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Beyond the reaction pathways of *ortho*-phenylene diamine and thiosemicarbazide

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Abstract: Reports have shown that solvent free reaction between *ortho*-phenylene diamine and thiosemicarbazide could lead to the production of a heterocyclic compound, which is an important product in pharmaceutics. In this project, the theoretical approaches that contain the reaction pathways and the mechanism to study them have been used in order to find both the mechanism and possible products that might emerge. In the course of examining the mechanism of that reaction, a scheme, containing eight minor pathways were devised and fifteen different transition states were found as well. Regardless of the mechanism, the relative potential energy surface showed that in each path, the substitution process on the carbon center of the aromatic ring appeared to be much more difficult than substitution on the thioamide carbon center (thiosemicarbazide). The results showed that the phenylene diamine and thiosemicarbazide reaction would produce benzimidazole-2-thione.

Keywords: Reaction pathways, Thiosemicarbazide, Phenylene diamine, Benzimidazole-2-thione, DFT.

Introduction

Benzotriazine derivatives are used directly as antibacterial [1] and antitumor [2] agents. Those compounds have usually a high surface biological activity [3] and due to that factor, many researchers have tried to develop new procedures for synthesizing different types of Benzotriazines [4]. Therefore; it is clear why many researches throughout the world have been trying to find less expensive and easier procedures for producing main Benzotriazine as a raw substance to be used in synthesizing those derivatives.

There have been some papers which have claimed on developing fast, quick and inexpensive methods in synthesizing this product, and have argued that Benzotriazine could be produced through phenylene diamine and thiosemicarbazide fusion in the absence of any additional solvent and without catalysts [5-8]. Regarding the importance of this method, scientists could focus on applying that method to produce Benzotriazine as the major compound for further synthesis of other drugs.

Two separate reports have recently claimed that the phenylene diamine and thiosemicarbazide reaction would produce benzimidazole-2-thione rather than benzotriazine-2-thione [9,10]. If this claim is proved true, there will be a concern that efforts to synthesize new derivatives of the triazines via that method would lead to defective results. On the other hand, benzotriazine-2-thione is essentially a highly important compound as it serves as the base for synthesizing benzimidazole derivatives. Hence; understanding the emergence of the product in this reaction becomes very important. Therefore; it will be reasonable to realize what products would emerge through phenylene diamine and thiosemicarbazide fusion (see Scheme **1**).

As we know, many theoretical studies on elementary reactions [11] and multi-step reaction pathways [12] have been already used successfully to present time to

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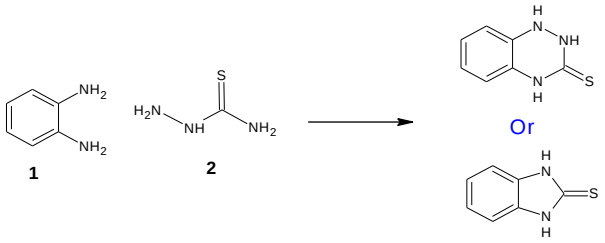
proximate the mechanism of reactions. In addition, the mechanism of the reaction of urea and *ortho*-phenylene Diamine has been investigated previously [13].



Scheme 1: The reaction of ortho-phenylenediamine with thiosemicarbazide.

According to this assumption, in its first step, the present study has used theoretical calculations and devised a scheme on the reaction path, followed by pursuing lower energy pathway, this study has tried to determine which one of the mentioned reports contain more scientific truth and application. .

The calculation was performed by Gaussian 03 software [14]. The Density Functional theory DFT method was used to approximate the entire hypothetical paths of the reaction by using B3LYP level [15] and 6-311+g (d,p) basis set as it is reliable for these approximations [16]. Different geometry models of each species consisted of reactants, Intermediates, products and the transition states were proposed as the input files, and have been optimized to develop several stationary states of each species. In order to find the transition states structure, the synchronous transit- guided quasi-Newton (STQN) method [17] was used. The frequencies of all structures were extracted to acquire the thermodynamic energies of each state. The accuracy of all transition states was confirmed by the IRC intrinsic reaction coordinates [18,19].

