

Theoretical Study of the Acidity and Basicity of the Cytosine Tautomers and Their 1:1 Complexes with Water

Asit K. Chandra,^{†,||} Danuta Michalska,^{‡,⊥} Rafat Wysokiński,[‡] and Thérèse Zeegers-Huyskens^{*,§}

Department of Chemistry, North-Eastern Hill University, Shillong 793022, India, Institute of Inorganic Chemistry, Wrocław University of Technology, Wybrzeże Wyspińskiego 27, 50-370 Wrocław, Poland, and Department of Chemistry, University of Leuven, 200F Celestijnenlaan, B-3001 Heverlee, Belgium

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This work deals with a theoretical study of the acidity and basicity of the amino–oxo, amino–hydroxy, and imino–oxo tautomers (including their rotamers) along with their interaction with one water molecule. The calculations are carried out using the DFT/B3LYP functional combined with the 6-31++G(d,p) or 6-311++G(d,p) basis sets. The proton affinities (PA) of the O and N atoms and the deprotonation enthalpies (DPE) of the OH and NH bonds of the cytosine tautomers are calculated as well. The results suggest that the amino–oxo tautomer may be the most stable form in the gas phase. The optimized geometries, binding energies, and harmonic vibrational frequencies of the cyclic structures of the monohydrated cytosine tautomers are calculated. Complex formation results in a moderate change of the pyramidal character of the amino group. For the cyclic C=O...HO...HN structures, the binding energies depend on the PA and DPE of the sites involved in the interaction. The perturbations of selected vibrational modes such as the stretching vibrations and the inversion mode of the amino group along with the blue shift of the NH stretching vibration in the imino–oxo complexes are discussed. The natural bond orbital analysis shows that there is an increase of the occupancy of the σ^* antibonding orbitals of the proton donor groups involved in the interaction.

I. Introduction

A large amount of work has been performed on the tautomerism of nucleic acid bases using both experimental and theoretical approaches. Much of the interest is due to the fact that the tautomers induce alterations in the normal base pairing leading to the possibility of spontaneous mutations in the DNA or RNA sequences.¹

There have been numerous computational studies on the tautomeric equilibrium of cytosine. On the basis of these theoretical studies, the lowest energy conformers of this nucleobase in the gas phase have been unambiguously identified. In addition to the canonical form amino–oxo (a–o), two enol (a–h(1) and a–h(2)) and two imino (i–o(1) and i–o(2)) forms shown in Figure 1 have been identified in a relatively narrow energy range. The amino–oxo tautomer is the “canonical” form found in DNA.² In aqueous solution, this form is also found to be predominant, by a factor of $10^{4.5}$.³ Since the tautomers are very close in energy, their relative stabilities are very sensitive to the level of theory.⁴ High-level calculations have been carried out recently. From MP2 calculations, it appears that the enol form (1) is the global minimum at almost all theoretical level^{4h} while the canonical form represents the first local minimum. DFT favors slightly the amino–oxo form.^{4g} Comparison of theoretical values with experimental data is difficult because there is no fully conclusive evidence yet. The canonical, enol, and a small amount of imino forms have been detected by infrared spectrometry in low-temperature matrices.⁵ The mi-

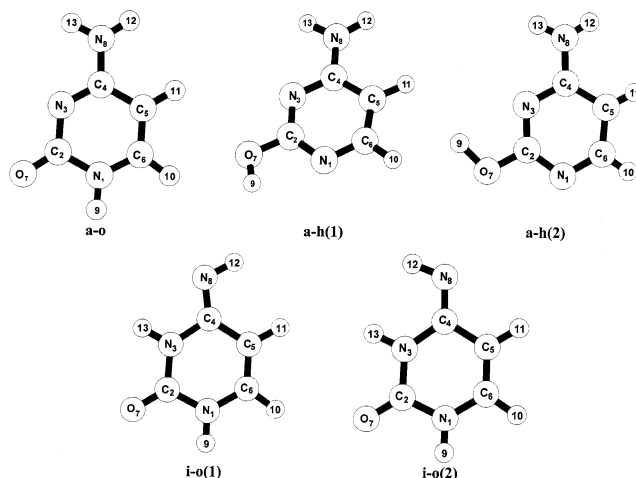


Figure 1. Tautomers and rotamers of cytosine investigated indicating the numbering of the atoms.

crowave investigation has also identified all three tautomers.⁶ Taking into account the small energy differences between the amino–oxo and amino–hydroxy tautomers, both of them can be considered in assigning the vibrational modes.^{4b,e,g,h,5} It must be further mentioned that the energy difference between two rotamers seems to be practically independent of the level of calculation.^{4g,h} In recent works,⁷ we have investigated the interaction between the mono- and dihydroxuracil tautomers with water. In the present work, we want to discuss the interaction between the three-low energy tautomers of cytosine with water.

The first part of the present paper deals with the relative stabilities of the tautomers. The second section describes the interaction between cytosine and one water molecule. It must

* Corresponding author. E-mail: therese.zeegers@chem.kuleuven.ac.be.

[†] North-Eastern Hill University.

[‡] Wrocław University of Technology.

[§] University of Leuven.

^{||} E-mail: akchandra@nehu.ac.in.

[⊥] E-mail: michalska@ichn.ch.pwr.wroc.pl.

be mentioned that the interaction between the canonical form of cytosine and one water⁸ or two water⁹ molecules has been investigated in several theoretical works. Theoretical studies have also shown that the interaction with water changes the relative energies of the other tautomers, the canonical tautomer being better hydrated than the other tautomers.^{4g,10} However, the binding energies of the a-h and i-o tautomers complexed with water have been reported only for water interacting at the (N1, O7) side of cytosine. In the present work, the binding energies for water interacting at the other sites are calculated as well. In previous works,¹¹ the binding energies of nucleobases and water were shown to depend both on the PA and DPE of the sites involved in complex formation. These correlations are discussed for the complexes investigated in the present work.

The vibrational properties of monohydrated a-h and i-o have not been reported so far and selected vibrational modes sensitive to complex formation are discussed. Finally, we discuss some results of the NBO analysis, more specifically, the occupancies of antibonding orbitals of the bonds participating to complex formation along with the changes of hybridization of relevant orbitals.

