Theoretical investigation for synthesis and characterization of two novel disubstituted imidazoles using microwave

Conference Paper *in* AIP Conference Proceedings · March 2020

DOI: 10.1063/5.0000128

CITATIONS
11

READS
75

3 authors, including:

Dhafer Saber Zinad
University of Technology - Iraq
45 PUBLICATIONS **822** CITATIONS

SEE PROFILE

Omar Adil
University of Mosul
20 PUBLICATIONS **60** CITATIONS

SEE PROFILE

Theoretical investigation for synthesis and characterization of two novel disubstituted imidazoles using microwave

Cite as: AIP Conference Proceedings **2213**, 020188 (2020); https://doi.org/10.1063/5.0000128
Published Online: 25 March 2020

Dhafer S. Zinad, Omar A. Shareef, and Ahmed Mahal

Theoretical Investigation for Synthesis and Characterization of Two Novel Disubstituted Imidazoles Using Microwave

Dhafer S. Zinad[1, a)],Omar A. Shareef [2, b)] and Ahmed Mahal [3,4,c)]

[1]*Applied Science Department, University of Technology, Baghdad 10001, Iraq.*
[2] *Department of Chemistry, College of Science, University of Mosul, Mosul 41002, Iraq.*
[3]*Key Laboratory of Plant Resources Conservation and Sustainable Utilization and Guangdong Provincial Key Laboratory of Applied Botany, South China Botanical Garden, Chinese Academy of Sciences, Guangzhou, 510650, People's Republic of China.*
[4]*Guangzhou HC Pharmaceutical Co., Ltd, Guangzhou 510663, People's Republic of China*

[a)] dhafer.utech.78@gmail.com
[b)] omaradel75a@gmail.com
[c)] ahmed.mahal@scbg.ac.cn

Abstract. The theoretical studies were carried out for the previous synthesized compounds including [N-(4-morpholinophenyl)-4-(4-(naphthalen-2-yl)-1*H*-imidazol-5-yl) pyridin-2-amine] (5a) and [3-(4-cyclopropyl-1*H*-imidazol-5-yl)-N-(4-morpholinophenyl) aniline] (5b) and their intermediates 4a and 4b as well. The calculations were revealed that the target compound 5b is more stable than 5a based on the molecular orbital energy gap between HOMO and LUMO (ΔE= 0.1364 eV). Thermodynamic studies were calculated to investigate the formation process of compounds which showed that compound 5b has formed faster and easier than 5a (ΔH_f= 129.317 Kcal/mol.k).

INTRODUCTION

The heterocycle molecule with the formula of $C_3H_4N_2$ is called imidazole and classified as an alkaloid type compound [1]. Beyond the attractive features of the imidazole ring itself, the synthesis of imidazole presents an opportunity to modify the ring substitution selectively at various positions. Many compounds containing imidazole ring exhibit important pharmacological and biological activities, like antibacterial, antimicrobial and antifungal activities [2]. Imidazoles are prevalent in other pharmaceutical contexts, including antibiotics (nitroimidazoles), central nervous system stimulants (theophyllines), and anticancer medication (mercaptopurines). Moreover, compounds containing imidazole moiety may involve in a few inhibitors of a sub-group of mitogen-activated protein kinases (p38 MAP kinases) that are considered to be associated with a diversity of immunological disorders and inflammatory [3-5]. The high imidazole therapeutic characteristics related medications have urged the chemists towards the development of newly chemotherapeutic agents. Numerous strategies for the synthesis of imidazole derivatives were achieved using various conventional methods [6]. Recently, green synthesis methods have acquired more interest owing to their benefits over the traditional methods, increased selectivity, cleaner reaction profiles, simplicity of employment and almost mild circumstances [7].

Microwave irradiation creates an efficient internal heat transfer, causing a uniform heating through the specimen in comparison with the wall heat transfer that takes place if oil or water bath is employed as an energy source [8,9]. Moreover, microwave-assisted organic synthesis (MAOS) reaction became a significant tool for a fast synthetic route to avoid side products formation [10].

