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## Statistical study for the prediction of pKa values of substituted benzaldoximes based on quantum chemical methods

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### 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 Mulliken charges on the atoms of hydroxyl group and C=N bond, the angle C<sub>6</sub>-C<sub>1</sub>-C<sub>7</sub>, and length of O-H bond. Molecular properties are also used like energies of HOMO and LUMO orbitals, hardness ( $\eta$ ), chemical potential ( $\mu$ ), total energy, dipole of molecule, and electrophilicity index (W). The relation 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 correlation coefficient R<sup>2</sup> obtained and the consistency between the experimental and the calculated values. © 2011 Trade Science Inc. - INDIA

### 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 quonone. 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 were used as analytical reagents<sup>[1]</sup>. Cyclohexanone oxime is converted into its isomer epsilon-caprolactam

which represents the raw material for the synthesis of nylon-6<sup>[2]</sup>. The amides obtained by Beckmann rearrangement can be converted into amine by hydrolysis, which could be employed as starting materials for the manufacture 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 medicine application, oxime structure is found to be effective in cholinesterase reactivators to treat the poisoning by organo-phosphates<sup>[3]</sup>.

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<sup>[4]</sup>. 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<sup>[5]</sup>. 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<sup>[8-11]</sup>, certain parameters might serve as useful descriptors for understanding

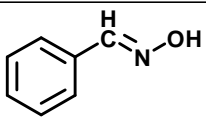
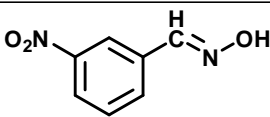
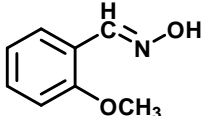
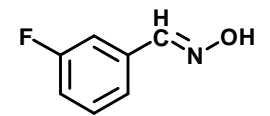
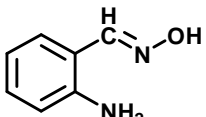
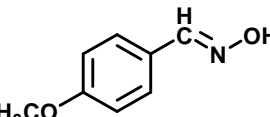
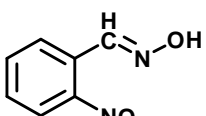
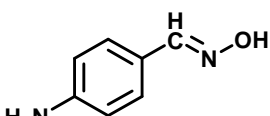
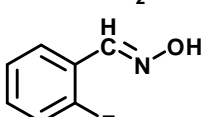
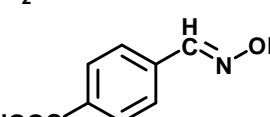
the physical and chemical effects of substituents on the pKa values of the benzaldoxime compounds under consideration.

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 were derived for the theoretical predictive of pKa values by regression analysis.

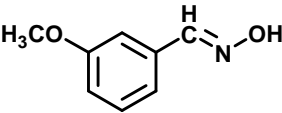
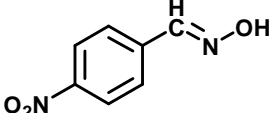
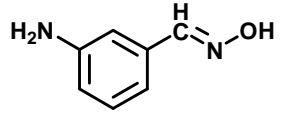
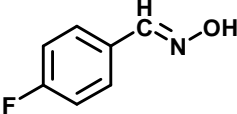
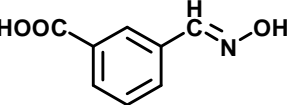
## METHODS

In order to determine the conformation of the lowest energy for each molecule of the fifteen benzaldoxime compounds listed in TABLE 1, full geometrical optimization was carried out at the level of semi-empirical PM3 methods as well as Hartree-Fock (HF) using gradient technique<sup>[13,14]</sup> 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.

