Theoretical Study of Uracil Tautomers. 2. Interaction with Water

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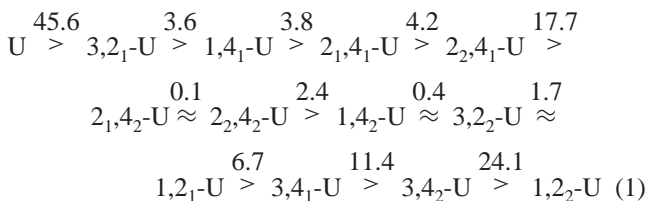
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The interaction of 2-hydroxy, 4-hydroxy, and 2,4-dihydroxy tautomers of uracil with a water molecule is studied at the B3LYP/6-31+G(d,p) computational level. Depending on the nature of the tautomers, cyclic or open structures are formed. In most of the cyclic structures, water accepts the OH or NH protons and donates its proton to the O or N atoms of the uracil tautomers. Two anticooperative structures where water acts as a biacceptor are also formed. The intermolecular distances, binding energies, and frequency shifts of the stretching vibrations are rationalized in terms of the deprotonation energies and the proton affinities of the sites involved in complex formation. The relative order of stability of the uracil tautomers, free and complexed with water, is compared. Deprotonation of the $O_{10}H$ bond of the $3,4_2$-U tautomer greatly influences the geometry and the binding energies of the water complexes. Complex formation with water also results in a decrease of the deprotonation energy. The concerted double-proton transfer of the tautomerization process U ⟷ $1,4_1$-U mediated by a water molecule is also examined. The lowering of the proton-transfer barrier because of excess entropy is discussed.

Introduction

In the Watson−Crick model of RNA, uracil (U) adopts the dioxo tautomeric form to be in the complementary conformation to the normal amino tautomer of adenosine[1] (see Figure 1). However, it has been known for a long time that uracil may also exist in other tautomeric forms whose appearance in RNA causes the formation of the nucleobase pairing mismatches.[2] The appearance of tautomeric forms depends on their relative order of stability, which has been the subject of numerous studies in the last two decades, at both experimental[3,4] and theoretical[5−8] levels. However, most of these studies have been focused on examining the relative order of stability of uracil tautomers in the gas phase, despite the fact that the most intriguing biochemical processes of the RNA functioning occur in solutions, e.g., water, and besides, these studies have been also restrained to only five tautomers in the gas phase and to the continuum model of solvent.

In the last two years, there has been a breakthrough in the study of uracil and its tautomers which has been developed in two directions.[9,10] One of them is related to an enlargement of the possible uracil tautomers. Two additional tautomers of uracil have been found in ref 9a at the B3LYP/6-31G(d) computational level, and the complete list of the 12 uracil tautomers has been then accomplished in ref 9b. The relative order of stability of all uracil tautomers at the B3LYP/6-31+G(d,p) level is as follows:

$$\begin{array}{ccccccc} & 45.6 & & 3.6 & & 3.8 & & 4.2 & & 17.7 \\ U & > & 3,2_1\text{-U} & > & 1,4_1\text{-U} & > & 2_1,4_1\text{-U} & > & 2_2,4_1\text{-U} & > \end{array}$$

$$\begin{array}{cccccc} & & 0.1 & & 2.4 & & 0.4 & & 1.7 \\ 2_1,4_2\text{-U} & \approx & 2_2,4_2\text{-U} & > & 1,4_2\text{-U} & \approx & 3,2_2\text{-U} & \approx \end{array}$$

$$\begin{array}{ccccc} & 6.7 & & 11.4 & & 24.1 \\ 1,2_1\text{-U} & > & 3,4_1\text{-U} & > & 3,4_2\text{-U} & > & 1,2_2\text{-U} \quad (1) \end{array}$$

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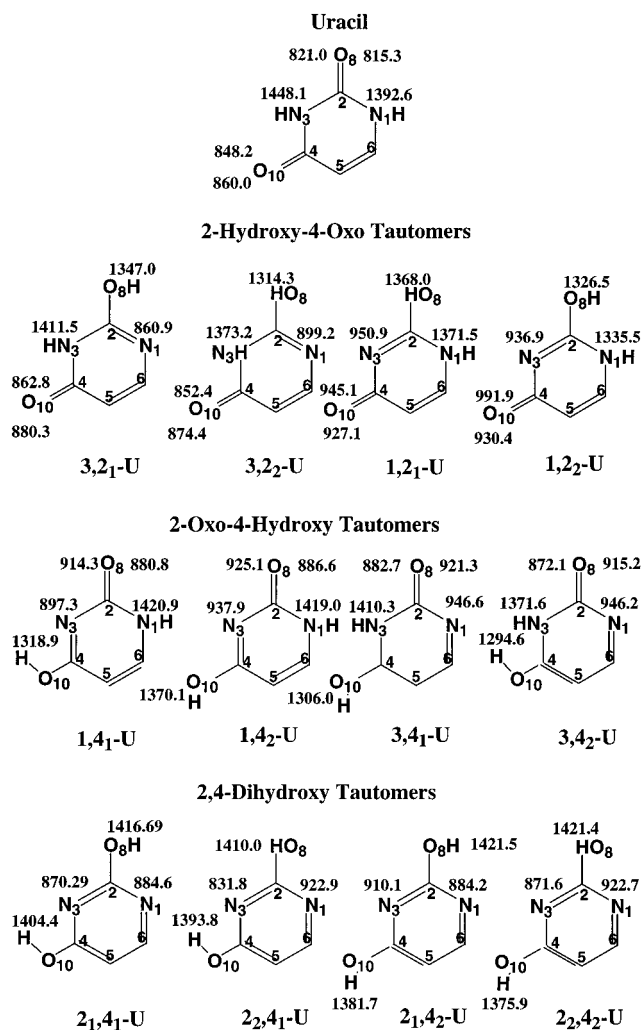† On leave from Bogoliubov Institute for Theoretical Physics, Kiev, Ukraine 03143.

Figure 1. Uracil and its tautomers. The proton affinities of the O and N atoms and deprotonation enthalpies of the O−H and N−H bonds are indicated.

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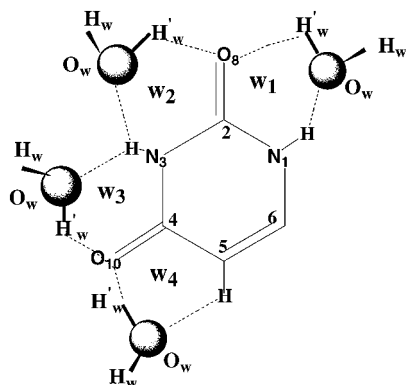*J. Phys. Chem. A, Vol. 105, No. 10, 2001* **1935**

Figure 2. Preferential sites of water molecules in the uracil vicinity.

In eq 1, the quantity above the inequality or $\approx$ sign indicates the corresponding energy difference, in kcal/mol, between the right-hand complex and its left-hand one and the notations analogous to ref 9b for uracil tautomers are employed, viz., the 2-hydroxy-4-oxo tautomers are referred to as $N,2_n$-U, 2-oxo-4-hydroxy as $N,4_n$-U ($N = 1$ and 3), and 2,4-dihydroxy as $2_n,4_k$-U ($1 \leq n, k \leq 2$). This list includes the $3,4_2$-U and $1,2_2$-U tautomers whose B3LYP/6-31+G(d,p) energies relative to uracil are equal to 98.0 and 122.1 kJ mol^{-1}, respectively, after the zero-point vibrational energy (ZPVE) correction. They show unusual acidic or basic properties[9b] (see Figure 1 where the proton affinity (PA) and deprotonation enthalpy (DPE) of each uracil tautomer are indicated).

The other direction focuses on the study of the interaction of uracil with water[10] (see also ref 8c,d). In ref 10a, the authors reveal three favorable sites w_1, w_2, and w_3 of a single water molecule to be placed in the uracil vicinity (see Figure 2). Their findings are consistent with analogous studies on the uracil−water complexes.[8c,10c,d] The fourth site w_4 between the $C_4=O_{10}$ and C_5-H_{11} bonds has been recently found in ref 10c,d. At the B3LYP/6-31+G(d,p) computational level, the binding energy of uracil with water molecule placed at the w_4 site is equal to 23.4 kJ mol^{-1}, in good agreement with the binding energy of 25.3 kJ mol^{-1} calculated at the MP2/DZP level[10c] and 29.7 kJ mol^{-1} at the MP2/6-311++G(d,p) level.[10d] The order of stability of these four uracil−water complexes is as follows (see also ref 10d):

$$\overset{6.5}{U-w_1} > \overset{2.4}{U-w_3} > \overset{4.1}{U-w_2} > U-w_4 \qquad (2)$$

However, the question of how the tautomeric order of stability is influenced by a presence of water has not been fully answered so far.

