Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2014, 5(1):9-17

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Semi-empirical and DFT computational studies of mechanism of reaction of phenylpropan-2-one and ethylamine

[*]Siaka A. A.[1], Uzairu A.[2], Idris S. O.[2] and Abba H.[2]

[1]*Department of Pure and Applied Chemistry Kebbi State University of Science and Technology, Aliero, Kebbi State, Nigeria*
[2]*Department of Chemistry, Ahmadu Bello University, Zaria Kaduna State, Nigeria*

ABSTRACT

The mechanism of reaction between phenylpropan-2-one and ethylamine was investigated using semi-empirical/Austin model (AM1) and Density functional theory [RB3LYP/6-31G(d)] calculations in SPARTAN,2009 program suit. The mechanism was found to involve four elementary steps comprising one intermediate and two transition states. According to transition state theory, the mechanism comprises of two reversible reaction schemes. Scheme I involves two molecules while scheme II involves only a molecule. The unimolecular was the rate determining step (k_1 =56.9214 x $10^{-25}s^{-1}$). The mechanism suggests that the reaction occurs in two steps: at first, a fast pre-equilibrium between the reactants and the prereactive complex is established, followed by an internal rearrangement leading to the elimination of a water molecule. There was a good agreement between the semi-empirical and DFT [RB3LYP/6-31G(d)] calculations. The overall reaction was found to be exothermic.

Keywords: bimolecular, catalysis, phenylpropan-2-one, intermediate and transition state.

INTRODUCTION

Nitrogen containing compounds are very widely distributed in nature and are essential to life, playing a vital role in the metabolism of all living cells. Imine is the compound formed when an amine reacts with aldehyde or ketone in which the C=O double bond is replaced with C=N double bond. Imines and their derivatives have long been recognized as key intermediates for the synthesis of nitrogen heterocycles, especially in the area of alkaloid synthesis [1]. Over the years there has been a keen interest in developing new applications of imine chemistry that enable the facile construction of the nitrogen heterocyclic frameworks found in alkaloids and other biologically active nitrogen heterocycles [2].Diversity-oriented synthesis (DOS) and various manifestations thereof constitute areas of considerable importance at the interface of the fields of organic synthesis and chemical biology [3].

One of the critical challenges in DOS is the efficient generation of collections of functionally and stereochemically diverse small molecules, especially those possessing skeletons found in natural products or drug-like molecules [4]. One attractive and powerful method that has recently emerged for generating such collections of molecules comprises using multicomponent reactions (MCRs) is to create suitably substituted intermediates that may be readily transformed by cyclizations and refunctionalizations that lead to further increases in molecular complexity and diversity[5]. Schiff base (imine) formation is a very important reaction in biological chemistry. For example pyridoxal phosphate (PLP), a derivative of pyridoxine, commonly known as vitamin B_6, binds to a number of

specific enzymes and plays a critical role in helping these enzymes to catalyze their reactions. Most enzymes that interact with PLP catalyze reactions involved in the metabolism of amino acids [6].

Since its introduction by Ellman in 1997 as a chiral ammonia equivalent, enantiopure 2-methyl-2-propanesulfinamide (*tert*-butanesulfinamide) has been demonstrated to be a versatile chiral auxiliary and has found extensive use both in academics and industry. [7] The *tert*-butanesulfinyl imines have been used in the asymmetric synthesis of many versatile building blocks including *syn*- and *anti*- 1,2- or 1,3-amino alcohols*α*-branched and *α,α*-dibranched amines, and *α*- or *β*-amino acids and esters[8]. Another recent report describes the intermolecular self-condensation of chiral *tert*-butanesulfinyl imines in a synthesis for the pyrrolizidine alkaloid [9].

The chemistry of quinone imines and N-acylated quinol imines resulting from biological oxidation (Cytochrome P-450) of aromatic nitrogen compounds (generally amides) is thought to be important in many biological processes. Quinone imines are intermediates in the oxidation of catecholamines leading to the formation of melanoid pigments. The anti-tumor compound N-methylellipticium acetate is proposed to form a tetracylic quinone imine linkage which then reacts with nucleosides and amino acids. The chemistry of N-acylated quinone imine linkage with nucleophiles is proposed to be involved in the toxic effects associated with analgesics such as phenacetin. [10]. At present, greater than 75% drugs and drug candidates incorporate imine functionality [11]. In these compounds, the nitrogen-containing units are known to play important roles for their bioactivities. For the synthesis of these chiral nitrogen-containing buildingblocks, use of imines as electrophiles is the most promising and convenient route [12].

The synthesis of these nitrogen-containing compounds by the easily available imine is one of the most important and convenient routes. However, as compared with the counterpart, C.O double bond, C.N double bond is a less explored area. Today the Lewis acid-promotedaddition of allylstannane to aldehyds is well established as a powerful synthetic method. On the contrary, only a handful of papers on the allylation reaction of imines by allylstannane were reported [13]. General imines and activated imines have also show relevance in stereo chemistry, especially in stereoselective reactions of aziridination, allylation and aldo reaction – a powerful synthetic route.. This stereo selectivity of imines has been used in the synthesis of peptidic antibiotics as well as other biologically active molecules.

