Ab-initio and semi-empirical study of tree mechanisms for the indole synthesis

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ABSTRACT

Indole is a benzopyrrole resulting from the fusion of a benzene ring on (α) and (β) carbons of pyrrole. It is a substance that is related to a great number of natural compounds, which play a considerable biochemical role. [1] [2]. The theoretical study of Fischer reaction, which is a general way of indole synthesis, was carried out by means the semi-empirical (AM$_1$, PM$_3$ and MNDO) and ab-initio methods (STO-3G, 3-21G, 6-31G and 6-31G*) to analyze the three mechanisms proposed for this reaction. Energies and heats of formation obtained are based on primarily on geometries optimization calculation for different hypothetical intermediates in the three mechanisms. Transition states calculations allows the clarification of Fischer reaction regioselectivity. The comparative theoretical study made on the proposed mechanisms, shows that the Robinson's mechanism is the most favorable.

Keywords: Indole, theoretical study, Fischer reaction, semi-empirical methods, ab-initio methods.
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INTRODUCTION

The most well known mechanism of the Fischer reaction is one established by Robinson [3]. In this mechanism a phenylhydrazine is reacted with an aldehyde or ketone to yield the phenylhydrazone, the latter isomerizes to the corresponding enamine.

After protonation in acidic medium, sigmatropic Cope rearrangement occurs, involving a nucleophilic attack of the aromatic benzene ring.

Cyclization of the resulting aniline / imine followed by the loss of NH3, always by the catalysis of an acid, produce the energetically favorable aromatic system (indol).

Kereselidze (1994) [4] reported a mechanism different from that of Robinson. In its mechanism, it does not rule out the possibility of rupture of the NN bond (weakened by the second nitrogen protonation) prior to nucleophilic attack of the benzene in contrast with the idea of Robinson suggests that the two steps are synchronous and that the process involved is a concerted Cope rearrangement.

The next step is the recombination of the two fragments by a nucleophilic attack of the vinylamine on aromatic ring depleted of electrons by NH$^+$ group.

At last, the attack of the ammonium by the amine group results pyrrole ring witch by elimination of ammoniac leads to the indole ring.

In addition to the classic mechanism of Robinson and the mechanism proposed by Kereselidze, and based on both experimental and theoretical observations, we tried to propose a third mechanism for the Fischer reaction.

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This mechanism differs from the two other, essentially, in the first step, wherein the initial protonation is on the nitrogen bonded to the benzene nucleus, similarly involving the early rupture of the NN bond.

This hypothesis is based on the following two facts:
-    Observation of the calculated transition state of the ene-hydrazine protonation which shows that the proton located at equal distances from the two atoms of nitrogen.

The transition structure shows one imaginary frequency which corresponds to the displacement of the proton H^+ between the two nitrogens, confirming the possibility of protonation on both sites, and justified our choice of the mechanism that the protonation is carried out on nitrogen N_7 .
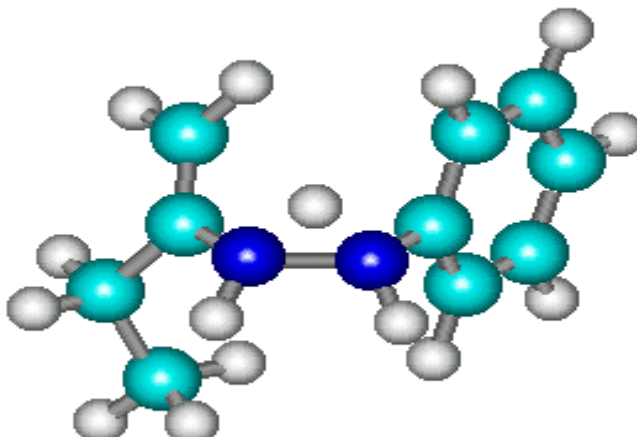

Fig I. The transition structure of the protonation step

-    The obtaining of aniline as by-product of the Fischer reaction mentioned by Zhao and Hughes.

Unlike Kereselidze mechanism, rupture of the N-N bond is in favor of the first nitrogen atom, leading to two fragments: aniline and carbocation.

Recombination of the resulting fragments is, this time, by the electrophilic attack of the positive carbon of the first fragment on the benzene ring of aniline.

The réarromatisation of the formed intermediate leads to a common intermediate, and after the formation of the indole ends with the same procedure described by Robinson.

