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Full-length paper

Analyzing toxicity through electrophilicity

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Summary

The toxicological structure-activity relationships are investigated using conceptual DFT based descriptors like global and local electrophilicities. In the present work the usefulness of electrophilicity in predicting toxicity of several polyaromatic hydrocarbons (PAH) is assessed. The toxicity is expressed through biological activity data (pIC_{50}) defined as molar concentration of those chemicals necessary to displace 50% of radiolabeled tetrachlorodibenzo-p-dioxin (TCDD) from the arylhydrocarbon (Ah) receptor. The experimental toxicity values (pIC_{50}) for the electron acceptor toxin like polychlorinated dibenzofurans (PCDF) are taken as dependent variables and the DFT based global descriptor electrophilicity index (ω) is taken as independent variable in the training set. The same model is then tested on a test set of polychlorinated biphenyls (PCB). A good correlation is obtained which vindicates the importance of these descriptors in the QSAR studies on toxins. These toxins act as electron acceptors in the presence of biomolecules whereas aliphatic amines behave as electron donors some of which are also taken into account for the present work. The toxicity values of the aliphatic amines in terms of the 50% inhibitory growth concentration (IGC_{50}) towards ciliate fresh-water protozoa *Tetrahymena pyriformis* are considered. Since there is no global nucleophilicity we apply local nucleophilicity (ω^{+}_{max}) as the descriptor in this case of training set. The same regression model is then applied to a test set of amino alcohols. Although the correlation is very good the statistical analysis reflects some cross validation problem. As a further check the amines and amino alcohols are used together to form both the training and the test sets to provide good correlation. It is demonstrated that the toxicity of several toxins (both electron donors and acceptors) in the gas and solution phases can be adequately explained in terms of global and local electrophilicities. Amount of charge transfer between the toxin and the biosystem, simulated as nucleic acid bases and DNA base pairs, indicates the importance of charge transfer in the observed toxicity. The major strength of the present analysis *vis-à-vis* the existing ones rests on the fact that it requires only one descriptor having a direct relationship with toxicity to provide a better correlation. Importance of using the information from both the toxin and the biosystem is also analyzed.

Abbreviations: DFT, Density Functional Theory; PCDF, polychlorinated dibenzofuran; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; QSAR, quantitative structure activity relationship.

Introduction

Various quantum chemical descriptors like charges, orbital energies, frontier orbital densities, polarizabilities, dipole moments etc. have been used in developing different quantitative structure activity relationships (QSARs) for predicting reactivity in terms of the structure and physicochemical properties of molecules. Density functional theory (DFT) provides a number of global reactivity descriptors such as electronegativity (χ), chemical potential (μ), hardness (η), polarizability (α) and softness (S) as well as local reactivity descriptors like Fukui function (FF) and local softness, which have been used in the development of QSARs [1–5]. Global electrophilic power of a molecule is quantified in terms of an electrophilicity index (ω) [6] which has been shown to be related to the rates of reactions [7]. A local version of this has also been proposed [8]. The power of the electrophilicity and other related quantities has been analyzed in the context of QSAR [9, 10] and also in describing the toxicity of polychlorinated biphenyls [11, 12] and benzidine

[12] wherein the conformational flexibility of toxins is highlighted.

Polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) are chemicals of concern because of their elevated concentrations, wide distribution and toxicity. Biochemical and pathological studies on aquatic organisms have consistently revealed that the lateral substituted congeners are more potent than the non-lateral congeners [13–15]. Polychlorinated dibenzofurans (PCDFs) are ubiquitous contaminants, which are present in various environmental systems and biota [16]. PCDFs are released directly into the atmosphere from a variety of combustion sources and manufacturing processes, such as municipal solid waste incinerators [17], automobile emissions [18] and chemical production processes [16]. They are mainly transported over long distances and/or deposited to the terrestrial and aquatic ecosystems through dry or wet deposition. Therefore, atmospheric transport and deposition constitute the primary distribution pathway in moving PCDFs from numerous emission sources to the environmental compartments [19].

Toxicity of polychlorinated biphenyls (PCB) has seen an upsurge of interest in recent years [20–24]. These compounds exhibit toxicity similar to that of polychlorinated dibenzo-*p*-dioxin (PCDD). This information on PCB has prompted several investigators to understand the toxic nature of PCB and their interaction with cellular components [25]. The marine aquatic contamination leads to increased concentration of these toxic compounds in sea-fish and others. The edible varieties accumulate the toxicities in different cells and produce contaminated fish oils and products and subsequent health hazards, instead of health benefits of uptake. Further, accumulation of these health hazardous toxic products may lead to various diseases including increased incidence of carcinogenesis particularly involving urinary bladder and other organs [13]. The origin of toxicity of PCDDs in living cells has been attributed to the electron accepting nature in charge transfer complex formalism with a receptor [26]. Hence, electron affinity of PCDDs/PCBs is used as an important quantity in understanding their toxic effects. Due to their extreme toxicity and the existence of many isomers, experimental investigations on toxic PCDDs are difficult.

