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Hydrogen-Bonded Dimers of 2-Thiouracil: Insights from Computational Analyses

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Abstract: The dominant roles of hydrogen bond (HB) interactions are known in biologically related systems, in which their characterizations could be considered at a high level of importance. 2-Thiouracil (2TU) is a biologically derived structure with known anti-thyroid pharmaceutical functions. This work investigated formations of hydrogen-bonded dimers of 2TU for providing insights from density functional theory (DFT) based computational analyses. The models were optimized, and their features were evaluated to learn details of interactions for formations of dimers of 2TU. Twelve dimers were found, and their evaluated configurations and features showed different properties for the models. Two types of S…H and O…H interactions were involved in the dimers, in which the hydrophobic hydrogen atoms of 2TU were also involved in interactions with the S and O atoms. The strengths of obtained dimers were different, meaning the dominant roles of relaxations configurations of dimers and strengths of each of involving interactions. But it should be noted that all models were in reasonable levels of energy strengths of formations. As a consequence, the dimers of 2TU could be known with their obtained specifications, and they could be conducted for working in future desirable applications.

Keywords: 2-thiouracil; anti-thyroid; DFT; hydrogen bond; molecular interactions.

1. Introduction

The structural determination of DNA by the pioneering work of Watson and Crick has raised intensive interest in investigating nucleobase structures and their derivatives to this time [1-3]. The nucleobases are indeed the building blocks of livening systems, and their configurations are very important for maintaining the ordered functions of such systems and situations [4]. Adenine (A) and guanine (G) are the purine-type of nucleobases, and Cytosine (C), Thymine (T), and Uracil (U) is the pyrimidine-type of nucleobases [5, 6]. Besides the

existence of original nucleobases, exploring the existence of other derivatives of nucleobases has been found very interesting up to now regarding their recognized roles in pharmaceutical applications [7]. Accordingly, considerable efforts have been dedicated to investigating features of such structures for developing new derivatives and functions [8-12]. Indeed, the biological-related systems are very complicated, and several unknown issues are still remained to be solved by employing various techniques and approaches [13-15]. To this aim, modifications of atomic sites of nucleobases were found achievable for approaching the expected pharmaceutical applications, in which 2-thiouracil (2TU) was found as a product of the urea-type oxygen atomic substitution of U by a sulfur atom (Figure 1) [16]. Further analyses indicated an anti-thyroid function for 2TU by inhibiting the activity of the thyroid peroxidase enzyme [17, 18]. In this regard, the importance of 2TU was found based on its specific role in controlling the human health system [19]. Earlier reports on 2TU showed various features of this sulfated uracil compound in different media and interaction with different substances [20-23]. This work investigated formations of the hydrogen-bonded dimers of 2TU to reveal insights from computational analyses.

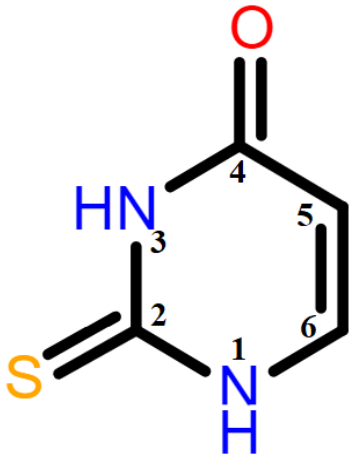

Figure 1. 2-Thiouracil (2TU).

The hydrogen bond (HB) interactions play dominant roles in chemical and biochemical systems to provide communications among the molecular and biomolecular systems [24-28]. In the case of nucleobases and their derivatives, HB interactions are crucial for creating lattices and macromolecular structures [29]. Besides the formation of hetero-molecular interactions, the formation of homo-molecular interactions between similar molecules was seen as important for defining their original properties and features [30]. The reports of earlier works indicated possibilities of participation of 2TU in HB interactions [31-33]. However, a lack of a systematic investigation remains for this important molecular system. Hence, the current research work aimed to reveal insights from computational analyses for the hydrogen-bonded dimers of 2TU. To investigate this topic, computational analyses were used to recognize the molecular systems and their involving interactions at the smallest scales [34-37]. It should be noted that drug development is a very wide area of research involving several techniques and methodologies in which the known substances could be investigated for approaching new insights regarding the desired goal [35-40]. In this regard, several attempts have been made to recognize the details of therapeutic systems; however, the field of research is still endless to be investigated further [44-48]. To this aim, the current work aimed to investigate the bimolecular models of 2TU, in which the molecular models were optimized and their features were evaluated to reach the targeted purpose (Tables 1 and 2 and Figures 1 and 2).

