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Comparative Study of Various Quantum Mechanical Descriptors for Prediction of Ionization Constant (pKa) of Substituted Anilines

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Abstract: In this work we studied comparative study of various quantum mechanical descriptors of subsituted anilines which are correlated with its ionization constant(pKa).The quantum mechanical descriptor studied are mulliken and ZDO (Zero Differential Overlap) electron population on nitrogen atom, global electrophilicity index, golobal softness and global hardness. All above quantum mechanical descriptors were calculated at PM3 level for aniline as well as protonated form of aniline and the descriptor of aniline and protonated form of aniline were correlated with pKa. The best descriptors was chosen based on coerrelation coefficient value. The Zero Differential Overlap charge densuty on base nitriogen atom is the best descriptor to calculate pKa among the studied descriptor.
Key Words : pKa, ZDO charge, Global electrophilicity index.

Introduction

Ammae et al has established the relationship between Ionization constant of phenol with its global electrophilicity,[1] which was calculated in DFT level but pKa of phenol had also been correlated with mulliken population on acidic hydrogen, which was calculated in PM3 level. The pKa of sulfonamide were correlated,[2] with its calculated surface tension. The carbon acids (CH_3Z) pKa were correlated,[3] with its deprotonation energy and also they proved that STO-3G basis set itself giving good correlation and correlation coefficient were not improved by higher basis set and diffusion function in DFT calculation. So in this work we studied comparative study of descriptors of aniline and protonated form of aniline which were calculated at semi-empirical level. The acids and bases pKa value are very important property,[4] and it have the profound effect on the physiochemical properties of a compound. In rational drug discovery pKa value are essential for optimization of ADME characteristics since compounds in their unionized form tend to be less soluble but can more easily penetrate lipophilic barrier existing between them. Furthermore,[5] Ionization constant have the effect on rate of reaction and reactivity of order of acids and bases towards specific reagent depends upon (based on HSAB principal) its pKa value.

Experimental

All the aniline and protonated form of aniline were geometry optimized using PM3(semi-empirical) hamiltonian in RHF method with convergence limit of 10×10^{-10} kcal/ mol. The Geometry optimization of molecule were done,[6] using arguslab 4.0.1 software. The descriptor were calculated from the appropriate value and descriptor were taken for linear rgression analysis for pKa calculation. The comparison of descriptors were done based on correlation coefficient value.

Result and Discussion

In quantum mechanical calculation we can generate the following information pertaining the molecule they are energy , dipole moment, electron population on individual atoms, energy of all molecular orbital and bond order between the atoms. From the knowledge of

above value we can generate so many local and global descriptors like hardness, softness, electrophilicity index, fukui function, and group electrophilicity and so on. The descriptors of molecule are calculated based on property of molecule to be correlated. Here mulliken and ZDO (Zero differential overlap) electron population on base nitrogen atom, energy of HOMO, energy of LUMO, chemical potential, hardness, softness, electrophilicity index are calculated for aniline and protonated form of aniline. The protonation energy is calculated from the energy of aniline and protonated aniline.The global descriptors of molecules such as Hardness (η), chemicalpotential(μ), Softness(S), electrophilicity index (ω) and energy of protonation are defined, [7-15] as follow.

$\eta = ½ (I - A)$ (1)

$\mu = -½ (I + A)$ (2)

$S = 1/ \eta$ (3)

$\omega = \mu^2/2\eta$ (4)

Energy of protonation $= E(NH^{+}) - E(N)$ - (5)

{$E(NH^{+})$= Enery of protonated aniline, E(N)= Energy of aniline}

According to koopman' theorem for closed shell molecular system, Ionization energy(I) and Electron affinity (A) can be written as [4]
(I= - Energy of HOMO and A= - Energy of LUMO)

The table 1 shows, [16] the pKa value of anilines. The minimum and maximum pKa value of aniline taken for this study are 1 and 4, value 1 for 4-nitroaniline and value 4.73 for 3-methyl aniline. Table 2 shows the mulliken and ZDO electron population on base nitrogen atom, energy of HOMO, energy of LUMO, chemical potential ,hardness, softness and electrophilicity index of protonated aniline. The equations 6 to 10 shows correlation coefficient (r) and standard deviation(s) of linear regression analysis for pKa of aniline with mulliken population on base nitrogen, ZDO population on base nitrogen, hardness, softness and electrophilicity index of protonated form of aniline respectively. Table 3 shows the protonation energy of aniline. The equation 11 is the linear regression analysis for pKa with protonation energy.

TABLE 1 : The pKa value of compounds.

