are stabilized by solvent in the same way, the relative order between them does not change. Thus, for these two systems the heterolytic process remains the most favorable one.

Finally, it should be mentioned that solvation has not been considered for dG(Cu^+) and dG(Cu^{2+}) systems. In these cases, the introduction of the first shell of solvation is mandatory since redox behavior of copper cations is largely influenced by the coordination sphere.[41]

Despite that, the present calculations in gas phase provide the first clues on the intrinsic chemistry of these systems and may be useful for following studies focused on the hydrolysis mechanism, which could proceed by a two-step mechanism, the first one being the cleavage of the N-glycosidic bond.[3,8,43,44]

4. Conclusions

In the present work, we have evaluated the influence of oxidation, protonation, and cationization with Cu^+ and Cu^{2+} on the strength of the N-glycosidic bond in 2′-deoxyguanosine. Previous calibration using two model systems (9-methylguanine and its radical cation) has validated the use of B3LYP methodology to treat our target system.

Geometrical changes in guanine due to the presence of X^{n+} can be understood by means of electrostatic and oxidative effects and differ depending on the system. In all cases, however, the N9−C1′ bond distance increases (from 0.03 to 0.06 Å) upon introducing positive charge in the guanine moiety, the observed variations being more important for the dicationic systems.

With respect to the 2′-deoxyribose ring, it has been found that metal binding, oxidation, and protonation do not produce significant changes in the values of the phase angle of pseudorotation *P*, the C(2′)-endo conformation of the sugar remaining in all cases. However, it has been shown that the glycosyl torsion angle χ varies considerably (between 242.0° and 189.8°). This has been attributed to the appearance of a stabilizing guanine−sugar (H8−O4′) interaction due to the increase of acidity of guanine C8−H8 upon cationization.

Binding energies show that the effect of X^{n+} hinders the homolytic dissociation, whereas it favors significantly the heterolytic process to such a large extent that for the dicationic systems dissociation energy values are negative. As a consequence of these changes (sugar puckering and strength of N9−C1′), metal cation binding, protonation, and oxidation may largely influence the hydrolysis mechanism of the N-glycosidic bond in DNA. Such studies are now under development in our laboratory.

Acknowledgment. Financial support from DGICYT and DURSI, through the BQ2002-04112-C02-01 and SGR00182 projects, and the use of the computational facilities of the Catalonia Supercomputer Center (CESCA) are gratefully acknowledged. R.R.-F. acknowledges the Ministerio de Educación y Ciencia for a FPU scholarship.

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