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Theoretical Investigation of Hydrogen Atom Transfer in the Cytosine-Guanine Base Pair and Its Coupling with Electronic Rearrangement. Concerted vs Stepwise Mechanism

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The transformation of the DNA base pairs from the Watson−Crick (WC) structures to its tautomers having imino−enol form can be achieved via two types of hydrogen atom transfer processes: (i) concerted, and/or (ii) stepwise (step by step). Here, we have studied and compared these two mechanisms in the cytosine-guanine (C-G) system. In the first mechanism there is the concerted movement of two hydrogen atoms along two of the three H-bridges that bond the bases, one from the cytosine to guanine and the other in the opposite direction. This movement must be coupled to an electronic reorganization, with some bond orders that pass from single to double and vice versa, in order to preserve the neutrality of these new structures. In the stepwise mechanism the movement of the hydrogen atoms and the electronic reorganization are not concerted, and it implicates the movement of a hydrogen atom at a time with the identification of two or more steps in this reaction. There are two possible neutral imino−enol structures in the C-G system, and both have been considered here. The principal result from this paper is that a different behavior is observed if the hydrogen transfer begins with a H of the guanine or of the cytosine and that a concerted (synchronic in the N−N and asynchronic in the N−O) double-hydrogen transfer can be activated only when the first H atom to move is that of the guanine, in particular. This is different from the A-T system[1] studied previously where the movement in a N−N bridge produces a zwitterionic structure and that in the N−O the concerted double-hydrogen transfer. In both cases a general conclusion can be given: the concerted double-hydrogen process begins with a hydrogen atom of a purinic base.

1. Introduction

The relevance of hydrogen bonds in DNA base pairing, and in providing structure and directionality of these bonds, is well-known and studied, but at the moment not completely understood. In particular, the role and mechanism of the hydrogen transfer and its coupling with the electronic reorganization are not completely clear. In general, both single and double hydrogen atom transfer are possible in DNA base pairs: the first creates zwitterionic (charged structures) tautomers, and the second creates neutral complexes. In the second case, there is the formation of the so-called "rare tautomers", the imino−enol forms of Watson−Crick (WC) base pairs, and these structures are thought to be responsible for genetic instabilities. The mechanism of two or more hydrogen atom transfer can be classified as concerted or stepwise when one or more steps can be identified. In these reactions there is also a correlation among the movement of the hydrogen atoms and the reorganization of the electronic structure. In the case of DNA base pairs, the correlation with the motions of the solvent molecules,[2,3] the sequence dependence,[4,5] and the environmental factors can also be important.[6−8]

The generation of these tautomers can be described as follows: the movement of a hydrogen atom from a base to the other base in a H-bridge of the C-G base pair induces the opposite motion in another H-bridge. These atomic movements are correlated also with a change in the electronic configuration that preserves the electrical neutrality. Figure 1 shows the concerted processes of hydrogen atom transfer and the electronic reorganization in the C-G system in a schematic manner. It is well-known that the C-G system, differently from the A-T base-pair, gives two imino−enol tautomers. The first one is similar to that of A-T base-pair[1] and is the only one stable. The other one can be obtained only by the movements of several atoms and does not have a well-defined minimum in the potential energy curve in the quantum calculation. In any case the amount of this tautomer can also be important, as demonstrated by us,[9,10] and hence it can play a role in the biological action of this base pair.

A complex process must be realized for generating both imino−enol tautomers, if the concerted process occurs. In fact, when a first hydrogen atom moves in a bridge, a second moves in the opposite direction in another bridge and some atomic distances (and charges) change from single to double bonds and vice versa. If these changes are not found in the computation, or a large amount of energy is necessary for this process, the nonconcerted movement becomes the more probable mechanism also in the generation of the neutral imino−enol tautomers of the CG base pair.

The electronic part of these systems can be described with diabatic or adiabatic states. In particular, the diabatic states are those where, following the chemical scenario, the structures of Figure 1 can be clearly identified along the reaction path of these processes, whereas the adiabatic state in this context has the conventional meaning that there is sufficiently strong electronic coupling between the diabatic (noninteracting) reactant and product states that electron or proton transfer involves a change of coordinates within a single electronic state and not a transition between states.

The relation between charge transfer (CT) and proton transfer (PT) in DNA has been experimentally underscored by Giese

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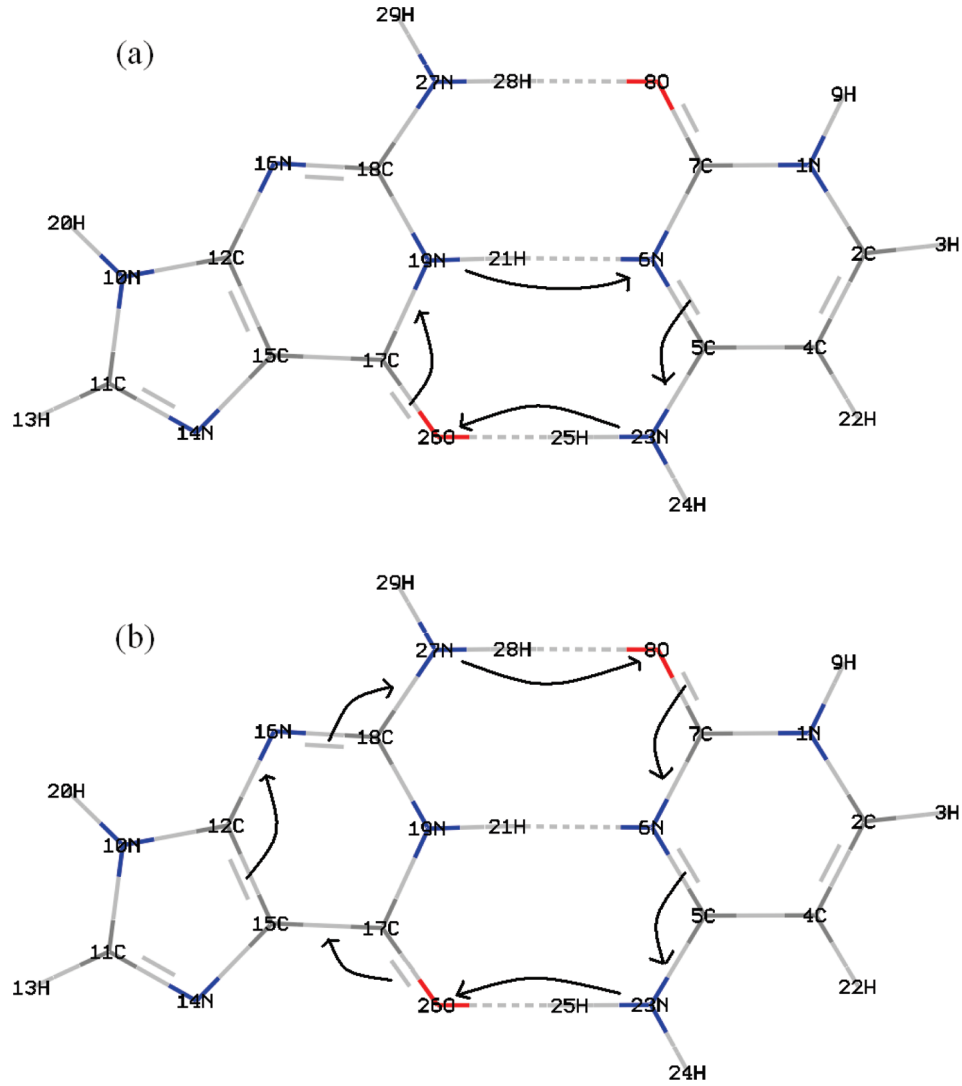

