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Theoretical Study of Some Chemical Kinetics and Physical Properties for some bnzohydrazide derivatives by using Semi-Empirical calculation (PM3 Method)

الدراسة النظرية للحركيات الكيميائية وبعض الخواص الفيزيائية لبعض مشتقات البنزوهيدرازيت باستخدام الحسابات الشبه التقريبية (طريقة PM3)

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Abstract

A theoretical study in the present work involved program(Gaussian 03W) to use the method of calculating the total Semi-Empirical calculations(PM3 Method) of two benzohydrazide derivatives [N'-(4-aminobenzylidene) benzohydrazide] ,[N'-(4-(dimethylamino benzylidene) benzohydrazide] , in order to elucidate the inhibition efficiencies and reactive sites of these compounds . They include calculations of dimensional geometry (lengths and bond angles) when the geometry of balanced. For these compounds some physical properties were calculated such as orbital energies (E_{LUMO}, E_{HOMO}), energy gap (ΔE), dipole moment (μ), IP (ionization energy) , hardness. Functions thermodynamic and IR intensity and absorption frequencies for tow compounds were also investigated. The purpose of this study to compare the possible sites for nucleophilic and electrophilic attacks and which compounds can be used anti-bacterial and anti-fungusthe . The results showed compound [N'-(4-(dimethylamino benzyliden) benzohydrazide] have lower electronegative, higher hardness(η) ,lower energy gap (ΔE) , and high vibrational frequencies of IR absorption compared with the other compound, which may be used as a highest anti- inflammatory. this difference in this results come according to the effect of subsisted groups of studied compounds .

الخلاصة

اعتمدت الدراسة النظرية في هذا العمل برنامج (Gaussian 09 W) , وباستخدام طريقة الحساب شبه التجريبية PM3 لأثنين من مشتقات البنزوهيدرازيت[N'-(4-aminobenzylidene bnzohydrazide] [N'-(4-(dimethylaminobenzylidene)bnzohydrazide ,من اجل القاء الضوء على فعالية التثبيطوالمواقع الفعالة لهذين المركبين , حيث تضمنت الدراسة الحسابات للابعاد الهندسية (اطوال وزوايا التآصر) عند الشكل الهندسي المتوازن وتم حساب بعض الخصائص الفيزيائية لهذه المركبات مثل طاقة الاوربيتالات (E_{LUMO}, E_{HOMO}) , فجوة الطاقة (ΔE) ,عزم ثنائي القطب (μ) , طاقة التأين IP , الصلابة, كما تم تشخيص الدوال الثرموداينميكية وشدة الامتصاص لاشعة IR لهذين المركبين . ان الغرض من الدراسة هو المقارنة بالمواقع الفعالة التي يمكن مهاجمتها للنيوكليوفيلات والالكتروفيلات وأي المركبات يمكن استخدامها كمضاد للبكتريا والفطريات. أظهرت النتائج ان المركب [N'-(4-) benzohydrazide dimethylamino benzylidene)ي متلك اقل كهروسلبية , اعلى صلابة (η), اقل فجوة طاقة (ΔE) ,اعلى تردد اهتزازي في منطقة امتصاص IR مع المركب الاخر , لذا يمكن ان يستخدم كاعلى مضاد حيوي . هذا التغاير في النتائج يعزى لتأثير المجموعة المعوضة للمركبات التي تم دراستها.

Introduction

Hydrazones have been demonstrated to possess antimicrobial, anticonvulsant, analgesic, antiinflammatory, antiplatelet, anti-tubercular, anticancer and antitumor activities [1,2]. Hydrazones possessing an azomethine – NHN=CH– proton constitute an important class of compounds for new drug development. Many researchers have therefore synthesized these compounds as target structures and evaluated their biological activities . These observations have served as guides for the development of new hydrazones that possess various biological activities[3] . Hydrazide and their heterocyclised products display diverse biological activities including antibacterial,antifungicidal,

analgesic, anti-inflammatory properties1-15. These heterocyclic systems find wide use in medicine, agriculture and industry.

