DNA Mutations Induced by Proton and Charge Transfer in the Low-Lying Excited Singlet Electronic States of the DNA Base Pairs: A Theoretical Insight

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In the present paper, we consider the formation of rare tautomeric forms of the neutral base pairs adenine−thymine (A−T) and cytosine−guanine (C−G) in low-energy excited singlet electronic states. Ab initio calculations (6-31G basis set) have been carried out at the Hartree−Fock level of theory for the ground electronic states and using a configuration interaction among all single excitations (CIS) technique for the excited electronic states. The obtained results indicate that the double proton transfer is not a feasible process in the ground electronic states. For the excited singlet electronic states, which can be directly accessed upon photoexcitation, the excitation energy is localized in the π system of one of the monomers of the pair. In these states, especially in the A−T base pair, the double proton transfer becomes energetically more accessible. However, it is unlikely that the rare tautomer may live long enough to perturb the duplication of the genetic code. Our theoretical results also show the existence of charge-transfer excited electronic states in both A−T and C−G base pairs. These states are found at a considerable high energy in the region corresponding to the ground-state minimum-energy configuration. These structures, which can be accessed only upon internal conversion from another excited electronic state, have a remarkable minimum of energy in the region corresponding to a single proton transfer that eventually neutralizes the charge separation induced by the electronic transition. We discuss the possibility that such metastable structures may play a key role in altering the DNA unwinding and strand separation (that is, in mutagenesis).

1. Introduction

The living world is constantly being irradiated by many different kinds of radiation. Two types of radiation are especially dangerous because they can alter DNA: ultraviolet light and the ionizing radiations (X-rays and atomic particles). Sea level sunlight is composed of wavelengths longer than 290 nm, which just barely overlap the long-wavelength absorption tail of the bases in DNA.[1] As a result of ozone depletion, the amount of the UV radiation is progressively increasing on the Earth.[2] Ultraviolet light can photostimulate the DNA, with the formation of pyrimidine dimers, most frequently between two adjacent thymine bases (which become joined by a cyclobutyl ring) in the same DNA strand, being the most common damage.[3,4] These dimers interfere with both transcription and replication of DNA. Because the damage occurs in one chain of the double helix, it can be repaired by removing the thymine−thymine dimer and recopying the missing bases from the other chain.[3]

Repair is less efficient for certain types of DNA damage than for others. However, if the harm affects the two chains of DNA it is more difficult to properly repair and can lead to mutations. As first pointed out by Watson and Crick and later by Löwdin, the double proton transfer reaction along two parallel hydrogen bonds joining the DNA chains could originate rare tautomers disturbing the genetic code, which is based on the sequence of base pairs: adenine (A)−thymine (T) and cytosine (C)−guanine (G).[5,6] This hypothesis assumes that a significant number of rare tautomers will be formed in that way and that they will remain stable during the DNA unwinding and strand separation, with the consequent loss in genetic information.

Several theoretical papers have been devoted to study the single and double proton transfer reactions along the hydrogen bonds in the ground electronic state S_0 of the neutral adenine−thymine and cytosine−guanine base pairs.[7−10] The double proton transfer process was found to be concerted or two-step depending on the level of calculation, but always with a high energy barrier. As expected, the single proton transfer reaction turned out to be less favorable than the double proton transfer one, because it produces a charge separation as a result of the formation of an ion-pair complex, while in the double proton transfer the electroneutrality of each base is preserved. On the contrary, a recent theoretical work has shown that the double proton transfer is less favorable (and it is not expected to be detected in the experiments) than the single one in monoionized Watson−Crick base pairs.[11] In fact, single proton transfer reactions for adenine−thymine and cytosine−guanine base pair radical cations are favorable processes both from a thermodynamic and a kinetic point of view, due to the increased acidity of the ionized monomer. In addition to this, the proton transfer does not imply a separation of charges in those radical cations but just a transfer of a positive charge.