The present work aims to use semi-empirical and ab-initio calculations to realize a comparative theoretical study of the previous three mechanisms; for better understanding of electronic factors influencing the course of the Fischer reaction. In a first step, we examined the structural and thermodynamic parameters of various reactionels intermediate by optimization of geometry calculation; after that, we studied Fischer reaction regioselectivity through the Transition states calculations.
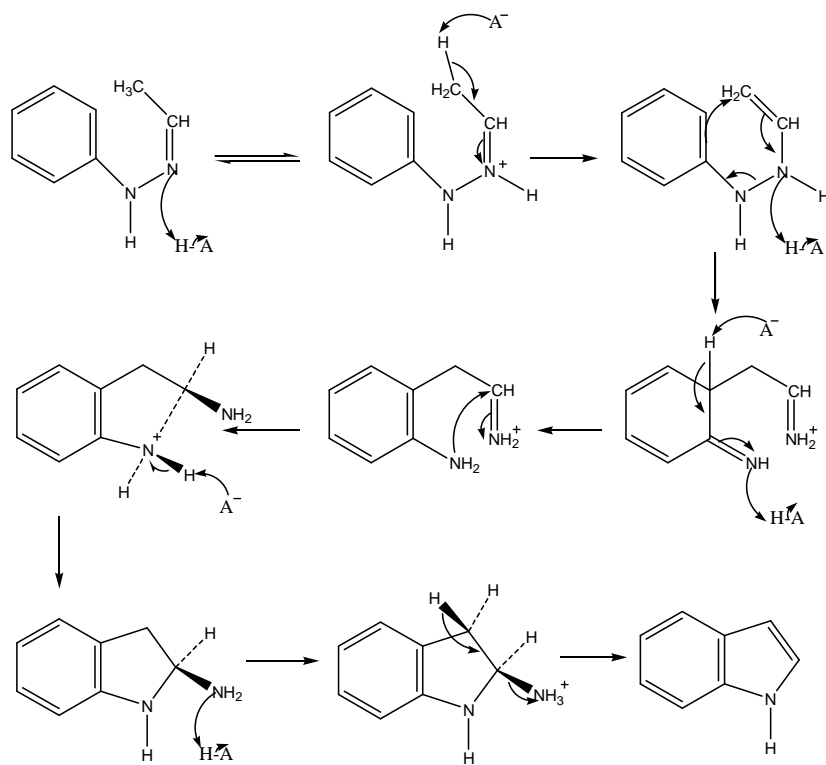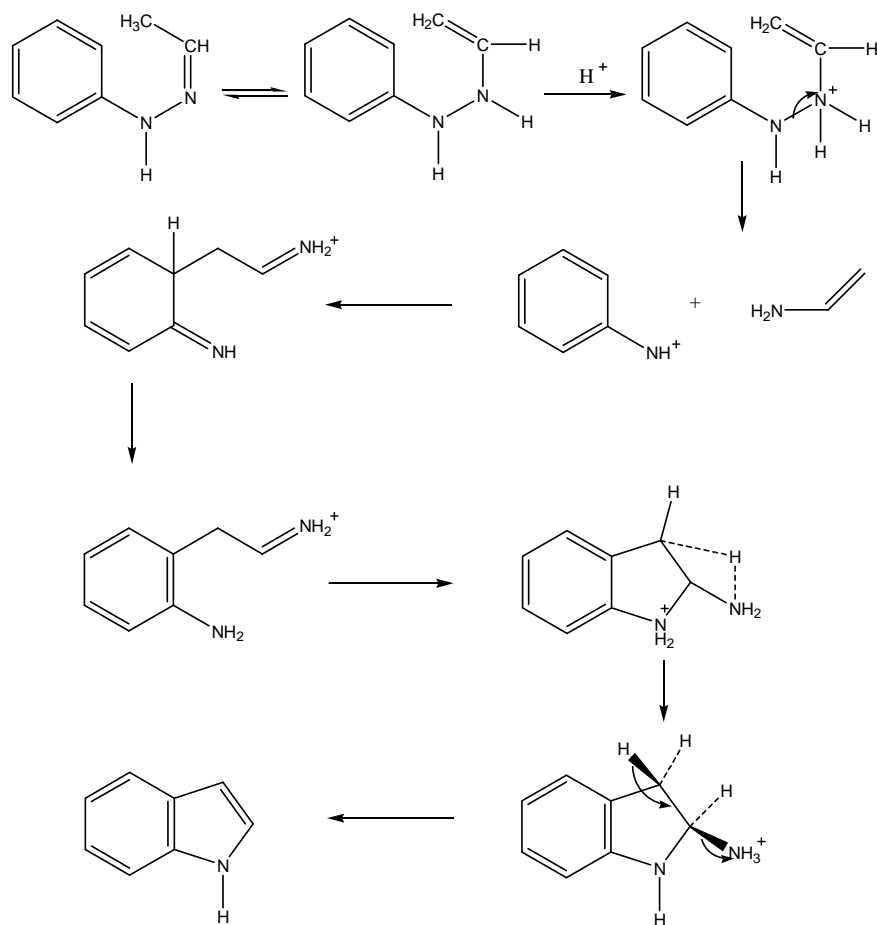
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Fig. II. Robinson mechanism for the Fischer reaction [5]

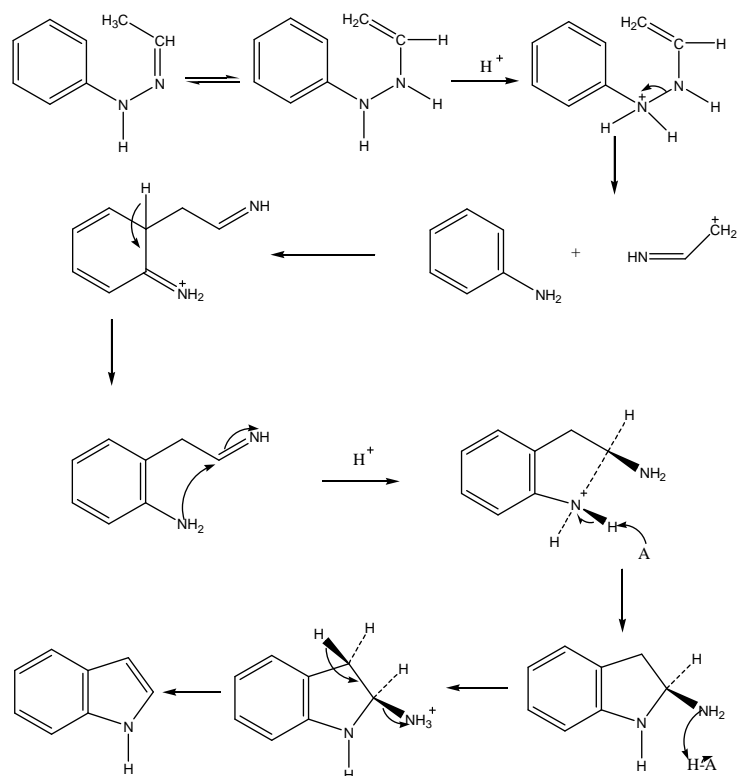**FigIV. Kereselidze mechanism for the Fischer reaction** [4]

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Fig. V. Proposed mechanism for the Fischer reaction

Computational methods
All calculations were performed essentially using Hyperchem (version 7.5) on Windows XP using the semi-empirical (AM$_1$, PM$_3$ and MNDO) [6] [7] and ab-initio methods (STO-3G, 3-21G, 6-31G and 6-31G*). [8] [9].

All the structures were characterized by vibrational analysis in the harmonic approximation,

All the structures were fully optimized until vibration analysis showed the absence of imaginary frequencies and a single one for transition states.

In our calculations we have used the following approaches:
-       Acidic catalysts simulation, using a proton.
-       The solvent effect was ignored.

Theoretical background
The regioselectivity of the Fischer reaction
When the ketone reactant of the Fischer reaction contains two enolizable sites, the régiocontrôle becomes a problem.
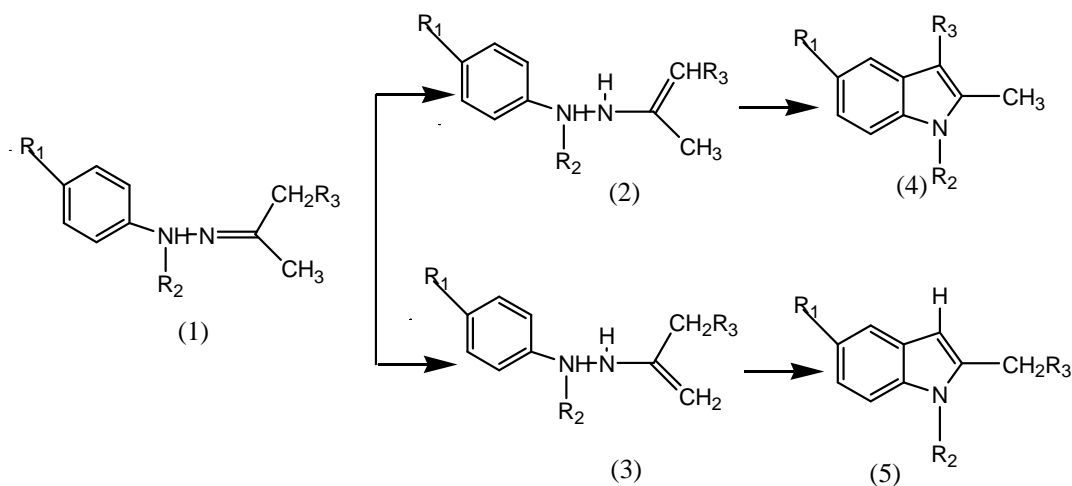
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Fig. VI. Direction of Indolisation of arylhydrazones unsymmetrical ketones [27]

