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Theoretical Study of Substituent Effects on Electronic and Structural Properties of 2,4-Diamino-5-*para*-substituted-phenyl-6-ethyl-pyrimidines

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Density functional theory (DFT) method at the level of B3LYP with 6-311G(d) basis set was used to investigate the effects of a variety of substituents (H, NH_2, NMe_2, OCH_3, CH_3, Cl, Br, CN, NO_2) on the electronic and structural properties of 2,4-diamino-5-*p*-substituted-phenyl-6-ethyl-pyrimidines. The investigation showed that the atomization energy was affected by substitution. Likewise, the molecular orbitals HOMO and LUMO and energy gap ΔE were affected by the substituent. Dipole moment was also affected by the introduction of the substituent. On the other hand, the Mulliken charges at only C1', C2 and N7, were correlated with both MSP and DSP models.

Keywords: Substituent effect, HOMO and LUMO, Pyrimethamine, DFT method, MSP and DSP models

INTRODUCTION

In recent years, the theoretical study of the electronic structure has proved to be very conducive to predict physico-chemical properties of a large number of donor-acceptor systems. Moreover, theoretical calculations such as geometry optimizations are very important for understanding the pathways of electron and/or energy transfer processes in photoactive assemblies [1].

The substituents attached to the molecular framework can enhance or diminish the reactivity. The mechanistic conclusions based on the linear relationships with free energy have been extremely fruitful. Accordingly, changes in reactivity in one reaction series caused by changes in substitution are related to changes in equilibrium or reactivity in another series caused by the same changes in substitution [2]. The most typical and the most useful mono-substituent parameter (MSP) is the Hammett model, which correlates with rates and equilibria of side-chain reactions of *para-* and *meta-*substituted aromatic compounds. The story of the applications, modifications, and extensions of the Hammett equation is well known and has been cited briefly or in detail in numerous articles and books [2-6]. On the other hand, the dual-substituent parameter (DSP) model is the Taft model which is a good tool for describing the transition of substituent electronic effect along the organic molecule [7].

In our previous studies on the substituent effect on the electronic and structural properties of some important aromatic compounds, we reported that the electronic and structural properties greatly depend on the substituents of the phenyl ring [1,8-10], namely, the substituents on the phenyl ring affect the electronic and structural properties *via* the field

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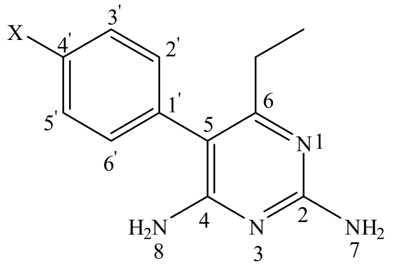


2,4-diamino-5-*para*-substituted-phenyl-6-ethyl-pyrimidine
X = H, NH_2, NMe_2, OCH_3, CH_3, Cl, Br, CN, NO_2

Scheme 1

and resonance effects.

Since malarial drug resistance may become a serious problem in the treatment of malaria [11], the selection of antimalarial drugs is necessarily dependent on the species and the reported resistance pattern in each setting [12]. Admittedly, the biological activity and the pharmaceutical properties of drugs are strongly dependent on their structure [13]. In this work, the full DFT method of investigation of the pyrimthamine and its derivatives has been conducted. Various donating and accepting substituents at *para* position of the phenyl ring of 2,4-diamino-5-phenyl-6-ethyl-pyrimidine have been introduced to study the substituent effects on structural and electronic properties (Scheme 1).

CALCULATION METHOD

The geometries of all 2,4-diamino-5-*para*-substituted-phenyl-6-ethyl-pyrimidine molecules were fully optimized by the 6-311G(d) basis sets with the DFT/B3LYP method using Gaussian 03 software [14], and some molecular properties were also calculated by B3LYP/6-311G(d). Regression analysis calculations were made using MINITAB data analysis software release 11.11 standard version [15]. In this study, the Hammett parameter was used as an MSP model [16] and the Taft parameter as a DSP model [17].

RESULTS AND DISCUSSION

Structural and Electronic Properties

Atomization energy (AE) and some molecular information about HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies, energy gap (ΔE) about the 4'-substituted-pyrimethamine molecules are given in Table 1.

