Tautomeric Equilibria of 2- and 4-Thiouracil in Gas Phase and in Solvent: A Density Functional Study

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ABSTRACT: The relative stabilities of the five favored tautomers of 2- and 4-thiouracil in gas phase and in water solution were determined by density functional theory employing the Becke, Lee, Yang, and Parr (B3LYP) exchange–correlation potential and the three 6-31G(d,p), 6-311++G(d,p), and triple-zeta valence (TZVP) basis sets. Zero-point vibrational corrections were also computed. Bulk solvent effects were studied in the framework of the self-consistent reaction field approach by the polarizable continuum model. All calculations indicate that the most stable tautomer for both species, in the gas phase as well as in solution, has the oxo-thione form, in full agreement with the previous ab initio and experimental studies. The tautomeric stability orders obtained in the aqueous solution are sensibly different from that in the gas phase. At B3LYP/6-311++G(d,p) level in the gas phase, the following orders of stability for 2- and 4-thiouracil tautomers were observed, respectively: S2U1 > S2U2 > S2U4 > S2U5 > S2U3 and S4U1 > S4U2 > S4U3 > S4U4 > S4U5. The corresponding trends in the aqueous phase are S2U1 > S2U3 > S2U2 > S2U5 > S2U4 and S4U1 > S4U2 > S4U3 > S4U5 > S4U4. On the basis of the computed energy differences we can hypothesize that only the oxo-thione forms of 2- and 4-thiouracil should exist in the gas phase and in water solution. Int J Quantum Chem 82: 44–52, 2001

Key words: thiouracil; tautomeric equilibria; density functional theory; solvent effects

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Introduction

The protomeric equilibria of heterocyclic molecules are the subject of continuing theoretical and experimental studies because of the biological implications that these phenomena cause on DNA and RNA base-pairs interactions [1–5]. In particular, the study of tautomeric equilibria of the nucleobases and of some of their analogs constitutes the starting point to explain the relationships between the contemporary occurrence of the rare enol tautomeric forms and the point mutations during DNA replication due to the ability of nucleic acids to accommodate noncanonical hydrogen bonds [3, 6].

Thiated derivatives can influence the structure of DNA and, although the picture of such changes is not completely known at the molecular level, some attempts to clarify their unusual functioning have already been made [7–12]. The introduction of the sulfur atom in the molecule of the uracil may induce changes in the properties of the base and modify its interactions, even if it retains the same distribution of hydrogen donors and acceptors as the standard base [7]. In particular, in a recent work of Kryachko and Nguyen [12], these changes are substantially attributed to the enhancement of the polarizability of nucleobases that, in turn, influences the induction and dispersion contributions to the stabilization energy of base pairs. No less significant are the structural changes mainly due to the C=S bonds that are longer than the C=O ones. Furthermore, because the sulfur atom is a weaker acceptor of H bonds than the oxygen one [13], the resulting thiobase pairings are influenced both from structural and energetic points of view. The structural and energetic variations depend on the formation of hydrogen bonds that are longer and weaker when sulfur replaces the oxygen atom in the uracil.

Thiouracils have been identified as minor components of transfer-RNA, and they are used as anticancer and antithyroid drugs, thus playing an important role in both the biological and pharmacological activities [13, 14]. Actually the 2-thiouracil is used as highly specific melanoma seeker, and it shows a mechanism of selective incorporation into growing melanins both *in vitro* and *in vivo* [15]. Moreover, the triorganophosphinegold (I) complexes of 2-thiouracil display promising antiarthritic activity [16]. 4-thiouracil presents cytostatic properties and is used as the cross-linking agent in RNA transcriptional regulation [17].

