

Theoretical Study for the Estimation of Pka Values of a Number Ofschiff Bases Using Parameters Derived from Quantum Mechanical Methods

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Abstract

This study included correlation analysis of the experimentally determined pKa values of nine Schiff bases with theoretically derived parameters based on three models of quantum mechanical calculations. Two of them are semi empirical (Austin Method 1 (AM1), and Parameterized Model 3 (PM3)) and the third is an ab initio (Hartree Fock (HF) method, The last method is determined at 6.311 G (d, p) basis set level of theory. The suggested parameters to undergo this study are electronic and energetic in nature, involving the atomic charges (Mullikan and Lowding), the total energy of molecule, bend, stretch, torsion, length of the imine bond (C=N) and other bonds connected to imine. Other parameters are represented by the energies of the HOMO and LUMO orbitals, Kinetic Energy (KE) and two types of Vander Waals interactions, of the 1,4 type (VDW1,4) and non1, 4 type (Non 1,4 VDW). The procedure followed for achieving this work is first by simple correlation between the pKa values with each of the suggested parameters. Relying on the obtained results, multiple Linear Regression Analysis (LRA) is performed. Three sets of parameters are derived from the applied methods AM1, PM3 and HF. The selected set of each method is used to estimate the pKa values of the compounds under consideration theoretically. Comparison of the experimental pKa with those determined theoretically are achieved. A preference is given in favor of AM1 over the other two methods in terms of correlation coefficient (R2) and Standard Error (SE). Additional test is introduced for verifying this method of calculation. The pKa for a number of compounds found in the literature and not involved in the regression analysis are calculated by the derived equations and compared with their experimental results. Good agreement between the practical and calculated pKa (s) are obtained. This procedure of calculation is proved to be of greet forecasting power and sufficient confidence level.

Keywords: pKa; Schiff bases; Correlation analysis; AM1; PM3; HF

Introduction

Schiff Bases are compounds of great importance due their various applications in many fields; and because of their physiological and biological activities [1,2]. They have been used in the field of industrial applications as corrosion inhibitors and in the manufacture of polymers and dyes [3,4]. They were also use as selective and sensitive reagents in the determination of metals by forming colored complexes with a number of metal ions [5]. Schiff bases were used in the field of medicine and pharmacy applications as they were used as antimicrobials; anti-bacteria and antifungal. In addition; they were used in the field of biological application [6,7].

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Schiff bases have gained great importance especially in the field of pharmacy and pharmaceutical compounds [8]; due to the presence of imine ($C=N$) groups in their structures and ease of preparation from a wide range of substituted amines and aromatic aldehydes. For this reason; Schiff bases have acquired superb activities and become of great importance in such type of applications; which motivated many researchers and encouraged them to work in this field [7,9].

The value of the acid dissociation constant (pK_a) is an important chemical function that helps in determining the chemical behavior of many types of compounds such as Schiff bases [10]. They estimate the ionization ratio of these compounds in the aqueous solution that result in hydronium ion and the conjugate base of the dissociated compound. Of the most important applications of this function is the determination of the stability of a drug; its distribution in the body; and its absorption [11]. This function can also be used as a measure of the acid strength. Mathematically; the pK_a values are equal to the negative value of the logarithm of the acid ionization constant (K_a). The low value of pK_a indicates to the strength of the acid and to the farthest dissociation of the acid in water. The acidity in this case is related to the stability of the resulted conjugate base of the ionization process; which in turn its stability depends on its ability to circulate the new pair of electrons found on its structure due to ionization. The value of pK_a therefore affected by electronic (inductive and electronegativity) factors represented by electrons donating or withdrawing substituents. The presence of an imine group ($C=N$) in the structure of the Schiff base makes the aromatic ring rotate in order to minimize the strain that could be raised as a result of substitution of large molecules spatially adjacent on the rings. The pK_a values are sensitive to change in electronic effects as well as to the geometry resulting from the spatial distribution of the molecule. Such factor can be estimated by quantum mechanical methods [7,12] in term of parameters such as electronic density and charges. Total energy of the molecule; energies of the molecular orbitals HOMO and LUMO and other descriptors will be presented later in this paper [13]. Although there are several practical methods were employed for the estimation the pK_a values; but they are all incapable of presenting the effects of these factors quantitatively.

This case gives preference to theoretical methods as well as it obviates the need for laboratory devices and chemicals in the absence of them. In this work three methods of quantum mechanics have been used to test the ability of such methods to evaluate the pK_a values of the Schiff base selected for this study and to predict the value of pK_a for compounds of related structures without need to the lab work [14]. Two of these methods designated as semi empirical methods Austin (AM1); Parameterized (PM3) methods. The third one known as an ab-initio method and named as Hartree Fock (HF) [15]. The pK_a value has become one of the most commonly used physicochemical functions especially due to its relation to the concept of the acidity function pH. Several experimental methods have been employed for the determination of the pK_a values [18]; and its calculation is of interest for many researchers in the field.

Calculation Methods

As an initial step; experimental pK_a values of nine Schiff bases were collected for doing this work [16]. According to their pK_a values five of them behave as strong bases; and the other four are weak acids. The name; pK_a values; and structures of the selected compounds are listed in **TABLE 1**; according to **FIG 1**.

The procedure of calculation is carried out by employing Chem. Office package (version 12; 2010; of Cambridge software; USA) for evaluating the selected parameters and SPSS (V.18) program is used for correlating these parameters with the practical pK_a values in order to determine the most effective parameters those giving the best description and predicting the pK_a values by multiple regression analysis results in terms of Standard Error (SE) which should be less than 5% of the experimental values and correlation coefficient (R^2) close to unity. These procedures were achieved as follow:

The most stable conformers (with minimum energy) of the nine Schiff bases were obtained by energy minimization. The methods

AM1 and PM3 are performed starting from this level of energy while the ab initio method HF is carried out by employing gradient technique at 6-311G (d,p) basis set; starting from the most stable conformer obtained by the semi empirical methods. This procedure is followed to ensure that; all the applied methods are achieved by starting from the same energy level represented by the conformer with minimum energy.

