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Thiouracils: Acidity, Basicity, and Interaction with Water

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The optimized geometries, harmonic vibrational frequencies, and the energies of the cyclic structures of monohydrated 2-thiouracil, 4-thiouracil, and 2,4-dithiouracil are calculated using density functional theory (B3LYP) combined with the 6-31+G(d,p) basis set. In the three most stable cyclic structures, the water molecule accepts the NH proton and donates a proton to the carbonyl oxygen or thiocarbonyl sulfur atoms. The intermolecular distances between the water molecule and the acceptor atom of thiouracils are about 0.5 Å longer for hydrogen bonds involving a sulfur atom. Less stable cyclic complexes involving the O4 atom and the C5H bond are also formed. The frequency shifts of the ν(OH) stretching vibrations of water and the ν(NH) stretching vibrations of thiouracils are compared with recent data on the 1:1 adducts of uracil and water. The proton affinity of the oxygen and sulfur atoms and the deprotonation enthalpy of the NH bonds of thiouracils are calculated at the same level of theory. Although intrinsic acidities and basicities are larger in thiouracils than in uracils, the binding energies with one water molecule do not differ markedly for uracil and thiouracils. Comparison with previous data obtained for the 1:1 adducts of uracil and thymine with water suggests that the same binding energy is obtained for a much larger proton affinity of the sulfur atom as compared with the oxygen atom. The complexes of the thiouracils with three water molecules are also investigated and the hydrogen bonding cooperativity is discussed. Comparison with uracil indicates an alteration of the first hydration shell caused by the substitution of the oxygen atom by the sulfur one.

Introduction

Continuous interest has been expressed in the structural properties of modified nucleic acid bases because most of them have been widely implicated for a variety of biological activities.[1−3] For example, incorporation of heavier atoms into DNA bases leads to a therapeutically important class of nucleic acid component.[4−7] One important class of such derivatives originates from the substitution of the thio group in place of the exocyclic oxo group in both purines and pyrimidines. More specifically, 2-thiouracils are frequently studied for their numerous pharmacological and biochemical capabilities such as mutagenic, anticancer, and antithyroid activities.[8−20] 2-Thiouracil constitutes an important derivative of the thiated pyrimidines. It is used as the cross-linking agent in RNA transcriptional regulation[21] and exists in prokaryotic tRNAs.[22,23] Thiobases influence the structure of DNA,[24] although hydrogen bonding involving thioguanine should not differ dramatically from guanine-containing complexes. The base stacking properties of thioguanine and thiouracils have been investigated recently,[25] and it has been shown that the hydrogen-bonded base pairs containing thiobases are only slightly less stable, viz. = 8 kJ mol^{-1}, than the unmodified ones. The N···S distances are larger by 0.4−0.7 Å than the N···O distances in the standard base pairs. In addition to the structural changes caused by C═S bonds being longer that the C═O bonds, the differences between oxygen and sulfur bases can also result from the lower electronegativity of sulfur relative to oxygen. Steric hindrance can also interfere with the formation of the diaminopurine−thiouracil base pair.[26,27]

Interaction with water is vital in DNA base pair interaction.[28,29] The interaction between conventional nucleobases and one water molecule has been discussed,[30−36] but very little is known about the hydration of thiated nucleobases. The hydration of the 6-position of thioguanine with respect to guanine has been investigated recently.[25] To the best of our knowledge, the interaction of thiouracils with one or several water molecules has not been studied theoretically. This article was undertaken to address this issue. Further, despite their biological importance, information is almost completely lacking regarding the intrinsic properties of thiouracils, such as the gas-phase acidity and basicity. As shown recently, they control, to a large extent, the interaction energy of conventional nucleobases with one water molecule.[34]

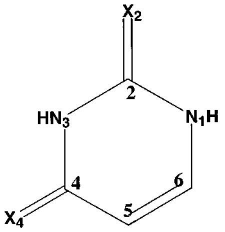

Figure 1. Atom numbering in thiouracils. 2TU (X2 = S, X4 = O), 4TU (X2 = O, X4 = S), and 2,4DTU (X2 = S, X4 = S).

The main objective of this work is to investigate the interaction between 2-thiouracil (2TU), 4-thiouracil (4TU), and 2,4-dithiouracil (2,4DTU) and one water molecule, to compare the results with those reported for uracil,[32] and to draw some conclusions on the biochemical diversity of thiouracils and uracil. The interaction between the thiouracils and three water molecules is investigated as well. All the data have been calculated using density functional theory (DFT) (B3LYP) combined with the 6-31+G(d,p) basis set.

Figure 1 indicates the molecular structure and the atom numbering of the studied molecules.

Because detailed theoretical[37−40] and experimental[41−44] data have shown that the thione-oxo or dithione forms of thiouracils

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TABLE 1: Results of B3LYP/6-31+G(d,p) Geometry Optimization of 2TU and the 2TU-water Complexes A, B, and C (Lengths in Å, Angles in Degrees)

relevant vibrational frequencies (in cm^{-1})

	2TU	complex A	complex B	complex C
N1H	1.011	1.028	1.011	1.011
N3H	1.014	1.014	1.031	1.028
C=O	1.222	1.222	1.221	1.233
C=S	1.664	1.680	1.681	1.664
N1C2	1.379	1.370	1.377	1.383
C2N3	1.371	1.368	1.362	1.371
N3C4	1.416	1.417	1.417	1.405
C4C5	1.457	1.455	1.459	1.453
C5=C6	1.352	1.353	1.351	1.354
N1C6	1.376	1.374	1.376	1.372
$O_wH_w'^{a}$		0.979	0.975	0.977

intermolecular parameters

	complex A	complex B	complex C
(N)H$\cdots O_w$	1.839	1.877	1.937
$H_w'\cdots X$	2.435	2.491	1.951
$\angle NH\cdots O_w$	159.5	157.7	144.6
$\angle O_wH_w'\cdots X$	140.4	136.4	141.0
$\angle C{=}X\cdots H_w'$	92.O	92.4	111.9
$\angle H_wO_wH_w'\cdots X$	177.7	175.6	174.9

vibrational frequencies[b]

assignment	2TU	complex A	complex B	complex C
$\nu3(H_2O)$		3882[c]	3890	3901
$\nu1(H_2O)$		3593	3662	3641
ν(N1H)	3636	3326	3634	3632
ν(N3H)	3599	3597	3304	3367
ν(C=O)	1779	1780	1781	1752
ν(C=S)	1160	1161	1160	1174
γ(N3H)	704	699,733	915	878
γ(N1H)	612	877	614	627

[a] The OH distance in free water calculated at the same level is 0.965 Å. [b] ν = stretching; γ = out-of-plane deformation vibration. [c] The ν(OH) frequencies in the free water molecule calculated at the same level of theory are equal to 3931 and 3809 cm^{-1}.