In Fig. 1, the atomization energy was plotted against σ_P. It indicates the stability of a molecule; the larger the energy, the more stable the molecule. The figure shows that the substitution on *para* position of 2,4-diamino-5-*para*-substituted-phenyl-6-ethyl-pyrimidine leads to an increase in the stability of the molecule compared to the unsubstituted one. Strictly speaking, the substitution of halogen Br (and Cl)

Table 1. Hammett's σ_P Values, Calculated Atomization Energy (AE), HOMO and LUMO Energies, the HOMO-LUMO Band Gap (ΔE) in eV, and the Dipole Moment (μ) in Debye of Pyrimethamine Molecules

X			MO Energies			
	σ_P	AE	HOMO	LUMO	ΔE	μ
H	0.00	135.0	-5.720	-0.555	5.166	1.7974
NH_2	-0.66	141.8	-5.428	-0.372	5.057	3.0563
NMe_2	-0.83	165.0	-5.226	-0.294	4.932	3.8271
OCH_3	-0.27	150.6	-5.612	-0.462	5.150	3.4189
CH_3	-0.17	146.9	-5.667	-0.480	5.188	2.1231
Cl	0.23	134.2	-5.866	-0.873	4.994	1.7832
Br	0.23	133.7	-5.861	-0.867	4.995	2.1422
CN	0.66	143.6	-6.059	-1.763	4.289	4.7229
NO_2	0.78	142.8	-6.101	-2.634	3.467	4.9370

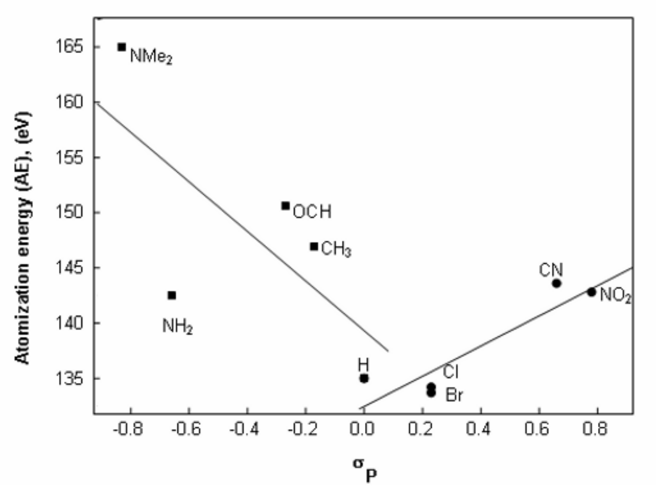


Fig. 1. Correlation between Hammett constants and atomization energy (AE).

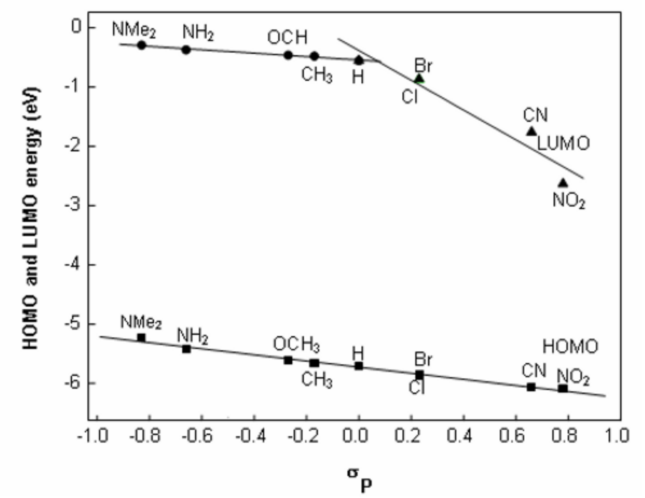


Fig. 2. Correlation between Hammett constants and HOMO and LUMO energies.

leads to the smallest atomization energy which may be of significance in antimalarial activity. Substitution with dimethylamino and with nitro and cyano has a big influence, but the electron-donating (ED) substituent is more effective than the electron-withdrawing (EW) substituent. The Hammett plot correlations for the two lines are given in Eqs. (1a) and (1b), respectively:

$$AE = 139.2 - 22.4\,\sigma_P \qquad \text{(ED)} \qquad (1a)$$
$n = 5$, $s = 9.34$, $r = 0.693$

$$AE = 139 - 33.2\,\sigma_P \qquad \text{(ED, after deleting } NH_2\text{)}$$
$n = 4$, $s = 3.89$, $r = 0.966$

$$AE = 133.6 + 13.7\,\sigma_P \qquad \text{(EW)} \qquad (1b)$$
$n = 5$, $s = 2.34$, $r = 0.910$

where n is the number of compounds, r is the correlation coefficient, s is the standard deviation.