II. Computational Methods

The geometries of the isolated cytosine tautomers and their corresponding water complexes were fully optimized by the density functional three-parameter model (B3LYP)¹² using the 6-311++G(d,p) basis set. The proton affinity defined as the negative enthalpy change associated with the gas-phase protonation reaction $B + H^+ \rightleftharpoons BH^+$ and the deprotonation enthalpy defined the enthalpy change associated with the gas-phase deprotonation reaction $AH \rightleftharpoons A^- + H^+$ were calculated. These quantities refer to 298.15K and 1 atm of pressure. As shown recently,¹³ the B3LYP/6-31+G(d,p) method gives very reliable results for predicting the acidities of nucleobases. The cytosine-water binding energy was calculated as the difference of the energy of the complex and the sum of the energies of the separated monomers. The counterpoise method of Boys and Bernardi¹⁴ was applied to correct for the basis set superposition errors. In addition, the deformation energies of cytosine tautomer and water molecule were estimated in a few complexes, by a procedure described for the uracil-water complexes.^{9b} The charges on individual atoms, orbital occupancies, and hybridizations were obtained by using the natural bond orbital analysis (NBO).¹⁵ The harmonic frequencies and infrared intensities of the isolated cytosine tautomers and their 1:1 water complexes were computed at the B3LYP/6-31++G(d,p) level of theory. To make an unequivocal comparison of the frequency shifts of the corresponding modes in the isolated tautomers and their complexes, it was necessary to perform a rigorous normal coordinate analysis. The potential energy distributions (PEDs) have been calculated for all the isolated molecules and their complexes, according to the procedure described in our earlier papers.¹⁶ The barrier height for the OH rotation about the C2O7 bond in a-h tautomers was calculated as the difference between the energy of the transition state for the internal rotation and the energy of the more stable rotamer, a-h(1). In optimization of the transition state we have used a synchronous transit-guided quasi-Newton (STQN) method (implemented in the Gaussian 98 set of programs).¹⁷

III. Results and Discussion

1. Proton Affinities, Deprotonation Enthalpies and Relative Stabilities of the Three Low-Energy Cytosine Tautomers. Table 1 contains the proton affinities of the O and N

TABLE 1: B3LYP/6-311++G(d,p) Proton Affinities (kJ mol⁻¹) of the O and N Atoms of the a-o, a-h, and i-o Tautomers of Cytosine

tautomer	O7 (N1 side)	O7 (N3 side)	N1	N3	N8
a-o	919.6 ^a	954.7 ^a		956.0 ^a	
a-h(1)			923.8	923.3	
a-h(2)			962.2	882.8	
i-o(1)	839.0	844.5			964.0
i-o(2)	832.0	833.2			970.9

^a The B3LYP/6-31++G(d,p) values are larger by 1–2 kJ mol⁻¹.^{8c}

TABLE 2: B3LYP/6-311++G(d,p) Deprotonation Enthalpies (kJ mol⁻¹) of the NH and OH Bonds of the a-o, a-h, and i-o Tautomers of Cytosine (Results of B3LYP/6-311++G(d,p) Calculations)

tautomer	N8H13	N8H12	N1H9	O7H	N3H13
a-o	1482.7 ^a	1458.4 ^a	1446.5 ^a		
a-h(1)	1488.1	1471.1		1442.2	
a-h(2)	1478.9	1465.2		1439.0	
i-o(1)			1414.2		1474.8
i-o(2)			1414.8		1443.5

^a The B3LYP/6-31++G(d,p) values are lower by 1–2 kJ mol⁻¹.^{8c}

atoms of the a-o, a-h, and i-o tautomers (including the two corresponding rotamers) of cytosine. The deprotonation enthalpies of the NH and OH bonds in the same molecules are indicated in Table 2.

Let us at first examine the basicities of the tautomers. Our calculations indicate that the PA values of the a-o form at the O7(N3 side) and N3 atoms are very similar in agreement with gradient-corrected density functional computations with a triple- ζ type basis set which predict that the N3 atom has higher basicity than the O one by less than 1 kJ mol⁻¹.¹⁸ Recent data obtained at the MP4 level show the coexistence of O7 (N3 side) and N3-protonated species with approximately equal concentrations.¹⁹ Our values are somewhat lower than the experimental values which comprise between 936 and 945 kJ mol⁻¹.²⁰ This may be accounted for by the coexistence of both a-o and a-h tautomers in the gas phase, the PA of the a-h(1) form being lower and equal, according to our calculations, to 923 kJ mol⁻¹. The large difference in PA of the N1 and N3 atoms in the two a-h rotamers may be rather surprising, the PA of the N1 atom in a-h(2) is by ca. 40 kJ mol⁻¹ larger in a-h(2) and the PA of the N3 atom is larger by the same amount in a-h(1). This may be due to a repulsion between the OH and NH⁺ dipoles in the protonated species. The energy required for the internal rotation of the O7H9 bond on going from the a-h(1) to the a-h(2) rotamer (38 kJ mol⁻¹, calculations at the MP2/6-31++G(d,p) level, this work) is similar to the difference in PAs of the N1 and N3 atoms, but this coincidence may be fortuitous. It is worth mentioning that the PA of the O atoms of the two i-o forms is very low, between 832 and 845 kJ mol⁻¹; this value is close to the PA of aliphatic unsaturated ketones such as CH₂=CHCOCH₃ (838 kJ mol⁻¹).²¹ Also noteworthy is the very large PA of the N8 atom (964–971 kJ mol⁻¹); this value is similar to the PA of the PA of aliphatic imines (R)₂C=NR (960 kJ mol⁻¹).¹⁹

Despite their fundamental importance, very few experimental data are available for the deprotonation enthalpies of nucleobases, and results from ion cyclotron resonance mass spectroscopy give only the relative order of acidity.²² Recently, the gas-phase acidities of the N1 and N3 sites of uracil have been bracketed to provide an understanding of the intrinsic reactivity of this nucleobase.¹³ Deprotonation energies of the CH bonds of the five nucleobases which may be relevant for their binding

properties with guest molecules have been recently calculated at the B3LYP/6-31+G(d) level.²³

