Molecular Structure, Reactivity, and Toxicity of the Complete Series of Chlorinated Benzenes

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The structure and chemical reactivity profiles of all 12 chlorobenzenes have been investigated using the density functional theory and ab initio molecular orbital calculations. Global and local reactivity descriptors such as electrophilicity index and local philicity, respectively, of the selected systems have been calculated in order to gain insights into the reactive nature and the reactive sites of these compounds. Also, the effects of chlorine substitution on the aromaticity of the compounds have been analyzed by calculating the nucleus-independent chemical shift. Interaction through charge transfer between chlorobenzenes and nucleic acid bases/selected base pairs are determined using Parr's formula. The results revealed that the chlorobenzenes act as electron acceptors in their interaction with biomolecules. Structure−toxicity analysis of this entire set of chlorobenzenes demonstrates the importance of the electrophilicity index in the prediction of reactivity/toxicity.

Introduction

Chlorobenzenes have a wide range of industrial and domestic uses, such as intermediates in the synthesis of other chemicals, solvents, hygiene products, and components of dielectric fluids.[1] They are toxic and pose threats to aquatic environments, leading to trichlorobenzenes and hexachlorobenzene being placed on the EU "Red List" of dangerous compounds.[2] Being semivolatile organic compounds, these pollutants can undergo long-range atmospheric transport and partition between air and other environmental compartments. The compounds cover a log K_{ow} range of 2.98−5.03 and tend to accumulate in tissues with a high fat content. Even though they are of moderate toxicity to wildlife and humans, various effects on internal organs have been observed following acute exposure. Some chlorobenzenes are carcinogenic and teratogenic.[3] Hexachlorobenzene (HCB) is a major air-borne organochlorine in arctic air present at relatively uniform picogram per cubic meter concentrations.[4−6] Qian et al.[5] have shown that chlorobenzenes caused significant changes of the serum testosterone concentration and hepatic glutathione *s*-transferase (GST) and uridine 5'-diphosphate glucuronosyltransferase (UDPGT) activity in crucian carps. The literatures related to the series of chlorobenzenes demonstrated the profound effects of aromatic chlorinated species and urge us to perform this detailed investigation.

The environmental effects of chlorobenzenes depend on their physical and chemical properties, and it is therefore important to understand the structure−property relationships that allow a complete understanding of their environmental consequences. In the present study, the molecular structures of the complete series of chlorobenzenes (12 possible molecules) have been studied with the density functional theory (DFT) and ab initio methods. The global reactivity descriptor, namely, electrophilicity index (ω) has been calculated to understand the reactive nature of these compounds. Schleyer et al.[7] introduced nucleus-independent chemical shifts (NICSs), the negative of the absolute magnetic shieldings, usually computed at the ring centers, as a means of evaluating the aromaticity/antiaromaticity of appropriate candidates. To correspond to the familiar NMR chemical shift convention, the signs of the computed values are reversed: negative NICSs denote aromaticity; positive NICSs denote antiaromaticity. NICS values can be obtained at a central point in the plane of the rings (NICS(0))[7] or at points above the ring, for example, NICS(1)[8] refers to calculations at a distance of 1.0 Å above the ring. We have also calculated the amount of charge transfer between chlorobenzenes and various bases, namely, adenine (A), guanine (G), thymine (T), cytosine (C), uracil (U), DNA base pairs GC Watson−Crick pairing (GCWC),[9,10] and AT Hoogsteen pairing (ATH)[9,10] to know about the possible interaction of chlorobenzenes with the biosystems.

Further, in view of the importance of quantitative structure−toxicity relationship (QSTR) studies in the field of aquatic toxicology from the facet of ecological safety assessment, fish toxicity (pC) of various chlorobenzenes against *Poecilia reticulata*[11] has been modeled by the linear regression technique using the DFT-based global reactivity descriptor ω.

Theoretical Background

According to the density functional theory,[12,13] the chemical potential (μ) and chemical hardness (η) are defined as

$$\chi = -\mu = -(\partial E/\partial N)_{v(\vec{r})} \tag{1}$$

and

$$\eta = (^1/_2)(\partial^2 E/\partial N^2)_{v(\vec{r})} = (^1/_2)(\partial \mu/\partial N)_{v(\vec{r})} \tag{2}$$

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

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identified as the negative of the electronegativity (χ) as defined by Iczkowski and Margrave.[14]

To save computational time, we have calculated chemical potential and chemical hardness by using Koopmans' theorem[12] as

$$\mu = (E_{\mathrm{LUMO}} + E_{\mathrm{HOMO}})/2 \tag{3}$$

and

$$\eta = (E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}})/2 \tag{4}$$

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

The global interactions between the constituents of chlorobenzenes and NA bases/base pairs have been determined using the parameter ΔN, which represents the fractional number of electrons, transferred from system A to system B, and is represented by[15]

$$\Delta N = \frac{\mu_{\mathrm{B}} - \mu_{\mathrm{A}}}{2(\eta_{\mathrm{A}} + \eta_{\mathrm{B}})} \tag{5}$$

where μ_{A}, μ_{B} and η_{A}, η_{B} are the chemical potentials and chemical hardness of systems A and B, respectively.