It has also been reported that enantioselectivity of imines is employed in chemical, pharmaceutical and agrochemical industries especially in the synthesis of chiral herbicide (S)-Metolachlor [14]. Anakumar et. al (2010) [15] also reported that stereoselectivity has been employed in the preparation of a well-known drug, rivastigmine which has been used to treat mild to moderate dementia associated with Alzheimer's and Parkinson's disease. Attempt to find, in literature any work (either empirical or theoretical) on imine formation from ethylamine and phenylpropan-2-one is yet to yield. Hence this work attempts to provide some information on this reaction mechanism theoretically.

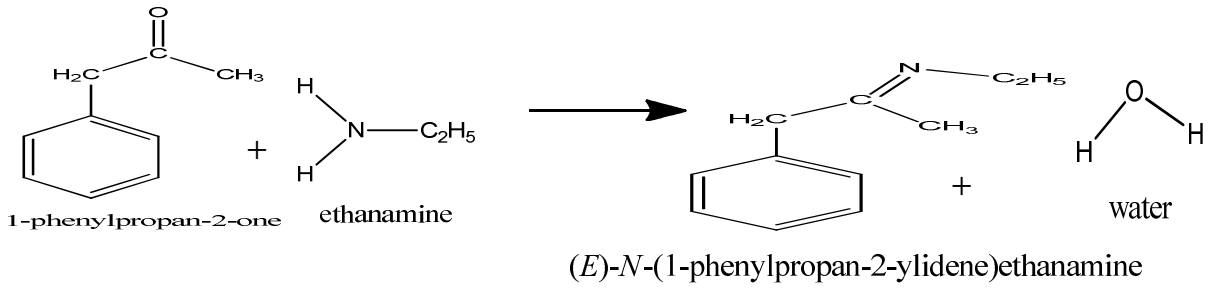

Fig.1: General reaction scheme

Computational Methods

The geometries of the reactants, transition states, intermediate and products were optimized using Molecular mechanics to remove strain energies. This was followed by semi empirical optimizations at AM theory level. Finally, DFT Becke's three parameter nonlocal exchange functional with the nonlocal correlation functional of Lee, Yang, Parr (B3LYP) with 6-31G(d) basis set calculations was employed. Furthermore, heat of formation was calculated for all the stationary points using thermochemical recipe at T_1theory level. For equilibrium geometries and transition states, the nature of the critical points was confirmed by an analytic frequency computation, and all the transition states have imaginary frequencies. Intrinsic reaction coordinate calculations were carried out to

confirm that the transition states connect to the right minima. All thermodynamic and kinetic parameters were calculated according to expression in the literature [16].

RESULTS AND DISCUSSION

Reaction Mechanism

Semi empirical Calculation

The outline of the reaction mechanism between ethylamine and phenylpropan-2-one is as shown in scheme I. The reaction starts by interaction between N1 of ethylamine and C8of the ketone; and O1 of the ketone and H1 of the ethylamine leading to the formation of stationary point I. The reaction proceeds via bond breakages between H1 and N1 of ethylamine, and O1 and C8 of phenylpropan-2-one, and bond formation between N1 and C8, leading to the formation of a second stationary point which was found to be an intermediate through frequency calculations. This intermediate is 222.17kJ/mol lower than the transition state. Next are the interactions between O1 of phenylpropan-2-one and H1 of ethylamine and N1of ethylamine and C8 of phenylpropan-2-one, forming another transition state stationary point with imaginary frequency 1723i. The standard heat of formation of all the stationary points and heat of reaction as presented in table 1 are depicted in figs. 2 and 3 below. The transition state II is 301.49kJ/mol higher than the intermediate I. Finally, the transition state II cleaved to form imine and water as the products with 284.27kJ energy lower than the transition state II.

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

Species	S^o(J/molK)	$\Delta_f H^o$(kJ/mol)	$\Delta_{rxn}H$(kJ/mol)	IR imaginary
$C_6H_5CH_2COCH_3$	+399.7990	-92.0300	0	
$C_2H_5NH_2$	+272.4160	-56.5450		
TSI, A-$B^{\#}$	+462.3000	+65.3010	+213.876	1885i
INT, C	+471.9236	-156.8640	-222.1650	
TSII, $C^{\#}$	+471.0500	+144.6244	+301.4884	1785i
Major product, P	+449.2180	+102.468	-42.1564	

