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Estimation of transition state and Synthesis of Barbituric Acid with their derivatives of 1,3,4-Thiadiazole

Fadhel Omran Essa, Kadhum Jwad Kadhum, and *Abbas A-Ali Drea

*College of Essential education / Science Department, Babylon University.
College of Medicine / Science Department, Babylon University.
College of Science / Science Department, Babylon University.

E-mail : aadreab@yahoo.com

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ABSTRACT

Quantum calculation method have been used to estimate the real transition state for the synthesis of Barbituric Acid and their derivatives of 1,3,4-Thiadiazole using semiemperical calculation methods. Optimized structures, electronic transition spectrum and vibration spectrum have been calculated for the preparative compounds compared with their experimental spectrums. Theoretical examination of transition state has been done to know the real transition state of reaction through zero point energy, total binding energy and first imaginary frequency. Three suggested transition states have been proposed for the reaction of 2-amino-5-mercapto-1, 3, 4-thiadiazol with 4-dimethylamino benzaldehyde. First transition state is the real state due their energy values comparatively with other states. Barbituric Acid and some of new derivatives of 1, 3, 4-Thiadiazol have been prepared as new medical agents. Good agreements has been found between the experimental and theoretical spectrums for the synthetic products, likes N-{5-(2, 2-Dimethylisopropylidenyl) thio-1,3,4-thiadiazolyl}-N-Benzoyl-amino-(4-(N-Dimethylamino)benzyl–aminobarbituric acid as final product.

Keywords: Quantum calculation methods, transition states, Barbituric Acid, Thiadiazole Semi-empirical and PM_3.

INTRODUCTION

Thiadiazole have a variety of potential biological activities [1-3], utilities as technologically useful[4-6], and number of methods for their preparation have been developed. A useful preparative method have been used for 2-amino-5-mercapto-1,3,4-thiadiazole was carbon disulphide and potassium hydroxide[7-9].Heterocyclic amines have been widely used for the synthesis of Schiff's base[10,11]. The barbituric acid derivatives comprise an important and valuable group of central nervous system depressants[12-16]. Its first member was synthesized by Fisher in 1903 and was called barbital (Veronal) which is a diethyl

barbiturate. The next to be synthesized was Phenobarbital (Luminal) which is an ethyl, phenyl derivative. In the following years, many hundreds of new derivatives have been produced but barbital and especially Phenobarbital still enjoy a deserved preference for many purposes. The chief advantage of several of the newer members of this group is their quicker onset of action and a shorter duration of action. Synonyms: Sleeping pills, goof balls, yellow jackets, red devils, etc. Uses: Sedation, hypnotic, anesthesia, preoperative. The properties are odorless, bitter, white crystalline powder, acidic and insoluble in water, but soluble as the sodium salt[17-18]. The estimation study of chemical synthesis reactions required optimized structures of the chemical moieties and their transition states for the reactions of synthesis. The structural properties are elementary keys to understand the chemical reactivity during the potential energy surface calculations. The first-order saddle point for minimal transitions must be taken care to get on the most probable states than others[19,20]. In present work, we are interested in study of the transition state of reaction synthesis for Schiff's base compound using different conditions and reactant species. Simulation studies are taken in several stages of calculation. To estimate at the last spectroscopic comparative study made and suggested the real transition state for the reaction.

MATERIALS AND METHODS

All chemicals used supplied from Fluka and Merck companies and used without any further purification .Infrared spectra were performed using a Shimadzu (FT-IR) -8400S spectrophotometer in the range (4000-400cm^{-1}).Spectra were recorded as potassium bromide discs . The electronic spectra of the compounds were obtained using a U.V-Visible spectrophotometer type(UV-VIS-2601 Double beam – Biotech engineering management.co.ltd) using quartz cell of (1.0)cm length with concentration (10^{-3}) mole $L^{-1}$of samples in acetone at 25^0Ć and melting points were obtained using an electro thermal apparatus Stuart melting point.