The energy minimization process helps to calculate the atomic charges and evaluating different structural parameters such as; total energy (TE); bond lengths and bond angles; two types of Vander Waals interactions (1,4VDW and Non 1,4VDW) torsion, stretch, bond. Two types of atomic charges are determined (Mullikan and lowding charges). The Energies Of The Highest Occupied Molecular Orbital (EHOMO) and the Lowest Unoccupied Molecular Orbital (ELUMO) are calculated. Other parameters as will be mentioned later are evaluated for the three methods considered in this work.

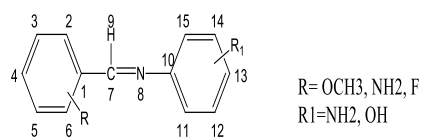


FIG. 1. Structure and numbering atoms of the selected compounds listed in TABLE 1.

TABLE 1. Experimental values of pKa [16]; and structure of Schiff bases selected for this study according to FIG. 1.

| No | Compound | pKa (Exp) |
|----|---|-----------|
| 1 | R=4-OH; R ₁ =13-NH ₂ | 5.5703 |
| 2 | R=4-OCH ₃ ; R ₁ =13-NH ₂ | 12.0071 |
| 3 | R=4-OCH ₃ ; R ₁ =14-NH ₂ | 12.6649 |
| 4 | R=11-NH ₂ ; R ₁ =11-OH | 6.0452 |
| 5 | R=6-NH ₂ ; R ₁ =12-OH | 5.0654 |
| 6 | R=6-NH ₂ ; R ₁ =13-OH | 6.4392 |
| 7 | R=6-F; R ₁ =11-OH | 10.839 |
| 8 | R=6-F; R ₁ =12-OH | 12.0386 |
| 9 | R=6-F; R ₁ =13-OH | 11.0559 |

Linear Regression Analysis (LRA)[13,17]

LRA is carried out in order to correlate the practical values of pKa for the collected compounds [16]; with the descriptors used as parameters obtained from the AM1; PM3 and HF methods; calculated by using Chem. Office program (version 12; 2010 Cambridge; USA).

Statistical analysis is then performed by applying simple (eq.1) and multiple (eq.2) LRA which can be expressed by the following equations.

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$$Y = b + ax \dots\dots(1)$$

$$Y = b + \sum_i aX_i \dots\dots(2)$$

Where Y is the experimental pKa values; b is a constant; Xi is the parameters determined by quantum mechanical methods; and ai(s) are the coefficient of X representing the weight of X that affecting Y. The estimation of the success of the derived equation is determined in terms of the correlation coefficient (R2) and Standard Error (SE); in which R2 should be close to unity and SE Less than 5% of experimental value in addition; the selected parameters must have a physical significance in terms of the theoretical aspects.

Results and Discussion

The practical values of pKa selected for undertaking this study are determined by potentiometric calculations [16]. These values are thought to be affected by the steric energies raised due to the geometrical distortion produced as a result of the spatial congestion; and the electronic nature of the substituents; existing on the structure of the compounds under consideration; as being electron withdrawing or donating groups. The descriptors suggested as parameters are therefore presented to describe these effects depending on quantum mechanical methods. The energetic parameters resulted from geometrical distortion such as Vander Waals interactions; total energy of the compounds; torsion; bond length; bond angles especially those connected to the (C=N) and the ionized bonds (O-H) are determined. Other parameters thought to be important for this study; such as the energies of the molecular orbital HOMO and LUMO are calculated. The electronic factor is expressed by atomic charges (Mullikan and lowding) on the hetro atoms (O,N) of the compounds. The net charges are raised as result of electron donating and withdrawal nature of the substituents and their ability to circularizing charges overall the molecular structures by resonance and inductive effect. The positions thought to be effective on the pKa values of the Schiff bases selected for this study are shown in FIG 1.

TABLE 2. Results obtained from applying AM1 method.

| Comp. | pKa | TE | H | L | L-H | MC-N8 |
|-------|----------|------------|-----------|----------|-----------|---------|
| 1 | 5.5703 | -59101.443 | -10.021 | -3.711 | 6.31 | -0.1578 |
| 2 | 12.0071 | -62681.651 | -10.052 | -3.722 | 6.33 | -0.156 |
| 3 | 12.6649 | -62680.768 | -10.044 | -4.47 | 5.574 | -0.1678 |
| 4 | 6.0452 | -59098.686 | -7.377 | -3.492 | 3.885 | -0.1917 |
| 5 | 5.0654 | -59100.365 | -9.68 | -4.292 | 5.388 | -0.2122 |
| 6 | 6.4392 | -59100.593 | -9.533 | -3.951 | 5.582 | -0.2103 |
| 7 | 10.839 | -64868.375 | -9.959 | -4.476 | 5.483 | -0.1112 |
| 8 | 12.0386 | -64873.049 | -10.008 | -4.68 | 5.328 | -0.1638 |
| 9 | 11.0559 | -64873.886 | -10.008 | -4.335 | 5.673 | -0.1521 |
| Comp. | bondC7N8 | bondC1C7 | bondN8C10 | Torsion | Non1;4VDW | VDW1;4 |
| 1 | 1.2909 | 1.4697 | 1.405 | -15.4224 | 0.2303 | 13.6183 |
| 2 | 1.2914 | 1.469 | 1.4058 | -15.3702 | 1.1341 | 17.6256 |
| 3 | 1.291 | 1.4691 | 1.4091 | -15.3366 | 1.1535 | 17.6696 |

