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Research Article

# THEORETICAL STUDY OF 1, 4-DIAZEPINES SYNTHESIS: THE REACTION MECHANISM AND TAUTOMERISM IN GAS PHASE AND IN SOLUTION

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**ABSTRACT**

The reaction mechanism in the synthesis of diazepines by the action of aliphatic diamines on the pyrone ring, which presents very important pharmacological properties, has been investigated using PM3 and DFT methods. The geometries for reactants, intermediates, transition states and products were completely optimized. All the transition states were verified by the vibrationnal analysis and the intrinsic reaction coordinate calculations. The reactivity of aliphatic diamines on DHA is done by using DFT-based reactivity descriptors. To identify the reactional and selectivity sites of these compounds towards electrophilic and nucleophilic attacks, various global reactivities and Fukui functions (FF) were used to probe the local reactivity and site selectivity. The dual descriptors $\Delta f_k$ , $\Delta S_k$ and multiphilic $\Delta w_k$ , give an aiding hand. The reaction of obtaining the diazepines is done according to two ways and two paths of synthesis. The results are in favour of way 1 and path 1 of synthesis.

**Keywords:** Dehydroacetic acid, Enaminones, Diazepines, DFT, Tautomerism.

## INTRODUCTION

The diazepine nucleus is a pharmacophoric scaffold and represents a class of heterocycles with a wide range of biological applications[1]. Many of them are widely used as anticonvulsant, antianxiety, sedative, antidepressive, hypnotic and neuroleptic agents[2-5]. Some heterocycles containing diazepines moiety were reported to possess anti-inflammatory[6], antiviral[7], anti-HIV-1[8], antimicrobial[9] and antitumor[10] activities.

A number of synthetic pathway to diazepines ring systems, including condensation reactions of diamines with unsaturated carbonyl compounds[11] or halocetones, have been described. So, it is not surprising if a lot of patents have described the use of this attractive skeleton for a range of activity which covers from compounds for biological use.

Besides these conventional methods used for their synthesis, we have shown, in a previous work[12], that 1,4-diazepine ring could be easily obtained from reaction of cetimine intermediates with aromatic aldehydes using $H_2SO_4$, $CF_3COOH$ or heteropolyacids as catalysts**.** Due to the considerable utility of these compounds in drug design, we want to report here a physical study of this reaction, using theoretical tools specifying reaction mechanism, different species involved and their relative stability. As extension of this reaction we have consider also similar reaction using propan-1, 2-diamine compound **3** in order to specify the steric effect.

The title compounds were synthesized from Three versatile compounds, dehydroacetic acid **1** 1,2-diamine and aromatic aldehyde in two steps. First, treatment of dehydroacetic acid **1** with 1,2-diamine allowed access to cetimine intermediates (product A or product B). Thus depending on the nucleophilic nature of the nitrogen $N_4$ or $N_5$, attack occurred either through nitrogen $N_5$ to give product A, or through nitrogen $N_4$ yielding to product B (Scheme 1). Second, intermediate cetimine was subsequently transformed into 1,4-diazepine derivative by reaction with benzaldehyde (Scheme 4).

Our aim is to investigate the two proposed paths and to determine the best path of synthesis using chemical descriptors[13-17] issue of the functional density theory (DFT). We also used the frontier orbitals (O.F), the atomic charge of Mulliken, natural charge NPA (Natural Population Analysis). We studied the stability of the tautomeric forms which constitute intermediate reaction compounds[18, 19].

**COMPUTATIONNAL DETAILS**

The Gaussian 03[20] program has been used for all calculations presented in this work. Geometries of compounds (DHA and aliphatic diamines) were fully optimized; we undertook calculation of quantum chemistry at various levels of precision. We used semi-emperical method PM3[21] and the density functional theory (DFT) with functional B3LYP[22]. To improve the accuracy of the calculation, we set a larger basis, such as the polarized double zeta 6-31G*. To predict the site selectivity of these compounds towards electrophilic and nucleophilic attack, various reactivity, selectivity descriptors and appropriate local quantities have been calculated from Mulliken Population analysis (MPA)[23], natural population analysis (NPA)[24], electrostatic potential – drived charges using the Merz-Kollman-Singh (MK)[25] scheme and Hirshfeld population analysis (HPA)[26]. To determine the various states (intermediate, transitions and final) in this reaction, we used the following techniques of calculations: Scan[27], QSTN[28] and IRC[29]. The obtained results are in good agreement with experimental values[12].

