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## Comparison of Global Reactivity Descriptors Calculated Using Various Density Functionals: A QSAR Perspective

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**Abstract:** Conceptual density functional theory (DFT) based global reactivity descriptors are used to understand the relationship between structure, stability, and global chemical reactivity. Furthermore, these descriptors are employed in the development of quantitative structure–activity (QSAR), structure–property (QSPR), and structure–toxicity (QSTR) relationships. However, the predictive power of various relationships depends on the reliable estimates of these descriptors. The basic working equations used to calculate these descriptors contain both the ionization potential and the electron affinity of chosen molecules. Therefore, efficiency of different density functionals (DFs) in predicting the ionization potential and the electron affinity has to be systematically evaluated. With a view to benchmark the method of calculation of global reactivity descriptors, comprehensive calculations have been carried out on a series of chlorinated benzenes using a variety of density functionals employing different basis sets. In addition, to assess the utility of global reactivity descriptors, the relationships between the reactivity–electrophilicity and the structure–toxicity have been developed. The ionization potential and the electron affinity values obtained from M05-2X method using the  $\Delta$ SCF approach are closer to the corresponding experimental values. This method reliably predicts these electronic properties when compared to the other DFT methods. The analysis of a series of QSTR equations reveals that computationally economic DFT functionals can be effectively and routinely applied in the development of QSAR/QSPR/QSTR.

### Introduction

The conceptual DFT based global reactivity and the local reactivity descriptors are useful quantities to understand the global reactivity and the local site selectivity, respectively. Reliable calculation of global reactivity descriptors is important in conceptual DFT, as these values are used as input for understanding the relationships between structure, stability, and reactivity as well as for QSAR/QSPR/QSTR development.<sup>1,2</sup> The working equations used to calculate the various global reactivity descriptors involve the ionization potential and the electron affinity of selected molecules.

Computationally, the ionization potential and the electron affinity are calculated from total electronic energy calculations on the  $N - 1$ ,  $N$ , and  $N + 1$  electron systems at the neutral geometry. This method is referred to as “delta SCF” or “ $\Delta$ SCF” method. Since, this approach is computationally demanding, these quantities are also calculated using Koopmans’ approximation.<sup>3</sup> However, this approximation is suitable for molecules with positive electron affinity but is less appropriate for systems with negative electron affinity. De Proft et al. have addressed this issue, and various new working relations have been proposed to compute absolute hardness from the ionization potential and the electron affinity.<sup>4,5</sup>

Both conventional ab initio wave function theory<sup>6</sup> and Kohn–Sham DFT methods<sup>7</sup> have been employed to predict the ionization potential and the electron affinity and, thus,

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**Table 1.** List of Different DFT Methods Evaluated in This Study

functional	type	percentage of Hartree–Fock exchange	exchange/correlation functional	ref
SVWN5	LSDA	0	Slater's local ex/VWN no.5	41–43
BLYP	GGA	0	Becke88/Lee–Yang–Parr	44, 45
B3LYP	HGGA	20	Becke88/Lee–Yang–Parr	44–46
MPWB1K	HMGGA	44	modified PW91/Becke95	15, 47, 48
BB1K	HMGGA	42	Becke88/Becke95	16, 44, 47
MPW1B95	HMGGA	31	modified PW91/Becke95	15, 47, 48
MO5	HMGGA	28	self-correlation-free	17
MO5-2X	HMGGA	56	self-correlation-free	18

global reactivity descriptors. Prediction of these electronic properties using wave function theory and DFT approaches has several limitations.<sup>8,9</sup> In this context, DFT methods have been shown to be more efficient than conventional ab initio methods due to their excellent cost-to-performance ratio.<sup>10,11</sup> The most popular hybrid DFT based B3LYP methods have been employed in several studies to predict the global and local reactivity descriptors.<sup>12</sup>

Numerous studies have been carried out to develop new exchange and correlation functionals to enhance the quality of prediction and expand the applicability of DFT methods.<sup>7,13</sup> Scuseria and Staroverov have reviewed the various strategies used to refine functionals for DFT.<sup>14</sup> Truhlar and co-workers have made seminal contributions to the development and refinement of functionals with wide applicability in chemistry using diverse set of training and test sets.<sup>8,10,11,13,15–18</sup> In general, two different approaches have been used for the development of new functionals, viz, nonempirical, and semiempirical. A nonempirical approach leads to the development of ab initio DFT (or pure DFT) in which functionals are constructed from the first principles with exact constraints. In the semiempirical DFT approach, the new functionals depend on the one or more parameters which are obtained from fitting to different sets of experimental data. The following strategies have been applied to design and develop different new density functionals: (i) local spin density approximation (LSDA), (ii) generalized gradient approximation (GGA), (iii) constraint satisfaction, (iv) modeling exchange–correlation hole, (v) empirical fits, and (vi) mixing Hartree–Fock and approximate DFT exchanges.

Different functionals used in the literature are referred to as various rungs of “Jacob’s ladder”.<sup>19,20</sup> They are classified on the basis of the number and the types of the constituents used in the functionals. The lowest rung is the LSDA in which the density functional depends only on density, and the second rung is the GGA in which the density functional depends on density and its reduced gradient. The third rung is meta GGA in which the functional also depends on kinetic energy density. The fourth rung is hybrid GGA, which employs some percentage of HF exchange. There are two kinds of DFT methods that fit into the fourth rung of the Jacob’s ladder, and they are called hybrid GGA (a combination of GGA with Hartree–Fock exchange). The typical examples are B3LYP, PBE0, and MPW1K. The other type is hybrid meta GGA (a combination of meta GGA with Hartree–Fock exchange). The MPWB1K, MPW1B95, and TPSSH functionals belong to this category. Both hybrid GGA and hybrid meta GGA are semiempirical, and they have been

very successful in chemistry. Recently, new density functionals have been developed by combining the method of constraint satisfaction with parametrization for thermochemistry, thermochemical kinetics, and noncovalent interactions.<sup>18</sup> These functionals are denoted as M05 and M05-2X. Subsequently, the same authors have developed M06, M06-2X, M06-HF, and M06-2L using large energetic databases. Since several functionals have been developed in the last five years, it is necessary to analyze the performance of various categories of DFT methods to predict the global reactivity descriptors. In this context, the DFT method which reliably predicts the ionization potential and the electron affinity is necessary. Hence, we have selected functionals from different categories. The selected functionals are presented in Table 1. Various basis sets such as 6-31G\*, 6-31G\*\*, 6-31+G\*, 6-31+G\*\*, 6-31++G\*\*, 6-311++G\*\*, aug-CC-PVDZ, and aug-CC-PVTZ have been chosen in this study. To explore the performance of various new functionals, the calculated ionization potential and electron affinity values have been compared with available experimental values. To benchmark the appropriate method for the calculation of global reactivity descriptors from QSAR/QSPR/QSTR perspectives, a series of chlorine-substituted benzenes have been considered as model systems, and QSTR has been developed for fish toxicities of these compounds against *Poecilia reticulata*.<sup>21</sup>

**Theoretical Background.** The chemical potential ( $\mu$ ) and chemical hardness ( $\eta$ ) are defined within DFT as the first- and second-order derivatives, respectively, of the Kohn–Sham (KS) energy to the number of particles at constant potential  $\nu(\vec{r})$ .<sup>3,22–24</sup>