S.No	Compound name	Exp,. pKa Value
1	3-fluro aniline	3.5
2	3- chloroaniline	3.46
3	4- chloro aniline	4.15
4	2- Bromo aniline	2.53
5	3- Bromo aniline	3.58
6	4- Bromo aniline	3.86
7	3,5 Dibromo aniline	2.34
8	3-Ethoxy aniline	4.18
9	2-Iodo aniline	2.6
10	2-methyl aniline	4.44
11	3-methyl aniline	4.73
12	3- nitro aniline	2.46
13	4-Nitro aniline	1

TABLE 2 : The descriptor of protonated aniline.

S.No	Mulliken charge on nitrogen	ZDO charge on nitrogen	Homo energy (au)	Lumo energy (au)	Hardness	Softness	Electrophilicity index
1	0.882	0.9537	-0.5234	-0.1845	0.1695	5.9014	0.3697
2	0.8848	0.9561	-0.4876	-0.1789	0.1544	6.4788	0.3598
3	0.8971	0.9667	-0.4877	-0.1787	0.1545	6.4725	0.3593
4	0.8823	0.9538	-0.5204	-0.1807	0.1699	5.8875	0.3617
5	0.8894	0.9602	-0.5039	-0.1787	0.1626	6.1501	0.3582
6	0.8874	0.9582	-0.5044	-0.1799	0.1623	6.1633	0.3608
7	0.8891	0.9602	-0.5035	-0.1828	0.1604	6.2364	0.3672
8	0.8783	0.9499	-0.4816	-0.1681	0.1568	6.3796	0.3366
9	0.8799	0.951	-0.4808	-0.1783	0.1513	6.6116	0.359
10	0.8903	0.9593	-0.5121	-0.1707	0.1707	5.8582	0.3414
11	0.88	0.9585	-0.5068	-0.17	0.1684	5.9382	0.34
12	0.8894	0.9606	-0.551	-0.1986	0.1762	5.6754	0.3986
13	0.8726	0.946	-0.5458	-0.2083	0.1688	5.9259	0.4212

TABLE 3 The protonation energy of aniline.

S.No	Free aniline energgy(au)	Protonated aniline energy(au)	Proronation energy(au)
1	-51.6298	-51.7849	-0.1551
2	-47.1017	-47.2762	-0.1745
3	-47.1017	-47.2811	-0.1794
4	-48.4537	-48.7044	-0.2507
5	-48.455	-48.688	-0.233
6	-48.4555	-48.6533	-0.1978
7	-60.8738	-61.055	-0.1812
8	-57.6443	-58.1245	-0.4802
9	-46.0481	-46.2754	-0.2273
10	-41.5384	-41.715	-0.1766
11	-41.4612	-41.6569	-0.1957
12	-62.9216	-63.0326	-0.111
13	-62.8224	-63.219	-0.3966

pKa = 63.57 x Mulliken population of protonated aniline - 52.95 —(6)

(r = 0.39, Std.Dev,. = 1.01)

pKa = 92.35 x ZDO population of protonated aniline - 85.04 —(7)

(r = 0.48, Std.Dev,. = 0.96)

pKa = - 22.3 x Hardness of protonated aniline + 6.94 —(8)

(r = 0.16, Std.Dev,. = 1.08)

pKa = - 3.85 x Softnes of protonated aniline + 27.32 —(9)

(r = 0.15, Std.Dev,. = 1.08)

pKa = - 38.78 x Global electrophilicity index of protonated anine + 7.91 —(10)

(r = 0.85, Std.Dev,. =0.57)

pKa = - 1.86 x Protonation energy + 3.71 —(11)

(r = 0.18, Std.Dev,. = 1.0)

TABLE 4 : The descriptors of aniline.

S.No	Mulliken charge on Nitrogen	ZDO Charge on Nitrogen	Homo energy (au)	Lumo energy (au)	Hardness	Softness	Electro-philicityindex
1	-0.0043	0.074	-0.3268	0.0029	0.1649	6.0661	0.0796
2	-0.0038	0.0744	-0.325	0.0037	0.1644	6.0846	0.0785
3	-0.0043	0.0731	-0.3191	0.003	0.1611	6.2093	0.0776
4	0.0036	0.0818	-0.3231	-0.0017	0.1607	6.2228	0.0821
5	-0.0031	0.0749	-0.3257	0.0003	0.163	6.135	0.0812
6	-0.0096	0.0732	-0.3239	0.0025	0.1632	6.1275	0.0791
7	0.0024	0.0812	-0.3325	-0.0138	0.1594	6.2755	0.0941
8	-0.009	0.0687	-0.3196	0.0102	0.1649	6.0643	0.0726
9	0.002	0.08	-0.3171	-0.0145	0.1513	6.6094	0.0908
10	-0.0102	0.0658	-0.315	0.0148	0.1649	6.0643	0.0683
11	-0.0097	0.0674	-0.3162	0.0148	0.1655	6.0423	0.0686
12	0.0023	0.0803	-0.3425	-0.0394	0.1516	6.5985	0.1203
13	0.0117	0.0942	-0.3475	-0.0377	0.1549	6.4558	0.1197

TABLE 5 : : The comparison of correlation coefficient and standard deviation of linear regression analysis of variuos descriptors. The values in table are in the descending order of correlation coefficient and ascending order of standard deviation.

