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REGULAR ARTICLE

Effects of protonation on proton transfer processes in Watson–Crick adenine–thymine base pair

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Abstract Intermolecular proton transfer processes in the Watson and Crick adenine–thymine neutral and protonated base pairs have been studied using the density functional theory (DFT) with the non-local hybrid B3LYP density functional. Protonated systems subject to study are those resulting from protonation at the main basic sites of the base pair model, namely N_7 and N_3 of adenine and O_2' and O_4' of thymine. Protonation of adenine induces a strengthening by about 4–5 kcal/mol of the base pair and does not significantly modify the double proton transfer energy profile obtained for the unprotonated system. On the other hand, protonation at the O_4' and O_2' thymine moiety causes thymine's N_3 proton to spontaneously transfer to adenine while non-transferred minima disappear at this level of theory. The different behaviour between protonated adenine–thymine and protonated guanine–cytosine is discussed.

1 Introduction

Hydrogen bonding among complementary bases, in their canonical forms, is the main responsible for the double stranded DNA specific pairing, which allows storing of genetic information. Because of that, the hydrogen bonding patterns and their behaviour have been the subject of many studies since its structure was first reported by Watson and Crick [1]. In particular, tautomeric equilibria of each nucleobase has attracted much of attention [2–7]. Moreover, many other studies have focused on the acid–base properties of nucleobases [2,8–14] and on the influence of different factors such as metal coordination, [15,16] protonation [17,18] or ionization [19,20] on these properties, since they could stabilize rare tautomers and thus, induce mispairings.

Löwdin's hypotheses, [21,22] which suggested that intermolecular proton transfer processes within base pairs could be the cause of point mutations in DNA, because non-canonical tautomers could be formed, have also been the subject of many theoretical studies [18,23–26]. The single and double proton transfer reactions in neutral base pairs, particularly in guanine–cytosine, have been the processes most often considered, result in a correlated level indicating that the concerted double proton transfer is the preferred mechanism and that the reaction energy is about 10 kcal/mol. However, as already indicated by Löwdin in his seminal papers, the introduction of a positive charge in the base pair either through ionization, [27,28] protonation [18,23] or coordination of a metal cation to the guanine [29] moiety, can significantly enhance the single proton transfer reaction, which becomes exothermic in some cases. As a matter of fact, protonated nucleobases can be found in DNA [30–33] and experimental results have detected proton transfers within base pairs, which may have been induced by an acidic environment [30].

Proton transfer processes in adenine–thymine (AT) base pair have received less attention [25,34–37] and have mainly focused on the neutral system. As for

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guanine–cytosine, electron correlation was found to be essential to properly describe the topology of the potential energy surface; the single proton transfer intermediate located at the HF level [37] being probably an artifact of the method.

The effects of introducing a positive charge to adenine–thymine have also been considered, but only through ionization. To our knowledge, the effects of protonation on proton transfer processes in adenine–thymine has not been reported in the literature. Since it is of interest to analyze whether or not protonation will induce similar effects than ionization, as found for guanine–cytosine, in this work we present our results on single and double proton transfer processes on the neutral and protonated AT base pair.

2 Computational details

Full geometry optimizations, without any symmetry constraints, have been carried out both for the neutral and protonated base pairs using the three-parameter B3LYP [38,39] density functional method with the triple zeta plus polarization and diffuse functions 6–311++G(d,p) basis set. The reliability of density functional methods for studying hydrogen bonded systems has been analysed in several papers, which have shown that the non-local hybrid B3LYP functional, provide results comparable to the MP2 method when similar basis sets are used [40,41].

The nature of the stationary points has been checked out by vibrational frequency calculations. Thermodynamic corrections have been obtained with the same basis set assuming an ideal gas, unscaled harmonic vibrational frequencies and the rigid rotor approximation, by standard statistical methods [42]. Net atomic charges have been obtained using the natural population analysis of Weinhold et al. [43], while basis set superposition error (BSSE) has been calculated using the Boys and Bernardi procedure [44,45].

3 Results and discussion

First, we will show the results corresponding to the neutral AT base pair. Second, results for the protonated AT base pair and the corresponding proton transfer processes will be presented. In both cases, the single and double proton transfer reactions shown in Scheme 1 have been analyzed. Finally, results obtained for AT will be compared with those previously published for GC.