TABLE 1 : Structure and experimental pKa values of the benzaldoximes considered for this study

Compd.	Name	Exp. pKa	Compd.	Name	Exp. pKa
	Benzaldoxime (B)	11.195		m-NO <sub>2</sub>	10.733
	o-OCH <sub>3</sub>	11.858		m-F	10.490
	o-NH <sub>2</sub>	11.577		p-OCH <sub>3</sub>	11.875
	o-NO <sub>2</sub>	11.503		p-NH <sub>2</sub>	-
	o-F	10.578		p-COOH	6.866

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Compd.	Name	Exp. pKa	Compd.	Name	Exp. pKa
	m-OCH <sub>3</sub>	-		p-NO <sub>2</sub>	10.366
	m-NH <sub>2</sub>	-		p-F	10.930
	m-COOH	-			

The optimized geometries were used for evaluation of natural atomic charges and structural parameters such as total energy (TE), dipole moment (DM), Angles, O-H bond length, the highest occupied molecular orbital energy ( $E_{\text{HOMO}}$ ), the lowest unoccupied molecular orbital energy ( $E_{\text{LUMO}}$ ). The values of  $E_{\text{HOMO}}$  and  $E_{\text{LUMO}}$  were used for the calculation of other molecular properties, namely; hardness ( $\eta$ )<sup>[15]</sup>, chemical potential ( $\mu$ )<sup>[16]</sup>, and electrophilicity index ( $W$ ) as illustrated in the following equation:

$$\mu = (E_{\text{HOMO}} + E_{\text{LUMO}})/2 \quad (1)$$

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

$$W = \mu^2/2 \eta \quad (3)$$

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

### Multiple linear regression (MLR)<sup>[18]</sup>

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:

$$\text{pKa} = b + \sum a_i x_i \quad (4)$$

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 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 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<sup>[19,20]</sup>. 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<sup>[21-23]</sup>.

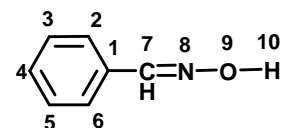
In this paper the experimental pKa values of benzaldoxime derivatives considered have been evaluated using a half integral potentiometric method<sup>[12]</sup>. These values are correlated with some descriptors derived by the help of quantum chemical calculation which are basically electronic and energy related values and they are thought to be capable of describing the effect of substituents on pKa values successfully. The parameters used as descriptors for pKa variation in this work are derived by two methods namely, PM3 (as a semi empirical model) and HF carried out at base set [6-311 G(d,p)] as an Ab initio model.

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<sup>[24]</sup>. 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<sup>[9-11]</sup>. 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<sup>[18,25,26]</sup>. 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<sup>[26]</sup>. The other pa-

rameters 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<sub>6</sub>-C<sub>1</sub>-C<sub>7</sub>) (see the structure below):