Benzohydrazide and their derivatives are poly functional molecules [4,5] bearing C=O , –NH– and $–NH_2$ functionalities in their structures. Therefore, we can expect these compounds to behave as ambident nucleophiles in several reactions [6]. The scarce data about their kinetics and reaction mechanisms prompted us to perform experimental and theoretical studies in order to gain insight in the corresponding reaction mechanisms towards carbonylic electrophiles, p-nitrophenyl acetate in the present case. We have shown that experimental and theoretical integrated research may become a very useful methodology to describe reaction mechanisms in organic chemistry [7] .

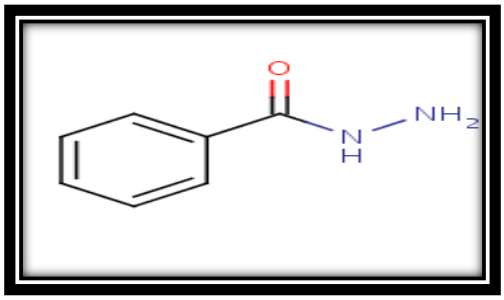

Figure 1: Benzohydrazide structure

Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties1-15. These heterocyclic systems find wide use in medicine, agriculture and industry [8, 9].

Methods of calculation.

The present study is based on G09 program (14) using PM3 (Modified Neglect of Diatomic Overlap Parametric Method Number 3) model which was developed and the treatment of organic molelcules (10,11). Such treatment yields the equilibrium geometry energy values of the molecules in addition to their fundamental vibration frequencies (3N-6) and IR absorption intensities(12) . Solution of this equation yields vibration frequencies $\lambda=4\pi^2\ \upsilon^2\ c^2$) (13) . Depending on this method some physical properties were calculated according to these equations $E_A = - E_{LUMO}$, $\eta=1/2 (E_{HOMO} - E_{LUMO})$, $(G^0 = H^O - ST)$, $(A^0 = G^0 – ST)$.

G09 program of J. Frisch, G. W. Trucks, et al(**14, 15)** was applied throughout .

Results and Discussion

The benzohydrazide derivatives investigated in the present work are:

Compound 1 **N'-(4-aminobenzylidene)benzohydrazide**

Chemical Formula: $C_{14}H_{13}N_3O$

Molecular Weight: 239.27

Comopound 2

N'-(4-(dimethylamino)benzylidene)benzohydrazide

Chemical Formula: C16H17N3O

Exact Mass: 267.14

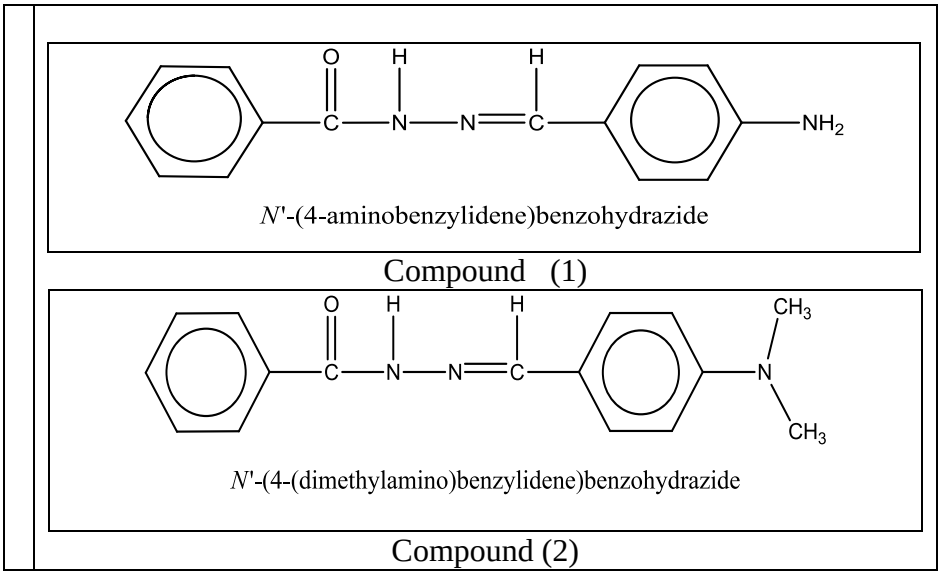

Figure 2: The geometric equilibrium for N'-(4-aminobenzylidene)benzohydrazide and N'-(4-(dimethylamino benzylidene) benzohydrazide

