

Theoretical study of the interaction between cytosine and hydrogen peroxide

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Abstract

This work deals with a theoretical study of the interaction between the amino-oxo (a-o) and *cis* amino-hydroxy (a-h) tautomers of cytosine with one hydrogen peroxide molecule (HP). The optimized geometries, binding energies and harmonic vibrational frequencies are calculated using DFT/B3LYP functional combined with the 6-31++G(d,p) basis set. The results of a NBO analysis are reported as well. Four stable a-o-HP and six stable a-h-HP complexes are found on the potential energy surface. The structures are cyclic, some of them being stabilized by weak intermolecular CH...O interactions. The binding energies range from −12.9 to −47.7 kJ mol^{−1}. HP binds to a-o cytosine 5.4–7.9 kJ mol^{−1} stronger than to the enol form. The data are compared with uracil–H₂O and uracil–HP complexes. The binding energies corresponding to the formation of C=O...HO...HN hydrogen bonds depend exponentially on the proton affinities of the O atoms of the carbonyl and hydroxyl groups and on the deprotonation enthalpies of the OH and NH bonds. The frequencies of the inversion mode of the NH₂ group are very sensitive to the pyramidal character of this group. The ν(CH) stretching vibrations of the CH bonds involved in the interaction show the characteristic features of the blue-shifted hydrogen bonds. The frequency shifts of the ν(OH) vibration of HP and of the ν(CH) vibration of cytosine are discussed in terms of the occupation of the corresponding antibonding orbitals and the rehybridization occurring upon complex formation. © 2005 Elsevier B.V. All rights reserved.

1. Introduction

As outlined in a previous work, hydrogen peroxide (HP) is of considerable interest in several biochemical processes [1]. More specifically, different modified DNA bases have been identified by treating mammalian cells with HP and it has been proven that the biological effect of HP is mediated by hydrogen-bond adducts [2,3]. The above considerations justify the interest of studying all the nucleobases–HP adducts. Up to now, only the interaction between adenine and HP [1] and

uracil and HP [4] has been investigated. It must be mentioned that compared with water relatively few experimental or theoretical data have been reported on the complexing ability of HP. Theoretical calculations have been carried out on HP complexed with water [5], hydrogen halides [6] and urea [7].

In the present work, we expand our studies on HP to the cytosine complexes. It is well known that cytosine exists as a mixture of several tautomers, the amino-oxo (a-o) and the amino-hydroxy (a-h) forms being the most stable ones. These two major tautomers have been identified by infrared spectroscopy in low-temperature matrices [8], by microwave spectroscopy [9] and more recently by double resonance laser spectroscopy [10]. Numerous calculations have been carried out on the relative energies of these two tautomers. Since the

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tautomers are very close in energy, their relative stabilities are very sensitive to the level of theory applied in computations. MP2 calculations have shown that the *cis*-enol form (a-h) is slightly more stable than the *trans*-enol form and represents the global minimum at almost all theoretical levels while the canonical oxo form found in DNA represents the first local minimum [11,12]. In contrast, DFT favours slightly the a-o form [13]. This conclusion is in agreement with calculations of Gibbs free energies performed at advanced levels of theory (MP4(SDQ)) and MP4(SDQ)/6-31 + G(d,p)//MP2/6-31 + G(d,p) indicating that the a-o tautomer is slightly more stable than the a-h one [14]. Owing to their similar stabilities, the interaction between both a-o and a-h tautomers and HP will be investigated in the present work. Our main objective is to systematically analyze the optimized structures, the binding energies, vibrational properties along with the charge redistribution resulting from complex formation. The results are compared with the data obtained for the interaction between the cytosine tautomers and water [15]. As shown by experimental data, H₂O is a better proton acceptor than HP but HP is a better proton donor than H₂O [16]. It seemed interesting to discuss to what extent the basicity/acidity of these two amphoteric molecules influences the properties of the complexes they are forming at the different sites of cytosine. The energies of the complexes can also be influenced by the proton donor and proton acceptor abilities of the different sites of cytosine which have been reported in a recent work [15]. In order to have a reliable comparison with the cytosine–H₂O complexes [15], all the calculations are carried at the B3LYP/6-31++G(d,p) level. It should be mentioned that to the best of our knowledge, no experimental data in the gas phase or in low-temperature materials have been reported for these interactions.

2. Computational methods

The structures of the cytosine–HP complexes were fully optimized by the density three-parameter hybrid model (DFT/B3LYP) [17,18] using the 6-31++G(d,p) basis set. It has been demonstrated that this level of theory is very reliable in predicting the acidities of nucleobases [19–21] along with the geometrical and vibrational features of their complexes with water [22,23]. Of several assumed conformations of the cytosine–HP complexes, several cyclic complexes proved to be stationary points (all real frequencies) on the potential energy surface. The binding energies were calculated as the difference of the energies of the complex and the sum of the energies of the separated monomers. The counterpoise method of Boys and Bernardi [24] was applied to correct for the basis set superposition error (BSSE) similar to our earlier studies [22,23]. The zero

point vibrational energy correction (ZPE) has also been included.

