

## A DFT computational study on the [3+2] cycloaddition between parent thionitrone and nitroethene

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### ABSTRACT

A molecular mechanism of the [3+2] cycloaddition has been explored using various DFT theoretical levels. It was found that the reaction proceeds via transition states with different synchronicity, but no intervention of the theoretical possible zwitterionic intermediates. Additionally, regioselectivity of the cycloaddition process has been analysed using vibrational analysis of localised TSs.

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## 1. Introduction

Five-membered heterocycles are widely used as biologically active compounds.<sup>1-5</sup> Heterocyclic compounds with two different heteroatoms particularly are the object of growing research interest of chemists. In particular, compounds bearing the thiazole ring in the molecular structure, such as isothiazolidines or isothiazolines, have antitumor, anti-allergic, anti-diabetic, anti-inflammatory, anthelmintic and anti-HIV activity.<sup>6-10</sup> The isothiazole ring is present in compounds with biological activity such as the pharmaceutical drugs ziprasidone and perospirone.<sup>11,12</sup> Subsequently, it should be noted, that the presence of nitro-group in the organic molecule generally stimulates additive functions of bioactivity.<sup>13-16</sup> Furthermore, nitro-group is an exceedingly attractive starting point for further transformation into many important organic groups and moieties.<sup>17-20</sup>

Nitroisothiazolidines can be prepared via [3+2] cycloaddition reaction involving thionitrones and conjugated nitroalkenes as addends. Unfortunately, there has been no relevant research so far dedicated the cycloaddition reaction of conjugated nitroalkenes with thionitrones. Moreover, chemistry thionitrones is nearly unknown today.<sup>21</sup> This work initiates the comprehensive study in this area.

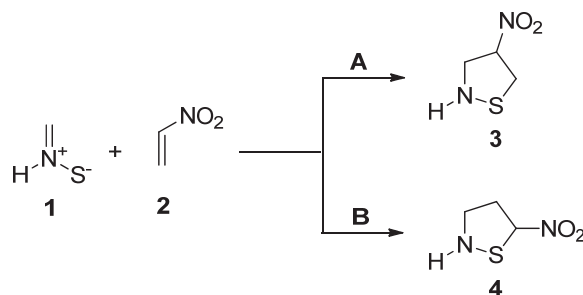
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Depending on the condition and nature of the reagent, the studied reaction (**Scheme 1.**) may furnish two isomeric products following the path A or B. The structure of the product could be predicted based on quantum chemical studies of the reaction mechanism we are presented herein.



**Scheme 1.** Theoretically possible paths of [3+2] cycloaddition reaction between parent thionitronone and nitroethene.

## 2. Results and Discussion

### 2.1 Computational details

For the simulation of the reaction paths hybrid functional B3LYP with the 6-31G(d), basis set included in the GAUSSIAN 09 package<sup>22</sup> was used. It was found previously that the B3LYP/6-31G(d) calculations illustrate well the structure of TSs in [3+2] cycloadditions involving conjugated nitroalkenes.<sup>23-26</sup> The critical points on reaction paths were localized in an analogous manner as in the case of the previously analyzed reaction of diazafluorene with cyanonitroethenes.<sup>26</sup> In particular, for structure optimization of the reactants and the reaction products the Berny algorithm was applied. First-order saddle points were localized using the QST2 procedure. The TSs were verified by diagonalization of the Hessian matrix and by analysis of the intrinsic reaction coordinates (IRC). In addition, similar simulations using more advanced B3LYP/6-31+G(d), B3LYP/6-31G(d,p) theoretical levels were performed. For optimized structures the thermochemical data for the temperature  $T = 298\text{K}$  and pressure  $p = 1\text{ atm}$  were computed using vibrational analysis data.