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|---------------------------------------|--------|--------|--------|----------|--------|---------|
| 4 | 1.2655 | 1.3528 | 1.2706 | -13.3185 | 0.7637 | 13.7787 |
| 5 | 1.2928 | 1.4627 | 1.4085 | -13.3064 | 0.9039 | 13.7989 |
| 6 | 1.2923 | 1.4643 | 1.4051 | -13.295 | 0.9168 | 13.8125 |
| 7 | 1.2907 | 1.4688 | 1.407 | -12.2788 | 0.8553 | 14.0255 |
| 8 | 1.2906 | 1.4711 | 1.4074 | -12.2777 | 0.9309 | 14.0616 |
| 9 | 1.2908 | 1.4697 | 1.4062 | -12.2783 | 0.9125 | 14.0831 |
| H: HOMO; L: LUMO; MC: Mullikan Charge | | | | | | |

TABLE 3. Results obtained from applying PM3 method.

| Comp. | pKa | TE | H | L | L-H | MC- N8 |
|--------------------------------------|----------|------------|-----------|----------|-----------|---------|
| 1 | 5.5703 | -54014.785 | -10.167 | -3.731 | 6.436 | -0.0594 |
| 2 | 12.0071 | -57450.611 | -10.194 | -3.744 | 6.45 | -0.0562 |
| 3 | 12.6649 | -57450.298 | -10.203 | -4.374 | 5.829 | -0.0679 |
| 4 | 6.0452 | -54010.597 | -9.095 | -4.222 | 4.873 | -0.064 |
| 5 | 5.0654 | -54012.768 | -9.437 | -4.324 | 5.113 | -0.0964 |
| 6 | 6.4392 | -54013.04 | -9.24 | -3.999 | 5.241 | -0.0826 |
| 7 | 10.839 | -59703.501 | -10.015 | -4.364 | 5.651 | 0.0014 |
| 8 | 12.0386 | -59708.132 | -10.162 | -4.58 | 5.582 | -0.0586 |
| 9 | 11.0559 | -59708.549 | -10.161 | -4.254 | 5.907 | -0.0437 |
| Comp. | bondC7N8 | bondC1C7 | bondN8C10 | Torsion | Non1;4VDW | VDW1;4 |
| 1 | 1.2959 | 1.4645 | 1.4273 | -15.4224 | 0.2303 | 13.6183 |
| 2 | 1.2958 | 1.465 | 1.4284 | -15.3702 | 1.1341 | 17.6256 |
| 3 | 1.2963 | 1.4646 | 1.4309 | -15.3366 | 1.1535 | 17.6696 |
| 4 | 1.3006 | 1.461 | 1.429 | -13.3185 | 0.7637 | 13.7787 |
| 5 | 1.3012 | 1.4581 | 1.4351 | -13.3064 | 0.9039 | 13.7989 |
| 6 | 1.3014 | 1.4598 | 1.4323 | -13.295 | 0.9168 | 13.8125 |
| 7 | 1.2944 | 1.4646 | 1.4282 | -12.2788 | 0.8553 | 14.0255 |
| 8 | 1.2956 | 1.4656 | 1.4298 | -12.2777 | 0.9309 | 14.0616 |
| 9 | 1.2961 | 1.4651 | 1.4292 | -12.2783 | 0.9125 | 14.0831 |
| H: HOMO; L:LUMO; MC: Mullikan Charge | | | | | | |

The values of the parameters mentioned above obtained using AM1, PM3 and HF are listed in TABLES 2, 3 and 4 respectively. These methods were used to derive three equations and testing their abilities for the determination of theoretical pKa values for the Schiff bases considered. Those methods are semi empirical (AM1 and PM3) and the ab initio (HF) models. The target equations are determined by three stages as follow:

TABLE 4. Results obtained from applying HF method.

| pKa | KE $\times 10^3$ | TE $\times 10^3$ | H | L | L-H | LC-N8 |
|--------|------------------|------------------|--------|--------|-------|---------|
| 5.5703 | 425.412 | -426.211 | -9.672 | -3.108 | 6.564 | -0.1972 |

| | | | | | | |
|--|-----------------|-----------------|------------------|----------------|------------------|---------------|
| 12.0071 | 449.68 | -450.566 | -9.685 | -3.091 | 6.594 | -0.1964 |
| 12.6649 | 449.682 | -450.566 | -9.711 | -3.898 | 5.813 | -0.2074 |
| 6.0452 | 425.412 | -426.214 | -8.736 | -3.773 | 4.963 | -0.2205 |
| 5.0654 | 425.427 | -426.216 | -8.894 | -3.857 | 5.037 | -0.2379 |
| 6.4392 | 425.428 | -426.215 | -8.981 | -3.532 | 5.449 | -0.2308 |
| 10.839 | 452.623 | -453.561 | -9.519 | -3.961 | 5.558 | -0.1539 |
| 12.0386 | 452.64 | -453.571 | -9.695 | -4.144 | 5.551 | -0.1957 |
| 11.0559 | 452.647 | -453.571 | -9.626 | -3.822 | 5.804 | -0.1889 |
| MC-N8 | bondC7N8 | bondC1C7 | bondN8C10 | Torsion | Non1;4VDW | VDW1;4 |
| -0.7478 | 1.2602 | 1.4693 | 1.4167 | -15.4224 | 0.2303 | 13.6183 |
| -0.7449 | 1.2602 | 1.4682 | 1.417 | -15.3702 | 1.1341 | 17.6256 |
| -0.753 | 1.2601 | 1.4666 | 1.421 | -15.3366 | 1.1535 | 17.6696 |
| -0.8013 | 1.2647 | 1.4555 | 1.4059 | -13.3185 | 0.7637 | 13.7787 |
| -0.8243 | 1.2681 | 1.4563 | 1.4166 | -13.3064 | 0.9039 | 13.7989 |
| -0.8198 | 1.2671 | 1.4594 | 1.4191 | -13.295 | 0.9168 | 13.8125 |
| -0.6883 | 1.2569 | 1.4684 | 1.4143 | -12.2788 | 0.8553 | 14.0255 |
| -0.7399 | 1.26 | 1.4666 | 1.4185 | -12.2777 | 0.9309 | 14.0616 |
| -0.7367 | 1.2593 | 1.4672 | 1.4152 | -12.2783 | 0.9125 | 14.0831 |
| H: HOMO; L: LUMO; MC: Mullikan Charge ; LC: Lowding Charge | | | | | | |