In this research calculated the geometry (bond lengths) of the two molecules o N'-(4-aminobenzylidene)benzohydrazide and N'-(4-(dimethylamino benzylidene) benzohydrazide , using the semi-empirical PM3 methods. According to the results calculated and recorded in the (**table 1 and Fig. 3)**

Show that each th bonds C_{10}-N_{13} compound 2] N'-(4-(dimethylamino benzylidene)] has high value compared to other compound 1 [N'-(4-aminobenzylidene)benzohydrazide] may be caused by the less electron- negative of $N(CH_3)_2$. Also the change of the group substituted had effect on the value of th angles of the studied compound in this research have shown calculation in the (**table 1 and Fig 3**) .That the angle ($\angle$ C_9 C_{10} N_{13}) showed that in compound 2 has high value compared to compound 1 . May be due to the big size of substitution groups on the angles.

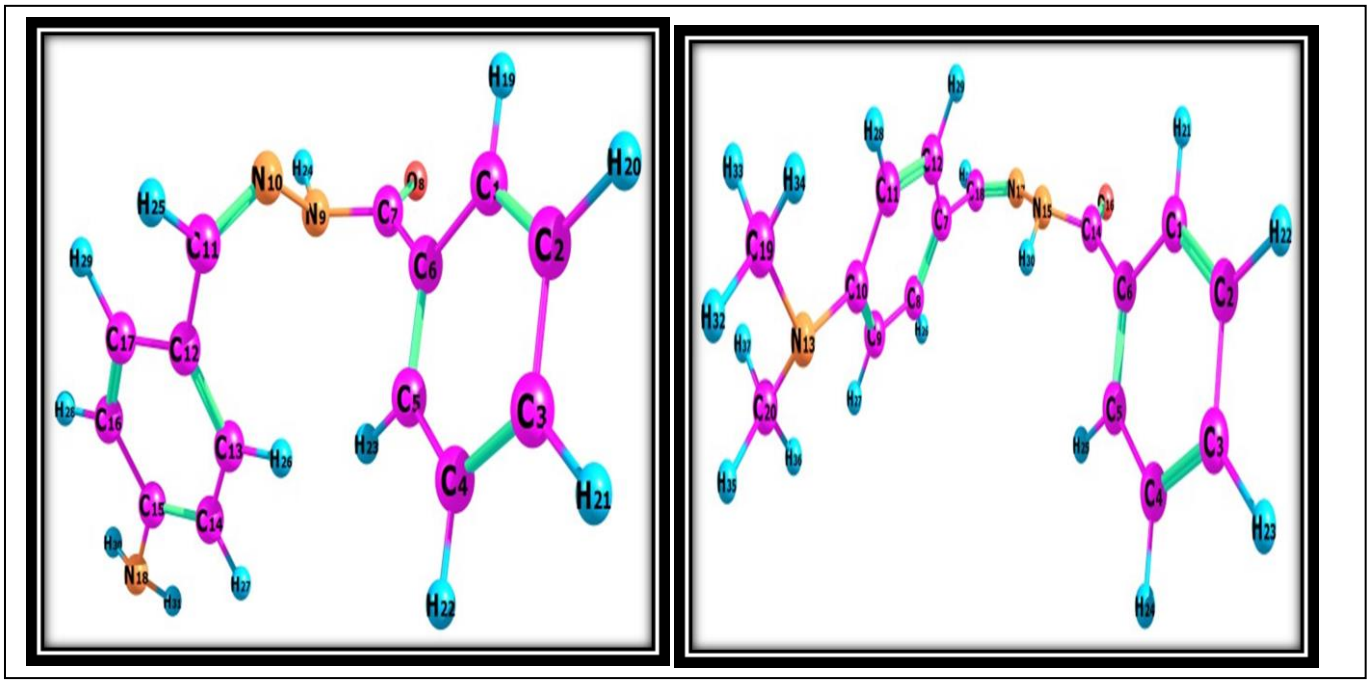

Figure 3: The geometric equilibrium (3D) the N'-(4-aminobenzylidene)benzohydrazide (Compound 1) and N'-(4-(dimethylamino benzylidene) benzohydrazide(Compound 2)