The present work is undertaken to address two issues. The first one is to study the complexes of uracil tautomers with water and to show how water affects their relative order of stability, whereas the second issue is to rationalize this relative order of stability of tautomer complexes with water in terms of the acidity and basicity of the different sites involved in the complex formation.

Computational Methodology

The computational methodology remains the same as that in part 1,[9b] namely, the computations were performed at the B3LYP/6-31+G(d,p) computational level using the Gaussian 98 suit of packages.[11] No constraints were imposed on a possible planarity of the tautomer−water complexes. The harmonic frequencies and ZPVEs were kept unscaled. All reported energy values were rescaled to the energy + ZPVE given in kJ mol^{-1}. The basis set superposition error (BSSE) effect was not accounted for because of its smallness, varying between 0.7 and 3.5 kJ mol^{-1}.[10a,12]

Complexes of Uracil Tautomers with Water

It is useful to remember here that if a water molecule is involved in a sequential hydrogen bonding, or in the other words, if water acts both as proton acceptor and proton donor, the relevant structure is energetically favored over the alternative double donor or double acceptor hydrogen bonding.[1b,13] These structures are cooperative and the binding energies with water are expected to be larger than the energies of the two open structures. In some of the complexes of the uracil tautomers, water acts as a bidonor toward the N or O atoms; in two tautomer complexes where two neighboring OH and NH groups are formed, water acts as a biacceptor. These structures are anticooperative, and the interaction energies with water are expected to be lower than the energies of the two open structures.

A. Optimized Geometries and Energies of Uracil Tautomer−Water Complexes. The optimized H-bond geometries of twenty-nine complexes of uracil tautomers with water are given in Table 1 where a few of them are compared with the geometries optimized at the MP2/DZP[10c] and MP2/6-311++G-(d,p)[10d] computational levels. Some representative structures are shown in Figures 3 and 4. Table 2 lists the interaction energies E_{HB} of the studied complexes of uracil tautomers with water. They are classified into cyclic and open structures. In the former ones, the water molecule mainly acts as a proton donor and as a proton acceptor. These H bonds form six-membered rings. In the open structures, water acts only as a proton donor.

Five cyclic complexes $3,2_1$-U−w_3, $3,2_2$-U−w_3, $1,4_1$-U−w_1, $1,4_2$-U−w_1, and 4-T_4-w_2 involving the N−H bond and the carbonyl oxygen atom of the corresponding tautomer are formed and shown in Figures 3 and 4. It is worth mentioning that the tautomers $3,2_1$-U and $3,2_2$-U structurally differ from each other by the different position of the O_8−H group being on the N_1 and N_3 side, respectively. A similar difference exists between the $1,4_1$-U and $1,4_2$-U tautomers relative to the position of the O_{10}−H group nearby the N_3 or C_5 atom, respectively. In the former case, as shown in Figure 1, the deprotonation enthalpies of the N_3−H and O_8−H groups of the $3,2_2$-U tautomer are smaller than those of the $3,2_1$-U because of a larger repulsion of these two bond dipoles. It is seen in Table 1 that the (N)H···O_w intermolecular distances vary from 1.867 to 1.924 Å and the $(O_w)H'_w$···O(=C) ones from 1.839 to 1.884 Å, where H'_w indicates the hydrogen atom of water molecule H bonded to the tautomer. They are somewhat shorter than those in the corresponding complexes of any dioxo tautomer with water. The N−H···O_w and $O_w H'_w$···O bond angles do not markedly differ from each other and range between 141.0° and 148.1°. Except the $3,2_1$-U−w_3 complex, the interaction energies E_{HB} of these uracil tautomers with water are larger than those involving the conventional uracil−water structures, ranging from 40.0 to 45.9 kJ mol^{-1}. The latter corresponds to the binding energy of the 4-T_4-w_2 complex, which possesses the smallest H-bond lengths among the aforementioned ones. Besides, it is also interesting to notice that the 4-T_4 tautomer has the smallest DPE at the w_2 site among the other five mentioned tautomers. This is also due to the large dipole−dipole repulsion of the N_3−H bond with the neighboring O_{10}−H bond. The energy E_{HB} of the $3,2_1$-U−w_3 complex is equal to 36.1 kJ mol^{-1}.

TABLE 1: Optimized Hydrogen-Bond Geometries of Uracil−Water and Uracil Tautomer−Water Complexes (Bond Lengths in Angstroms, Bond Angles in Degrees)]

T	$r(X^a-H\cdots O_w)$	$\angle X^a HO_w$	$r(O_w - H'_w\cdots X^a)$	$\angle O_w H'_w X^a$	$r(O_w - H'_w)$	$\angle H'_w O_w H_w$
U−w$_1$[b]	1.929	144.3	1.943	142.6	0.978	107.6
	(1.890)[c] (1.926)[d]	(143.4)[c]	(1.889)[c] (2.002)[d]	(149.1)[c]	(0.970)[d]	
U−w$_2$[b]	1.989	142.6	1.964	141.6	0.976	107.6
	(1.950)[c] (1.977)[d]	(141.7)[c]	(1.897)[c] (2.023)[d]	(148.9)[c]	(0.968)[d]	
U−w$_3$[b]	1.969	143.0	1.923	141.0	0.979	107.6
	(1.929)[c] (1.959)[d]	(142.4)[c]	(1.874)[c] (1.990)[d]	(150.9)[c]	(0.969)[d]	
U−w$_4$	2.401	129.8	1.902	157.8	0.977	106.8
	(2.219)[c] (2.374)[d]	(129.7)[c]	(1.865)[c] (1.946)[d]	(159.8)[c]	(0.969)[d]	
3,2$_1$-U−w$_1$	1.700	159.3	1.977	136.5	0.976	108.1
	(1.717)[d]		(2.032)[d]		(0.973)[d]	
3,2$_1$-U−w$_2$	2.077	145.1	2.128	130.2	0.968	106.2
3,2$_1$-U−w$_3$	1.922	142.6	1.884	145.6	0.981	107.7
3,2$_1$-U−w$_4$	2.486	128.0	1.888	160.3	0.977	106.6
3,2$_2$-U−w$_1$			1.983 X = N$_1$	161.9	0.976	106.1
3,2$_2$-U−w$_2$	1.842 X = O$_8$	168.6			0.967	106.6
	2.228 X = N$_1$	138.5				
3,2$_2$-U−w$_3$	1.880	146.0	1.870	146.4	0.984	107.7
1,2$_1$-U−w$_1$	1.944	149.8	2.176	126.1	0.969	107.7
1,2$_1$-U−w$_2$	1.688	159.1	1.965	135.4	0.985	107.8
	(1.710)[d]		(2.012)[d]		(0.975)[d]	
1,4$_1$-U−w$_1$	1.924	144.3	1.855	147.8	0.984	107.5
1,4$_1$-U−w$_2$			1.939 X = O$_8$	174.0	0.975	104.4
1,4$_1$-U−w$_3$	1.731	160.1	1.974	135.5	0.983	107.7
	(1.749)[d]		(2.030)[d]		(0.973)[d]	
1,4$_2$-U−w$_1$	1.918	144.4	1.848	148.1	0.984	107.5
1,4$_2$-U−w$_2$			2.089 X = O$_8$	153.4	0.971	102.2
1,4$_2$-U−w$_3$			2.128 X = N$_3$	160.8	0.973	103.9
3,4$_2$-U−w$_1$			1.958 X = N$_1$	167.9	0.978	105.4
3,4$_2$-U−w$_2$	1.867	146.7	1.839	147.8	0.986	107.5
3,4$_2$-U−w$_3$	1.823 X = O$_{10}$	168.3			0.967	106.7
	2.264 X = N$_3$	136.7				
2$_1$,4$_1$-U−w$_1$	1.777	160.4	1.956	139.6	0.983	107.8
2$_1$,4$_1$-U−w$_2$			2.016 X = O$_8$	166.0	0.970	105.7
2$_1$,4$_1$-U−w$_3$	1.755	160.8	2.010	135.0	0.980	107.7
2$_2$,4$_1$-U−w$_1$			1.965 X = N$_1$	163.1	0.977	105.9
2$_2$,4$_1$-U−w$_2$	1.794	161.8	2.028	138.4	0.978	107.8
2$_2$,4$_1$-U−w$_3$	1.764	160.9	2.027	137.7	0.979	107.9
2$_1$,4$_2$-U−w$_1$	1.785	160.6	1.959	139.6	0.982	107.8
2$_1$,4$_2$-U−w$_2$			2.083 X = N$_3$	170.9	0.974	104.4
2$_1$,4$_2$-U−w$_3$			2.098 X = N$_3$	167.8	0.973	104.2
2$_2$,4$_2$-U−w$_1$			1.963 X = N$_1$	160.5	0.978	106.0
2$_2$,4$_2$-U−w$_2$	1.778	161.9	2.018	135.3	0.979	107.6