Calculation details: Semiemperical methods according to molecular orbital theory have been used to find the optimized structures of barbituric acid and their derivatives structural configuration interaction (3 X 3) of microstate .Bond stability (length & torsion) for main bonds have been examined using PM3 method. The transition state for the reaction path techniques have been studied using quadratic synchronous transit method (**QST**) of Hyperchem 8.02[21]. It searches for a maximum along a parabola connecting reactants and products, and for a minimum in all directions perpendicular to the parabola. Vibration frequencies of the proposed transition state structures have been calculated at UHF/RHF/3-21++G level of theory for characterization of the nature of stationary points and zero point energy (ZPE) calculations to compute the quantum energies of these reactions.

Synthesis:

1. The compound of 2-amino-5-mercapto-1,3,4-thiadiazol has been prepared by mixing of 2.0gm(0.02mol)of thiosemicarbazide with 2.33gm(0.02mol) of anhydrous sodium carbonate[18]. The final product formed as yellow needles. The yield is 1.6g (55%) and m. p is 233-235^0 Ć.

2. 5-(4-Dimethylamino)benzylidene)amino-1,3,4-thiadiazole-2-thiol has been prepared through a mixture of compound **1**. 0.5gm (0.006mol) of compound **1** in absolute ethanol added to the appropriate aldehyde 0.56gm (0.006mol) in acidic medium. The final product was red crystals with yield of 75% and m.p is 259-260.5˚C)[19,20].

3. The Preparation of *N*-{chloro[4-(dimethylamino)phenyl]methyl}-*N*-(5-mercapto-1,3,4-thiadiazol-2-yl)benzamide has been done by dissolving 0.5 gm (0.0019mol) of compound **2** in 5ml of dry benzene. The product formed as red crystals with an yield of 65% and m.p is 224-226˚C [25].

4. The Preparation *of* *N*-{carbamimidamido[4-(dimethylamino)phenyl]methyl}-*N*-(5-mercapto1,3,4thiadiazol-2-yl)benzamide has been done by mixing 0.096gm (0.0011mol) of sodium acetate and guanidine hydrochloride 0.0248gm (0.00029mol) in absolute ethanol. The product formed as yellow crystals with the percentage yield of 70% and m.p is 217-218.5˚C [26].

5. The compound of N-{5-mercapto(1,3,4-thiadiazol-2-yl)-N-benzoyl-amino-4-(N-dimethylaminobenzyl) amino barbituric acid has been prepared by addition of 0.27mmol of dimethyl malonate to the solution of sodium methoxide .The final product is red crystals with an yield of 60% and m.p is 233.5-235 ˚C [27].

6. The preparation of N{5((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)thio-1,3,4-thiadiazol-2-yl} N -benzoyl-amino(4-(N-dimethyl aminobenzyl) amino barbituric acid has been done by pouring the mixture of 0.1gm(0.21mmol) compound **5** and 0.02gm (0.188mmol) sodium carbonate solution into 15ml of dry dioxane . After stirring for 20min., 2,2-dimethyl-4-[(phenylsulfonyl)methyl]-1,3-dioxolane was added and refluxed for three hours .The solvent was evaporated and extracted by ethyl acetate .The organic layer has been evaporated and the final product is syrup .

RESULTS AND DISCUSSION

Figure.1 shows the geometries of the only possible three proposed transition state structures have been optimized and Compound .**1** was IR-tested. The Probable transition state of prepared compounds comes out through confirmation. Table 1. Show that the activation energy for the forward reaction is less than the activation energy for the backward reaction. This means the reaction tends to the products for all transition states. The interaction of 2-amino-5-mercapto-1,3,4-thiadiazol with 4-dimethylamino benzaldehyde in transition state, which are expected to yield TS1 is the real transition state and first transition state is the most probable state to give up the reaction products than other states due to lowest energy value of the reaction barrier 21.556 kcal mol^{-1}, highest value of zero point energy 154.7413kCal mol^{-1} and highest energy stability -65435.9980 kCal mol^{-1}[21].