3.1 Neutral system

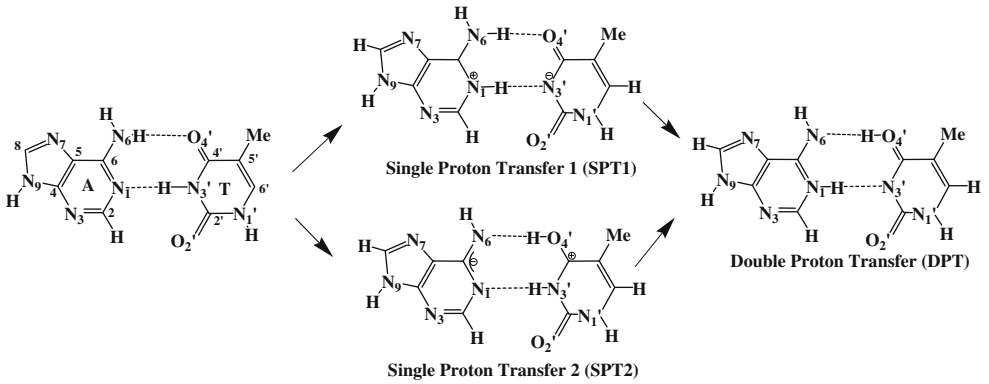
For the neutral system only the minimum corresponding to the double proton transferred structure (ATDPT) was located. Our results are in very good agreement with previous published results and confirm the need for using a level of theory that includes electron correlation.

Geometries for the non-transferred minima (AT), transition state and the double proton transfer product (ATDPT) are shown in Fig. 1. As expected, geometrical parameters of the nucleobases within the base pair remain very similar to those of the unpaired monomers (see Supplementary material). Most important changes correspond to those atoms directly involved in the pairing. That is, C_6–N_6 of adenine suffers a slight shortening (0.01 Å), whereas in the thymine moiety, the C_4'–O_4' bond increases by 0.014 Å and the N_3'–C_4' bond distance decreases by 0.017 Å. Geometrical changes occurring along the double proton transfer mainly affect these atoms. In fact, the double proton transfer can be understood as an amino/imino-keto/enol equilibria involving the N_6, O_4', N_1 and N_3' atoms of the nucleobases. Changes occurring in the base pair are less pronounced than in the isolated nucleobases. For instance, the C_4'–O_4' bond distance increases 0.128 Å from the canonical isolated thymine to the thymine DPT "rare" tautomer, while this increase is 0.071 Å, when considering thymine paired to adenine.

Variations in hydrogen bonding distances along de DPT process are significant. The N_6–O_4' hydrogen bond dramatically decreases by 0.367 Å, thus indicating the acidic behaviour of the O_4' bound proton in the DPT product, which in turn, stresses out the intrinsic unstability of such product. In fact, DPT minimum disappears when considering Gibbs energy corrections.

Transition state geometry shows a highly asyncronous intermediate situation between the reactant and the product. The TS geometry is closer to the DPT product than to the reactant. That is, both protons are closer to those centers that accept the proton along the reaction, the N_1–N_3' proton showing a more advanced situation. Finally, distances between heavy atoms (N_6–O_4' and N_1–N_3') are shortened in the transition state, which is a common trend in proton transfer processes.

Figure 2 shows the energy profile for the concerted double proton-transfer reaction. Even though no single proton-transferred intermediates have been located as minima on the potential energy surface, the energy of ATSPT1 and ATSPT2 single proton transferred species has been estimated by performing restricted optimizations in which the N_1–H bond distance was fixed at