Table 1 : Calculated geometric parameters (bond lengths in Angstrom length angles in degree) of the N'-(4-aminobenzylidene)benzohydrazide and N'-(4-(dimethylamino benzylidene) benzohydrazide

Para. Geo.	Bond length and Angle	Para. Geo.	Bond length and Angle	Para. Geo.	Bond length and Angle	Para. Geo.	Bond length and Angle
Compound 1		Compound 2		Compound 1		Compound 2	
R(1-2)	1.391	R(1-2)	1.391	R(12-17)	1.397	R(10-13)	1.443
R(1-6)	1.395	R(1-6)	1.394	R(13-14)	1.387	R(11-12)	1.387
R(1-19)	1.096	R(1-21)	1.096	R(13-26)	1.102	R(11-28)	1.101
R(2-3)	1.391	R(2-3)	1.391	R(14-15)	1.403	R(12-29)	1.096
R(2-20)	1.095	R(2-22)	1.095	R(14-27)	1.097	R(13-19)	1.481
R(3-4)	1.391	R(3-4)	1.391	R(15-16)	1.404	R(13-20)	1.481
R(3-21)	1.095	R(3-23)	1.095	R(15-18)	1.426	R(14-15)	1.447
R(4-5)	1.390	R(4-5)	1.390	R(16-17)	1.386	R(14-16)	1.214
R(4-22)	1.095	R(4-24)	1.095	R(16-28)	1.097	R(15-17)	1.390
R(5-6)	1.395	R(5-6)	1.395	R(17-29)	1.096	R(15-30)	1.002
R(5-23)	1.101	R(5-25)	1.096	R(18-30)	0.995	R(17-18)	1.295
R(6-7)	1.488	R(6-14)	1.495	R(18-31)	0.995	R(18-31)	1.099
R(7-8)	1.219	R(7-8)	1.397	A(2-1-6)	119.7	R(19-32)	1.098
R(7-9)	1.447	R(7-12)	1.395	A(2-1-19)	120.2	R(19-33)	1.101
R(9-10)	1.426	R(7-18)	1.469	A(1-2-3)	120.2	R(19-34)	1.102
R(9-24)	1.000	R(8-9)	1.386	A(1-2-20)	119.8	R(20-35)	1.098
R(10-11)	1.292	R(8-26)	1.096	A(6-1-19)	120.1	R(20-36)	1.102
R(11-12)	1.468	R(9-10)	1.405	A(1-6-5)	120.1	R(20-37)	1.101
R(11-25)	1.100	R(9-27)	1.101	A(1-6-7)	119.4	A(2-1-6)	119.7
R(12-13)	1.396	R(10-11)	1.404	A(3-2-20)	120.0	A(2-1-21)	120.3
A(2-3-4)	120.0	A(1-2-3)	120.2	A(13-14-15)	120.0	A(8-9-10)	120.5
A(2-3-21)	120.0	A(1-2-22)	119.8	A(13-14-27)	119.4	A(8-9-27)	119.5
A(4-3-21)	120.0	A(6-1-21)	120.0	A(15-14-27)	120.6	A(10-9-27)	120.0
A(3-4-5)	120.2	A(1-6-5)	120.2	A(14-15-16)	119.7	A(9-10-11)	118.7
A(3-4-22)	120.0	A(1-6-14)	119.5	A(14-15-18)	120.1	A(9-10-13)	120.5
A(5-4-22)	119.8	A(3-2-22)	120.0	A(16-15-18)	120.0	A(11-10-13)	120.6
A(4-5-6)	119.8	A(2-3-4)	120.1	A(15-16-17)	119.9	A(10-11-12)	120.6
A(4-5-23)	119.9	A(2-3-23)	120.0	A(15-16-28)	120.6	A(10-11-28)	120.0
A(6-5-23)	120.3	A(4-3-23)	119.9	A(15-18-30)	112.0	A(10-13-19)	116.6
A(5-6-7)	120.5	A(3-4-5)	120.1	A(15-18-31)	112.0	A(10-13-20)	116.6
A(6-7-8)	124.3	A(3-4-24)	120.0	A(17-16-28)	119.5	A(12-11-28)	119.4
A(6-7-9)	119.3	A(5-4-24)	119.9	A(16-17-29)	119.8	A(11-12-29)	119.4
A(8-7-9)	116.2	A(4-5-6)	119.7	A(30-18-31)	111.5	A(19-13-20)	111.7
A(7-9-10)	115.5	A(4-5-25)	119.8			A(13-19-32)	108.5
A(7-9-24)	113.9	A(6-5-25)	120.4			A(13-19-33)	113.2
A(10-9-24)	107.9	A(5-6-14)	120.2			A(13-19-34)	110.4
A(9-10-11)	121.4	A(6-14-15)	114.0			A(13-20-35)	108.5