Let us examine at first the acidity of the NH₂ group. Our calculations reveal that the DPE values of the NH₂ group in the a-o and a-h tautomers comprise between 1458 and 1488 kJ mol⁻¹. These values are markedly lower than the DPE of the NH₂ group in aniline (1536 kJ mol⁻¹).²⁴ This can be accounted for by the larger pyramidal character of the NH₂ group in aniline. A second remark concerns the difference between the DPE values of the N8H12 and N8H13 bonds. As indicated in Table 2, the DPE of the N8H13 bonds are larger by 14–25 kJ mol⁻¹ than those of the N8H12 bonds. The nonequivalence of the two NH bonds of the NH₂ group is also reflected by the C5C4N8H12 and N3C4N8H13 dihedral angles (pyramidal rotated geometry) which slightly increase on going from the a-o tautomer to the two a-h rotamers. It should also be noticed that there are small differences between the DPE of the N8H13 bonds in the three amino forms, the lowest DPE (1479 kJ mol⁻¹) being predicted for the a-h(2) rotamer and the largest DPE (1488 kJ mol⁻¹) being calculated for the a-h(1) rotamer. This effect cannot be accounted for pyramidal character of the NH₂ group which, as shown by the sum of the angles around the N8 atom, decreases slightly in the order a-o > a-h(1) > a-h(2).^{4h}

The acidic properties of the two i-o rotamers show also interesting features. The DPE of the N3H bond of i-o (2) is lower by ca. 30 kJ mol⁻¹ than the DPE of this bond in its parent rotamer. This can be accounted for by an electrostatic repulsion between the two nearly parallel NH dipoles in this tautomeric form. This is in agreement with the fact that the N8H12 distance in i-o(2) (1.020 Å) is slightly longer than in i-o(1) (1.017 Å) and that the C4N8H12 angle is slightly larger in i-o(2) (112.5°) than in i-o(1) (110.9°).

Finally, it appears from our calculations that the DPEs of the O7H9 groups in the two a-h rotamers are nearly the same (1439–1442 kJ mol⁻¹). The acidity of this hydroxylic group is larger than that of phenol (1481 kJ mol⁻¹)²⁵ which is very often taken as reference proton donor in hydrogen bond studies.

The relative stabilities of the a-o, a-h(1), and i-o(1) tautomers have been calculated by DFT methods.^{4g} Depending on the basis set, the a-o was found to be the most stable tautomer, with 1–8 kJ mol⁻¹ below a-h(1) and 5–9 kJ mol⁻¹ below i-o(1). To have a reliable comparison, the relative stabilities of the five forms have been calculated at the BLYP/6-311++G(d,p) level not used in ref 4g. Our results show that the relative stabilities (in kJ mol⁻¹, in brackets) of the five forms are ordered as follows:

a-o [0] > a-h(1) [4.8] > a-h(2) [8.2] > i-o(1) [9.0] > i-o(2) [15.8]

Calculations of the total electronic energies using different MP2 methods^{4h} have shown that the hydroxy tautomer a-h(1) is more stable by 6–11 kJ mol⁻¹ than the a-o one. However, it should be emphasized that calculations of Gibbs free energies of cytosine tautomers (the neutral species at 298.15 K) performed at the advanced levels of theory (MP4(SD)/6-31+G(d,p)//MP2/6-31+G(d,p) and MP4(SQD)/6-31+G(d,p)//MP2/6-31+G(d,p) indicate that the a-o tautomer is more stable than the a-h(1) one by about 0.7 and 4 kJ mol⁻¹, respectively,^{19b} in relatively good agreement with the data of the present work. Although the DFT methods may not be the best choice for calculating relative energies of nucleobases, for the 2-hydroxypyridine/2(1H)-pyridone system, only the DFT/B3LYP method predicts correctly the oxo-hydroxy stabilities of 2-oxopyri-

dine.²⁶ As concluded in ref 4g, the final answer to the question of stabilities of the low-energy tautomers of cytosine remains.

Finally, the relative energies of the four imino-hydroxy rotamers calculated in this work at the B3LYP/6-311++G(d,p) level are by 55–105 kJ mol⁻¹ above the most stable a-o tautomer. The low-stability of these rotamers is also reflected by the low PA value of the O7 atom at the N1 side (832 and 839 kJ mol⁻¹).

2. Interaction of Cytosine Tautomers with Water. a. Optimized Geometries. The interaction of a-o cytosine with one water molecule has been the subject of several theoretical investigations performed by different methods and levels.⁷ There are much less data on the interaction between the a-h and i-o tautomers with water. The optimized geometries and dissociation energies or interaction energies have been reported at different levels of theory only for water interacting at the N1,O7 side of the tautomers.^{4h,10} It has also been shown that the hydration of cytosine tautomers changes their relative order of stability, the a-o native form being better hydrated than the other tautomers.^{4h,10}

The cyclic complexes considered in the present work are the ones involving the N, C=O, NH, or OH bonds of cytosine. Their optimized structures are shown in Figure 2. We must mention that the 1:1 complex between a-o cytosine and water has not been investigated at the B3LYP/6-311++G(d,p) level and in order to have a reliable comparison with the other tautomers, its geometry and other properties are described here. An open complex characterized by a lower stability can also be formed between the N8H12 bond of the a-o tautomer and the O atom of water. I-o(2) cytosine can also interact with water to give a closed complex involving the N8 atom and the C5H11 bond. These structures will no more be considered hereafter. Tables 3–5 contain selected geometrical parameters for the isolated cytosine tautomers and their corresponding water complexes.²⁷ In complexes B involving the two a-h rotamers, the NH bonds of the amino group are elongated by 0.007–0.008 Å and the O7H9 bonds in complexes A are elongated by 0.015–0.016 Å. This reflects the larger proton donor ability of the O7H9 bond as compared with that of the amino group. Our results show that in the two A structures, complex formation results in a very small increase of the planarity of the NH₂ group. In the two B complexes where the NH₂ group participates to the bonding with water, the NH₂ group becomes nearly planar.

In the i-o complexes, the N1H and N3H13 bonds involved in the interaction are elongated by 0.011–0.012 Å and the C4=N8 bond by 0.009 Å. As indicated by the value of the dihedral angle N3C4N8H12, complex formation does not result in marked change of the planar structure of the imine function. It must be noticed that in complex C where the lone pair of the N8 atom of the imino group acts as a proton acceptor, complex formation results in an elongation of the C4=N8 bond by 0.009 Å and a very small increase of the C4N8H12 angle. A similar effect has been predicted theoretically for the complexes involving aliphatic imines and water.²⁸

The shortest intermolecular distances are the O7H9...O_w distances in the a-h(1) and a-h(2) complexes which comprise between 1.816 and 1.831 Å. The O7H9...O_w angles are also markedly larger than the intermolecular angles in the other structures which are all predicted between 142 and 149°.

