



Correlation Study for the Determination of Pka of A Number of Schiff Bases Derived from N-Formyl Pyridine Using Quantum Mechanical Methods



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Abstract

Statistical analysis employing multi parametric regression analysis was used to correlate the pKa values of 16 substituted Schiff bases (imines) derived from hetero generous carbonyl compounds with various descriptors as parameters. These parameters are based on quantum mechanical methods, four sets of parameters are used for these treatments. Two of them were derived depending on the semi empirical calculation represented by Austin method1 (AM₁) and parameterized method3 (PM₃).

The other two sets were chosen as Ab initio models, expressed by Hartree fock (HF) and MP2 calculation models performed at 6.311G (d, p) level of theory. The descriptors employed to test their impact on the variation of the experimental pka(s) are of two kinds, electronic and spatial properties including atomic charges (Mulliken and Lowding), length of the imine (C=N) and connected bonds. Other molecular characteristic are also used such as energies of the HOMO and LUMO orbitals, total energies (TE), kinetic energy (KE), torsion, Vander Waals interactions of the 1,4 type (VDW 1,4) and non 1,4 type (Non 1,4 VDW).

The correlation between the pKa values of the studied compounds and each of the selected parameters are first investigated. Depending on the obtained results, several sets (two, three and so on) were constructed. The best set of parameters for every models used to calculate the pKa value of the studied compounds theoretically. Comparison are carried out between the experimental pKa values with the calculated ones from AM₁, PM₃, MP₂, and HF methods.

The Ab initio models, HF and to less extent MP₂ showed better consistency between the experimental and the calculated pKa(s) of the compounds considered in the study indicated by the value of multiple correlation coefficient (R²) and standard error (SE). This proved the high predictive power and sufficient reliability of such model to study the effect of substituents on the pKa values of the compound under investigation.

Hypothetical compounds of similar structures but with different substituents not included in the regression analysis are used to test the success of the derived equations. Good results are obtained.

Keywords : Theoretical Calculation, HF, MP₂, PM₃, AM₁

Introduction

Schiff bases are organic compounds formed from the reaction of primary amine with an aldehyde or ketone under certain conditions. Structurally, Schiff based are characterized by the presence of an imine (C=N) group.

This type of compounds are present in various forms. They were used as catalysts, dyes and pigments. They also employed as intermediates in organic synthesis and for stabilizing polymers⁽¹⁾. The existence of

imine group in such compounds, and being affected by the structural geometry and type of substituents, made this type of compounds liable and critical to wide range of biological activities such as anti-bacterial, anti-viral, anti-fungal, anti-malarial and other activities (2-4).

The acid dissociation constant (pKa) is one of the most common and well known chemical functions. Recognizing the values of pKa is the basis of understanding many of the chemical reactions, especially those occur between compounds to be

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studied with different pharmaceutical compounds, in addition to complexes formation as well as many analytical methods^(5,6).

The values of pKa are important chemical functions among other values, those affected by chemical properties of different compounds such as their chemical activities and spectral properties⁽⁷⁾. Therefore, the values of pKa are sensitive to the inductive effects resulting from the electron donating and withdrawing effect on various substituents, and steric effect that resulting from spatial interference resulting from the proximity of specific groups in the geometrical distribution, which play an important role in determining the shape of the molecule and causing structural deformations by interfering with each other^(8,9).

Since such effects can be evaluated by using several methods of quantum mechanics, many researchers have resorted to using a number of variables that can give a description to help understanding the physical and chemical effects of different substituents on pKa values⁽⁹⁾.

The possibility of calculating pKa values for hypothetical compounds is of great importance as they can help to understand the mechanism of organic reactions by getting knowledge about the intensity of the ionization process of the acid in the solution, knowing the percentage of the proton resulting from the ionization process is also of great importance in the study of absorption, diffusion and then secretion of the drug taken by patients based on active substance of the drug, which contain an acid or alkali group in its composition. This varies in certain proportions according to the physiological effect of the acid function pH^(10,11).

In order to test the possibility of the theoretical calculations using quantum mechanical methods to achieve a match with the values calculated experimentally, four quantum mechanical methods, were used to calculate the values of pKa theoretically. These methods included the Hartree fock (HF) and MP2 as Ab initio methods and Austin method1 (AM1) and parametric methods (PM3) as semi-empirical methods by employing Chem office program (version 12, 2010), then conducting statistical analysis using SPSS program (version 18) aiming for developing mathematical equations

representing the best relationships those giving an accurate description of the studied variables⁽¹²⁻¹⁴⁾.

Method of calculations

The first step of achieving these calculations requires to find out the most stable conformation (with the lowest energy) for the (16) compounds listed in Table (1) by geometry optimization. Energy minimization is achieved at level for two of the semi empirical AM1 and PM3 in addition to two of the Ab initio MP2 and HF methods using gradient technique and 6-311 G (d,p) basis set. In order to undergo this job all the possible conformers at the semi empirical level were optimized, while at the Ab initio methods carried out at 6-311 G (d,p) level, the optimization process is performed only for the most stable conformer obtained by the semi empirical methods. All the steps mentioned above is aimed to ensure that, the followed calculation is carried out by starting from the conformer with minimum energy^(15,16).