A(10-11-12)	128.6	A(6-14-16)	124.2			A(13-20-36)	110.4
A(10-11-25)	114.2	A(8-7-12)	119.4			A(13-20-37)	113.2
A(12-11-25)	117.2	A(8-7-18)	118.7			A(15-14-16)	121.7
A(11-12-13)	121.6	A(7-8-9)	120.4			A(14-15-17)	117.9
A(11-12-17)	118.7	A(7-8-26)	119.7			A(14-15-30)	114.0
A(13-12-17)	119.8	A(12-7-18)	121.8			A(17-15-30)	114.7
A(12-13-14)	120.3	A(7-12-11)	120.3			A(15-17-18)	123.1
A(12-13-26)	120.1	A(7-12-29)	120.3			A(17-18-31)	114.7
A(12-17-16)	120.4	A(7-18-17)	127.6			A(32-19-33)	108.4
A(12-17-29)	119.8	A(7-18-31)	117.7			A(32-19-34)	108.2
A(14-13-26)	119.6	A(9-8-26)	119.8			A(33-19-34)	108.1
						A(35-20-36)	108.2
						A(35-20-37)	108.3
						A(36-20-37)	108.1

Physical properties

Depending on the Semi-empirical method of calculation according to the (PM3) is calculate some physical properties of the molecules studied in this research; Dipole moments (μ in Debye) , energies(e V)of the high Occupied Molecular Orbital (E_{HOMO}) and the Lower Unoccupied Molecular Orbital (E_{LUMO}) IP (ionization energy) . The higher HOMO energy values show the molecule is a good electron donor, in other hand, the lower HOMO energy values indicate that, a weaker ability of the molecules for donating electron. LUMO energy presents the ability of a molecule for receiving electron[17-19] . the negative E_{HOMO} is equal to the ionization potential) the calculation has been ionization energies (e V) , Also calculated the energy difference (ΔE , e V), And finally calculated (Molecular Hardness)Hardness(η) = ½(E_{HOMO} - E_{LUMO}) , (Electron Affinity) E_A = - E_{LUMO} according Koopmans theorem for N system of electrons [20] . The HOMO and LUMO of a molecule play important roles in intermolecular interactions , through the interaction between the HOMO of the drug with the LUMO of the receptor and vice versa. The interactions stabilized inversely with energy gap between the interacting orbitals. Increasing HOMO energy and decreasing LUMO energy in the drug molecule lead to enhancement stabilizing interactions, and hence, binding with the receptor enhancement stabilizing interactions, and hence, binding with the receptor [20,21] . . The HOMO and LUMO of a molecule play important roles in intermolecular interactions , through the interaction between the HOMO of the drug with the LUMO of the receptor and vice versa. The interactions stabilized inversely with energy gap between the interacting orbitals [22,23].

