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The computational study of the tautomerization of Dacarbazine in a biological system: The DFT approach

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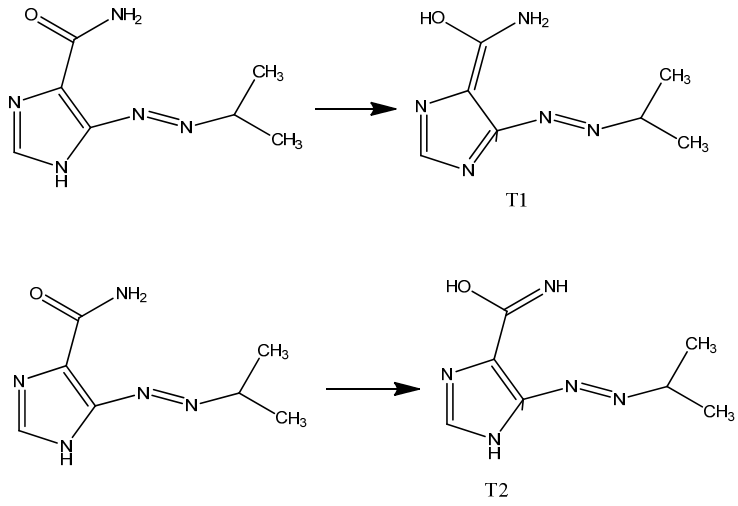
HIGHLIGHTS

- Applying a theoretical investigation to the tautomerization mechanism
- Applying an accurate method by diffuse orbitals
- Calculation of physico-chemical parameters
- Simulation of biochemistry media

GRAPHICAL ABSTRACT



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ABSTRACT

The aim of this study was to examine dacarbazine tautomerization with the density functional theory, where two tautomer structures have been indicated. The B3LYP/6-311G++ (d, p) , 6-311(d, p), and 6-311 quantum methods were considered to calculate the relative energies transferred between two structures. Also, calculations of the HOMO, LUMO, as well as the structures' band gap energy were performed. Estimation of electronic parameters, such as electrophilicity, electronegativity, softness, and hardness, were also investigated to determine the compound's reactivity in a biological media.

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1. Introduction

Dacarbazine has no or ivory color and belongs to the alkylating agents of antineoplastic drugs, which has been primarily focused on anticancer functions. The six main classes of agents found in this family of medications and dacarbazine belong to triazenes [1]. The use of dacarbazine [5-(3,3-dimethy-1-triazenyl) imidazole-4-carboxamide; DTIC] is predominately used as an anticancer medication. Different studies have previously examined DTIC's electrochemical features and DNA binding behaviors [2,3]. This agent is cell-cycle, non-specific, anti-neoplastic, and indicates a wide range of antitumor activities in mice tumor models; however, its function has so far been limited in human beings. This agent also contributes to chemotherapy as a single antitumor drug and has shown potential when the food and drug administration approved its application in treating metastasis in melanoma in 1975 [4,5].

Thus, pre-clinical and clinical trials are performed considering DTIC as the reference medication. DTIC induces just 15% of the melanoma instances (although this is low, no better level has yet been identified). Application of DTIC is usually in combined form, such as in combination with Adriamycin-Bleomycin-Vinblastine-Dacarbazine or ABVD for the treatment of Hodgkin [6-10]. Every nitrogen atom has the potential of donating or accepting classical or dual hydrogen bonds, making it highly suitable for the flexibility of structures as well as biologic activities. DTIC has wide-ranging uses in the clinical context and can be injected or infused in solution forms; unfortunately, normal ambient temperature leads to its instability. Therefore, the powder form of DTIC has the most common application. When different sites of a single molecule have the potential of interacting with proton transfer, crystalline packing will usually be the result [11,12].

2. Experimental study

2.1. Computational method

The DFT framework with spin unlimited setting at Becke's three parameter hybrids function along with the Lee-Yang-Parr correlation function was used to perform the calculations and to examine the reactivity of tautomer of dacarbazine (D). The 6-311, 6-311++g(d, p), and 6-311g(d, p) pople basis sets were also used to describe B3LYP at the computational level for all atoms. Gaussview 5.0 was considered to build the primary structures, and their optimization took place with Gaussian 09 revision A02 [13]. Various configurations of tautomer underwent examination. The same technique was used to calculate the stability energy, structural parameters, dipole moment, electronegativity, thermal characteristic, and IR frequency features of reactivity as well.