Indexes of  $\sigma$ -bonds development ( $l$ ) were calculated according to the formula<sup>27</sup>:

$$l_{A-B} = 1 - \frac{r_{A-B}^{\text{TS}} - r_{A-B}^{\text{P}}}{r_{A-B}^{\text{P}}}, \quad (1)$$

where  $r_{A-B}^{\text{TS}}$  is the distance between the reaction centers A and B at the TS and  $r_{A-B}^{\text{P}}$  is the same distance at the corresponding product.

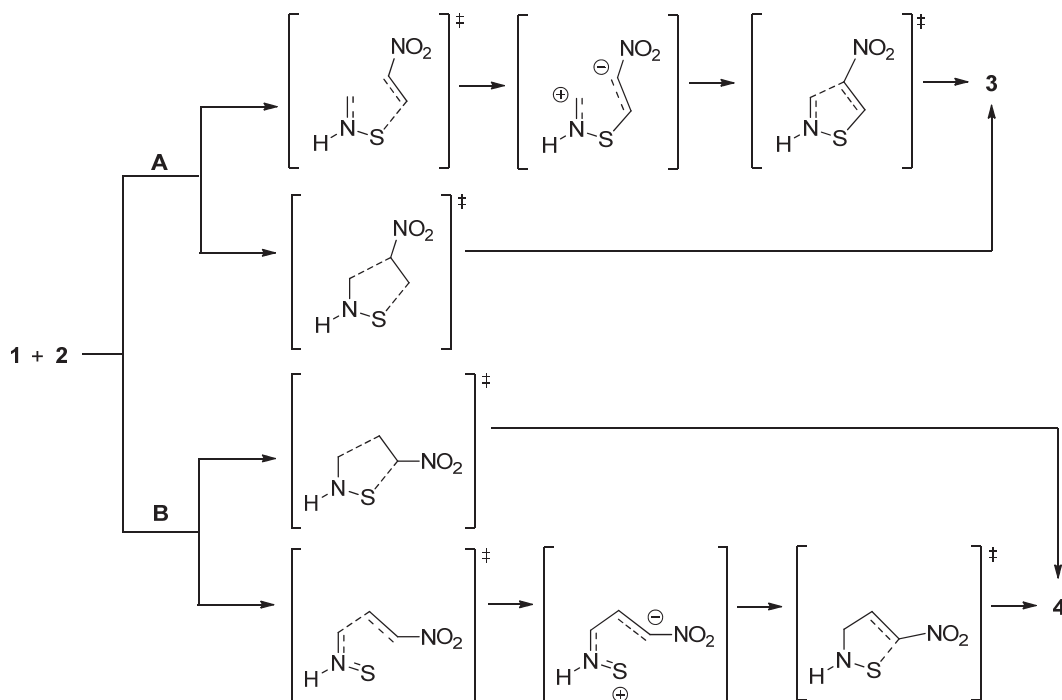
The kinetic parameters as well as essential properties of critical structures are displayed in **Tables 1** and **2**.

### 2.2 Energetical aspects of the [3+2] cycloaddition reaction between parent thionitronone and nitroethene

The [3+2] cycloaddition between parent thionitronone (**1**) and nitroethene (**2**) theoretically may proceed via two competitive regioisomeric channels leading to 4-nitro-1,2-thiazolidine (**3**) and 4-nitro-1,2-thiazolidine (**4**) (**Scheme 1**). The performed B3LYP/6-31G(d) calculations show clearly that both transformation are allowed from a thermodynamic point of view. In particular, Gibbs free energies of these reactions equals about 19kcal/mol. So, reaction's equilibria are completely shifted in to reaction products.