The charges on individual atoms and orbital occupancies were calculated by using the natural bond population scheme [25]. All calculations were performed with the Gaussian 98 package [26]. To make an unequivocal comparison of the frequencies in the isolated molecules and in their complexes, a rigorous normal coordinate analysis was performed. The non-redundant set of 33 internal coordinates for the isolated cytosine tautomers and 45 internal coordinates for the HP complexes has been derived as recommended by Fogarasi and Pulay [27]. The potential energy distribution (PED) has been calculated for all the systems, according to the procedure described in our earlier papers [28,29]. The BSSE-corrections on the frequencies are usually weak and were not taken into account.

3. Results and discussion

3.1. Optimized geometries and binding energies of the cytosine–HP complexes

The optimized structures of the a-o–HP and a-h–HP complexes are shown in Figs. 1 and 2. It must be mentioned that for the a-o–HP interaction, one stable open complex formed at the O7 carbonyl atom is obtained (O7...H16 = 1.808 Å, ∠O16H16O7 = 173.3°). This complex characterized by a binding energy (including BSSE- and ZPE-corrections) of $-31.3 \text{ kJ mol}^{-1}$ will no more be considered in the present work which is mainly intended to discuss the bonding trends in the cyclic complexes. Geometrical parameters which are relevant for the discussion are indicated in Table 1.

Table 2 contains the binding energies including the BSSE- and ZPE-corrections of the a-o and *cis* a-h cytosine–HP complexes.

We will consider at first the a-o–HP systems. In the A₁ complex, the interaction with HP results in an increase of the planarity of the amino group (despite to the fact that this group is not bonded to HP). The sum of the angles around the N8 atom increases from 358.0° to 359.7° and the C5C4N8H10 and N3C4N8H9 dihedral angles which are equal to 10.3° and -6.4° in the free molecule decrease to -3.6° and 2.4° in the A₁ complex. When the interaction occurs at the (N3, N8H9) side of cytosine, two stable complexes can be formed. Complex B₂ having a binding energy of $-46.7 \text{ kJ mol}^{-1}$ is more stable than complex B₁ characterized by a binding energy of $-42.9 \text{ kJ mol}^{-1}$. This can be accounted for by a more linear arrangement of the two hydrogen bonds in complex B₂. It is worth mentioning that in the complexes between urea and HP, the binding energy of the seven-membered structure calculated at the B3LYP/6-31G(d,p) level is equal to

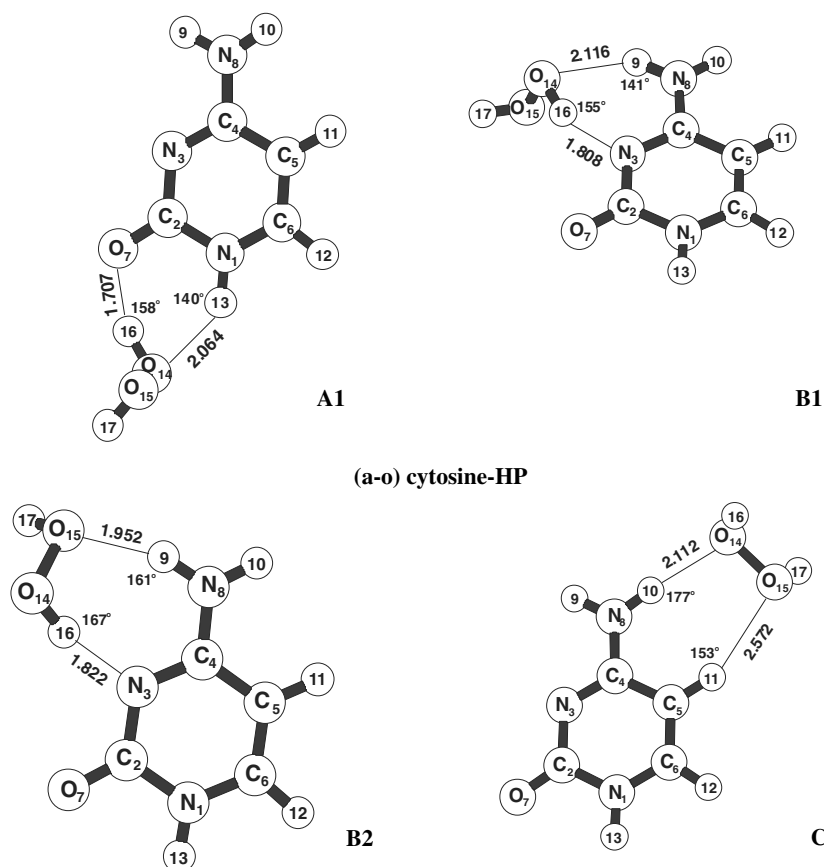


Fig. 1. B3LYP/6-31++G(d,p) optimized structures for the complexes between amino-oxo cytosine and hydrogen peroxide.

$-44.6 \text{ kJ mol}^{-1}$, about 6 kJ mol^{-1} larger than the six-membered one [7]. Further, as indicated by the H11...O15 intermolecular distance of 2.572 \AA and the C5H11O15 angle of 153.3° , the a-o-HP(C) complex, is stabilized by a C5H11...O15 hydrogen bond. This complex is characterized by a binding energy of $-13.6 \text{ kJ mol}^{-1}$. This small value can be explained by the low acidity of the C5H11 bond (DPE = 1573 kJ mol^{-1}) [20] and by the fact that the structure is anticooperative, the two O atoms of HP acting both as electron donor [30]. The O14H16 bond is elongated by $0.0277\text{--}0.0378 \text{ \AA}$ in structures A₁, B₁ and B₂ but remains practically unchanged in the anticooperative structure C.

