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Exploring Formations of Thio-Thiol and Keto-Enol Tautomers for Structural Analysis of 2-Thiouracil

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ABSTRACT

Formations of thio-thiol and keto-enol tautomers of 2-thiouracil (2TU) were investigated in this work for performing structural analysis by means of density functional theory (DFT) calculations. To this aim, existence of all possible structures were examined by movement of hydrogen atoms of amine groups to each of original thio and keto groups for formation of thiol and enol groups for new structures. Optimization calculations were performed to reach the minimum energy level for each investigated structure. The results showed that occurrence of such tautomerism processes could yield new features for the corresponding structures, in which variations were more or less significant in comparison with the original features. The important note is that formations of tautomers were possible meaning changes of expected activities regarding occurrence of such process in order to the concept of structure-activity relationship. Therefore, such computer-based works could provide information for examining such features in the tautomers of 2TU, as a compound related to pharmaceutical applications, to manage somehow the structural features for the specified purposes.

KEYWORDS 2-Thiouracil, Tautomer, Thio-thiol, Keto-enol, DFT.

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INTRODUCTION

After characterizing nucleobase structures, considerable efforts have been dedicated to investigate existence of other possible derivatives with specific applications especially related to pharmaceutical compounds production.[1-3] To this aim, several modified models of nucleobases have been introduced, in which 2-thiouracil (2TU) has been seen as a useful compound obtained by uracil nucleobase.[4-6] 2TU has been seen useful for medication of thyroid disorders and some types of cancers in addition to its role as an initiating structure for synthesizing other pharmaceutical compounds.[7-9] One of issues with almost all pharmaceutical compounds is their unwanted side effects after consumption or their low efficacy for medication.[10] As known by structure-activity relationship (SAR), each structure would assign an specified activity, in which changes of structural features could change the expected activity for that compound.[11] Therefore, performing structural analysis is an important step for characterizing those structural parameters affecting the specified activity for the investigated models.[12] To do such analysis, computational chemistry approach could help very well to analyze structures at the lowest molecular and atomic scales avoiding the existence of any interferers.[13] Hence, such approach was used in this work to analyze structure of 2TU regarding formation of thio-thiol and keto-enol tautomers as shown in Fig. 1.

Tautomerism is a common process happening in almost all organic compounds changing their structural feaures.[14] Such tautomers formation are also possible for 2TU, in which hydrogen atoms of two amine groups of heterocyclic nucleobase ring could move to sulfur (thio) or oxygen (keto) sites of the parent structure to construct new thiol or enol tautomeric structures. In such processes, the structural stability of tautomer is expected to be changed during such hydrogen movement yielding new features for the resulted tautomer structure. As a result, not only one tautomer, but five tautomers were achieved for 2TU in addition to the parent 2TU by movement of hydrogen atoms of amine groups between thio or keto groups of the parent 2TU (Fig. 1). To reach the purpose of this work, all possibilities of such tautomer formations were examined and their features were evaluated for providing required information for discussing the subject (Table1).

