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Development of new methods for calculation of ionization constants of a number of Schiff base compounds using quantum mechanics methods

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Abstract

Two of the quantum mechanical methods, semi-empirical calculation represented by the AM1 model and an Abinitio method DFT, were used to accomplish a theoretical study to estimate the ionization constant (pKa) for several benzaldoximes substitution(BS). During the discussion of the theoretical variables selected for achieving this study by the two ways mentioned above. The results showed that the methods of basic calculations (Abinitio) were more suitable than the semi-empirical method for such calculation, since the calculated pKa values were consistent with their experimental values.

The difference between the theoretical and practical (pKa) is used as an indication to the mesomeric, inductive and steric effects of substituents. Such effects can not be determined by classical methods quantitatively. These theoretically calculated variables were derived by quantum chemical methods (DFT, AM1) and then correlated with the experimental values of pKa using multi parametric linear regression analysis by trial and error. The results obtained by correlation were well indicated by the values of the correlation coefficient (R^2) and standard deviation (SE) values in both methods. The success of this procedure is reflected by the large agreement between the practical pKa values with the theoretical computed values. The great convergence between the theoretical pKa values and the practical values for both methods(AM1, DFT) indicates the suitability and accuracy for such calculation applied in this paper.

Keywords: *Ionization constant, benzaldoximes substitution, quantum mechanics methods, AM1, DFT.*

1. Introduction

Schiff bases are organic compounds produced by the reaction of a primary amine with aldehyde or ketone under certain conditions. The term Schiff bases is applied to compounds containing the imine group or what is known as the exciting azo methen (C=N) and was first prepared by Schiff in 1864 [1,2].

The attachment of the hydroxyl group with azomethine compound yields oximes, which are well-known compounds with general functional group (-C=N-OH). Oximes have wide applications and were used as anti-skinning agents, anti-inflammatory agents, antibiotics, and antioxidants [3,4].

pKa is one of the most familiar and well-known chemical functions. Acknowledge the pKa values is the basis for understanding a great of the chemical reactions, especially those between compounds being studied with different pharmaceutical compounds, in addition to forming complexes and many analytical methods [5].

One of the most important chemical functions is the pKa value which is affected by the different chemical properties of the different compounds such as chemical activates and spectral properties [6].

The calculation of pKa values for compound theoretically is of great importance since it enables us to understand the mechanism of organic reaction by presenting an idea about the intensity of the ionization of the acid in solution [7].

2. Method of calculations

First, it is necessary to find the most stable conformation (which is of the lowest energy) for the studied compounds listed in Table(1) by employing geometry optimization.

Two methods of quantum mechanical carried out the geometrical optimization, the semi-empirical (AM1) and Abinitio methods (DFT)[8,9], starting from the semi-empirical AM1 level. The geometries of all possible matches are optimized, whereas Abinitio method [DFT: grid-based, method: B3LYP].

The natural atomic charges and structural

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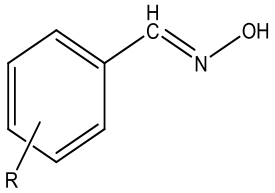
parameters like Angles, O-H bond length, total energy (TE), dipole moment (DM), the highest occupied molecular orbital energy (E_{HOMO}) and the lowest unoccupied molecular orbital energy (E_{LUMO}) were evaluated by using the optimized geometries [10].

The Chem. Office Program (version 12, 2010 of Cambridge software, USA) was utilized to calculate the quantum chemical descriptors.

Table 1: Structures of the considered compound in this study.



Comp. No.	R	Exp. pKa
1	H	11.195
2	o-CH_3	11.858
3	o-NH_2	11.577
4	o-NO_2	11.503
5	o-F	10.578
6	m-OCH_3	11.400
7	m-NH_2	12.410
8	m-COOH	6.715
9	m-NO_2	10.733
10	m-F	10.490
11	p-OCH_3	11.875
12	p-NH_2	12.590
13	p-COOH	6.866
14	p-NO_2	10.366
15	p-F	10.930

3. Results and Discussion

In this work, the experimental pKa values of the investigated compounds considered have been estimated using a half-integral potentiometric method [11].

