Chemical Reactivity Indices for the Complete Series of Chlorinated Benzenes: Solvent Effect

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We present a comprehensive analysis to probe the effect of solvation on the reactivity of the complete series of chlorobenzenes through the conceptual density functional theory (DFT)-based global and local descriptors. We propose a multiphilic descriptor in this study to explore the nature of attack at a particular site in a molecule. It is defined as the difference between nucleophilic and electrophilic condensed philicity functions. This descriptor is capable of explaining both the nucleophilicity and electrophilicity of the given atomic sites in the molecule simultaneously. The predictive ability of this descriptor is tested on the complete series of chlorobenzenes in gas and solvent media. A structure−toxicity analysis of these entire sets of chlorobenzenes toward aquatic organisms demonstrates the importance of the electrophilicity index in the prediction of the reactivity/toxicity.

Introduction

In the last several decades, halogenated aromatic hydrocarbons have been used extensively as intermediates in the chemical industry and agriculture. Some of these chemicals are carcinogenic and have deleterious effects on organisms. Because these chemicals are being introduced into the environment, pollution effects by these kinds of compounds should be anticipated.[1,2] Agricultural developments have led a parallel growth in the use of chemical agents for plague controls, which are known as pesticides. These compounds are released into the environment, and due to their physicochemical properties, such as water solubility, vapor pressure, or partition coefficients between organic matter (in soil or sediment) and water, they can disperse in various environmental media, provoking serious health problems.[3]

Many of the chlorobenzenes have been classified by the Environmental Protection Agency as hazardous waste, priority toxic pollutants, and carcinogens.[4] The chlorobenzenes are often used as intermediates in the manufacture of certain dyestuffs, and many pesticides and are formed from the degradation of other organochlorine compounds.[4] They are toxic and pose threats to aquatic environments, leading to trichlorobenzenes and hexachlorobenzene being placed on the EU "Red List" of dangerous compounds.[5] 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 man, various effects on internal organs have been observed following acute exposure. Chlorobenzenes have a nonspecific toxicological mode of action that can be significantly described with traditional parameters by means of a simple relationship with the octanol/water partition coefficient (K_{ow}).[6]

Hexachlorobenzene is a major air-borne organochlorine compound in arctic air present at relatively uniform picogram per cubic meter concentrations.[7,8] Qian et al.[7] have shown that chlorobenzenes caused significant changes in the serum testosterone concentration and hepatic Glutathione s-transferase (GST) and UDP−glucuronosyltransferase (UDPGT) activity in crucian carps. The literatures related to the series of chlorobenzenes demonstrated the profound effects of aromatic chlorinated species and urged us to do this detailed investigation. Recently, we have made a detailed theoretical study on the structure, properties, and toxicity for the complete series of chlorobenzenes in the gas phase.[9]

In the present study, the effect of solvation on the reactivity of the complete series of chlorobenzenes is analyzed using the global descriptors such as energy (E), hardness (η), chemical potential (μ), and electrophilicity index (ω). Fukui functions (FF) are utilized to understand the sites that are prone to nucleophilic or electrophilic attack. A multiphilic descriptor ($\Delta\omega_k$) is proposed in this study, and its predictive ability is tested on the complete series of chlorobenzenes in gas and solvent media. Further, in view of the importance of quantitative structure−toxicity relationship (QSTR) studies in the field of aquatic toxicology, toxicity (12 h − $\log(1/LC_{50})$)[10] values, which are logarithms of inverse of median lethal concentrations after 12 h exposure of the chlorobenzenes against *Rana japonica* tadpoles, have been modeled by the linear regression technique using the density functional theory (DFT)-based global reactivity descriptor ω in gas and solvent media.

Theoretical Background

According to the DFT,[11,12] the chemical potential (μ) and chemical hardness (η) are defined as,

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

and

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

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 identified as the negative of the electronegativity (χ), as defined by Iczkowski and Margrave.[13]

