Statistical Study For The prediction Of pKa Values Of Substituted Benzaldoxime Based On Quantum Chemicals Methods

Emad A.S. Al-Hyali[1] , Nezar A. Al-Azzawi[1] , Faiz M.H. Al-Abady[2]

[1] *Chem. Dept., College of Education, Univ. of Mosul , Mosul , Iraq*

[2] *Chem. Dept., College of Science, Univ. of Tikrit , Iraq*

(**Received:** 5 / 12 / 2010 ---- **Accepted:** 16 / 3 / 2011)

Abstract:

Multiple regression analysis was used for the calculation of pKa values of 15 substituted benzaldoximes by using various types of descriptors as parameters. These descriptors are based on quantum mechanical treatments. They were derived by employing semi-empirical calculation represented by the PM3 model and an Ab initio method expressed by Hartree-Fock (HF) model performed at the 6-311 G (d, p) level of theory. The parameters tested for their ability to represent the variations observed in the experimental pKa(s) are atomic and structural properties including Muliken charges on the atoms of hydroxyl group and C=N bond, the angle C_6-C_1-C_7, and length of O-H bond. Molecular properties are also used like energies of HOMO and LUMO orbitals, hardness (η), chemical potential (□), total energy, dipole of molecule, and electrophilicity index (ω). The relationship between pKa values and each of these parameters of the studied compounds is investigated. Depending on these relations, two sets of parameters were constructed for comparison between the PM3 and HF methods. The results obtained favor the Ab initio method for such applications although both models proved to have high predictive power and have sufficient reliability to describe the effect of substituents on pKa values of benzaldoxime compounds under consideration which is clear from the values of multiple correlation coefficient R^2 obtained and the consistency between the experimental and the calculated values

Introduction:

Oximes are well known compounds with a general functional group (-C=N-OH). They are the condensation products of hydroxyl amines with aldehydes (forming aldoxime), ketones (forming ketoxime), or quinone. The aldoxime exists only as a syn isomer, where as benzaldoxime as (aromatic aldoximes) exist in syn and anti isomers. These two geometrical isomers have very different properties. Oximes are very important compounds. They have wide application and were used in various fields. They are used as analytical reagents [(1)]. Cyclohexanone oxime is converted into its isomer ε-caprolactam which represents the raw material for the synthesis of nylon-6[(2)]. The amides obtained by Beckmann rearrangement can be converted into amine by hydrolysis, which could be employed as starting materials for the synthesis of dyes, plastic, fibers and pharmaceuticals. Oximes can be used as peel-preventing additives in paints and lacquers. They act as antioxidants against oxidative drying materials which form sticky skin with air oxygen. Another effect of anti-skinning offers drying time delay which can be used in formulating paints. Oximes are also used as chemical building block for the synthesis of agrochemicals and pharmaceuticals. In medicinal application, oxime structure is found to be effective in cholinesterase reactivators to treat the poisoning by organo-phosphates[(3)]. Oximes are used as ligands in transition metal complex catalyst chemistry. Oxime acts as anti oxidant, radical scavenger which found applications in textile, plastic, paint, detergent, and rubber industry. They have therefore, long been the goal of many researchers in different areas of chemistry. The knowledge of pKa values provides a basis for understanding the chemical reactions between the compound of interest and pharmacological target. Additionally, they play a major role in acid-base titration, complex formation and many other analytical procedures[(4)]. The pKa value of a compound is therefore, a very important chemical phenomenon (among others) that influences many characteristics such as its reactivity and spectral properties. Its importance lies in that such value is affected by the nature and location of substituents present on the compound [(5)]. The pKa values are therefore sensitive to the variation of inductive effect (which may result from formal charges or dipole within a molecule) and steric effect that arise from spatial interaction between adjacent groups within the molecule. Since such effects can be evaluated by quantum chemical methods [(7-11)], certain parameters might serve as useful descriptors for understanding the physical and chemical effects of substituents on the pKa values of the benzaldoxime compounds under consideration. The assessment of pKa values of hypothetical compounds is of prime interest. The knowledge strength of acid which required to protonate a compound is of great importance for the investigation of the kinetic and mechanism of organic reactions[(12-13)]. The protonated fraction is also of special significance in the studies of absorption, distribution and eventual excretion of drugs, depending on the active substance which contains acidic of basic functional groups, which are ionized to varying degrees at physiological pHs. The influence of acidity constant on biological activity has been reviewed by many researcher groups[(14-16)]. In order to find how far experimental finding are reflected in theoretical predictions and what kind of information can be extracted from such investigation, the present work examines the applicability of quantum chemical parameters derived from PM3 and HF methods as descriptors for substituents effects on the pKa values of benzaldoximes. Several sets of parameters will be derived for the theoretical predictive of pKa values by regression analysis.

Methods:

In order to determine the conformation of the lowest energy for each molecule of the fifteen benzaldoxime compounds listed in Table (1), full geometry optimization was carried out at the level of semi-empirical PM3 methods as well as Hartree-Fock (HF) using gradient technique[17-18] and 6-311 G(d,p) basis set. At the semi-empirical PM3 level, geometries of all possible conformers were optimized, while Ab initio [HF/6-311 G(d,p)] optimization was performed only for the most stable conformer found with PM3 method. In all cases, the completion of optimization in order to ensure obtaining geometry with minimum energy was examined. The optimized geometries were used for the evaluation of natural atomic charges and structural parameters such as total energy (TE), dipole moment (DM), Angle (C6-C1-C7), O-H bond length, the highest occupied molecular orbital energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}). The values of E_{HOMO} and E_{LUMO} were used for the calculation of other molecular properties, amely; ardness (η)[19], chemical potential (□)[20], and electrophilicity index (ω) as illustrated in the following equation :