Our data indicate further that there is no single correlation between the O7...H_w distances and the PA of the corresponding lone pair of the O7 atom. This can be accounted for by the fact that the NH...O_w bond participating to the binding in the closed complex will reinforce the O7...H_w bond by cooperative effect.

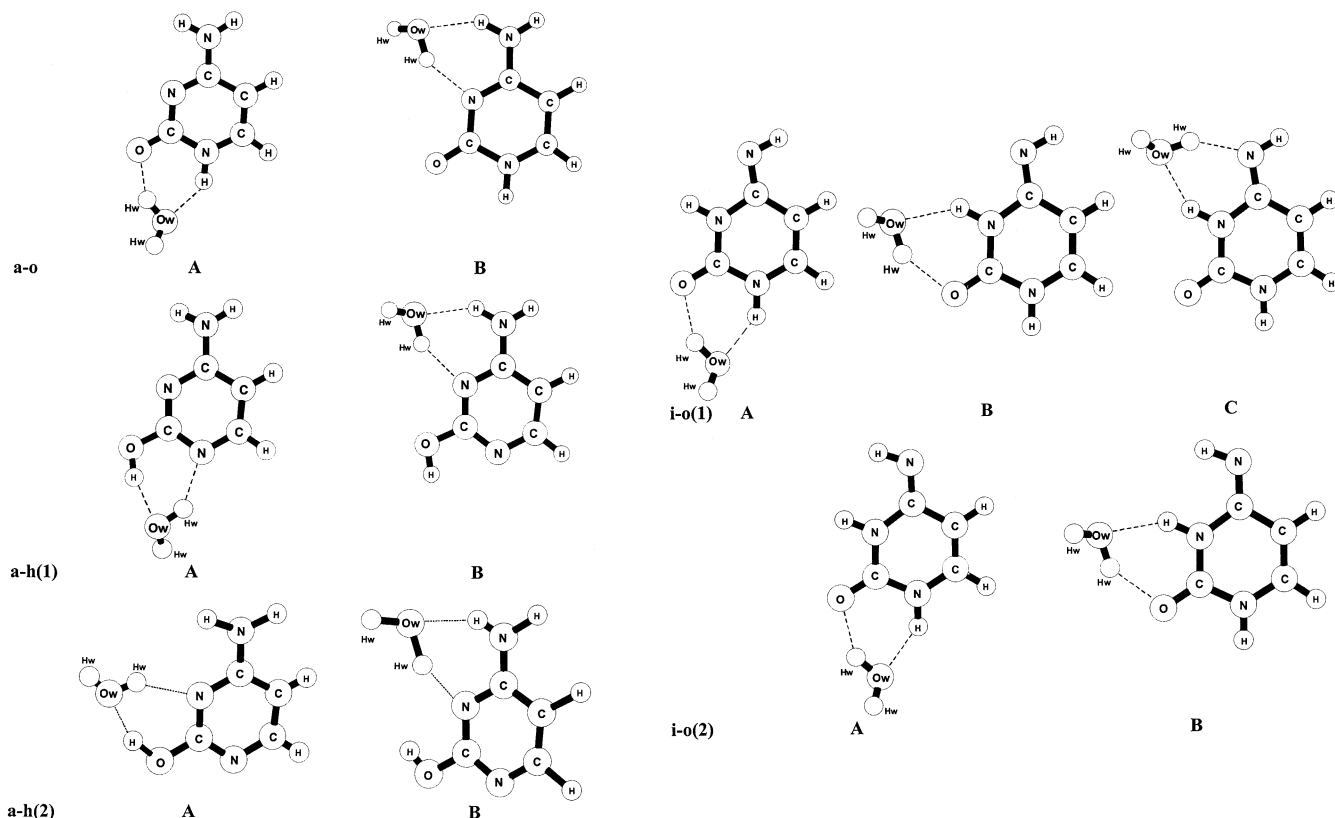


Figure 2. B3LYP/6-311++G(d,p) optimized structures of the investigated complexes between cytosine tautomers and water.

TABLE 3: Selected Optimized Distances (Å) and Angles (deg) in Free a-o Cytosine and the 1:1 Complexes with Water

	free a-o	complex A	complex B
N1H9	1.010	1.021	1.010
N8H12	1.005	1.005	1.005
N8H13	1.008	1.008	1.018
C4N8H12	120.3 ^a	120.6	119.9
C4N8H13	117.4 ^a	118.2	118.8
H12N8H13	117.8 ^a	118.3	118.9
C5C4N8H12	-12.7 ^a	-7.6	-2.4
N3C4N8H13	8.4 ^a	3.3	1.7
	free water	complex A	complex B
H ₂ O	0.962	0.982	0.981
intermolecular parameters			
	complex A		complex B
H _w ···O7	1.837	H _w ···N3	1.930
O _w H _w O7	149.7	O _w H _w N3	147.2
H9···O _w	1.953	H13···O _w	1.998
N1H9O _w	143.5	N8H12O _w	144.5

^a RIMP2/TZVPP calculations^{4h} reveal a larger nonplanarity of the NH₂ group (sum of the angles around the N8 atom = 352.6° and dihedral angles = -20.6° and 12.2°)