The step of geometrical optimization helps to estimate the value of atomic charges and calculating various structural parameters like the total energy (TE), torsion, Vander waals interactions of the 1,4 type (VDW 1,4) and non 1,4 type (non 1,4 VDW), atomic charges (Mullikan and lowding) and others will be mentioned later⁽¹³⁾.

Other parameters such as the energy of highest occupied molecular orbital (E_{HOMO}) and the energy of the lowest unoccupied molecular orbitals (E_{LUMO}) were determined. Various descriptors as parameters are calculated for the four methods selected to achieve this study. All these calculation were carried out by employing the Chem. Office package (version 12, 2010 of Cambridge software , USA).

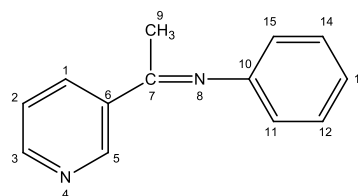
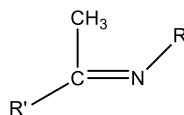


Fig. 1: Structure diagram of the compound studied with number on atoms as used in the parameter

Table1: structures of the considered compound in this study



Comp. No.	R'	R	Heat of Formation PM3 Kcal/Mol	Total Energy HF Kcal/Mol $\times 10^3$
1	m-pyridine	OH	31.009	-282.939
2	m-pyridine	o-phenol	25.975	-426.203
3	m-pyridine	m-phenol	25.658	-426.201
4	m-pyridine	p-phenol	25.347	-426.201
5	m-pyridine	o-aniline	68.827	-413.829
6	m-pyridine	m-aniline	67.923	-413.829
7	m-pyridine	p-aniline	68.099	-413.829
8	p-pyridine	o-phenol	26.803	-426.203
9	p-pyridine	m-phenol	25.7046	-426.201
10	p-pyridine	p-phenol	25.811	-426.201
11	p-pyridine	o-aniline	69.332	-413.829
12	p-pyridine	m-aniline	68.479	-413.829
13	p-pyridine	p-aniline	68.542	-413.829
14	o-pyridine	o-pyridine- 3-ol	32.106	-436.191
15	m-pyridine	o-pyridine- 3-ol	31.486	-436.180
16	p-pyridine	o-pyridine- 3-ol	32.258	-436.180

Statistical Analysis

Statistical Analysis is used to correlate the experimental values of pKa obtained by potentiometric method^(9,13,19), with various parameters determined by quantum mechanical methods using the Chem. Office program.

The Statistical method used is expressed by multiparametric linear regression analysis (MRA), which can be presented by the following equation:

$$pKa = b + \sum_i a_i X_i \dots \dots \dots (1)$$

Where b is a reference value, $X_i(s)$ are the descriptors selected as parameters to calculate the pKa values theoretically, and $a_i(s)$ are the coefficient of x representing the gradient of the X that affect the value of X (s).

Results and Discussion

In this work, the experimental values of pKa were obtained by potentiometric⁽⁸⁾ method and calculated by correlating these values with parameters derived and estimated by quantum mechanical methods. These parameters are energetic and electronic in nature. They are basically thought to be good representative for describing their effect on the pKa values. For these reasons, this work is concentrated on two types of parameters; First, the energies resulted from distortion that rise up due to geometry optimization and spatial arrangements, such as Vander Waals interactions, torsion and total energy of the

molecule, as well as, the bond angle and bond length around the C=N group and the ionized bond (O-H) which is thought to be important for undergoing this study. Other parameters such as energy of the HOMO and LUMO orbitals are evaluated.

The second type of parameters are electronic represented by the electronic charges on the hetro atoms (O and N) in the possion affecting the value of pKa by electron donating and withdrawing resulting from the various substituents present on rings of the studied compounds.

Four quantum mechanics methods are used for performing this study, two of them are semi empirical methods (AM1 and PM3) and the others are Ab initio methods (MP2 and HF). The reason for employing four methods is that, each method is efficient in doing some types of calculations and has deficiencies in other sides, therefore, its aimed to test these methods in order to choose the most suitable one for achieving our objective. The results obtained from the methods mentioned above are listed in table (2-5). Figure (1) show the structure and atom numbering of the studied compounds.