In the present work, an attempt has been made to explore the uses of DFT based reactivity descriptors to investigate the structure-activity relationship in the series of PCDFs, and PCBs. All the previously determined biological activity data [27], that is the negative of the log of molar concentration of chemical necessary to displace 50% of radiolabeled TCDD from Ah receptor (pIC_{50}), are utilized for this purpose. Experimental biological activity (pIC_{50}) for PCDFs and PCBs are correlated with their corresponding calculated pIC_{50} values determined using one parameter regression analysis in gas phase using Mulliken Population Analysis (MPA), Natural Population Analysis (NPA) and Hirshfeld Population Analysis (HPA) (Stockholder partitioning scheme) schemes. Sets of aliphatic amines and amino alcohols, which act as electron donors in their interaction with biomolecules have also been studied for their toxicity values in terms of 50% inhibitory growth concentration (IGC_{50}) towards tear-drop shaped, unicellular, fresh water protozoa *Tetrahymena pyriformis* [28] using one parameter regression analysis in gas phase using the NPA scheme. The amount of charge transfer between a toxin and nucleic acid bases/DNA base pairs is also calculated to gain insights into the origin of toxicity vis-à-vis the charge transfer between a toxin and a biosystem.

Theoretical background

Electronegativity (χ) and hardness (η) are defined within the conceptual DFT framework as [2, 29]

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

and

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

where E and $v(\vec{r})$ are respectively the total energy and the external potential of an N- electron system with chemical potential [30], μ, which is the Lagrange multiplier associated with the normalization constraint of DFT.

Operational definitions for χ and η may be written [2] using a finite difference approximation in terms of the ionization potential (I) and electron affinity (A) as

$$\chi = \frac{I + A}{2} \tag{3}$$

and

$$\eta = \frac{I - A}{2} \tag{4}$$

which may be further approximated by using Koopmans' theorem as

$$\chi = -\frac{\epsilon_H + \epsilon_L}{2} \tag{5}$$

and

$$\eta = \frac{\epsilon_L - \epsilon_H}{2} \tag{6}$$

where ϵ_L and ϵ_H are energies of the lowest unoccupied and highest occupied orbitals respectively.

Parr et al. [6] introduced the global electrophilicity index (ω) as follows

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

The Fukui function is a local reactivity descriptor defined as [31, 32]

$$f(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{v(\vec{r})} = \left(\frac{\delta \mu}{\delta v(\vec{r})}\right)_N \quad (8)$$

which may be approximated as follows [33–35] due to the discontinuities in the above derivatives

$$f^+(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}) \text{ for nucleophilic attack} \quad (9a)$$

$$f^-(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \text{ for electrophilic attack} \quad (9b)$$

$$f^0(\vec{r}) = (\rho_{N+1}(\vec{r}) - \rho_{N-1}(\vec{r}))/2 \text{ for radical attack} \quad (9c)$$

The concept of a generalized philicity has been developed [8] which can tackle the electrophilic, nucleophilic and radical reactions. The condensed-to-atom philicity at atom k in a molecule may be written as [8]

$$\omega_k^\alpha = \omega . f_k^\alpha \quad (10)$$

where f_k^α ($\alpha = +, -$ and 0 refer to nucleophilic, electrophilic and radical attacks respectively) is the condensed Fukui function for the atom k.

The fractional number of electrons transferred from a system A to a system B is given by [36]

$$\Delta N = \frac{\mu_B - \mu_A}{2(\eta_A + \eta_B)} \quad (11)$$

which is an important quantity in analyzing the global interactions between the AHH receptors and NA bases/DNA base pairs. Flow of electrons can also be predicted by using the Sanderson's electronegativity equalization principle [37] which dictates that the electron will flow from the molecule with lower electronegativity to that with higher electronegativity.

In order to check the effects of both the donor and the acceptor in analyzing toxicity we define a type of quantum dissimilarity as follows:

$$\Delta_\omega^{ij} = \left(\omega^+_{\max(i)}(\text{electrophile}) - \omega^-_{\max(j)}(\text{nucleophile})\right)^2 \quad (12)$$

For the set of electron acceptor toxins like PCDFs and PCBs, the corresponding nucleophile is taken to be guanine and for the set of electron donor toxins like aliphatic amine, the electrophile is taken to be uracil. The $\omega^-_{\max(j)}$ of guanine is calculated at the N-center whereas the $\omega^+_{\max(i)}$ for uracil is calculated at the C-center. The philicity based quantity (Equation 12) is known to serve better than its local softness variant [38]. The smaller the value of Δ_{ij}^ω the stronger the electrophile-nucleophile interaction will be.

Computational details

The geometries of polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) are optimized using 6–31G* basis set in the framework of B3LYP theory comprising Becke's three–parameter hybrid exchange and LYP correlation functionals whereas the geometries of aliphatic amines are minimized at the Hartree-Fock (HF) level using 6-311G** basis set in gas phase [39, 40]. All calculations are performed using the G98W & G03W suites of programs [41]. The atomic charges for all the above molecules are obtained in the framework of B3LYP theory using MPA [42] and NPA schemes [43, 44]. Also Hirshfeld population scheme [45] as implemented in the DMOL^3 package [46] employing BLYP/DND method is used to obtain atomic charges for all molecules studied in the present work. Since it provides negative charges on H-atoms in some cases it is ultimately not used. One parameter QSAR is performed [47] using the least square error estimation method to predict the toxicity values. The ΔN values are calculated using eq. 11 in which μ ($-\chi$) and η of both the toxins and NA bases/DNA base pairs are calculated using Equations 5 and 6 respectively.

