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Theoretical study of The Reaction mechanisms of Thiazolidine formation from 2-aminoethanthiol and Formaldehyde

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Abstract

Two possible have been proposed to account for the condensation of 2-aminoethanthiol with formaldehyde to thiazolidine. The first is suggested to proceed through a similar Schiff base intermediate. The second mechanism for thiazolidine formation involves initial attack on formaldehyde by the sulfur atom, the formation of sulfonium ion intermediate, and cyclization. By using computational chemistry, the MP2/6-311++G(2d,2p) level of theory was selected from HF,MP2 and DFT as the best method to describe the geometry of reactants , products, intermediates and transition state. At this level of theory, geometry optimization, vibrational frequencies, intrinsic reaction coordinate (IRC).Thermodynamic properties ΔH^o and ΔG^o have been calculated for this reaction.

Keyword: Thiazolidine, Transition state, IRC, Basis set

1.Introduction

Thiazolidine (TC) formation from carbonyl compounds and aminothiols has been studied [1] (Eq.1)

due to its relevance to the binding of carbonyl compounds to proteins containing sulfhydryl and amino groups in close proximity [2].

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TC

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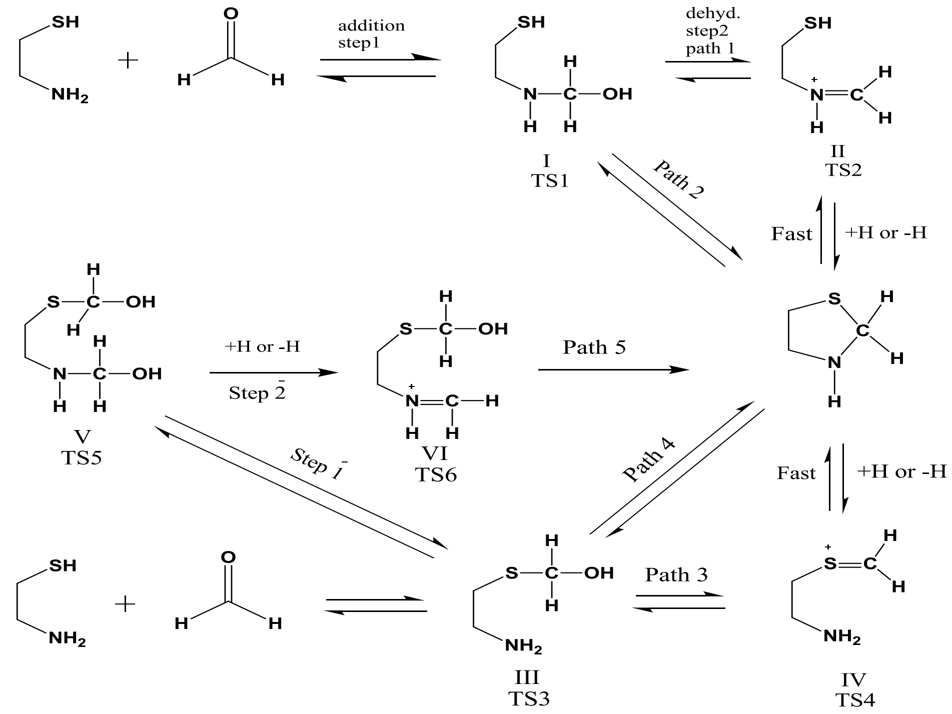


Scheme 1

Thiazolidine formation has been suggested to proceed through a similar Schiff base intermediate [3] II (Path I, Scheme I) in the condensation of 2–aminoethanthiol with Formaldehyde [4]. An alternative mechanism for thiazolidine formation involves initial attack on Formaldehyde by the sulfur and cyclization (Path 3, Scheme I). Two less plausible possibilities involve S_N2 displacements of hydroxide from the carbinolamine(Path2) and hemithioactal[5] (Path 4), respectively.

to the incomplete nature of the earlier studies, and the lack of kinetic information on reactions of aliphatic amines with aliphatic aldehydes, we have reexamined the mechanism of TC from 2-aminoethanthiol and Formaldehyde by computational chemistry. [6]

A transition structure is the molecular configuration that separates reactants and products. In a one-dimensional system, this point is a maximum of the potential energy function.

