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Simulation Study of Adrenaline Synthesis from Phenylalanine

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ABSTRACT

Simulation study of Adrenaline synthesis from Phenylalanine has been carried out using semi-empirical methods (PM3) and density functional theory (DFT) STO-3G level of theory . Geometrical properties and vibration mods have been calculated for all structures. Different probable products have been suggested for each reaction and the most probable products being selected depending upon the electronic properties to prove the pathway of reactions that's needed to synthesis adrenaline in the human body.

The calculations show the most probable product than other structurs due its energetic values of total energy, energy barrier value, heat of formation, zero point energy, imaginary frequency and rate constant that's equal to ($5.554*10^{12}$, $5.572*10^{12}$, $7.857*10^{12}$, $1.331*10^{13}$,$1.116*10^{13}$) respectively by s^{-1} units. Thermodynamic functions (ΔH, ΔS, ΔG) have been calculated for five steps reactions of Adrenaline synthesis . In reaction 1 equal to (-69.468, $1.37*10^{-4}$, -66.610), reaction 2 (-46.453, $3.044*10^{-3}$, -64.710), reaction 3 (-63.734, 0.022, 138.900), reaction 4 (87.036, $8.631*10^{-3}$, -451.510) and reaction 5 (-6.722,-0.025, 346,800) respectively by kCal/mol, kCal/mol/deg, and kCal/mol respective units. The chemical reactivity or energy gap has been calculated for the most probable products in the pathway of adrenaline synthesis .

Keywords: Simulation Study; Semi-empirical method; DFT; Adrenaline.

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1. INTRODUCTION

Adrenaline (Epinephrine or 4,5-β-trihydroxy phenethylamine) has formula chemical formula $C_6H_{13}NO_3$. It,s a hormone and a neurotransmitter secreted by the inner part of the adrenal gland, which produces in the heart of the adrenal in response to physical or mental stress [1]. Adrenaline has one amino group that is associated with an aromatic ring with a two-carbon chain, -CH_2-CH_2-). Epinephrine classified in the class of compounds called catecholamine which is a monoamine derived from the amino acid tyrosine, and also the same case derived from phenylalanine[2]. Figure 1 shows the chemical structure of Adrenaline.

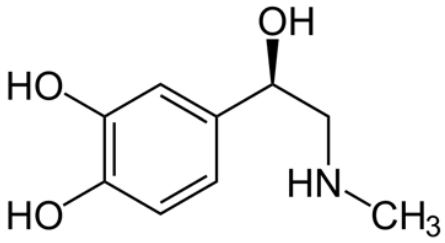
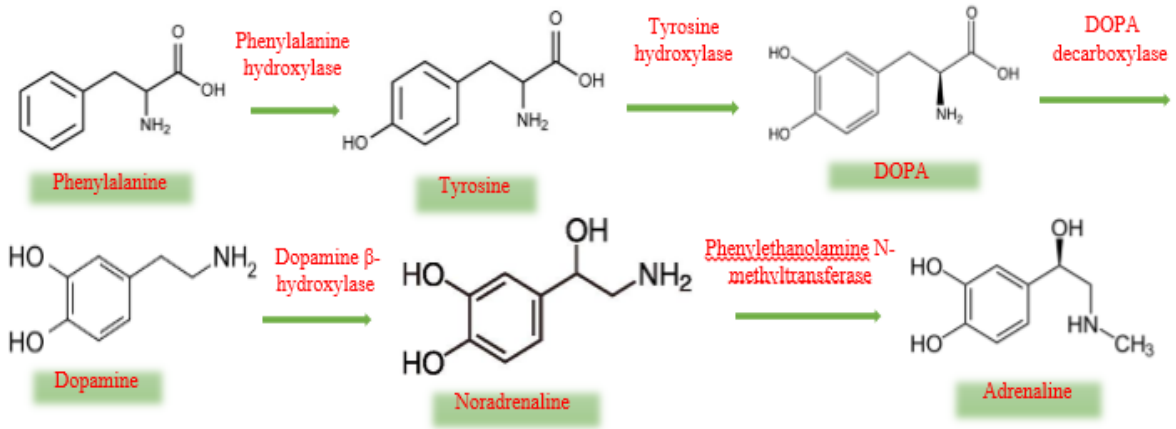


Figure 1: Chemical structure of Adrenaline.

Adrenaline was discovered as a substance produced from adrenal gland in 1886 by William Bates reported, than was isolated and recognized in 1895 by Napoleon Cybulski[3], and synthesized of adrenaline for the first time artificially in 1904 by Friedrich Stolz[4]. Metabolic reactions that occur in Adrenaline synthesis in the human body from Phenylalanine are Oxidation of Phenylalanine to Tyrosine, Oxidation of Tyrosine to L-DOPA, Decarboxylation of L-DOPA to Dopamine, Oxidation of Dopamine to Noradrenaline, And at the last methylation of Noradrenaline to Adrenaline [5] through the following steps:



The present study tends to prove the beast's path of Adrenaline synthesis from Phenylalanine theoretically through the quantum calculations treatment of the electronic and geometrical structure by using PM3 of semi-empirical calculations and DFT minimal STO-3G. Different probables products will be suggested in each reaction to find the most probable product.