2. Materials and Methods

The B3LYP-D3/6-31+G* density functional theory (DFT) calculations were performed using the Gaussian program [49] to investigate formations of hydrogen-bonded dimers of 2TU. DFT methods were used in several research works, and their ability was suitable for investigating complicated systems in chemical and biochemical media [50-52]. As shown in Figure 2, twelve models of dimers were obtained by examining the possibilities of interactions for all molecular/atomic sides of 2TU. The models were optimized to obtain the stabilized structures and energies. The effects of basis superposition error (BSSE) were also considered for evaluating the interaction energies of the models [53].

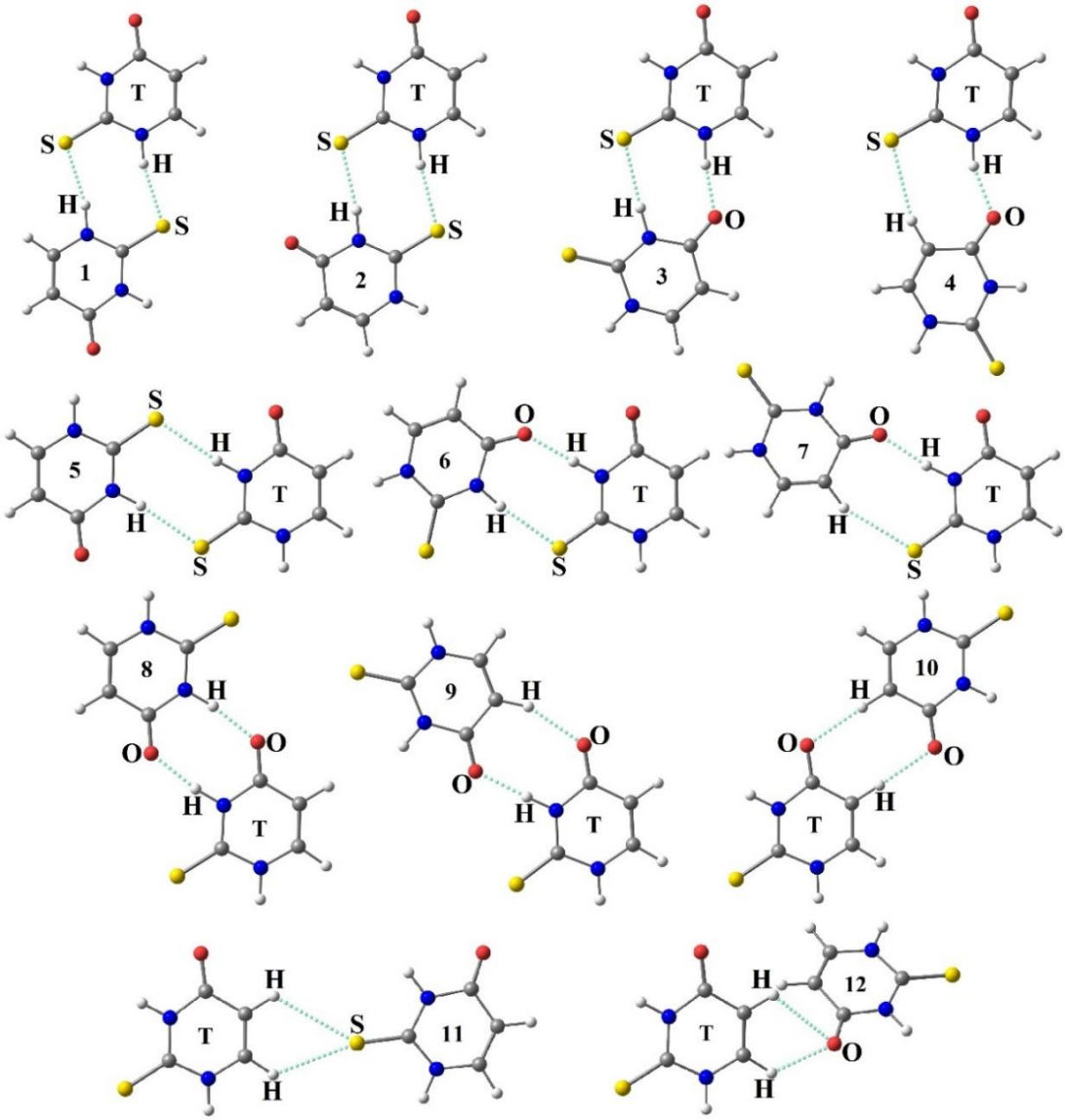

Figure 2. The optimized dimers of 2-Thiouracil (2TU). T stands for one fixed 2TU molecule and the numbers 1-12 show the rotation of another 2TU molecule around the fixed molecule of dimers T1-T12.