Eqs. (1) to (4) were used to calculate the descriptors of the chemical reactivity and stability based on DFT, including electronic chemical potential (μ), chemical hardness (η), chemical softness (S), and electrophilicity (ω) with regard to the Koopmans theorem.

$$\mu = \left(\frac{\partial E}{\partial N}\right)V\ (r),T \tag{1}$$

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)V\ (r),T \tag{2}$$

$$S = 1/2\eta \tag{3}$$

$$\omega = \mu^2 / 2\eta \tag{4}$$

In which, μ shows the chemical potential, η indicates the chemical hardness, S shows the global softness, and ω indicates the electrophilicity index.

3. Results and discussion

Two tautomer configurations are known to make dacarbazine biologic, as well as promote hydrogen bonding with its DNA and other chemical compounds. Since any alterations in the position of hydrogen in the chemical configuration have the potential of changing the effects of the medication, investigations were performed on the T1 and T2 tautomer configurations of dacarbazine in the gas phase to identify any such potential. Table 1 indicates the energy values associated with dacarbazine and tautomer configurations. Fig. 1 shows the tautomer after reaching equilibrium. Figs. 2 and 3 indicate the optimum structures for D, T1, and T2, while Figures 4-6 indicate the compound's HOMO and LUMO plots. The electron's negative density is shown by the red area, and its positive density is represented by the green area. The former indicates the electrophilicity, and the latter indicates electron affinity zones in the compound, which can possibly

Table 1. Energy of dacarbazine, T1 and T2 by all basis sets.

Basis set	**6-311++g(d, p)**			**6-311(d, p)**			**6-311**		
	D	**T1**	**T2**	**D**	**T1**	**T2**	**D**	**T1**	**T2**
Energy (kJ)	-1675.98	-1677.53	-1677.95	-1675.98	-1677.52	-1675.95	-1675.38	-1676.92	-1675.34

alter the hybridization of atoms in the molecules. In 1968, Gyftopoulos and Hatsopoulos, following the statistics of ensembles and considering a free atom or ion as a thermodynamic system, put forward a quantum thermodynamic definition of electronegativity. Given the electron density function ($\rho(r)$) in a chemical system (atom or molecule) and the energy functional ($E(\rho)$), the chemical potential (μ) of that system in equilibrium is defined as the derivative of the energy with respect to the number of electrons at fixed molecular geometry.

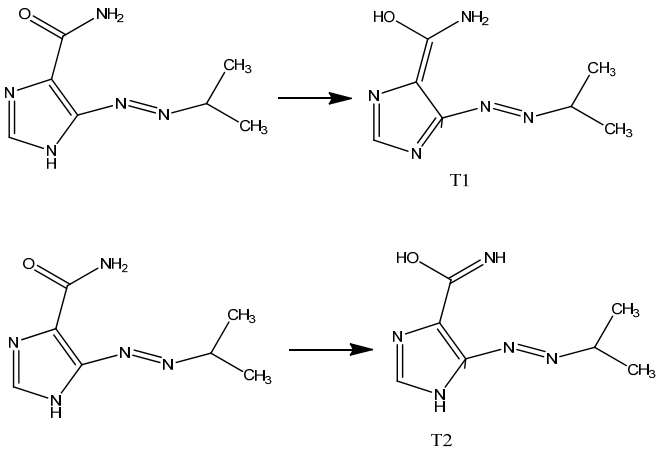

Fig. 1. Structure of dacarbazine and tautomers.

