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Electronic Transitions of Thiouracils in the Gas Phase and in Solutions: Time-Dependent Density Functional Theory (TD-DFT) Study

M. K. Shukla and Jerzy Leszczynski*

*Computational Center for Molecular Structure and Interactions, Department of Chemistry,
Jackson State University, Jackson, Mississippi 39217*

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Comprehensive theoretical investigations were performed on the electronic singlet and triplet $\pi\pi^*$ and $n\pi^*$ transition energies of 2-thiouracil, 4-thiouracil, 2,4-dithiouracil, and their methyl derivatives in the gas phase and in water and acetonitrile solutions. The computed results were compared with the corresponding properties of uracil. The ground state geometries of different tautomers were optimized at the B3LYP level with use of the 6-311++G(d,p) basis set. Single point energy calculations were performed at the MP2/cc-pVTZ level by using the B3LYP/6-311++G(d,p) geometries. Geometry optimizations for the most stable tautomers of each species were also performed at the MP2/cc-pVTZ level. Vertical electronic transition energies were computed at the time-dependent density functional theory level (TD-DFT), using the B3LYP functional and the 6-311++G(d,p) basis set and utilizing the B3LYP/6-311++G(d,p) geometries. The effects of water and acetonitrile solutions on the ground and excited states were computed by using the Polarizable Continuum Model (PCM). Computed electronic transition energies were found to be in good agreement with the corresponding experimental data. It was found that thiouracils would exist mainly in the keto-thione tautomeric form in the gas phase and in solutions. The similarity and differences with uracil are also discussed.

1. Introduction

The knowledge about the structure and function of biopolymers requires detailed information not only for their constituents but also for their substituted analogues since these substituted analogues are also found in some natural biopolymers or they can be formed under certain conditions, e.g., change in environment, UV radiation. Further, substituted analogues can also be used in different important applications such as a probe in studying the dynamics of biopolymers, drugs against diseases; on the other hand they can be lethal since they may disrupt the helical structure and may cause mutation.[1] Structure and functions of nucleic acid bases (NABs) are significantly modified by the incorporation of a heavier analogue of oxygen such as sulfur and selenium.[2] The thio substitutions of NABs are subjected to several experimental[3] and theoretical investigations[4] due to their therapeutic and other biological importance. Although the thio-substituted bases have the same distribution of hydrogen bond donors and acceptors as the standard bases, the sulfur atom induces the change in the property and interaction of bases due to the fact that it is heavier and a weaker hydrogen bond acceptor than the oxygen atom.[5] Interestingly, the 6-thioguanine is suggested to block the formation of G tetrads in the guanine-rich oligodeoxyribonucleotides. However, the formation of G.GC triple helixes is not destabilized by the thioguanine.[6] Further, hydration of guanine around the carbonyl group is destabilized when the oxygen is replaced by a sulfur atom.[7]

Significant change in the photophysical property of molecules is also revealed when the carbonyl groups are substituted by thiocarbonyl groups. Consequently, the lowest singlet $\pi\pi^*$ and $n\pi^*$ states of thiocarbonyl-containing molecules have significantly lower energy than the corresponding carbonyl-containing molecules.[8] The thio analogues of uracil, namely, 2-thiouracil (2TU), 4-thiouracil (4TU), and 2,4-dithiouracil (DTU), have also been found to possess notable biological and pharmacological activities. Thiouracils can be used as anticancer and antithyroid drugs.[1] The investigation of t-RNA shows the presence of a small amount of thiouracil.[9] The 4-thio-substituted analogues of dUMP are known as good substrates of thymidilate synthase.[10] They are used as the cross-linking agents in RNA transcriptional regulation and are known to exhibit cytostatic activity.[11]

The thio analogues of uracil, namely, 2TU, 4TU, and DTU, have been the subject of several experimental and theoretical studies.[3a,5a,b,12] A comprehensive analysis of the experimental and theoretical investigations of thiouracils can be found in a recent review article.[3a] All theoretical investigations have suggested that these molecules exist in the keto-thione (dithione in the case of DTU) form, both in the gas phase and in aqueous solution. In the crystalline environment these molecules were also found to be in the keto-thionic tautomeric form.[13] Rostkowska et al.[5a] on the basis of low-temperature IR spectroscopic and ab initio theoretical investigations on thiouracils and their N1 and N3 methyl derivative have shown that these species exist in the keto-thione tautomeric form. Rubin et al.[14] on the basis of the results of ab initio theoretical and electronic absorption and emission experimental investigations on 4TU have predicted that the molecule exists in the keto-thione form in the aqueous medium; however, in an ethanol solution, the occurrence of the minor tautomeric form (thiol or enol obtained by involving the N1 or N3 hydrogen on the sulfur or oxygen atom) has also been suggested. Lamsabhi et al.[15] have studied the gas-phase proton affinity of 2TU, 4TU, and DTU using Fourier transform ion cyclotron resonance (FTICR) mass spectrometry and the G2(MP2) level of theoretical calculations. It was revealed that thiouracils are moderate bases with almost

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* Corresponding author. E-mail: jerzy@ccmsi.us.

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equal strength (DTU has the lowest strength among thiouracils) and protonation takes place at the atom attached to C4 in all thiouracils. Milder and Kliger[16] by performing the photolysis of 4-thiouridine (4TUrd), 1,3-dimethyl-4-thiouracil (DMTU), and uracil (U) have shown that quenching of the lowest triplet state of 4TUrd and DMTU by quenchers is due to the electron-transfer process. Further, it was also revealed that phosphorescence in 4TUrd originates from the thione tautomeric form. Marino et al.[5b] have performed a theoretical study on tautomeric stability of 2TU and 4TU in the gas phase and in aqueous solution at the B3LYP level using 6-31G(d,p), 6-311++G(d,p) and TZVP basis sets. On the basis of these calculations the keto-thione tautomeric form of 2TU and 4TU was found to be the most stable in the gas phase and in aqueous solution.