The formation of complexes between *cis* a-h cytosine and HP also results in a larger planarity of the NH₂ group. The H9N8H10 angle increases by ca. $0.5\text{--}2^\circ$ and there is also a decrease of the dihedral angles H9N8C4N3 and H10N8C4C5 by ca. $2\text{--}5^\circ$. The binding energies for the A₂ and A₁ complexes are equal to -47.7 and $-39.0 \text{ kJ mol}^{-1}$, respectively. Again, this difference can be accounted for by a more linear arrangement in the seven-membered structure. As indicated by the H11...O15 distance of 2.637 \AA and the C5H11...O15 angle of 149.8° , structure C is stabilized by a weak

CH...O hydrogen bond. Structure D is stabilized by a relatively short N1...H16O14 hydrogen bond (1.8289 \AA); the H12...O15 distance equal to 2.784 \AA is too long to be classified as a hydrogen bond but a weak electrostatic interaction between the C6H12 and the O15 atom cannot be ruled out. Interestingly, complex formation results in a marked contraction of the C6H12 bond equal to 0.011 \AA . This will be discussed in the following section.

The results of Table 2 indicate that the binding energies of HP with the a-o tautomer are larger than the binding energies with the a-h tautomer. For the comparable structures A₁, B₁ and B₂, the binding energies of the a-o tautomer with HP are larger by 7.9 , 6.3 and 5.4 kJ mol^{-1} , respectively. This is in agreement with our data on the cytosine–water complexes where the binding energies of the a-o(A₁) complex was calculated to be larger by 6.7 kJ mol^{-1} and the (a-o)B₁ complex by 5.5 kJ mol^{-1} than in the corresponding a-h complexes [15]. Recent data have also shown that the dissociation energy of the a-o cytosine–water A₁ complex (including BSSE) is significantly lower (7.1 kJ mol^{-1}) than the a-h cytosine–water complex [31].

Let us now discuss the bonding trends in the a-o cytosine–HP and a-o cytosine–H₂O complexes in the A₁

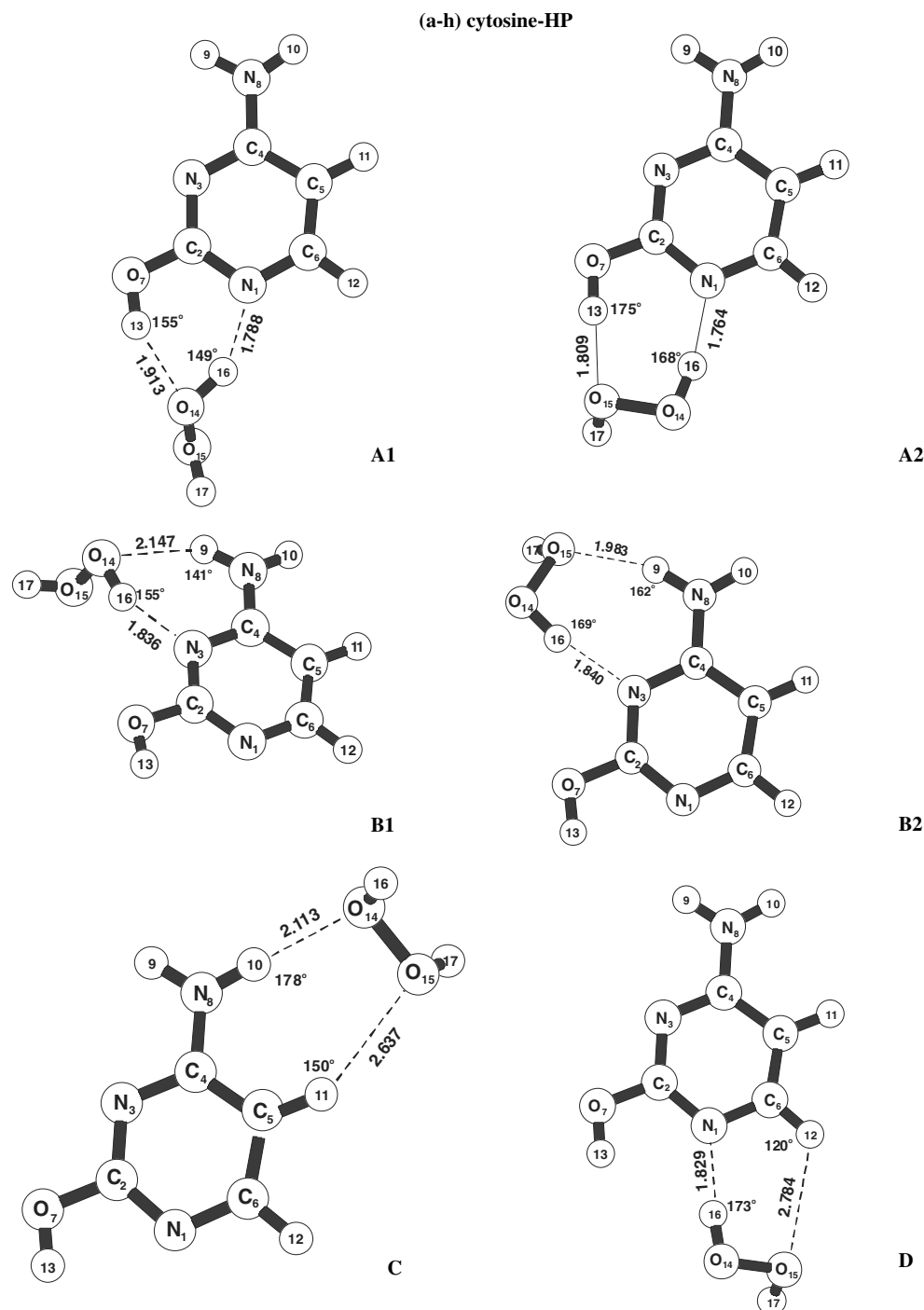


Fig. 2. B3LYP/6-31++G(d,p) optimized structures for the complexes between amino-hydroxy cytosine and hydrogen peroxide.