TABLE 2: Results of B3LYP/6-31+G(d,p) Geometry Optimization of 4TU and the 4TU−Water Complexes A, B, and C (Length in Å, Angles in Degrees)

	4TU	complex A	complex B	complex C
N1H	1.011(1.009)[b]	1.023	1.011	1.011
N3H	1.015(1.014)[b]	1.015	1.027	1.031
C=O	1.219(1.224)[b]	1.231	1.230	1.219
C=S	1.662(1.646)[b]	1.662	1.661	1.677
N1C2	1.392(1.388)[b]	1.382	1.386	1.395
C2N3	1.388(1.390)[b]	1.382	1.380	1.388
N3C4	1.392(1.390)[b]	1.394	1.392	1.383
C4C5	1.444(1.445)[b]	1.441	1.446	1.442
C5=C6	1.356(1.355)[b]	1.357	1.354	1.356
N1C6	1.375(1.376)[b]	1.373	1.377	1.372
$O_w.H_w'\_$		0.978	0.975	0.977

intermolecular parameters[c]

	complex A	complex B	complex C
(N)H$\cdots O_w$	1.916	1.963	1.868
$H'_w\cdots X$	1.961	1.994	2.437
$\angle NH\cdots O_w$	144.5	144.2	157.7
$\angle O_wH'\cdots X$	141.4	138.6	139.1
$\angle C{=}X\cdots H_w'\_$	109.2	110.3	93.9
$\angle H_wO_wH_w'\cdots X$	177.7	175.2	176.5

vibrational vrequencies

assignment	4TU	complex A	complex B	complex C
$\nu3(H_2O)$		3901	3905	3887
$\nu1(H_2O)$		3631	3679	3615
ν(N1H)	3645	3415	3646	3643
ν(N3H)	3594	3592	3384	3293
ν(C=O)	1809	1782	1779	1811
ν(C=S)[d]	1156	1160	1170	1153
γ(N1H)	562	803	556	572

[a] Same remarks as in footnotes to Table 1. [b] MP2/6-31G(d,p) calculations.[40] [c] X is the O atom in complexes A and B and the sulfur atom in complex C. [d] Coupled with the δ(N3H) vibration. [e] Two modes with important γ(N3H) contribution.

are largely predominant in the vapor, solid, and low-temperature argon or nitrogen matrixes, only these tautomers will be investigated in this article.

Computational Method

The geometries of isolated, protonated, and deprotonated 2TU, 4TU, and 2,4DTU and their corresponding complexes with one or three water molecules were optimized without any constraint using DFT-type, B3LYP exchange-correlation functional with 6-31+G(d,p) basis set. Harmonic vibrational frequencies and zero-point vibrational energies (ZPE), also calculated at the B3LYP/6-31+G(d,p) level, were retained unscaled. The proton affinities and deprotonation enthalpies were calculated at the standard conditions of pressure of 1 atm and a temperature of 298 K. The Gaussian 98 package[45] was used for all the calculations. Although the B3LYP method strongly underestimates the stacking interaction in DNA base pairs,[46] it is comparable with the MP2 level in the calculations of the hydrogen bond energies and protonation and deprotonation energies; it gives even better results for the vibrational frequencies via using larger scaling factors. This has been thoroughly discussed in previous works.[34,35]

Results and Discussion

To proceed with the study of the interaction of thiouracils with one or three water molecules, we begin with analyzing briefly their properties in the gas phase and comparing our data with reported values. The geometries of the thiouracils are optimized at the B3LYP/6-31+G(d,p) level. Relevant geometrical parameters and unscaled vibrational frequencies of the free thiouracils are reported in Tables 1, 2, and 3.[47] In the gas phase, free 4TU is more stable than 2TU by 7.0 kJ mol^{-1}. The dipole moments of free 2TU, 4TU, and 2,4DTU calculated in this work are equal to 4.8, 5, and 5D, respectively, and do no differ strongly from the values of 4.6, 4.8, and 4.9 D obtained at the MP2/6-31G(d) level.[25] The polarizabilities of 2TU, 4TU, and 2,4DTU evaluated in this work are equal to 89, 91, and 121 au; they are significantly larger than the polarizability of 67 au of uracil. This implies a larger contribution of the dispersion interaction for thiouracils. The polarizabilities of uracils and thiouracils recently obtained at the HF/6-31G(d) level[25] are about 20% smaller; our calculated value for uracil is in good agreement with the one of 65 au evaluated at the MP2/6-31G(d,p) level.[48]

Bond lengths and bond angles optimized at the HF/6-31G-(d) level have been compared with the crystallographic data of thiouracils.[49] The HF/6-31G(d,p) level underestimates the N1C2 distance by 0.015 Å and overestimates the C4C5 distance by 0.025 Å. The differences between the experimental and theoretical data have been assigned to crystal-packing forces and intermolecular hydrogen bonds. In Table 2, the distances in isolated 4TU are compared with the ones calculated recently at the MP2/6-31G(d,p) level[40]; they differ by only 0.001−0.004 Å, except the C=O distance that is predicted to be 0.005 Å longer and the C=S distance that is predicted to be 0.016 Å shorter than those calculated in the present work. This indicates

TABLE 3: Results of B3LYP/6-31+G(d,p) Geometry Optimization of 2,4DTU and the Water Complexes A, B, and C (Lengths in Å, Angles in Degrees)

relevant vibrational frequencies (cm^{-1})				
	2,4DTU	complex A	complex B	complex C
N1H	1.011	1.028	1.011	1.011
N3H	1.015	1.015	1.032	1.033
N1C2	1.379	1.370	1.376	1.381
C2N3	1.375	1.372	1.367	1.375
N3C4	1.395	1.396	1.396	1.387
C4C5	1.443	1.441	1.444	1.442
C5=C6	1.356	1.357	1.354	1.357
N1C6	1.375	1.373	1.375	1.371
C2=S	1.662	1.678	1.678	1.663
C4=S	1.660	1.661	1.660	1.675
O_wH_w'_		0.978	0.974	0.976
intermolecular parameters				
		complex A	complex B	complex C
(N)H···O_w		1.832	1.849	1.839
H'_w...S		2.451	2.527	2.465
∠NH···O_w		159.6	156.5	159.2
∠O_wH_w'···S		139.3	132.6	135.8
∠C=S···H'_w		91.9	92.9	94.2
∠$H_wO_wH_w'$···X		177.7	172.7	174.8
vibrational frequencies				
assignment	2,4DTU	complex A	complex B	complex C
ν3(H_2O)		3883	3893	3888
ν1(H_2O)		3607	3687	3641
ν(N1H)	3634	3314	3633	3630
ν(N3H)	3585	3583	3269	3255
ν(C=S)	1241[a]	1226	1240	1238

[a] Modes with predominant ν(C2=S) and ν(C4=S) contributions. [b] Two modes with predominant γ(N1H) character.