In 1902, Plancher and Bonavia[10] [11] [12] have issued general rules governing the direction of the indolisation of the arylhydrazones of unsymmetrical ketones.

The principle is that the hydrazone of methyl alkyl ketones give 2-methyl indole 3-substituted on 3, as the major product.

In the following years, many examples have supported the idea that the methyl alkyl ketones provide 2-methyl indole 3-substituted as a unique or principal product.

To orient the reaction towards the formation of indole unsubstituted in position 3, Trofimov used the thioether group which it eliminates later.

Since this procedure requires two additional steps in the overall synthetic way, efforts have been made to direct the reaction towards the unsubstituted indole 3 directly from methyl ketones[13].

The consensus of these investigations is that the production of indole unsubstituted 3 increases by the use of strong acids.

This procedure does not present a general method for the regiospecific formation of indole unsubstituted 3 with a considerable yield, indeed, the regiocontrôle of the Fischer reaction seems to be dependent on several factors such as the nature of the phenylhydrazone and the acidity of the medium.

Since the donor effect (+ M) to the nitrogen atom, the carbon 3 of the indole manifest increased nucleophilicity, allowing a diversity substitution on this site, hence the need to orient the Fischer reaction to obtain the unsubstituted derivatives in this position.

We can conclude from all studies on this subject that the experimental conditions needed to achieve this goal are:
- Use of a strong acid
- The use of a polar solvent and non-basic
- Phenylhydrazine carries the larger N-substituent.

Establishment of a reactionel mechanism [14]
The development of a reactionel mechanism is a delicate task that requires a researcher imagination and rigor.

There is no method or procedure to be followed to the letter to arrive at a mechanism hypothesis. We can only indicate here some useful rules and principles;

The first rule is absolute: the proposed mechanism must be consistent with all available observations.

The other rules or principles set out below are only guides.

Economy principle; we primarily look for the simplest mechanism; the one with the fewest of elementary steps.

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Principle of simplicity of elementary processes; whenever possible, the simplest possible be invoked elementary steps (principle of least change of structure).

Microscopic reversibility principle; at the microscopic level, each elementary step must take place in both directions.

We can never prove that a mechanism is correct. We can only prove otherwise, so reject mechanism is still (in suspended) until it has been invalidated by a new experience.

It is the very nature of scientific theories or models to be thus likely to be defeated by new observations.
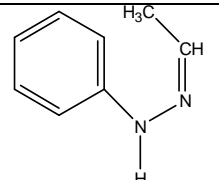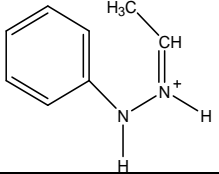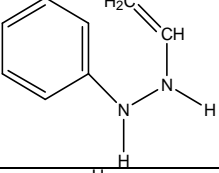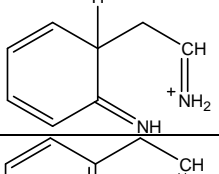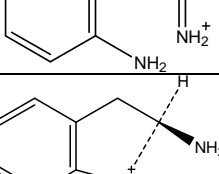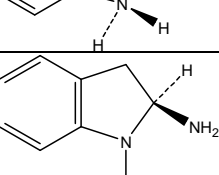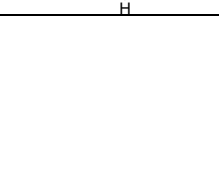
RESULTS AND DISCUSSION

Energies and heats of formation
The following tables show the intermediate heats of formation for the three mechanisms, obtained using the methods AM_1, PM_3 and MNDO.

The data in the literature concerning the mechanisms of Robinson and Kereselidze are also summarized in these tables.

Table. I. Heats of formation of the various intermediaries in the Robinson mechanism

Intermédiaire	Chaleurs de formation (calculées) en (Kcal /mol)			Chaleurs de formation (littérature) en (Kcal /mol)		
	AM_1	PM_3	MNDO	AM_1	PM_3	MNDO
	58.21	55.12	51.35	59.61	55.40	51.55
	221.19	222.50	221.71	221.47	235.17	249.60
	73.57	66.27	68.50	73.33	69.58	68.92
	201.35	208.02	215.27	201.62	208.29	216.11
	174.72	187.35	193.33	174.97	187.61	193.54
	178.52	172.99	182.66	178.79	173.26	182.87
	31.40	23.57	23.95	31.66	23.03	24.16

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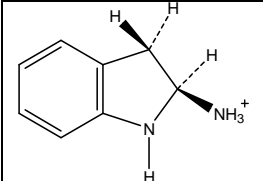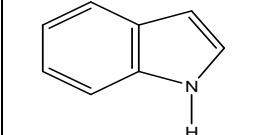
	182.45	174.19	183.95	182.72	174.47	184.16
	54.94	42.38	44.06	55.15	42.44	44.15

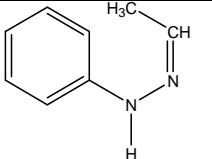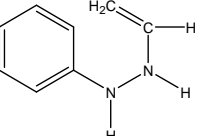**Table .II. Heats of formation of the various intermediaries in the Kereselidze mechanism**
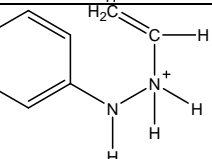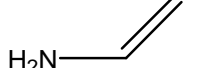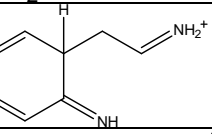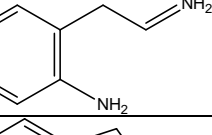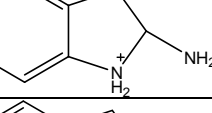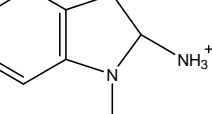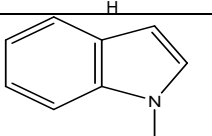
Intermédiaire	Chaleurs de formation calculées (Kcal/mol)			Chaleurs de formation (littérature) (Kcal/mol)
	AM₁	**PM₃**	**MNDO**	**AM₁ (single point)**
	85.21	55.12	51.35	---
	73.57	66.27	68.50	---
	232.88	227.41	240.63	---
	246.70	244.65	241.38	246.56
	12.51	18.73	18.75	11.50
	200.25	212.88	215.27	252.99
	177.32	185.14	193.31	252.99
	178.52	172.99	182.66	264.68
	182.45	174.19	183.95	---
	54.94	42.38	44.06	---