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

$$\eta = (\partial^2 E / \partial N^2)_{\nu(\vec{r})} = (\partial \mu / \partial N)_{\nu(\vec{r})} \quad (2)$$

where  $E$  and  $N$  are the total energy and the number of electrons in the system, respectively, and  $\nu(\vec{r})$  is the external potential. The global hardness is an indicator of the overall stability of the system. A maximum hardness principle (MHP) relating hardness to stability at a constant chemical potential has been proposed by Pearson.<sup>3,22,25</sup> The proof of the same has been provided by Parr and Chattaraj.<sup>26–29</sup> The chemical potential,  $\mu$ , is identified as the negative of the electronegativity ( $\chi$ ) by Iczkowski and Margrave.<sup>30</sup> Although, these quantities have been defined based on the KS energy, the same definitions have been routinely used in the canonical molecular orbital theory. The most popularly used formulas for the computation of these quantities use the three point finite difference approximation

and express  $\mu$  and  $\eta$  through the ionization potential ( $I$ ) and the electron affinity ( $A$ ).

$$\mu = -\chi = -\frac{1}{2}(I + A) \quad (3)$$

$$\eta = (I - A) \quad (4)$$

Ionization potential and electron affinity can be calculated using  $\Delta$ SCF method using the formulas given below:

$$I \approx E(N - 1) - E(N) \quad (5)$$

$$A \approx E(N) - E(N + 1) \quad (6)$$

where  $I$  and  $A$  are obtained from total electronic energy calculations on the  $N - 1$ ,  $N$ , and  $N + 1$  electron systems at the neutral geometry. Another DFT approximation originating from the Koopmans' theorem<sup>3</sup> is

$$I \approx -\varepsilon_{\text{HOMO}}, A \approx -\varepsilon_{\text{LUMO}} \quad (7)$$

where  $\varepsilon_{\text{HOMO}}$  and  $\varepsilon_{\text{LUMO}}$  are the KS one electron eigenvalues associated with the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), respectively, from approximate DFT calculations on neutral molecules. These approximations have also been widely used in the canonical molecular orbital theory. Various problems in the calculation of  $\mu$  and  $\eta$  have been highlighted in a recent study.<sup>4</sup> Other methods of calculation of global hardness have been reported in the literature.<sup>4,31–33</sup> Compact finite difference schemes with spectral-like resolution have been used to calculate hardness as second derivatives of energy with respect to the electron number.<sup>31</sup> An algorithm for computation of density functional based orbital reactivity indices, such as orbitally resolved hardness and softness tensors, and total hardness, and the Fukui functions have been extended to degenerate electronic states.<sup>32</sup> Recently, Tozer and De Proft have described the problems associated with the calculation of absolute hardness.<sup>4</sup> A simple correction to the Koopmans' expression is highlighted on the basis of a consideration of integer discontinuity. The resulting expression does not require the explicit computation of the electron affinity. The alternative expression for the hardness provided by Tozer and De Proft is

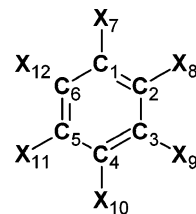
$$\eta = \frac{\varepsilon_{\text{LUMO}} - \varepsilon_{\text{HOMO}}}{2} + \varepsilon_{\text{HOMO}} + I \quad (8)$$

where  $I = I_0$  is the experimental ionization potential. It can be further written as

$$\eta = \frac{\varepsilon_{\text{LUMO}} + \varepsilon_{\text{HOMO}}}{2} + I \quad (9)$$

Although there has not been a rigorous definition, the concept of electrophilicity has been known for several decades. In 1999, Parr et al. proposed a rigorous definition based on the energy lowering associated with a maximum amount of electron flow between two species.<sup>34</sup> It is defined as

$$\omega = \frac{\mu^2}{2\eta} \quad (10)$$



**X = H or Cl**

**Figure 1.** Chlorobenzene template structure with atom numbering.

Subsequently, a number of studies have been made to understand the global reactivity and site selectivity of systems using this new index. A detailed account on various aspects of this new electrohilicity index has been summarized in a recent review and update.<sup>35</sup>

**Computational Details.** The geometries of the benzene and 12 chlorine-substituted benzenes are optimized using various DFT methods listed in Table 1 with 6-31G\*, 6-31G\*\*, 6-31+G\*, 6-31+G\*\*, 6-31++G\*\*, 6-311++G\*\*, aug-CC-PVDZ, and aug-CC-PVTZ basis sets. The harmonic vibrational frequencies are calculated for all the geometries, which confirm that the obtained structures are minima on the potential energy surface. The global electronic properties are calculated using the eqs 3, 4, and 10. Both the ionization potential and electron affinity values are calculated using  $\Delta$ SCF procedure (eqs 5 and 6) and Koopmans' theorem (eq 7). With a view to assess how various reactivity indices evolve, the global reactivity descriptors computed from different schemes are also compared with Tozer and De Proft's expression for  $\eta$  (eq 8). All calculations are carried out using Gaussian 03 suite of programs.<sup>36</sup>

## Results and Discussion

Various chlorinated benzenes (CBs) selected in this study are schematically represented in Figure 1 along with the atom numbering. Since, the objective of the present investigation is to explore efficiencies of various DFs, a systematic analysis has been carried out on the structure, the energy, and the electronic properties of chlorobenzenes.

**Energetics and Structural Details of Chlorobenzenes.** It is well-known that the sterical interaction between any two adjacent chlorine atoms in substituted benzenes decreases the stability of the respective isomers. As a consequence, the lowest stability can be expected for the CBs with chlorine at ortho and meta positions. The calculated total energies, the thermodynamic quantities (enthalpy and free energy), and the relative energies using various methods with 6-31++G\*\* basis set for all chlorobenzenes along with benzene are presented in Tables 2–4. The stability of a conformer with a given number of chlorine atoms is determined by its relative energy ( $\Delta E$ ) with respect to the most stable isomer. For dichlorobenzenes, all the chosen methods predict the para isomer (1,4-C2B) of dichlorobenzene as the most stable isomer, except in the SVWN5 method. It can be found that SVWN5 method predicts 1,3-C2B as the most stable isomer (Table 2). This discrepancy may be attributed to the problems in the treatment of exchange and correlation interactions

**Table 2.** Calculated Energies  $E$  (Hartree) and Relative Energy ( $\Delta E$ , kcal/mol) with respect to the Most Stable Isomer with a Given Number of Chlorine Atoms using 6-31++G\*\* Basis Set

