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Theoretical study of the tautomerization of Carmustine in a biological media as an anti-cancer drug

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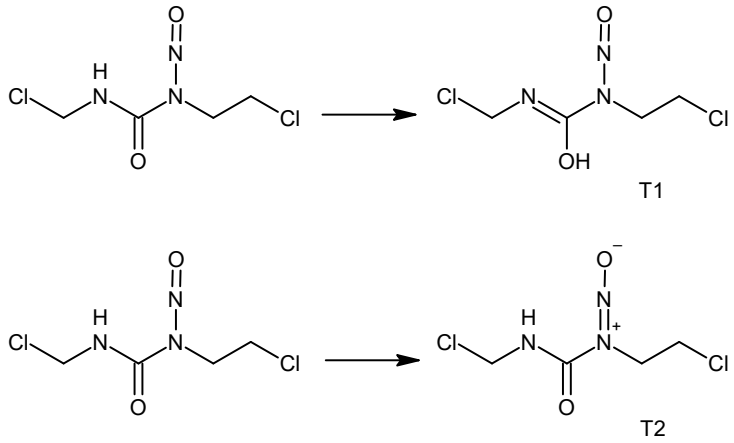
HIGHLIGHTS

- Considering gas catalysis tautomerism.
- Applying Carmustine as anti-cancer drug.
- Applied DFT method for considering drug behavior.
- Use different basis sets for analysis.
- Calculation of thermodynamic energy of tautomerism.

GRAPHICAL ABSTRACT



Structure of Carmastine and tautomers

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ABSTRACT

Tautomers can be defined as isomers of single molecules existing in solutions or cells. Tautomers have the ability to interchange due to numerous spontaneous arrangements of chemical bonds, unlike chirality, whose molecules represent mirror images of enantiomers of one another. Tautomerization of the carmustine mechanism as a potential anti-cancer medication was examined using the DFT method. Two conformational tautomers were identified in the structure of carmustine, and the structure of both tautomers was shown to consider the contribution of atom changes to carmustine conformation. It was possible to obtain the relative energies B3LYP/6-311G++ (d,p), Aug-cc-pVDZ, and 6-311++g(2d,2p) basis sets. Calculations of the highest occupied molecular orbital (HOMO), the lowest unoccupied orbital (LUMO), and bandgap energies of structures were performed while also obtaining the electronics parameters, electrophilicity, electronegativity, softness, and hardness in order to determine the compounds' reactivity within the biological medium. Based on the results, the carmustine structure and both tautomer conformations showed stability, but T1 had greater stability than T2.

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1. Introduction

Given its decomposition mechanisms and distinctive characteristics, it is possible to regard carmustine or [1,3-bis(2-chloroethyl)-1-nitrosourea] as a DNA-modifying agent and a suitable antitumor medication [1-3]. This medication can be categorized into a group of drugs belonging to a class of alkylating anticancer agents, which significantly contribute to treating different human cancers, including leukemia, malignant melanoma, and secondary brain tumors [4-8]. Like other components of nitrosourea derivatives, carmustine shows high lipophilic properties with a lower molecular weight, facilitating its penetration into the CNS and easy crossing through the blood-brain barrier [9-10]. Additionally, the cytotoxic effects of nitrosoureas (CNUs) can be employed to inhibit cancer cell growth.

The primary mechanism of action is exerted through DNA binding and DNA alkylation by a nitrogenous base within a duplex [11,12]. This process inhibits some fundamental processes such as DNA replication, transcription, and translation [13-18]. The two chloroethyl groups make carmustine a bifunctional alkylating agent and enable it to establish intra- and inter-cellular DNA cross-linking [19-22]. Typically, nitrosoureas containing carmustine show extreme instability, undergoing rapid spontaneous transformations that result in several products [23-30]. As a result of such transformations, rapidly converting the alkylating chlorocarbonium ion (active species) produces highly unstable 2-chloroethyldiazene hydroxide [31-33]. The chlorocarbonium ion can be described as a potent alkylating agent capable of cross-linking DNA, which results in high levels of toxicity compared to simple monoalkylation. There are several studies in the relevant literature on dacarbazine tautomerization [34].

The current paper seeks to examine the mechanisms of carmustine degradation and its decomposition pathways in an aqueous medium while investigating the drug's degradation mechanisms the effects from a molecular perspective. Given the interactions of carmustine with DNA, the carmustine tautomer configuration was investigated in a biological media to obtain the best structure of carmustine for the study.