- The first stage included the determination of the parameters suggested for this study and related to the pKa values by employing the Chem Office program. The values of these parameters are listed in **TABLES (2, 3 and 4)** for AM1, PM3 and HF methods respectively. A prior energy minimizations are achieved when applying the semi empirical methods (AM1 and PM3) while the optimization by HF method is carried out at 6-311 G (d, p) basis set and initiating from the most stable conformer obtained by the semi empirical methods so can guarantee that all the calculations in the various methods are started from the same level (molecule with minimum energy).
- As an initial step for the statistical treatment. Correlation between the pKa values and each of the suggested parameters are investigated by using simple regression analysis (**eq.2**). This step helps to understand the nature and the strength of the relation between the pKa and each of the determined parameters and the relations among the parameters themselves. This process can give an idea and helps to making the correct choice of parameters in the next step when applying the multiple LRA. The results of the simple regression analysis carried out on the data obtained from AM1 and PM3 (**Tables 2 and 3**) of the semi empirical models are given in **TABLE 5** and **TABLE 6** respectively.

TABLE 5 indicates that; the best relation of pKa is found with the total energy of the molecule; Mullikan charge existing on the imine nitrogen atoms (MC-N8) and with the Vander Waals interactions. Good relationships are also noticed between the energy of HOMO orbitals with the bond lengths (C7-N8); (C1-C7) and (N8-C10) (**FIG.1**). These bonds are

well related to the energy gaps (LUMO-HOMO) (L-H). The imine bond (C7- N8) is related to the bonds attached to it (C1-C7 and C10-N8). These bonds representing the central part of the studied compounds (**FIG. 1**) which is mostly affected by the electronic movement across the two rings in the structures of Schiff bases by resonance and inductive effects. Electronic movement could also increases the attraction and/or repulsion between the adjacently located substituents reflecting the steric effect. Results of the correlation carried out among the data obtained by PM3 method; are listed in **TABLE 6**. Approximately the same relations as in AM1 model are seen but with weaker strengths.

- The results of the simple LRA mentioned above in point 2 representing a primary step for achieving the multiple LRA and can give a clue when selecting the parameters which best affecting the pKa values in order to derive the required equations as the aim of this work. Several attempts have been undertaken by the application of multiple LRA using two and three parameters **TABLE 7**. No more than three parameters were used for deriving the final equation in order to ensure adequate degree of freedom for the statistical analysis since nine compounds were only used in this study. The results of the various attempts when applying data obtained by AM1 and PM3 are listed in **TABLE 8** and **TABLE 9** respectively. The results of the multiple LRA using data of both methods were unsatisfactorily. Low correlation coefficient (R²) and high SE are noticed. Looking carefully at the values of pKa of the considered Schiff bases; it can be seen that; four of them behaves as weak acids (pKa range from 5.61-5.97) and the other five behaving as strong bases (pKa range from 11.00-12.66). This wide range of variation could not be distinguished by the applied parameters. The higher values of pKa are an indication to the stability of the conjugate base resulted from the ionization process. Their values may be represented as pKb values.

The LRA of these data seems to be not sensitive enough to such variations. It is therefore gives weak relations in the LRA analysis. In order to overcome this problem; a Discriminating Factor (DF) is used as a parameter to distinguish between the acidic and basic (pK) values. This factor is represented by value of unity when (pKa<7.0) and by zero when (pKa>7) as shown **TABLE 7** and **TABLE 8**. The results acquired by applying the AM1 and PM3 after adding the discriminating Factor are shown in **TABLE 8**.

TABLE 5. Values of the correlation coefficients (R) resulted from simple regression of AM1 method.

| parameters | pKa | TE | H | L | L-H | MC-N8 | bondC7N8 | bondC1C7 | bondN8C10 | Torsion | Non1;4VDW | VDW1;4 |
|-----------------|--------|--------|--------|--------|-------|-------|----------|----------|-----------|---------|-----------|--------|
| pKa | 1.000 | | | | | | | | | | | |
| TE | -0.892 | 1.000 | | | | | | | | | | |
| H | -0.483 | 0.491 | 1.000 | | | | | | | | | |
| L | -0.553 | 0.688 | 0.579 | 1.000 | | | | | | | | |
| L-H | 0.264 | -0.195 | -0.878 | -0.118 | 1.000 | | | | | | | |
| MC-N8 | 0.623 | -0.751 | -0.414 | -0.299 | 0.328 | 1.000 | | | | | | |
| bondC7N8 | 0.299 | -0.313 | -0.958 | -0.547 | 0.846 | 0.194 | 1.000 | | | | | |
| bondC1C7 | 0.402 | -0.421 | -0.988 | -0.580 | 0.864 | 0.317 | 0.988 | 1.000 | | | | |
| bondN8C1 | 0.365 | -0.382 | -0.978 | -0.589 | 0.845 | 0.263 | 0.996 | 0.997 | 1.000 | | | |

| | | | | | | | | | | | | |
|------------------|-------|--------|--------|--------|--------|--------|--------|--------|--------|--------|-------|-------|
| 0 | | | | | | | | | | | | |
| Torsion | 0.029 | -0.392 | 0.147 | -0.475 | -0.458 | 0.082 | -0.097 | -0.097 | -0.089 | 1.000 | | |
| Non1;4VDW | 0.630 | -0.436 | -0.134 | -0.400 | -0.071 | -0.061 | 0.156 | 0.136 | 0.159 | 0.107 | 1.000 | |
| VDW1;4 | 0.644 | -0.262 | -0.300 | -0.029 | 0.348 | 0.173 | 0.200 | 0.228 | 0.221 | -0.642 | 0.634 | 1.000 |