structure where H_2O or HP interact with a-o cytosine at the (N1–H13, O7) side to give a six-membered ring [10]. The H13...O14 distance in the H_2O complex equal to 1.947 Å is shorter by 0.117 Å than the corresponding distance in the a-o cytosine–HP complex. In contrast, the O7...H16 distance equal to 1.813 Å is longer by 0.106 Å than the corresponding distance in the a-o cytosine–HP system. This can be explained by the fact that the O atom of water is more basic than that of HP; in-

versely, the OH bond of HP is a better proton donor than that of water. It must be mentioned that the six-membered ring involving the $\text{C}=\text{O}\cdots\text{HO}\cdots\text{HN}$ hydrogen bonds is nearly planar and the intermolecular angles do not markedly differ which allows for a valuable comparison. Further, the binding energy of cytosine with H_2O ($-37.2 \text{ kJ mol}^{-1}$) [15] is smaller by more than 9 kJ mol^{-1} than that of the corresponding a-o cytosine–HP complex ($-46.9 \text{ kJ mol}^{-1}$). In previous works

Table 1

Selected optimized distances (Å) and angles (deg) in isolated a-o and a-h cytosine and HP and their 1–1 complexes

	Free a-o cytosine or HP	Complex A ₁	Complex B ₁	Complex B ₂	Complex C
<i>r</i> (N1H13)	1.0114	1.0207	1.0114	1.0110	1.0111
<i>r</i> (N8H9)	1.0093	1.0090	1.0175	1.0198	1.0088
<i>r</i> (N8H10)	1.0065	1.0061	1.0064	1.0065	1.0108
<i>r</i> (C5H11)	1.0825	1.0825	1.0822	1.0823	1.0824
<i>r</i> (C6H12)	1.0849	1.0846	1.0848	1.0848	1.0851
<i>r</i> (O14H16)	0.9712	1.0009	0.9992	0.9989	0.9720
∠H9N8C4	117.6	118.2	118.7	119.0	117.6
∠H10N8C4	121.5	122.0	121.1	121.0	122.3
∠H9N8H10	118.9	119.5	119.8	119.9	120.0

	Free a-h cytosine or HP	Complex A ₁	Complex A ₂	Complex B ₁	Complex B ₂	Complex C	Complex D
<i>r</i> (O7H13)	0.9702	0.9828	0.9855	0.9703	0.9703	0.9700	0.9693
<i>r</i> (N8H9)	1.0093	1.0090	1.0091	1.0160	1.0180	1.0090	1.0090
<i>r</i> (N8H10)	1.0069	1.0064	1.0066	1.0063	1.0062	1.0106	1.0064
<i>r</i> (C5H11)	1.0840	1.0837	1.0837	1.0838	1.0838	1.0837	1.0837
<i>r</i> (C6H12)	1.0876	1.0871	1.0872	1.0873	1.0873	1.0878	1.0865
<i>r</i> (O14H16)	0.9712	1.0006	1.0031	0.9952	0.9960	0.9720	0.9921
∠H9N8C4	117.3	118.1	117.8	119.1	119.5	118.0	118.2
∠H10N8C4	120.4	121.2	121.1	120.6	120.6	121.9	121.3
∠H9N8H10	118.1	118.9	118.7	119.5	119.8	119.9	119.0

Results from B3LYP/6-31++G(d,p) calculations.

Table 2

Binding energies (E_{HB}) (kJ mol^{−1}) of a-o and a-h cytosine with HP with BSSE- and ZPE-corrections

	Complex A ₁	Complex A ₂	Complex B ₁	Complex B ₂	Complex C	Complex D
a-o E_{HB}	−46.9		−42.9	−46.7	−13.6	
BSSE	−0.9		0.2	1.1	2.3	
ZPE	6.7		7.4	8.6	5.2	
a-h	−39.0	−47.7	−36.6	−41.3	−12.9	−27.3
BSSE	−0.6	0	1.2	1.7	2.2	1.5
ZPE	6.1	7.7	6.6	7.7	4.4	5.0

Results of B3LYP/6-31++G(d,p) calculations.

[23,32], we have correlated the hydrogen-bond energies of different hydrated nucleobases to the proton affinities (PA) and the deprotonation enthalpies (PA(A[−])) of the sites involved in the interaction. Thus for the considered complexes, PA(A[−]) are the deprotonation enthalpies of the NH bonds and PA(B) the PA of the carbonyl oxygen atom forming the six-membered ring. In a small range, the correlation can be considered as linear [23]. In a broader range, the best fit is an exponential expression of the form [32]

$$E_{\text{HB}} = A e^{B(\text{CPA}(\text{A}^-) - \text{PA}(\text{B}))}. \quad (1)$$

It should be noticed that exponential expressions between binding energies and proton affinities have been obtained for strong ionic hydrogen bonds [33–35]. Further, an exponential expression between the binding energies and the difference in proton affinities has been recently deduced from a valence bond analysis [36].