The interest in the gas-phase equilibria of such molecular systems can be helpful for modeling the real situation in the condensed phase. Solvent effects of biomolecules are extremely important in DNA base-pair interactions because several biological processes occur following the displacement of water of hydration [18]. Although a modulation of the tautomeric equilibria is possible upon solvation especially in heterocyclic systems, recent calculations, concerning DNA and RNA bases derivatives [19], have pointed out that the enol forms are very minor in water with respect to the dioxo ones. The tautomeric equilibria of uracil and its derivatives have been extensively studied at experimental [20–23] and quantum mechanical [2, 12, 24–30] level, but no comparison work, devoted to the stability order of the tautomers of both 2- and 4-thiouracils in water, is known until now.

The analysis of the relative population of all 4-thiouracil tautomers in solvent without geometry optimization has been performed theoretically in a work including the MP4(SDQ/6-311G(2d,2p)//MP2/6-31G(d,p) computations [28]. The interaction of the most stable tautomer of 2- and 4-thiouracil with few water molecules has been examined at B3LYP/6-31+G(d,p) level by Kryachko et al. [12, 31]. The stability order of 2-thiouracil tautomers into aqueous solution was never examined.

For these reasons and taking into account their biological relevance, we have considered it interesting to investigate the tautomeric behavior of 2- and 4-thiouracil in gas phase and mainly in water. Our density functional study, performed using the B3LYP hybrid functional and different basis sets, should represent the first theoretical study in which the five lower lying tautomers of both thiobases are contemporarily investigated at the same level of theory and their behavior compared.

Method

All calculations were carried out using the GAUSSIAN 98 [32] code. Geometry optimizations, without imposing any symmetry constraints, were performed using the Becke [33] and Lee, Yang, and Parr [34] (B3LYP) functional.

Triple-zeta valence (TZVP) all-electron orbital and the corresponding auxiliary [35], 6-31G(d,p) [36], and 6-311++G(d,p) [37] basis sets were employed for the computations. Harmonic vibrational frequencies were computed using

the analytical B3LYP/6-311++G(d,p) second derivatives. The polarizable continuum model (PCM) approach [38, 39] was used for the full optimized calculations in water, employing the same functional and basis sets as in the gas-phase study. The PCM model [38–41] allows one to work with cavities of realistic molecular shape with the surface of the cavity subdivided in small portions (tesserae). The solute–solvent electrostatic interaction is represented by a set of polarization point charges, placed in the center of each tessera.

Results and Discussion

From previous theoretical studies [2, 6, 12, 14, 23–30], only the five lower-lying of the six possible tautomers of the two 2- and 4-thiouracil derivatives were considered in our work: the di-keto (U1), the keto-enol (U2 and U3), and the di-enolic (U4 and U5) forms depicted in Figure 1. Results obtained for the 2- and 4-thiouracil tautomers will be discussed separately.

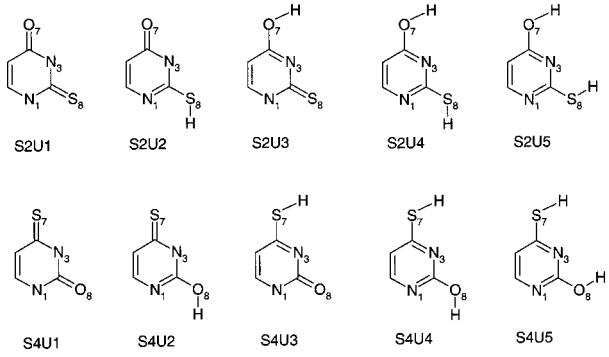

FIGURE 1. Schematic drawing of the 2- and 4-thiouracil tautomers.

2-THIOURACIL

Gas-phase stabilities of the 2-thiouracil tautomers are reported in Table I. The oxo-thione S2U1 and the keto-enol S2U3 tautomers are the most and the less stable ones at all levels of theory, respectively.

In our and in previous studies, it is noteworthy that the relative stability values of S2U2, S2U4, and S2U5 forms fall always in a narrow range of energy.

TABLE I

Gas phase total (in a.u.) and relative energies (ΔE in kcal/mol) at 0 K, for the five tautomers of 2-thiouracil, obtained at B3LYP level with different basis sets.