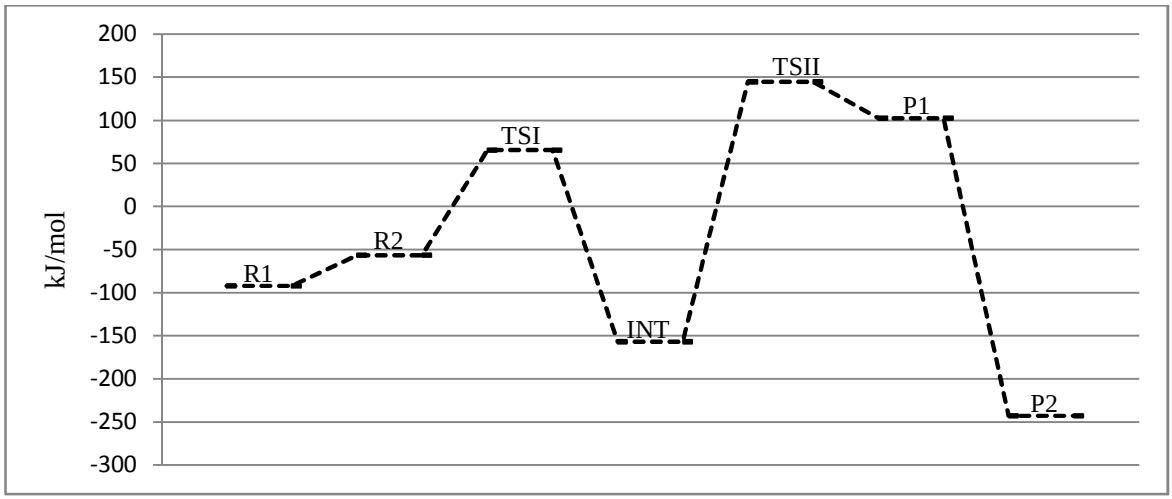

Fig.2: Energy curves for standard heat of formation for reaction mechanism using AM1 calculation

Density Functional Theory Calculations

DFT calculation results at RB3LYP/6-31G(d) level of electronic energy (E_e) in au, entropy (S^o) in J/molK, and heat content(enthalpy) in kJ/mol at 298.15K of the species involved in the general mechanism are as presented in the table 7 below. Based on the enthalpy values, the transition state I(1590i) has stabilization energy of -17.42kJ/mol compared to the reactants. The bimolecular transition process (step I) is reversible with $\Delta G^{\#}$ of +41.8514kJ/mol and entropy decreased of -198.7974J/molK. The step also has activation energy of +145.6025kJ/mol. The intermediate surpasses transition state II (with imaginary frequency of 1723i and stabilization energy of -184.64kJ/mol) to give the products with stabilization energy of +86.95kJ/mol. The transition state reaction step II is characterized with entropy increase of +10.5326J/molK and Gibb's energy of -12.1203kJ/mol. The transition reaction step II

(unimolecular) was found to have the low rate constant value of 56.9214 x $10^{-25}s^{-1}$, and hence the rate determining step of the reaction mechanism. Thermodynamic data are as presented in table 2.

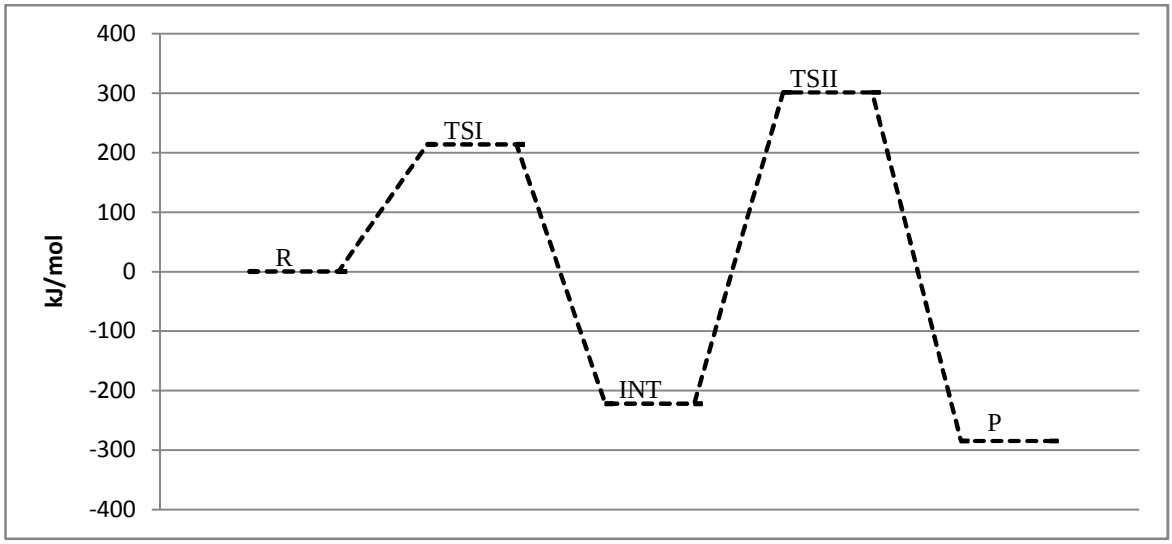

Fig.3: Energy curves for heat of reaction for reaction mechanism using AM1 calculation

