A theoretical study on protonation of some halogen substituted pyridine derivatives

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Abstract

The geometries of 12 multi-halogenated pyridine derivatives were optimized using theoretical methods. The Hartree–Fock (HF) method with the 6-31G(d) and B3LYP method with 6-31G(d) basis sets were found to be adequate in calculation of absolute acidity constants, pK_a values. A perfect correlation between the computed and experimentally obtained acidity constants, pK_a values, was observed.
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1. Introduction

Proton transfer reactions play a basic role in chemistry, in particular in biochemistry. Due to existence of pyridine ring in the structure of many biologically active compounds like herbicides such as *nicosulfuron*; pesticides such as *ivin*; insecticides such as *anabasine*, *nicotine* and *imidadoprid*; fungicides such as *ethidium bromide*; cardiovascular drugs such as *nifedipine*; analgesics such as *nichetamide*; sulfadrugs such as *sulfapyridine*; synthetic alcoloids such as *chloroquine* and *plasmocid*; antiseptics such as *proflavine*, *ethacidine* and *isoniazid*; natural alcoloids such as *quinine*, *emetine* and *papavarine*; vitamin B5, *nicotinic acid*, *nicotinamide vitamin B6*, *pyridoxal* and *pyridoxamine*; *nicotinamide adenin dinucleotide*, the pyridine ring has been studied extensively both experimentally [1–23] and theoretically [24–30]. However, we believe that the potentially active pyridine derivatives deserve more detailed and systematic theoretical studies using updated computer programs and recently available knowledge on structure activity relations.

It has been well established that one of the versatile approach to have an idea on the structure and the activity of any molecules is learning about the knowledge of the acidity constants, pK_a values, and tautomeric structure of ionizable molecules. They are of particular interest for elucidating reaction mechanisms, especially those having proton transfers and for interpreting binding of substrates or inhibitors to enzymes. The experimental determinations of individual pK_a values are difficult in complex systems and kinetic assignments of pK_a values are often concealed by uncertainties in interpreting the pH dependence of the measured parameters. It is useful, therefore, to have reliable and accurate means of calculating relative and/or absolute pK_a values and to have an understanding is essential for the measured effective pK_a values in complex poly ions [31].

As an extension of our previous studies on pyridine derivatives [29,30] we now are reporting on the protonation behaviour of some di, tri, tetra, penta and hexa halogenated pyridine derivatives.

2. Computational methods

Since nowadays both microscopic and macroscopic theoretical methods are available for the estimation of solvation free energies it is possible, in principle, to determine theoretical relative or absolute acidity constants, pK_a values, Scheme 1 explains the interrelationship between the thermodynamic parameters of gas and solution phases.

The acidity constant, pK_a, can be computed by using Eqs. (1) and (2):

$$\Delta G = -RT \ln K_a \tag{1}$$

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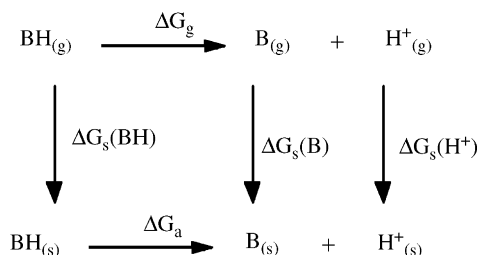
Scheme 1. Interrelationship between the gas phase and solution thermodynamic parameters.

and rearranging Eq. (1) we obtain Eq. (2):

$$pK_a = \frac{\Delta G_a}{2.303RT} \qquad (2)$$

The *ab initio* calculation of the absolute pK_a values can be made by using Eq. (3) in which

$$pK_a = \frac{\Delta G_g + \Delta G_a}{2.303RT} \qquad (3)$$

ΔG_g and $\Delta G_a = \Delta G_s(B) - \Delta G_s(BH) + \Delta G_s(H^+)$ are the gas phase and solution free energies of the ionization and ΔG_s's are solvation free energies, respectively.

The geometry optimizations were performed by the *ab initio* Hartree–Fock (HF) and density functional geometry (DFT) methods which were implemented in the Gaussian 03 program [32]. The calculation of solvation free energies was carried out using at HF/6-31G(d) and B3LYP/6-31G(d) methods, respectively. The total energies are given in Hartree using the conversation factor 1 Hartree = 627.5095 kcal mol^{-1}. The value of $\Delta G_s(H^+)$ was taken between -250 and -275 kcal mol^{-1}.