For a quantitative comparison between the complexes of the nucleobases uracil and cytosine with H₂O and HP, the intrinsic acidities and the basicities of these

molecules must also be considered. In other words, we must consider the PAs of the O atoms of H₂O and HP (PA(O)) and the deprotonation enthalpies of the OH groups (PA(O[−])) of these two molecules. Table 3 contains the binding energies of uracil and cytosine with H₂O and HP. This table also reports the PA(A[−]), PA(B) values of the nucleobases along with the experimental PA(O[−]) and PA(O) of H₂O and HP. These data show that the PA of H₂O is larger by ca 20 kJ mol^{−1} than the PA of HP. This is in agreement with the larger electron withdrawing character of OH as compared with H [37]. Taking these basicities/acidity data into account, the binding energies have been fitted to an exponential function of the form:

$$E_{\text{HB}} = 24.77 \times 10^3 e^{-0.0044[\text{PA}(\text{A}^-) + \text{PA}(\text{O}^-) - (\text{PA}(\text{B}) + \text{PA}(\text{O}))]} \quad (r = 0.9792), \quad (2)$$

illustrated in Fig. 3.

Interestingly, a double exponential equation similar to Eq. (2) has been recently used in order to evaluate the interaction energies of triazoles clusters involved in

Table 3

Binding energies of uracil and a-o cytosine with H₂O and HP (C=O...HO...HN hydrogen bonds), deprotonation enthalpies (PA(A[−])) of the NH bonds and proton affinities of the O atoms

Uracil–H ₂ O ^a	Uracil–HP ^b	PA(A [−]) ^a	PA(B) ^a
−32.7 ^c	−37.0 ^c	1391	815
−24.4 ^d	−28.1 ^d	1447	820
−26.7 ^e	−31.0 ^e	1447	849
Cytosine–H ₂ O ^f	Cytosine–HP ^g	PA(O [−]) ^h	PA(O) ^h
−37.2	−46.9	1446	922
H ₂ O		1635	697
HP		1573	678

Deprotonation enthalpies of the OH bonds of water and HP (PA(O[−])) and PA of the O atoms H₂O and HP (PA(O)). All data in kJ mol^{−1}. The PAs are defined as the negative enthalpy changes associated with the gas-phase protonation reaction. The deprotonation enthalpies are defined as the enthalpy changes associated with the gas-phase deprotonation reaction.

^a Ref. [32].

^b Ref. [15].

^c Complex formed at the (N1H1, O4) side of uracil.

^d Complex formed at the (N3H3, O4) side of uracil.

^e Complex formed at the (N3H3, O2) side of uracil.

^f Ref. [32].

^g This work.

^h Ref. [16].

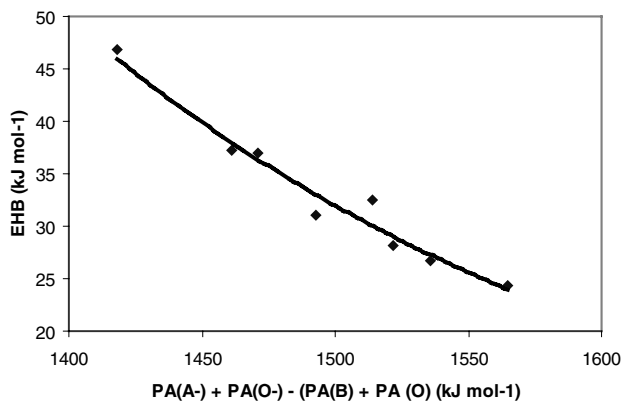


Fig. 3. E_{HB} as a function of $PA(A^-) + PA(O^-) - (PA(B) + PA(O))$ (kJ mol^{−1}).

double proton transfer processes [38]. It must be noticed that Eq. (2) has been deduced for cyclic NH...OH...O=C hydrogen-bonded systems. The coefficients of this equation must depend on the nature of the hydrogen bond.

3.2. Vibrational frequencies and NBO analysis of the cytosine–HP complexes

In this section, we will discuss the harmonic vibrational frequencies and infrared intensities of selected vibrational modes in the complexes involving the two

cytosine tautomers with HP. The vibrational data dealing mainly with the vibrations of the OH, NH₂ and CH groups are summarized in Table 4. Results of a NBO analysis for the two tautomers complexes which are relevant for the discussion are summarized in Table 5 [39].

