


**Original Article**

# Density Functional Theory Study of 1, 4-Bis(methane sulfonyloxy)butane Tautomerization Mechanism as Anticancer Drug

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**ARTICLE INFO**
**Article history**

Received: 2020-11-01

Received in revised: 2020-11-28

Accepted: 2020-11-29

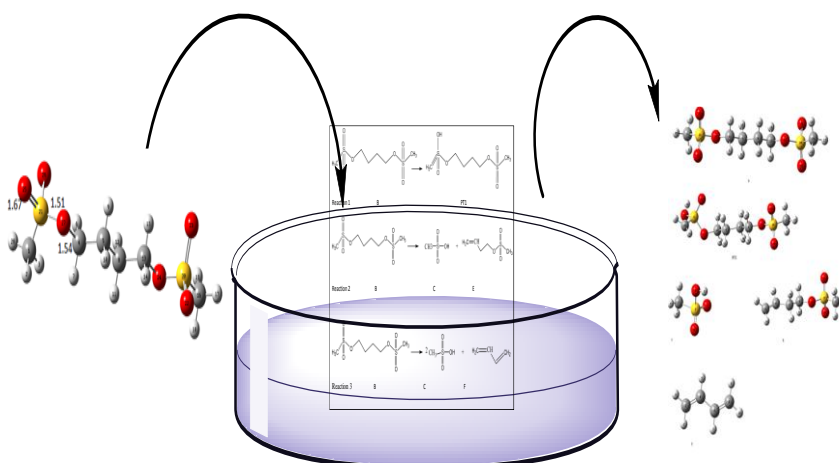
 Manuscript ID: [JMCS-2011-1130](#)

 DOI: [10.26655/JMCHMSCI.2021.1.7](https://doi.org/10.26655/JMCHMSCI.2021.1.7)
**KEYWORDS**

 Busulfan  
 Theoretical calculation  
 Tautomer  
 Reactivity  
 Stability energy  
 Anticancer drug

**ABSTRACT**

This study discussed the prediction of tautomerization manner of the 1,4-bis(methane sulfonyloxy)butane in chemical reactions with an excellent and accurate quantum methods in gas phase. H transition and H migration for the O-H to nearby C=S was theoretically elaborated. The thione tautomer isomer structure formation was investigated as a novel work in recent years. The accurate energy of optimized molecule structures in gas-phase was surveyed by two basis sets of 6-31++G(d) and 6-31++G (d,p) to determine the best reactivity in the biochemical and chemical media. According to the defined computational results, the 1,4-bis(methane sulfonyloxy)butane has been followed by three reactions. Activation and formation energy of reaction was calculated and showed logical way to tautomerization manner. Three predicted reactions state that dissociation of 1,4-bis(methane sulfonyloxy)butane to alkene and sulfonyloxy functional groups is more occruable than tautomer transition in chemical and biochemical media.

**GRAPHICAL ABSTRACT**


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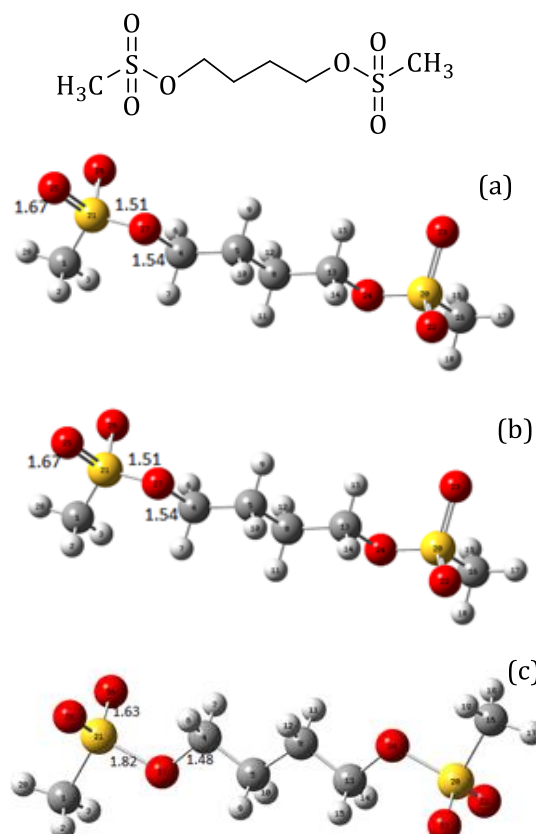
## Introduction