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[13]

$$f(\vec{r}) = (\partial\rho(\vec{r})/\partial N)_{v(\vec{r})} = (\delta\mu/\delta v(\vec{r}))_N \tag{6}$$

Since the above derivatives are discontinuous, three different types of Fukui functions have been defined[16−18]

For nucleophilic attack

$$f^{+}(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}) \tag{7a}$$

For electrophilic attack

$$f^{-}(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \tag{7b}$$

For radical attack

$$f^{0}(\vec{r}) = (\rho_{N+1}(\vec{r}) - \rho_{N-1}(\vec{r}))/2 \tag{7c}$$

Parr et al. have introduced a global electrophilicity index ω as[19]

$$\omega = \frac{\mu^2}{2\eta} \tag{8}$$

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 nucleocapsid protein p7 when reacted with a variety of electrophilic agents.[20]

Recently, Chattaraj et al.[21] 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

$$\omega_{\mathrm{k}}^{\alpha} = \omega f_{\mathrm{k}}^{\alpha} \tag{9}$$

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

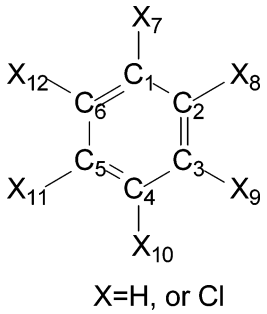

Figure 1. Structure along with atom numbering for the chlorobenzene template.

Computational Details

The structure along with atom numbering for the chlorobenzene template is shown in Figure 1. The geometries of benzene and all 12 chlorobenzenes are optimized by using both Hartree−Fock, HF/6-31G*, and Becke's three parameter hybrid density functional, B3LYP/6-31G*, which includes both Hartree−Fock exchange and DFT exchange correlation functionals.[22−24] The above calculations are carried out using the *Gaussian 98W* suite of programs.[25] The optimized geometries are characterized by harmonic vibrational frequencies, which confirmed that the structures obtained are minimum on the potential energy surface. The global electrophilicity index is calculated for all the selected systems using eq 8. For aromaticity analysis upon stepwise addition of chlorine, nucleus-independent chemical shift (NICS-(1))[8] calculations are carried out. The amount of charge transfer[15] between chlorobenzenes and various bases, namely, adenine (A), guanine (G), thymine (T), cytosine (C), uracil (U), DNA base pairs GCWC,[9,10] and ATH[9,10] is calculated using eq 5 to know about the possible nature of interaction of chlorobenzenes with the biosystems. The Hirshfeld[26] population scheme (Stockholder partitioning scheme) has been used to calculate FF values as implemented in the *DMOL*[3] package[27] package employing the BLYP/DN method. Then the local philicity (ω_{k}^{+}) is obtained for all atoms of the selected systems using eq 9. One parameter, QSARs,[28] is performed using a least-squares error estimation method[29] to calculate and compare the fish toxicity (pC)[11] of various chlorobenzenes.

Results and Discussion

Energies of Chlorobenzenes. The calculated energies, thermodynamic quantities (enthalpy and free energy), and dipole moments of all chlorobenzenes along with benzene 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 dichlorobenzenes, the para isomer (1,4-C2B) is the most stable, whereas the ortho isomer (1,2-C2B) is the least stable with a difference of 2.48 kcal/mol in their energy values. The meta isomer is less stable than the para isomer by an amount of 0.09 kcal/mol. Similarly, 1,3,5-C3B and 1,2,4,5-C4B are shown to be the most stable isomers, whereas 1,2,3-C3B and 1,2,3,4-C4B are the least stable isomers for the tri- and tetrachlorobenzenes, respectively. The chlorine substituent at the adjacent positions seems to destabilize the isomers, and the resulting steric effect may be one of the important sources of

