Theoretical Study on the Complete Series of Chloroanilines

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The environmental effects of chloroanilines depend on their physical and chemical properties, and it is therefore important to know their structure−property relationships that allow a complete understanding of their environmental consequences. The chemical reactivity profiles of all 19 chloroanilines have been investigated using the density functional theory for the first time. Global reactivity descriptors, such as hardness, chemical potential, electrophilicity index, and polarizability, and local reactivity descriptors, namely, local philicities, have been calculated in order to gain insights into the reactive nature and the reactive sites of the selected systems. Using AIM theory, the presence of hydrogen bond critical points (HBCPs) and the values of electron density and Laplacian of electron density at the HBCPs have been analyzed to appreciate the presence of intramolecular hydrogen bonding in the selected systems. Structure−toxicity analysis of the selected set of chloroanilines demonstrates the importance of the electrophilicity index in the prediction of reactivity/toxicity.

Introduction

Halogenated derivatives of aniline are important intermediates in the manufacture of dyes and agricultural products.[1,2] Aniline and 2-chloroaniline are anthropogenic organic compounds primarily used in the manufacture of polymers, rubbers, pharmaceuticals, and dyes. Both are suspected carcinogens and are highly toxic to aquatic life.[3] Chloroanilines can be formed by the microbial decay of herbicides such as phenyl-carbamate and phenylurea.[4]

The molecular prototype of an aromatic amine is the aniline. It has been the subject of several studies during the past two decades.[5−9] Aniline, an extensively used industrial chemical, causes selective toxicity to the spleen.[10,11] The toxicity is manifested by splenomegaly, elevated erythropoietic activity, hyperpigmentation, hyperplasia, fibrosis,[10,11] and a variety of primary sarcomas of the spleen after chronic exposure in rats.[10,12]

Aniline exposure has been shown to lead to iron overload (increases in both total and free iron), and induction of oxidative stress (lipid peroxidation and malondialdehydeprotein adducts) in the spleen.[13] The induction of oxidative stress in the spleen is also accompanied by such morphological changes as vascular congestion, increased red pulp cellularity due to increased sinusoidal macrophages and fibroblasts, capsular thickening, and formation of fibrous tissue in the capsule and throughout the parenchyma.[10]

Previous work has demonstrated that mono-chloroanilines have been more potent nephrotoxicants than aniline following acute administration to Fischer 344 (F344) rats.[14] Lo et al.[15] have further reported that acute administration of dichloroanilines has been associated with alterations to the kidney and established that the dihaloanilines have been more nephrotoxic than the monohaloanilines. Acute administration of 3,5-DCA to F344 rats or Sprague−Dawley rats[16] produced decreased urine output, elevated blood urea nitrogen concentration, and diminished renal cortical slice accumulation of *p*-aminohippurate and tetraethylammonium. 3,5-Dichloroaniline (3,5-DCA), a specific chlorinated aniline derivative, is an intermediate in the production of some fungicides. Many chloroanilines, including 3,5-DCA, have been quantitated in water samples collected from rivers.[17] Consequently, exposure to halogenated anilines can occur through environmental or occupational exposure.

In the present study, the complete series of chloroanilines (19 possible molecules) have been studied within a density functional theory (DFT) framework. The global reactivity descriptors, namely, hardness (η), chemical potential (μ), electrophilicity index (ω), and polarizability (α), and local reactivity descriptors, such as local philicities (ω^+ and ω^-), have been calculated to understand the reactive nature of these compounds and the possible reactive sites in them. The theory of atoms-in-molecules (AIM) allows one to understand the concept of a chemical bond and its strength in terms of electron density distribution.[18,19] In the present study, we utilize the AIM theory in analyzing the intramolecular hydrogen bonding in the selected systems.

Further, in view of the importance of quantitative structure−toxicity relationship (QSTR) studies in the field of aquatic toxicology, toxicity ($\log(\mathrm{IGC}_{50}{}^{-1})$) of various chloroanilines against *Tetrahymena pyriformis*[20] has been modeled by the linear regression technique using the DFT-based global reactivity descriptor ω.

Theoretical Background

According to density functional theory,[21,22] the chemical potential (μ) and chemical hardness (η) are defined as

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right)_{\upsilon(\bar{r})} \tag{1}$$

and

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{\upsilon(\bar{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{\upsilon(\bar{r})} \tag{2}$$

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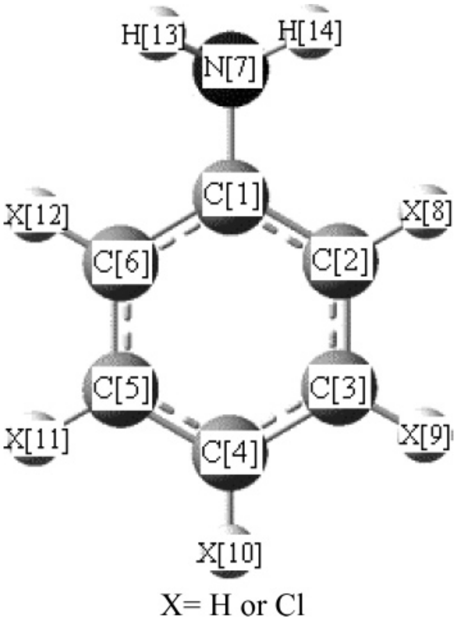


Figure 1. Structure along with atom numbering for the chloroaniline template.

