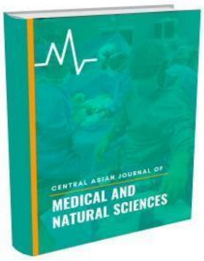

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Article

Ionization Constants of Oximes Using HF and PM3 Quantum Methods

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Abstract: This study investigates the ionization constants of various chemical compounds using two theoretical methods, HF/6-31G and PM3, coupled with multiple regression analysis to correlate these constants with theoretically calculated physical variables. The variables considered include energy functions (HOMO, LUMO, hardness, chemical potential, electrophilicity index, ductility), thermodynamic functions (ΔH, ΔG, ΔS), and dipole moments. The research aims to address the gap in accurately predicting ionization constants through theoretical calculations. The correlation coefficients (R2) were used to evaluate the relationship between practical ionization constants and theoretical variables. The strongest correlations were found with thermodynamic functions, particularly enthalpy (ΔH). Multiple regression analysis identified the best predictors for ionization constants, achieving high R2 values (0.980 for HF/6-31G and 0.993 for PM3). These findings demonstrate a strong alignment between practical and theoretical ionization constants, highlighting enthalpy as the most influential variable. The study underscores the potential of computational chemistry methods to accurately predict ionization constants, aiding in the efficient design and analysis of chemical compounds.

Keywords: HOMO, Hartree-Fock, Ionization constant, LUMO, Quantum methods

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1. Introduction

Ionization constant

The ionization constant is a measure of the strength of the acid and base, equal to the ratio between the concentration of the products to the concentration of the reactants, that is, the concentration of the ionized (disintegrated) acid or base to the concentration of the non-disintegrated or ionized substance [1].

Methods for determining the ionization constant

There are several ways to determine the values of ionization constants for aromatic ketones and organic compounds, including theoretical and practical methods.

Practical methods

These methods depend on practical experiments in the laboratory through which the ionization constant is measured, including:

First - conductivity method, second - optical spectroscopy, third - electrochemical methods, fourth - thermal methods, fifth - stress plating method

Theoretical methods: Due to the progress made in the field of computers and software, many researchers have been forced to use computer programs to create many chemical calculations, including calculating PKa values for many basic and acidic organic compounds. The theoretical methods study the inductive electronic effects, the solubility of compounds, and the resonance of compounds that carry... Negative or positive charge, as well as studying hydrogen bonds and their effect [2]. The scientist Liptak and his group found the values of the ionization constant for the substituted phenolic compounds through standard free energy according to the following equation [3].

$pKa = \Delta G° / 2.303\ RT$ ………..(2)

Since:-

$\Delta G°$: expresses the standard free energy.

R: expresses the general constant for gases.

T: expresses temperature.

Computational Chemistry

Computational theoretical chemistry is one of the advanced, modern, and distinguished branches of chemistry at present. Its goal is to find the most important characteristics of a chemical compound and compare them with the values measured by practical methods. Computational chemistry aims to create effective mathematical approximations to solve theoretical chemistry problems in the fastest time and at the lowest cost and to develop algorithms and computer programs that Calculate properties of molecules such as total energy, dipole moment, van der Waals bonds, and other properties by developing a large number of approximate methods that balance accuracy and computational cost. The term computational chemistry is used when the mathematical method has been developed sufficiently to be applied using a computer. [5,4].

Harty-Fock (HF) method:

Most elementary calculations (ab initio) rely on the orbital approximation method represented by the Hartree-Fock method, which can be abbreviated as (HF), which is one of the basic calculation methods in quantum mechanics and gives good results in finding the energy potential. The value of atomic orbitals when calculating multi-electron wave functions Based on the reduction of nonlinear coupled differential equations to ideal shapes of molecular orbitals using the Variation Method.

Calculations using the Hartree-Fock method are good when this method can accurately estimate the heat of formation of a compound within a few kilocalories per mole, and this method is often not accurate enough to accomplish this. This type of calculation with the required accuracy. In order to be a good measure for this method, the binding energy is considered, which, according to the Hartree-Fock concept, is the amount of acceptable error in this method, the value of which should not exceed (1ev = 1.602 10 J) for each (valence) electronic double [7,6].