The benzaldoxime structure

Additional parameters were also tested such as the energy of HOMO and LUMO orbitals and the values of  $\mu$ ,  $\eta$  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	N 8 Charge	C7 Charge	Angle C6-C1-C7	TE	DM	O-H Length (Å)	E <sub>HOMO</sub> (ev)	E <sub>LUMO</sub> (ev)	$\eta$ (ev)	$\mu$ (ev)	W (ev)
B	0.2147	-0.2638	-0.0205	-0.0532	122.581	-4.229	-1.159	0.9507	-0.3422	-0.0043	0.169	-0.1733	-0.0824
o-OCH3	0.2132	-0.2621	-0.0313	-0.0431	120.292	4.6952	-1.229	0.9509	-0.3261	-0.0048	0.1606	-0.1655	-0.078
o-NH2	0.2211	-0.2831	-0.0661	-0.0029	129.807	0.3202	-1.305	0.9504	-0.2924	-0.001	0.1457	-0.1467	-0.0724
o-NO2	0.2219	-0.2682	0.0187	-0.1333	120.168	4.1084	-1.167	0.9525	-0.3738	-0.0697	0.1521	-0.2218	-0.0521
o-F	0.1703	-0.2152	0.0717	-0.1404	119.375	-0.897	1.9289	0.9591	-0.3433	-0.0149	0.1642	-0.1791	-0.0753
m-OCH3	0.1738	-0.2189	0.0652	-0.1447	122.951	2.9215	1.3784	0.9578	-0.3319	-0.0072	0.1624	-0.1695	-0.0777
m-NH2	0.2130	-0.2610	-0.0336	-0.0445	123.908	-5.340	-1.154	0.9511	-0.2972	-0.0001	0.1486	-0.1487	-0.0742
m-COOH	0.2158	-0.2586	-0.0163	-0.0574	122.615	-3.232	0.6424	0.9506	-0.3553	-0.0266	0.1644	-0.191	-0.0707
m-NO2	0.2211	-0.2624	-0.0078	-0.0587	124.004	-5.690	-0.939	0.9507	-0.372	-0.0716	0.1502	-0.2218	-0.0509
m-F	0.2173	-0.2574	-0.0174	-0.0559	123.801	-2.213	-1.126	0.9513	-0.346	-0.0168	0.165	-0.1818	-0.0749
p-OCH3	0.2135	-0.2600	-0.0357	-0.0380	124.349	3.5678	-1.110	0.9510	-0.323	-0.0044	0.159	-0.1641	-0.0777
p-NH2	0.2113	-0.2631	-0.0523	-0.0240	124.259	-5.331	-1.170	0.9513	-0.293	0.0045	0.148	-0.1444	-0.0767
p-COOH	0.2170	-0.2586	-0.0063	-0.0674	122.682	-3.274	0.6322	0.9509	-0.356	-0.0354	0.160	-0.1958	-0.0657
p-NO2	0.2220	-0.2558	0.0055	-0.0756	124.741	-6.131	-0.925	0.9520	-0.377	-0.0761	0.150	-0.2268	-0.0501
p-F	0.2168	-0.2596	-0.0237	-0.0487	124.159	-2.284	-1.182	0.9515	-0.34	-0.023	0.162	-0.1855	-0.0712

TABLE 3 : Values of the descriptors used as parameters calculated by HF method

Compd.	H10 Charge	O9 Charge	N8 Charge	C7 Charge	Angle C6-C1-C7	TE	DM	O-H	E <sub>HOMO</sub> (ev)	E <sub>LUMO</sub> (ev)	$\eta$	$\mu$	W
B	0.4156	-0.60162	-0.12728	0.10852	121.10	-398.32	-1.159	0.9452	0.0861	-0.3153	-0.2007	-0.1146	-0.0327
o-OCH3	0.4148	-0.60405	0.09806	0.09807	116.27	-512.13	-1.229	0.9453	0.0865	-0.3158	-0.2012	-0.1147	-0.0327
o-NH2	0.4111	-0.60305	-0.20689	0.19416	117.38	-453.35	-1.305	0.9450	0.0964	-0.2813	-0.1889	-0.0925	-0.0226
o-NO2	0.4251	-0.59135	-0.07262	0.10919	118.05	-601.72	-1.167	0.946	0.0514	-0.3523	-0.2019	-0.1505	-0.0561
o-F	0.4206	-0.6014	-0.08013	0.10181	118.48	-497.17	1.9289	0.9453	0.0797	-0.3252	-0.2025	-0.1228	-0.0372
m-OCH3	0.4206	-0.6014	-0.0801	0.1018	119.29	-497.17	1.3784	0.9455	0.0817	-0.3107	-0.1962	-0.1145	-0.0334

