



Computational study of reaction mechanism of formaldehyde and glycine Schiff base

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ABSTRACT

Theoretical study of reaction mechanism of formaldehyde and glycine was conducted with regard to formation of Schiff base using Spartan '08 software semi-empirical/parametric model (PM3) and Density Functional Theory [RB3LYP/6-31G (d)] calculations. The mechanism was found to contain four elementary steps comprising two transition states and one intermediate. The transition states are reversible. The consecutive reaction (scheme 3) involves a bimolecular and unimolecular steps. The unimolecular is the rate determining step with a lower k_1 value of $1.665 \times 10^{21} \text{ s}^{-1}$. There was a good agreement between the two methods calculations and the overall reaction was found to be second order and exothermic.

Keywords: DFT, PM3, Unimolecular, Schiff base, Transition state

INTRODUCTION

The reaction between the lower amino acids and formaldehyde has been reported by several authors e.g. Tomiyama [1]. The Sorenson formol titration[2] of amino acids in 10% formaldehyde solutions is based upon the assumption of a condensation reaction as originally postulated by Schiff[3] to give azimethine groups -C=N-. They are condensation products of aldehyde or ketones with primary amines and were first reported by Hugo Schiff[3]. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable [4], while those of aromatic aldehydes having effective conjugation are more stable. The direct demonstration of Schiff's base formation between glycine and formaldehyde is complicated by the unstable nature of the compound together with the strong polymerizing tendency [5]. Some Schiff's bases are stabilized by metal-complexation as found for copper (ii) salicylaldehyde-glycine as reported by Eichhorn [6]. Schiff bases are found to be an intermediate formed in some biological reactions have been studied as a chelating agents [7-9]. The Schiff bases are reported by many workers to possess antibacterial, antifungal, antiviral, anti HIV, anti protozoal and anthelmintic activities and also exhibit significant anticonvulsant activity apart from other pharmacological properties [10-11]. Many Schiff bases were reported to have possess biological activities such as antimicrobial, anti-HIV, anti fungal, antibacterial, anti-inflammatory, anticonvulsant ,antitumor and antihypertensive activity[10-17].

Braun stein and Snell [18-19] proposed the accepted mechanism for this reaction. It consists of the addition of an amine to a carbonyl compound to give an intermediate carbinolamine which loses a molecule of water to produce the imine [20]. The carbinolamine proved to be difficult to observe in the formation of Schiff base but experimental

evidence supported its existence [21] and location of rate determining step of the reaction in its dehydration. Theoretical calculations based on quantum mechanics onto a reactive system can provide the detail description of the geometries of the intermediate and transition states involved in the reaction.

Semi-empirical and DFT computational studies of mechanism of reaction of phenylpropan-2-one and ethylamine have been reported [22]. They concluded that it involves four elementary steps comprises of an intermediate and two transition states and dehydration of one of the transition complex to form the imine. A comprehensive study was carried out for the water-assisted transamination of glycine and formaldehyde [23]. The work allowed for the description of all the geometries of all the intermediates and transition states of the reactions, which can be described by five steps: carbinolamine formation, dehydration, 1, 3 proton transfer, hydrolysis and carbinolamine elimination. Among the five steps of the reaction, hydrolysis and elimination occur with the existence of general acid catalysis related to the carboxylic group.

A theoretical study was carried out based on DFT calculation of the formation of Schiff base of pyridoxamine analogues with two different aldehydes [24]. The reaction was found to be two steps reaction; formation of carbinolamine and dehydration of the carbinolamine to give the final imine. Attempt to find in literature on any theoretical work on imine formation from glycine and formaldehyde is yet to find.

Hence in the present work, the reaction between glycine and formaldehyde as regards to Schiff base formation will be discussed by means of description of geometry, energy, intermediate and transition state structures involved in such reaction. This will provide some information of the reaction mechanism theoretically.