Cancer is the name of the ailment caused by the deterioration of some organs or tissue cells by dating of control and tending to singularity in a harmonious state of our body which is governed by strict control mechanisms [1, 2]. Every three people today, caught for the life by cancer that has become a common disease. There are too many candidate molecules with cogency to be drug, the experiments that have to be performed for each cause the drug cost to increase and the prolongation of the duration of the drug to be taken [3-6]. 1,4-bis(methane sulfonyloxy)butane is one of anticancer drugs that has several structures to react in any situation. All the chemical compounds in biological media have OH, S, O and N group function, causing the drug behaviour. The presence of these group functions with double bond may result in tautomerism transition in chemical and biochemical media. Change of atom place in molecule resulted different chemical activity because of different density of electron, different chemical manner, and different physical chemical properties. Intramolecular single-proton transfer process or thiol-thione tautomerization reactions have been profited. Due to their essential role in biological and chemical processes and its importance in understanding their mechanisms caused considerable experimental and theoretical attention [7-9]. Several theoretical and experimental studies were performed to warble the information concerning H-transfer mechanism and properties relevant to such tautomeric-equilibrium processes [10-14]. The tautomeric single H-transfer in many compounds, determining the thiol-thione favoured structure was concerned in several areas of biochemistry, pharmacy and chemistry [15-17]. Quantum chemical approaches especially density functional theory (DFT)-calculation is helpful to corroborate the reacting of each molecules activity. The present study considers the mechanism of tautomerization reaction of 1,4-bis(methane sulfonyloxy)butane thermodynamically. Three reactions suggested

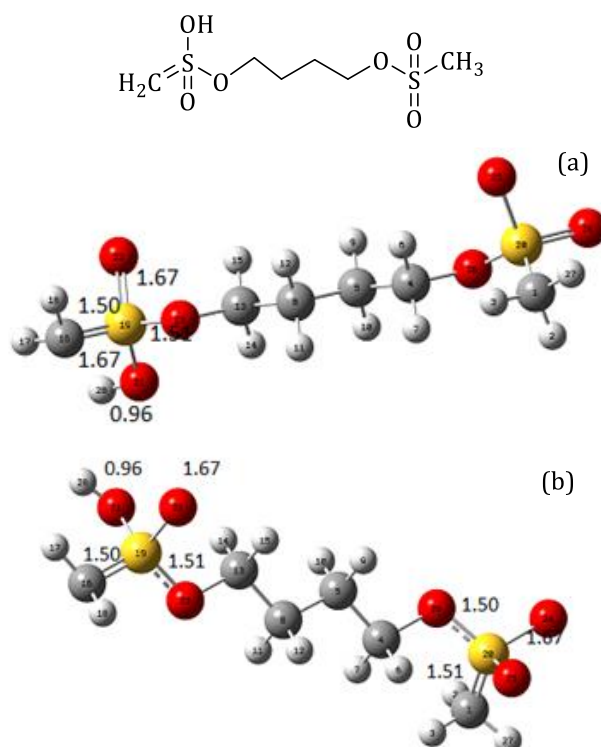
for this consideration and activity energy for all reactions were calculated by DFT method. Structural parameters and the probability of single proton intermigration in the thiol-thione tautomerism reaction have been computed.