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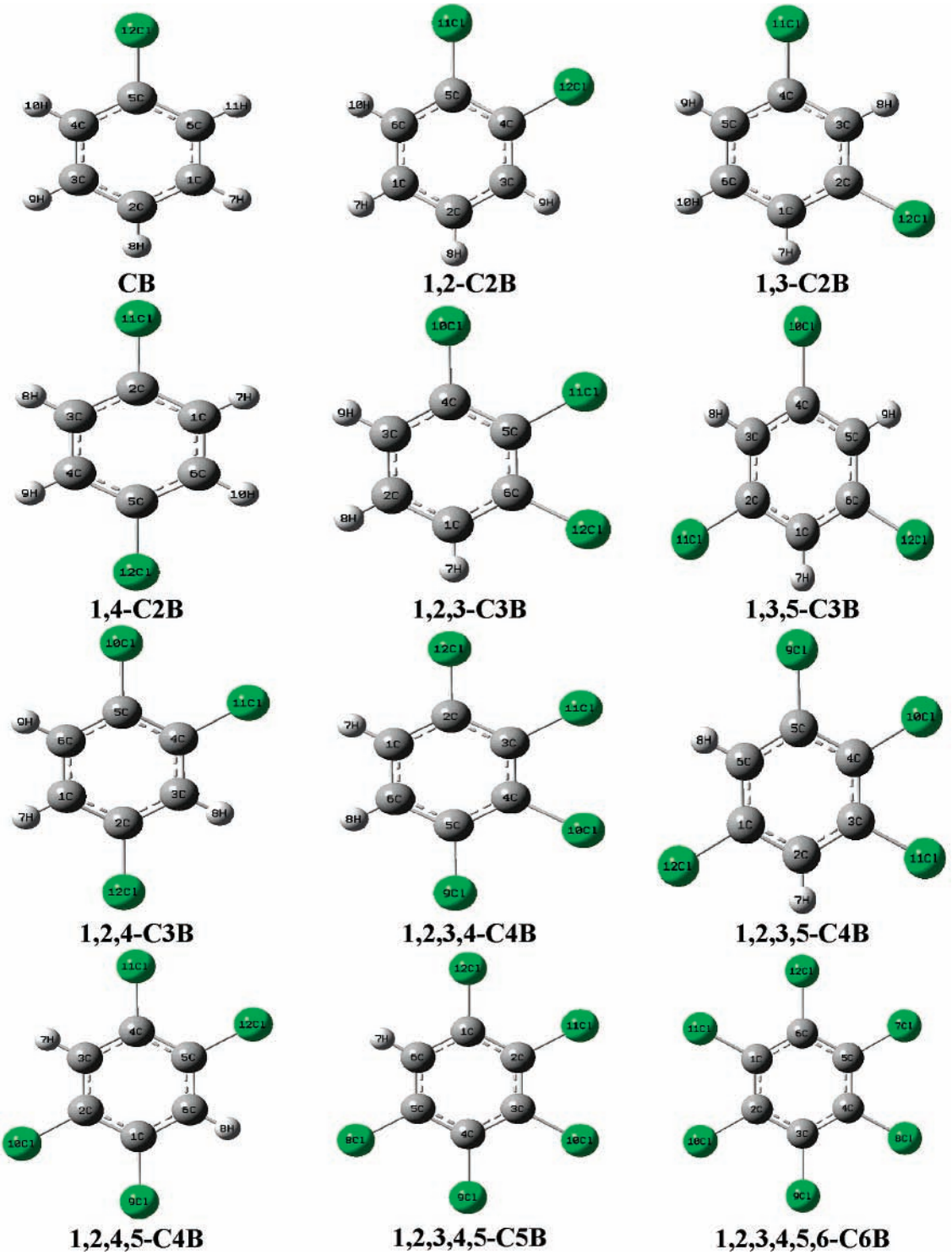


Figure 1. Structures along with atom numbering for the complete series of chlorobenzenes.

To save computational time, we have calculated the chemical potential and chemical hardness by using Koopmans' theorem[11] 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 energy of the lowest unoccupied molecular orbital and E_{HOMO} is the energy of the highest occupied molecular orbital.

The FF, which measures the sensitivity of a system's chemical potential to an external perturbation at a particular site, is defined as[12]

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

Because the above derivatives are discontinuous, three different

TABLE 1: Calculated Energy *E* (hartree), Hardness η (au), Chemical Potential μ (au), and Electrophilicity Index ω (au) for All Chlorobenzenes Both in Solvent and Gas Phases from the BLYP/DNP Method