TABLE 6 . Values of the correlation coefficients (R) resulted from simple regression of PM3 method.

| parameters | pKa | TE | H | L | L-H | MC-8 | bondC7N8 | bondC1C7 | bondN8C10 | Torsion | Non1;4VDW | VDW1;4 |
|------------------|------------|------------|------------|------------|------------|------------|----------|----------|-----------|---------|-----------|--------|
| pKa | 1 | | | | | | | | | | | |
| TE | - 0.885 | 1 | | | | | | | | | | |
| H | -0.73 | 0.697 | 1 | | | | | | | | | |
| L | - 0.324 | 0.478 | - 0.025 | 1 | | | | | | | | |
| L-H | 0.436 | - 0.326 | - 0.847 | 0.553 | 1 | | | | | | | |
| MC-N8 | 0.492 | - 0.691 | - 0.462 | - 0.131 | 0.316 | 1 | | | | | | |
| bondC7N8 | -0.74 | 0.78 | 0.923 | 0.039 | - 0.749 | - 0.747 | 1 | | | | | |
| bondC1C7 | 0.784 | - 0.761 | - 0.887 | - 0.008 | 0.735 | 0.648 | -0.946 | 1 | | | | |
| bondN8C10 | - 0.336 | 0.365 | 0.502 | - 0.334 | - 0.596 | - 0.705 | 0.709 | -0.774 | 1 | | | |
| Torsion | 0.029 | - 0.404 | 0.255 | - 0.663 | - 0.566 | 0.31 | 0.089 | 0.121 | 0.167 | 1 | | |
| Non1;4VDW | 0.63 | - 0.428 | - 0.057 | - 0.387 | - 0.159 | - 0.061 | 0.014 | 0.025 | 0.37 | 0.107 | 1 | |
| VDW1;4 | 0.644 | - 0.247 | - 0.461 | 0.166 | 0.473 | 0.025 | -0.335 | 0.382 | 0.092 | -0.642 | 0.634 | 1 |

TE= Total Energy; H=HOMO; L=LUMO; L-H =LUMO-HOMO

TABLE 7. Multiple LRA attempts using data obtained by AM1 and PM3 methods.

| AM1 | | | | PM3 | | | |
|----------------|--------|----------------|--------|----------------|--------|----------------|--------|
| Parameter | Coeff. | R ² | SE | Parameter | Coeff. | R ² | SE |
| TE | -0.001 | 0.916 | 1.0669 | TE | -0.001 | 0.912 | 1.0931 |
| Torsion | -0.887 | | | Torsion | -0.92 | | |
| TE | -0.001 | 0.976 | 0.5768 | TE | -0.001 | 0.976 | 0.5765 |
| VDW1;4 | 0.845 | | | VDW1;4 | 0.869 | | |

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|----------------------------|---------|-------|--------|----------|--------|-------|--------|
| TE | -0.001 | 0.977 | 0.6153 | TE | -0.001 | 0.962 | 0.6217 |
| VDW1;4 | 0.86 | | | VDW1;4 | 0.893 | | |
| H | 0.154 | | | H | 0.292 | | |
| TE | -0.001 | 0.977 | 0.6168 | TE | -0.001 | 0.976 | 0.6238 |
| VDW1;4 | 0.854 | | | VDW1;4 | 0.88 | | |
| bondC7N8 | -13.298 | | | bondC7N8 | 46.339 | | |
| TE | -0.001 | 0.979 | 0.5915 | TE | -0.001 | 0.977 | 0.6151 |
| VDW1;4 | 0.841 | | | VDW1;4 | 0.894 | | |
| MC-N8 | -8.393 | | | L | -0.467 | | |
| VDW1;4 | 0.23 | 0.979 | 0.587 | VDW1;4 | 0.219 | 0.977 | 0.6082 |
| MCN8 | -9.887 | | | MCN8 | -8.558 | | |
| DF* | 5.963 | | | DF* | 5.822 | | |
| DF*: Discriminating Factor | | | | | | | |

TABLE 8. Multiple LRA result from AM1 and PM3 methods.

| AM1 | | PM3 | |
|----------------------------|--------|-----------------------|--------|
| Parameter | Coeff | Parameter | Coeff |
| VDW1;4 | 0.23 | VDW1;4 | 0.219 |
| MC-N8 | -9.887 | MC-N8 | -8.558 |
| DF* | 5.963 | DF* | 5.822 |
| (Constant)=0.704 | | (Constant)=2.123 | |
| R ² =0.979 | | R ² =0.977 | |
| Std. Error=0.5870 | | Std. Error=0.6082 | |
| No of observation=9 | | No of observation=9 | |
| DF*: Discriminating Factor | | | |

The results of TABLE 8 showed considerable improvement in the LRA (R²=0.979; SE=0.587 for AM1 and R²=0.977; SE=0.608 for PM3 methods). These results can be expressed as in equations (3) and (4) respectively.

$$pK_a = 0.704 + 0.230(\text{VDW1;4}) - 9.887\text{Muliken charge N8} + 5.963\text{DF} \dots (3)$$

$$pK_a = 2.123 + 0.219\text{VDW} - 8.558\text{Muliken charge N8} + 5.822\text{DF} \dots (4).$$

Equations (3 and 4) are used to estimate the values of pK_a. The calculated values are given in TABLE 9.