TABLE 1: Calculated Energies E (hartree), Zero-Point Energies (ZPE, kcal/mol), Enthalpies H (hartree), and Dipole Moments D (debye) of All Chloroanilines from the B3LYP/6-311++ g Level[a]**

system	E	ZPE	ΔE	ΔE_0	H	ΔH	D
aniline	−287.6877	73.11			−287.5644		1.59
2-CA	−747.3117	67.32	0.00	0.00	−747.1966	0.00	1.91
3-CA	−747.3113	67.19	0.29	0.17	−747.1962	0.20	3.01
4-CA	−747.3103	67.17	0.89	0.74	−747.1953	0.81	3.44
2,3-C2A	−1206.9295	61.29	3.03	2.84	−1206.8228	2.88	3.24
2,4-C2A	−1206.9328	61.32	0.96	0.81	−1206.8260	0.86	3.05
2,5-C2A	−1206.9340	61.30	0.26	0.08	−1206.8272	0.13	1.79
2,6-C2A	−1206.9344	61.48	0.00	0.00	−1206.8274	0.00	0.69
3,4-C2A	−1206.9284	61.19	3.72	3.43	−1206.8218	3.52	4.21
3,5-C2A	−1206.9332	61.13	0.72	0.37	−1206.8266	0.46	3.42
2,3,4-C3A	−1666.5456	55.29	5.34	5.21	−1666.4471	5.22	3.96
2,3,5-C3A	−1666.5506	55.23	2.16	1.96	−1666.4523	2.00	2.84
2,3,6-C3A	−1666.5512	55.31	1.78	1.67	−1666.4528	1.66	1.57
2,4,5-C3A	−1666.5500	55.28	2.56	2.42	−1666.4515	2.45	3.18
2,4,6-C3A	−1666.5541	55.42	0.00	0.00	−1666.4554	0.00	1.93
3,4,5-C3A	−1666.5451	55.10	5.61	5.29	−1666.4469	5.37	4.45
2,3,4,5-C4A	−2126.1615	49.25	3.69	3.67	−2126.0714	3.64	3.77
2,3,4,6-C4A	−2126.1661	49.25	0.83	0.81	−2126.0760	0.78	2.59
2,3,5,6-C4A	−2126.1674	49.27	0.00	0.00	−2126.0772	0.00	1.91
PCA	−2585.7770	43.55			−2585.6948		2.88

[a] The relative energies (ΔE, ΔE_0, ΔH) in kcal/mol are with respect to the most stable isomer with a given number of chlorine atoms.

where E is the total energy of the system, N is the number of electrons in the system, and $v(\vec{r})$ is the external potential. μ is identified as the negative of the electronegativity (χ) as defined by Iczkowski and Margrave.[23]

To save the computational time, we have calculated the chemical potential and chemical hardness by using Koopmans' theorem[21] as

$$\mu = \frac{E_{\mathrm{LUMO}} + E_{\mathrm{HOMO}}}{2} \tag{3}$$

and

$$\eta = \frac{E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}}}{2} \tag{4}$$

where E_{LUMO} is the lowest unoccupied molecular orbital's energy and E_{HOMO} is the highest occupied molecular orbital's energy.

TABLE 2: Calculated Global Reactivity Descriptors for Chloroanilines from the B3LYP/6-311++ g Method[a]**

system	μ	η	ω	α
aniline	−0.1129	0.0995	0.0641	78.37
2-CA	−0.1230	0.0981	0.0771	90.67
3-CA	−0.1247	0.0990	0.0785	91.52
4-CA	−0.1223	0.0948	0.0789	91.53
2,3-C2A	−0.1305	0.0980	0.0869	103.47
2,4-C2A	−0.1313	0.0935	0.0923	104.54
2,5-C2A	−0.1334	0.0969	0.0917	104.65
2,6-C2A	−0.1314	0.0972	0.0888	104.53
3,4-C2A	−0.1308	0.0944	0.0907	104.42
3,5-C2A	−0.1350	0.0989	0.0921	107.26
2,3,4-C3A	−0.1363	0.0936	0.0993	116.81
2,3,5-C3A	−0.1402	0.0973	0.1010	117.51
2,3,6-C3A	−0.1382	0.0966	0.0989	117.05
2,4,5-C3A	−0.1392	0.0927	0.1045	118.11
2,4,6-C3A	−0.1390	0.0926	0.1043	118.21
3,4,5-C3A	−0.1388	0.0941	0.1023	117.15
2,3,4,5-C4A	−0.1439	0.0929	0.1114	131.02
2,3,4,6-C4A	−0.1437	0.0923	0.1118	131.23
2,3,5,6-C4A	−0.1446	0.0965	0.1084	128.19
PCA	−0.1493	0.0910	0.1224	144.11

[a] All data are in au.

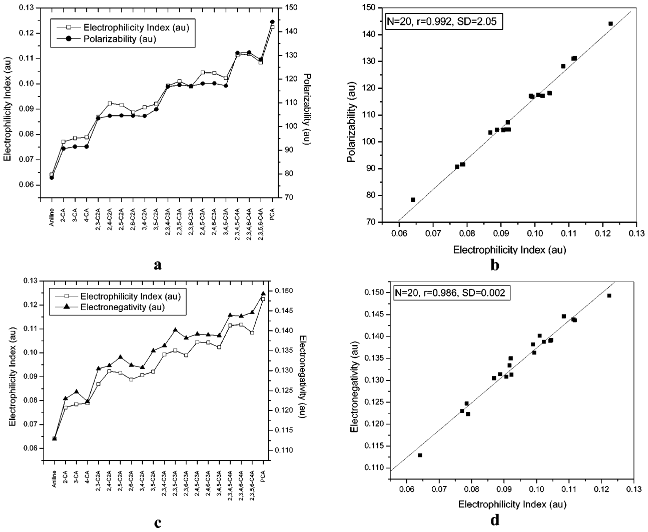


Figure 2. Relationships between various global reactivity descriptors from the B3LYP/6-311++ g** method.