[a] X = N, O of uracil or its tautomer T. [b] B3LYP/6-31+G(d,p) calculations.[10b] [c] MP2/DZP calculations.[10c] [d] MP2/6-311++G(d,p) calculations.[10d]

Nine closed complexes 3,2$_1$-U−w$_1$, 1,2$_1$-U−w$_2$, 1,4$_1$-U−w$_3$, 2$_1$,4$_1$-U−w$_1$, 2$_1$,4$_1$-U−w$_3$, 2$_2$,4$_1$-U−w$_2$, 2$_2$,4$_1$-U−w$_3$, 2$_1$,4$_2$-U−w$_1$, and 2$_2$,4$_2$-U−w$_2$ are formed between the O−H group and the N atom of the uracil tautomer and the water molecule (see Figure 3). By comparison of the 3,2$_1$-U−w$_1$ complex with the U−w$_1$ one, where, placed at the most energetically preferable site w$_1$, the water molecule donates its H atom to the O$_8$ atom and accepts the N$_1$−H$_7$ bond, the most stable tautomer 3,2$_1$-U behaves in a different way because its O$_8$−H bond is turned out directly to this site. This bond possesses a DPE smaller by 45.6 kJ mol^{-1} than the N$_1$−H bond of uracil. Therefore, as seen in Table 2, the binding energy of the 3,2$_1$-U−w$_1$ complex is larger by 5.4 kJ mol^{-1} than the one of the parental U−w$_1$ complex. A similar structure in the vicinity of the w$_1$ site is predicted by the present calculations for the 2$_1$,4$_1$-U tautomer, although it appears to be less stable than that of U−w$_1$ because the DPE of the 2$_1$,4$_1$-U group O$_8$−H is higher by 28.9 kJ mol^{-1} than the DPE of the N$_1$−H group. In these nine cyclic complexes, the (O)H···O$_w$ distances ranging between 1.688 and 1.794 Å are significantly larger than the (O$_w$)H'$_w$···N ones, which fall in the interval of 1.956 and 2.028 Å. The O−H··· O$_w$ bond angles varying from 159.1° to 161.9° are also larger

than the O$_w$ − H'$_w$···N ones taking values between 135.0° and 139.6°. These geometrical data show that the cyclic N···H$_w$−O$_w$···H−O-type complexes are more asymmetric than the (C═)O···H'$_w$ − O$_w$···H − N ones. Their interaction energies with water are spread over a rather broad interval, from 26.3 kJ mol^{-1} which corresponds to the 2$_2$,4$_1$-U−w$_2$ complex to 49.1 kJ mol^{-1}, the interaction energy of the 1,2$_1$-U−w$_2$ one. It is the largest interaction energy revealed in the present study. Notice that this complex is characterized by the shortest (O)H···O$_w$ bond length equal to 1.688 Å.

Ten open structures of the uracil tautomers with water are also predicted by the present calculations. In the seven structures 3,2$_2$-U−w$_1$, 1,4$_2$-U−w$_3$, 2$_1$,4$_1$-U−w$_2$, 2$_2$,4$_1$-U−w$_1$, 2$_1$,4$_2$-U−w$_2$, 2$_1$,4$_2$-U−w$_3$, and 2$_2$,4$_2$-U−w$_1$, the water molecule resides between the N atom and the O−H group in the trans position with respect to this atom (see Figure 3). In these structures, the N atom acts as a proton acceptor. In the 1,4$_1$-U−w$_2$ and 1,4$_2$-U−w$_2$ complexes, the oxygen atom of the carbonyl group becomes the preferential site for the hydrogen bonding. The latter possesses the largest total dipole moment of 11.2 D among all of the studied complexes. In the 3,4$_2$-U−w$_1$ complex where the water molecule lies between the carbonyl group and the N$_1$

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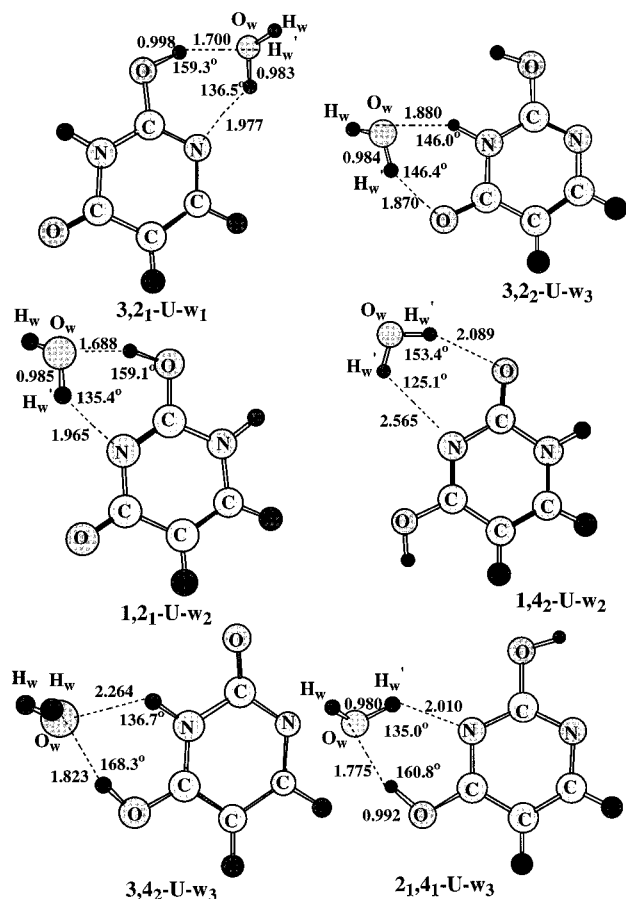*J. Phys. Chem. A, Vol. 105, No. 10, 2001* **1937**

Figure 3. Examples of cyclic and biacceptor complexes of uracil tautomers with a water molecule.
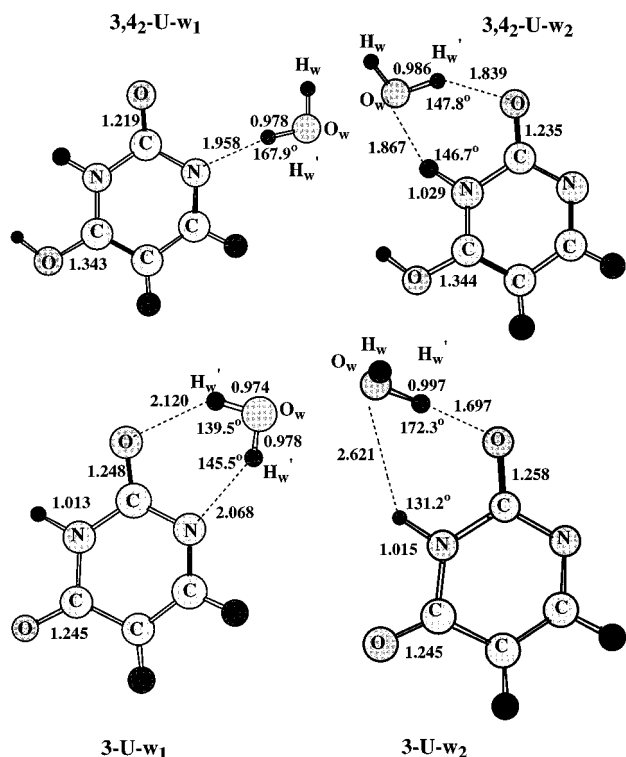

Figure 4. Complexes of the $3,4_2$-U tautomer and their O_{10}-deprotonated analogue with a water molecule at the w_1 and w_2 sites.

atom (see Figure 4), the hydrogen bond is formed on the latter one. This may be accounted for by the larger PA of the N_1 atom (946.2 kJ mol^{-1}) as compared with that of the O_8 atom

TABLE 2: Binding Energy E_{HB} (kJ mol^{-1}) and Total Dipole Moment (D) of Uracil Tautomer−Water Complexes[a]