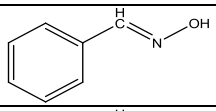
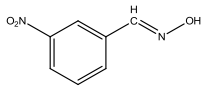
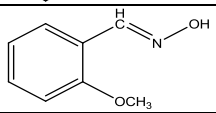
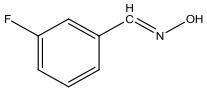
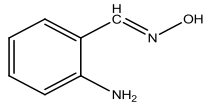
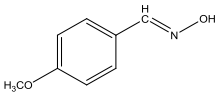
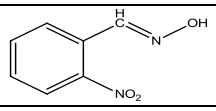
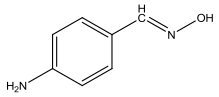
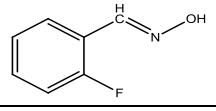
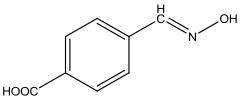
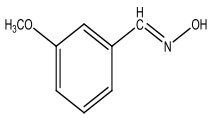
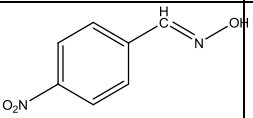
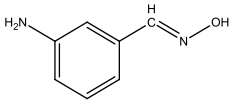
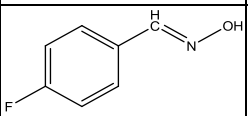
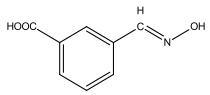
$$□ = (E_{HOMO} + E_{LUMO})/2 \quad \ldots\ldots (1)$$

$$\eta = 1/2\ (E_{HOMO} - E_{LUMO}) \quad \ldots\ldots (2)$$

$$\omega = □^2/2\ \eta \quad \ldots\ldots (3)$$

The Chem Office Program (V.11, 2008 of Cambridge Software, USA) was employed for the performance of conformational analysis and determination of the final equilibrium geometries and the calculations of all the quantum chemical descriptors[21]

Table (1): Structure and experimental pKa values of the substituted benzaldoximes.

Compd.	Symbol	Exp. pKa	Compd.	Symbol	Exp. pKa
	Benzaldoxime (B)	11.195		m-NO_2	10.733
	o-OCH_3	11.858		m-F	10.490
	o-NH_2	11.577		p-OCH_3	11.875
	o-NO_2	11.503		p-NH_2	-
	o-F	10.578		p-COOH	6.866
	m-OCH_3	-		p-NO_2	10.366
	m-NH_2	-		p-F	10.930
	m-COOH	-			

Multiple Linear Regression (MLR)[22] :

MLR analyses were carried out in order to correlate the experimental pKa values to the electronic and structural variables obtained by quantum chemical calculations. The MLR can be expressed by the following equation:

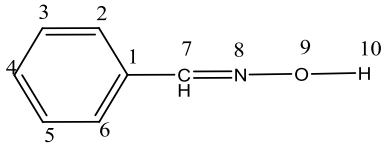
$$pKa = b + \sum a_i x_i \quad \ldots (4)$$

Where b is a constant and represents a reference value, x_i (s) the parameters selected for the regression and a_i (s) the coefficients of the parameters. The MLR calculations were performed by the SPSS package V.12 for windows. The multiple correlation coefficient (R) and standard error (SE) were utilized as an indication of the linearity and stability of the chosen model.

Results and Discussion:

The experimental pKa values of benzaldoxime derivatives considered have been evaluated using a

half integral potentiometric method[23]. These values are correlated with some descriptors derived by the help of quantum chemical calculation which are basically electronic and energy related values and they are thought to be capable of describing the effect of substituents on pKa values successfully. In developing pKa models, it is reasonable to expect that variations in the pKa should be correlated in some way with the electronic charges at the dissociating positions[24]. For the benzaldoximes, we found that atomic charges on the functional group heavy atoms (O of the OH) and the acidic hydrogen in OH can serve as good regression parameters which is consistent with other studies[9-11]. The pKa values of OH group vary with substitution, increasing with electron donating groups and decreasing with electron withdrawing groups. The substitution on the benzene ring affect the charge on the C=N group in addition to the length of O-H bond and determine the type of interactions that OH group undergoes (specially at the ortho position) which in turn affect the energy and geometry of the molecules and pKa value as a result. A variety of parameters were used for the calculation of pKa theoretically[8,25,26]. These parameters are based on quantum chemical methods (non of these studies used these parameters for the calculation of pKa of benzaldoximes) namely PM3 and HF. The Muliken partial atomic charges on the H and O atoms (of the OH group), N and C (of the C=N group) are thought to correlate well to the pKa values of the studied compounds in spite of their shortcoming [26]. The other parameters considered as descriptors for the pKa values and employed in this analysis are the total energy of molecule (TE), dipole of molecule (DM) and angle (C_6-C_1-C_7) (the structure below illustrate the position of the selected angle):



The benzaldoxime structure Additional parameters were also tested such as the energy of HOMO and LUMO orbitals and the values of μ, η and W which are calculated as illustrated in equations (1), (2) and (3) respectively.The values of all the mentioned descriptors calculated by PM3 and HF methods are given in Tables (2) and (3) respectively.