The Fukui function (FF), which measures the sensitivity of a system's chemical potential to an external perturbation at a particular site, is defined as[22]

$$f(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{v(\vec{r})} = \left(\frac{\delta \mu}{\delta v(\vec{r})}\right)_N \tag{5}$$

Since the above derivatives are discontinuous, three different types of FFs have been defined using a finite difference approximation[24−26] as

$$f^{+}(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}) \qquad \text{for nucleophilic attack} \tag{6a}$$

$$f^{-}(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \qquad \text{for electrophilic attack} \tag{6b}$$

$$f^{0}(\vec{r}) = (f^{+}(\vec{r}) + f^{-}(\vec{r}))/2 \qquad \text{for radical attack} \tag{6c}$$

where $\rho_N(\vec{r})$, $\rho_{N+1}(\vec{r})$, and $\rho_{N-1}(\vec{r})$ are the electron densities of the N, $N + 1$ and $N - 1$ electron systems, respectively, all calculated at the same external potential $v(\vec{r})$ of the N electron system.

Yang and Mortier[24] introduced the condensed-to-atom variant of the FF, i.e., the Fukui function on atom k in a molecule using

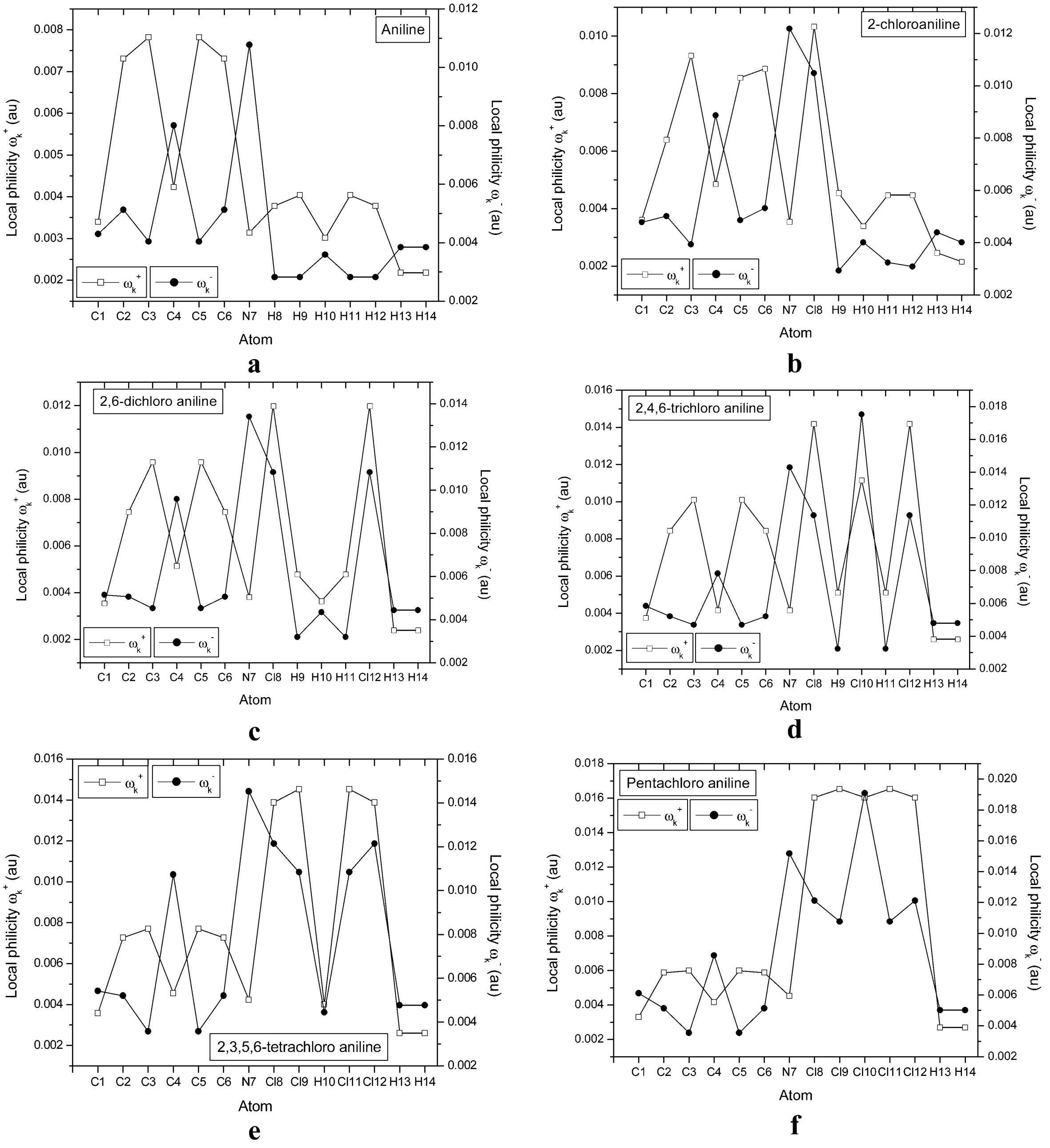


Figure 3. Plots of local reactivity descriptors for selected chloroanilines obtained from the BLYP/DND method.

