Theoretical Study of Tautomeric Forms of Uracil. 1. Relative Order of Stabilities and Their Relation to Proton Affinities and Deprotonation Enthalpies

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The potential-energy surface of the uracil tautomerization is comprised of 12 different tautomeric forms, except uracil itself. Their optimized structures are determined at the B3LYP/6-31+G(d,p) computational level. Five structures are reported for the first time, although four of them fall into the relative-energy interval already investigated in the past. The relative order of stability of all uracil structures is established. The proton affinities (PAs) and the deprotonation enthalpies (DPEs) of the atoms or bonds involved in the tautomerization process are calculated at the same computational level. The PAs and DPEs values sensitively depend on the tautomeric form, with the PAs of the oxygen and nitrogen atoms ranging from 815 to 947 kJ mol^{-1} and the DPEs of the OH and NH groups from 1295 to 1448 kJ mol^{-1}. The relative energies of the uracil structures with respect to uracil are then rationalized in terms of a second-order polynomial of the difference between their mean PAs and DPEs.

1. Introduction

Uracil is one of the building pyrimidine nucleobases of RNA.[1] In DNA, it is replaced by thymine, its 5-methyl derivative. It has been recently synthesized via the proton irradiation of CO−N$_2$−H$_2$O and obtained by quenching this high-temperature plasma.[2]

Uracil manifests itself in its most stable diketo form (see Figure 1). Nevertheless, it has been known for a long time that uracil may also exist in some tautomeric forms. They result from proton-transfer reactions, whose activation barriers control their formation and determine actually their relative population. In the Watson−Crick model of RNA, uracil in uridine must take its dioxo tautomeric form in order to be in the complementary conformation with the normal, amino tautomer of adenosine. Because of the highly probable link between the spontaneous point mutations developing during RNA replication and the occurrence of the rare enol tautomers of uracil[3] viewed as a major factor responsible for the formation of the nucleobase-pairing mismatches, the uracil tautomers have been the subject of many experimental[4−7] and theoretical[8−11] studies in the past. NMR,[3] UV,[4−5] IR and Raman,[6] and microwave[7a] spectroscopic studies of uracil tautomers led to the conclusion that the 2,4-dioxo tautomer is the most stable one in the gas and solid states and in solution as well. Calorimetric experiments revealed that the 2-oxo-4-hydroxy tautomer of uracil is less stable compared to its 2,4-dioxo form by 79.5 ± 25.1 kJ mol^{-1}.[7b] Fujii and coworkers[5b,c] concluded that the most stable hydroxy tautomer lies above the main form by less than 40.2 kJ mol^{-1} (see also ref 7c). Since then, the problem of the relative stability of rare enol-type tautomers of uracil, primarily in water, has become the subject of a major concern.

The six uracil tautomers were the subject of numerous studies performed at both semiempirical and ab initio computational levels.[8−11] As a matter of fact, one easily finds out combinatorially that there are actually $\binom{6}{2} - 2 - 1 = 12$ possible sites for two hydrogen atoms to reside on the atoms N$_1$, N$_3$, O$_8$, and O$_{10}$. This results from two possible orientations of the O−H bond, leading to different rotamers. Therefore, there exist 12 different structures, excluding uracil, of which four are monohydroxy tautomers with one dihydroxy tautomer and seven are the different planar rotamers of the hydroxy groups. Of these structures, only seven have been calculated previously. Two new tautomeric forms of uracil have been recently predicted at the B3LYP/6-31G(d) computational level.[11c]

One of the aims of the present work is to investigate the potential-energy surface (PES) of the uracil tautomerization at the B3LYP/6-31+G(d,p) computational level. The PES search reveals the 12 structures of uracil. The properties of five rotamers are reported in the present paper for the first time. It is interesting to notice that four of them fall into the energy interval examined recently in ref 11c.

Much less attention has been paid in the past to the relative stabilities of protonated and deprotonated structures of uracil, although double proton transfer between the nucleobases in DNA may play the key role in the appearance of rare tautomers. This was first pointed out by Watson and Crick[12], and this was the basic idea of the molecular mechanism of point mutations proposed by Löwdin[13a,b] (see also refs 14 and 15 for current review). Furthermore, the protonated and deprotonated forms of the uracil structures are of considerable interest in view of the potential protonation sites of DNA base radical ions[16] and their interaction with water as well. There is, however, a complete lack of information regarding the intrinsic acidity and basicity of the uracil tautomers, which can be considered as fundamental properties.

The present work is organized in the following manner. Section 2 briefly discusses the computational methodology, and section 3.A presents the relative order of stability of the 12 possible structures of uracil. Section 3.B deals with their proton affinities (PAs) and deprotonation enthalpies (DPEs). The relative order of stability of the uracil structures are rationalized in terms of their mean PAs and mean DPEs.