This effect has been discussed in our previous papers,^{8d,11} where the cooperativity factor calculated for the interaction between nucleobases with water has been shown to be equal to 0.3. Let us notice that the perturbation of the distances has been shown, more than 25 years ago, to be the leading factor determining the cooperativity.²⁹

b. Binding Energies. Table 6 reports the binding energies including the BSSE- and ZPE-corrections for the cytosine tautomers complexed with one water molecule. To have a reliable comparison with other systems, the binding energies

do not include the deformation energies which describe the energy required to distort a free cytosine or water molecule to a particular geometry in the complex. As asked by one of the reviewers, the deformation energies have been estimated for a few complexes. For the A and B complexes of the a-o tautomer, they are equal to 3.2 and 2.4 kJ mol⁻¹ and for the A and B complexes of the a-h(1) tautomer, they take the values of 4.0 and 1.9 kJ mol⁻¹, respectively. The binding energies which span a large range, from 21.5 (i-o(B)) to 36 kJ mol⁻¹ (a-o(A)) can be discussed as a function of the intrinsic acidity and basicity of the sites involved in the interaction. In isolated i-o(1), the PA of the lone pair of the O atom (839.0 kJ mol⁻¹) is much lower than the PA of the lone pair in isolated a-o (919.6 kJ mol⁻¹); furthermore, the acidity of the N1H bond in a-o (DPE = 1446.5 kJ mol⁻¹) is markedly larger than the acidity of the N3H bond (DPE = 1474.8 kJ mol⁻¹) in isolated i-o(1). For the cyclic O7···H_wO_w···H9N1 complexes, this dual dependence can be expressed by the following exponential expression:

$$-E_{\text{HB}} = 4244e^{-0.0038(1.5\text{DPE}-\text{PA})} \quad (n = 6) \quad r = 0.9912 \quad (1)$$

The predominance of the proton donor in determining the hydrogen bond energies has been predicted theoretically by Desmeules and Allen in 1980.³⁰ Recently, this predominance has been demonstrated in strong asymmetrical (O···H···O)⁻ hydrogen bonds involving enols and enolates.^{31a} A recent statistical analysis, illustrating the generality of eq 1, has shown that proton donor is more important in determining hydrogen bond strength than proton acceptor.^{31b}

Owing to the limited number of theoretical data, it was not possible to deduce similar correlations for the other complexes. We must notice, however, that for the closed O7H9···O_wH_w···N1 complexes, the same binding energies with water are obtained at lower (1.5DPE - PA) values or, in other words, at

TABLE 4: Selected Optimized Distances (Å) and Angles (deg) in Free a-h(1) and a-h(2) Cytosine and Their 1:1 Complexes with Water (Results of B3LYP/6-311++G(d,p) Calculations)

distances or angles	free a-h(1) ^a	complex A	complex B
N8H12	1.006	1.006	1.005
N8H13	1.008	1.008	1.016
O7H9	0.967	0.983	0.967
C4N8H12	119.3 ^b	120.5	120.4
C4N8H13	116.2 ^b	117.3	119.1
H12N8H13	117.0 ^b	118.2	119.8
C5C4N8H12	-14.8 ^b	-12.1	-5.3
N3C4N8H13	10.6 ^b	9.1	3.8
	free water	complex A	complex B
O _w H _w	0.962	0.981	0.979
intermolecular parameters	complex A	complex B	
N1...H _w	1.927		
N1H _w O _w	142.1		
O _w ...H9	1.816		
O7H9O _w	160.3		
N3...H _w			1.963
N3H _w O _w			146.9
H13...O _w			2.021
N8H13O _w			145.2
	free a-h(2)	complex A	complex B
N8H12	1.006	1.005	1.005
N8H13	1.008	1.007	1.015
O7H9	0.966	0.981	0.965
C4N8H12	118.6	119.7	120.3
C4N8H13	116.2	118.0	119.9
H12N8H13	116.9	117.8	119.7
C5C4N8H12	-16.9	-13.9	-3.2
N3C4N8H13	12.2	10.2	1.9
	free water	complex A	complex B
	0.962	0.979	0.978
intermolecular parameters	complex A	complex B	
N3...H _w	1.957		1.967
N3O _w H _w	142.9		151.8
H9...O _w	1.831		
O7H9O _w	160.8		
H13...O _w			2.040
N8H13O _w			144.9

^a Skeletal bond lengths and bond angles calculated at the B3LYP/6-311++G(d,p) level have been reported in ref 4g. ^b RIMP2/TZVPP data^{4h} indicate a larger nonplanarity of the NH₂ group (sum angles around the N8 atom = 349.2°, dihedral angles = -23 and +16.4°).

higher acidities or basicities of the corresponding sites. It can be concluded that the coefficients of eq 2 are only valuable for closely related complexes. It has been shown experimentally³² that for open complexes, the slopes and intercepts of the correlation between infrared frequency shifts, enthalpies or free energies of complex formation depend on the nature of the hydrogen bonds.

c. Vibrational Properties of the 1:1 Complexes between Cytosine Tautomers and Water. The vibrational spectrum of the free a-o and a-h tautomers of cytosine have been studied experimentally in low-temperature matrixes,⁵ in the solid state by conventional infrared and Raman spectroscopies,³³ and by inelastic neutron scattering spectroscopy.^{4d} To the best of our knowledge, no vibrational data in low-temperature matrices have been reported so far for cytosine complexed with water. This can be accounted for by experimental difficulties to observe

TABLE 5: Selected Optimized Distances (Å) and Angles (deg) in Free i-o (1) and i-o (2) Cytosine and Their 1:1 Complexes with Water (Results of B3LYP/6-311++G(d,p) Calculations)

	free i-o(1)	complex A	complex B	complex C
N1H9	1.008	1.020	1.008	1.008
N3H13	1.012	1.012	1.022	1.025
C4N8H12	110.9	110.9	110.7	111.5
N3C4N8H12	0	0	0.1	0.2
	free H ₂ O	complex A	complex B	complex C
O _w H _w	0.962	0.976	0.973	0.982
intermolecular parameters	complex A	complex B	complex C	
H9...O _w	1.952			
N1H9O _w	143.9			
O7...H _w	1.934		1.946	
O7H _w O _w	143.9		143.7	
H13...O _w			2.032	1.974
N3H13O _w			141.6	145.0
N8...H _w				1.902
N8O _w H _w				147.5
	free i-o (2)	complex A	complex B	
N1H9	1.008	1.019	1.008	
N3H13	1.011	1.011	1.022	
N8H12	1.020	1.020	1.020	
C4N8H12	112.5	112.6	112.2	
	free H ₂ O	complex A	complex B	
	0.962	0.975	0.975	
intermolecular parameters	complex A	complex B		
H9...O _w	1.960			
N1H9O _w	143.6			
O7...H _w	1.941		1.942	
O7H _w O _w	143.5		144.0	
H13...O _w				1.985
N3H13O _w				144.8