the corresponding electronic population (q_k) as

$$f_k^+ = q_k(N+1) - q_k(N) \qquad \text{for nucleophilic attack} \qquad (7a)$$

$$f_k^- = q_k(N) - q_k(N-1) \qquad \text{for electrophilic attack} \qquad (7b)$$

$$f_k^0 = (f_k^+ + f_k^-)/2 \qquad \text{for radical attack} \qquad (7c)$$

Parr et al. have introduced a global electrophilicity index ω as[27]

$$\omega = \frac{\mu^2}{2\eta} \qquad (8)$$

According to this definition, ω measures the ability of a molecular species to soak up electrons and is used in understanding the reactivity of the human immunodeficiency virus type 1 (HIV-1) nucleocapsid protein p7 (NCp7) when reacted with a variety of electrophilic agents.[28]

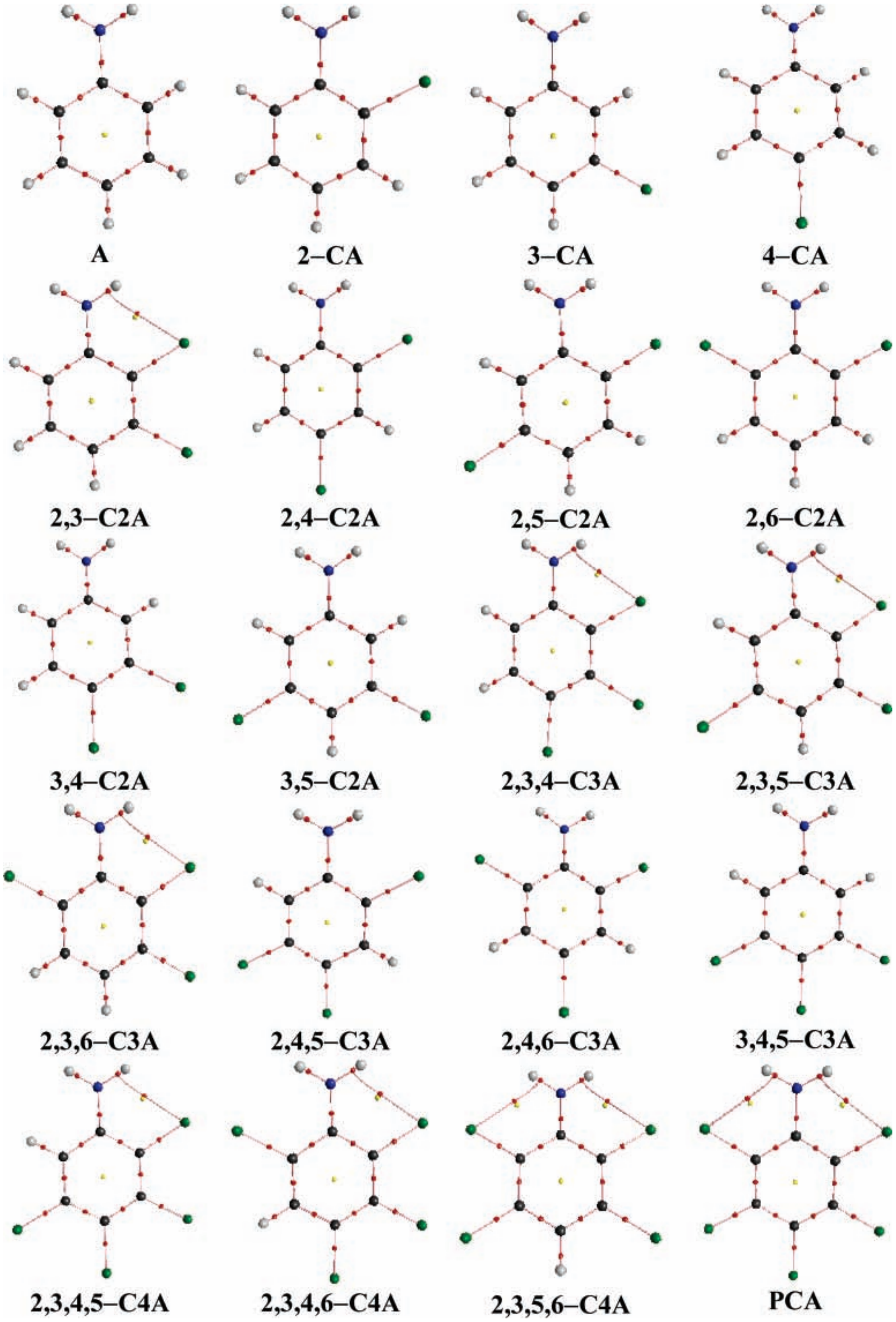
Recently, Chattaraj et al.[29] have proposed a generalized concept of philicity containing electrophilic, nucleophilic, and radical reactions. The condensed-to-atom variants for the atomic site "k" have been written as

$$\omega_k^\alpha = \omega f_k^\alpha \qquad (9)$$

where $\alpha = +, -,$ and 0 refer to nucleophilic, electrophilic, and radical attacks, respectively. The ω_k^α will vary from atom to atom in a molecule, but the sum of any ω_k^α over all atoms is conserved.