Amino substituent has irregular and a small amount of atomization energy in the ED groups. Hence, the deletion of NH_2 substituent improves the linearity of the plot (see Eq. (1a)). On the other hand, the ED substituents with a large amount of atomization energy belong to the methyl group. The inner rotation of the methyl group makes it hard to estimate the accurate value of the zero-point energy, so that the atomization energy may have some ambiguity.

Energies of the HOMO and the LUMO are very popular quantum chemical descriptors. The energy of the HOMO is directly related to the ionization potential and characterizes the susceptibility of the molecule to attack by electrophiles. On the other hand, the energy of the LUMO is directly related to the electron affinity and characterizes the susceptibility of the molecule to attack by nucleophiles [18].

The HOMO and LUMO energies and the difference between the HOMO and LUMO energies known as energy band gap ($\Delta E = E_{LUMO} - E_{HOMO}$) are all given in Table 1. It can be seen from the data in the table that the substituents have significant effect on both HOMO and LUMO levels. In order to gain insight into the origin of the effects of the substituent in 2,4-diamino-5-*para*-substituted-phenyl-6-ethyl-pyrimidine on HOMO and LUMO energies, the Hammett plots of their energies against σ_P were constructed (Fig. 2). The Hammett plot correlations for HOMO and LUMO energies are given in Eqs. (2) and (3), respectively:

$$HOMO = -5.73 - 0.517\,\sigma_P \qquad (2)$$
$n = 9$, $s = 0.03788$, $r = 0.992$

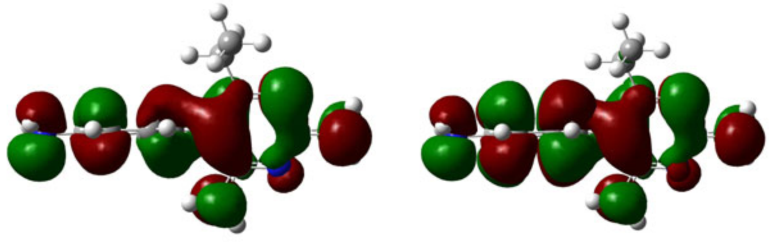
$$LUMO = -0.544 - 0.288\,\sigma_P \qquad \text{(ED)} \qquad (3a)$$
$n = 5$, $s = 0.01645$, $r = 0.990$

$$\text{LUMO} = -\,0.383 - 2.519\,\sigma_P \qquad (\text{EW}) \qquad (3b)$$

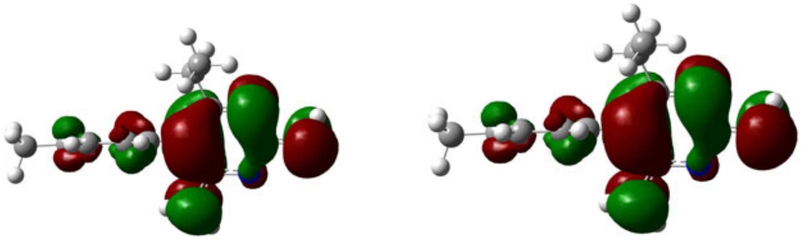
$n = 5$, $s = 0.2635$, $r = 0.964$

Figure 2 and Eq. (2) show significant linear relationship between HOMO and σ_P with the correlation coefficient $r = 0.992$. The negative slope ($\rho = -0.517$) means that the ED substituent (*e.g.* NH_2, NMe_2 or OCH_3) causes an increase in the energy level, while the EW substituent (*e.g.* CN or NO_2) decreases the energy level. The low value of ρ suggests that the introduction of substituents has modest effect on HOMO.