2. COMPUTATIONAL DETAILS

Theoretical calculations were completed by using the computational implemented in the Hyperchem Version 8.0.9 program [6,7]. Geometry optimization, electronic energies, heat of formation for all chemical compounds that's needed to Adrenaline synthesis from Phenylalanine have been optimized at semi empirical method and DFT- STO-3G. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are studied to calculate the Energy gap (ΔE) [8,9]. Thermodynamic parameters (ΔG, ΔH, ΔS) were calculated at semi-empirical method PM3 level[10]. Table 1 shows the chemical structures and abbreviations of all compounds.

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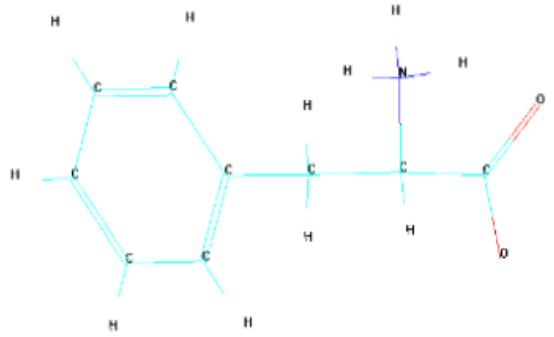
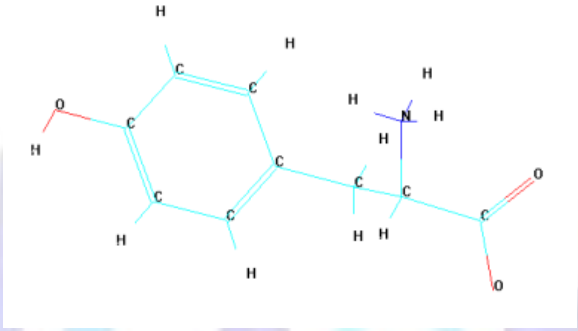
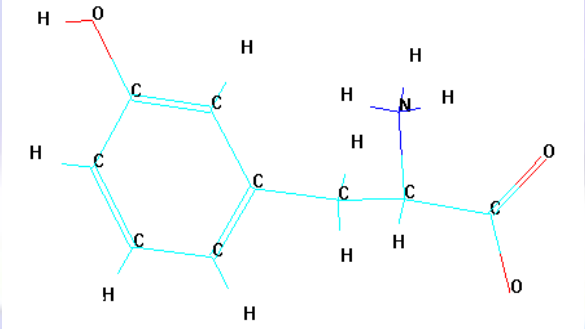
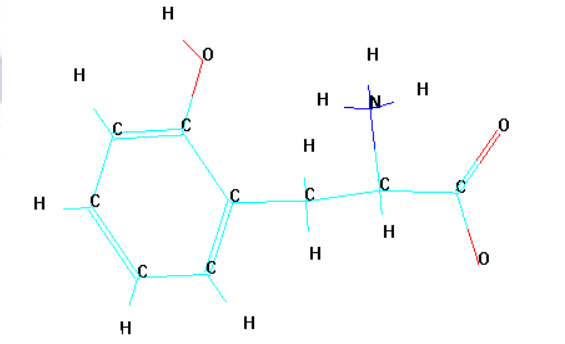
Table 1: List of chemical structures and abbreviations.

Phe		Phenylalanine
4-HP		4-hydroxy phenylalanine
3-HP		3-hydroxy phenylalanine
2-HP		2-hydroxy phenylalanine

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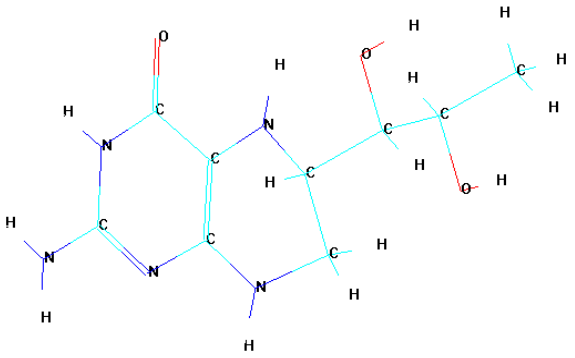
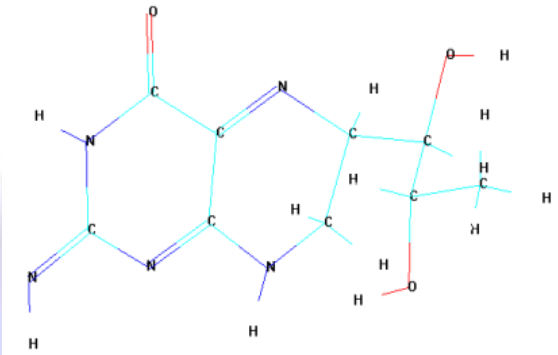
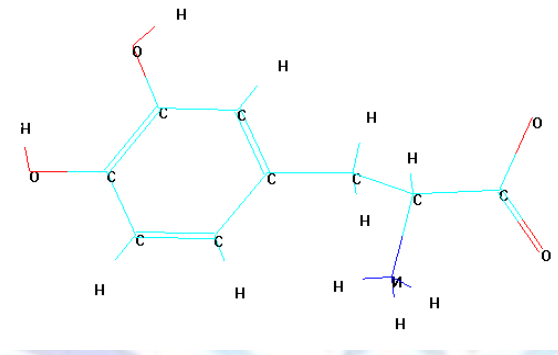
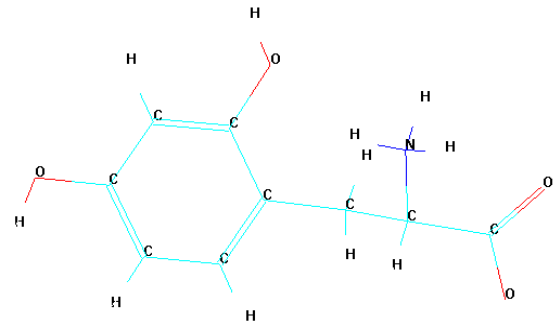
THBP		5,6,7,8-Tetrahydrobiopterin
DHBP		7,8-Dihydrobiopterin
DOPA-3		3,4-Dihydroxyphenylalanine
DOPA-2		2.4-Dihydroxyphenylalanine