Among the other methods the Hammett equation has been one of the widely used method to search for the effect of substituent on an equilibrium process [33]. When a heteroatom of a heteroaromatic compound acts as reaction site as in the case of protonation or deprotonation process (Scheme 2; Eq. (4)) n can have positive, negative or zero value:

$$BH^{n+} \rightleftharpoons B^{(n+1)+} + H^+ \qquad (4)$$

The Hammett equation can be used in elucidation of reaction mechanisms. A general form of the Hammett equation can be written as follows:

$$\log \frac{K}{K_0} = \rho\sigma \qquad (5)$$

where K and K_0 values are acid dissociation equilibrium constants of substituted and unsubstituted molecules, respectively. The slope of the correlation line of σ versus $\log K/K_0$ is referred to as ρ the reaction constant. It is a measure of the sensitivity of the reaction or equilibrium to electronic substituent effect. A large ρ value for an equilibrium implies the strong interaction between the substituent and positive heteroatom. The parameter σ is referred as the substituent constant and it consists of inductive and mezomeric effects and they are mathematically addible (i.e. $\sigma_T = \sigma_{mezomeric} + \sigma_{inductive}$). So we can make use of the σ_T values in interpreting the obtained results (i.e. when a substituent has a value $\sigma_T < 0$ that means this substituent is an electron donating one) (Scheme 2).

3. Results and discussions

The *ab initio* calculated thermal and solvation free energies, ΔG_g and ΔG_s values, of the natural molecules and their protonated cations were depicted in Table 1.

The size and the absolute values of solvation free energy changes both with HF/6-31G(d) and B3LYP/6-31G(d) methods had indicated that, with the exception of molecule 12, enormous increase of total free energies seem to occur in protonation. The very same trend was observed in nucleophilicity increase. The compound 12 was found to be most powerful nucleophiles both in gas and in solution phase both with HF/6-31G(d) and B3LYP/6-31G(d) methods (Table 2).

Both gas and aqueous phase calculations had revealed that the electronic charges on nitrogen atom is the least in molecule 6 and the most in molecule 11 by B3LYP/6-31G(d) gas and aqueous phase calculations. On the other hand HF/6-31G(d) aqueous phase calculations revealed that on nitrogen atom in molecule 1 is the biggest (Table 3).

The latter case is more understandable and more explainable by traditional way. Since molecule 1 has no substituent that means no atom or group exist to withdraw electron of nitrogen atom. Whereas in molecule 11 there are four brom atoms to withdraw electrons from the pyridine nitrogen atom inductively making this atom electron poor. Similarly the lesser extent of electronic charges, with both methods and in both gas and aqueous phases of molecule 6 than that of molecule 12 reflects the bigger electronic withdrawing effect of chlor atom than brom atom. Although both molecules contain penta halogen atoms in molecule 6 the chlorine atoms are more electronegative than the bromine atoms which are present in molecule 12. And in this way electron density of the pyridine nitrogen atom in molecule 6 lowered more than molecule 12.

The gas and liquid phase calculated dipole moments were depicted in Table 4.

As one immediately can realize that the highest dipolarization occurs, both in gas and aqueous phase, in molecule 4. This is an expected situation because two chlor atoms are located as

Scheme 2. Nomenclature and protonation pattern of studied compounds. (1) Pyridine; (2) 3,5-dichloropyridine; (3) 2,3-dichloropyridine; (4) 2,6-dichloropyridine; (5) 2,3,5,6-tetrachloropyridine; (6) pentachloropyridine; (7) 3,4,5-tribromopyridine; (8) 2,3,4-tribromopyridine; (9) 2,3,6-tribromopyridine; (10) 2,3,4,5-tetrabromopyridine; (11) 2,3,5,6-tetrabromopyridine; (12) pentabromopyridine.

Table 1

Ab initio and aqueous phase calculated thermal and solvation free energies, investigated compounds at 298 K