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Compd.	H10 Charge	O9 Charge	N8 Charge	C7 Charge	Angle C6-C1-C7	TE	DM	O-H	E <sub>HOMO</sub> (ev)	E <sub>LUMO</sub> (ev)	η	μ	W
m-NH2	0.4181	-0.5961	-0.1223	0.10692	119.48	-585.88	-1.154	0.9438	-0.0001	-0.2972	-0.1486	-0.1487	-0.0744
m-COOH	0.4212	-0.5961	-0.1223	0.1069	119.48	-585.88	0.6424	0.9438	0.0481	-0.3405	-0.1943	-0.1462	-0.055
m-NO2	0.4212	-0.5930	-0.1254	0.11999	118.89	-601.74	-0.939	0.9453	0.0325	-0.345	-0.1887	-0.1563	-0.0647
m-F	0.4190	-0.5972	-0.1208	0.1100	119.24	-497.18	-1.126	0.945	0.0738	-0.328	-0.2009	-0.1271	-0.0402
p-OCH3	0.4136	-0.6030	-0.1384	0.1168	119.63	-512.18	-1.110	0.945	0.0927	-0.2992	-0.196	-0.1033	-0.0272
p-NH2	0.4108	-0.6063	-0.1488	0.1191	119.76	-453.35	-1.170	0.944	0.0045	-0.2932	-0.1489	-0.1444	-0.07
p-COOH	0.4202	-0.5967	-0.1134	0.1058	119.41	-585.90	0.6322	0.945	-0.0354	-0.3562	-0.1604	-0.1958	-0.1195
p-NO2	0.4237	-0.5926	-0.1067	0.10560	119.24	-601.74	-0.925	0.945	-0.076	-0.377	-0.1505	-0.2265	-0.1704
p-F	0.4176	-0.5992	-0.1271	0.1118	119.11	-497.18	-1.182	0.945	-0.023	-0.34	-0.1585	-0.1815	-0.1039

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 statistics 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<sub>9</sub> and H<sub>10</sub>) and the C=N group (C<sub>7</sub> and N<sub>8</sub>) 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 <sub>HOMO</sub> (ev)	E <sub>LUMO</sub> (ev)	η	μ	W
pKa	1.000													
H10 Charge	0.014	1.000												
O9 Charge	0.196	-0.931	1.000											
N 8 Charge	-0.239	-0.757	0.875	1.000										
C 7 Charge	0.156	0.660	-0.764	-0.965	1.000									
C6-C1-C7	0.037	0.403	-0.516	-0.612	0.662	1.000								
TE	0.175	-0.261	0.130	0.197	-0.301	-0.271	1.000							
DM	-0.536	-0.798	0.832	0.776	-0.671	-0.420	0.080	1.000						
Length O-H	-0.021	-0.941	0.926	0.885	-0.823	-0.442	0.2747	0.771	1.000					
E <sub>HOMO</sub>	0.354	-0.140	-0.157	-0.497	0.507	0.424	0.092	-0.193	-0.080	1.000				
E <sub>LUMO</sub>	0.237	-0.340	0.087	-0.304	0.535	0.154	0.197	0.034	0.065	0.857	1.000			
η	-0.130	-0.369	0.457	0.371	-0.299	-0.511	0.193	0.426	0.270	-0.291	0.243	1.000		
μ	0.301	-0.248	-0.037	-0.416	0.477	0.301	0.149	-0.083	-0.008	0.964	0.963	-0.027	1.000	
W	-0.205	0.410	-0.207	0.167	-0.299	0.013	-0.229	-0.127	-0.136	-0.687	-0.962	-0.492	-0.854	1.000

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	23.59	8.825	0.325	1.468
N8	34.901			
O9	-82.173	6.626	0.420	1.409
H10	-80.352			
Angl	0.195	-2.137	0.528	1.318
TE	0.106			
Len O-H	-31.294	41.262	0.026	1.552
H10	-3.503			
DM	-1.658	27.743	0.702	1.105
O9	70.192			
DM	-1.584	28.189	0.815	0.961
O9	71.080			
TE	0.151			
DM	-2.006	-667.708	0.885	0.773
O9	-7.954			
Len O-H	709.092			
DM	-2.247	-315.128	0.970	0.434
O9	-36.785			
Len O-H	355.361			
H10	-109.984			
DM	-2.499	43.545	0.991	0.245
O9	-47.041			
W	47.006			
H10	-203.749			
DM	-2.498	44.015	0.991	0.268
O9	-45.962			
W	48.129			
H10	-204.321			
N8	-0.804			
DM	-2.443	53.226	0.994	0.249
O9	-20.750			
N8	5.993			
H10	-159.064			
Angl	-0.046			
H	-62.042			