Results and discussion

As illustrated in Scheme **2**, it is possible to initially consider four different paths (leading to formation of three intermediates) for the interaction between phenylene diamine (compound 1) and thiosemicarbazide (compound 2). The two separated paths (paths 1 and 4) lead to the formation of Intermediate 3. In the path 1, the amine nitrogen of compound **2** attacks the carbon center of **1** and in turn, the amine of **1** leaves its position. However; in path 4, nitrogen of **1** attacks the carbon of **2**, and the amine of **2** leaves (shown in Scheme **2**). These two paths result in the formation of Intermediate 3. Nevertheless, when calculating the two considered pathways, it was found that there are two transition States, TS (A) with 73.2 kcal mol^{-1} and TS (C) 76.4 kcal mol^{-1} in path 4. After comparing the energy of TSs A and C, it was found that TS of A is a much lower energy than TS (C) which had 76.4 kcal mol^{-1}. It shows that the hydrogen bond in TS (C) could not make up for the steric congestion to decrease the energy surface.

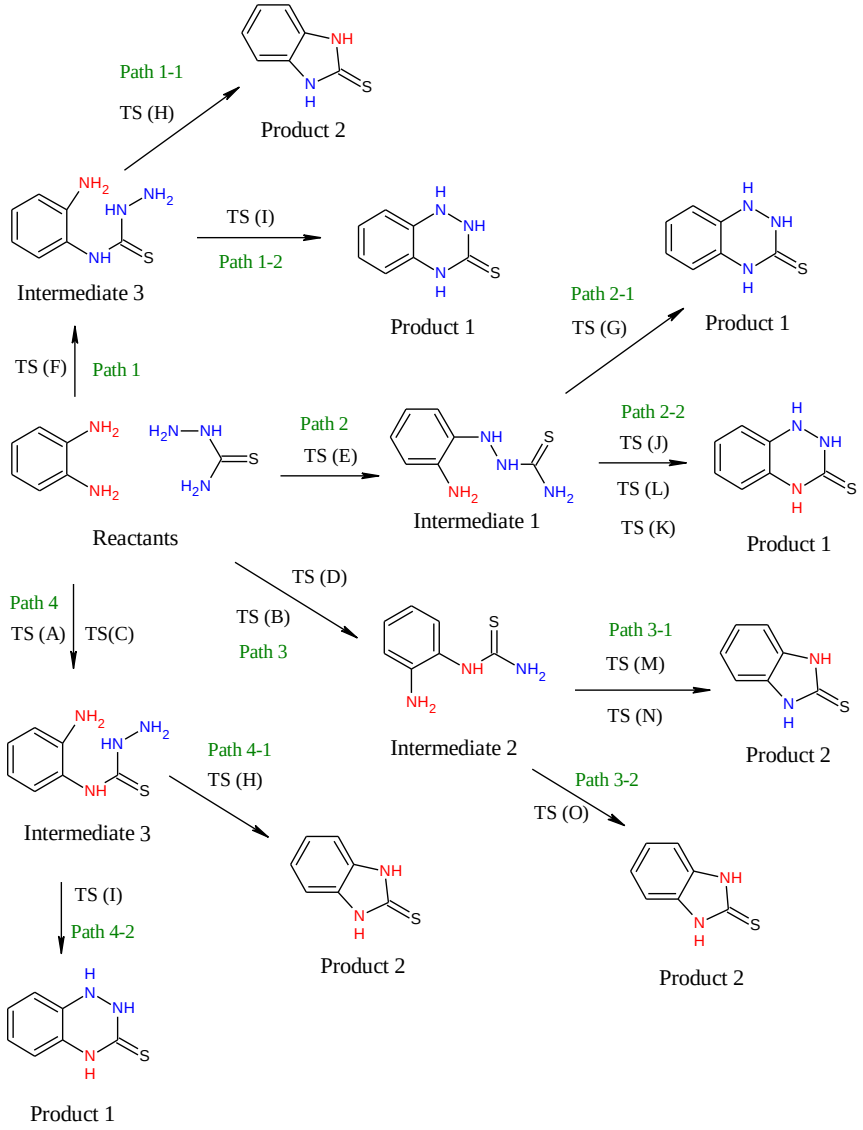
Table 1: The values of relative Gibbs free energy (Kcal/mol) of all species.