system	B3LYP		MPW1B95		MPWB1K		BB1K		SVWN5		BLYP		M05		M05-2X	
	$E$	$\Delta E$	$E$	$\Delta E$	$E$	$\Delta E$	$E$	$\Delta E$	$E$	$\Delta E$	$E$	$\Delta E$	$E$	$\Delta E$	$E$	$\Delta E$
CB	-691.86		-691.82		-691.82		-691.81		-689.37		-691.74		-691.68		-691.81	
1,2-C2B	-1151.45	2.44	-1151.47	1.85	-1151.47	1.85	-1151.45	1.95	-1147.82	1.31	-1151.32	2.47	-1151.28	2.24	-1151.38	1.94
1,3-C2B	-1151.46	0.05	-1151.47	0.01	-1151.47	0.00	-1151.46	0.01	-1147.83	0.00	-1151.32	0.01	-1151.28	0.06	-1151.38	0.08
1,4-C2B	-1151.46	0.00	-1151.47	0.00	-1151.47	0.00	-1151.46	0.00	-1147.83	0.02	-1151.32	0.00	-1151.28	0.00	-1151.38	0.00
1,2,3-C3B	-1611.04	4.74	-1611.12	3.74	-1611.12	3.64	-1611.09	3.96	-1606.27	2.44	-1610.89	4.86	-1610.88	4.21	-1610.95	3.65
1,2,4-C3B	-1611.04	2.14	-1611.12	1.73	-1611.12	1.64	-1611.09	1.83	-1606.27	1.13	-1610.90	2.22	-1610.88	1.89	-1610.95	1.63
1,3,5-C3B	-1611.05	0.00	-1611.12	0.00	-1611.12	0.00	-1611.10	0.00	-1606.28	0.00	-1610.90	0.00	-1610.88	0.00	-1610.95	0.00
1,2,3,4-C4B	-2070.63	2.82	-2070.76	2.13	-2070.76	2.15	-2070.73	2.27	-2064.72	1.33	-2070.47	2.86	-2070.48	2.52	-2070.51	2.10
1,2,3,5-C4B	-2070.63	0.40	-2070.77	0.33	-2070.77	0.34	-2070.73	0.36	-2064.72	0.19	-2070.47	0.36	-2070.48	0.30	-2070.52	0.30
1,2,4,5-C4B	-2070.63	0.00	-2070.77	0.00	-2070.77	0.00	-2070.73	0.00	-2064.72	0.00	-2070.48	0.00	-2070.48	0.00	-2070.52	0.00
1,2,3,4,5-C5B	-2530.21		-2530.41		-2530.41		-2530.37		-2523.17		-2530.05		-2530.07		-2530.08	
1,2,3,4,5,6-C6B	-2989.79		-2990.05		-2990.05		-2990.00		-2989.61		-2989.62		-2989.67		-2989.64	
benzene	-232.27		-232.17		-232.16		-232.17		-230.92		-232.15		-232.07		-232.23	

**Table 3.** Enthalpies  $H$  (Hartree) and Free Energies  $G$  (Hartree) Calculated from B3LYP, MPW1B95, MPWB1K, and BB1K Methods with 6-31++G\*\* Basis Set<sup>a</sup>

system	B3LYP				MPW1B95				MPWB1K				BB1K			
	$H$	$\Delta H$	$G$	$\Delta G$	$H$	$\Delta H$	$G$	$\Delta G$	$H$	$\Delta H$	$G$	$\Delta G$	$H$	$\Delta H$	$G$	$\Delta G$
CB	-691.77		-691.80		-691.72		-691.76		-691.72		-691.76		-691.72		-691.75	
1,2-C2B	-1151.36	2.45	-1151.40	2.55	-1151.38	1.91	-1151.42	1.96	-1151.38	1.91	-1151.42	1.80	-1151.36	2.00	-1151.41	1.93
1,3-C2B	-1151.37	0.04	-1151.41	0.04	-1151.38	0.00	-1151.42	0.00	-1151.38	0.00	-1151.42	0.00	-1151.37	0.00	-1151.41	0.00
1,4-C2B	-1151.37	0.00	-1151.41	0.00	-1151.38	0.02	-1151.42	0.09	-1151.38	0.03	-1151.42	0.15	-1151.37	0.02	-1151.41	0.13
1,2,3-C3B	-1610.96	4.82	-1611.00	5.03	-1611.04	3.80	-1611.08	4.07	-1611.04	3.79	-1611.08	4.05	-1611.01	4.03	-1611.05	4.27
1,2,4-C3B	-1610.96	2.19	-1611.01	2.28	-1611.04	1.73	-1611.08	1.76	-1611.04	1.72	-1611.08	1.60	-1611.01	1.84	-1611.06	1.73
1,3,5-C3B	-1610.97	0.00	-1611.01	0.00	-1611.04	0.00	-1611.09	0.00	-1611.04	0.00	-1611.09	0.00	-1611.02	0.00	-1611.06	0.00
1,2,3,4-C4B	-2070.55	2.75	-2070.60	2.87	-2070.69	2.08	-2070.74	2.13	-2070.69	2.10	-2070.74	2.09	-2070.66	2.22	-2070.70	2.22
1,2,3,5-C4B	-2070.56	0.37	-2070.60	0.41	-2070.70	0.32	-2070.74	0.34	-2070.69	0.34	-2070.74	0.36	-2070.66	0.35	-2070.71	0.38
1,2,4,5-C4B	-2070.56	0.00	-2070.61	0.00	-2070.70	0.00	-2070.74	0.00	-2070.69	0.00	-2070.74	0.00	-2070.66	0.00	-2070.71	0.00
1,2,3,4,5-C5B	-2530.15		-2530.20		-2530.35		-2530.40		-2530.35		-2530.40		-2530.30		-2530.35	
1,2,3,4,5,6-C6B	-2989.74		-2989.79		-2990.00		-2990.05		-2990.00		-2990.05		-2989.94		-2990.00	
benzene	-232.16		-232.20		-232.06		-232.09		-232.06		-232.09		-232.06		-232.10	

<sup>a</sup> The relative energies of  $\Delta H$  and  $\Delta G$  (in kcal/mol) are with respect to the stable isomer of given number of chlorine atoms.

when compared to other functionals. In fact, it can be noted that the Hartree–Fock exchange in SVWN5 and BLYP is zero. However, BLYP predicts the trend which is similar to that of other functionals and is discussed in the subsequent section. Hence, the inherent features of Slater's exchange and the VWN's correlation functionals may be responsible for the incorrect experimental trend. Further, the results clearly show that an intricate balance between the exchange and correlation terms is necessary for the appropriate prediction of the structure.

The calculated energy difference between the para and the ortho isomers from MPW1B95, MPWB1K, BB1K, and M05-2X methods are similar. It ranges from 1.85 to 1.95 kcal/mol. When compared to these methods, B3LYP, BLYP, and M05 methods predict marginally higher energy differences of 2.24 to 2.47 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 predicted energy difference between the isomers of tri- and tetrachlorobenzenes follows the same trend as that observed for dichlorobenzenes. It has been found from the above analysis that the MPW1B95, MPWB1K, BB1K, and M05-2X methods predict similar trends, whereas B3LYP, BLYP, and M05 methods show similar trends, which is different from the former. The SVWN5 predicted energy does not show any agreement with the other chosen methods. The

thermodynamic quantities, such as enthalpy and free energy, as well as their relative values are shown in Tables 3–4. The trends observed in the  $\Delta H$  and  $\Delta G$  calculations are more or less parallel to that of  $\Delta E$ .

Tables S1–S2 shown in the Supporting Information provides the details of both the calculated bond lengths and angles using various methods with 6-31++G\*\* basis set along with the experimental values for comparison.<sup>37,38</sup> It is evident from the tables that the calculated geometrical properties are in good agreement with the experimental values. It can be found from the Supporting Information (Table S1) that chlorine substitution in the  $C_1$  reduces the bond length of the  $C_1$ – $C_2$  and  $C_1$ – $C_6$  to 0.002 Å, which is observed in all the methods. The bond lengths predicted by the M05 and M05-2X methods are closer to the experimental values when compared to the other methods. The BLYP method slightly overestimates the bond distances.