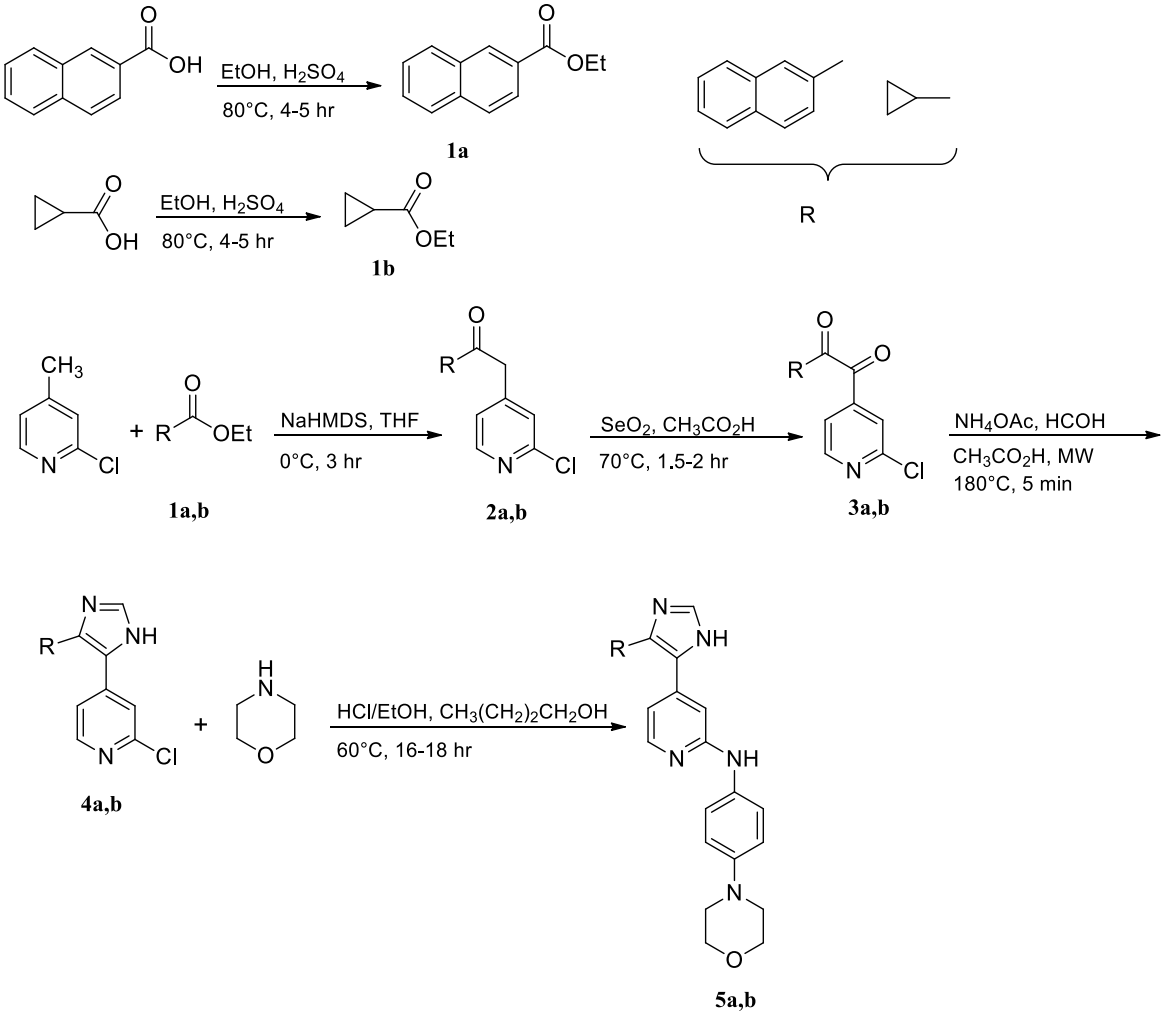
Herein and in a continuity to our previous research study, the effort for theoretical investigation of the synthesis of novel imidazo-aminopyridinyl derivatives using 2-chloro-4-methyl pyridine moiety as starting material have been studied. The theoretical approach is used to investigate the formation and stability for the targets during synthesis processes.

2nd International Conference on Materials Engineering & Science (IConMEAS 2019)
AIP Conf. Proc. 2213, 020188-1–020188-6; https://doi.org/10.1063/5.0000128
Published by AIP Publishing. 978-0-7354-1964-3/$30.00

RESULTS AND DISCUSSION

Chemistry

Scheme 1 outlined the steps for the preparation of novel imidazo-aminopyridinyl derivatives starting from 2-chloro-4-methyl pyridine [11].