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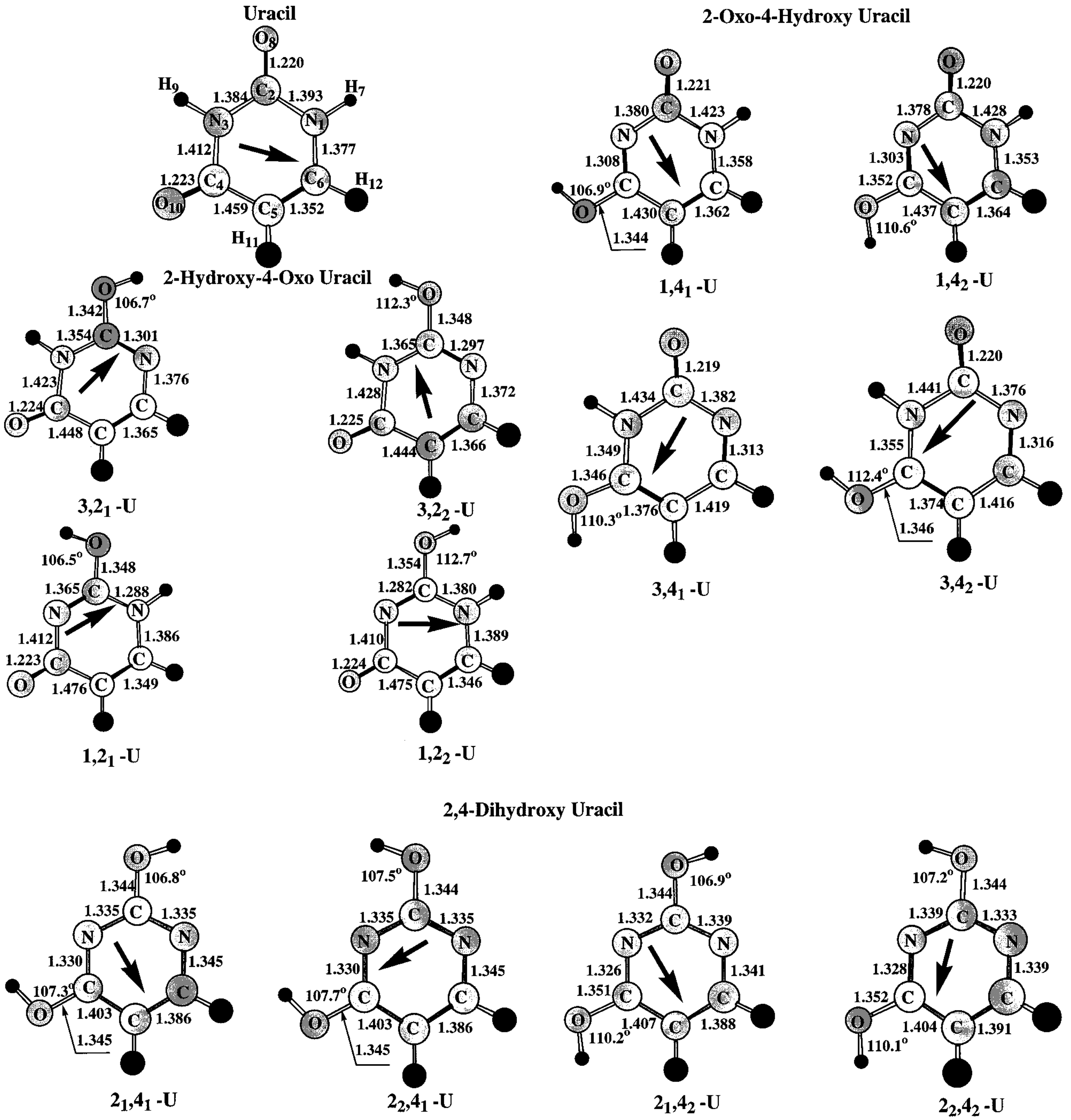


Figure 1. B3LYP/6-31G(d,p) optimized geometries of uracil and the different forms of 2-hydroxy-4-oxo uracil, 2-oxo-4-hydroxy uracil, and 2,4-dihydroxy uracil. Bond lengths are given in angstroms, bond angles in degrees. The arrow indicates the direction of the total dipole moment.

The following notations of the tautomers and rotamers of uracil U are employed throughout the whole work by indicating the atoms where the hydrogen is attached. Because there are two rotamers for each OH group in the tautomer, they are specified by a "1" or "2" subscript. Uracil itself is then indicated by 1,3-U. 2-Hydroxy-4-oxo tautomers are referred to as 3,2_1-U and 1,2_1-U, whereas their rotamers are referred to as 3,2_2-U and 1,2_2-U, respectively. 2-Oxo-4-hydroxy tautomers are 1,4_1-U and 3,4_1-U, and the corresponding rotamers are 1,4_2-U and 3,4_2-U, respectively. The 2,4-dihydroxy tautomer is then referred as 2_1,4_1-U, whereas its rotamers are labeled as 2_2,4_1-U, 2_1,4_2-U, and 2_2,4_2-U.

2. Computational Methodology

All computations were performed at the DFT B3LYP computational level with the 6-31+G(d,p) basis set, using the Gaussian 98 suit of packages.[17] This level is somewhat superior to that employed recently in ref 11c. The geometries of the uracil structures and their protonated and deprotonated forms were fully optimized without the constraint on a possible planarity. The harmonic vibrations were also calculated in order to characterize the structures of tautomeric forms of uracil and further analyze their vibrational spectra and thermodynamic properties. The harmonic frequencies and zero-point vibrational energies (ZPVE) were retained unscaled. The reported energy values were rescaled to the energy + ZPVE and given in kJ mol^{-1} unless otherwise noted, as, for example, in Table 2. Gas-phase PAs and DPEs were calculated under standard conditions of temperature $T = 298.15$ K and pressure $P = 1$ atm.

The reliability of the chosen DFT-type computational level has already been verified (see, e.g., refs 9e, 10b,d, 11a,c, 18, and references therein). It adequately describes the experimental

TABLE 1: Optimized Geometries of the New Rotamers of Uracil[a]