U−w	E_{HB}	D
U−w_1	36.40 (38.87)[b] (37.2)[c]	4.1
U−w_2	27.49 (30.79)[b] (29.7)[c]	5.1
U−w_3	29.87 (32.42)[b] (31.0)[c]	4.6
U−w_4	23.35 (25.31)[b] (24.3)[c]	2.9
2-hydroxy−w		
$3,2_1$-U−w_1	41.80 (42.3)[c]	4.3
$3,2_1$-U−w_2	16.23	5.1
$3,2_1$-U−w_3	36.11	2.3
$3,2_1$-U−w_4	22.68	3.7
$3,2_2$-U−w_1	18.62	4.5
$3,2_2$-U−w_2	42.73	5.7
$3,2_2$-U−w_3	43.14	2.0
$1,2_1$-U−w_1	27.15	8.0
$1,2_1$-U−w_2	49.08 (48.5)[c]	5.5
4-hydroxy−w		
$1,4_1$-U−w_1	40.00	3.8
$1,4_1$-U−w_2	20.75	8.3
$1,4_1$-U−w_3	42.55 (43.1)[c]	4.3
$1,4_2$-U−w_1	40.79	6.5
$1,4_2$-U−w_2	22.68	11.2
$1,4_2$-U−w_3	17.32	10.8
$3,4_2$-U−w_1	23.97	7.9
$3,4_2$-U−w_2	45.94	4.8
$3,4_2$-U−w_3	43.72	8.3
2,4-dihydroxy−w		
$2_1,4_1$-U−w_1	34.31	2.9
$2_1,4_1$-U−w_2	11.38	3.3
$2_1,4_1$-U−w_3	37.53	1.6
$2_2,4_1$-U−w_1	21.09	4.6
$2_2,4_1$-U−w_2	26.28	3.8
$2_2,4_1$-U−w_3	26.36	2.5
$2_1,4_2$-U−w_1	33.18	5.6
$2_1,4_2$-U−w_2	17.82	6.3
$2_1,4_2$-U−w_3	16.86	7.0
$2_2,4_2$-U−w_1	21.67	4.0
$2_2,4_2$-U−w_2	34.69	5.1

[a] The B3LYP/6-31+G(d,p) energy of uracil is equal to −414.8473621 hartree, and its ZPVE = 54.5703 kcal/mol. [b] MP2/DZP + ZPVE energies.[10c] [c] MP2/6-311++G(d,p) + ZPVE energies.[10d]

(915.2 kJ mol^{-1}). In these open complexes, the N···H$'_w$ or O···H$'_w$ distances range between 1.939 and 2.089 Å. The hydrogen bond is not linear, as seen from the corresponding N···H$'_w$ − O$_w$ or O···H$'_w$ − O$_w$ angles varying between 153.3° and 174.0°. The interaction energies of these uracil tautomers with water are substantially lower compared to those of the cyclic complexes and take values from 11.4 to 22.7 kJ mol^{-1}.

In the $3,2_1$-U−w_2 and $1,2_1$-U−w_1 complexes, the O−H group of the 2-hydroxy-4-oxo tautomers functions as a proton acceptor. In these closed structures, the (O_w)H$'_w$···O distances which are equal to 1.977 and 2.176 Å, respectively, are markedly longer than the (N)H···O$_w$ distances which are 1.700 and 1.944 Å long. Their binding energies of 16.2 and 27.1 kJ mol^{-1}, respectively, are lower than in those in the other cyclic structures involving these tautomers. These features can be explained by the lower proton acceptor ability of the lone pairs of the oxygen atom of the OH group.

In the $3,2_2$-U−w_2 and $3,4_2$-U−w_3 complexes, water acts as a double-proton acceptor, being bonded to both the N−H and O−H groups of these monohydroxy tautomers (see Figure 3). In these anticooperative structures,[13] the (O_w)H$'_w$···N distances are rather large, viz., 2.228 and 2.264 Å, respectively, whereas the corresponding (O_w)H$'_w$···O ones are relatively short, 1.880 and 1.870 Å. Their interaction energies with water comprise 42.7 and 43.7 kJ mol^{-1}, respectively. The origin of such an anticooperative structure is likely due to the lower DPEs of the

N_3−H and O−H groups of the $3,2_1$-U and $3,4_2$-U tautomers (see Figure 1) which enable them to form a cyclic structure with a water molecule. The large E_{HB} of the $3,4_2$-U tautomer at the w_3 site can be explained by the exceptionally large acidity of the O_{10}−H group of the $3,4_2$-U tautomer whose DPE appears to be equal to 1294.6 kJ mol^{-1}, which is much lower compared with the DPEs of the other O−H groups of the hydroxy tautomers. It follows that the less stable $3,4_2$-U tautomer can be considered as a "super acid". The lone pairs of water molecule are bonded asymmetrically to the O−H and N−H groups. A similar situation is found in "super bases" such as proton sponges, where the proton donor is bridged symmetrically or asymmetrically to the two vicinal N atoms of the base.[14]

No stable cyclic structure at the w_3 site of the $1,2_1$-U tautomer are predicted by the present calculations.

The last complex studied in the present work is that formed by the $3,2_1$-U tautomer with a water molecule placed at the w_4 site (see Figure 2). The (C)H···O_w distance is slightly longer, whereas the $(O_w)H'_w$···O one is slightly shorter than in the corresponding U−w_4 complex. Its interaction energy with water is lower by 0.7 kJ mol^{-1} compared with that of the U−w_4 complex. These data indicate that the less favorable C−H···O_w interaction is not very sensitive to the tautomeric structure of the molecule, and this is likely the case for the complexes containing the other tautomers with water molecule at the w_4 site.

The optimized O_w−H_w distance in the free water molecule is equal to 0.965 Å at the present B3LYP/6-31+G(d,p) computational level. As indicated in Table 1, the O_w − H'_w distances in the cyclic complexes of the uracil tautomers with water range between 0.976 and 0.985 Å and in the open ones from 0.970 to 0.978 Å. The larger elongation in the cyclic complexes results from the cooperativity. This will be discussed more quantitatively in the next section. When a water molecule acts as a mono- or bi-acceptor, as in the $3,2_1$-U−w_2, $1,2_1$-U−w_1, and $3,4_2$-U−w_3 complexes, the O_w − H'_w bond length is slightly elongated by 0.002−0.003 Å.

B. Correlation Between the Hydrogen-Bond Parameters PA and DPE. The correlation between the hydrogen-bond parameters and the PAs are well-documented in the literature for the neutral H bonds and the ionic ones as well.[15a] Much less data related to cyclic complexes where the interacting species act both as proton donor and proton acceptor are available. In a recent work,[10b] the stabilities of the different uracil−water and thymine−water complexes have been rationalized in terms of the differences in the PAs of the oxygen lone pairs and DPEs of the N−H bonds. In the hydrogen bonds between simple substituted carbonyl bases (HRC=O) and water, their parameters are correlated with the PAs of the corresponding sites, and positive departures from the correlations are observed for the cyclic dimers where the distance between the hydrogen atom of the R substituent and the oxygen atom of water is lower than 2.5 Å. As demonstrated in Table 1, this is actually the case for the complexes of uracil and its tautomers with water.

Let us now consider the closed (N)H···O_w − H'_w···O(=C) complexes formed by uracil and its tautomers with a water molecule. Table 1 and Figure 1 indicate that the intermolecular distances r((O_w)H'_w···O) are not ordered according to their PAs and DPEs values. In these six-membered rings, the two hydrogen bonds are mutually strengthened because of a cooperativity effect. It can be then expected that these distances will also depend, although to a lesser extent, on the acidity of the N−H bonds involved in the formation of the closed structure. The
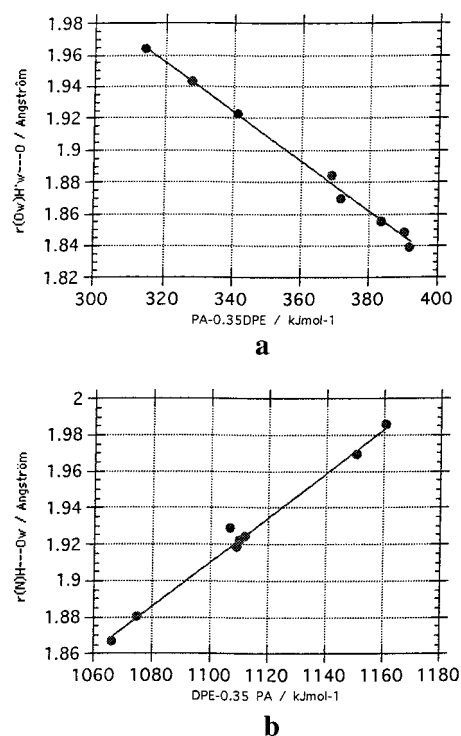

Figure 5. (a) $r((O_w)H'_w$···O) bond length as a function of PA − 0.35DPE; (b) $r((N)H$···$O_w)$ bond length as a function of DPE − 0.35PA.

best correlation coefficients are then found for the following exponential expressions which include the conventional uracil−water complexes as well (bond lengths in Å, PA and DPE in kJ mol^{-1}):

$$r((O_w)H'_w···O) = 2.55 \exp[-0.83 \times 10^3(PA - 0.35DPE)],$$
$$r = 0.9979 \quad (3)$$

$$r((N)H···O_w) = 0.944 \exp[0.64 \times 10^3(DPE - 0.35PA)],$$
$$r = 0.9935 \quad (4)$$

They are displayed in Figure 5. Such correlations, very similar to those proposed for the conventional complexes of nucleobases with water, can thus be extended to the less stable tautomeric complexes with water. As indicated by the corresponding coefficients for PA and DPE, the mutual influence of the two N−H···O_w and O_w − H'_w···O hydrogen bonds is the same. This likely results from the fact that, as previously studied, the intermolecular distances and angles do not markedly differ in both cases. We could not deduce expressions similar to eqs 3 and 4 for the cyclic (N)H···O_w − H'_w···N structures. The reason is probably because the intermolecular distances and angular properties in these structures vary within much broader limits.