**Ionization Potential and Electron Affinity.** The ionization potentials and the electron affinities calculated from various methods using 6-31++G\*\* basis set employing Koopmans' theorem are shown in Table 5, and the results obtained from the remaining basis functions are shown in Supporting Information (Tables S3–S8). The experimental ionization potentials and the electron affinities of CBs obtained from the NIST standard reference database are also presented in the same table. It can be found that all selected



**Table 4.** Enthalpies  $H$  (Hartree) and Free Energies  $G$  (Hartree) Calculated from SVWN5, BLYP, M05, and M05-2X Methods with 6-31++G\*\* Basis Set<sup>a</sup>

system	SVWN5				BLYP				M05				M05-2X			
	$H$	$\Delta H$	$G$	$\Delta G$	$H$	$\Delta H$	$G$	$\Delta G$	$H$	$\Delta H$	$G$	$\Delta G$	$H$	$\Delta H$	$G$	$\Delta G$
CB	-689.28		-689.31		-691.64		-691.68		-691.58		-691.62		-691.71		-691.75	
1,2-C2B	-1147.74	1.39	-1147.78	1.51	-1151.23	2.50	-1151.27	2.60	-1151.19	2.29	-1151.23	2.45	-1151.29	1.96	-1151.33	2.03
1,3-C2B	-1147.74	0.00	-1147.78	0.00	-1151.23	0.00	-1151.27	0.00	-1151.19	0.08	-1151.23	0.16	-1151.29	0.01	-1151.33	0.00
1,4-C2B	-1147.74	0.02	-1147.78	0.02	-1151.23	0.01	-1151.27	0.01	-1151.19	0.00	-1151.23	0.00	-1151.29	0.00	-1151.33	0.01
1,2,3-C3B	-1606.19	2.64	-1606.24	2.88	-1610.82	4.95	-1610.86	5.17	-1610.80	4.35	-1610.84	4.67	-1610.87	3.69	-1610.91	3.75
1,2,4-C3B	-1606.19	1.22	-1606.24	1.32	-1610.82	2.27	-1610.86	2.36	-1610.80	1.97	-1610.84	2.12	-1610.87	1.67	-1610.91	1.70
1,3,5-C3B	-1606.20	0.00	-1606.24	0.00	-1610.82	0.00	-1610.87	0.00	-1610.80	0.00	-1610.85	0.00	-1610.87	0.00	-1610.91	0.00
1,2,3,4-C4B	-2064.65	1.30	-2064.69	1.42	-2070.40	2.78	-2070.45	2.89	-2070.40	2.51	-2070.45	2.69	-2070.44	2.08	-2070.49	2.30
1,2,3,5-C4B	-2064.65	0.18	-2064.70	0.22	-2070.40	0.34	-2070.45	0.37	-2070.41	0.34	-2070.45	0.50	-2070.44	0.25	-2070.49	0.39
1,2,4,5-C4B	-2064.65	0.00	-2064.70	0.00	-2070.41	0.00	-2070.45	0.00	-2070.41	0.00	-2070.45	0.00	-2070.44	0.00	-2070.49	0.00
1,2,3,4,5-C5B	-2523.10		-2523.15		-2529.98		-2530.03		-2530.01		-2530.06		-2530.02		-2530.07	
1,2,3,4,5,6-C6B	-2981.56		-2981.61		-2989.56		-2989.62		-2989.61		-2989.66		-2989.59		-2989.64	
benzene	-230.82		-230.85		-232.05		-232.08		-231.97		-232.00		-232.13		-232.16	

<sup>a</sup> The relative energies of  $\Delta H$  and  $\Delta G$  (in kcal/mol) are with respect to the stable isomer of given number of chlorine atoms.**Table 5.** Ionization Potential ( $I$ ) and Electron Affinity ( $A$ ) of Chlorinated Benzenes in eV Calculated from Various Methods with 6-31++G\*\* Basis Set using Koopmans' Theorem

system	expt <sup>a</sup>		B3LYP		MPWB1K		MPW1B95		BB1K		SVWM		BLYP		M05		M05-2X	
	$I$	$A$	$I$	$A$	$I$	$A$	$I$	$A$	$I$	$A$	$I$	$A$	$I$	$A$	$I$	$A$	$I$	$A$
CB	9.07 ± 0.02	— <sup>c</sup>	6.95	0.80	6.02	1.40	6.02	1.43	5.98	1.35	6.76	2.13	5.97	1.41	7.15	0.49	8.34	-0.32
1,2-C2B	9.06 ± 0.02	0.093	7.07	1.08	6.08	1.64	6.09	1.67	6.04	1.59	6.82	2.37	6.07	1.67	7.23	0.78	8.44	-0.03
1,3-C2B	9.10 ± 0.02	— <sup>c</sup>	7.13	1.13	6.16	1.70	6.17	1.73	6.12	1.64	6.90	2.43	6.15	1.73	7.32	0.83	8.51	0.03
1,4-C2B	8.92 ± 0.03	— <sup>c</sup>	6.95	1.16	5.96	1.74	5.97	1.77	5.92	1.68	6.70	2.47	5.97	1.76	7.12	0.84	8.31	0.05
1,2,3-C3B	9.18 ± 0.03	— <sup>c</sup>	7.29	1.30	6.29	1.82	6.29	1.85	6.25	1.77	7.02	2.55	6.29	1.87	7.46	1.03	8.68	0.21
1,2,4-C3B	9.04 ± 0.03	— <sup>c</sup>	7.11	1.40	6.09	1.94	6.10	1.97	6.05	1.89	6.83	2.68	6.12	1.98	7.27	1.10	8.46	0.31
1,3,5-C3B	9.30 ± 0.06	0.34	7.43	1.39	6.42	1.92	6.43	1.96	6.39	1.87	7.17	2.66	6.42	1.97	7.62	1.12	8.84	0.32
1,2,3,4-C4B	8.9	— <sup>c</sup>	7.23	1.52	6.18	2.02	6.20	2.06	6.15	1.97	6.93	2.77	6.23	2.11	7.37	1.24	8.58	0.45
1,2,3,5-C4B	9.02	— <sup>c</sup>	7.29	1.60	6.24	2.10	6.26	2.14	6.21	2.05	6.98	2.84	6.29	2.16	7.44	1.33	8.65	0.54
1,2,4,5-C4B	9	0.45	7.19	1.64	6.14	2.15	6.16	2.18	6.11	2.10	6.88	2.89	6.20	2.20	7.33	1.35	8.53	0.58
1,2,3,4,5-C5B	8.8	0.729	7.32	1.75	6.26	2.21	6.27	2.25	6.22	2.17	7.00	2.96	6.32	2.45	7.46	1.48	8.67	0.70
1,2,3,4,5,6-C6B	9.0 ± 0.1	0.92 ± 0.10	7.45	2.00	6.36	2.46	6.38	2.53	6.33	2.41	7.11	3.16	6.44	2.80	7.58	1.61	8.81	0.82
benzene	9.24	-1.12 ± 0.03 <sup>b</sup>	7.01	0.42	6.19	1.05	6.18	1.07	6.15	0.99	6.94	1.77	6.04	1.04	7.26	0.11	8.43	-0.72