Results and discussion

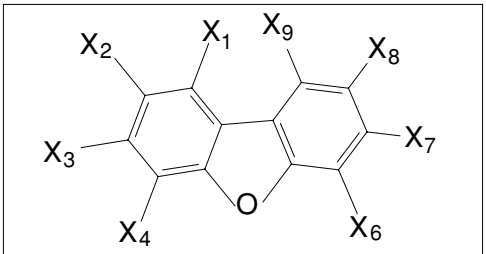
The structural templates of PCDFs, and PCBs with required atom numbering are presented in Tables 1 and 2 respectively alongwith the identity (ID) of the molecules with substitution pattern. Previous studies [11–13] have revealed the fact that PCDFs, and PCBs are electron acceptors in their interaction with biomolecules. Hence for regression analysis, the atom with the maximum value of local electrophilic power ($\omega^+_{\max}$) in a molecule alongwith the electrophilicity index (ω) have been considered as independent variables.

Charge transfer analysis (ΔN)

The global interactions between the constituents of selected systems namely, PCDFs, PCBs and amines (A) and NA bases/DNA base pairs (B) have been determined using the parameter ΔN, which represents the fractional number of electrons, transferred from a system A to a system B. Charge transfer data between PCDFs, PCBs and amines (A) and NA bases/DNA base pairs (B) are presented in Tables 3–5. Generally, electron flows from less electronegative system to more electronegative and this fact along with the definition of ΔN clearly shows that charge transfer values are positive for PCDFs and PCBs representing them as electron acceptors and for amines ΔN is negative showing them as electron donors.

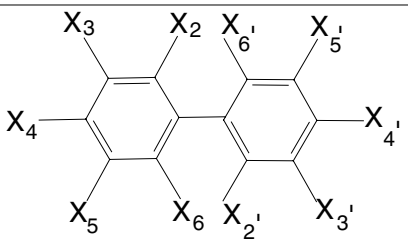
In the case of interaction with PCDFs and PCBs, Guanine and GCWC donate maximum charge among the selected bases and base pairs respectively and Uracil (base) and ATH (base pair), the minimum (Tables 3 and 4). Figure 1A shows the correlation between the amount of charge transfer

Table 1. Polychlorinated dibenzofurans with identity number (ID) representing the substitution pattern.



ID	X_1	X_2	X_3	X_4	X_6	X_7	X_8	X_9
1	H	Cl	H	H	H	H	H	H
2	H	H	H	Cl	H	H	H	H
3	H	Cl	H	H	Cl	H	H	H
4	H	Cl	H	H	H	H	Cl	H
5	Cl	H	Cl	H	Cl	H	H	H
6	Cl	H	Cl	H	H	H	Cl	H
7	H	Cl	Cl	Cl	H	H	H	H
8	H	Cl	Cl	H	H	H	Cl	H
9	H	Cl	H	H	Cl	Cl	H	H
10	H	Cl	Cl	Cl	Cl	H	H	H
11	H	Cl	Cl	Cl	H	H	Cl	H
12	H	Cl	Cl	H	H	Cl	Cl	H
13	Cl	Cl	H	Cl	Cl	Cl	H	H
14	Cl	Cl	Cl	Cl	H	H	Cl	H
15	Cl	Cl	Cl	H	H	Cl	Cl	H
16	H	Cl	Cl	Cl	H	Cl	Cl	H
17	Cl	Cl	Cl	Cl	H	Cl	Cl	H
18	H	Cl	Cl	Cl	Cl	Cl	Cl	H
19	H	Cl	Cl	H	Cl	H	Cl	H
20	Cl	Cl	Cl	H	Cl	H	H	H
21	Cl	Cl	Cl	H	H	Cl	H	H
22	Cl	H	Cl	Cl	H	Cl	Cl	H
23	H	Cl	Cl	Cl	H	Cl	H	Cl
24	Cl	Cl	Cl	H	H	Cl	H	Cl
25	Cl	Cl	Cl	H	H	Cl	H	H
26	Cl	H	Cl	Cl	H	Cl	Cl	H
27	H	Cl	Cl	Cl	H	Cl	H	Cl

Table 2. Polychlorinated biphenyls with identity number (ID) representing the substitution pattern.



ID	X_2	X_3	X_4	X_5	X_6	$X_{2'}$	$X_{3'}$	$X_{4'}$	$X_{5'}$	$X_{6'}$
28	Cl	H	H	H	H	H	Cl	Cl	Cl	H
29	Cl	Cl	Cl	H	H	H	Cl	Cl	H	H
30	Cl	H	Cl	Cl	H	H	Cl	Cl	H	H
31	Cl	Cl	Cl	Cl	H	H	Cl	Cl	H	H
32	Cl	H	Cl	H	H	Cl	H	Cl	H	H
33	Cl	H	Cl	H	Cl	H	Cl	Cl	Cl	H

computed as ΔN (see Table 3) and the electrophilicity index. A good linear relationship is found with correlation coefficient $R = 0.991$. Figure 1B shows the correlation obtained between the experimental biological activity (pIC_{50}) (see Table 5) of polychlorinated dibenzo furans with the

Table 3. Charge transfer (ΔN) between different polychlorinated dibenzofurans and nucleic acid bases/base pairs in gas phase.