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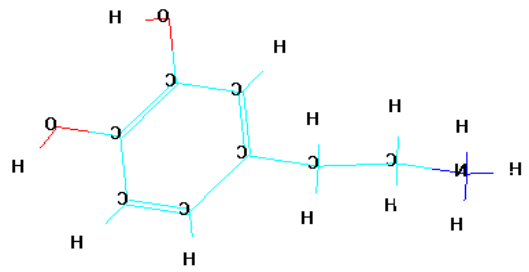
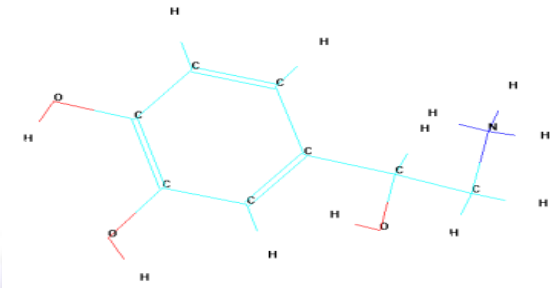
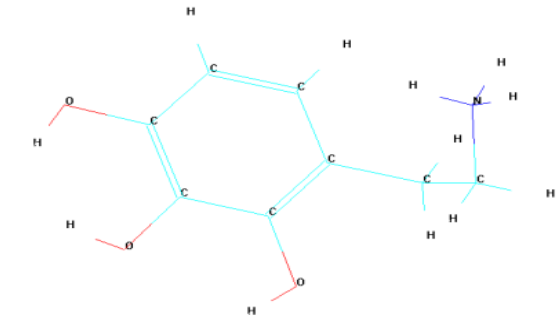
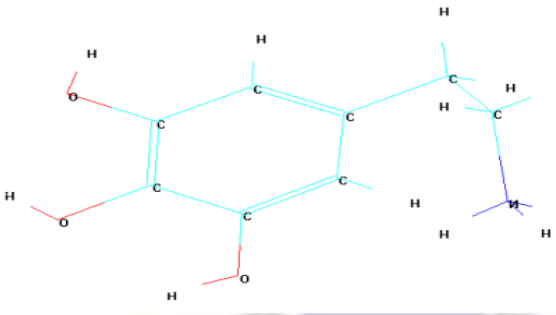
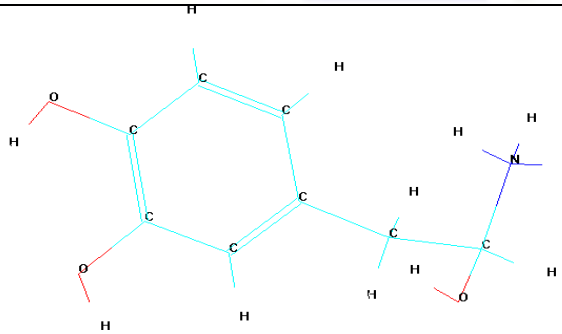
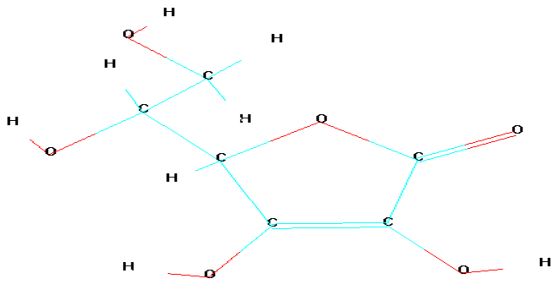
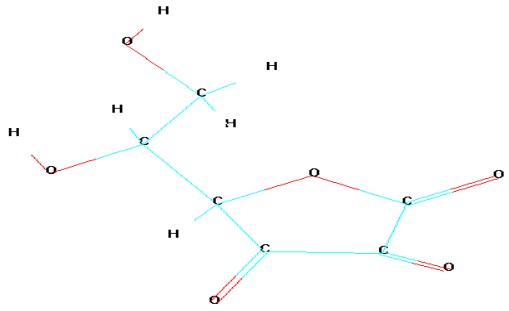
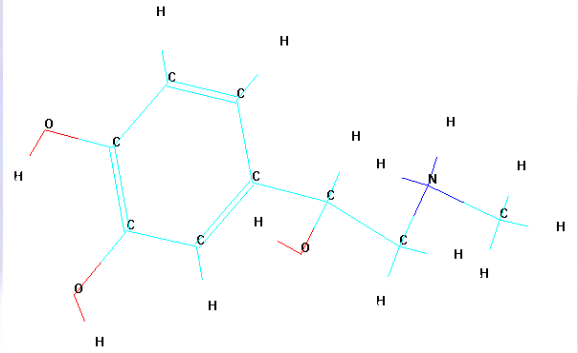
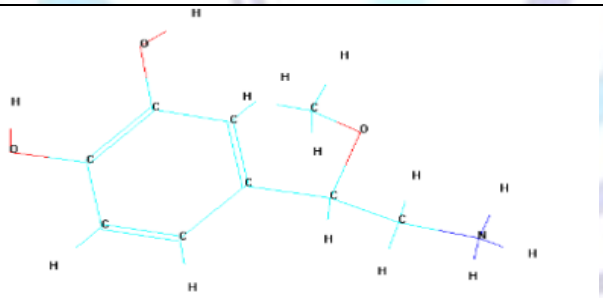
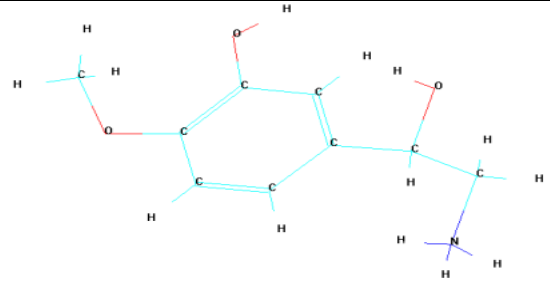
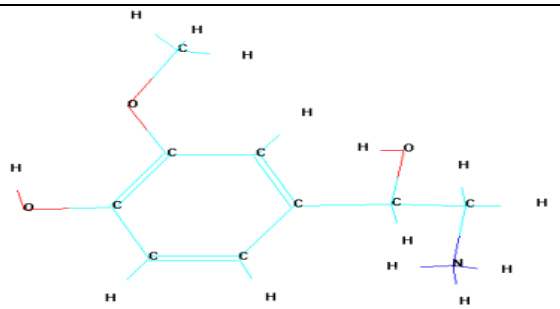
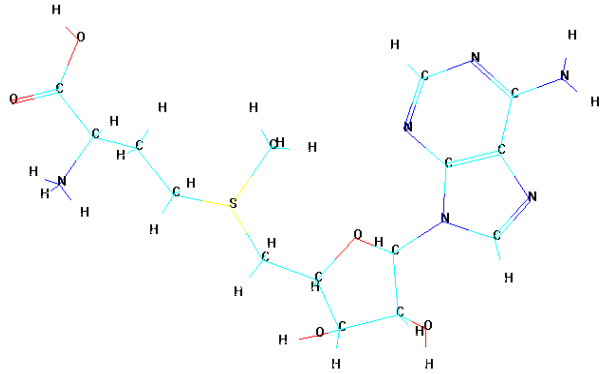
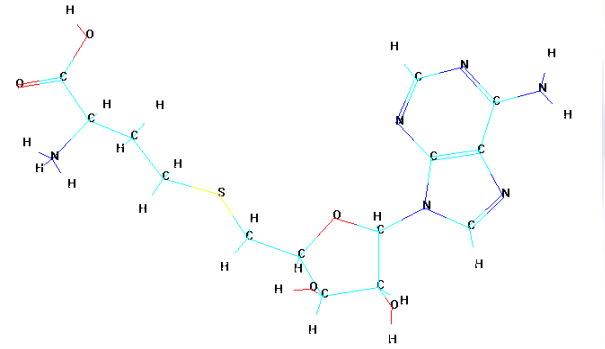
DA		Dopamine
2-A-1-HEBDIOL		Norepinephrine 4-[2-amino-1-hydroxyethyl]benzene-1,2-diol
2-AEB-2.3,4-TRIOL		4-[2-aminoethyl]benzene-2,3,4-triol
2-AEB-3,4,5-TRIOL		4-[2-aminoethyl]benzene-3,4,5-triol
2-A-2-HEB-1,2-DIOL		4-[2-amino-2-hydroxyethyl]benzene-1,2-diol