Let us at first discuss the vibrations of the NH₂ group. In the complexes where the NH₂ group is not involved in the interaction with HP a-o cytosine (A₁), a-h cytosine (A₁, A₂, D), the frequencies of the $\nu^{as}(\text{NH}_2)$ and $\nu^s(\text{NH}_2)$ vibrations increase by a few wavenumbers (3–9 cm^{−1}) which is related to the small decrease of pyramidalization of the NH₂ group induced by the interaction with HP. The NBO analysis for these free NH₂ groups indicate that the s-character of the N atom bonded to H increases by ca. 0.5% and that there is no change in the occupation of the corresponding $\sigma^*(\text{NH})$ orbital. Not surprisingly, when the NH₂ group is involved in hydrogen bonding, both the $\nu^{as}(\text{NH}_2)$ and $\nu^s(\text{NH}_2)$ vibrations are shifted to lower frequencies and their corresponding infrared intensities increase. As indicated by the PED, the low-frequency vibration in the B₁ and B₂ complexes involving the two tautomers is predominantly the $\nu(\text{N8H10})$ vibration. The lowering of the frequencies can be mainly accounted for by a marked change of the occupation of the $\sigma^*(\text{N8H9})$ orbital which increases from 0.009e in the free tautomers to 0.034e (a-o(B₂)) or 0.032e (a-h(B₂)). The same remark also holds when the N1H13 or the O7H13 bonds are involved in the interaction with HP.

The frequencies of the $\tau(\text{NH}_2)$ vibration coupled with other vibrational modes increase by about 10–20 cm^{−1}. Interesting features are predicted for the $\text{inv}(\text{NH}_2)$ vibration. It should be mentioned that the frequency of this mode is very sensitive to the method and level of calculation. Indeed, calculations carried out at the B3LYP/6-31G(d,p) level predict the $\text{inv}(\text{NH}_2)$ mode at 275 cm^{−1} in a-o and at 326 cm^{−1} in a-h [40–42]. These values are by ca. 70–100 cm^{−1} higher than the values calculated in the present work. Furthermore, it has been shown that the $\text{inv}(\text{NH}_2)$ mode in heteroaromatic molecules cannot be properly described within the harmonic approximation [40–42]. Therefore, their relative frequency variations are more significant than their absolute values. Our calculations indicate that the frequency of the $\text{inv}(\text{NH}_2)$ mode decreases by ca. 80 cm^{−1} in the a-o(A₁) complex and by 50–90 cm^{−1} in the a-h(A₁, A₂, D) complexes, in agreement with the increase of planarity of the NH₂ group resulting from the interaction with HP. The high sensitivity of the frequency of the $\text{inv}(\text{NH}_2)$ appears from our data showing that an increase of the sum of the angles around the N8 atom by one degree results in a decrease of the frequency of the $\text{inv}(\text{NH}_2)$ mode by 40 cm^{−1}.

Interesting features are predicted for the $\nu(\text{CH})$ vibrations. The apparent infrared intensity increase of the $\nu(\text{C5H11})$ vibration in a-o(B₁, B₂) complexes result from

Table 4

Unscaled frequencies (cm^{-1}) and infrared intensities (km mol^{-1} , in parentheses) of selected vibrational modes in free a-o cytosine, a-h cytosine and HP and their complexes

a-o Cytosine	Complex A ₁	Complex B ₁	Complex B ₂	Complex C	Assignment ^a		
3750 (51)	3757 (57)	3722 (96)	3716 (98)	3719 (155)	$\nu^{\text{as}}(\text{NH}_2)$		
3629 (71)	3474 (614)	3631 (87)	3631 (88)	3632(71)	$\nu(\text{N1H13})$		
3609 (92)	3614 (90)	3501 (471)	3457 (631)	3572 (261)	$\nu^{\text{s}}(\text{NH}_2)$		
3236 (3)	3237 (2)	3241 (41)	3238 (288)	3240 (4)	$\nu(\text{C5H11}) + \nu(\text{O14H16})^{\text{B2}} + \nu(\text{C6H12})^{\text{B1}}$		
3212 (3)	3218 (69)	3216 (1)	3216 (1)	3210 (6)	$\nu(\text{C6H12}) + \nu(\text{C5H11})^{\text{A1}}$		
1774 (775)	1731 (906)	1778 (727)	1779 (704)	1767 (803)	$\nu(\text{C2=O7})$		
1638 (147)	1639 (225)	1653 (62)	1663 (30)	1655 (105)	$\delta(\text{NH}_2)$		
1088 (42)	1101 (25)	1118 (58)	1119 (41)	1102 (49)	$r(\text{NH}_2) + \nu(\text{C2=O7})$		
626 (66)	793 (20)	614 (25)	617 (33)	596 (40)	$\gamma(\text{N1H13})$		
526 (11)	540 (14)	667 (101)	693 (84)	637 (28)	$\tau(\text{NH}_2) + \gamma(\text{N1H13})^{\text{B1,C}}$		
174 (195)	93 (198)	303 (145)	313 (95)	364 (253)	$\text{inv}(\text{NH}_2)$		
<i>HP</i>							
3769 (11)	3216 (809)	3234 (925)	3242 (651)	3762 (34)	$\nu(\text{O14H16})$		
3768 (60)	3773 (37)	3770 (32)	3774 (38)	3758 (70)	$\nu(\text{O15H17})$		
1445 (1)	1516 (14)	1515 (61)	1574 (32)	1439 (1)	$\delta\text{H16O14O15}$		
945 (1)	962 (155)	954 (25)	940 (4)	949 (2)	$\nu\text{O14O15} + \delta(\text{O14H16O7})^{\text{A1}} + \nu(\text{N1C2})^{\text{B1}}$		
373 (222)	249 (133)	261 (134)	354 (130)	441 (224)	$\tau\text{H16O14O15H17}$		
a-h Cytosine	Complex A ₁	Complex A ₂	Complex B ₁	Complex B ₂	Complex C	Complex D	Assignment
3787 (93)	3533 (940)	3469 (1180)	3787 (103)	3787 (105)	3788 (87)	3798 (102)	$\nu(\text{O7H13})$
3745 (48)	3753 (53)	3750 (52)	3726 (95)	3722 (99)	3725 (149)	3754 (55)	$\nu^{\text{as}}(\text{NH}_2)$
3609 (73)	3614 (82)	3612 (81)	3526 (386)	3487 (586)	3577 (251)	3616 (91)	$\nu^{\text{s}}(\text{NH}_2)$
3217 (8)	3221 (7)	3221 (4)	3221 (8)	3220 (9)	3225 (1)	3223 (7)	$\nu(\text{C5H11})$
3179 (16)	3185 (62)	3185 (30)	3183 (16)	3183 (17)	3175 (22)	3199 (2)	$\nu(\text{C6H12})$
1640 (20)	1645 (45)	1649 (155)	1676 (566)	1681 (448)	1671 (567)	1645 (22)	$\delta(\text{NH}_2) + \nu(\text{C5C6}) + \nu(\text{C2N3})$
1245 (56)	1306 (4)	1313 (14)	1245(69)	1242 (73)	1248 (52)	1244 (75)	$\delta(\text{O7H13}) + \nu(\text{C2N3})$
492 (6)	513 (11)	510 (12)	625 (49)	663 (33)	610 (6)	507 (2)	$\tau(\text{NH}_2) + \delta(\text{C2O7})$
258 (254)	167 (232)	207 (248)	285 (169)	277 (106)	331 (255)	169 (227)	$\text{inv}(\text{NH}_2) + \tau(\text{H}_2\text{O}_2)^{\text{B2,C}}$
<i>HP</i>							
3769 (11)	3779 (38)	3773 (45)	3773 (32)	3774 (38)	3759 (65)	3777 (32)	$\nu(\text{O15H17})$
3768 (60)	3204 (985)	3144 (1276)	3308 (892)	3293 (919)	3763 (34)	3350 (1357)	$\nu(\text{O14H16})$
1445 (1)	1515 (137)	1631 (83)	1510 (77)	1575 (51)	1440 (1)	1575 (5)	$\delta(\text{H16O14O15})$
945 (1)	959 (38)	942 (3)	950 (7)	942 (4)	1004 (7)	943 (4)	$\nu(\text{O14O15})$
374 (222)	236 (113)	396 (135)	251 (125)	343 (133)	430 (231)	258 (138)	$\tau(\text{H16O14O15H17}) + \tau\text{HB ring}^{\text{A2,B2,D}}$