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Table. III. Heats of formation of the various intermediaries in the proposed mechanism
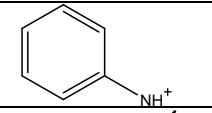**Energy diagrams**

Intermédiaire	Chaleurs de formation en Kcal/mol)		
	AM$_1$	**PM$_3$**	**MNDO**
(structure)	58.21	55.12	51.35
(structure)	73.57	66.27	68.50
(structure)	231.42	224.87	240.14
(structure)	21.31	25.58	21.58
(structure)	258.38	261.84	256.04
(structure)	195.55	207.76	208.95
(structure)	34.82	37.72	39.96
(structure)	178.52	172.99	182.66
(structure)	182.45	174.19	183.95
(structure)	54.94	42.38	44.06

For the three mechanisms, we used to draw the energy diagrams, calculation results obtained by AM$_1$ method because were the only ones that are reported in the literature for Kereselidze mechanism.

It is found that the changes of energy in passing from one to another intermediate in the three mechanisms and using different methods are very similar.

Our calculation results for Robinson mechanism and that of Kereselidze, are in good agreement with literature data.

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Fig. VII. Energy Path of Robinson mechanism
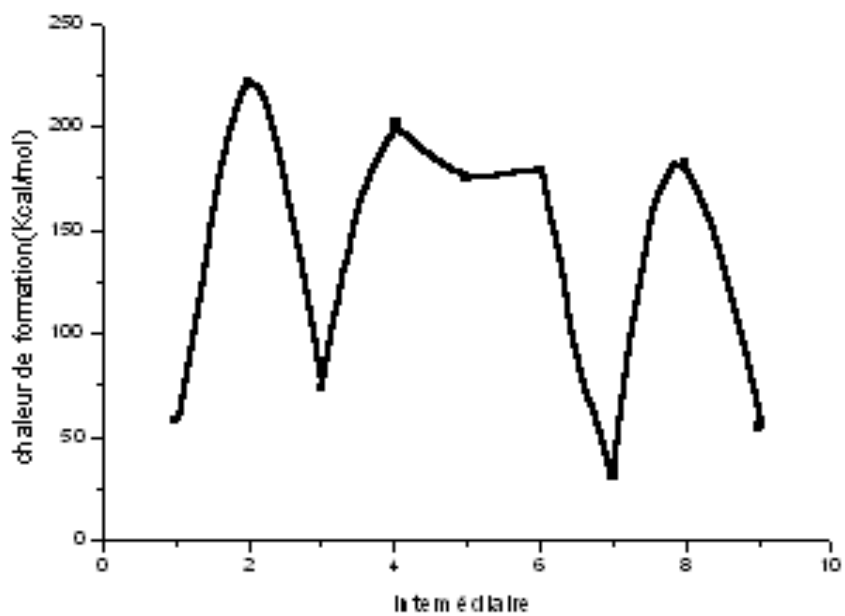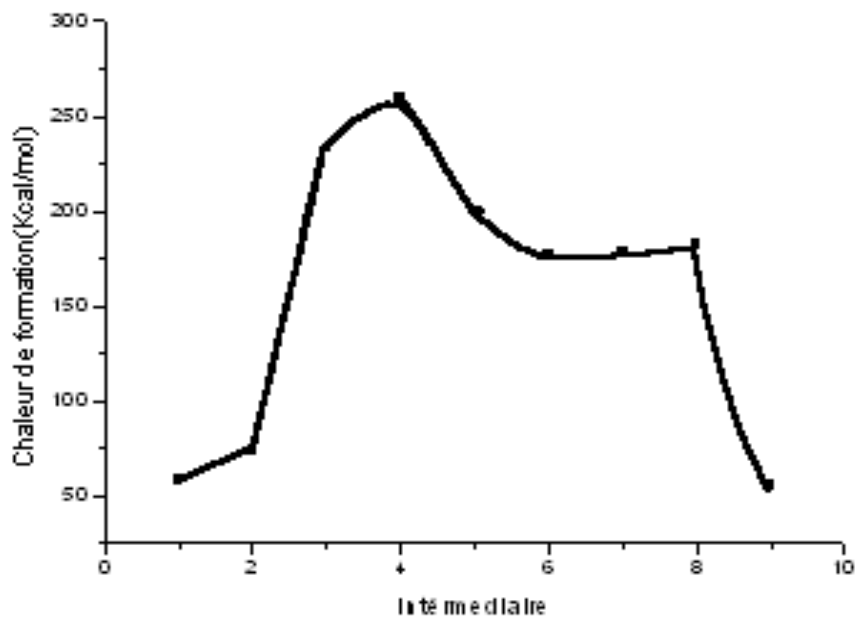

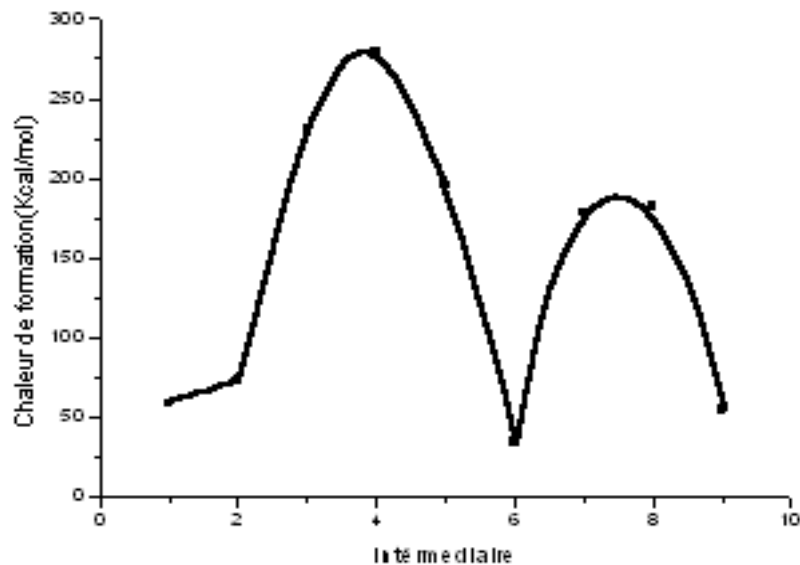**Fig.VIII. Energy Path of Kereselidze mechanism**

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Fig. IX. Energy Path of proposed mechanism

Transition state
The transition structures study of the key steps of the three mechanisms
In order to obtain a coherent picture of the Fischer reaction for all the mechanisms, we decided to carry out a detailed study of the transition states of the key steps for the three mechanisms by the AM1 method.