In the present paper, we intend to analyze the feasibility of the formation of rare tautomers of the neutral Watson−Crick base pairs in low-energy excited singlet electronic states. As a matter of fact, excited electronic states are in the middle of the way leading from the ground electronic state to an ionized state, which exhibits an opposite behavior. To this aim, we have

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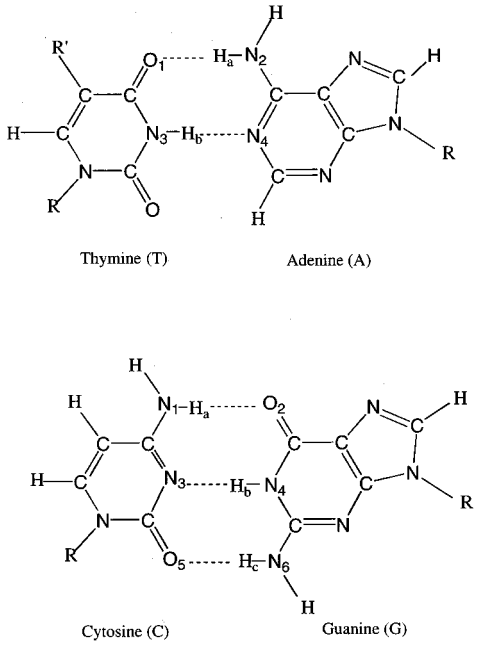
SCHEME 1



theoretically studied the single and double proton transfer reactions in several excited singlet electronic states of the neutral adenine−thymine and cytosine−guanine base pairs.

2. Methods

All calculations have been performed with the split-valence 6-31G basis set[12] within the Gaussian 94 series of programs.[13]

The ground electronic state has been studied through the restricted Hartree−Fock method (RHF). For the excited singlet electronic states, the CI all-single-excitations with a spin-restricted Hartree−Fock reference ground state (CIS) has been employed.[14] Note that, taking into account the Brillouin's theorem, the Hartree−Fock ground-state calculations are equivalent to CI among single-substituted determinants calculations. Ten spin-restricted singlet states have been included in the CIS calculation. Full geometry optimization and direct localization of transition states have been performed both at the RHF and CIS levels through the Schlegel gradient optimization algorithm using redundant internal coordinates[15] as implemented in the Gaussian 94 package. The use of a larger basis set and the introduction of the correlation energy has not been feasible here given the size of the studied base pairs and the fact that we have to deal with excited electronic states. Several previous works have shown that introduction of correlation energy with a perturbative method systematically reduces the energy barriers for the proton transfer processes in both the ground and singlet excited electronic states.[16] As discussed in the following section, the main conclusions of our work do not depend on the actual values of the energy barriers.

Analytical second derivatives of the energy with respect to Cartesian coordinates[17] have been used to obtain the nature of the stationary points; no negative eigenvalues indicate a minimum, whereas one negative eigenvalue identifies a transition state.

3. Results and Discussion

As stated in the Introduction, we will only consider the "normal" base pairs A−T and C−G. Scheme 1 depicts the hydrogen bonds of the two base pairs in their more stable configuration in the ground electronic state. In the scheme, R indicates the points where the base pair is linked to the rest of the nucleoside. R′ in thymine indicates the position of a methyl group. In our calculations, a hydrogen has been placed in these positions. This implies that, in fact, thymine has been modeled by a Uracil molecule, a change that is not likely to affect the proton transfer process. We will first deal in this section with the A−T system as the double proton transfer here follows a somewhat simpler scheme. Later on, we will carefully analyze also the C−G base pair. Finally, we will conclude by discussing the feasibility of the different processes and their possible role in mutagenesis.