Table (2): Values of descriptors calculated by PM3 method

Compd.	H10 Charge	O9 Charge	N8 Charge	C7 Charge	Angle C6-C1-C7	TE	DM	O-H	E_{HOMO} (ev)	E_{LUMO} (ev)	η	μ	ω
B	0.4156	-0.60162	-0.12728	0.10852	١٢١,١٠	-398.32	-1.159	٠,٩٤٥٢	0.0861	-0.3153	-0.2007	-0.1146	-0.0327
o-OCH3	0.4148	-0.60405	0.09806	0.09807	١١٦,٢٧	-512.13	-1.229	٠,٩٤٥٣	0.0865	-0.3158	-0.2012	-0.1147	-0.0327
o-NH2	0.4111	-0.60305	-0.20689	0.19416	١١٧,٣٨	-453.35	-1.305	٠,٩٤٥٠	0.0964	-0.2813	-0.1889	-0.0925	-0.0226
o-NO2	0.4251	-0.59135	-0.07262	0.10919	١١٨,٠٥	-601.72	-1.167	٠,٩٤٦	0.0514	-0.3523	-0.2019	-0.1505	-0.0561
o-F	0.4206	-0.6014	-0.08013	0.10181	١١٨,٤٨	-497.17	1.9289	٠,٩٤٥٣	0.0797	-0.3252	-0.2025	-0.1228	-0.0372
m-OCH3	0.4206	-0.6014	-0.0801	0.1018	١١٩,٢٩	-497.17	1.3784	٠,٩٤٥٥	0.0817	-0.3107	-0.1962	-0.1145	-0.0334
m-NH2	0.4181	-0.5961	-0.1223	0.10692	١١٩,٤٨	-585.88	-1.154	٠,٩٤٣٨	-0.0001	-0.2972	-0.1486	-0.1487	-0.0744
m-COOH	0.4212	-0.5961	-0.1223	0.1069	١١٩,٤٨	-585.88	0.6424	٠,٩٤٣٨	0.0481	-0.3405	-0.1943	-0.1462	-0.055
m-NO2	0.4212	-0.5930	-0.1254	0.11999	١١٨,٨٩	-601.74	-0.939	٠,٩٤٥٣	0.0325	-0.345	-0.1887	-0.1563	-0.0647
m-F	0.4190	-0.5972	-0.1208	0.1100	١١٩,٢٤	-497.18	-1.126	٠,٩٤٥	0.0738	-0.328	-0.2009	-0.1271	-0.0402
p-OCH3	0.4136	-0.6030	-0.1384	0.1168	١١٩,٦٣	-512.18	-1.110	٠,٩٤٥	0.0927	-0.2992	-0.196	-0.1033	-0.0272
p-NH2	0.4108	-0.6063	-0.1488	0.1191	١١٩,٧٦	-453.35	-1.170	٠,٩٤٤	0.0045	-0.2932	-0.1489	-0.1444	-0.07
p-COOH	0.4202	-0.5967	-0.1134	0.1058	١١٩,٤١	-585.90	0.6322	٠,٩٤٥	-0.0354	-0.3562	-0.1604	-0.1958	-0.1195
p-NO2	0.4237	-0.5926	-0.1067	0.10560	١١٩,٢٤	-601.74	-0.925	٠,٩٤٥	-0.076	-0.377	-0.1505	-0.2265	-0.1704
p-F	0.4176	-0.5992	-0.1271	0.1118	١١٩,١١	-497.18	-1.182	٠,٩٤٥	-0.023	-0.34	-0.1585	-0.1815	-0.1039

Table (3): Values of the descriptors used as parameters calculated by HF method

Compd.	H10 Charge	O9 Charge	N 8 Charge	C 7 Charge	Angle C6-C1-C7	TE	DM	O-H Length (A)	E_{HOMO} (ev)	E_{LUMO} (ev)	η (ev)	μ (ev)	(ev)
B	0.2147	-0.2638	-0.0205	-0.0532	١٢٢,٥٨١	-4.229	-1.159	٠,٩٥٠٧	-0.3422	-0.0043	0.169	-0.1733	-0.0824
o-OCH3	0.2132	-0.2621	-0.0313	-0.0431	١٢٠,٢٩٢	4.6952	-1.229	٠,٩٥٠٩	-0.3261	-0.0048	0.1606	-0.1655	-0.078
o-NH2	0.2211	-0.2831	-0.0661	-0.0029	١٢٩,٨٠٧	0.3202	-1.305	٠,٩٥٠٤	-0.2924	-0.001	0.1457	-0.1467	-0.0724
o-NO2	0.2219	-0.2682	0.0187	-0.1333	١٢٠,١٦٨	4.1084	-1.167	٠,٩٥٢٥	-0.3738	-0.0697	0.1521	-0.2218	-0.0521
o-F	0.1703	-0.2152	0.0717	-0.1404	١١٩,٣٧٥	-0.897	1.9289	٠,٩٥٩١	-0.3433	-0.0149	0.1642	-0.1791	-0.0753
m-OCH3	0.1738	-0.2189	0.0652	-0.1447	١٢٢,٩٥١	2.9215	1.3784	٠,٩٥٧٨	-0.3319	-0.0072	0.1624	-0.1695	-0.0777
m-NH2	0.2130	-0.2610	-0.0336	-0.0445	١٢٣,٩٠٨	-5.340	-1.154	٠,٩٥١١	-0.2972	-0.0001	0.1486	-0.1487	-0.0742
m-COOH	0.2158	-0.2586	-0.0163	-0.0574	١٢٢,٦١٥	-3.232	0.6424	٠,٩٥٠٦	-0.3553	-0.0266	0.1644	-0.191	-0.0707
m-NO2	0.2211	-0.2624	-0.0078	-0.0587	١٢٤,٠٠٤	-5.690	-0.939	٠,٩٥٠٧	-0.372	-0.0716	0.1502	-0.2218	-0.0509
m-F	0.2173	-0.2574	-0.0174	-0.0559	١٢٣,٨٠١	-2.213	-1.126	٠,٩٥١٣	-0.346	-0.0168	0.165	-0.1818	-0.0749
p-OCH3	0.2135	-0.2600	-0.0357	-0.0380	١٢٤,٣٤٩	3.5678	-1.110	٠,٩٥١٠	-0.323	-0.0044	0.159	-0.1641	-0.0777
p-NH2	0.2113	-0.2631	-0.0523	-0.0240	١٢٤,٢٥٩	-5.331	-1.170	٠,٩٥١٣	-0.293	0.0045	0.148	-0.1444	-0.0767
p-COOH	0.2170	-0.2586	-0.0063	-0.0674	١٢٢,٦٨٢	-3.274	0.6322	٠,٩٥٠٩	-0.356	-0.0354	0.160	-0.1958	-0.0657
p-NO2	0.2220	-0.2558	0.0055	-0.0756	١٢٤,٧٤١	-6.131	-0.925	٠,٩٥٢٠	-0.377	-0.0761	0.150	-0.2268	-0.0501
p-F	0.2168	-0.2596	-0.0237	-0.0487	١٢٤,١٥٩	-2.284	-1.182	٠,٩٥١٥	-0.34	-0.023	0.162	-0.1855	-0.0712

