Asian Journal of Chemistry; Vol. 23, No. 1 (2011), 215-218

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Investigation of Quantitative Structure Activity Relationship Parameters on the *m*-Substituted Pyridine Compound: A GAMMESS Study

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(*Received*: 1 February 2010; *Accepted*: 25 August 2010) AJC-9023

The influence of the *meta* substituents on the electronic properties of the pyridine compound were studied using GAMMESS package with Hartree-Fock at basis set (STO-3G) level. Hartree-Fock was used to find the minimization 3D-geometry of the molecules. It can be seen a direct relationship between Hammett constants (σ) and the experimental values (pKa). The charges, HOMO, LUMO, hardness (η), electronic chemical potential (μ), the maximum electronic charges (ΔN_{max}) and global electrophilicity index (ω) were determined and used for prediction the pK_a values.

Key Words: QSAR, Substituent effect, Pyridine compound, pKa Values, Hardness, Global electrophilicity index, HOMO, LUMO.

INTRODUCTION

Resonance plays a more important role as can be seen by resonance structures of pyridine compound. So, pyridine compound has a complete electron delocalization (aromaticity) in the ring as shown in Fig. 1.

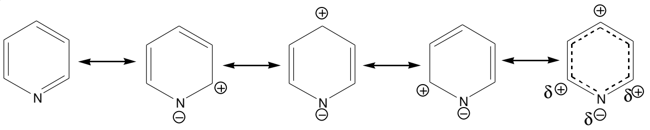


Fig. 1. Resonance phenomenon of pyridine

Quantitative structure activity relationship (QSAR) is commonly used to predict of organic compound. The aim of QSAR is to relate fundamental or surrogate characteristics of a compound and account for variation for related group of chemicals. A secondary aim, if the primary is accomplished is to predict the additional effect of molecular substitutions[1].

Most work employing quantum chemical descriptors has been carried out in the field of quantitative structure activity relationship. The descriptors have been correlated with biological activities such as enzyme inhibition activity and hallucinogenic activity[2,3]. The pharmacological activities of the 2-, 3- and 4-mono derivatives of 1,4-dihydropyridine have been correlated with classical and various quantum chemical parameters[4].

The quantitative structure activity relationship is a widely used approach for organic compounds. Its application to inorganic toxicants is poorly represented in the environmental toxicology literature[5,6]. The quantitative structure activity relationship models are mathematical equation relating chemical structure to their biological activity. They give useful information for drug design and medicinal chemistry[7,8].

Theoretical modeling and simulation methods based on the quantum chemical and statistical theories play a crucial role in understanding the fundamental aspect of a vast range of problems of chemical interest. The major goal of theoretical chemistry is the prediction of structure and properties of simple molecules[9,10].

Electronegativity, hardness and softness are realized in terms of the basic parameters in the DFT[11]. Reinhoudt *et al.*[12] published a linear Hammett relationship for the complex stability of an array of *para*-substituted pyridines complexed to cationic SCS-pincer palladium complexes.

The ^{14}N NQR parameters of 5-R-tetrazolo pyridine and its corresponding tautomer, on the tetrazole-azide isomerization, were calculated at the B3LYP/6-311++G** level of theory and compared with each other[13]. Since most studies have looked at the effect of substitution at the/8/position on the tetrazole-azide equilibrium[14].

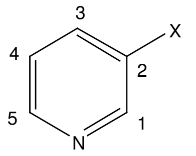
EXPERIMENTAL

All the calculations have been performed using the GAMMESS package. The GAMMESS program was employed for the calculation of different descriptor including dipole moment, charges, bond length, angles, torsion, HOMO, LUMO, hardness (h), electronic chemical potential (m), the maximum electronic charges (ΔN_{max}) and global electrophilicity index (ω).

The regression equations were obtained by the (spss) software. The correlation coefficient (R), standard error (se) and Fisher constant (F) were employed to judge the validity of regression equation. All calculations were run on a Pentium (IV) personal computer (2.4 MB CPU) with the Windows XP operating system.

RESULTS AND DISCUSSION

In this paper, the experimental acidity constant (pK_a) of substituted pyridine compound was calculated its physical properties as shown in Fig. 2.



X= H, CH_3, Cl, CN, NH_2, NO_2, OCH_3, Ph, SCH_3

Fig. 2. Substituted pyridine compound which accounted theoretically

The experimental pK_a values for the substituted pyridine and (σ) values are given in Table-1.