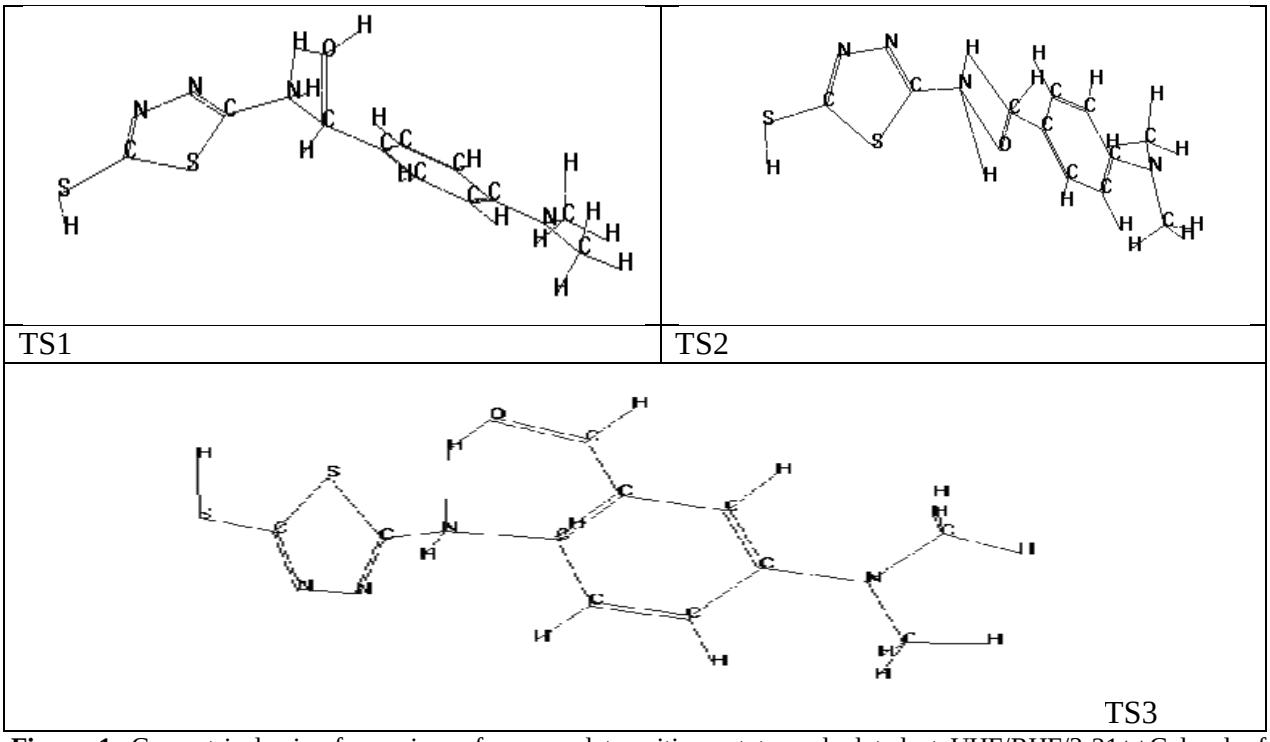


Figure 1. Geometrical wire form view of proposed transitions states calculated at UHF/RHF/3-21++G level of theory.

Table 1. Energy properties of probable transition states for 2-amino-5-mercapto-1,3,4-thiadiazol with 4-dimethylamino benzaldehyde calculated at UHF/RHF/3-21++G level of theory.

Transition State	Zero Point Energy KCal/mol	Total Energy KCal/mol	Heat of Formation KCal/mol	IR-Frequency (Imaginary)
TS1	154.7413	-65435.9980	280.38	-
TS2	141.4692	-65049.8452	312	-
TS3	148.5204	-65111.4203	251	-