Scheme 1

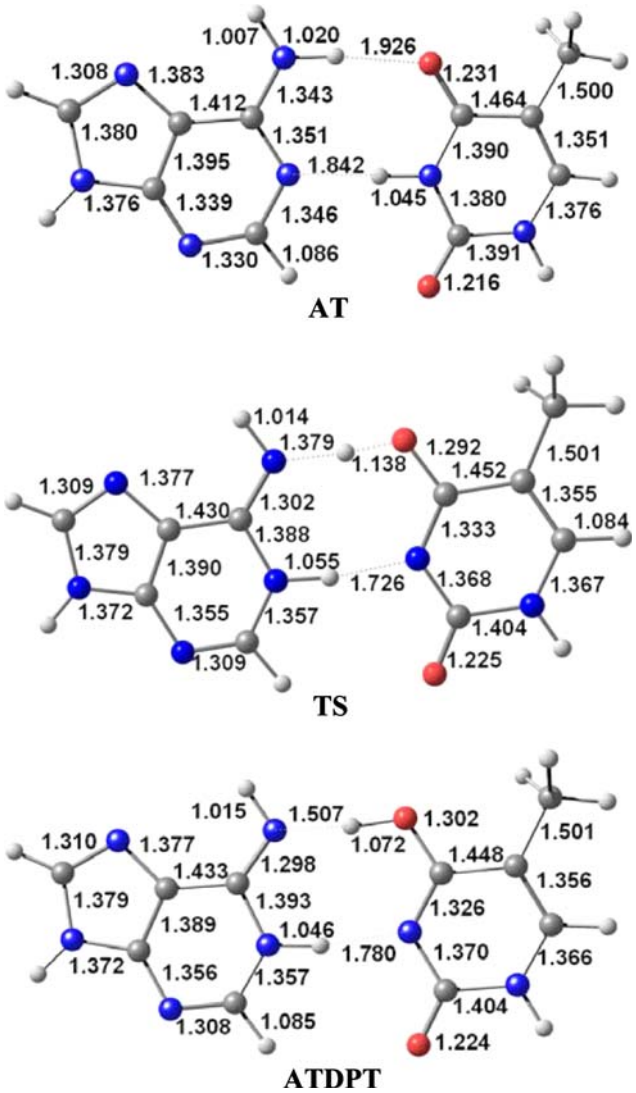


Fig. 1 Optimized geometries for AT and ATDPT minima and for the transition state (*TS*). Distances are in Amstrongs

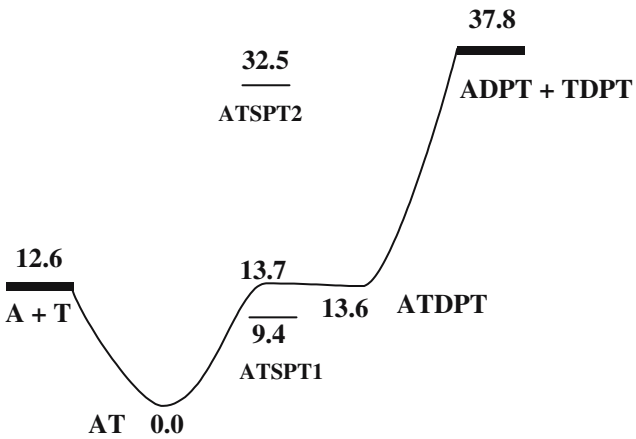


Fig. 2 Energy profile for the double proton transfer process (*DPT*) within the neutral adenine–thymine base pair. Energies in kcal/mol

1.095 Å (ATSPT1), or the N_3'–H and the O_4'–H bond distances were fixed at 1.025 and 0.984 Å (ATSPT2). As in the case of guanine–cytosine base pair, single proton transfer reactions in the neutral base pair implies the creation of an ion-pair-like structure, which is highly destabilized in gas phase. Moreover, the SPT2 structure is higher in energy than the SPT1 one. This is not surprising, considering that SPT2 structure implies the deprotonation of adenine's amino group (deprotonation enthalpy of 354 kcal/mol) and the subsequent protonation of thymine's carbonyl group (proton affinity of 202 kcal/mol), while SPT1 corresponds to the deprotonation of thymine's N_3' (deprotonation enthalpy of 345 kcal/mol) and the protonation of adenine N_1 atom (proton affinity of 224 kcal/mol) [46]. Thus, as these single proton transfer processes close a thermodynamic cycle in which acidity and basicity of the moieties play the predominant role, the smaller the difference between protonation and deprotonation enthalpies of the involved tautomers, the less endothermic the process is. Therefore, any factor capable of reducing this difference will enhance the feasibility of single proton transfer processes. On the other hand, since dipole moments of the SPT ion pair intermediates are larger than those

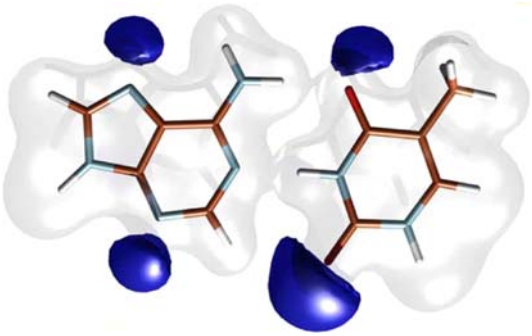


Fig. 3 Electrostatic potential map of adenine–thymine base pair. *Blue regions* indicate favoured regions for the interaction with a point positive charge

of the non-transferred and double proton-transferred products, these ion pair structures are expected to be stabilized by a polar solvent.

3.2 Protonated systems

Figure 3 depicts the electrostatic potential map of AT base pair. Blue (dark) colour indicates the regions that are favourable towards an interaction with a positive charge. It appears that N_7 and N_3 are suitable sites for such an interaction. In addition, two other regions near O_2' and, to a lesser extent, O_4' centers on thymine are also found to be suitable for the interaction with a positive charge. It is expected that the preference for these sites will be similar to that for protonation.