Robinson mechanism
The key step in the Robinson mechanism is a [3,3] sigmatropic rearrangement of Cope.
This type of rearrangement is related to Electrocyclic transformations that are collaborative processes governed by the symmetry of the orbitals.

These reactions are discussed in terms of electrophiles or nucleophiles interactions, even if there is charge separation in some cases.

The feasibility of an electrocyclic reaction can be correlated to the stability of the transition state.

These reactions are generally independent of external influences such as the effects of solvent, the concentrations, the nature of the catalysts ... etc, which frequently complicate the course of the reactions.

The transition structures, distances and activation energies for the sigmatropic rearrangement in Robinson mechanism are displayed in **Fig. X.** The results of the calculations show an increase of the (N_7-N_8) bond length to achieve 3.4 A°, While the C_{10} and C_4 carbons initially unbound approach until a distance of 1.9 A to form a bond.

These results are in good agreement with the experimental data since the activation energy for the sigmatropic rearrangement of the kinetic enhydrazine's is greater.
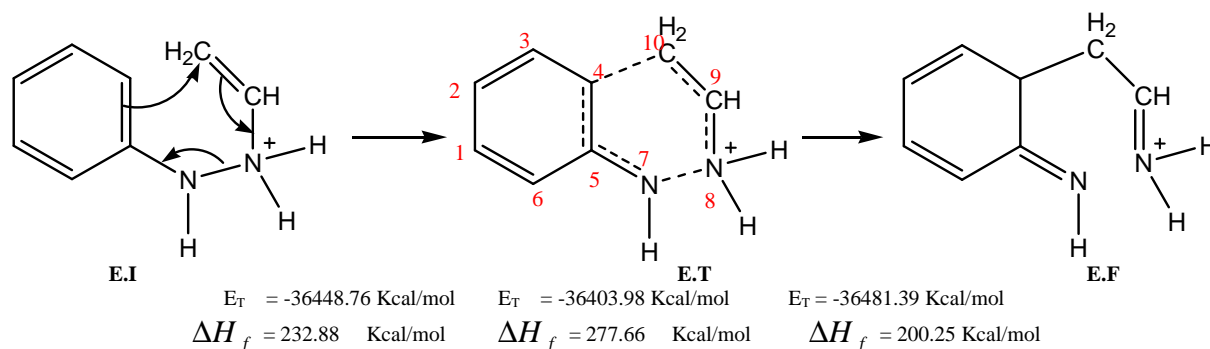
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E_T = -36448.76 Kcal/mol E_T = -36403.98 Kcal/mol E_T = -36481.39 Kcal/mol

ΔH_f = 232.88   Kcal/mol ΔH_f = 277.66   Kcal/mol ΔH_f = 200.25 Kcal/mol

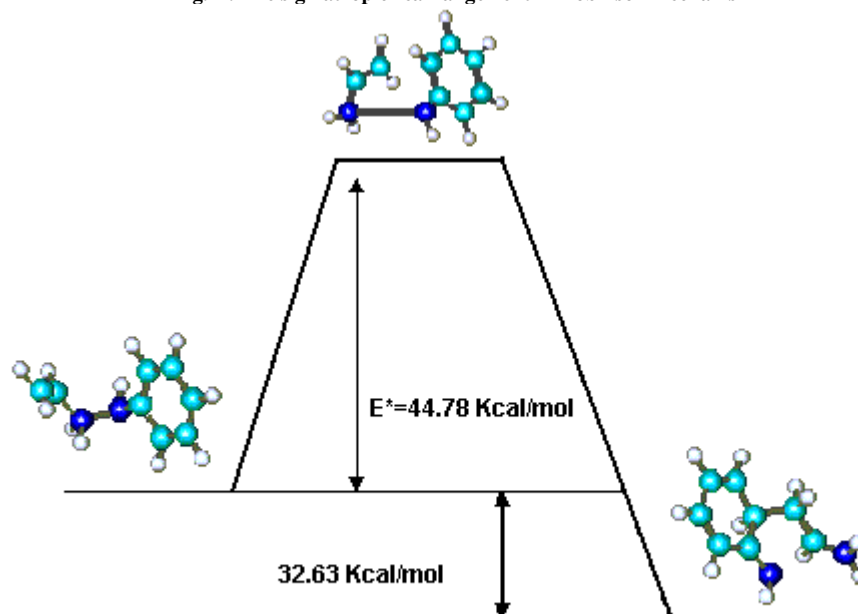**Fig. X. The sigmatropic rearrangement in Robinson mechanism**

Fig. XI. Energy diagram of sigmatropic rearrangement in the Robinson mechanism

Kereselidze mechanism

In Kereselidze mechanism, the key step is the recombination of the two fragments, the process being a nucleophilic substitution on the benzene ring.

This type of reaction is difficult in the unactivated benzene, indeed the electron cloud of the benzene ring and the nucleophilic repel leading to transition states of very high energies.

The presence of NH + activating group on the benzene ring indicates the positive partial charges on the atoms in the ortho and in the para (2,4 and 6). Which create attractive forces with the nucleophilic reagent and thus facilitate the reaction and which justifies the activation energy 39.68 Kcal / mol. See (**Fig. XII).**

The results of calculation are gathered in **Table.V.**

The distance between the two carbons C_6 and C_7 and their net charge in the transition state shown that there is indeed an attractive force between them, binder the two fragments.

In the transition state, there is also a reduction of the C_8-C_9 bond which indicates the formation of a double bond between the atoms, by elongation against C_7- C_8-binding certifies that turns in a single bond.