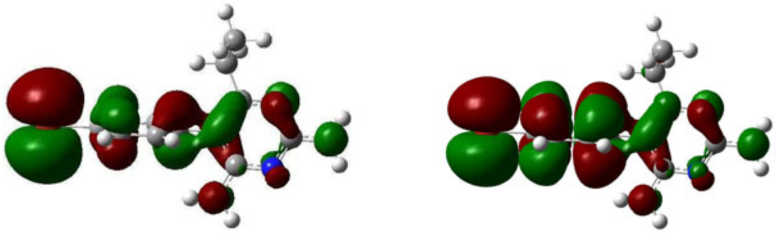
Figure 2 and Eq. (3a) indicate that the substitution with an ED substitutuent slightly raises the LUMO level ($\rho = -0.288$), whereas the substitution with an EW substituent significantly lowers the LUMO level ($\rho = -2.519$). The high negative ρ value of EW (see Eq. (3b)) suggests that the substitution on the molecule has an effect on LUMO. The molecular HOMO and LUMO orbitals of some compounds are graphically displayed in Fig. 3. This figure shows that both HOMO and



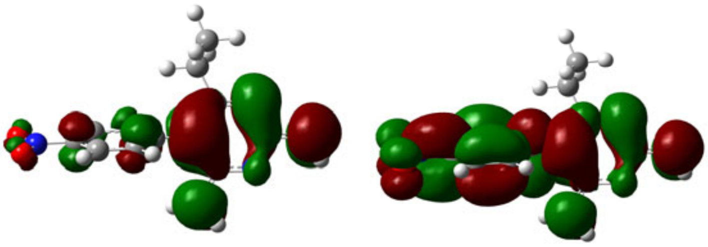
HOMO NH_2 LUMO NH_2



HOMO CH_3 LUMO CH_3



HOMO Br LUMO Br



HOMO NO_2 LUMO NO_2

Fig. 3. Three dimensional pictures of HOMO and LUMO of NH_2, CH_3, Br and NO_2 substituents.

LUMO are distributed along the 2,4-diamino-5-*para*-substituted-phenyl-6-ethyl-pyrimidine molecular skeleton.

The HOMO-LUMO gap (ΔE) is well known to be an important stability index [19]. In order to show the substituent effect on ΔE, it is plotted against σ_P (Fig. 4). The obtained correlation is given in Eq. (4).

$$\Delta E = 5.21 + 0.284\ \sigma_P \qquad \text{(ED)} \qquad (4a)$$
$n = 5$, $s = 0.1458$, $r = 0.932$

$$\Delta E = 5.36 - 2.04\ \sigma_P \qquad \text{(EW)} \qquad (4b)$$
$n = 5$, $s = 0.1267$, $r = 0.942$

It can be seen from Fig. 4 and Eq. (4) that the substitution on 2,4-diamino-5-*para*-substituted-phenyl-6-ethyl-pyrimidine skeleton exerts a significant effect on ΔE. Figure 4 shows that the introduction of ED substituents leads to a slight fall in ΔE, whereas the introduction of EW substituents leads to a large fall in ΔE. This can be attributed to the fact that the HOMO energies linearly decrease, while LUMO undergoes a small change in ED and a large fall in EW (see Fig. 2).

The polarity of the molecule is well known to be crucial for various physicochemical properties, and many descriptors have proposed to quantify the polarity effects. The most obvious and the most frequently used quantity to describe the polarity is the electric dipole moment (μ) of molecule [20]. To illustrate the effect of the substituent on μ, the quantitative relationship between μ and the electronic parameter of the substituents (σ_P) (Fig. 5 and Eq. (5)) has been studied. Figure 5 and Eq. (5) show two linear lines; the first one indicates that the substitution with ED substituent increases the dipole moment with negative slope, while the second one indicates that the substitution with EW substituent increases the dipole moment with positive slope.

$$\mu = 2.05 - 2.05\ \sigma_P \qquad \text{(ED)} \qquad (5a)$$
$n = 5$, $s = 0.2247$, $r = 0.828$

$$\mu = 1.28 + 4.73\ \sigma_P \qquad \text{(EW)} \qquad (5b)$$
$n = 5$, $s = 0.1026$, $r = 0.962$

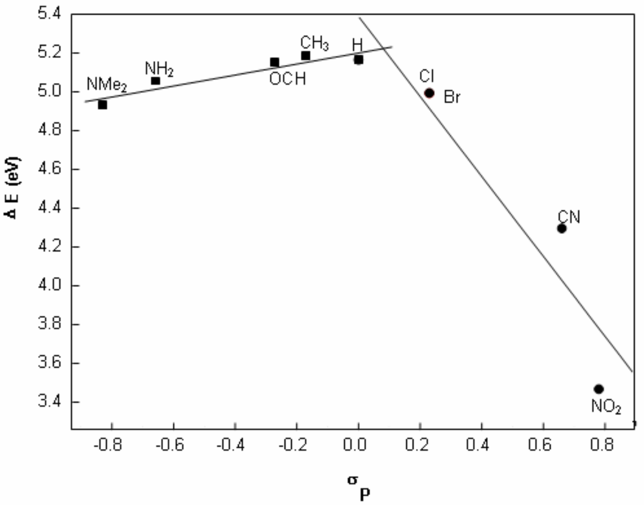


Fig. 4. Correlation between Hammett constants and ΔE.