2. Computational model

The effect of two configurations of tautomer on carmustine (C) reactivity was examined using the DFT framework to perform all calculations while considering unrestricted spin settings at Becke's 3-parameter hybrid functional together with the Lee-Yang-Parr correlation functional (B3LYP) and describing the atoms' computational level using the Aug-cc-pVDZ, 6-311++g(d,p), and 6-311++g(2d,2p) people basis set. Gauss View 5.0 software was used to build the basic structure, then Gaussian 09 revision A02 was employed to optimize the structures [35]. Various configurations of tautomers were taken into account. The following procedure was used to calculate the energy of stability, structural parameters, dipole moment, electronegativity, thermal features, IR frequency, and reactivity characteristics. The calculation of DFT-based chemical reactivity, along with stability descriptors, consisting of electronic chemical potential (μ), chemical hardness (η) and global softness (S), and electrophilicity index (ω) was performed using Eqs. (1) through (4) under Koopmans theorem.

$$\mu = -\chi \tag{1}$$

$$\eta = (I-A) / 2 \tag{2}$$

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

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

where χ, I, and A, represent the electronegativity, ionization potential, and electron affinity, respectively.

3. Results and discussion

There are two tautomer arrangements for carmustine that establish biological and hydrogen binding to the DNA and different chemical mixtures. Since every change in the hydrogen position within the chemical structure can lead to changes in the effects of the drug, the gas-phase of T1 and T2 tautomer arrangements of carmustine were investigated. Table 1 illustrates the geometric properties of carmustine and tautomers, although the geometric properties of all compounds changed when using 6-311++(d,p) and 6-311++(2d,2p). However, the compounds showed their most desirable and precise structure using the Aug-cc-pVDZ basis set. Fig. 1 shows the energy of the optimal structures of C, T1, and T2.

Table 1. The geometry of carmustine, T1, and T2 using all basis sets..

Bond	6-311++(d,p)			6-311++(2d,2p)			Aug-cc-pVDZ		
	C	T1	T2	C	T1	T2	C	T1	T2
C7-N17	1.35	1.25	1.35	1.35	1.25	1.35	1.35	1.26	1.35
C7-O20	1.21	1.36	1.21	1.21	1.36	1.21	1.22	1.36	1.22
N18-N19	1.35	1.36	1.35	1.35	1.36	1.35	1.35	1.36	1.35
N19-O21	1.21	1.20	1.21	1.21	1.20	1.21	1.21	1.21	1.21

According to the obtained data, carmustine and T2 had similar structures and the potential to function similarly in chemical media; the calculation of the electronics parameters better illustrates this possibility. Fig. 2 indicates the tautomer when it reaches equilibrium. The optimal structures of C, T1, and T2 are shown in Figs. 3 and 4. The compound HOMO and LUMO plots are illustrated in Figs. 5 through 7. The negative electron density has been highlighted using red, while positive patterns are indicated using green. Negative and positive densities reflect the compound's electrophilicity and electron affinity zones, respectively. The mentioned zones can change the atom hybridization in the molecules. Figs. 8 through 10 indicated the IR spectra of C, T1, and T2 to determine the enol and imine forms of tautomerization.

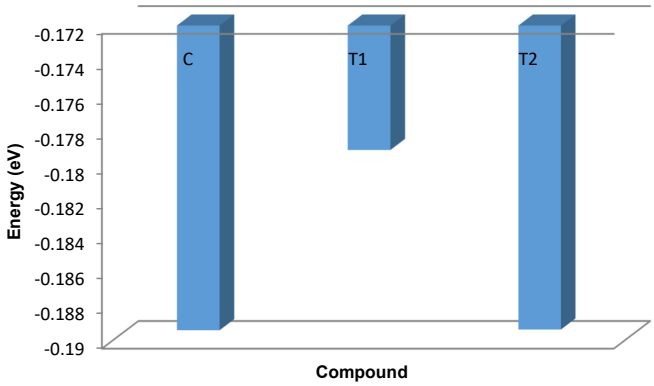

Fig. 1. The energy of the optimal structures of C, T1, and T2.