geometry	U	$2_1,4_2$-U	$2_2,4_2$-U	$1,4_2$-U	$3,2_2$-U	$1,2_2$-U
			Bond Length			
$r(N_1, C_2)$	1.393	1.339	1.333	1.428	1.297	1.380
$r(N_1, C_6)$	1.377	1.341	1.339	1.353	1.372	1.389
$r(N_1, H_7)$	1.010			1.012		1.010
$r(C_2, N_3)$	1.384	1.332	1.339	1.378	1.365	1.282
$r(C_2, O_8)$	1.220	1.344	1.344	1.220	1.348	1.354
$r(N_3, C_4)$	1.412	1.326	1.328	1.303	1.428	1.411
$r(N_3, H_9)$	1.014				1.015	
$r(C_4, C_5)$	1.459	1.407	1.404	1.437	1.444	1.475
$r(C_4, O_{10})$	1.223	1.351	1.352	1.352	1.225	1.223
$r(C_5, C_6)$	1.352	1.388	1.391	1.364	1.366	1.346
$r(C_5, H_{11})$	1.081	1.084	1.084	1.083	1.083	1.083
$r(C_6, H_{12})$	1.084	1.087	1.087	1.085	1.087	1.084
$r(H_7, O_8)$		0.970	0.970		0.967	0.967
$r(O_8, H_{11})$		0.967	0.967	0.967		
			Bond Angle			
$\angle N_1C_2N_3$	113.2	127.8	127.8	116.1	123.8	124.9
$\angle N_1C_2O_8$	122.7	116.9	115.8	118.5	117.8	116.8
$\angle N_1C_6C_5$	121.8	123.0	123.6	119.7	125.3	119.8
$\angle N_1C_6H_{12}$	115.4	116.2	116.0	117.1	114.4	115.7
$\angle C_2N_1H_7$	115.1			115.0		121.7
$\angle C_2O_8H_7$		106.9	107.2		112.3	112.7
$\angle C_2N_3C_4$	127.9	115.7	116.1	120.0	123.5	120.0
$\angle N_3C_4C_5$	113.7	122.8	122.2	125.0	111.9	116.6
$\angle C_4N_3H_9$	149.2				114.2	
$\angle C_4C_5C_6$	119.8	115.6	115.6	115.7	119.7	120.1
$\angle C_4O_{10}H_9$		110.2	110.1	110.6		
$\angle C_5C_4O_{10}$	126.1	122.7	123.1	119.6	129.0	122.3
$\angle C_6C_5H_{11}$	122.0	121.7	121.8	121.3	122.3	121.4

[a] Bond lengths are in angstroms, and bond angles are in degrees.

TABLE 2: Relative B3LYP/6-31+G(d,p) Energy E_{rel} in kJ mol^{-1}, with and without ZPVE, and the Total Dipole Moment in D of the Different Structures of Uracil, with Respect to Uracil[a]

structure	E_{rel}	E_{rel} + $ZPVE_{rel}$	D
	2-Hydro-4-oxo		
$3,2_1$-U	46.4 (51.9)[b] (43.5)[c]	45.6 (51.0)[b] (43.9)[c]	3.4 (3.2)[b]
$3,2_2$-U	81.3	78.3	2.4
$1,2_1$-U	81.8 (90.4)[b]	80.0 (87.0)[b]	6.7 (4.6)[b]
$1,2_2$-U	127.5	122.1	9.4
	2-Oxo-4-hydro		
$1,4_1$-U	50.0 (56.5)[b] (49.4)[c]	49.2 (52.2)[b] (50.2)[d]	5.1 (4.6)[b]
$1,4_2$-U	80.2	77.9	7.9
$3,4_1$-U	89.5 (94.6)[b]	86.6 (91.6)[b]	7.5 (7.5)[b]
$3,4_2$-U	102.3 (108.0)[b]	98.0 (104.2)[b]	6.1 (5.8)[b]
	2,4-Dihydroxy		
$2_1,4_1$-U	53.5 (64.0)[b] (44.5)[c]	53.1 (64.0)[b]	1.3 (1.1)[b]
$2_2,4_1$-U	58.5 (69.0)[b]	57.7 (69.0)[b]	2.5 (2.5)[b]
$2.3,4_1$-U	76.7	75.4	4.2
$2_2,4_2$-U	76.9	75.5	3.8

[a] The B3LYP/6-31+G(d,p) energy of uracil is equal to −414.847 362 1 hartree. Its ZPVE = 54.5703 kcal mol^{-1}. [b] B3LYP/6-31G(d) + 0.9804ZPVE computational level.[11c] [c] MP2(fc)/6-31G(d,p)//HF/6-31G(d,p) computational level.[10d] [d] MP2/DZP + 0.91ZPVE computational level.[10e]

geometry of uracil U (see Table 1 and also Table 1 in ref 11a,c) and the rotational constants of uracil and its tautomeric forms $3,2_1$-U, $1,4_1$-U, and $2_1,4_1$-U (see Table 1 in ref 9e), and, moreover, it is in fact energetically closer to the MP4 level than to the MP2 one.[9e] It is also worth noting that the experimental values of the acidity of uracil are very close (to within 4 kJ mol^{-1}) to the one predicted at B3LYP/6-31+G(d,p), thus validating that computational method and level.[18d] However, by comparison with the MP2/6-31G(d) level (see Table 3 in ref 11a and Table 2 in ref 19), the B3LYP/6-31+G(d,p) level overestimates the total dipole moment of uracil (see also ref 9e), whose experimental value varies from 3.86[7a] to 4.16 D.[7d] The calculated ν(NH) stretching vibrations of uracil are compared with the experimental data in Table S1 of the Supporting Information (see also ref 18). It is worth noticing that such a comparison leads to scaling factors of 0.9509 and 0.9490.

3. Results and Discussion

3.A. Optimized Geometries and Relative Energies of Uracil Tautomeric Forms The 12 structures of uracil displayed in Figure 1 and lying within ca. 122 kJ mol^{-1} above its global energy minimum are found in the present work on the PES of the uracil tautomerization. Seven of them have geometries matching the geometries calculated at the B3LYP/6-31G(d) level in ref 11c. The properties of five rotamers are considered here for the first time. Their optimized geometries are collected in Table 1. As is discussed in ref 8d, the keto−enol tautomerism is accompanied by significant changes of the corresponding C−O bond length. In the present case, the C_2-O_8 bond is elongated by 0.12−0.13 Å and the C_4-O_{10} bond by ∼0.13 Å. There is also a decrease of the $N_1-C_2-O_8$ bond angle from 4.6 to 6.9°. For all of the structures except the $1,2_2$-U one, we observe a pronounced elongation of the C_5-C_6 double bond. It is worth noticing that in the two dihydroxy structures, all of the intra-ring distances, with the exception of the C_5-C_6 one, become smaller. This may be accounted for by the increasing aromatic character of the six-membered ring. In the $2_2,4_2$-U structure, the distances are very similar to those experimentally observed in pyrimidine[20], where the shortest distance N_1-C_2 is 1.33 Å and the largest one of the C_4-C_5 bond is equal to 1.41 Å. A similar remark also holds for the angles, varying from 115.1° of the $C_2-N_3-C_4$ bond angle to 128.2°, which corresponds to the $N_1-C_2-N_3$ bond angle.