Method (PM3):

The (PM3) method uses the same equations used in the (AM1) method. The (PM3) method is more accurate than the (AM1) method in calculating the angles of hydrogen bonds, while the (AM1) method is better than the (PM3) method when calculating the energies of hydrogen bonds. The (AM1) method also gives better results than the (PM3) method when measuring compounds at high temperatures. The difference between the (PM3) method and (AM1) is that each method has an advantage when calculating some elements in the periodic table over the other method, as the (AM1) method can find calculations for the elements falling within the second group of the periodic table, while the (PM3) method is specific to heavy elements. The (PM3) method gives the lowest percentage of error. It gives the best relationship with laboratory measurements, especially the bond lengths, as the calculated and resulting values in this method rely on laboratory experimental methods, and its calculations do not require a very long time when compared to basic calculation methods that require a very long time [9,8].

2. Materials and Methods

Theoretical calculations: Theoretical Calculation

The development taking place in the field of computers and software has prompted many researchers to use theoretical methods to find pka values, and among these programs are (Chem. Office) and the program (Gaussian program Gauss View Gaussian 09). These programs are based on the use of quantum mechanics and molecular mechanics [10].

Two methods (HF/6-31G and PM3) were used. The information obtained using the (Gaussian 09) program is numerous and is:

- Energy of atomic orbitals (HOMO, LUMO)
- Atomic charges.
- transitional status bodies.
- Bacterial dissociation energy.
- Heat of formation.
- Voltage or electrostatic energy.
- The angles between atoms.
- The lengths of the bonds between atoms.
- Total energy.
- Thermodynamic functions.
- Dipole moment.

The distinctive thing about the (Gaussian 09) program is that it contains a huge amount of information. The reason for choosing multiple theories is to conduct a comprehensive survey of most theoretical methods in the fields of computational chemistry and choose the best of these methods and theories in order to obtain the best (pKa) values theoretically [11].

In this study, many variables were calculated using basic methods, including:

- Thermodynamic functions (ΔS, ΔG, ΔH)
- Dipole moment.
- Values of atomic orbital energies (HOMO, LUMO)
- Hardness values, electronic potential, spherical electrophilicity index, and flexibility. Which was calculated based on the values of atomic orbitals (HOMO, LUMO).

Calculations were performed in the following ways:

- HF, Basis set (6-31G).
- PM3

Gaussian 09W program

Steps for theoretical calculations of components in Gaussian 09W program):

- Drawing the molecular formula of compounds using the Chem. Office program.
- Transferring the compound drawn in the Chem. Office program to the)Chem program. 3D)
- Save the compound in the)Chem program. 3D) in file format (Input File)
- Open Gauss View 6.0; after that, the file saved in Input File format will be opened.
- Choose the (Calculate) button, and then choose Gaussian Calculation Setup.
- From the Job Type button, we choose Optimization, and from there, we choose Minimum to obtain the lowest energy, and then the compound will be more stable and have the best vacuum form.
- After that, from the Method button, the theoretical method is chosen, and the basis set is determined.
- After that, we choose Submit, and then the work will be done in the Gaussian 09W program.
- After completing the results, they will be saved via Notepad.

The 10-Statistical analysis is performed using SPSS

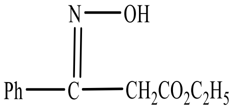
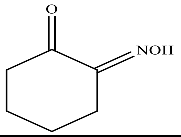
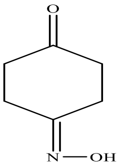
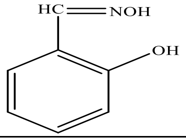
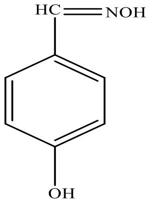
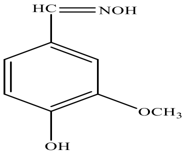
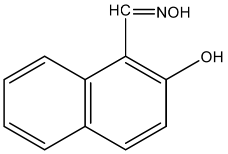
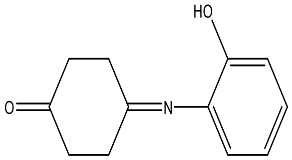
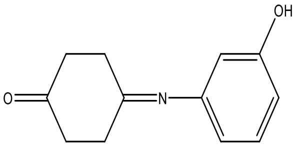
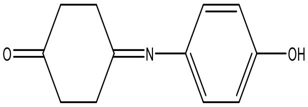
Statistical Analysis

Statistical analysis was done between the selected and calculated variables (hardness, electronic potential, spherical electrophilic index, flexibility, HOMO, LUMO, dipole moment, ΔH, ΔG, ΔS) by theoretical methods with practical (pKa) values using (SPSS) program. The values of the correlation coefficient (R2) were adopted to determine the strength and type of relationship between the calculated variables and the practical (pKa) values [12]. Statistical analysis was conducted between the variables with each other and with the practical (pKa) values using the five methods used according to the following steps:

- The calculated variables (hardness, electronic potential, spherical electrophilicity index, flexibility, HOMO, LUMO, dipole moment, ΔH, ΔG, ΔS) that were studied were entered as unsupported variables with the values of practical ionization constants, which are considered variables. Accredited.
- The calculated variables are analyzed with the values of ionization constants through several steps in the statistical program (SPSS) in the following steps:

  Linear + Regression + Analysis
- After that, the values of the correlation coefficient (R2) are obtained, and through the values of the correlation coefficient (R2), it is known which variables have a significant impact on the values of (pKa) in the simple regression analysis.
- We then conduct a multiple statistical analysis process to determine the strength of the relationship between the variables that were used with each other and with the values of the practical ionization constants.