As a primary step, correlation among the selected parameters and the pKa values of the benzaldoxime compounds and among the parameters themselves are performed. The statistical results obtained for the performance of these parameters are listed in Table (4). The correlation coefficient assumes a value between (-1) and (+1). If one variable tends to increase the other decrease, the correlation coefficient is negative. Conversely, if the variables tend to increase together the correlation coefficient is positive. The results of Table (4) show weak simple relations among the pKa values and the other parameters. As expected substituents cause changes in the electronic density at the dissociating functional groups in benzaldoximes. Good correlation among the atomic charges of the hydroxyl group (O_9 and H_{10}) and the C=N group (C_7 and N_8) are noticed. The relations among the atomic charges of these groups and the length of O-H bond were also strong. Additionally, satisfactory relations are seen between charges and the dipole of the molecules. Observation of the global electrophilicity index values show that, substitution of benzaldoxime with electron acceptor group increases its electrophilic activity, while, substitution with electron donor group results in electrophilic deactivation. Table (4) and Figure (1) show that, the relation between the pKa values and the global electrophilicity index is negative slope. This is because, strong electrophilic reagent leads to low substrate selectivity in the form of low pKa value. According to this variations we expected to find these parameters effective in the calculation of pKa values statistically. The theoretical estimation of the pKa values of the 15 substituted benzaldoximes considered in this study based on the quantum chemical parameters as descriptors for pKa are carried out statistically by multiple regression analysis method.

Table (4): Correlation coefficients among the parameters evaluated by PM3 method

Parameters	pKa	H10 Charge	O9 Charge	N 8 Charge	C 7 Charge	C6-C1-C7	TE	DM	O-H Length	E_{HOMO} (ev)	E_{LUMO} (ev)	η	μ	ω
pKa	**1.000**													
H10 Charge	**0.014**	١,٠٠٠												
O9 Charge	**0.196**	−٠,٩٣١	١,٠٠٠											
N 8 Charge	**-0.239**	−٠,٧٥٧	٠,٨٧٥	١,٠٠٠										
C 7 Charge	**0.156**	٠,٦٦٠	−٠,٧٦٤	−٠,٩٦٥	١,٠٠٠									
C6-C1-C7	**0.037**	٠,٤٠٣	−٠,٥١٦	−٠,٦١٢	٠,٦٦٢	١,٠٠٠								
TE	**0.175**	−٠,٢٦١	٠,١٣٠	٠,١٩٧	−٠,٣٠١	−٠,٢٧١	١,٠٠٠							
DM	**-0.536**	−٠,٧٩٨	٠,٨٣٢	٠,٧٧٦	−٠,٦٧١	−٠,٤٢٠	٠,٠٨٠	١,٠٠٠						
Length O-H	**-0.021**	−٠,٩٤١	٠,٩٢٦	٠,٨٨٥	−٠,٨٢٣	−٠,٤٤٢	٠,٢٧٤٧	٠,٧٧١	١,٠٠٠					
E_{HOMO}	**0.354**	−٠,١٤٠	−٠,١٥٧	−٠,٤٩٧	٠,٥٠٧	٠,٤٢٤	٠,٠٩٢	−٠,١٩٣	−٠,٠٨٠	١,٠٠٠				
E_{LUMO}	**0.237**	−٠,٣٤٠	٠,٠٨٧	−٠,٣٠٤	٠,٥٣٥	٠,١٥٤	٠,١٩٧	٠,٠٣٤	٠,٠٦٥	٠,٨٥٧	١,٠٠٠			
η	**-0.130**	−٠,٣٦٩	٠,٤٥٧	٠,٣٧١	−٠,٢٩٩	−٠,٥١١	٠,١٩٣	٠,٤٢٦	٠,٢٧٠	−٠,٢٩١	٠,٢٤٣	١,٠٠٠		
μ	**0.301**	−٠,٢٤٨	−٠,٠٣٧	−٠,٤١٦	٠,٤٧٧	٠,٣٠١	٠,١٤٩	−٠,٠٨٣	−٠,٠٠٨	٠,٩٦٤	٠,٩٦٣	−٠,٠٢٧	١,٠٠٠	
ω	**-0.205**	٠,٤١٠	−٠,٢٠٧	٠,١٦٧	−٠,٢٩٩	٠,٠١٣	−٠,٢٢٩	−٠,١٢٧	−٠,١٣٦	−٠,٦٨٧	−٠,٩٦٢	−٠,٤٩٢	−٠,٨٥٤	١,٠٠٠

Depending on this statistical method, two predictive models have been build up for comparison between the Ab initio [HF/6-311 G(d,p)] and semi empirical (PM3) methods, with the help of the variables used as descriptors and presented in Tables (2 and 3). The first MLR model generated by variables based on the PM3 method. The results and the multiple regressions are given in Table (5)

Table (5): Summary of the regression analysis results between pKa values and descriptors calculated by PM3 method

Parametar	a	b	R	S.E
C7 N8	−٢٣,٥٩ −٣٤,٩٠١	٨,٨٢٥	٠,٣٢٥	١,٤٦٨
O9 H10	−٨٢,١٧٣ −٨٠,٣٥٢	٦,٦٢٦	٠,٤٢٠	١,٤٠٩
Angl TE	٠,١٩٥ ٠,١٠٦	−٢,١٣٧	٠,٥٢٨	١,٣١٨
Len O-H H10	−٣١,٢٩٤ −٣,٥٠٣	٤١,٢٦٢	٠,٠٢٦	١,٥٥٢
DM O9	-١,٦٥٨ ٧٠,١٩٢	٢٧,٧٤٣	٠,٧٠٢	١,١٠٥
DM O9 TE	-١,٥٨٤ ٧١,٠٨٠ 0.١٥١	٢٨,١٨٩	٠,٨١٥	٠,٩٦١
DM O9 Len O-H	-٢,٠٠٦ -٧,٩٥٤ ٧٠٩,٠٩٢	-٦٦٧,٧٠٨	٠,٨٨٥	٠,٧٧٣
DM O9 Len O-H H10	-٢,٢٤٧ -٣٦,٧٨٥ ٣٥٥,٣٦١ -١٠٩,٩٨٤	-٣١٥,١٢٨	٠,٩٧٠	٠,٤٣٤
DM O9 ω H10	-٢,٤٩٩ -٤٧,٠٤١ ٤٧,٠٠٦ -٢٠٣,٧٤٩	٤٣,٥٤٥	٠,٩٩١	٠,٢٤٥