Table 2: results obtained from applying AM1 method

Comp.	pKa	TE	HOMO	LUMO	LUMO-HOMO	MullikenCharges N8
1	9.4592	-40098.4489	-8.4570	-2.4950	5.9620	-0.0620
2	5.6851	-59092.5009	-9.4890	-3.1740	6.3150	-0.1537
3	4.9479	-59093.5332	-9.0520	-4.6230	4.4290	-0.1648
4	6.2875	-59093.9565	-9.4550	-3.4720	5.9830	-0.0586
5	5.1803	-56797.9460	-9.0500	-2.7060	6.3440	-0.1568
6	5.3394	-56797.5702	-9.4040	-4.2220	5.1820	-0.1742
7	6.8191	-56797.8856	-9.1040	-2.7190	6.3850	-0.1458
8	5.4738	-59091.8220	-9.5430	-3.2170	6.3260	-0.1468
9	4.8891	-59093.2704	-9.6330	-3.2550	6.3780	-0.1506
10	6.2218	-59093.3419	-9.4290	-3.7100	5.7190	-0.0428
11	5.2280	-56797.5454	-9.0790	-2.7210	6.3580	-0.1469
12	5.2361	-56797.1205	-7.0740	-4.3390	2.7350	-0.1572
13	6.2664	-56797.7891	-9.0720	-2.7000	6.3720	-0.1319
14	9.0129	-60583.8119	-9.5390	-2.7310	6.8080	-0.1338
15	9.0349	-60583.6654	-8.9990	-1.4890	7.5100	-0.1393
16	8.8539	-60584.9575	-9.4800	-2.6230	6.8570	-0.1222
Comp.	bondC7N8	bondC6C7	bondN8C10	Torsion	Non14VDW	VDW14
1	1.3147	1.4744	1.4971	-1.9634	1.3151	8.9569
2	1.2969	1.4811	1.4102	.4242	1.3529	15.2964
3	1.2959	1.4873	1.3979	-7.4413	3.7514	15.0549
4	1.2972	1.4803	1.4060	-7.3266	3.7169	15.1131
5	1.2952	1.4814	1.4145	1.3650	2.5517	15.9181
6	1.2969	1.4855	1.4063	-9.5065	4.0133	15.9340
7	1.2949	1.4796	1.4076	-9.4467	3.9653	15.8658
8	1.2964	1.4860	1.4112	-.1037	1.2665	15.5132
9	1.2939	1.4851	1.4109	-7.4445	3.7135	15.2756
10	1.2955	1.4866	1.4043	-7.3123	3.6409	15.3226
11	1.2962	1.4875	1.4149	.7974	2.6149	16.1271
12	1.2721	1.3605	1.2719	-9.5153	3.9642	16.1691
13	1.2946	1.4851	1.4082	-9.4819	3.8315	16.0984
14	1.2965	1.4790	1.4259	6.8474	1.9487	16.2451
15	1.2902	1.5055	1.4179	5.9284	1.2752	15.3847
16	1.2947	1.4853	1.4275	12.4729	-2.3305	15.6070

Table 3: results obtained from applying PM3 method

Comp.	PKa1	TE	HOMO	LUMO	LUMO-HOMO	MullikenCharges N8
1	9.4592	-36175.6110	-9.2410	-2.6970	6.5440	-0.0281
2	5.6851	-54010.3559	-9.4600	-3.0890	6.3710	-0.0476
3	4.9479	-54011.4331	-9.1200	-4.4760	4.6440	-0.0576
4	6.2875	-54011.1345	-9.4230	-2.7140	6.7090	-0.0586
5	5.1803	-51337.8675	-9.2220	-2.4100	6.8120	-0.0532
6	5.3394	-51337.2439	-9.2480	-4.1100	5.1380	-0.0666
7	6.8191	-51337.0244	-9.1900	-2.5430	6.6470	-0.0599
8	5.4738	-54009.9990	-9.5350	-2.7870	6.7480	-0.0404
9	4.8891	-54012.0267	-9.5740	-2.7010	6.8730	-0.0471
10	6.2218	-54011.5302	-9.3290	-3.0920	6.2370	-0.0428
11	5.2280	-51337.8026	-9.2110	-2.4980	6.7130	-0.0472
12	5.2361	-51336.8873	-9.2230	-4.6280	4.5950	-0.0645
13	6.2664	-51336.5210	-9.1190	-2.4670	6.6520	-0.0542
14	9.0129	-54661.9123	-9.2010	-3.1170	6.0840	-0.0211
15	9.0349	-54663.8133	-9.4910	-2.7000	6.7910	-0.0261
16	8.8539	-54662.3772	-9.3250	-1.9860	7.3390	-0.0445
Comp.	bondC7N8	bondC6C7	bondN8C10	Torsion	Non14VDW	VDW14
1	1.3063	1.4782	1.3948	-1.9634	1.3151	8.9569
2	1.2984	1.4769	1.4311	.4242	1.3529	15.2964
3	1.2997	1.4819	1.4230	-7.4413	3.7514	15.0549
4	1.2970	1.4798	1.4273	-7.3266	3.7169	15.1131
5	1.2975	1.4788	1.4323	1.3650	2.5517	15.9181
6	1.2986	1.4811	1.4257	-9.5065	4.0133	15.9340
7	1.2975	1.4791	1.4285	-9.4467	3.9653	15.8658
8	1.2984	1.4804	1.4320	-.1037	1.2665	15.5132

9	1.2960	1.4817	1.4283	-7.4445	3.7135	15.2756
10	1.2967	1.4818	1.4246	-7.3123	3.6409	15.3226
11	1.2968	1.4815	1.4317	.7974	2.6149	16.1271
12	1.2992	1.4865	1.4247	-9.5153	3.9642	16.1691
13	1.2962	1.4815	1.4275	-9.4819	3.8315	16.0984
14	1.2952	1.4896	1.4196	6.8474	1.9487	16.2451
15	1.2977	1.4776	1.4277	5.9284	1.2752	15.3847
16	1.2951	1.4819	1.4276	12.4729	-2.3305	15.6070