TABLE 9. Comparison between the experiment and calculated pK_a values obtained from AM1 and PM3 methods.

| pK _a (exp) | AM1 | | PM3 | |
|-----------------------|-----------------------|---------|-----------------------|-------|
| | pK _a (cal) | *Resd | pK _a (cal) | *Resd |
| 5.5703 | 5.3964 | 0.1739 | 5.6138 | -0.04 |
| 12.0071 | 12.2633 | -0.2562 | 12.286 | -0.28 |
| 12.6649 | 12.39 | 0.2749 | 12.3957 | 0.27 |

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| | | | | |
|--------------------------|---------|---------|---------|-------|
| 6.0452 | 5.7684 | 0.2768 | 5.6882 | 0.36 |
| 5.0654 | 5.9758 | -0.9104 | 5.97 | -0.9 |
| 6.4392 | 5.9601 | 0.4791 | 5.8548 | 0.58 |
| 10.839 | 10.9923 | -0.1533 | 11.0046 | -0.17 |
| 12.0386 | 11.5207 | 0.5179 | 11.526 | 0.51 |
| 11.0559 | 11.4099 | -0.354 | 11.4032 | -0.35 |
| *Resd= pKa Exp - pKacalc | | | | |

Comparing the results obtained from the multiple LRA of AM1 and PM3; listed in **TABLE 8** and the calculated pKa with the experimental values in **TABLE 9**; a preference is given to AM1 method in terms of R² and SE. These results reflected a good prediction power of the calculated pKa and more consistency with experimental values.

The HF Method

This is one of the most important ab initio methods; and is commonly applied in such studies. The parameters determined by applying this method are listed in **TABLE 4**. These parameters are treated in the same way as AM1 and PM3 methods. Simple LRA between the experimental pKa and the parameters determined by HF method **TABLE 4** is carried out. The results are listed in **TABLE 10**. The results in **TABLE 10** reveals that; the pKa values of the considered Schiff bases are highly related to their kinetic and total energies indicated by values of (R) close to unity and to less extent related to the energy of HOMO orbital; Mullikan charges; and with bond length C7N8. The practical pKa also showed mild relation with the bond length of C1C7; Non 1;4 VDW and VDW1; 4 interactions.

Additional relations are noticed among the other parameters themselves. The total energy (TE) is related to the Kinetic energy (KE). The energies of HOMO orbitals are related to Mullikan charges; bond length (C7N8) and (C1C7). The lowing charges are involved with the Mullikan charges and bond length of (C7 N8). The Mullikan charges are related with the bond lengths of (C7N8) and (C1C7). Finally the bond length (C7N8) showed good relationship with the bond length of (C1C7).

The above mentioned results do not largely differ from the AM1 and PM3 methods. They seem to vary in the same trend. This encouraged us to go further for achieving multiple LRA. The same parameters were found to be effective on the pKa values as in the multiple LRA in the semi empirical methods (AM1 and PM3). Samples of the results obtained from various attempts of multiple LRA when applying data obtained by HF method are listed in **TABLE 11**.

TABLE 10. Results of simple LRA applied on data obtained by HF method.

| Parameters | pKa | K E | TE | H | L | L-H | L C | M C- N8 | Bond C7N8 | Bond C1C7 | Bond N8C10 | Torsion | Non1; 4VDW | VDW1; 4 |
|------------|-------|-------|----|---|---|-----|-----|---------|-----------|-----------|------------|---------|------------|---------|
| pKa | 1.000 | | | | | | | | | | | | | |
| KE | 0.966 | 1.000 | | | | | | | | | | | | |

Citation: Al. Hyali E.A.S et al. Theoretical Study For The Estimation Of Pka Values Of A Number Ofschiff Bases Using Parameters Derived From Quantum Mechanical methods. Phys Chem Ind J. 2021;16(2):137.

| | | | | | | | | | | | | | | |
|------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|-------|-------|
| TE | 0.965 | -1.000 | 1.000 | | | | | | | | | | | |
| H | -0.751 | -0.751 | 0.751 | 1.000 | | | | | | | | | | |
| L | -0.276 | -0.348 | 0.348 | -0.120 | 1.000 | | | | | | | | | |
| L-H | 0.344 | 0.297 | -0.297 | -0.770 | 0.726 | 1.000 | | | | | | | | |
| LC | 0.600 | 0.721 | -0.721 | -0.675 | 0.098 | 0.404 | 1.000 | | | | | | | |
| MC-N8 | 0.701 | 0.794 | -0.794 | -0.803 | -0.093 | 0.497 | 0.977 | 1.000 | | | | | | |
| bondC7N8 | -0.735 | -0.796 | 0.796 | 0.851 | 0.042 | -0.562 | -0.932 | -0.981 | 1.000 | | | | | |
| bondC1C7 | 0.666 | 0.696 | -0.696 | -0.966 | 0.217 | 0.808 | 0.790 | 0.874 | -0.899 | 1.000 | | | | |
| bondN8C10 | 0.375 | 0.298 | -0.298 | -0.545 | 0.049 | 0.409 | -0.021 | 0.106 | -0.110 | 0.446 | 1.000 | | | |
| Torsion | 0.029 | 0.198 | -0.199 | 0.266 | -0.720 | -0.647 | 0.199 | 0.085 | 0.020 | -0.235 | -0.285 | 1.000 | | |
| Non1;4VDW | 0.630 | 0.544 | -0.543 | -0.057 | -0.366 | -0.196 | -0.065 | -0.013 | 0.016 | -0.075 | 0.282 | 0.107 | 1.000 | |
| VDW1;4 | 0.644 | 0.479 | -0.478 | -0.469 | 0.232 | 0.474 | 0.077 | 0.211 | -0.294 | 0.362 | 0.402 | -0.642 | 0.634 | 1.000 |

TABLE 11. Multiple LRA attempts using data obtained by HF method.