A.A		Ascorbic acid
DHA		Dihydroascorbic acid
4(1-H,2-MAE)B1,2-DIOL		Epinephrine 4-(1-Hydroxy-2-(methylamino)ethyl)benzene-1,2-diol
4(2-A-1-ME)B-1,2DIOL		4-(2-amino-1-methoxy ethyl)benzene-1,2- diol
5(2-A-1-HE)-2-MP		5-(2-amino-1-hydroxy ethyl)-2-methoxy phenol

4(2-A-1-HE)-2-MP		4-(2-amino-1-hydroxy ethyl)-2-methoxy phenol
SAM		S-adenosyl methionine
SAH		S-adenosyl honocysteine

3. RESULTS AND DISCUSSION

The study included the adrenaline synthesis from phenylaniline in vacuum taking into account the factors of the reaction at 25℃ and 1M concentration for all chemical compounds by different quantum calculation methods. The energetic properties of Adrenaline synthesis were calculated by semi empirical PM3 method and listed in Table 2. Table 2 show that the rate constant of raction of aquired values is very high, thats mean these ractions are very fast, because the values of the rate constant equal to the speed of the reaction at the concentrations used. These reactions are very fast because they are nerve reactions [11]. In very fast reactions that cannot control the value of the energy barrier which equal to the value of activation energy is negative [12]. Thermodynamic parameters indicate that the reactions 1 and 3 are exothermic and spontaneous, reaction 2 and 5 are exothermic and nonspontaneous while reaction 4 is endothermic and spontaneous according to the concept of thermodynamic[13,14].

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Table 2: Energetic properties for synthetic reactions of Adrenaline.