SCHEME 1. Preparation of imidazo-aminopyridinyl derivatives.

The first step included the reaction of 2-chloro-4-methyl pyridine as a starting material with ethyl-2-naphthoate and/or ethyl cyclopropanecarboxylate (1a,b) produced β-keto aniline (2a,b) which was oxidized via selenium dioxide to form 1,2-dione (3a,b). Imidazole cyclization step was achieved using MAOS reaction [12]. Treatment of the 1,2-dione with ammonium acetate and formaldehyde using MW synthesizer yielded the cyclized intermediate (4a,b). The functionalization of the pyridine ring at carbon two (C2) position was achieved by the nucleophilic aromatic substitution reaction (SNAr) that produced the designed compounds (5a,b) in a good yield.

D Molecular Modeling Study

The studies of molecular modeling are essential for understanding the compound's molecular arrangement. The two intermediates 4a and 4b and the final products 5a and 5b were optimized with the help of B3LYP [13] level with 6-311G (d) basis set Fig. 1.

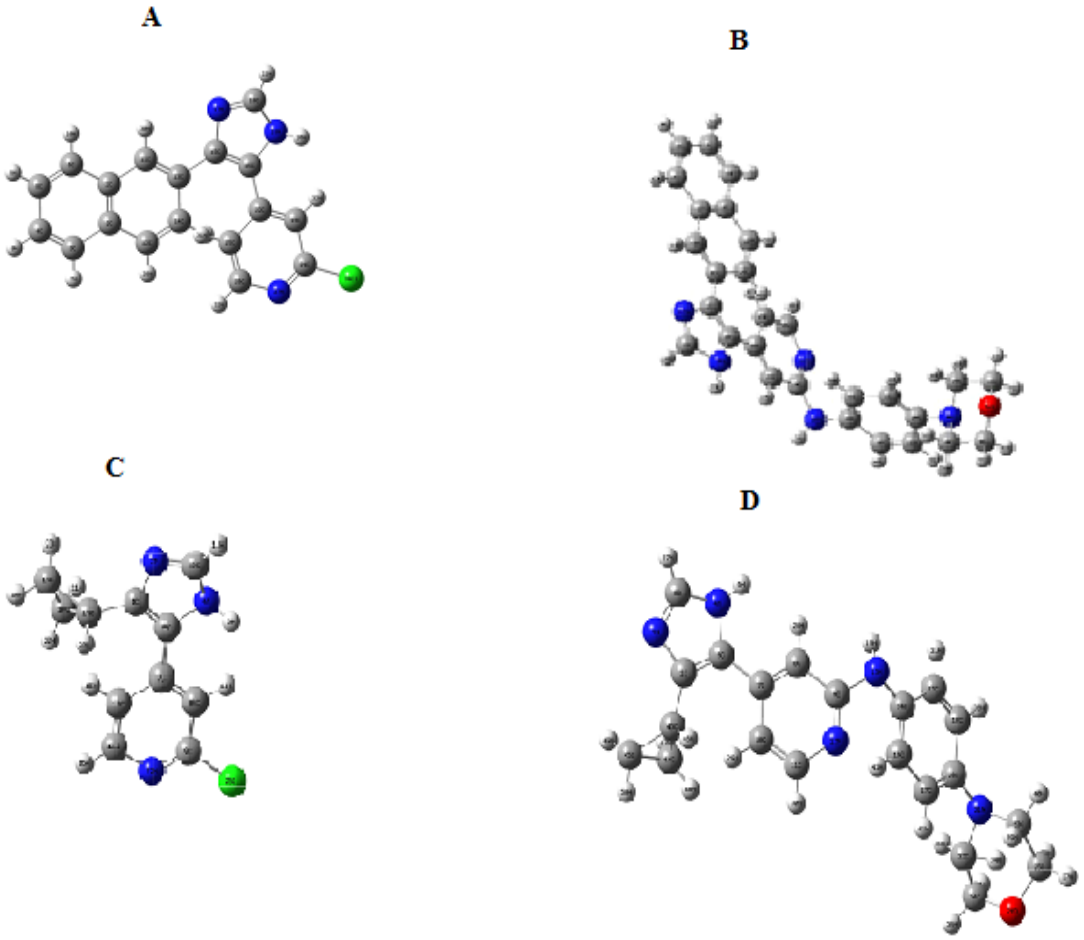


FIGURE 1. The optimized geometry of: (A) compound 4a, (B) 5a, (C) 4b and (D) 5b.