## Theoretical Method

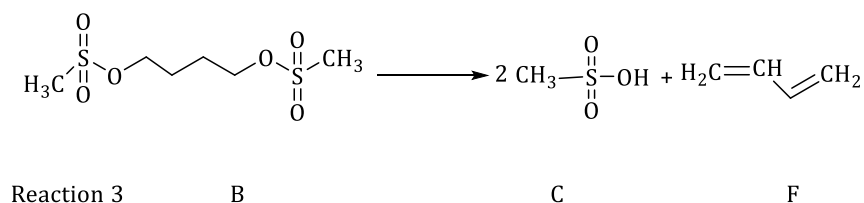
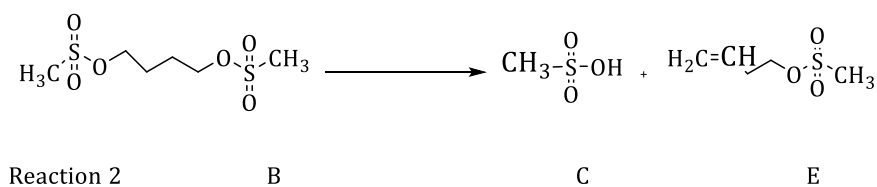
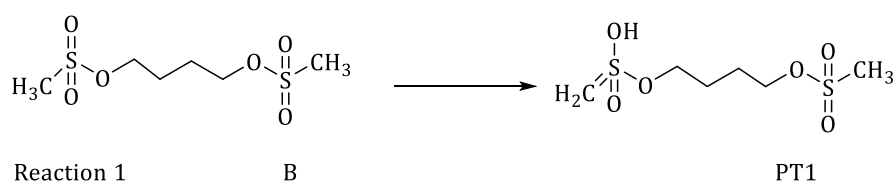
In order to investigate the reactivity of tautomer of the 1,4-bis(methane sulfonyloxy)butane, all the calculations were performed in framework of density functional theory (DFT). For this purpose, Becke's three parameter hybrids function combined with the Lee-Yang- Parr correlation function, B3LYP, were applied using the 6-31++G(d) and 6-31++(d,p) pople basis set. The initial structures were built by gauss view 5.0 and the structures were optimized with Gaussian 03[18]. Different configuration tautomer was considered. Stability energy, structural parameters were calculated using the same method.



**Figure 1:** Structure of Busulfan (a), input of software before optimization (b), output of software after optimization by B3LYP/6-31++G(d,p)



**Figure 2:** Predicted tautomer of Busulfan (PT1), (a) input, (b) output by B3LYP/6-31++G(d,p)



**Scheme 1:** three mechanism reaction of changing tautomer

### Result and Dissection

Figure 1 and Figure 2 demonstrated the chemical structure of the **1**, 4-bis(methane sulfonyloxy)butane named busulfan as anticancer drug and probable thiol-thione tautomer structure. The difference in the bond length in the

chemical structure (Figure 1) and bond length of tautomer structure (Figure 2) states these two structures have different ability to participate in chemical reaction. Due to the presence of the donor atom (O), busulfan is a special property of the tautomeric process. This research has tried to

introduce the most stable isomer in terms of energy by computing the busulfan tautomerization in the gas phase and comparing the results of their calculations with each other. Therefore, a tautomeric structure was considered (Schema 1). Three different reaction may happen when the busulfan participate in chemical reaction. Reaction 1 demonstrates the tautomer transition by changing place of H in two situations PT1 recognized. Reaction 2 states one functional active group of busulfan separated and in reaction 3 separation of two active function groups of busulfan happened. These three reactions are probable reactions can occur in chemical and biological media. In Schema 2, the label of all atoms in the software is shown, in which the structure B is transformed by hydrogen transfer [19] to PT1 forms. C, E, and F form by dissociation intermolecular bond. The three suggested reactions in Schema 1 show a

variety of modes of tautomerization of the busulfan. For recognition of which reaction has most probability to happened formation energy of each compound calculated by B3LYP/6-31++g(d) and B3LYP/6-31++g(d,p) Table 1 states calculated energy. B3LYP/6-31++g(d,p) basis set showed accurate amount of energy and compound B has most stability amongst the other compounds. According to calculated energy tautomer structure is less stable than busulfan that resulted busulfan has most activity in chemical and biochemical media. Energy of E (-2154.44 kJ) states the most stability amongst the other suggested compounds.. Table 3-1 reveal the results for total energy and relative stability calculated by DFT method. According to the calculated results, by computing the energy using B3LYP/6-31++g(d) and B3LYP/6-31++g(d,p), for any compound, the most stable structure is B. B has the negative lowest energy.