	S2U1	S2U2	S2U3	S2U4	S2U5
			B3LYP/6-31G(d,p)		
Total energy	−737.695862	−737.679524	−737.676719	−737.679990	−737.680458
ΔE	0.0	10.25	12.01	9.96	9.66
			B3LYP/6-311++G(d,p)		
Total energy	−737.815017	−737.800434	−737.795114	−737.799617	−737.799022
ΔE	0.0	9.15	12.48	9.66	10.03
			B3LYP/TZVP		
Total energy	−737.800577	−737.786839	−737.781602	−737.786888	−737.786252
ΔE	0.0	8.62	11.91	8.58	8.99
			SCF/6-31G(d,p)+MBPT[a]		
ΔE	0.0	8.64	11.93	6.46	—
			B3LYP/6-31+G(d,p)[b]		
ΔE	0.0	9.34	12.03	9.38	9.76
			MP2/6-31G(d)[c]		
ΔE	0.0	9.80	13.6	9.30	9.80

[a] From Ref. [2].
[b] From Ref. [12].
[c] From Ref. [30].

This can be the reason for the slight discrepancies in the stability order obtained by using different basis sets as a consequence of their different reliability in the orbital description. Starting from the B3LYP/6-31(d,p) values, the introduction of only one diffuse function (see B3LYP/6-31+(d,p) of Ref. [12]) produces the "most relevant" changes in the stability order. On the contrary, a different contraction scheme and a further diffuse function introduction [set B3LYP/6-311++(d,p)] leaves the stability order unaffected with respect to that of Kryachko and Nguyen [12]. B3LYP/TZVP data show that S2U2 and S2U4 forms are practically degenerate and, except for the relative position of S2U2, yield results very similar to those of Lamsabhi et al. [30] (see MP2/6-31G* results in Table I). The convergence of our B3LYP/6-311++(d,p) and B3LYP/6-31+(d,p) [12] results allows us to assume, with sufficient confidence, the S2U1 > S2U2 > S2U4 > S2U5 > S2U3 order of stability as the most probable one in gas phase.

The equilibrium geometry of the S2U1 absolute minimum obtained at B3LYP/6-311++(d,p) is reported in Table II. The computed structural parameters are quite in agreement with experimental data [42]. The only remarkable difference can be observed in the case of N3C4 distance that, in all our computations, is longer than that obtained at the Hartree–Fock (HF) level (1.404 Å) [2] and by the experimental measurement [42]. It is worth noting that experimental data are referred to the 2-thiouridine (i.e., the respective nucleoside), and gas-phase theoretical calculations cannot take into account the crystal forces, thus, small differences in the bond lengths are justified. In any case, considering the electronic situation of the S2U1 tautomer, the N3C4 bond should have preferentially a single-bond character. The slight discrepancy can be also ascribed to the fact that experimental measurement is the result of an average length assignable to all the tautomers with very similar stability. Unscaled vibrational frequencies computed at the B3LYP/6-311++G(d,p) level, available upon request from the authors, are slightly smaller (less than the 10%) than the experimental ones [14] and confirm indirectly the reliability of our geometrical parameters.

TABLE II
Optimized geometry of the most stable tautomer (S2U1) of 2-thiouracil at B3LYP/6-311++G(d,p) level in vacuum and in solvent.[a]

Parameter	Gas phase	Water	Exp[b]
N1C2	1.378	1.367	1.368
C2N3	1.369	1.366	1.360
N3C4	1.417	1.407	1.388
C4C5	1.456	1.446	1.435
C5C6	1.345	1.351	1.337
C6N1	1.374	1.371	1.381
C2S8	1.661	1.675	1.677
C4O7	1.214	1.224	1.228
N1C2N3	113.2	114.1	116.0
C2N3C4	128.1	127.3	126.6
N3C4C5	113.4	114.1	114.4
C4C5C6	119.6	119.2	119.5
C5C6N1	121.8	121.8	122.6
C6N1C2	123.8	123.4	120.8
N1C2S8	122.5	122.7	123.4
N3C4O7	120.0	119.5	119.2

[a] Distances are in Å and angles in degrees.
[b] From Ref. [42].