Figure 1. Schematic representation of the concerted hydrogen atom transfer and electronic reorganization in the C-G base pair. The two imino−enol structures are shown.

and Wessely.[11] There is confusion in the name of the process where protons and electrons are transferred. Following the review of Meyer,[12] the term proton-coupled electron transfer (PCET) will be used to describe the general class of these reactions where a generic couple between the transfer of these two types of particles can be underscored. The terms ET-PT and PT-ET can be used when the electron transfer is followed by the proton transfer and vice versa, and it has been proposed in the literature to name the concerted pathway that describes the electron transfer-proton transfer as ETPT[13] or electron−proton transfer EPT[14] or even concerted proton−electron transfer CPET.[15] The term H-atom transfer (HAT) can be used when both the transfer of electron and proton comes from the same bond, and hydride transfer when two electrons and a proton are transferred from the same chemical bond. There is a type of EPT pathway in which concerted electron−proton transfer occurs but involving more than one site. In this case, one says a multiple site-electron proton transfer (MS-EPT) with an electron−proton donor simultaneously transfers electrons and protons to different acceptors, or an electron−proton acceptor simultaneously accepts electrons and protons from different donors. This MS-EPT process appears to be the biological pathway in which long-range electron transfer[16] is coupled to short-range proton transfer. On the other side, the addition to the G-C WC base pair of the of electron or hydride are found to be able to trigger the proton transfer.[17−19]

As reported for the adenine-thymine (A-T) system in our paper,[1] a double-hydrogen transfer has been observed in the electronic ground state of dual hydrogen-bonded dimers such as formic acid dimer,[20−24] benzoic acid dimer,[25−27] and (2-pyridone)−(2-hydroxypyridine) dimer.[28−30] These molecules exhibit reversible excited-state double-hydrogen transfer reactions due to tunneling and, on the other hand, several dual hydrogen-bonded dimers undergo irreversible transfer reactions.[31−35] The study of the proton transfer (PT) between the DNA bases is well documented in the literature. Florian and Leszczynski reported ab initio calculations of several tautomers of C-G[36] formed from the WC base pair both by simultaneous transfer of two protons and ion pairs produced by single proton transfer between the nucleobases. The relative stabilities and dissociation energies of the base pairs were determined at the MP2/6-31G**//HF/6-31G* level. These computations indicate the importance of electron correlation for reliable estimation of the relative energy of the tautomers. They demonstrate also that one ion pair and one neutral pair resulting from single- and double PT within CG are energetically accessible. The stable tautomers of the A-T and C-G WC pairs (at the B3LYP/6-31G** level) have been recently reported by Hayashi and Mukamel.[37]

Bertran et al.[38] and Li et al.[39] demonstrate that among several types of single and double PT that might occur in the radical cations of WC pairs, just one single proton transfer (SPT) and one double PT (DPT) reaction are feasible for each WC pair. No stationary point corresponding to the DPT structure was found for C-G$^{\bullet+}$. However, recent experimental ESR study[40] and theoretical calculation with the inclusion of 11 water molecules[41] show the evidence of a facile proton transfer from G$^{\bullet+}$ to C in the C-G$^{\bullet+}$ base pair. Even though that system is different from that of this paper, those studies support the generation of these tautomers. Here, we cannot discuss the effect of the interaction of the C-G base pair with the water molecules since several H-bridges must be added to the three considered in this paper, but a detailed study on a hydrated system is in progress and it will be published later.

In a recent model study, Siebrand et al.[42] showed the analytical solution of the transfer dynamics in the instanton techniques for arbitrary coupling strength when the hydrogen bonds are represented by quartic potentials. In this case, the concerted transfer proton always takes place and the tunneling splittings can be assigned exclusively to this mechanism. A synchronous 1D tunneling occurs in the low-temperature limit and a asynchronous 2D tunneling is prevalent only when the temperature is close to the point of crossover to the classical regime, when the coupling is sufficiently weak. These are precisely the conditions where stepwise transfer provides an alternative mechanism. Otherwise, entropically the synchronous concerted motion will be very unlikely[43−47] unless the dynamics of this concerted motion (or nonconcerted) is the consequences of symmetric (or asymmetric) nuclear vibrations.[48] In any case, only in the femtosecond dynamics can the nuclear motions be studied, allowing for a true definition of a concerted or nonconcerted process and a clear distinction between transition state(s) and intermediate(s).

In a previous paper,[1] we analyzed the mechanism of the hydrogen atom transfer in the two H-bridges that bond the adenine and thymine bases and its coupling with the electronic reorganization in order to obtain the imino−enol neutral tautomer. The goal of this paper is to extend this study to the cytosine-guanine system, to determine the mechanism of the imino−enol tautomer generation (in this system there are two of these structures), and to compare this mechanism with the scheme in Figure 1. In particular, in Theoretical Method we describe the method utilized, and in Results and Discussion we show the results and discuss the chemical and biological meaning. Finally, in Conclusion we summarize the results and compare with both the literature data for the C-G system and with that for the A-T base pair.

2. Theoretical Method

As in our previous papers[1,9,10,49−51] this theoretical investigation of the cytosine-guanine (C-G) base pair is based (in Gaussian 2003 package[52]) on the density functional theoretical (DFT) approach (b3lyp) in the cc-pVDZ basis set. The DFT, in fact, is an efficient alternative to conventional ab initio theory for accurately describing the hydrogen bonds involved in DNA base pairs, and the basis set used is reliable for these systems.[53−55] Besides, the B3LYP density functional theory has been utilized in a broad range of investigations on hydrogen bonding and proton transfer dynamics in DNA base pairs,[6,7,36,39,41,56,57] and the results indicated that the B3LYP calculations predict the energetics of these systems comparable to the MP2.[58]

In order to study the correlation between the movement of a hydrogen atom in a bridge with the positions of the other atoms, we have optimized the positions of all atoms of the C-G system at each fixed position of this hydrogen atom. Since each hydrogen atom moves in a bridge as a consequence of the tunneling process, with this approach we can follow the reorganization of the global system as a consequence of this movement. This method is equal to that used in the A-T system,[1] but it is different from the method utilized in our other previous papers on the C-G base pair.[14,50] In fact, since in the previous cases our aim was the construction of the multidimensional PES (three-dimensional or six-dimensional) as a function of the different hydrogen positions in each bridge, the optimization of the other atomic positions has been done for each position of these three hydrogen atoms.

In order to understand the real mechanism of the hydrogen transfer in this system, four types of properties have been analyzed:

• The potential energy curves as a function of the position of one hydrogen atom in a H-bridge. This property is related to the real possibility of a process. A high barrier of energy of a specific mechanism means the impossibility of following it, of course.

• Selected interatomic distances that must change considerably in this process. The simple mechanism depicted in Figure 1 can be a good model of the real process only if these distances change when the bonds move from single to double or vice versa.

• The atomic Mulliken charges of the main atoms involved in the process. In the electronic reorganization the behavior of these atomic charges is very important.

• Finally, the global dipole moment of these systems. This property can be important in order to understand if a general structural change can happen, and it is necessary in this case more than one diabatic state in the description of this process.