The hydrogen-bond energies in the closed (N)H···O_w − H'_w···O complexes, where, as suggested by the intermolecular distances, both hydrogen bonds contribute equally to the binding energies, can also be represented as a function of the intrinsic acidities or basicities of the groups involved in the hydrogen-bond formation. The analysis of the data collected in Table 2 and Figure 1 leads to the following exponential expression for the interaction energy E_{HB} (E_{HB}, PA, and DPE in kJ mol^{-1}):

$$E_{HB} = 2419 \exp[-0.003\ 322(1.5DPE - PA)], \quad r = 0.9847$$
$$(5)$$

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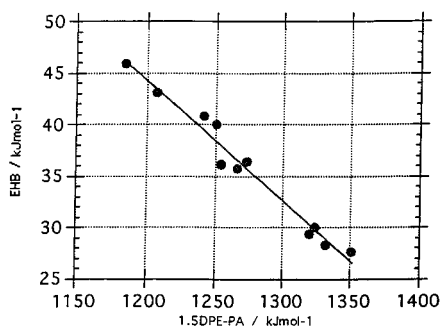
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Figure 6. E_{HB} as a function of $1.5DPE - PA$.

The data illustrated in Figure 6 show that the correlation established for the interaction energy between five nucleobases such as uracil, thymine, cytosine, adenine, and guanine, on the one side, and the water molecule, on the other one, is now extended to the complexes of the less stable tautomers of uracil with water. An analogous correlation has been recently proposed for the enol−enolate hydrogen bonds.[16] The dominant contribution of the proton donor to the interaction energy has been discussed in refs 10a,b and 15a.

For the $N{\cdots}H_w-O_w{\cdots}H-O$ cyclic structures, eq 5 is characterized by a worse correlation coefficient, $r = 0.9238$. This is likely because the $(O)H{\cdots}O_w$ bond provides a larger contribution to E_{HB}. This $(O)H{\cdots}O_w$ bond is indeed significantly shorter and its deviation from linearity is significantly lower than in the $O_wH'_w{\cdots}N$ hydrogen bond.

For the open complexes where the water molecule acts as a proton donor, the interaction energies are correlated to the PA of the acceptor atom. This has been discussed for numerous hydrogen-bond systems.[15b] In a small range, the correlation is generally linear. In the present complexes where, on one hand, the E_{HB} values range between 11 and 24 kJ mol^{-1} and the PA, on the other one, varies between 870 and 950 kJ mol^{-1}, the best fit is given by the exponential expression (energies and PAs in kJ mol^{-1})

$$E_{HB} = 0.002\,13 \exp[-0.009\,97PA], \quad r = 0.9557 \quad (6)$$

It must be mentioned at last that the large binding energy of 43.7 kJ mol^{-1} calculated for the $3,4_2$-U−w$_3$ complex is due to the exceptionally large acidity of the O_8−H bond. Only two complexes where water acts as a biacceptor are predicted by the present calculations, and therefore, these data are insufficient to deduce a correct correlation.

The v(OH) and v(NH) stretching frequencies of the free uracil tautomers and the frequency shifts resulting from complex formation with water are presented in Table 3. In the cyclic $N)H{\cdots}O_w - H'_w{\cdots}O$ complexes, the v(NH) stretching vibration is shifted to lower wavenumbers by 191−267 cm^{-1} and substantially enhanced by a factor of 4−9. As expected, the largest shift of 267 cm^{-1} is predicted for the strongest complex $3,4_2$-U−w$_2$ (see Figure 4). The second group of cyclic $(O)H{\cdots}O_w - H'_w{\cdots}N$ complexes is characterized by red shifts of the v(OH) stretching vibration ranging from 357 to 604 cm^{-1}. The lower limit corresponds to the $2_2,4_1$-U−w$_2$ complex, which is the least stable one, whereas the upper limit is assigned to $1,2_1$-U−w$_2$, the strongest complex. For open complexes, the frequency shifts of the v(XH) stretching vibrations are related to the PA of the acceptor atom.[15c] So far no correlations between these shifts and the PA have been established for cyclic complexes. As shown in our previous works,[10b,15a] the frequency shifts are related to the elongation of the XH bond involved in

hydrogen-bond formation, and as discussed in ref 1b, the elongations of the XH bond are inversely related to the intermolecular $H{\cdots}B$ distances. From these considerations, it can be anticipated that the frequency shift of the v(OH) and v(NH) vibrations of the present complexes will be governed by both the DPE and PA of the interacting sites. Furthermore, the coefficients of DPE and PA are expected to be very similar to those of eq 4. For the complexes between the hydroxy tautomers and water, the correlation is indeed as follows (Δv(OH) in cm^{-1}, DPE and PA in kJ mol^{-1}):

$$\Delta v(OH) = 3.36 \times 10^5 \exp[-0.0063(DPE - 0.40PA)],$$
$$r = 0.9727 \quad (7)$$

where DPE and PA refer, in this case, to the DPE of the OH bonds and the PA of the N atoms. It must be mentioned that in some other complexes the v(NH) and the v(OH) stretching vibrations are strongly coupled. In the case of the $3,2_1$-U−w$_1$ complex belonging to the group of cyclic complexes, the v_1^w and v_3^w stretching vibrations of water are shifted toward lower wavenumbers by 275 and 47 cm^{-1}, respectively, and enhanced by a factor of 6−9. The formation of the $1,2_1$-U−w$_2$ complex results in a red shift of the v_1^w stretching vibration of water by 304 cm^{-1} and a very large increase of its IR intensity.

It is also interesting to analyze the stretching vibrations in the uracil tautomer−water complexes where water acts as a biacceptor of the hydrogen bond. These are the $3,2_2$-U−w$_2$ and $3,4_2$-U−w$_3$ complexes. One may expect then that the red shifts of the v_1^w and v_3^w stretching vibrations of water are quite small and actually equal to 7 and 18 cm^{-1} for the v_1^w and v_3^w vibrations, respectively.

The out-of-plane deformation of the OH bond (γ(OH)) is predicted around 600 cm^{-1}, with an infrared intensity of 60 km/mol. This mode is very sensitive to the interaction with water. In the $1,4_1$-U−w$_3$ complex for example, it is computed at 925 cm^{-1}, with an intensity of 130 km/mol.

C. Relative Order of Stability of the Tautomer−Water Complexes. As discussed in sections A and B, the interaction between the uracil tautomers and water leads to various cyclic or open complexes. We have shown that the interaction energies are ruled by the acidity or basicity of the groups or atoms involved in the formation of the hydrogen bonds or, in other words, by the *local properties* of the tautomers. In a previous work,[9b] we have demonstrated that the relative stability of the uracil tautomers is inversely related to the difference $\overline{DPE} - \overline{PA}$, where $\overline{DPE}$ refers to the mean value of the deprotonation enthalpies of the two functional N−H or O−H groups and $\overline{PA}$ to the mean value of the proton affinities of the two O or N atoms. Thus, the relative order of stability of the tautomers is governed by the acidic or basic properties of *all* of the sites present in the tautomers. From this, it can be anticipated that the relative order of stability of the tautomer−water complexes will not be the same as that established for the free tautomers. For instance, the calculated order of the interaction energies of the most stable tautomers with water molecule w$_1$ becomes as follows:

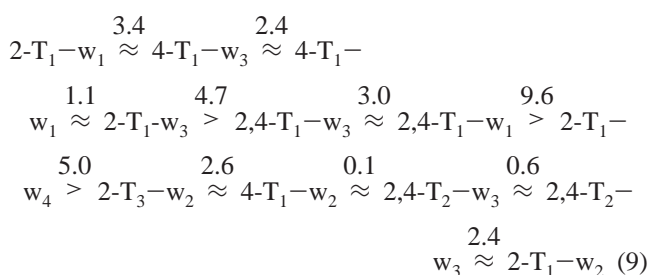$$2\text{-}T_1-w_1 \overset{1.8}{\approx} 4\text{-}T_1-w_1 \overset{5.7}{\approx} 2,4\text{-}T_1-w_1 \overset{13.2}{>} 2,4\text{-}T_2-w_1 \quad (8)$$

In eq 8, $E_{HB} = 41.80$ kJ mol^{-1} of the $3,2_1$-U−w$_1$ complex is chosen as the reference energy. In general, the relative order of