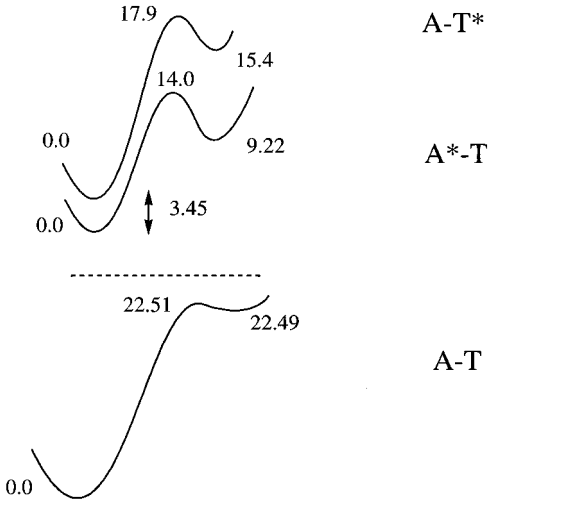


Figure 1. Schematic energy profile for the double proton-transfer reaction in the adenine−thymine base pair. A−T refers to the ground electronic state, whereas A*−T and A−T* refer respectively to the lowest excited singlet electronic state with the excitation localized in the adenine or the thymine moieties. Relative energies of the stationary points are also provided (in kcal/mol).

3.1. Adenine−Thymine (A−T) Base Pair. For this system, as shown in the upper part of Scheme 1, there are two hydrogen bonds linking both unities, $O_1\cdots H_a-N_2$ and $N_3-H_b\cdots N_4$. The depicted configuration is the more stable one, at least in the ground electronic state. The double proton transfer process has been analyzed in several low-lying electronic states. Figure 1 shows schematically the potential energy profile along the double proton transfer process in the ground singlet electronic state S_0 (indicated as A−T in Figure 1) and two excited singlet electronic states**.** Of these two, the lowest in energy is in fact the first excited singlet state S_1 and corresponds to a $\pi-\pi^*$ electronic excitation localized in the adenine moiety so that it is labeled as A*−T. The other electronic state considered is the first excited singlet state with the excitation localized in the π system of thymine and is labeled accordingly as A−T*. At the reactant configuration this corresponds to S_3. Between both excited states there is another singlet electronic state with the excitation localized in the adenine π system.

In accordance with previous results,[9] we have found that in the ground electronic state the double proton transfer takes place in a concerted way through only one transition state involving a high energy barrier of 22.51 kcal/mol. The final product has also a high energy, the whole process being endothermic by 22.49 kcal/mol. The first three rows in Table 1 show the evolution of the distances of the transferring H atoms along the three located stationary points: reactant, transition state, and product (respectively RE, TS, and PR in Table 1; a subscript A−T is used to indicate the ground electronic state). It can be seen that the two hydrogen atoms have almost transferred synchronically, as in the transition state both are very close to

TABLE 1: Main Bond Distances (in Å) for the Stationary Points Located in the A−T, A*−T, A−T*, and A^+-T^- Electronic States

	O_1-H_a	H_a-N_2	N_3-H_b	H_b-N_4
RE_{A-T}	2.02	1.00	1.02	1.86
TS_{A-T}	1.08	1.43	1.76	1.02
PR_{A-T}	1.04	1.53	1.80	1.02
RE_{A^*-T}	1.94	1.00	1.02	1.89
TS_{A^*-T}	1.20	1.26	1.75	1.03
PR_{A^*-T}	0.99	1.71	1.93	1.01
RE_{A-T^*}	1.95	1.00	1.02	1.87
TS_{A-T^*}	1.17	1.29	1.73	1.03
PR_{A-T^*}	1.00	1.70	1.86	1.01
INT_{A+T-}	0.99	2.03	1.02	1.93

their final positions. This resemblance of the transition state to the high-energy product configuration is also in good agreement with the Hammond postulate.[18] Our results are similar to those previously reported by Florián et al.[9] using a smaller basis set, though they found a lower energy barrier and also a lower endothermicity. It is important to note that as the barrier for the reverse process is only 0.02 kcal/mol at our level of calculation, it is quite unlikely that the energy well of the product may support any bound state so that the tautomerization process will not take place in the ground electronic state for the A−T base pair.