The consideration of the solvent effects can be very important because, sometime, the solvent can introduce significant changes in the molecular structure both in terms of nuclear and electronic distributions. In fact a polar solvent, such as water, has the tendency to displace the tautomeric equilibria so as to increase the population of the most polar tautomer. This effect can reverse the stability order in gas phase.

Dipole moments (μ) of 2-thiouracil tautomers obtained at the various levels of theory are practically the same. Thus, in the course of our discussion, only the B3LYP/6-311++G(d,p) values will be explicitly reported. The results of the calculations performed in water solution for 2-thiouracil tautomers are collected in Table III.

Although the stability orders in solution are different from those in the gas phase, the data show that the S2U1 remains the most stable tautomer, at all levels of theory. The geometry optimization does not introduce sensible changes with respect to the gas-phase structures as can be concluded by the values of geometrical parameters reported in Table II for the most stable S2U1 tautomer.

Aside from the used basis set, the presence of the solvent stabilizes the S2U3 form having the larger dipole moment ($\mu = 5.708$ D) but is not able to reverse the stability of S2U1 ($\mu = 4.746$ D) and S2U3 forms notwithstanding the difference in their dipole values. The contributions of cavitation, repulsion, and dispersion energy are not decisive because they are very similar for all tautomers. The total of non-

TABLE III

Relative stabilities (ΔE in kcal/mol) and free hydration energies (ΔG in kcal/mol) for the five tautomers of 2-thiouracil in water, obtained by the PCM model.

Method	ΔE(S2U1-S2U2)	ΔE(S2U1-S2U3)	ΔE(S2U1-S2U4)	ΔE(S2U1-S2U5)
B3LYP/6-31G(d,p)	17.40	9.13	17.98	19.45
B3LYP/6-311++G(d,p)	15.24	10.11	17.25	17.21
B3LYP/TZVP	17.47	9.02	17.95	18.00
	ΔG(S2U1-S2U2)	ΔG(S2U1-S2U3)	ΔG(S2U1-S2U4)	ΔG(S2U1-S2U5)
B3LYP/6-31G(d,p)	6.02	−4.69	7.51	6.56
B3LYP/6-311++G(d,p)	5.67	−3.71	7.91	6.94
B3LYP/TZVP	6.57	−2.90	7.19	6.80

electrostatic interactions range from 2.05 (S2U1) to 1.70 (S2U2) to 1.89 (S2U3) to 1.52 (S2U4) to 1.54 (S2U5) kcal/mol in the B3LYP/6-311++G(d,p) computations, but it is very similar when the 6-31G(d,p) or TZVP basis sets are used. The large energy difference between the S2U1 and S2U3 isomers in gas phase probably accounts for keeping this stability order.

The 6-31G(d,p) and TZVP basis sets propose the same trend of relative energy with S2U2, S2U4, and S2U5 tautomers all present within 2 kcal/mol. On the contrary, the more extended 6-311++G(d,p) set stabilizes the S2U2 form with respect to the other two, which appear almost degenerate. This latter result seems to be the most reliable, taking into account both the dipole moment values of the three systems [4.746 (S2U2), 1.337 (S2U4), and 2.105 (S2U5) D] and the fact that a net effect of the polar solvent, such as water, is the destabilization of the conformations with intramolecular hydrogen bonds [41]. In S2U4 as well as in S2U5 tautomer, two intramolecular H bonds between the —SH and the —OH groups and the N1 and N3 lone pairs (see Fig. 1) are present, thus, they are the less hydrated forms with free hydration energy values of about 6.5–7.0 kcal/mol lower than that of S2U1 system taken as reference. Only in the case of S2U3 tautomer the free hydration energy assumes a more negative sign with respect ot S2U1 (see Table III).