Since the intrinsic reaction coordinate (IRC) was defined as the mass-weighted steepest decent pathway (MW-SDP) starting from a transition structure (TS) and practical for computation of IRC were developed, [7,8] reaction pathways of numerous chemical reaction have been elucidated by calculations of IRC. To calculate an IRC, one has to locate the TS on a potential energy surface (PES) as the starting point. Hence, there have been considerable efforts to develop efficient methods locating TS [9]. The most fundamental tools are geometry optimization methods, which can locate one TS starting from an initial guess when the guess is appropriate [10]. The geometry of a transition structure is an important piece of information for describing the reaction mechanism. To understand if we need to generalize the one dimensional picture above to many dimensions. The transition structure is mathematically defined as a saddle point the first derivative of the potential with respect to any nuclear coordinate is zero, and the second derivative is positive for all but one coordinate. Thus, such a point looks like a minimum on the potential energy surface in every direction except one. Along that particular direction (that actually defines the reaction coordinate at the transition state) this point is a maximum of the potential.

The aim of this paper is to investigate the mechanism of the reaction between Formaldehyde and 2-aminoethanthiol through theoretical calculations using DFT, HF and MP2 methods of quantum chemistry. A better understanding of the chemistry of thiazolidine formation reaction will help the selection of catalysis and will improve the reaction condition to achieve better yields.

2. Computational Details

The calculations were performed using Gaussian 05 program package [11]. The geometries of reactants and products were fully optimized at the Hatree - Fock (HF) , Density Functional theory (DFT) by Beck's Three-Parameter hybrid functional (B3LYP) and MØller-Plesest second order (MP2) using 6-31G(d), 6-31++G(d, p) and 6-311++(2d,2p) basis set. The stability of the obtained structures is confirmed by vibration analysis. QST method was used to search for transition states.

3. Results and Discussion

3.1 Energies and Geometries

The energies of reactants and products were calculated at DFT and MP2 levels as shown in tables 1 and 2 respectively. The energies sensitive to the basis set used. It is clear that the calculated values of the energies depend on the basis set used. Accordingly the energy decreases from −71857.166 and −358599.064 kcal/mole for the Formaldehyde and thiazolidine respectively at the B3LYP/6-31++G(d,p) level to −71878.163 and −358651.058 kcal/mole at the B3LYP/6-311++G(2d,2p) level.. The geometric structures of reactants and intermediates are shown in Figs. 1 and 2. The structural parameters of various compounds used in the thiazolidine formation are listed in table 3. The energies of transition state structures were calculated at MP2 level only as shown in table 4, the zero-point energies are calculated by two basis sets and listed in table 5. The potential energy calculation showed that the bond length of C-S and C-N of 2-aminoethanthiol are consistent through converting from reactants to product (see table 3). On the other hand the transition states or intermediates are characterized by their higher energies compared to the reactants and products. In all cases the energy of TS2 and TS4 are higher than the energy of the TS1, TS3, TS5 and TS6.

Table 1 Total energy of the reactants and products used in thiazolidine formation calculated at DFT level with three basis sets.

Compounds	DFT6-31G(d)	DFT6-31++G(d ,p)	DFT6-311++G(2d,2p)
Formaldehyde	−71846.795	−71857.166	−71878.163
2-Aminoethanethiol	−334684.228	−334699.660	−334740.221
Water	−47947.379	−47963.107	−47980.601
Thiazolidine	−358594.571	−358599.064	−358651.058

Table 2 Total energy of the reactants and products used in thiazolidine formation calculated at MP2 level with four basis sets.

Compounds	MP2/ 6-31G(d)	MP2/ 6-31++G(d ,p)	MP2/ 6-311++G(2d,2p)	MP2/ 6-311++G(2df,2p)
Formaldehyde	−71639.370	−71655.699	−71676.866	−71724.415

2-aminoethanethiol	−334023.674	−334071.372	−334153.578	−334193.947
Water	−47814.283	−47837.1527	−47876.687	−47888.388
Thiazolidine	−357865.578	−357910.576	−357943.404	−358051.846

Table 3 MP2/6−31++(2d,2p) structural parameters of reactants and products.