Table 2: DFT energy parameters of the species in the reaction mechanism

Species	E_e(au)	S^o(J/molK)	ΔH_f^0(kJ/mol)	$\Delta_{rxn}H$(kJ/mol)
A	-424.2052	+406.2031	-104.87	0
B	-135.1701	+270.8286	-44.98	
TSI, (A-$B^{\#}$)	-559.3198	+478.2343	-167.27	-17.42
INT, C	-559.3717	+481.6443	-175.66	-8.39
TSII, $C^{\#}$	-559.2955	+492.1769	-184.64	-8.98
Product, P	-559.3561	+475.3816	+86.95	+271.59

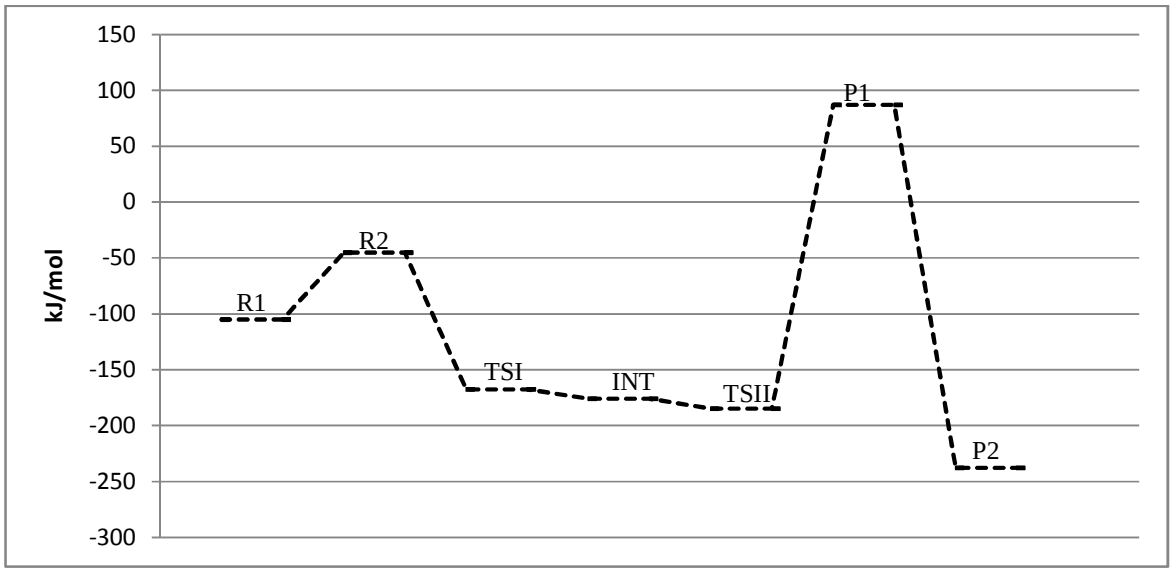

Fig.4: Energy curves for standard heat of formation for reaction mechanism using DFT RB3LYP/6-31G(d) calculation

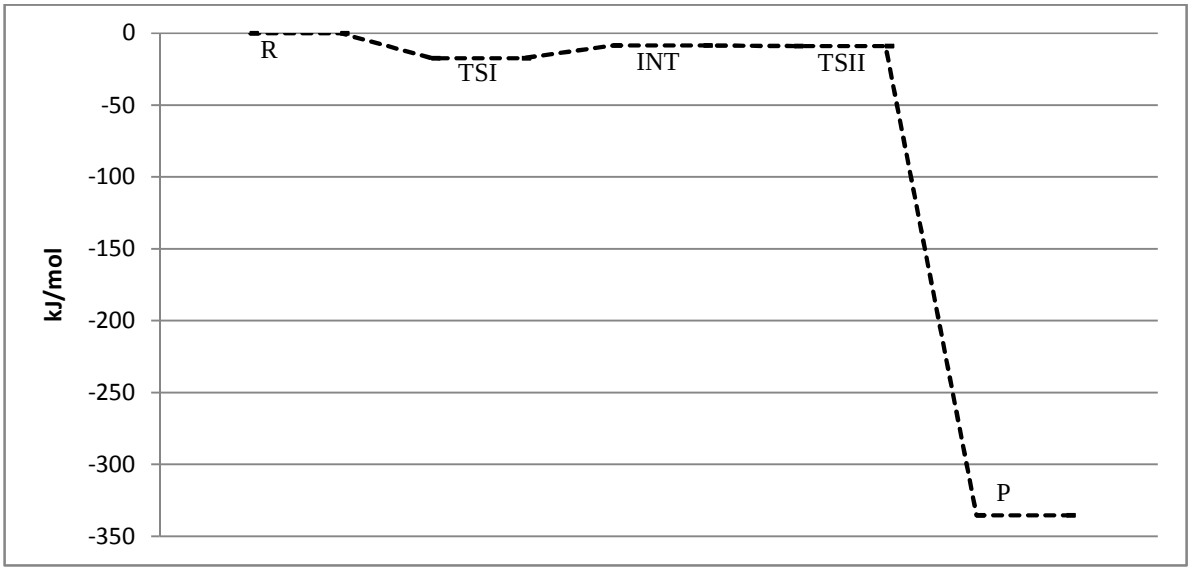

Fig.5: Energy curves for heat of reaction for the mechanism using DFT calculation