Igarashi-Yamamoto et al.[17] have performed extensive experimental electronic absorption, circular dichroism (CD), and magnetic circular dichroism (MCD) spectroscopic investigations on 2TU, 4TU, DTU, and their substituted analogues in the aqueous and acetonitrile solutions. They have found that although 4TU exists only in the keto-thione tautomeric form, for 2TU and DTU the observed experimental transitions were explained in terms of the thione-thiol tautomeric forms. Based on the NMR investigation of 2TU in the deuterated dimethyl sulfoxide solution, Kokko et al.[18] have suggested that the molecule exists in the thiol form. On the other hand all theoretical calculations[3a,5a,b,14] and X-ray crystallographic investigations[13] suggest that thiouracils should exist in only the keto-thionic tautomeric form in the gas phase and in aqueous solution. Further, there are some contradictory opinions regarding the nature of the lowest triplet state of thiouracils. Salet et al.[19] have suggested that the $n\pi^*$ state is the lowest triplet state in the case of 4TUrd. On the other hand Taherian and Maki[20] on the basis of optically detected magnetic resonance (ODMR) study on 1-methyl-2-thiouracil, 1-methyl-4-thiouracil, and 1-methyl-2,4-dithiouracil and Milder and Kliger[16] on the basis of a laser photolysis study on uracil, 4-thiouridine, and 1,3-dimethyl-4-thiouracil in different solvents along with INDO/S calculations have suggested that the lowest triplet state of thiouracils is of the $\pi\pi^*$ type. The MCQDPT2/MCSCF level of theoretical calculation also indicated that the $\pi\pi^*$ state is the lowest triplet state in 4TU.[21]

In view of the above-discussed inconsistencies, we have performed a time-dependent density functional theory investigation on thiouracils and selected methyl derivatives in the gas phase and in aqueous and acetonitrile solutions to shed some light on the tautomeric properties and on the nature of the lowest triplet state of titled molecules.

2. Computational Details

Ground-state geometries of uracil, 2TU, 4TU, DTU, thiol tautomeric forms, and methyl derivatives of thiouracils and the anionic form of DTU were optimized at the B3LYP level of theory by using the 6-311++G(d,p) basis set. Single point energy calculations and geometry optimizations were also performed at the MP2 level with the cc-pVTZ basis set. The electronic vertical singlet and triplet transition energies were computed by using the time-dependent density functional theory (TD-DFT) method and the 6-311++G(d,p) basis set employing the B3LYP functional and B3LYP/6-311++G(d,p) geometries. The effects of aqueous and acetonitrile solvations on the relative stability of tautomers and on the electronic transition energies were modeled with use of the PCM model.[22] All theoretical calculations were performed with the Gaussian 03 program.[23] The molecular orbitals were visualized with the MOLEKEL program.[24]

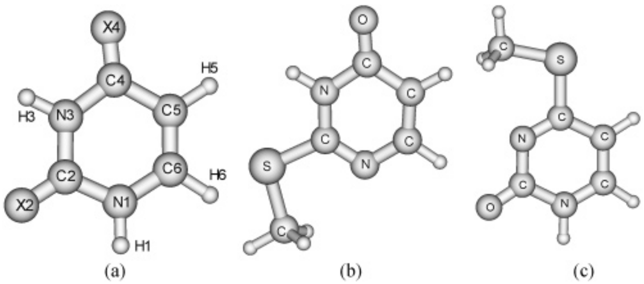

Figure 1. General structure and atomic numbering scheme of uracil (X2 = X4 = O), 2TU (X2 = S, X4 = O), 4TU (X2 = O, X4 = S), and DTU (X2 = X4 = S) (a), structure of 2MTU (b), and structure of 4MTU (c). The N1 and N3 methyl derivatives can be obtained by the substitution of a methyl group at the relevant site of the corresponding molecule.

3. Results and Discussion

The ground-state geometry optimizations and subsequent vertical singlet and triplet transition energy calculations were performed for uracil and thiouracils (2TU, 4TU, DTU). To resolve the existing ambiguity regarding the possibility of occurrence of the thiol tautomeric form of thiouracils in aqueous media, different methyl derivatives and thiol tautomeric forms were also studied and computed transition energies were compared with those for the corresponding tautomeric form. The atomic numbering schemes and general structure of molecules are shown in Figure 1. The nomenclature TU-SmHn (or TU-OmHn) refers the thiol tautomeric form of TU where the Hn hydrogen is attached to the Sm (Om) atom. Since the ground-state properties of thiouracils have been discussed already by several researchers in detail,[3a,5a,12−15] we will describe ground-state properties only very briefly.

3.1. Ground-State Properties. It is established from the theoretical and experimental investigations that 4TU exists only in the keto-thione tautomeric form in the gas phase and in water solution.[3a,5a,b,14,17] Therefore, we have studied tautomeric stability of only 2TU and DTU in the gas phase and in water and acetonitrile solutions. The relative stability of different tautomers of 2TU and DTU in the gas phase and in water and acetonitrile solutions at the B3LYP/6-311++G(d,p) and MP2/cc-pVTZ//B3LYP/6-311++G(d,p) levels is shown in Table 1. It is evident from this table that the keto-thione (dithione for DTU) form of both molecules is the most stable in the gas phase and in solutions. Given the high relative energy of other tautomers it is unlikely that minor tautomers would be present in the gas phase and in solutions in significant amounts (Table 1). This result is also in agreement with other theoretical results.[3a,5b,14,15]

The computed rotational constants and dipole moment of thiouracils and uracil in the gas phase at the B3LYP/6-311++G(d,p) and MP2/cc-pVTZ levels are presented in Table 2. The experimental data for rotational constants (shown in Table 2) are available only for uracil and were obtained by using microwave spectroscopy.[25] It should be noted that the experimental rotational constants for TU are not yet available. The experimental dipole moments of TU are also shown in Table 2. It is evident from Table 2 that the computed rotational constants of uracil at the B3LYP and MP2 levels are in very good agreement with the corresponding experimental data. However, comparing theoretical results with the experimental data, one can find that B3LYP computed results are better than the MP2 results with regard to the rotational constants of uracil.

The Stark effect measurements have predicted that the uracil dipole moment would be 3.87 D[25] while in dioxane solution it is measured as 4.16 D.[26] The experimental dipole moments of

TABLE 1: Relative Total Energy (kcal/mol) of Tautomers of 2TU and DTU in the Gas Phase and in Water and Acetonitrile Solutions Obtained at the B3LYP/6-311++G(d,p) and MP2/cc-pVTZ//B3LYP/6-311++G(d,p) Levels

	B3LYP			MP2//B3LYP[a]		
molecule/tautomer	gas	water	acetonitrile	gas	water	acetonitrile
2TU (keto-thione)	0.0	0.0	0.0	0.0	0.0	0.0
2TU-S2H1	11.65	15.16	15.09	10.34	12.56	11.89
2TU-S2H3	20.56	17.64	17.74	19.33	18.61	17.47
2TU-O4H3	12.69	10.35	10.43	11.26 (11.2)	8.64 (8.64)	9.46
DTU (keto-thione)	0.0	0.0	0.0	0.0	0.0	0.0
DTU-S2H1	11.00	13.89	13.88	9.39	10.41	10.65
DTU-S2H3	20.85	16.96	17.18	19.73	18.42	17.45
DTU-O4H3	14.03	12.75	12.78	13.14	13.27	11.95

[a] Values in parentheses correspond to the MP2/cc-pVTZ geometry.