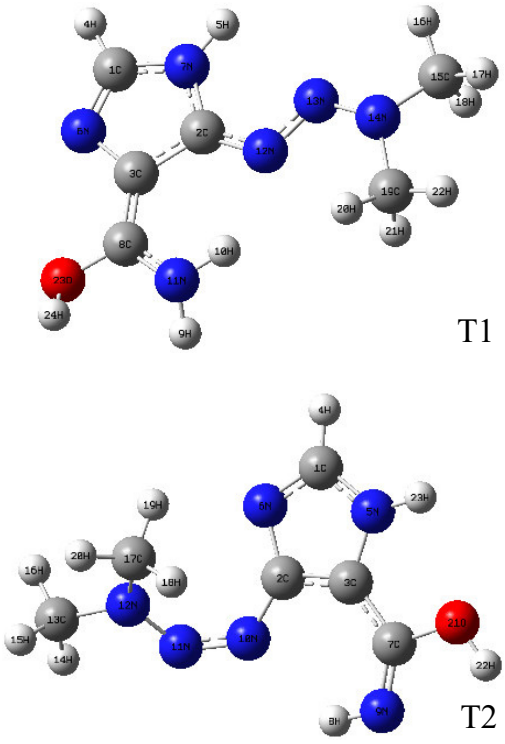

Fig. 2. Optimized structure of tautomer T1 and T2 by 6-311++(d, p).

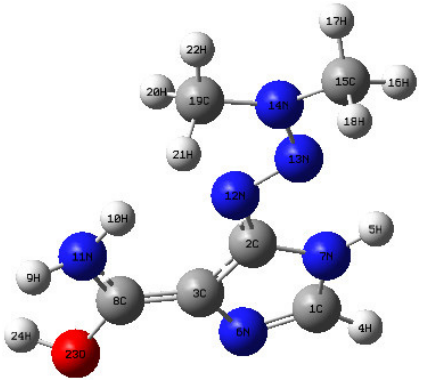

Fig. 3. Optimized structure of dacarbazine 6-311++(d, p).

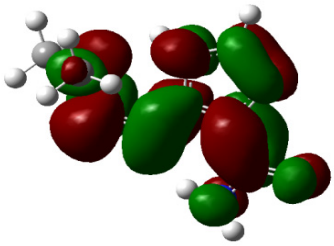

Fig. 4. HOMO-LUMO plot of dacarbazine by 6-311++(d, p).

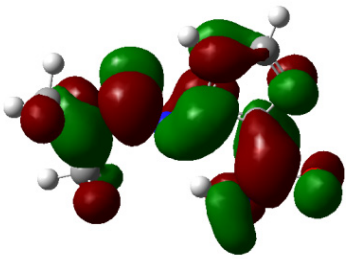

Fig. 5. HOMO-LUMO plot of T1 by 6-311++(d, p).

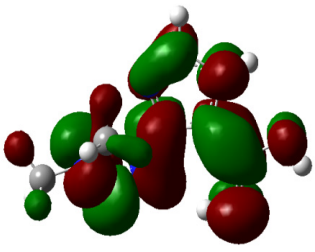

Fig. 6. HOMO-LUMO plot of T2 by 6-311++(d, p).

Figs. 7-9 show the D, T1, and T2's IR spectrum used to determine the tautomerization's enol and imine forms.

According to the data shown in Table1, the D, T1, and T2 energy showed little change given the different values of approximately 0.03 kJ. Based on the values obtained for energy calculations, 6-311++ (d, p) was employed for the other computation parameters. Negative energy led to stability in formation conditions. Thus, T2 shows higher stability compared to other molecules.

Geometric parameters, such as the length of the bond in Table 2, indicate that the D, T1, and T2 active sites

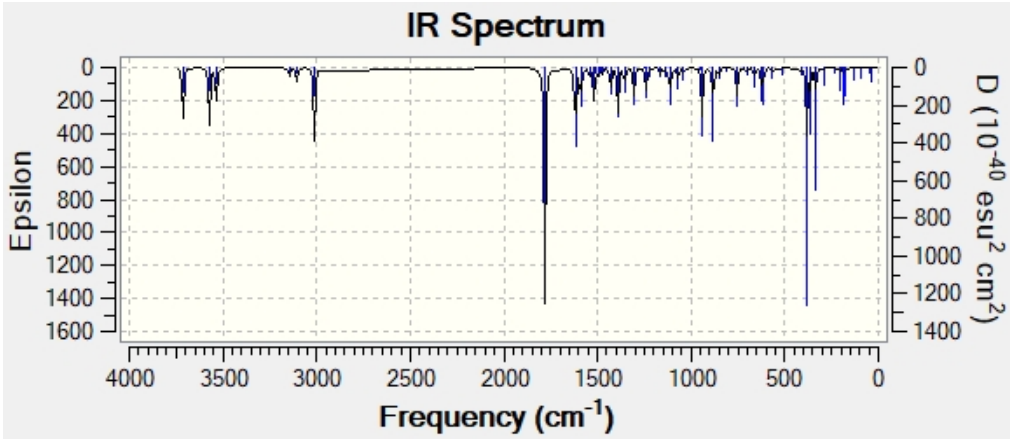

Fig. 7. IR of dacarbazine by 6-311++(d, p).