The calculations and observations were investigated utilizing the Gauss 0W9 platform and analyzed with Gauss view 5.0.9 program. The bond lengths and angels observed for both intermediates and products, as shown in Table 1.

Table 1. Various bond lengths (A) and bond angles (°) for different compounds.

Compound (4a) B3LYP/6.311G (d, p)		**Compound (4b) B3LYP/6.311G (d, p)**	
Bond length (A)	**Bond angle (°)**	**Bond length (A)**	**Bond angle (°)**
C_1-C_2 (1.352)	C_1-C_2-C_3 (120.0)	C_1-N_2 (1.396)	C_1-N_2-C_3 (106.51)
C_2-C_3 (1.540)	C_2-C_3-C_4 (120.0)	N_2-C_3 (1.328)	N_2-C_3-N_4 (111.4)
C_3-C_4 (1.355)	C_3-C_4-C_5 (120.0)	C_3-N_4 (1.368)	C_3-N_4-C_5 (109.60)
C_4-C_5 (1.540)	C_4-C_5-C_6 (120.0)	N_4-C_5 (1.392)	C_7-C_8-C_9 (118.01)
C_5-C_6 (1.355)	C_{11}-C_{12}-C_{13} (120.0)	C_7-C_8 (1.408)	C_8-C_9-C_{10} (121.75)
C_{11}-C_{12} (1.540)	C_{12}-C_{13}-C_{14} (120.0)	C_8-C_9 (1.388)	C_9-C_{10}-C_{11} (119.55)
C_{12}-C_{13} (1.355)	C_{13}-C_{14}-C_{15} (120.0)	C_9-C_{10} (1.412)	C_{10}-C_{11}-N_{12} (125.34)
C_{13}-C_{14} (1.355)	C_{14}-C_{15}-C_{16} (120.0)	C_{10}-C_{11} (1.387)	C_{17}-C_{18}-C_{19} (60.23)
C_{14}-C_{15} (1.540)	C_{15}-C_{16}-N_{17} (125.5)	C_{11}-N_{12} (1.319)	
C_{16}-N_{17} (1.304)	C_{16}-N_{17}-C_{18} (106.25)	C_{17}-C_{18} (1.532)	
N_{17}-C_{18} (1.304)	N_{17}-C_{18}-N_{19} (108.7)	C_{18}-C_{19} (1.506)	
C_{18}-N_{19} (1.463)	C_{22}-C_{23}-C_{24} (119.3)		
C_{22}-C_{23} (1.349)	C_{23}-C_{24}-C_{25} (120.5)		
C_{23}-C_{24} (1.539)	C_{24}-C_{25}-C_{26} (119.45)		
C_{24}-C_{25} (1.539)	C_{25}-C_{26}-C_{27} (120.4)		
C_{25}-C_{26} (1.355)			
C_{26}-N_{27} (1.349)			

Table 2. Various bond lengths and bond angles for different compounds.

