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Additivity of substituent effects on the proton affinity and gas-phase basicity of pyridines

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ABSTRACT

The change in the proton affinity (PA) and basicity (GB) of pyridine with substituents have been considered by quantum mechanical methods at the B3LYP/6-311++G(d,p) level of theory. The PA and GB values increase by the electron-donating substituents and decrease by the electron-withdrawing substituents. The effects of substituents on the PA and GB are approximately additive. The deviations of changes that are predicted from the additivity of substituent effects are generally lower than 30% from the calculated changes. Linear relationships are observed between the calculated PA values of substituted pyridines and the topological properties of electron density, the molecular electrostatic potentials (MEP), and the N–H bond lengths. In addition, well-defined relations are established between the calculated PA values and the Hammett constants, and the reaction constant (ρ) has been calculated for the protonation reaction. With some exceptions, the effect of substituents are also additive on the electron density and its Laplacian calculated at N–H BCP, and the MEP values calculated around the N atom.

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1. Introduction

The gas-phase basicity (GB) and proton affinity (PA) of M (a molecule or atom) are both defined in terms of the gas-phase reaction



The GB is the negative of the free energy change associated with this reaction, while the PA is the negative of the enthalpy change [1].

The absolute PA is one of the most fundamental thermodynamic properties of bases [2–5], which provides valuable hints about the electrophilic reactivity [6]. PA reflects the intrinsic basicity of a chemical compound in absence of any solvent effects, and is of prime theoretical importance [7]. PA can be applied to different aspects such as determination of the stability of cationic species [8,9], the hydrogen-bonding ability, acidity of solid catalysts [10], and relation between PA and pK_a [11–13].

Conventionally, the PA values of pyridine and its derivatives were measured in the gas phase using experimental methods (such as spectrometric techniques, kinetic methods, etc.) [1,2,14–23], ab initio methods, and density functional theory (DFT) [2,7,24–27].

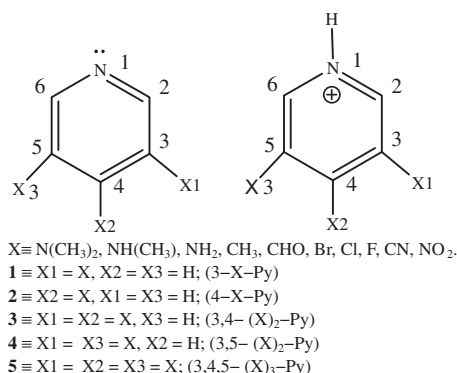
The additivity of substituents on different properties is an interesting subject that has been considered from both experimental and theoretical viewpoints. The concept of additivity was introduced [28], developed [29] and used [6,30–40] for the proton affinities of the ring carbons in polysubstituted benzenes.

The relationships between PAs and other properties, such as ionization energy and binding energy were previously investigated [41–44] for some aromatic and nonaromatic (and noncyclic) compounds. Linear relationships with high correlation coefficients were observed in many cases.

In this paper, the additivity of the effects of electron-donating and electron-withdrawing substituents on the PA and GB of pyridine (see Scheme 1) have been studied using quantum mechanical calculations. The categories 1–5 correspond to meta, para, meta-para, meta-meta, and meta-meta-para substituted cases. The importance of resonance and polar effects can be investigated by comparison of the effects of substituents in different positions on the ring. Also, it is the purpose of this work to investigate the relationships between PA and different properties including topological properties of electron density at the N–H bond critical points (BCP) calculated by the atoms in molecules (AIM) method [45], the molecular electrostatic potentials (MEP), the structural parameters, and the Hammett σ -constants. In the present work, the additivity of substituent effects has also been considered on the topological properties of electron density and MEP values. The reaction constant has been calculated from the relationship between the PA values and the Hammett σ -constants of substituents.

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Scheme 1. Numbering of the positions in the pyridine and the pyridinium ion derivatives.

2. Computational methods

All calculations were carried out using the Gaussian03 [46] program package. The structures were optimized using the B3LYP [47] functional with the 6-311++G(d,p) [48] basis set. Single point calculations have been performed on the optimized structures at the B3LYP/aug-cc-pVTZ [49] and MP2/6-311++G(d,p) [50] levels of theory. Vibrational frequency calculations have been performed at the B3LYP/6-311++G(d,p) level of theory on the structures optimized at the same level, when the harmonic frequencies were scaled by 0.962 [51,52]. The ΔE values have been corrected for zero point energy $\Delta E_{ZPE} (= \Delta E + \Delta ZPE)$ at the B3LYP/6-311++G(d,p) level.