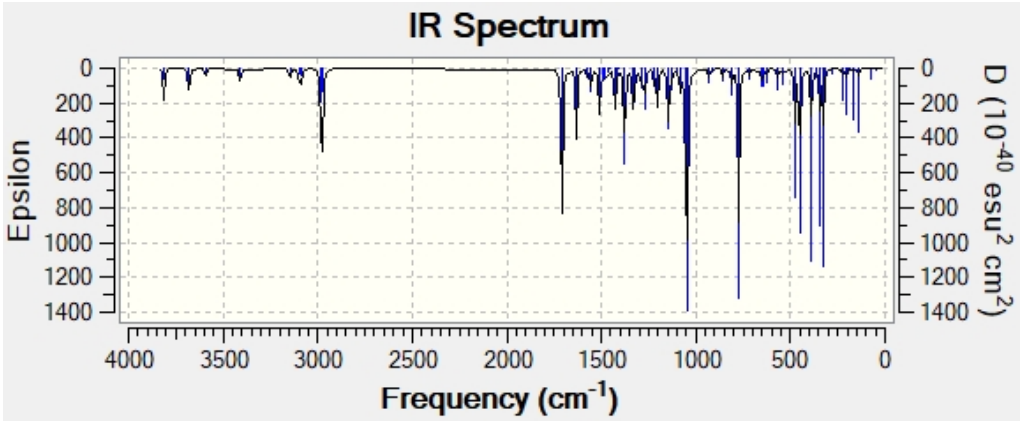

Fig. 8. IR of T1 by 6-311++(d, p).

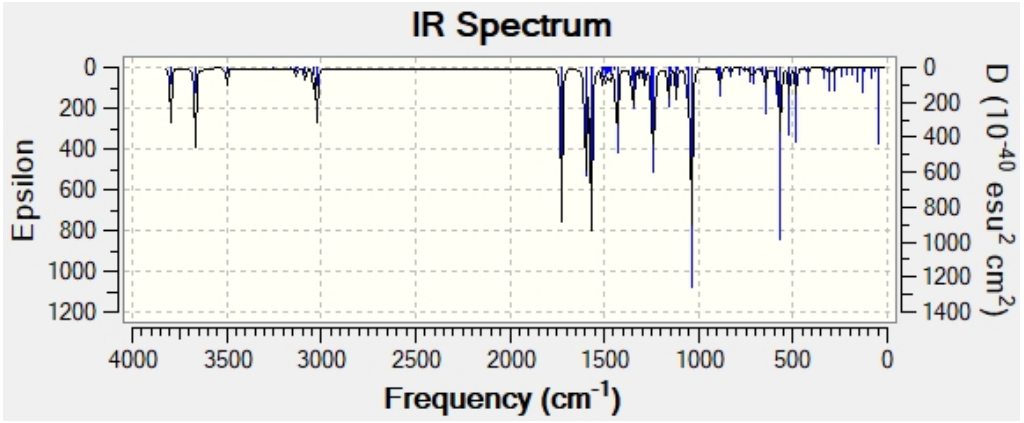

Fig. 9. IR of T2 by 6-311++(d, p).

Table 2. Geometry of D, T1 and T2 by 6-311++(d, p)

T1	Bond lenght	T2	Bond lenght	D	Bond lenght
C8-O23	1.34	C7-N9	1.26	C8-O23	1.21
C8-N11	1.37	C7-O21	1.36	C8-N11	1.35
C8-C3	1.37	C3-C7	1.44	C3-C8	1.5
C1-N6	1.29	N5-C3	1.37	C2-C3	1.39
C1-N7	1.37	C1-N5	1.35	C3-N6	1.35
C2-C3	1.43	C1-N6	1.31	C1-N6	1.31
N7-C2	1.38	C2-N6	1.37	C2-N7	1.38
		C2-C3	1.39	C1-N7	1.35

underwent changes when the molecule's configuration was altered. Geometric alterations led to changes in energy for every compound. Short bond length led to a more desirable and rapid function in chemical reactions. Thus, the C-N bond in D is shorter compared to others, the C-N bond in D is shorter compared to others, and the C-C bond in T1 is shorter compared to others. In line with the data of Table 2, D and T1 participated more conveniently in chemical reactions.