TABLE 2: Computed Rotational Constants (*A*, *B*, *C*, all in MHz) and Dipole Moments (μ, in D) of Uracil and Thiouracils at the B3LYP/6-311++G(d,p) and MP2/cc-pVTZ Levels

parameters	B3LYP	MP2	experiment[a]
	uracil		
A	3885.40	3907.01	3883.87825(110)
B	2012.72	2018.72	2023.73267(101)
C	1325.89	1331.00	1330.92380(60)
μ	4.58	4.18	4.16, 3.87
	2-thiouracil		
A	3556.06	3569.76	
B	1301.98	1313.61	
C	953.04	960.25	
μ	4.75	4.42	4.21
	4-thiouracil		
A	3573.44	3591.24	
B	1293.92	1304.45	
C	949.95	956.88	
μ	4.95	4.56	4.47
	2,4-dithiouracil		
A	2857.42	2876.86	
B	947.85	957.83	
C	711.75	718.58	
μ	4.93	4.61	4.67

[a] For the experimental rotational constant of uracil see ref 25, for the dipole moment of uracil see refs 25 and 26, for the dipole moment of thiouracils see ref 27.

2TU, 4TU, and DTU are found to be 4.21, 4.47, and 4.67 D, respectively, in the dioxane solution.[27] Our computed dipole moments for uracil, 2TU, 4TU, and DTU are 4.18, 4.42, 4.56, and 4.61 D at the MP2/cc-pVTZ level and 4.58, 4.47, 4.95, and 4.93 D at the B3LYP/6-311++G(d,p) level, respectively. Therefore, the MP2/cc-pVTZ computed dipole moments are in very good agreement with the corresponding experimental dipole moment obtained in dioxane solution. Surprisingly, for uracil the computed dipole moment is not in as good agreement with the gas-phase data obtained by using Stark effect technique as that obtained in the dioxane solution (Table 2). Comparing computed and experimental dipole moments, one can find that MP2 results are better than the B3LYP values for compounds studied in the present work. Since experimental data for rotational constants of thiouracils are not available and given the good agreement between the experimental and theoretical data discussed earlier, we believe that our computed rotational constants would be reliable and may provide an alternative to experimental results.

3.2. Singlet Electronic Transitions. Vertical singlet and triplet transition energies of thiouracils and uracil were computed at the time-dependent density functional theory (TD-DFT) level by using the B3LYP functional and the 6-311++G(d,p) basis set in the gas phase and in the aqueous and acetonitrile solutions by using the ground-state optimized geometries at the B3LYP/6-311++G(d,p) level. These transition energies ($\pi\pi^*$ and nπ^*) are shown in Tables 3−6. It should be noted that in these tables, some transitions are shown to be contaminated with Rydberg transitions. Generally, electronic spatial extent ($\langle R^2 \rangle$) values are used to identify the Rydberg states. The $\langle R^2 \rangle$ values for Rydberg states are larger than that in the ground and valence excited states. The $\langle R^2 \rangle$ values for the ground and valence excited states are similar. Since implementation of the TDDFT method in Gaussian 03 is limited to the calculation of transition energies only, we have characterized different states by the visualization of orbitals using the MOLEKEL program.[24] The percent contribution of Rydberg character in a state was calculated by taking the summation of the squire of the coefficient of the wave function of each excitation and then calculating the percent contribution of Rydberg character of the relevant orbital excitation of that state. If the Rydberg contribution was found to be more than 30%, we have indicated those transitions as Rydberg contaminated in the tables. We will discuss each molecule separately.

3.2.1. 2-Thiouracil. Computed vertical singlet and triplet $\pi\pi^*$ and nπ^* transition energies of 2TU, 1-methyl-2-thiouracil (1M2TU), 2-methylthiouracil (2MTU), 3-methyl-2-methylthiouracil (3M2MTU), and thiol forms of 2TU are presented in Table 3 along with the corresponding experimental transition energies. In this table, the computed electronic transitions of 2TU in water and acetonitrile solutions are explained in terms of the experimental transitions of 2TU and 2-thiouridine (2TUrd) in water and in acetonitrile.[17] It is clear from the table that the computed singlet $\pi\pi^*$ transition energies are in good agreement with the corresponding experimental data of 2TU and 2TUrd. The calculation predicted that the third singlet $\pi\pi^*$ transition in the 5.3−5.4 eV region would be very weak. This prediction is also in good agreement with the experimental observation that a transition in the range of 5.1−5.3 eV is only observed in the MCD spectra of 2TU and 2TUrd.[17] Further, in view of the agreement between the theoretical and experimental data of 2TU, it is clear that the first singlet $\pi\pi^*$ transition of 2TU and 2TUrd does not belong to the thiol form of the molecule as suggested in earlier experimental work.[17] The nπ^* transitions of 2TU shown in Table 3 are localized at the thiocarbonyl group. Our calculations predict that the lowest singlet nπ^* transition of 2TU in water and in acetonitrile solutions would be near 3.9 eV. This prediction is also in good agreement with the experimental observation of an nπ^* transition in the range of 3.7−3.8 eV in the CD and MCD spectra of 2TUrd in water and acetonitrile solutions.[17]

The computed electronic transitions of 1M2TU are explained in terms of the experimental data of 2TUrd. Theoretical calculation predicts a very weak transition near 5.25 eV in the water and acetonitrile solutions. In the experimental study, only