The tautomerization or relative energy E_{rel} of a given uracil structure is defined as a difference between its total energy and that of uracil. The relative energies of all different structures of uracil and their total dipole moments are listed in Table 2. One expects the energies of the tautomers to be different, with a relatively small difference between rotamers. This is the case for the dihydroxy tautomers but not for the 2-hydroxy and 4-hydroxy tautomers, where the energy difference between the rotamers varies between 13 and 41 kJ mol^{-1}. In terms of their relative energies, they are partitioned into the three following groups.

The first group includes the most stable tautomer $3,2_1$-U of the 2-hydroxy-4-oxo form, with a total dipole moment of 3.4 D and an energy higher than uracil by 45.6 kJ mol^{-1}. The $3,2_1$-U tautomer is followed by the 2-oxo-4-hydroxy tautomer $1,4_1$-U and the 2,4-dihydroxy tautomer $2_1,4_1$-U. They are located at 3.6 and 7.4 kJ mol^{-1} above $3,2_1$-U, respectively, and have total dipole moments of 5.1 and 1.3 D. Both these tautomers have the O_8−H group in the cis position with respect to the N_3 atom.

The second group falls within an interval of energies of approximately 75−98 kJ mol^{-1} above uracil. It is separated from the first group by 17.7 kJ mol^{-1} and particularly contains two nearly isoenergetic 2,4-dihydroxy conformers $2_1,4_2$-U and $2_2,4_2$-U and also a pair of nearly isoenergetic structures $1,4_2$-U and $3,2_2$-U. They are placed above uracil by respectively 75.4, 75.5, 77.9, and 78.3 kJ mol^{-1}. As seen in Figure 1, $2_1,4_2$-U and $2_2,4_2$-U are interconnected to each other by the O−H group flipping around the C_2-O_8 bond. The four mentioned lower-energy structures have not been studied so far, despite the fact that the other ones, $1,2_1$-U and $3,4_1$-U, belonging to this group and lying above uracil by 80.0 and 86.6 kJ mol^{-1} have recently been reported.[11c] It is also seen in Figure 1 that in the $2_1,4_2$-U, $2_2,4_2$-U, and $1,4_2$-U structures the $O_{10}-H$ group is in the cis position with respect to the C_5 atom. The second group also includes the structures $1,4_2$-U, $1,2_1$-U, and $3,4_1$-U, with rather large dipole moments of 7.9, 6.7, and 7.5 D, respectively. Comparing these values of the total dipole moment with those calculated in ref 11c at the B3LYP/6-31G(d) computational level and also collected in Table 2, one finds that the B3LYP/6-31G(d) level predicts less accurately the dipole moment of $1,2_1$-U, whereas its present magnitude correlates well with other reported theoretical values ranging from 6.5 to 6.7 D.[8d,10e] Finally, the $3,4_2$-U structure lies above uracil by ~98.0 kJ mol^{-1}.

The third group of the uracil structures consists of a single structure $1,2_2$-U, which is higher in energy than uracil by 122.1 kJ mol^{-1} and is also reported for the first time in the present work. It has the largest dipole moment of 9.4 D among all tautomeric forms of uracil, and its O_8-H bond is pointing out of the uracil ring by 0.13 Å, whereas the N_1-H bond takes the opposite direction and lies partly out of the ring plane by 0.10 Å. The corresponding transition structure lies above $1,2_2$-U by 0.56 kJ mol^{-1} only. It is planar and characterized by the imaginary frequency 76*i* cm^{-1}, describing the asymmetric out-of-plane libration of the O_8-H and N_1-H bonds.

Therefore, the relative stability order of the different structures of uracil becomes the following at the present computational level:

$$\begin{aligned} 1{,}3\text{-U} &\overset{45.6}{>} 3{,}2_1\text{-U} \overset{3.6}{>} 1{,}4_1\text{-U} \overset{3.8}{>} 2_2{,}4_1\text{-U} \overset{4.2}{>} \\ &\qquad 2_2{,}4_1\text{-U} \overset{17.7}{>} 2_1{,}4_2\text{-U} \overset{0.1}{\approx} 2_2{,}4_2\text{-U} \\ &\overset{2.4}{>} 1{,}4_2\text{-U} \overset{0.4}{\approx} 3{,}2_2\text{-U} \overset{1.7}{\approx} 1{,}2_1\text{-U} \overset{6.7}{>} 3{,}4_1\text{-U} \overset{11.4}{>} \\ &\qquad 3{,}4_2\text{-U} \overset{24.1}{>} 1{,}2_2\text{-U} \end{aligned} \quad (1)$$

where the quantity above the inequality indicates the corresponding energy difference. This order is preserved at ambient temperatures. The present order of stability can be compared with previous theoretical findings:

B-LYP/6-31G(d,p)//MP2/6-31G(d,p)[9e]

$$1{,}3\text{-U} \overset{47.9}{>} 3{,}2_1\text{-U} \overset{3.0}{>} 1{,}4_1\text{-U} \overset{6.6}{>} 2_1{,}4_1\text{U} \quad (2)$$

MP2/DZP + 0.91ZPVE[10e]

$$1{,}3\text{-U} \overset{43.9}{>} 3{,}2_1\text{-U} \overset{6.3}{>} 1{,}4_1\text{-U} \quad (3)$$

MP4(SDTQ)/6-31G(d,p)//HF/6-31G(d,p) + 0.9ZPVE[HF/6-31G(d,p)][9e]

$$1{,}3\text{-U} \overset{48.1}{>} 3{,}2_1\text{-U} \overset{5.7}{>} 2_1{,}4_1\text{-U} \overset{0.4}{\approx} 1{,}4_1\text{-U} \quad (4)$$

and finally, with

MP2/6-31G(d,p)//HF/6-31G(d,p) + 0.9ZPVE[HF/6-31G(d,p)][10d]

$$1{,}3\text{-U} \overset{43.3}{>} 3{,}2_1\text{-U} \overset{1.0}{>} 1{,}4_1\text{-U} \overset{5.2}{>} 2_1{,}4_1\text{-U} \quad (5)$$