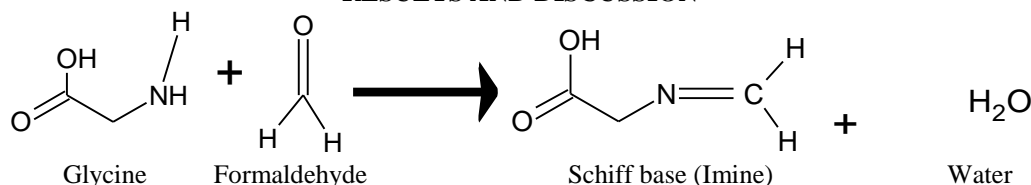
MATERIALS AND METHODS

Computational Methods

All computations were made using the standard version of PM3 semi-empirical MO methods and Density Functional Theory (DFT) method in the Spartan 08 software package as run on a HP Pavilion computer Intel(R) Celeron(R) Dual CPU, 6.00GB RAM.

The structures of the reactants, transition state, intermediates and products were built and minimized with the MM2 method in the Spartan 08. All the geometries were optimized using AM1, followed by parametric method 3 (PM3) and MNDO and finally by DFT Becke's three parameter non-local exchange functional with nonlocal correlation function of Lee, Yang and Parr (B3LYP) with 6-31G (d) basis set calculations were employed. The optimized geometries of all species in the reaction were confirmed in terms of vibration analysis [25]. Transition state for each step was located and confirmed by animating the vibration corresponding the coordinate by selecting the imaginary frequency at the top of the IR tab. Heat of formation (ΔH_f) of the reactants, transition states, intermediate and products were all calculated. Infra-red (IR), thermodynamic and kinetics parameters were also calculated according to the expression in the literature [26].