3. Results and Discussion

The main aim of this paper is to study the mechanism that, starting from the most stable structure (the WC tautomer) of the C-G system, gives their imino−enol tautomers. In particular, we would like to compare the concerted hydrogen atom transfer and the electronic reorganization in the C-G system for obtaining these neutral structures with the processes where the different hydrogen atoms move separately and, hence, also where the electronic reorganization is uncorrelated. There is also an additional problem: beginning from a neutral structure, one arrives at another neutral tautomer, but there is a restriction of neutrality at every moment of this process, or is this condition reached only at the end of the process? To give an answer to this question is an important goal of this paper. As reported in the previous paper on the A-T system,[1] the terms *stepwise* and *concerted* in this double-hydrogen reaction are often considered equal to the terms *asynchronous* and *synchronous*[47,59] as described in the literature. A distinction between these terms is necessary since the first two, *concerted* and *stepwise*, are related to the PES, and the second two, *asynchronous and synchronous*, to the movement of the hydrogen atoms. In particular, concerted double-hydrogen transfer refers to a single chemical reaction step involving the transfer of both hydrogen atoms, and hence *concerted* means that the reaction occurs without an intermediate in this context. In the *stepwise* reaction, a stable intermediate state exists and the potential energy surface (PES) exhibits a minimum, with a well deep enough to support a bound state (which is the origin of the double-exponential decay profiles of the femtosecond transients[60]), between those of the reagent and the product. Of course, the real mechanism can mix these

different characteristics. For example, two cases of this mix can be a concerted process which is not completely synchronic (see later) and a case where the PES does not show a minimum but rather a region with small inclination, and the time-dependent calculation shows a significant probability that the system is trapped in this region.[12] This means that while extreme cases of model mechanisms can be depicted, the real mechanism may be more complex. As a consequence, detailed information of this very important process of the hydrogen movement and of the electronic reorganization in the C-G base pair can be obtained only with a theoretical/computation quantum mechanical study.

Figures 2−6 and 10 comprise three parts, each one related to the movement of a hydrogen atom in a specific H-bridge: (a) in the $N_{19}-N_6$ bridge, (b) in the $N_{23}-O_{26}$ bridge, and finally (c) in the $N_{27}-O_8$ bridge. Also Figures 7−9 comprise three parts, but in these cases all parts of Figure 7 are related to $N_{19}-N_6$, those of Figure 8 to $N_{23}-O_{26}$, and those of Figure 9 to $N_{27}-O_8$ H-bridges. In all these figures, we have the N−H distance on the *x*-axis, due to the different positions of the hydrogen atoms in the direction of the N−H bond. Of course, this does not mean an assumption of a linear hydrogen movement in the H-bridge and that the role of the out-of-plane movement of this atom is neglected since the optimization of the other atomic positions also changes the angle in the H-bridges.

Figure 2 shows the potential energy curves of the C-G base pair as a function of the hydrogen position in the three H-bridges. The differences among these cases are evident. When the hydrogen atom moves from the guanine to the cytosine base in the $N_{19}-N_6$ bridge (Figure 2a), a well-defined barrier can be identified. Different are the two cases where the hydrogen atom moves in one of the two N−O bridges. In the case of the movement of the hydrogen atom from the cytosine to the guanine base (Figure 2b) a region (N(C)−H > 1.3 Å) exists where the interaction of theH atom with N(G) gives a relative stabilization of this system, but there is not a stable configuration (minimum of PES) with this atom on N(G). Instead, in the case of the movement of the hydrogen atom from the guanine to the cytosine base (Figure 2c) in the N−O bridge, there is a stable configuration when the hydrogen atom of the guanine reaches the cytosine base (N(G)−H > 1.8 Å). Moreover, there is a general question about the three curves of Figure 2. These curves of energy are adiabatic, of course, but in a diabatic description, is this the energy of only one or of more states? We believe that the different behavior of these curves can be a consequence of the different number of diabatic states involved: we suppose that, in the case of the movement of the hydrogen atom in the $N_{19}-N_6$ bridge (Figure 2a) and in the $N_{27}-O_8$ bridge (Figure 2c), the potential energy curves plotted are those of two diabatic states, but when the hydrogen atom moves in the $N_{23}-O_{26}$ bridge, only a diabatic state can be activated for all positions of this atom. This supposition can be verified with the analysis of the charges of the atoms directly involved in this movement.

In order to compare the two mechanisms of concerted and stepwise movement of the hydrogen atoms in the bridges, we analyze in Figures 3 and 4 the modifications of equilibrium distances of the heavy atoms of the three H-bridges and of the hydrogen atoms in the bridges not directly involved in the H-movement, respectively. In all cases for Figure 3, the behavior of the atomic distances of the heavy atoms in the H-bridge with H-movement is similar: a decrease until N−H = 1.3−1.5 Å and then an increase. This behavior can be interpreted in the following way. The movement of a hydrogen atom in a H-bridge is helped by the decrease of the distance between the corresponding heavy atoms (as we have demonstrated in our previous calculations[1,11,12,48−50]), and afterward when this hydrogen atom moves predominantly on the arrival base, a relaxation to the original distance of the heavy atoms can be found. The behavior of the atomic distances in the other H-bridges (indirectly involved in the hydrogen movement) is different as a conse-

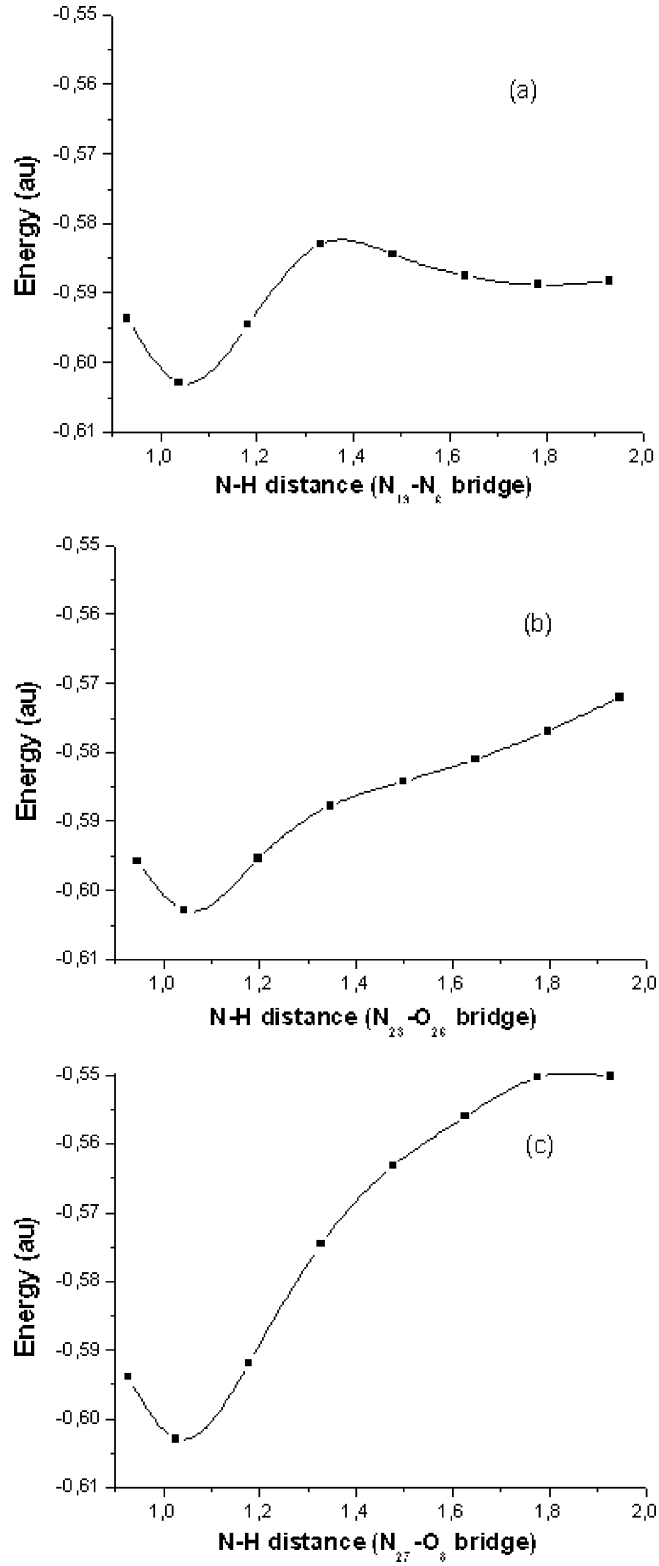

Figure 2. Potential energy curves as a function of the N−H distance in the three H-bridges: (a) $N_{19}-N_6$, (b) $N_{23}-O_{26}$, and (c) $N_{27}-O_8$. The distances are in angstroms (Å) and the energy in atomic units (au). The computed points and the spline fitting are shown. In this figure, −937 au must be added to the value of the energy.