TABLE-1
HAMMETT CONSTANTS (σ) AND EXPERIMENTAL pK_a OF PYRIDINE SUBSTITUENTS

Substituent	pK_a	σ
H	5.2	0.00
m-CH_3	5.7	-0.07
m-Cl	2.8	0.37
m-CN	1.4	0.56
m-NH_2	6.1	-0.16
m-NO_2	0.6	0.71
m-OCH_3	4.9	0.12
m-Ph	4.8	0.06
m-SCH_3	4.4	0.15

Table-2 was showed the calculated parameters like total energy, dipole, HOMO and LUMO.

TABLE-2
CALCULATED RESULTS FOR SUBSTITUENTS OF PYRIDINE USING (STO-3G) BASIS SET

Substituent	Total energy [eV]	Dipole	HOMO [eV]	LUMO [eV]
H	-243.639	2.058	-8.1879	6.5443
m-CH_3	-282.224	2.235	-7.8695	6.6178
m-Cl	-697.645	2.070	-8.1634	6.0001
m-CN	-334.189	3.131	-8.5852	5.1130
m-NH_2	-297.960	2.703	-7.0124	6.6260
m-NO_2	-444.343	3.409	-7.5974	4.1443
m-OCH_3	-356.058	3.211	-7.1947	6.5525
m-Ph	-470.393	2.145	-6.8029	5.5021
m-SCH_3	-675.424	3.518	-7.1838	6.3539

The calculated hardness (η), electronic chemical potential (μ), the maximum electronic charges (ΔN_{max}) and global electrophilicity index (ω) of the molecules[15-17] are shown in Table-3.

TABLE-3
CALCULATED RESULTS FOR HARDNESS (η), ELECTRONIC CHEMICAL POTENTIAL (μ), THE MAXIMUM ELECTRONIC CHARGES (ΔN_{max}) AND GLOBAL ELECTROPHILICITY INDEX (ω) OF PYRIDINE USING (STO-3G) BASIS SET

Substituent	μ [eV]	η [eV]	ω [eV]	ΔN_{max}
H	-0.8218	7.3661	0.0458	0.1116
m-CH_3	-0.6259	7.2437	0.0270	0.0864
m-Cl	-1.0817	7.0818	0.0826	0.1527
m-CN	-1.7361	6.8491	0.2200	0.2535
m-NH_2	-0.1932	6.8192	0.0027	0.0283
m-NO_2	-1.7266	5.8709	0.2539	0.2941
m-OCH_3	-0.3211	6.8736	0.0075	0.0467
m-Ph	-0.6504	6.1525	0.0344	0.1057
m-SCH_3	-0.4150	6.7688	0.0127	0.0613

Selected charge of nitrogen atom, charges of carbon atoms at different positions are collected in Table-4.

TABLE-4
SELECTED CHARGES OF NITROGEN AND DIFFERENT CARBON ATOMS OF PYRIDINE SUBSTITUENTS

Substituent	Charge					
	N	C1	C2	C3	C4	C5
H	-0.239	0.034	-0.073	-0.050	-0.073	0.034
m-CH_3	-0.239	0.026	0.006	-0.058	-0.072	0.030
m-Cl	-0.228	0.038	0.008	-0.047	-0.066	0.036
m-CN	-0.231	0.054	-0.004	-0.031	-0.070	0.047
m-NH_2	-0.231	0.011	0.096	-0.074	-0.064	0.019
m-NO_2	-0.226	0.048	0.068	-0.036	-0.067	0.049
m-OCH_3	-0.230	0.019	0.117	-0.087	-0.063	0.018
m-Ph	-0.240	0.031	-0.005	-0.053	-0.074	0.032
m-SCH_3	-0.231	0.037	-0.028	-0.061	-0.066	0.029

Hammett constants of mentioned substituents have been used as the measure of the electronic effect. According to the plotted graphs, it can be seen a direct relationship between σ and pK_a as shown in Fig. 3.

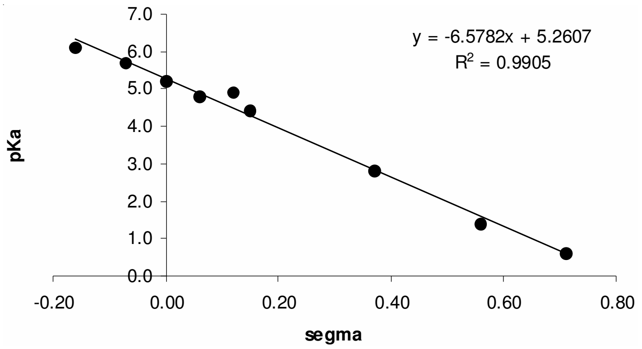


Fig. 3. Correlation between (σ) and the (pK_a) values

Correlation of the experimental (pK_a) with the calculated LUMO energy afforded an even better fit (R = 0.887). This correlation is graphically presented in Fig. 4.