Compound	HF/6-31G(d)						B3LYP/6-31G(d)					
	Thermal free energy, G_g (kcal mol⁻¹)	Solvation free energy, $G_s(B)$ (kcal mol⁻¹)	Total solvation free energy, $\Delta G_s(B)$[a] (kcal mol⁻¹)	Thermal free energy, $G_g(BH^+)$ (kcal mol⁻¹)	Solvation free energy, $G_s(BH^+)$ (kcal mol⁻¹)	Total solvation free energy $\Delta G_s(BH^+)$[b] (kcal mol⁻¹)	Thermal free energy, G_g (kcal mol⁻¹)	Solvation free energy, $\Delta G_s(B)$[a] (kcal mol⁻¹)	Total solvation free energy $\Delta G_s(B)$[a] (kcal mol⁻¹)	Thermal free energy, $G_g(BH^+)$ (kcal mol⁻¹)	Solvation free energy, $G_s(BH^+)$ (kcal mol⁻¹)	Total solvation free energy, $\Delta G_s(BH^+)$[b] (kcal mol⁻¹)
1	−154803.46	−154808.54	−5.08				−155798.06	−155804.33	−6.27			
1p				−155039.31	−155094.88	−55.57				−156030.24	−155094.88	−56.47
2	−730728.47	−730734.75	−6.28				−732600.34	−732605.48	−5.14			
2p				−730948.65	−731011.01	−62.36				−732821.19	−731011.01	−60.14
3	−730727.53	−730734.81	−7.28				−732600.27	−732608.18	−7.91			
3p				−730948.40	−731004.64	−56.24				−732821.22	−731004.64	−57.1
4	−730731.97	−730734.81	−2.84				−732604.33	−732611.63	−7.3			
4p				−730950.69	−731004.64	−53.95				−732822.93	−731004.64	−54.07
5	−1306647.73	−1306650.48	−2.75				−1309396.4	−1309398.28	−1.88			
5p				−1306856.40	−1306907.76	−51.36				−1309606.98	−1306907.76	−53.41
6	−1594602.25	−1594595.77	6.48				−1597789.79	−1597787.72	2.07			
6p				−1594809.20	−1594859.32	−50.12				−1597999.75	−1594859.32	−47.32
7	−4991588.03	−4991587.07	0.96				−4995972.98	−4995975.87	−2.89			
7p				−4991808.04	−4991863.17	−55.13				−4996195.87	−4991863.17	−53.59
8	−4991588.07	−4991593.34	−5.27				−4995973.67	−4995978.57	−4.9			
8p				−4991808.86	−4991856.90	−48.04				−4996192.99	−4991856.90	−54.59
9	−4991593.09	−4991593.34	−0.25				−4995977.38	−4995973.36	4.02			
9p				−4991806.70	−4991856.90	−50.20				−4996197.63	−4991856.90	−45.56
10	−6603846.98	−6603849.61	−2.63				−6609362.41	−6609363.66	−1.25			
10p				−6604063.09	−6604116.99	−53.90				−6609582.04	−6604116.99	−44.55
11	−6603849.56	−6603853.00	−3.44				−6609364.29	−6609366.80	−2.51			
11p				−6604063.09	−6604116.43	−53.34				−6609580.78	−6604116.43	−51.27
12	−8216044.63	−8216105.31	−60.68				−8222751.84	−8222750.45	1.39			
12p				−8216318.73	−8216364.66	−45.93				−8222968.89	−8216364.66	−44.86

[a] $\Delta G_s(B) = G_s(B) - G_g$.

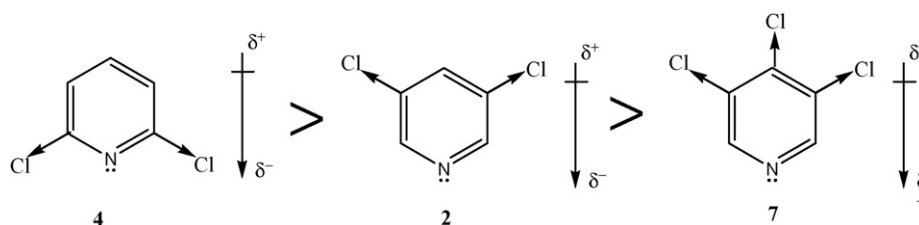[b] $\Delta G_s(BH^+) = G_s(BH^+) - G_g(BH^+)$.

Fig. 1. Polarization of molecules **2**, **4** and **7**—μ(D) HF(gas): 4.25 > 0.56 > 0.08; μ(D) HF(aqueous): 6.54 > 0.66 < 1.35; μ(D) B3LYP(gas): 3.87 > 0.61 > 0.28; μ(D) B3LYP(aqueous): 6.29 > 0.74 < 1.02.