Table 4: results obtained from applying HF method

Comp.	pKa	KE × 10 ³	TE × 10 ³	HOMO	LUMO	LUMO-HOMO	Lowding Chareg
1	9.4592	282.346	-282.939	-9.4410	-2.2680	7.1730	-0.0692
2	5.6851	425.397	-426.203	-9.1340	-2.7040	6.4300	-0.2238
3	4.9479	425.404	-426.198	-8.8670	-3.6680	5.1990	-0.2227
4	6.2875	425.401	-426.199	-8.9680	-2.9950	5.9730	-0.2164
5	5.1803	413.106	-413.829	-8.7160	-2.4740	6.2420	-0.2174
6	5.3394	413.089	-413.826	-9.3110	-2.6180	6.6930	-0.2210
7	6.8191	413.092	-413.827	-8.5680	-2.7640	5.8040	-0.2092
8	5.4738	425.395	-426.202	-9.2370	-2.6850	6.5520	-0.2136
9	4.8891	425.405	-426.198	-9.3010	-3.2000	6.1010	-0.2122
10	6.2218	425.403	-426.199	-9.0370	-3.1830	5.8540	-0.2060
11	5.2280	413.086	-413.829	-8.7900	-2.5870	6.2030	-0.2077
12	5.2361	413.090	-413.826	-8.7580	-4.0990	4.6590	-0.2109
13	6.2664	413.094	-413.828	-8.6550	-2.9560	5.6990	-0.1989
14	9.0129	435.348	-436.180	-8.4950	-2.7960	5.6990	-0.2186
15	9.0349	435.342	-436.177	-8.8080	-2.4920	6.3160	-0.2261
16	8.8539	435.390	-436.178	-8.9510	-2.2960	6.6550	-0.2316
Comp.	Mulliken ChargesN8	bondC7N8	bondC6C7	bondN8C10	Torsion	Non14VDW	VDW14
1	-0.3567	1.2626	1.4886	1.4422	-1.9634	1.3151	8.9569
2	-0.7575	1.2655	1.4898	1.4162	.4242	1.3529	15.2964
3	-0.8317	1.2625	1.4930	1.4130	-7.4413	3.7514	15.0549
4	-0.8243	1.2614	1.4895	1.4104	-7.3266	3.7169	15.1131
5	-0.7383	1.2637	1.4906	1.4247	1.3650	2.5517	15.9181
6	-0.8308	1.2607	1.4888	1.4119	-9.5065	4.0133	15.9340
7	-0.8236	1.2627	1.4925	1.4105	-9.4467	3.9653	15.8658
8	-0.7568	1.2634	1.4961	1.4171	-1.037	1.2665	15.5132
9	-0.8240	1.2589	1.4956	1.4078	-7.4445	3.7135	15.2756
10	-0.8172	1.2610	1.4957	1.4107	-7.3123	3.6409	15.3226
11	-0.7347	1.2631	1.4962	1.4245	.7974	2.6149	16.1271
12	-0.8236	1.2618	1.5057	1.4122	-9.5153	3.9642	16.1691
13	-0.8170	1.2610	1.4991	1.4113	-9.4819	3.8315	16.0984
14	-0.7722	1.2578	1.4940	1.3928	6.8474	1.9487	16.2451
15	-0.7302	1.2623	1.4894	1.4063	5.9284	1.2752	15.3847
16	-0.7026	1.2618	1.4912	1.4140	12.4729	-2.3305	15.6070

Table 5: results obtained from applying MP2 method

Comp.	pKa	KE × 10 ³	TE × 10 ³	HOMO	LUMO	LUMO-HOMO	Lowding Chareg
1	9.4592	282.756	-283.537	-10.3290	-4.3170	6.0120	-0.0278
2	5.6851	426.013	-427.124	-9.7980	-3.3270	6.4710	-0.1347
3	4.9479	425.978	-427.118	-9.3010	-4.6480	4.6530	-0.1405
4	6.2875	425.986	-427.119	-9.6820	-3.6920	5.9900	-0.1437
5	5.1803	413.677	-414.745	-9.3490	-3.2540	6.0950	-0.1391
6	5.3394	413.649	-414.737	-10.0360	-3.3840	6.6520	-0.1382
7	6.8191	413.650	-414.739	-9.1300	-3.4800	5.6500	-0.1449
8	5.4738	426.009	-427.126	-9.9770	-3.6780	6.2990	-0.1424
9	4.8891	425.986	-427.118	-9.4930	-4.8890	4.6040	-0.1428
10	6.2218	425.990	-427.119	-9.7810	-4.0080	5.7730	-0.1468
11	5.2280	413.687	-414.745	-9.4230	-3.5190	5.9040	-0.1393
12	5.2361	413.656	-414.738	-9.5420	-4.7980	4.7440	-0.1409
13	6.2664	413.656	-414.740	-9.2620	-3.7920	5.4700	-0.1483
14	9.0129	435.955	-437.116	-9.5210	-3.4840	6.0370	-0.1355
15	9.0349	435.966	-437.112	-9.6210	-3.3030	6.3180	-0.1350
16	8.8539	435.965	-437.112	-9.6480	-3.5520	6.0960	-0.1375
Comp.	Mulliken ChargesN8	bondC7N8	bondC6C7	bondN8C10	Torsion	Non14VDW	VDW14