TABLE 3: Electronic Transition Energies (Δ*E*, eV) and Oscillator Strength (*f*) of 2TU, 1M2TU, 2MTU, and 3M2MTU and Thiol Tautomeric Forms of 2TU in the Gas Phase and in Water and Acetonitrile (ACN) Solutions

	theoretical						experimental Δ*E*[a]									
	gas		W		ACN		W		ACN		W_{2TUrd}			ACN_{2TUrd}		
state	Δ*E*	*f*	Δ*E*	*f*	Δ*E*	*f*	Abs	MCD	Abs	MCD	Abs	CD	MCD	Abs	CD	MCD
2TU																
S1(ππ*)	4.08	0.0506	4.33	0.1445	4.32	0.1443	4.22	4.28	4.25	4.25	4.34	4.34	4.25	4.30	4.28	4.28
S2(ππ*)	4.87	0.3146	4.81	0.3638	4.81	0.3659	4.52	4.71	4.63	4.64	4.51	4.59	4.68	4.63	4.61	4.68
S3(ππ*)	5.27	0.0084	5.40	0.0026	5.40	0.0026		5.32		5.10			5.12			5.08
S4(ππ*)	6.15[b]	0.2434	6.05[b]	0.4048	6.05[b]	0.4039	5.85				5.66	5.61	5.74	5.69	5.69	5.64
S1(nπ*)	3.58	0.0	3.91	0.00	3.90	0.0						3.81	3.72		3.71	
S2(nπ*)	4.14	0.0001	4.50	0.0002	4.49	0.0002										
T1(ππ*)	3.00		3.24		3.23											
T2(ππ*)	3.54		3.71		3.70											
T1(nπ*)	3.35		3.70		3.69											
T2(nπ*)	4.00		4.40		4.39											
1M2TU																
S1(ππ*)	4.12	0.0665	4.31	0.1465	4.31	0.1459	4.22	4.28	4.25	4.25	4.34	4.34	4.25	4.30	4.28	4.28
S2(ππ*)	4.95	0.2807	4.88	0.3308	4.88	0.3337	4.52	4.71	4.63	4.64	4.51	4.59	4.68	4.63	4.61	4.68
S3(ππ*)	5.12	0.0313	5.26	0.0059	5.25	0.0062		5.32		5.10			5.12			5.08
S4(ππ*)	6.04	0.3376	5.93	0.4448	5.93	0.4435	5.85				5.66	5.61	5.74	5.69	5.69	5.64
S1(nπ*)	3.54	0.0001	3.82	0.0001	3.81	0.0001						3.81	3.72		3.71	
S2(nπ*)	4.16	0.0	4.43	0.0	4.42	0.0										
2MTU																
S1(ππ*)	4.52	0.2125	4.50	0.2650	4.49	0.2669	4.34	4.59	4.28	4.34						
S2(ππ*)	5.28	0.0087	5.34	0.0019	5.34	0.0018	5.08	5.08	5.23	5.21						
S3(ππ*)	5.77	0.1032	5.61	0.1559	5.61	0.1552	5.39		5.58							
S1(nπ*)	4.72	0.0001	5.09	0.0001	5.08	0.0001										
S2(nπ*)	5.15	0.0003	5.21	0.0003	5.20	0.0003										
3M2MTU																
S1(ππ*)	4.51	0.1920	4.50	0.2561	4.50	0.2575	4.28	4.34								
S2(ππ*)	5.35	0.0262	5.37	0.0082	5.37	0.0087	5.21	5.14								
S3(ππ*)	5.73	0.0757	5.60	0.1203	5.60	0.1200	5.58									
S1(nπ*)	4.79	0.0	5.05	0.0	5.04	0.0										
S2(nπ*)	5.15	0.0003	5.24	0.0004	5.23	0.0004										
2TU-O4H3																
S1(ππ*)	3.36	0.0089	3.99	0.0366	3.97	0.0358										
S2(ππ*)	4.49[b]	0.1453														
S3(ππ*)	4.65[b]	0.2501	4.60	0.4912	4.59	0.4942										
S4(ππ*)	5.95	0.0916	5.97	0.0814	5.97	0.0907										
2TU-S2H1																
S1(ππ*)	4.58	0.1847	4.60	0.2589	4.60	0.2602	4.28	4.34								
S2(ππ*)	5.61	0.0369	5.58	0.0098	5.58	0.0105	5.21	5.14								
S3(ππ*)	5.84	0.1098	5.68	0.1566	5.69	0.1570	5.58									
2TU-S2H3																
S1(ππ*)	5.07	0.0311	5.16	0.0567	5.16	0.0582										
S2(ππ*)	5.53	0.0054	5.60	0.0016	5.60	0.0018										
S3(ππ*)	5.66	0.1127	5.39	0.1951	5.39	0.1921										

[a] For singlet transition energies see ref 17. Abs = absorption, CD = circular dichroism, MCD = magnetic circular dichroism, W_{2TUrd} = 2-thiouridine in water, ACN_{2TUrd} = 2-thiouridine in acetonitrile. [b] Rydberg contamination.

MCD spectra of 2TUrd showed a transition near 5.1 eV in water and acetonitrile solutions.[17] Therefore, our theoretical prediction is in good agreement with the experimental data in this regard. In general, there is good agreement between the computed and experimental data (Table 3). This agreement is generally somewhat better than those between the theoretical data of 2TU and the experimental transitions of 2TUrd discussed earlier. Further, the computed transition energies of 2TU and 1M2TU are generally similar; the methyl substitution at the N1 site of 2TU has generally little effect on the transition energies. Comparison of the computed singlet ππ* transition energies of 3M2MTU with the corresponding experimental data also reveals the good agreement (Table 3).

Theoretically, 2MTU can possess two tautomers depending upon whether hydrogen is attached at the N1 or N3 site. Further, these tautomers are structurally similar to the 2TU-S2H3 and 2TU-S2H1 thiol tautomeric forms of 2TU. It is evident from Table 1 that the 2TU-S2H1 tautomeric form is more stable than the 2TU-S2H3 form in the ground state both in the gas phase and in water and acetonitrile solutions. Therefore, it is expected that the N3H tautomeric form of 2MTU would be more stable than the N1H tautomer. Computed singlet ππ* transition energies of 2MTU (N3H form) were compared with corresponding transition energies of the 2MTU. There is good agreement between the theoretical and experimental data (Table 3). The TD-DFT calculation of the 2TU-S2H1 thiol tautomeric form in aqueous medium shows singlet ππ* transitions near 4.6, 5.58, and 5.68 eV while for 2TU-S2H3 in aqueous medium the corresponding transitions are predicted to be near 5.16, 5.4, 5.60, and 5.82 eV. The computed transitions of 2TU-S2H1 and