**RESULTS AND DISCUSSION**

In the scheme 2 following compounds were studied.

**1- Molecular geometries**

The predicted bond lengths, bond angles, and dihedral angles are collected in Tables 1, 2 following the labeling of the atoms reported in scheme 3.

**a- Molecular geometries of compound 1 (DHA)**

**RESULT**

-The PM3 method underestimates the values of $C_2$-$O_9$, $C_3$-$C_4$, $C_2$-$C_3$ and $C_3$-$C_7$ in about 2.00%, 0.20%, 2.14%, and 1.80% respectively. While it overestimates the distances $O_1$-$C_2$, $C_6$-$C_{12}$, $C_4$-$C_5$, and $C_6$-$O_1$ by 2 .72%, 5.36%, 2.58% and 4.25% respectively.

-DFT method DFT underestimates distances of $O_1$-$C_2$, $C_2$-$O_9$, $C_6$-$O_1$ and $C_6$-$C_{12}$ by 0.8%, 0.16%, 0.75% and 0.33%. While it overestimates distances of $C_3$-$C_4$, $C_4$-$C_5$ and $C_3$-$C_7$ by 5.70%, 4.22% and 6.9% respectively. These results are in good agreement with other theoretical results[19].

According to our analysis results (dihedral angles), the geometry of the DHA is plane; this result is in good agreement with the experience[30].

**b- Molecular geometries of compounds 2 and 3**

Unfortunately, we have no available experimental data for current comparison. We can say that the PM3 and DFT methods give the same order of geometrical parameters (Bond Angles and Dihedral angles) for compounds **2** and **3**, except when we replaced the atom $C_6$ (compound **2**) with an atom $H_6$ (compound **3**), the bond $C_2$-$H_6$ is transformed into bound $C_2$-$C_6$ with a difference on the level of bond angles and dihedral angles.

**2- Energy Gap**

Within Fukui's Frontier Molecular Orbital (FMO) theory, the highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) play fundamental roles in the Interpretation of chemical reactivity, especially toward electrophiles and nucleophiles. We propose theoretically to determine the energy values of the Frontier Molecular Orbital HOMO and LUMO as well as the variation $|HOMO - LUMO|$ of the compound **1**, compound **2** and **3** using various levels of calculations.

Note: $\Delta E_{AB} = \left| E_{HOMO}(A) - E_{LUMO}(B) \right|$ The values of energy gap of studied compounds presented in Table 3.

Results show that aliphatic 1, 2-diamines will play the part of nucleophilic and the DHA the good electrophile.

The obtained results concerning stability, structure and electronic properties of the DHA and aliphatic 1, 2-diamines (compound **2**, compound **3**) can be used for the reactivity study of these compounds. Indeed, the reactivity theoretical study of the DHA (compound **1**) as well as aliphatic 1,2-diamines (compound **2**, compound **3**) which will be the subject of the continuation of our work, rest primarily on the knowledge of their geometrical structures.

**3- Chemical descriptors**

**a. Study of the global reactivity**

We calculated the reactivity descriptors by the DFT method, in order to confirm the electrophilic or nucleophilic nature of these compounds. In the table 4, we gave the values of the chemical potential μ, hardness ŋ, mollesse S and the electrophilic capacity ω[31, 32].

The obtained results indicate that the transfer of electrons will take place on compound **2** (or compound **3**) towards compound **1**. The studied reaction is in character hard – hard and the reactivity descriptors value of the electrophilic confirms that compound **1** is more electrophile that compounds **2** and **3**.

**b. Study of the local reactivity**

**α. Fukui reactivity descriptors of compound 1.**

Table 5 lists the calculated values of local reactivity descriptors (Fukui) using B3LYP/6-311G* method for Mulliken and NPA derived charges.

The atoms with the maximal value of condensed Fukui function are the carbon $C_7$ atom, then the DHA is the species electrophile of the reaction and the specificity of the obtained product indicates that the nucleophilic attack will be done on carbon $C_7$. This result is in good agreement with the experience[12].

**β. Frontier orbital coefficients of compound 2.**

Generally, an electrophilic reaction will take place preferably in the molecular sites with the largest values for the HOMO density. Likewise, a nucleophilic reaction is more likely to place where the LUMO electron density is the largest within the substrate. The important Frontier orbital coefficients for compound 2 shown in equation:

$$\Phi_{HOMO} = -0,13167C_1 - 0,22868C_2 + 0,39534N_5 - 0,04168\varphi N_4 - 0,07032C_3 + 0,10555C_6$$

This equation indicates that highest HOMO coefficient is on $N_5$ atom. The electrophilic substitution should preferentially occur at the $N_5$ position.