The PA and GB at 298.15 K are defined as the enthalpy change (Eq. (2)) and the free energy change (Eq. (3)), respectively, during the protonation process.

$$PA = \Delta H_g^0(A) + \Delta H_g^0(H^+) - \Delta H_g^0(AH^+), \quad (2)$$

$$GB = \Delta G_g^0(A) + \Delta G_g^0(H^+) - \Delta G_g^0(AH^+), \quad (3)$$

Table 1
Calculated energy values in kcal mol⁻¹ for protonation process and N-H bond lengths (in Å).

	1	2	3	4	5	1	2	3	4	5
	$-\Delta E^a$					$-\Delta E^b$				
N(CH ₃) ₂	249.27	242.2				245.8	242.6			
NH(CH ₃)	247.3	239.8	251.3	247.7	251.3	243.2	236.9		244.4	-246.0
NH ₂	244.1	237.3	245.8	242.3	247.5	239.3	234.0	240.4	238.4	-242.4
CH ₃	235.4	234.3	238.4	237.5	241.2	231.9	231.5	234.8	234.6	-237.8
H	230.8		230.8		230.8	228.2		228.2		-228.2
Br	227.8	225.4	224.2	220.7	220.9	225.1	223.1	221.6	218.7	-218.5
Cl	227.3	224.8	222.8	219.3	218.7	224.9	222.5	220.9	218.0	-217.2
F	226.2	223.6	219.7	216.6	213.0	223.8	221.5	217.6	214.9	-211.3
CHO	223.8	223.2	217.5	217.1	213.9	222.1	221.5	216.6	216.0	-212.2
CN	218.8	217.1	207.3	204.8	197.0	216.6	215.0	205.3	203.1	-196.5
NO ₂	215.8	215.3	204.1	201.5	193.2	215.1	213.8	202.1	201.0	-191.4
	$-\Delta E^c$					r_{N-H}				
N(CH ₃) ₂	240.7	233.6				1.0118	1.0152			
NH(CH ₃)	238.4	231.2	242.8	239.2	242.9	1.0121	1.0155	1.0119	1.0147	1.0117
NH ₂	235.4	228.9	237.4	234.5	239.2	1.0126	1.0157	1.0125	1.0152	1.0122
CH ₃	226.9	225.7	230.0	229.0	232.6	1.0153	1.0159	1.0149	1.0156	1.0147
H	222.3		222.3		222.3	1.0163		1.0163		1.0163
Br	219.5	217.1	216.0	212.5	212.7	1.0155	1.0168	1.0159	1.0172	1.0163
Cl	218.9	216.4	214.6	211.1	210.5	1.0156	1.0169	1.0160	1.0172	1.0164
F	217.7	215.2	211.2	208.1	204.7	1.0158	1.0170	1.0164	1.0175	1.0170
CHO	215.4	214.9	209.4	209.0	205.7	1.0166	1.0171	1.0174	1.0179	1.0176
CN	210.4	208.8	199.2	196.7	189.0	1.0169	1.0172	1.0177	1.0182	1.0185
NO ₂	207.6	207.1	196.2	193.7	185.6	1.0174	1.0175	1.0180	1.0188	1.0191

^a The protonation energies calculated at the B3LYP/6-311++G(d,p) level in kcal/mol.

^b Single point energies calculated at the MP2/6-311++G(d,p) level.

^c The ΔE values calculated at the B3LYP/6-311++G(d,p) level and corrected by zero point energy.

We used $\Delta H_g^0(H^+) = 2.5RT = 1.48$ kcal/mol and $\Delta G_g^0(H^+) = 2.5RT - T\Delta S^0 = 1.48 - 7.76 = -6.28$ kcal/mol from the literatures [7,13,53].