<sup>a</sup> The experimental  $I$  and  $A$  were obtained from NIST standard reference database webbook <http://webbook.nist.gov/chemistry>. <sup>b</sup> Ref 47.<sup>c</sup> Not listed in NIST database.**Table 6.** Ionization Potential ( $I$ ) and Electron Affinity ( $A$ ) in eV Calculated using  $\Delta$ SCF Method

system	B3LYP/6-31G*		M05-2X/6-31++G**		expt <sup>a</sup>	
	$I$	$A$	$I$	$A$	$I$	$A$
CB	8.68	-1.54	9.01	-1.09	9.07 ± 0.02	— <sup>c</sup>
1,2-C2B	8.69	-0.14	9.07	0.01	9.06 ± 0.02	0.093
1,3-C2B	8.75	-0.16	9.12	-0.60	9.10 ± 0.02	— <sup>c</sup>
1,4-C2B	8.56	-0.92	8.92	-0.58	8.92 ± 0.03	— <sup>c</sup>
1,2,3-C3B	8.86	0.17	9.24	0.29	9.18 ± 0.03	— <sup>c</sup>
1,2,4-C3B	8.65	0.16	9.04	0.27	9.04 ± 0.03	— <sup>c</sup>
1,3,5-C3B	9.00	0.15	9.39	-0.28	9.30 ± 0.06	0.34
1,2,3,4-C4B	8.73	0.44	9.12	0.52	8.9	— <sup>c</sup>
1,2,3,5-C4B	8.78	0.44	9.17	0.21	9.02	— <sup>c</sup>
1,2,4,5-C4B	8.66	0.07	9.08	0.05	9	0.45
1,2,3,4,5-C5B	8.76	0.70	9.19	0.75	8.8	0.729
1,2,3,4,5,6-C6B	8.86	0.77	9.29	0.87	9.0 ± 0.1	0.92 ± 0.10
benzene	8.86	-2.10	9.15	-1.48	9.24	-1.12 ± 0.03 <sup>b</sup>

<sup>a</sup> The experimental  $I$  and  $A$  were obtained from NIST standard reference database webbook <http://webbook.nist.gov/chemistry>. <sup>b</sup> Ref 49.<sup>c</sup> Not listed in NIST database.

methods underestimate the ionization potentials. Further, the magnitudes and signs of the electron affinities have not been predicted properly by these methods. The values predicted from the M05-2X method are much closer to the experimental values. The discrepancy in the prediction of these values may be due to the parametrization of different density functionals and the limitations of Koopmans' theorem. In order to assess the importance of electron relaxation upon

ionization and electron attachment, the  $\Delta$ SCF approach are used employing M05-2X/6-31++G\*\* method. The results are depicted in Table 6. It can be observed that  $\Delta$ SCF values are in good agreement with the experimental values.

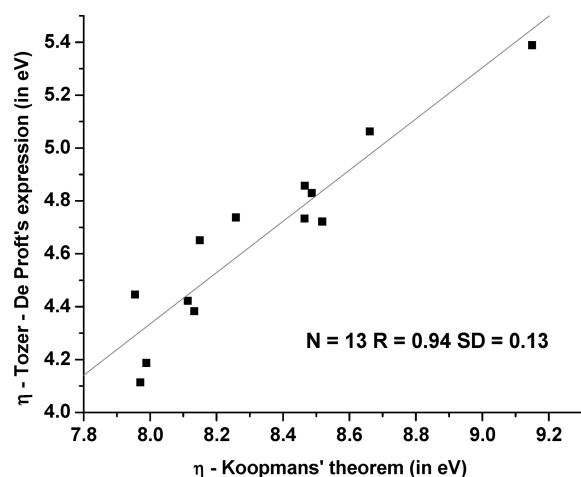
**Global Descriptors of Chlorobenzene.** The calculated chemical hardness, chemical potential, and electrophilicity index from various methods using 6-31++G\*\* basis functions employing Koopmans' approximation and different

**Table 7.** Global Reactivity Properties, Hardness ( $\eta$ ), Chemical Potential ( $\mu$ ), and Electrophilicity ( $\omega$ ) in eV, Calculated from B3LYP, MPW1B95, MPWB1K, and BB1K Methods with 6-31++G\*\* Basis Set using Koopmans' Theorem

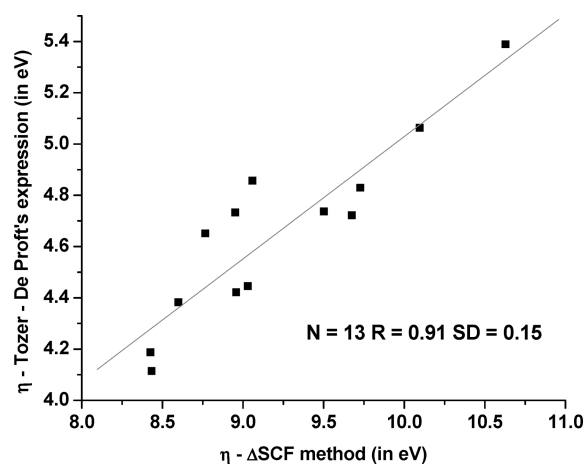
system	B3LYP			MPW1B95			MPWB1K			BB1K		
	$\eta$	$\mu$	$\omega$	$\eta$	$\mu$	$\omega$	$\eta$	$\mu$	$\omega$	$\eta$	$\mu$	$\omega$
CB	6.15	-3.88	1.22	4.59	-3.73	1.51	4.62	-3.71	1.49	4.63	-3.66	1.45
1,2-C2B	5.99	-4.07	1.39	4.42	-3.88	1.71	4.44	-3.86	1.68	4.46	-3.82	1.63
1,3-C2B	6.00	-4.13	1.42	4.44	-3.95	1.76	4.46	-3.93	1.73	4.48	-3.88	1.68
1,4-C2B	5.80	-4.05	1.42	4.20	-3.87	1.78	4.22	-3.85	1.76	4.24	-3.80	1.71
1,2,3-C3B	5.99	-4.29	1.54	4.44	-4.07	1.87	4.46	-4.05	1.84	4.48	-4.01	1.80
1,2,4-C3B	5.71	-4.26	1.59	4.13	-4.04	1.97	4.15	-4.01	1.94	4.17	-3.97	1.89
1,3,5-C3B	6.04	-4.41	1.61	4.47	-4.19	1.96	4.50	-4.17	1.93	4.52	-4.13	1.89
1,2,3,4-C4B	5.70	-4.37	1.68	4.14	-4.13	2.06	4.17	-4.10	2.02	4.17	-4.06	1.98
1,2,3,5-C4B	5.69	-4.45	1.74	4.12	-4.20	2.14	4.14	-4.17	2.10	4.16	-4.13	2.05
1,2,4,5-C4B	5.55	-4.42	1.76	3.97	-4.17	2.19	3.99	-4.15	2.16	4.01	-4.10	2.10
1,2,3,4,5-C5B	5.57	-4.54	1.85	4.02	-4.26	2.26	4.04	-4.23	2.22	4.05	-4.20	2.17
1,2,3,4,5,6-C6B	5.45	-4.72	2.05	3.85	-4.46	2.58	3.90	-4.41	2.50	3.92	-4.37	2.44
benzene	6.59	-3.72	1.05	5.11	-3.63	1.29	5.15	-3.62	1.27	5.16	-3.57	1.23