**γ-Charges distribution of compound 3.**

In order to get some insight in the charge distribution of this compound, the atomic electronic population was computed using Mulliken (MPA) and NPA population analysis. The results are displayed in Table

Our results considered in the table 6, confirm that compound **3** is the nucleophilic species of the reaction and it indicates that the nucleophilic attack could be done not only by $N_5$ but also by $N_4$ because of the steric effect on $N_4$ is less important. This explains why in this case we obtain the mixture A+B by experience[33].

**4- Dual index of compound 1 (DHA)**

Table 7 presents the values of dual descriptors through B3LYP/6-31G* method for Milliken (MK) derived charges.

The results of table 7 obtained by the use of the MK (Mulliken) population analysis, indicate that the dual descriptors highlight that a nucleophilic attack is done preferably on the carbon atoms: $C_2$, $C_6$ and $C_7$. As for the local reactivity, it is notable that the site competitive for a nucleophilic attack is the carbon atom $C_7$.

The synthesis of diazepines via cetimine A was described[12]. The extention of this reaction to diamine compound **3** ($R_1$=H, $R_2$ =$CH_3$) leads to mixture of compound A and B according to

scheme 3. Thus depending on the nature of the substuant on $N_4$ nucleophilic occurred either through $N_5$ to give product A or through both $N_4$ and $N_5$ to yield the mixture A and B.

**5- Stability of the products obtained by the two ways in gas phase and in solution**

In Table 8, the results showed that the obtained product by way 1 is characterized by weak enthalpy formation on PM3 method. Consequently, the most preferred way of synthesis is the way 1 in gas phase and in solution. This means that the reaction of **1** with **2** gave exclusively intermediate A, while **1** with **3** could lead to the mixture of A + B, with A as major product. Thus is in good agreement with experiment.

**6- Synthesis of diazepines**

This stage is a synthesis of the diazepines, for this purpose the treatment of cetimine intermediate (product A) with benzaldehyde give the intermediate $I_1$, this intermediate was subsequently transformed into 1, 4-diazepine (Scheme 4). The reaction of obtaining the diazepines is according to two possible synthesis paths:

**a. Tautomeric equilibrium**

The tautomeric equilibrium between the tautomeric forms $I_1$ and $I_2$ is represented in scheme 6 and the computed molar fractions for the two predominant forms in gas phase and in solution are given in Table 9. Constants equilibrium $K_t$ is calculated using the usual equation [19]: $K_t = \exp\left(\frac{-\delta G^0_{I_1,I_2}}{RT}\right)$ were $\delta G^0_{I_1,I_2}$ is the difference of Gibbs free energies of tautomers $I_1$ and $I_2$ : $\delta G^0_{I_1,I_2} = \Delta G^0_{I_2} - \Delta G^0_{I_1}$.

The R value is equal to 1.987 cal $K^{-1}mol^{-1}$ and T is 298.15K. The molar fractions $[I_1]$ and $[I_2]$ of tautomers ($I_1$) and ($I_2$) were calculated using the following equations:

$$[a] = \frac{1}{1+K_t},\ [b] = \frac{K_t}{1+K_t}$$

In scheme 5 are shown the different tautomeric forms exhibited by these compounds and in table 9 are given the results of calculation with molar fractions for $I_1$ and $I_2$ tautomers in gas phase and in solution.

We can conclude that the tautomeric form $I_2$ is the most dominating, in gas phase and by the presence of solvent CH3OH.