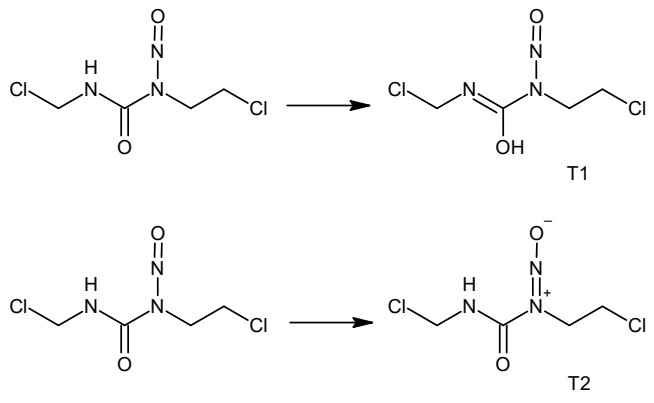

Fig. 2. Structure of carmustine and tautomers upon reaching equlibrium.

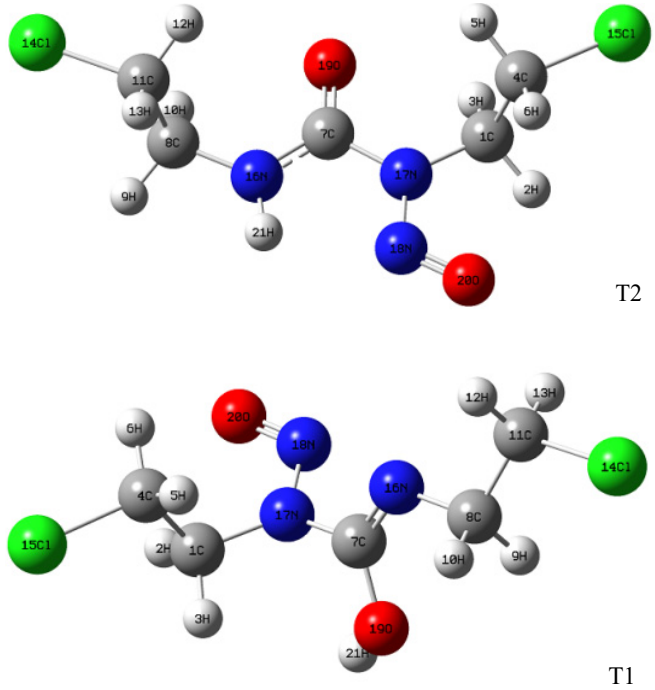

Fig. 3. Optimized structure of tautomer T1 and T2 by Aug-cc-pVDZ.

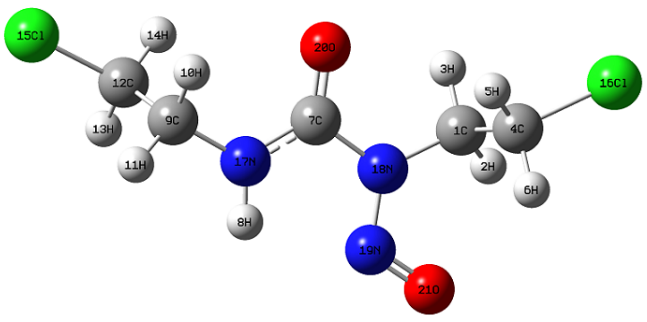

Fig. 4. Optimized structure of carmustine by Aug-cc-pVDZ.

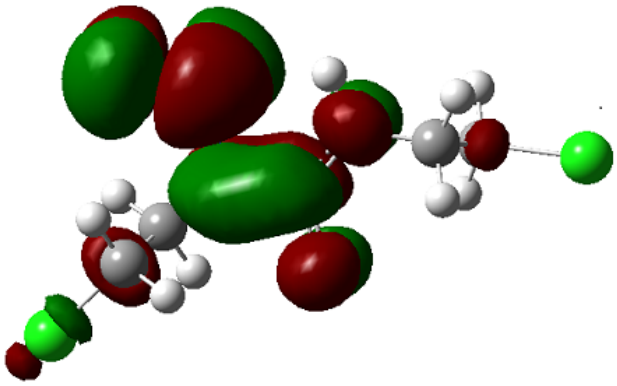

Fig. 5. HOMO-LUMO plot of carmustine by Aug-cc-pVDZ.