TABLE 4: Electronic Transition Energies (ΔE, eV) and Oscillator Strength (f) of 4TU, 1M4TU, 4MTU, and 1M4MTU in the Gas Phase and in Water and Acetonitrile (ACN) Solutions

	theoretical						experimental ΔE^a									
	gas		W		ACN		W		ACN		W_{4TUrd}			ACN_{4TUrd}		
state	ΔE	f	ΔE	f	ΔE	f	Abs	MCD	Abs	MCD	Abs	CD	MCD	Abs	CD	MCD
4TU																
S1($\pi\pi^*$)	4.20	0.2976	4.16	0.4372	4.15	0.4397	3.78	3.84	3.79	3.81	3.75	3.59	3.78	3.75	3.72	3.72
S2($\pi\pi^*$)	4.82	0.0076	4.91	0.0346	4.91	0.0331		4.68		4.68		4.61	4.73		4.59	4.64
S3($\pi\pi^*$)	5.12	0.1237	5.23	0.0611	5.22	0.0623	5.08	5.32	5.02		5.08	5.34		5.06	5.32	5.39
S1(nπ^*)	2.78	0.0	3.20	0.0	3.19	0.0									3.10	
S2(nπ^*)	4.61	0.0004	5.04	0.0005	5.02	0.0005										
T1($\pi\pi^*$)	2.37		2.68		2.67						2.29					
T2($\pi\pi^*$)	3.76		3.87		3.87						3.03					
T1(nπ^*)	2.47		2.95		2.93											
T2(nπ^*)	4.54		4.98		4.97											
1M4TU																
S1($\pi\pi^*$)	4.08	0.3322	4.07	0.4843	4.06	0.4860	3.78	3.84	3.79	3.81	3.75	3.59	3.78	3.75	3.72	3.72
S2($\pi\pi^*$)	4.82	0.0082	4.90	0.0260	4.89	0.0247		4.68		4.68		4.61	4.73		4.59	4.64
S3($\pi\pi^*$)	4.99[b]	0.0380	5.14	0.0832	5.13	0.0849	5.08	5.32	5.02		5.08	5.34		5.06	5.32	5.39
S4($\pi\pi^*$)	5.03[b]	0.1169														
S1(nπ^*)	2.81	0.0001	3.20	0.0001	3.19	0.0001									3.10	
S2(nπ^*)	4.56	0.0003	4.98	0.0004	4.97	0.0004										
4MTU																
S1($\pi\pi^*$)	4.46	0.1120	4.50	0.2645	4.50	0.2625	4.15	4.22								
S2($\pi\pi^*$)	4.64	0.1432	4.86	0.1050	4.85	0.1069	4.64	4.59								
S3($\pi\pi^*$)	5.66	0.0366	5.62	0.0386	5.62	0.0379	5.56	5.46								
S1(nπ^*)	4.41	0.0015	4.73	0.0024	4.70	0.0024										
S2(nπ^*)	4.90	0.0004	5.46	0.0001	5.43	0.0001										
1M4MTU																
S1($\pi\pi^*$)	4.41	0.1881	4.44	0.3180	4.44	0.3158	4.09	4.15								
S2($\pi\pi^*$)	4.66	0.1032	4.86	0.0872	4.85	0.0885	4.59	4.56								
S3($\pi\pi^*$)	5.59	0.0429	5.54	0.0466	5.54	0.0461	5.58	5.32								
S1(nπ^*)	4.48	0.0014	4.78	0.0023	4.75	0.0022										
S2(nπ^*)	4.92	0.0005	5.41	0.0001	5.37	0.0001										

[a] For singlet transition energies see ref 17, for triplet transition energies see ref 16. Abs = absorption, CD = circular dichroism, MCD = magnetic circular dichroism, W_{4TUrd} = 4-thiouridine in water, ACN_{4TUrd} = 4-thiouridine in acetonitrile. [b] Rydberg contamination.

2TU-S2H3 can be compared with the experimental transitions of 2MTU. The experiment suggests that 2MTU in water solution would have absorption near 4.34, 5.08, and 5.39 eV.[17] Therefore, the computed transition of 2TU-S2H1 is in good agreement with the experimental data of 2MTU (Table 3). On the other hand computed transition energies of the 2TU-S2H3 tautomer are not in agreement with the experimental data of 2MTU. Therefore, we conclude that in aqueous media, 2MTU exists in the N3H tautomeric form. This assertion is also confirmed from the fact that computed transition energies of 2TU-S2H1 are also in good agreement with the corresponding experimental data of 3M2MTU near 4.28, 5.21, and 5.58 eV in an aqueous solution (Table 3).

3.2.2. 4-Thiouracil. Computed vertical singlet and triplet $\pi\pi^*$ and nπ^* transition energies of 4TU, 1-methyl-4-thiouracil (1M4TU), 4-methylthiouracil (4MTU), and 1-methyl-4-methylthiouracil (1M4MTU) are presented in Table 4 along with the corresponding experimental data. Computation predicted singlet $\pi\pi^*$ transitions in water for 4TU near 4.16, 4.91, and 5.23 eV, for 1M4TU near 4.07, 4.90, and 5.14 eV, for 4MTU near 4.50, 4.86, and 5.62 eV, and for 1M4MTU near 4.44, 4.86, and 5.54 eV. Computed transition energies of 4TU, 1M4TU, 4MTU, and 1M4MTU in acetonitrile solution are generally similar to those of corresponding transition energies obtained in the water (Table 4). The absorption, CD, and MCD spectra of 4TU and 4TUrd in water and acetonitrile solutions have shown that the singlet $\pi\pi^*$ transition energies are generally in the 3.8, 4.7, and 5.1−5.3 eV region (Table 4).[17] Further, the experimental transition energies of 4MTU are found near 5.2, 4.6, and 5.6 eV and for 1M4MTU near 4.1, 4.6, and 5.6 region (Table 4).[17] Therefore, the computed transition energies of 4TU, 1M4TU, 4MTU, and 1M4MTU are generally in good agreement with the corresponding experimental data except for the first singlet $\pi\pi^*$ transition for which the theoretical error is a bit large. However, it should be noted the theoretical error is predicted consistently for all molecules shown in Table 4. Igarashi-Yamamoto et al.[17] have reported the existence of a weak CD band near 3.1 eV (400 nm) in 4TUrd in an acetonitrile solution that was assigned as due to the nπ^* transition. Our calculation predicted a vertical singlet nπ^* transition in the 3.2 eV region in water and acetonitrile solutions for 4TU and 1M4TU, which is in good agreement with the experimental data (Table 4). Further, computed nπ^* transitions are localized at the thiocarbonyl group of the molecule.