Compounds	C−H A^0	C=O A^0	C−C A^0	C−N A^0	C−S A^0	S−H A^0	N−H A^0	O−H A^0
Formaldehyde	1.104	1.221						
2-Aminoethanethiol	1.07		1.54	1.47	1.78	1.31	1.00	
Water								0.959
Thiazolidine	1.07		1.530	1.486 1.478	1.766 1.780		1.00	

Table 4 Total energies (Kcal/mole) of Transition state structures used in the formaldehyde and 2−aminoethanethiol reaction calculated at MP2 level with three basis sets.

TS	MP2/6-31G(d)	MP2/6-31++G(d,p)	MP2/6-311++G(2d,2p)
TS1	-405674.254	-405740.132	-405870.157
TS2	-358073.288	-358119.916	-358209.871
TS12	-405680.522	-405745.970	-405217.08
TS3	-405678.271	-405744.174	-405873.504
TS4	-358038.851	-358100.057	-358190.170
TS34	-405494.022	-405566.643	-405620.204
TS5	-477328.842	-477412.913	-477591.619
TS6	-429726.091	-429790.619	-429928.148

Table 5 Zero point energy ZEP (Kcal/mole) Calculated at HF/6-31G(d) and HF/6-31++G(2d,2p) levels.

Molecule	Zep at HF/6-31G(d)	Zep at HF/6-31++G(2d,2p)
Formaldehyde	18.326	17.74253
2-aminoethanethiol	62.899	62.173
Water	14.415	14.294
Thiazolidine	69.613	68.799
TS1	86.756	85.435
TS2	75.198	74.155
TS12	81.743	83.071
TS3	86.409	85.877
TS4	75.021	74.218
TS34	86.570	85.547
TS5	109.518	108.468
TS6	98.613	97.775

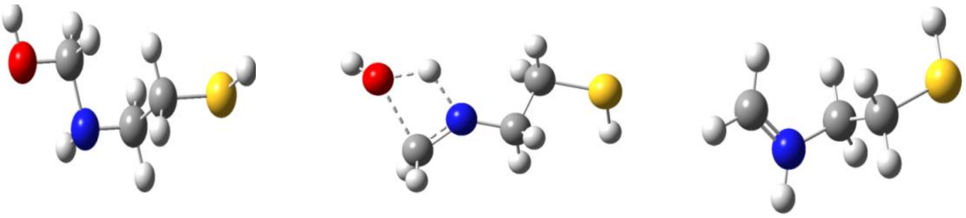
Formaldehyde

2-aminoethanethiol

Thiazolidine

Water

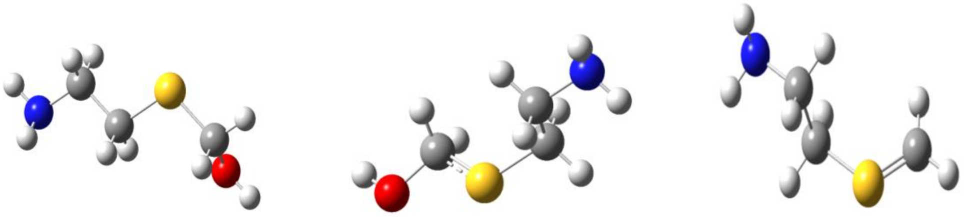
Fig.1 Geometries of reactants and products



TS1

TS12

TS2



TS5 TS6

Fig. 2 Geometries of transition states

3.2 Reaction mechanism

The route of aliphatic aldehyde with 2-aminoethanethiol has been examined via the three possible reaction paths, namely, addition reaction of amine with carbonyl compound to form Carbinolamine intermediate I then converted to form cationic Schiff base intermediate II (Path1, scheme 1) , and addition reaction of thiol with carbonyl compound to form hemithioacetal then the formation of sulfonium ion intermediate and cyclization (Path 3), three route two less plausible possibilities involve S_N2 displacements of hydroxide from the carbinolamine (Path 2) and hemithioacetal (Path 4), respectively [5] as shown in scheme 1 .

The enthalpy and Gibbs free energy change and the final energies for these reaction are calculated at HF and DFT high level using basis sets 6-31++G(2d,2p) which tabulated in Table 3-6 . This table concentrated on path one and path three species. DFT level of calculation gave more accurate results of energies than MP2 level for configurationally structures and transition state structures of table 6.

Table 6 The Quantum mechanical energy, ΔG° and ΔH° of the pathways reaction at different levels (Kcal/mol).