RESULTS AND DISCUSSION

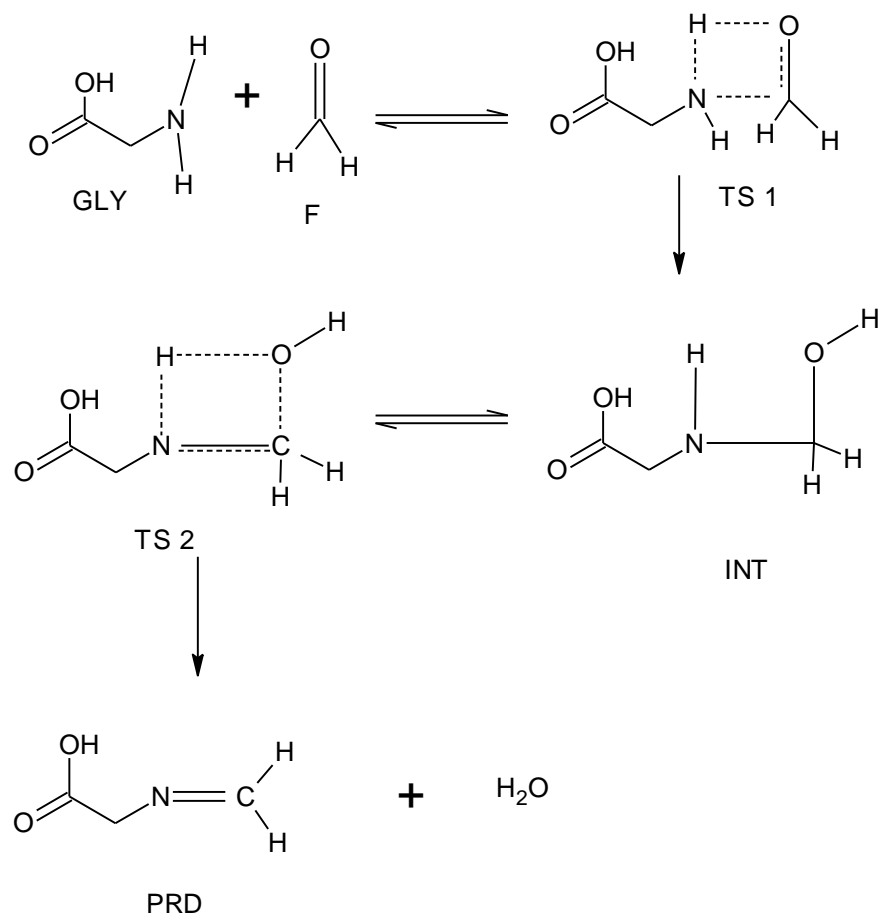


Scheme 1: General Scheme of the Reaction

Reaction Mechanism

The reaction mechanism of reaction between glycine and formaldehyde is outlined and shown in scheme 2. The reaction is initiated by interaction between nitrogen (N) of glycine and C1 of formaldehyde, and the O1 of formaldehyde and H1 of glycine leading to the formation of transition state (TS1). The reaction goes on through bond breaking between H1 and N of glycine, and O1 and C1 of formaldehyde and formation of bond between N and C1, leading to the formation of an intermediate (INT). The intermediate is 198.8Kj/mol lower than the transition state (TS1). Next are the interaction between O1 of formaldehyde and H1 of glycine and N of glycine and C1 of

formaldehyde, forming another transition state (TS2) with an imaginary frequency of $i1738$. Standard heat of formation of all species is presented in table 1 are depicted in figures 1 and 2 shown below. The transition state 2 cleaved finally to produce a Schiff base (imine) and water as the products with 171.71Kj/mol energy lower than transition state 2(TS2).



Scheme 2: Reaction Mechanism

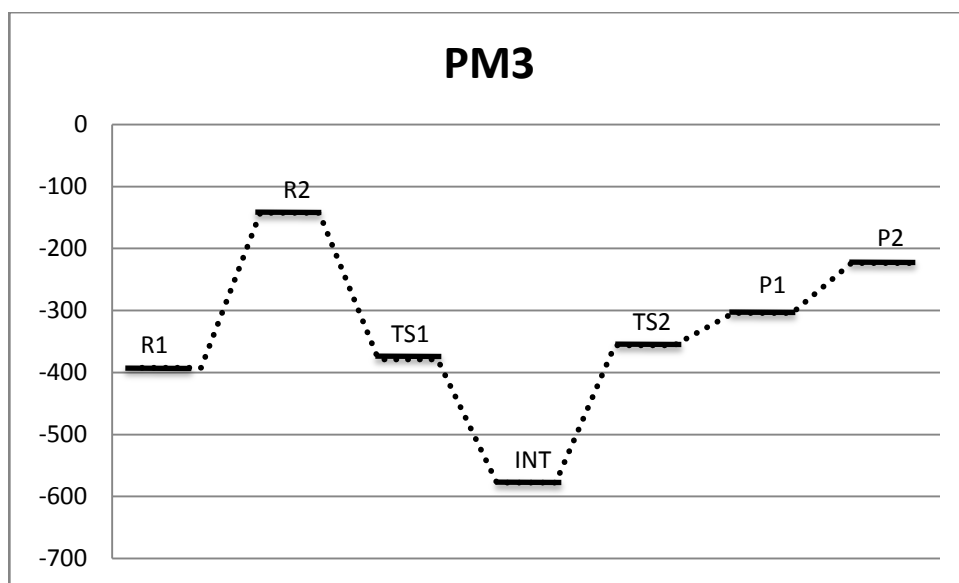


Fig 1: Energy curve for standard heat of formation for the reaction mechanism using PM3