The topological properties of electron charge density were analyzed by the AIM method using AIM2000 package [54] at the wave functions obtained at the B3LYP/6-311++G(d,p) level. The cube files containing the MEP data have been generated for the X_n -py compounds at the B3LYP/6-311++G(d,p) level using the Gaussian03 package. The freely available MOLEKEL program has been used [55] to visualize the MEP. The most negative-valued MEP point (V_{min}) can be obtained from the visual inspection of MEP data for the lone-pair region of the nitrogen atom in the pyridine.

3. Results and discussion

Substituted pyridines and related pyridinium ions are categorized in five groups as are shown in Scheme 1. The common numbering scheme has been used to indicate the positions on the ring. The protonation energies calculated at different levels of theory are gathered in Table 1. The values calculated at the B3LYP/aug-cc-pVTZ level are not listed because they do not significantly differ from the reported values at the B3LYP/6-311++G(d,p) level of theory. The protonation energies calculated at the the B3LYP/6-311++G(d,p) level of theory are in the range of -193.22 to -251.32 kcal mol⁻¹ (see Table 1). The minimum and maximum values correspond to NO₂ and NH(CH₃), respectively, in the category 5. As can be seen, the electron-withdrawing (EW) substituents decrease the protonation energies and the stability of protonated compounds relative to the pyridine, while the reverse is true for the electron-donating (ED) substituents. Linear relationships with good correlation coefficients ($R \geq 0.94$) are observed between the ΔE values and the N-H bond lengths (and the Hammett constants) for all categories presented in Scheme 1.

Although the zero point energy correction decreases the absolute values of ΔE , the order does not change by this correction since ZPE is approximately independent of the substituent (see Table 1). This is in agreement with the previous finding [56], which

Table 2

Experimental and calculated proton affinities and gas phase basicities.

	1	2	3	4	5	1	2	3	4	5
	PA					GB				
N(CH ₃) ₂	234.9 (231.7)	242.0 (238.4)				227.6 (225.4)	234.6 (232.1)			
NH(CH ₃)	232.5	239.9	244.1 30	240.4 10	244.4 54	225.0	232.0	236.7 21	233.2 5	237.0 62
NH ₂	230.2 (228.1)	236.9 (234.2)	238.8 30	235.5 10	240.7 54	221.6 (220.5)	228.7 (226.5)	231.1 21	228.9 -14	232.9 41
CH ₃	227.2 (225.5)	228.4 (226.4)	231.3 7	230.4 5	234.1 12	219.4 (217.9)	220.6 (218.8)	223.8 2	222.7 0	226.4 8
H	223.7	(222.3)				(214.7)	216.0			
Br	218.5 (217.6)	220.9 (219.4)	217.4 27	212.5 6	214.2 38	210.8 (209.9)	213.2 (211.8)	209.7 27	206.2 6	206.4 37
Cl	217.8 (215.9)	220.3 (219.0)	216.0 20	209.5 5	212.5 29	210.2 (208.3)	212.7 (211.3)	208.3 20	204.8 5	204.2 28
F	216.6 (215.6)	219.1 (218.2)	212.7 6	210.4 0	206.2 7	208.9 (208.0)	211.5 (210.6)	205.0 6	201.9 0	198.5 7
CHO	216.2	216.8 (216.2)	210.8 11	210.0 12	207.2 32	208.7	209.3 (208.6)	203.2 9	202.9 11	199.5 33
CN	210.2 (209.6)	211.8 (210.5)	200.5 10	198.0 5	190.4 17	202.6 (202.0)	204.3 (202.9)	193.0 10	190.5 5	182.8 16
NO ₂	208.5	209.0 (209.0)	197.6 14	195.0 6	187.1 23	200.7	201.5 (201.4)	190.1 15	187.3 6	180.1 25

Experimental data given in the parentheses were taken from reference [14]. The bold data are equal to $D\% = (\Delta X_p - \Delta X_c) \times 100 / \Delta X_p$, where ΔX_p is the change in the proton affinity calculated by the additivity of substituents effects and ΔX_c is the change calculated by the usual method (the value calculated for substituted pyridine minus the value calculated for pyridine).

the proton had a constant contribution to PAs of carbons of some planar (aromatic) rings.