Steps	Reactants	Probabilities Products	Energy barrier (kCal/mol)	HΔ (kCal/mol)	ΔS (kCal/mol/deg)	ΔG (kCal/mol)	k (s^{-1})
Reaction 1	O_2+Phe+ THBP	H_2O+4-HP + DHBP	69.469-	-69.468	$1.37*10^{-4}$	-66.610	$5.554*10^{12}$
		H_2O+3-HP + DHBP	-69.561	-69.560	$4.63*10^{-4}$	-66.810	$5.552*10^{12}$
		H_2O+2-HP + DHBP	-69,427	-69.426	$-2.428*10^{-3}$	-65.810	$5.561*10^{12}$
Reaction 2	4-HP+O_2+ THBP	DOPA-3+H_2O+ DHBP	-17880	-49.453	$-3.044*10^{-3}$	-64.710	$5.572*10^{12}$
		DOPA-2+H_2O+ DHBP	-17878.727	-48.18	$-2.5791*10^{-3}$	-66.110	$5.558*10^{12}$
Reaction 3	DOPA-3	DA+CO_2	131.563	-63.734	0.022	138.900	$7.857*10^{12}$
Reaction 4	DA+A.A+O_2	2-A-1-HEBDIOL +DHA+H_2O	-461.941	87.036	$8.631*10^{-3}$	-451.510	$1.331*10^{13}$
		2-AEB-2.3,4-TRIOL +DHA+H_2O	-469.354	169.623	$6.864*10^{-3}$	-456.810	$2.874*10^{12}$
		2-AEB-3,4,5-TRIOL +DHA+H_2O	-469.195	169.782	$4.247*10^{-3}$	-456.910	$2.874*10^{12}$
		2-A-2-HEB-1,2-DIOL +DHA+H_2O	-469.845	169.132	$6.543*10^{-3}$	-457.710	$2.871*10^{12}$
Reaction 5	2-A-1-HEBDIOL+SAM	4(1-H,2-MAE)B1,2-DIOL +SAH	346.857	-6.722	-0.025	346.800	$1.116*10^{13}$
		4(2-A-1-ME)B-1,2DIOL +SAH	359.71	6.131	-0.026	351.900	$1.125*10^{13}$
		5(2-A-1-HE)-2-MP +SAH	355.929	2.35	0.024-	356.800	$1.135*10^{13}$
		4(2-A-1-HE)-2-MP +SAH	352.812	-0.768	-0.021	352.900	$1.127*10^{13}$

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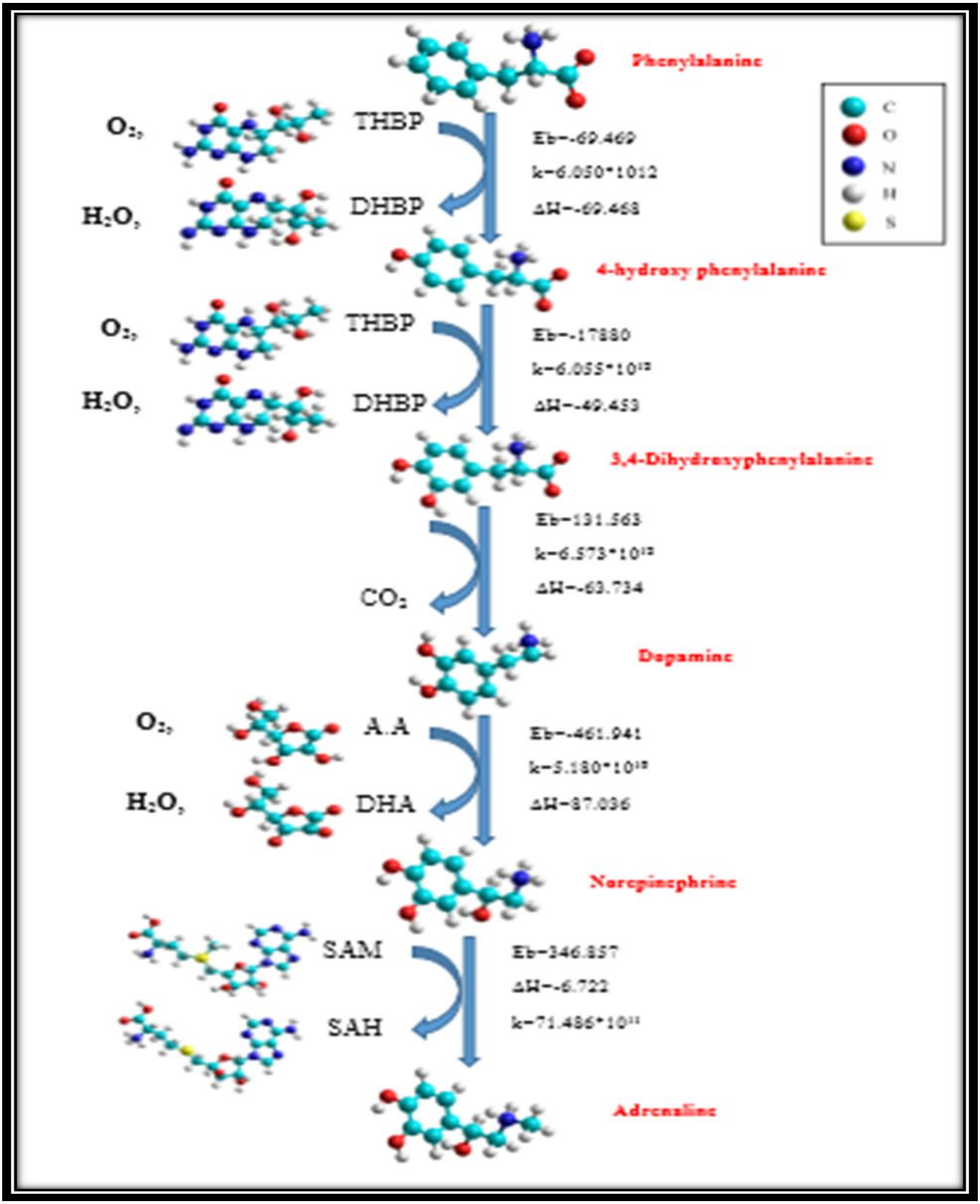
Scheme 1 show the pathway of Adrenaline synthesis accourding to energetic properties . Scheme 1