TABLE 3: ν(OH) and ν(NH) Stretching Frequencies in Free Uracil Tautomers and Water and Corresponding Frequency Shifts in the Water Complexes (cm^{-1})

U−w	$\nu_{N_1-H_7}{}^a$, $\Delta\nu_{N_1-H_7}$	$\nu_{N_3-H_9}{}^a$, $\Delta\nu_{N_3-H_9}$	$\nu_1^{w\,a}$, $\Delta\nu_1^w$	$\nu_3^{w\,a}$, $\Delta\nu_3^w$
U	3649 (109)	3607 (69)	ν_1^w = 3809 (6)	ν_3^w = 3931 (57)
U−w$_1$	−222 (−193)^b (508)	−1 (−4)^b (94)	−192 (360)	−32 (108)
U−w$_2$	0 (−5)^b (131)	−191 (360)	−152 (238)	−28 (104)
U−w$_3$	−2 (−5)^b (104)	−206 (−165)^b (356)	−196 (386)	−31 (100)
U−w$_4$	−2 (97)	−1 (81)	−182 (483)	−29 (102)

2-T−w	ν_{O_8-H}, $\Delta\nu_{O_8-H}$	ν_{N-H}, $\Delta\nu_{N-H}$	ν_1, $^w\Delta\nu_1^w$	ν_3, $^w\Delta\nu_3^w$
3,2$_1$-U	3777 (123)	3593 (71)		
3,2$_1$-U−w$_1$	−554 (947)	1 (69)	−275 (710)	−47 (117)
3,2$_1$-U−w$_2$	−6 (128)	−147 (359)	−24 (24)	−20 (120)
3,2$_1$-U−w$_3$	−1 (125)	−239 (398)	−239 (398)	−33 (96)
3,2$_1$-U−w$_4$	0 (131)	−1 (85)	−32 (131)	−30 (96)
3,2$_2$-U	3826 (91)	3575 (37)		
3,2$_2$-U−w$_1$	1 (102)	3 (45)	−176 (630)	−36 (110)
3,2$_2$-U−w$_2$	−224 (805)	−29 (24)	−7 (25)	−18 (125)
3,2$_2$-U−w$_3$	−12 (106)	−236 (338)	−297 (569)	−38 (95)
1,2$_1$-U	3775 (115)	3648 (115)		
1,2$_1$-U−w$_1$	−9 (122)	−167 (590)	−26 (33)	−7 (132)
1,2$_1$-U−w$_2$	−604 (893)	−2 (112)	−304 (708)	−45 (102)

4-T−w	$\nu_{O_{10}-H}$, $\Delta\nu_{O_{10}-H}$	ν_{N-H}, $\Delta\nu_{N-H}$	ν_1, $^w\Delta\nu_1^w$	ν_3, $^w\Delta\nu_3^w$
1,4$_1$-U	3744 (90)	3624 (81)		
1,4$_1$-U−w$_1$	2 (91)	−227 (343)	−291 (694)	−35 (93)
1,4$_1$-U−w$_2$	5 (100)	−3 (98)	−128 (437)	−39 (66)
1,4$_1$-U−w$_3$	−484 (760)	4 (81)	−272 (672)	−44 (102)
1,4$_2$-U	3828 (77)	3621 (83)		
1,4$_2$-U−w$_1$	−4 (80)	−237 (341)	−301 (727)	−36 (92)
1,4$_2$-U−w$_2$	−3 (95)	−5 (89)	−57 (165)	−67 (39)
1,4$_2$-U−w$_3$	−1 (95)	−4 (88)	−99 (330)	−43 (75)
3,4$_2$-U	3809 (88)	3585 (47)		
3,4$_2$-U−w$_1$	1 (62)	−1 (98)	−213 (769)	−43 (96)
3,4$_2$-U−w$_2$	−12 (107)	−267 (349)	−333 (661)	−38 (93)
3,4$_2$-U−w$_3$	3577 (660)^c	3553 (257)^c	−7 (25)	−18 (127)

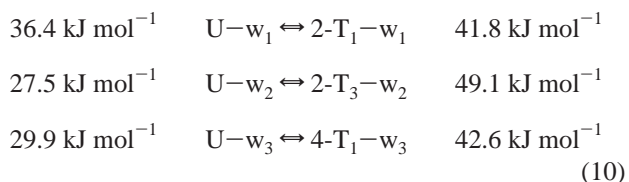| 2,4-T−w	ν_{O_8-H}, $\Delta\nu_{O_8-H}$	$\nu_{O_{10}-H}$, $\Delta\nu_{O_{10}-H}$	ν_1, $^w\Delta\nu_1^w$	ν_3, $^w\Delta\nu_3^w$
2$_1$,4$_1$-U	3785 (101)	3758 (92)		
2$_1$,4$_1$-U−w$_1$	−404 (504)	−3 (91)	−274 (936)	−45 (107)
2$_1$,4$_1$-U−w$_2$	−4 (130)	3 (175)	−51 (138)	−26 (146)
2$_1$,4$_1$-U−w$_3$	1 (102)	−425 (767)	−223 (573)	−43 (110)
2$_2$,4$_1$-U	3796 (96)	3766 (78)		
2$_2$,4$_1$-U−w$_1$	1 (105)	1 (84)	−202 (725)	−38 (102)
2$_2$,4$_1$-U−w$_2$	−357 (558)	18 (71)	−194 (601)	−47 (126)
2$_2$,4$_1$-U−w$_3$	28 (78)	−390 (681)	−208 (570)	−47 (121)
2$_1$,4$_2$-U	3787 (103)	3766 (78)		
2$_1$,4$_2$-U−w$_1$	−393 (482)	0 (77)	−269 (937)	−45 (107)
2$_1$,4$_2$-U−w$_2$	0 (115)	1 (88)	−114 (422)	−43 (96)
2$_1$,4$_2$-U−w$_3$	−1 (116)	1 (86)	−107 (390)	−43 (90)
2$_2$,4$_2$-U	3787 (99)	3822 (77)		
2$_2$,4$_2$-U−w$_1$	1 (108)	0 (85)	−203 (708)	−37 (102)
2$_2$,4$_2$-U−w$_2$	−395 (666)	2 (79)	−209 (587)	−42 (114)

^{a} Frequencies are taken relative to the corresponding frequencies of uracil tautomers or water molecule displayed in the first line of each tautomer. IR intensities in km/mol are indicated in parentheses. ^{b} Experimental frequencies.[17] ^{c} ν(OH) and ν(NH) modes are strongly coupled.

stability of tautomer−water complexes appears to be as follows:

$$2\text{-T}_1\text{−w}_1 \overset{3.4}{\approx} 4\text{-T}_1\text{−w}_3 \overset{2.4}{\approx} 4\text{-T}_1\text{−}$$

$$\text{w}_1 \overset{1.1}{\approx} 2\text{-T}_1\text{−w}_3 \overset{4.7}{>} 2,4\text{-T}_1\text{−w}_3 \overset{3.0}{\approx} 2,4\text{-T}_1\text{−w}_1 \overset{9.6}{>} 2\text{-T}_1\text{−}$$

$$\text{w}_4 \overset{5.0}{>} 2\text{-T}_3\text{−w}_2 \overset{2.6}{\approx} 4\text{-T}_1\text{−w}_2 \overset{0.1}{\approx} 2,4\text{-T}_2\text{−w}_3 \overset{0.6}{\approx} 2,4\text{-T}_2\text{−}$$

$$\text{w}_3 \overset{2.4}{\approx} 2\text{-T}_1\text{−w}_2 \quad (9)$$

The noticeable changes in the order in (2) taking place under the concerted double-proton transfer via a bridging water molecules in the uracil−water complexes are worth mentioning.

As seen in Figure 2, these double-proton transfers describe the following tautomerization processes (see also ref 10d):

$$36.4 \text{ kJ mol}^{-1} \quad \text{U−w}_1 \leftrightarrow 2\text{-T}_1\text{−w}_1 \quad 41.8 \text{ kJ mol}^{-1}$$

$$27.5 \text{ kJ mol}^{-1} \quad \text{U−w}_2 \leftrightarrow 2\text{-T}_3\text{−w}_2 \quad 49.1 \text{ kJ mol}^{-1}$$

$$29.9 \text{ kJ mol}^{-1} \quad \text{U−w}_3 \leftrightarrow 4\text{-T}_1\text{−w}_3 \quad 42.6 \text{ kJ mol}^{-1}$$

$$(10)$$

where the left- and right-hand numbers indicate the binding energies of the reactants and products relative to the corresponding channels. If the reactant side is characterized by the order in (2), the product side of (10) takes a different order of the binding energies, viz., the second tautomerization reaction appears to be stronger than the third one which, in turn, is

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stronger than the first reaction. However, the reactant and product channels in (10) have different reference energies. For instance, in the case of the second tautomerization reaction, if the reactant channel reference energy corresponds to zero, the product channel reference energy is equal to the tautomerization energy of 81.8 kJ mol^{-1} of the $1,2_1$-U$-$w$_2$ tautomer. Therefore, summarizing, water substantially facilitates this tautomerization double-proton-transfer reaction by 21.6 kJ mol^{-1}.