Unfortunately, the analysis of thermodynamical factors does not give any information about the reaction's mechanism. It should be noted at this point that, in the case of [3+2] cycloadditions involving conjugated nitroalkenes, a one-step-mechanism may compete with a two-step, zwitterionic mechanism. This has been recently explored with regards to [3+2] cycloadditions of (Z)-C-anthryl-N-arylnitrones

with (E)-3,3,3-trichloro-1-nitroprop-1-ene,<sup>28</sup> (Z)-C-(3,4,5-trimethoxyphenyl)-N-methylnitron with 1-EWG-3,3,3-trichloro-1-nitroprop-1-enes<sup>23,29</sup> and (Z)-C-(4-methoxyphenyl)-N-phenylnitron with 1-chloro-1-nitroethene.<sup>27</sup> In consequence two different mechanisms should be considered for the considered reaction studied (**Scheme 2**).

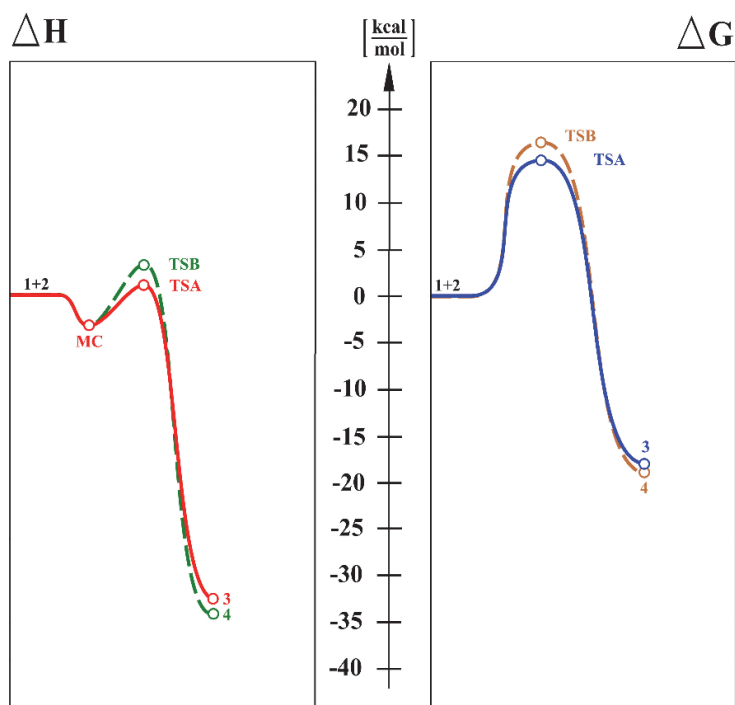


**Scheme 2.** Mechanism of [3+2] cycloaddition reaction between parent thionitron and nitroethene

The results obtained from B3LYP/6-31G(d) calculations show that energy profiles of both considered reactions are similar. In particular, between the valley of starting materials and the valley of final product, only one maximum of the transition state (TS) was localized. Additionally, before the transition state, a valley of pre-reaction complex was identified (**Table 1**, **Fig. 1**). All attempts of localization of alternative transition states which may be connected with hypothetical zwitterionic mechanism, were not successful.

**Table 1.** Eyring parameters for [3+2] cycloaddition between parent thionitron (1) and nitroethene (2) according to DFT calculations

Theory level	Transition	$\Delta H$ [kcal/mol]	$\Delta S$ [cal/molK]	$\Delta G$ [kcal/mol]
B3LYP/6-31g(d)	1+2 $\rightarrow$ MC	-3.5	-23.2	3.4
	1+2 $\rightarrow$ TSA	1.8	-43.6	14.8
	1+2 $\rightarrow$ 3	-32.2	-44.7	-18.9
	1+2 $\rightarrow$ TSB	3.5	-43.5	16.5
	1+2 $\rightarrow$ 4	-33.1	-46.8	-19.2
B3LYP/6-31g(d,p)	1+2 $\rightarrow$ MC	-3.6	-24.1	3.6
	1+2 $\rightarrow$ TSA	1.8	-43.7	14.9
	1+2 $\rightarrow$ 3	-31.6	-44.6	-18.3
	1+2 $\rightarrow$ TSB	3.5	-43.5	16.5
	1+2 $\rightarrow$ 4	-32.5	-46.7	-18.6
B3LYP/6-31g+(d)	1+2 $\rightarrow$ MC	-2.8	-24.2	4.4
	1+2 $\rightarrow$ TSA	2.8	-43.6	15.8
	1+2 $\rightarrow$ 3	-30.1	-44.4	-16.9
	1+2 $\rightarrow$ TSB	4.9	-43.5	17.9
	1+2 $\rightarrow$ 4	-30.8	-46.5	-17.0