ID	Adenine	Thymine	Guanine	Cytosine	Uracil	GCWC	ATH
1	0.0570	0.0021	0.0984	0.0324	−0.0190	0.0756	0.0454
2	0.0550	0.0005	0.0961	0.0305	−0.0200	0.0730	0.0433
3	0.0845	0.0290	0.1258	0.0601	0.0074	0.1084	0.0746
4	0.0799	0.0244	0.1213	0.0554	0.0029	0.1029	0.0697
5	0.0905	0.0349	0.1317	0.0661	0.0132	0.1155	0.0810
6	0.0906	0.0345	0.1323	0.066	0.0126	0.1159	0.0810
7	0.0877	0.0321	0.1291	0.0633	0.0104	0.1123	0.0781
8	0.0950	0.0390	0.1365	0.0705	0.0171	0.1211	0.0857
9	0.1095	0.0533	0.1510	0.0852	0.0312	0.1384	0.1012
10	0.1043	0.0483	0.1457	0.0800	0.0262	0.1322	0.0957
11	0.1079	0.0516	0.1494	0.0835	0.0294	0.1365	0.0994
12	0.1070	0.0502	0.1489	0.0823	0.0279	0.1357	0.0984
13	0.1195	0.0632	0.1607	0.0952	0.0409	0.1502	0.1118
14	0.1162	0.0592	0.1580	0.0916	0.0368	0.1467	0.1082
15	0.1174	0.0603	0.1593	0.0928	0.0378	0.1483	0.1095
16	0.1205	0.0635	0.1622	0.0959	0.04100	0.1518	0.1128
17	0.1293	0.0719	0.1712	0.1047	0.0491	0.1626	0.1221
18	0.1331	0.0760	0.1747	0.1087	0.0534	0.1669	0.1262
19	0.1128	0.0566	0.1542	0.0885	0.0344	0.1423	0.1047
20	0.1035	0.0475	0.1449	0.0792	0.0255	0.1312	0.0948
21	0.1007	0.0440	0.1426	0.076	0.0218	0.1281	0.0917
22	0.1163	0.0592	0.1583	0.0917	0.0367	0.1470	0.1083
23	0.1178	0.0609	0.1595	0.0933	0.0385	0.1486	0.1100
24	0.1178	0.0607	0.1597	0.0932	0.0382	0.1487	0.1099
25	0.1007	0.0440	0.1426	0.076	0.0218	0.1281	0.0917
26	0.1163	0.0592	0.1583	0.0917	0.0367	0.1470	0.1083
27	0.1178	0.0609	0.1595	0.0933	0.0385	0.1486	0.1100

Table 4. Charge transfer (ΔN) between different polychlorinated biphenyls and nucleic acid bases/base pairs in gas phase.

ID	Adenine	Thymine	Guanine	Cytosine	Uracil	GCWC	ATH
28	0.0932	0.0380	0.1341	0.0690	0.0165	0.1184	0.0840
29	0.1089	0.0535	0.1497	0.0849	0.0317	0.1371	0.1006
30	0.0879	0.0345	0.1276	0.0645	0.0137	0.1113	0.0787
31	0.0975	0.0435	0.1375	0.0739	0.0223	0.1229	0.0887
32	0.1012	0.0469	0.1414	0.0776	0.0255	0.1275	0.0927
33	0.1111	0.0567	0.1512	0.0876	0.0353	0.1391	0.1032

amount of charge transfer between the toxin and Guanine. A correlation coefficient R of 0.881 is obtained. Figure 1C reports the correlation obtained between the experimental activity and that obtained from the linear equation using charge transfer and electrophilicity. A fair correlation is found with $R = 0.892$. For the interaction of PCDFs with GCWC pairs, the analogous correlations give $R = 0.991$, 0.880 and 0.892 (Figure 2) respectively. A good correlation is obtained from above studies showing the significance of the charge transfer in toxicity analysis on PCDFs. It may, however, be mentioned that ΔN is an intermolecular descriptor because it possesses

Table 5. Experimental and calculated biological activity (pIC_{50}) in gas phase for the training set of polychlorinated dibenzofurans.

ID	ω (eV)	ω^+_{max} (NPA) (eV)	Observed pIC_{50}	Calculated pIC_{50}
1	2.763	0.888	4.061	3.800
2	2.699	0.720	3.429	3.583
3	3.101	0.883	4.125	4.947
4	3.180	0.893	4.103	5.216
5	3.366	1.306	6.123	5.847
6	3.425	1.007	4.653	6.047
7	3.331	1.156	5.396	5.728
8	3.486	1.488	6.858	6.254
9	3.659	1.551	7.255	6.841
10	3.748	1.551	7.379	7.144
11	3.769	1.633	7.657	7.215
12	3.785	1.824	8.444	7.269
13	3.952	1.717	8.194	7.836
14	3.967	1.683	7.911	7.887
15	4.005	1.756	8.147	8.016
16	4.046	1.902	8.943	8.155
17	4.263	1.612	7.587	8.892
18	4.293	1.756	8.376	8.994
19	3.828	1.621	7.610	7.415
20	3.642	1.57	7.379	6.784
21	3.657	1.718	7.954	6.835
22	3.989	1.629	7.657	7.962
23	3.988	1.629	7.657	7.958
24	4.010	1.575	7.313	8.033
25	3.657	1.718	7.954	6.835
26	3.989	1.621	7.623	7.962
27	3.988	1.622	7.623	7.958

Table 6. Experimental and predicted biological activity (pIC_{50}) in gas phase for the test set of polychlorinated biphenyls.