	E			η			μ			ω		
system	solvent phase	gas phase	ΔE^a	solvent phase	gas phase	$\Delta\eta^b$	solvent phase	gas phase	$\Delta\mu^c$	solvent phase	gas phase	$\Delta\omega^d$
CB	−691.8644	−691.8591	−0.0053	0.0859	0.0844	0.0016	−0.1362	−0.1384	0.0022	0.1080	0.1135	−0.0055
1,2-C2B	−1151.4874	−1151.4819	−0.0055	0.0831	0.0812	0.0019	−0.1411	−0.1447	0.0036	0.1198	0.1289	−0.0091
1,3-C2B	−1151.4911	−1151.4859	−0.0052	0.0827	0.0815	0.0012	−0.1424	−0.1473	0.0049	0.1226	0.1331	−0.0105
1,4-C2B	−1151.4913	−1151.4859	−0.0055	0.0794	0.0776	0.0018	−0.1395	−0.1445	0.0050	0.1225	0.1345	−0.0120
1,2,3-C3B	−1611.1087	−1611.1034	−0.0053	0.0824	0.0811	0.0013	−0.1471	−0.1522	0.0052	0.1313	0.1428	−0.0115
1,2,4-C3B	−1611.1126	−1611.1076	−0.0051	0.0777	0.0761	0.0016	−0.1449	−0.1511	0.0062	0.1351	0.1500	−0.0149
1,3,5-C3B	−1611.1156	−1611.1112	−0.0044	0.0824	0.0817	0.0007	−0.1500	−0.1569	0.0069	0.1365	0.1507	−0.0141
1,2,3,4-C4B	−2070.7291	−2070.7242	−0.0049	0.0768	0.0754	0.0014	−0.1489	−0.1551	0.0062	0.1443	0.1595	−0.0152
1,2,3,5-C4B	−2070.7325	−2070.7282	−0.0043	0.0768	0.0755	0.0013	−0.1505	−0.1574	0.0069	0.1475	0.1641	−0.0166
1,2,4,5-C4B	−2070.7332	−2070.7288	−0.0044	0.0747	0.0732	0.0015	−0.1490	−0.1563	0.0073	0.1486	0.1669	−0.0183
1,2,3,4,5-C5B	−2530.3482	−2530.3443	−0.0039	0.0743	0.0732	0.0012	−0.1532	−0.1603	0.0071	0.1579	0.1755	−0.0176
1,2,3,4,5,6-C6B	−2989.9623	−2989.8557	−0.1066	0.0707	0.0674	0.0034	−0.1606	−0.1716	0.0110	0.1824	0.2185	−0.0361

[a] Difference between solvent- and gas-phase energy values. [b] Difference between solvent- and gas-phase chemical hardness values. [c] Difference between solvent- and gas-phase chemical potential values. [d] Difference between solvent- and gas-phase values of electrophilicity index.

TABLE 2: Sites with Maximum Value of Fukui Functions (f^+_{max}, f^-_{max}) with the Respective Atomic Sites in Bracket for the Complete Series of Chlorobenzenes Calculated Using HPA Charges from the BLYP/DNP Method[a]

	f^+_{max}		f^-_{max}	
system	solvent phase	gas phase	solvent phase	gas phase
CB	0.1101 (C1/C3)	0.1608 (Cl)	0.2162 (Cl)	0.2454 (Cl)
1,2-C2B	0.1293 (Cl)	0.1533 (Cl)	0.1820 (Cl11)	0.2023 (Cl)
1,3-C2B	0.1198 (Cl)	0.1533 (Cl)	0.1853 (Cl)	0.2111 (Cl)
1,4-C2B	0.1054 (C4)	0.1416 (Cl)	0.1933 (Cl12)	0.2183 (Cl)
1,2,3-C3B	0.1345 (Cl11)	0.1465 (Cl12)	0.1592 (Cl10)	0.1778 (Cl10/Cl12)
1,2,4-C3B	0.1268 (Cl11)	0.1463 (Cl11)	0.1677 (Cl12)	0.1909 (Cl12)
1,3,5-C3B	0.1203 (Cl10/Cl12)	0.1464 (Cl)	0.1575 (Cl10/Cl11)	0.1806 (Cl)
1,2,3,4-C4B	0.1310 (Cl10/Cl11)	0.1392 (Cl10/Cl11)	0.1471 (Cl9)	0.1648 (Cl9/Cl12)
1,2,3,5-C4B	0.1256 (Cl9/Cl11)	0.1412 (Cl9/Cl11)	0.1461 (Cl10)	0.1589 (Cl10)
1,2,4,5-C4B	0.1114 (Cl)	0.1308 (Cl)	0.1449 (Cl)	0.1620 (Cl)
1,2,3,4,5-C5B	0.1285 (Cl10)	0.1349 (Cl10)	0.1306 (Cl9/Cl11)	0.1463 (Cl8/Cl12)
1,2,3,4,5,6-C6B	0.1108 (Cl9/Cl12)	0.1195 (Cl)	0.1176 (Cl10)	0.1345 (Cl)

[a] The Fukui functions (f^+ and f^-) for all atoms for the complete series of chlorobenzenes are presented in the Supporting Information.

types of FFs have been defined[14−16]

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

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

$$f^0(\vec{r}) = (\rho_{N+1}(\vec{r}) - \rho_{N-1}(\vec{r}))/2 \quad \text{for radical attack} \tag{6c}$$