Compound (4a) B3LYP/6.311G (d, p)		Compound (4b) B3LYP/6.311G (d, p)	
Bond length (A)	**Bond angle (°)**	**Bond length (A)**	**Bond angle (°)**
C_1-C_2 (1.354)	C_1-C_2-C_3 (119.96)	C_1-N_2 (1.397)	C_1-N_2-C_3 (106.47)
C_2-C_3 (1.540)	C_2-C_3-C_4 (119.96)	N_2-C_3 (1.327)	N_2-C_3-N_4 (110.95)
C_3-C_4 (1.355)	C_3-C_4-C_5 (119.98)	C_3-N_4 (1.370)	C_3-N_4-C_5 (109.66)
C_4-C_5 (1.539)	C_4-C_5-C_6 (120.0)	N_4-C_5 (1.390)	C_7-C_8-C_9 (120.04)
C_5-C_6 (1.354)	C_{11}-C_{12}-C_{13} (120.02)	C_7-C_8 (1.397)	C_8-C_9-C_{10} (121.15)
C_{11}-C_{12} (1.539)	C_{12}-C_{13}-C_{14} (119.99)	C_8-C_9 (1.414)	C_9-C_{10}-C_{11} (118.61)
C_{12}-C_{13} (1.351)	C_{13}-C_{14}-C_{15} (119.99)	C_9-C_{10} (1.415)	C_{10}-C_{11}-N_{12} (124.06)
C_{13}-C_{14} (1.355)	C_{14}-C_{15}-C_{16} (125.71)	C_{10}-C_{11} (1.385)	C_{11}-N_{12}-N_{13} (118.69)
C_{14}-C_{15} (1.354)	C_{15}-C_{16}-N_{17} (125.71)	C_{11}-N_{12} (1.352)	N_{12}-N_{13}-C_{14} (131.47)
C_{14}-C_{15} (1.539)	C_{16}-N_{17}-C_{18} (106.29)	N_{12}-N_{13} (1.383)	N_{13}-C_{14}-C_{15} (116.91)
C_{15}-C_{16} (1.345)	N_{17}-C_{18}-N_{19} (108.69)	N_{13}-C_{14} (1.415)	C_{14}-C_{15}-C_{16} (124.95)
C_{16}-N_{17} (1.470)	C_{22}-C_{23}-C_{24} (119.33)	C_{14}-C_{15} (1.409)	C_{15}-C_{16}-C_{17} (120.20)
N_{17}-C_{18} (1.300)	C_{23}-C_{24}-C_{25} (120.0)	C_{15}-C_{16} (1.401)	C_{16}-C_{17}-C_{18} (121.35)
C_{18}-N_{19} (1.460)	C_{24}-C_{25}-C_{26} (119.45)	C_{16}-C_{17} (1.397)	C_{20}-N_{21}-C_{22} (119.25)
C_{22}-C_{23} (1.349)	C_{25}-C_{26}-N_{27} (120.47)	C_{17}-C_{18} (1.387)	N_{21}-C_{22}-C_{23} (118.86)
C_{23}-C_{24} (1.349)	C_{26}-N_{27}-N_{28} (119.5)	C_{20}-N_{21} (1.420)	C_{22}-C_{23}-C_{24} (109.71)
C_{24}-C_{25} (1.534)	N_{27}-N_{28}-N_{29} (109.25)	N_{21}-C_{22} (1.470)	C_{23}-C_{24}-C_{25} (110.14)
C_{25}-C_{26} (1.354)	N_{28}-C_{29}-C_{30} (120.24)	C_{22}-C_{23} (1.477)	C_{24}-C_{25}-O_{26} (111.11)
C_{26}-N_{27} (1.299)	C_{29}-C_{30}-C_{31} (119.76)	C_{23}-C_{24} (1.527)	C_{43}-C_{44}-C_{45} (60.63)
N_{27}-N_{28} (1.470)	C_{30}-C_{31}-C_{32} (119.9)	C_{23}-C_{24} (1.527)	
N_{28}-C_{29} (1.469)	C_{31}-C_{32}-C_{33} (119.9)	C_{24}-C_{25} (1.524)	
C_{29}-C_{30} (1.540)	C_{32}-C_{33}-C_{34} (120.06)	C_{25}-O_{26} (1.459)	
C_{30}-C_{31} (1.354)	C_{33}-C_{34}-C_{35} (109.2)	C_{43}-C_{44} (1.524)	
C_{31}-C_{32} (1.355)	C_{38}-C_{39}-C_{40} (109.26)	C_{44}-C_{45} (1.508)	
C_{33}-C_{34} (1.466)	C_{39}-C_{40}-C_{41} (109.61)		
C_{37}-C_{38} (1.539)			
C_{38}-C_{39} (1.539)			
C_{39}-C_{40} (1.539)			
C_{40}-C_{41}(1.432)			

The importance of the theoretical approach is to explain the chemical reactivity and selectivity of the active site of compounds under investigation. According to frontier molecular orbitals approach, the gap of energy between HOMO and LUMO orbitals explains the electron transfer interaction [14] and some factors are called the chemical reactivity magnitudes [15].