. Pathway of Adrenaline synthesis within sevral steps.

The energetic properties for all chemical compounds were calculated by the DFT- STO-3G level of theory as show in Table 3.

Table 3: The properties of energy for all chemical compounds.

Reactions		Total energy kCal/mol	ZPE kCal/mol	Molecular orbital energy		
				HOMO (eV)	LUMO (eV)	ΔE_{gab} (eV)
Reaction 1	Phe	-296103.504	85.94813	14.062	14.932	0.870
	4-HP	-331815.725	-795.942	15.546	16.334	0.787
	3-HP	-337296.732	76.934	14.336	15.205	0.868
	2-HP	-313882.509	69.241	19.857	20.422	0.564
	THBP	-347533.704	-404.734	42.418	43.648	1.229
	DHBP	-431753.039	-1795.760	16.393	16.784	0.390
Reaction 2	L-DOPA-3	-342495.390	-118.740	19.614	19.715	0.101
	L-DOPA-2	-378502.277	79.769	14.515	15.343	0.827
Reaction 3	DA	-218124.785	-992.327	15.566	15.686	0.119
Reaction 4	A.A	-33256.054	-842.535	16.201	17.123	0.922
	DHA	-368366.966	-225.570	18.587	18.897	0.310
	2-A-1-HEBDIOL	-317459.957	91.849	8.232	10.207	1.915
	2-AEB-2.3,4-TRIOL	-306639.698	-993.124	13.978	15.015	1.037
	2-AEB-3,4,5-TRIOL	-314215.161	-617.481	9.999	10.117	0.117
	2-A-2-HEB-1,2-DIOL	-317442.890	91.312	8.870	10.367	1.497
Reaction 5	SAM	-799039.175	-3448.226	-0.205	6.474	6.680
	SAH	-722545.307	-2988.044	65.772	65.871	0.065
	4(1-H,2-MAE)B1,2-DIOL	-267243.197	-96.147	29.879	30.473	0.593
	4(2-A-1-ME)B-1,2DIOL	-289960.017	-299.302	5.573	7.312	1.738
	5(2-A-1-HE)-2-MP	-338039.050	108.338	8.242	10.158	1.915
	4(2-A-1-HE)-2-MP	-338033.276	104.902	8.794	10.523	1.728

The energy band gap of all compounds through the adrenaline synthesis pathway was calculated[15] and showed as below:

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Phe → 4-HP → L-DOPA-3 → DA →

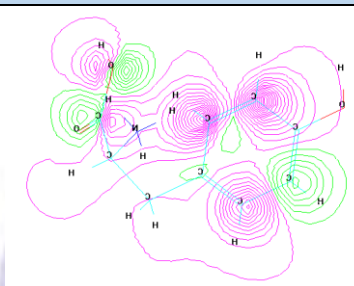
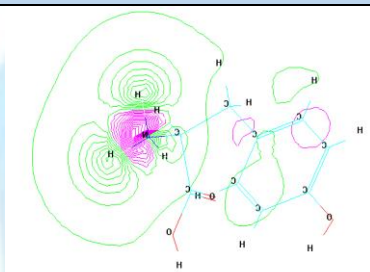
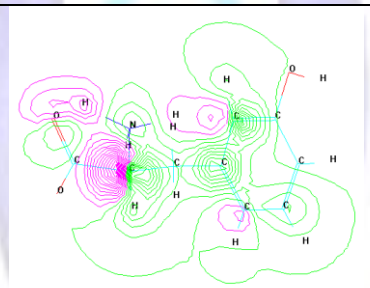
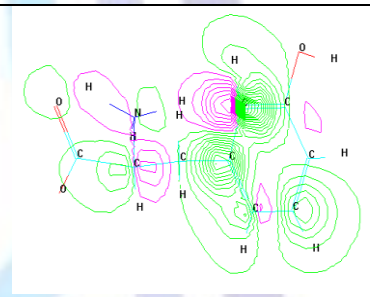
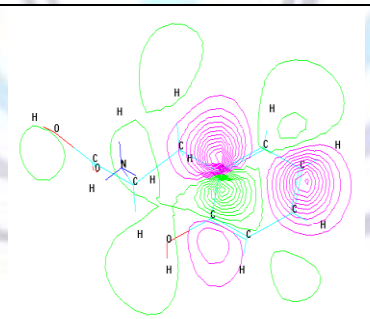
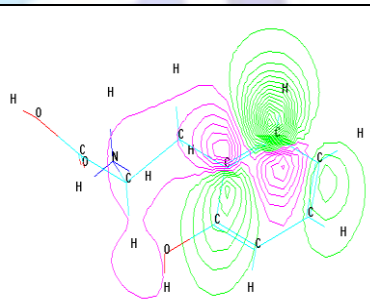
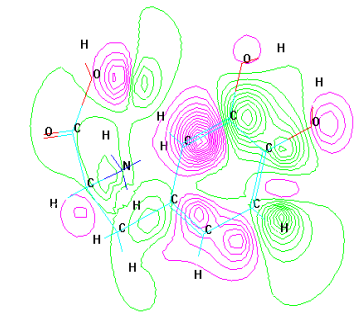
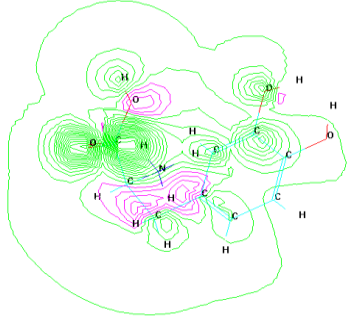
(0.870 eV) **(0.787 eV)** **(0.101 eV)** **(0.119 eV)**