ID	ω	ω^+_{max}(NPA) (eV)	Observed pIC_{50}	Calculated pIC_{50}
28	3.109	0.476	5.584	4.975
29	3.329	0.432	6.134	5.721
30	3.424	0.440	5.762	6.044
31	3.597	0.461	6.057	6.631
32	2.866	0.318	4.442	4.150
33	3.112	0.406	4.577	4.985

information regarding both the toxin and the biosystem. Figures 1C and 2C refer to 2-descriptor models with possible collinearity. They are included because of the suggestion made by the referee.

For interaction with amines, Uracil (base) and ATH (base pair) accept maximum charges among respectively the bases and base pairs considered here and Guanine and GCWC accept the minimum (Table 7).

QSAR analysis

Initially for carrying out QSAR analysis on different sets of molecules, the given data set is divided into a training set and a test set. Regression analyses are carried out on the training set and the developed model is used to predict the compounds in the test set.

Polychlorinated dibenzofurans (PCDFs)

The gas phase data of the set of 27 PCDFs are used as the training set. Linear regression analysis is carried out on the training set and the results are presented in Table 8. The model obtained is then applied to the test set comprising 6 polychlorinated biphenyls (PCBs). The observed along with calculated values of pIC_{50} for the training set of PCDFs are presented in Table 5 and observed and predicted pIC_{50} values of the test set of PCBs are presented in Table 6. The ω values are capable of providing (Figure 3) a correlation R for the training (test) set equal to 0.891 (0.834). This QSAR model is used to predict the pIC_{50}values of molecules in the test set.

For the set of 27 PCDFs, a relatively good correlation was found, characterized by $R = 0.891$. The adjusted R^2 equals 0.7864 for the equation $pIC_{50} = 3.3944^*(0.3451)\omega - 5.5788$ (1.2804) where values between brackets indicate standard errors. Both variables, ω and the constant were found to be significant by a t-test. The standard error of the estimate was found to be 0.7206. As an internal measure of validation, a leave 25% out Q^2 value was computed (note: 7 values were left out) and the value of 0.7559 suggests that the model has good predictive capacity. The F-ratio was found to be 96.7427, which is very good compared to the value of F for the given number of parameters and data points. In order to check that the correlation is not due to chance, the probability that a random distribution of the points would yield the same correlation coefficient was computed in the way proposed by Ponec et al [48]. The probability was found to be less than 10^{-6} meaning that the correlation is not a chance correlation.

Although the ω along with ω^+_{max} values provide a much better correlation ($R = 0.99$, $Q^2 = 0.99$) we refrain from using that in order to avoid possible collinearity and overfitting [49].

Polychlorinated biphenyls (PCB)

The gas phase data of the test set of PCBs are used for the linear regression analysis using the QSAR model developed for the training set of PCDFs. The observed along with calculated values of pIC_{50} are presented in Table 6. The ω values provide a correlation (R) of 0.834.

This external test set does reveal that indeed the correlation above can be used as a prediction model. The correlation equation $y = 1.0034x - 0.0268$ is indeed relatively close to $y = x$.

The quantum dissimilarity, Δ^{ω}_{ij}, for both PCDFs (Figure 3C) and PCBs (Figure 3D) correlates well with pIC_{50}.