The calculation of the transition states of the two key steps of Kereselidze mechanism (**Fig. XVII**) shows that the gap between the two activation energy values is infinitely small, this step is indifferent to the degree of substitution of the second fragment, it which does not correlate with the regioselectivity of the reaction in favor of the substituted indole in position 3.
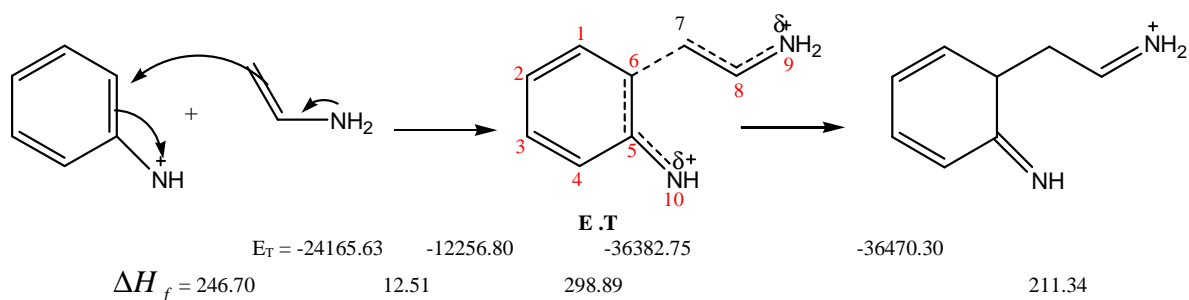
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E_T = -24165.63   -12256.80   -36382.75   -36470.30

ΔH_f = 246.70   12.51   298.89   211.34

Fig. XII. The recombination of the two fragments in the Kereselidze mechanism
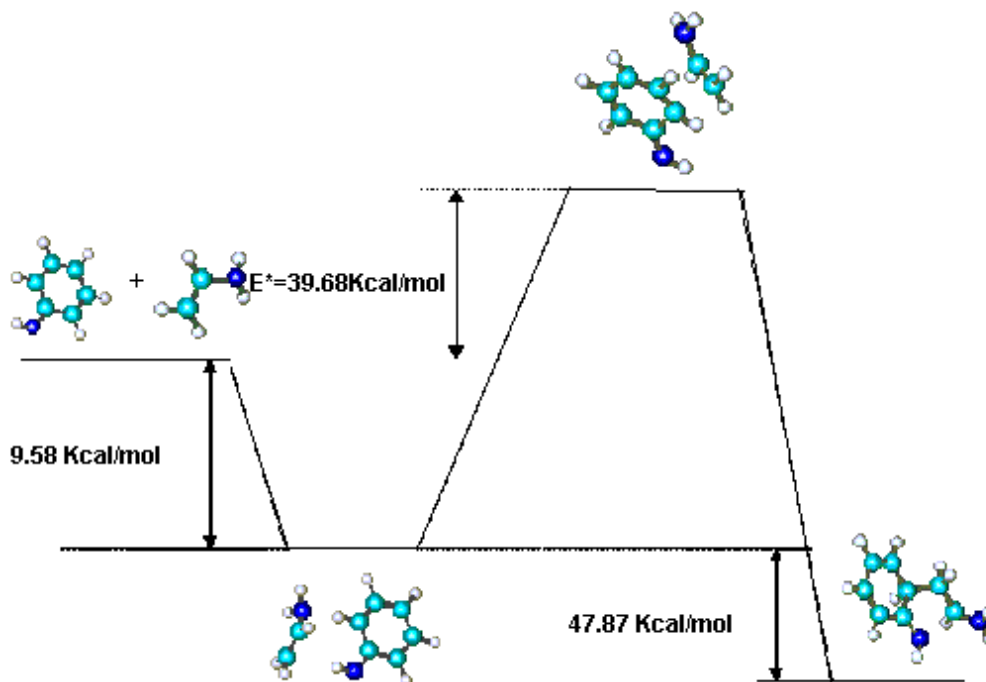

Fig. XIII. Energy diagram of the recombination of the fragments in the Kereselidze mechanism

Proposed mechanism

In this mechanism, the key step is the recombination of the two fragments by electrophilic substitution on the aromatic ring, such substitution is activated by the presence of donor Π group are ortho and para directors. See figure 14

La présence du groupement amino (NH_2) oriente donc la réaction en ortho et en para et active la réaction, et ce qui est en accord avec les charges nettes négatives qui apparaissent sur les atomes de carbone C_2, C_4 et C_6.

The geometrical parameters of the two transition structures are displayed in table 6.

From the AM_1 results obtained, If we compare the net charges of two carbons (C6 and C7) in the two transition structures, we can see that the attractive force between them is more important in the proposed mechanism, (-0.14 and 0.44) anti (0.79 and -0.24) in that of Kereselidze.

The results of the calculations show also a decrease of C_5-N_{10} bond length, which indicates the formation of a double bond between these atoms.

We find that the energy barrier required for recombination of the fragments is 39.68 kcal / mol for Kereselidze mechanism and 16.59 kcal / mol, this value is greater in the case of Robinson, it is 44.78 Kcal/mol, which is predictable given the instability of the reagents in the first two mechanisms.

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- **Mécanisme proposé :**

E_T = -24705.92   -11696.02   -36385.35   -36486.09

ΔH_f = 21.31   258.38   296.28   195.55
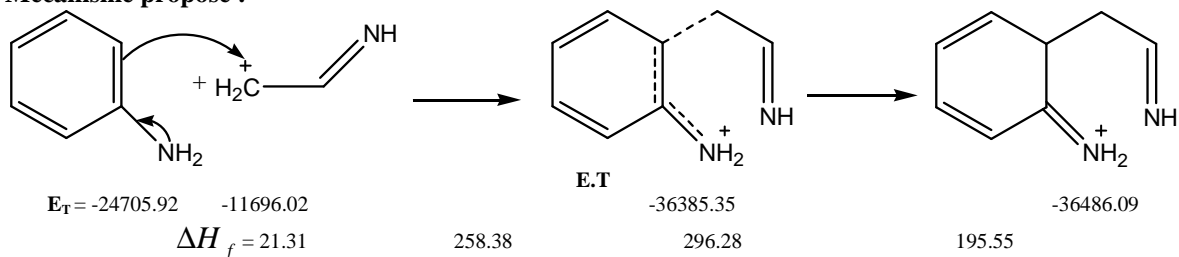
Fig. XIV The recombination of the two fragments in the proposed mechanism
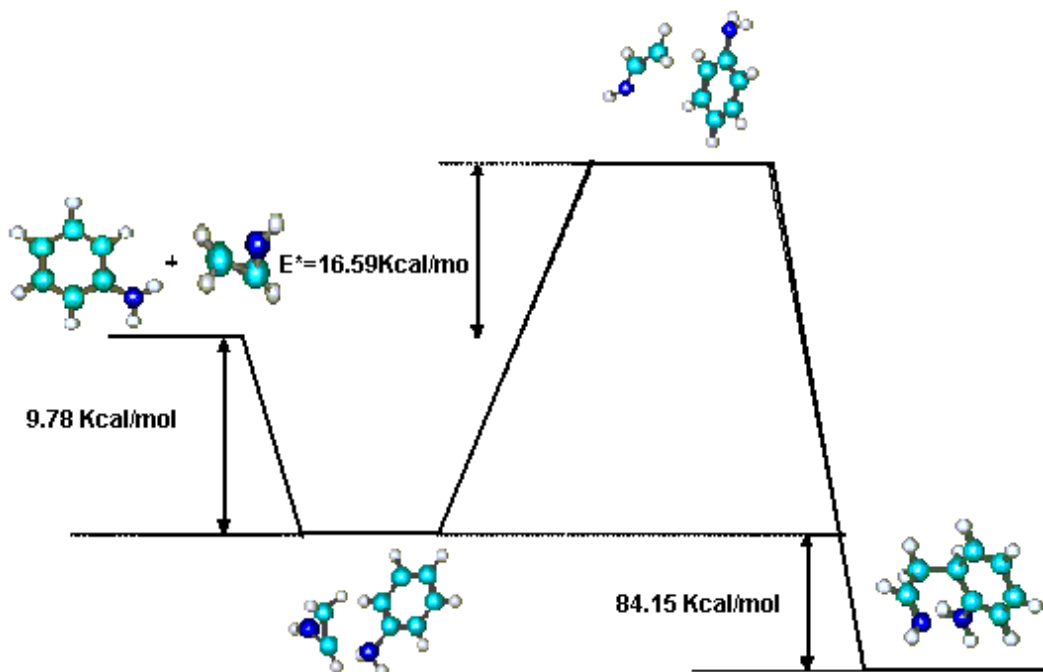
Fig. XV. Energy diagram of the recombination of the fragments in the proposed mechanism