Parr et al. have introduced a global electrophilicity index ω as[17]

$$\omega = \frac{\mu^2}{2\eta} \tag{7}$$

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.[18]

Recently, Chattaraj et al.[19] 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,

$$\omega_k^{\alpha} = \omega f_k^{\alpha} \tag{8}$$

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

Toro-Labbé and co-workers[20] have recently proposed a new dual descriptor ($\Delta f(r)$), which is defined as the difference between the nucleophilic and electrophilic FFs and is given by,

$$\Delta f(\mathrm{r}) = [(f^+(r) - (f^-(\mathrm{r})] \tag{9}$$

If $\Delta f(r) > 0$, then the site is favored for a nucleophilic attack, whereas if $\Delta f(r) < 0$, then the site may be favored for an electrophilic attack.

In light of the local philicity concept proposed by Chattaraj et al.[19] and a dual descriptor derived by Toro-Labbé and co-workers,[20] it is interesting to propose here a multiphilic descriptor using the global and unified philicity concept, which can concurrently characterize both the nucleophilic and electrophilic nature of a chemical species. It is defined as the difference between the nucleophilic and electrophilic condensed philicity functions. It is an index of selectivity toward nucleophilic attack, which can as well characterize an electrophilic attack and is given by,

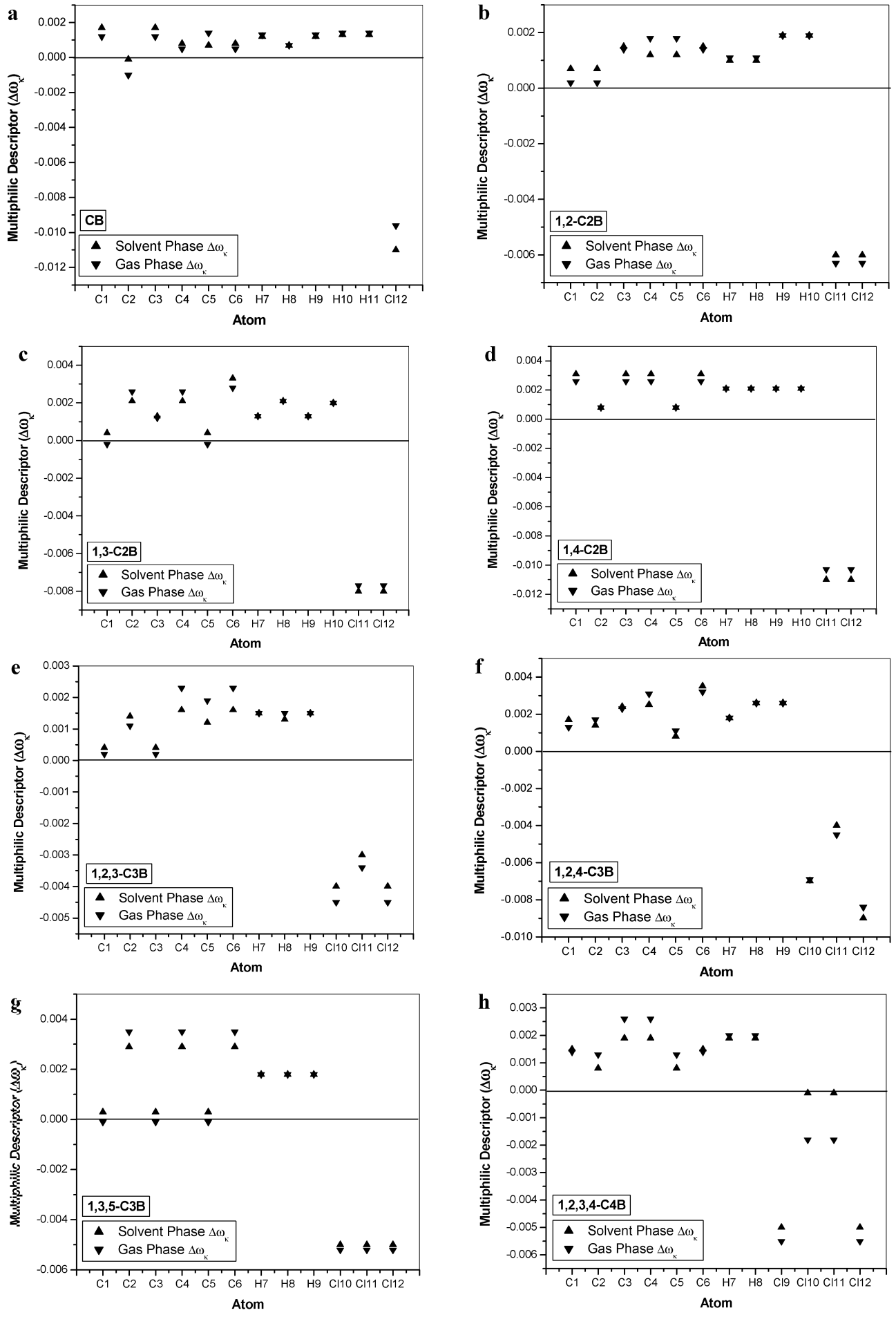
$$\Delta\omega_k = [\omega_k^{+} - \omega_k^{-}] = \omega\,[\Delta f_k] \tag{10}$$