TABLE 1: Calculated Energies *E* (hartree), Zero-Point Energies (ZPE, kcal/mol), Enthalpies *H* (hartree), Free Energies *G* (hartree), and Dipole Moments μ (debye) of All Chlorobenzenes from the B3LYP/6-31 g* Level[a]

system	*E*	ZPE	ΔE	ΔE_0	*E* (HF)	ΔE (HF)	*H*	ΔH	*G*	ΔG	μ
benzene	−232.25	63.22			−230.70		−232.14		−232.18		0.00
CB	−691.85	57.25			−689.60		−691.75		−691.78		1.93
1,2-C2B	−1151.44	51.22	2.48	2.51	−1148.50	3.1	−1151.35	2.48	−1151.39	2.58	2.77
1,3-C2B	−1151.44	51.19	0.09	0.09	−1148.50	0.19	−1151.35	0.08	−1151.39	0.08	1.81
1,4-C2B	−1151.44	51.19	0.00	0.00	−1148.50	0.00	−1151.35	0.00	−1151.39	0.00	0.00
1,2,3-C3B	−1611.03	45.14	4.72	4.78	−1607.39	5.9	−1610.94	4.74	−1610.99	4.95	2.81
1,2,4-C3B	−1611.03	45.13	2.10	2.15	−1607.39	2.55	−1610.95	2.13	−1610.99	2.22	1.40
1,3,5-C3B	−1611.03	45.08	0.00	0.00	−1607.40	0.00	−1610.95	0.00	−1610.99	0.00	0.00
1,2,3,4-C4B	−2070.61	39.03	2.82	2.82	−2066.28	3.72	−2070.54	2.79	−2070.59	2.93	2.11
1,2,3,5-C4B	−2070.62	39.01	0.42	0.40	−2066.28	0.61	−2070.55	0.40	−2070.59	0.43	1.01
1,2,4,5-C4B	−2070.62	39.03	0.00	0.00	−2066.29	0.00	−2070.54	0.00	−2070.59	0.00	0.94
1,2,3,4,5-C5B	−2530.20	32.91			−2525.17		−2530.14		−2530.19		0.00
1,2,3,4,5,6-C6B	−2989.78	26.78			−2984.05		−2989.73		−2989.78		0.00

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

TABLE 2: Ranges of Bond Lengths and Bond Angles of Chlorobenzenes and Benzene Optimized with B3LYP and HF Methods Using the 6-31 g* Basis Set[a]

	chlorobenzenes (Å)		benzene (Å)		observed value for benzene[b]		chlorobenzene (degrees)		benzene (degrees)		observed value for benzene[b]
parameter	B3LYP	HF	B3LYP	HF	(Å)	parameter	B3LYP	HF	B3LYP	HF	(degree)
$r(C_1-C_2)$	1.394−1.405	1.383−1.392	1.397	1.386	1.391	$\angle C_1C_2C_3$	118.0−120.1	118.2−120.1	120.0	120.0	120.0
$r(C_1-C_6)$	1.391−1.404	1.383−1.391	1.397	1.386		$\angle C_2C_3C_4$	119.5−121.7	119.5−121.8	120.0	120.0	
$r(C_2-C_3)$	1.394−1.410	1.383−1.397	1.397	1.386		$\angle C_3C_4C_5$	118.0−121.0	118.2−121.0	120.0	120.0	
$r(C_3-C_4)$	1.392−1.407	1.380−1.394	1.397	1.386		$\angle C_4C_5C_6$	119.1−122.0	119.1−121.0	120.0	120.0	
$r(C_4-C_5)$	1.391−1.401	1.379−1.391	1.397	1.386		$\angle C_5C_6C_1$	118.0−120.7	118.2−120.8	120.0	120.0	
$r(C_5-C_6)$	1.388−1.404	1.377−1.391	1.397	1.386		$\angle C_6C_1C_2$	119.5−121.7	119.6−121.8	120.0	120.0	
$r(C_1-X_7)$			1.087	1.075	1.080	$\angle C_2C_1X_7$			120.0	120.0	
X = H						X = H					
X = Cl	1.734−1.761	1.723−1.745				X = Cl	118.9−121.6	119.0−122.0			
$r(C_2-X_8)$	1.083−1.085	1.071−1.073	1.087	1.075		$\angle C_3C_2X_8$	120.3−121.0	120.3−120.9	120.0	120.0	
X = H						X = H					
X = Cl	1.734−1.748	1.729−1.735				X = Cl	118.3−120.9	118.1−120.8			
$r(C_3-X_9)$	1.083−1.087	1.072−1.075	1.087	1.075		$\angle C_4C_3X_9$	119.7−120.9	119.6−120.7	120.0	120.0	
X = H						X = H					
X = Cl	1.736−1.757	1.723−1.741				X = Cl	117.9−120.3	117.6−120.2			
$r(C_4-X_{10})$	1.083−1.087	1.071−1.075	1.087	1.075		$\angle C_5C_4X_{10}$	120.1−121.1	120.1−122.0	120.0	120.0	
X = H						X = H					
X = Cl	1.734−1.756	1.729−1.741				X = Cl	118.5−121.7	118.1−120.3			
$r(C_5-X_{11})$	1.084−1.087	1.073−1.075	1.087	1.075		$\angle C_6C_5X_{11}$	119.0−120.4	119.4−120.4	120.0	120.0	
X = H						X = H					
X = Cl	1.734−1.753	1.723−1.737				X = Cl	118.1−119.4	118.4−120.0			
$r(C_6-X_{12})$	1.083−1.087	1.071−1.075	1.087	1.075		$\angle C_1C_6X_{12}$	118.9−121.0	119.0−120.9	120.0	120.0	
X = H						X = H					
X = Cl	1.734	1.723				X = Cl	120.0	120.0			

[a] Complete geometric details of these systems are provided in Supporting Information. [b] References 30 and 31.

the relative instabilities of the chlorobenzene isomers apart from the associated electrostatic effects.