Table. IV. Charges and bond lengths of the initial state and the transition state of the sigmatropic rearrangement

Longueur de liaison L (A°)	E .I	E.T
C_1-C_2	1.41	1.44
C_2- C_3	1.41	1.40
C_4- C_5	1.41	1.50
C_5-N_7	1.44	1.30
N_7-N_8	1.44	3.40
N_8-C_9	1.48	1.37
C_9-C_{10}	1.31	1.40
C_{10}-C_4	3.91	1.90
Charges nettes		
C_1	-0.06	-0.08
C_2	0.01	0.16
C_4	-0.03	0.26
C_5	-0.14	-0.03
N_7	-0.11	-0.08
N_8	0.11	-0.28
C_9	-0.17	0.20
C_{10}	0.08	-0.27

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Table.V. Main geometric parameters of the transition structure for the Kereselidze mechanism

L (A°)	E.T
C_1-C_2	1.39
C_1- C_6	1.42
C_3- C_4	1.37
C_4- C_5	1.49
C_6-C_7	1.90
C_7-C_8	1.40
C_8- N_9	1.35
C_5-N_{10}	1.30
Charges nettes	
C_1	-0.18
C_2	0.17
C_3	-0.12
C_4	0.08
C_5	-0.04
C_6	0.19
C_7	-0.24
C_8	0.18
N_9	-0.28
N_{10}	-0.05

Table. VI. Main geometric parameters of the transition structure for the proposed mechanism

L (A°)	E.T
C_1-C_2	1.39
C_2- C_3	1.42
C_3- C_4	1.40
C_4- C_5	1.43
C_5-N_{10}	1.41
C_6-C_7	1.90
C_7-C_8	1.45
C_8- N_9	1.30
Charges nettes	
C_1	-0.03
C_2	-0.07
C_3	0.03
C_5	0.08
C_6	-0.17
C_7	0.44
C_8	-0.08
N_9	-0.04
N_{10}	-0.26

Study results of the regioselectivity of the Fischer reaction

$E_1^*=19.28$

E_T **(Kcal/mol)** = -43637.18   -43617.90   -43671.90

ΔH_f **(Kcal/mol)** = 218.13   237.40   183.68

$E_2^*=13.76$

E_T **(Kcal/mol)** = -43641.92   -43628.15   -43666.50

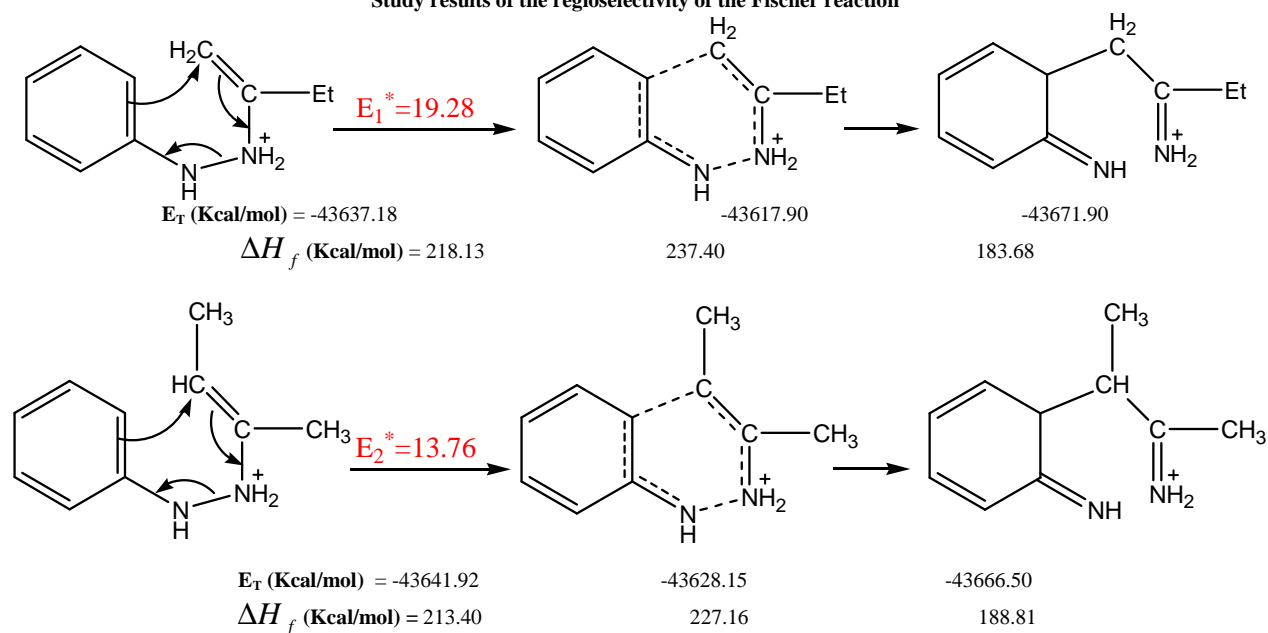ΔH_f **(Kcal/mol)** = 213.40   227.16   188.81