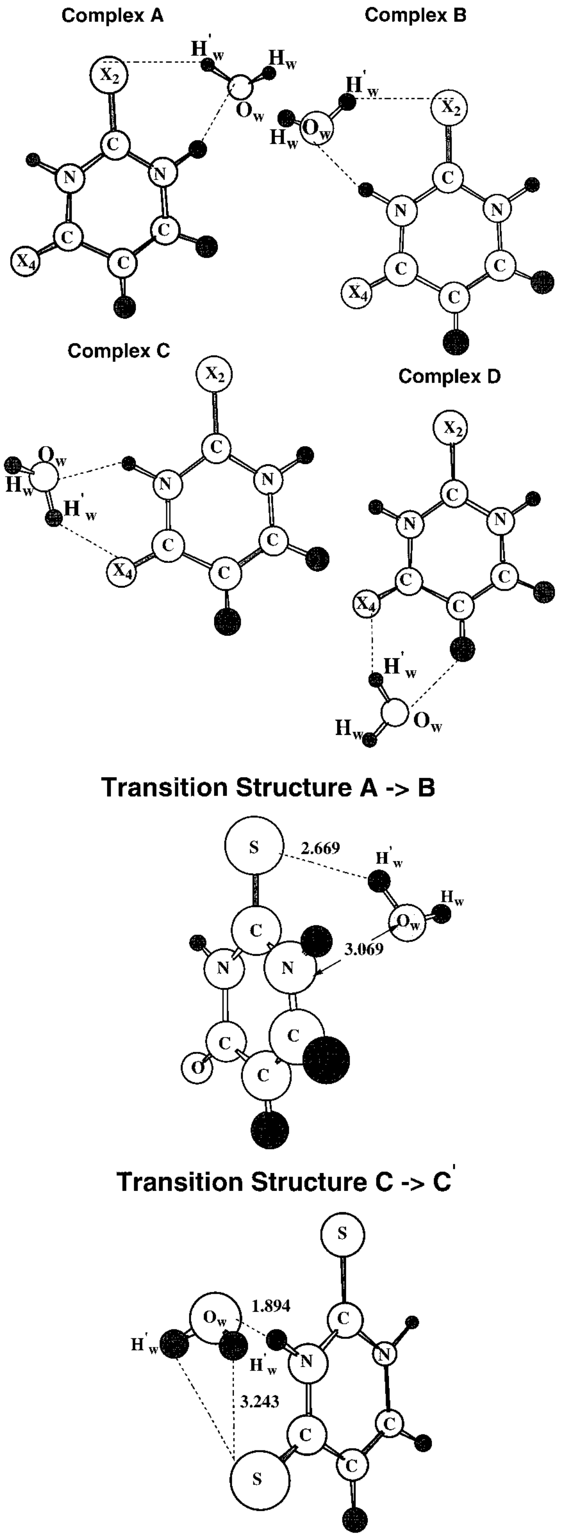

Figure 2. Structures A, B, C, and D of the complexes between the thiouracils and one water molecule. Transition structures in the 2TU−H_2O and 2,4DTU−H_2O complexes.

the reliability of the present computational level in comparison with the MP2/6-31G(d,p) one.

The N1H, N3H, C=O, and C5=C6 distances in uracil and in the three thiouracils are very similar. Larger differences are found for the N1C2 and C2N3 intra-ring distances. In uracil, the N1C2 and C2N3 distances are 1.393 and 1.383 Å, respectively,[32] and are 0.018 and 0.005 Å longer than in 2TU. Further, the N3C4 and C4C5 distances of 1.412 and 1.459 Å are 0.020 and 0.015 Å longer than in 4TU. This shows that the substitution of the carbonyl by a thiocarbonyl group results in a decrease the NC or CC distances of the adjacent bonds.

The infrared spectra of thiouracils have been studied in argon and nitrogen matrixes.[42−44] The vibrational frequencies and intensities have been calculated there at the B3LYP/6-31G(d,p) level,[42,44] and the frequencies have been scaled uniformly by a factor of 0.98. Comparison with the present results shows that the inclusion of diffuse functions provides a slightly better agreement with the experimental frequencies. For instance, the ν(NH) frequencies are 5−10 cm^{-1}, the ν(C=O) frequencies are 35−37 cm^{-1}, and the γ(NH) frequencies are 8−40 cm^{-1} lower than those calculated at the B3LYP/6-31G(d,p) level.[44]

1. Interaction between 2TU, 4TU, and 2,4-DTU and One Water Molecule. Structure and Vibrational Frequencies. We will now discuss the properties of the 1:1 adducts of thiouracils and water. The structure of the complexes of one water molecule with the investigated thiouracils is shown schematically in Figure 2. Their geometries and vibrational frequencies are gathered in Table 2. By analogy with the uracil−water 1:1 adduct, the most stable cyclic complexes, A, B, and C, are the ones in which one water accepts the acidic NH proton and donates its H_w'_ proton to the carbonyl oxygen or thiocarbonyl sulfur atoms. These complexes are characterized by the C_1 symmetry. The nonbonded hydrogens of water are pointing out of the plane of the thiouracils. As indicated by the values of the $H_wO_wH_w'$···O or $H_wO_wH_w'$···S dihedral angles falling between 172.7 and 177.8°, the bonded hydrogen atoms of water are slightly out-of-plane. The binding energies of the thiouracils with one water molecule are given in Table 4 which, for the purpose of comparison, also reports the interaction energies of the corresponding uracil−water 1:1 adducts.[34]

TABLE 4: B3LYP/6-31+G(d,p) Binding Energies (kJ mol^{-1}) for the 2TU−H_2O, 4-TU−H_2O, and 2,4DTU−H_2O Complexes[a,b]

system	complex A	complex B	complex C	complex D
2TU−H_2O	−44.5(−35.7)	−33.3(−26.5)	−38.0(−29.1)	−30.9(−23.0)
4TU−H_2O	−46.0(−36.7)	−35.2(−26.7)	−35.9(−27.9)	−24.4(−17.0)
2,4DTU−H_2O	−44.7(−35.9)	−33.1(−25.3)	−34.8(−27.9)	−25.3(−18.6)
uracil−H_2O[c]	−45.9(−36.2)	−36.3(−27.5)	−39.0(−29.8)	−31.2(−23.4)[d]

[a] The total energies of free 2-TU, 4-TU, and 2,4DTU are equal to −737.769609, −737.799614, and −1060.749204 hartree, respectively. The total energy of the free water molecule is −76.749204 hartree. [b] The values in parentheses indicate the binding energies with ZPE corrections. [c] From ref 34, without BSSE corrections. [d] From ref 63.