$$\boldsymbol{\chi = -\frac{(E_{LUMO} + E_{HOMO})}{2}}$$

$$\boldsymbol{\mu = -\chi = \frac{(E_{LUMO} + E_{HOMO})}{2}}$$

$$\boldsymbol{\eta = \frac{(E_{LUMO} - E_{HOMO})}{2}}$$

$$\boldsymbol{S = \frac{1}{2\eta}}$$

$$\boldsymbol{\omega = \frac{\mu^2}{2\eta}}$$

$$\boldsymbol{\sigma = \frac{1}{\eta}}$$

To understand the compound's chemical reactivity, the comparison of orbital energy must be required. The HOMO orbital always works as electron donor orbital, which possess greater energy and works as the electron donor. The LUMO orbital always works as electron acceptor orbital, which possess less energy and acts as the electron acceptor. The results clarify that the hardness value for the final products (the larger gap between HOMO and LUMO energy) leads to the more stability of the products and intermediates. The calculated energy

gaps (ΔE) of synthesized compounds confirms the stability of products 5a,b in comparison with the intermediates 4a,b. Compound 4a has the highest energy gap with (ΔE= 0.14432 eV) as compared to the compound 5a (ΔE= 0.11912 eV) which clearly indicates the highest stability of compound 4a than compound 5a as following 4a>5a. On the other hand, compound 4b (ΔE= 0.1675 eV) is more stable than compound 5b (ΔE= 0.1364 eV) as indicated by the calculated energy gaps. The calculated energy gaps confirm that the compound 4b has the highest stability among others as following 4b>4a>5b>5a (Table 3).

Table 3. Quantum chemical factors of the targets.

Compound	HOMO eV	LUMO eV	ΔE eV	η eV	ω eV	χ	μ eV	S	σ
5a	-0.18175	-0.06263	0.11912	0.05956	0.125339	0.12219	-0.12219	8.39489	16.78979
4a	-0.21965	-0.07533	0.14432	0.07216	0.150729	0.14749	-0.14749	6.92904	13.85809
5b	-0.1831	-0.0467	0.1364	0.0682	0.096788	0.1149	-0.1149	7.33137	14.66276
4b	-0.2351	-0.0676	0.1675	0.08375	0.136757	0.15135	-0.15135	5.97014	11.94029

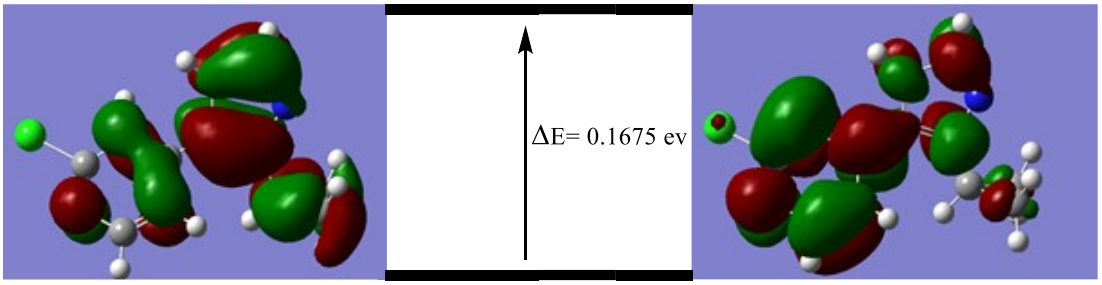


Figure 2. HOMO and LUMO molecular energy gap of **4b**

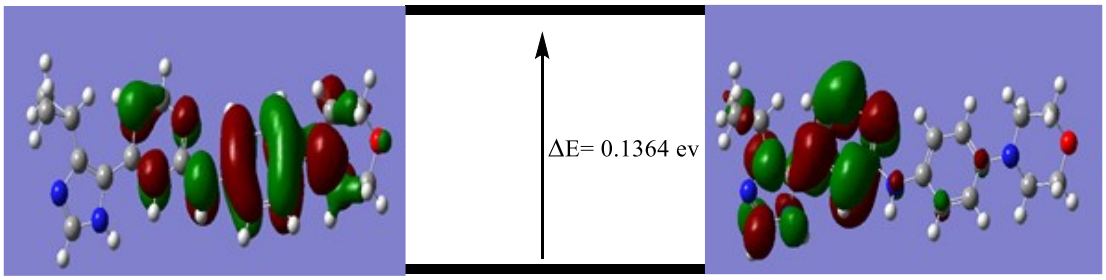


Figure 3. HOMO and LUMO molecular energy gap of **5b**

Thermodynamic Study

Heat of formation has been studied in order to investigate the energy needed for the formation of the target compounds and intermediates and table 4 shows the heat of formation data of each compound.