The thermodynamic energies such as enthalpy and free energy as well as their relative values are shown in Table 1. The relative values, ΔH and ΔG, follow the same trend and remain nearly constant as ΔE. These thermodynamic data are valuable in characterizing the molecular properties of chlorobenzene in the gas phase. The dipole moment has been expected to be related to the bulk properties of chlorobenzene, and they seem to arise mainly from the vector sum of the contributing C−Cl bond dipoles.

Structural Details. Table 2 provides ranges of calculated bond lengths and bond angles of 12 chlorobenzenes from B3LYP and HF calculations with the 6-31 g* basis set along with benzene geometries. Complete geometric details of these systems are provided as Supporting Information (Tables S1−S5). Table 3 gives bond lengths and bond angles for selected systems, namely, CB and 1,3,5-C3B along with the observed values for comparison. As seen from the above tables, the calculated and observed geometries of benzene, CB, and 1,3,5-C3B are in good agreement. The calculated geometries for chlorobenzenes are thus expected to be reasonable. It can be noted from Tables 2 and 3 that the geometry is distorted by the chlorine substituent, so that the C−C bonds adjacent to chlorine are shorter than the others and C−C−C bond angles at the substituted carbon atom are larger than 120°. In the case of benzene, the HF method provides closer values to the observed data. That is, the C−C bond distance is 1.386 Å, which is closer to the observed value[30,31] of 1.391 Å. Also, C−H bond distances and C−C−C bond angles are closer to the observed values.[30,31]

In the case of chlorobenzene (CB), the C−C bond distance obtained using the B3LYP method is 1.394 Å, which is closer to the observed value[32] of 1.391 Å. For C−Cl bond distances, HF provides a value (1.745 Å) closer to the observed value (1.739 Å) compared to the B3LYP method. The C6−C1−C2 bond angles were obtained by B3LYP and HF methods at the chlorine-substituted position, respectively, as 121.4° and 121.3° which are larger than the 120° as expected and are closer to the observed value[32] (121.65°). For 1,3,5-trichlorobenzene (1,3,5-C3B), the C−C bond distance obtained by the B3LYP method exactly matches with observed value[33] of 1.394 Å. For

TABLE 3: Bond Lengths and Bond Angles of CB and 1,3,5-C3B Optimized with B3LYP and HF Methods Using the 6-31 g* Basis Set along with Observed Results

	CB (Å)		observed	1,3,5-C3B (Å)		observed		CB (degrees)		observed	1,3,5-C3B (degrees)		observed
parameter	B3LYP	HF	value[a] (Å)	B3LYP	HF	value[b] (Å)	parameter	B3LYP	HF	value[a] (degrees)	B3LYP	HF	value[b] (degrees)
$r(C_1-C_2)$	1.394	1.383	1.391	1.394	1.383	1.394	$\angle C_1C_2C_3$	119.0	119.1	119.05	118.0	118.2	
$r(C_1-C_6)$	1.394	1.383		1.394	1.383		$\angle C_2C_3C_4$	120.5	120.4	120.24	122.0	121.8	
$r(C_2-C_3)$	1.396	1.386	1.394	1.394	1.383		$\angle C_3C_4C_5$	119.8	119.8	119.79	118.0	118.2	
$r(C_3-C_4)$	1.396	1.386	1.400	1.394	1.383		$\angle C_4C_5C_6$	120.5	120.4		122.0	121.8	
$r(C_4-C_5)$	1.396	1.385		1.394	1.383		$\angle C_5C_6C_1$	119.0	119.1		118.0	118.2	
$r(C_5-C_6)$	1.396	1.386		1.394	1.383		$\angle C_6C_1C_2$	121.4	121.3	121.65	122.0	121.8	122.36
$r(C_1-X_7)$							$\angle C_2C_1X_7$						
X = H							X = H						
X = Cl	1.761	1.745	1.739	1.753	1.737	1.728	X = Cl	119.3	119.4		119.0	119.1	
$r(C_2-X_8)$	1.085	1.073	1.078	1.083	1.071	1.081	$\angle C_3C_2X_8$	121.0	120.8		121.0	120.9	
X = H							X =H						
X = Cl							X = Cl						
$r(C_3-X_9)$	1.087	1.075	1.087				$\angle C_4C_3X_9$	120.2	120.2				
X = H							X = H						
X = Cl				1.753	1.737		X = Cl				119.0	119.1	
$r(C_4-X_{10})$	1.086	1.075	1.080	1.083	1.071		$\angle C_5C_4X_{10}$	120.1	120.1		121.0	120.9	
X = H							X = H						
X = Cl							X = Cl						
$r(C_5-X_{11})$	1.087	1.075					$\angle C_6C_5X_{11}$	119.3	119.4				
X = H							X = H						
X = Cl				1.753	1.737		X = Cl				119.0	119.1	
$r(C_6-X_{12})$	1.085	1.073		1.083	1.071		$\angle C_1C_6X_{12}$	120.1	120.1		121.0	120.9	
X = H							X = H						
X = Cl							X = Cl						