For the A, B, and C complexes, the largest variations in the ring distances are predicted for N1C2 in complex A, C2N3 in complex B, and N3C4 in complex C, in other words, for the CN bonds involved in the formation of the pseudo-ring structure. Hydrogen bond formation results in an elongation by 0.011−0.012 Å of the C═O bond and by 0.015−0.017 Å of the C═S bond. Somewhat similar results were obtained for self-associated 2TU. In the heterodimer of 2TU, in which the C2═S and C4═O bonds are both involved in the dimer formation, the equilibrium C2═S bond length is elongated by about 0.013 Å, whereas the C4═O bond becomes longer by about 0.007 Å than in the corresponding monomer.[25]

The intermolecular H_w'···S distances lie between 2.435 and 2.527 Å; that is, they are 0.48−0.53 Å longer than the corresponding H'_w···O distances, which are between 1.951 and 1.994 Å. The O_wH_w'···S and O_wH_w'···O angles do not differ substantially and lie in the interval between 132° and 141°. Very large differences are predicted for the C═X···H'_w angles, which vary from 109° to 112° for the carbonyl complexes and from 92° to 94° for the thiocarbonyl complexes. In the 1:1 adducts of uracil and water A, B, and C, the (N)H···O_w distances range between 1.940 and 1.999 Å and the corresponding angles between 141° and 144°. In the three thiouracils complexed with one water molecule, the (N)H···O_w distances range between 1.839 and 1.963 Å, and the corresponding NH···O_w angles vary between 144.5° and 159.5°. In the 2TU and 4TU complexes where both the NH group and the S atom of the thiocarbonyl group are involved in complex formation [2TU(A), 2TU(B), 4TU(C)], the (N)H···O_w distances are shorter, between 1.839 and 1.868 Å, and the NH···O_w angles, between 157.7° and 159.6°, are larger than in complexes where the carbonyl group acts as a proton acceptor.

Complexes D are 6−9 kJ mol^{-1} less stable than complexes C. This difference is of the same order of magnitude as the one of 7 kJ mol^{-1} recently reported for the analogous uracil−water complex.[31] The CH···O hydrogen bonds are weaker than the NH···O bonds, mainly because of a large reduction in the electrostatic contribution. Marked differences reflecting the weaker nature of the CH···O hydrogen bond are also observed for the geometries. The water is now coplanar with the ring of the thiouracil derivative, the $H_wO_wH_w'$···O4 or $H_wO_wH_w'$···S4 dihedral angles being close to 180°. A similar structure has been reported recently for the uracil−water complex.[31] Further, the O_w...H5 distances that are equal to 2.369 Å in 2TU−H_2O, 2.353 Å in 4TU−H_2O, and 2.261 Å in 2,4DTU−H_2O are considerably longer than the (N)H···O_w distances. The CH···O angle, which appears to be equal to 129.9° in the 2TU−H_2O complex D, is smaller than the (N)H···O_w angles of 144°−160° in the other studied structures. The elongation of the C═S bond, also smaller in the D structures than in the other ones, takes values of 0.001 Å in the 2TU−H_2O adduct and 0.007 Å in the 2,4DTU−H_2O complex. The C5H bond length equal to 1.081 Å in the free molecules becomes elongated by 0.001−0.002 Å in the D complexes. Because one of the main objectives of this work is to discuss the stability of the complexes in terms of the intrinsic acidities or basicities of the NH groups and the O or S atoms involved in complex formation, the D complexes will be not be discussed further.

Figure 2 also includes two typical transition structures of the thiouracil-H_2O complexes. The first one describes the migration of a water molecule between the 2TU complexes A and B. It lies above the lower-energy complex B by 14.9 kJ mol^{-1} and is characterized by the imaginary frequency 27i cm^{-1}. The other transition structure is related to the flipping of water throughout the thiouracil plane in the 2,4DTU−H_2O water complex C. It is placed above C by 6.7 kJ mol^{-1} and possesses the imaginary frequency of 208i cm^{-1}. As depicted in Figure 2, the two O_wH_w bonds are pointing out symmetrically toward the sulfur atom relative to the plane. This actually makes such transition structure different from the corresponding ones for the uracil−H_2O adducts which are perfectly planar.[56]

In complexes A, B, and C, the ν(CH) and the ring vibrations are rather insensitive to hydrogen bond formation with one water molecule. As we expected, the ν_1 and ν_3 vibrations of water, the ν(NH) vibrations, and the ν(C═O) vibrations of the bonds involved in the interaction with one water molecule are red-shifted, and the γ(NH) vibrations that are generally strongly sensitive to hydrogen bond formation are blue-shifted by 160−240 cm^{-1}. The in-plane deformation vibrations, δ(NH), are coupled with ring modes. In isolated 2TU, the mode calculated at 1572 cm^{-1} contains δ(N1H) and δ(N3H) contributions, and the mode at 1455 cm^{-1} shows a predominant δ(N3H) character. This is in agreement with the assignment in ref 44. In the 2TU−H_2O complex A, the predominant δ(N3H) mode appears at 1460 cm^{-1} and two modes at 1680 and 1640 cm^{-1} involve mainly the δ(N1H) vibration. The same remarks also hold for the other molecules, and these modes will not be discussed further in this article. As outlined in previous works,[42,44] the ν(C═S) vibrations are strongly coupled with other modes and, therefore, their frequency shifts do not reflect the strength of the hydrogen-bonding interaction with water.