TS	Path Route	DFT/6-31 G(d)	DFT/ 6-31++G(2d,2p)	ΔG° HF/6-311++G (2d, 2p)	ΔH° HF/6-311++G (2d, 2p)

TS12	Path12	−406377.633	−406411.612	7.055	4.071
TS34	Path34	−406332.120	−406360.759		

3.3

Transition state calculations

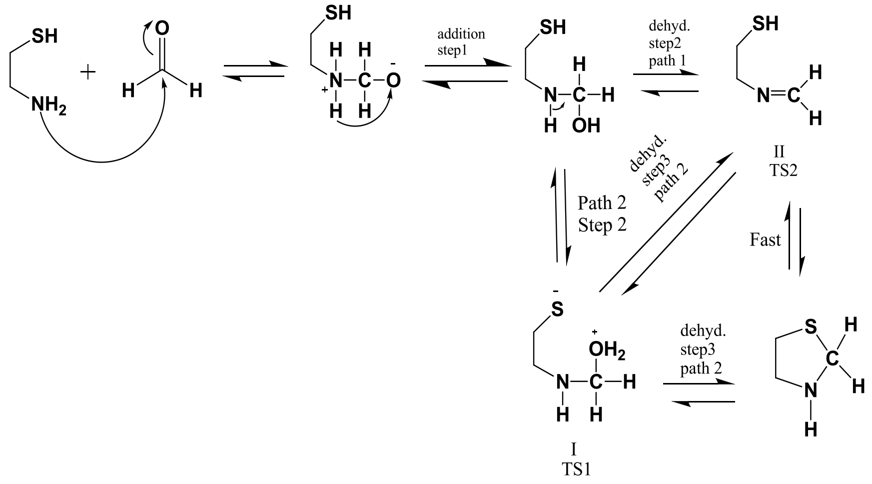
Two different techniques have been to look into the transition state. The first technique is using the quadratic synchronous method (QST) of Hyperchem 7.52 or Gauss 05 which searches for a maximum a long a parabola connecting reactants and products and for a minimum in all directions perpendicular to the parabola. This method will calculate the overall energy barrier between the reactant and product but it cannot identify the structure of the transition state. The energy barrier calculated by MP2 at three levels for the thiazolidine formation reaction.

The second method used for searching transition state structure is based on chemical guess in which one can suppose several possible transition states and the examined by IR calculation. This method is good for a well-known reaction mechanism [12].

For investigation six transition state structures are proposed for reaction aliphatic aldehyde with 2-aminoethanthiol. Among these possible transition state structures only TS2 of path I is proved to be a real transition state with one negative frequency at −55.65 cm^{-1} and gave a positive energy barrier, while TS1 in the same path is proved to be a real transition state with two negative frequencies at −428.59 cm^{-1} and 155.23 cm^{-1} but has a negative energy barrier.

The calculated energy barrier of these transition state structures TS2, TS4, TS5 and TS6 for the reaction formaldehyde with 2-aminoethanethiol are 47607.154, 47627.014, 71685.842 and 24063.548 Kcal/mole respectively. The TS1 and TS3 gave a negative energy barrier −13.016 and −17.103 Kcal/mole respectively as listed in table 7. Because high energy of the TS2 and TS4 to do perform to high energy barrier , we suggested transition states TS12 and TS34 between TS1 and TS2, TS3 and TS4 respectively. The TS12 and TS34 gave the energy barrier −18.899 and 160.428 Kcal/mole respectively. Also we suggested the proposed mechanism for the formation of thiazolidine is shown in scheme 2. The mechanism includes the nucleophilic amine group attacks the

positively induced carbonyl carbon to form a hemicetal, then intrinsic protonation of the hydroxyl group by amine group leads to the formation of a good leaving group (H_2O) and gives a Schiff base II (path 1), or protonation by proton transfer from thiol group to hydroxyl group to give intermediate I. Another nucleophilic attack of the thiolate ion on the induced carbo-cationic carbon leads to the formation of a thiazolidine. This mechanism includes two transition state. TS1 (scheme2) was characterized by two imaginary frequency at −606.37 cm^{-1} and −141.38 cm^{-1}, while no imaginary frequency was found in the calculated vibrational spectra of TS2 (scheme 2). The results agree with the experimentally observed reaction thiazolidine formation reactions [13].