2-A-1-HEBDIOL → 4(1-H, 2-MAE)B1,2-DIOL

(1.915 eV) **(0.593 eV)**

The energy gap value for all chemical compounds in the pathway of Adrenaline synthesis indicates they are good conductors [16], this enables to transfer electrical signals in the nervous system. The HOMO and LUMO orbitals were calculated by the DFT- STO-3G level of theory, they showed in Table 3.

Table 3: The molecular properties of chemical meoties calculated by the DFT- STO-3G level of theory.

	Reactants	Probabilities Products	HOMO at 2D contours	LUMO at 2D contours
Reaction 1	O_2+Phe+ THBP	4-HP		
		3-HP		
		2-HP		
Reaction 2	4-HP+O_2 + THBP	DOPA-3		

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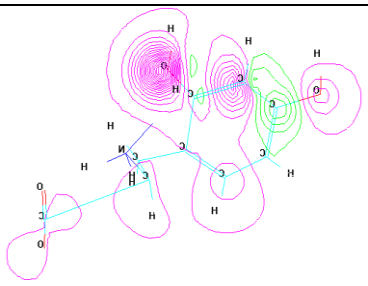
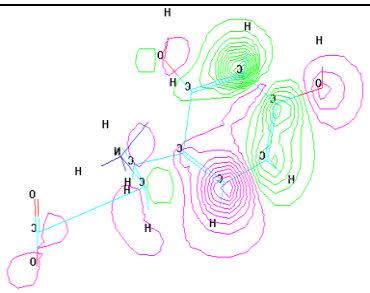
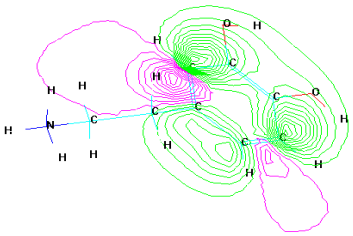
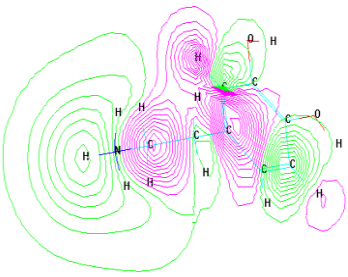
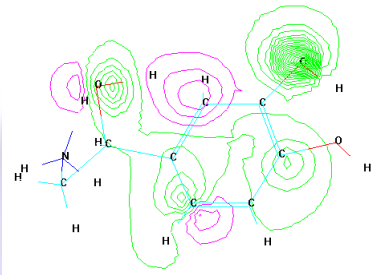
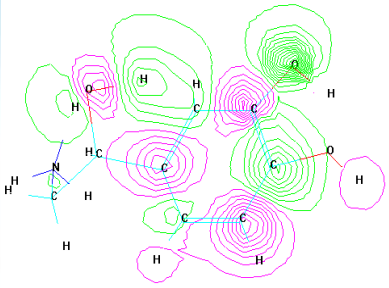
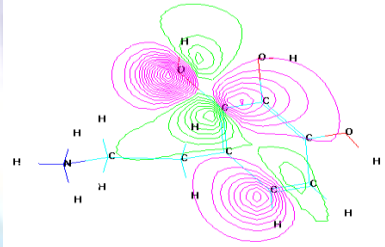
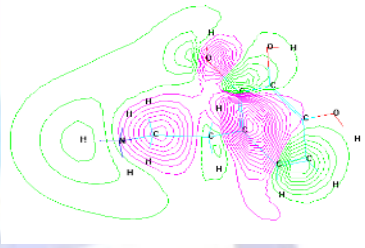
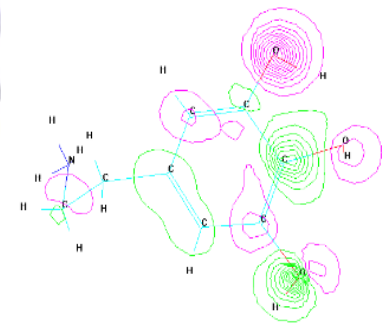
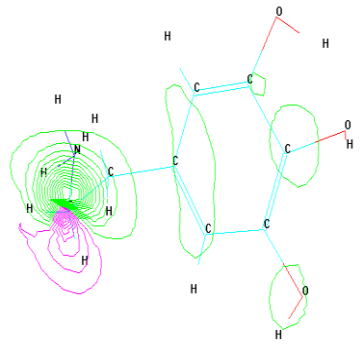
		DOPA-2		
Reaction 3	DOPA-3	DA		
Reaction 4	DA+A.A+O2	2-A-1-HEBDIOL		
		2-AEB-2.3,4-TRIOL		
		2-AEB-3,4,5-TRIOL		