Furthermore, a comparison of eqs 1 and 8 dealing with the relative orders of stability of uracil tautomers, free and complexed with water, shows that water substantially affects the relative order of stability of uracil tautomers in the gas phase in two different manners. First, as mentioned above, it enhances their occurrence. This is also seen, e.g., in that the most stable tautomer $3,2_1$-U becomes less stable than its $3,2_1$-U$-$w$_1$ complex by 5.4 kJ mol^{-1}, while $1,2_1$-U becomes less stable by 12.7 kJ mol^{-1}, enhancing its occurrence, by a factor of nearly 2. Second, water changes the relative stability between tautomers themselves. For example, it raises the relative stability of the $3,2_1$-U and $1,4_1$-U tautomers by a factor of 2 relative to the $2_1,4_1$-U one. With regards to the base pairing in DNA and RNA, water also favors the binding to the $1,4_1$-U and $2_1,4_1$-U tautomers on the major groove side, whereas the site in the vicinity of the sugar$-$phosphate backbone remains a more favorable one only for uracil and its $3,2_1$-U tautomer.

We conclude this section by making a rough estimation of the stability of the lower-energy tautomers of uracil surrounded by the first hydration shell consisting of three water molecules at the w$_1$, w$_2$, and w$_3$ sites. Summing the interaction energies of uracil $3,2_1$-U, $1,4_1$-U, and $2_1,4_1$-U with these three water molecules, we obtain the following energies:

$$E_{HB}(U - \sum_{i=1}^{3} w_i) = 93.8 \text{ kJ mol}^{-1}, E_{HB}(2\text{-}T_1 - \sum_{i=1}^{3} w_i) =$$

$$94.1 \text{ kJ mol}^{-1}, E_{HB}(4\text{-}T_1 - \sum_{i=1}^{3} w_i) = 103.3 \text{ kJ mol}^{-1},$$

$$E_{HB}(2,4\text{-}T_1 - \sum_{i=1}^{3} w_i) = 83.2 \text{ kJ mol}^{-1} \quad (11)$$

Hence, the $1,4_1$-U tautomer surrounded by the first hydration shell is more stable than the $3,2_1$-U one by $\sim$9.2 kJ mol^{-1}, which is larger, as follows from eq 1, than their relative energy equal to 3.6 kJ mol^{-1}. It therefore implies that the hydrated $1,4_1$-U tautomer of uracil is more stable than the hydrated $3,2_1$-U tautomer by 5.6 kJ mol^{-1}. This is in accord with the conclusion made in ref 8e that the Onsager-type solvent favors the $1,4_1$-U tautomer rather than the $3,2_1$-U one by 6.2 kJ mol^{-1}. In other words, we may conclude that the first hydration shell stabilizes the $1,4_1$-U tautomer by ca. 90% with respect to the most stable $3,2_1$-U tautomer in the gas phase. On the contrary, water destabilizes the $2_1,4_1$-U tautomer by $\sim$10 kJ mol^{-1} relative to the $3,2_1$-U one. This is also in agreement with the conclusion drawn in ref 8e.

D. Transition Structures. In contrast to the w$_4$ complexes, all of the studied w$_1$, w$_2$, and w$_3$ complexes of the uracil tautomers with water are nonplanar, i.e., the oxygen O$_w$ and nonbonded hydrogen H$_w$ atoms of the water molecule which forms its "free" O$_w$$-H_w$ bond are pointing out of the tautomer plane. A similar trend has been already noticed for uracil in ref 10. For example, in the case of the $1,4_1$-U$-$w$_1$ complex, the hydrogen atom H$_w$ is placed out of plane by $\sim$0.5 Å. This results in the out-of-plane dipole moment component of 1.1 D of the
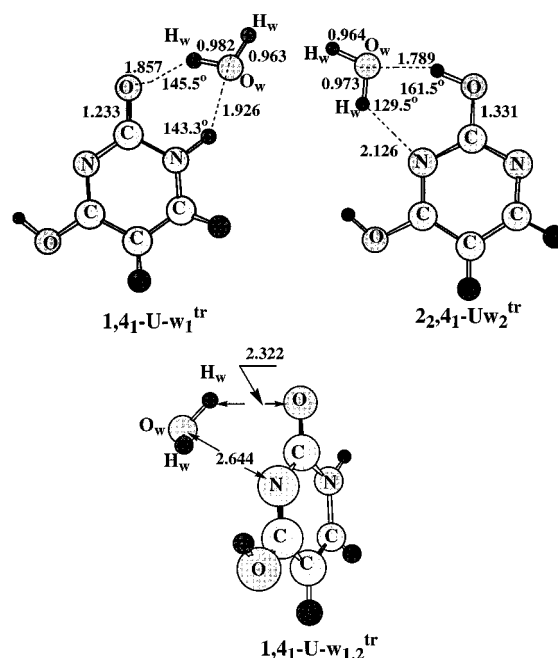

Figure 7. Characteristic transition structures of uracil tautomer$-$water complexes.

total dipole moment of 3.8 D of the $1,4_1$-U$-$w$_1$ complex. Therefore, there are actually two isomers of the complex $1,4_1$-U$-$w$_1$ distinguished by the position of the free O$_w$$-H_w$ bond of water relative to the $1,4_1$-U ring. Their interchange is governed by the transition structure $1,4_1$-U$-$w$_1^{tr}$ which is perfectly planar (see Figure 7) and lies by 1.0 kJ mol^{-1} above the $1,4_1$-U$-$w$_1$ complex. Its imaginary frequency of 170i cm^{-1} describes the out-of-plane rotation of the free O$_w$$-H_w$ bond. Such a small transition barrier becomes accessible at $T > 100$ K and thus implies a nearly free flipping of these isomers into each other. A higher transition barrier is found in the w$_2$ region. For instance, the transition structure $2_2,4_1$-U$-$w$_2^{tr}$ displayed also in Figure 7 resides above the $2_2,4_1$-U$-$w$_2$ minimum by 4.5 kJ mol^{-1}. The transition structure between $1,4_1$-U$-$w$_1$ and $1,4_1$-U$-$w$_2$ is also shown in Figure 7. It is characterized by the imaginary frequency of 59i cm^{-1} assigned to the out-of-plane motion of the whole water molecule, whU$-$wich forms two rather weak and bent H-bonds with the O$_8$ and N$_3$ atoms. This transition structure $1,4_1$-U$-$U$-$w$_{1,2}^{tr}$ is located by 8.7 kJ mol^{-1} above $1,4_1$-U$-$w$_2$.

E. Complexes of the Deprotonated $3,4_2$-U Tautomer with Water. The radical anion of uracil has been recently investigated and it has been shown that geometric changes resulting from electron attachment are small.[18] In the conventional anionic complexes with water, the NH$\cdots$O$_w$ hydrogen bonds are broken and the remaining C=O$\cdots$H$_w'$ bonds, while remaining linear, are much shorter that they are in the neutral.[10b] For the w$_1$, w$_2$, and w$_3$ complexes, the hydrogen-bond energy increases by a factor of 1.15$-$1.49. The influence of the detachment of a proton of uracil, leading to a deprotonated species, on the geometry and energy of the complexes with water has not been investigated so far. The $3,4_2$-U tautomer, which has the lowest DPE of 1294.6 kJ mol^{-1}, is chosen for this purpose.

The geometries of the mono anion $3,4_2$-U$-$O$_{10}^-$ (4-T_4^d) complexed with water at the w$_1$ and w$_2$ sites are displayed in Figure 4. The geometries of the neutral complexes are shown for the comparison. As discussed in section A, the $3,4_2$-U$-$w$_1$ complex has an open structure, the O$_w$H$_w'$$\cdots$N distance is 1.958 Å, and the complex is perfectly planar. The corresponding

$[U\text{-}w_3 \rightleftharpoons 1,4_1\text{-}U\text{-}w_3]^{tr}$
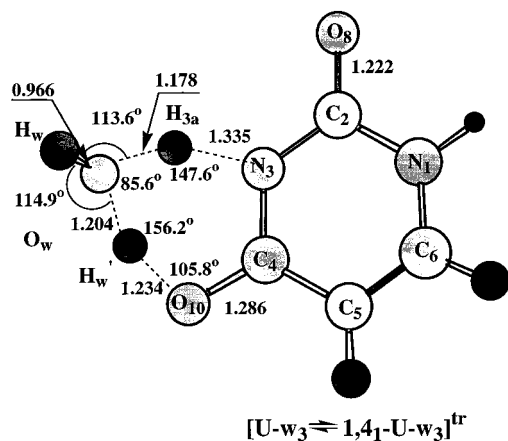
Figure 8. Transition state of the concerted double-proton transfer of the tautomerization process $U-w_3 \leftrightarrow 1,4_1\text{-}U-w_3$ mediated by a water molecule at the w_3 position.

binding energy amounts to ~24.0 kJ mol^{-1}. In contrast, the $3,4_2$-U$-w_2$ complex is cyclic and the binding energy with water is 45.9 kJ mol^{-1}. The geometries of the $4\text{-}T_4^d$ complexes are drastically different. The $4\text{-}T_4^d\text{-}w_1$ complex becomes now cyclic, and the $O_wH'_w\cdots N$ distance is elongated by 0.010 Å. The interaction energy with water is increased by a factor of more than 2 and becomes now 57.3 kJ mol^{-1}.