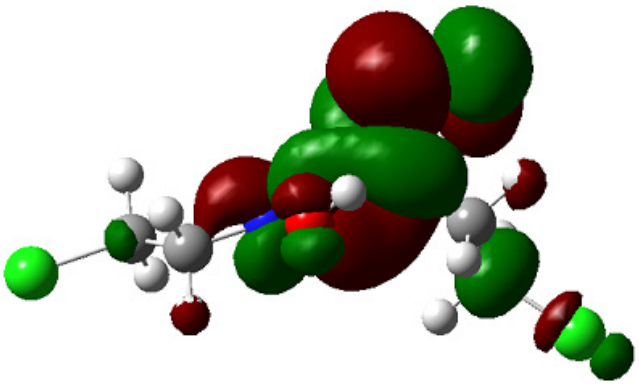

Fig. 6. HOMO-LUMO plot of T1 by Aug-cc-pVDZ.

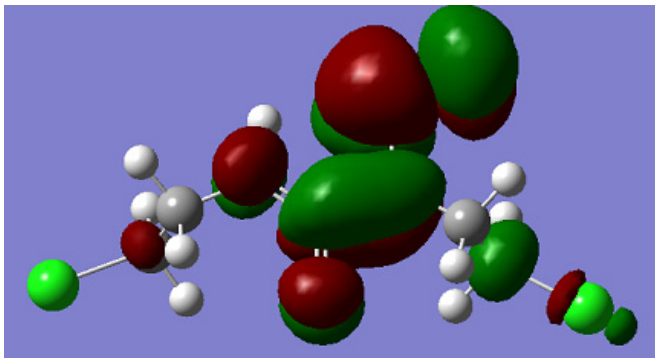

Fig. 7. HOMO-LUMO plot of T2 by Aug-cc-pVDZ.

In Table 2, the dipole moment of T1 is more than the dipole moment of C and T2, which refers to electronegativity and the position of the heteroatom and a hydrogen atom. When heteroatoms, like N, O, and halides, gather in the same position, the dipole moment vector gets bigger.

HOMO energy shows a molecule's capability of donating electrons; therefore, higher E_{HOMO} values indicate a greater possibility of donating electrons by the molecule. On the other hand, LUMO energy represents a molecule's ability to accept electrons, which means that lower E_{HOMO} values result in the greater possibility

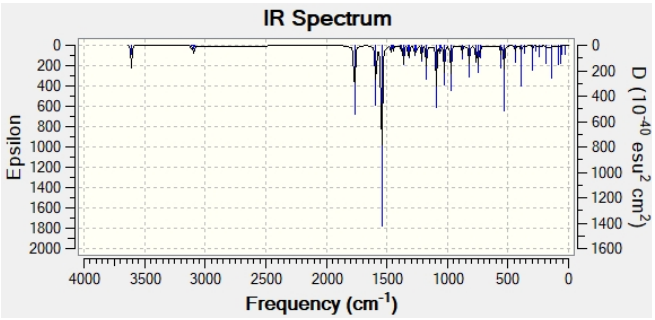

Fig. 8. IR spectrum of carmustine by Aug-cc-pVDZ.

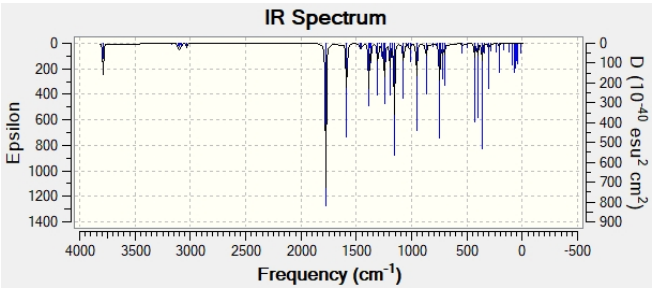

Fig. 9. IR spectrum of T1 by Aug-cc-pVDZ.