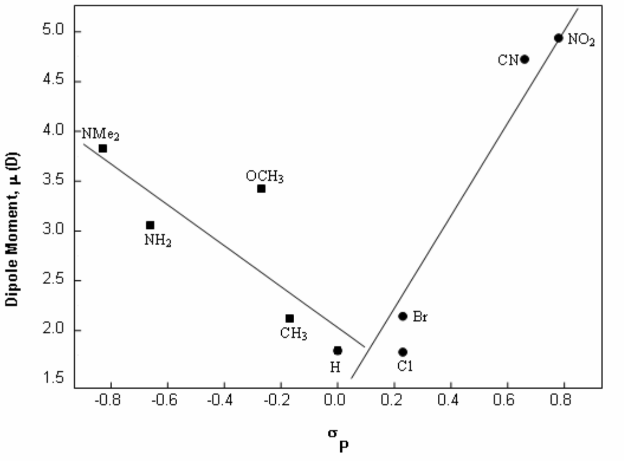


Fig. 5. Correlation between Hammett constants and dipole moment.

The main structural parameters of molecules on ground states obtained at the B3LYP/6-311G(d) are presented in Table 2. Table 2 shows that there is no significant substituent effects marked on all bonds length of the pyrimidine ring (C6-N1, N3-C4, C2-N3, N1-C2) and C1'-C5. The C4-C5-C1'-C2' dihedral angles θ (*i.e.* rotation between *para*-substituted phenyl ring and pyrimidine ring) are also given in Table 2. The dihedral angle is evidently affected by different substituents. The obtained results imply that all molecules are non-coplanar which can be attributed to the bulky 6-ethyl and

Table 2. Selected Structural Parameters (Bond Lengths and Dihedral Angles) of Pyrimethamine Molecules

	Bond distance (Å)					Dihedral angle (°)
X	C6-N1	N3-C4	C2-N3	N1-C2	C1'-C5	θ
H	1.343	1.334	1.339	1.333	1.491	70.020
NH_2	1.344	1.335	1.339	1.336	1.494	72.170
NMe_2	1.345	1.335	1.339	1.336	1.490	71.721
OCH_3	1.344	1.334	1.340	1.336	1.491	75.226
CH_3	1.343	1.334	1.339	1.336	1.491	70.134
Cl	1.343	1.333	1.340	1.337	1.490	68.617
Br	1.342	1.334	1.340	1.337	1.490	72.249
CN	1.341	1.333	1.340	1.338	1.487	67.294
NO_2	1.340	1.333	1.340	1.338	1.486	65.325

Table 3. The Mulliken Charges (Q_M) of C1', C5, C4, N1, N3, C6, C2, N7 and N8 Atoms

Subs.	$C1'$	C5	C4	N1	N3	C2	C6	N7	N8
H	-0.130	-0.192	0.542	-0.395	-0.411	0.516	0.260	-0.786	-0.832
NH_2	-0.141	-0.192	0.540	-0.397	-0.410	0.512	0.260	-0.786	-0.822
NMe_2	-0.139	-0.192	0.538	-0.397	-0.411	0.511	0.261	-0.786	-0.822
OCH_3	-0.133	-0.192	0.545	-0.397	-0.412	0.516	0.252	-0.786	-0.824
CH_3	-0.126	-0.194	0.542	-0.397	-0.411	0.515	0.263	-0.786	-0.832
Cl	-0.130	-0.193	0.542	-0.395	-0.410	0.521	0.265	-0.787	-0.823
Br	-0.119	-0.191	0.546	-0.396	-0.411	0.522	0.253	-0.788	-0.824
CN	-0.092	-0.194	0.547	-0.395	-0.411	0.530	0.254	-0.790	-0.824
NO_2	-0.088	-0.187	0.546	-0.395	-0.411	0.533	0.252	-0.790	-0.824

4-NH_2 groups. Smaller rotations of the phenyl ring, compared to the unsubstituted one (70.02) were for the EW substituents NO_2, CN and Cl with 65.325, 67.294 and 68.617 degrees, respectively, while larger rotations of the phenyl ring were for the ED substituents CH_3, NMe_2, NH_2 and OCH_3 70.134, 71.721, 72.17 and 75.226 degrees, respectively.