As for the uracil− and thymine−H_2O complexes,[32] the mean frequency shifts, $\Delta\nu$(OH), of the ν_3 and ν_1 vibrations of water are related to the elongations of the OH bond. A similar picture is valid for thiouracil−H_2O adducts. For O_wH_w'···S bonds formed between 2TU, 4TU, and 2,4DTU and water, the following correlation can be derived:

$$-\Delta\nu(\mathrm{OH\cdots S})(\mathrm{cm}^{-1}) = -12 + 10.6 \times 10^3\,\Delta r(\mathrm{OH})(\text{Å}) \qquad r = 0.9897 \quad (1)$$

For the OH···O bonds formed between uracil or thymine and water, the following correlation was previously deduced:[32]

$$-\Delta\nu(\mathrm{OH\cdots O})\ (\mathrm{cm}^{-1}) = -19 + 10 \times 10^3\,\Delta r(\mathrm{OH})\ (\text{Å}) \qquad r = 0.9987 \quad (2)$$

Figure 3 compares the frequency shifts and the elongations of the OH distance for OH···O and OH···S hydrogen bonds. It can be predicted from eqs 1 and 2 that the same elongation of

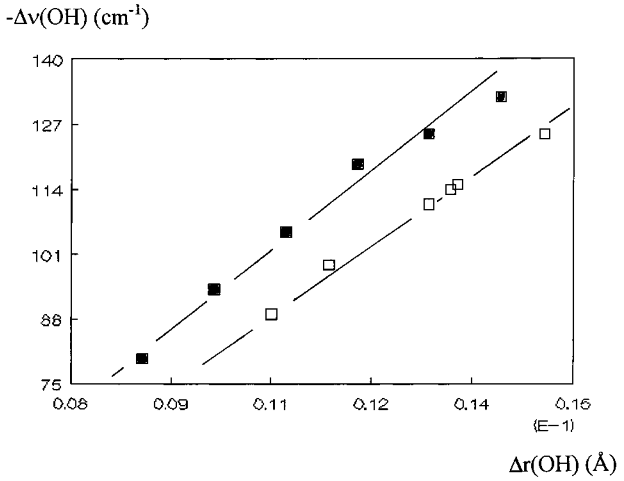

Figure 3. $-\Delta\nu$(OH) (cm^{-1}) as a function of Δr(OH) (Å) for OH···O (□) and OH···S (■) hydrogen bonds between uracil and thiouracils and one water molecule.

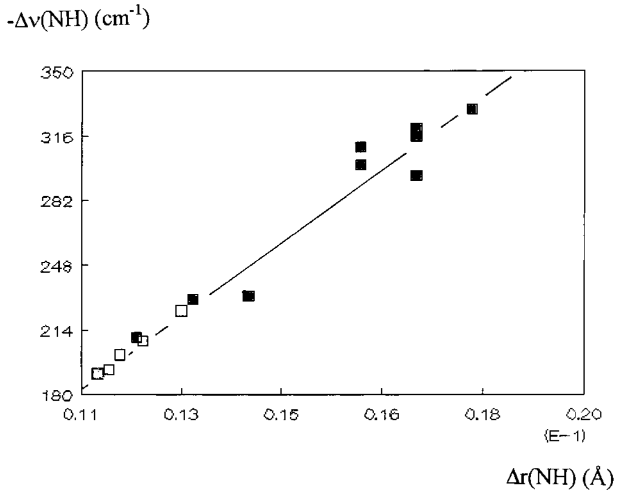

Figure 4. $-\Delta\nu$(NH) (cm^{-1}) as a function of Δr(NH) (Å) for the NH···O hydrogen bonds in uracil and thymine (□) and thiouracil (■) complexed with one water molecule.

the OH bond causes larger frequency shifts of the νOH vibration in OH···S than in OH···O systems. Experimental[50,51] and theoretical data[52−56] have shown that for a given proton donor, the OH···S bonds are weaker than the OH..O ones. However, for the same enthalpy of complex formation, the elongation of the OH bonds is larger for OH···S than for OH···O hydrogen bonds.[50] This has been explained by the fact that more charge is transferred to the OH bond with the more polarizable sulfur bases.[50,51] This in agreement with the aforementioned values of the polarizabilities of thiouracils compared with uracil.

In the 1:1 adducts of uracil and thymine with water, the elongations of the NH bond involved in this interaction with water vary between 0.015 and 0.013 Å and, thus, the frequency shifts of the ν(NH) vibration, which is actually a fairly unmixed mode, range between 191 and 232 cm^{-1}. In the thiouracil complexes, the elongation of the NH bond and the frequency shift of the corresponding ν(NH) frequency are larger, ranging between 0.012 and 0.018 Å and 210−330 cm^{-1}, respectively. This can be attributed to the larger acidic character of the NH bonds in the thiouracils that will be discussed in the next section. Figure 4, where the frequency shift has been plotted against the elongation of the NH bond, indicates that the same correlation holds for uracil− and thiouracil−H_2O complexes, in contrast to eqs 1 and 2.

TABLE 5: B3LYP/6-31+G(d,p) Proton Affinities [PA(B)] and Deprotonation Enthalpies [PA(A$^-$)] (kJ mol^{-1}) of 2TU, 4TU, and 2,4DTU

PA(B) of the X2 and X4 atoms				
	X2 (N1 side)	X2 (N3 side)	X4 (N3 side)	X4 (C5 side)
2TU[a]	840.6	843.0	845.4	858.6
4TU	814.5	819.1	871.9	874.4
2,4DTU[b]	841.0	843.1	869.9	872.4
uracil[c]	815.1	820.1	849.0	859.8

PA(A$^-$) of the N1$^-$ and N3$^-$ anions		
	N1H	N3H
2TU	1364.2	1401.0
4TU	1359.6	1418.2
2,4DTU	1338.8	1392.4
uracil*c*	1391.0	1447.1

[a] Experimental value determined by the bracketing method is 874 kJ mol^{-1}.[36] [b] Experimental value = 907.1 kJ mol^{-1}.[36] [c] From ref 34.

The IR spectra of 2TU and 4TU have been investigated in argon matrixes.[57] In the presence of small amounts of water, the ν(N3H) and ν(N1H) of 2TU vibrations are shifted downward by 146 and 186 cm^{-1}, respectively, and the ν(N1H) and ν(N3H) vibrations of 4TU by 190 and 120 cm^{-1}. In 4TU, blue shifts of the γ(N1H) and γ(N3H) vibrations of 130 and 125 cm^{-1} have also been observed. Water also induces a downward shift of the ν(C=O) vibration of 21 cm^{-1} in 2TU and 18 cm^{-1} in 4TU. These observations suggest that the N1H, N3H, and C=O groups are involved in complex formation with water. No shift of the ν(C=S) vibration indicative of an interaction between the thiocarbonyl group and water could be observed in these low-temperature materials.

2. Proton Affinities, Deprotonation Enthalpies, and Bonding Trends. We begin this section by noticing that complex formation of 2TU and 4TU with one water molecule does not significantly affect the relative stabilities of 2TU and 4TU. The A complex 4TU−H_2O is 8.6 kJ mol^{-1} more stable that the 2TU−H_2O one, and this value does not differ greatly from the value of 7.0 kJ mol^{-1} for the free molecules. The results reported in Table 4 indicate that the binding energies of the three thiouracils with one water molecule are ordered as follows: complex A > complex C > complex B. It is remarkable that, when a water molecule binds the thiouracils at a given A, B, or C site, the binding energies including the ZPE corrections are nearly the same, within the limits ca. of 1−2 kJ mol^{-1}, and appear further to be also rather insensitive to the substitution of a carbonyl by a thiocarbonyl group. In the thioguanine−H_2O complex, where the water molecule water acts as a bidonor, the optimized geometry of the complex is similar to that of the guanine−water complex, but the S6···O_w distance is 0.8 Å larger than the O6···O_w one.[25] Despite this fact, the thioguanine−water complex is only 1.7 kJ mol^{-1} less stable than the guanine−water complex.[25] Our results on the thiouracils display the same trend.