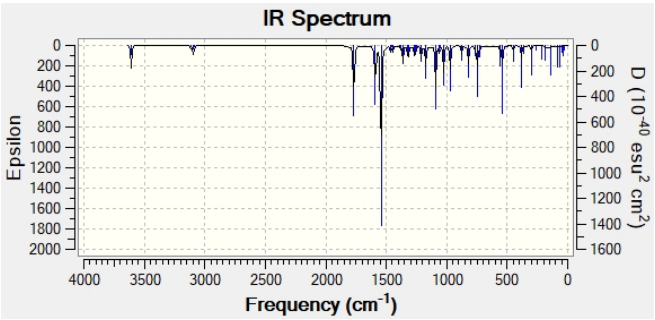

Fig. 10. IR spectrum of T2 by Aug-cc-pVDZ.

of receiving electrons by the molecule. The main parameter is the energy gap that exists among the energy levels of HOMO and LUMO (Fig. 11); it is a function of the molecules' reactivity. Ionization potential basically describes atom chemical reactivity, and the high ionization potential of molecules reflects their highly stable status. Hard molecules possess more significant energy gaps, while their soft counterparts show higher reactivity associated with their higher potential for electron donation. The electrophilicity index describes the molecule's capability for election acceptance. The compounds' electronic parameters are presented in Table 2. As shown in this table, C donates electrons in a chemical media, and T1 shows the most favorable structure to receive electrons in those conditions. Considering the bandgap energy, T1 had higher reactivity, acting better in a biological chemical media.

Table 2. Electronics parameters of C, T1, and T2 by AUG-CC-PVDZ.

Molecular parameters	C	T1	T2
E_{HOMO}	-0.27823	-0.27123	-0.27821
E_{LUMO}	-0.10061	-0.08698	-0.10056
$\Delta E_{HOMO-LUMO}$	0.17762	0.18425	0.17765
IP (Ioniziation energy)	0.27823	0.27123	0.27821
Electron affinity (EA)	0.10061	0.08698	0.10056
Electronegativity (χ)	0.18942	0.179105	0.18938
Chemical potential (μ)	-0.18942	-0.179105	-0.18938
Chemical softness (S)	11.26	21.709	11.258
Chemical hardness (η)	0.0888	0.0460	0.888
Global electrophilicitiy index (ω)	0.2020	0.3482	0.2018
Dipole moment (Debye)	2.2072	2.8056	2.2057
C_v (kcal/mol)	45.459	46.384	45.439
S (kcal/mol)	122.031	124.665	122.043

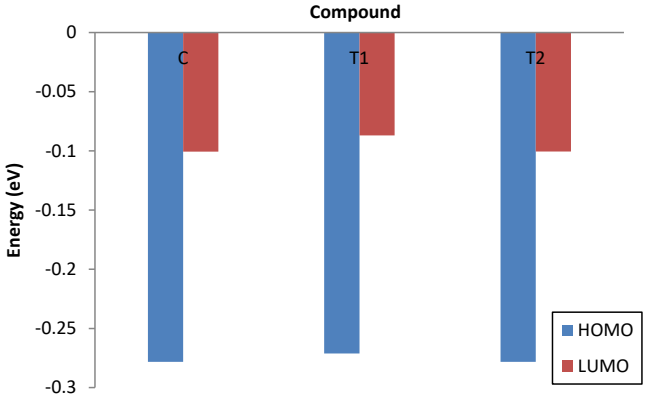

Fig. 11. HOMO and LUMO energy of the optimal structures of C, T1, and T2.

This result was supported by other thermodynamic and electronic parameters of the compounds. According to Figs. 8, 9 and 10, all the IR spectra showed the presence of the same functional groups in the compound and its tautomerization structures.

Thermodynamic properties showed stability and reactivity in the chemical media. The obtained negative chemical potential showed the stability of the compound. In Table 2, the chemical potentials -0.18942, -0.1791, and -0.18938 for C, T1, and T2, respectively, show that C is more stable than T1 and T2. The amount of entropy can help to confirm the chemical potential.

4. Conclusions

T1 can be considered the most stable bioactive form in the tautomer of carmustine. The interconversion between various tautomeric forms should be considered to understand carmustine's physical characteristics and chemical reactivity. The use of computational instruments that can predict the best tautomer stability will be effective, but quantum calculations seem to be highly time-consuming. However, generalization of the results is not recommended when deciding if the same counts of different molecules will demonstrate better stability for T1 tautomers. In addition, since the solvent and other circumstances will affect the equilibrium, attention is required when performing the estimations. Our results suggest that a large sample (hundreds or even thousands) of various molecules should be used in high-level computational tautomerism analysis. The results of those analyses could be helpful in developing models for quantitative structure-tautomerism relationships that can predict tautomers with the greatest stability for every molecule (in the application range of the model) through suitable molecular descriptors.

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