where Δf_k is the condensed-to-atom-*k* variant of $\Delta f(r)$ (eq 9). If $\Delta\omega_k > 0$, then the site *k* is favored for a nucleophilic attack, whereas if $\Delta\omega_k < 0$, then the site *k* may be favored for an electrophilic attack. Because FFs are positive ($0 \le \Delta f_k \le 1$), $-1 \le \Delta f_k \le 1$, and the normalization condition for $\Delta\omega_k$ is

$$\sum_k \Delta\omega_k \, \mathrm{d}r = \omega \sum_k \Delta f_k \, \mathrm{d}r = 0 \tag{11}$$

Computational Details

The geometries of chlorobenzenes are initially optimized at the semiempirical level using the GAUSSIAN 98W suite of programs[21] in the gas phase followed by reoptimization at the


a
Multiphilic Descriptor ($\Delta\omega_k$)
CB
Solvent Phase $\Delta\omega_k$
Gas Phase $\Delta\omega_k$
C1 C2 C3 C4 C5 C6 H7 H8 H9 H10 H11 Cl12
Atom
b
1,2-C2B
C1 C2 C3 C4 C5 C6 H7 H8 H9 H10 Cl11 Cl12
c
1,3-C2B
d
1,4-C2B
e
1,2,3-C3B
C1 C2 C3 C4 C5 C6 H7 H8 H9 Cl10 Cl11 Cl12
f
1,2,4-C3B
g
1,3,5-C3B
h
1,2,3,4-C4B
C1 C2 C3 C4 C5 C6 H7 H8 Cl9 Cl10 Cl11 Cl12