S.No	Name of Descriptor taken for linear regression analysis	correlation Coefficient (r)	Std., Deviation
1	ZDO Population on base nitrogen atom	0.97	0.22
2	Mulliken population on base nitrogen atom	0.94	0.35
3	Gobal electrophilicity index	0.86	0.54
4	Gobal electrophilicity index of protonated aniline	0.85	0.57
5	Hardness of aniline	0.74	0.72
6	Softness of aniline	0.74	0.73
7	ZDO Population on base nitrogen atom of protonated aniline	0.48	0.96
8	Mulliken population on base nitrogen atom of protonated aniline	0.39	1.01
9	Protonation energy	0.18	1
10	Hardness of protonated aniline	0.16	1.08
11	Softness of protonated aniline	0.15	1.08

Table 4 shows the mulliken and ZDO population on base nitrogen atom, energy of HOMO, energy of LUMO, chemical potential, hardness, softness and electrophilicity index of aniline. The equation 12-16 shows the correlation coefficient (r) and standard deviation of linear regression analysis for pKa with mulliken population on base nitrogen, ZDO population on base nitrogen, hardness, softness and electrophilicity index of aniline. Table 5 shows the value of coerrelation coefficient (r)and standard deviation of linear regression analysis for pKa with various descriptor .

pKa = - 164.82 x Mulliken population of aniline - 52.95 —(12)

(r = 0.94, Std.Dev,. = 0.35)

pKa = - 136.46 x ZDO population of aniline + 13.67 —(13)

(r = 0.97, Std.Dev,. = 0.22)

pKa = 155.84 x Hardness of aniline - 21.76 —(14)

(r = 0.74, Std.Dev,. = 0.72)

pKa = - 3.85 x Softnes of aniline + 27.32 —(15)

(r = 0.74, Std.Dev,. = 0.73)

pKa = - 54.01 x Global electrophilicity index of aniline + 7.91 —(16)

(r = 0.86, Std.Dev,. = 0.54)

TABLE 6 : The calculated pKa from equation 13 and experimental pKa.

S.No.	Compound name.	Exp,.pKa value.	Calculated pKa from ZDO charge.	Residual value
1	3-fluro aniline	3.5	3.57	0.07
2	3- chloroaniline	3.46	3.51	0.05
3	4- chloro aniline	4.15	3.69	-0.46
4	2- Bromo aniline	2.53	2.5	-0.03
5	3- Bromo aniline	3.58	3.44	-0.14
6	4- Bromo aniline	3.86	3.68	-0.18
7	3,5 Dibromo aniline	2.34	2.58	0.24
8	3-Ethoxy aniline	4.18	4.29	0.11
9	2-Iodo aniline	2.6	2.75	0.15
10	2-methyl aniline	4.44	4.69	0.25
11	3-methyl aniline	4.73	4.47	-0.26
12	3- nitro aniline	2.46	2.71	0.25
13	4-Nitro aniline	1	0.81	-0.19

In Table 5, the correlation coefficient and standard deviation of linear regression of analysis various descriptor are shown in the decreasing order of correlation coefficient and increasing order of standard deviation. It is very clear from table 5 that the descriptor calculated for the protonated form of aniline other than global electrophilicity index are have very poor coerrelation coefficeint value between 0.48 to 0.15.The coerrelation coefficient of global electrophilicity index of aniline(0.86) and global electrihpilicity index of protonated form of aniline are have same coerrelation coefficient(0.85).The ZDO electron population on base nitrogen atom (coerrelation coefficient .0.97) is superior descriptor to mulliken electron population on nitrogen base atom(coerrelation coefficient.0.95) of aniline but ZDO and mulliken electron poulation on base nitrogen of protonated aniline are have poor correlation coefficient 0.48 and 0.39 respectively. The ZDO electron population is the better descriptor than mulliken population for pKa value.

Conclusion

The global electrophilicilty index, hardness, mulliken charge on base nitrogen, ZDO charge on base nitrogen, softness of aniline and protonated form of aniline were calculated and correlated with pKa by linear reression analysis. The ZDO charge on base nitrogen atom of aniline is the best descriptor to calculate pKa of aniline at semi-empirical level of calculation with PM3 hamiltonian among the aforementioned descriptors. Protonation energy of aniline and hardness, sofness of protonated form of aniline are giving very poor correlation.

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