1	-0.2624	1.4952	1.5182	1.5182	-1.9634	1.3151	8.9569
2	-0.5262	1.3088	1.4962	1.4433	.4242	1.3529	15.2964
3	-0.6040	1.3034	1.5086	1.4325	-7.4413	3.7514	15.0549
4	-0.6081	1.3054	1.4984	1.4332	-7.3266	3.7169	15.1131
5	-0.5265	1.3068	1.4965	1.4464	1.3650	2.5517	15.9181
6	-0.6018	1.3034	1.4992	1.4413	-9.5065	4.0133	15.9340
7	-0.6126	1.3058	1.4490	1.4305	-9.4467	3.9653	15.8658
8	-0.5217	1.3095	1.4973	1.4414	-.1037	1.2665	15.5132
9	-0.6083	1.3042	1.5096	1.4327	-7.4445	3.7135	15.2756
10	-0.6127	1.3054	1.4993	1.4329	-7.3123	3.6409	15.3226
11	-0.5264	1.3077	1.4994	1.4462	.7974	2.6149	16.1271
12	-0.6079	1.3038	1.5098	1.4357	-9.5153	3.9642	16.1691
13	-0.6181	1.3065	1.5002	1.4319	-9.4819	3.8315	16.0984
14	-0.5232	1.3022	1.4976	1.4301	6.8474	1.9487	16.2451
15	-0.5002	1.3062	1.4958	1.4398	5.9284	1.2752	15.3847
16	-0.5025	1.3065	1.4981	1.4408	12.4729	-2.3305	15.6070

AM1 method:

A primary test is carried out to examine the nature of the relation between the pKa and the selected parameters and among the parameters themselves, by simple regression analysis. The value of correlation coefficient (R), which located

between (+1 and -1), is used as a measure of the relation between the correlated parameters. The value close to (+1) gives indication to the direct and linear relation while values near (-1) means inverse linear relationship.

Table 6: shows the results obtained from the application of AM1 method.

parameters	pKa	TE	HOMO	LUMO	LUMO-HOMO	Mulliken ChargeN8	bondC7N8	bondC6C7	bondN8C10	Torsion	Non14VDW	VDW14
pKa	1.000											
TE	0.286	1.000										
HOMO	-0.028	0.397	1.000									
LUMO	0.654	0.122	-0.202	1.000								
LUMO-HOMO	0.487	-0.136	-0.708	0.835	1.000							
Mulliken Charges N8	0.416	0.349	-0.081	0.142	0.148	1.000						
bondC7N8	0.362	0.572	-0.495	0.299	0.494	0.422	1.000					
bondC6C7	0.207	-0.128	-0.858	0.443	0.802	0.124	0.668	1.000				
bondN8C10	0.516	0.429	-0.585	0.544	0.721	0.361	0.944	0.790	1.000			
Torsion	0.601	-0.167	-0.266	0.615	0.593	0.024	0.160	0.304	0.380	1.000		
Non14VDW	-0.604	-0.001	0.210	-0.516	-0.490	-0.073	-0.240	-0.238	-0.407	-0.896	1.000	
VDW14	-0.447	-0.890	-0.187	-0.171	-0.018	-0.516	-0.690	-0.066	-0.585	-0.009	0.202	1.000

Good relations are noticed between the pKa values of Vander Waals interactions, which in turn affect the bond length of the compounds as well as among the bonds themselves around the ionization area. Other good relations were also noticed such as those between the energies of HOMO and LUMO orbitals and bond lengths. All the good relations mentioned above can be considered as starting points for the multiple regression and for deriving linear equations for calculating pKa values.

The next step of this study included achieving multiparametric regression analysis, starting from correlating the values of pKa of the studied compounds with two, three, four, five, and six parameters. Tens of attempts were carried out. A number of these trials are listed in Table (7), shows the set of parameters chosen for calculating pKa by

AM1, which can be represented as in the following equation (eq.2).

$$pKa = 1.550 + 0.003 VDW + 0.101 Torsion + 12.685 \text{ Mulliken charge N8} + 0.510 E_{LUMO} + 0.900 E_{HOMO} + 11.866 \text{ bond length N8 - C10} \dots\dots(2)$$

Table 7: Multiple regression analysis results of several attempts by AM1 method

Var	Coeff	R ²	Std.E
LUMO	1.221	0.543	1.189
VDW14	-0.328		
LUMO	0.731	0.631	1.113
VDW14	-0.364		
Torsion	0.0899		
LUMO	0.671	0.674	1.092
VDW14	-0.248		
Torsion	0.095		
MullikenCharges N8	10.041		
LUMO	0.696	0.690	1.117
VDW14	-0.205		
Torsion	0.103		
MullikenCharges N8	11.420		
HOMO	0.363		
VDW14	0.003	0.697	1.165
Torsion	0.101		
MullikenCharges N8	12.685		
LUMO	0.510		
HOMO	0.900		
bondN8C10	11.806		

Table 8: The selected results for calculating pKa values by AM1 method

Parameter	Coeff
VDW14	0.003
Torsion	0.101
MullikenCharges N8	12.685
LUMO	0.510
HOMO	0.900
bondN8C10	11.806
(Constant) =1.550	
R ² =0.697	
Std. Error =1.165	
No of observation =9	

Using equation(2), the theoretical value of pKa were calculated. The differences between the experimental and calculated values of pKa are listed in table (9).

Table 9: Comparision between the experimental and calculated values from AM1 method

Comp. No.	Pka(ex)	Pka(th)	Res
1	9.4592	9.3797	0.0795
2	5.6851	6.1773	-0.4922
3	4.9479	4.7411	0.2068
4	6.2875	6.4212	-0.1337
5	5.1803	6.9208	-1.7405
6	5.3394	4.4011	0.9383
7	6.8191	5.8207	0.9984
8	5.4738	6.1528	-0.6790
9	4.8891	5.2512	-0.3621
10	6.2218	6.5055	-0.2837
11	5.2280	6.9601	-1.7321
12	5.2361	5.0671	0.1690
13	6.2664	6.0397	0.2267
14	9.0129	7.4545	1.5584
15	9.0349	8.3146	0.7203
16	8.8539	8.3007	0.5532

PM3 method:

The parameters calculated by PM3 method (listed in table (3)) are treated in the same way as in AM1 method. The results of the analyses are listed in Tables 10, 11 and 12. The results of table (12) can be written in equation (3).