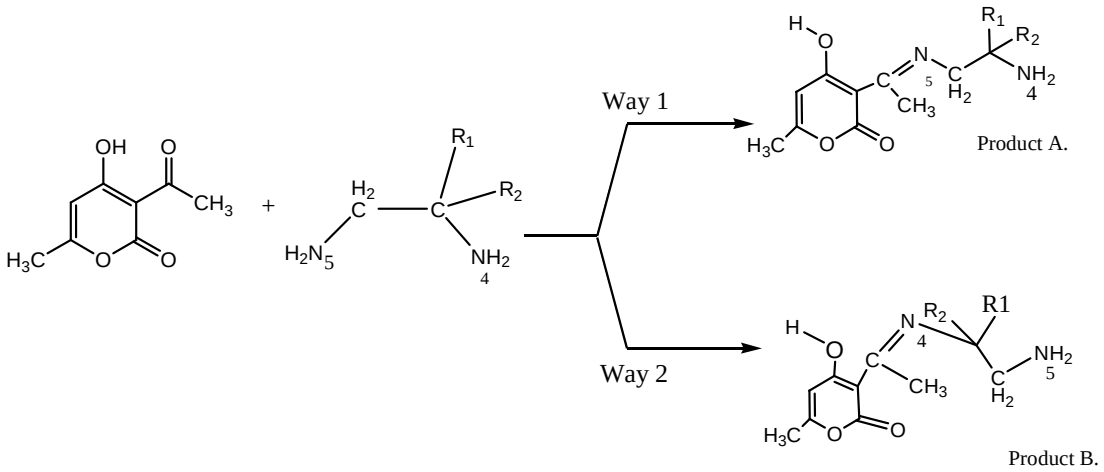
**b. Stability of the products in gas phase and in solution**

Table 10 presents the values of total energies and values of the formation enthalphy by DFT and PM3 methods respectively.

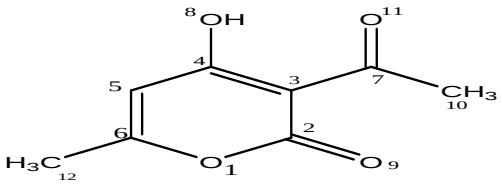
The obtained product with path 1 is more stable than the obtained product with path 2, the experimenters gave an output of 60% of the diazepines.

The steric effects play a very great part in obtaining diazepines, the prevalence of the repulsion interactions makes difficult cyclization. The obtaining of diazepines is easier according to path 1 in gas phase and in solution.

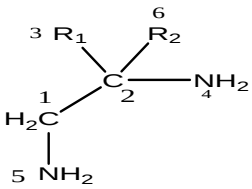
We represent in scheme 6, favorised way and path of the obtaining diazepines reaction:




**Scheme 1: Synthesis of products A and B**



*Compound 1.*



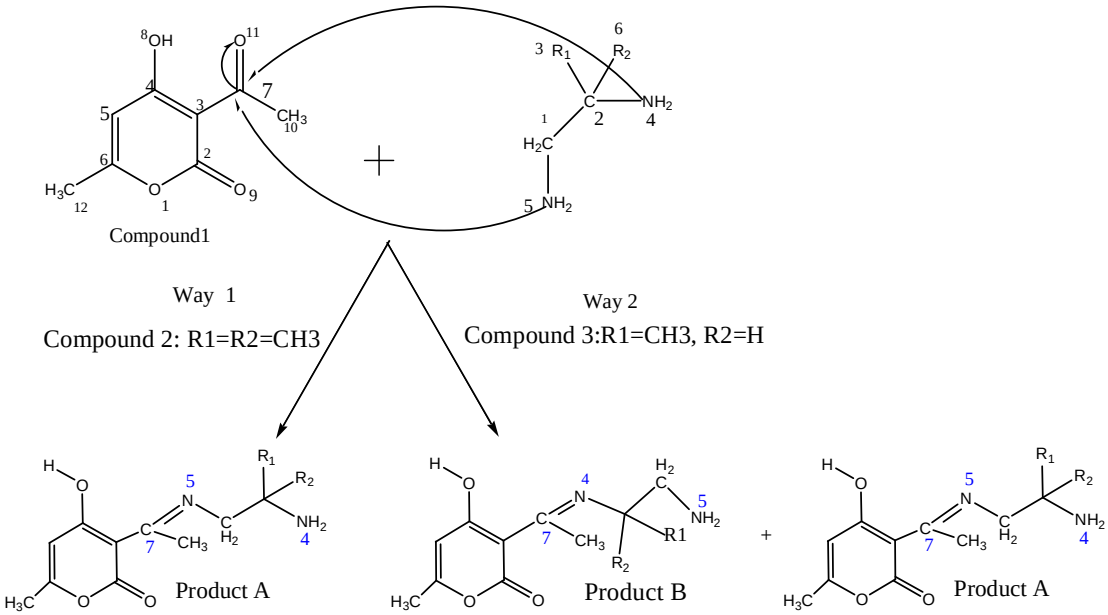
*Compound 2 or 3.*

- **Compound 1:** *3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one (DHA).*