Now we analyze the results in the two excited electronic states. As already stated, Figure 1 shows the energy profile, whereas the more relevant geometrical parameters for the double proton transfer process are also given in Table 1. In both cases, the energy profile indicates a concerted process with only one transition state linking the normal tautomer (reactant) with the rare one (product). In this way, the results are qualitatively similar to the process just described for the ground electronic state. However, important numerical differences can be observed in both states; the endothermicity is much lower than that obtained in the ground electronic state. The energy barriers are also lower when considered from the reactant well. The reverse barriers from the excited product to the excited reactant are not negligible now so that the rare tautomers can probably exist (the energy well of the product in both A*−T and A−T* electronic states will support bound vibrational states). The geometries of the transition states also reflect these differences as the two hydrogens are transferring more asynchronically in both excited electronic states than in the ground electronic state. In both cases, the hydrogen atom H_b, which jumps from thymine to adenine, has already been totally transferred in the transition state, whereas the second hydrogen atom H_a is still in flight, though closer to the final destination, the O_1 atom of thymine. The Hammond postulate remains valid. Interestingly, the asynchrony suggests that adenine is a better proton acceptor than thymine, a fact well documented for the DNA bases in their ground electronic state.[19] Our results suggest that this ordering is not modified when one of the two bases is in its first excited singlet electronic state.

We also analyze the double proton transfer process upon photoexcitation to one of the considered electronic states of the A−T base pair. First of all, we have calculated the energy of the different excited electronic states at the geometry of the ground-state minimum-energy structure. This point, reached by vertical excitation, corresponds to the geometry to be accessed assuming that the electronic excitation is very fast in comparison with the nuclear reorganization (Franck−Condon principle). Obviously, vertical excitations lead to structures higher in energy than the corresponding optimized minima, implying an excess of vibrational energy in the excited electronic state. Relative energies of 10.6 and 12.6 kcal/mol over the corresponding minimum have been obtained respectively for the A*−T and A−T* excited electronic states. From these points, the energy barriers for the double proton transfer are much lower (3.4 and 5.3 kcal/mol respectively for A*−T and A−T*). It is also important to note that for the low-lying excited-state A*−T the structure corresponding to a vertical excitation has a higher energy than the product for the double proton transfer so that in this case the double proton transfer may take place through tunneling.

Up to now, we have only considered the double proton transfer process. As in the three electronic states, the process turns out to be concerted, the single proton transfer has not appeared as an intermediate step of the whole process. Several attempts to locate the product of a hypothetic single proton transfer, a zwiterionic structure with the two transferring hydrogens in one side of the dimer, have failed. This result is not surprising for the ground electronic state, as the same finding has already been reported in previous studies.[7−9] The inability to find such a product even in the excited electronic states is surprising given that for A−T radical cation a recent theoretical work has found that the single proton transfer is by far the more advantageous process.[11] A possible explanation is the reluctance of isolated neutral species to evolve into a charge separation structure, which prevents the single proton transfer process in the ground electronic state. This difficulty is not present in radical cations, where the single proton transfer only implies a displacement of a charge but no additional charge separation is produced. Because in both A*−T and A−T* states the electronic excitation is localized in one of the two monomers, there is no charge separation induced by electronic excitation so that a single proton transfer in these states would also lead to a very unsatisfactory charge separation. Things would be different if the electronic excitation produced a charge separation. That is, if the excited electronic states were of the charge-transfer type. In light of these considerations, we focused our attention on these charge-transfer excited states. Initially, we obtained promising data: the HOMO → LUMO excitation for the starting A−T geometry would lead to a charge-transfer excited state as the HOMO is localized in the adenine fragment and the LUMO in the thymine one. This excitation, which we will denote as A^+-T^-, is also to be expected prior to the A^--T^+ one, as adenine has an ionization potential lower than that of thymine.[20] However, the CIS calculation of the vertical excitation does not show the presence of a charge-transfer state among the first 10 excited singlet electronic states considered in the calculation. This does not mean that such an electronic state does not exist, but it puts a lower limit to its energy, 42.2 kcal/mol above the lowest A*−T excited singlet electronic state.