$pK_a = 1454.444 + 18.604 MC(N8) - 377.648 \text{ bond}(N8-C10) + 0.112 (\text{Torsion}) - 305.880 \text{ bond}(C7-N8) - 357.630 (\text{bond } C6-C7) + 1.196 (\text{VDW } 1,4)$ (3).

The results of Table (13) obtained by the application of PM3 model showed better results than AM1 indicated by higher values of R² (0.878) and lower value of SE (0.739). Good consistency are noticed between the experimental and the calculated value of pKa (Table 13).

Concentrating on the parameters of equation (3), it can be seen that, the most effected parameters on pKa values are the bonds connected the two rings of the studied Schiff bases in addition to charge on the nitrogen atom of the imine bond. These bonds representing the center of electronic movement across the two rings and determine the spatial arrangement of the compound. These kinds of parameters affect the values of pKa as a result.

Table 10: Simple regression analysis results of the application of PM3 method

Parameters	pKa	TE	HOMO	LUMO	LUMO-HOMO	Mulliken Charge N8	bondC7N8	bondC6C7	bondN8C10	Torsion	Non14VDW	VDW14
pKa	1.000											
Total Energy	0.318	1.000										
HOMO	0.019	0.298	1.000									
LUMO	0.393	0.057	-0.263	1.000								
LUMO-HOMO	0.365	-0.000	-0.428	0.985	1.000							
Mulliken Charge N8	0.731	0.166	-0.272	0.402	0.426	1.000						
bondC7N8	0.165	0.857	0.137	-0.274	-0.282	0.096	1.000					
bondC6C7	0.035	-0.242	0.342	-0.384	-0.422	0.069	-0.344	1.000				
bondN8C10	-0.563	-0.838	-0.257	0.108	0.147	-0.407	-0.773	-0.050	1.000			
Torsion	0.601	-0.139	-0.212	0.487	0.494	0.677	-0.206	0.025	0.022	1.000		
Non14VDW	-0.604	-0.019	0.274	-0.494	-0.512	-0.547	0.024	0.137	0.093	-0.896	1.000	
VDW14	-0.447	-0.873	0.014	-0.103	-0.099	-0.378	-0.862	0.352	0.889	-0.009	0.202	1.000

Table 11: Multiple regression analysis results of several attempts by PM3 method

var	Coeff	R ²	Std.E
MullikenCharges N8	73.211	0.619	1.086
bondN8C10	-59.038		
MullikenCharges N8	27.114	0.712	0.983
bondN8C10	-89.461		
Torsion	0.109		
MullikenCharges N8	15.619	0.764	0.929
bondN8C10	-152.295		
Torsion	0.107		
bondC7N8	-245.121		
MullikenCharges N8	9.956	0.807	0.882
bondN8C10	-199.073		
Torsion	0.103		
bondC7N8	-424.845		
bondC6C7	-136.728		
MullikenCharges N8	18.604	0.878	0.739
bondN8C10	-377.648		
Torsion	0.112		
bondC7N8	-305.880		
bondC6C7	-357.630		
VDW14	1.196		

Table 12: The selected results for calculating pKa values by PM3 method

Parameter	Coeff
Mulliken Charges N8	18.605
bondN8C10	-377.648
Torsion	0.112
bondC7N8	-305.881
bondC6C7	-357.631
VDW14	1.196
(Constant) =	1454.444
R ² =	0.878
Std. Error =	0.739
No of observation =	16

Table 13: Comparison between the experimental and calculated pKa from by PM3 method

Comp. No.	Pka(ex)	Pka(th)	Res
1	9.4592	9.4478	0.0114
2	5.6851	6.1072	-0.4221
3	4.9479	5.6246	-0.6767
4	6.2875	5.6414	0.6461
5	5.1803	5.9946	-0.8143
6	5.3394	5.8801	-0.5407
7	6.8191	5.9242	0.8949
8	5.4738	4.8498	0.6240
9	4.8891	5.2853	-0.3962
10	6.2218	6.5837	-0.3619
11	5.2280	5.7677	-0.5397
12	5.2361	4.4623	0.7738
13	6.2664	6.2215	0.0449
14	9.0129	9.2342	-0.2213
15	9.0349	8.4771	0.5578
16	8.8539	8.4289	0.4250

HF and MP2 methods:

The two Ab initio methods of HF and MP2 are also treated in the same way as in the semi empirical (AM1 and MP3) methods. The results of the analysis of HF and MP2 are portrayed in Tables (14-17) and (18-21) respectively. Similar trends in the relation between pKa and Mullikan charges, Vander waals interactions, and torsion. Both Mullikan and lowding charges showed good relation with the kinetic (KE) and total (TE)

energies indicated by the values of correlation coefficient close to unity⁽¹⁷⁾.

These charges are inversely related to the KE and directly related to the TE.

These charges are also inversely related to the Vander waals forces.