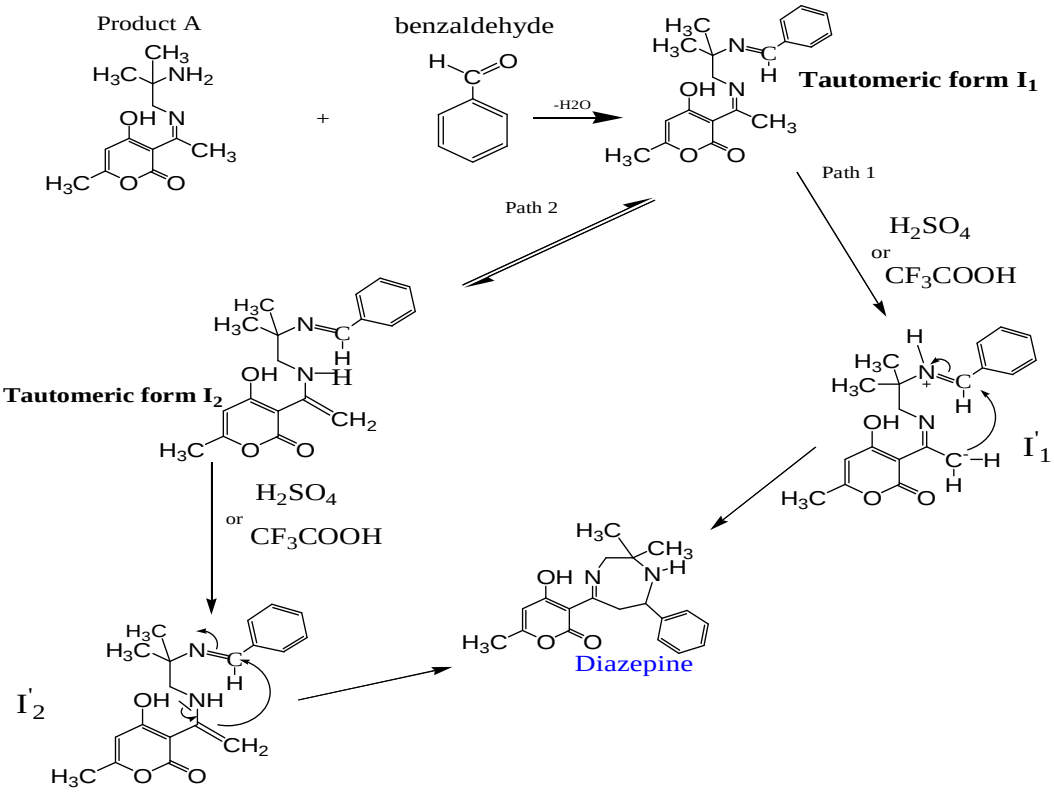
- **Compound 2:** ($R_1$=$R_2$=CH3), *2-methylpropan-1, 2-diamine.*

- **Compound 3:** ($R_1$=CH3, $R_2$ = H), *Propan-1, 2-diamine.*

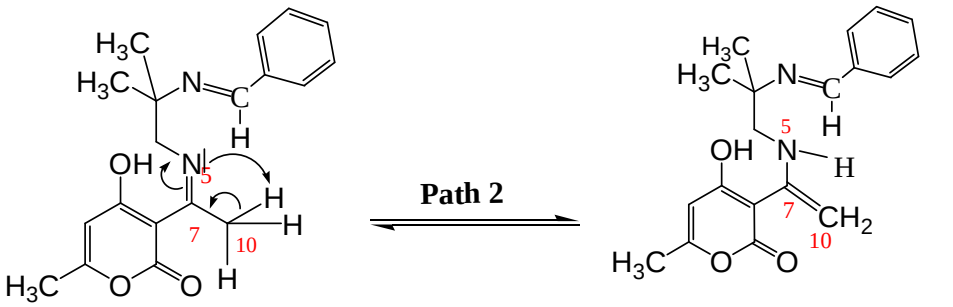
**Scheme 2: Presentation of the studied compounds**