Table 1. of compound names with practical pKa values for the compounds studied

No	Nomenclature	pKa	
1	Ethyl benzoyl acetate oxime	4.88	 $\mathrm{Ph{-}C({=}N{-}OH){-}CH_2CO_2C_2H_5}$
2	cyclohexanone oxime-2-one	6.59	
3	cyclohexanone oxime-4-one	6.49	
4	2-hydroxy-benzaldoxime	11.39	
5	4-hydroxy-benzaldoxime	11.34	
6	3-methoxy-4-hydroxy-benzaldoxime	10.68	
7	2-Hydroxy-1-naphthyl aldoxime	11.29	
8	2-hydroxy phenyl cycloheximide-4-one	7.14	
9	3-hydroxy phenyl cycloheximide-4-one	7.26	
10	4-hydroxy phenyl cycloheximide-4-one	7.00	

3. Results and Discussion

Theoretical Calculations

The compounds were studied theoretically and their pKa values were extracted theoretically, as a group of variables were calculated for them. Among the variables that were calculated were the thermodynamic functions (HΔ, ΔG, ΔS), the dipole moment, the energy of the orbitals (HOMO, LUMO), the energy functions, hardness, electronic potential, flexibility, and evidence of Spherical electrophilicity, as the ionization constant was calculated for a number of compounds in light of obtaining the best relationship between the variables with each other, and with the ionization constan [13].

Table 2. values of energy functions with dipole moments for the compounds studied using the HF/6-31G method

Comp.	HOMO (e.v)	LUMO (e.v)	Di (e.v)	μ (e.v)	ŋ (e.v)	σ (e.v)	ω (e.v)
1	-0.34110	-0.08613	6.8235	-0.21362	0.127485	0.872515	0.002909
2	-0.39440	-0.11077	4.0127	-0.25259	0.141815	0.858185	0.004524
3	-0.39480	-0.13292	2.5949	-0.26386	0.130940	0.869060	0.004558
4	-0.32127	-0.08761	0.9958	-0.20444	0.116830	0.883170	0.002441
5	-0.31134	-0.10049	2.1287	-0.20592	0.105425	0.894575	0.002235
6	-0.30174	-0.09859	3.1352	-0.20017	0.101575	0.898425	0.002035
7	-0.29100	-0.07178	1.6376	-0.18139	0.109610	0.890390	0.001803
8	-0.30911	-0.10116	1.3698	-0.20514	0.103975	0.896025	0.002188
9	-0.31259	-0.11258	0.8351	-0.21259	0.100005	0.899995	0.002260
10	-0.30173	-0.12439	2.0242	-0.21306	0.088670	0.911330	0.002013

Table 3. values of energy functions with dipole moments for the compounds studied using the PM3 method

Comp.	HOMO (e.v)	LUMO (e.v)	Di (e.v)	μ (e.v)	ŋ (e.v)	σ (e.v)	ω (e.v)
1	-0.35706	-0.01621	4.4687	-0.18664	0.170425	0.829575	0.002968
2	-0.37707	-0.00108	2.5488	-0.18908	0.187995	0.812005	0.003360
3	-0.38617	-0.01337	1.9949	-0.19977	0.186400	0.813600	0.003719
4	-0.33605	-0.01705	0.5459	-0.17655	0.159500	0.840500	0.002486
5	-0.33050	-0.01217	1.5604	-0.17134	0.159165	0.840835	0.002336
6	-0.32313	-0.01288	2.1629	-0.16801	0.155125	0.844875	0.002189
7	-0.31791	-0.03180	0.8797	-0.17486	0.143055	0.856945	0.002187
8	-0.33281	-0.01153	1.2900	-0.17217	0.160640	0.839360	0.002381
9	-0.33591	-0.01511	0.8881	-0.17551	0.160400	0.839600	0.002470
10	-0.32845	-0.01237	1.8977	-0.17041	0.158040	0.841960	0.002295