Results from B3LYP/6-31++G(d,p) calculations.

^a ν , stretching; δ , deformation; r , rocking; γ , out-of-plane bending; τ , torsional; inv , inversion mode.

a coupling with the $\nu(\text{O14H16})$ or $\nu(\text{C6H12})$ vibrations and will no more be discussed hereafter. The intermolecular H11...O15 distances of 2.572 and 2.637 Å in the a-o(C) and a-h(C) complexes indicate that weak intermolecular CH...O hydrogen bonds are present in these systems. As shown by the PED, the $\nu(\text{C5H11})$ and $\nu(\text{C6H12})$ vibrations are 90–98% pure and can be considered as intrinsic properties of these complexes [43].

A thorough discussion of blue-shifted hydrogen bonds in which hydrogen bond formation leads to a CH bond shortening, a blue shift and an infrared intensity decrease of the CH stretching vibration lies out of the scope of the present work (see for example [44–58]). Let us notice that in a-o(C), the $\nu(\text{C5H11})$ vibration is blue shifted by 4 cm^{-1} , corresponding to a small contraction of the bond by 0.1 mÅ. Further, in a-h(C), the C5H11 bond is contracted by 0.3 mÅ, the $\nu(\text{C5H11})$ vibration is blue shifted by 8 cm^{-1} and

its infrared intensity decreases from 8 to 1 km mol^{-1} . These effects are weak but are thought to be significant. Indeed CH bond contractions between 0.1 and 0.5 mÅ have been predicted for weak hydrogen-bond complexes [49,50,53]. One of the most attractive explanation of the blue shift has been provided by Alabugin et al. [52] who have suggested that the CH bond length is controlled by two effects which act in opposite directions: the CH bond lengthening due to increased occupation of the $\sigma^*(\text{CH})$ antibonding orbital and the CH bond contraction due to the increasing s-character of the CH bond. Our results are in good qualitative agreement with this statement. Indeed, in the a-o(C) and a-h(C) complexes, our calculations (Table 5) predict a small increase of the $\sigma^*(\text{C5H11})$ occupation by 0.002–0.003e and a weak increase of the s-character of the CH bond by 0.5%. In a-h(D), where the blue shift ($+20 \text{ cm}^{-1}$) and the contraction of the C6H12