DM O9 ω H10 N8	-٢,٤٩٨ -٤٥,٩٦٢ ٤٨,١٢٩ -٢٠٤,٣٢١ −0.٨٠٤	٤٤,٠١٥	٠,٩٩١	٠,٢٦٨
DM O9 N8 H10 Angl η	-٢,٤٤٣ -٢٠,٧٥٠ ٥,٩٩٣ -١٥٩,٠٦٤ −0.٠٤٦ -٦٢,٠٤٢	٥٣,٢٢٦	٠,٩٩٤	٠,٢٤٩

Looking at the results of Table (5), the relation between pKa and the charges on O_9, N_8, length of O-H bond, and DM are of negative correlation coefficient, which means that, the increase of the values of these descriptors increases the value of pKa and decrease the ionization efficiency of the molecules. The values of the coefficients of O_9, N_8 and length of O-H bond indicate great influence of such descriptors on pKa values, which suppose that, the withdrawing substituents increase the ionization efficiency of the molecules. The charge on the atoms C_7, H_{10}, angle and TE have opposite effect on the pKa values. The simple correlation coefficients obtained from correlating the pKa values and each of these descriptors found separately are weak but was found to increase significantly in the multiple regression analysis. The results of the regression analysis of pKa values build up with the help of the parameters calculated by the PM3 method are summarized in Table (5). In this model we have generated various equations by employing the entire variables shown in Table (2). The best fitted equations of this class are the following two in which 4 and 6 variables are used respectively.

pKa = 43.545 - 2.499 DM – 47.041 Charge of O_9 + 47.006 ω – 203.749 charge of H_{10} ….. (5)

pKa = 53.226 - 2.443 DM – 20.750 charge of O_9 + 5.993 charge of N_8 –159.064 charge of H_{10} – 0.046 Angle – 62.042 η …(6)

Preference is given to equation (5) in which less number of parameters is used to describe the substituents effect on pKa with negligible differences to that of 6 parameters. This model (eq.5) includes the partial Muliken charges on the atoms of OH group, DM and W. these values are electronic and molecular properties and have been tested as pKa descriptors for other types of compounds in previous studies[26-28]. Comparison between the calculated pKa values according to equation 5 and 6 and the experimental values of the considered benzaldoximes are reported in Table (6). On the basis of the statistical quality of result, it is clear that, one can use this equation to predict the pKa values of hypothetical compounds of similar type as was done for the compounds m-OCH_3, m-NH_2, m-COOH and P-NH_2 which were not included in the regression analysis. A linear relation is obtained (with R> 0.97) from the plot of the experimental pKa versus the calculated values indicating to high prediction power and reliable method for such applications.

Table (6): Comparison between the observed and calculated pKa values evaluated by the PM3 method

Compd.	Obs.pKa	Calc. pKa (Eq.5)	*Res	Calc.pKa (Eq.6)	*Res
B	11.195	11.088	-0.017	11.234	-0.039
o-OCH3	11.858	12.020	-0.162	11.842	0.016
o-NH2	11.577	11.662	-0.٠٨٥	11.675	-0.098
o-NO2	11.503	11.451	0.٠٥٢	11.417	0.086
o-F	10.578	10.594	-0.٠١٦	10.611	-0.033
m-OCH3	.	11.369	.	11.332	.
m-NH2	.	12.414	.	11.819	.
m-COOH	.	6.713	.	6.811	.
m-NO2	10.733	10.677	0.٠٥٦	10.796	-0.063
m-F	10.490	10.673	-0.١٨٣	10.676	-0.186
p-OCH3	11.875	11.482	0.٣٩٣	11.398	0.477
p-NH2	.	12.620	.	12.187	.
p-COOH	6.866	6.849	0.017	6.828	0.038