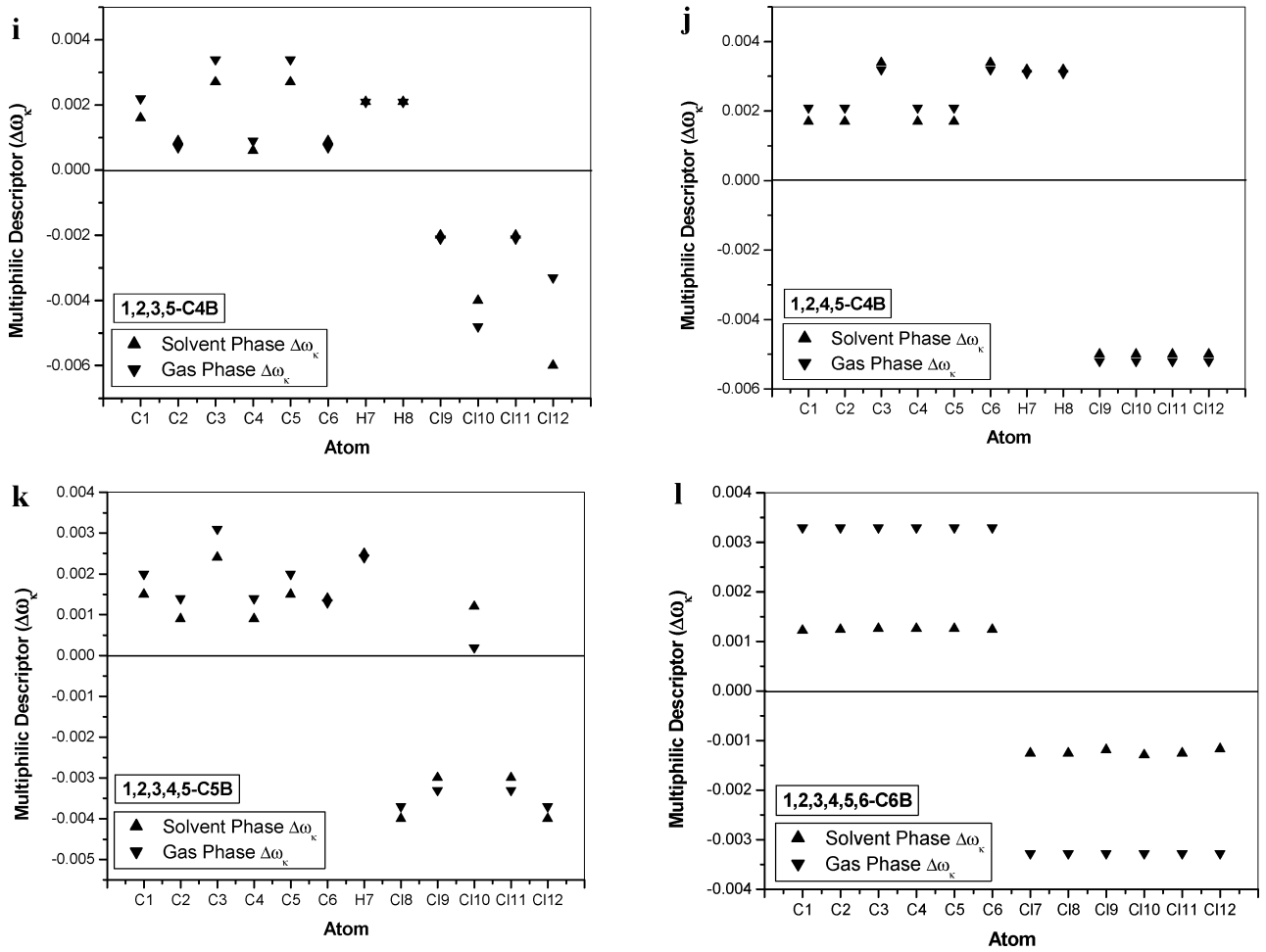


Figure 2. (a−l) Plots representing the values of the multiphilic descriptor of all atoms for the complete series of chlorobenzenes.

BLYP/DNP level using the DMOL^3 program[22] both in the gas phase and solvent media. The DNP level basis set is of double-numeric quality (i.e., there are approximately two atomic orbitals for each one occupied in the free atom) augmented with polarization functions (i.e., functions with angular momentum one higher than that of the highest occupied orbital in free atom). The structures along with atom numbering for the complete series of chlorobenzenes are presented in Figure 1. The COSMO solvation model as included in the DMOL^3 program is used to compute global and local reactivity parameters in the solvent (water) environment. The Hirshfeld[23] population scheme (Stockholder partitioning scheme) has been used to get FF values as implemented in the DMOL^3 package employing the BLYP/DNP method. The FFs (f^+ and f^-) and local philicities (ω_k^+ and ω_k^-) are calculated for all atoms of the selected systems using eq 6 and eq 8, respectively, and are provided in the Supporting Information (Tables S1−S12), and a multiphilic descriptor for all atoms of various chlorobenzenes is calculated using eq 10. One parameter QSAR[24] analysis is performed using a least-squares error estimation method [25] to calculate and compare the tadpole toxicity (12 h − log(1/LC$_{50}$))[10] of various chlorobenzenes.

Results and Discussion

Analyzing the effect of solvation on the reactivity of chlorobenzenes plays a vital role in understanding their interacting capabilities with the biological systems.

Global Reactivity of Chlorobenzenes. Table 1 lists the energy (E), hardness (η), chemical potential (μ), and electrophilicity index (ω) for the complete series of chlorobenzenes both in gas and solvent media with ΔE, $\Delta\eta$, $\Delta\mu$, and $\Delta\omega$ representing their corresponding differences between solvent- and gas-phase values. It is interesting to note from the ΔE values that all chlorobenzenes are stabilized in going from gas to solvent medium. Among the isomers of dichlorobenzene, 1,2-C2B and 1,4-C2B show a greater increase in stabilization compared to 1,3-C2B in solvent medium. Similarly, 1,2,3-C3B and 1,2,3,4-C4B show higher variations in energy and, hence, increased stability compared to their respective counterparts in moving from gas to solvent media. Also, 1,2,3,4,5-C5B and 1,2,3,4,5,6-C6B are more stabilized in solvent medium. Though such trends are not fully reflected by $\Delta\eta$, $\Delta\mu$, and $\Delta\omega$ values, they are in overall support of the fact that all chlorobenzenes display increased stabilization in solvent medium.

Local Reactivity on Chlorobenzenes. The sites with the maximum value of FFs, viz. f^+_{max}, f^-_{max}, respectively for nucleophilic attack (NAK) and electrophilic attack (EAK) both in solvent and gas phases for the complete series of chlorobenzenes, are presented in Table 2. For CB, the Cl site is prone to NAK in the gas phase and C1/C3 is favored in solvent medium compared to all other sites whereas EAK is favored only at Cl sites. It is quite interesting to note that in all the remaining chlorobenzenes, only chlorine sites are highly prone to both NAK and EAK, with the exception of the C4 site in 1,4-C2B, which is more prone to NAK in solvent medium. Also, from the magnitude of FF values, EAK is more favored at Cl sites compared to NAK both in gas and solvent media. Further, there is a decrease in the attacking nature at the respective Cl sites in

moving from gas to solvent medium for both EAK and NAK. To have a closer look at the nature of attack at different atomic sites in a molecule using a single descriptor, we have proposed a multiphilic descriptor in the following section that can describe NAK and possibly EAK simultaneously.