3.2.3. 2,4-Dithiouracil. Computed electronic transitions of DTU, 1-methyl-2,4-dithiouracil (1MDTU), and thiol tautomers of DTU are shown in Table 5 along with the corresponding experimental data. Experimentally, the spectral profile of DTU is complicated and solvent dependent.[17] In an aqueous solution, DTU shows two absorption peaks near 3.53 (351 nm) and 4.40 eV (282 nm). However, in the acetonitrile solution three absorption peaks near 3.53 (351 nm), 4.32 (287 nm), and 5.28 eV (235 nm) were obtained.[17] The observed spectral transitions in water and acetonitrile solutions were explained in terms of the thione-thiol tautomeric forms of DTU.[17] The speculation about the existence of the thione-thiol tautomerism was based on the MCD spectra of the compound near 238 nm, which

TABLE 5: Electronic Transition Energies (Δ*E*, eV) and Oscillator Strength (*f*) of DTU, 1MDTU, Thiol, and Anionic Forms of DTU in the Gas Phase and in Water (W) and Acetonitrile (ACN) Solutions.

	theoretical						experimental ΔE^a									
	gas		W		ACN		W		ACN		W_{DTUrd}			ACN_{DTUrd}		
state	Δ*E*	*f*	Δ*E*	*f*	Δ*E*	*f*	Abs	MCD	Abs	MCD	Abs	CD	MCD	Abs	CD	MCD
DTU																
S1(ππ*)	3.55	0.0137	3.70	0.0629	3.69	0.0631	3.53	3.54	3.53	3.53		3.51	3.57	3.53	3.47	3.53
S2(ππ*)	4.00	0.0768	4.18	0.2306	4.17	0.2300					3.96	3.96		3.72	3.75	
S3(ππ*)	4.51	0.3266	4.44	0.3264	4.43	0.3292	4.40	4.32	4.32	4.28	4.43	4.46	4.37	4.40	4.46	4.30
S4(ππ*)	4.78	0.3893	4.75	0.4272	4.75	0.4291		5.14	5.28	5.21					5.58	5.46
S1(nπ*)	2.76	0.0	3.13	0.0	3.11	0.0						3.16			3.04	
S2(nπ*)	3.49	0.0001	3.80	0.0002	3.79	0.0002										
T1(ππ*)	2.35		2.63		2.62											
T2(ππ*)	3.02		3.22		3.22											
T1(nπ*)	2.44		2.87		2.86											
T2(nπ*)	3.31		3.61		3.60											
1MDTU																
S1(ππ*)	3.62	0.0360	3.72	0.0953	3.71	0.0953	3.53	3.54	3.53	3.53		3.51	3.57	3.53	3.47	3.53
S2(ππ*)	3.91	0.0536	4.13	0.1640	4.12	0.1643					3.96	3.96		3.72	3.75	
S3(ππ*)	4.47	0.3883	4.40	0.3763	4.39	0.3783	4.40	4.32	4.32	4.28	4.43	4.46	4.37	4.40	4.46	4.30
S4(ππ*)	4.83	0.3494	4.77	0.4267	4.77	0.4281		5.14	5.28	5.21					5.58	5.46
S1(nπ*)	2.77	0.0	3.14	0.0	3.12	0.0						3.16			3.04	
S2(nπ*)	3.47	0.0001	3.72	0.0001	3.71	0.0001										
DTU-S4H3																
S1(ππ*)	3.14	0.0178	3.67	0.0561	3.65	0.0556										
S2(ππ*)	4.42^b	0.1594														
S3(ππ*)	4.59^b	0.1862	4.57	0.5082	4.56	0.5147										
S4(ππ*)	4.77	0.2675	4.73	0.3434	4.72	0.3403										
S5(ππ*)	5.27	0.0234	5.09	0.0045	5.09	0.0049										
DTU-S2H1																
S1(ππ*)	3.58	0.0930	3.82	0.2451	3.81	0.2440										
S2(ππ*)	4.45	0.0870														
S3(ππ*)	4.57	0.2200	4.55	0.2137	4.55	0.2217										
S4(ππ*)	5.04	0.0391	4.82	0.0706	4.82	0.0671										
S5(ππ*)	5.69^b	0.1018														
S6(ππ*)	5.77^b	0.2232	5.45	0.3377	5.46	0.3295										
DTU-S2H3																
S1(ππ*)	3.86	0.0011	4.33	0.0117	4.31	0.0106										
S2(ππ*)	4.26	0.3665	4.20	0.5143	4.19	0.5196										
S3(ππ*)	4.96	0.0616	4.61	0.0917	4.61	0.0914										
S4(ππ*)	5.61	0.2236	5.43	0.2442	5.44	0.2361										
1MDTU-anion (N3-anion)																
S1(ππ*)	3.46	0.0738	3.83	0.1020	3.82	0.1068										
S2(ππ*)	3.75	0.0224	4.28	0.0073	4.27	0.0078										
S3(ππ*)	4.02	0.3041	4.10	0.5130	4.09	0.5112										
S4(ππ*)	4.46	0.2275	4.63	0.3934	4.62	0.3949										
DTU-N1 anion																
S1(ππ*)	3.31	0.1164	3.55	0.2238	3.54	0.2246										
S2(ππ*)	3.95	0.0705	4.19	0.0602	4.18	0.0621										
S3(ππ*)	4.43	0.2139	4.53	0.2523	4.53	0.2547										
S4(ππ*)	4.65	0.3487	4.76	0.3981	4.76	0.3965										
DTU-N3 anion																
S1(ππ*)	3.36	0.0611	3.75	0.0853	3.74	0.0888										
S2(ππ*)	3.84^b	0.0279	4.35	0.0188	4.34	0.0141										
S3(ππ*)	4.12^b	0.4593	4.13	0.4995	4.12	0.5021										
S4(ππ*)	4.46^b	0.2569	4.61	0.3849	4.60	0.3891										

[a] For singlet transition energies see ref 17. Abs = absorption, CD = circular dichroism, MCD = magnetic circular dichroism, W_{DTUrd} = dithiouridine in water, ACN_{DTUrd} = dithiouridine in acetonitrile. [b] Rydberg contamination.

showed a different sign of the MCD band in water and in acetonitrile solutions. Our theoretical data shown in Table 1 and other theoretical calculations[3a,5a,12c] clearly show that DTU would be present only in the thione form in the gas phase and in water and acetonitrile solutions. Therefore, the spectral analysis of DTU by Igarashi-Yamamoto et al.[17] in terms of the thione-thiol tautomeric form does not appear convincing.