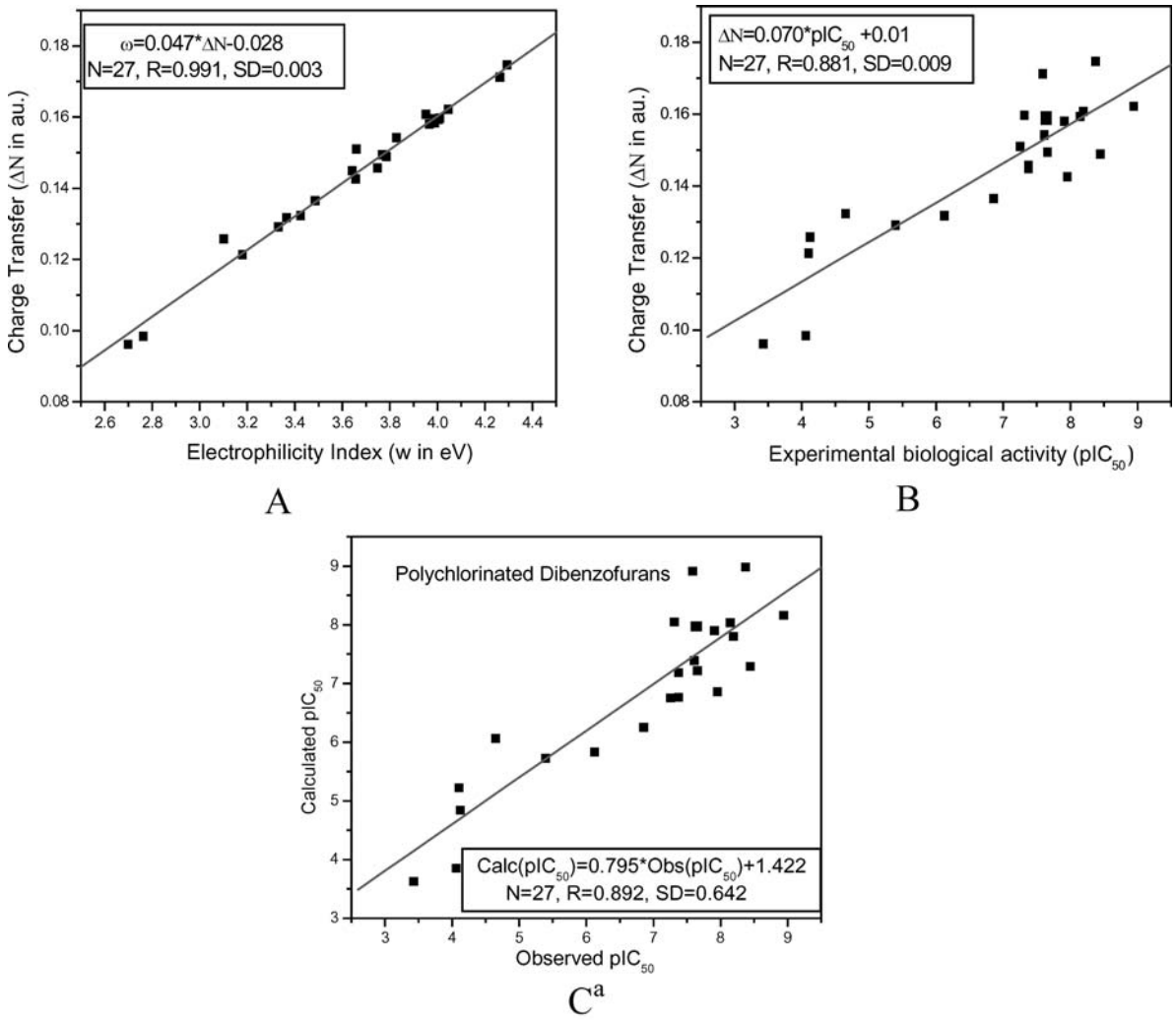


Figure 1. Variation of charge transfer with (A) electrophilicity index (ω), (B) the experimental biological activity (pIC_{50}) during interaction of polychlorinated dibenzo furan with guanine and (C) Observed versus calculated pIC_{50} values of polychlorinated dibenzo furan using electrophilicity index (ω) and ΔN with guanine.

Greater interactions (smaller Δ_{ij}^{ω}) between the toxin and the biosystem leads to a more toxic behavior of the toxin. Note the intermolecular nature of this descriptor.

A comparison of the descriptors used in the present study with those reported elsewhere for describing the toxicity of the same type of molecule is in order. This will bring out the strength and weakness of the descriptors used in the present study and that of others. In line with this idea, we first consider the work carried out by Arulmozhiraja et al [50] in the toxicity prediction of PCDFs. In that study, they have selected a set of 33 PCDFs alongwith their experimental binding affinities (BA) for aryl hydrocarbon receptors (AhR), aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin *O*-deethylase (EROD) induction potencies [log ($1/EC_{50}$)]. They have taken DFT based descriptors such as global softness (S), electronegativity (χ) and electrophilicity index (ω) separately as independent variables and have obtained a correlation, R of 0.732, 0.687 and 0.694 respectively with BA of PCDFs with rat hepatic cytosol Ah receptor. Almost a similar correlation has been seen with AHH induction potencies of PCDFs in rat hepatoma H-4-II E cells and EROD induction potencies of PCDFs in rat cells. In our case using electrophilicity index (ω) for a set of 27 PCDFs, we get correlation coefficients of 0.891 with the toxicity (pIC_{50}) values in gas phase. Similar results are obtained for the descriptors of PCDFs studied in the solvent phase. Further Arulmozhiraja et al have also tried in the same paper two and three parameter QSARs using a combination of DFT based descriptors (S, χ, ω) alongwith a hydrophobic term (log P) and a topological parameter, $L_{\max}$ defined as the greatest interatomic distance in PCDFs. They have obtained correlation coefficients in the range of 0.794 to 0.881, lower than that obtained using only DFT based one parameter QSARs in the present study. The electrophilicity index (ω), tells us about