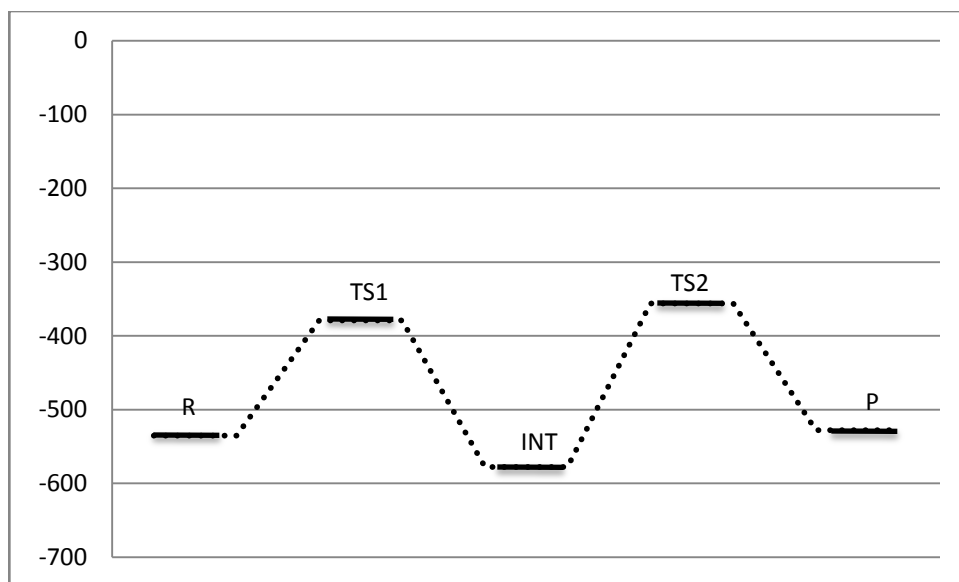


Fig 2: Energy curve for standard heat of formation for the reaction mechanism using PM3

Table 1: Semi-empirical energy parameters of the species in the reaction mechanism

Species	S°(J/mol K)	ΔH_f° (Kj/mol)	ΔH_{rxn} (Kj/mol)	IR imaginary
Glycine	314.25	-392.55	0	
Formaldehyde	218.69	-142.6	0	
TS1, GF [#]	363.99	-378.9	156.25	i1976
INT, C	370.3	-577.7	-198.8	
TS2, GF ^{2#}	362.29	-356.07	221.63	i1738
P (imine)	336.92	-304.24	-171.71	
Water	188.24	-223.54		

Density Functional Theory (DFT) calculation:

Table 2 below shows the results of DFT RB3LYP/6-31G (D) theory of electronic energy (E_a) in au, entropy S° in J/mol and enthalpy H° in KJ/mol at 298.15K of the species involved in the mechanism. The TS1 (i1568) has stabilization energy of -738941 KJ/mol as compared to the reactant. The bimolecular transition state process (step1) is reversible with ΔG^\ddagger of 160 KJ/mol and decrease of entropy of -157.47J/mol. This step has activation energy of -733983KJ/mol. The intermediate surpass TS2 (i1911) and stabilization energy of -1047180KJ/mol to give the products with activation energy of 2317KJ/mol. The transition state reaction in step 2(unimolecular) is characterized with increase in entropy of 160.81J/mol and Gibb's energy of -210KJ/mol. The transition state in step 2 was found to have a lower rate constant value of $1.6605 \times 10^{21} s^{-1}$ and hence the rate determining steps of the reaction. Kinetic data are presented in table 5.

Table 2: Density Functional Theory energy parameters of the species in the reaction mechanism

Species	E(au)	S°(J/mol K)	ΔH_f° (Kj/mol)	ΔH_{rxn} (Kj/mol)	IR imaginary
Glycine	-284.420434	310.24	-746785	0	
Formaldehyde	-114.500474	218.56	-300621	0	
TS1, GF [#]	-398.876780	371.8	-1047252	154	i1568
INT, C	-398.942886	356.94	-1047425	-173	
TS2, GF ^{2#}	-398.849617	365.37	-1047180	245	i1911
P (imine)	-322.504380	337.33	-846736	-168	
Water	-76.408946	188.85	-200612		

During the reaction N-H, N-H2 and N-CA bonds in the glycine stretch by 0.008Å, 0.185 Å and 0.011 Å respectively in the TS1. Similarly, O1-C1, C1-H3 bonds in formaldehyde are increased by 0.128 Å, and 0.002 Å, while C1-H2 bond does not stretched in TS1. As the reaction progress from TS1 to TS2, C1-H2, C1-H3 and N-CA decreased by 0.017 Å, 0.019 Å and 0.017 Å respectively. TS2 also undergoes bond stretching and shrinkage on transforming into

the products with C1-H2 and C1-2HA stretched and N-C1 shrinks due to formation of a double bond as presented in table 3.