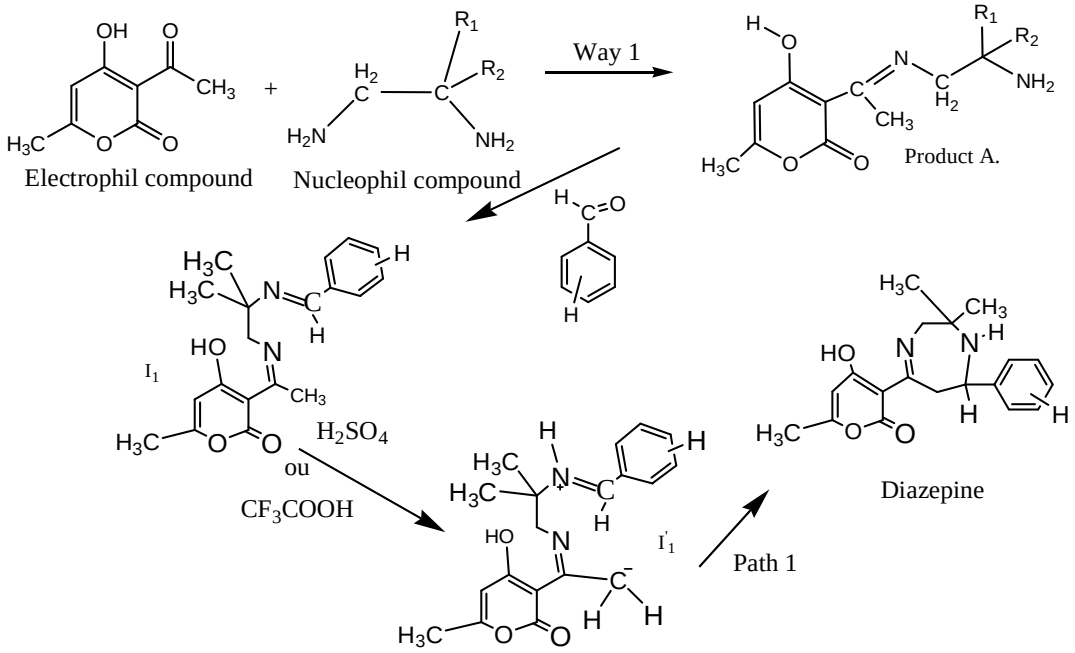

**Scheme 3: Route to reaction intermediates**




**Scheme 4: Reaction mechanism of the synthesis of Diazepine**




**Scheme 5: Tautomeric form of I1 and I2**




**Scheme 6: Way and path of the reaction for obtaining diazepines**

**Table 1: Optimized geometrical parameters of compound 1 (DHA)**

| Geometrical parameters. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Bond lengths (A⁰) | | | | Bond Angles (⁰) | | | Dihedral Angles (⁰) | | |
| Distances | PM3 | DFT | Expérimental | Angles | PM3 | DFT | Angles | PM3 | DFT |
| $O_1$-$C_2$ | 1.396 | 1.370 | 1.359 | $C_3\,C_2\,O_1$ | 122.5 | 116.3 | $H_{18}\,C_{10}C_7C_3$ | 179.99 | -179.99 |
| $C_2$-$C_3$ | 1.465 | 1.454 | 1.426 | $C_4\,C_3\,C_2$ | 117.7 | 118.1 | $H_{18}\,C_{10}C_7O_{11}$ | -0.003 | -0.003 |
| $C_3$-$C_4$ | 1.395 | 1.438 | 1.359 | $C_5\,C_4\,C_3$ | 114.8 | 125.5 | $C_{10}\,C_7C_3C_4$ | -179.99 | 180.00 |
| $C_4$-$C_5$ | 1.415 | 1.427 | 1.494 | $C_6\,C_5\,C_4$ | 128.4 | 111.2 | $O_{11}\,C_7C_3C_4$ | 0.002 | 0.006 |
| $C_5$-$C_6$ | 1.345 | 1.352 | 1.326 | $O_1\,C_6\,C_5$ | 117.7 | 127.6 | $O_{11}\,C_7C_3C_2$ | -179.99 | -179.99 |
| $C_6$-$O_1$ | 1.373 | 1.419 | 1.434 | $C_3C_7C_{10}$ | 120.7 | 121.8 | $C_7C_3C_2O_9$ | 0.017 | 0.00 |
| $C_2$-$O_9$ | 1.212 | 1.230 | 1.232 | $O_{11}C_7C_{10}$ | 120.7 | 116.2 | $C_4C_3C_2O_9$ | -179.99 | 180.00 |
| $C_3$-$C_7$ | 1.473 | 1.445 | 1.509 | $O_{11}C_7C_3$ | 118.5 | 121.9 | $H_{19}\,O_8C_4C_3$ | 180.00 | 0.002 |
| $C_7$-$O_{11}$ | 1.233 | 1.261 | 1.269 | $C_7C_3C_2$ | 122.4 | 120.6 | $O_8\,C_4C_5C_6$ | -179.99 | 180.00 |
| $C_7$-$C_{10}$ | 1.496 | 1.519 | 1.509 | $O_8C_4C_3$ | 126.5 | 117.9 | $C_4C_5C_6O_1$ | 0.00 | 0.00 |
| $C_4$-$O_8$ | 1.331 | 1.339 | 1.335 | $C_5C_6C_{12}$ | 126.6 | 125.7 | $C_4\,C_5C_6C_{12}$ | -180.00 | -180.00 |
| $C_6$-$C_{12}$ | 1.479 | 1.505 | 1.509 | | | | $H_{15}\,C_{12}C_6O_1$ | 179.99 | 180.00 |
| | | | | | | | $C_{12}\,C_6O_1C_2$ | -180.00 | -180.00 |
| | | | | | | | $C_6\,O_1C_2O_9$ | -180.00 | -180.00 |