TABLE 6: Binding Energies (-E_{HB}) (kJ mol⁻¹) Including BSSE and ZPE Corrections for the 1:1 Complexes of Cytosine Tautomers with Water (Results of B3LYP/6-311++G(d,p) Calculations)

tautomers	complex A	complex B	complex C
a-o	36.0 ^a	34.5 ^a	
a-h(1)	29.3 ^{b,c}	29.0	
a-h(2)	23.7	21.5	
i-o(1)	31.2 ^{b,c}	21.8	29.7
i-o(2)	30.4 ^c	27.6	

^a The binding energies calculated at the B3LYP/6-31++G(d,p) level are 37.2 and 34.8 kJ mol⁻¹, respectively.^{8d} ^b The dissociation energies including BSSE but excluding ZPE corrections at the CCSD(T)/TZP level are 39.2 and 37.2 kJ mol⁻¹, respectively.¹⁰ ^c The binding energies calculated at the MP2/aug TZVPP level are 41.3, 43.6, and 42.7 kJ mol⁻¹, respectively.^{4h}

the νNH₂, νNH, νO7H9, and νO_wH_w vibrations of the different a-o and a-h(1) complexes which, owing to their small energy differences, are likely to coexist in these low-temperature materials. Vibrational frequencies and infrared intensities, assignments and PED of selected vibrational modes in the a-o, a-h(1), and i-o(1) isolated tautomers and in their corresponding water complexes are listed in Tables 7-9.²⁷

As mentioned above, the frequencies of the νNH and νCH vibrations are by ca. 5 cm⁻¹ higher than the ones calculated at the B3LYP/6-31G(d,p) level. More surprisingly, the inversion modes of the NH₂ group calculated at this level are respectively

TABLE 7: Vibrational Frequencies (cm⁻¹) and Infrared Intensities (km mol⁻¹, in Parentheses) and Assignment and PED (in Brackets) for Selected Vibrational Modes in the 1:1 Complexes between a-o Cytosine and Water (Results of B3LYP/6-31++G(d,p) Calculations)

free a-o	assignment and PED ^a	complex A	assignment and PED ^a	complex B	assignment and PED ^a
3750 (51)	ν N8H12 [62+], ν N8H13[38-]	3754 (53)	ν N8H12[62+], ν N8H13[38-]	3720 (90)	ν N8H12[92]
3629(71)	ν N1H9[99]	3404(83)	ν N1H9[76+], ν O _w H _w [25+]	3632(84)	ν N1H9[100]
3609(92)	ν N8H13[61+], ν N8H12[38+]	3613(82)	ν N8H13[62+], ν N8H12[38+]	3447(2)	ν N8H13[57+], ν O _w H _w [38+]
1774(775)	ν C2=O7[74]	1746(702)	ν C2=O7 [55], δ N1H9[11]	1775(750)	ν C2=O7 [72]
1638(147)	δ NH ₂ [80]	1641(66)	δ NH ₂ [65], δ H ₂ O[13]	1664(17)	δ NH ₂ [53], ν C5C6[18+]
626(66)	γ N1H[82]	836(153)	γ N1H9[43], δ (O _w ...H9N1)[30]	612(32)	γ N1H9[82]
526(11)	tNH ₂ [50], δ C2O7[23]	535(16)	tNH ₂ [82]	675(90)	tNH ₂ [53], δ (O _w H _w ...N3)[13]
174(195)	invNH ₂ [84]	135(209)	invNH ₂ [83]	309(135)	invNH ₂ [80]
free water	assignment and PED ^a	complex A	assignment and PED ^a	complex B	assignment and PED ^a
3929(54)	ν^{as} (H ₂ O)	3892(80)	ν O _w H' _w [98+]	3891(78)	ν O _w H' _w [98+]
3806(5)	ν^{s} (H ₂ O)	3470(1090)	ν O _w H _w [75+], ν N1H9[27-]	3498(1008)	ν O _w H _w [62+], ν N8H13[34-]

^a ν = stretching, δ = in-plane bending, γ = out-of plane bending, r = rocking, t = twisting, inv = inversion mode, Cring = six-ring mode, HBring = hydrogen bond ring mode. The plus or minus sign indicates the relative phases of vibrations

TABLE 8: Vibrational Frequencies (cm⁻¹) and Infrared Intensities (km mol⁻¹, in Parentheses) and Assignment and PED (in Brackets) for Selected Vibrational Modes in the 1:1 Complexes between a-h(1) Cytosine and Water (Results of B3LYP/6-31++G(d,p) Calculations)

free a-h(1)	assignment and PED ^a	complex A	assignment and PED ^a	complex B	assignment and PED ^a
3786(93)	ν O7H9[100]	3400(113)	ν O7H9[65+], ν O _w H _w [33+]	3787(99)	ν O7H9[100]
3745(48)	ν N8H12[60+], ν N8H13[40-]	3750(50)	ν N8H12[61+], ν N8H13[39-]	3724(90)	ν N8H12[90+], ν N8H13[10-]
3609(73)	ν N8H13[60+], ν N8H12[40+]	3612(74)	ν N8H13[61+], ν N8H12[34+]	3480(54)	ν N8H13[77+], ν O _w H _w [16+]
1640 (20)	δ NH ₂ [55], ν Cring [30]	1644(71)	δ NH ₂ [66], ν (C4N8)[10]	1682(394)	δ NH ₂ [62], ν C4N8[12]
1245(55)	δ O7H9[51], ν C2N3[16+]	1439(143)	δ O7H9[33], ν C2O7[14+]	1245(65)	δ O7H9[52], ν C2N3[17+]
557(106)	γ O7H9[98]	860(187)	γ O7H9[72], γ HB ring	555(97)	γ O7H9[98]
492(6)	tNH ₂ [56+], δ C2O7[14+]	504(11)	tNH ₂ [76]	651(83)	tNH ₂ [86]
451(12)	γ Cring[55], tNH ₂ [18]	454(11)	γ Cring[57], tNH ₂ [14]	460(12)	γ Cring[64]
260(257)	invNH ₂ [94]	200(246)	invNH ₂ [95]	295(159)	invNH ₂ [51-], γ HBring[21+]
free water	assignment and PED ^a	complex A	assignment and PED ^a	complex B	assignment and PED ^a
3929(54)	ν^{as} (H ₂ O)	3882(93)	ν O _w H' _w [98]	3890(86)	ν O _w H' _w [97]
3806(5)	ν^{s} (H ₂ O)	3495(1435)	ν O _w H _w [65+], ν O7H9[34-]	3540(867)	ν O _w H _w [83+], ν N8H13[14-]

^a Abbreviations are the same as in Table 8.