The electric dipole polarizability is a measure of the linear response of the electron density in the presence of an infinitesimal electric field F, and it represents a second-order variation in energy,

$$\alpha_{a,b} = -\left(\frac{\partial^2 E}{\partial F_a \, \partial F_b}\right) \qquad a, b = x, y, z \qquad (10)$$



A **2–CA** **3–CA** **4–CA**

2,3–C2A **2,4–C2A** **2,5–C2A** **2,6–C2A**

3,4–C2A **3,5–C2A** **2,3,4–C3A** **2,3,5–C3A**

2,3,6–C3A **2,4,5–C3A** **2,4,6–C3A** **3,4,5–C3A**

2,3,4,5–C4A **2,3,4,6–C4A** **2,3,5,6–C4A** **PCA**

Figure 4. AIM-derived molecular graphs of chloroanilines as obtained from B3LYP/6-311++ g** calculation. Bond critical points are denoted by small red dots, and the yellow dots represent ring critical points.

The polarizability α is calculated as the mean value as given in the following equation:

$$\langle\alpha\rangle = (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})/3 \qquad (11)$$

Computational Details

The structure along with atom numbering for the chloroaniline template is shown in Figure 1. The geometries of aniline and all 19 chloroanilines are optimized using Becke's three parameter hybrid density functional, B3LYP/6-311++G**, which includes both Hartree–Fock exchange and DFT exchange correlation functionals.[30–32] The above calculations are carried out using the *Gaussian 98W* suite of programs.[33] The optimized geometries are characterized by harmonic vibrational frequencies, which confirmed that the structures obtained are minima on the potential energy surface. Complete geometric details of all the selected systems are provided in the Supporting Information (Tables S1–S10). The electrophilicity index is calculated for all the selected systems using eq 8. The Hirshfeld[34] population scheme (Stockholder partitioning scheme) has been used to calculate FF values as implemented in the *DMOL*^{3} package employing the BLYP/DND method.[35] Then the local

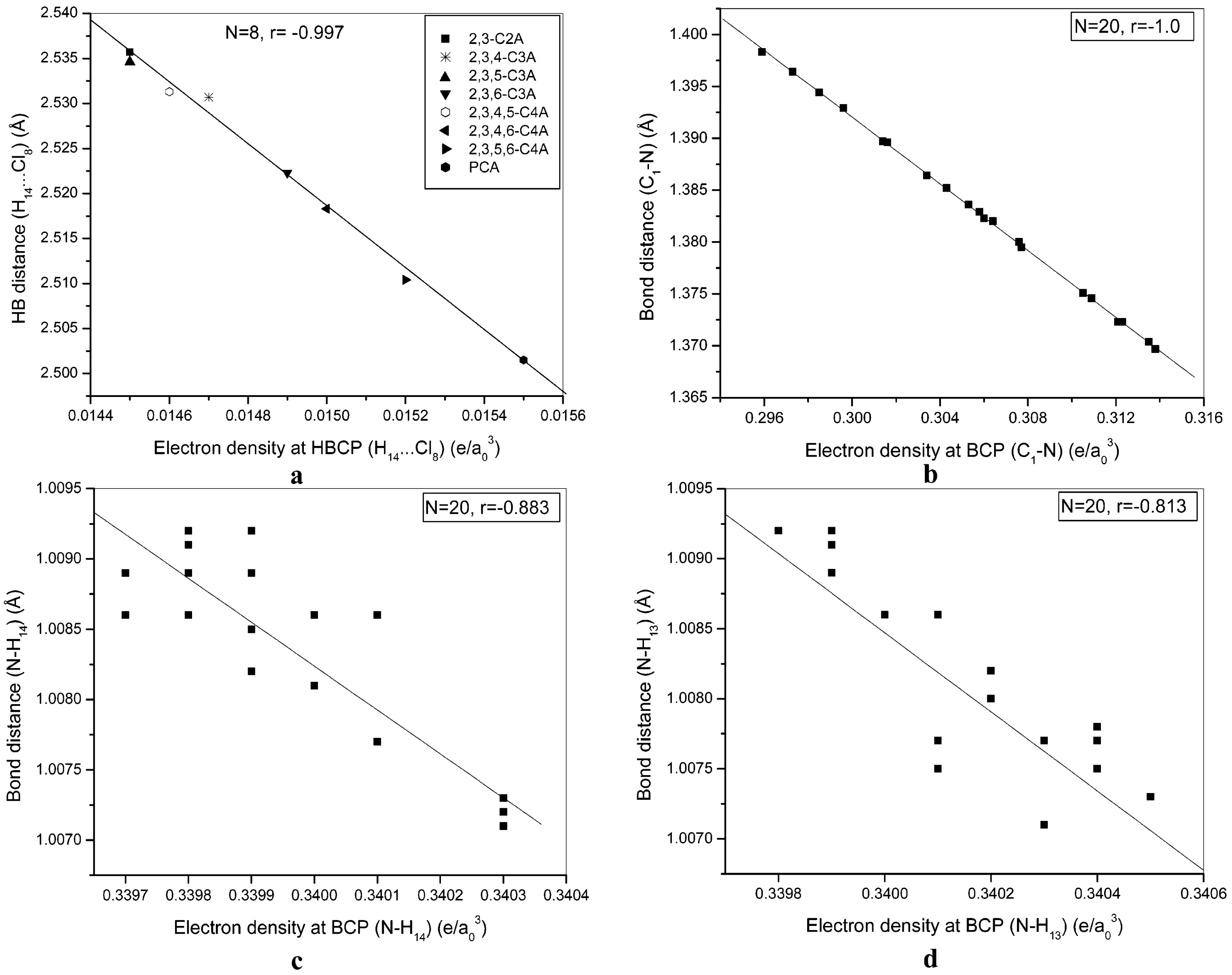


Figure 5. Relationships between electron density at the selected BCP and their respective bond distances.