Species	Energy	Species	Energy
Reactants	8.22	TS (M)	88.1
RC	11.4	TS (N)	83.7
TS (A)	73.2	TS (O)	70.9
TS (B)	69.4	IC (2-2)	13.6
TS (C)	76.4	IC (1-2)	8.95
TS (D)	75.0	IC (3-2)	11.3
TS (E)	75.5	IC (2-1)	13.2
TS (F)	75.8	IC (3-1)	11.1
TS (G)	79.0	IC (1-1)	6.37
TS (H)	60.6	PC (1-1)	5.96
TS (I)	84.0	PC (2-1)	0.00
TS (J)	61.6	Product (2-2)	7.89
TS (K)	67.1	Product (1-3)	4.94
TS (L)	66.5	Product (1-4)	8.39

In path 2, the hydrazine group of thiosemicarbazide attacks carbon center of phenylenediamine through TS (E) (75.5 kcal mol^{-1}) and generates intermediate 1. Besides, in path 3, the compound **2** pushes the hydrazine group from the compound **1** (TS B with 69.4 kcal mol^{-1} and D with 75.0 kcal mol^{-1}). As previously mentioned, the TS (E) (path 2) contains higher energy than TS (B and D), which is in agreement with the theory that suggests the substitution reaction occurs easier on the carbon of thiosemicarbazide than on an aromatic carbon center of phenylene diamine. The mentioned points indicate that it is easier to find out why paths 3 and 4 take place faster than path 1 and 2.

After the first step and acquiring the intermediates, it is observed that every path bifurcates into two different minor routes. The path 1 reaches the minor paths (1-1) and (1-2) lead to benzimidazole-2-thione and benzotriazine-2-thione products; respectively. The channels (2-1) and (2-2) which are divided from path 2, merely produces benzimidazole-2-thione. As shown in Figure **5**, any transition state in the channel (2-2) has less energy compared to the TS of path (2-1). Comparing paths bifurcation into intermediate 2 we

can find out that channel (3-1) (containing TS M with 88.1 kcal mol^{-1} and N with 83.7 kcal mol^{-1}) has higher energy than path (3-2) which consisted of TS (O) that has 70.9 kcal mol^{-1}. Moreover, in continuation of path 4, the path (4-1) which gives benzimidazole-2-thione is in lower energy compared path (4-2) that gives benzotriazine-2-thione.



Scheme 2: All of the possible pathways for the reaction.

As shown in Figure **1**, two different transition states were found between reactant complex and intermediate in path 3 and 4, namely TS (A) and TS (C). Despite the presence of same mechanism of the two species, it seems that the steric congestion of the hydrazine group in the TS (C) results in a lower stability compared to TS (A); and even the N···HNH hydrogen bond (2.60Å) could not decrease the TS (C) energy compared to TS (A).

In addition, two TSs were found in the case of path 3. Here, the hydrazine group leaves its position during a substitution process. In spite of N···HNH hydrogen bond (2.28 Å) in TS (D), one can consider this as the repulsion of nonbonding electron pairs and/or steric congestion responsible for leaving hydrazine which makes TS (D) to be more unstable than TS (B) (Figure **2**).