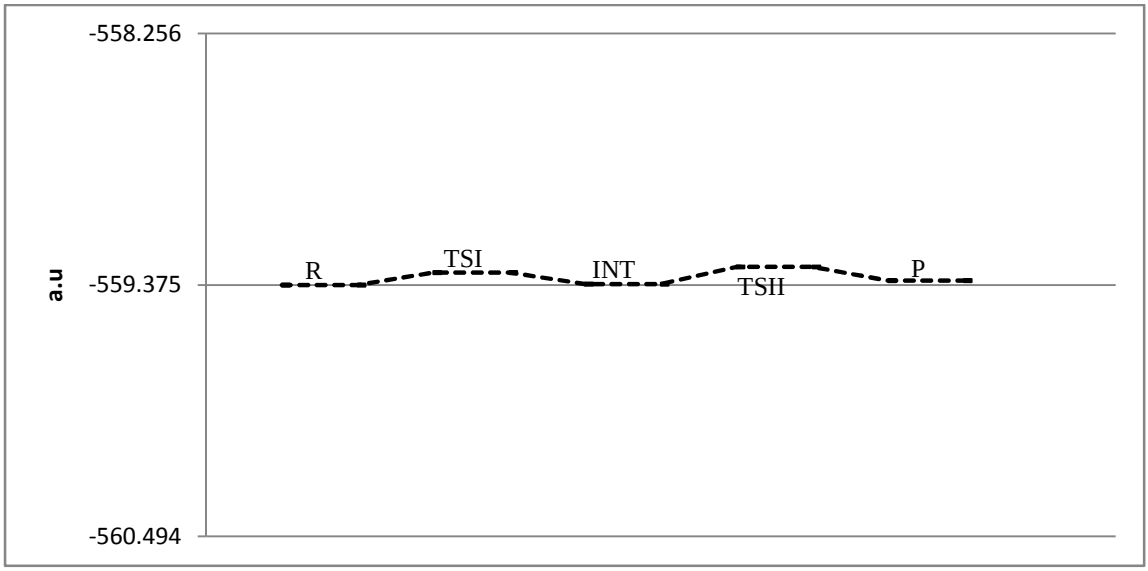

Fig.6: Electronic energy curve for reaction mechanism from DFT calculation

During the reaction O1 – C8, C7 – C8 and C8 – C9 bonds in phenylpropan-2-one stretched by 0.14A^o, 0.09 and 0.12 respectively, in the transition state I. Similarly, N1 – C2 and N1 – H1 bonds in ethylamine are decreased by 0.11 and 0.01A^o, while N1 – H7 bond is stretched by 0.24A^o in transition state I. as the reaction progresses from transition state I to transition state II, C7 – C8, C8 – C9 and N1 – C8 are decreased by 0.32A^o, 0.23A^o and 0.22A^o respectively. Finally, bond stretching and shrinking are observed as the transition state II eventually gives rise to products, with C7 – C8, and C8 – C9 bonds stretching, and C1 –C7, N1 –C8 and N1 – C10 (consequent of double bond) bonds shrinking as presented in the table 3 below.