p-NO2	10.366	10.379	-0.٠١٣	10.306	0.060
p-F	10.930	11.032	-0.١٠٢	11.194	-0.264

*Res = Calc. pKa – Obs. pKa

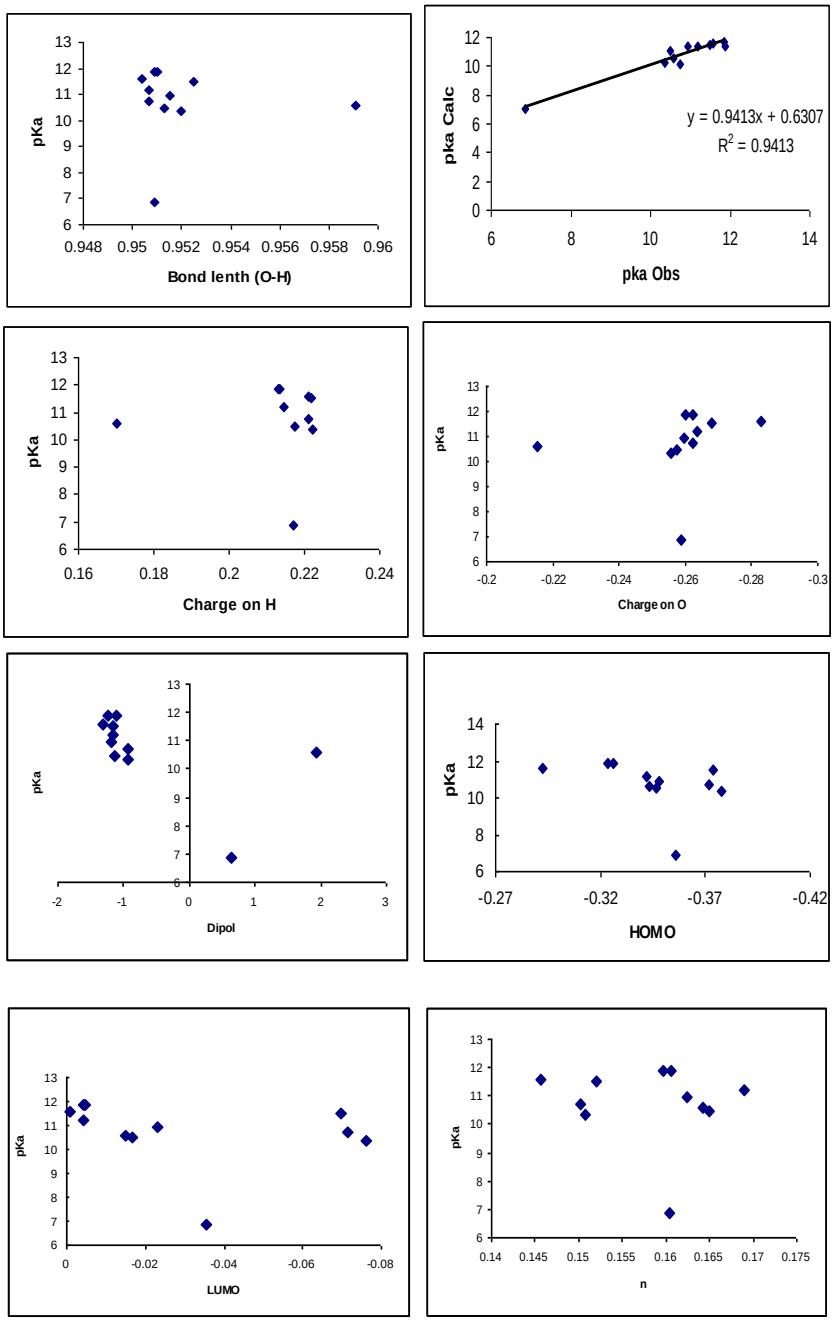


Figure (1): Relations among pKa values and selected descriptors calculated by PM3 method

The second MLR model has been formed with the help of the descriptors derived by HF [6-311 G(d_1p)] method. In this model, various equations have been generated (Table (7)). The best fitted equations are the following two:

pKa = -1665.177-195.988 Charge of O_9-2.435 DM + 1632.195 Length of O-H – 0.007 TE… (7)

pKa = -1660.158 – 2.436 DM – 0.007 TE + 1637.221 Length of OH – 196.374 Charge of O_9 – 0.059 W (8)

Preference is given to equation (7) for the same reason used previously to compare equations (5) and (6). The predicted pKa values from equation (7) and (8) are given in Table (8). On the basis of this model, we can also justify the validity of the selected descriptors for such applications. A linear relationship (Figure 2) is obtained from the plot of the experimental pKa against the calculated values with high correlation coefficient (R > 0.99). A final conclusion can be driven in which, the comparison between the Ab initio [HF/6-311 G(d,p)] and the semi empirical (PM3) indicates reasonable correspondence between the two methods. Both of them gave high correlation coefficients and acceptable deviation.

Table (7): Results of the regression analysis between the pKa values and parameters estimated by HF method

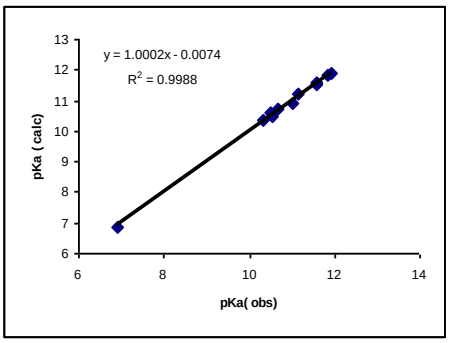
Parameter	a	b	R	S.E
C7 N8	٢٥,٦٠٧ ٨,٠٥٧	٨,٥٦٢	٠,٤١٦	١,٤١٢
O9 H10	-٢,٩٩٤ -١١١,٤٧٤	٥٥,٥٧٥	٠,٣٥٦	١,٤٥١
Angl TE	0.٠٠٩ -0.٤١٤	٦٤,٦٤٣	٠,٥٢٤	١,٢٣٢
Len O-H H10	-٢١٢,٩١٩ ٢٨٢٠,٠١٥	- ٢٥٦٥,٦٤١	٠,٦٣٨	١,١٩٦
H10 Len O-H O9	-٢٤٥,٩٧٦ ٢٨٤٩,٣٧١ ٣٣,٩٧٨	- ٢٥٥٩,٢٢٢	٠,٦٤٠	١,١٢٧
C7 O9 DM	-٣,٦٥٦ -٧٥,٢٩٦ -٢,٣٣٥	-٣٥,٨٩٨	٠,٩٢٤	٠,٦٣٦
O9 DM H10	-١٥٨,١٨٨ -٢,٤٣٠ ١٠٧,٠٦٧	-١٣٠,٨١١	٠,٩٣٣	٠,٥٩٨
O9 DM Len O-H	-١١٦,٧١٣ -٢,١٧٤ ١٧٠٣,٦٤٧	- ١٦٧١,٢٤٥	٠,٩٨١	٠,٣٤٥
O9 DM N8 H10	-٧٣,٣٦٨ -٢,٤١٩ ٤,٥٥٣ ١٦,٢٠٨	-٤١,٥٥٩	٠,٩٥٥	٠,٥٣٠
O9 DM Len O-H W	-١٣٤,٢٧٠ -٢,٢١٣ ١٨٨١,١٧٦ -٢,١٣٥	- ١٨٤٩,٧٢٣	٠,٩٨٢	٠,٣٤٣
O9 DM Len O-H TE	-١٩٥,٩٨٨ -٢,٤٣٥ ١٦٣٢,١٩٥ -0.٠٠٧	- ١٦٥٥,١٧٧	٠,٩٩٩	٠,٠٧٦
N8 O9 H10 DM Ang	١,٨٨٧ -١٠٧,٦٧٩ ٦٣,٦١٤ -٢,٤٢٩	-٥٥,٠٥٠	٠,٩٤٠	٠,٤٨٢