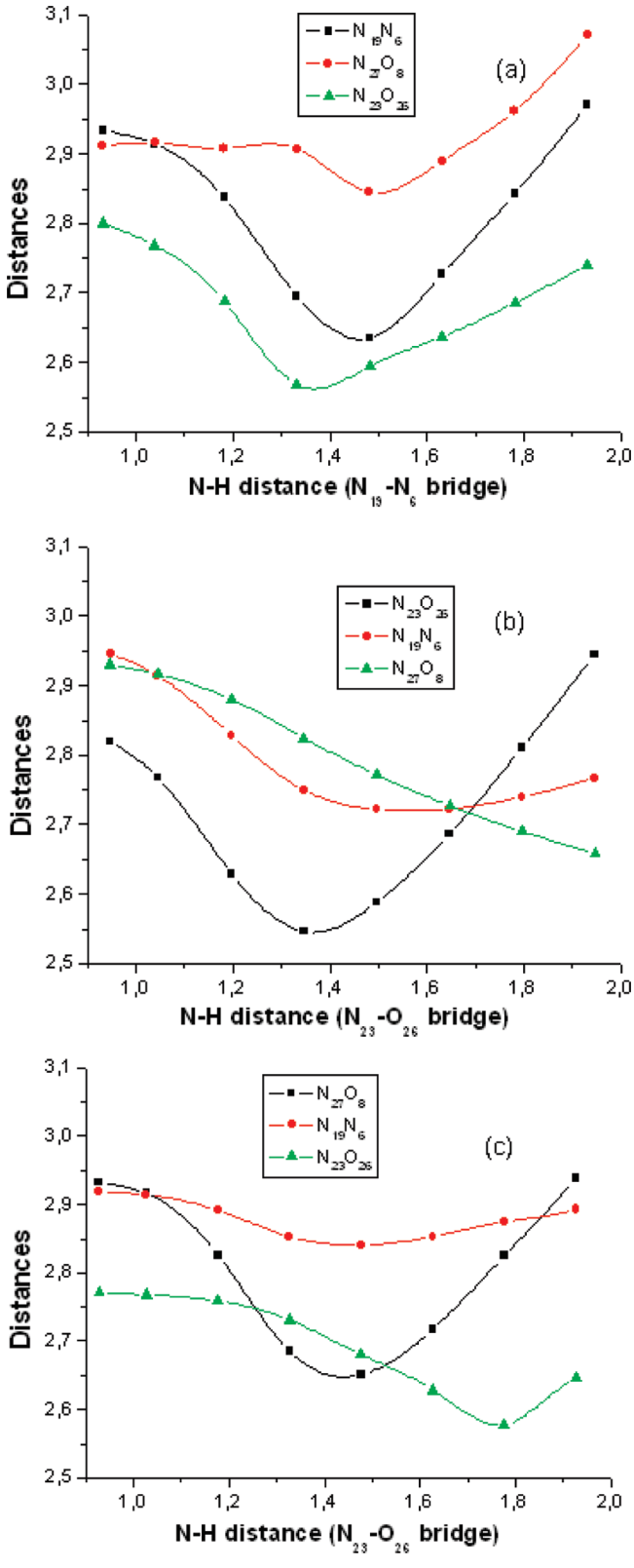

Figure 3. Distances of the heavy atoms in the three bridges as a function of the N−H distance in the N_{19}−N_6 bridge (a), in the N_{23}−O_{26} bridge (b), and in the N_{27}−O_8 bridge (c). The distances are in angstroms (Å). The computed points and the spline fitting are shown.

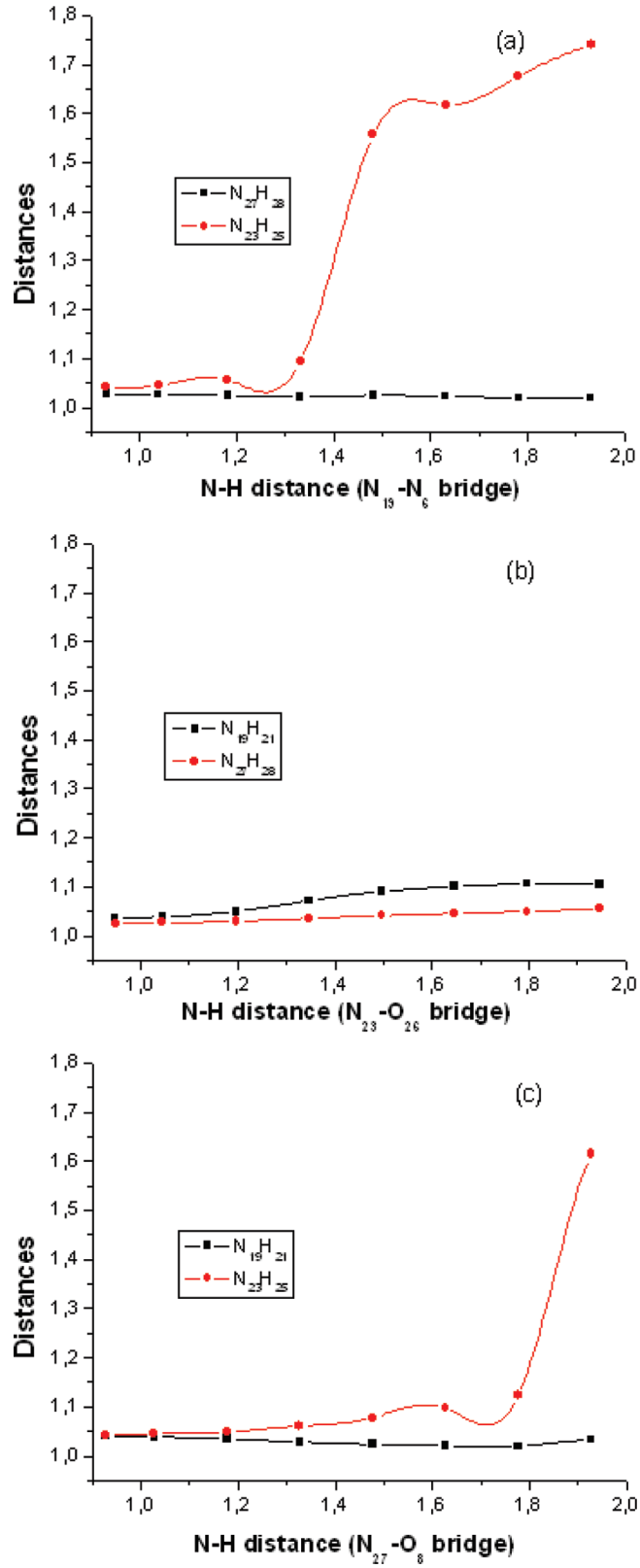

Figure 4. N−H distances in the bridges not directly involved in the H-movement. The *x*-axis is equal to that in Figure 3. The distances are in angstroms (Å). The computed points and the spline fitting are shown.

quence of the specific H-bridge where the hydrogen atom moves. In particular, the distance between the heavy atoms conveys the same behavior (decrease and then increase) in the N_{23}−O_{26} bridge and (with a less change) in the N_{27}−O_8 bridge, when the hydrogen moves in the N_{19}−N_6 bridge (Figure 3a). When the hydrogen moves in the N_{23}−O_{26} bridge (Figure 3b), the distances of the heavy atoms in the other bridges decrease monotonically (N_{27}−O_8) or until a practically constant value is reached (N_{19}−N_6). Finally, when the hydrogen moves in the

$N_{27}-O_8$ bridge (Figure 3c), the change of $N_{19}-N_6$ distance is small and the $N_{23}-O_{26}$ distance has a discontinuity around 1.8 Å.