Looking at the results of TABLE 5, the relation between pKa and the charges on O<sub>9</sub>, N<sub>8</sub>, length of O-H bond, and DM are of negative slope, 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<sub>9</sub>, N<sub>8</sub> 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<sub>7</sub>, H<sub>10</sub>, 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.

$$\text{pKa} = 43.545 - 2.499 \text{ DM} - 47.041 \text{ Charge of O}_9 + 47.006 \text{ W} - 203.749 \text{ charge of H}_{10} \quad (5)$$

$$\text{pKa} = 53.226 - 2.443 \text{ DM} - 20.750 \text{ Charge of O}_9 + 5.993 \text{ charge of N}_8 - 159.064 \text{ Charge of H}_{10} - 0.046 \text{ Angle} - 62.042 \eta \quad (6)$$

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<sup>[26-28]</sup>.

The values of the experimental and calculated pKa using (eq. 5 and 6) with comparison between the experimental and predicted values of pKa 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<sub>3</sub>, m-NH<sub>2</sub>, m-COOH and P-NH<sub>2</sub> which were not included in the regression analysis.

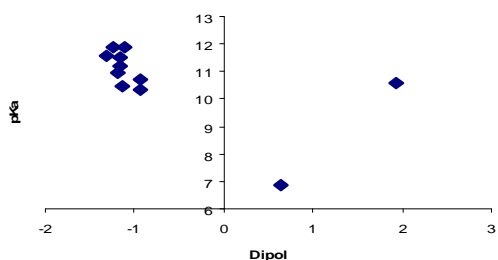
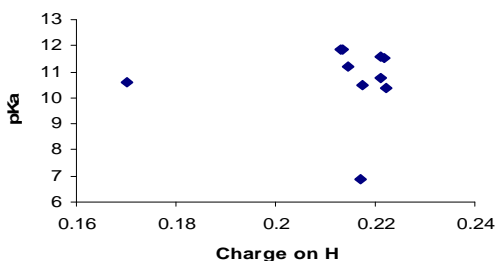
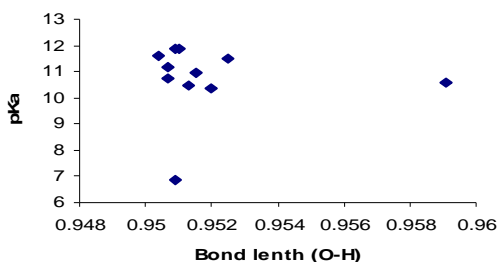
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A linear relation is obtained (with  $R > 0.97$ ) from the plot of the experimental pKa versus the calculated values indicating to high prediction power and reliable method for such applications.

**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	-0.085	11.675	-0.098
o-NO2	11.503	11.451	0.052	11.417	0.086
o-F	10.578	10.594	-0.016	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	0.056	10.796	-0.063
m-F	10.490	10.673	-0.183	10.676	-0.186
p-OCH3	11.875	11.482	0.393	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	-0.013	10.306	0.060
p-F	10.930	11.032	-0.102	11.194	-0.264