3.1. The proton affinity and basicity

The calculated PA values for pyridine derivatives are reported in Table 2. It is equal to 223.7 kcal mol⁻¹ for pyridine at the B3LYP/6-311++G(d,p) level that is in good agreement with the reported experimental data 222.3 kcal mol⁻¹ (taken from the NIST database). For those substituted pyridines that the experimental data are available, the order of calculated PA values is similar to the experimental results. The calculated values and the available experimental data show a very good linear correlation with $R^2 = 0.99$ for the categories **1** and **2**. Thus, the B3LYP/6-311++G(d,p) level can be employed as a reliable method in the calculation of PA in pyridine derivatives.

The maximum PA value, 244.4 kcal mol⁻¹, corresponds to 3,4,5-(NH(CH₃))₃-py, and the minimum value, 187.1 kcal mol⁻¹, corresponds to 3,4,5-(NO₂)₃-py (see Table 2). Nitro group is a strong electron-withdrawing substituent, which decreases the electron density substantially on the N atom of the pyridine ring. In each category, the ED substituents increase the electron density on the N atom, which makes the nitrogen lone pair more available for the proton and increase the PA values relative to pyridine. This behavior is reversed by the EW substituents. The PA value decreases more with increasing the electron-withdrawing ability of substituents. Thus, the maximum values of PA for the ED and EW substituents correspond to the categories **5** and **2**, respectively.

The most important resonance structures of pyridine ring in the presence of ED substituents are shown in Scheme 2. As can be seen, the negative charge can be placed on the N atom in one resonance structure for 4-position substituted cases. The ED substituents affect the center of reaction (N atom) by charge transfer and increase the PA value. Although the substituents in position 3 (or 5) do not increase the negative charge on the N atom by resonance, they increase the electron density near the N atom and increase the PA values relative to pyridine.

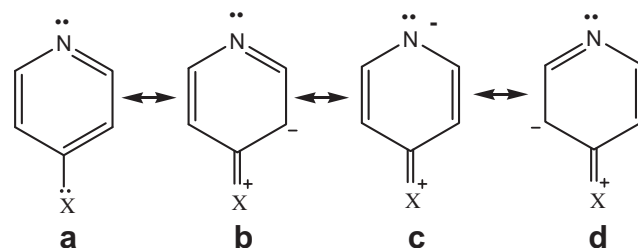
The PA values of 4-position substituted pyridines are greater than those of 3 (or 5)-position substituted cases, which could be

attributed to higher charge transfer in the former derivatives. The calculations reveal that the 4-position substituted pyridine is more basic relative to the 3 (or 5)-position substituted case.

The EW substituents can be divided into two groups: (a) F, Cl, and Br are electron-withdrawing due to the polar and electron-donating due to the resonance effects. (b) NO₂, CN, and CHO are electron-withdrawing due to both the induction and resonance effects. When, the EW substituents are located in positions 4 and 3 (or 5), the induction is more effective than the resonance. Since the inductive effect is in reverse relationship with the distance between the substituent and the center of reaction (N atom), the inductive effect for position 4 is lower than 3 (or 5). Thus, PA is greater for the 4-position substituted cases of EW substituents in both sets a and b.

Because of considerable σ -and- π -electron withdrawing power of CHO, CN, and NO₂ substituents, and the σ -acceptor and weak π -donor character of halogen atoms, a further reduction in the PA value is observed with the substituents of group b in comparison with a.

The PA values calculated for the group **3** are greater than the group **4** for all the ED and EW substituents. On the other hand, in the presence of ED substituents with resonance effects (and with charge transfer ability), the calculated PA value in the group **3** (3,4-(X)₂-Py) is greater than that in the group **4** (3,5-(X)₂-Py). Thus, the polar effect is more effective when two EW substituents are located in positions 3 and 5, such that the PA in the group **4** is lower



Scheme 2. Resonance structures in the 4-position substituted cases.

in comparison with the group **3**. The order of PA values is **1 < 2 < 4 < 3 < 5** for the ED substituents and **5 < 4 < 3 < 1 < 2** for the EW substituents.

By the additivity formula [29], which is based on the independent-substituent concept and was rationalized by homodesmotic reactions, the PAs of polysubstituted benzenes were estimated from the PA of unsubstituted benzene plus increments I

$$\text{PA}(\text{substituted benzene}) = \text{PA}(\text{benzene}) + \sum_N I(N)_{\alpha(N)} \quad (4)$$

where the summation runs over all substituents N , and $\alpha(N)$ denotes the position of the substituent relative to the protonation site (α = ortho, meta, para, and ipso).