The results showed that compound 1 [N'-(4-aminobenzylidene)benzohydrazide] has high value for each of (Dipole moment , IP, Electron Affinity E_A) , And less value (E_{LUMO}) , this means that this compound has more ability to loss electrons and easier ionization compared to compound 2 [N'-(4-(dimethylamino benzylidene) benzohydrazide]. Also the results showed compound 2 has higher hardness (**η**) , lower energy gap (**ΔE**) (Table 2) , which may be explained the highest anti-inflammatory compound (Table 2)

Table 2:Calculated , μ (in Debye) ,orbital energies (E_{HOMO}, E_{LUOM}, ΔE in eV) , IP(in eV) , E_A (in eV) , and η (in eV) for the derivatives of bnzohydrazide.

Comp.	μDebye	E_{HOMO}	E_{LOMO}	ΔE	IP	E_A	η
$C_{14}H_{13}N_3O$ (1)	3.3475	-8.8563	-0.3282	8.5281	8.8563	0.3282	-4.26405
$C_{16}H_{17}N_3O$ (2)	5.8520	-8.6582	-0.2166	8.4416	8.6582	0.2166	-4.2208

Thermodynamics functions

Thermodynamics functions for the studied molecules were listed in **Table 3**. Compared with **$C_{14}H_{13}N_3O$ (1) $C_{16}H_{17}N_3O$ (2)** , molecules along with the rotational constants, obtained in this study, Both NH_2 , $N(CH_3)_2$ substituent's in same compound causes an increase in the all thermodynamics functions [E^o, H^o, G^o, A^o, C_V , C_P , S^o] due to its stabilization by resonance effect.

$N(CH_3)_2$ > NH_2

The deferent thermodynamics functions values due to deferent substituted groups.Future studies must aim to computationally dock these conformers to the active site of the adrenergic receptor in order to determine which conformer has the greatest biological effect.where used to calculate the vibration and rotation contributions to the thermodynamic functions according to the statistical thermodynamic equations

$$U_{vib}^{0} = \sum_{i=1}^{3N-6} \frac{R\,T\,X_i}{e^{X_i} - 1} \qquad \text{.....(1)}$$

$$X_i = \frac{1.44\bar{\nu}}{T} \qquad \text{.....(2)}$$

$$S_{vib}^{0} = R \sum_{i=1}^{3N-6} \left[\frac{X_i}{e^{X_i} - 1} - \ln\left(1 - e^{-X_i}\right) \right] \qquad \text{.....(3)}$$

$$S_{rot}^{0} = R \left[\frac{3}{2} + \ln \frac{8\pi^2 \left(8\pi^2 I_X I_Y I_Z\right)^{\frac{1}{2}} (KT)^{\frac{3}{2}}}{\sigma \hbar^3} \right] \qquad \text{.....(4)}$$

(20, 21)

I : Moment of inertia Symmetry Coefficient σ

h : Planck's constant , N_o : Avocado's number

K : Boltzmann constant , R : gas constant

Table 3: The calculated standard thermodynamics functions at 298.15oK of the derivatives of bnzohydrazide.

Comp.	E^0 kJ/Mol	H^0 kJ/mol	G^0 kJ/mol	S^0 kJ/mol.deg	A^0 kJ/mol	Cv kJ/mol.deg
Compound (1) $C_{14}H_{13}N_3$ O	683.954	686.431	525.511	0.5408	364.5915	0.2507
Compound (2) $C_{16}H_{17}N_3$ *O*	832.431	834.909	647.467	0.6290	460.0250	0.2955

Frequencies IR Intensity of Absorption .

Table 4: Frequencies of Absorption of IR Intensity of Compound (1) $C_{14}H_{13}N_3$ O and Compound (2) $C_{16}H_{17}N_3O$

Type of bond	Compound 1 $C_{14}H_{13}N_3$ O		Compound 2 $C_{16}H_{17}N_3$ *O*	
C=N St.	Frequency cm^{-1}	IR intensity	Frequency cm^{-1}	IR intensity
	1869.6667	105.6905	1856.2778	115.6890
C=O St.	1945. 8476	439.8104	1954.1520	400.8234
C-H St.	3002.1298	15.1314	3016.3847	12.3456
N-H St.	3368.1215	13.3575	3315.2427	15.1123

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