Contrary to what happens in the case of GC base pair, when protonating at the purine moiety of AT, no single proton transfer product can be found, and only double proton transfer products are located. On the other hand, when AT base pair is protonated at the basic O_2' and O_4' centers of the thymine moiety, the non-transferred minima disappears as thymine's N_3' proton is transferred to adenine's N_1 in a spontaneous process. Relevant geometrical parameters for the non-transferred, double-transferred product and transition structures for N_3 and N_7 protonated adenine, as well as the SPT-like structures obtained upon protonating thymine at the O_4' and O_2' sites are shown in Fig. 4. Complete geometries can be found in the supplementary material.

Intramolecular changes upon protonation of the base pair are similar to those occurring when isolated nucleobases are protonated. For the N_7 protonated system, major changes are found in N_7–C_8–N_9 distances while for N_3 protonation, significant changes are located at the N_1–C_2–N_3–C_4 bond distances. These variations arise from the electronic reorganization produced to accommodate the positive charge of the protonated systems. Population analysis shows that charge changes for the N_7 protonated system are heavily located at C_8 and N_9 atoms (mean charge increase of 0.15 a.u. in these atoms), whereas for the N_3 protonated system, the major changes are found on C_2, N_1 and N_6 with a charge increase of 0.21 a.u. Similar to what happened on protonated GC base pair, the charge distribution of N_7 protonated systems is almost totally localized at the five-membered ring, while protonation at N_3 is spread through the six-membered ring of adenine. Nevertheless, since the proton associated to the SPT2 transfer is not directly bond to the aromatic ring of the nucleobase, the acidification of NH is rather similar regardless of the site of protonation.

For thymine protonated species, the charge is driven to the adenine moiety through the N_3' to N_1 proton transfer process. NPA shows a 0.92 a.u. charge on the adenine moiety after the transfer. Moreover, as charge is mainly distributed on the 6-membered ring of adenine, intra adenine geometrical changes are similar to those occurring to the N_3 protonated AT base pair. In addition, C–O_4' or C–O_2' bonds are elongated as protonation causes the enolization of the carbonyl group.

As expected, changes in hydrogen bonding for the protonated base pair compared to the neutral system are determined by the change in acidity of the protonated nucleobases. That is, adenine protonation induces a strengthening of the hydrogen bond where adenine acts as proton donor (N_6–O_4'), which is shortened by an average value of 0.17 Å, whereas the hydrogen bond where adenine acts as proton acceptor (N_1–N_3') increases by 0.13 Å and is weakened. It is remarkable that changes in hydrogen bonding are almost equivalent for N_7 and N_3 protonated systems. This is in contrast to protonated GC since, for this base pair, different sites of protonation led to different elongations or shortenings of hydrogen bonds. On the other hand, for thymine protonated species, where the spontaneous proton transfer occurs, the N_1–N_3' hydrogen bond is not significantly modified and the N_6–O_4' one is shortened or lengthened depending on whether thymine is protonated at the O_2' or O_4' center. That is, $H^+AT_{O_4'}$ has a much longer N_6–O_4' hydrogen bond than $H^+AT_{O_2'}$, due to the lower basicity of O_4' in the former case.

Geometry changes occurring along the double proton transfer reaction in adenine protonated AT are similar to those found in the neutral system. That is, atoms involved in the amino/imino-keto/enol equilibria suffer the same increase or decrease in their bonding both qualitatively and quantitatively. Moreover, as the DPT process does not imply a net charge transfer between moieties, charge is maintained on adenine in the DPT products. Therefore, hydrogen-bond, where adenine acts as the proton donor, will still be strengthened when