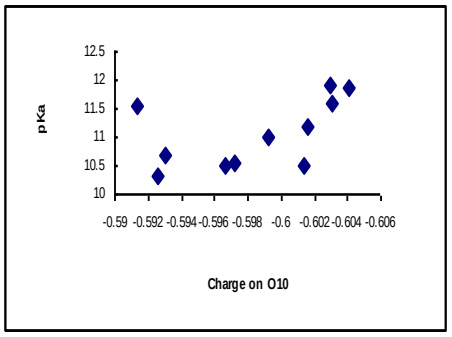
	-0.٢٢٩			
DM TE Len O-H O W	-٢,٤٣٦ −0.٠٠٧ ١٦٣٧,٢٢١ -١٩٦,٣٧٤ −0.٠٥٩	- ١٦٦٠,١٥٨	٠,٩٩٩	٠,٠٨٣٧

Table (8): Comparison between the observed and calculated pKa values estimated by the HF method

Compd.	Obs. pKa	Calc. pKa (Eq.8)	*Res	Calc.pKa (Eq.7)	*Res
B	11.195	11.167	-0.027	١١,٠٩٧	−٠,٠٩٨
o-OCH3	11.858	11.841	-0.016	١١,٦٦٩	−٠,١٨٩
o-NH2	11.577	11.599	0.022	١١,٤١٩	-٠,١٥٨
o-NO2	11.503	11.563	0.060	١١,٤٠٠	-٠,١٠٣
o-F	10.578	10.509	-0.068	١٠,٣٧٧	-٠,٢٠١
m-OCH3	.	12.332	.	١٢,٢٥٥	.
m-NH2	.	9.225	.	٩,٠٢٩	.
m-COOH	.	4.885	.	٤,٦٥٤	.
m-NO2	10.733	10.675	-0.057	١٠,٥١٧	-٠,٢١٦
m-F	10.490	10.527	0.037	١٠,٣٦٧	-٠,١٢٣
p-OCH3	11.875	11.924	0.049	١١,٨٥٣	-٠,٠٢٢
p-NH2	.	10.514	.	١٠,٣٩٧	.
p-COOH	6.866	6.903	0.037	٦,٧٥١	-٠,١١٥
p-NO2	10.366	10.327	-0.038	١٠,١٦١	-٠,٢٠٥
p-F	10.930	10.995	0.065	١٠,٨٥٤	-0.076

*Res = Calc. pKa – Obs. pKa





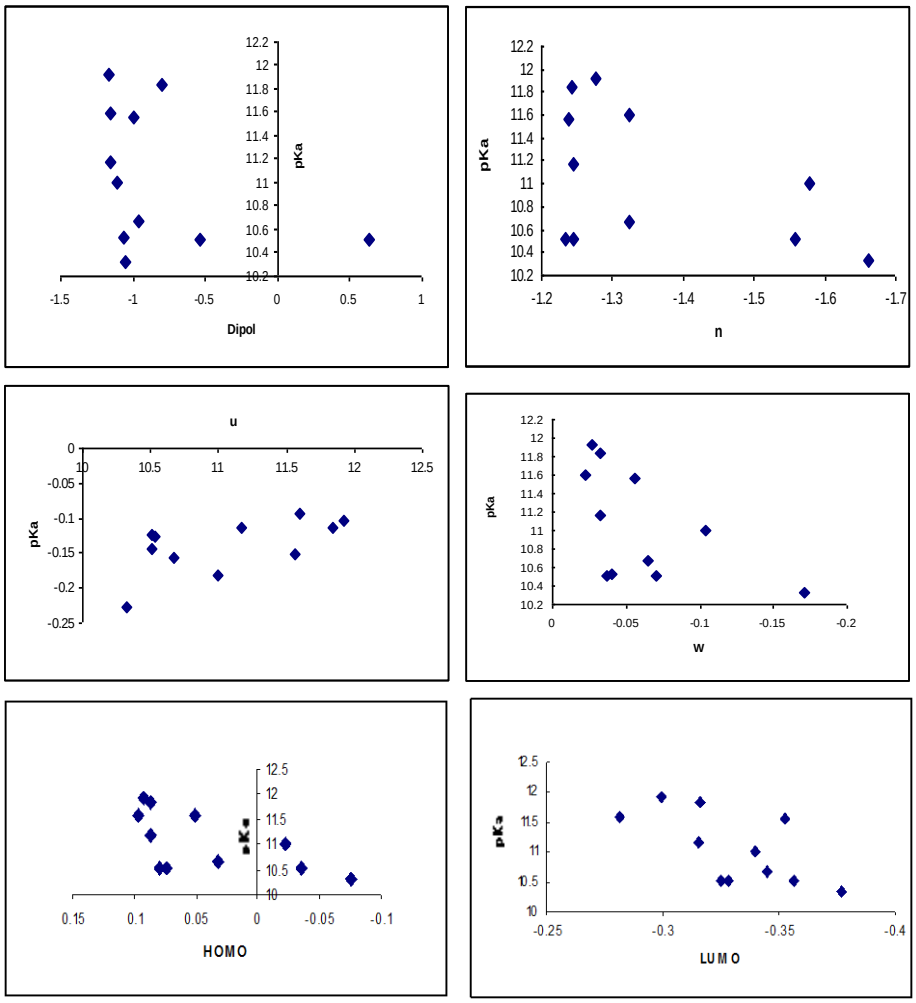


Figure (2): Relations among pKa values and selected descriptors calculated by HF method