The $4\text{-}T_4^d\text{-}w_2$ complex is linear, and the $O_wH'_w\cdots N$ distance is, by 0.142 Å, shorter than that in the $3,4_2$-U$-w_2$ complex. In the $4\text{-}T_4^d\text{-}w_2$ complex, the O_w atom of a water molecule resides out of the molecular plane with the dihedral angle of 6.4°, and its H_w atom lies nearly perpendicular to this plane with the dihedral angle of 95.3°. The binding energy of 46.2 kJ mol^{-1} is about the same as the one of 45.9 kJ mol^{-1} in the $3,4_2$-U$-w_2$ complex.

The formation of a ring structure in the $4\text{-}T_4^d\text{-}w_1$ complex and the shortening of the $O_wH'_w\cdots O$ bond in the $4\text{-}T_4^d\text{-}w_2$ complex suggest a strong increase of the proton acceptor ability of the O_8 atom in the deprotonated species. As indicated in Figure 4, deprotonation results in a decrease of the N_3C_2 distance and an increase of the C_2O_8 bond length, which indicate a larger electronic delocalization within the $N_3C_2O_8$ skeleton. The changes of the complex structures upon electron attachment have been explained by charge accumulation in the $C_5C_4O_{10}$ region.[10b]

Our calculations also reveal that complex formation with water affects significantly the DPE of the $O_{10}H$ bond. In the $3,4_2$-U$-w_1$ complex, the DPE is equal to 1255 kJ mol^{-1} and is thus lowered by 39.6 kJ mol^{-1} with respect to the free tautomer. This effect may be due to the charge transfer taking place from the tautomer to the water molecule. In contrast, in the $3,4_2$-U$-w_2$ complex, the DPE of the $O_{10}H$ bond is 1288.1 kJ mol^{-1}, i.e., lower by only 6.5 kJ mol^{-1} than that in the free tautomer. In this cyclic complex, the electronic delocalization is mainly confined to the six-membered ring.

F. Double-Proton Transfer in the $1,4_1$-U Tautomer. We consider the concerted double-proton transfer of the tautomerization process $U-w_3 \leftrightarrow 1,4_1\text{-}U$ in the presence of a bridging water molecule. Such a process can be viewed as the key mechanism leading to the base pairing mismatch[2] in the Watson−Crick A−U pair.[1] The tautomer $1,4_1$-U which is the most stable one in polar solvents (see ref 8e and section C) and is thus of relevant biophysical importance[9b] is chosen for this purpose.

The transition structure $[U-w_3 \leftrightarrow 1,4_1\text{-}U-w_3]^{tr}$ governing this process is displayed in Figure 8. This concerted double-

proton transfer of the tautomerization process $U-w_3 \leftrightarrow 1,4_1\text{-}U$ in the presence of a bridging water molecule is described by the asymmetric double-well potential which possesses two minima corresponding to the $U-w_3$ and $1,4_1$-U$-w_3$ complexes separated by an activation barrier. Their energies are equal to 61.6 and 25.1 kJ mol^{-1} relative to the barrier height (see Figure 8). Their energy offset is equal to 36.5 kJ mol^{-1}, that is, by 12.7 kJ mol^{-1} lower than the gas-phase tautomerization energy of $U-w_3 \leftrightarrow 1,4_1\text{-}U-w_3$. This implies that a water molecule placed on the minor groove of the Watson−Crick adenine−uracil base pair substantially facilitates the aforementioned tautomerization process. It is interesting to compare the present activation barrier of 61.6 kJ mol^{-1} with the similar one governing the tautomerization of guanine[19a] and cytosine[19b] mediated by a water molecule. At $T \neq 0$ K, an excess entropy due to the proton transfer from the lower well to the transition structure is calculated to be 32.6 J mol^{-1} T^{-1}, whereas from the upper well to the transition structure it becomes equal to 24.5 J mol^{-1} T^{-1}. At $T = 298.15$ K, these excess entropies lower the activation barrier free energy of the double-proton transfer to 47.6 and 14.5 kJ mol^{-1}, respectively, for the lower and upper wells (see Figure 8).

The transition structure $[U-w_3 \leftrightarrow 1,4_1\text{-}U-w_3]^{tr}$ is characterized by interesting geometrical and intrabond properties. As shown in Figure 8, the $O_w - H'_w$, O_w-H_{3a}, and $O_{10} - H'_w$ distances which range between 1.178 and 1.234 Å, respectively, are considerably elongated with respect to the free water molecule. The $O_w - H'_w$ and $O_{10} - H'_w$ distances of 1.204 and 1.234 Å are nearly the same, and the $O_{10}\cdots O_w$ distance of 2.385 Å is very short. These geometrical parameters indicate a very strong, nearly symmetrical OHO hydrogen bond. The H_3O^+ moiety has a strongly distorted pyramidal structure, the $H'_w - O_w - H_{3a}$ angle being equal to 85.6° and the two others are 114.9° and 113.6°. The N_3-H_{3a} distance of 1.335 Å is intermediate between that of a valence bond (1.05 Å) and an intermolecular hydrogen bond ($\approx$1.8 Å).

This transition structure possesses the imaginary frequency 1488i cm^{-1} assigned to the simultaneous double-proton transfer of H'_w and H_{3a} (see Figure 8). This vibrational mode corresponds to a contraction of the $O_w - H'_w$ bond and to a stretching of the N_3-H_{3a} one. The vibrational modes predicted at 1974 and 1717 cm^{-1} with respective IR intensities of 73 and 580 km/mol describe some stretching motions of the $O_w - H'_w$, O_w-H_{3a}, and $O_{10}-H_w^1$ bonds. The ν(OH) vibrations are red-shifted by about 2000 cm^{-1} from the free water molecule. The out-of-plane deformation vibrations of the $O_w - H'_w$ and O_w-H_{3a} bonds are also predicted at 1457 cm^{-1}, an unusually high frequency. It is also worth mentioning that two modes at 1008 and 1297 cm^{-1} are coupled with the intermolecular mode $\nu_\sigma(N_3\cdots H_{3a})$. This frequency is lower than the ν(NH) frequency predicted at about 3600 cm^{-1} but much larger than the frequency of the intermolecular mode usually observed at wavenumbers lower than 200 cm^{-1}.[20]

Conclusions

We have studied the interaction of uracil tautomers with water in order to find a rationale expressing the relative order of stability of uracil tautomers in the presence of water. Twenty-nine complexes of uracil tautomers with a water molecule have been chosen for this purpose. Their complete classification in terms of cyclic and open structures has been elaborated, and their comparison with the parental uracil−water structures has been carried out in terms of their geometries and energies.

We have particularly shown that the cyclic structures are partitioned into two types. One of them is the typical case of

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the donor−acceptor functioning of water molecule. The other one corresponds to the cyclic anticooperative structures where the water molecule acts as a biacceptor of the hydrogen bond. The origin of the cyclic structures has been rationalized in terms of the PAs and DPEs of the corresponding tautomers. We have extended the correlation established earlier for the interaction energies of uracil, thymine, cytosine, adenine, and guanine with water in terms of the function of 1.5PA − DPE to the tautomers of uracil.

One of the spectacular properties of water is its ability to mediate the tautomerization process. In the present work, it has been studied for the tautomerization U−w_3 ⟷ 1,4$_1$-U−w_3 which, as shown, is facilitated by a bridging water molecule w_3. In this context, it is interesting to notice that the corresponding activation barrier of 61.6 kJ mol^{-1} is nearly identical to those governing the tautomerizations in guanine and cytosine. We have also shown that such a double-proton-transfer mediated by a water molecule results in excess entropies which at $T =$ 298.15 K reduce the activation barrier free energy by 14.0 and 10.6 kJ mol^{-1} for the lower well U−w_3 and the upper one 1,4$_1$-U−w_3, respectively.

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