A better correlation (R = 0.918) was obtained between Hammett constant (σ) and the calculated global electrophilicity index (ω) as shown in Fig. 5. While calculated hardness (η) did not correlate linearly (R = -0.494) with (σ) values.

Also, a better correlation (R = -0.869), (R = -0.754) and (R = -0.869) was obtained between (pK_a) values and the calculated (charge-C1), (charge-C3) and (charge-C5), respectively.

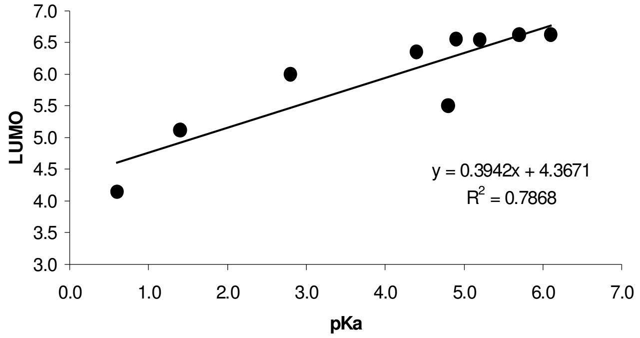


Fig. 4. Correlation between the calculated LUMO energy of pyridine substituents and their corresponding (pK_a) values

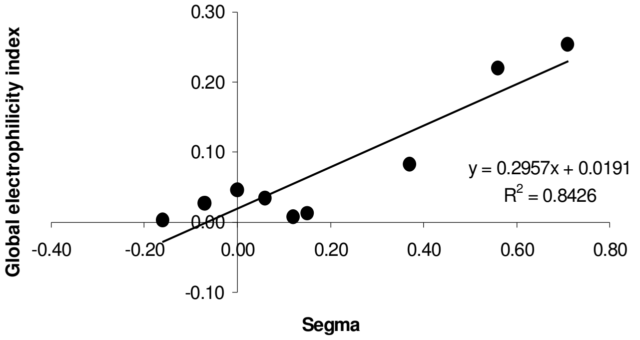


Fig. 5. Correlation between (σ) and the global electrophilicity index

While did not correlate linearly with (charge-C2), (charge-C4) and (charge-N).

The charge of carbon atom and nitrogen has different value according to the difference of the substituted on the pyridine ring as shown in Figs. 6 and 7.

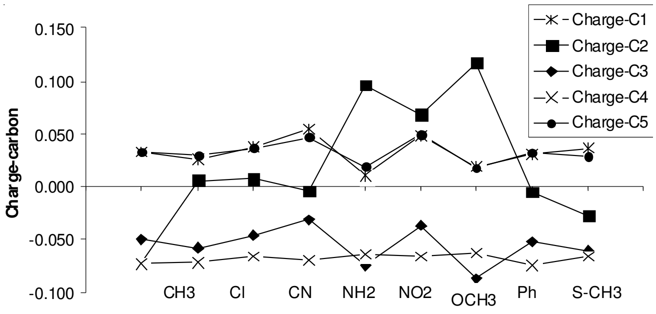


Fig. 6. Graph of different charges of carbon atoms of pyridine ring at different substituents

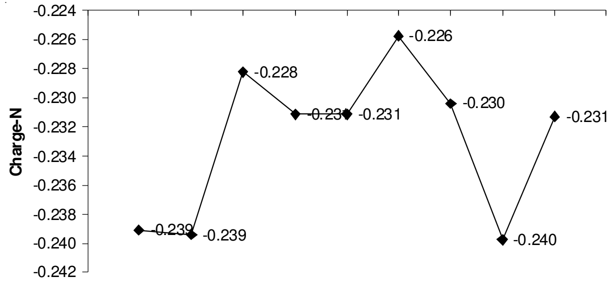


Fig. 7. Graph of charges of nitrogen atom of pyridine ring at different substituents

A better correlation (R = -0.941) was obtained between the (pK_a) values and the calculated global electrophilicity index (ω) as shown bellow:

We observed from the Figs. 8 and 9, that the relationship between the (pK_a) values and the global electrophilicity index shows a negative slope. This is because strongly electrophilic reagent leads to low substrate selectivity in the form of low pK_a values (Table-5).