[a] Reference 32. [b] Reference 33.

TABLE 4: Calculated Global Reactivity Descriptors for Chlorobenzenes and Nucleic Acid Bases/Selected Base Pairs from the B3LYP/6-31 g* Method

system	η (eV)	μ (eV)	ω (eV)
benzene	3.400	−3.302	1.603
CB	3.182	−3.523	1.950
1,2-C2B	3.093	−3.748	2.271
1,3-C2B	3.099	−3.823	2.358
1,4-C2B	3.001	−3.741	2.331
1,2,3-C3B	3.074	−4.019	2.627
1,2,4-C3B	2.950	−3.970	2.672
1,3,5-C3B	3.097	−4.149	2.780
1,2,3,4-C4B	2.912	−4.138	2.941
1,2,3,5-C4B	2.921	−4.200	3.020
1,2,4,5-C4B	2.865	−4.160	3.015
1,2,3,4,5-C5B	2.844	−4.319	3.279
1,2,3,4,5,6-C6B	2.781	−4.517	3.669
adenine	2.850	−3.103	1.689
thymine	2.894	−3.689	2.351
guanine	2.916	−2.648	1.202
cytosine	2.785	−3.370	2.039
uracil	2.962	−3.919	2.593
GCWC	2.018	−3.030	2.275
ATH	2.526	−3.256	2.098

C−Cl bond distances, the HF method provides a value (1.737 Å) closer to the observed value (1.728 Å). The C−C−C bond angles were obtained by B3LYP and HF methods at the chlorine-substituted positions, respectively, as 122.0° and 121.8° which are also larger than the 120° as expected and are closer to the observed value[33] (122.36°). These results confirm the appropriateness of the basis set chosen for the investigation.

Global Descriptor on Chlorobenzene. Calculated values of global reactivity descriptors, namely, chemical hardness, chemical potential, and electrophilicity index from the B3LYP/6-31 g* method have been presented in Table 4. Among the selected systems, the most stable structure (benzene) has the maximum hardness in accordance with the maximum hardness principle (MHP) and the hardness decreases with an increase in the number of chlorine substitutions. Also, there is an increase in the value of the electrophilicity index with an increase in the number of chlorine substitutions, indicating an increase in reactivity of more substituted chlorobenzenes.

TABLE 5: Charge Transfer between Chlorobenzenes and Nucleic Acid Bases/ Selected Base Pairs from the B3LYP/ 6-31 g* Method

system	adenine	thymine	guanine	cytosine	uracil	GCWC	ATH
benzene	0.016	−0.031	0.052	−0.006	−0.049	0.025	0.004
CB	0.035	−0.014	0.072	0.013	−0.032	0.047	0.023
1,2-C2B	0.055	0.005	0.091	0.032	−0.014	0.070	0.043
1,3-C2B	0.061	0.011	0.097	0.038	−0.008	0.077	0.05
1,4-C2B	0.055	0.004	0.092	0.032	−0.015	0.071	0.043
1,2,3-C3B	0.078	0.028	0.114	0.055	0.008	0.097	0.068
1,2,4-C3B	0.075	0.024	0.112	0.052	0.004	0.095	0.065
1,3,5-C3B	0.088	0.038	0.125	0.066	0.019	0.109	0.079
1,2,3,4-C4B	0.095	0.044	0.133	0.073	0.024	0.118	0.086
1,2,3,5-C4B	0.090	0.039	0.128	0.067	0.019	0.112	0.081
1,2,4,5-C4B	0.092	0.041	0.130	0.070	0.020	0.115	0.083
1,2,3,4,5-C5B	0.107	0.055	0.145	0.084	0.034	0.132	0.099
1,2,3,4,5,6-C6B	0.126	0.073	0.164	0.103	0.052	0.155	0.118