Multiphilic Descriptor on Chlorobenzenes. The multiphilic descriptor ($\Delta\omega_k$) of all atoms for the complete series of chlorobenzenes both in gas and in solvent media is presented (Figure 2a−l). For CB, the Cl12 site is more prone to EAK, and all other sites except for the C2 site show preference toward NAK both in gas and solvent media. From the magnitude of $\Delta\omega_k$, it is seen that EAK at the Cl12 site of CB is increased in solvent medium. In the case of dichlorobenzenes, EAK is possible mostly at chlorine sites (Figure 2b−d) and they have a greater chance of NAK at C sites than H sites in both media. Also, the Cl site shows an increased preference toward EAK in solvent medium for all dichlorobenzenes except for the 1,2-C2B, where it shows a decrease. It is interesting to note that the C1 and C5 sites of 1,3-C2B change their preference from EAK to NAK marginally in solvent medium. On looking at C3B's (Figure 2e−g), it is clear that Cl sites are prone to EAK and most other sites toward NAK, with a few exceptions. There is a decrease in EAK at most of the Cl sites in solvent medium.

In case of C4B's (Figure 2h−j), again Cl sites are prone to EAK and all other sites toward NAK. With the exception of the Cl12 site in 1,2,3,5-C4B, other Cl sites in all C4B's show a decrease in fondness toward EAK in solvent medium. Further, in C5B's (Figure 2k), all Cl sites except for the Cl10 site have a liking for an EAK, whereas all other sites are vulnerable toward NAK. In hexachlorobenzene (Figure 2l), Cl (C) sites are prone to EAK (NAK), and the magnitude of their susceptibility toward EAK (NAK) decreases in solvent medium.

Structure−Toxicity Analysis on Chlorobenzenes. The quantitative structure−toxicity relationship (QSTR) for the selected set of six chlorobenzenes against *Rana japonica* tadpoles is analyzed. Table 5 lists the experimental[10] and calculated tadpole toxicity data (12 h − $\log(1/LC_{50})$) for the selected set of six chlorobenzenes. Considering the experimental toxicity data (12 h − $\log(1/LC_{50})$) as a dependent variable and DFT-based global descriptor, namely electrophilicity index (ω) obtained from the BLYP/DNP method as independent variable, linear regression analyses are carried out for both solvent and gas phase-derived data (ω) separately, and the regression equations are given by

$$12\text{ h} - \log(1/LC_{50}) = -2.298 + 50.365^*\omega \quad \text{Solvent phase}$$

$$N = 6,\ r^2 = 0.951,\ r^2_{CV} = 0.901,\ SD = 0.121 \qquad (12)$$

and

$$12\text{ h} - \log(1/LC_{50}) = -1.144 + 37.756^*\omega \quad \text{Gas phase}$$

$$N = 6,\ r^2 = 0.926,\ r^2_{CV} = 0.857,\ SD = 0.150 \qquad (13)$$

A selected descriptor is capable of explaining a 95.1% (92.6%) variation in data with a leave one out cross-validated squared correlation coefficient (r_{cv}^2) of 0.901 (0.857) and root-mean-square error (SD) of 0.121 (0.150) in the solvent (gas) phase. A plot between the experimental and calculated toxicity values (Figure 3a,b) provides a correlation coefficient (r) of 0.975 (0.962). This reveals the fact that the electrophilicity index can be effectively used as a descriptor in the prediction of aquatic toxicity. It is also interesting to note that solvent-derived ω provides a marginally better correlation with toxicity than gas phase-derived ω. Further, the developed regression model is utilized to predict the toxicity of the remaining CB's whose experimental toxicity data are not available and are presented in italics (Table 3).