Table 5

Results of NBO analysis for isolated a-o cytosine, a-h cytosine and HP and their complexes

	a-o Cytosine or HP	Complex A ₁	Complex B ₁	Complex B ₂	Complex C
<i>NBO charges (e)</i>					
C5	−0.400	−0.395	−0.393	−0.393	−0.400
H11	0.248	0.250	0.252	0.251	0.260
C6	0.067	0.076	0.070	0.070	0.060
H12	0.242	0.247	0.245	0.245	0.238
O14	−0.493	−0.538	−0.537	−0.502	−0.500
H16	0.493	0.516	0.513	0.508	0.505
<i>CT (e)^a</i>					
		0.036	0.037	0.029	−0.020
<i>% s-Character</i>					
C5H11	32.7	32.8	32.7	32.7	33.2
C6H12	32.1	32.3	32.2	32.2	32.1
O14H16	22.3	29.1	29.6	29.2	22.8
<i>Occupation of σ^* orbitals (e)</i>					
$\sigma^*(\text{C5H11})$	0.011	0.011	0.010	0.010	0.014
$\sigma^*(\text{C6H12})$	0.013	0.012	0.012	0.012	0.013
$\sigma^*(\text{O14H16})$	0.004	0.066	0.064	0.062	0.004

	a-h Cytosine	Complex A ₁	Complex A ₂	Complex B ₁	Complex B ₂	Complex C	Complex D
<i>NBO charges (e)</i>							
C5	−0.390	−0.388	−0.388	−0.386	−0.385	−0.393	−0.383
H11	0.244	0.246	0.246	0.246	0.247	0.254	0.248
C6	0.064	0.076	0.078	0.068	0.068	0.058	0.074
H12	0.229	0.233	0.232	0.231	0.231	0.225	0.249
O14	−0.493	−0.506	−0.539	−0.504	−0.534	−0.501	−0.527
H16	0.493	0.503	0.514	0.506	0.511	0.505	0.502
<i>CT (e)^a</i>							
		0.023	0.028	0.028	0.035	−0.021	0.049
<i>% s-Character</i>							
C5H11	32.3	32.4	32.4	32.2	32.3	32.7	32.4
C6H12	30.6	30.8	30.7	30.7	30.7	30.5	31.3
O14H16	22.3	29.9	29.6	28.8	29.0	22.6	28.8
<i>Occupation of σ^* orbitals (e)</i>							
$\sigma^*(\text{C5H11})$	0.012	0.012	0.012	0.012	0.012	0.014	0.012
$\sigma^*(\text{C6H12})$	0.020	0.018	0.018	0.019	0.020	0.020	0.018
$\sigma^*(\text{O14H16})$	0.004	0.074	0.069	0.059	0.058	0.004	0.057

^a Sum of the NBO charges on the cytosine tautomer.

bond (1.1 mÅ) which is not hydrogen bonded are the largest, both effects are acting in the same direction, the occupation of the $\sigma^*(\text{C6H12})$ orbital decreasing by 0.002e and the percentage of s-character of the bond increasing by 0.7% with respect to isolated a-h. More quantitative results dealing with the rehybridization model have been obtained for the interaction between methylhalides and HP where the CH distances have been expressed by a dual equation [59].

The vibrational modes (stretching, deformation and torsional vibrations) of HP are also perturbed. The $\nu(\text{O14H16})$ vibration is red shifted by ca. 525–550 cm^{−1} in the a-o–HP complexes and 420–625 cm^{−1} in a-h–HP complexes. Their infrared intensities markedly increase, in agreement with the polarity enhancement of the O14H16 bond. In all the complexes, our calculations predict a marked increase of the occupation

of the $\sigma^*(\text{O14H16})$ orbital which is equal to 0.004e in the isolated HP molecule and increases up to 0.057–0.074e in the corresponding complexes. The frequency shift of the $\nu(\text{O14H16})$ vibrations are correlated to the increase of the occupation of the $\sigma^*(\text{O14H16})$ orbital by the equation:

$$\Delta\nu(\text{O14H16}) \text{ (cm}^{-1}\text{)} = 1.7 + 8.7 \times 10^3 \Delta\sigma^*(\text{O14H16})(e) \quad (3)$$

($r = 0.9966$).

It should be mentioned that the % s-character of the O atom in the O14H16 bond in the complexes varies between 28.8% and 29.6%. Even though the s-character change (1.3%) is rather significant, the OH bonds are such great σ -acceptors [60] that increase of the population of the $\sigma^*(\text{O14H16})$ orbital outweighs the effect of rehybridization. We must further notice that the slope of Eq. (3) is much larger than the one obtained for the

complexes between the cytosine tautomers and water ($4.59 \times 10^{-3} \text{ e cm}^{-1}$) [10]. This may be related to the larger acidity of the OH bond in HP.

Finally, it must be mentioned that some amount of charge is transferred from cytosine to HP in all the complexes at the exception of the anticooperative structures a-o(C) and a-h(C) systems where HP acts as an electron donor. This charge transfer is moderate (0.023–0.037e) and does not markedly differ for the complexes.

4. Concluding remarks

The present work deals with a theoretical study of the interaction between the amino-oxo and *cis* amino-hydroxy tautomers of cytosine and one hydrogen peroxide molecule. In our previous studies on the interaction between nucleobases and water, we have shown the the binding energies depend on the acidity and on the basicity of the nucleobases. In the present work, it is shown that the binding energies are correlated to the proton acceptor and proton donor ability of water or hydrogen peroxide as well. Further, the perturbation of some relevant vibrational modes are discussed. More specifically, the red shift of the $\nu(\text{OH})$ vibration of hydrogen peroxide and the blue shift of the $\nu(\text{CH})$ vibration of cytosine are discussed in terms of the occupation of the corresponding antibonding orbitals and the rehybridization occurring upon complex formation.

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