THEORETICAL AND EXPERIMENTAL STUDIES OF ANTIOXIDANT PROPERTIES OF ANTIPYRINETHIOSEMICARBAZONE DERIVATIVES

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دراسة نظريه وتجريبيه للصفات المضاده للاكسده لمشتقات
ANTIPYRINETHIOSEMICARBAZONE DERIVATIVES

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الخلاصة

تناول البحث الحالي دراسة مشتقات Antipyrinethiosemicarbazone كمضادات للاكسدة حيث اثبتت النتائج بان جميع هذه المركبات لها فعاليه جيدة كمضادات للاكسده . بينت دراسة العلاقه بين معاملات الكيمياء الكمي (الفرق بين حرارة التكوين للجزيئة وجذرها االموجب) وفعالية المركبات كمضادات للاكسدة ان القيمة الاكبر للفرق في حرارة التكوين تقابل القيمة الاكبرللفعاليه ضد الاكسده

ABSTRACT

Antipyrinethiosemicarbazone derivatives have been investigated as antioxidant in this work. The results of antioxidant activity coefficient (K) proved that all investigated compounds have good antioxidant activity.

Investigation of the relation between antioxidant activity (K) and quantum-chemical parameters difference of heats of formation of a molecule and its cation radical ΔH_f shows that the ΔH_f values proportional with K values of investigated compounds.

Key words : Thiosemicarbazone derivatives , Antioxidant , Quantum-chemical parameters

INTRODUCTION

Antipyrine was one of the first major synthetic compound to be used in medicine as an analgesic and antipyretic drugs [1]. The derivatives of antipyrine were reported to be more active and less toxic than the parent drugs [2-4].

Oxidative stress arises in a biological system after an icreased exposure to oxidants or decrease in the antioxidant capacity of this system . It often leads to generation of reactive oxygen species including free radicals [5].

Protection of human against oxidative stress as well as prophylactic of incurable diseases are important fields in medicine and biochemistry over the world. Antioxidants play a major role in protecting biological systems against many incurable diseases. The antioxidants have been widely used in different fields of medicine such as a substances which interrupt radical-chain oxidation processes that improve general health and prevent incurable diseases [6].

In this work antipyrinethiosemicarbazone derivatives have been investigated as antioxidants . These substances are effective pharmaceuticals for prophylactic and treatment of virus diseases, which it was confirmed by clinical test. The relation between antioxidation activity and quantum-chemical parameters of these substances has been investigated in this work too.

EXPERIMENTAL PARTS

(1) Synthesis of antipyrinethiosemicarbazone derivatives

The antipyrinethiosemicarbazone derivatives were synthesized according to a general procedure [7] and Figure 1 shows the structures of prepared compounds . 0.01 mol of 4-formylantipyrine and 0.01 mol of p-aminodiphenylamine in 50 ml of ethanol were treated with few drops of acetic acid .The reaction mixture was refluxed for ½ h. , the solid product was collected crystallized from ethanol. 0.01 mol of the solid and few drops of triethylamine in 50 ml of dry toluene were treated with acetic acid by adding it dropwise at room temperature followed by refluxing for 1h. . Trituration of the residue with light petrol (40-60°C), furnished products which on crystallization from the proper solvent . 0.01 mol from each products prepared previously with 0.02 mol of sulphat powder and 0.1g of iodiun in : (1) 20 ml of o-dichlorobenzene followed by refluxing for 2 h. . Trituration with light petrol (40-60^{o}C) , furnished products which on crystallization from the proper solvent to give {N-(benzalidene) amino antipyrinthiosemicarbazone} (A) compound . (2) 20 ml of $NaOCH_3$ followed by refluxing for 2 h. . The products were triturated to give {N-(methoxybenzalidene) amino antipyrinethiosemicarbazone} (B) compound . The structures of studied compounds are shown in Figure 1. .

(2) Antioxidantion activity determination

The principle of method involves recording the absorbance values in visible region using U.V-Visible Spectrophotometer for prepared of compounds . The spectra were recorded on a shimatzu-260 at wavelength 540 nm and by using quartize cell for measuring the absorbance values for the {N-(benzalidene) amino antipyrinthiosemicarbazone}(A) and {N-

(methoxybenzalidene) amino antipyrinethiosemicarbazone} (B) compounds at concentrations 0.012, 0.024, 0.036, 0.048 and 0.060 mg/ml and these were mixed with 0.1M of $NaClO_4$ in ethanol . Exposure time to oxidant (visible light) was about 30 – 60 sec .