Scheme 2

Table 7 Transition state calculated at MP2 level with three basis sets.

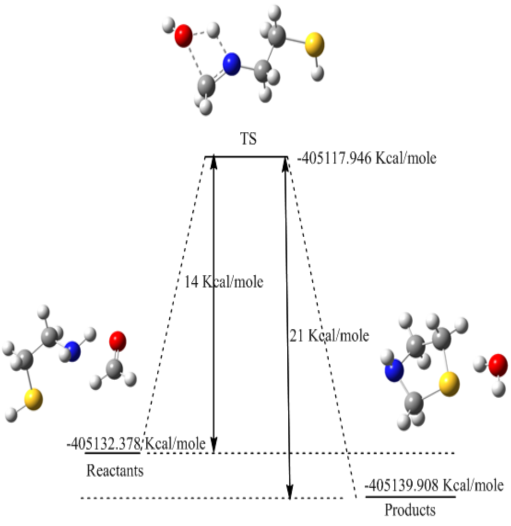
Compound	MP2/6−31G(d)	MP2/6−31++G(d,p)	MP2/6−31++G(2d,2p)
Formaldehyde	−71639.370	−71655.699	−71676.866
aminoethanethiol	−334023.674	−334071.372	−334153.578
Total	−405663.044	−405727.071	−405830.444
TS1	−405674.254	−405740.132	−405870.157
Energy Barrier	−11.210	−13.061	−39.713
TS2	−358073.288	−358119.916	−358209.871
Energy Barrier	47589.756	47607.154	47453.173
TS12	−405680.522	−405745.970	−405850.08
Energy Barrier	−17.478	−18.899	−19.636
TS3	−405678.271	−405744.174	−405873.504
Energy Barrier	−15.227	−17.103	−43.060
TS4	−358038.851	−358100.057	−358190.170
Energy Barrier	47624.193	47627.014	47640.274
TS34	−405494.022	−405566.643	−405620.204
Energy Barrier	169.022	160.428	210.240
TS5	−477328.842	−477412.913	−477591.619
Energy Barrier	71665.798	71685.842	71761.175
TS6	−429726.091	−429790.619	−429928.148
Energy Barrier	24063.047	24063.548	24097.704

3.4 Intrinsic Reaction Path (IRC)

The starting point of studying chemical reactions in computational chemistry is to locate and characterize the reactants, products, and transition states on the potential energy surface (PES). For some reactions, the PES can be rather complicated so that it is not obvious to determine if the transition state (TS) connects to desired reactants and products. In such cases, tracing the reaction path from the TS to reactants and products becomes essential for understanding the reactions. Besides, the information of the PES along the reaction path is also desired for deailed kinetic and dynamic studies. A natural definition of the reaction path is the steepest descent path from the TS down to bath reactant and product sides on the PES. When mass-weighted Cartesian coordinates are used, this path is the so-called intrinsic reaction coordinate (IRC) [14] . Physically; the IRC is the solution of equation of motion of the nuclei, which move on the PES with infinitesimal velocity. Mathematically, IRC proves to be a quasi-geodesic curve in the Riemannian space corresponding to the PES and hence the shortest path connecting the reactant to product via the TS. The IRC is thus a simple yet rigorous approach for probing complicated reaction processes [15].

The IRC results for thiazolidine formation reaction in path I in scheme 1 at UHF/6-31++G(2d,2p) level gave an activation energy of 14 and 21 Kcal/mole

for forward and reverse reaction as shown in Figs.3 & 4. While IRC results for thiazolidine formation reaction according to scheme 2 for TS2 at the same level gave an activation energy of 9.86 and 17.39 Kcal/mole for forward and reverse reaction as shown in Figs.5 & 6.