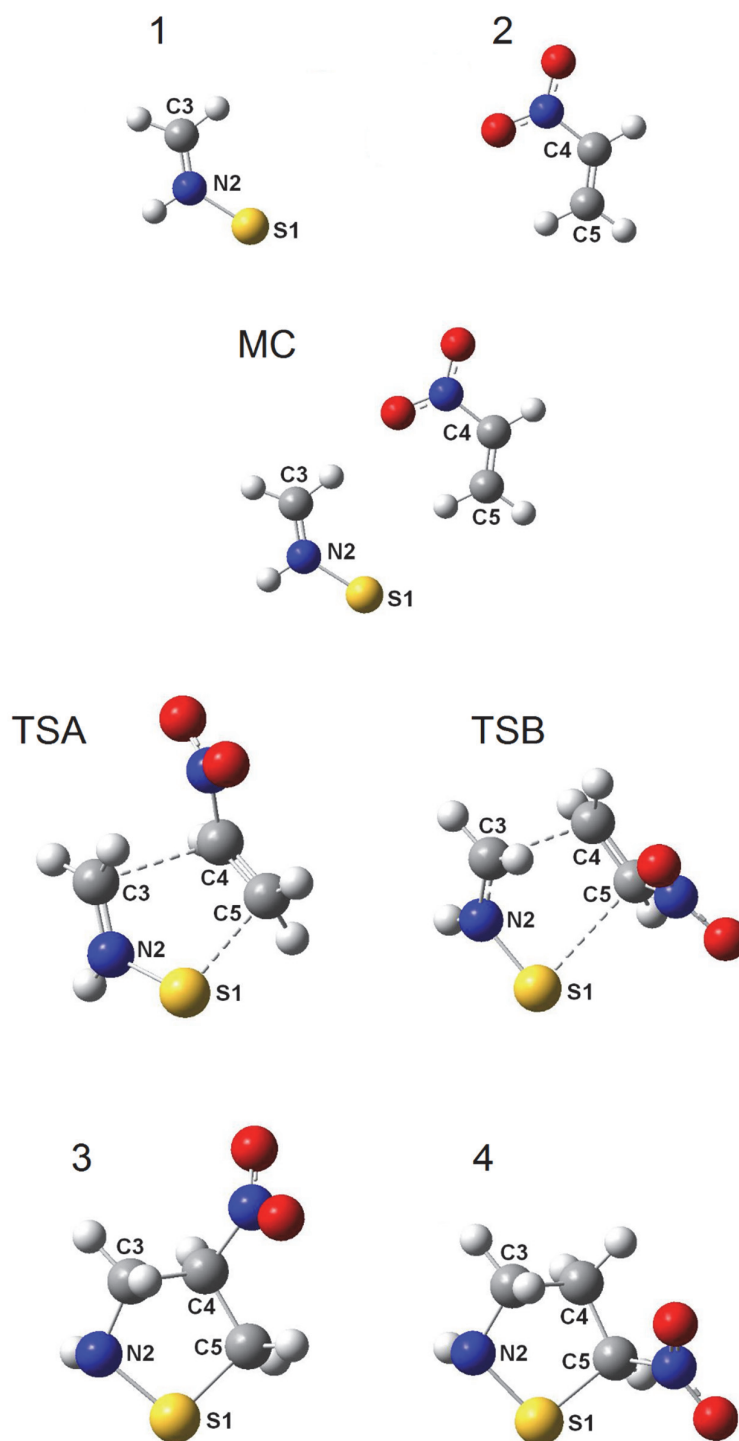


**Fig. 1.** Energy profiles for [3+2] cycloaddition between parent thionitron (1) and nitroethene (2) according to DFT calculations