B3LYP/6-31+G(d) + 0.9804ZPVE[B3LYP/6-31G(d)][11c]

$$\begin{aligned} 1{,}3\text{-U} &\overset{51.0}{>} 3{,}2_1\text{-U} \overset{42.0}{>} 1{,}4_1\text{-U} \overset{8.8}{>} 2_1{,}4_1\text{-U} \overset{5.0}{>} 2_2{,}4_1\text{-U} \overset{18.0}{>} 1{,}2_1\text{-U} > \\ &\qquad \overset{4.6}{} 3{,}4_1\text{-U} \overset{12.6}{>} 3{,}4_2\text{-U} \end{aligned} \quad (6)$$

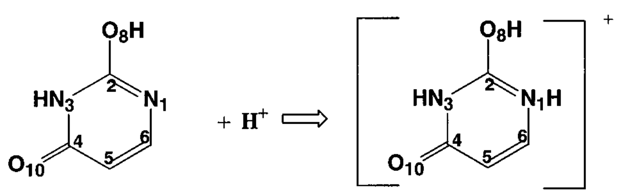
One sees that, at any computational level, the $3,2_1$-U structure is certainly the most stable one. It is followed by the $1,4_1$-U structure, which lies very close to the 2,4-dihydroxy one $2_1,4_1$-U. A comparison of the structures of $1,4_1$-U and $2_1,4_1$-U presented in Figure 1 suggests that the corresponding proton transfer from O_8 in $1,4_1$-U to the N_1 site in $2_1,4_1$-U which can be facilitated by the adjacent water molecule occurs via a nearly symmetrical double well reaction path. Because the dipole moment of the 2-oxo-4-hydroxy tautomer $1,4_1$-U exceeds that of $2_1,4_1$-U by a factor of about four (see Table 2), its occurrence in a polar solvent is highly probable compared with the occurrence of the $2_1,4_1$-U tautomer (see ref 11d). The next stable structure is $2_2,4_1$-U, which is placed by ~4.6−5.0 kJ mol^{-1} above $2_1,4_1$-U (see eqs 1 and 6). It is followed by the two rotamers $2_1,4_2$-U and $2_2,4_2$-U, which are almost isoenergetic, according to (1). The relative order of stability goes further to $1,4_2$-U, $1,2_1$-U, $3,4_1$-U, and $3,4_2$-U and finally ends by the $1,2_2$-U rotamer. All of the uracil structures can also be characterized by their vibrational properties and IR intensities given in Table S1.

One of the main factors determining the relative stability of the different forms of uracil is certainly the repulsion interaction between two neighboring O−H and N−H groups. As is demonstrated by the present data, the $3,2_2$-U rotamer is less stable by 32.7 kJ mol^{-1} than the $3,2_1$-U one because of the repulsive dipole−dipole interaction of the nearly parallel N_3-H and O_8-H bond dipoles. A simple estimation of the difference of their dipole−dipole interaction as pointlike dipoles in $3,2_1$-U and $3,2_2$-U gives 21.6 kJ mol^{-1}, which is about 66% of the aforementioned energy difference. A similar remark holds for $1,2_1$-U and $1,2_2$-U, whose difference in relative energies is equal to 42.1 kJ mol^{-1}. Another factor is the attractive interaction between the O−H or N−H bonds, on the one side, and the lone pair(s) of the adjacent N or O atoms, on the other one.[21] Here, the existence of intramolecular hydrogen bonds can be ruled out for geometrical reasons. In all cases, the intramolecular H···N distances are short, i.e., smaller than the sum of the van der Waals radii of the H and N atoms. However, the OH···N angles which appear to be smaller than 90° decline an efficient overlapping between the OH bond and the N lone pair. In $1,4_1$-U, the $N_3 \cdots H_9$ distance is indeed equal to 2.253 Å and the corresponding angle $\angle O_{10}H_9N_3$ is found to be 78.8°. A similar conclusion can be also drawn for $2_1,4_1$-U and $2_2,4_1$-U, where the $N_3 \cdots H_9$ (O_{10}) distance is equal to 2.262 Å ($2_1,4_1$-U) and to 2.275 Å ($2_2,4_1$-U) with the corresponding $O_{10}H_9N_3$ angle of 72.1° ($2_1,4_1$-U) and 78.7° ($2_2,4_1$-U). In $2_1,4_1$-U, the $N_1 \cdots H_8$ (O_4) distance is equal to 2.254 Å, with the corresponding $O_4H_8N_1$ angle of 79.7°, whereas in $2_2,4_1$-U, the $N_3 \cdots H_8$ (O_4) distance is equal to 2.256 Å, with the corresponding O_4 H_8 N_3 angle of 79.5°.

It is worth noticing that, although the tautomerization of uracil has been a subject of numerous studies, the relative order of stability of the tautomeric forms of uracil has not been so far rationalized in terms of their physicochemical properties. An important property is the intrinsic basicity, and as a rule,[22] the tautomeric form of the lowest basicity is predominant in the gas phase. It is known, e.g., that the tautomers 2-hydropyridine and 2-pyridone both exist in the gas phase and that their PAs do not differ by more than 2.4 kJ mol^{-1}.[23] Furthermore, the fact that $1,4_2$-U is more stable than $3,4_1$-U and $3,4_2$-U implies that the proton at the N_3 atom is more acidic than that residing at the N_1 atom. These features suggest that the energies of the tautomers depend on their intrinsic acidities and basicities. This will be discussed in the next section.