Table 2
Gas and aqueous phase HF/6-31G(d) and B3LYP/6-31G(d) calculated HOMO, LUMO and nucleophilicity, n, values of investigated molecules

Compound	HF/6-31G(d)			B3LYP/6-31G(d)		
	HOMO	LUMO	n	HOMO	LUMO	n
Gas phase						
1	−0.3440	0.1270	−0.4710	−0.2526	−0.0224	−0.2302
2	−0.3549	0.0937	−0.4486	−0.2667	−0.0517	−0.2150
3	−0.3528	0.0968	−0.4496	−0.2629	−0.0486	−0.2143
4	−0.3541	0.0960	−0.4501	−0.2645	−0.0496	−0.2149
5	−0.3592	0.0717	−0.4309	−0.2670	−0.0691	−0.1979
6	−0.3654	0.0624	−0.4278	−0.2717	−0.0751	−0.1966
7	−0.3535	0.0814	−0.4349	−0.2636	−0.0574	−0.2062
8	−0.3546	0.0827	−0.4373	−0.2618	−0.0566	−0.2052
9	−0.3470	0.0828	−0.4298	−0.2556	−0.0585	−0.1971
10	−0.3527	0.0712	−0.4239	−0.2604	−0.0653	−0.1951
11	−0.3488	0.0723	−0.4211	−0.2570	−0.0666	−0.1904
12	−0.3529	0.0622	−0.4151	−0.2599	−0.0717	−0.1882
Aqueous phase						
1	−0.3462	0.1223	−0.4685	−0.2610	−0.0261	−0.2349
2	−0.3444	0.1058	−0.4502	−0.2575	−0.0406	−0.2169
3	−0.3461	0.1086	−0.4547	−0.2587	−0.0380	−0.2207
4	−0.3467	0.1056	−0.4523	−0.2585	−0.0403	−0.2182
5	−0.3494	0.0884	−0.4378	−0.2583	−0.0548	−0.2035
6	−0.3549	0.0761	−0.4310	−0.2633	−0.0637	−0.1996
7	−0.3422	0.0928	−0.4350	−0.2550	−0.0484	−0.2066
8	−0.3466	0.0950	−0.4416	−0.2579	−0.0465	−0.2114
9	−0.3399	0.0974	−0.4373	−0.2538	−0.0525	−0.2013
10	−0.3433	0.0837	−0.4270	−0.2537	−0.0563	−0.1974
11	−0.3410	0.0878	−0.4288	−0.2505	−0.0538	−0.1967
12	−0.3452	0.0738	−0.4190	−0.2544	−0.0636	−0.1908

Table 3
Gas and aqueous phase HF/6-31G(d) and B3LYP/6-31G(d) calculated charge on nitrogen atom, q_N, values of investigated molecules

Compound	HF/6-31G(d)		B3LYP/6-31G(d)	
	Gas phase	Aqueous phase	Gas phase	Aqueous phase
1	−0.5152	−0.5705	−0.4057	−0.4576
2	−0.5018	−0.5621	−0.3943	−0.4463
3	−0.4982	−0.5578	−0.3978	−0.4515
4	−0.4877	−0.5457	−0.3973	−0.4524
5	−0.4828	−0.5326	−0.3916	−0.4360
6	−0.4828	−0.5269	−0.3913	−0.4311
7	−0.5038	−0.5562	−0.3956	−0.4413
8	−0.5143	−0.5651	−0.4250	−0.4717
9	−0.5179	−0.5693	−0.4448	−0.4822
10	−0.5112	−0.5606	−0.4221	−0.4677
11	−0.5191	−0.5683	−0.4462	−0.4909
12	−0.5173	−0.5621	−0.4455	−0.4871