Attempts to find minimum-energy structures for a charge-transfer state also failed when exploring the regions corresponding to the reactant and product of the double proton transfer process. However, a minimum-energy structure corresponding to the A^+-T^- electronic state was located with the two transferable hydrogen atoms H_a and H_b in the thymine part. This structure is only 3.42 kcal/mol above the more stable minimum of the lowest lying A*−T excited singlet electronic state. The Mulliken charges of this structure reveal that there is almost no charge transfer between both moieties. This result confirms that a proton, and not a hydrogen atom, has been transferred in that A^+-T^- excited state and accounts for the remarkable stability of this structure, as in this case the single proton transfer fully compensates for the electronic charge separation initially brought about by the electronic excitation (as a matter of fact,

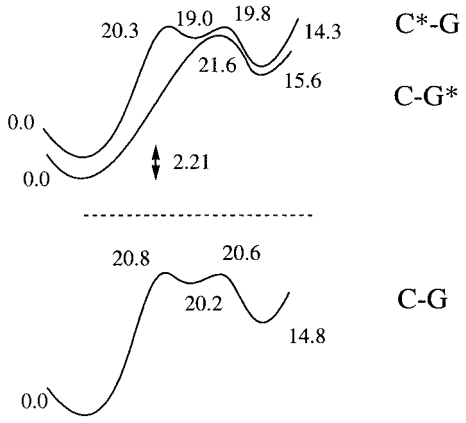


Figure 2. Schematic energy profile for the double proton-transfer reaction in the cytosine−guanine base pair. C−G refers to the ground electronic state, whereas C*−G and C−G* refer respectively to the lowest excited singlet electronic state with the excitation localized in the cytosine or the guanine moieties. Relative energies of the stationary points are also provided (in kcal/mol). Note that for clarity purposes a crossing of the energy profiles corresponding to the two electronic excited states has been artificially avoided.

TABLE 2: Main Bond Distances (in Å) for the Stationary Points Located in the C−G, C*−G, C−G*, and C⁻−G⁺ Electronic States

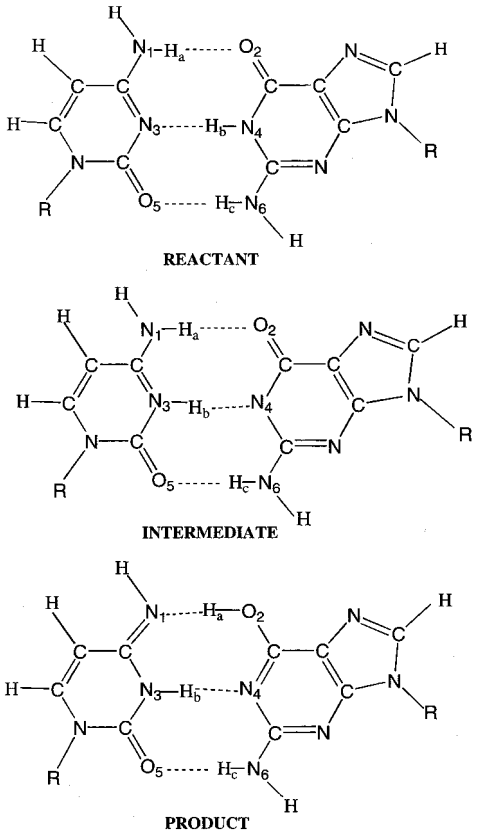
	N_1-H_a	H_a-O_2	N_3-H_b	H_b-N_4	O_5-H_c	H_c-N_6
RE_{C-G}	1.01	1.83	1.96	1.01	1.93	1.00
$TS1_{C-G}$	1.05	1.49	1.17	1.47	1.89	0.99
INT_{C-G}	1.08	1.43	1.07	1.70	2.01	0.99
$TS2_{C-G}$	1.19	1.26	1.05	1.75	2.07	0.99
PR_{C-G}	1.75	0.98	1.02	1.94	2.05	1.00
RE_{C-G*}	1.01	1.84	1.95	1.01	1.95	1.00
TS_{C-G*}	1.21	1.23	1.06	1.67	2.03	1.00
PR_{C-G*}	1.82	0.97	1.02	1.90	1.97	1.00
RE_{C*-G}	1.01	1.88	1.98	1.01	2.01	1.00
$TS1_{C*-G}$	1.02	1.69	1.20	1.38	1.97	0.99
INT_{C*-G}	1.04	1.57	1.06	1.72	2.08	0.99
$TS2_{C*-G}$	1.22	1.22	1.04	1.77	2.11	0.99
PR_{C*-G}	1.76	0.98	1.02	1.94	2.04	1.00
INT_{C-G^+}	0.99	2.12	0.99	2.05	1.86	1.01