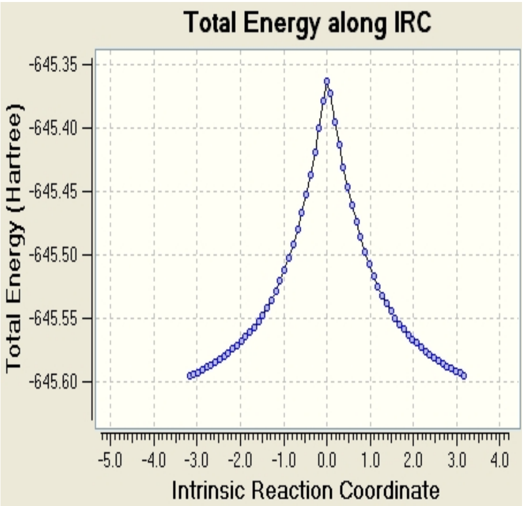
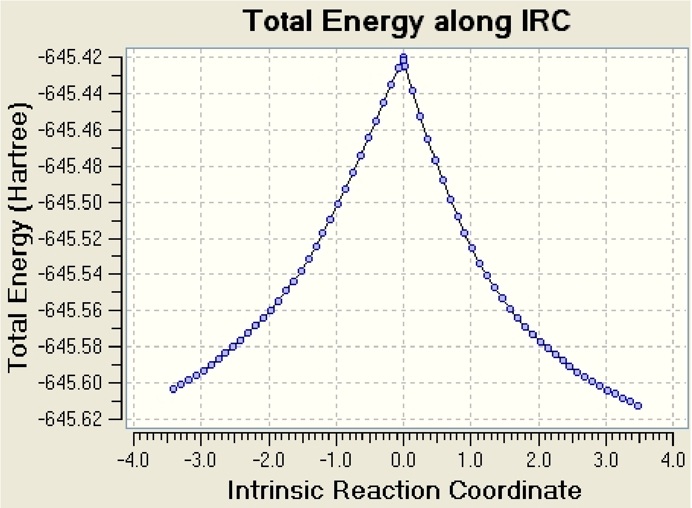


Fig. 3 The Geometry of TS12 Transition state structures of Formaldehyde with 2-aminoethanthiol from IRC Calculation at RHF/6-31++g(2d,2p).

Fig. 5 The Geometry of TS2 (scheme 2) Transition state structures of Formaldehyde with 2-aminoethanthiol from IRC Calculation at RHF/6-31G(d).

Fig. 4 Thiazolidine formation reaction at UHF/6-31++G (2d, 2p) according to scheme 1.



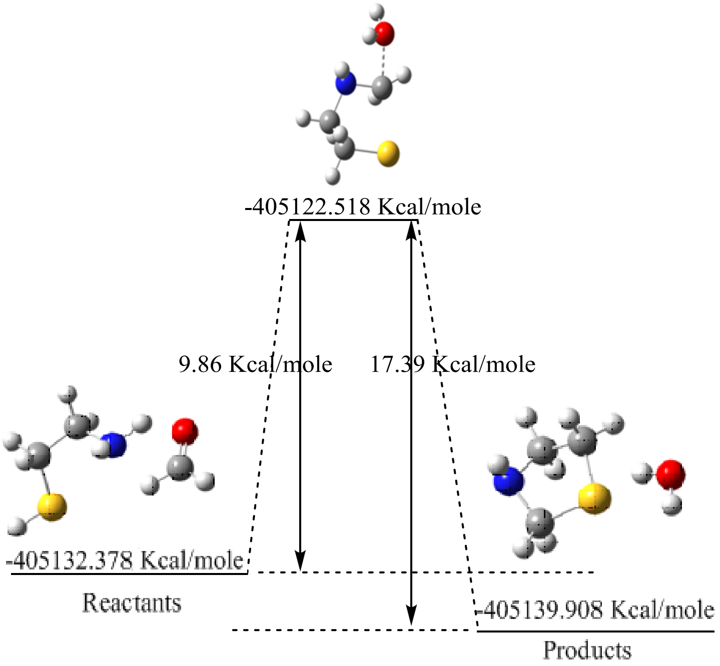


Fig. 6 Thiazolidine formation reaction at UHF/6-31++G (2d, 2p) according to scheme 2.

4.Conclusions

This article has described the first theoretical study on thiazolidine formation reaction from 2- aminoethanthiol and formaldehyde. Our results on gas phase calculation, indicate the mechanism of reaction involving cyclic cationic Schiff base (TS12) intermediate which leads to Schiff base. At UHF/6-31++G(2d,2p) level gave an activation energy of 14 and 21 Kcal/mole for forward and reverse reaction, While second mechanism of reaction used (TS2, scheme2) which leads to thiazolidine and gave an activation energy of 9.86 and 17.39 Kcal/mole.

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