ortho to the pyridine nitrogen atom (i.e. 2,6-dichloropyridine) and both chlor atoms withdraw electrons from the pyridine ring and 2 and 6 positions become more negative than the other positions of the ring. On the other hand the lowest polarization seems to occur in molecule **7** in gas phase and in molecule **2** in aqueous phase. It is not difficult to understand this situation because two chlor atoms are placed at third and fifth positions of the pyridine ring (i.e. both chlor atoms are *meta* to the nitrogen atom) and withdraws electrons less than other positions (i.e. *ortho-* and *para-*). Therefore, three chlor atoms in molecule **7** which are located at third, fourth and fifth positions are much more effectively withdraw electrons because of the chlor atom which is located at *para* position and withdraw electrons much more strongly than other two (i.e. both of them at *meta*) and in this way polarization will be more effective. The differences in gas and aqueous phase dipole moments reflects the solvation extent of those molecules (Fig. 1).
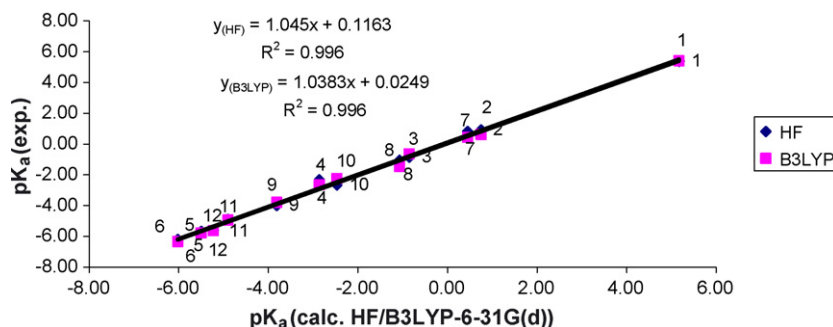
Fig. 2. The correlation plot of experimental and HF/B3LYP calculated pK_a values.
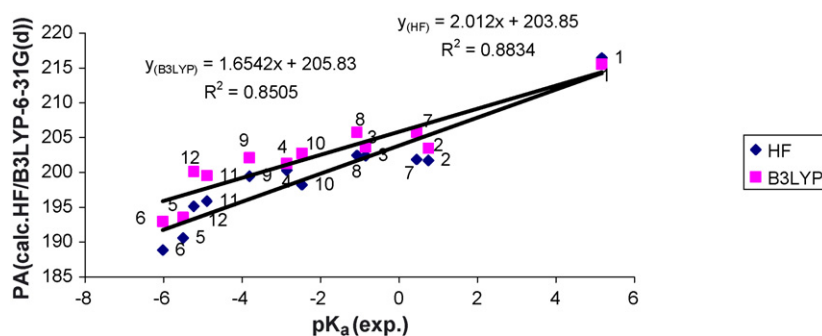
Fig. 3. Correlation plot for experimental pK_a and gas phase HF/B3LYP calculated proton affinities (PA).

3.1. Acidity

The calculated acidity constants were depicted in Table 5. Both HF/6-31G(d) and B3LYP/6-31G(d) methods reproduced very similar data and both of them are seem to be successful to describe the true value when the experimental values were taken as reference. A perfect correlations between computed and experimental values was observed (Fig. 2).

Similarly gas phase proton affinity values of studied molecules has indicated that there is no effect in molecule **1** (i.e. have no substituent) to decrease the proton affinity whereas in molecules **5** and **6** withdrawal of electrons on azo nitrogen of pyridine ring reaches the highest power with tetra and penta chlor atoms, respectively. Consequently the proton affinities of

these two molecules are lowered considerably comparing to others (Fig. 3; Table 6).

It is now possible to discuss, the position and the extent of substituent effects on the acidities of studied compounds by evaluating the calculated σ values (Table 7).

3.2. Linear free energy relationship

As it was described in Section 2 the Hammett equation can be used to elucidate the reaction pathways and in discussing the effect of substituents. In the present work we have worked on an experimentally studied reaction namely the protonation reaction of some halogenated pyridine derivatives. We aimed in

Table 4

Gas and aqueous phase HF/6-31G(d) and B3LYP/6-31G(d) calculated dipole moment, $\mu(D)$, values of investigated molecules

Compound	HF/6-31G(d)		B3LYP/6-31G(d)	
	Gas phase	Aqueous phase	Gas phase	Aqueous phase
1	2.3141	3.0343	2.1922	2.9263
2	0.5615	0.6646	0.6171	0.7454
3	3.8170	6.2967	3.4639	6.1797
4	4.2533	6.5494	3.8777	6.2927
5	2.3487	3.7916	2.1735	3.7067
6	1.3483	1.6682	1.3969	1.7554
7	0.0868	1.3581	0.2813	1.0265
8	2.5931	4.7376	2.3030	4.5494
9	3.2401	5.5916	2.8910	4.4244
10	1.2783	2.1118	1.3274	2.1318
11	2.2107	3.7776	2.0489	3.7101
12	1.5392	1.9031	1.6256	2.0485

Table 5

HF/6-31G(d) and B3LYP/6-31G(d) calculated and experimental pK_a values

Compound	pK_a		
	HF/6-31G(d)	B3LYP/6-31G(d)	Experimental[a]
1	5.38	5.41	5.17
2	0.92	0.62	0.75
3	−0.86	−0.63	−0.85
4	−2.32	−2.66	−2.86
5	−5.66	−5.79	−5.50
6	−6.20	−6.34	−6.02
7	0.81	0.43	0.45
8	−1.06	−1.46	−1.07
9	−3.99	−3.79	−3.81
10	−2.65	−2.25	−2.47
11	−4.89	−4.95	−4.90
12	−5.61	−5.64	−5.23

[a] Taken from Ref. [34] with exception of compound **1** which is taken from Ref. [35].