This study included theoretically calculating the number of the compounds' physical variables under investigation and calculating ionization constants for all compounds by obtaining the best relationship between these variables with the ionization constant (pKa).

The Millikan atomic charge [12,14] for the investigated compounds for (C7, N8, O9, H10), which are thought to be the most effective atoms on the theoretical calculation by the two quantum mechanical methods (AM1, DFT).

The total energy(TE), angle(C6-C1-C7), the dipole of molecule(DM), OH Length, the energy of HOMO and LUMO orbitals [15] and the values of chemical potential (μ) [16-18], hardness (η) [19] and electrophilicity index (W) [20,21]. These parameters were illustrated as descriptors for pKa values and employed in this analysis.

The obtained results from the methods mentioned above are listed in Tables (2 and 3). Fig(1) shows the structure and atomic numbering for the investigated compound.

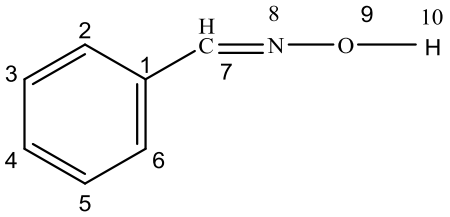


Table 2. The physical parameters calculated theoretically for the investigated compounds using the AM1 method.

Comp. No.	H10 Charge	O9 Charge	N8 Charge	C7 Charge	Angle C6-C1-C7	TE	DM	O-H Length(A)	E_{LUMO} (ev)	E_{HOMO} (ev)	η	μ	W
1	0.2383	-0.2538	-0.0586	0.0946	118.429	-4.2374	-1.1650	0.9785	-0.0042	-0.3602	0.1780	-0.1822	0.0932
2	0.2372	-0.2537	-0.0606	-0.0933	120.000	4.2210	-1.1849	0.9420	-0.0084	-0.3569	0.3485	-0.1827	0.0957
3	0.2367	-0.2617	-0.0707	-0.0775	120.143	-4.8036	-1.1310	0.9774	0.0032	-0.3427	0.1730	-0.1698	0.0833
4	0.2421	-0.2409	-0.0978	-0.1104	120.162	4.1121	-0.5885	0.9794	-0.0779	-0.3978	0.1600	-0.2379	0.1768
5	0.2388	-0.2498	-0.0566	-0.0959	122.139	-2.7671	-0.9661	0.9786	-0.0135	-0.3618	0.1742	-0.1877	0.1011
6	0.2381	-0.2530	-0.0580	-0.0957	118.010	1.4719	-1.1839	0.9779	-0.0052	-0.3501	0.1725	-0.1777	0.0915

7	0.2368	-0.2550	-0.0605	-0.0937	118.145	-7.3927	-1.1428	0.9781	0.0022	-0.3409	0.1716	-0.1694	0.0836
8	0.2443	-0.2490	-0.0409	-0.1067	118.017	2.4226	3.8776	0.9791	-0.0295	-0.3804	0.1755	-0.2050	0.1197
9	0.2457	-0.2463	-0.0400	-0.1080	118.580	-2.2394	-1.0517	0.9798	-0.0751	-0.3993	0.1621	-0.2372	0.1735
10	0.2411	-0.2505	-0.0502	-0.1007	118.358	-4.2475	-1.0968	0.9791	-0.0141	-0.3606	0.1733	-0.1874	0.1013
11	0.2375	-0.2556	-0.0638	-0.0877	118.349	1.3699	-1.1533	0.9779	-0.0025	-0.3629	0.1802	0.1827	0.0926
12	0.2347	-0.2587	-0.0757	-0.0772	118.978	-7.3905	-1.1445	0.9779	0.0085	-0.3569	0.1827	0.1742	0.0830
13	0.2429	-0.2457	-0.0458	-0.1075	118.300	2.3494	3.8328	0.9789	-0.0389	-0.3823	0.1717	-0.2106	0.1292
14	0.2451	-0.2442	-0.0365	-0.1142	118.203	-2.8289	-1.0761	0.9797	-0.0759	-0.3918	0.1580	-0.2339	0.1731
15	0.2397	-0.2518	-0.0567	-0.0952	118.538	-4.2641	-1.1041	0.9787	-0.0139	-0.3726	0.1794	-0.1933	0.1041

Table 3: The parameters calculated theoretically using B3LYP method of DFT with Basis set: 3-21G.