Our data concerning the stability order in solution cannot be compared with other previous studies because in the work of Kryachko and Nguyen [12] the interaction with the water molecules regards only the most stable tautomer of 2- and 4-thiouracil. In their study, the authors conclude that, although the S4U1 is more stable by 1.67 kcal/mol than S2U1 tautomer in gas phase, and that the situation remains almost the same when these tautomers interact with only one water molecule, their trihydrated complexes have a reversed stability order with the S2U1–$(H_2O)_3$ system, favored by 0.7 kcal/mol over the S4U1–$(H_2O)_3$ one. Extracting the same information from our PCM computations we obtain that the S4U1 tautomer is always more stable than S2U1 both *in vacuo* and in solution, at all levels of theory. The disagreement is certainly due to the different approaches used in the treatment of the interaction with the solvent. While the PCM model does not allow the estimation of the specific interactions with water, on the other hand, a hydration shell consisting of three water molecules cannot be considered as the complete first hydration shell in the thiouracils.

4-THIOURACIL

Gas-phase stabilities of the five 4-thiouracil tautomers are reported in Table IV together with previous theoretical data [2, 12, 28, 30]. A first glance at the table shows that, except for the most S4U1 and the less S4U5 stable systems, our computations give slightly different orders. B3LYP/6-31G(d,p) and B3LYP/TZVP stability trends are quite homogeneous between them, although the TZVP basis set reduces the energy differences among S4U2, S4U3, and S4U4. The 6-311++G(d,p) set gives the same results than the 6-31+G(d,p) [12] one but enhances the energy difference between S4U3 and S4U4 tautomers. The MP2/6-31G(d) data of Lamsabhi

TABLE IV

Gas phase total (in a.u.) and relative energies (ΔE in kcal/mol) at 0 K, for the five tautomers of 4-thiouracil, obtained at various levels of theory.

	S4U1	S4U2	S4U3	S4U4	S4U5
			B3LYP/6-31G(d,p)		
Total energy	−737.698662	−737.682390	−737.678865	−737.679389	−737.678510
ΔE	0.0	10.21	12.42	12.09	12.64
			B3LYP/6-311++G(d,p)		
Total energy	−737.817260	−737.799995	−737.799424	−737.798581	−737.798171
ΔE	0.0	10.85	11.31	11.81	11.98
			B3LYP/TZVP		
Total energy	−737.803622	−737.787195	−737.786380	−737.786504	−737.785573
ΔE	0.0	10.31	10.82	10.74	11.32
			B3LYP/6-31+G(d,p)[a]		
ΔE	0.0	10.30	11.43	11.41	12.00
			MP2/6-31G(d)[b]		
ΔE	0.0	11.2	12.8	11.5	12.1
			MP2/6-31G(d,p)[c]		
ΔE	0.0	10.26	16.59	11.89	—
			MP4(SDQ)/6-311G(2d,2p)//MP2/6-31G(d,p)[c]		
ΔE	0.0	10.39	15.27	12.72	—
			MP2/6-311++G(2d,2p)//MP2/6-31G(d,p)[c]		
ΔE	0.0	9.13	14.19	9.88	—
			SCF/6-31G(d,p)+MBPT[d]		
ΔE	0.0	10.08	11.80	9.10	—

[a] From Ref. [12].
[b] From Ref. [30].
[c] From Ref. [28].
[d] From Ref. [2].

et al. [30] propose a stability order with S4U1 > S4U2 ≈ S4U4 > S4U5 > S4U3. This result differs with respect to all B3LYP calculations, essentially for the relative positions of the latter two tautomers, and is in disagreement with those coming from the previous MP2/6-31G(d,p) optimization and from MPn ($n = 2, 4$)/6-311G(2d,2p)//MP2/6-31G(d,p) single-point computations [28], in the energy difference estimation. As in the case, of 2-thiouracil and because MP2 computations seem to be more influenced by the basis set effect, we can hypothesize that the B3LYP/6-311++G(d,p) order of stability is quite reliable.