The pK_a analysis of 2,4-dithiouridine (DTUrd) indicated the possibility of the presence of an anionic and a neutral form of DTU in the neutral solution.[28] It is possible that in the neutral solution, DTU may also be present in the mixture of the neutral and anionic forms. Therefore, ground state geometries of anions of DTU were also optimized at the B3LYP/6-311++G(d,p) level. The N1-anion of DTU obtained by the deprotonation of the N1H group is about 13.0 kcal/mol more stable in the gas phase and about 3.4 and 3.7 kcal/mol more stable in water and acetonitrile solutions, respectively, than the N3-anion of DTU obtained by the deprotonation of the N3H group. Computed electronic transition energies of the N1-anion of DTU and the anion of 1MDTU (obtained by the deprotonation of the N3H group) are also presented in Table 5. Further, absorption spectra of DTU and DTUrd are generally similar except that a strong absorption peak is also observed near 3.96 eV (313 nm) in an aqueous solution of DTUrd. This peak (313 nm) is red-shifted to near 3.72 eV (333 nm) in acetonitrile. The 313-nm peak was explained as due to the existence of the thione form of the DTUrd while that of the 333-nm peak was explained in terms of the thiol form of the DTUrd.[17]

The observed experimental transition energies of DTU in water near 3.53 and 4.40 eV and in acetonitrile near 3.53 and 4.32 eV can be explained in terms of the computed transition energies of DTU in water at 3.70 and 4.44 eV and in acetonitrile at 3.69 and 4.43 eV, respectively (Table 5). Therefore, it appears that the 4.32-eV transition of DTU in acetonitrile, which was assigned to the thiol tautomeric form,[17] is actually from the thione tautomeric form. Further, the computed electronic transition energies of the N1-anion of DTU in water (at 3.55 and 4.53 eV) and in acetonitrile (at 3.54 and 4.53 eV) are also very close to the computed and experimental transition energies of DTU in water and in acetonitrile (Table 5). Theoretical calculation predicts a strong transition near 4.2 eV for DTU in water and in acetonitrile solutions (in the gas phase this is a weak transition near 4.0 eV); however, the N1-anion of DTU yields a weak transition in the same region (Table 5). Surprisingly, no such transition was revealed in the experimental study of DTU.[17] However, a transition near 3.96 eV (313 nm) was found in the absorption spectra of DTUrd in water and near 3.72 eV (333 nm) in acetonitrile.[17] The transition in water was assigned to the thione form while that in acetonitrile was assigned to the thiol tautomeric form of the molecule.[17]

Since the pK_a of DTUrd suggests the possibility of the coexistence of the neutral and the anionic form of DTUrd in solution, the transition energy calculations were also performed for the neutral and anionic form of 1-methyl-2,4-dithiouracil (1MDTU) and are shown in Table 5. The computed transition energies of 1MDTU in water and acetonitrile solutions near 3.7, 4.1, and 4.4 eV are in excellent agreement with the corresponding experimental data of DTUrd in water near 3.5, 4.0, and 4.4 eV and in acetonitrile near 3.5, 3.7, and 4.4 eV, except for the second transition in acetonitrile for which the agreement is poor (Table 5). The computed transition energies of the anion of 1MDTU in water and acetonitrile solutions near 3.8, 4.1, and 4.6 eV are also close to the experimental data of DTUrd and computed transition energies of 1MDTU (Table 5). It should be noted that the computed intensity of the 4.1-eV transition of 1MDTU is appreciably increased under anionic formation while in the case of the DTU the intensity of the corresponding transition (near 4.2 eV) is appreciably decreased in the anionic formation of the molecule (Table 5). Therefore, the experimental appearance of a strong transition near 4.0 eV in DTUrd and the nonexistence of such a transition in DTU may be attributed to the existence of a different proportion of neutral and anionic forms of DTU and DTUrd in solutions. The experimental investigation also shows a transition near 5.2 eV in DTU and near 5.6 eV in DTUrd.[17] However, theoretical calculations of DTU and 1MDTU and their anions show a transition in the 4.6−4.8 eV region (Table 5).

Igarashi-Yamamoto et al.[17] have explained the 5.2- and 5.6-eV transitions of DTU and DTUrd in terms of the thiol form of the molecule. Although the calculation shows that DTU-S4H3 and DTU-S2H3 thiol forms have a transition near 5.3 eV, given the relative stability of these tautomers, it is unlikely that they would be present in the gas phase and in aqueous solution. Theoretical calculation predicts that the lowest singlet nπ* transition of DTU and 1MDTU would be near 3.1 eV in water (Table 5). The computed first nπ* transition is localized mainly at the C4S4 group while the second nπ* transition is localized mainly at the C2S2 thiocarbonyl group. The theoretical prediction is in very good agreement with the experimental data of DTUrd which show the existence of a nπ* transition near 3.16 eV in water.[17]

3.3. Triplet Electronic Transitions. The lowest two triplet $\pi\pi$* and nπ* transition energies of 2TU, 4TU, and DTU in the gas phase and in water and acetonitrile solutions are shown in Tables 3−5, respectively. It is evident from the data that for all thiouracils, the lowest $^3\pi\pi$* state has a lower energy than the lowest ^{3}nπ* state both in the gas phase and in solutions. The excitation energies of the lowest $^3\pi\pi$* and ^{3}nπ* states of 2TU are larger than the corresponding states of 4TU and DTU, both in the gas phase and in solution. Further, the excitation energies of the lowest $^3\pi\pi$* and ^{3}nπ* states of 4TU and DTU are generally similar. As mentioned in the Introduction, there are somewhat contradictory results regarding the nature of the lowest triplet state of 4TU.[16,19−21] Our computed result that the lowest $^3\pi\pi$* state has a lower energy than the corresponding ^{3}nπ* state (Tables 3-5) is in agreement with the experimental findings of Taherian and Maki[20] and Milder and Kliger[16] that the lowest triplet state of TU is of the $\pi\pi$* type. The computed triplet $\pi\pi$* transition energies of 4TU near 2.68 and 3.87 eV in water can be explained in terms of the experimental transition energies of 4TUrd near 2.29 and 3.0 eV in water.[16] It should be mentioned that a triplet transition near 1.70 eV was also reported in the experiment; however, our calculated results do not support the existence of such a transition.[16] The quantitative information regarding the experimental triplet transition energies of 2TU and DTU is not available to the best of our knowledge and, therefore, we cannot compare our computed data with the experiment.