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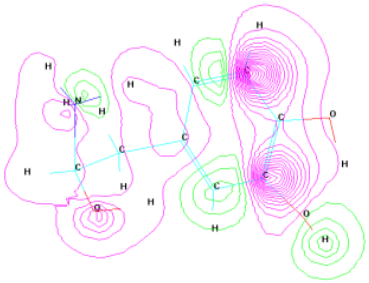
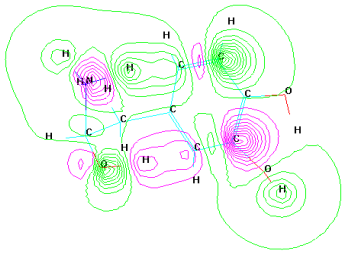
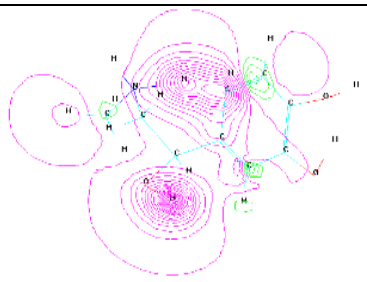
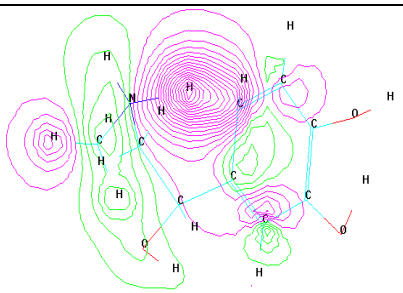
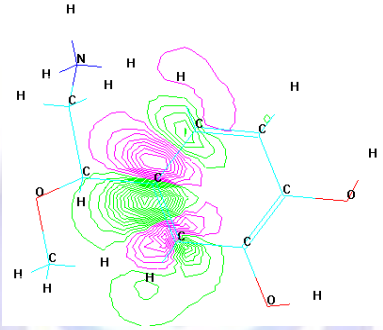
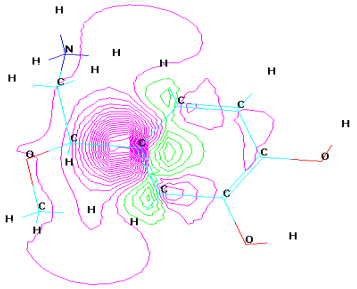
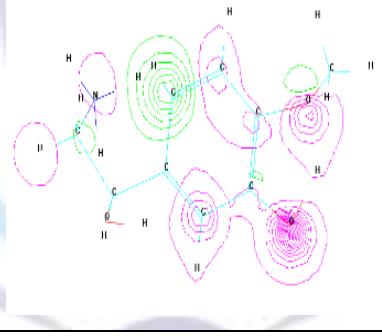
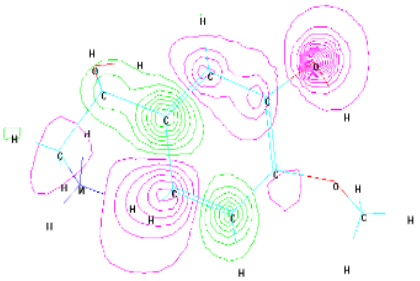
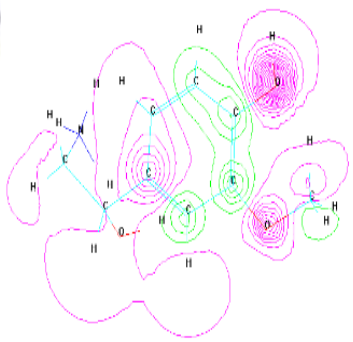
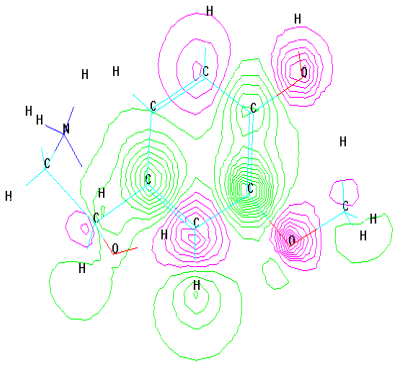
		2-A-2-HEB-1,2-DIOL +DHA+H_2O		
Reaction 5	2-A-1-HEBDIOL +SAM	4(1-H,2-MAE)B1,2-DIOL		
		4(2-A-1-ME)B-1,2DIOL		
		5(2-A-1-HE)-2-MP		
		4(2-A-1-HE)-2-MP		

4. CONCLUSIONS

- The pathway of Adrenaline synthesis have been investigated accourding to theoretical calculations.
- Comparitive of chemical recations are achevied dependiong on the energetic phenomena for every stepwise reaction.
- Molecular orbital behavoure have been estimated through DFT calculation and the reactivity been determinated for all chemical mioties of chemical synthesis in vaccum.
- The reactions of synthesis are spontinously takeplaces due the biological signal transfer in brine.

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