SCHEME 1

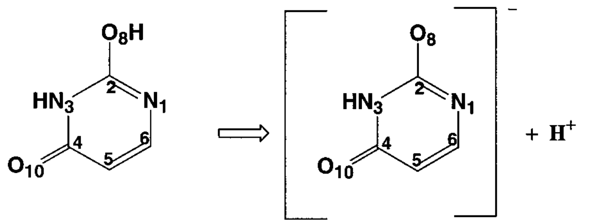
Protonation of the $3,2_1$-U uracil at the N_1 atom



PA(N_1): $3,2_1\text{-U} + H^+ \longrightarrow 1,3,2_1\text{-U}^+$

The proton affinity is the negative value of the enthalpy of the protonation process: PA(A) = [E(A) - E(AH$^+$)] + [ZPVE(A) - ZPVE(AH$^+$)] + 5RT/2

Deprotonation of the $3,2_1$-U uracil at the O_8 atom



DPE(O_8): $3,2_1\text{-U} \longrightarrow 3\text{-U}^- + H^+$

The deprotonation enthalpy is the enthalpy of the deprotonation process: DPE(A) = [E(A) - E(A$^-$)] + [ZPVE(A) - ZPVE(A$^-$)] + 5RT/2

3.B. PAs and DPEs of Uracil Tautomeric Forms

In this section, we will discuss the protonation affinities and DPEs of the atoms or bonds participating in the tautomerization process, namely, the protonation of the carbonyl oxygen and nitrogen atoms and the deprotonation of the N−H and O−H bonds as well.

The protonation of uracil and its 12 different structures leads to 12 protonated forms UH^+, which, for a convention, bear the names of their most stable parental uracil tautomeric form. We also use the notations defined in the Introduction and based on listing the atoms where the hydrogen atoms and the added proton are attached. An example of protonation and deprotonation reactions in the $3,2_1$-U tautomer is shown in Scheme 1.The former reaction can be also considered as the protonation of the 1,3-U at the O_8 atom on the N_1 side. This implies that the sum of energies for these two reactions, $3,2_1\text{-U} + H^+ \rightarrow 1,2_1,3\text{-U} + H^+$, is equal to the tautomerization energy of $3,2_1$-U.

The PAs of uracil structures are presented in Table 3. The most stable prototautomeric form is $1,2_2,4_1\text{-U}^+$ with a PA of 914.3 kJ mol^{-1} for the O_8 atom on the N_3 side. This might be of importance for a possible proton transfer in base pairs containing the uracil tautomeric form $1,2_2,4_1\text{-U}^+$, which may cause, according to the Löwdin model,[13] a base pair mismatch. The latter PA exceeds the largest PA of uracil at the O_{10} position on the C_5 side ($1,3,4_2\text{-U}^+$) by 54.3 kJ mol^{-1}, which coincides rather well with the energy difference of 49.4 kJ mol^{-1} between uracil and its $1,4_1$-U tautomer shown in eq 1. Apparently, the difference of ca. 5 kJ mol^{-1} between these values is mainly attributed to the more preferable arrangement of the X−H bond dipoles (X = O and N) in $1,2_2,4_1\text{-U}^+$ residing at the N_1, O_8, , and O_{10} atom (N_3 side) compared with that in $1,3,4_2\text{-U}^+$ at N_1, N_3, and O_{10} (C_5 side). The aforementioned energy difference of ∼5 kJ mol^{-1} can be significantly reduced or even reversed in polar solvents because of the larger dipole moment of $1,3,4_2\text{-U}^+$ of 5.7 D compared with that of $1,2_2,4_1\text{-U}^+$, which is equal to 2 D. The other prototautomeric forms are arranged in the following manner

$$\begin{aligned}
&1,2_2,4_1\text{-U}^+\\
&\quad\overset{5.2}{>} 1,3,4_2\text{-U}^+ \overset{11.8}{>} 1,3,4_1\text{-U}^+ \overset{1.0}{\approx} 1,2_2,4_2\text{-U}^+ \overset{12.5}{\approx} 3,2_1,4_2\text{-U}^+\\
&\quad\overset{3.1}{>} 1,2_1,4_1\text{-U}^+ \overset{10.6}{>} 1,2_2,3\text{-U}^+ \overset{3.8}{>} 3,2_1,4_1\text{-U}^+ \overset{1.9}{\approx} 1,2_1,3\text{-U}^+\\
&\quad\overset{6.5}{>} 1,2_1,4_2\text{-U}^+ \overset{12.7}{>} 2_2,3,4_2\text{-U}^+ \overset{22.0}{>} 2_2,3,4_1\text{-U}^+ \qquad (7)
\end{aligned}$$

It might also be mentioned that the 2,4 forms can be considered as 2,4-dihydroxy pyrimidines. The PA of $2_1,4_1$-U does not markedly differ from that of pyrimidine equal to 880 kJ mol^{-1}.[25] The lowest PA of 831.8 kJ mol^{-1} is found for the N_3 atom of $2_2,4_1$-U. This results from the repulsion between the three O_8−H, N_3−H, and O_{10}−H bond dipoles. Finally, it is worth mentioning that the PA of the O_{10} atom on the N_3 side of the least stable $1,2_2$-U rotamer is equal to 991.9 kJ mol^{-1}. Therefore, it appears to be one of the *strongest organic bases* because its PA is similar to that of aliphatic diamines and is about 20 kJ mol^{-1} lower than that of the proton sponges.[25]

The DPEs of the N−H and O−H bonds of uracil and its 12 different forms are collected in Table 4. There exists actually six possible forms of deprotonated uracil and its 12 tautomers and rotamers. They are displayed in Figure 2. By analogy with the prototautomeric form convention, the deprotonated conformer is referred to its more stable neutral parental tautomeric

TABLE 3: PAs[a] in kJ mol^{-1} of the O and N Atoms of the Different Structures of Uracil

structure	O_8 (N_1 side)	O_8 (N_3 side)	O_{10} (N_3 side)	O_{10} (C_5 side)	N_1	N_3
U	815.3	821.0	848.2	860.0[b]		
$3,2_1$-U			862.3	880.3	860.9	
$3,2_2$-U			852.4	874.4	899.2	
$1,2_1$-U			945.1	927.1		950.9
$1,2_2$-U			991.9	930.4		936.9
$1,4_1$-U	880.8	914.3				897.3
$1,4_2$-U	886.8	925.1				937.9
$3,4_1$-U	921.3	882.7			946.6	
$3,4_2$-U	915.2	872.1			946.2	
$2_1,4_1$-U					884.6	870.2
$2_2,4_1$-U					922.9	831.8
$2_1,4_2$-U					884.2	910.1
$2_2,4_2$-U					922.7	871.6