(3) Quantum-chemical calculations

Al-chem 2000 program was used to draw geometrical structure of {N-(benzalidene) amino antipyrinthiosemicarbazone}(A) and {N-(methoxybenzalidene) amino antipyrinethiosemicarbazone} (B) compounds and geometrical optimization has been doing to calculate the charge density over the molecule structure of (A) and (B) compounds then by using hyperchem program / MNDO semiempirical method, which permits to make quantum-chemical calculations of difference of heats of formation of molecule and its cation radical ΔH_f which as shown in Figure 2. .

RESULTES AND DISCUSSION

(1) Characterization of antipyrinethiosemicarbazone derivatives:-

(A) Elemental analysis

The elemental analysis (CHN) of investigated compounds has been shown in Table 1. Which shows that practical values of (CHN) are in good agreement with the calculated values, but there are some differences between the practical values and calculated values reache about 2% due to impurities , thus the structures of prepared compounds are confirmed .

(B) Infra-red spectra (IR)

IR spectra were recorded by using KBr disc of investigated compounds, which are shown in Table 1. The strong band observed at 3440-3270 cm^{-1} region has been assigned to υ(HN) vibration and the absorption at ~ 1600 cm^{-1} can be attributed to C=N or C=C aromatic stretching vibration of imino group .The bands observed in 1330-1305 cm^{-1}, 1050-1060 cm^{-1} and 820-760 cm^{-1} regions may be assigned to {υ(C=S)+υ(C=N)+υ(C-N)}, υ(N-N) and υ(C=S-) stretching respectively .

(2) Antioxidant activity and quantum-chemical parameters of antipyrinethio-semicarbazone derivatives

Investigation of the relation between antioxidant properties and structure of antioxidant seems to be very interesting problem, It could be a key to comprehensive mechanisms of biochemical oxidation of these substances in tissues[8].

Quantum-chemical parameters help to describe the properties of antioxidation in detail. Data of distribution of charge density over the molecule structure would help to determine active atom groups, which are responsible for oxidation of whole molecule. Data of distribution of charge density over the molecule structure have been calculated for investigated compounds Table 2. shows that high charge density (-0.311)-(-0.298) is located near (-N-N-) bond in antipyrine ring in molecule, which gives possibility to oxidation of this group in molecule .

The difference between heats of formation of a molecule and its cation radical ΔH_f could be used as parameter for cation radical stability of the substances .

Oxidation processes for all investigated compounds could be connected with the stability of cation radicals of substances (i.e oxidation of the investigated compounds procced via cation radical formation and reversible process according a mechanism shows in Figure 2.) . Quantum-chemical calculation of ΔH_f has been shown in Table 2. These data show that the high tendency to oxidation of substances corresponding to low value of ΔH_f .

Investigation of the influence of pharmaceuticals on the process oxygen reduction and its kinetics in tissues [9] could be treated as the modeling of antioxidant activity of the sample in vitro , therefore the reduction of the oxygen quantity in solution depende on the antioxidant concentration . Thus coefficient of antioxidant activity (K) has been suggested as[10]:

$$K = \frac{\Delta I_0 / I}{\Delta C}$$

where ΔC is the change of antioxidant concentration, I_0 is the incidence light without antioxidant compounds {N-(benzalidene) amino antipyrinthiosemicarbazone}(A) and {N-(methoxybenzalidene) amino antipyrinethiosemicarbazone} (B) , I is the transmitted light from $NaClO_4$ in ethanol with antioxidant compounds (A) and (B) , the ratio of I_0/I was calculated by the equation [11]:

$$I_0 / I = e^{2.303A}$$

where A is the absorbance value . The scan of U.V. Spectra of all investigated compounds show absorption at 540 nm in visible region which can be identified as a electronic transition ($\Pi \rightarrow \Pi^*$) [12] which was mainly localized on N & N of two azomethine groups and in thio-keto group .

Curve of I_0/I against antioxidant concentration has been plotted Figure 3. for compounds A and B respectively [13] . The result of this curve was shown the ratio I_0/I depend on concentration of antioxidant compounds (A) and (B) . At low concentration of antioxidant compounds high I_0/I ratio at high absorbance then (I) will be decreasing (i.e: most of (I_0) was absorbed in the solution of $NaClO_4$ in ethanol with antioxidant compounds (A) and (B)) , thus most of oxygen was contributed in oxidant process (i.e: if (I) was decreased the oxygen reduction in the solution of antioxidant compounds (A) and (B)) will be decreasing . If the concentration of antioxidant compounds (A) and (B) are

increasing the absorbance will be decreasing , then I_0/I ratio will be decreasing too (i.e: (I) will be increasing , thus the reduction of oxygen will be increasing) , therefore we can expecte that these compounds which were studied in this work have a good antioxidant properties , then antioxidant activity of the investigated compounds has been determined (Table 2.). For this aim, from curve of I_0/I against antioxidant concentration Figure 3. for compounds A and B respectively , the slope of lines gives the coefficient of the antioxidant activity (K) . As it is expected these substances have shown excellent antioxidant activity in comparison with the standard antioxidant (methyl-2,6-di-tert-buthyl- phenal)(K=58.99 ml/g) [6] . Compound (B) with electron with donator property have higher effect (K) than compound (A) with electron with drawing property , These observation are in accord with charge density on carbon atoms which it binds to R substitute (OCH_3 or H) as obtained from molecular orbital calculation and this finding in accord with (ΔH_f) which are calculated by semiemperical molecular orbital calculation / MNDO method as shown in table 2. .