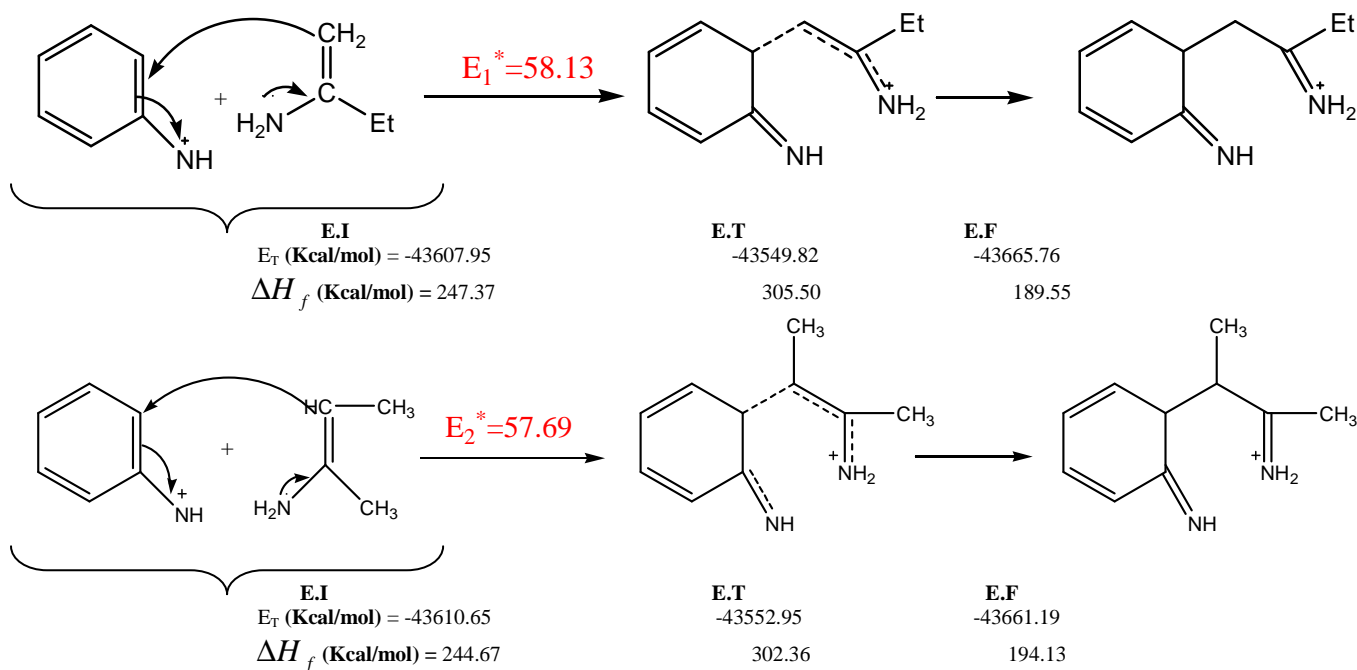**Fig. XVI. The sigmatropic reaction of kinetics and thermodynamics enhydrazine**

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Fig. XVII. Transition states of both key steps of Kereselidze mechanism
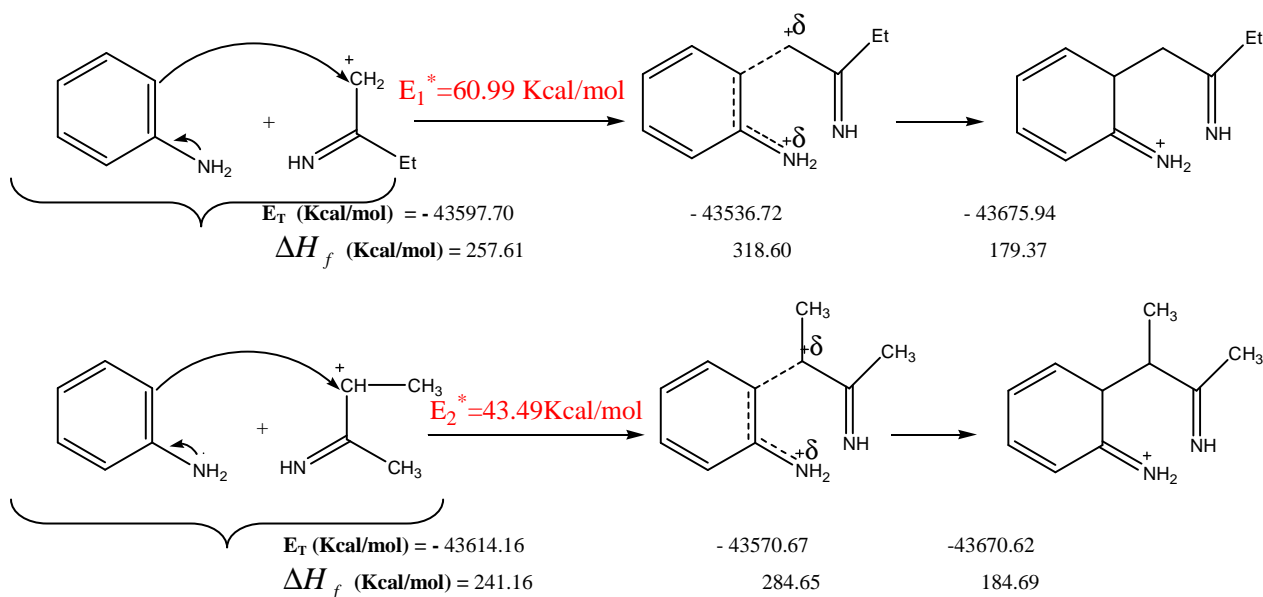

Fig. XVIII. Transition states of both key steps of proposed mechanism

CONCLUSION

It is very important to understand that a mechanism is only a hypothesis which must take account of all the experimental and theoretical observations available.

As a hypothesis, a mechanism is still likely to be challenged and changed according to new or more accurate observation that could be made.

The chemical literature abounds with such reactions whose mechanism, considered as well established for many years, and had to be revised as more accurate observations allowed by the evolution of technical analysis methods.

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The optimization calculation of the geometry of the three intermediate mechanisms of the Fischer reaction has allowed us to see that Robinson mechanism requires the lowest energy path, it shows that there are more stable intermediates that indole itself, which probably explains the failure of this method for the synthesis of this compound.

The calculation of the transition state of the initial protonation, as well as products resulting from the cleavage of the N-N bond that were experimentally detected inspired us to propose the third mechanism for the Fischer.

The study of the transition states of the key steps of the three mechanisms, the study shows that the regioselectivity e Robinson mechanism which is consistent with experimental data is more likely.

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