Our previous works[32,34] have shown that the binding energies of conventional nucleobases with one water molecule depend on the proton affinities of the O atoms [PA(B)] and on the deprotonation enthalpies of the NH bonds [PA(A$^-$)] involved in the formation of the cyclic complexes. The intrinsic acidity also emerges as a common property of the diverse hydrogen donors in the protein α-helix and enzymes. This property may in part be responsible for the natural selection of these molecules as principal biological hydrogen donors.[58,59] Table 5 reports the proton affinities of the oxygen and sulfur atoms and the deprotonation enthalpies of the N1H and N3H bonds of 2TU, 4TU, and 2,4DTU. The data for uracil, calculated at the same level,[28] are also indicated in this table.

Our results show that the heteroatom in 4-position is the most basic site of the molecules, contrary to the results ref 37. Furthermore, the substitution of O by S in 2TU and 4TU does not significantly affect the PA(B) value of the other O atom, which is nearly the same as for uracil. As demonstrated in other works,[60−64] thiocarbonyl derivatives are considerably more basic than their carbonyl homologues. In the present case, the PA(B) value of the S2 atom is 23−26 kJ mol^{-1} larger than that of the O2 atom, and the PA(B) value of the S4 atom is 13−20 kJ mol^{-1} larger than that of the O4 atom. The basicity difference of carbonyl and thiocarbonyl bases has been thoroughly discussed in the literature in terms of field, resonance, and polarizability effects.[63] No experimental or theoretical data are available for the acidity of the NH bonds of thiouracils. The data of Table 5, reported for the first time, indicate that the substitution of carbonyl group(s) by thiocarbonyl group(s) increases the acidity of the NH bond by 25−55 kJ mol^{-1}. Experimental data on intrinsic acidities and basicities have been reported for carboxamides and thiocarboxamides.[64] Compared with carboxamides, the thiocarboxamides are stronger bases (by 19 kJ mol^{-1}) and much stronger acids (by 65 kJ mol^{-1}).[64] These results are in line with the present data. Protonation or deprotonation of thiouracils also result in spectacular changes of the geometric and vibrational parameters, similar to those reported recently for uracil[33] and uracil−H_2O anionic complexes.[36] This will be discussed in a forthcoming article.[65] Further, recent B3LYP calculations have shown that anion formation leads to significant geometrical changes in the nucleobases.[66]

Inspection of Tables 4 and 5 reveals that the most stable hydrogen bonds present in complexes A are formed at the lone pair of the O2 or S2 atoms (N1 side) characterized by the lowest PA(B) and with the N1H bond characterized by the highest acidity. Despite the larger basicity of the S atom and much larger acidity of the NH bonds in thiouracils, their binding energies with one water molecule do not differ significantly in thiouracils and uracil. In these cyclic structures, the strength of the NH···O hydrogen bonds must depend on the acidity of the NH bond and is therefore expected to be larger in thiouracils than in uracil. In contrast, the OH···S hydrogen bonds are weaker than the OH···O ones despite the larger PA(B) value of the S atom. This is nicely illustrated by the interaction between one water molecule and $H_2C{=}O$ or $H_2C{=}S$ where the hydrogen bond energies are 23 and 13.8 kJ mol^{-1}, respectively,[54] and the PA(B) values of the two bases are 717.7 and 756.5 kJ mol^{-1}.[67] The energy of the hydrogen bond involving the carbonyl base is ca. 9 kJ mol^{-1} larger although its PA(B) is ca. 39 kJ mol^{-1} lower. It follows from these considerations that the same hydrogen bond energies should be obtained for larger PA(B) values for OH···S than for OH···O hydrogen bonds. Similar trends are obtained from theoretical or experimental data on ionic $AH^+\cdots B$ hydrogen bonds. Desmeules and Allen[68] have correlated the energies of these hydrogen bonds to ΔPA, the difference in monomer PAs. The same energy is obtained at significantly higher ΔPA values for hydrogen bonds involving acceptor atoms of the second row than of the third one. Experimental data are also available for $AH^+\cdots O$ and $AH^+\cdots S$ hydrogen bonds.[69] From the linear correlation observed between the hydrogen bond energies and ΔPA, reported in ref 69, we could estimate that the same hydrogen bond energies are obtained when the PA(B) values of the S bases are at least 100 kJ mol^{-1} larger than those of the O bases.

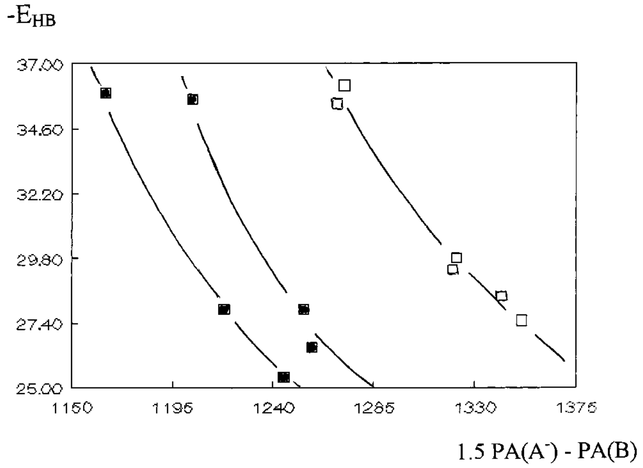

Figure 5. Binding energies ($-E_{HB}$) (kJ mol^{-1}) as a function of 1.5 PA(A^-) − PA(B) (kJ mol^{-1}) for uracil and thymine (□) (ref 34) and thiouracils (■) complexed with water. The right curve refers to 2TU and 4TU and the left curve to 2,4DTU.