[a] See Scheme 1 for the definition of PA. [b] The experimental PA of uracil.[24]

TABLE 4: DPEs[a] in kJ mol^{-1} of the NH and OH Bonds of the Different Structures of Uracil

structure	N_1	N_3	O_8 (N_1 side)	O_8 (N_3 side)	O_{10} (N_3 side)	O_{10} (C_5 side)
U	1392.6	1448.1				
$3,2_1$-U		1411.5	1347.0			
$3,2_2$-U		1373.2		1314.3		
$1,2_1$-U	1371.5			1368.1		
$1,2_2$-U	1335.5		1326.5			
$1,4_1$-U	1420.5				1398.9	
$1,4_2$-U	1419.9					1370.1
$3,4_1$-U		1410.3				1306.0
$3,4_2$-U		1371.6			1294.6	
$2_1,4_1$-U			1416.6		1404.0	
$2_2,4_1$-U				1412.0	1393.8	
$2_1,4_2$-U			1421.5			1381.7
$2_2,4_2$-U				1421.4		1375.9

[a] See Scheme 1 for the definition of DPE.

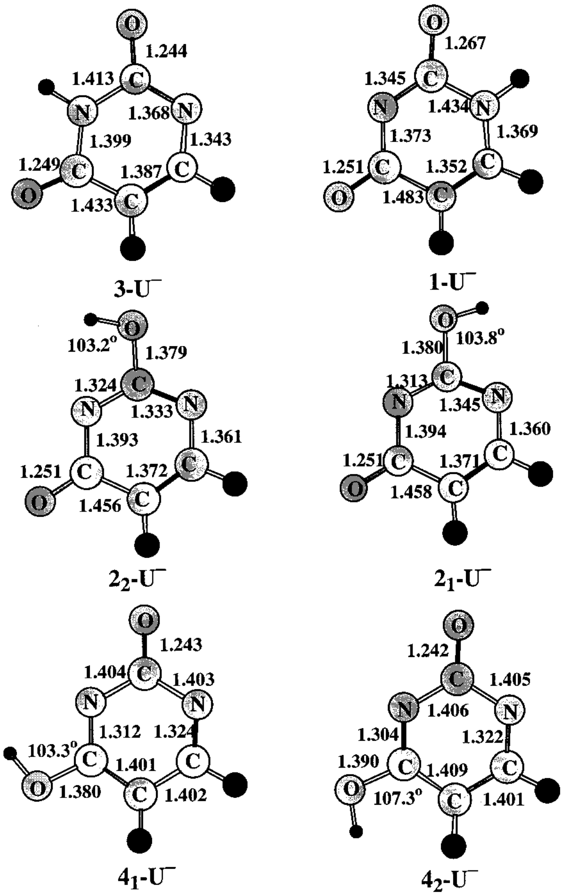


Figure 2. B3LYP/6-31G(d,p) optimized geometries of deprotonated uracil and deprotonated monohydroxy and dihydroxy uracil.

form supplied by the subscript "1" or "2" related to two different rotamers. Deprotonation results in noticeable changes in the geometries. In the N_1 or N_3 anions of uracil and the monohydroxy forms, there is a significant contraction of 0.025−0.041 Å of the two C−N_1 and C−N_3 bonds and an elongation of 0.024−0.047 Å of the neighboring C═O bonds. These features are connected with a strong electronic delocalization within the N−C═O group. In the monohydroxy uracils, the C−O bond is also elongated by 0.036−0.038 Å. An inverse trend is observed in the dihydroxy structures. Deprotonation of the C−O−H bond results in a strong contraction of 0.094−0.102 Å of the C−O bonds and a significant elongation of 0.053−0.074 Å of the (O)C−N bond. Both the C−O and C−N distances are very similar to those obtained in deprotonated uracil 3-U^-. Large perturbations of the vibrational spectrum, analogous to those observed for uracil,[26] are also predicted by the present calculations. The stability order of the deprotonated forms is as follows

$$3\text{-U}^-(2.4) \overset{55.4}{>} 1\text{-U}^-(8.0) \overset{4.0}{>} 2_2\text{-U}^-(2.6) \overset{5.6}{>} 2_1\text{-U}^-(5.3) \overset{12.6}{>} 4_1\text{-U}^-(5.7) \overset{27.2}{>} 4_2\text{-U}^-(7.9) \quad (8)$$

where the total dipole moment in debyes of the corresponding structure is indicated in parentheses.

The results of Table 4 indicate that the N_1−H bond of uracil is more acidic by 55.5 kJ mol^{-1} than the N_3−H one. This difference can be accounted for by the Mulliken charges on the N_3 and N_1 atoms, which are equal to −0.55 and −0.45, respectively. However, it is obvious that the deprotonation of the N_1−H bond cannot occur in normal nucleobases where N_1 is bonded to the sugar−phosphate backbone. A comparison of the data in Tables 2 and 4 indicates that the lowest DPE values are calculated for the less stable 3,4_2-U and 1,2_2-U forms. However, for the other structures, there is no systematic correlation between the relative energies and intrinsic acidities. It should also be noticed that the acidity of the O−H bond in the 1,2_2-U and 3,4_2-U forms is very large. Their DPEs are larger by ca. 75 kJ mol^{-1} than the DPE of 1375 kJ mol^{-1} for 4-NO_2 phenol[27], which is often taken as a reference acid in hydrogen bond studies.