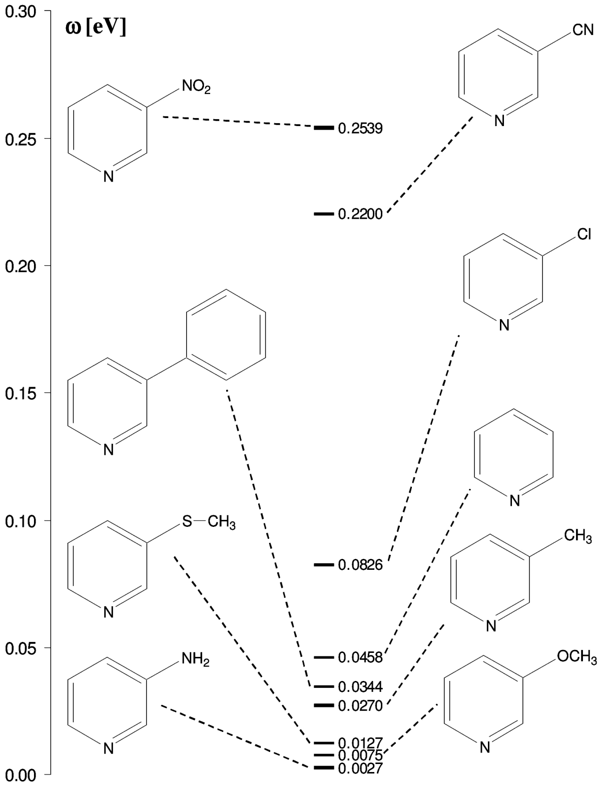


Fig. 8. Theoretical global electrophilicity index (w) for pyridine's substituents

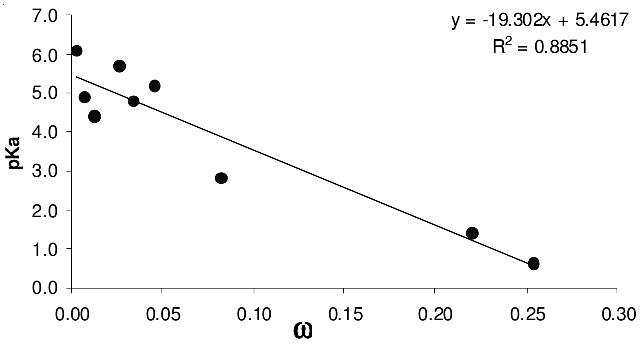


Fig. 9. Comparison between pK_a and the global electrophilicity index

TABLE-5
CORRELATION BETWEEN GLOBAL ELECTROPHILICITY INDEX (ω) AND THE EXPERIMENTAL VALUES OF (pK_a)

Calcd. of the substituent	Slope	Constant	R	pK_a (Exp.)	pK_a (Pred.)
H	-18.998	5.359	0.945	5.2	4.5
m-CH_3	-18.689	5.315	0.946	5.7	4.8
m-Cl	-19.195	5.586	0.961	2.8	4.0
m-CN	-19.920	5.474	0.921	1.4	1.1
m-NH_2	-18.427	5.300	0.941	6.1	5.2
m-NO_2	-19.518	5.468	0.893	0.6	0.5
m-OCH_3	-19.788	5.554	0.942	4.9	5.4
m-Ph	-19.299	5.460	0.939	4.8	4.8
m-SCH_3	-20.172	5.636	0.954	4.4	5.4

Conclusion

Theoretical developments made towards the broad subject of chemical parameters using quantum chemical methods. Chemical potential, hardness, softness *etc*., has been theoretically studied within GAMMESS method. The comparison between the experimental (pK_a) values and global electrophilicity index shows a linear relationship ($R^2 = 0.842$). The values of (pK_a) predicted from the knowledge of the global electrophilicity index.

The influence of substituents on the (pK_a) values can be rationalized by considering substituent effects in Hammett relations. The (nitro) substituent withdraws electron density from the aromatic ring thus makes the (nitrogen atom) more positive charged.

ACKNOWLEDGEMENTS

The author wishes to thank Dr. Eid A. Abdalrazaq of Department of Chemistry, College of Science, Al-Hussein Bin Talal University, Ma'an, Jordan for his advice on various aspects of this research.

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