During the course of the reaction the bond distances and the bond angles undergoes changes in the transformation of the reactants through the transition states into products. These variations are shown in table 3 and 4 respectively.

Table 3: Variation in bond distance between transition state 2 and product(imine)

Transition state 2 bonds distance Å		Product bonds distance Å	
N-C1	1.352 Å	N-C1	1.266 Å
N-CA	1.449 Å	N-CA	1.449 Å
CA-2HA	1.099 Å	CA-2HA	1.106 Å
C1-H2	1.096 Å	C1-H2	1.101 Å
CA-1HA	1.106 Å	CA-1HA	1.095 Å

Table 4: Variation in bond angles between transition state 2 and product (imine)

Transition state 2 bonds angles		Product bonds angles	
N-C1-H3	117.78°	N-C1-H3	124.03°
N-CA-1HA	113.98°	N-CA-1HA	109.36°
N-CA-2HA	111.29°	N-CA-2HA	113.84°
CA-N-C1	116.67°	CA-N-C1	117.40°
N-CA-C	118.82°	N-CA-C	110.82°

Table 5: Rate constant k_1 and k_2 , Arrhenius factor A, and activation energy for step 1 and 2

Step 1(bimolecular)	K_2 1.075×10^{134}
	A 272876
	E_a -733983
Step2 (unimolecular)	K_1 1.665×10^{21}
	A 4.2414×10^{21}
	E_a 2317.819

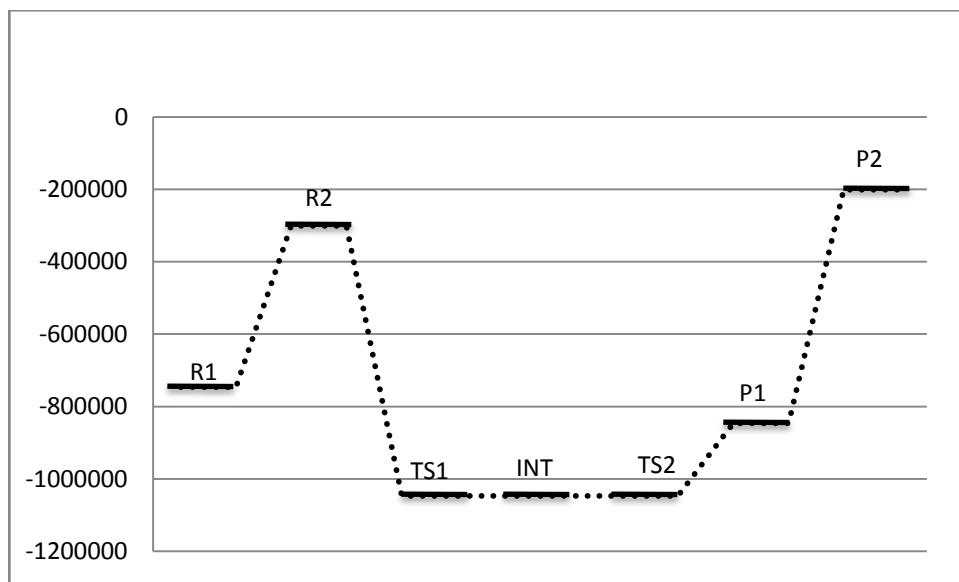


Fig3: Energy curve for standard heat of formation for reacting species in the reaction mechanism using DFT RB3LYP/6-31G (d)