**Table 2: Optimized geometrical parameters of compounds 2 and 3**

| Bond lengths (A⁰), Angles (⁰) | | | | | |
|---|---|---|---|---|---|
| Compound 2 | | | Compound 3 | | |
| Method | PM3 | DFT | Method | PM3 | DFT |
| $C_1$-$C_2$ | 1.550 | 1.551 | $C_1$-$C_2$ | 1.541 | 1.546 |
| $C_1$-$N_5$ | 1.471 | 1.460 | $C_1$-$N_5$ | 1.472 | 1.463 |
| $C_2$-$C_3$ | 1.534 | 1 .534 | $C_2$-$C_3$ | 1.541 | 1.523 |
| $C_2$-$N_4$ | 1.495 | 1.479 | $C_2$-$N_4$ | 1.493 | 1.473 |
| $C_2$-$C_6$ | 1.530 | 1.540 | $C_2$-$H_6$ | 1.122 | 1.106 |
| $N_5\,C_1\,C_2$ | 116.7 | 116.8 | $N_5\,C_1\,C_2$ | 116.7 | 116.4 |
| $C_1\,C_2\,N_4$ | 108.8 | 106.5 | $C_1\,C_2\,N_4$ | 109.8 | 107.9 |
| $C_1\,C_2\,C_3$ | 110.7 | 110.9 | $C_1\,C_2\,C_3$ | 111.7 | 112.5 |
| $C_3\,C_2\,C_6$ | 108.6 | 110.0 | $C_3\,C_2\,H_6$ | 107.6 | 107.8 |
| $C_6\,C_2\,N_4$ | 111.7 | 112.6 | $H_6\,C_2\,N_4$ | 110.8 | 112.5 |
| $N_4\,C_2C_1\,N_5$ | 54.4 | 56.0 | $N_4\,C_2C_1\,N_5$ | 56.3 | 58.2 |
| $C_3\,C_2C_1\,N_5$ | -65.1 | -60.8 | $C_3\,C_2C_1\,N_5$ | -65.9 | -62.2 |
| $C_6\,C_2C_1\,N_5$ | 175.9 | 177.8 | $H_6\,C_2C_1\,N_5$ | 176.5 | 179.5 |

**Table 3: Energy gap in PM3 and DFT methods**

| Compounds | $\Delta E_{AB}$ | |
|---|---|---|
| | **PM3 (kcal/mol)** | **DFT (a.u.)** |
| Compound 1—Compound 2 | 273.72 | 0.284 |
| Compound 2—Compound 1 | 20.57 | 0.154 |
| Compound 1—Compound 3 | 272.68 | 0.284 |
| Compound 3—Compound 1 | 20.37 | 0.154 |

**Table 4: Calculated Global Reactivity Properties of compounds 1, 2 and 3**

| reactivity indexes | $\mu$ kcal/mol | $\eta$ kcal/mol | $S$ kcal/mol | $\omega$ kcal/mol |
|---|---|---|---|---|
| Compound **1** | -168.6 | 40.4 | 9753.5 | 352.0 |
| Compound **2**, Compound **3** | -127.8 | 96.9 | 4059.7 | 84.2 |

**Table 5: Fukui reactivity descriptors $f_k^+$ of DHA using MPA and NPA population analysis**

| Atom | $f_k^+$ | |
|---|---|---|
| | ***Mulliken*** | ***NPA*** |
| $C_2$ | -0.157 | -0.053 |
| $C_4$ | -0.186 | -0.129 |
| $C_6$ | -0.109 | 0.025 |
| $C_7$ | 0.130 | 0.060 |