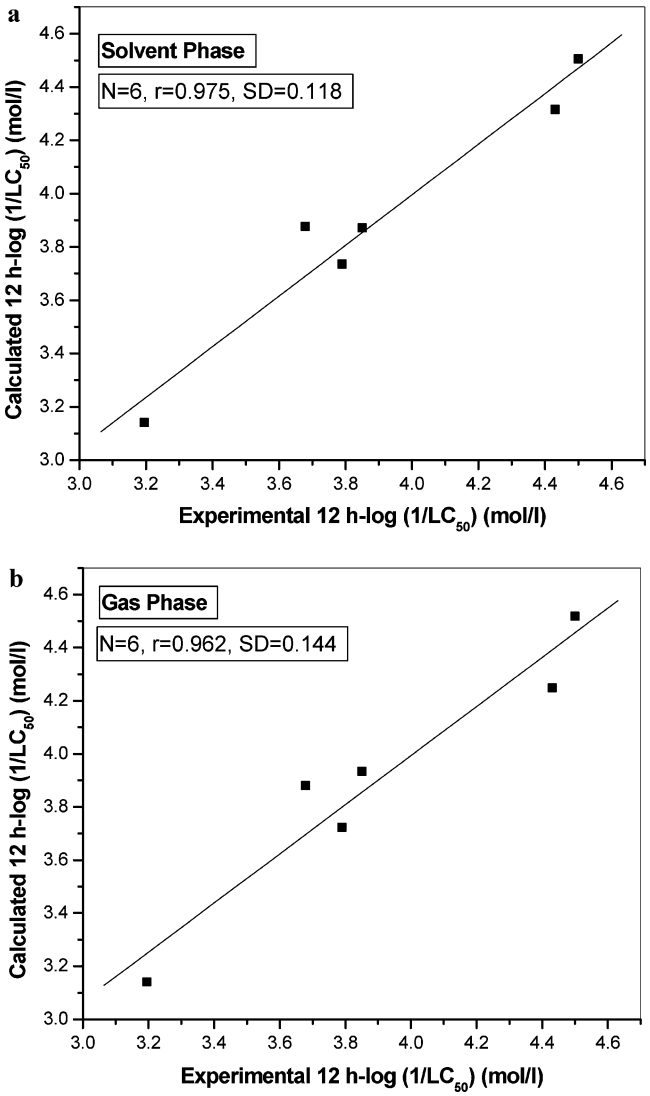


Figure 3. Plots between experimental and calculated values of toxicity (12 h − $\log(1/LC_{50})$) in (a) solvent phase and (b) gas phase for the selected set of chlorobenzenes against *Rana japonica* tadpoles.

Conclusions

A systematic investigation has been made to study the effect of solvation on global and local reactivity descriptors for the complete series of chlorobenzenes. It is seen from global descriptors that all chlorobenzenes are stabilized in solvent medium compared to gas phase. Using Fukui functions, sites that are prone to nucleophilic and electrophilic attacks are analyzed. The proposed multiphilic descriptor is capable of successfully identifying the possible nature of attack at each atomic site in all chlorobenzenes, both in solvent and gas phases. A structure−toxicity study has been carried out with existing experimental tadpole toxicity of chlorobenzenes as a dependent variable and their electrophilicity index as an independent variable. Results revealed that the electrophilicity index could be effectively used as a descriptor in explaining the toxicity of chlorobenzenes. It is also interesting to note that solvent-derived ω provides a better correlation with toxicity than gas phase-derived ω. Due to the success of the developed regression

TABLE 3: Experimental and Calculated Toxicity (12 h − log(1/LC_{50})) Values of the Chlorobenzenes against *Rana japonica* Tadpoles from the BLYP/DNP Method

		calculated 12 h − log(1/LC_{50}) (mol/L)	
system	experimental 12 h − log(1/LC_{50})[a] (mol/L)	solvent phase[b]	gas phase[c]
CB	3.195	3.141	3.141
1,2-C2B	3.790	3.736	3.723
1,3-C2B	3.679	3.877	3.881
1,4-C2B	3.850	3.872	3.934
1,2,3-C3B	4.431	4.315	4.248
1,2,4-C3B	4.500	4.506	4.519
1,3,5-C3B	−	*4.577*	*4.546*
1,2,3,4-C4B	−	*4.970*	*4.878*
1,2,3,5-C4B	−	*5.131*	*5.052*
1,2,4,5-C4B	−	*5.186*	*5.157*
1,2,3,4,5-C5B	−	*5.655*	*5.482*
1,2,3,4,5,6-C6B	−	*6.889*	*6.494*

[a] Taken from ref 10. [b] Calculated using ω as a descriptor in solvent phase; the predicted values for the missing compounds are in italics. [c] Calculated using ω as a descriptor in gas phase; the predicted values for the missing compounds are in italics.

model, it is utilized to predict the toxicity of the remaining CB's whose experimental toxicity data are not available.

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Supporting Information Available: Tables S1−S12 contain the Fukui functions (f^+ and f^-) and local philicities (ω_k^+ and ω_k^-) for all chlorobenzenes using HPA charges from BLYP/DNP calculations both in solvent and gas phases.

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