| Parameter | Coef | R ² | SE |
|------------------|--------|----------------|---------|
| KE | 0.000 | 0.948 | 0.84277 |
| Non1;4VDW | 1.763 | | |
| KE | 0.000 | 0.975 | 0.5824 |
| VDW1;4 | 0.452 | | |
| KE | 0.000 | 0.976 | 0.6313 |
| VDW1;4 | 0.422 | | |
| NonVDW1;4 | 0.375 | | |
| KE | 0.000 | 0.976 | 0.6323 |
| VDW1;4 | 0.528 | | |
| Torsion | 0.097 | | |
| K.E | 0.000 | 0.977 | 0.6121 |
| VDW1;4 | 0.419 | | |
| MC-N8 | -5.532 | | |
| VDW1;4 | 0.240 | 0.977 | 0.6117 |
| MC-N8 | -5.957 | | |
| DF | -5.915 | | |

TABLE 12. Results of the multiple LRA applied on data obtained from HF method.

| HF | |
|-----------|-------------|
| Parameter | Coefficient |

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| | |
|---|--------|
| VDW1;4 | 0.24 |
| MC-N8 | -5.957 |
| DF | -5.915 |
| Constant =3.643; R2=0.977; Std. Error=0.6117; No of observation=9 | |

Same problem was precluded the analysis as that encountered us when applying PM3 and AM1 methods. The discriminating factor was added to the regression analysis as a parameter in order to differentiate two pKa features; acidic (pKa<7) and basic (pKa>7). This helped to overcome this problem. The results in **TABLE 12** can be formulated as in equation(5).

$$\text{pKa}=3.643+0.240(1;4\text{VDW})-5.957 \text{ MC-N8 } -5.915 \text{ DF} \dots(5)$$

Theoretical pKa values are calculated by using equation (5) that derived by HF method. The calculated pKa are then compared with experimental pKa values. Results are given in **TABLE 13**.

TABLE 13. Comparison between the experimental and calculated pKa values by applying HF method.

| Comp. No | Pka (ex) | Pka (th) | Res |
|----------|----------|----------|---------|
| 1 | 5.4512 | 5.5703 | 0.1191 |
| 2 | 12.3107 | 12.0071 | -0.3036 |
| 3 | 12.3691 | 12.6649 | 0.2958 |
| 4 | 5.8082 | 6.0452 | 0.2370 |
| 5 | 5.9502 | 5.0654 | -0.8848 |
| 6 | 5.9267 | 6.4392 | 0.5125 |
| 7 | 11.1093 | 10.8390 | -0.2703 |
| 8 | 11.4252 | 12.0386 | 0.6134 |
| 9 | 11.4115 | 11.0559 | -0.3556 |

The results obtained from HF method and those collected from AM1 are compared with the experimental pKa values of the studied compounds in terms of R2 and SE. The results were in favors of AM1 method which gave values (R2=0.979; SE=0.587) while the HF method gave (R2=0.977 and SE=0.611). As a results; the experimental pKa were more consistent with the calculated values when applying AM1 method.

In order to introduce a further assessment for the success of the selected parameters as a test for these methods for such calculation. The derived equation (eq3) by AM1 method is applied to estimate the pKa values for a number of Schiff bases found in the literature [16] (listed in **TABLE 15**) with similar structures (**FIG 2**); and not involved in the regression analysis. The values of the parameters of these compounds needed to apply eq.(3) are listed in **TABLE 14**. The calculated pKa values are then compared with the experimental ones. This comparison is presented in **TABLE 15**.

TABLE 14. Parameters of the compounds given in TABLE 15 and FIG. 2 used for testing the AM1 method (eq.3).

| NO. | pKa (exp) | VDW1;4 | MC-N8 | DF* |
|-----|--------------|---------|---------|-----|
| 1 | 9.4592 | 8.9569 | -0.062 | 1 |
| 2 | 5.6851 | 15.2964 | -0.1537 | 0 |
| 3 | 4.9479 | 15.0549 | -0.1648 | 0 |
| 4 | 6.2875 | 15.1131 | -0.0586 | 0 |
| 5 | 5.1803 | 15.9181 | -0.1568 | 0 |
| 6 | 5.3394 | 15.934 | -0.1742 | 0 |
| 7 | 6.8191 | 15.8658 | -0.1458 | 0 |
| 8 | 5.4738 | 15.5132 | -0.1468 | 0 |
| 9 | 4.8891 | 15.2756 | -0.1506 | 0 |
| 10 | 6.2218 | 15.3226 | -0.0428 | 0 |
| 11 | 5.228 | 16.1271 | -0.1469 | 0 |
| 12 | 5.2361 | 16.1691 | -0.1572 | 0 |
| 13 | 6.2664 | 16.0984 | -0.1319 | 0 |
| 14 | 9.0129 | 16.2451 | -0.1338 | 1 |
| 15 | 9.0349 | 15.3847 | -0.1393 | 1 |
| 16 | 8.8539 | 15.607 | -0.1222 | 1 |

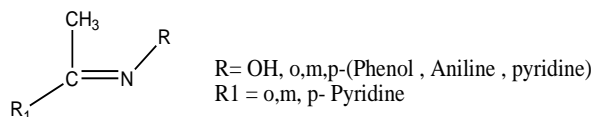


FIG 2. Structure of Schiff bases found in the literature and used to test this procedure.