CONCULSIONS

The results of this work allow to determine the relation between quantum-chemical parameters and antioxidant activity of antipyrinethiosemicarbazone derivatives . It was noted on the complicated oxidation mechanism of the substances, the differences between heats of formation of molecule and its cation radical ΔH_f and the antioxidant activity (K) and the high ΔH_f value is the greater (K) value are related at investigated compounds have good antioxidant activity.

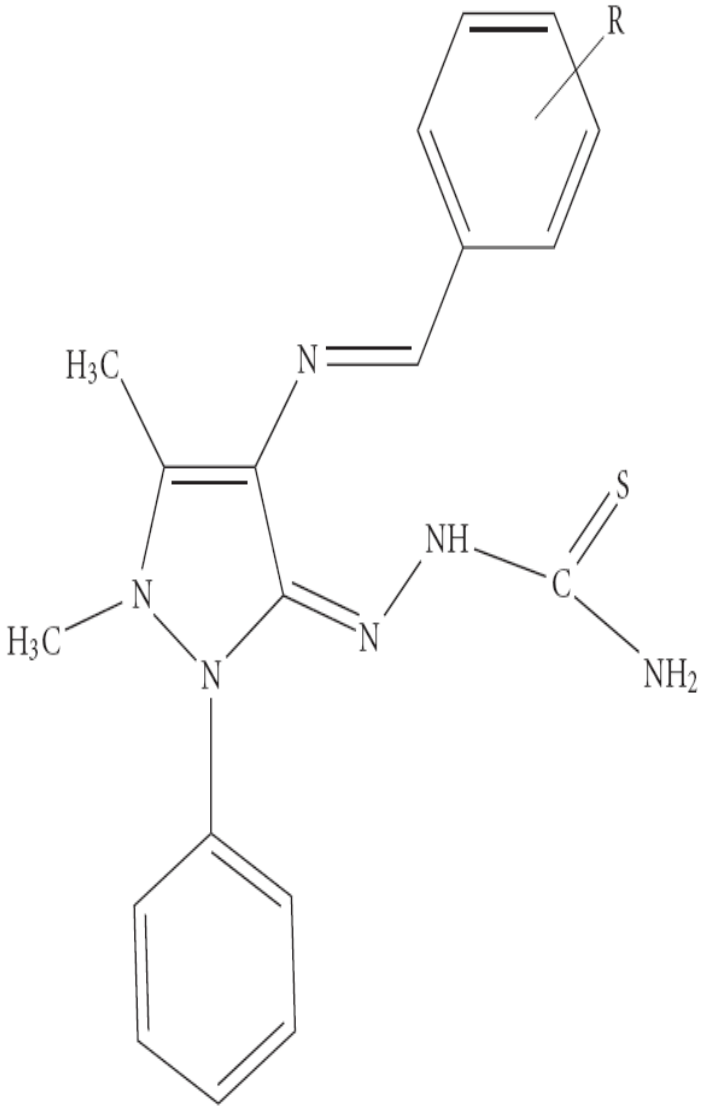

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Figure 1. The structure of {N-(benzalidene) amino antipyrinthiosemicarbazone}(A) at R = H and {N-(methoxybenzalidene) amino antipyrinethiosemicarbazone} (B) at R = OCH_3 compounds