Table 6
Gas phase HF/6-31G(d) and B3LYP/6-31G(d) calculated E, zero point correction energy, ZPE and proton affinities (PA) values of investigated molecules

Compound	HF/6-31G(d)			B3LYP/6-31G(d)		
	E (kcal mol^{-1})	ZPE (kcal mol^{-1})	PA	E (kcal mol^{-1})	ZPE (kcal mol^{-1})	PA
1	−154741.5837	59.8889	216.4148	−155742.5868	55.8735	215.5364
1p	−154967.4243	69.3147		−155967.0470	64.7973	
2	−730677.3956	47.2389	201.7004	−732552.5195	43.7751	203.4637
2p	−730888.2388	56.3817		−732764.6177	52.4096	
3	−730676.5799	47.1385	202.3969	−732552.4568	43.7374	203.6143
3p	−730888.1761	56.3378		−732764.7432	52.4096	
4	−730681.1607	47.0193	200.3136	−732556.5983	43.6558	201.2925
4p	−730890.6234	56.1684		−732766.5003	52.2653	
5	−1306608.2503	34.1804	190.5871	−1309359.3774	31.4382	193.5114
5p	−1306807.8610	43.2040		−1309561.3727	39.9222	
6	−1594568.5948	27.6983	188.8301	−1597758.1001	25.3263	192.9592
6p	−1594766.4485	36.7219		−1597959.5306	33.7977	
7	−4991543.3313	39.6712	201.8509	−4995931.0032	36.7344	205.7541
7p	−4991754.2372	48.7261		−4996145.2977	45.2748	
8	−4991543.5823	39.4452	202.4534	−4995931.8190	36.5524	205.7666
8p	−4991755.1785	48.5881		−4996146.1762	45.1430	
9	−4991546.1551	39.3448	199.4476	−4995933.9525	36.4771	202.0832
9p	−4991754.7392	48.4814		−4996144.6074	45.0489	
10	−6603808.5097	32.5552	198.2114	−6609326.2635	30.0765	202.7169
10p	−6604015.7761	41.6102		−6609537.4832	38.5793	
11	−6603811.1453	32.4485	195.8583	−6609328.4598	30.0138	199.5355
11p	−6604016.0899	41.5349		−6609536.4792	38.4977	
12	−8216073.1861	25.4079	195.1178	−8222721.2100	23.3873	200.1128
12p	−8216277.3777	34.4816		−8222929.7942	31.8587	

this work to see which theoretical method can describe this process better and how close the obtained results to literature results. The application of the Hammett equation to heterocyclic systems was described in detail in the literature [33]. It was suggested that since the reaction occurs via formation of an azonium cation the size ρ value of this reaction should be great to show the extent of interaction between the substituent and the reaction side. The value of equilibrium constant ρ was found to be big and the sign was found negative [33]. The calculated total substituent constants, σ_T values, were depicted in Table 7.

In compound **2** the σ_T values for two chlor atoms which are located as *meta* to the reaction center (i.e. azo nitrogen atom of pyridine ring) have a value of 0.77, 0.83 and 0.76, respectively

by using HF, B3LYP calculated and experimentally determined pK_a values. In the literature σ_m values for Cl atoms is reported as +0.37 and its very close to σ_T values of σ_m(Cl) of this work (i.e. since they are addible in 3,5-dichloropyridine σ_m(Cl) = 0.77/2, 0.83/2, 0.76/2 with the different methods, respectively). It seems that HF method perform better in this calculation. In molecule **4** however both chlor atoms are located as *ortho* the reaction center and σ_T values of σ_o(Cl) were found as 1.33/2, 1.39/2, 1.39/2, respectively by using HF, B3LYP calculated and experimental pK_a values. There is no σ_o values reported in the literature therefore we cannot compare to find out how realistic these values are but we can say that σ_T(Cl) values in *ortho* position is nearly doubled. In molecule **3** we

Table 7
Calculated substituent constants, σ values[a] for the investigated compounds