\*Res = Calc. pKa – Obs. pKa



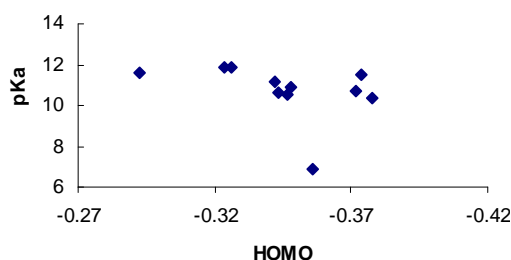
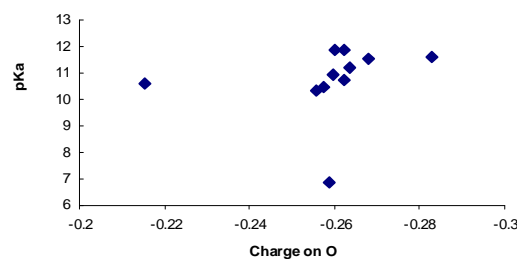
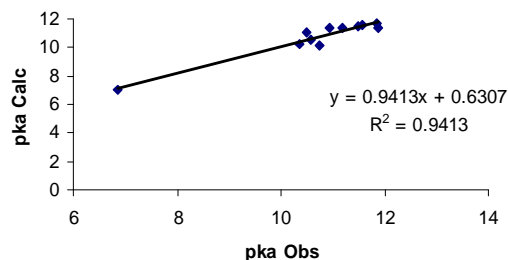
The second MLR model has been formed with the help of the descriptors derived by HF [6-311 G(d,p)] method. In this model, various equations have been generated (TABLE 7). The best fitted equations are the following two:

$$\text{pKa} = -1665.177 - 195.988 \text{ Charge of O}_y - 2.435 \text{ DM} + 1632.195 \text{ Length of O-H} - 0.007 \text{ TE} \quad (7)$$

$$\text{pKa} = -1660.158 - 2.436 \text{ DM} - 0.007 \text{ TE} + 1637.221 \text{ Length of OH} - 196.374 \text{ Charge of O}_y - 0.059 \text{ W} \quad (8)$$

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.



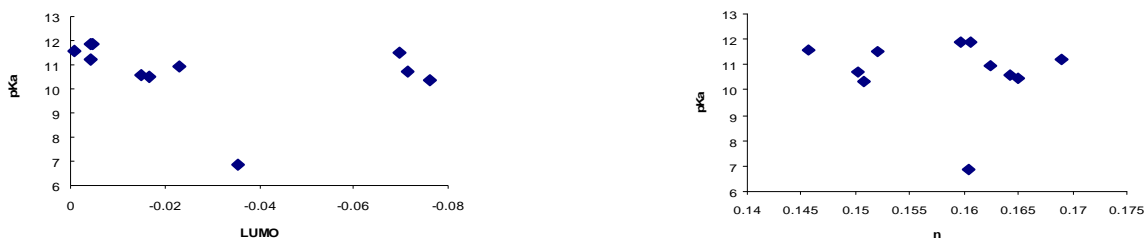


Figure 1 : Relations among pKa values and selected descriptors calculated by PM3 method

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	Compd.	Obs. pKa	Calc. pKa (Eq.8)	*Res	Calc.pKa (Eq.7)	*Res
B	11.195	11.167	-0.027	11.097	-0.098	m-NO2	10.733	10.675	-0.057	10.517	-0.216
o-OCH3	11.858	11.841	-0.016	11.669	-0.189	m-F	10.490	10.527	0.037	10.367	-0.123
o-NH2	11.577	11.599	0.022	11.419	-0.158	p-OCH3	11.875	11.924	0.049	11.853	-0.022
o-NO2	11.503	11.563	0.060	11.400	-0.103	p-NH2	.	10.514	.	10.397	.
o-F	10.578	10.509	-0.068	10.377	-0.201	p-COOH	6.866	6.903	0.037	6.751	-0.115
m-OCH3	.	12.332	.	12.255	.	p-NO2	10.366	10.327	-0.038	10.161	-0.205
m-NH2	.	9.225	.	9.029	.	p-F	10.930	10.995	0.065	10.854	-0.076
m-COOH	.	4.885	.	4.654	.						