**Table 1:** Energy of compounds by DFT

Compound	E(Kj) B3LYP/6-31++g(d)	E(Kj) B3LYP/6-31++(d,p)
B	-3897.26	-3899.18
PT1	-3897.11	-3898.95
C	-1743.80	-1744.67
E	-2153.40	-2154.44
F	-409.55	-409.72

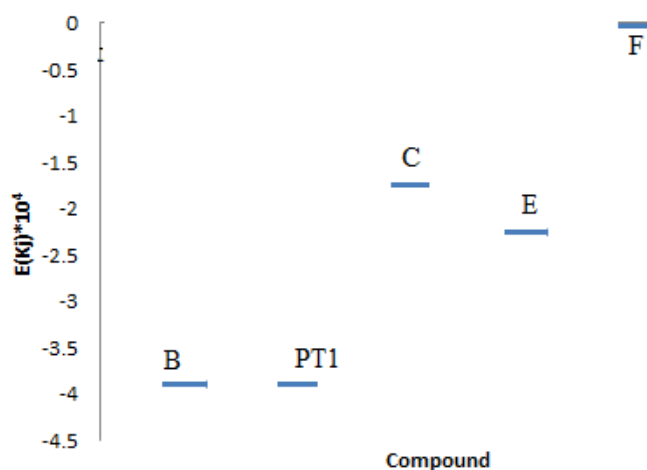
The assortment of energy was found to be B, PT1, E, C, and F, respectively. Therefore B has the lowest energy and suitable structure for presenting and reacting in chemical and biological media.

To satisfy and adjust the minimum energy with relative energy, relative energy of each reaction has been calculated. Table 2 contributes the relative energy for three reactions. The reaction 2 has the lowest energy, so reaction 2 has been done faster as the other ones. In tautomerization

process C and E is more probability than the other products. The reason of stability is diffusion of negative charge in molecule. Therefore, it can be concluded that the busulfan first changes the structure intermolecularly, and then participates in the reaction in all media. Schema 3 depicts the different energy level of compounds. This Schema distinguishes stability of compound clearly. However, B and PT1 specify the minimum energy but in reaction, relative energy shows the probability reaction.

**Table 2:** Relative energy of reactions by DFT

Reaction	$\Delta_r E(\text{Kj})\text{-B3LYP/6-31++g(d)}$	$\Delta_r E(\text{Kj})\text{-B3LYP/6-31++(d,p)}$
1	+0.15	+0.23
2	+0.06	+0.07
3	+0.11	+0.12



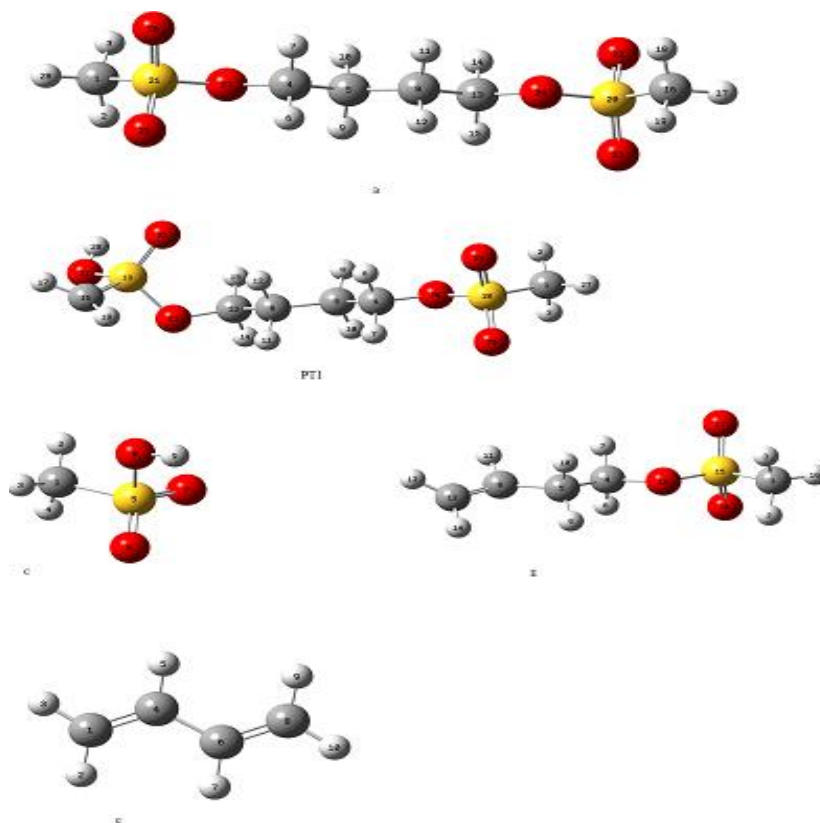
Scheme 3: energy level of compounds by DFT