TABLE 3: Electron Density $\rho(r_c)$ (e/a$_0^3$) and Laplacian of Electron Density $\nabla^2\rho(r_c)$ (e/a$_0^5$) at the Hydrogen BCPs and Their Respective Bond Distances (Å)

	distance		HBCP			
			$H_{14}\cdots Cl_8$		$H_{13}\cdots Cl_{12}$	
molecule	$H_{14}-Cl_8$	$H_{13}-Cl_{12}$	$\rho(r_c)$	$\nabla^2\rho(r_c)$	$\rho(r_c)$	$\nabla^2\rho(r_c)$
aniline						
2-CA	2.5689					
3-CA						
4-CA						
2,3-C2A	2.5357		0.0145	0.016		
2,4-C2A	2.5731					
2,5-C2A	2.5694					
2,6-C2A	2.5552	2.5548				
3,4-C2A						
3,5-C2A						
2,3,4-C3A	2.5307		0.0147	0.016		
2,3,5-C3A	2.5347		0.0145	0.016		
2,3,6-C3A	2.5223	2.5449	0.0149	0.016		
2,4,5-C3A						
2,4,6-C3A	2.5596	2.5596				
3,4,5-C3A						
2,3,4,5-C4A	2.5313		0.0146	0.016		
2,3,4,6-C4A	2.5183	2.5504	0.0150	0.016		
2,3,5,6-C4A	2.5104	2.5104	0.0152	0.016	0.0152	0.016
PCA	2.5015	2.5015	0.0155	0.017	0.0155	0.017

philicities (ω^+ and ω^-) are obtained for all atoms of the selected systems using eq 9. The wave functions obtained from the B3LYP/6-311++G** method are used with the AIM2000 program[36] to calculate the topological properties of the systems under investigation. Hence the critical points (CPs) may be localized, and their properties such as electron densities at CPs and their Laplacians may be analyzed. The 6-311++G** basis set is applied because the inclusion of the diffuse components in the basis set is desired to describe properly the hydrogen bonding interaction.[37] One parameter QSARs[38] are performed using a least-squares error estimation method [39] to calculate and compare the toxicity ($\log(IGC_{50}^{-1})$) of various chloroanilines against *T. pyriformis*.[20]

Results and Discussion

Energies of Chloroanilines. The calculated energies, thermodynamic quantity (enthalpy), and dipole moments of all chloroanilines along with aniline are presented in Table 1. The stability of a conformer with a given number of chlorine atoms is determined by its relative energy ΔE or ΔE_0 (including the zero-point energy correction), with respect to the most stable isomer.

For monochloroanilines, the ortho isomer (2-CA) is the most stable, whereas the para isomer (4-CA) is the least stable with a difference of 0.89 kcal/mol in their energy values. The meta isomer is less stable than the ortho isomer by an amount of 0.29 kcal/mol. In the case of dichloroanilines, the isomer with both ortho positions substituted with chlorine atoms (2,6-C2A) is the most stable and that with no ortho chlorine substitution

TABLE 4: Electron Density $\rho(r_c)$ (e/a_0^3) and Laplacian of Electron Density $\nabla^2\rho(r_c)$ (e/a_0^5) at the Ring CP and Selected BCPs

			BCP					
	ring CP		N−H_{14}		N−H_{13}		C_1−N	
molecule	$\rho(r_c)$	$\nabla^2\rho(r_c)$	$\rho(r_c)$	$\nabla^2\rho(r_c)$	$\rho(r_c)$	$\nabla^2\rho(r_c)$	$\rho(r_c)$	$\nabla^2\rho(r_c)$
aniline	0.0212	0.0395	0.3399	−0.3930	0.3399	−0.3930	0.2959	−0.2150
2-CA	0.0211	0.0391	0.3398	−0.4078	0.3402	−0.3982	0.3034	−0.2224
3-CA	0.0212	0.0393	0.3398	−0.3955	0.3399	−0.3956	0.2985	−0.2182
4-CA	0.0213	0.0393	0.3398	−0.3943	0.3398	−0.3943	0.2973	−0.2167
2,3-C2A	0.0208	0.0384	0.3399	−0.4109	0.3404	−0.4006	0.3053	−0.2242
2,4-C2A	0.0211	0.0388	0.3397	−0.4088	0.3402	−0.3995	0.3043	−0.2235
2,5-C2A	0.0211	0.0388	0.3398	−0.4106	0.3403	−0.4014	0.3060	−0.2250
2,6-C2A	0.0210	0.0386	0.3401	−0.4136	0.3401	−0.4136	0.3105	−0.2285
3,4-C2A	0.0211	0.0387	0.3399	−0.3970	0.3399	−0.3969	0.2996	−0.2192
3,5-C2A	0.0211	0.0390	0.3401	−0.3989	0.3401	−0.3989	0.3014	−0.2211
2,3,4-C3A	0.0206	0.0378	0.3399	−0.4119	0.3404	−0.4013	0.3058	−0.2249
2,3,5-C3A	0.0207	0.0381	0.3400	−0.4138	0.3405	−0.4038	0.3077	−0.2265
2,3,6-C3A	0.0206	0.0379	0.3403	−0.4168	0.3401	−0.4156	0.3121	−0.2298
2,4,5-C3A	0.0209	0.0382	0.3397	−0.4109	0.3403	−0.4021	0.3064	−0.2256
2,4,6-C3A	0.0209	0.0383	0.3401	−0.4142	0.3401	−0.4142	0.3109	−0.2291
3,4,5-C3A	0.0208	0.0381	0.3400	−0.3992	0.3400	−0.3992	0.3016	−0.2214
2,3,4,5-C4A	0.0203	0.0372	0.3399	−0.4139	0.3404	−0.4036	0.3076	−0.2267
2,3,4,6-C4A	0.0204	0.0373	0.3403	−0.4174	0.3401	−0.4158	0.3123	−0.2302
2,3,5,6-C4A	0.0203	0.0372	0.3403	−0.4187	0.3403	−0.4187	0.3138	−0.2311
PCA	0.0198	0.0363	0.3403	−0.4190	0.3403	−0.4190	0.3135	−0.2312