Conducting the multiple regression analysis for both HF method (Table (15)) and MP2 method (Table (19)), better results are obtained by HF method ($R^2 = 0.929$, $SE = 0.563$) (Table (16)).

The results of Table (16) obtained from HF method can be expressed by equation (4).

$$pK_a = 361.978 - 0.727 \text{ Non } 1,4 \text{ VDW} + 43.209 \text{ Lowding charge} - 117.860 \text{ bond N8} - \text{C10} + 2.144$$

Table 14: Simple regression analysis results of the application of HF method

Parameters	pKa	KE	TE	HOMO	LUMO	LUMO-HOMO	Lowding Chareg	Mulliken Charge sN8	Bond C7N8	Bond C6C7	Bond N8C10	Torsion	Non14VDW	VDW14
pKa	1.000													
KE	-0.327	1.000												
TE	0.326	-1.000	1.000											
HOMO	0.097	0.438	-0.438	1.000										
LUMO	0.521	-0.268	0.268	-0.187	1.000									
LUMO-HOMO	0.373	-0.419	0.418	-0.615	0.890	1.000								
LowdingChareg	0.390	-0.980	0.980	-0.419	0.246	0.392	1.000							
MullikenCharge sN8	0.599	-0.865	0.865	-0.401	0.548	0.626	0.864	1.000						
bondC7N8	-0.212	-0.161	0.161	-0.126	0.221	0.236	0.064	0.234	1.000					
bondC6C7	-0.377	0.200	-0.200	0.318	-0.704	-0.713	-0.144	-0.366		1.000				
bondN8C10	-0.017	-0.787	0.787	-0.474	0.346	0.498	0.714	0.742	0.602		1.000			
Torsion	0.601	0.130	-0.130	0.126	0.605	0.427	-0.114	0.370	0.091	0.335	-0.017	1.000		
Non14VDW	-0.604	0.041	-0.040	0.138	-0.612	-0.555	-0.046	-0.496	0.231	0.336	-0.181	-0.896	1.000	
VDW14	-0.447	0.920	-0.920	0.569	-0.294	-0.500	-0.931	-0.891	0.148	0.373	-0.703	-0.009	0.202	1.000

Table 15: Multiple regression analysis results of several attempts by HF method

Var	Coeff	R ²	Std..E
Non14VDW	-0.564	0.4963	1.250
LowdingChareg	15.870		
Non14VDW	-0.682	0.810	0.798
LowdingChareg	41.185		
bondN8C10	-128.822		
Non14VDW	-0.700	0.863	0.706
LowdingChareg	43.227		
bondN8C10	-114.803		
HOMO	1.540	0.927	0.540
Non14VDW	-0.621		
LowdingChareg	43.265		
bondN8C10	-116.253		
HOMO	1.967		
bondC6C7	-100.719	0.929	0.563
Non14VDW	-0.727		
LowdingChareg	43.209		
bondN8C10	-117.860		
HOMO	2.144		
bondC6C7	-106.430		
Torsion	-0.029		

HOMO – 106.430 bond (C6-C7) – 0.029 torsion (4).

While the results given by MP2 method (Table 22). Can be written as in equation (5).

$$pK_a = 167.317 - 18.094 \text{ MC} - 178.628 \text{ bond (N8-C10)} + 77.627 \text{ bond (C7-N8)} + 1.121 \text{ LUMO} + 0.235 \text{ Torsion} + 78.363 \text{ lowding charge} \dots (5)$$

Using eqs (4) and (5) to calculate the values of pKa gave the results listed in

Tables (17 and 21) respectively. Good consistency is noticed between the experimental and calculated pKa⁽⁵⁾.

Table 16: The selected results for calculating pKa values by HF method

Parameter	Coeff
Non14VDW	-0.727
LowdingChareg	43.209
bondN8C10	-117.860
HOMO	2.144
bondC6C7	-106.430
Torsion	-0.029
(Constant) = 361.978	
R ² = 0.929	
Std. Error = 0.563	
No of observation = 16	

Table 17: Comparison between the experimental and calculated pKa from by HF method

Comp. No.	pka(ex)	pka(th)	Res
1	9.4592	9.4367	0.0225
2	5.6851	6.2533	-0.5682
3	4.9479	5.3905	-0.4426
4	6.2875	6.1483	0.1392
5	5.1803	5.4371	-0.2568
6	5.3394	4.9584	0.3810
7	6.8191	6.8655	-0.0464
8	5.4738	5.7744	-0.3006
9	4.8891	5.2800	-0.3909
10	6.2218	5.8092	0.4126
11	5.2280	5.0955	0.1325

12	5.2361	4.7824	0.4537	15	9.0349	7.9606	1.0743
13	6.2664	6.4277	-0.1613	16	8.8539	8.7521	0.1018
14	9.0129	9.5404	-0.5275				