The behavior of the N−H distances in the H-bridges not directly involved in the hydrogen movement can be seen in Figure 4. It is evident that, when the hydrogen atom moves from the guanine to the cytosine, the hydrogen atom on the cytosine follows it synchronically (if the first H moves in the N−N H-bridge) or asynchronically (if the first H moves in the N−O bridge) but not vice versa. The meaning of this behavior is clear: only when the H-movement begins with an atom on the guanine base are the concerted double-hydrogen transfers (schematized in the Figure 1a and 1b) possible in the C-G base pair system, and these processes can be synchronous or asynchronous. When the process begins with the H atom of the cytosine, the other hydrogen atoms do not follow it and a zwitterionic structure is created. This case cannot be a first step of a stepwise double-hydrogen transfer since there is not a minimum in the PES (see Figure 2b). These results have not been reported in the literature, and we believe that they can be also of biological interest since it is possible to influence the selectivity of the H-bridges and with a different mechanism to produce different quantities of isomers. This idea cannot be followed here but can be a stimulus to experimental studies.

Figures 5 and 6 show the change of the interatomic distance of the four covalent bonds (two singles and two doubles) O_8-C_7, C_7-N_6, N_6-C_5, and C_5-N_{23} of the cytosine base and the corresponding bonds $O_{26}-C_{17}$, $C_{17}-N_{19}$, $N_{19}-C_{18}$, and $C_{18}-N_{27}$ of the guanine, as a function of the hydrogen position in the three bridges, $N_{19}-N_6$ (Figure 5a and 6a), $N_{23}-O_{26}$ (Figure 5b and 6b), and $N_{27}-O_8$ (Figure 5c and 6c). These bonds must change from single to double and vice versa in the concerted mechanism or they are important in structural considerations. In Figures 5 and 6 it is evident that some bonds increase and others decrease these interatomic distances, and this behavior can be easy correlated to the decrease or increase of the bond order. In any case, from the analysis of these figures also it appears the limit of the proposed scheme in Figure 1. For example, Figure 5a shows the practically perfect opposite behavior of the two bonds N_6-C_5 and C_5-N_{23} when H_{21} moves in the $N_{19}-N_6$ bridge, as in accord with the scheme of Figure 1a, but Figure 5a also shows that in the WC tautomer these two bonds are equal and this is not the situation described in the depiction. Another important consideration is evident in the analysis of these two figures (Figures 5 and 6). In Figures 5a, 5c, 6a, and 6c, the discontinuity in the behavior of the distances (and hence of the bond orders) of these bonds is evident but not in Figures 5b and 6b. This means that the movement of H_{21} in the $N_{19}-N_6$ bridge and H_{28} in the $N_{27}-O_8$ bridge involves two diabatic states, whereas that of H_{25} in the $N_{23}-O_{26}$ bridge involves only one state. The number and the nature of these diabatic states can be understood by understanding other molecular properties (atomic charges and dipole moment) shown in the Figures 7−10.

Figures 7−9 show the atomic charges of the atoms in the hydrogen bridges involved directly or indirectly in the movement of the hydrogen atom. From the comparison between Figure 7a, 8b, and 9c, we can see that the qualitative behavior of these atomic charges (those of the atoms in the bridge where the hydrogen moves) is similar. Two differences are in any case present: a discontinuity in the charge variation of Figure 7a and 9c (discontinuity similar to that of the previous figures) and a larger variation of the N and H atomic charges when the hydrogen moves from the guanine to the cytosine compared

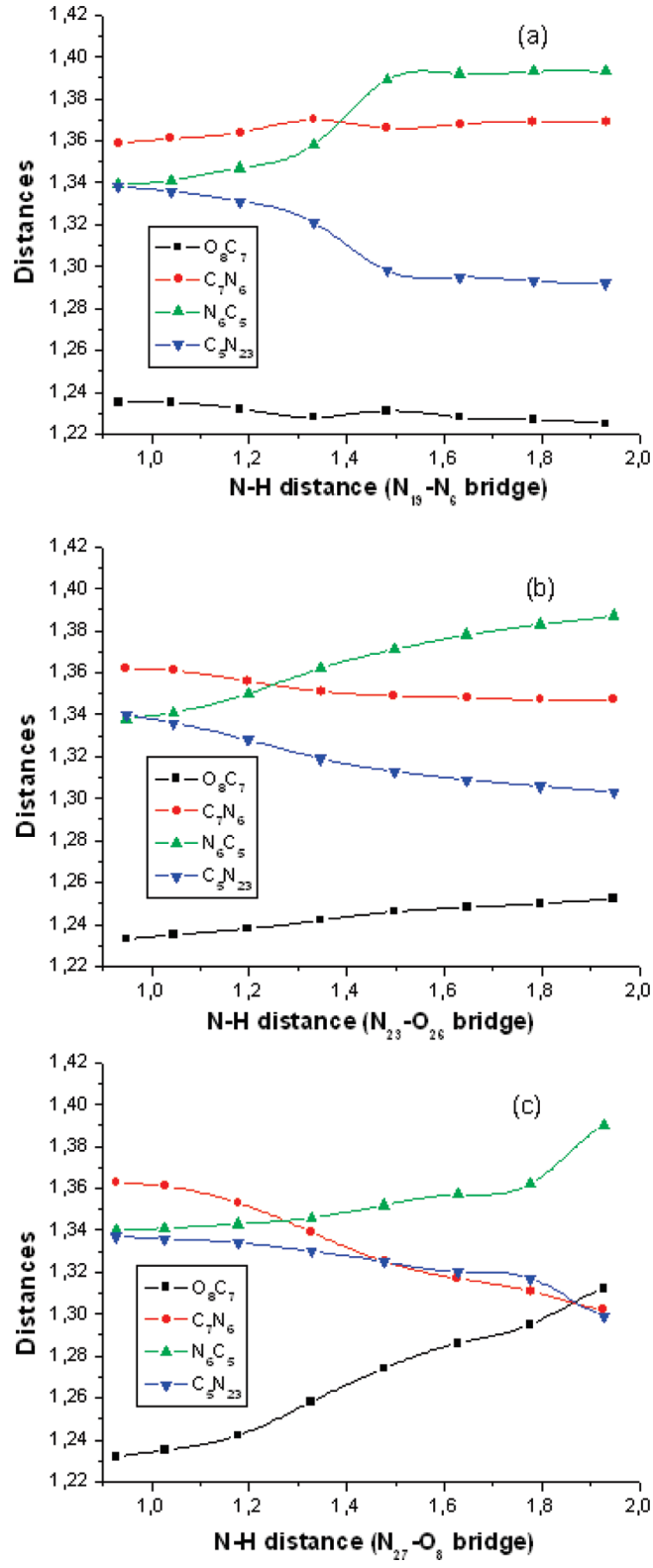

Figure 5. Atomic distances in angstroms (Å). The computed points and the spline fitting are shown.

with the opposite direction of the hydrogen movement. Instead, the atomic charges of the atoms in the bridges not directly involved in the H-movement have different variations if the hydrogen atom moves in one bridge or in the other. In particular, the atomic charges of N_{27}, H_{28}, and O_8 in Figures 7c and 8c and that of N_{19}, H_{21}, and N_6 in Figures 8a and 9a have little continuous variations. More interesting are the cases of Figure 7b and 9b. These atomic charges are those of the atoms N_{23},