References

1. Z. Hdzbecher, L. Divis, M. Kral, L. Sucha, and F. Vlacil. "Hand book of organic reagents in inorganic analysis". Jhon Wiley and Sons. In. 1976, 691.
2. L.C. Jhaveri and H.B. Nalk, J. Indian Chem. Soc., V.2, No.2, 1978, 183.
3. D. Vavaprasad and Mahaderau, J. Poly. Sci. Part A. Polymer Chemistry, 24, 1986, 3279-3290.
4. Y. H. Ebead, H.M. Salman and M.A. Abdellah, Bull. Korean Chem. Soc., V.31, No.4, 2010, 850-858.
5. T.H. Lowry and K.S. Richardson. "Mechanism and Theory in Organic Chemistry, 3rd. ed. Harper Collins ; New York, 1987.
6. S.H. Pine, J.B. Hendrickson, D.J. Carm and G.S. Hammond, "Organic chemistry", 4th. Ed., McGraw-Hill, London, 1981, 196-236.
7. A. Strietwieser, and Jr. C.H. Heathcock. "Introduction to Organic Chemistry", 2nd. Ed., Macmillan Publishing Co., New York, 1981, 60-65.
8. K.C. Kross, P.G. Seybold, Z. Peralta-Inga and P. Politzer, J. Org. Chem., 66, 2001, 6919-6925.
9. K.C. Kross and P.G. Seybold, Int. J. Quantum Chem., 80, 2000, 1107-1115.
10. K.C. Gross, P.G. Seybold, and C.M. Hadad, Int. J. Quantum Chem., 90, 2002, 445-458.
11. K.G. Gross and P.G. Seybold, Int. J. Quantum Chem. 85, 2001, 569-579.
12. C.H. Rochester, "Acidity function", Academic Press, London, 1970.
13. M. Liler, "Reaction mechanisms in aulfuric acid and other strong acid media". Academic Press. London, 1970.
14. A. Albert, "Selective toxicity", Methuen, London, 1968.
15. D. Bieger and O. Wassermann, J. Pharm. Pharmacol., 19, 1967, 844.
16. A. Albert. "Selective toxicity". 6th ed., Chapman and Hall, London, Methuen, New York, 1979.
17. H.B. Ed. Schlegel. "Molar electronic structure, theory, geometry optimization on potential energy surface, World Scientific". Singapore, 1994.
18. J. Baker, J. Comput. Chem., l7, 1986, 385.
19. R.G. Parr and R.G. Pearson, J. Am. Chem. Soc., 105, 1983, 7512.
20. R.P. Iczkowski, and J.L. Margrave, J. Am. Chem. Soc., 83, 1961, 3547.

21. R.G. Parr, L.V. Szentpaly and S. Lin. J. Am. Chem. Soc., 121, 1999, 1922.
22. J. Shorter. "Correlation analysis of organic chemistry". Research studies Press, New York, 1982.
23. Nezar A. Al-Azzawi. "The role of hydrogen bonding and other parameters on ionization constants of benzaldoximes". Ph. D. Thesis, Mosul, Iraq. 1998.
24. J.M. Park, K.T. No, M.S. Jhon and H.A. Scheraga, J. Compud. Chem., 14, 1993, 1482-1490.
25. Amar A. Ibrahim and Eid A. Abdalrazaq, Am. J. of Appli. Sci., k6(7), 2009, 1385-1389.
26. Chad A. Hollingsworth, P.G. Seybold, C.M. Hadad, In. J. of Quantum Chem., 90, 2002, 1396-1403.
27. P.P. Singh, H.K. Srivastava and F.A. Pasha, Bio. Org. Med. Chem., 12 (1), 2004, 171.
28. F.A. Pasha, H.K. Srivastava and P.P. Singh Int. J. Quantum Chem. 104(1), 2005, 87.

دراسة إحصائية للتنبؤ عن قيم pKa لمعوضات البنزالدوكزيمات بالاستناد على متغيرات مشتقة من طرق ميكانيك الكم

عماد عبدالاله صالح الحيالي[١] ، [١]نزار عبد الله العزاوي[١] ، فائز محسن ألعبادي[٢]

[١] *قسم الكيمياء ، كلية التربية ، جامعة الموصل ، الموصل ، العراق*

[٢] *قسم الكيمياء ، كلية العلوم ، جامعة تكريت ، تكريت ، العراق*

(تاريخ الاستلام: ٥ / ١٢ / ٢٠١٠ ---- **تاريخ القبول:** ١٦ / ٣ / ٢٠١١ **)**

الملخص

تضمن هذا البحث استخدام التحليل الانحداري متعدد المتغيرات لحساب قيم ثابت تفكك الحامض pKa لخمسة عشر معوضا من مركبات البنزالدوكزيمات وباستعمال متغيرات وصفية متنوعة. هذه المتغيرات تستند على استخدام معالجات طرق ميكانيك الكم، وهي مشتقة من الحسابات شبه التجريبية Semi-empirical ممثلة بطريقة PM3 فضلا عن طرق الحسابات الأساسية Ab-initio والتي عبر عنها بطريقة هارتري فوك Hartree Fock (HF) المنجزة عند مستوى نظري 6-311G (d,p) .ان المتغيرات التي تم اختيارها لاختبار مدى إمكانية تمثيلها للتباين الملاحظ في قيم pKa التجريبية هي متغيرات تمثل صفات ذرية وتركيبية. هذه المتغيرات هي شحنات موليكن على ذرات مجموعتي الهيدروكسيل والازوميثان (C=N) وقيمة الزاوية (C_1-C_6-C_7) وطول الآصرة O-H. كذلك تم استخدام صفات جزيئية مثل طاقات الاوربيتالات HOMO و LUMO وصلابة الجزيئة (η) والجهد الكيميائي (μ) والطاقة الكلية (TE) والعزم الجزيئي ثنائي القطب (DM) ودليل الالكتروفيلية (ω). وقد تم دراسة العلاقة بين قيم pKa وكل من هذه المتغيرات للمركبات قيد الدراسة. وبالاعتماد على هذه العلاقات تم بناء مجموعتين من المتغيرات والتي تم استخدامها للتنبؤ عن قيم pKa نظريا في محاولة لإجراء مقارنة بين طريقتي PM3 و HF في إمكانية انجاز هذه الدراسة. وقد أشارت النتائج التي تم الحصول عليها إلى أفضلية طريقة الحسابات الأساسية في هذا النوع من التطبيقات بالرغم من قدرة كلا الطريقتين على انجاز هذا النوع من الحسابات وبدرجة كافية من الكفاءة في وصف تأثير المعوضات على قيم pKa للمركبات المأخوذة بنظر الاعتبار، هذه النتيجة تم الإشارة إليها بوضوح بوساطة قيم معاملات الارتباط العالية (R^2) والتطابق المحصل عليه بين القيم العملية لـ pKa وتلك المحسوبة نظريا.