The variation of electrophilicity index with nucleus-independent chemical shift (NICS(1)) calculated using B3LYP and HF /6-31 g* has been depicted in Figure 2. Electron delocalization and aromaticity play a vital role in deciding the stability of the selected systems. Hence, we have carried out NICS(1) analysis to test the aromaticity and the stability of the selected systems. The more negative the NICS(1) value of a system, the more aromatic and more stable it will be.[8] Accordingly, benzene is the most aromatic, and the aromaticity decreases with an increase in the number of chlorine substituents. Electrophilicity index, which is a measure of the global reactivity of the system, increases with an increase in the number of chlorine substituents. It may be noted from the Figure 2 that benzene, which is the most aromatic, has the least value for electrophilicity index and the most negative value for NICS(1) and C6B, which is the least aromatic, has the highest value for electrophilicity index and the least negative value for NICS(1) showing maximum

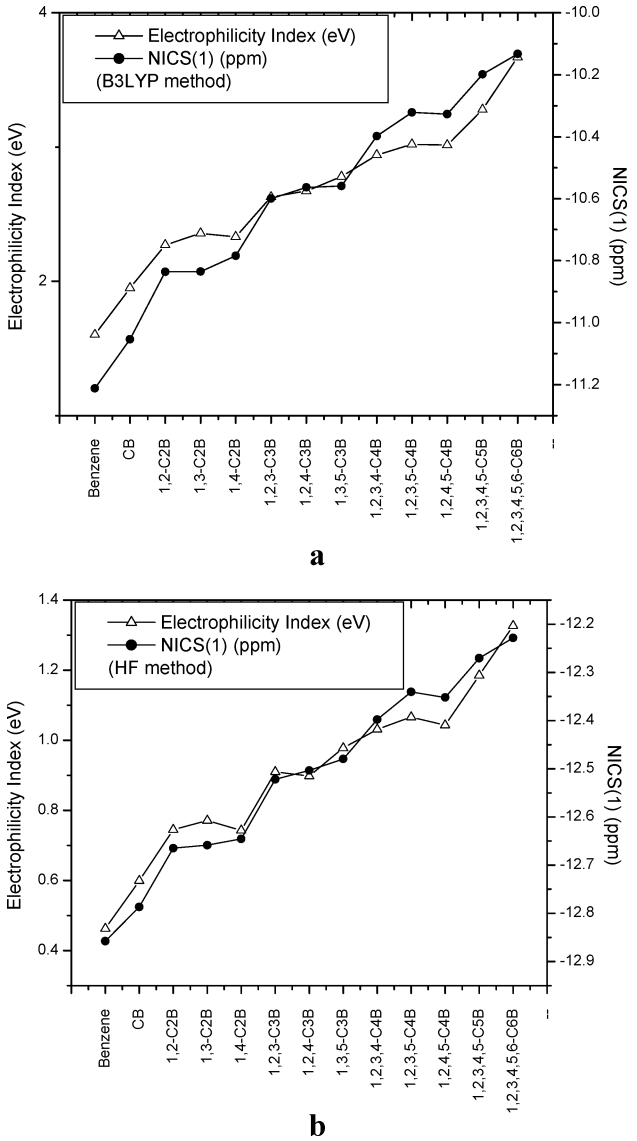

Figure 2. Relationship between the electrophilicity index ω and nucleus-independent chemical shift (NICS(1)) for the complete series of chlorobenzenes from the (a) B3LYP and (b) HF /6−31 g* levels.

reactivity among the selected chlorobenzenes. This fact is in conformity with a proposed minimum electrophilicity principle.[34]

Interaction with Biomolecules. The amount of charge transfer between chlorobenzenes and various bases, namely, adenine (A), guanine (G), thymine (T), cytosine (C), uracil (U), DNA base pairs GCWC, [9] and ATH[10] is calculated to discover the possible interaction of chlorobenzenes with the biosystems (Table 5). If two systems X and Y are brought together, as in a reaction, they must form a single system with a constant value of chemical potential. The negative chemical potential can be called the absolute electronegativity, and there is always a transfer of electrons from a less electronegative system to a more electronegative system. It is seen from Table 4 that chlorobenzenes act as electron acceptors in their interaction with bases/selected base pairs with a few exceptions. For instance, monochlorobenzene (CB) acts as electron donor in its interaction with thymine and uracil (Table 5). This electron-accepting nature prompted us to analyze the toxic characteristics of chlorobenzenes in terms of their ω values.