**Table 6: Charge distribution of compound 3 using PM3 and DFT (B3LYP) methods**

| Atom | $PM_3$ | DFT | |
|---|---|---|---|
| | ***Mulliken*** | ***Mulliken*** | ***NPA*** |
| $C_1$ | -0.144 | -0.146 | -0.269 |
| $C_2$ | -0.112 | -0.335 | -0.077 |
| $C_3$ | -0.116 | -0.451 | -0.690 |
| $N_4$ | -0.043 | -0.726 | -0.913 |
| $N_5$ | -0.035 | -0.710 | -0.894 |

**Table 7: Calculated local reactivity properties of carbon atoms of compound 1 (DHA) using Mulliken (MK) derived charges**

| Atom | $f_k^+$ | $f_k^-$ | $\Delta f_k$ | $w_k^+$ | $w_k^-$ | $\Delta w_k$ |
|---|---|---|---|---|---|---|
| $C_2$ | -0.1570 | -0.2090 | 0.0520 | -0.0880 | -0.1170 | 0.0290 |

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_4$ | -0.1860 | -0.0760 | -0.1100 | -0.1041 | -0.0425 | -0.0616 |
| $C_6$ | -0.1090 | -0 .3050 | 0.1960 | -0.0610 | -0.1708 | 0.1098 |
| $C_7$ | 0.1300 | 0.1000 | 0.0300 | 0.0728 | 0.056 | 0.0168 |

**Table 8: Enthalpy formation in PM3 method, total energies in DFT method in Gas phase and in solution**

| | | Gas phase | | Solution (methanol solvent) |
|---|---|---|---|---|
| | | PM3 | DFT | DFT |
| **Way** | **Product** | **(Kcal / mol)** | $E$ **(a.u.)** | $E$ **(a.u.)** |
| **1** | Product A | 56.5 | -878,144743 | -882.296466 |
| **2** | Product A | 125.5 | -839.098831 | -863.012088 |
| | Product B | 62.74 | -893.113164 | -893.417917 |

**Table 9: Calculated molar fractions for $I_1$ and $I_2$ tautomers in gas phase and solution**

| $K_t$ | | | | | |
|---|---|---|---|---|---|
| gas phase | | | | Solution | |
| $PM_3$ | | DFT | | DFT | |
| $[I_1]$ | $[I_2]$ | $[I_1]$ | $[I_2]$ | $[I_1]$ | $[I_2]$ |
| $1.08\ 10^{-8}$ | 0.89 | $1.74\ 10^{-8}$ | 0.99 | $1.80\ 10^{-10}$ | 0.99 |

**Table 10: Total energies by DFT method and formation enthalphy by PM3 method**

| | Gas phase | | Solution (methanol solvent) |
|---|---|---|---|
| | PM 3 | DFT | DFT |
| | $\Delta H_f$ **(Kcal / mol)** | $E$ **(a.u.)** | $E$ **(a.u.)** |
| Intermediate $I'_1$ | 194.9 | -1072.878 | -1072.896 |
| Intermediate $I'_2$ | 199.5 | -1072.870 | -1072.864 |
| Product of path 1 | 176.8 | -1072.262 | -1072.504 |
| Product of path 2 | 189.4 | -1072.260 | -1072.488 |

**CONCLUSION**

We have described a mechanism for obtaining of 1, 4-benzodiazepines by ring closure of intermediate A or B, resulting from reaction between compound **1** and 1, 2-diamines **2** or **3**. However in the two cases, the $C_7$ of **1** was the initial target of the amino group attack. But while reaction with **2** gave product A exclusively, **3** led to the mixture A and B. these results are in good agreement with the experience. The results of this study indicate: The nature of the reaction was identified by calculating the energy gap between the frontier orbitals. The calculated reactivity descriptors were used to predict the preferred sites of electrophiles and nucleophiles attack in the molecule under investigation. In all cases, the atoms with the maximal value of condensed Fukui function, local softness and local philicity are predicted to be the preferred sites of electrophilic and nucleophilic attack. Dual descriptors are shown to be very efficient in predicting nucleophilic and electrophilic attacks. We were interested in this synthesis reaction by

studying the tautomeric forms that constitute the intermediate compounds. The results are in favor of way 1 and path 1 of the synthesis reaction. We are giving the favorite way and path of the reaction to obtain diazepines.

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