**Table 8.** Global Reactivity Properties, Hardness ( $\eta$ ), Chemical Potential ( $\mu$ ), and Electrophilicity ( $\omega$ ) in eV, Calculated from SVWN5, BLYP, M05, and M05-2X Methods with 6-31++G\*\* Basis Set using Koopmans' Theorem and Tozer-De Proft's Expression for Hardness

system	SVWN5			BLYP			M05			M05-2X			
	$\eta$	$\mu$	$\omega$	$\eta$	$\mu$	$\omega$	$\eta$	$\mu$	$\omega$	$\eta$	$\eta^a$	$\mu$	$\omega$
CB	4.63	-4.45	2.14	4.56	-3.69	1.50	6.66	-3.82	1.09	8.66	5.06	-4.01	0.93
1,2-C2B	4.45	-4.60	2.37	4.41	-3.87	1.70	6.46	-4.00	1.24	8.47	4.86	-4.20	1.04
1,3-C2B	4.47	-4.67	2.44	4.42	-3.94	1.75	6.49	-4.08	1.28	8.49	4.83	-4.27	1.07
1,4-C2B	4.23	-4.58	2.49	4.21	-3.87	1.77	6.28	-3.98	1.26	8.26	4.74	-4.18	1.06
1,2,3-C3B	4.47	-4.79	2.56	4.42	-4.08	1.88	6.44	-4.24	1.40	8.46	4.73	-4.45	1.17
1,2,4-C3B	4.15	-4.75	2.72	4.15	-4.05	1.98	6.17	-4.18	1.42	8.15	4.65	-4.39	1.18
1,3,5-C3B	4.51	-4.92	2.68	4.46	-4.20	1.98	6.50	-4.37	1.47	8.52	4.72	-4.58	1.23
1,2,3,4-C4B	4.16	-4.85	2.82	4.11	-4.17	2.11	6.13	-4.31	1.51	8.13	4.38	-4.52	1.25
1,2,3,5-C4B	4.14	-4.91	2.92	4.13	-4.23	2.16	6.11	-4.38	1.57	8.11	4.42	-4.60	1.30
1,2,4,5-C4B	3.99	-4.88	2.99	4.00	-4.20	2.21	5.98	-4.34	1.58	7.95	4.45	-4.55	1.30
1,2,3,4,5-C5B	4.04	-4.98	3.07	3.87	-4.38	2.48	5.98	-4.47	1.67	7.97	4.11	-4.69	1.38
1,2,3,4,5,6-C6B	3.95	-5.14	3.34	3.64	-4.62	2.93	5.97	-4.59	1.77	7.99	4.19	-4.81	1.45
benzene	5.17	-4.35	1.83	5.00	-3.54	1.25	7.15	-3.68	0.95	9.15	5.39	-3.85	0.81

<sup>a</sup> Tozer-De Proft's hardness expression using eq 10.**Figure 2.** Plot between the hardness obtained from the Koopmans' theorem and the Tozer-De Proft's expression using M05-2X/6-31++G\*\* method.

equations (eqs 3, 4, 7 and 10) are shown in Tables 7 and 8. The results obtained using the remaining basis functions are shown in Supporting Information (Tables S9–S19). The hardness of most of the CBs decreases with an increase in the number of chlorine atoms. The overall observation of the hardness profile indicates that for any of the chosen

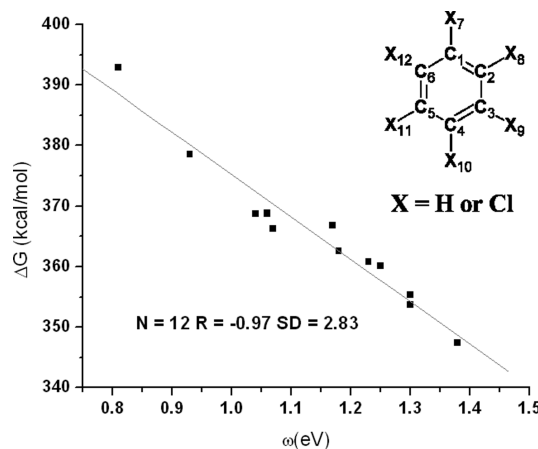
**Figure 3.** Plot between the hardness obtained from the  $\Delta$ SCF method and the Tozer-De Proft's expression using M05-2X/6-31++G\*\* method.

method with different basis sets, the maximum and minimum hardness values lie within  $\sim 0.30$  eV in most cases. The hardness predicted by MPW1B95, MPWB1K, BB1K, BLYP, and SVWN5 are in close agreement with each other. There is no such agreement in the values obtained from the other methods. The hardness and the relative energies of different CBs have been compared to understand the validity of

**Table 9.** Electrophilicity ( $\omega$ ), Calculated from M05-2X/6-31++G\*\* Method, and Experimental Free Energy ( $\Delta G_g^0$  in kcal/mol) of Deprotonation of Benzene and CBs

system	$\omega$ (eV)	$\Delta G_g^0$
CB	0.93	378.6
1,2-C2B	1.04	368.7
1,3-C2B	1.07	366.3
1,4-C2B	1.06	368.8
1,2,3-C3B	1.17	366.8
1,2,4-C3B	1.18	362.6
1,3,5-C3B	1.23	360.8
1,2,3,4-C4B	1.25	360.1
1,2,3,5-C4B	1.30	355.4
1,2,4,5-C4B	1.30	353.7
1,2,3,4,5-C5B	1.38	347.4
benzene	0.81	392.9

maximum hardness principle (MHP). The stability (relative energies in Table 2) of dichloro systems vary as 1,4-C2B > 1,3-C2B > 1,2-C2B. The hardness calculated from all the methods applying Koopmans' approximation of these isomers vary as 1,3-C2B > 1,2-C2B > 1,4-C2B (Tables 7 and 8). In contrast, the hardness indices predicted from B3LYP/6-31G\* method employing  $\Delta$ SCF approach follow the order of 1,4-C2B > 1,3-C2B > 1,2-C2B (Supporting Information, Table S20), which is in parallel with the trend in the stabilities of these dichlorobenzenes. It can be noted that M05-2X/6-31G\* method using  $\Delta$ SCF does not yield the same trend. The 1,2,4-C3B isomer shows lowest hardness among the 1,2,3-C3B and 1,3,5-C3B isomers. The hardness of 1,2,4,5-C4B isomer of tetrachlorinated benzene marginally decreases when compared with the other tetrachlorinated benzenes. For each group of chlorobenzene isomers, in some cases, as the energy and electrophilicity decreases, the

**Figure 4.** Plot between the electrophilicity ( $\omega$ ) calculated from M05-2X/6-31++G\*\* method and the free energy ( $\Delta G_g^0$ ) of deprotonation.

hardness increases as expected from the principles of maximum hardness and minimum electrophilicity. These principles are not very effective in analyzing the relative stabilities of isomers.<sup>3</sup>

The hardness values calculated for benzene and CBs using Tozer and De Proft's expressions (eq 8) employing M05-2X/6-31++G\*\* method are also given in Table 8. The calculated hardness values using Koopmans' approximation,  $\Delta$ SCF method, and Tozer-De Proft's expression are compared in Figures 2 and 3. It can be seen that the relative trends in these values are similar.

The chemical potential and the electrophilicity index increase with an increase in the number of chlorine atom substitutions, which is in line with the results observed in