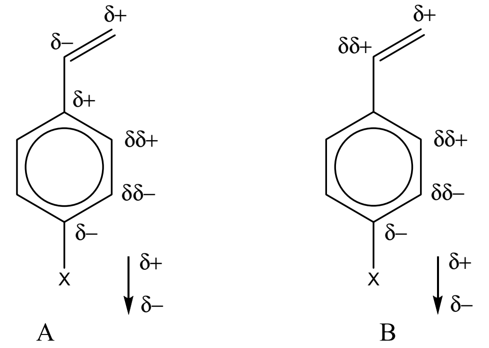
Correlation Analysis of Mulliken Charges

The Mulliken charges Q_M for some of the pyrimidine ring atoms of the studied molecules are listed in Table 3. Table 3 shows that the atoms C1', N1, N3, C5, N7 and N8 have negative Mulliken charges, whereas the atoms C2, C4 and C6 have positive Mulliken charges.

It is well known that the electronic substituent effects in aromatic network transfer in three ways: inductive, resonance and field effects. The inductive effect is an electrical influence of a group which is transmitted primarily by polarization of the bonding electrons from one atom to the next. Since this effect disappears after the third carbon-carbon sigma-bond, it was not introduced into our study since its focus is on the substituent effects on far atoms (pyrimidine ring). The field effect includes two transmission ways the first of which is the substituent field effect transfers by space *i.e.* each π-unit (a double or triple bond or aromatic system) is thought to be polarized separately, the polarization being induced by the substituent dipole in another part of the molecule (Scheme 2A). This interaction can be transmitted either through the molecular framework or through the solvent continuum and is accordingly called localized or direct polarization because each π-unit in the side-chain is polarized separately. On the other hand, conjugated π-system shows some additional polarizations (proportional σ_F) that can best be explained in terms of substituent-induced polarization of whole π-network. This component is termed extended polarization (Scheme 2B) [9,21-22].

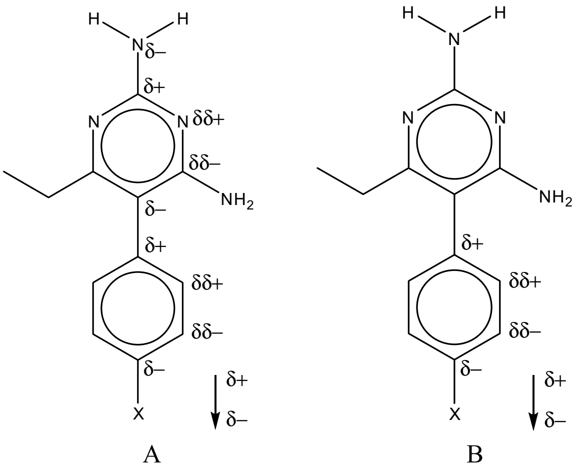
At this point, we would like to focus on the resonance and field effects. As was mentioned above, the pyrimidine ring is not coplanar with *para*-substituted phenyl ring, hence, the π-interaction between the two rings is prevented. Therefore, only localized or direct polarization would affect pyrimidine atoms. The atoms which well correlated with MSP and DSP parameters were C1', C2 and N7 with the exception of C5 (Table 4). In other words, only atoms which had a direction parallel to the substituent dipole moment experienced a substituent effect [21a], while the atoms which took a direction perpendicular to the substituent dipole moments (*i.e.* C4, C6, N1, N3 and N8) did not feel a substituent effect. A reverse effect was observed at N7, while a normal effect was observed at C1' and C2. However, the Q_M data were analyzed by both MSP and DSP parameters. The DSP parameter had a better correlation than the MSP parameter. Therefore, the correlation relationships obtained by DSP parameter were adopted for the experiment. The excellent to satisfactory fits seen in Table 4 indicate that the substituent effects were electronic in origin.