Table 4. Thermodynamic properties of compounds

Compound	ΔH_f (Kcal/mol)	ΔS (Kcal/mol.K)	ΔG (Kcal/mol)
5a	305.12	177.488	-1429.36
4a	172.99	133.30	-1317.36
5b	275.65	166.58	-1162.59
4b	129.317	113.520	-1049.73

The values of heat of formation confirm the formation rate of the intermediates along with the products. The above results (Table 3) indicate that the compound of 4b (ΔH_f= 129.317) is formed faster than compound 4a (ΔH_f= 172.99) based on the calculations of ΔH_f as 4b needs less energy than compound 4a. Accordingly, compound 5b (ΔH_f= 275.65) can be formed faster than compound 5a (ΔH_f= 305.12) and we conclude the formation of compounds is proceeding as following sequence 4b>4a>5b>5a. The above results are an agreement with the results of the stability (Hardness measurement).

The obtained data of entropy (ΔS) shows that the more rigid cyclic structure can lead to the faster product formation (Table 3). The decrease in this value gives a significant indication to the compound stability and thus provides a proper support to explain the cause of the discrepancies in the heat of formation values for the final

products. The data shows that the compound 4b has a higher value of ΔS (higher degree of freedom) than compound 4a. Compound 5a has a lower value of ΔS (lower degree of freedom) than compound 5b. For this reason, it can be concluded that the compound 5b will be formed faster than compound 5a and its stability rate is higher as well.

CONCLUSION

The theoretical calculations, including DFT study and thermodynamic studies were investigated the stability and formation rate of the synthesized products. The obtained results confirmed that compound 5b is more stable and formed faster than compound 5a.

ACKNOWLEDGEMENT

We acknowledge the support provided by University of Tübingen/ Germany and the support by CAS President's International Fellowship Initiative (2016PM032) as well.

CONFLICT OF INTEREST

The author declares that there is no conflict of interests

REFERENCES

1. R. Katritzky and C. W. Rees, Com. Het. Chem. **5**, 469-498 (1984).
2. M. Boiani and M. González, Mini-Rev. Med. Chem. **5**, 409-424 (2005).
3. S. W. Wright, R. R. Harris, R. J. Collins, R. L. Corbett, A. M. Green, E. A. Wadman, and D. G. Batt, J. Med. Chem., **35**, 3148-3155 (1992).
4. P. F. Jackson and J. L. Bullington, Curr. Top. Med. Chem., **2**, 1011-1020 (2002).
5. F. Muth, A. El-Gokha, F. Ansideri, M. Eitel, E. Döring, A. Sievers-Engler, A. Lange, F. M. Boeckler, M. Lämmerhofer**,** P. Koch, and S**.** A. Laufer, *J. Med. Chem*., **60**, 594-607 **(**2017**).**
6. R. K. Jat, Pharmacophore, **1**, 167-177 (2010).
7. G. B. Helen, S. B. Laura, and T. L. Mark, J. Org. Prep. Proc. Intern., **50,** 2 (2018).
8. P. Lidstrom, J. Tierney, B. Wathey, and J. Westman, Tetrahedron, **57**, 9225 (2001).
9. G. Manoj, N. S. Sharad, Z. Radek, and S. V. Rajender, Acc. Chem. Res., **47**, 1338-1348 (2014).
10. S. Ravichandran and E. Karthikeyan, Inter. J. ChemTech Res. **3**, 466-470 (2011).
11. F. Ansideri, J. T. Macedo, M. Eitel, A. El-Gokha, D. S. Zinad, C. Scarpellini, M. Kudolo, D. Schollmeyer, F. Boeckler, B. S. Blaum, S. A. Laufer, and P. Koch, ACS Omega, **3**, 7809-7831 (2018).
12. S. E. Wolkenberg, D. D. Wisnoski, W. H. Leister, Y. Wang, Z. Zhao, and C. W. Lindsley, Org. Lett., **6**, 1453-1456 (2004).
13. M. W. Peter, B. G. Johnson, and J. A. Pople, Chem. Phys. Lett. **197**, 499-505 (1992).
14. M. J. Frisch, G. W. Trucks, and H. B. Schlegel, Gaussian 09, Revision A.02, Gaussian, Inc., PA, Wallingford CT. (2009).
15. J. W. Peters, W. N. Lanzilotta, J. Lemon, and L. C. Seefeldt, Science **282**, 1853-1858 (1998).