**Table 10.** Regression Analysis of Global Reactivity Descriptors, Hardness ( $\eta$ ), Chemical Potential ( $\mu$ ), and Electrophilicity ( $\omega$ ), Calculated from Various Methods/Basis Set Using Koopmans' Theorem

method	basis set	$R$			method	basis set	$R$		
		$\eta$	$\mu$	$\omega$			$\eta$	$\mu$	$\omega$
B3LYP	6-31G*	-0.933	-0.887	0.949	SVWN5	6-31G*	-0.910	-0.862	0.966
	6-31G**	-0.929	-0.886	0.945		6-31G**	-0.903	-0.861	0.966
	6-31+G*	-0.909	-0.880	0.955		6-31+G*	-0.892	-0.848	0.971
	6-31+G**	-0.900	-0.880	0.960		6-31+G**	-0.887	-0.847	0.973
	6-31++G**	-0.900	-0.880	0.960		6-31++G**	-0.887	-0.846	0.973
	6-311++G**	-0.895	-0.877	0.959		6-311++G**	-0.877	-0.841	0.973
	AUG-CC-PVDZ	-0.892	-0.876	0.963	BLYP	6-31G*	-0.921	-0.889	0.957
	AUG-CC-PVTZ	-0.903	-0.868	0.957		6-31G**	-0.915	-0.889	0.961
MPWB1K	6-31G*	-0.910	-0.868	0.961		6-31+G*	-0.897	-0.882	0.966
	6-31G**	-0.905	-0.867	0.961		6-31+G**	-0.892	-0.882	0.969
	6-31+G*	-0.889	-0.855	0.969		6-31++G**	-0.893	-0.883	0.969
	6-31+G**	-0.883	-0.854	0.971		6-311++G**	-0.888	-0.875	0.969
	6-31++G**	-0.883	-0.854	0.971	M05	6-31G*	-0.945	-0.867	0.938
MPW1B95	6-31G*	-0.915	-0.871	0.960		6-31G**	-0.943	-0.864	0.934
	6-31G**	-0.908	-0.870	0.960		6-31+G*	-0.930	-0.854	0.942
	6-31+G*	-0.895	-0.859	0.966		6-31+G**	-0.924	-0.854	0.946
	6-31+G**	-0.888	-0.857	0.971		6-31++G**	-0.927	-0.854	0.946
	6-31++G**	-0.888	-0.857	0.971		6-311++G**	-0.916	-0.850	0.946
BB1K	6-31G*	-0.913	-0.870	0.961	M05-2X	6-31G*	-0.937	-0.869	0.931
	6-31G**	-0.905	-0.868	0.962		6-31G**	-0.936	-0.870	0.931
	6-31+G*	-0.895	-0.856	0.968		6-31+G*	-0.916	-0.861	0.938
	6-31+G**	-0.885	-0.855	0.968		6-31+G**	-0.912	-0.864	0.938
	6-31++G**	-0.885	-0.855	0.968		6-31++G**	-0.912	-0.864	0.938
						6-311++G**	-0.908	-0.861	0.944

**Table 11.** Regression Equations Obtained for  $\omega$  from Various Methods/Basis Sets using Koopmans' Theorem

method	basis set	$pC$	$R$	SD	method	basis set	$pC$	$R$	SD
B3LYP	6-31G*	(0.582)+3.248 $\omega$	0.949	0.219	SVWN5	6-31G*	(-0.209)+2.204 $\omega$	0.966	0.178
	6-31G**	(0.539)+3.259 $\omega$	0.945	0.227		6-31G**	(-0.318)+2.237 $\omega$	0.966	0.180
	6-31+G*	(-0.285)+3.337 $\omega$	0.955	0.205		6-31+G*	(-0.976)+2.223 $\omega$	0.971	0.165
	6-31+G**	(-0.409)+3.391 $\omega$	0.960	0.194		6-31+G**	(-1.113)+2.258 $\omega$	0.973	0.160
	6-31++G**	(-0.409)+3.391 $\omega$	0.960	0.194		6-31++G**	(-1.113)+2.258 $\omega$	0.973	0.160
	6-311++G**	(-0.505)+3.368 $\omega$	0.959	0.196		6-311++G**	(-1.217)+2.228 $\omega$	0.973	0.161
	AUG-CC-PVDZ	(-0.607)+3.401 $\omega$	0.963	0.186					
MPWB1K	AUG-CC-PVTZ	(-0.571)+3.441 $\omega$	0.957	0.200	BLYP	6-31G*	(0.785)+2.553 $\omega$	-0.889	0.201
	6-31G*	(0.331)+2.868 $\omega$	0.961	0.191		6-31G**	(0.658)+2.617 $\omega$	-0.889	0.191
	6-31G**	(0.302)+2.868 $\omega$	0.961	0.191		6-31+G*	(-0.074)+2.577 $\omega$	-0.882	0.179
	6-31+G*	(-0.446)+2.836 $\omega$	0.969	0.171		6-31+G**	(-0.192)+2.619 $\omega$	-0.882	0.171
	6-31+G**	(-0.589)+2.886 $\omega$	0.971	0.165		6-31++G**	(-0.192)+2.619 $\omega$	-0.883	0.171
	6-31++G**	(-0.589)+2.886 $\omega$	0.971	0.165		6-311++G**	(-0.352)+2.628 $\omega$	-0.875	0.170
MPW1B95					M05	6-31G*	(0.645)+3.476 $\omega$	-0.867	0.240
	6-31G*	(0.426)+2.762 $\omega$	0.960	0.195		6-31G**	(0.624)+3.481 $\omega$	-0.864	0.247
	6-31G**	(0.315)+2.808 $\omega$	0.960	0.194		6-31+G*	(-0.081)+3.558 $\omega$	-0.854	0.232
	6-31+G*	(-0.427)+2.779 $\omega$	0.966	0.178		6-31+G**	(-0.177)+3.607 $\omega$	-0.854	0.224
	6-31+G**	(-0.547)+2.818 $\omega$	0.971	0.167		6-31++G**	(-0.177)+3.607 $\omega$	-0.854	0.224
	6-31++G**	(-0.547)+2.818 $\omega$	0.971	0.167		6-311++G**	(-0.386)+3.725 $\omega$	-0.850	0.225
BB1K					M05-2X	6-31G*	(0.454)+4.328 $\omega$	-0.869	0.253
	6-31G*	(0.377)+2.854 $\omega$	-0.870	0.190		6-31G**	(0.454)+4.328 $\omega$	-0.870	0.253
	6-31G**	(0.263)+2.903 $\omega$	-0.868	0.190		6-31+G*	(-0.539)+4.639 $\omega$	-0.861	0.239
	6-31+G*	(-0.407)+2.886 $\omega$	-0.856	0.175		6-31+G**	(-0.539)+4.639 $\omega$	-0.864	0.239
	6-31+G**	(-0.497)+2.911 $\omega$	-0.855	0.173		6-31++G**	(-0.539)+4.639 $\omega$	-0.864	0.239
	6-31++G**	(-0.497)+2.911 $\omega$	-0.855	0.173		6-311++G**	(-0.689)+4.618 $\omega$	-0.861	0.228

the case of hardness. The chemical potential predicted by MPW1B95, MPWB1K, BB1K, BLYP, and M05 are similar. There is only a marginal variation in the electrophilicity index predicted by the MPW1B95, MPWB1K, and BB1K methods.

**Relation Between Reactivities and Electrophilicity.** With a view to assess how electrophilicity index predicts the reactivity of a series of molecules, the relationship between the deprotonation free energies<sup>39</sup> of benzene and chlorobenzenes (Table 9) and the electrophilicity has been explored, and it is depicted in Figure 4. It can be seen that deprotonation free energies vary linearly with electrophilicity, and thus, electrophilicity provides valuable information about the relative reactivities of a series of homologous compounds.

**Structure-Toxicity Analysis of Chlorobenzenes.** With a view to benchmark the level of calculation of different global reactivity descriptors for QSTR development, the toxicity ( $pC$ ) values of the selected set of nine chlorobenzenes against *Poecilia reticulata* have been used. In the development of QSTR, the experimental toxicity data ( $pC$ ) have been considered as dependent variables and global reactivity descriptors obtained from all the methods (Tables 7–8, and Supporting Information, Tables S9–S19) as independent variables. The QSTRs derived from the multiple regression analysis employing different global reactivity descriptors obtained from various levels of calculations are presented in Tables 10–11.