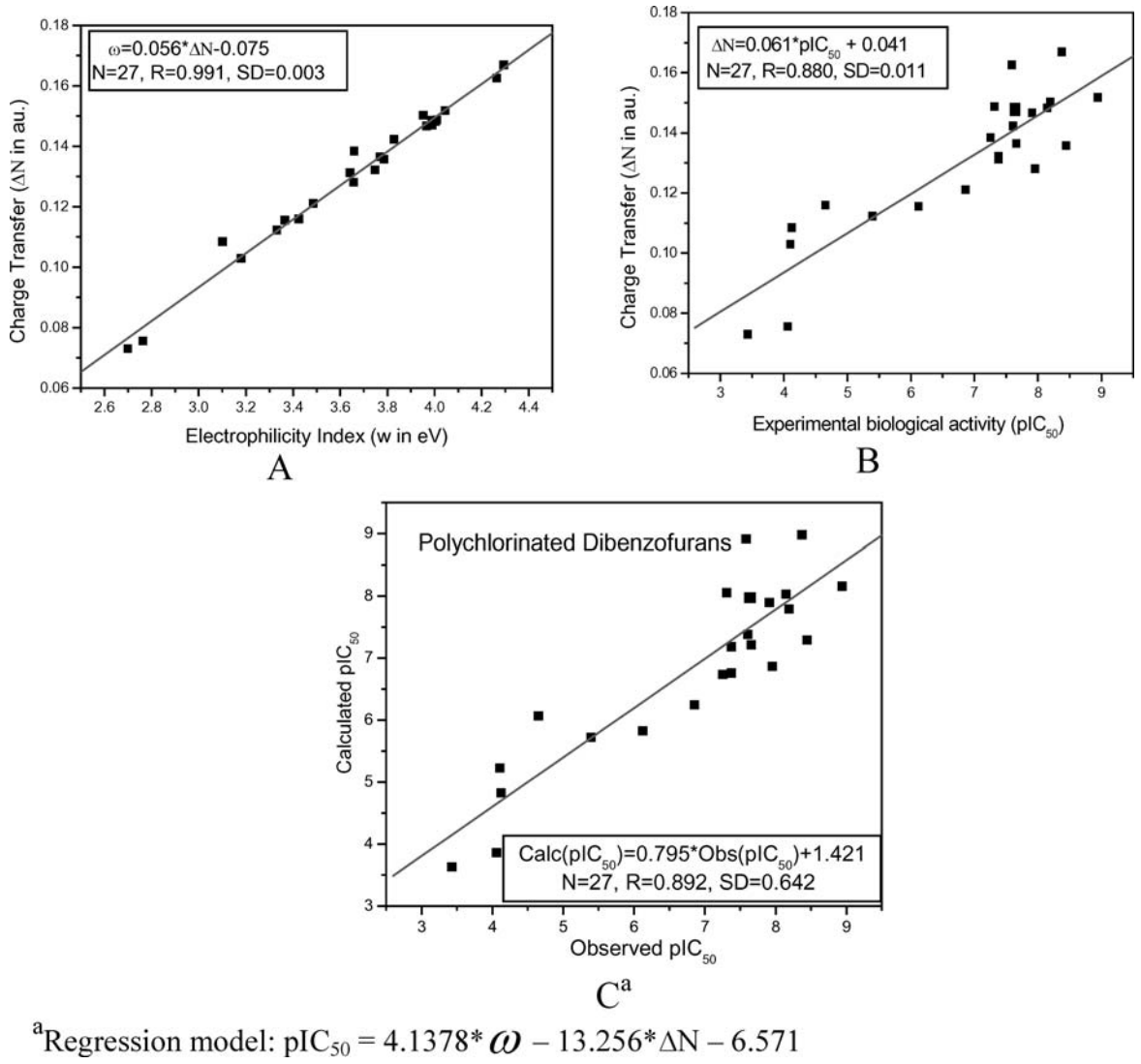


Figure 2. Variation of charge transfer with (A) electrophilicity index (ω), (B) the experimental biological activity (pIC_{50}) during interaction of polychlorinated dibenzo furan with GCWC base pair and (C) Observed versus calculated pIC_{50} values of polychlorinated dibenzo furan using electrophilicity index (ω) and ΔN with GCWC base pair.

the global reactivity of the selected molecules thereby having a direct relationship with toxicity unlike other parameters. Thus with only one descriptor we are able to get a better correlation with the experimental toxicity values. Further interrelationship among the selected descriptors is good enough compared to their descriptors. This shows the significance of the selected descriptor in the toxicity analyses on PCDFs and PCBs.

Waller et al [27] have also carried out QSAR analysis on dioxins and dioxin like compounds using comparative molecular field analysis (CoMFA), a three dimensional QSAR paradigm, to explore the physico-chemical requirements for binding to the Ah (dioxin) receptor. The relative success or failure of any CoMFA/QSAR model is dependent on the procedure adopted for the alignment or superposition, of molecules in the data set. The working hypothesis for them has been that there might be a stacking interaction operating in the molecular recognition event in which the most highly halogenated ring would be considered to be the preferred stacking plane for unsymmetrically substituted molecules. They have obtained partial atomic charges at AM1 level of calculation, whose reliability is itself questionable compared to MPA/NPA/HPA derived charges obtained by us at B3LYP/6–31G* level DFT calculations. They have obtained a correlation coefficient ($R = 0.950$) using a combined set of dioxins, furans and biphenyls through the related toxicity (pIC_{50}) values. Using only one parameter electrophilicity index (ω) obtained correlation is sufficiently high for the set of 27 PCDFs (0.891) which is used as the training set and for the set of PCBs (0.834) which is used as the test set of the PCDFs. Similar trend is obtained also in solvent phase optimized descriptors with pIC_{50} values for the combined set

Table 7. Charge transfer (ΔN) between different amines and nucleic acid bases/base pairs in gas phase.