Additionally, the interaction details were examined by performing the quantum theory of atoms in molecules (QTAIM) analyses. To this point, the models were recognized by their stabilized dimers and details of interactions. Furthermore, frontier molecular orbital energy levels were evaluated for the models, including the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) and their related features, such as chemical potential, chemical hardness, and electrophilicity index. The obtained molecular features of the models including E (energy of formation), H (HOMO), L (LUMO), G (energy gap of HOMO and

LUMO levels), U (chemical potential), H (chemical hardness), W (electrophilicity index), and V (molar volume), were summarized in Table 1. Furthermore, the obtained QTAIM features of the models, including INT (interaction type), DIS (interaction distance), ρ (total electron density), $\nabla^2\rho$ (Laplacian of electron density), and H (energy density), were summarized in Table 2. As a consequence, the models were analyzed based on their evaluated molecular and QTAIM features to provide insights into the formations of 2TU dimers from the employed DFT computations [54-57].

3. Results and Discussion

This work was done to provide insights on the hydrogen-bonded dimers formations of 2TU from computational analyses. The importance of investigating 2TU is because of its pharmaceutical roles, which has made it the topic of several research works up to now [17]. Accordingly, formations of homo-molecular dimers of 2TU were investigated in this work to learn details of the interaction feasibility of this molecule in a single-standing state. The models of possible formations of dimers through HB interactions were examined to find twelve finalized models by the results of optimization calculations. The models were stabilized, and their features were evaluated to learn their details. As shown in Figure 1, the original 2TU has appropriate atomic sites for involvement in HB interactions, and such features were examined within this work. Such possibilities were examined by fixing one 2TU molecule, as indicated by T in Figure 2, and rotating the other 2TU molecule around the fixed molecule. To this aim, the models were optimized in different configurations yielding twelve models in Figure 2. Based on the evaluated molecular features, different strengths of formations of dimer models were obtained for T1-T12 models, as included in Table 1.

Table 1. Molecular features of the models.*

Model	E	H	L	G	U	H	W	V
2TU	n/a	-6.62	-2.01	4.61	-4.31	2.31	4.02	91.95
T1	-11.83	-6.92	-2.21	4.72	-4.57	2.36	4.42	166.26
T2	-8.10	-6.57	-2.14	4.43	-4.35	2.21	4.28	171.74
T3	-11.35	-6.49	-2.21	4.28	-4.35	2.14	4.42	186.39
T4	-10.09	-6.45	-2.38	4.07	-4.41	2.03	4.79	183.39
T5	-5.24	-6.57	-1.91	4.66	-4.23	2.34	3.83	174.60
T6	-7.31	-6.38	-1.92	4.46	-4.15	2.23	3.86	168.38
T7	-5.64	-6.43	-2.01	4.42	-4.22	2.21	4.03	182.33
T8	-9.34	-6.26	-1.89	4.37	-4.07	2.18	3.80	182.60
T9	-6.92	-6.20	-1.95	4.24	-4.08	2.12	3.92	165.58
T10	-5.39	-6.60	-1.95	4.65	-4.27	2.33	3.92	159.30
T11	-4.39	-6.41	-2.34	4.07	-4.37	2.03	4.70	169.36
T12	-2.15	-6.50	-2.32	4.17	-4.41	2.09	4.66	172.19

*The models are shown in Figures 1 and 2. E is in kcal/mol. H, L, G, U, H, and W are in eV. V is in cm^3/mol.

The models were found to interact with each other, and their molecular features were obtained to learn about their states in the dimer form compared to the original single form. Analyzing the results of Table 1 could show the highest levels of strengths for T1 and T3 with -11.83 kcal/mol and -11.35 kcal/mol for the evaluated E values. On the other hand, the lowest levels of strength were found for T11 and T12, with -4.39 kcal/mol and -2.15 kcal/mol for the evaluated E values. The rest of the models were found between these two levels according to their evaluated strengths as shown by this order: T1 > T3 > T4 > T8 > T2 > T6 > T9 > T7 > T10 > T5 > T11 > T12. Different stabilities of strength formations for the dimer models showed the importance of the roles of atomic sites for determining the feasibility of 2TU for participating in interactions. In this regard, the model with a lower dimer strength could be