TABLE 15. Comparison between the experimental values of a number of Schiff bases (as in FIG. 2) found in the literature [16] and calculated by equation(3) (AM1).

| NO. | Comp. | pKa (exp) | pKa (cal) | Resd* |
|-----|-------------------------------|-----------|-----------|---------|
| 1 | R1=m-pyridine; R=OH | 9.4592 | 9.3401 | 0.1191 |
| 2 | R1=m-pyridine; R=o-phenol | 5.6851 | 5.7418 | -0.0567 |
| 3 | R1=m-pyridine; R=m-phenol | 4.9479 | 5.796 | -0.8481 |
| 4 | R1=m-pyridine; R=p-phenol | 6.2875 | 4.7594 | 1.5281 |
| 5 | R1=m-pyridine; R=o-aniline | 5.1803 | 5.9154 | -0.7351 |
| 6 | R1=m-pyridine; | 5.3394 | 6.0911 | -0.7517 |

| | | | | |
|---------------------------|--------------------------------------|--------|---------|---------|
| | R=m-aniline | | | |
| 7 | R1=m-pyridine; R=p-aniline | 6.8191 | 5.7947 | 1.0244 |
| 8 | R1= p-pyridine; R=o-phenol | 5.4738 | 5.7234 | -0.2496 |
| 9 | R1= p-pyridine; R=m-phenol | 4.8891 | 5.7064 | -0.8173 |
| 10 | R1=p-pyridine; R=p-phenol | 6.2218 | 4.6514 | 1.5704 |
| 11 | R1=p-pyridine; R=o-aniline | 5.228 | 5.8656 | -0.6376 |
| 12 | R1=p-pyridine; R=m-aniline | 5.2361 | 5.9771 | -0.741 |
| 13 | R1=p-pyridine; R=p-aniline | 6.2664 | 5.7107 | 0.5557 |
| 14 | R1=o-pyridine; R=o-pyridine; o-OH | 9.0129 | 11.7263 | -2.7134 |
| 15 | R1=m-pyridine; R=o-pyridine; o-OH | 9.0349 | 11.5827 | -2.5478 |
| 16 | R1=p-pyridine; R=o-pyridine; o-OH | 8.8539 | 11.4648 | -2.6109 |
| *Resd=pKa (exp)-pKa (cal) | | | | |

If we check the results listed in **TABLE 15**; it is possible to come up with important information that; the theoretical results refer to which cannot be practically deduced quantitatively. The increase in the ionization process of the acid indicates an increase in the acidity of the considered compound. The acidity (ionization process); in other words; is increasing when the resulting conjugate base is more stable. The magnitude of this ionization is relative since it varies with the presence of different obstacles that weaken the strength of the ionization process such as the formation of the inter and intra molecular hydrogen bonds with the ionizing group; steric effect; and the nonlinearity of the molecule.

The increase in the strength of the hydrogen bond weakens the ionization process and reduces the acidity; i.e. increases the pKa values. When this bond is not represented as a variable in the statistical analysis; its effect will appear as a deviation in the calculated pKa from the practical value. The existence of the spatial effect on the ionized group; as well as the nonlinearity of the molecule; weakens the strength of the hydrogen bonds; thereby increasing the ionization process. As a result; the theoretical pKa value is decreased and shows a positive deviation from the practical values. This deviation representing the average effect resulting from the steric congestion and the nonlinearity of the molecule. The results in **TABLE 15**; showed good consistency between the observed and the practical values of pKa. The differences in the pKa values of the compounds selected to complete this study are related to their structural variation; as follows:

- The compounds with the numbers 2, 5, 8, and 11 have either an OH or NH₂ group at the ortho position and can form an intra-molecular hydrogen bond, except those hindered by the methyl group existing on the carbon atom of the imine bond which cause a small deviation in the calculated pKa values
- Compounds 3, 6, 9 and 12 each has either an OH or NH₂ group at the meta position. The ionization process is impeded by the nonlinearity of the molecules which resulting from the presence of substituents at the meta positions in the phenol, amine and meta-pyridine rings. Their calculated pKa are deviated from the practical values by a magnitude almost equal to that noticed in the compounds mentioned in point 1
- Inter molecular hydrogen bonds are formed by compounds 4, 7 and 10 in which the OH and NH₂ groups are located in para position with respect to an imine bond attached to benzene ring. Its strength varies relatively in the similar compounds when they are substituted at the ortho and meta positions [19]. The theoretical pKa values show a positive deviation from their practical values. This deviation is proportional to the forces resulted from the formation of the hydrogen bond and the nonlinearity of the molecule supporting this result it is found that, the deviation caused by the OH group in compounds 4 and 10 is greater than that caused by the NH₂ group in compound number 7
- Compounds 14, 15 and 16, each has two pyridine rings connected to two ends of the imine bond. An OH group and a nitrogen atom exist in one of the two pyridine rings at ortho positions on the both sides of the imine bond. This arrangement in addition to the presence of N atom in positions o, m, and p in the other pyridine ring could impose non-linear shapes with proximity and direction enables the OH group to interact strongly with the nitrogen atom of the imine bond to form an intra-molecular hydrogen bond which impairs the ionization process and resulting in a deviation in the pKa calculated with respect to the practical values by a magnitude proportional to the strength of the hydrogen bond which as a result decreasing the ionization process and reduces the acidity of these compounds [20]. The increase in the calculated pKa compared to the practical value could be considered as a measure of the strength of the hydrogen bond. The results of (TABLE 15) showed high consistency between the practical pKa values of the compounds used for testing the success of the derived equation (eq3) with their calculated values when using AM1 method.

Conclusion

The results obtained throughout this study concluded that, the quantum mechanical methods can be successfully used for calculation of functions such as pKa values by correlation with theoretically derived parameters estimated by quantum chemical methods. Such calculation of statistical correlation analysis depending on parameters based on quantum mechanical methods could form a high prediction power for evaluation of pKa values as chemical function and may be other functions, saving chemicals, reducing efforts and instruments of different techniques. Additional advantage in favor of the theoretical calculation is obtained. The theoretical method could quantitatively assess the effect of the descriptors (X(s)) indicated by their coefficients (a(s)) values as in equation (2). The coefficient value (a) is representing the weight of the parameter (X) that affecting Y(pKa). This could not be possible to estimate experimentally.

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