The B3LYP/6-311++G(d,p) geometrical parameters of the S4U1 most stable tautomer are reported in Table V. The situation appears to be analogous to that of 2-thiouracil. Again, the structural parameters are well reproduced, except the N3C4 distance, which is considerably longer than the experimental one [44]. The same arguments, as in the case of 2-thiouracil, can be advanced for explaining the disagreement. On the other hand the vibrational frequency for the stretching relative to the N3C4 bond is very close to experimental value (1357 vs. 1344–1350 cm^{-1}, Ref. [14]), although this distance is abundantly overestimated. All other frequencies, available upon request to authors, are in good agreement with the comparison data [12, 14].

In Table VI are collected the relative stabilities (ΔE) and the free hydration energies (ΔG) of

TABLE V
Optimized geometry of the most stable tautomer (S4U1) of 4-thiouracil at B3LYP/6-311++G(d,p) level in vacuum and in solvent.[a]

Parameter	Gas phase	Water	Exp[b]
N1C2	1.391	1.381	1.396
C2N3	1.387	1.385	1.373
N3C4	1.391	1.382	1.349
C4C5	1.441	1.431	1.445
C5C6	1.351	1.356	1.353
C6N1	1.374	1.365	1.372
C2O8	1.211	1.219	1.214
C4S7	1.659	1.675	1.656
N1C2N3	112.9	113.8	114.5
C2N3C4	127.9	127.2	127.7
N3C4C5	114.1	114.8	115.3
C4C5C6	120.1	119.7	119.0
C5C6N1	121.4	121.5	122.2
C6N1C2	123.3	123.0	121.1
N1C2O8	123.1	123.4	123.4
N3C4S7	120.9	120.5	119.2

[a] Distances are in Å and angles in degrees.
[b] From Ref. [44].

the 4-thiouracil tautomers in solution. Dipole moment trends are practically the same in all the three computations, so only B3LYP/6-311++G(d,p) values will be given along the discussion.

The results show that the S4U1 (μ = 4.944 D) species is the most stable one also in solvent. B3LYP/6-31G(d,p) and B3LYP/TZVP full-optimized computations indicate the same stability order for the five tautomers. The only difference in the B3LYP/6-311++G(d,p) order regards the S4U4 (μ = 1.784 D) and S4U5 (μ = 2.281 D) forms, with the first favored over the second by 0.82 kcal/mol. Both these tautomers are characterized by two intramolecular hydrogen bonds and, as in the case of 2-thiouracil, are those less solvated with ΔG values sensibly lower with respect to that of S4U1. Because the dipole moment of S4U5 is higher than that of S4U4, the B3LYP/6-311++G(d,p) result seems to be much more reasonable than our other findings.

The S4U2 (μ = 4.138 D) tautomer keeps the same stability order as in the gas phase at all levels of theory, while the S4U3 (μ = 5.299 D) system gains a position in both B3LYP/6-31G(d,p) and B3LYP/TZVP computations. The ΔG value for S4U3

TABLE VI
Relative stabilities (ΔE in kcal/mol) and free hydration energies (ΔG in kcal/mol) for the five tautomers of 4-thiouracil in water, obtained by the PCM model.