Comp. No.	H10 Charge	O9 Charge	N8 Charge	C7 Charge	Angle C6-C1-C7	TE	DM	O-H Length(A)	E_{LUMO} (ev)	E_{HOMO} (ev)	η	μ	W
1	0.2385	-0.2484	-0.0437	-0.0495	118.9380	-4.2374	-1.1650	0.9958	-0.0267	-0.2341	0.1037	-0.1304	0.0820
2	0.2382	-0.2538	-0.0519	-0.0571	115.6290	10.3440	-1.0310	0.0996	-0.0213	-0.2228	0.1008	-0.1221	0.0739
3	0.2370	-0.2554	-0.0563	-0.0505	118.6300	-4.8025	-1.1298	0.9959	-0.0170	-0.2174	0.1000	-0.1172	0.0685
4	0.2435	-0.2302	-0.0323	-0.0683	117.5920	4.1121	0.5885	0.9965	-0.1117	-0.2452	0.0668	-0.1785	0.2385
5	0.2393	-0.2452	-0.0409	-0.0546	123.9540	-2.7671	-0.9661	0.9967	-0.0323	-0.2357	0.1017	-0.1340	0.0885
6	0.2388	-0.2466	-0.0493	-0.0454	120.5190	1.4719	-1.1839	0.9970	-0.0254	-0.2259	0.1003	-0.1257	0.0787
7	0.2367	-0.2505	-0.0499	-0.0455	119.9830	-7.3927	-1.1428	0.9961	-0.0175	-0.2123	0.0974	-0.1149	0.0678
8	0.2440	-0.2407	-0.0310	-0.0514	119.8290	2.4226	3.8776	0.9960	-0.0512	-0.2460	0.0974	-0.1486	0.1134
9	0.2456	-0.2373	-0.0326	-0.0506	120.4190	-2.2394	-1.0517	0.9971	-0.1098	-0.2530	0.0716	-0.1814	0.2298
10	0.2417	-0.2431	-0.0400	0.0480	120.4290	-4.2475	-1.0968	0.9963	-0.0340	-0.2400	0.1028	-0.1372	0.0916
11	0.2368	-0.2522	-0.0531	-0.0486	119.9500	1.3699	-1.1533	0.9957	-0.0172	-0.2290	0.1059	-0.1231	0.0715
12	0.2339	-0.2574	-0.0640	-0.0483	120.5040	-7.3910	-1.1445	0.9968	-0.0027	-0.2183	0.1078	-0.1105	0.0566
13	0.2441	-0.2373	-0.0365	-0.0490	120.5450	2.3490	3.8328	0.9973	-0.0633	-0.2510	0.0939	-0.1572	0.1316
14	0.2463	-0.2337	-0.0309	-0.0498	120.0520	-2.2842	-1.0500	0.9977	-0.1110	-0.2505	0.0697	-0.1808	0.2345
15	0.2403	-0.2457	-0.0461	-0.0480	120.2800	-4.2641	-1.1040	0.9964	-0.0278	-0.2370	0.1046	-0.1324	0.0838

The results listed in Table (2,3) indicate that electronic charge values are affected by the location of substituted groups. These groups were electron-donating and withdrawing in nature. These charges increase in the presence of electron-donating substituents and decrease with the withdrawing groups.

As noted that the value of the nitrogen charge (N8) is lower than the rest of the atoms due to the presence of the withdrawing group (NO_2) meta, Para position. The lowest value of the nitrogen charge at compound 14 is due to the presence of the group

(NO_2) in Para position because of resonance effect [21] .

In general, any substituent that affects the O-H bond will affect the pKa value of the compound. Electrons withdrawing group weaken the O-H, increasing the ionization process and decreasing the value of pKa and vice versa. It was found that the highest charge value on (N8) was in Ortho position due to inductive effect, while the N8 charge values were lower in Para positions due to the mesomeric effect.

Other calculated variables express the amount of distortion in pKa values that occur in the compounds under consideration, which works to vary the total, kinetic, and steric energies, which affects the heat of formation values and reflect the variation in pKa values.

This theoretical study is aimed to investigate the extent to which its results correspond to practical results according to the scientific bases.