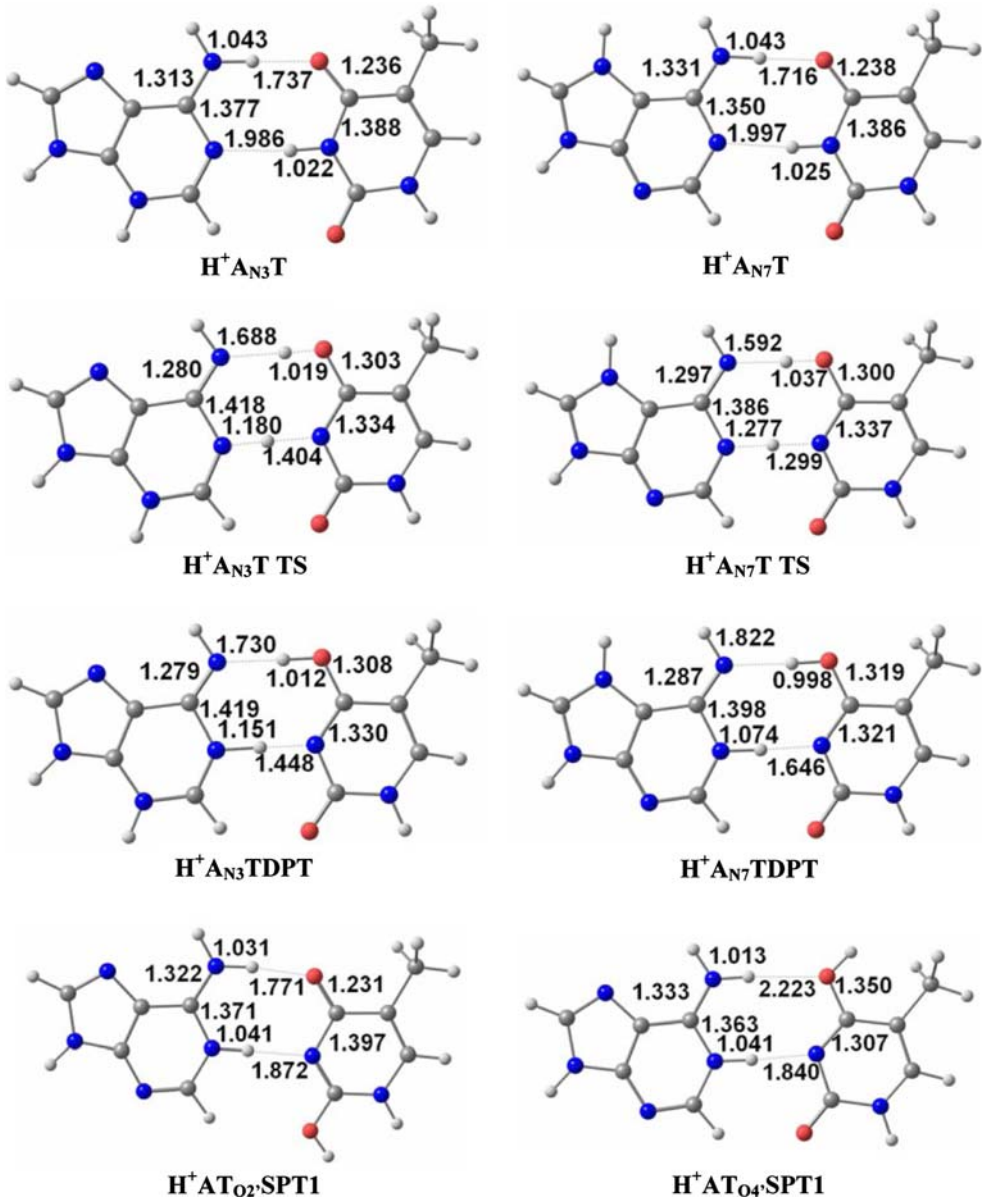


Fig. 4 Main geometry parameters of $H^+A_{N_3}T$, H^+AN_7T, $H^+AT_{O_2}$ and $H^+AT_{O_4}$ and the minima and transition structures involved in the single proton transfer (*SPT*) and DPT processes. Distances are in Amstrongs (complete geometries can be found in supporting material)

compared to the neutral ATDPT and those where it acts as the proton acceptor will be weakened.

Transition state structures leading to the DPT products for protonated adenine base pairs show that in the $H^+A_{N_3}T$ case, both protons are more displaced towards DPT product than in the $H^+A_{N_7}T$ case, whereas in both cases there is a general shortening of the hydrogen bonding pattern in order to facilitate the transfer. Moreover, there is a significant difference between protonated and neutral DPT transition states concerning the synchronycity of the double transfer. That is, while in the neutral system the DPTTS structure shows that the N_1–N_3' is almost totally transferred and the N_6–O_4' proton is "half-way" transferred, this situation is exchanged in the adenine protonated base pair, due to the presence of the positive charge on adenine.

Proton affinity values for isolated adenine and thymine and for AT base pair at all basic centers are shown in Table 1. These values are in good agreement with experimental results [47] as well as with previous theoretical calculations [14]. As shown, protonation at N_3 center is favored over protonation at N_7, both on the isolated nucleobase and the base pair. Proton affinity values for the base pair, protonated at adenine, are 3–5 kcal/mol

Table 1 Proton affinity values (kcal/mol) for adenine and adenine–thymine base pair at different basic sites

		PA[a]
A	N_7	215.5
	N_3	221.2
	N_1	222.7
Exp.[b]		225.5
T	O_4'	203.6
	O_2'	195.2
Exp.[b]		210.7
AT	N_7	218.7
	N_3	226.2
	O_4'[c]	224.1
	O_2'[c]	220.0

[a] After correction for translational, rotational and vibrational energies determined at the B3LYP/6-311++G(d, p) level
[b] Taken from Ref. [46,47]
[c] After the SPT1 proton transfer

larger than those corresponding to the isolated nucleobase due to the stabilization of the positive charge by polarization effects. Moreover, thymine's proton affinity is larger when it is paired than when it is isolated since proton transfer process largely stabilizes thymine protonation.