Table 18: Simple regression analysis results of the application of MP2 method

Parameters	pKa	KE	TE	HOMO	LUMO	LUMO-HOMO	Lowdin g Chareg	Mulliken Charges N8	bondC 7N8	bondC 6C7	bondC3 C10	Torsi on	Non14V DW	VD W14
pKa	1.000													
KE	-0.327	1.000												
TE	0.327	-1.000	1.000											
HOMO	-0.285	0.532	-	1.000										
LUMO	0.259	0.248	-	-0.003	1.000									
LUMO-HOMO	0.366	-0.049	0.049	-0.498	0.868	1.000								
LowdingChareg	0.522	-0.948	0.948	-0.629	-0.187	0.150	1.000							
MullikenChargesN8	0.632	-0.771	0.771	-0.608	0.086	0.376	0.901	1.000						
bondC7N8	0.477	-0.972	0.972	-0.609	-0.223	0.109	0.989	0.864	1.000					
bondC6C7	-0.034	-0.308	0.308	-0.466	-0.512	-0.213	0.380	0.329	0.354	1.000				
bondN8C10	0.421	-0.948	0.948	-0.656	-0.110	0.230	0.974	0.913	0.970	0.388	1.000			
Torsion	0.601	0.130	-	-0.130	0.478	0.479	0.123	0.507	0.037	0.065	0.141	1.000		
Non14VDW	-0.604	0.041	-	0.321	-0.344	-0.458	-0.266	-0.586	-0.208	-0.105	-0.299	-	1.000	
VDW14	-0.447	0.920	-	0.633	0.287	-0.065	-0.962	-0.821	-0.974	-0.386	-0.932	-	0.202	1.000

Table 19: Multiple regression analysis results of several attempts by MP2 method

var	Coeff	R ²	Std.E
MullikenCharges N8	27.571	0.584	1.184
bondN8C10	-73.904		
MullikenCharges N8	32.127	0.736	0.941
bondN8C10	-231.560		
bondC7N8	63.839		
MullikenCharges N8	26.921	0.798	0.861
bondN8C10	-248.159		
bondC7N8	81.828		
LUMO	0.936		
MullikenCharges N8	-12.448	0.868	0.729
bondN8C10	-175.530		
bondC7N8	113.415		
Torsion	0.232		
LUMO	1.000		
MullikenCharges N8	-18.094	0.892	0.695
bondN8C10	-178.628		
bondC7N8	77.623		
LUMO	1.121		
Torsion	0.236		
LowdingChareg	78.363		

Table 20: The selected results for calculating pKa values by MP2 method

Parameter	Coeff
MullikenCharges N8	-18.094
bondN8C10	-178.628
bondC7N8	77.622
LUMO	1.121
Torsion	0.235
LowdingChareg	78.363
(Constant)	=167.317
R ²	=0.892
Std. Error	=0.695
No of observation	=16

Table 21: Comparision between the experimental and calculated pKa from by MP2 method

Comp. No.	pka(ex)	pka(th)	Res
1	9.4592	9.4527	0.0065
2	5.6851	6.4323	-0.7472
3	4.9479	5.5601	-0.6122
4	6.2875	6.5106	-0.2231
5	5.1803	5.6888	-0.5085
6	5.3394	5.0551	0.2843
7	6.8191	6.7458	0.0733
8	5.4738	5.6244	-0.1506
9	4.8891	5.2075	-0.3184
10	6.2218	6.0555	0.1663
11	5.2280	5.3475	-0.1195
12	5.2361	4.3972	0.8389
13	6.2664	6.0280	0.2384
14	9.0129	9.4994	-0.4865
15	9.0349	7.6858	1.3491
16	8.8539	8.6447	0.2092

Conclusion

Comparison of the results obtained from the four methods AM1, PM3, HF and MP2 in terms of R² and SE values can be concluded as in Table (22).

Table 22: comparison of the results obtained from AM1, PM3, HF and MP2 methods

Method	R ²	SE
AM1	0.697	1.165
PM3	0.879	0.739
HF	0.929	0.563
MP2	0.892	0.695

Looking at Table (22) and the comparison between the experimental and the calculated values of pKa listed in tables (9, 13, 17 and 21), it can be concluded that, A preference is given to method among the other used for achieving this study⁽¹⁸⁾. Best matching among the experimental and the theoretical values of pKa are observed by HF method. According to these results, the validity of the chosen parameters for such application are justified.

Relying on the quality of the statistical results obtained so far, additional test is carried out for this method by calculating the values of pKa for a number of hypothetical compounds of similar structure but with different substituents and were not included in the regression analysis (with studied compounds). These compounds have the structures shown in figure (2)

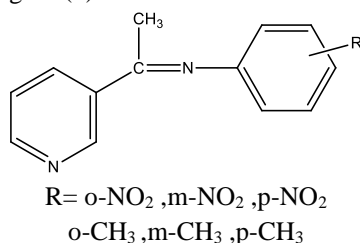


Fig. 2: hypothetical compound used to test the applied methods for calculating pKa value

The values of the parameters involved in equations (2-5) for these compounds are listed in Table (23). The calculated pKa of these compounds are listed in Table (23).

Table 23: the parameters of the hypothetical compounds calculated by using AM1, PM3, HF and MP2 methods, and involved in eq. 2-5.

Comp	pka (AM1)	pka (PM3)	pka (HF)
o-NO ₂	6.1961	15.1261	5.9959
m-NO ₂	4.6854	8.9076	4.9932
p-NO ₂	4.4511	10.1218	6.1354
o-CH ₃	6.1655	8.8746	5.2989
m-CH ₃	5.0303	7.6183	5.8411
p-CH ₃	4.7198	7.7236	6.0226

The pKa values of the hypothetical compounds calculated by eq (2-5) are listed in Table (23). The obtained values of pKa appearing to be of acceptable and consistent range indicating good prediction power and may be good reliability.

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