Table 4. values of thermodynamic functions using HF/6-31G

Comp.	ΔH Hartree/particle	ΔG Hartree/particle	ΔS cal. K^{-1} .mol^{-1}
1	0.258862	0.201464	120.804
2	0.168754	0.127186	87.488
3	0.168970	0.127132	88.055
4	0.149372	0.107574	87.972
5	0.150289	0.107542	89.968
6	0.188046	0.139329	102.534
7	0.204405	0.156745	100.310
8	0.261180	0.208998	109.827
9	0.260560	0.207324	112.046
10	0.260512	0.207127	112.358

Table 5. values of thermodynamic functions by PM3

Comp.	ΔH Hartree/particle	ΔG Hartree/particle	ΔS cal. K^{-1} .mol^{-1}
1	0.239552	0.179030	127.380
2	0.156754	0.114123	89.725
3	0.156543	0.113585	90.411
4	0.141285	0.096365	94.542
5	0.140739	0.095470	95.277
6	0.174190	0.123924	105.793
7	0.191848	0.142475	103.915
8	0.242515	0.188346	114.008
9	0.242011	0.186154	117.560
10	0.242032	0.186739	116.373

Table 6. values of the correlation coefficient R2 for the relationship between variables were calculated theoretically using the (HF/6-31G) method

HF	pka	HOMO	LUMO	Di	ΔH	ΔG	ΔS	μ	ŋ	σ	ω
pka	1	0.2607	0.2002	0.2323	0.0202	0.0197	0.0227	0.3184	0.1214	0.1214	0.2446
HOMO	0.2607	1	0.1846	0.1542	0.1894	0.1775	0.2806	0.9002	0.808	0.808	0.9963
LUMO	0.2002	0.1846	1	0.0544	0.0472	0.0405	0.1158	0.4802	0.9E-05	0.9E-05	0.2142
Di	0.2323	0.1542	0.0544	1	0.0009	0.0001	0.0364	0.0538	0.3003	0.3003	0.1325
ΔH	0.0202	0.1894	0.0472	0.0009	1	0.9987	0.9092	0.1793	0.1418	0.1418	0.1883
ΔG	0.0197	0.1775	0.0405	0.0001	0.9987	1	0.8876	0.1655	0.1361	0.1361	0.1754
ΔS	0.0227	0.2806	0.1158	0.0364	0.9092	0.8876	1	0.2937	0.1777	0.1777	0.29
μ	0.3184	0.9002	0.4802	0.0538	0.1793	0.1655	0.2937	1	0.5105	0.5105	0.9195
ŋ	0.1214	0.808	0.9E-05	0.3003	0.1418	0.1361	0.1777	0.5105	1	1	0.7758
σ	0.1214	0.808	0.9E-05	0.3003	0.1418	0.1361	0.1777	0.5105	1	1	0.7758
ω	0.2446	0.9963	0.2142	0.1325	0.1883	0.1754	0.29	0.9195	0.7758	0.7758	1

Table 7. values of the correlation coefficient R2 for the relationship between variables were calculated theoretically using the (PM3) method

PM3	pka	HOMO	LUMO	Di	ΔH	ΔG	ΔS	μ	ŋ	σ	ω
pka	1	0.3284	0.0018	0.3262	0.0186	0.0202	0.0075	0.3671	0.2683	0.2683	0.3325
HOMO	0.3284	1	0.0759	0.168	0.0862	0.0756	0.1654	0.9462	0.9578	0.9578	0.9935
LUMO	0.0018	0.0759	1	0.005	0.0359	0.0467	7E-05	0.002	0.2182	0.2182	0.0434
Di	0.3262	0.168	0.005	1	0.0091	0.0056	0.0525	0.1672	0.1538	0.1538	0.1612
ΔH	0.0186	0.0862	0.0359	0.0091	1	0.9979	0.8983	0.1231	0.0527	0.0527	0.1043
ΔG	0.0202	0.0756	0.0467	0.0056	0.9979	1	0.8689	0.1141	0.0427	0.0427	0.0931
ΔS	0.0075	0.1654	7E-05	0.0525	0.8983	0.8689	1	0.177	0.1413	0.1413	0.1827
μ	0.3671	0.9462	0.002	0.1672	0.1231	0.1141	0.177	1	0.8178	0.8178	0.9713
ŋ	0.2683	0.9578	0.2182	0.1538	0.0527	0.0427	0.1413	0.8178	1	1	0.9242
σ	0.2683	0.9578	0.2182	0.1538	0.0527	0.0427	0.1413	0.8178	1	1	0.9242
ω	0.3325	0.9935	0.0434	0.1612	0.1043	0.0931	0.1827	0.9713	0.9242	0.9242	1