Table .2 shows comparison between the experimental and theoretical vibration spectrum of the all six synthetic compounds. The compound.1 was confirmed according to data, they found in good agreement by two bands at 3338 cm^{-1} and 3257 cm^{-1} due to asymmetric and symmetric stretching vibrations of ν NH_2 group respectively. The frequency of NH tautomer. form stretching revealed absorbing band at 3103 cm^{-1}. Absorption bands at 2922 cm^{-1} and 2771cm^{-1} were attributed to intermolecular hydrogen bonding of NH group .Bond absorption at 1604 cm^{-1} was due to ν C=N stretching. The sharp bands at 1546 and 1475 are due to the ν N-H bending and ν N-N stretching vibration respectively. SH showed weak absorption at 2499 cm^{-1}, but the stretching band is characteristically weak and may go undetected in the spectra of dilute solution or thin film. Absorption at 1288, 1172 are due to ν C=S and NCS stretching respectively; absorption of ν SH and ν C=S indicated thiol- thione tautomerism. ν C-S showed absorption at 675, 615 cm^{-1}.

Table 3. Shows another comparison between experimental and theoretical U.V spectrum of the six synthetic compounds. The absorption band at 333nm is due to n-π* transition and at 255nm due to π- π* transition. The infrared spectrum of compound .2, indicate that the characteristic absorption band frequency of (C=N) at 1612 cm^{-1} with disappearance of bands at 3338 cm^{-1} and 3257 cm^{-1}. Stretching vibrations of ν NH_2 group and absence of band at 1674 cm^{-1} which correspond to carbonyl group of aldehyde. Data shows that U.V spectrum proved the structure by revealing absorption bands at 430nm due to (n-π*) and at 278nm due to (π- π*) transitions. In Compound.3, the band of carbonyl amide group at 1671 cm^{-1} and the absorption band of C-Cl group at 798 $cm^{-1.}$. The two electronic transition peaks are observed at 278 nm (π- π*) and 458 nm (n- π*), (in ethanol solvent). FT-IR spectrum of Compound .4, reveals that bands at 3352 cm^{-1}, 3251 cm^{-1} form a double peak for ν (NH_2), while bands at 3136 cm^{-1} and 3093 cm^{-1} were attributed to –NH str. (tautomeric form). Bands at 2920 cm^{-1} and 2854 c Bands at 1608 cm^{-1}, 1651 cm^{-1} for ν (C=N), 1550 cm^{-1} for (NH bend), 1465 cm^{-1} ν (N-N str.), 1361 cm^{-1} ν (C-N bend.), 1053 cm^{-1}, 1033 m^{-1} due to the intermolecular hydrogen band of –NH, and absence absorption band at 798 $cm^{-1}$to group of the C-Cl. U.V spectrum in ethanol solvent showed absorption at 280 nm (π- π*) and at 432 nm (n- π*) . The confirmation of the product structure of Compound .5, reveals that the band at 3275 cm^{-1} for ν (NH as stretching.), at 3174 cm^{-1} for ν (NH symmetric), at1753 cm^{-1} and1732 cm^{-1} for ν(C=O stretching, cyclo) and at 1647 cm^{-1} ν(C=N stretching, cyclo). The appearance of two electronic transition peaks at 278 nm (π- π*) and 438 nm (n- π*), (ethanol as a solvent) is another evidence. The confirmation of the product structure of compound .6, is proved by revealing band at 3174 cm^{-1} for (NH as stretching). Note that there are three bands at (2987, 2935, 2899) cm^{-1} as evidence of a group isopropylidine in the compound as shown in table 2. Band at 1732 cm^{-1} for ν(C=O stretching, cyclo), at 1680 cm^{-1} for (C=O, amide2) , at1662 cm^{-1} for (C=O, cyclo amide1) and at 1647 cm^{-1} for (C=N stretching ,cyclo) .

Table 2. Comparative of experimental and theoretical vibration spectrum analysis of synthetic compounds.