In the cyclic complexes involving conventional nucleobases and one water molecule, we have demonstrated that the binding energies are correlated to the function 1.5 PA(A^-) − PA(B), showing the predominance of the acidity of the proton donor in determining the hydrogen bond energies.[34] Figure 5 displays difference plots for OH···O (in uracil and thymine)[34] and OH···S bonds in thiouracils. The curves depicting the OH···O and OH···S systems are nearly parallel, but the OH···S systems are displaced to the left of 1.5 PA(A^-) − PA(B) values, which are about 100 kJ mol^{-1} lower. This means that to obtain the same binding energy, the PA(B) value of the S atoms of thiouracils must be about 100 kJ mol^{-1} larger than the PA(B) value of the O atoms of uracil. This conclusion agrees well with the experimental data on ionic hydrogen bonds discussed above. This illustrates also the usefulness of establishing quantitative relations between the hydrogen bond parameters and the acidity or basicity of the sites involved in the formation of cyclic complexes. In addition, when the water molecule is restricted to interacting with the O(S)6 position of guanine, the 6-thioguanine−water complex is much less stable (7.9 kJ mol^{-1}) than the guanine−water complex (20.5 kJ mol^{-1}).[25]

3. Complexes between Thiouracils and Three Water Molecules. The B3LYP/6-31+G(d,p) optimized structures of the most stable complexes formed between 2TU, 4TU, and 2,4DTU and three water molecules are illustrated in Figure 6. In this case, 4TU is 2.7 kJ mol^{-1} less stable than 2TU, in contrast to the free molecules or their 1:1 adducts with water. This can be explained by the small differences in acidities or basicities of 2TU and 4TU, the 2TU−$(H_2O)_3$ and 4TU−$(H_2O)_3$ complexes having different types of hydrogen bonding with water. Table 6 lists important intra- or intermolecular distances and vibrational frequencies together with the binding energies of the thiouracils complexed with three water molecules. Two nearly isoenergetical structures I and II are predicted for the 2,4DTU−$(H_2O)_3$ complex. As shown in ref 70, in uracil, the two C=O groups and the N1H, N3H, and C5H bonds are involved in the interaction with three water molecules. Therefore, the hydration shell consisting of three waters can be considered as the complete first hydration shell for uracil. In the present thiouracil−$(H_2O)_3$ complexes, the C5H bond in the four structures and the S4 atom in 4TU−$(H_2O)_3$ and 2,4DTU−$(H_2O)_3$(I) are not hydrogen-bonded to water. Thus, our study suggests an alteration of the first hydration shell under the substitution of the oxygen atom(s) by the sulfur one(s). The different behavior

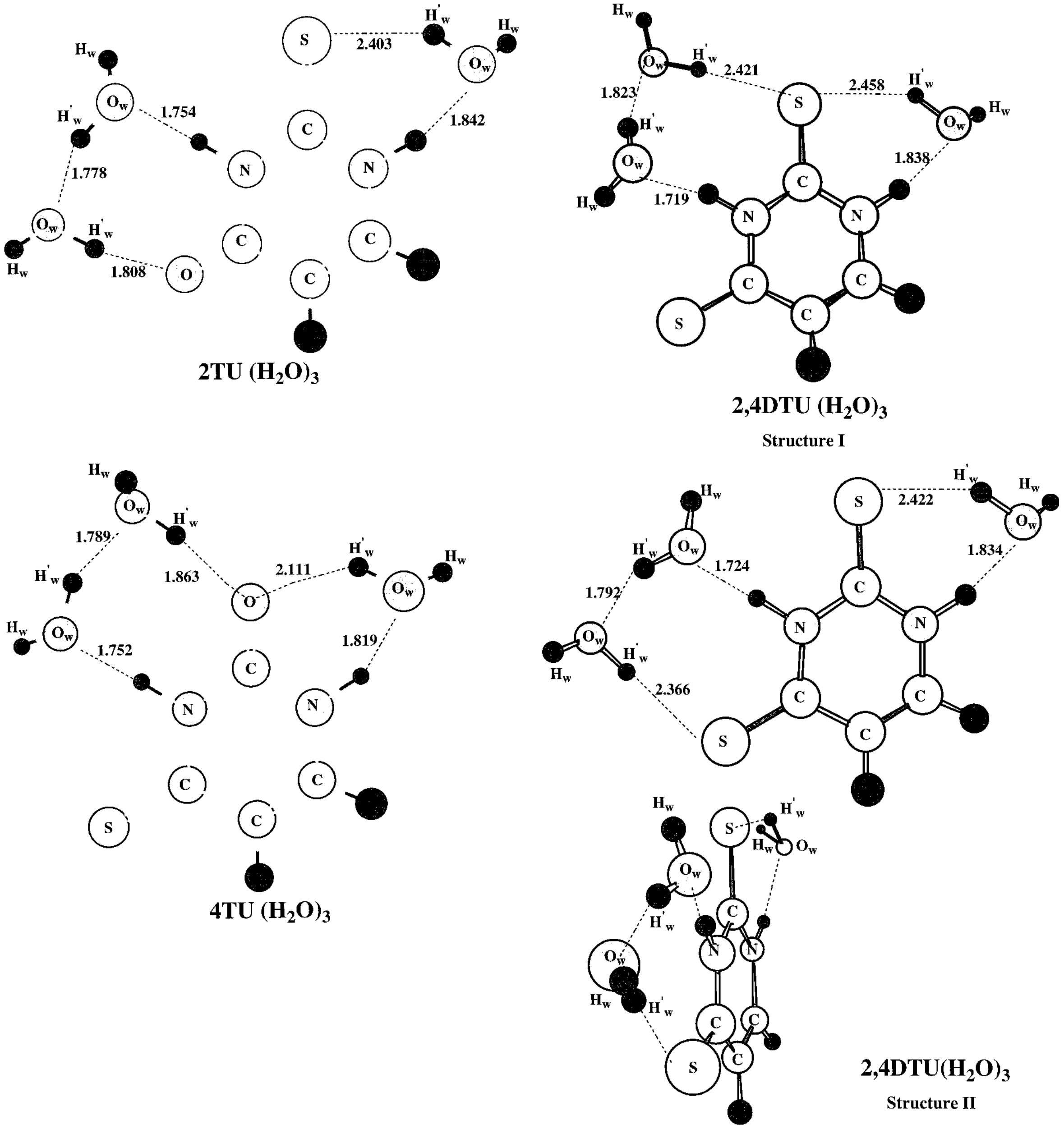

Figure 6. B3LYP/6-31+G(d,p) optimized structures for complexes involving 2TU, 4TU, and 2,4DTU and three water molecules.