Interactions of addends at first lead to formation of the pre-reaction complex **MC**. This is a common intermediate for both considered reaction channels. The formation of **MC** is accompanied by a reduction of the enthalpy system by about 3.5kcal/mol. **MC** however may not exist as a stable intermediate, because Gibbs free energy of its formation is positive. Within the **MC**, any new bonds are not formed. Distances between reaction centres (**Table 2**) exist beyond areas, typical for new bonds in the transition state.

**Table 2.** Key parameters of critical structures for [3+2] cycloaddition between parent thionitron (1) and nitroethene (2) according to DFT calculations.

Theory level	Structure	Interatomic distances				$\Delta I$
		C3-C4		C5-S1		
		r [Å]	l	r [Å]	l	
B3LYP/6-31g(d)	<b>MC</b>	3.927		5.041		
	<b>TSA</b>	2.428	0.441	2.483	0.670	0.23
	<b>3</b>	1.557		1.867		
	<b>TSB</b>	2.235	0.553	2.765	0.519	0.03
	<b>4</b>	1.545		1.866		
B3LYP/6-31g(d,p)	<b>MC</b>	4,577		4,980		
	<b>TSA</b>	2.423	0.444	2.475	0.674	0.23
	<b>3</b>	1.558		1.866		
	<b>TSB</b>	2.229	0.557	2.752	0.525	0.03
	<b>4</b>	1.545		1.866		
B3LYP/6-31g+(d)	<b>MC</b>	4,558		5,020		
	<b>TSA</b>	2.459	0.423	2.449	0.688	0.27
	<b>3</b>	1.560		1.867		
	<b>TSB</b>	2.238	0.553	2.757	0.524	0.03
	<b>4</b>	1.546		1.869		



**Fig. 2.** Views of critical structures for [3+2] cycloaddition between parent thionitron (1) and nitroethene (2) according to DFT calculations.

A further conversion of **MC** on both considered paths lead to the transition state (**TSA** for path **A**, and **TSB** for path **B**). This is accompanied by an increasing of the enthalpy by 1.8 kcal/mol and 3.5 kcal/mol for paths **A** and **B** respectively. Subsequently, entropy of the reaction system dramatically decreased. In consequence, Gibbs free energies of the activation are equal 14.8 kcal/mol and 16.5

kcal/mol for paths **A** and **B** respectively. Thus, the regioisomeric channel leading to the 4-nitroadduct (**3**) is favoured, however both theoretically possible paths should be considered as if it was allowed from the kinetic point of view. Within TSs two new sigma bonds are formed. There are C3-C4 and C5-S1 bonds. These bonds are formed simultaneously, however the degrees of their development are different. In particular, the more synchronous is less favoured by TS on the path B ( $\Delta I=0.03$ ).

A further transformation of TSs lead to a valley which should be connected with the final product. This was confirmed by the IRC calculations. A similar picture of the considered reaction provides analogous DFT calculations on more advanced theoretical levels (**Tables 1** and **2**).

### 3. Conclusions

The DFT calculations, independently of theoretical level suggest that a favoured direction of [3+2] cycloaddition between parent thinitrone and nitroethene is the reaction leading to the 4-nitro-1,2-thiazolidine. Competitive reaction channels leading to the 4-nitro-1,2-thiazolidine are less favoured, but allowed from the kinetic point of view. A detailed exploration of the reaction paths confirmed without any doubts that all competitive reactions should proceed according to a one-step, but asynchronous mechanism. The synchronicity of the formation of new sigma bonds is depends on the orientation of addends substructures in the transition state.

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