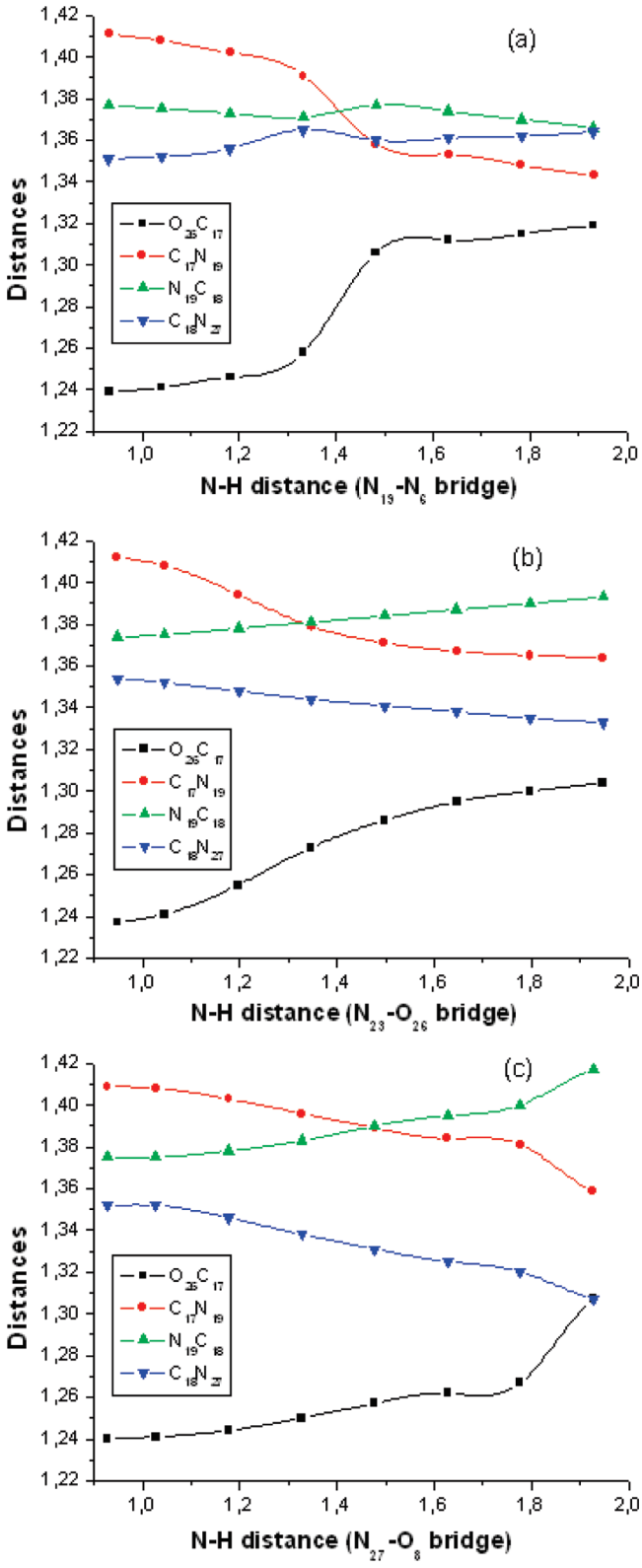

Figure 6. Atomic distances in angstroms (Å). The computed points and the spline fitting are shown.

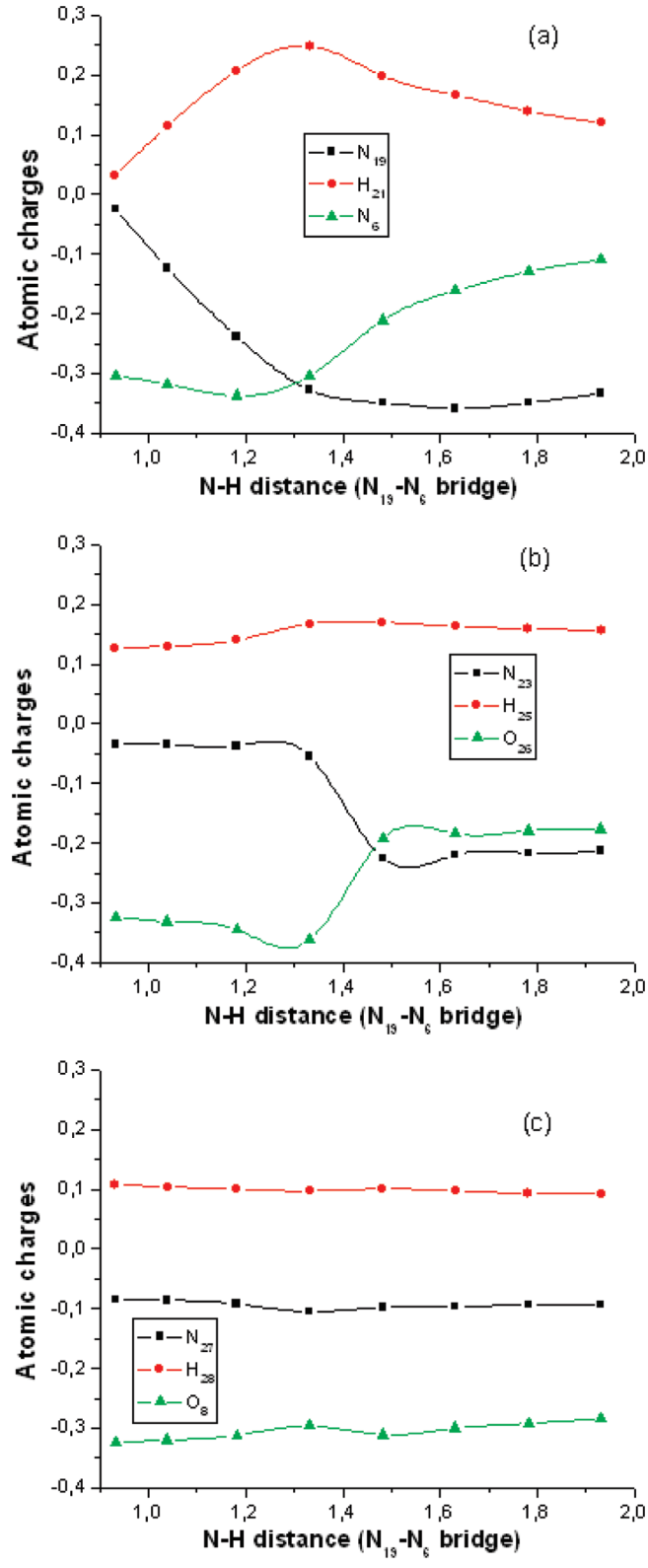

Figure 7. Atomic charges as a function of the N−H distance in the N_{19}−N_6 H-bridge. The distances are in angstroms (Å). The computed points and the spline fitting are shown.

H_{25}, and O_{26}, when H_{21} or H_{28} moves from the guanine to the cytosine. In these cases discontinuous and larger variations are evident, over all of the heavy atoms, due to the correlated movement of two hydrogen atoms (see Figures 4a and 4c).

This different behavior can also be connected to the different number of diabatic states involved in the two processes: only one diabatic state is involved in the H_{25} hydrogen transfer in the N_{23}−O_{26} bridge, and two diabatic states in the movement of the hydrogen atom in the other bridges.