of uracil and thiouracils in the presence of three water molecules certainly has an implication for their different biochemical activities. In the four structures, two water molecules are bonded together and the hydrogen bonds formed at the X2,N3H side of the thiouracils become more linear than in the monohydrated species. The intermolecular distances between the two water molecules are equal to 1.778 Å (2TU), 1.789 Å (4TU), 1.823 Å (2,4DTU I), and 1.792 Å (2,4DTU II). A common feature of the four studied complexes is that the $H_w \cdots O_w$ distances in the hydrogen-bonded water molecules are significantly shorter than in the water dimer, where this distance calculated at the same computational level is equal to 1.919 Å. A similar contraction of the $H_w \cdots O_w$ distance has been found in guanine complexed by two water molecules at the N1H, C6=O side of guanine.[71] Figure 6 shows that in 2TU and 2,4DTU(II), the two basic sites S2 and O4 and the two NH bonds are involved in the interaction with three water molecules. In contrast, in 4TU and 2,4DTU, the two lone pairs of the O2 or S2 atoms are bonded to water. In comparison with the monohydrated species, we observe that the interaction with three water molecules results in a shortening by 0.032 Å of the $H_w' \cdots S2$ distance in 2TU and to respective lengthenings by 0.143 and 0.007 Å of these distances in 4TU and 2,4DTU(I). The occupation of the two lone pairs of the O or S atoms results in an anticooperative effect.[72,73] This effect is not operating for the $H_w' \cdots O2$ or $H_w' \cdots S2$ distances (N3 side) which are both elongated with respect to the monohydrated species. We suggest that such feature results probably from the increased proton donor ability of the water dimer.[74] A substantial decrease of the stretching vibrations of water is also predicted. In 2TU$-(H_2O)_3$, for example, the mean value of the $\nu(H_wOH_w')$ frequencies of 3683 cm^{-1} is markedly lower than the value of 3776 cm^{-1} in the corresponding B complex.The same remark also holds for the ν(N3H) frequency which is equal to 3304 cm^{-1} in the monohydrated species and lowers to 3093 cm^{-1} when 2TU is complexed by three water molecules. For all the trihydrated thiouracils, a spectacular increase of the frequency of the γ(N3H) vibration and a moderate decrease of the ν(C=O) frequency are also noticed.

Cooperative phenomena also influence the binding energies. In the three thiouracils complexed with three water molecules,

TABLE 6: Intra- and Intermolecular Distances (in Å), Vibrational Frequencies (in cm^{-1}) and Binding Energies (in kJ mol^{-1}) for the Complexes Involving 2TU, 4TU, and 2,4DTU with 3 H_2O Molecules

inter- and intramolecular distances				
distances	2TU−$(H_2O)_3$	4TU−$(H_2O)_3$	2,4DTU−$(H_2O)_3$	distances
			I	II
N1H	1.028	1.026	1.028	1.029
N3H	1.042	1.041	1.045	1.045
C2=X	1.683	1.246	1.696	1.683
C4=X	–	1.665	1.666	1.677
(N1)H···O_w	1.849	1.819	1.838	1.834
H_w'···X2[a]	2.403	2.111	2.458	2.422
(N3)H···O_w	1.754	1.752	1.719	1.724
H_w'···O_w	1.778	1.789	1.823	1.792
H_w'···O4	1.808	–	–	2.366
H_w···X2[b]		1.863	2.421	–
vibrational frequencies				
assignment				
ν3(H8O7H9)[a]	3880	3904	3883	3880
ν1(H8O7H9)[a]	3563	3675	3628	3582
ν3(H11O10H1 2)[c]	3894	3886	3883	3882
ν1(H11O10H1 2)[c]	3472	3586	3618	3505
ν3(H14O13H1 5)*d*	3891	3894	3866	3880
ν1(H14O13H1 5)*d*	3553	3500	3549	3572
ν(N1H)	3324	3351	3323	3311
ν(N3H)	3093	3109	3031	3037
ν(C4=O)/ν(C2 =O)	1748	1754	–	–
γ(N1H)	880	853	880	885
γ(N3H)	991	984	1030	1022
ν3(H8O7H9)[a]	3880	3904	3883	3880
ν1(H8O7H9)[a]	3563	3675	3628	3582
binding energies[e]				
	−132.1(−104.2)	−123.3(−94.4)	−119.0(−92.6)	−122.3(−95. 6)
Σ(A + B + C)	−115.8(−91.3)	−117.1(−91.3)	−112.6(−89.1)	−112.6(−89. 1)

[a] N1 side. [b] N3 side. [c] Water molecule bonded to the X2 atom or N3H group. [d] Water molecule bonded to the N3H group or to the X4 atom. [e] The values in parentheses indicate the binding energies with ZPE corrections.

the binding energies become larger by 3−12% than the sum of the binding energies of the monohydrated complexes A, B, and C.

These percentages cannot actually be considered as the real values of the cooperativities because the occupation of the sites in the trihydrated complexes is not the same as in the monohydrated species. Nevertheless, they certainly show this trend. The energy of the hydrogen bond in the water dimer calculated at the same level is only −15.3 kJ mol^{-1} and, as suggested by the decrease of the intermolecular distances discussed above, the strength of this bond increases in the trihydrated thiouracils.

4. Concluding Remarks. This study represents the first theoretical analysis of the interaction between the three thiouracils and one or three water molecules. The geometries, relevant vibrational properties, and the binding energies with water are discussed in terms of the proton affinities and the deprotonation enthalpies of the different sites of the thiouracils, which are also reported for the first time. In particular, the binding trends are rationalized in terms of 1.5 PA(A^-) − PA(B). We have also shown that, compared with the uracil−$(H_2O)_3$ complex, the substitution of O by S leads to the alteration of the first hydration shell consisting of three water molecules. This is an interesting effect which might have far-reaching consequences to be explored in biochemistry and pharmacology.

Note Added after Submission of the Manuscript. The gas-phase acidities of the N1 and N3 sites of uracil have been bracketed recently to provide an understanding of the intrinsic reactivity in this nucleic base.[75] These measurements are closest (within 4 kJ mol^{-1}) to our values predicted at the B3LYP/6-31/G(d,p) level,[34] thus validating the choice of our computational method and level. Further, the gas-phase proton affinities of the three thiouracils have been measured by means of Fourier transform ion cyclotron resonance mass spectroscopy.[76] In all cases, the protonation takes place attached to position 4, although thiocarbonyls generally are stronger bases than carbonyl in the gas phase. This is in complete agreement with the conclusions of our work.

One of the referees asked if we could extrapolate our results to the interaction of the studied molecules with bulk water. As a matter of fact, we do not think that it is possible; our results on intrinsic reactivities and interaction with water deal with the gas-phase chemistry and not with the molecular interactions in media of very high polarity. From this point of view, an interesting article on the acidity of uracil in the gas phase and in solution appeared recently.[75] In the gas phase, the N3 site of uracil is far less acidic than the N1 site, in direct contrast to what occurs in solution (dielectric constant of 78.5), where the two sites are so close in acidity as to be unresolvable. About the same behavior can be expected for the thiouracils. Moreocer, in bulk water, the OH groups are hydrogen-bonded to each other and this certainly affects their proton donor or proton acceptor abilities. Thus, any extrapolation of the present results to bulk water would be highly speculative.

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