Molecule	Substituent	Calculated by using HF-calculated pK_a values	Calculated by using B3LYP-calculated pK_a values	Calculated by using experimental pK_a values
1	Hydrogen	–	–	–
2	3,5-Dichloro	0.77	0.83	0.76
3	2,3-Dichloro	1.08	1.04	1.04
4	2,6-Dichloro	1.33	1.39	1.39
5	2,3,5,6-Tetrachloro	1.91	1.94	1.84
6	Pentachloro	2.00	2.03	1.93
7	3,4,5-Tribromo	0.79	0.86	0.81
8	2,3,4-Tribromo	1.11	1.19	1.08
9	2,3,6-Tribromo	1.62	1.59	1.55
10	2,3,4,5-Tetrabromo	1.39	1.32	1.32
11	2,3,5,6-Tetrabromo	1.77	1.79	1.74
12	Pentabromo	1.90	1.91	1.80

[a] Calculated using Eq. (5) and taking ρ value as −5.77 for pyridine protonation, ρ value as 5.77 for pyridine deprotonation [33].

have the combination of *meta* and *ortho* effect so the values of $\sigma_T(Cl)$ were found as 1.03, 1.04, 1.04 by HF, B3LYP calculated and experimental pK_a values, respectively. Addition of chlor atom to any position seems to increase the electron withdrawing effect and consecutively makes molecule less basic (i.e. more acidic). This point is also has reflected here and σ_T for molecule **6** which contains five chlor atoms as substituent found as 2.00, 2.03 and 1.93, respectively with the same methods of calculation. This is the biggest σ_T value within the studied compounds as expected.

A very similar trend was observed for compounds **7–12** which have brom atoms as substituent. From the obtained values (Table 7) we can immediately see that molecule **12** which has five brom atoms as substituents has the σ_T values of 1.90, 1.91 and 1.80, respectively by the same methods of calculations. If we compare these σ_T values with that of σ_T values of compound **6** we easily can conclude the greater effect of chlor atoms than that of brom atoms. The literature values for σ_m and σ_p are 0.39 and 0.23 [33]. Whereas they were found as 0.37 and 0.23 for chlor atoms. So the main differences come from σ_o values which are included in σ_T values. But not from the σ_m and σ_p values. We can conclude that which are also included in σ_T values.

3.3. Correlation attempts

It is customary to compare the computed parameters with experimental values for mapping purpose when experimental data is available. However, most of the time there may exist no experimental data and the computational data may be used in prediction. This method sometimes may be very useful in synthetic chemistry and in quantitative structure activity relationship (QSAR) and quantitative structure property relationship (QSPR) studies.

As it was indicated earlier an excellent correlations between experimental and HF/6-31G(d) and B3LYP/6-31G(d) calculated pK_a values (i.e. R^2 values are 0.996 in both cases) were searched. The slopes of the correlation plots for both cases are about unity indicating the perfect correlations. Although the regression values dropped down for the correlations between experimental pK_a values and gas phase HF and B3LYP calculated proton affinities (PA) still acceptable correlations
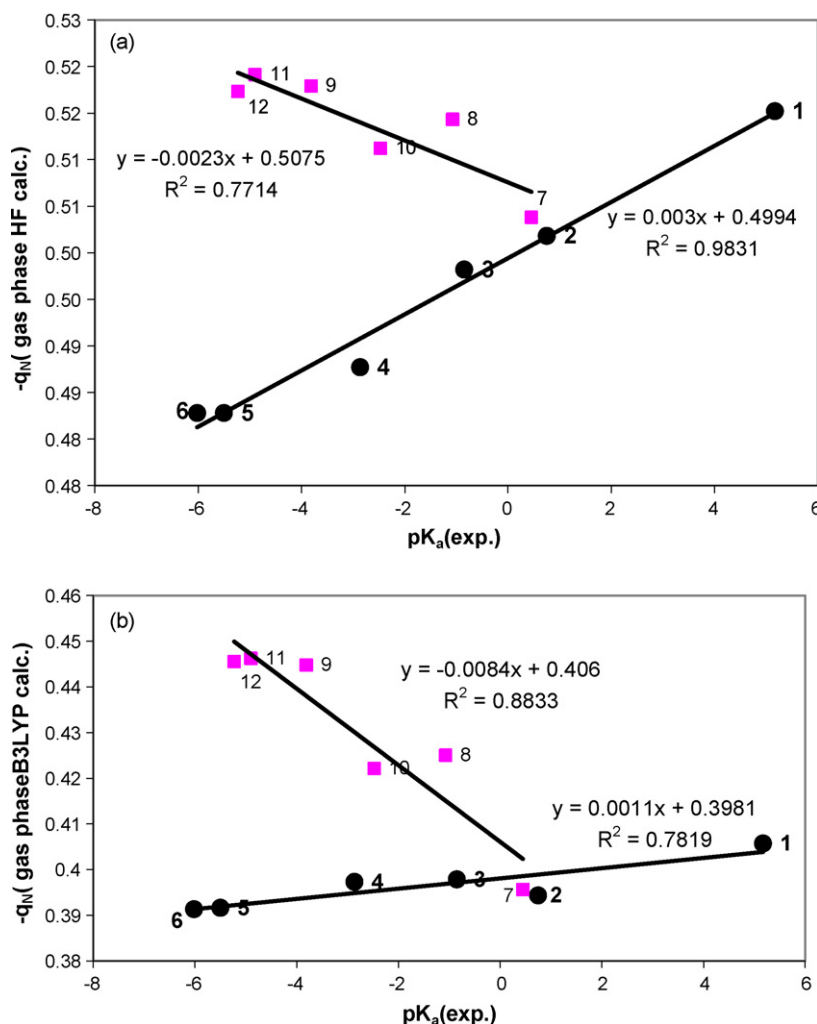