Finally, Figure 10 shows the global dipole moment of the C-G system as a function of the hydrogen movement in the N_{19}−N_6, N_{23}−O_{26}, and N_{27}−O_8 bridges. These figures show very clearly one of the most important results of this paper: the change of the dipole moment, as a function of the hydrogen

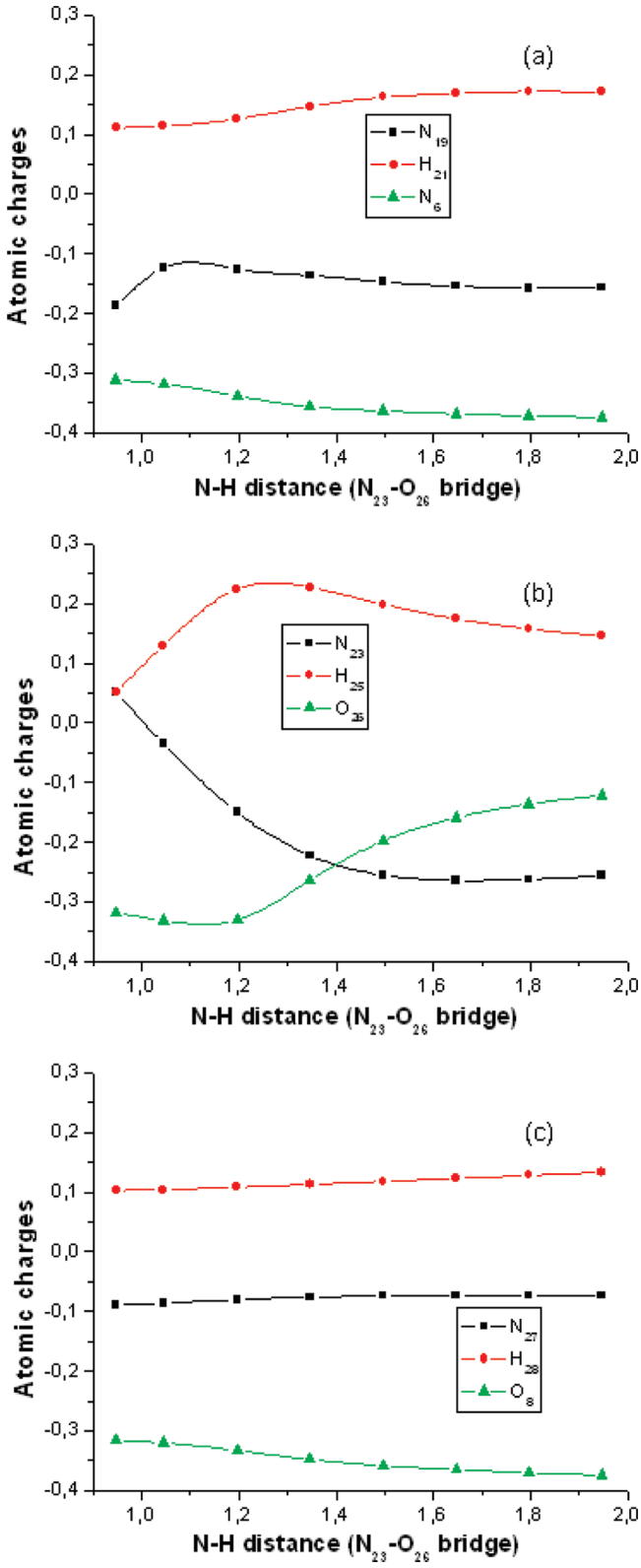

Figure 8. Atomic charges as a function of the N−H distance in the N_{23}−O_{26} H-bridge. The distances are in angstroms (Å). The computed points and the spline fitting are shown.

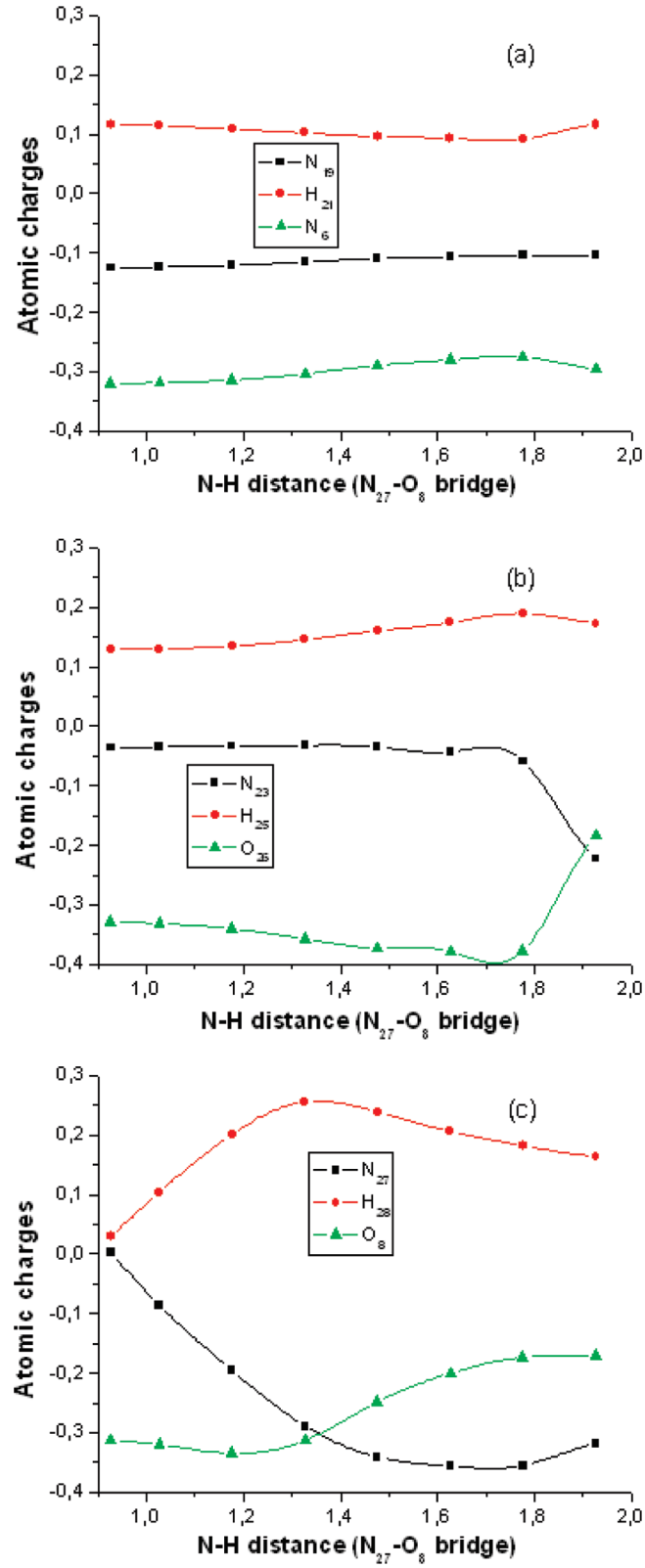

Figure 9. Atomic charges as a function of the N−H distance in the N_{27}−O_8 H-bridge. The distances are in angstroms (Å). The computed points and the spline fitting are shown.

position in a H-bridge, has a discontinuity when the hydrogen moves from the guanine to the cytosine (Figure 10a and 10c). This means a global change of the atomic charges, with the conclusion that one diabatic state is sufficient for describing the movement from the cytosine to the guanine but not the movement in the opposite direction. In this figure, more so than in the previous figures, the discontinuity (Figure 10a and 10c) versus the continuity (Figure 10b) is evident. The central and final (as a function of the H movement) position of the discontinuity is also evident, correlated with synchronous and asynchronous dynamical process. These results in the diabatic picture can be tested with a mathematical transformation from