The deviation of a predicted change in a property by additivity of the effect of substituents from the calculated change has been determined by the following equation (see bold data in Table 2 for proton affinity and basicity).

$$\%D = (\Delta X_p - \Delta X_c) \times 100 / \Delta X_p \quad (5)$$

where ΔX_p is the predicted change by the additivity of substituents effects and ΔX_c is the change calculated by the usual method (the value calculated for substituted pyridine minus the value calculated for pyridine). As can be seen in Table 2, $D\%$ is lower than 30 in many cases. Thus, with the exception of several cases, in which the orientation of substituents is different from mono substituted cases for the steric effects, the additivity of the effects of substituents is observed for proton affinity.

The calculated GB values of pyridine derivatives are also reported in Table 2. The orders of the calculated GB values are similar to the calculated PA values. On the other hand, there is a linear relationship between the PA and GB values with a very good correlation coefficient, $R = 1.0$. Neither symmetry changes nor dramatic changes in geometries are imposed by protonation; thus, influence of entropy on GB is constant for all practical implications.

The additivity of substituents effects on the basicity is similar to the proton affinity. So, with some exceptions, the effects of substituents could be added up for the basicity.

3.1.1. AIM analysis

The values of electron density (ρ_{BCP}) and Laplacian of electron density ($\nabla^2\rho$) were evaluated at the N-H BCP by the means of AIM approach at the B3LYP/6-311++G(d,p) level of theory. The ρ and $\nabla^2\rho$ values lie in the ranges of 0.334 to 0.341 e/au³ and -1.761 to -1.814 e/au⁵, respectively (see Table 3). The lowest and highest values correspond to NO₂ and NH(CH₃) substituents, respectively, in category **5**. The ED substituents increase the ρ and $\nabla^2\rho$ values calculated at the N-H BCP in comparison with pyridine. The observations are reversed for the EW substituents. The values of ρ and $\nabla^2\rho$ in the 4-position substituted derivatives are higher than those in the 3-position substituted cases. The values of both properties are in linear relationship with the calculated PA values ($R \geq 0.93$). Fig. 1 shows the relationship between PA and ρ (and $\nabla^2\rho$) in group **3**. Linear relationships with good correlation coefficients are observed between the ρ values and the N-H bond lengths for different categories ($R \geq 0.97$).

As can be seen in Table 3, $D\%$ for the ρ values calculated at N-H BCP is lower than 30 for the most pyridine derivatives; so, the substituent effect is approximately additive for the $\rho_{\text{N-H BCP}}$ values. A similar behavior is observed for the Laplacian of electron charge density at the above mentioned point (see Table 3).

3.1.2. MEP analysis

The molecular electrostatic potential (MEP) originally invoked to study electrophilic reactivity [57]. The MEP of a molecule is a real physical property, and it can be determined experimentally by X-ray diffraction techniques [58]. $V(\vec{r})$ that is created at a point \vec{r} by electrons and nuclei of a molecule is given as:

$$V(\vec{r}) = \sum_A \frac{Z_A}{|\vec{R}_A - \vec{r}|} - \int \frac{\rho(\vec{r}')}{|\vec{r} - \vec{r}'|} d\vec{r}' \quad (6)$$

Table 3
Electron density ρ (in e/au³), Laplacian of electron density $\nabla^2\rho$ (in e/au⁵), the results of MEP analysis and the value of $\log(K/K_0)$ calculated at the B3LYP/6-311++G(d,p) level of theory.