Compound	Experimental cm^{-1}.	Theoretical (PM3-CI(3X3)cm^{-1}	Intensity	Descriptions
Compound (1)	3338	3546	10.303	□ N-H Asymmetric
	3257	3490	8.96	□ N-H symmetric
	2490	1677	12	□ S-H
	1608	1613	116	Cyclic C=N ,NH_2 Bending
	1564	1507	243	□ C=N
Compound (2)	3088	3175	0.289	C-H Ar
	3010	3123	2.57	=C-H
	2958	3116	0.013	N-CH3
	1591	1842	342	C=C
	1617	1547	17.56	C=N Schiff + Cyclo
	821	1111	2.289	Para-sub
Compound(3)	3088	3078	10.5	C-H Aromatic-Asymmetric
	3010	3068	26.39	C-H Aromatic Symmetric
	2954	3030	1.1	N-CH
	1668	1999	94	C=O Amide1
	1594	1512	257	C=N
	1533	1777	0.6	C=C
	891	724	49.5	C-Cl
Compound(4)	3336	3522	3.2	NH_2 Asymmetric
	3290	3459	3.0	=N-H
	3213	3402	0.48	NH_2 Asymmetric
	3111	3344	8.0	N-H
	1664	1946	175.6	C=O Amide1
	1647	1677	507	C=N
	1533	1794	4.98	C=C
Compound(5)	3336	3312	44	N-H Cyclic
	3290	3274	15.5	N-H
	3078	3077	10.9	C-H Aromatic
	3059	3066	28.6	C-H Aromatic Symmetric
	1669	1992	93.5	C=O Amide1
	1748	1975	106.5	C=O Amide2
	1734	1940	178.8	C=O Cyclic
	1763	1797	28.5	C=C
	1647	1704	356	C=N Cyclic
Compound(6)	3336	3354	10.8	N-H Amide
	3091	3307	6.7	N-H uncyclic
	3064	3066	23.8	C-H Aromatic Symmetric
	2954-2935-2895	2973	0.178	Isopropyl dine
	1730	1974	95	C=O Amide2

	1680	1944	213.8	C=O
	1662	1993	130.6	C=O Amide1
	1597	1700	411	C=N
	1533	1620	50	C=C

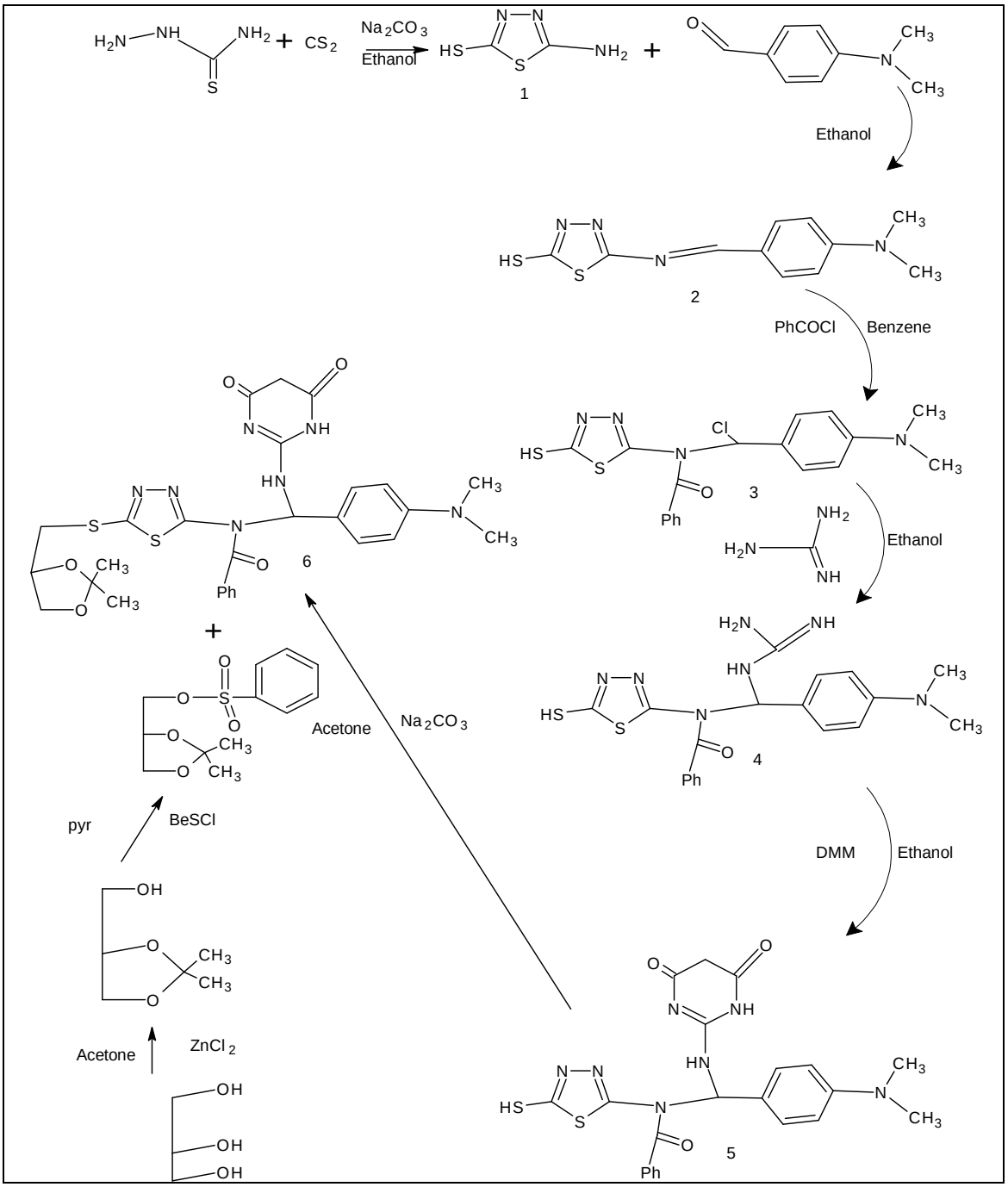
Table 3. Experimental and theoretical UV/Visible spectra of synthetic compounds.