Pairing energies for neutral and protonated base pairs are shown in Table 2. In both adenine protonated systems, base pairing energies are larger than that of the neutral system by approximately 4–5 kcal/mol. Note that base pairing energies for both adenine protonated systems are very similar, in agreement with the fact that both systems show very similar hydrogen bond distances. However, thymine protonated base pairs show interaction energies that are much larger (15–20 kcal/mol) than those of the neutral system or adenine protonated base pairs. We have to take into account that these values account for the energy gain associated to the proton transfer. The interaction energy is larger for O_2' protonated base pair than for O_4', which agrees with the fact that the N_6–O_4' hydrogen bond is larger for the latter system.

Figure 5 shows the energy profile for the considered proton transfer processes. The relative stability of DPT products depends on the protonation site. Comparing DPT energy values with those of the neutral system (see Fig. 2), it can be observed that protonation at N_3 increases the reaction energy by 3.6 kcal/mol, whereas protonation at N_7, stabilizes the DPT product by 1.6 kcal/mol. For thymine protonated base pair, reaction energies associated to single proton transfer processes are determined with respect to the H^+AT_{Ox}' ($X = O_2', O_4'$) species, for which the N_3'–H bond distance is frozen at the neutral system value. In these two cases, reaction energy values are very similar, regardless of whether protonation takes place at O_2' or O_4'. This fact points out that thymine's N_3' is acidified in a similar way by protonating either at O_2' or O_4'. However, the base pairing energy becomes weaker if protonation occurs at O_4', which is in good agreement with the fact that N_6–O_4' hydrogen bond is largely affected in this case, due to the decrease of basicity upon protonating O_4'.

Reaction energies associated to the [$H^+A + T \rightarrow H^+ADPT + TDPT$] process are determined by the relative stability of the involved tautomers. Note, in Fig. 5 that the relative order of N_7 and N_3 protonation asymptotes is exchanged when going from reactants to products. In this case, as protonation occurs only in adenine, energy difference between thymine tautomers (E[T]− E[TDPT] = 13.3 kcal/mol) makes no difference when considering reaction energy differences between N_7 and N_3 systems. However, relative tautomeric stability of H^+A and H^+ADPT is important. That is, for $H^+A_{N_7}$, the energy difference between $H^+A_{N_7}$ and $H^+A_{N_7}DPT$ is about 9.6 kcal/mol, while for $H^+A_{N_3}$ the same relation is 23.5 kcal/mol. This means that N_7 protonation stabilizes the rare ADPT tautomer, while protonation at N_3 destabilizes it with respect to the non protonated nucleobase system, for which the same difference is 11.9 kcal/mol. In the base pair system, values for E[$H^+A_{N_7}T$]−E[$H^+A_{N_7}TDPT$] and E[$H^+A_{N_3}T$]− E[$H^+A_{N_3}TDPT$] are 12.0 and 17.2 kcal/mol, respectively, while this value is 13.6 for the non-protonated base pair. That is, protonation at N_7 stabilizes the DPT product both for the isolated base and base pair, whereas N_3 protonation highly destabilizes the nucleobase and base pair DPT product. As explained, for $H^+A_{N_7}$ and $H^+A_{N_7}T$ the positive charge is mainly distributed on the five-membered ring whereas for $H^+A_{N_3}$ and $H^+A_{N_3}T$ the charge is mainly localized on the six-membered ring of adenine, which largely influences the stability of the corresponding $H^+A_{N_x}TDPT$ product.

3.3 Adenine–thymine versus guanine–cytosine

At this point, it is interesting to compare the influence of introducing a positive charge, either by protonation or by ionization, in adenine–thymine base pair, with that of guanine–cytosine. Since ionization takes place at the purine moiety, we will consider only protonation at this monomer. Figure 6 shows the energy profiles corresponding to the most favorable proton transfer processes in neutral, ionized and protonated GC and AT base pairs.