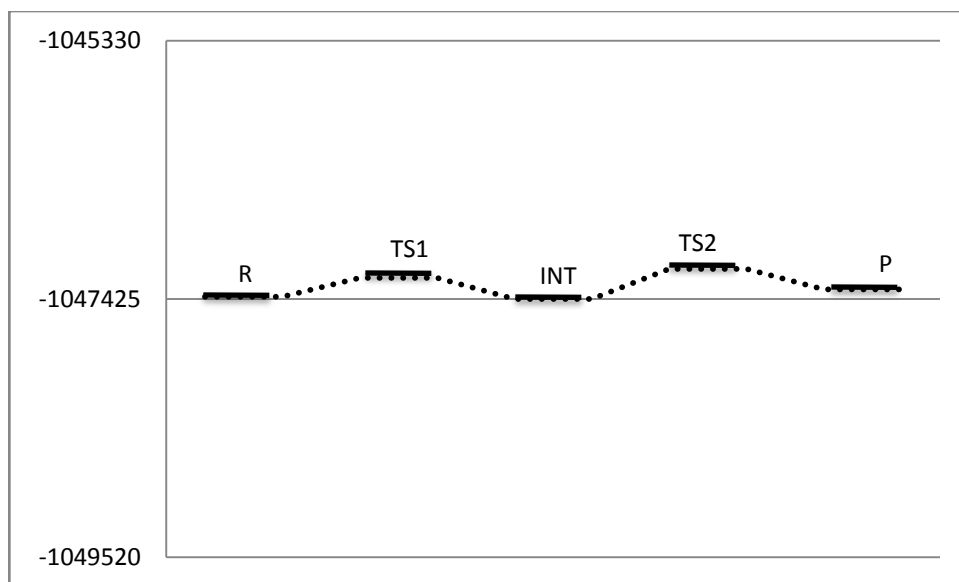


Fig4: Energy curve for standard heat of formation for the reaction mechanism using DFT RB3LYP/6-31G(d)

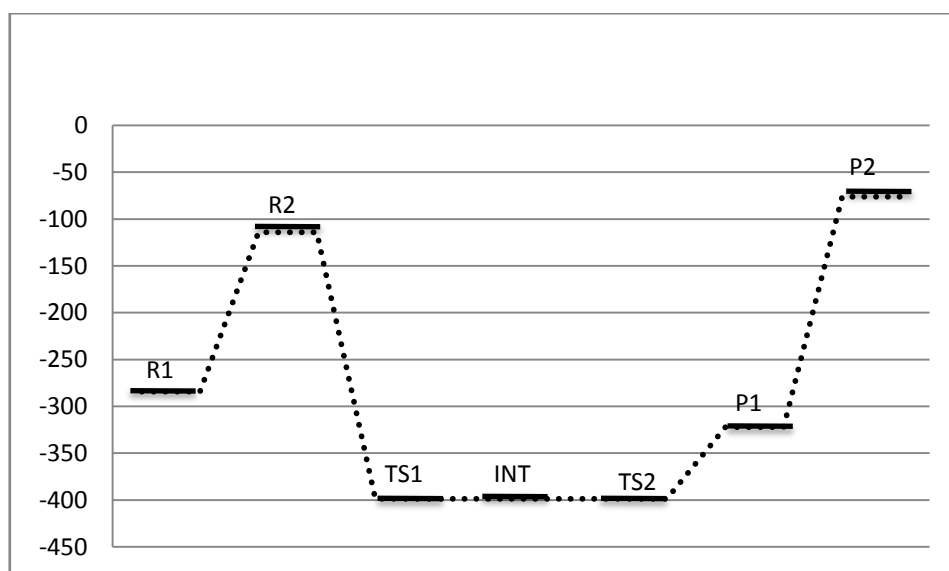
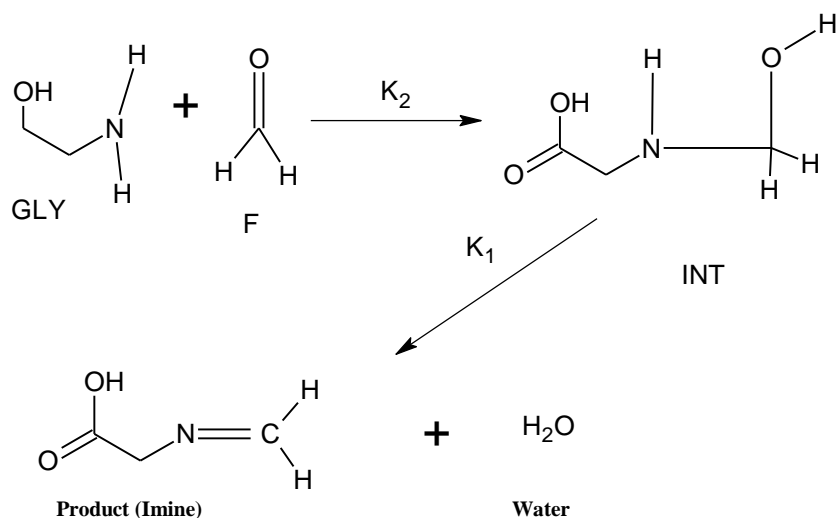