3.4. Comparison with Uracil. Computed transition energies of uracil in the gas phase and in water and acetonitrile solutions are presented in Table 6 along with the relevant experimental data.[29] Uracil in the gas phase shows three absorption peaks near 5.08, 6.05, and 6.63 eV.[29a] Our computed transition energies of uracil in the gas phase near 5.18, 5.9, and 6.47 eV are in good agreement with the experimental data (Table 6). Further, our computed transition energies of uracil in water near 5.12 and 6.16 eV are also in good agreement with the experimental transition energies near 4.81 and 6.11 eV in the aqueous environment.[29b] Calculation predicted that the first singlet nπ* transition of uracil in water would be near 5.12 eV while the second transition would be at 6.13 eV. It should be noted that the first nπ* transition is localized at the C4O4 group while the second is mainly localized at the C2O2 group. The first experimental nπ* transition of uracil is generally reported near 250 nm (4.96 eV).[29d,e] Therefore, the computed first nπ* transition near 5.12 eV in water is in good agreement with the experimental data. The computed second nπ* transition near 6.13 eV in water can be correlated with the nπ* transition of 1-methyluracil near 217 nm (5.71 eV).[29f] Among triplet transitions, calculation suggests that the lowest ^{3}nπ* state would be about 1.2 eV higher in energy than the corresponding $^3\pi\pi$* state of uracil. Our computed $^3\pi\pi$* transition energies of uracil in water and acetonitrile solutions near 3.6 and 4.9 eV can be correlated with the experimental triplet transition energies near 3.6 and 4.2 eV obtained in acetonitrile solution.[16] Further, experimental investigations have also suggested the existence

TABLE 6: Electronic Transition Energies (ΔE, eV) and Oscillator Strength (f) of U in the Gas Phase and in Water and Acetonitrile (ACN) Solutions

	theoretical									
	gas phase		water		ACN		experimental ΔE^a			
state	ΔE	f	ΔE	f	ΔE	f	Abs1	Abs2	CD	range
S1($\pi\pi^*$)	5.18	0.1317	5.12	0.1909	5.12	0.1920	5.08	4.79	4.73	4.6−5.1
S2($\pi\pi^*$)	5.90	0.0391	6.16	0.1539	6.16	0.1475	6.05	6.14	5.77	5.8−6.1
S3($\pi\pi^*$)	6.47^b	0.1186	6.26	0.0998	6.26	0.1062	6.63		6.36	6.3−6.6
S1(nπ^*)	4.67	0.0	5.12	0.0	5.10	0.0	4.96			
S2(nπ^*)	5.80	0.0	6.13	0.0	6.12	0.0	5.71			
T1($\pi\pi^*$)	3.43		3.55		3.55	3.55				
T2($\pi\pi^*$)	4.75		4.85		4.85		4.20			
T1(nπ^*)	4.29		4.76		4.74					
T2(nπ^*)	5.55		5.89		5.89					

[a] Abs1: absorption values for singlet $\pi\pi^*$ transitions are in the gas phase (see ref 29a); for singlet nπ^* transitions, see refs 29d,e and 29f; triplet $\pi\pi^*$ transition energies are in acetonitrile (see ref 16). Abs2: absorption transitions in water (see ref 29b). CD: CD spectra of uridine in an aqueous medium (see ref 29c). Range: range of experimental transitions (for review see refs 29d,e). [b] Rydberg contamination.

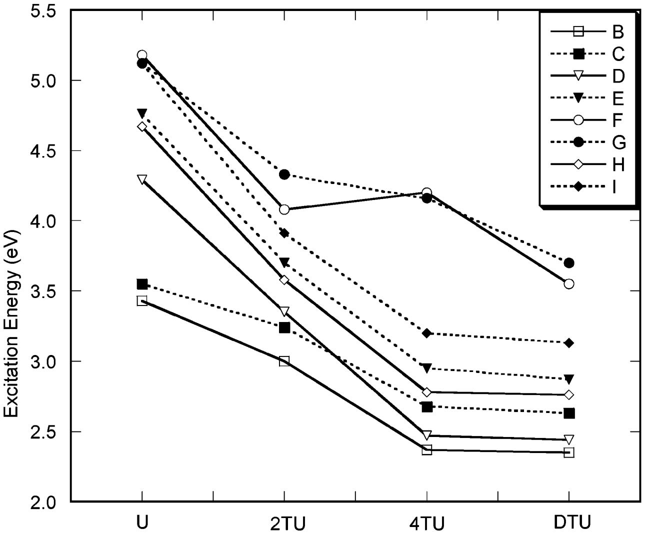

Figure 2. Variation of computed transition energies of uracil and thiouracils: (B) $^3\pi\pi^*$ in gas, (C) $^3\pi\pi^*$ in water, (D) ^{3}nπ^* in gas, (E) ^{3}nπ^* in water, (F) $^1\pi\pi^*$ in gas, (G) $^1\pi\pi^*$ in water, (H) ^{1}nπ^* in gas, and (I) ^{1}nπ^* in water.

of very weak $^3\pi\pi^*$ transitions near 1.8 and 2.1 eV, but our theoretical calculations do not support the existence of such transitions.[16]

The variation of the computed energies of the lowest singlet and triplet $\pi\pi^*$ and nπ^* transitions each of uracil, 2TU, 4TU, and DTU in the gas phase and in water is shown in Figure 2. This figure reveals that all but the lowest $^1\pi\pi^*$ states show a linear decrease in transition energy under the monothio substitution of uracil; the 4-thio substitution shows the largest decrease. Further, the 2-thio substitution of 4TU induces insignificant change in excitation energies (Figure 2). In the case of the lowest $^1\pi\pi^*$ state a significant change in transition energies between 2TU and 4TU is not revealed, although transition energy is significantly decreased in going from uracil to monothiouracils. The dithio substitution of uracil shows a further decrease in the transition energy.

4. Conclusions

The TD-DFT computations of thiouracils, methyl derivatives of thiouracils, and their comparison with uracil have led to the following important conclusions:

1. All thiouracils, namely, 2TU, 4TU, and DTU, studied here would be present in the keto-thione (dithione in the case of DTU) tautomeric form in the gas phase and in water and acetonitrile solutions.

2. The TD-DFT computed transition energies are generally in good agreement with the corresponding experimental data. In the case of 2,4-dithiouracil, an anionic form of the molecule obtained by the deprotonation of the N1H site may also be present in the water and acetonitrile solutions. Further, the spectral features of DTU were found to be complex.

3. Uracil and all thiouracils studied here have the $\pi\pi^*$ type of the lowest triplet state in the gas phase and in water and acetonitrile solutions.

4. In going from uracil to monothio-substituted uracil, the computed lowest singlet nπ^* and triplet $\pi\pi^*$ and nπ^* transition energies were found to decrease linearly: the transition energies for 2TU were found to be between the transition energies of uracil and 4TU. Further, the transition energies of 4TU and DTU were found to be similar. In the case of the lowest singlet $\pi\pi^*$ transition, the transition energy for 2TU and 4TU is similar, although it is decreased in going from uracil to monothio-substituted uracil. The dithiouracil has the lowest transition energy.

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