	1	2	3	4	5	1	2	3	4	5
$\rho_{\text{BCP}} \times 10$						$-\nabla^2\rho$				
N(CH ₃) ₂	3.397	3.401			3.412	1.775	1.762			
NH(CH ₃)	3.393	3.399	3.406	22	3.405	1.778	1.765	1.760	3	1.774
NH ₂	3.391	3.396	3.400	34	3.398	1.781	1.769	1.767	1	1.779
CH ₃	3.385	3.385	3.389	9	3.388	1.779	1.778	1.774	3	1.775
H		3.381					1.783			
Br	3.375	3.381	3.377	32	3.370	1.784	1.783	1.785	-28	1.785
Cl	3.374	3.380	3.375	25	3.370	1.786	1.784	1.787	-27	1.791
F	3.373	3.378	3.372	22	3.367	1.793	1.789	1.795	34	1.805
CHO	3.373	3.378	3.370	-7	3.366	1.790	1.790	1.792	45	1.792
CN	3.370	3.373	3.363	7	3.359	1.796	1.792	1.802	14	1.805
NO ₂	3.366	3.370	3.357	10	3.351	1.799	1.798	1.806	34	1.809
$-\text{MEP} \times 10^2$						$\log(K/K_0)$				
N(CH ₃) ₂	10.8	12.5				2.963	4.785			
NH(CH ₃)	10.7	11.3	11.5	35	11.3	2.309	4.111	5.318	4.409	5.396
NH ₂	10.6	11.0	11.0	58	10.8	1.418	3.270	3.888	3.305	4.345
CH ₃	10.1	10.3	10.5	8	10.3	0.857	1.179	1.993	1.708	2.672
H		9.9					0.000			
Br	8.6	8.9	8.1	24	7.5	-1.344	-0.728	-1.626	-2.532	-2.484
Cl	8.7	9.0	8.1	16	7.6	-1.514	-0.870	-1.993	-2.891	-3.047
F	8.8	9.1	8.2	6	7.8	-1.832	-1.172	-2.842	-3.647	-4.529
CHO	8.3	8.5	7.2	12	7.0	-1.883	-1.737	-3.317	-3.382	-4.146
CN	7.6	7.8	6.6	31	6.2	-3.463	-3.036	-5.934	-6.582	-8.555
NO ₂	7.4	7.5	5.5	10	5.3	-3.943	-3.733	-6.692	-7.410	-9.265

The bold data are equal to $D\% = (\Delta X_p - \Delta X_c) \times 100 / \Delta X_p$, where ΔX_p is the predicted change in property by the additivity of substituents effects and ΔX_c is the change calculated by the usual method (the value calculated for substituted pyridine minus the value calculated for pyridine).

where Z_A is the charge on nucleus A, located at R_A , and $\rho(\vec{r})$ is the molecule's electron density [59]. The sign of $V(r)$ at any point depends on whether the effects of the nuclei or the electron are dominant there. The most negative values are associated with the lone pairs of electronegative atoms, because of the larger value of the electronic term in Eq. (6) in comparison with the nuclear term, and these V_{\min} points represent the centers of negative charges on the molecule [60].

As can be seen in Table 3, the MEP (V_{\min}) value becomes more negative with the ED substituents and by the increase in the number of those groups, while the reverse is true with the EW substituents. As a result, the electrostatic term depends on the electron-donation or electron-withdrawal character of the substituents.

The comparison of 3 (or 5) and 4-position substituted cases shows that the MEP values in the former are less negative than those in the later derivatives. As can be seen in Fig. 2, there is a

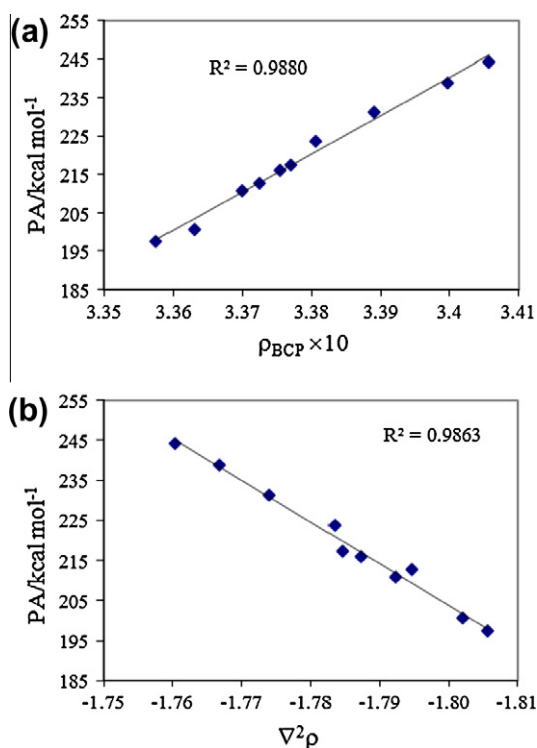


Fig. 1. Linear correlation between the PA and (a) the electron density, and (b) the Laplacian of electron density at the N-H BCP.