TABLE 9: Vibrational Frequencies (cm⁻¹) and Infrared Intensities (km mol⁻¹, in Parentheses) and Assignment and PED (in brackets) for Selected Vibrational Modes in the 1:1 Complexes between i-o(1) Cytosine and Water (Results of B3LYP/6-31++G(d,p) Calculations)

free i-o(1)	PED ^a	A	PED ^a	B	PED ^a	C	PED ^a
3657(113)	ν N1H9[100]	3447(455)	ν N1H9[100]	3658(110)	ν N1H9[100]	3654(114)	ν N1H9[100]
3614(63)	ν N3H13[100]	3613(52)	ν N3H13[100]	3433(291)	ν N3H13[99]	3374(93)	ν N3H13[99]
3523(9)	ν N8H12[100]	3523(7)	ν N8H12[100]	3517(8)	ν N8H12[100]	3543(13)	ν N8H12[100]
1802(824)	ν C2=O7[71]	1776(789)	ν C2=O7[58], δ N1H9[11]	1773(839)	ν C2=O7[60], ν C2N3[10]	1806(812)	ν C2=O7[70]
1719(500)	ν C4=N8[33+], ν C5=C6[29+]	1721(530)	ν C4=N8[33+], ν C5=C6[28+]	1722(402)	ν C4=N8[32+], ν C5=C6[30+]	1715(469)	ν C4=N8[33+], ν C5=C6[33+]
1660(16)	ν C4=N8[41+], ν C5=C6[35-]	1660(18)	ν C4=N8[41+], ν C5=C6[34-]	1663(12)	ν C4=N8[41+], ν C5=C6[34-]	1655(15)	ν C4=N8[35+], ν C5=C6[30-]
1502(84)	δ N1H9[30], ν C6N1[22]	1530(48)	δ N1H9[52], ν C6N1[18]	1499(71)	δ N1H9[25], ν C6N1[22]	1514(77)	δ N1H9[22], ν C6N1[20]
1399(20)	δ N3H13[33], ν C2N3[11]	1406(11)	δ N3H13[56], ν C2N3[13]	1457(36)	δ N3H13[57], ν C4N8[10]	1464(29)	δ N3H13[73], ν C4N8[20]
822(93)	γ N8H12[75+], γ C5H11[18-]	826(99)	γ N8H12[75+], γ C5H11[19-]	844(2)	γ N8H12[49+], γ N3H13[32+]	800(174)	γ N8H12[36+], γ C5H11[38-]
652(109)	γ N3H13[88]	646(106)	γ N3H13[54], γ Cring[16]	808(248)	γ N3H13[46], γ HBring[26]	762(124)	γ N3H13[66]
524(40)	γ N1H9[86]	778(154)	γ N1H9[56], γ HBring[26]	526(55)	γ N1H9[81]	545(50)	γ N1H9[64]
free water	PED ^a	A	PED ^a	B	PED ^a	C	PED ^a
3929(54)	ν^{as} OH	3894(98)	ν O _w H' _w [96]	3898(91)	ν O _w H' _w [95]	3889(74)	ν O _w H' _w [98]
3806(5)	ν^{s} OH	3588(517)	ν O _w H _w [100]	3634(319)	ν O _w H _w [97]	3454(922)	ν O _w H _w [87]

^a Abbreviations are the same as in Table 8.

equal to 275 cm⁻¹ (a-o) and 326 cm⁻¹ (a-h(1)) and are thus higher by 100 and 65 cm⁻¹ than the ones calculated at the B3LYP/6-31++G(d,p) level. As shown by the PED, this mode appears to be decoupled from the twisting vibration of the NH₂ group. We may note that the inversion mode of these two tautomers calculated at the HF/6-31G(d,p) level are 86 (a-o) and 224 cm⁻¹ (a-h(1)), respectively.³⁴

We want to discuss at first the spectral perturbations resulting from the interaction of the a-o and a-h(1) tautomers with water. In the A complexes where the NH₂ group is not involved in the interaction with water, the frequencies of the ν NH₂

vibrations increase by 4–5 cm⁻¹. This effect results from the small decrease of the pyramidalization of the NH₂ group induced by complexation with water (Tables 3 and 4). Note that an inverse effect is observed for the free tautomers. The lower frequency of the ν^{as} NH₂ vibration in isolated a-h(1) can be accounted for by the more pronounced pyramidal character of the NH₂ group in this tautomeric form. The δ NH₂, rNH₂, and tNH₂ vibrations are shifted to higher frequencies. However, in both the a-o and a-h(1) complexes, these vibrations appear to be coupled with other vibrational modes and as a consequence do not reflect the strength of the interaction. Interestingly,

TABLE 10: Occupancies of Selected Antibonding Natural Bond Orbitals in Free Cytosine Tautomers and in Their 1:1 Complexes with Water (Results of B3LYP/6-31++G(d,p) Calculations)

	free a-o		complex A		complex B	
σ^*N1H9	0.015		0.037		0.014	
σ^*N8H13	0.009		0.009		0.027	
$\pi^*N3=C4$	0.386		0.399		0.423	
$\pi^*C2=O7$	0.362		0.405		0.365	
$\sigma^*O_wH_w$ (water)	0		0.041		0.037	

	free a-h(1)	complex A	complex B	free a-h(2)	complex A	complex B
σ^*O7H9	0.010	0.048	0.010	0.010	0.045	0.010
σ^*N8H13	0.009	0.009	0.025	0.009	0.009	0.026
$\pi^*N3=C4$	0.459	0.452	0.501	0.472	0.484	0.488
$\sigma^*C2=O7$	0.052	0.044	0.051	0.052	0.044	0.054
$\sigma^*O_wH_w$	0	0.041	0.038	0	0.045	0.033

	free i-o(1)	complex A	complex B	complex C	free i-o(2)	complex A	complex B
σ^*N1H9	0.011	0.034	0.012	0.012	0.011	0.034	0.012
σ^*N8H13	0.015	0.015	0.033	0.038	0.014	0.014	0.035
$\pi^*C4=N8$	0.257	0.260	0.252	0.293	0.254	0.257	0.250
$\pi^*C2=O7$	0.368	0.403	0.403	0.362	0.368	0.403	0.405
$\sigma^*O_wH_w$	0	0.028	0.025	0.044	0	0.027	0.026