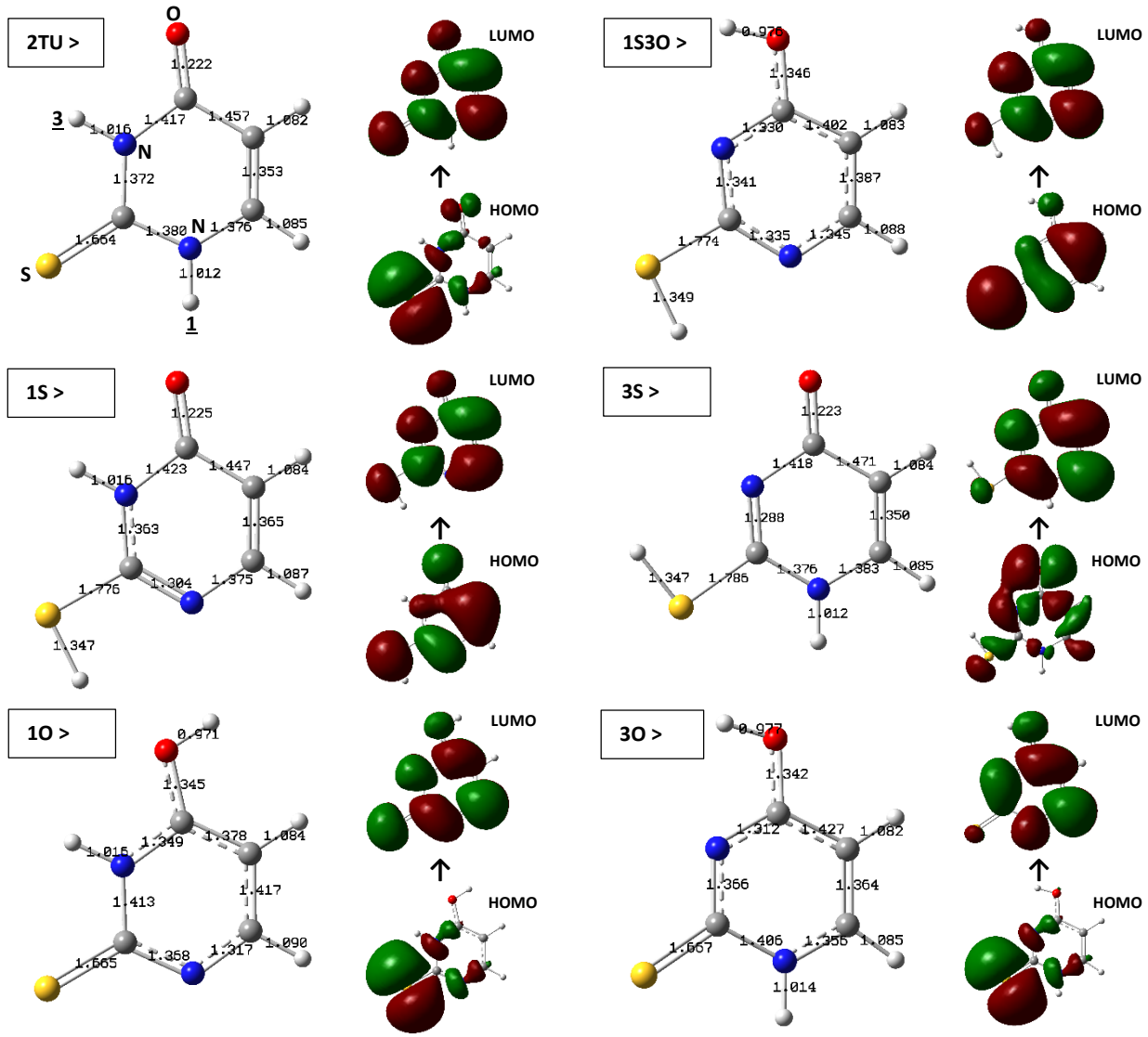

Fig. 1: Optimized models of 2TU and tautomers and representations of HOMO → LUMO distribution patters.

MATERIALS & METHODS

The main material of this work was 3D model of 2TU, in which other tautomeric structures were generated from the parent 2TU yielding 1S3O, 1S, 3S, 1O, and 3O tautomeric models as shown in Fig. 1. Tautomeric models were assigned by a number 1 or 3 meaning the hydrogen atom of nitrogen number 1 or number 3 moving between sulfur and/or oxygen atomic sites. For example, 1S3O means that the hydrogen number 1 moved to sulfur atomic site and the hydrogen number 3 moved to oxygen atomic site. Stabilized structures of all models were obtained by performing optimization calculations at the B3LYP/6-31+G* level of density functional theory (DFT) employing the Gaussian program.[15] Hence, all possible structures were prepared for evaluating describing features including various types of energies as summarized in Table 1. Total energy of structure was assigned by E, in which difference energy between each tautomer and the most stabilized structure was assigned by ΔE. Moreover, energy values of the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO), energy gap (Egap), chemical hardness and softness

(η and σ), and dipole moment (Dm) were obtained for the stabilized structures. Additionally, HOMO → LUMO distribution patterns were visualized for the models in addition to the optimized shapes and bond distances as shown in Fig. 1. As a consequence, the required information were obtained for analyzing structural features of 2TU among formations of thio-thiol and keto-enol tautomeric forms.

Table 1: Obtained descriptors for the optimized models.*

Model	E eV	ΔE eV	HOMO eV	LUMO eV	Egap eV	η eV	σ eV^{-1}	Dm Debye
2TU	-20076.665	0	-6.617	-2.002	4.615	2.307	0.433	4.838
1S3O	-20076.102	0.563	-6.836	-1.405	5.431	2.716	0.368	1.331
1S	-20076.161	0.505	-6.920	-1.820	5.100	2.550	0.392	3.054
3S	-20075.759	0.906	-6.917	-1.306	5.611	2.805	0.356	6.836
1O	-20075.649	1.016	-5.852	-2.063	3.788	1.894	0.528	8.253
3O	-20076.071	0.594	-5.902	-1.957	3.944	1.972	0.507	5.785

*Models were shown in Fig. 1.