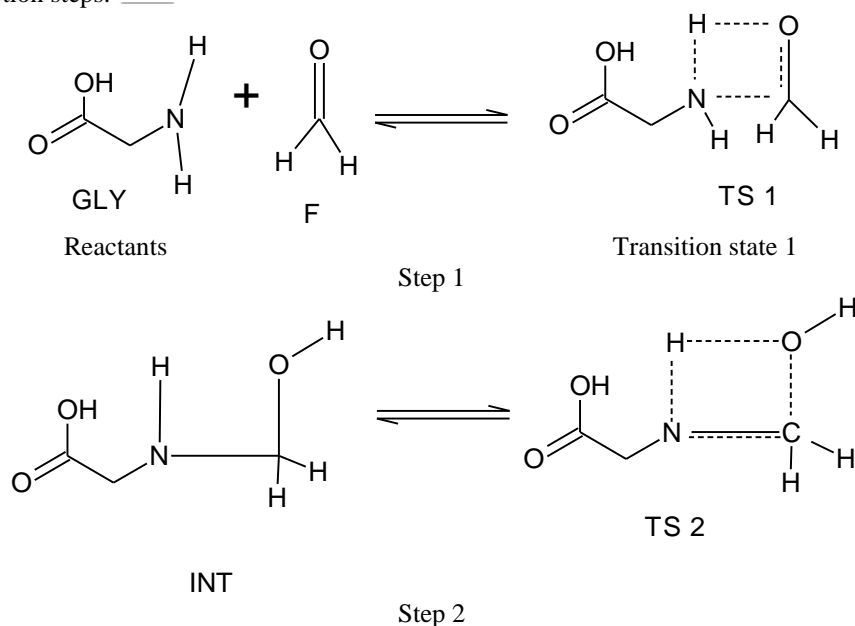
Fig 5: Electronic energy curve for reaction mechanism from DFT RB3LYP/6-31G (d) calculation

The consecutive step of this reaction can be illustrated as $G + F \xrightarrow{K_2} I \xrightarrow{K_1} P$ is shown in figure below. Kinetically, the first is the rate determining step with lower rate constant value of $k_1 1.665 \times 10^{21} \text{s}^{-1}$.