complex formation may cause a decoupling of some vibrational modes. This is the case of the νNH_2 mode coupled with the $\delta C2=O7$ vibration which is predicted at 532 cm^{-1} in isolated a-o cytosine and at 492 cm^{-1} in isolated a-h(1) cytosine. The formation of the A complexes decouples this mode which is calculated at 535 cm^{-1} with 82% contribution in monohydrated a-o cytosine and at 504 cm^{-1} with a contribution of 76% in monohydrated a-h(1) cytosine. Further, complex formation decreases the frequency of the inversion mode of the NH_2 group in the A complexes, by 40 cm^{-1} in a-o cytosine and by 60 cm^{-1} in a-h(1) cytosine. It is worth mentioning that the frequencies of this inversion mode are ordered as follows: a-o(A) < free a-o < a-h(1) < free a-h(1) which is the order of increasing pyramidal character of the NH_2 group. In complexes B where one of the bond of the NH_2 group is involved in the interaction with water, the frequency of the inversion mode increases by 135 cm^{-1} (a-o) and 35 cm^{-1} (a-h(1)) with respect to the isolated tautomers.

The infrared spectrum of isolated i-o(1) cytosine calculated at the MP2/tzp level has been discussed in two selected regions— $3700\text{--}3300$ and $1800\text{--}1500\text{ cm}^{-1}$ —but no PED was reported.^{4g} Our calculated nonscaled νNH and νCH and frequencies are lower by more than 150 cm^{-1} . Complex formation on the N1H9 bond results in a great frequency decrease by 210 cm^{-1} of the corresponding stretching frequency and an intensity increase by a factor of ca. 4 (Table 9). The same remark holds for the complex formed on the N3H13 bond, the stretching vibration of which decrease by 180 cm^{-1} . A spectacular shift of 250 cm^{-1} is predicted for the corresponding γNH vibrations. We note an interesting effect in the i-o(1) complex C where the O_wH_w bond of water interacts with the lone pair of the N8 atom of the imine function. The $\nu N8H12$ vibration predicted at 3523 cm^{-1} in isolated i-o(1) cytosine is blue-shifted by 20 cm^{-1} in the complex. It is worth mentioning that a blue shift of the νNH vibration of 11 cm^{-1} has been observed experimentally in the complex between diphenylketimine and phenol in a solvent of low polarity.^{28b} This frequency increase has been explained by the increase of the s character of the orbitals of the N atom of the imine function. According to our NBO analysis, hybridization of the orbital on the N8 atom changes from $sp^{3.4}$ (22.7% s-character) in free i-o(1) tautomer to $sp^{3.2}$ (23.7% s-character) in the complex. We are aware of the fact that any bond orbital analysis includes certain arbitrariness, but the relative increase of 1% may be significant.³⁵ We must also notice that in the A

and B complexes involving the i-o tautomers where the interaction occurs at the carbonyl group, the $\nu C2=O7$ vibration decreases by $26\text{--}29\text{ cm}^{-1}$. In contrast, when the interaction takes place on the imino nitrogen atom, the mode having a predominant $\nu C4=N8$ character at 1660 cm^{-1} is shifted by only 5 cm^{-1} , despite the fact that the $C4=N8$ bond is elongated by 0.009 \AA . This elongation does not differ markedly from the elongation of the $C=O$ bond (0.012 \AA). The great insensitivity of the $\nu C=N$ vibration to complex formation on the nitrogen lone pair has been observed experimentally.^{28b} Theoretical calculations carried out on the complex between methylenimine and water have shown that this great insensitivity can be accounted for by a coupling between the δNH and δCH_2 vibrations. In the present case, there appears to exist an important coupling between the $\nu C=N$ and the $\nu C5=C6$ vibration of the six-membered ring.

Finally, for all the complexes mentioned in Tables 7–9, the mean frequency shifts of the ν^{as} and ν^s vibrations ($\Delta\nu O_wH_w$) are between 101 (i-o(B)) and 191 cm^{-1} (a-o(C)). As expected, there is a marked infrared intensity increase. The larger frequency shift of the $\nu O7H9$ vibration in the a-h(1) complexes (386 cm^{-1}) can be accounted for by the larger acidity of the $O7H9$ bond, in agreement with our calculations.

d. NBO Analysis of the Complexes between Cytosine Tautomers and Water. As expected, in all the proton donor NH , O_wH_w , $O7H9$ groups participating to hydrogen bond formation, there is an increase of negative charge on the N or O atoms and an increase of positive charge on the hydrogen atoms, leading to an enhanced polarity of the bonds.²⁷ This is a general feature of all conventional hydrogen bonds. The occupancies of selected σ^* or π^* antibonding orbitals in the isolated cytosine tautomers and their monohydrated forms are indicated in Table 10.

We note that the increase of the occupancy of the $\pi^*C4=N8$ orbital in the i-o(1)(C) complex is equal to 0.036 e , which can be related to the elongation of this bond. The increase of the occupancy of the $\pi^*C2=O7$ orbital is nearly the same (0.035 e) in agreement with the previous discussion. The occupancy of the σ^* orbital of the bonded $NH\cdots$ group increases by $0.018\text{--}0.023\text{ e}$ and that of the $O7H9$ group by 0.038 e .

Finally, our results show that the increase of the occupancy of the $\sigma^*O_wH_w$ orbital of water, which is equal to zero in the

isolated molecule, strongly increases in the complexes. This occupancy ranges indeed from $0.026e$ ($i-o(2)B$) to $0.041e$ ($a-o(A)$).³⁵

As discussed in a recent work³⁶ the XH bond length in XH·Y hydrogen bonds is controlled by a balance of two main factors acting in opposite direction: the XH bond lengthening due to the $n \rightarrow \sigma^*(XH)$ hyperconjugative interaction and the XH bond shortening due to the increase in the s-character in the X hybrid orbitals. In the present complexes, the s-character of the orbital of the O atom in the bonded O_wH_w group varies within a very small range, from 23.4% in the $a-h(2)B$ complex to 24% in the two $i-o(A)$ complexes. Thus, the rehybridization of the O atom in the bonded O_wH_w group is weak compared with the increase of the occupation of the $\sigma^*(O_wH_w)$ orbital.

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