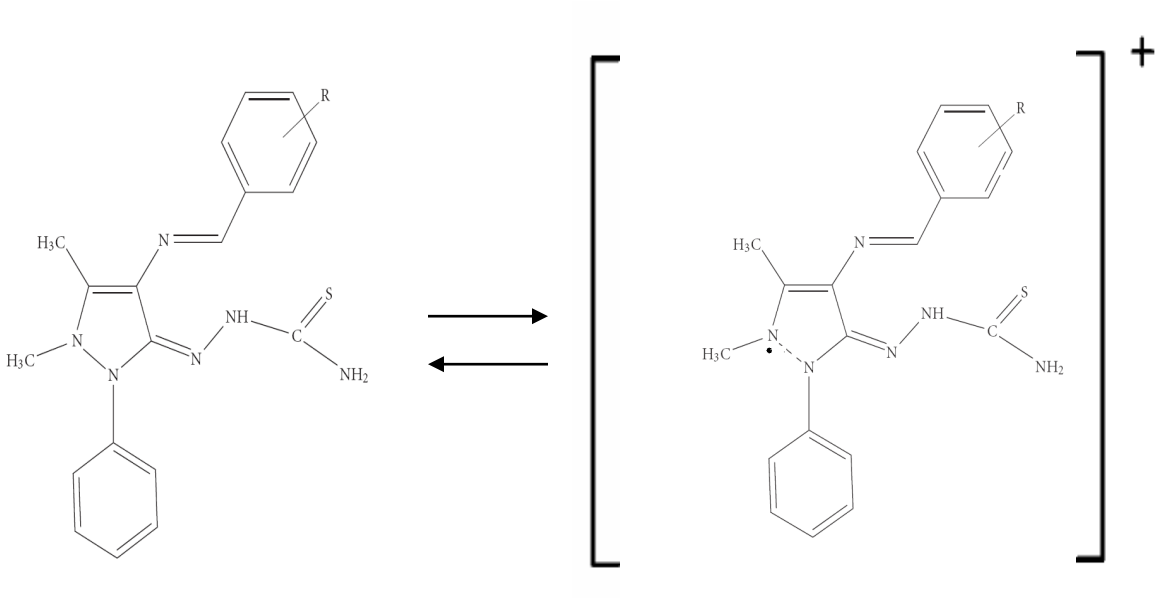

Figure 2 . Mechanism scheme of {N-(benzalidene) amino antipyrinthiosemicarbazone}(A) at R = H and {N-(methoxybenzalidene) amino antipyrinethiosemicarbazone} (B) at R = OCH_3 compounds and their cation radical

Table 1. Experimental and calculated values of CHN analysis and IR spectra data (cm^{-1}) of the investigated compounds

Compounds	Calculated Values			Experimental Values			υ(NH)	υ(C=N)	υ(N-N)	υ(C=S)	υ(C=S)+ υ(C=N)+ υ(C-N)
	C%	H%	N%	C%	H%	N%					
A	62.7	5.2	23.1	60.8	5.9	19.3	3440-3270	1600	1050	820-760	1330-1305
B	75.8	3.3	13.2	72.9	4.2	13.5	3420 - 3310	1600	1060	840-820	1320 - 1195

Table 2. Quantum-chemical parameters ((ΔH_f)and atomic charge density) and antioxidant activity of the investigated compounds (A) and (B) .

Compounds	(ΔH_f) (Kcal/mol)	(K) (ml/g)	Atoms	Charges (elementary charge)
A	160	125	N-N	(-0.311),(-0.298)
			N-C	(0.177),(-0.130)
			C=C	(0.081),(-0.083)
			C-C	(-0.074),(-0.030)
			C=N	(0.247),(-0.237)
			C-H	(-0.169),(0.060)
			C=S	(0.177),(-0.128)
			N-H	(-0.189),(0.160)
B	175	166	N-N	(-0.311),(-0.298)
			N-C	(0.177),(-0.130)
			C=C	(0.081),(-0.083)
			C-C	(-0.074),(-0.030)
			C=N	(0.247),(-0.237)
			C-O	(-0.083),(-0.195)
			C=S	(0.177),(-0.128)
			N-H	(-0.189),(0.160)

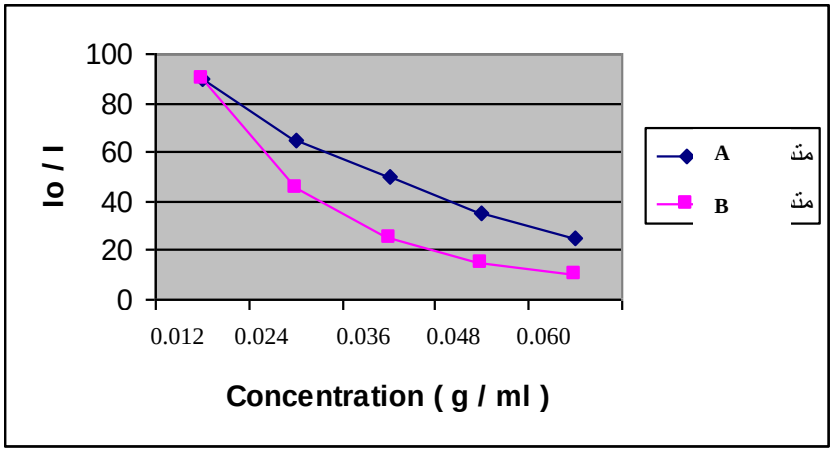

Figure 3. The relative decrease of oxygen against concentration of {N-(benzalidene) amino antipyrinthiosemicarbazone}(A) and {N- (methoxybenzalidene) amino antipyrinethiosemicarbazone} (B) compounds (1 cm cell) .

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