RESULTS & DISCUSSION

As shown in Fig. 1, six models were investigated in this work including the parent 2TU and five additional tautomers of 1S3O, 1S, 3S, 1O, and 3O, resulted by movement of hydrogen 1 and/or 3 among sulfur and/or oxygen atomic sites. A quick look at the face of tautomers and bond distances could show effects of occurrence of tautomerism on geometrical features of the models. Such observation was affirmed by evaluated values of total energy (E) for each structure, in which the parent model of 2TU was found to be the most stabilized structure (Table 1). Comparing values of E for other tautomers indicated different stabilities for the resulted tautomers, in which 1S was the most stabilized one and 1O was the least stabilized one among five tautomeric structures indicated by comparing magnitudes of ΔE. By changing stabilities of structures, their corresponding electronic features are also expected to be changed. To show this trend, obtained values of energies for HOMO and LUMO levels indicated significant variations among tautomeric structures in addition to comparing with the parent 2TU. Furthermore, differences of HOMO and LOMO levels assigned by Egap also detected significant changes of such electronic features for the investigated models. These features are almost the most important ones for defining the reactivity of compounds, in which each value of η and σ could somehow show tendency of a molecule for contributing to reactions in the modes of chemical hardness and softness. Lower values of η and higher values of σ could imply for better favorability of a molecule for contributing to reactions with other substances. For the model systems, such values were significantly changed for 1O model, in which it was shown earlier as the least stabilized tautomer among other tautomeric structures. It is worth to note that tautomerism might lead to mutation in living systems, in which the results here showed that the reactivity of tautomers were changed by movement of only one hydrogen atom. Moreover, unwanted side effects of such pharmaceutical related compounds might be arisen from the formation of such tautomeric structures with different tendency to contribute to reactions with other substances in comparison with the parent model. Therefore, such results could provide insightful information for preparing a compound of 2TU wit desirable reactivity.

Further analysis of the models by visualized HOMO and LUMO distribution patterns could show that changes of HOMO patterns among the models were more significant than those of LUMO patterns indicating that the tendency of positions of molecules for electron donating were remarkably changed whereas those positions for electron accepting were almost similar among the models. This trend could be mentioned in another words, in which the models of 2TU different features for initiating a contribution to a reaction as electron donors. Such changes of molecular orbitals patterns yielded different values of Dm, in which the largest value was found again for 1O tautomer. The results emphasized that only closed formulas of molecular models are not enough for analyzing their features, in which such open formulas could show possible variations of structural features and their corresponding electronic features as indicated by optimized geometries and evaluated descriptors. Additionally, careful examination of the results could reveal insight about how to modify next structures of 2TU avoiding formation of tautomers or managing formations of desired tautomers for specified purposes. Obtaining these results could be done by benefit of employing computer-based works for analyzing the pure models at the smallest molecular and atomic scales, which are not easily achievable in experiments.[16, 17] As a consequence, the obtained results of current work indicated possibility for existence of tautomers of 2TU for warring for its carful employing for further pharmaceutical applications.

CONCLUSION

This work was done for analyzing structural features of 2TU through formations of thio-thiol and keto-enol tautomers resulted by movement of hydrogen atoms of amine groups of parent molecule into sulfur and oxygen atomic sites. DFT calculations yielded five tautomeric structures with different optimized geometries and stabilities in comparison with the parent 2TU or among other tautomers. The most highlighted results of such variations were found for 1O model, in which hydrogen of nitrogen number 1 was moved to oxygen atomic site to make enol tautomer. The highest stability of tautomers was found for 1S model, in which hydrogen of nitrogen number 1 was moved to oxygen atomic site to make thiol tautomer. Molecular orbitals related features indicated that tendency of tautomers for contributing to reactions with other substances were significantly changed, in which such tendency was tremendously increased for 1O model with the lowest stability. Such achievement revealed the importance of structural features for defining their activity arising advantages or disadvantages for their further applications.

DISCLOSURE STATEMENT

The author(s) did not report any potential conflict of interest.

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