(3,4-C2A) is the least stable isomer. Similarly, 2,4,6-C3A and 2,3,5,6-C4A are shown to be the most stable isomers, whereas 3,4,5-C3A and 2,3,4,5-C4A are the least stable isomers for tri- and tetrachloroanilines, respectively.

The values of the thermodynamic quantity enthalpy as well as their relative values are shown in Table 1. The relative value, ΔH, follows the same trend and remains nearly constant as ΔE. These thermodynamic data are valuable in characterizing the molecular properties of chloroanilines in the gas phase. The dipole moment has been expected to be related to the bulk properties of chloroanilines, and they seem to arise mainly from the vector sum of the contributing C−Cl and C−N bond dipoles.

Global Descriptors of Chloroanilines. The calculated values of global reactivity descriptors, namely, chemical potential, chemical hardness, electrophilicity index, and polarizability, from the B3LYP/6-311++G** method are presented in Table 2. Among the selected systems, the most stable structure (aniline) has the maximum hardness in accordance with the maximum hardness principle (MHP),[40,41] and there is an average decrease in the hardness with an increase in the degree of Cl substitution.

Figure 2a shows the variation of ω and α of the chloroanilines. Values of ω and α increase with the increase in the degree of Cl substitution. Aniline has the minimum value for ω and α and hence is the least reactive, and PCA, which has the maximum value for ω and α, is the most reactive among the selected systems with a minimum value of hardness. This fact is in accordance with the minimum polarizability principle (MPP)[42] and the minimum electrophilicity principle (MEP).[43] A good linear relationship exists between ω and α (Figure 2b) with a correlation coefficient (r) of 0.992.

Variations of electronegativity (χ) and ω with increase in the degree of Cl substitution for the selected systems are shown in Figure 2c. χ follows the trend of ω. Also a good linear relationship exists between χ and ω (Figure 2d) with a correlation coefficient (r) of 0.986.

Local Descriptors of Chloroanilines. Local descriptors are useful in identifying the active sites in a molecule. The nucleophilic attack (NAK) and electrophilic attack (EAK) at a particular site are provided by the local philicities, ω^+ and ω^-, respectively. Figure 3 provides the ω^+ and ω^- values for the selected systems, viz., aniline, 2-CA, 2,6-C2A, 2,4,6-C3A, 2,3,5,6-C4A, and PCA, respectively. In the case of aniline, C_3 and C_5 sites are more prone to NAK than other sites, whereas the N_7 site is the most preferred site to EAK. The chlorine site is the most favored site to NAK and the N_7 site shows affinity toward EAK in 2-CA. In 2,6-C2A, again Cl sites are prone to NAK and the N_7 site is prone to EAK. For 2,4,6-C3A, Cl_8 and Cl_{12} are preferred sites to NAK and Cl_{10} is preferred to EAK. In 2,3,5,6-C4A, Cl_9 and Cl_{11} are the most favored sites to NAK and N_7 is the most favored site to EAK. Finally, in the case of PCA, Cl_9 and Cl_{11} sites are preferred sites to NAK and the Cl_{10} site is preferred to EAK. Thus, with the help of local philicities, one can identify the active sites in the selected systems.

AIM Calculations for Chloroanilines. Figure 4 presents the molecular graphs of all 19 chloroanilines along with that of aniline. These graphs are obtained from the B3LYP/6-311++G** wave functions. The application of the Bader theory indicates the bond path between the hydrogen atom of $-NH_2$ and chlorine atom at the ortho-position for some of the selected systems, and there exist bond critical points (BCPs) for such interactions (Figure 4). This may suggest that intramolecular hydrogen bonds (HBs) exist for 2,3-C2A, 2,3,4-C3A, 2,3,5-C3A, 2,3,6-C3A, 2,3,4,5-C4A, 2,3,4,6-C4A, 2,3,5,6-C4A, and PCA molecules. It is interesting to note that the intramolecular HB exists between ortho Cl and the H of $-NH_2$ wherever the respective meta-position is also occupied by a Cl atom. This may be attributed to the fact that the repulsive force between the adjacent Cl atoms (particularly at ortho- and meta-positions) may compel the ortho Cl to move closer to the H of $-NH_2$ resulting in the formation of a HB. Hence the use of the Bader theory may be treated as a decisive tool for the characterization of the type of interaction.

The topological criteria of hydrogen bonding have been given by Koch and Popelier.[44,45] According to them, the BCP and the bond path should exist for an X−H···Y hydrogen bond; the electron density $\rho(r_c)$ and its Laplacian $\nabla^2\rho(r_c)$ for an H···Y contact should be within the range 0.002−0.04 au for the electron density and 0.02−0.15 au for its Laplacian. We see that H···Cl interactions for those molecules fulfill these criteria (Table 3). A plot between the electron density at the hydrogen bond critical point (HCBP) of $H_{14}\cdots Cl_8$ and their corresponding bond distances provides a linear relationship with a good correlation coefficient (r) of −0.997 (Figure 5a).