Another step with two separated TSs is the path (3-1) which consisted of the ring closing intermediate 2 via substitution of amine in the carbon center of thioamide. There is a possibility that a weak hydrogen bond interaction between free hydrazine causes the TS (N)

be lower energy than its counterpart species. In fact, the TS (N) has two hydrogen bonds containing one N···H (1.98 Å) and S···H (2.59 Å); however, TS (M) has not any hydrogen bond (Figure **3**).

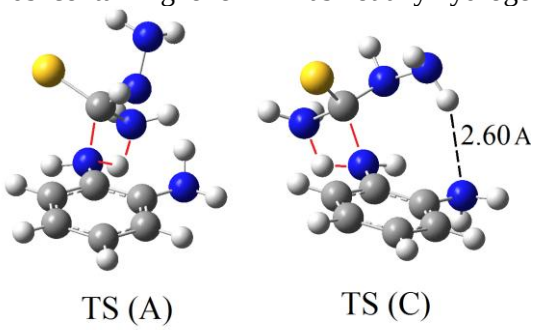


Figure 1: The structures of the transition states A and C.

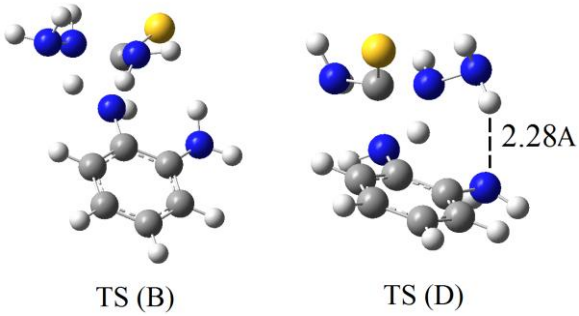


Figure 2: The structures of the transition states B and D.

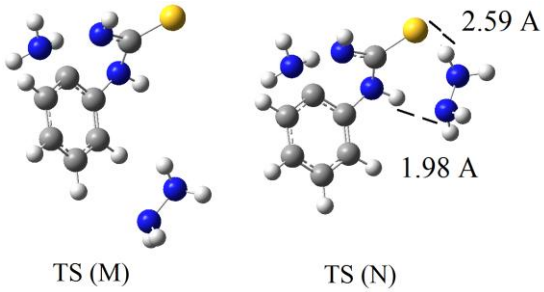


Figure 3: The structures of transition states M and N.

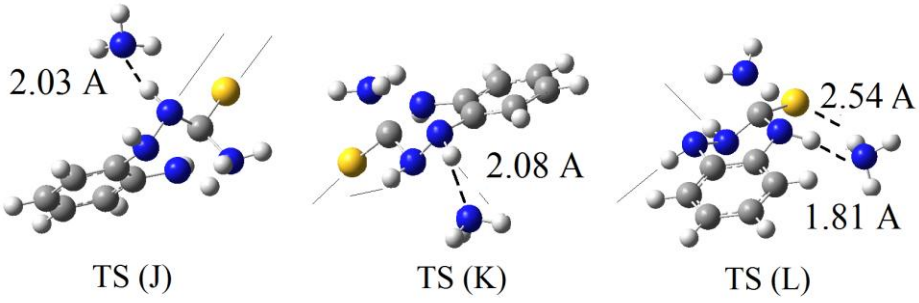


Figure 4: The structures of the transition states J and K and L.

As shown in Figure **4**, TS (J) (61.6 kcal mol^{-1}) with a 2.03 Å N···H hydrogen bond has a cyclohexane half-chair-like conformation; however, TS (K) (67.1 kcal mol^{-1}) with an N···H hydrogen bond (2.08 Å), and TS

(L) (65.4 kcal mol^{-1}) with an N···H, an S···H hydrogen bond (1.91 Å, and 2.54 Å receptivity), have a half-boat-like figure. In all three cases, there is a hydrogen bond interaction. However, what causes the half-chair structure of (J) to become more stable than the half-boat structure (K) and (L) is not clear. Furthermore; it seems that despite having the same mechanism and steric conformation, the structure (L) is more suitable in moving toward (K) due to an excessively weak hydrogen bond between sulfur and the hydrogen of amine (2.54 Å).