A statistical treatment followed these calculations to examine the nature of the relationship between the pKa and the selected parameters and among the parameters with each other by performing a simple regression analysis. The results obtained are listed in tables (4,5).

Table 4. The values of correlation coefficients of the relation between the parameters evaluated by AM1 method.

Parameters	pKa	H10 Charge	O9 Charge	N8 Charge	C7 Charge	Angle C6-C1-C7	TE	DM	O-H Length(A)	E_{LUMO} (ev)	E_{HOMO} (ev)	η	μ	W
pKa	1.000													
H10 Charge	-0.664	1.000												
O9 Charge	-0.478	0.838	1.000											
N8 Charge	-0.565	0.553	0.205	1.000										
C7 Charge	0.193	-0.325	-0.326	-0.100	1.000									
Angle C6-C1-C7	0.226	-0.251	-0.028	-0.427	-0.074	1.000								
TE	-0.403	0.344	0.483	-0.055	-0.275	0.065	1.000							
DM	-0.927	0.468	0.344	0.342	-0.201	-0.242	0.439	1.000						
O-H Length(A)	-0.210	0.288	0.185	0.073	0.029	-0.256	-0.387	0.140	1.000					
E_{LUMO}(ev)	0.457	-0.866	-0.869	-0.211	0.282	0.091	-0.414	-0.341	-0.226	1.000				
E_{HOMO} (ev)	0.337	-0.873	-0.893	-0.186	0.352	0.037	-0.375	-0.204	-0.199	0.928	1.000			
η	0.191	-0.326	-0.231	-0.060	0.011	0.237	0.361	-0.116	-0.993	0.257	0.269	1.000		
μ	0.394	-0.581	-0.556	-0.314	0.074	-0.088	-0.195	-0.206	0.030	0.332	0.503	0.027	1.000	
W	-0.310	0.857	0.879	0.161	-0.339	-0.040	0.359	0.185	0.209	-0.936	-0.998	-0.276	-0.462	1.000

Table 5. The values of correlation coefficients of the relation between the parameters evaluated by DFT method.

Parameters	pKa	H10 Charge	O9 Charge	N8 Charge	C7 Charge	Angle C6-C1-C7	TE	DM	O-H Length(A)	E_{LUMO} (ev)	E_{HOMO} (ev)	η	μ	W
pKa	1.000													
H10 Charge	-0.648	1.000												
O9 Charge	-0.519	0.925	1.000											
N8 Charge	-0.643	0.948	0.935	1.000										
C7 Charge	-0.045	0.038	-0.022	0.027	1.000									
Angle C6-C1-C7	-0.215	0.049	0.104	0.125	0.181	1.000								
TE	-0.274	0.287	0.241	0.254	-0.285	-0.537	1.000							

DM	-0.895	0.480	0.444	0.495	-0.151	0.004	0.383	1.000						
O-H Length(A)	-0.179	0.156	0.296	0.218	0.132	0.652	-0.663	0.111	1.000					
E_{LUMO}(ev)	0.672	-0.928	-0.882	-0.898	-0.051	-0.185	-0.250	-0.495	-0.247	1.000				
E_{HOMO} (ev)	0.327	-0.889	-0.914	-0.839	0.177	0.054	-0.240	-0.274	-0.175	0.815	1.000			
η	0.119	-0.756	-0.811	-0.702	0.260	0.163	-0.203	-0.131	-0.118	0.621	0.960	1.000		
μ	0.434	-0.934	-0.940	-0.887	0.119	-0.009	-0.252	-0.344	-0.201	0.897	0.987	0.904	1.000	
W	-0.231	0.838	0.877	0.781	-0.196	-0.078	0.208	0.196	0.173	-0.767	-0.993	-0.975	-0.969	1.000

The results are shown in Tables (4 and 5) showed good relationships between some variables, varying in their proximity and nature in terms of spatial position and electronic repulsion [22-24] by applying the AM1 method. Table (4) The best value of the correlation coefficient when applying simple regression between (HOMO, W), (O-H Length, η), (LUMO, HOMO) (pKa, DM) was -0.998, -0.993, 0.928, -0.927 respectively.