Table 4 lists the values of the electron density $\rho(r_c)$ and its Laplacian $\nabla^2\rho(r_c)$ for the selected BCP and benzene ring CP of

TABLE 5: Experimental and Calculated Toxicity ($\log(\mathrm{IGC}_{50}{}^{-1})$) Values against *T. pyriformis* of the Selected Chloroanilines from the B3LYP/6-311++ g Method**

	$\log(\mathrm{IGC}_{50}{}^{-1})$		
system	observed[a]	calculated	residual[b]
2-CA	−0.17	−0.09	−0.08
3-CA	0.22	−0.02	0.24
4-CA	0.05	0.01	0.04
2,5-C2A	0.58	0.72	−0.14
3,4-C2A	0.56	0.67	−0.11
3,5-C2A	0.71	0.75	−0.04
2,4,5-C3A	1.30	1.44	−0.14
2,3,4,5-C4A	1.96	1.83	0.13
2,3,5,6-C4A	1.76	1.66	0.10

[a] Reference 20. [b] Difference between the experimental and calculated toxicity ($\log(\mathrm{IGC}_{50}{}^{-1})$) values.

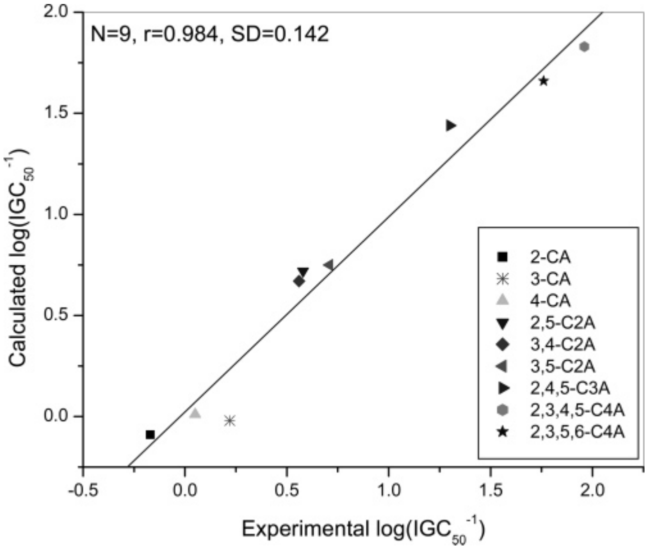


Figure 6. A plot between experimental and calculated toxicity ($\log(\mathrm{IGC}_{50}{}^{-1})$) values of the selected chloroanilines against *T. pyriformis*.

all chloroanilines. Ring CPs which are characteristic of a closed shell interaction have $\nabla^2\rho(r_c) > 0$ and a low positive value for $\rho(r_c)$. BCP at C_1−N, N−H_{14}, and N−H_{13} provides a $\nabla^2\rho(r_c) < 0$ and a high positive value for $\rho(r_c)$, which are characteristics of covalent type interactions. Figure 5b−d presents the plots between the electron density at BCP and the bond length in C_1−N, N−H_{14}, and N−H_{13} for aniline and all chloroanilines. A linear relationship with a good correlation coefficient (r) exists in all cases. That is, with increase in the $\rho(r_c)$, the respective bond length decreases.

Structure−Toxicity Analysis on Chloroanilines. Previous studies by our group have established the usefulness of DFT based descriptors in structure−activity/toxicity/property studies.[46−52] The QSTR for aquatic toxicity ($\log(\mathrm{IGC}_{50}{}^{-1})$) of the selected set of nine chloroanilines against *T. pyriformis*[20] has been analyzed. Table 5 lists the experimental and calculated aquatic toxicity ($\log(\mathrm{IGC}_{50}{}^{-1})$) for the selected set of nine chloroanilines. Considering the experimental toxicity data ($\log(\mathrm{IGC}_{50}{}^{-1})$) as a dependent variable and a DFT-based global descriptor, namely, the electrophilicity index (ω) obtained from the B3LYP method, as an independent variable, linear regression analysis has been carried out, and the regression equation is given by

$$\log(\mathrm{IGC}_{50}{}^{-1}) = -4.414 + 56.035\omega \qquad (12)$$

$$N = 9, \quad r^2 = 0.968, \quad \mathrm{SD} = 0.144$$

The selected descriptor ω is capable of explaining the 96.8% variation in data with a root-mean-square error of 0.144. A plot between the experimental and calculated toxicity values (Figure 6) provides a correlation coefficient (r) of 0.984, which reveals the fact that electrophilicity index can be effectively used as a descriptor in the prediction of toxicity.

Conclusions

Theoretical calculations have been carried out on all 19 chloroanilines in order to assess their structure, bonding, stability, reactivity, and toxicity. Ortho CAs are found to be more stable than the corresponding meta or para isomers. The number and position of the chlorine substituents play a vital role in deciding the structural stability/reactivity of CAs. The usefulness of AIM theory in understanding the intramolecular hydrogen bonding has been highlighted in this work. A structure−toxicity study has been carried out with the existing experimental aquatic toxicity values of chloroanilines against *T. pyriformis* as the dependent variable and their electrophilicity index as the independent variable. Results revealed that electrophilicity index could be effectively used as a descriptor in explaining the aquatic toxicity of chloroanilines.

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Supporting Information Available: Tables S1−S10 providing bond lengths and bond angles for the complete series of chlorinated anilines optimized with B3LYP method using the 6-311++ g** basis set. This material is available free of charge via the Internet at http://pubs.acs.org.

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