Table 8. Values of the correlation coefficient R2 for the relationship between pKa values with the variables calculated in the tripartite analysis in the HF/6-31G method

المتغيرات	R^2
HOMO+LUMO+ΔH	0.976
HOMO+LUMO+ΔG	0.968
HOMO+LUMO+ΔS	0.964
HOMO+ΔH+Di	0.980
HOMO+ΔG+Di	0.979
HOMO+ΔG+ΔH	0.980
ΔH+ΔG+ ω	0.973
ΔH+ΔG+ μ	0.954
ΔH+ ω+ μ	0.964
ΔH+ μ+ ŋ	0.976
ΔG+ μ+ ŋ	0.968

Table 9. values of the correlation coefficient R2 for the relationship between pKa values with variables calculated in the SWOT analysis in the PM3 method

المتغيرات	R^2
HOMO+LUMO+ΔH	0.990
HOMO+LUMO+ΔG	0.983
HOMO+ΔH+Di	0.984
HOMO+ΔG+Di	0.985
Di+ΔH+ ŋ	0.992
Di+ΔG+ ŋ	0.993
ΔH+HOMO+ΔG	0.977
ω +ΔG+ΔH	0.950
ŋ +ΔG+ΔH	0.988

Calculating pKa values using the (HF/6-31G) method, as it was found that the best and highest correlation is between the variables (ΔG, ΔH, HOMO) and with the practical (pKa) values, as the value of the correlation coefficient was (R2 = 0.980), as the values of a constant were calculated Ionization is theoretically according to the following equation:

pKa=39.648+(58.239* HOMO)+(108.983* ΔG)+(-142.341*ΔH)

Table 10. The theoretical pKa values calculated using the (HF/6-31G) method

HOMO	58.239			
ΔG	108.983			
ΔH	-142.341			
Constant	39.648			
Compound	HOMO	ΔG	ΔH	pKa
1	-0.34110	0.201464	0.258862	4.892152
2	-0.39440	0.127186	0.168754	6.519037
3	-0.39480	0.127132	0.168970	6.459111
4	-0.32127	0.107574	0.149372	11.39953
5	-0.31134	0.107542	0.150289	11.84383
6	-0.30174	0.139329	0.188046	10.4928
7	-0.29100	0.156745	0.204405	10.68778
8	-0.30911	0.208998	0.261180	7.246349
9	-0.31259	0.207324	0.260560	6.949492
10	-0.30173	0.207127	0.260512	7.56733

Calculating pKa values using the PM3 method, it was found that the best and highest correlation is between the variables (ΔG, Di, ŋ) and with the practical pKa values, as the value of the correlation coefficient was (R2 = 0.993) [14,15]. The ionization constant values were calculated theoretically according to the following equation. :

pKa=37.056+(-0.325* Di)+(-45.948* ΔG)+(-131.065* ŋ)

Table 11. of theoretical pKa values calculated using the PM3 method

Di	-0.325			
ΔG	-45.948			
ŋ	-131.065			
Constant	37.056			
Compound	Di	ΔG	ŋ	pKa
1	4.4687	0.179030	0.170425	5.040849
2	2.5488	0.114123	0.187995	6.344352
3	1.9949	0.113585	0.186400	6.758138
4	0.5459	0.096365	0.159500	11.54594
5	1.5604	0.095470	0.159165	11.30125
6	2.1629	0.123924	0.155125	10.32754
7	0.8797	0.142475	0.143055	11.47415
8	1.2900	0.188346	0.160640	6.928346
9	0.8881	0.186154	0.160400	7.191138
10	1.8977	0.186739	0.158040	7.145451

4. Conclusion

this study demonstrates a significant correspondence between the practical and theoretically calculated ionization constants of various chemical compounds, using HF/6-31G and PM3 methods. The analysis identified thermodynamic functions, particularly enthalpy (ΔH), as the most influential variable affecting ionization constants. The highest correlation coefficients ($R2 = 0.980$ for HF/6-31G and $R2 = 0.993$ for PM3) were obtained with the variables ΔG, ΔH, and HOMO, highlighting the robustness of the chosen theoretical models. These findings underscore the potential of computational chemistry methods in accurately predicting pKa values, which is crucial for the rational design of chemical compounds. Future research should focus on expanding the dataset of chemical compounds and exploring additional theoretical methods to further refine the predictive accuracy of ionization constants, thereby enhancing the applicability of these computational tools in various chemical and pharmaceutical applications.

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