The  $\Delta$ SCF method has also been used along with the Koopmans' approximation to understand the predictive power of global reactivity descriptors obtained from different strategies. The eqs 5 and 6 have been used to predict the ionization potential and the electron affinity using B3LYP and M05-2X methods with 6-31G\* and 6-31++G\*\* basis sets, respectively. The predicted regression values using  $\Delta$ SCF method is shown in the Table 12. The experimental

**Table 12.** Regression Analysis of Global Reactivity Descriptors, Hardness ( $\eta$ ), Chemical Potential ( $\mu$ ), and Electrophilicity ( $\omega$ ), Calculated from Various Methods/Basis sets using  $\Delta$ SCF Method

method/basis set	$\eta$		$\mu$		$\omega$	
	$R$	SD	$R$	SD	$R$	SD
B3LYP/6-31G*	-0.783	0.431	-0.693	0.499	0.734	0.470
M05-2X/6-31++G**	-0.738	0.467	-0.768	0.443	0.768	0.443

and calculated toxicity data ( $pC$ ) for the selected set of nine CBs are listed in Tables 13 and 14.

As shown in previous studies, electrophilicity index exhibits very good correlation with the toxicity values when compared to hardness and electronegativity.<sup>40</sup> Even though, the global reactivity descriptors calculated using different methods show significant variations as discussed above, the mean deviation of the properties between all the systems with respect to the chosen method/basis set is similar. That is the predicted global reactivity descriptors are varying with respect to the method and the basis set, but the magnitude of the difference in between the systems are similar in all the methods. This observation influences the final regression analysis and predicts the correlation coefficient without major deviation between each of the methods. Although the ionization potential and the electron affinity calculated using  $\Delta$ SCF methods produce good correlation with the experimentally observed data, they do not improve the correlation coefficient.

In general, the regression values obtained using various methods are comparable. The overall observation illustrates that the increasing the number of basis functions in any method refines the calculated values of the descriptors only. There is no marked variation in the correlation coefficient. It is an interesting observation that quantum chemical descriptors such as the global reactivity descriptors can be routinely used in the



**Table 13.** Experimental and Calculated Fish Toxicity ( $pC$ ) Values against *Poecilia Reticulate* of Selected Chlorobenzenes from B3LYP, MPW1B95, MPWB1K, and BB1K Methods with 6-31++G\*\* Basis Set using Koopmans' Theorem

system	observed	B3LYP			MPW1B95			MPWB1K			BB1K		
		$\omega$ (eV)	calc	res	$\omega$ (eV)	calc	res	$\omega$ (eV)	calc	res	$\omega$ (eV)	calc	res
CB	3.77	1.22	3.73	0.04	1.51	3.72	0.05	1.49	3.72	0.05	1.45	3.72	0.05
1,2-C2B	4.4	1.39	4.29	0.11	1.71	4.26	0.14	1.68	4.26	0.14	1.63	4.26	0.14
1,3-C2B	4.28	1.42	4.41	-0.13	1.76	4.40	-0.12	1.73	4.40	-0.12	1.68	4.40	-0.12
1,4-C2B	4.56	1.42	4.40	0.16	1.78	4.47	0.09	1.76	4.48	0.08	1.71	4.47	0.09
1,2,4-C3B	4.83	1.59	4.97	-0.14	1.97	5.01	-0.18	1.94	5.00	-0.17	1.89	5.01	-0.18
1,3,5-C3B	4.74	1.61	5.06	-0.32	1.96	4.99	-0.25	1.93	4.99	-0.25	1.89	5.00	-0.26
1,2,3,4-C4B	5.35	1.68	5.28	0.07	2.06	5.25	0.10	2.02	5.24	0.11	1.98	5.26	0.09
1,2,3,5-C4B	5.43	1.74	5.49	-0.06	2.14	5.48	-0.05	2.10	5.48	-0.05	2.05	5.48	-0.05
1,2,4,5-C4B	5.85	1.76	5.55	0.30	2.19	5.62	0.23	2.16	5.63	0.22	2.10	5.61	0.24

**Table 14.** Experimental and Calculated Fish Toxicity ( $pC$ ) Values against *Poecilia Reticulate* of Selected Chlorobenzenes from SVWN5, BLYP, M05, and M05-2X Methods With 6-31++G\*\* Basis Set using Koopmans' Theorem

system	observed	SVWN5			BLYP			M05			M05-2x		
		$\omega$ (eV)	calc	res	$\omega$ (eV)	calc	res	$\omega$ (eV)	calc	res	$\omega$ (eV)	calc	res
CB	3.77	2.14	3.71	0.06	1.50	3.73	0.04	1.09	3.77	0.00	0.93	3.76	0.01
1,2-C2B	4.4	2.37	4.25	0.15	1.70	4.26	0.14	1.24	4.30	0.10	1.04	4.30	0.10
1,3-C2B	4.28	2.44	4.39	-0.11	1.75	4.40	-0.12	1.28	4.44	-0.16	1.07	4.45	-0.17
1,4-C2B	4.56	2.49	4.50	0.06	1.77	4.45	0.11	1.26	4.38	0.18	1.06	4.38	0.18
1,2,4-C3B	4.83	2.72	5.03	-0.20	1.98	4.99	-0.16	1.42	4.94	-0.11	1.18	4.94	-0.11
1,3,5-C3B	4.74	2.68	4.95	-0.21	1.98	4.98	-0.24	1.47	5.13	-0.39	1.23	5.17	-0.43
1,2,3,4-C4B	5.35	2.82	5.26	0.09	2.11	5.35	0.00	1.51	5.29	0.06	1.25	5.28	0.07
1,2,3,5-C4B	5.43	2.92	5.47	-0.04	2.16	5.47	-0.04	1.57	5.49	-0.06	1.30	5.50	-0.07
1,2,4,5-C4B	5.85	2.99	5.63	0.22	2.21	5.59	0.26	1.58	5.50	0.35	1.30	5.51	0.34

development of QSAR/QSPR/QSTR approaches in the industries without any high computational time and cost.

## Conclusions

In this study, an attempt has been made to evaluate how various DFT methods predict the stability, the electronic properties, and the reactivities of CBs. In this investigation, some popular functionals belonging to the pure, GGA, hybrid, and meta and hybrid meta GGA have been selected. It is evident from the results that increase in the rigor in the level of calculation leads to good agreement between the calculated and experimental values of ionization potentials and electron affinities. Typically, M05-2X method outperforms the other functionals in the prediction of ionization potentials and electron affinities of CBs using Koopmans' approximation and  $\Delta$ SCF method. The ionization potential and the electron affinities calculated from  $\Delta$ SCF method are in good agreement with the experimental values when compared to the Koopmans' approximation. The trends in the hardness values of CBs calculated from various schemes are comparable.

The usefulness of global reactivity descriptors in the development of structure–activity/toxicity relationships has been illustrated. There is no drastic change in the correlation coefficients obtained from the linear/multiple regression analysis of toxicity vs calculated global reactivity descriptors from different levels of theory. The results clearly show that the reliable estimates of the trends in the global reactivity descriptors are sufficient enough to develop QSAR/QSPR/QSTR. This investigation, once again, reinforces the usefulness of global reactivity descriptors in QSAR/QSPR/QSTR parlance.

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**Supporting Information Available:** Provides the calculated bond lengths and bond angles of chlorobenzene and 1,3,5-C3B from various methods using 6-31++G\*\* basis set, the calculated ionization potential and electron affinity using various methods/basis sets, and the various global reactivity descriptors like hardness, chemical potential, electrophilicity index, etc., calculated using various methods/basis sets. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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