Table 3: Bond Length (Å) of compounds

Compound	R(Bond length/Å)
B	R(C1-S21) 1.79 R(S21-O26) 1.46 R(S21-O27) 1.64
PT1	R(H28-O21) 0.97 R(C16-H17) 1.08 R(C16-S19) 1.60 R(S19-O22) 1.48 R(S19-O23) 1.63
C	R(S5-O7) 1.45 R(S5-O8) 1.65 R(O8-H9) 0.97 R(C1-S5) 1.79
E	R(C12-C8) 1.33
F	R(C1-C4) 1.34

According to bond length results, by changing the place of H (transfer proton) on O atom bond length revolved. Short bond length distributes strong bond that has not been participated in reaction and long bond length introduced the weak bond that wants to break the bond for making better bond. So, C-S bond in B is 1.79 and in PT1 is 1.60. Strong bond in PT1 caused that PT1 has not partaken in reaction. Also O-H bond in PT1 is 0.97 that obtained this bond is strong and does not trepan to react. In F and E, C=C bond is 1.34 and 1.33 respectively. This bond caused

these compounds have been stable. Pathway 2 and 3 make the stable structure but are the probability condition for reaction.  $\mu$  shows the direction of dipole vector for leading compound to participate in reaction. PT1 by highest dipole momentum 4.446 Debye has bipolar and affected by polarity in solutions and biological condition. Dipole momentum in body case roles an important factor. F has 0 values that acquired in all conditions, it is neutral. Therefore pathway 3 has less chance for reaction.



**Schema 2:** Optimized structure of all reaction

### Conclusion

The tautomerization of B to PT1 happened because of conjugation between the hydroxyl and sulfonyl function in PT1. It makes the carbonyl possess high electronic density to have a nucleophilic attack on H. Therefore B is more stable in all media for acting in reaction. Three pathways were indicated for the tautomerization of busulfan. Energy of each reaction showed that the pathway 3 has stable product that does not create polarity for acting in the polar solution. Changing bond length in B and PT1 showed different ability to do reaction. Reaction energy of different pathway +0.23, +0.07 and +0.12 for reaction A, B and C respectively states the probability of each reaction. Since the biochemistry media always was applying in polar condition, the pathway 3 is not suitable for the biological reaction.

### Acknowledgements

This work was financially supported by the University of Jiroft as grant No: 3813-97-4.

### Conflict of Interest

We have no conflicts of interest to disclose.

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#### HOW TO CITE THIS ARTICLE

Razieh Razavi. Density Functional Theory Study of 1, 4-Bis(methane sulfonyloxy)butane Tautomerization Mechanism as Anticancer Drug *J. Med. Chem. Sci.*, 2021, 4(1) 53-59

DOI: 10.26655/JMCHMSCI.2021.1.7

URL: [http://www.jmchemsci.com/article\\_119823.html](http://www.jmchemsci.com/article_119823.html)