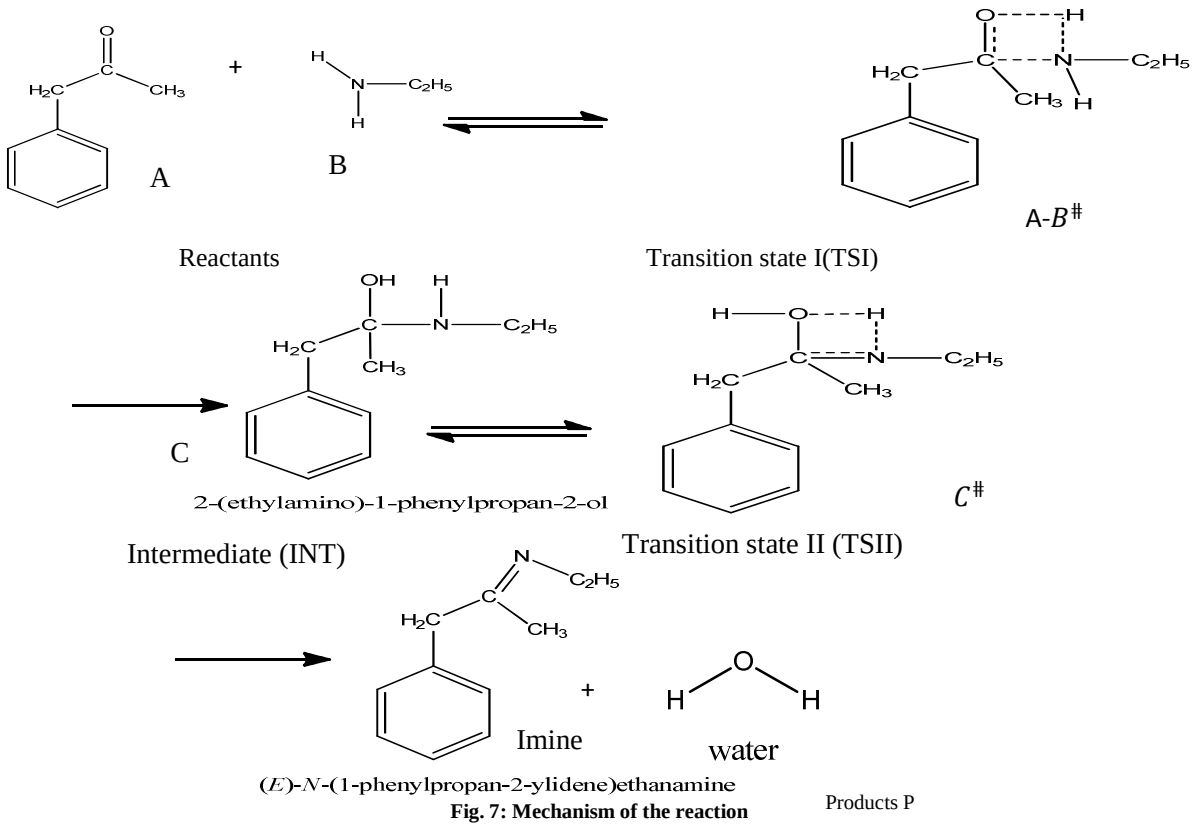

Fig. 7: Mechanism of the reaction

Also as the bond distances are undergoing variations during the transformation of the reactants through stationary points to products, the bond angles are not left out in the changes. Variations in the bond distances and bond angles are presented in the tables 3 and 4 below.

Table 3: Variations in bond distances between transition state II and product (major) imine

Transition state II	bond Distances Å	Product bonds	Distances Å
C1–C7	1.523A^{o}	C1–C7	1.520
C7–C8	1.514	C7–C8	1.534
C8–C9	1.503	C8–C9	1.513
C8–N1	1.325	C8–N1	1.276
N1–C10	1.465	N1–C10	1.453

Table 4: Variations in bond angles between transition state II and product (major) imine

Transition state II		Product	
∠C7C8N1	123.98	∠C7C8N1	127.74
∠C8N1C10	124.46	∠C8N1C10	123.68
∠C7C8C9	116.32	∠C7C8C9	114.62
∠C1C7C8	118.09	∠C1C7C8	112.84
∠N1C10C11	110.01	∠N1C10C11	109.91

The consecutive reaction step which can be illustrated as A + B $\xrightarrow{k_2}$ C $\xrightarrow{k_1}$ P is as shown in fig.8 below. From the kinetic parameters the first is the rate determining step with the lower rate constant value of k_1 = 56.9214 x $10^{-25}s^{-1}$

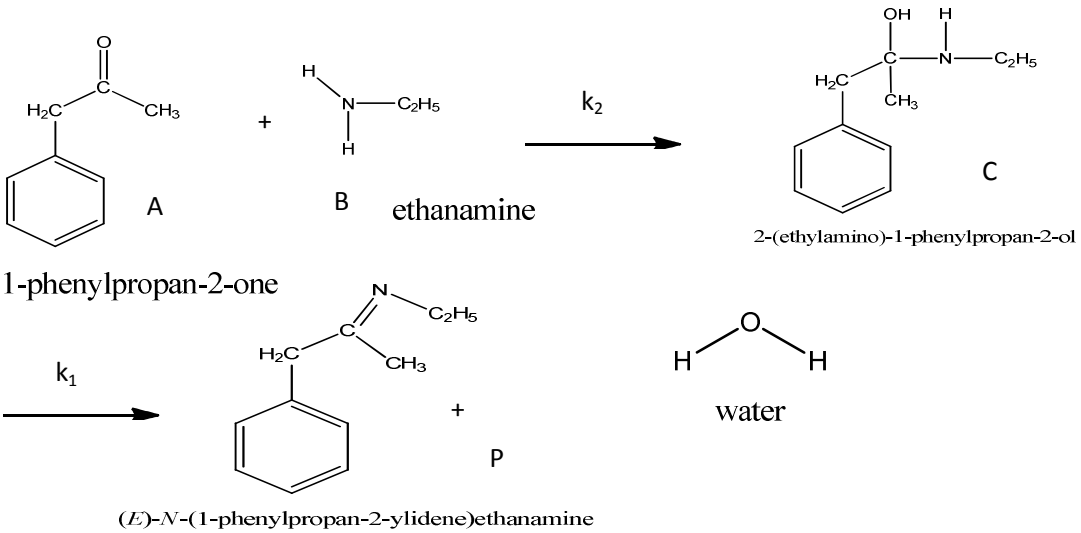

Fig.8: Consecutive step scheme of the reaction

From thermodynamic calculations, the consecutive step of the reaction is all irreversible. The step from reactants (A and B) to the intermediate (C) has Gibb's free energy change ($\Delta_{rxn}G^o$) of -14.261kJ/mol (<0). Then the step from the intermediate to product has Gibb's free energy change ($\Delta_{rxn}G^o$) of -345.948kJ/mol (<0), indicating the irreversibility of the reaction. Table.10 below shows the enthalpy of formation, ($\Delta_f H^o$) and entropy, (ΔS^o) at standard temperature and pressure of the species in the consecutive reaction step.