Compounds	Experimental transition(nm)	Theoretical transition(nm) Single point calculations(PM3)	Oscillator strength	Explanation
Compound(1)	250	248.9	0.1	**π → π***
	312	266	0.08	**π→π***
	338	349.5	0.545	**n→ π***
Compound(2)	278	267	0.216	**π → π***
	430	346	0.576	**n→ π***
Compound(3)	278	219	0.016	**π→ π***
	458	346	0.51	**n→ π***
Compound(4)	280	329	0.155	**π→ π***
	432	352	0.319	**n→ π***
Compound(5)	278	246	0.18	**π→ π***
	360	328	0.216	**π→ π***
	438	343.6	0.193	**n→ π***
Compound(6)	278	282	0.67	**π→ π***
	330	338	0.064	**π→ π***
	428	355.99	0.305	**n→ π***

The chemical formula and physical properties of prepared compounds have been listed in table 4. Different solvent have been used depending upon the chemical behavior of this products with different appearances for all them. Scheme 1.shows the diagrams of the consecutive reaction to synthesis different chemical compounds that may be useful as new agents in medical treatments.

Table 4. chemical formula and Physical properties of synthetic compounds .

Compounds	Chemical Formula	Solvent Purifications	Yield% Color	Melting point ˚C
1	$C_2H_4N_3S_2$	Water	67% yellow needles	233-235
2	$C_{11}H_{12}N_4S_2$	Ethanol+Acetone	80% Red	258-260
3	$C_{18}H_{17}N_4S_2ClO$	Ethanol	71% Pink	224-226
4	$C_{19}H_{21}N_7S_2O$	Ethanol	68%yellow	239-241
5	$C_{22}H_20N_7S_2O_3$	Ethanol	55%Yellow Peel	228-230
6	$C_{28}H_{31}N_7S_2O_5$	Ethanol	50%brown	Syrup



Scheme 1. Diagrammatic pathways of the synthesis reactions for the six compounds.

APPLICATION.

New medical agents can be synthesized according to the estimation study and performing through the comparative study between the experimental and theoretical results.

CONCLUSIONS

- First transition state is the most probable state to give up the reaction products than other transition states.
- All synthesis reactions are tend to the products to give up final products with lowest energy barrier value than energy barrier value of backward reaction.
- They found a good agreement between the experimental and theoretical values of vibration and electronic spectrums of synthetic compounds.

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