Scheme 3: Consecutive step of the reaction

Thermodynamic calculation shows that the consecutive steps are all irreversible. The step from the reactants (G + F) to intermediate I have a Gibbs's free energy change $\Delta_{\text{rxn}}G^\circ$ of -6.00Kj/mol (<0). The step from intermediate to product has a Gibbs's free energy change $\Delta_{\text{rxn}}G^\circ$ of -11.00Kj/mol (<0), which indicates the irreversibility of the reaction. Table 2 shows the entropy, (ΔS°) and enthalpy of formation (ΔH_f) at standard temperature and pressure of the species in the reaction steps. _____

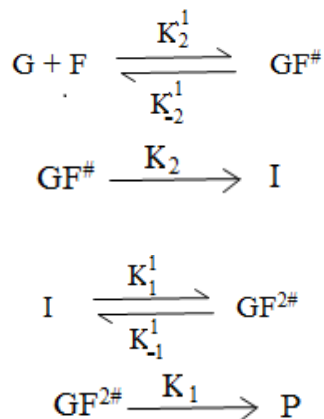


Scheme 4: Transition state reaction scheme

The energy values are presented in table 5. The activation energy values indicates that the steps are reversible due to low energy barriers as opposed the entropy change values. _____

Reaction Kinetics

The reaction mechanisms consist of the following steps



The rate laws for all products of the reaction can be written as follows

$$\begin{array}{ll}
 \frac{d[\text{P}]}{dt} = k_1[\text{GF}^{2\#}] & 1 \\
 \frac{d[\text{GF}^{2\#}]}{dt} = -k_1[\text{GF}^{2\#}] - k_{-1}^1[\text{GF}^{2\#}] + k_1^1[\text{I}] & 2 \\
 \frac{d[\text{I}]}{dt} = -k_1[\text{I}] - k_{-1}^1[\text{GF}^{2\#}] + k_2^1[\text{GF}^\#] & 3 \\
 \frac{d[\text{GF}^\#]}{dt} = -k_2[\text{GF}^\#] - k_{-2}^1[\text{GF}^\#] + k_1^1[\text{G}][\text{F}] & 4
 \end{array}$$

By using steady state approximation from equation 2

$$[\text{GF}^{2\#}] = \frac{K_1^1}{K_1^1 + K_{-1}^1} [\text{I}] \quad 5$$

By using equation 3 and 5 we have

$$\begin{array}{l}
 -k_1^1[\text{I}] + \frac{K_{-1}^1 K_1^1}{K_1^1 + K_{-1}^1} [\text{I}] k_2 [\text{GF}^\#] = 0 \\
 [\text{I}] = \left[\frac{K_2 (K_1^1 + K_{-1}^1)}{K_1^{12}} \right] [\text{GF}^\#] \quad 6
 \end{array}$$

From equation 4 we have

$$\text{GF}^\# = \frac{K_2^1}{K_2^1 + K_2} [\text{G}][\text{F}] \quad 7$$

$$[\text{I}] = \frac{K_2 K_2^1 (K_1^1 + K_{-1}^1)}{K_1^2 (K_2 + K_2^1)} [\text{G}][\text{F}] \quad 8$$

From equation 8 and 5 we have

$$[\text{GF}^{2\#}] = \frac{K_2 K_2^1}{K_1^1 (K_1^1 + K_{-1}^1)} [\text{G}][\text{F}]$$

$$\begin{aligned}
 \frac{d[\text{P}]}{dt} &= k_1 \frac{K_2 K_2^1}{K_2^1 (K_2 + K_2^1)} [\text{G}][\text{F}] \\
 &= k [\text{G}][\text{F}]
 \end{aligned}$$

k is the experimental rate constant.

CONCLUSION

The reaction between amino acid glycine and formaldehyde was found to occur in four stages with each stage has its own characteristic thermodynamic and kinetic parameters. The unimolecular step of the reaction was found to be the rate determining step. The kinetic of the reaction has been established but the overall rate constant is yet determined, likewise the experimental rate constant. The calculation was performed with Spartan 08 software by using the semi-

empirical PM3 and Density Functional Theory (DFT) smallest basis set RB3LYP/ 6-31G (d). The two methods are in agreement with one another since both predict the presence of two transition states in the mechanism of reaction that are all reversible and one intermediate. A better result may be obtained by using a higher level theory and larger basis set. The overall kinetic was found to be a second order.

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