DFT method, Table (5) The best value of the correlation coefficient between the two variables (HOMO, H), (μ, HOMO), (HOMO, W) (η, W) were 0.960, 0.987, -0.993, -0.975 respectively.

All the good relationships mentioned in previous tables can be considered the starting point of the multiple regression of linear equations to calculate the values of pKa.

Using the SPSS program in multiple linear regression analysis and using the sequential variables input method to find the best linear relationship through which the best result and the best equation for calculating values of pKa theoretically and comparing them with the practical value can be reached. Experience by entering two, three, four, five and six parameters.

Table(6) included a summary of the best relationships obtained from these attempts and by adopting the values of the correlation coefficient (R), which was dose to unity and with the low standard deviation(S.E) that was considered as a measure of the success the selection of the adopted variables in describing the studied systems.

Table 6. Results of the regression analysis between the pKa values and descriptors calculated by AM1, DET methods.

Method& Group	Parameter	A	b	R	S.E
AM1	DM	-0.649	83.781	0.984	0.363
	O9	-38.948			
	W	26.726			
	H10	-0.036			
DFT	DM	-0.730	111.686	0.960	0.575
	H10	-275.972			
	O9	154.185			
	N8	-66.838			

Equations eq.1 and eq.2 represent the models used to calculate the pKa values by the AM1 and DFT methods, respectively, whereas the two equations describe the effect of the substituents on pKa.

pKa= 83.781 + (-0.649DM) + (-38.948O9) + (26.726W) + (-0.036H10)….(1)

pKa=111.686+(-0.730DM)+(-275.972H10)+(154.185O9)+ (-66.838N8)….(2)

Tables (7,8) show the theoretical values of pKa obtained by the developed equations (1,2) and the differences between experimental and theoretical values

Table 7. Comparison between the observed and calculated pKa values evaluated by the (AM1) methods.

Compd.	pKa*	pKa**	ΔpKa
1	11.195	11.053	0.142
2	11.858	11.524	0.334
3	11.577	11.652	-0.075

4	11.503	11.070	0.433
5	10.578	10.809	-0.231
6	11.400	11.060	0.340
7	12.410	11.370	1.040
8	6.715	6.389	0.326
9	10.733	10.174	0.559
10	10.490	10.092	0.398
11	11.875	11.388	0.487
12	12.590	12.255	0.335
13	6.866	7.045	-0.179
14	10.366	10.312	0.054
15	10.930	10.726	0.204

pKa* = Experimental Values
pKa**= Calculated Values
ΔpKa = pKa* -pKa**

Table 8. Comparison between the observed and calculated pKa values evaluated by the (DFT) methods.

Compd.	pKa*	pKa**	ΔpKa
1	11.195	11.338	-0.143
2	11.858	11.039	0.819
3	11.577	11.490	0.087
4	11.503	10.723	0.780
5	10.578	11.279	-0.701
6	11.400	11.921	-0.521
7	12.410	11.910	0.500
8	6.715	6.478	0.237
9	10.733	10.266	0.467
10	10.490	10.975	-0.485
11	11.875	11.841	0.034
12	12.590	12.562	0.028
13	6.866	7.375	-0.509
14	10.366	10.513	-0.147
15	10.930	11.374	-0.444

Comparison between the calculated pKa value by employing equations and the practical values[19], in table (8) showed a high convergence between the two values, indicating the success in applying this method for such calculation with high accuracy.

4. Conclusions

Two methods semi-empirical calculation represented by the AM1 model and an Abinitio method DFT has been successfully conducted to determine the effect of the substituents on the pKa values of benzaldoximes compounds relying on some molecular properties derived from each of them.

A number of sets of parameters are obtained by correlating experimental pKa with the derived parameters from AM1 and DFT using simple and multiple regression analysis for both methods (AM1, DFT).

The best set of parameters was obtained from applying the multiple regression analysis when using

On the other hand, the best set of parameters derived from the DFT method and represented by equation (2) were used to calculate pKa value theoretically. The calculated values are compared with the practical values. The two values of both methods(AM1, DFT) were in good agreement, which indicates the accuracy of the calculation achieved in this study.

The method used in this research could be applied to the theoretical determination of pKa values for another family of organic compounds. Its save time, and chemicals.

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