Fig. 4. (a) Correlation plot for experimental pK_a values against gas phase HF calculated, electronic charges on nitrogen atom (q_N). (b) Correlation plot for experimental pK_a values against gas phase B3LYP calculated electronic charges on nitrogen atom (q_N).
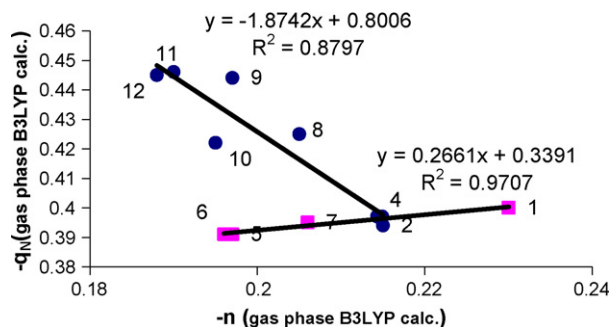
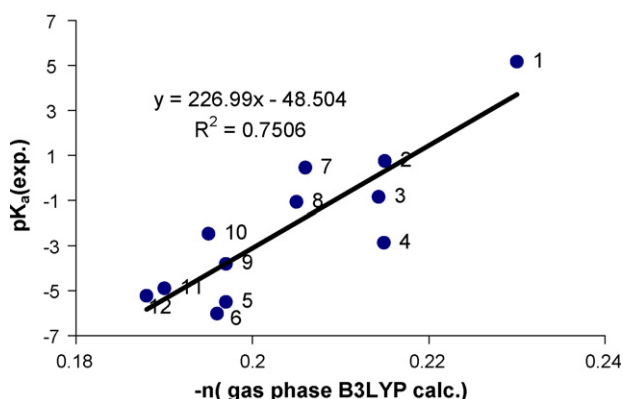Fig. 5. Correlation plot for gas phase B3LYP calculated nucleophilicities against.

Fig. 6. Correlation plot for experimental pK_a values against gas phase B3LYP calculated. Nucleophilicity values $(-n)$.

were observed (i.e. R^2 values are 0.883 and 0.850, respectively) (Fig. 3).

Correlation plot for experimental pK_a(exp.) values against gas phase calculated electronic charge on nitrogen atom q_N with both HF and B3LYP method indicate that brom substituted derivatives (compounds **7–12**) less effective in withdrawing electrons comparing to chlor substituted ones (compounds **2–6**) as expected. Therefore magnitude of the electronic charge on nitrogen atom is bigger in the brom substituted molecules (Fig. 4a and b).

A similar trend was observed for correlation search between gas phase B3LYP calculated nucleophilicity $(-n)$ against gas phase B3LYP calculated charges $(-q_N)$ (Fig. 5) against the gas phase B3LYP calculated nucleophilicities $(-n)$ with the exception of compound **7** charges on brom substituted molecules are bigger than that of chlor substituted ones.

A correlation search between nucleophilicities and experimental pK_a values revealed that B3LYP method performs slightly better than that of HF method (Fig. 6) with a correlation of $R^2 = 0.7506$ and in gas phase calculations.

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