To rationalize the relative order of stability of the different forms of uracil in terms of their PAs, let us consider the mean value $\overline{\text{PA}}$ of the PA of the two acceptor atoms. For the carbonyl oxygen atom, we introduce the average value of the PA of two inequivalent lone pairs. For instance, by means of Table 3, we readily find that $\overline{\text{PA}}$(U) = 837 kJ mol^{-1}, the mean value of the $\overline{\text{PA}}$ of the two carbonyl oxygens. For the 1,2_2-U structure, the $\overline{\text{PA}}$ value is equal to 949.1 kJ mol^{-1}, the average value of the PA of the carbonyl oxygen (961.2 kJ mol^{-1}) and the N_3 atom (936.9 kJ mol^{-1}). These are actually the smallest and the largest values of $\overline{\text{PA}}$ among all forms of uracil. A comparison of the data reported in Tables 2 and 3 shows a very rough correlation between the relative stability of the different structures and the corresponding $\overline{\text{PA}}$ values. However, one may also notice a strong departure for the 3,2_2-U structure, whose relative energy is much larger than that predicted from the $\overline{\text{PA}}$ value which is equal to 881.1 kJ mol^{-1}. Moreover, the 1,4_2-U, 3,4_1-U, and 3,4_2-U forms are characterized by the similar $\overline{\text{PA}}$ values, viz., 921.9, 924.3, and 919.9 kJ mol^{-1}, although their relative energies differ significantly from each other, cf. 77.9, 86.6, and 98.0 kJ mol^{-1}. The fact that 1,4_2-U is more stable than 3,4_1-U or 3,4_2-U implies that the proton at the N_3 atom is more acidic than that residing at the N_1 atom. The DPEs of the N−H and O−H bonds of uracil and its different forms show that this is indeed the case. The DPE of the N_1−H bond of 1,4_2-U is equal to 1419.0 kJ mol^{-1}, i.e., it is much larger than the DPE of the N_3−H bond in 3,4_1-U, which is equal to 1410.3 kJ mol^{-1} and that in 3,4_2-U, which is equal to 1371.6 kJ mol^{-1}. These considerations suggest that the relative order of stability of the different structures of uracil depend not only on the PA of the acceptor atoms but also on the acidity of the different proton-donor groups. Therefore, their order of stability can be rationalized in terms of the difference $\overline{\text{DPE}} - \overline{\text{PA}}$, where $\overline{\text{DPE}}$ is defined as the mean value of the DPEs of the two functional N−H or O−H groups. This is illustrated in Figure 3, where the relative energies of the uracil structures are plotted vs $\overline{\text{DPE}} - \overline{\text{PA}}$. The two curves displayed in Figure 3 correspond to the monohydroxy (the lower one) and the dihydroxy (the upper one) forms of uracil. The lower curve is fairly approximated by the second-order polynomial

$$E_{\text{rel}} = 168.2 + 0.168(\overline{\text{DPE}} - \overline{\text{PA}}) - 0.78 \times 10^{-3}(\overline{\text{DPE}} - \overline{\text{PA}})^2 \quad (9)$$

with the correlation coefficient $r = 0.9930$.

Equation 9 represents actually the first quantitative correlation between the intrinsic acidity or basicity of the atoms or groups involved in the tautomerization process and the relative stability of different forms. Such a correlation may also be useful for other molecules involved in a lactam−lactim tautomerism.

4. Concluding Remarks

In the present work, we have shown that the PES of the uracil tautomerization is comprised in total of the 12 structures,

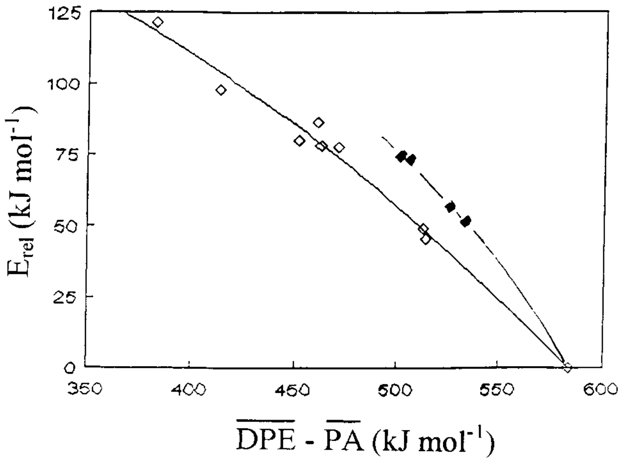


Figure 3. Relative energies E_{rel} of the uracil structures vs $\overline{DPE} - \overline{PA}$. The lower curve corresponds to the monohydroxy structures and the upper one to the dihydroxy structures of uracil.

excluding uracil, with five ones being reported for the first time. Their relative order of stability has been accomplished at the B3LYP/6-31+G(d,p) computational level. The most stable uracil structure is the 2-hydroxy-4-oxo form $3,2_1$-U, with the tautomerization energy $E_{rel} = 45.6$ kJ mol^{-1}, where the ZPVE contribution provides only 1.8%. Despite this fact, it is unable to function as a normal nucleobase because of the absence of the N_1-H_7 bond connected to the sugar−phosphate backbone. It appears, however, in the modified nucleobases, including pseudouridine.[28] In fact, among normal nucleobases, the 2-oxo-4-hydroxy $1,4_1$-U structure is the most stable one, lying above $3,2_1$-U by 3.8 kJ mol^{-1}. Its dipole moment exceeds that of $3,2_1$-U by 50%, and therefore, polar solvents favor $1,4_1$-U rather than $3,2_1$-U.[11d] For these two reasons and also because it has the N_1 atom linked to the sugar−phosphate backbone, it becomes a major biophysical interest. One also notices that the ZPVE contribution to the stabilization energy of the uracil structures ranges from 0.8 to 5.9 kJ mol^{-1}, with the latter being rather essential for the $1,2_2$-U one.

The PAs and DPEs of the 12 forms of uracil have been calculated at the same computational level. The major conclusion of the present theoretical study is that the relative energies of the 12 structures of uracil has been rationalized in terms of the difference of the mean DPEs and the mean PAs of the functional groups participating in the tautomerization process. It might be of interest to extend the present rationale to other nucleobase tautomers. In particular, it will be extended in part 2 of this work dealing with the geometries and interaction energies of different uracil structures complexed with water.

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Supporting Information Available: Table S1 listing ν(NH) and ν(OH) stretching vibrations of uracil and its structures. This material is available free of charge vis the Internet at http://pubs.acs.org.

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