separated easier than the model with a higher dimer strength. Consequently, the models were recognized based on their tendency to participate in dimer formations. Electronic features of the models were analyzed by the evaluated values of frontier molecular orbitals and their related parameters. Based on the evaluated values of H and L, standing as the edging levels of full and vacant molecular orbitals, movements of such edges were observed between the single and dimer models and among the dimer models. The obtained results indicated that the models were in different levels of electronic environments compared to each other. Not only the levels of the edges of molecular orbitals were changed, but also their energy distances were changed as indicated by different values of G. Parallel with these results, other parameters, including U, H, and W, were changed, showing varieties of electronic environments for the investigated dimers. This achievement is very important for recognizing the future behaviors of 2TU for participating in interactions with other substances. Different modes of strengths and electronic features are dominant for yielding behaviors of the models. The evaluated values of V also indicated that the combination of two 2TU molecules did not need a two-times space. A smaller space was found because of the relaxation and sharing of the electronic environments.

Table 2. QTAIM features of the models.*

2TU Dimer	INT	DIS	ρ	$\nabla^2\rho$	H	INT	DIS	ρ	$\nabla^2\rho$	H
T1	S…H	2.304	0.0249	0.0554	-0.0016	H…S	2.304	0.0249	0.0554	-0.0016
T2	S…H	2.354	0.0217	0.0518	-0.0008	H…S	2.334	0.0229	0.0543	-0.0010
T3	S...H	2.343	0.0225	0.0523	-0.0010	H…O	1.769	0.0385	0.1268	-0.0004
T4	S…H	2.737	0.0108	0.0315	-0.0012	H…O	1.828	0.0339	0.1105	-0.0005
T5	S…H	2.385	0.0199	0.0506	-0.0003	H…S	2.385	0.0199	0.0506	-0.0003
T6	S…H	2.351	0.0216	0.0530	-0.0007	H…O	1.824	0.0327	0.1096	-0.0001
T7	S…H	2.748	0.0101	0.0313	-0.0013	H…O	1.851	0.0304	0.1027	-0.0001
T8	O…H	1.814	0.0339	0.1123	-0.0002	H…O	1.814	0.0340	0.1123	-0.0002
T9	O…H	2.169	0.0167	0.0558	-0.0004	H…O	1.851	0.0311	0.1022	-0.0002
T10	O…H	2.197	0.0164	0.0514	-0.0001	H…O	2.199	0.0164	0.0512	-0.0001
T11	H…S	2.869	0.0059	0.0240	-0.0005	H…S	3.057	0.0049	0.0180	-0.0002
T12	H…O	2.381	0.0112	0.0420	-0.0002	H…O	2.805	0.0059	0.0235	-0.0001

*The models are shown in Figure 1. DIS is in Å. P, $\nabla^2\rho$, and H are in au.

Details of dimer formations were investigated by analyzing the evaluated QTAIM features (Table 2) as useful elements for describing the interacting systems [58-60]. The models involved two interactions for each of the T1-T12 dimers, in which all atomic sites of 2TU were participating in such interactions among different dimer configurations. In Figure 2, the dashed lines showed the available interactions for the dimer models between the interacting atoms of fixed T and rotating counterpart. As a general achievement, the participation of S…H interactions yielded higher strengths of dimers formations in comparison with the participation of O…H interactions as found by the values of E of Table 1. It was interesting that the hydrophobic hydrogens of 2TU, those connected to the carbon atoms in C-H bonds, were also feasible to participate in interactions, in which the pure participations of those hydrogen atoms of the fixed 2TU with the S and O atoms of the other 2TU found T11 and T12. Based on the relaxation configurations of the models and the strengths of each interaction, the models of 2TU were recognized in dimer forms with reasonable strengths.

4. Conclusions

This work was done to provide insights into the formation of hydrogen-bonded dimers of 2TU by performing DFT-based computational analyses. According to the obtained achievements, twelve dimers of 2TU were obtained by considering all possibilities of interactions between two TU molecules. The features of stabilized models indicated different

strengths of formations and electronic properties. Besides these variations, the QTAIM-based details of interactions provided information on each of the involved interactions, including S…H and O…H types. Interestingly, the hydrophobic hydrogens of 2TU were also interacting with the S and O atoms but in lower strength than other types of dimers formations. In this regard, the models were stabilized, and their features indicated the importance of molecular configurations for forming the hydrogen-bonded dimers. Consequently, conducting the formation of a dimer model or preventing the formation of another model could help to approach desirable features for 2TU in a dimer state.

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Conflicts of Interest

The authors declare no conflict of interest.

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