The HOMO energy shows the molecule's potential for electron donation; and therefore, higher values of E_{HOMO} would lead to a higher probability of electron donation by the molecules. The LUMO energy indicates the capability of the electron acceptance by a molecule; and therefore, lower values of E_{LUMO} would lead to a higher probability of electron acceptance by the molecules. One of the most important parameters is the energy gap between the HOMO and LUMO energy levels of a molecule as it is a function of the molecule reactivity. This means that the electronegativity will have a local dependency, with different values for different points over the molecule. This reflects the fact that when we reach the equilibrium state (and only in this state), there is no net charge transfer within the molecular fragments. Apart from its conceptual importance, this principle is used to determine atomic charges and in studies that combine quantum mechanics and molecular mechanics.

Ionization potential shows a fundamental characterization of the chemical reactivity of atoms and molecules, with high IP pertaining to significant stability. A hard molecule possesses a large energy gap, while a soft molecule shows higher reactivity compared to the hard molecules due to the convenient offering of electrons to the acceptors. The molecule's potential of accepting electrons can be probably characterized with the use of the electrophilicity index. The compound's electronics parameters are shown in Table 3. One of the most surprising features of these plots is the fact that the local hardness is sometimes negative, in seeming disagreement with the tendency for an increase in the electron density (ergo, increase in electron number) to increase the chemical potential. Recall, however, that the external potential is not being held constant: as one increases the electron density at the point r, there is a compensating decrease in the external potential, which can cause the chemical potential to decrease. It seems that this effect is most pronounced in electronic shells. It is interesting that the local hardness also clearly shows shell structure and that the exponential divergence that is mandated on mathematical grounds does not appear in our calculations. This latter feature is, no doubt, due to the inadequacy of our basis set for describing the

Table 3. Electronics parameters of D, T1 and T2 by 6-311++(d, p)

Molecular parameters	D	T1	T2
E_{HOMO}	-0.24555	-0.13784	-0.20849
E_{LUMO}	-0.10076	-0.03336	-0.05639
$\Delta E_{HOMO-LUMO}$	0.14479	0.10448	0.1521
IP (Ioniziation energy)	0.24555	0.13784	0.20849
Electron affinity (EA)	0.10076	0.03336	0.05639
Electronegativity (χ)	0.173155	0.0856	0.13244
Chemical potential (μ)	-0.173155	-0.0856	-0.13244
Chemical softness (s)	13.81	19.14	13.14
Chemical hardness (η)	0.07239	0.05224	0.07605
Global electrophilicitiy index (ω)	0.2070768	0.07013	0.1153211
Dipol momentum (Deby) (μ)	8.0563	3.66	4.88
C_v (kcal/mol)	46.613	49.33	46.223
S (kcal/mol)	111.93	114.62	111.66

asymptotic decay of the electron density and the linear response function.

As shown in Table 3, T1 donates an electron, while T2 shows the best structure for electron acceptance in chemical reactions. According to the band gap energy, T1 was more reactive compared to the others. Thus, it acts better in the biological chemical context, which is supported by the other thermodynamic and electronic parameters of each compound.

4. Conclusion

T1 shows the highest stability among the bioactive configurations of dacarbazine tautomer. It is only possible to understand dacarbazine's physical characteristics and chemical reactivity through the consideration of interconversions between various forms of tautomer. It would be helpful to use computational tools capable of predicting the highest stability of tautomer; however, performing the needed quantum calculations requires significant time. It is obvious that the present results cannot be generalized for the prediction of similar computations or finding T1 tautomer with the highest stability in other molecules. Furthermore, it is worth noting that the equilibrium is affected by the solvent and other conditions, whose consideration in the calculations may or may not be possible. In theory, with the use of proper molecular descriptors, such high-level computational tautomerism analyses should be performed on a large number (hundreds or even thousands) of different molecules, and the obtained results should be employed to establish quantitative structure-tautomerism association models with the potential to predict the tautomer with the highest stability for a very small molecule (in terms of the model's applicability)

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