\*Res = Calc. pKa - Obs. pKa

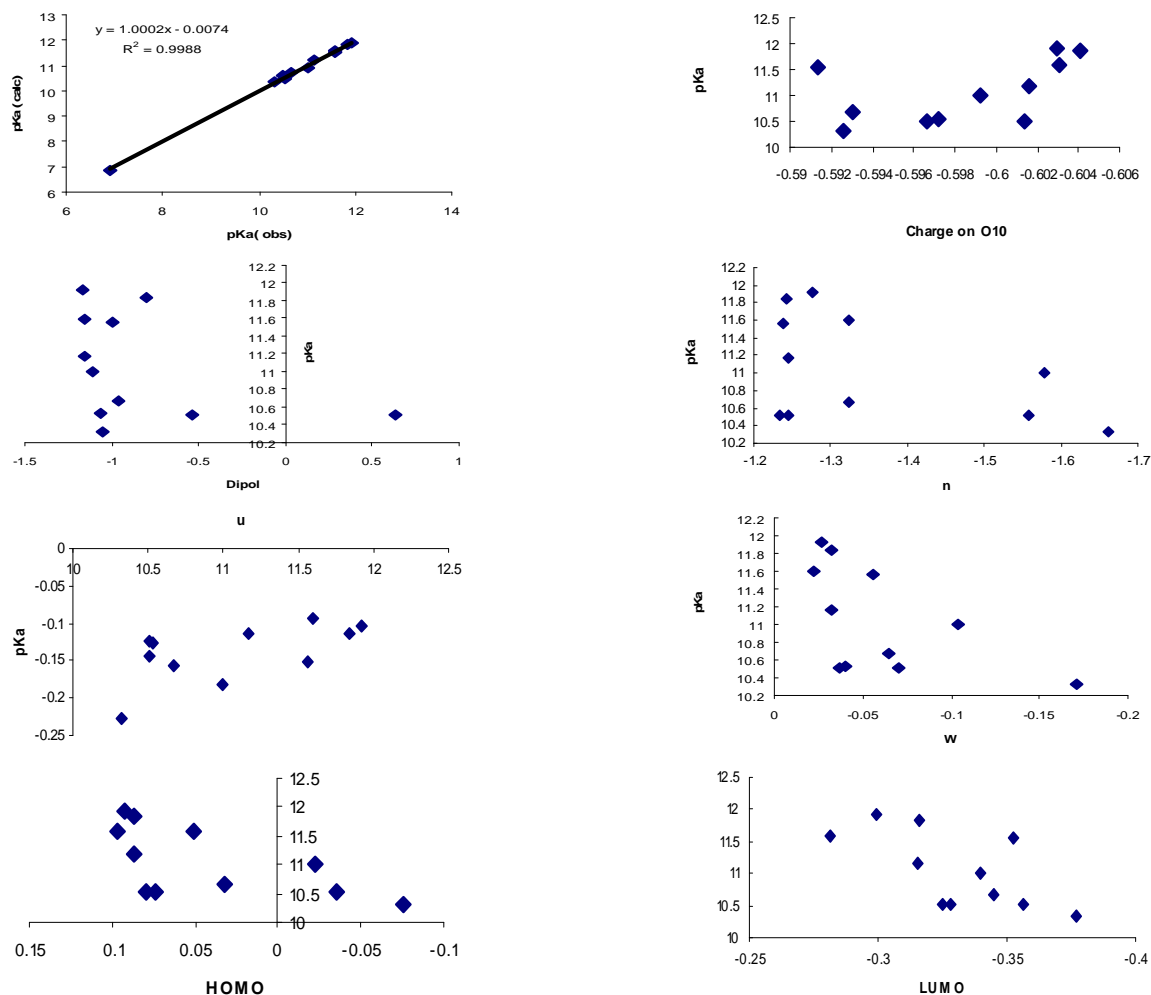


Figure 2 : Relations among pKa values and selected descriptors calculated by HF method



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