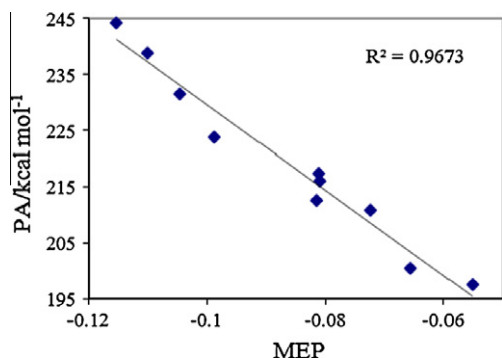


Fig. 2. Relationship between the molecular electrostatic potential around the nitrogen and the PA value.

good correlation between MEP and PA for group 3. This linear correlation is also observed for other groups ($R \geq 0.98$).

As can be seen in Table 3, $D\%$ for the MEP values calculated around the N atom of ring is lower than 30; so, the substituent effect is approximately additive for the MEP values calculated around the N atom.

3.1.3. The Hammett constants (σ)

The values of σ were defined by Hammett from the ionization constants of benzoic acids as follows:

$$\sigma_X = \log K_X - \log K_H \quad (7)$$

where K_H and K_X are the ionization constant for the benzoic acid and a meta- or para-substituted benzoic acid in water at 25 °C [61,62]. The values of Hammett constants σ_m and σ_p summarize the total electronic effects which consist of the resonance and the field polar effects, of X bound to a benzene ring [63]. The σ constant can often successfully predict the equilibrium and the rate constants for a variety of chemical reactions. For $X = H$, σ is equal to zero by definition. The EW substituents are characterized by positive values of σ (increasing the ionization constant relative to the benzoic acid) and the ED substituents by negative values (decreasing the ionization constant relative to the benzoic acid) [64].

In order to investigate the relationship between PA and σ , we assumed that the σ values measured for benzene ring to be proportional with the corresponding values for pyridine ring. The σ values were adopted from literature [65]. The σ_{total} values for the categories 3, 4, and 5 calculated using the following equations: $\sigma_{\text{total}} = \sigma_{\text{meta}} + \sigma_{\text{para}}$ for 3, $\sigma_{\text{total}} = 2 \times \sigma_{\text{meta}}$ for 4, and $\sigma_{\text{total}} = 2 \times \sigma_{\text{meta}} + \sigma_{\text{para}}$ for 5.

The correlation coefficients for the linear relationships between the PA values and the Hammett σ -constants in various categories are higher than 0.96. As can be seen in Fig. 3, there is a good linear correlation between σ and PA in the group 3. In the presence of an electron donating substituent, the increased negative charge on the nitrogen atom facilitates proton gain, thereby increasing the PA of substituted pyridine.

With respect to Hammett equation

$$\log(K/K_0) = \sigma \rho = -(\Delta G - \Delta G_0)/2.3RT \quad (8)$$

the slope of $\log(K/K_0)$ against σ , which is defined by ρ (reaction constant), represents the sensitivity of a reaction to the electronic withdrawal or donation in comparison with the benzoic acid ionization. In this study, K and K_0 are the equilibrium constants of protonation process for a substituted pyridine and pyridine itself, respectively. These values are reported in Table 3. The values denoted by ΔG and ΔG_0 are the Gibbs free energies of mentioned reactions.

The Hammett equation holds good when inductive effect is the only polar connection between a substituent and reaction center

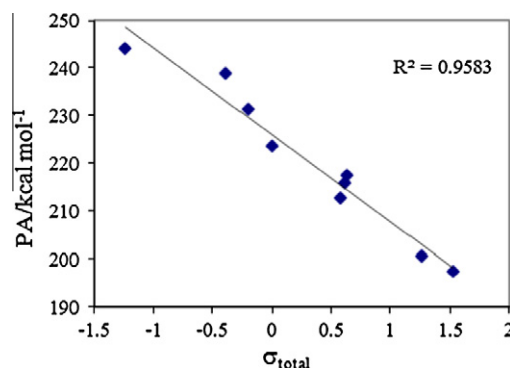


Fig. 3. Relationship between the PAs and the Hammett constants.