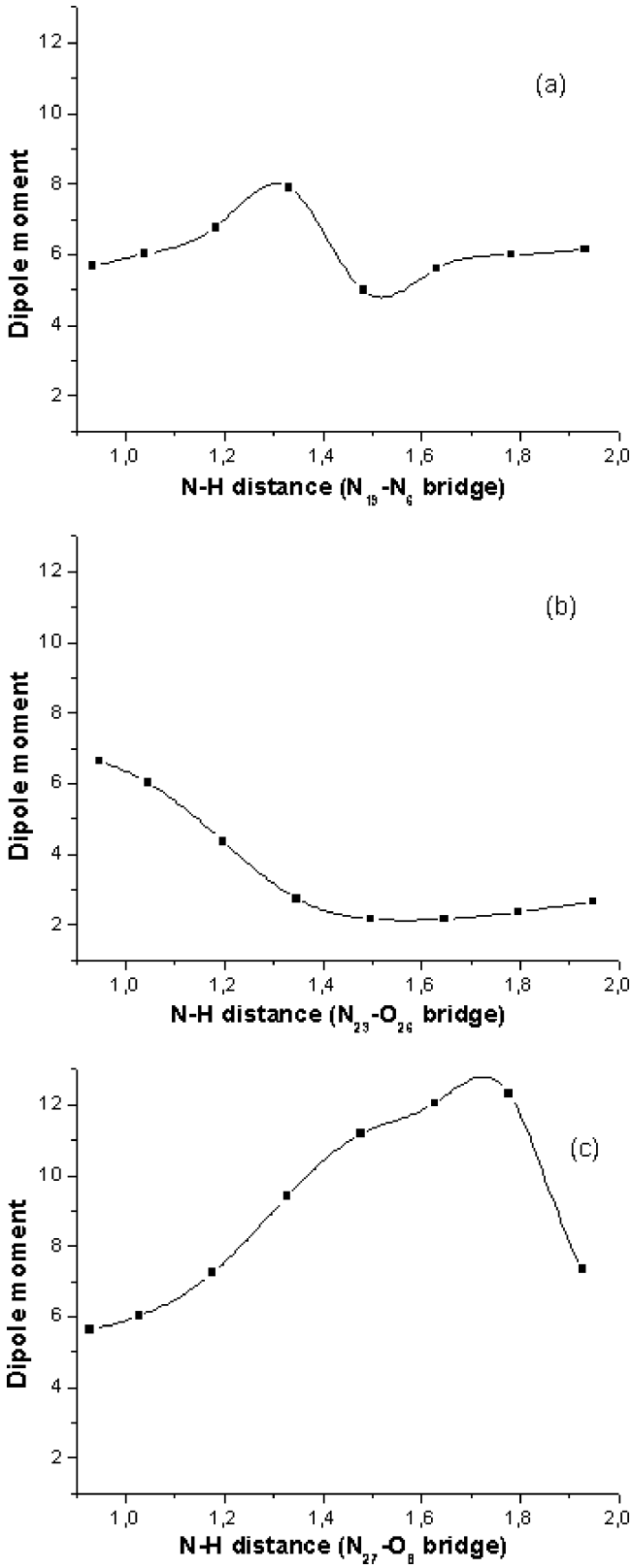

Figure 10. Dipole moment of the global CG system as a function of the N−H distance in angstroms (Å). The computed points and the spline fitting are shown.

the adiabatic to diabatic states, and the discontinuity in the dipole moment has been also studied experimentally by the help of stationary laser field or intense laser pulses but only for simpler systems.[61−63] The dipole moment behavior shown in the Figure 10 is similar to that of the A-T system[1] where one or two diabatic states can be involved as a function of the H-bridge considered (N−N or N−O, respectively).

In the Figure 4 of ref 10 we showed the monodimensional PES of the five H-bridges (the two of the A-T system and the three of the C-G system), when only one of these coordinates is changed and the other(s) is in the equilibrium position (all others coordinates of these systems are optimized, of course). The two monodimensional PES show in Figure 2 for the A-T system,[1] otherwise, are obtained without the assumption of equilibrium position in the H-bridge where there is not hydrogen atom movement, as in this paper. From the comparison of these three figures we can compare the behavior of the C-G system with that of A-T system. In particular, in the C-G system of this paper we find a minimum in the *soft* N_{19}−N_6 H-bridge and (in a less evident way) in the *hard* N_{27}−O_8 H-bridge, while in the A-T system the minimum of energy is in the *hard* N−O H-bridge, when we do not impose the equilibrium position in the other(s) H-bridge(s). These results are clearly connected to the different concerted double-hydrogen transfer or zwitterionic generation in the C-G and A-T systems. Similarly, the atomic charges and the dipole momentum are discontinuous or continuous in the same way.

4. Conclusion

In this paper we have analyzed concerted and stepwise hydrogen atom transfer and the electronic reorganization in order to generate the imino−enol forms from the most stable tautomer of the cytosine-guanine base pair (the WC structure). The driving force of the concerted process is the neutrality restriction, but this paper has underscored that this does not mean that the system remains neutral in every moment of the process. In fact, this is a very strong restriction that means not only a concerted process but also a synchronic one, and it can be assumed only as a limit case. The other limit case is the completely unrelated movement of each hydrogen atom and also unrelated movement among these atoms and the electronic reorganization. In this case a charged system is generated, of course, and the neutrality of this system is obtained only at the end of the process. Information about the real process of generation of the imino−enol forms of the C-G base pair can be obtained by a time-dependent analysis, but also some static properties (energy, charge, bond distance, etc.) give some important indications.

In this paper we have analyzed these properties, and some interesting results have been shown. In particular, we can summarize the results as follows:

1. There is a different behavior if the hydrogen transfer begins with a H atom of the guanine or a H atom of the cytosine. From the analysis of the data of this paper, we can conclude that the movement of the hydrogen atom in the N_{19}−N_6 bridge can generate only a concerted and synchronous double-hydrogen transfer, while a movement of the hydrogen in one of the two N−O bridges can generate a zwitterionic structure or an asynchronous concerted process as a consequence of the direction of the H-movement (from the cytosine to guanine or vice versa). This is different from the A-T system[1] where the movement in the N−N bridge generates a stepwise process and that in the N−O bridge the concerted process. In reality these concerted processes are also not synchronic since the movement of the first hydrogen does not affect the position of the other hydrogen atom until the first reaches a particular position. In particular, in the movement of the H_{28} atom, the other hydrogen atom (H_{25}) moves only when the first is completely transferred from one base to the other. Only at that moment, a practically instantaneous movement of the hydrogen atom in the N_{23}−O_{26}

bridge occurs. The three H-bridges were denoted *hard* ($N_{27}-O_8$) and s*oft* ($N_{19}-N_6$ and $N_{23}-O_{26}$) in our previous papers, hence, it is not true that only the H-movement in the soft bridge can be followed by the corresponding movement in the hard bridge in the C-G system, differently from that of the A-T case. In the C-G system, a concerted process can be activated only when the first H atom to move is that of the guanine.

2. In the movement of the hydrogen atom from the cytosine to the guanine only one diabatic state is involved, and two diabatic states in the case of the hydrogen movement from the guanine to the cytosine. This is evident from the charge variations (as a function of the hydrogen position in the bridge) but, mainly, by the variation of the global dipole moment. This is similar to the A-T system where the movement of the hydrogen atom from the thymine to the adenine involves one diabatic state, and the other from the adenine to thymine involves two diabatic states. Also in the C-G system, the discontinuity in the dipole momentum can be important for discovering a global change of molecular properties, as reported in the literature.[1,61]

From the analysis of the data of this paper and of the previous one on the A-T base pair,[1] a general conclusion can be made: the concerted double-hydrogen process in DNA base pairs begins with a hydrogen atom of a purinic base.

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