Method	ΔE(S4U1-S4U2)	ΔE(S4U1-S4U3)	ΔE(S4U1-S4U4)	ΔE(S4U1-S4U5)
B3LYP/6-31G(d,p)	9.86	15.65	18.92	21.09
B3LYP/6-311++G(d,p)	10.41	13.60	17.89	17.07
B3LYP/TZVP	11.38	13.53	18.20	19.25
MP4(SDQ)/6-311G(2d,2p)// MP2/6-31G(d,p) (SCI-PCM)[a]	12.02	18.13	20.28	—
MP4(SDQ)/6-311G(2d,2p)// MP2/6-31G(d,p) (AM1-SM2)[a]	13.11	13.16	18.58	—
MP2/6-311++G(2d,2p)// MP2/6-31G(d,p) (SCI-PCM)[a]	10.76	17.05	17.44	—
MP2/6-311++G(2d,2p)// MP2/6-31G(d,p) (SCI-PCM)[a]	11.84	12.08	15.74	—
	ΔG(S4U1-S4U2)	ΔG(S4U1-S4U3)	ΔG(S4U1-S4U4)	ΔG(S4U1-S4U5)
B3LYP/6-31G(d,p)	−0.49	0.65	6.99	6.36
B3LYP/6-311++G(d,p)	−0.12	−0.19	6.24	6.22
B3LYP/TZVP	−1.96	2.72	5.20	6.08
MP4(SDQ)/6-311G(2d,2p)// MP2/6-31G(d,p) (AM1-SM2)[a]	2.72	−2.11	5.86	—
MP4(SDQ)/6-311G(2d,2p)// MP2/6-31G(d,p) (SCI-PCM)[a]	1.63	2.86	7.56	—

[a] From Ref. [28].

is the most negative accordingly to the dipole moment trend.

The geometry optimization leaves the structural parameters of tautomers practically unchanged with respect to those obtained in vacuum. Furthermore the contributions due to nonelectrostatic interactions are much smaller than the ΔG values and very similar for all tautomers [2.12 (S4U1), 1.80 (S4U2), 1.72 (S4U3), 1.54 (S4U4), and 1.52 (S4U5) kcal/mol]; thus, they cannot decide the reversal of the stability trend. For these reasons, the stability order in water of the first three tautomers should be essentially conditioned by the energy differences in gas phase.

The B3LYP/6-311++G(d,p) geometrical parameters of the most stable S4U1 tautomer in solution are reported in Table V. Differences of less than 0.02 Å for bond lengths and 1.0° for valence angles are found in going from gas to condensed phase.

B3LYP results are in agreement with all the previous theoretical data reported in Table VI. However, it should be emphasized that the MPn ($n = 2, 4$) values concerning the S4U3 system are referred to a tautomer in which the N3C4O7H torsion (see Fig. 1) is 180° [28]. This means that the stability of S4U3 species, in the MPn computations, is estimated without the hydrogen bond contribution. Because normally the intramolecular hydrogen bonds play a significant role in the stabilization of a molecule, it is possible that taking into account this interaction, the order of stability between S4U3 and S4U2 can be influenced.

Conclusions

In this work we have studied the tautomeric equilibria of the 2- and 4-thiouracil derivatives both in gas phase and in solution employing the hybrid B3LYP functional and different basis sets. On the basis of the obtained results the following conclusions can be drawn:

1. All computations indicate the di-keto (U1) tautomer as the most stable and perhaps the unique form existing in the gas phase and in water for both 2- and 4-thiouracil systems. This observation suggests that mutations should not depend on the presence of unusual enol forms but on other circumstances and in particular on the different stability of the hydrogen bonds and the structural changes introduced by the sulfur atom.
2. The S4U1 species is more stable than S2U1 in both phases, and all other tautomers of 4-thiouracil appear to be better hydrated than those of 2-thiouracil.
3. The order of stability of tautomers depends on the basis set, especially in the presence of degenerate systems. The convergence of the data is obtained in correspondence with the 6-311++G(d,p) basis set from which we think to derive out best proposal for the stability trends.
4. The solvent effects modify partially the stability order of tautomers with respect to that in gas phase in the sense that only the enol forms are interested in the phenomenon. The energy differences in water of the U2, U3, U4, and U5 tautomers of both 2- and 4-thiouracils with respect to the U1 one become greater than those in gas phase, underlying a major difficulty to the tautomerism in this medium. The results do not depend on the very small variation of the geometrical structures but are substantially in line with dipole moment trends and with the pre-existent energetic situation in the gas phase.
5. The geometrical parameters and the harmonic vibrational frequencies are well reproduced.

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