this charge separation is the driving force of the proton transfer in this state). The main relevant bond distances of this structure, labeled as $INT_{A^+T^-}$, are given in the last row of Table 1. It is worth noting that, given that adenine becomes positively charged after photoexcittion, the proton jumps from adenine to thymine. In this way, this charge-transfer state behaves more like the recently studied A−T radical cation[11] where single proton transfer from adenine to thymine was the only favorable process. The difference is that in our case the initial A^+-T^- geometry has a very high energy and it might not exist as a stable configuration, the single proton transfer taking place without any energy barrier.

3.2. Cytosine−Guanine (C−G) Base Pair. The generic structure of the C−G dimer is shown in Scheme 1 above. In this case, there are three hydrogen bonds linking the two bases so that now there are three hydrogen atoms (labeled H_a, H_b, and H_c) to be considered as candidates to the transfer between the two bases. After preliminary calculations, we discarded the triple proton transfer as a not competitive process so that we restrict our study to the double proton transfer.

The corresponding theoretical results are presented in Figure 2 and Table 2. As in the A−T case, the figure schematically depicts the energy profile for the whole process in the ground and two low-lying excited singlet electronic states. The positions of the hydrogen atoms linking the base pair are given in Table 2 for the stationary points (minima, intermediates, and transition states) in the different electronic states to be studied here.

SCHEME 2



As in the A−T case, we first consider the ground electronic state. The results, schematically shown in Figure 2 and Scheme 2 indicate now a stepwise mechanism with a first transition state and a zwitterionic intermediate where the "central" H_b has been transferred from guanine to cytosine (see Scheme 2). In a second stage, H_a is transferred from cytosine to guanine through a second transition state to obtain the final rare tautomer. The whole process is endothermic by 14.8 kcal/mol. The intermediate is found at a quite high energy, 20.2 kcal/mol, and it is only slightly below the two transition states (found at 20.8 and 20.6 kcal/mol, respectively). Therefore, the intermediate may not survive more than one vibrational period. That is, the potential energy well of the intermediate is so flat that it probably does not support bound vibrational states. Our results are in qualitative agreement with the ones obtained by Florián et al.[10] with a slightly larger basis set (6-31G*). The fact that the first proton jumps from guanine to cytosine also agrees with the higher proton affinity of cytosine. This agrees with the recent result obtained using a high level of computation[21] though the experimental data is controversial at this point.[19,22] Parenthetically we note that in both A−T and C−G cases the hydrogen atom of the N−H···N fragment is the first to be transferred. In the A−T system this is the shortest H-bond, but for C−G system it is the largest one. Last but not least, we note that for the C−G system the rare tautomer arising from the double proton transfer is not only more energetically accessible than in the A−T case but the reverse process has now a nonnegligible barrier so that once the tautomer has been formed it may well survive for a relative long period of time (Figure 2).