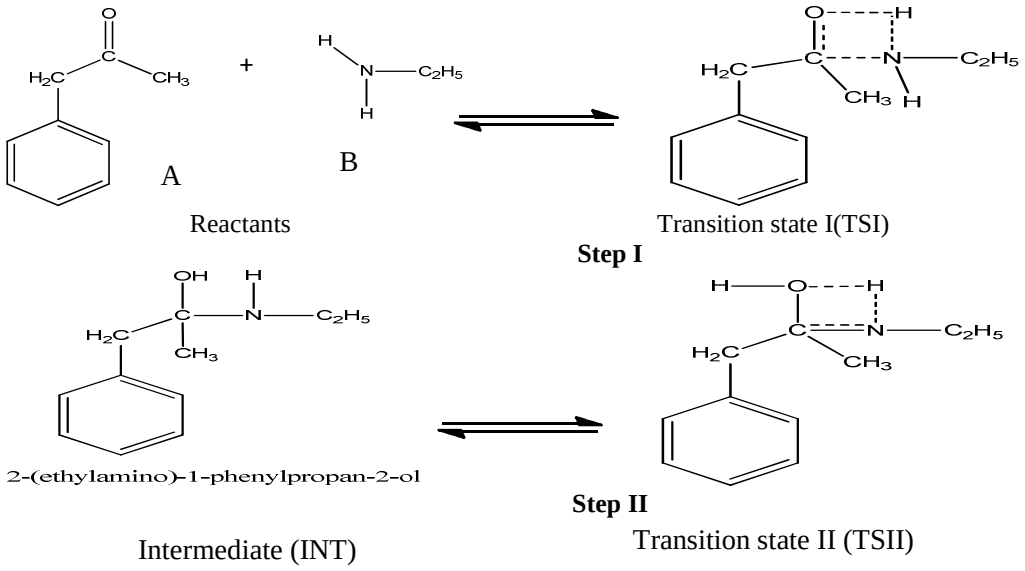

Fig.9: Transition state reaction scheme

The energy values are presented in the tables 5 and 6 below. The activation energy values also indicate that the steps are reversible due to low energy barriers as opposed to entropic change values.

Table 5: Entropy of formation S^o(J/molK) entropy of activation $\Delta S^{\#}$(J/molK)and Gibbs'free energy of activation $\Delta G^{\#}$(kJ/mol) at AM1 and RB3LYP/6-31G(d) theory levels

	Semi empirical (AM1)			DFTRB3LYP/6-31G(d)		
Species	S^o	$\Delta S^{\#}$	$\Delta G^{\#}$	S^o	$\Delta S^{\#}$	$\Delta G^{\#}$
A	+399.7990			+406.2031		
B	+272.8002			+270.8286		
C	+491.9337			+501.7844		
Step I		-180.6655	+276.4633		-198.7974	+41.6514
E	+471.9236			+485.3349		
F	+471.0500			+188.8535		
Step II		-0.8736	+301.7489		+10.5326	-12.1203

Table 6: Activation energy E_a, Arrhenius frequency factor A, and rate constants, k_1 and k_2 for the step I and step II

Step 1(bimolecular)	E_a	145.6025kJmol^{-1}
	A	1895.84mol^{-1}dm$_3$s^{-1}
	k_2	58.8116 x10^{-24}mol^{-1}dm^{3}s^{-1}
Step 2 (unimolecular)		
	E_a	199.9083kJmol^{-1}
	A	5.9914x10^{13}s^{-1}
	k_1	56.9214 x 10^{-25}s^{-1}

Kinetics of the Reaction

From fig.2 above the reaction mechanism consists of the following steps:

$$A + B \underset{k_{-2}}{\overset{k_2'}{\rightleftharpoons}} AB^{\#}$$

$$AB^{\#} \xrightarrow{k_2} C$$

$$C \underset{k_{-1}'}{\overset{k_1'}{\rightleftharpoons}} C^{\#}$$

$$C^{\#} \xrightarrow{k_1} P$$

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

$$\frac{d[P]}{dt} = k_1[C^{\#}] \quad \text{i}$$

$$\frac{d[C^{\#}]}{dt} = -k_1[C^{\#}] - k'_{-1}[C^{\#}] + k_1'[C] \quad \text{ii}$$

$$\frac{d[C]}{dt} = -k_1'[C] + k'_{-1}[C^{\#}] + k_2[AB^{\#}] \quad \text{iii}$$

$$\frac{d[AB^{\#}]}{dt} = -k_2[AB^{\#}] - k'_{-2}[AB^{\#}] + k_2'[A][B] \quad \text{iv}$$