The value of ρ_F of C1' atom (26.3×10^{-3}) is higher than that of C2 (17.7×10^{-3}) which may be due to the fact that the C1' is closer to the substituent than C2 and that the C1' suffers from local and extended π-polarization (Schemes 3A and 3B) while C2 suffers only from local polarization (Scheme 3A). As it was mentioned above, the dipole generated between the bonds N7-C2 coincides with the axis of dipole that goes through the *para*-substituent, thus C2 atom sensed normal field substituent effect, whereas N7 atom sensed reverse field substituent effect as shown in Scheme 3A.



Localized or direct polarization Extended polarization

Scheme 2

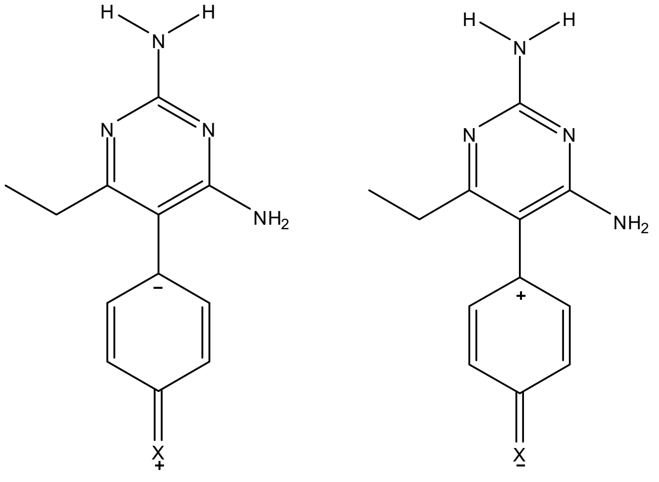


Localized or direct polarization Extended polarization

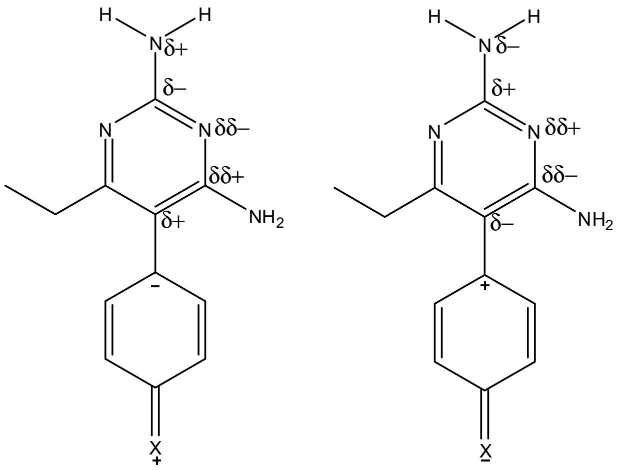
Scheme 3

Table 4. MSP and DSP Correlation Analysis for B3LYP/6-311G(d) Mulliken Charges of C1', C2 and N7 Atoms

	Hammett				Taft					
Atom	$\rho \times 10^3$	r	$s \times 10^2$	Scale for σ	$\rho_F \times 10^3$	$\rho_R \times 10^3$	R	Scale for σ_R	$s \times 10^2$	λ
C1'	27.8	0.939	0.7159	σ^-	26.3	43.2	0.976	σ^-_R	0.4873	1.64
C2	17.6	0.991	0.1079	σ°	17.7	12.5	0.994	σ^-_R	0.0972	0.71
N7	-3.8	0.932	0.0718	σ°	-4.0	-2.63	0.971	σ^-_R	0.0503	0.66



Scheme 4. The direct resonance



Scheme 5. The resonance induced polar effect

λ which represents the ratio of ρ_R/ρ_F shows that in C1' the resonance was predominant over field effect (1.64), whereas in C2 and N7 atoms the field effect was predominant over resonance effect (0.71 and 0.66, respectively). The question here is if there is no conjugation between *para*-substituted phenyl and pyrimidine rings, how C2 and N7 atoms could sense the resonance effect. The interpretation of the resonance effect is more complicated than that of the field effect [22]. Generally, two different transmission mechanisms have been considered: the (direct) resonance and the resonance-induced polar effect. C1' senses the direct resonance effect whereas; C2 and N7 atoms sense the resonance-induced polar effect as shown in Schemes 4 and 5, respectively.