Now we can proceed to analyze the excited singlet electronic states. As in the A−T system, we have first considered the lowest singlet states obtained through a $\pi-\pi^*$ electronic

excitation localized in each DNA base unit. In this way, the C−G* and C*−G excited states have been studied being, respectively, the first and second excited singlet electronic states. The energy profile for the double proton transfer and the evolution of distances of the hydrogen bonds along the stationary points localized for each system are presented in Figure 2 and Table 2. Figure 2 clearly shows a difference between both excited electronic states. For the lowest C−G* pair, the energy profile indicates a process in only one step, whereas for the C*−G pair the two-step energy profile is similar to that occurring in the ground electronic state. As Figure 2 schematically indicates and Table 2 numerically reports, the unique transition state for the C−G* pair greatly resembles the second transition state of the two-step process so that the two hydrogens are also transferring quite asynchronically in the C−G* electronic state. Contrary to the A−T system, it seems that the photoexcitation does not make the double proton transfer process much more easy in comparison with the ground electronic state. The energy barrier for the C−G* excited state is slightly higher. For the C*−G pair, the energies of the two transition states and of the intermediate, relative to the corresponding reactant minimum, are only about 1 kcal/mol smaller than the values found for the ground electronic state. However, at this point it must be reminded that to analyze the feasibility of any reaction in a given electronic state accessed upon photoexcitation, the more relevant result, taking into account the Franck−Condon principle, is the relative energy of the vertical excitation. For the C−G* state, the vertical excitation reaches a point located at 7.35 kcal/mol above the absolute minimum of this state, whereas for the C*−G case, the value is slightly larger, 9.95 kcal/mol. Thus, contrary to the A−T results, the final product in each case of C−G is still higher in energy so that the double proton transfer cannot directly occur even if a tunneling mechanism is invoked.

Beside that we have been able to identify the product of a single proton transfer as a minimum of energy in two electronic states, these structures are probably not stable if the zero-point energy is included. Again, to stabilize the product of such a single proton transfer, a charge-transfer electronic excitation is needed. As the ionization potential of guanine is lower and the HOMO of the neutral base pair at its minimum-energy conformation is also localized in the guanine moiety, the lowest charge-transfer excited singlet electronic state to be expected is of the C^-−G^+ type. In this case, the CIS calculation of the ground-state minimum energy configuration discloses the existence of such a C^-−G^+ state, though its energy (35.34 kcal/mol) lies well above that of the first excited singlet state, C−G*. Interestingly, as in the A−T pair, the high energy of this state could not be anticipated with a simple molecular orbital analysis, as this state comes from the HOMO−LUMO electronic excitation.

Analysis of this charge-transfer excited state has revealed, as in the previous A−T case, the occurrence of a minimum-energy structure in the region corresponding to the product of a single proton transfer from the now positively charged guanine moiety to cytosine. Its geometry, listed in the last row of Table 2 (as INT_{C-G^+}), indicates that the central proton H_b has been transferred from the N_4 atom of guanine to the N_3 atom of cytosine (see scheme). The structure of this minimum, then, resembles one of the intermediates found in the ground and excited C*−G electronic states, though it is far more stable given that it does not involve a charge separation. The proton transfer has neutralized the charge motion initially caused by photoexcitation. In fact, this structure is found 15.67 kcal/mol *below* the reactant minimum of the lowest-lying C−G* excited singlet electronic state so that this point is, in fact, the more stable structure found for the excited singlet electronic states of the C−G system. The situation is then very similar to the one previously found for the A−T pair. The only difference is that now this charge-transfer state is much more stable. In fact, we have been able to obtain a minimum-energy configuration for the C^-−G^+ state in the reactant zone. This point has an energy only 10.61 kcal/mol above the one corresponding to the C−G* minimum energy. However, we have not been able to find any transition state linking this minimum with the single proton transfer one, though it must exist, probably near the former minimum (as the whole process is clearly exothermic).

3.3. Concluding Remarks. In the ground electronic state S_0, the double proton transfer takes place in a concerted way (a single process) in the A−T base pair, whereas a two-step mechanism has been obtained for the C−G system. However, in both cases, the whole process is highly endothermic and the rare tautomer is quite unstable (especially in the A−T case where there is almost no energy barrier for the reverse double proton transfer leading back to the normal base pair form). Therefore, we conclude that double proton transfer in S_0 cannot account for the mutagenesis process (a point already noted in previous works[7−10]).