Table 2 Base pairing energies (in kcal/mol) for the neutral and protonated base pairs

	AT	H^+AT		$H^+ATSPT1$	
	Neutral	N_7	N_3	O_4'	O_2'
D_e	12.6(11.9)	17.3(16.5)	17.6(16.8)	32.7(31.9)	37.6(36.5)
D_0[a]	11.3(10.6)	16.2(15.4)	16.6(15.8)	31.4(30.6)	36.0(35.1)
$\Delta H^0_{298\,K}$[b]	11.2(10.5)	16.0(15.2)	16.2(15.4)	31.8(31.0)	35.9(35.0)
$\Delta G^0_{298\,K}$[b]	–0.9(–1.6)	5.0(4.2)	5.4(4.6)	21.2(20.4)	23.8(22.9)

Values in parenthesis correspond to BSSE corrected values
[a] Includes zero point energy computed from the unscaled harmonic B3LYP/6-311++G(d,p) frequencies
[b] After correction for translational, rotational and vibrational energies determined at the B3LYP/6-311++G(d,p) level

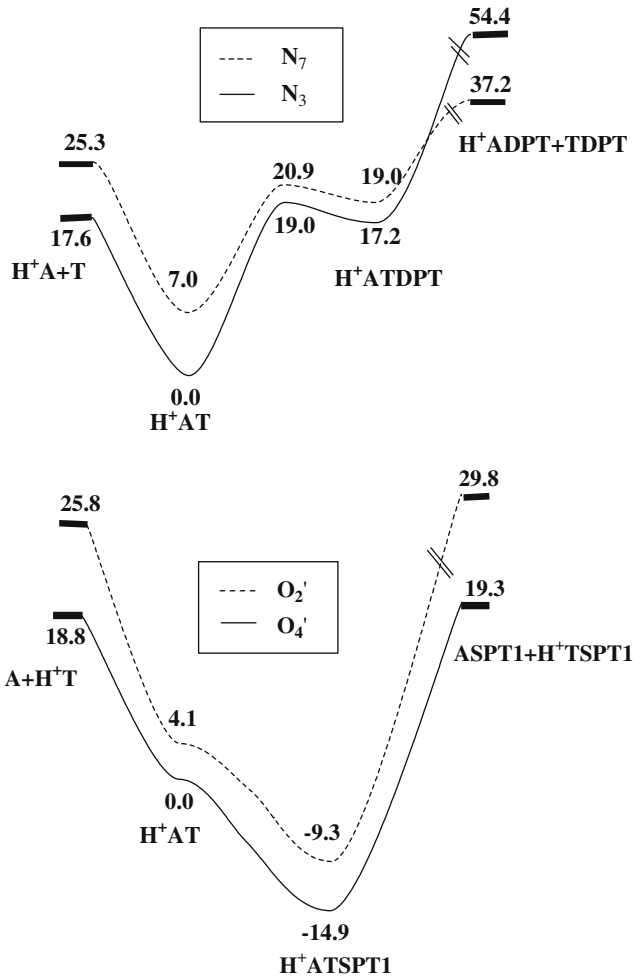


Fig. 5 Energy profiles corresponding to the DPT and single proton transfer (*SPT1*) processes in the adenine and thymine protonated systems, respectively. Energies are in kcal/mol

First, as already suggested by Löwdin in 1963, for neutral systems with equally charged bases the concerted double proton transfer reactions is the preferred process since it does not involve a charge separation. Reaction energies, 10.1 and 13.6 kcal/mol for GC and AT, respectively, are determined by the stability of the tautomers involved in the pairing and by the hydrogen bond interaction.

Let us now consider the situation in which the two bases are unequally charged as it is the case for the ionized or protonated systems. For GC and AT radical cations, for which the positive charge mainly lies at the purine moiety, due to their lower ionization energy compared to those of the pyrimidine monomers, the single proton transfer reaction from the purine to the pyrimidine monomer is the preferred process. For the two systems, GC and AT, the non proton transferred and single proton transferred structures are almost degenerate ($\Delta E = 1.2$ kcal/mol), and the process presents low energy barriers (4.3 kcal/mol for GC and 1.6 kcal/mol for AT). This is due to the increased acidity of the ionized monomers and to the fact that the single proton transfer reaction does not imply a charge separation but just the transfer of a positive charge.

The introduction of a positive charge through protonation at the purine monomer presents certain similarities to ionization but only in the case of GC, for which the single proton transfer from guanine to cytosine becomes the more favorable process. Again, this is due to the increased acidity of guanine upon protonation and to the fact that the transfer does not imply a charge separation. However, N_7 protonated adenine–thymine base pair behaves dramatically differently from the adenine–thymine radical cation [28], even though in both cases the purine moiety holds a positive charge. That is, for $AT^{\cdot+}$ the single proton transfer reaction is the preferred process, whereas for the protonated system, no single proton transfer product has been located and the observed process correspond to the double tautomerization.