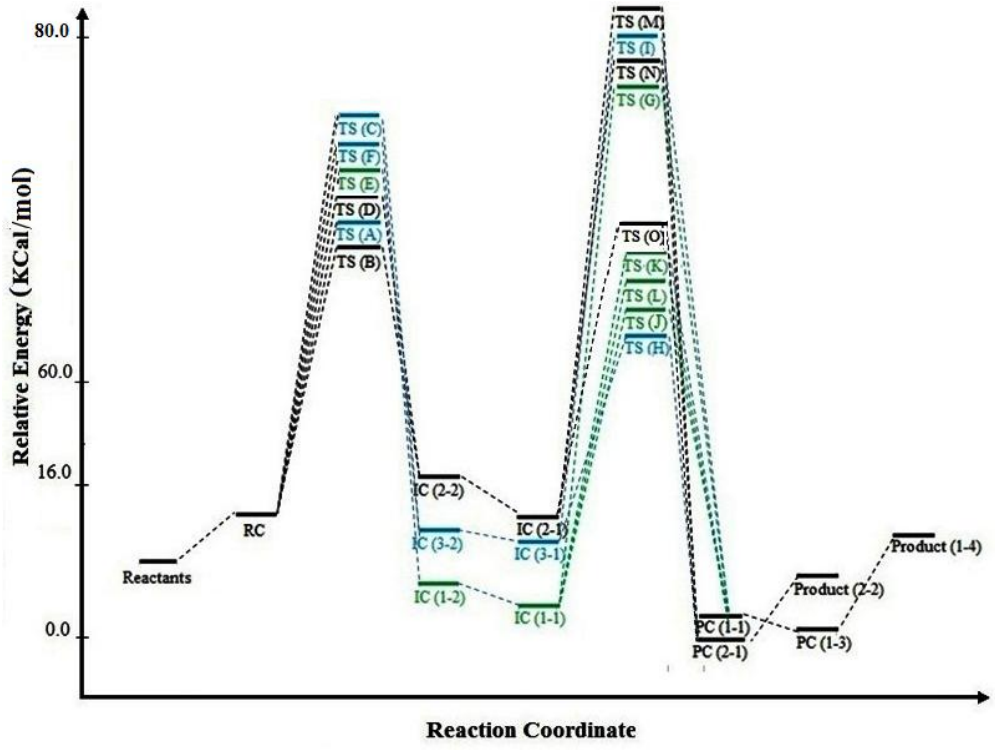


Figure 5: The relative Gibbs free energy surface of the all possible paths of the reaction.

Conclusion

Regardless of the diversity of the transition states in some steps, the relative potential energy surface (see Figure **5**) shows that in each step, the substitution process on the carbon center of aromatic ring appears to be more difficult than substitution on the carbon of thioamides. For example paths (1,1), (2,2), (3,2), (4,1) are faster with lower energy than paths (1,2), (2,1), (3,1), (4,2); respectively (Table **1**).

In addition the relative potential energy surface (RPES) shows that the pathway Reactants –> Reactant complex –> TS (A) –> Intermediate complex (3-2) –> Intermediate (3-1) –> TS (H) –> Product complex (2-1) is the less energy channel for this reaction and the product of this pathway is benzimidazole-2-thione.

In addition, the relative potential energy surface (RPES) shows that the pathway Reactants –> Reactant complex –> TS (A) –> Intermediate complex (3-2) –> Intermediate (3-1) –> TS (H) –> Product complex (2-1) is with the least energy way in this reaction and benzimidazole-2-thione is product of this pathway.

Moreover; comparing all transition states in the first step, it was revealed that in spite of making hydrogen bond interaction, stymieing the hydrazine group in endo position significantly increases the energy surface of each species (see A-C, and B-D structures in Figures **1**, and **2**).

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