Using steady state approximation, from equation (ii)

$$[C^{\#}] = \frac{k_1'}{k_1' + k'_{-1}}[C] \quad \text{v}$$

Using equations (iii) and (v), we have

$$-k_1'[C] + \frac{k'_{-1}k_1'}{k_1' + k'_{-1}}[C] + k_2[AB^{\#}] = 0$$

$$[C] = \left[\frac{k_2(k_1' + k'_{-1})}{k_1'^2}\right][AB^{\#}] \quad \text{vi}$$

Similarly, from equation (iv), we have,

$$[AB^{\#}] = \frac{k_2'}{k_2 + k_{-2}'}[A][B] \quad \text{vii}$$

Equations (vi) and (vii) gives,

$$[C] = \frac{k_2 k_2'(k_1' + k_{-1}')}{k_1'^2(k_2 + k_{-2}')}[A][B] \quad \text{viii}$$

From equations (viii) and (v), we have,

$$[C^{\#}] = \frac{k_2 k_2'}{k_1'(k_2 + k_{-2}')}[A][B] \quad \text{ix}$$

Therefore the overall rate law can be written as;

$$\frac{d[P]}{dt} = k_1 \frac{k_2 k_2'}{k_1'(k_2 + k_{-2}')}[A][B] \quad \text{x}$$

where $k_1 \frac{k_2 k_2'}{k_1'(k_2 + k_{-2}')} = K'$, experimental rate constant.

CONCLUSION

The reaction between benzylmethyl ketone has been found to occur through four steps, each step with its characteristic thermodynamics and kinetic parameters. Unimolecular step was the rate determining step of the reaction mechanism. A detailed kinetic of the reaction has been established but the overall reaction rate constant is yet to be determined. Experimental rate constant for the reaction is yet to be found. It's also worthy to note that that the calculation was performed using semi-empirical (AM1) and smallest basis set [RB3LYP/6-31G(D)] of the Density Functional Theory, a better result could be obtained using higher theory level and larger basis set. Also the results from the two methods are in good agreement with each other, as they both confirmed the presence of two transition states in the mechanism and the transition state reaction are all reversible.

REFERENCES

[1] Blumenkopf T. A., and Overman L. E., *Reactions Chemie Review*. **1986**; 86: 857.
[2] Rudolph A. C., Machauer R., and Martin S. F., *Tetrahedron Letters* **2004**; 45: 4895.
[3] Burke M. D. and Schreiber S. L., A Planning Strategy for Diversity-Oriented Synthesis Angewandte Chemie, International Edition. **2004**; 43: 46.
[4] Marcaccini S, Torroba T In: Multicomponent Reactions. Zhu J, Bienayme H, editors. Wiley- VCH; Weinheim: **2005**. p. 33.
[5] Sunderhaus, J. D., Dockendorff, C. and Martin, S. F.,*Org Lett*. **2007**;9:4223 – 4226
[6] Tim Soderberg (University of Minnesota, Morris), Organic Chemistry with a Biological Emphasis.
[7] EllmanJ. A., OwensT. D., and TangT. P., *Acounts of Chemical Research*.**2002**, 35(11), 984 - 95.
[8] (a) Jacobsen, M. F.; Skrydstrup, T. *J. Organic Chemistry*.**2003**, *68*, 7122; (b) Tang, T. P.; Ellman, J. A. *Journal of Organic Chemistry*.**2002**, *67*, 7819; (c) Tang, T. P.; Ellman, J. A. *J. Organic Chemistry*.**1999**, *64*, 12.
[9] Schenkel, L. B.; Ellman, *J. A. Organic. Letter*.**2004**, 6, 3621. 10.
[10] J S. Swenton, Ohio State University **1960** Kenny Road Columbus, Oh 43210, Chemistry of Biologically Relevant Quinone Imines
[11] Liu G., Cogan O. A., and Ellman J. A.; *Journal of the American Chemical. Society*. 119, 9913 (**1997**).
[12] E. F. Kleinman, Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, **1991**; Vol. 2, Chapter 4, p 893.
[13] Li-Xin Dai, Ying-Rui Lin, Xue-Long Hou. and Yong-Gui Zhou; Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, *China Pure and Applied Chemistry*, Vol. 71, No. 6, pp. 1033 – 1040, **1999**.
[14] Blaser H.U., Pugin B., F. Spinder F., Togni A., *Rendous. Chimie*. 2002, 5, 379.].
[15] Arunkumar K. Appi Reddy M. Sravan Kumar, B. Vijaya Kumar, K. B. Chandrasekhar, P. Rajender Kumar and Manojit Pal; *Beilstein J. Org. Chem.* **2010,** *6*, 1174–1179. doi:10.3762/bjoc.6.134
[16] E. Thomas and R. Philip, physical Chemistry, **2006** Revised Edition, pp 924 – 925 ISBN 0-8053-3842-X