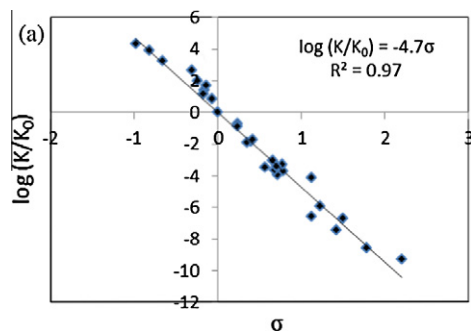


Fig. 4. All categories have been considered together in drawing the Hammett plot.

[66]. Resonance effect is the main cause of the failure of the Hammett equation. If σ^+ (or σ^-) values give a better fit in the Hammett equation, then this means that resonance is involved between the substituent and the reaction center. In the present work, we checked the Hammett equation by both σ and σ^+ (or σ^-) of substituents at para position. The correlation coefficient for relationship between $\log(K/K_0)$ and σ is higher than σ^+ (or σ^-); it is such because of low contribution of a resonance structure (for X-Py-H⁺) that is related to Scheme 2b. In all optimized X-Py-H⁺ structures, the N-H fragment is in the plane of ring.

We assume that the σ values of pyridine ring are proportional with those reported for benzene ring. With the exception of σ_p for F and σ_m for Cl and Br, there are good agreements between $\log(K/K_0)$ values and the σ values selected for substituents. $-(\Delta G - \Delta G^\circ)/2.3RT = \log(K/K_0)$ versus σ is shown in Fig. 4, where the above mentioned cases have not been considered in drawing the plot. As can be seen, a linear relationship is observed between $\log(K/K_0)$ and σ_{total} with a good correlation coefficient in which the slope (ρ) is equal to -4.7 and $R^2 = 0.97$. The negative value indicates that the ED substituents increase the protonation and the EW substituents decrease it. Linear relationships with good correlation coefficients are also observed between $\log(K/K_0)$ and σ for the singly- doubly- and triply-substituted cases separately. In addition, the reaction constant has been calculated for all categories. The slopes are equal to -5.1 , -5.0 and -4.4 for singly- (groups 1 and 2) doubly- (groups 3 and 4) and triply- (group 5) substituted pyridines, respectively. Thus, the absolute value of ρ decreases by increasing the number of substituents. This means that the sensitivity of reaction to the type of substituent decreases by the increase in the number of substituents. Linear relationships with good correlation coefficients are also observed between the Hammett constants and the ρ values calculated at the N-H BCP ($R \geq 0.96$).

The Hammett constants reflect the electronic effects of the substituents that can affect the V_{min} values [58,67,68]. It is found that the values of MEP are linearly proportional to σ .

4. Conclusion

The quantum mechanical studies show that the EW substituents at different positions on the pyridine ring increase the protonation energies of substituted pyridine and the ED substituents decrease that. For all ED and EW substituents, the calculated PA in 4-position substituted derivatives is greater than those in 3 (or 5)-position substituted cases. The effects of substituents on the proton affinity, the basicity, the topological properties of electron charge density, and the MEP values calculated around the N atom of pyridine are approximately additive. Generally, the deviation of a predicted change in the above mentioned properties by the additivity of the effects of substituents from the calculated changes are lower than 30%.

Linear relationships with very good correlation coefficients are observed between the PA values and the Hammett constants. The slope (ρ) for the plot of $-(\Delta G - \Delta G^\circ)/2.3RT$ versus σ in the singly, doubly and triply substituted derivatives is equal to -5.1 , -5.0 , and -4.4 , respectively. The ρ value is negative, thus, the protonation increases by the ED substituents and decreases by the EW groups. In addition, the slope in the singly substituted cases is steeper than the doubly, while the latter is also steeper than the triply substituted derivatives. Therefore, the sensitivity of reaction to the type of substituent decreases by the increase in the number of substituents.

Linear relationships are observed between the PA and ρ (and $\nabla^2\rho$) values calculated at the N-H BCP and the MEP values calculated around the N atom of the ring. The MEP around the nitrogen atom is an excellent measure for the proton donation potential in X_n-py.

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