Table 3 shows the deprotonation enthalpy values for neutral ionized and protonated adenine and guanine species. It can be observed that the deprotonation enthalpies of purines radical cations ($G^{\cdot+}$ and $A^{\cdot+}$) are much lower (by about 109–126 kcal/mol) than those of their respective neutral species. This is not surprising

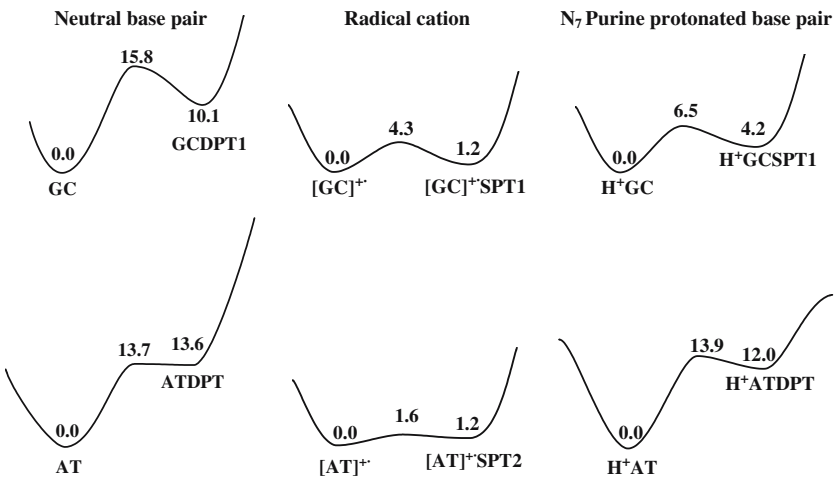


Fig. 6 Schematic representation of the energy profiles corresponding to proton transfer processes in neutral, radical cation and protonated GC and AT base pairs

Table 3 Deprotonation enthalpies (kcal/mol) and net charges

N_1			N_6		
	DE(kcal/mol)	charge		DE(kcal/mol)	charge
Gua	339.0	−0.63	Ade	355.8	−0.76
H^+Gua_{N7}	248.4	−0.61	H^+Ade_{N7}	261.2	−0.72
H^+Gua_{N3}	231.6	−0.61	H^+Ade_{N3}	255.1	−0.67
$[Gua]^{+\cdot}$	230.0	−0.61	$[Ade]^{+\cdot}$	229.2	−0.57

since acidification of the considered proton is related to the charge-increase in the corresponding nitrogen atom. Natural population analysis indicates that for the radical adenine system the depletion of electronic charge on N_6 is the largest. For guanine, we do not observe such an important decrease due to the different nature of the *N* atom and because it is compensated by π polarization. This important enhancement of acidity upon ionization is the main responsible factor for promoting the single proton transfer from the purine moiety to the pyrimidine. Although protonation at N_7 induces also an important decrease in the deprotonation energy (∼90–95 kcal/mol), the enhancement of acidity is not as important as in the case of ionization since now the charge partially remains on the proton. Moreover, proton affinity of thymine O_4 (203.6 kcal/mol) is smaller than that of cytosine N_3 (221.9 kcal/mol) in such a way that the energy difference between proton affinity and deprotonation energy of the centers involved in the proton transfer is 26.5 and 57.6 kcal/mol for $HG_{N_7}C$ and $HA_{N_7}T$, respectively. Therefore, the acidification of adenine amino proton caused by N_7 protonation is not sufficient to induce the SPT2 process, due to the low basicity of the O_6' center. This SPT2 process requires a larger acidification, which is indeed reached by oxidizing adenine.

4 Conclusions

Intermolecular proton transfer processes in the Watson and Crick adenine–thymine neutral and protonated base pairs have been studied using the density functional theory (DFT) with the non-local B3LYP hybrid density functional. Protonated systems subject to study are those resulting from protonation at the main basic sites of the base pair model, namely N_7 and N_3 of adenine and O_2' and O_4' of thymine. Protonation of adenine induces a strengthening of about 4–5 kcal/mol on the base pair but does not significantly modify the energy profiles of the unprotonated system, the most favorable reaction being the double proton transfer process. However, protonation at the O_4' and O_2' thymine moiety causes thymine's N_3 proton to spontaneously transfer to adenine while non-transferred minima disappear at this level of theory.

The behaviour of protonated AT is different from that of protonated GC in the sense that purine protonation only induces single proton transfer reactions in the case of GC. For AT, the acidification induced by protonating adenine, along with the lower basicity of the accepting center (O_4'), is not enough to stabilize the single proton transfer product. Thus, although according to Löwdin's hypothesis, the introduction of a positive

charge strongly favors the proton transfer from the more positively charged nucleobase to the other one, its feasibility depends on the acid/base nature of the involved nucleobases.

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