In the low-lying $\pi-\pi^*$ excited singlet electronic states, the electronic transition is localized in one of the two monomers. The energy profiles for the double proton transfer show some noticeable variations. For the A−T base pair, the whole process is also concerted, though the energy barrier is considerable lower, and, more remarkably, the rare tautomer becomes quite stable. On the other hand, the C−G system switches between a concerted and a stepwise process, depending on which side of the dimer is excited. In this case, the energy barrier and product stability do not suffer major modifications. From the point initially accessed upon photoexcitation (the vertical transition from the ground state minimum), the rare tautomer can be directly reached through a tunneling mechanism only for the A^*−T case whereas this process cannot take place in the other A−T and C−G excited electronic states considered. However, even in the former case, once the rare tautomer has been obtained, it can go back to the original form with, at least, the same rate at which it has been obtained. Besides this, it can also relax to the ground electronic state where, as stated above, it will quickly revert to the initial configuration too. Thus, the double proton transfer in these excited electronic states is not able to produce a rare tautomeric form which lasts long enough to interfere with the DNA unwinding and strand separation process.

Finally, we come to the analysis of the charge-transfer excited electronic states. As already stated, these states are very high in energy in the region corresponding to the ground state minimum of energy. However, exposition to quite high-energy radiations (X-rays and even atomic particles) make these states accessible. There is another point, though, we have not considered yet: the probability that a given electronic transition takes place is governed by strict quantum mechanical rules which can be accounted for by measuring the so-called oscillator strength. For the excited states localized in one monomer, the oscillator strength is clearly not null. However, the charge-transfer excitation, as it implies an excitation between two molecular orbitals centered in different regions of the whole dimer, shows a nearly zero oscillator strength. This result indicates that these charge-transfer states are not directly accessed upon a direct photoexcitation from the ground elec-

tronic state. However, these states can be populated through internal conversion from another electronic state initially obtained upon photoexcitation, which, at some geometry, crosses with the charge-transfer excited electronic state. Once this charge-transfer state has been obtained it will quickly evolve to its very deep minimum-energy structure which results from a single proton transfer (from guanine to cytosine or from adenine to thymine). This quite stable structure may live for a relatively long period of time. This is so for two main reasons. First, the oscillator strength between this state and the ground electronic state is zero (for the same reason stated above). Second, the ground electronic state has no minimum of energy in this region corresponding to a single proton transfer so that the Franck−Condon factor, which also governs the probablility of a given electronic transition, is also expected to be near zero. In addition to this, there are no other excited electronic states in this region, so a crossing cannot occur without an unlikely additional supply of energy. We must recall here that, even if the formation of the single proton transfer intermediate has a low probability, the DNA chain is actually under continuous sun irradiation so that there can be an uninterrupted pumping from the ground state to this single proton transfer excited state leading to a significant quantity of rare tautomers, enough to perturb the DNA duplication process if they are not repaired by the enzimatic machinery. Finally, it has to be kept in mind that it is not the rare tautomer properties in a vacuum but rather their characterization in solution that must be ultimately determined to really know if they have any role to play in mutagenesis. As indicated by previous theoretical studies on the solvation effects on proton transfer processes in DNA base pairs,[7,10] solvation must affect the equilibria of the base mispaired structures and the transition states of the polymerase active sites.[23] Anyway, we think that our gas-phase calculations are a first step in the understanding of the processes that lead to the formation of the rare tautomer structures under UV radiation.

Then, our results point out the possibility that the charge-transfer electronic states may play a significant role in the, up to now, quite mysterious process of mutagenesis. It would be quite interesting to carry out a detailed experimental exploration of these systems using femtochemistry techniques[24] to detect short-lived intermediates in order to assess the existence of these single proton transfer intermediates and their possible role in mutagenesis driven by photoirradiation,[25] as it has already been investigated in the model base pair 7-azaindole dimer.[26]

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Supporting Information Available: Tables 3S and 4S give the absolute energy (in au) of all the located stationary points for the A−T and C−G systems, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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