Local Descriptor on Chlorobenzene. Previous studies[35−38] have shown that the electron-accepting nature of a system is associated with possible nucleophilic attack at the reactive sites. So, the electron-accepting nature of chlorobenzenes as explained by the above charge-transfer analysis has revealed the fact that active sites in chlorobenzenes are those which are prone for nucleophilic attack. Therefore, in the present investigation, local philicity (ω^+) values for all the atoms of the selected systems, namely, benzene, CB, 1,4-C2B, 1,3,5-C3B, 1,2,4,5-C4B, 1,2,3,4,5-C5B, and C6B have been presented (Figure 3). In the case of benzene, carbon sites are prone to nucleophilic attack compared to hydrogen atoms. The carbon atom attached to the chlorine atom and the chlorine site shows affinity toward nucleophilic attack in monochlorobenzene (CB), and this leads to charge depletion at the carbon sites in the ortho positions. A similar situation prevails in 1,4-C2B with non-chlorine-substituted carbon sites predominating in nucleophilic attack. For 1,3,5-C3B, all the three chlorine atoms are potential sites for attracting a nucleophile. In 1,2,4,5-C4B, non-chlorine-substituted positions, namely, C3 and C6, are the most favored sites for electron acceptance. In 1,2,3,4,5-C5B and C6B, the chlorine site is the most favored site for nucleophilic attack. Thus, with the help of local philicity, one can identify the active sites in the selected systems.

TABLE 6: Experimental and Calculated Fish Toxicity (pC) Values against *Poecilia reticulata* of the Selected Chlorobenzenes from the B3LYP/6-31 g* Method

system	ω (eV)	observed pC value[a]	calculated pC value	residual[b]
CB	1.950	3.77	3.77	0.00
1,2-C2B	2.271	4.40	4.28	0.12
1,3-C2B	2.358	4.28	4.42	−0.14
1,4-C2B	2.331	4.56	4.38	0.18
1,2,4-C3B	2.672	4.83	4.93	−0.10
1,3,5-C3B	2.780	4.74	5.10	−0.36
1,2,3,4-C4B	2.941	5.35	5.36	−0.01
1,2,3,5-C4B	3.020	5.43	5.49	−0.06
1,2,4,5-C4B	3.015	5.85	5.48	0.37

[a] Reference 11. [b] Difference between the experimental and calculated fish toxicity (pC) values.

Structure−Toxicity Analysis on Chlorobenzenes. The QSTR for fish toxicity (pC) of the selected set of nine chlorobenzenes against *Poecilia reticulata* has been analyzed. Table 6 lists the experimental[11] and calculated fish toxicity data (pC) for the selected set of nine chlorobenzenes. Considering the experimental toxicity data (pC) as a dependent variable and DFT-based global descriptor, namely, 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

$$\mathrm{pC} = 0.6324 + 1.6076\omega$$

$$N = 9, \quad r^2 = 0.896, \quad \mathrm{SD} = 0.223 \qquad (10)$$

The selected descriptor ω is capable of explaining the 89.6% variation in data with a root-mean-square error of 0.223. A plot between the experimental and calculated toxicity values (Figure 4) provides a correlation coefficient (r) value of 0.95, which reveals the fact that electrophilicity index can be effectively used as a descriptor in the prediction of toxicity. It must be emphasized that the present approach can provide a guideline toward the possible toxicity of a molecule. However, the small differences in toxicity values of various isomers may not necessarily be properly reproduced by this essentially statistical technique. The energy values are reliable in the sense that the relative stabilities of isomers of any system are correctly taken