C5 showed very low correlations with both MSP and DSP parameters. This may be due to the bulky NH_2 and ethyl groups which are droopy on C5 atom. This creates confusion whether the substituent senses the field or the resonance-induced polar effects.

CONCLUSIONS

Various *para*-substituted 2,4-diamino-5-X-phenyl-6-ethylpyrimidines (X = H, NH_2, NMe_2, OCH_3, CH_3, Cl, Br, CN, NO_2) were investigated through the DFT calculations of B3LYP level with 6-311G(d) basis set. The results showed that the atomization energy, HOMO and LUMO energies, and energy gap ΔE were affected by the substituents. Dipole moment was also affected by introducing the substituent. All these molecular properties were linearly dependent on the Hammett parameter. On the other hand, the Mulliken charges at only C1', C2 and N7 correlated with both MSP and DSP models and were interpreted by the polarization models of p-X-phenyl moiety.

REFERENCES

[1] B.A. Saleh, J. Mol. Struct. THEOCHEM 915 (2009) 47.

[2] J. Shorte, Correlation Analysis of Organic Reactivity, Chaps. 3 and 4, Research Studies Press, Wiley, Chichester, 1982.

[3] L.P. Hammett, Physical Organic Chemistry, 2nd ed., Chap. 11, McGraw-Hill, New York, 1970.

[4] J. Shorter, Prog. Phys. Org. Chem. 17 (1990) 1.

[5] J. Shorter, Chem. Intelligencer 2 (1996) 39.

[6] O. Exner, Correlation Analysis of Chemical Data, Plenum, New York and SNTL, Prague, 1988.

[7] O. Exner, in: N.B. Chapman, J. Shorter (Eds.), Correlation Analysis in Chemistry, Recent Advances Plenum, New York, 1978.

[8] B.A. Saleh, A.H. Essa, S.A.O. Al-Shawi, A.F. Jalbout,

J. Mol. Struct. THEOCHEM 909 (2009) 107.

[9] B.A. Saleha, S.A. Al-Shawia, G.F. Fadhil, J. Phys. Org. Chem. 21 (2008) 96.

[10] A.H. Essa, B.A. Saleh, A.J. Hameed, J. Comput. Theoret. Nanosci. 6 (2009) 706.

[11] V. Wiwanitkit, Malaria Research in Southeast Asia, Nova Science Publishers, Inc., 2007, p. 47.

[12] National Center for Infectious Diseases, Division of Parasitic Diseases (2007) Internet references. Retrieved from http://www.cdc.gov/malaria/facts.htm

[13] E.B. Burgina, V.P. Baltakhinov, E.V. Boldyreva, T.P. Shakhtschneider, J. Struct. Chem. 45 (2004) 64.

[14] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision C.02, Gaussian, Inc., Wallingford, CT, 2004.

[15] R. Krishnan, J.S. Kinkley, R. Seeger, J.A. Pople, J. Chem. Phys. 72 (1980) 650.

[16] C. Hansch, A. Leo, R.W. Taft, Chem. Rev. 91 (1991) 165.

[17] S. Ehrensons, R.T.C. Brownlee, R.W. Taft, Prog. Phys. Org. Chem. 10 (1973) 1.

[18] K. Tuppurainen, S. Lötjönen, R. Laatikainen, T. Vartiainen, U. Maran, M. Strandberg, T. Tamm, Mutat. Res. 247 (1991) 97.

[19] D.F.V. Lewis, C. Ioannides, D.V. Parke, Xenobiotica 24 (1994) 401.

[20] M. Karelson, V.S. Lobanov, A.R. Katritzky, Chem. Rev. 96 (1996) 1027.

[21] a) G.K. Hamer, I.R. Peat, W.F. Reynolds, Can. J. Chem. 51 (1973) 897; b) G.K. Hamer, I.R. Peat, W.F. Reynolds, Can. J. Chem. 51 (1973) 915.

[22] a) J. Bromilow, R.T.C. Brownlee, D.J. Craik, P.R. Fiske, J.E. Rowe, M. Sadek, J. Chem. Soc., Perkin Trans. 2 (1981) 753; b) R.T.C. Brownlee, D.J. Craik, J. Chem. Soc., Perkin Trans. 2 (1981) 760; c) R.T.C. Brownlee, D.J. Craik, J. Org. Magn. Reson. 15 (1981) 248.