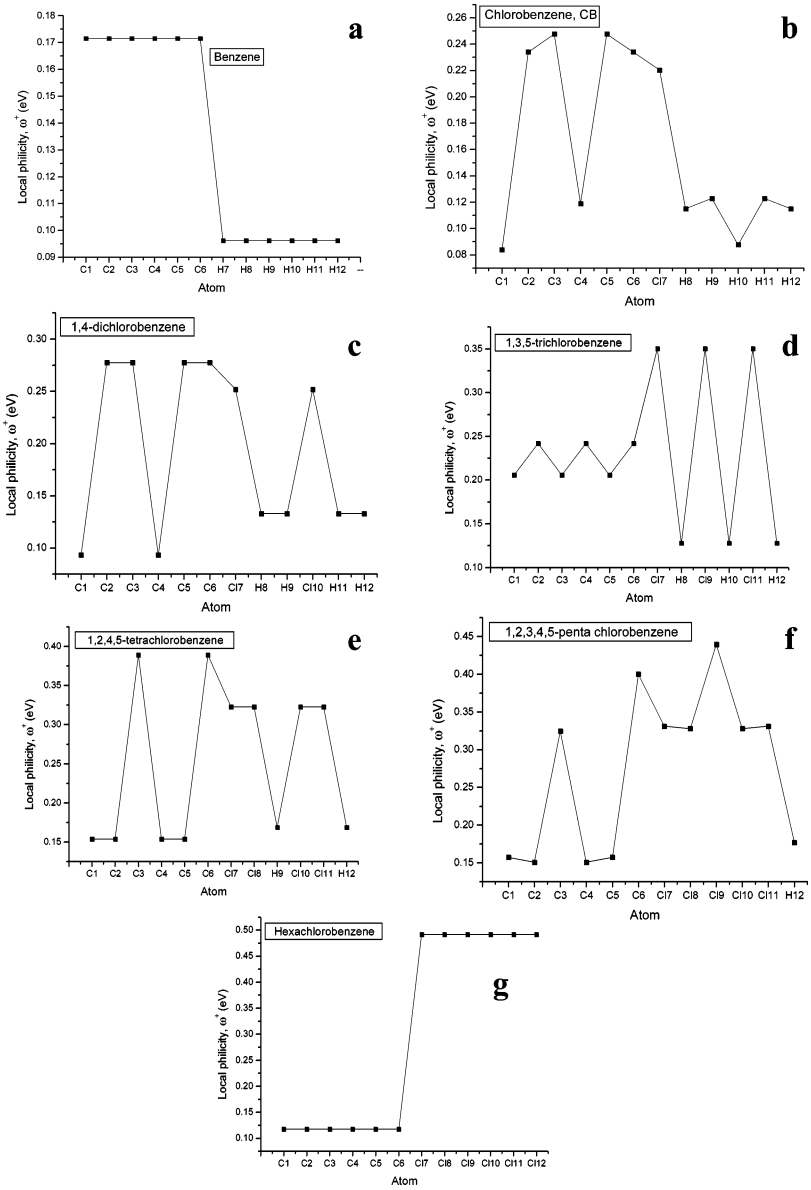

Figure 3. Local philicity (ω^+) of all the atoms in (a) benzene, (b) chlorobenzene, CB, (c) 1,4-dichlorobenzene, (d) 1,3,5-trichlorobenzene, (e) 1,2,4,5-tetrachlorobenzene, (f) 1,2,3,4,5-pentachlorobenzene, and (g) hexachlorobenzene obtained from BLYP/DN method.

care of. Even the increase in toxicity with an increase in the number of chlorine substituents is beautifully delineated by the present method. The power of the present method of toxicity prediction with only one descriptor becomes transparent when compared with other QSAR/QSTR techniques which use more descriptors, often disjoint and with no apparent connection with toxicity, to provide comparable or poorer correlations.

Conclusions

Chlorobenzenes are toxic, highly persistent, and ubiquitously distributed environmental contaminants. Theoretical calculations have been carried out in order to assess the stable structures and reactive properties of the complete series of 12 chlorobenzenes. Para CBs are found to be more stable than the corresponding ortho- or meta isomers. The number and position of the chlorine substituent plays a vital role in deciding the structural stability/reactivity of CBs. The relationship between electrophilicity index and aromaticity (NICS(1)) illustrates that the aromaticity decreases with an increase in the NICS(1) value (becoming less negative) and there is a corresponding increase in the electrophilicity index. Chlorobenzenes act as electron

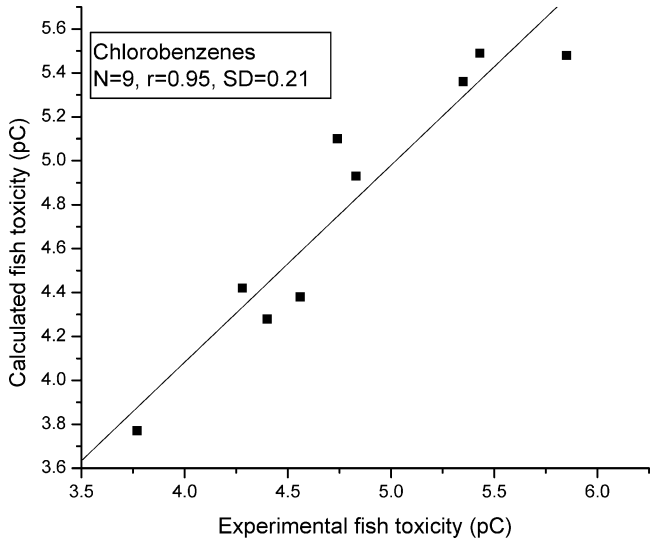

Figure 4. Plot between experimental and calculated fish toxicity (pC) of selected chlorobenzenes.

acceptors in their interaction with nucleic acid bases/selected base pairs and thereby exhibit their toxic characteristics. The reactive sites in the selected chlorobenzenes are also identified using the local philicity (ω^+). A structure toxicity study has been carried out with existing experimental fish toxicity values of chlorobenzene 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 fish toxicity of chlorobenzenes.

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Supporting Information Available: Tables S1−S5 provide bond lengths and bond angles for the complete series of chlorinated benzenes optimized with B3LYP and HF methods using the 6-31 g* basis set. This material is available free of charge via the Internet at http://pubs.acs.org.

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