S.No.	Molecule	Adenine	Thymine	Guanine	Cytosine	Uracil	GCWC	ATH
1	Propylamine	−0.0808	−0.1213	−0.0484	−0.1005	−0.1360	−0.0857	−0.0960
2	Butylamine	−0.0811	−0.1215	−0.0487	−0.1008	−0.1363	−0.0860	−0.0962
3	N-Methylpropylamine	−0.0979	−0.1392	−0.0646	−0.1182	−0.1541	−0.1053	−0.1143
4	Amylamine	−0.0815	−0.1225	−0.0486	−0.1015	−0.1375	−0.0865	−0.0969
5	N–Methylbutylamine	−0.1000	−0.1411	−0.0668	−0.1203	−0.156	−0.1076	−0.1164
6	N,N–Dimethylethylamine	−0.1067	−0.1487	−0.0728	−0.1275	−0.1638	−0.1155	−0.1238
7	(+/−)-sec-Butylamine	−0.0729	−0.1139	−0.0401	−0.0928	−0.1290	−0.0768	−0.0878
8	Isoamylamine	−0.0801	−0.1206	−0.0476	−0.0998	−0.1354	−0.0849	−0.0952
9	1–Methylbutylamine	−0.0733	−0.1144	−0.0405	−0.0932	−0.1294	−0.0773	−0.0883
10	1–Ethylpropylamine	−0.0759	−0.1169	−0.0431	−0.0958	−0.1319	−0.0802	−0.0910
11	N,N-Diethylmethylamine	−0.1076	−0.1495	−0.0736	−0.1283	−0.1646	−0.1164	−0.1247
12	tert–Amylamine	−0.0659	−0.1077	−0.0326	−0.0860	−0.1230	−0.0689	−0.0807
13	(+/−)-1,2–Dimethylpropylamine	−0.0742	−0.1156	−0.0411	−0.0943	−0.1308	−0.0783	−0.0894
14	Propargylamine	−0.0260	−0.0690	0.0077	−0.0462	−0.0851	−0.0235	−0.0392
15	N–Methylpropargylamine	−0.0478	−0.0921	−0.0128	−0.0690	−0.1085	−0.0484	−0.0627
16	2–Methoxyethylamine	−0.0696	−0.1104	−0.0371	−0.0894	−0.1254	−0.0731	−0.0843
17	3–Methoxypropylamine	−0.0746	−0.1157	−0.0418	−0.0945	−0.1307	−0.0788	−0.0897
18	3–Ethoxypropylamine	−0.0752	−0.1162	−0.0423	−0.0951	−0.1312	−0.0794	−0.0902

Table 8. Regression models, correlation coefficient (R) and the standard deviations (SD) for the polychlorinated dibenzo furans and aliphatic amines in gas phase for the training set using NPA.

System	Method	Regression Equation	N	R	SD
PCDFs		$pIC_{50} = 3.3944 * \omega - 5.5788$	27	0.891	0.642
Amines	NPA	$pIC_{50} = 2.1252 * \omega^{-}_{N\,max} - 1.6828$	18	0.936	0.140

of PCDFs and PCBs. Since the charge transfer process plays a vital role in toxicity analysis, electrophilicity (ω) values should have a direct relation with toxicity. Thus with less number of descriptors, reliable DFT based parameters, good contribution from individual descriptors to toxicity and good interrelationship among descriptors, have made our selection of descriptors better for the toxicity analysis of PCDFs and PCBs.

Tysklind et al [51] have analyzed the ethoxyresorufin *O*-deethylase (EROD) induction of polychlorinated dibenzofurans (PCDFs) in the H4IIE rat hepatoma cell bioassay. In order to establish a quantitative structure-activity relationship (QSAR) for the toxic equivalency factor (TEF) values, several physicochemical descriptor variables have been used by them to chemically characterize the tetra- to octachlorinated PCDFs. The predicted TEF indicates that a large number of congeners are potent EROD inducers. But the advantage in our present study over the above analysis is that using only one descriptor we are able to get good correlation for the selected sets of PCDFs and PCBs when compared to 37 descriptors used by them, which induces computational difficulties and the existence of very low individual contributions and a virtually no direct relationship of each descriptor with the toxicity.

Aliphatic amines

Aliphatic amines are known [52] to be electron donors in their interaction with biomolecules. Hence for the regression analysis, the ω^{-}_{max} of the atom with the maximum value of local

Table 9. Experimental and calculated biological activity (pIC_{50}) in gas phase for the training set of aliphatic amines.

Sl No.	Molecules	ω	ω^{-}_{max} (NPA)	Observed[a] $\log(IGC^{-1}_{50})$	Calculated $\log(IGC^{-1}_{50})$
1	Propylamine	0.636	0.459	−0.708	−0.673
2	Butylamine	0.634	0.457	−0.574	−0.678
3	N–Methylpropylamine	0.546	0.363	−0.809	−0.886
4	Amylamine	0.622	0.452	−0.485	−0.689
5	N-Methylbutylamine	0.542	0.359	−0.678	−0.895
6	N,N-Dimethylethylamine	0.477	0.294	−0.908	−1.039
7	(±)–sec-Butylamine	0.663	0.478	−0.671	−0.631
8	Isoamylamine	0.651	0.469	−0.577	−0.651
9	1–Methylbutylamine	0.655	0.471	−0.685	−0.647
10	1–Ethylpropylamine	0.631	0.456	−0.813	−0.680
11	N,N–Diethylmethylamine	0.489	0.303	−0.756	−1.019
12	tert–Amylamine	0.700	0.503	−0.698	−0.576
13	(+/−)-1, 2-Dimethylpropylamine	0.637	0.458	−0.710	−0.676
14	Propargylamine	0.690	0.495	−0.826	−0.594
15	N-Methylpropargylamine	0.636	0.419	−0.982	−0.762
16	2-Methoxyethylamine	0.659	0.002	−1.790	−1.685
17	3-Methoxypropylamine	0.661	0.003	−1.773	−1.683
18	3-Ethoxypropylamine	0.660	0.003	−1.703	−1.683

[a] Experimental data as given in reference [27].

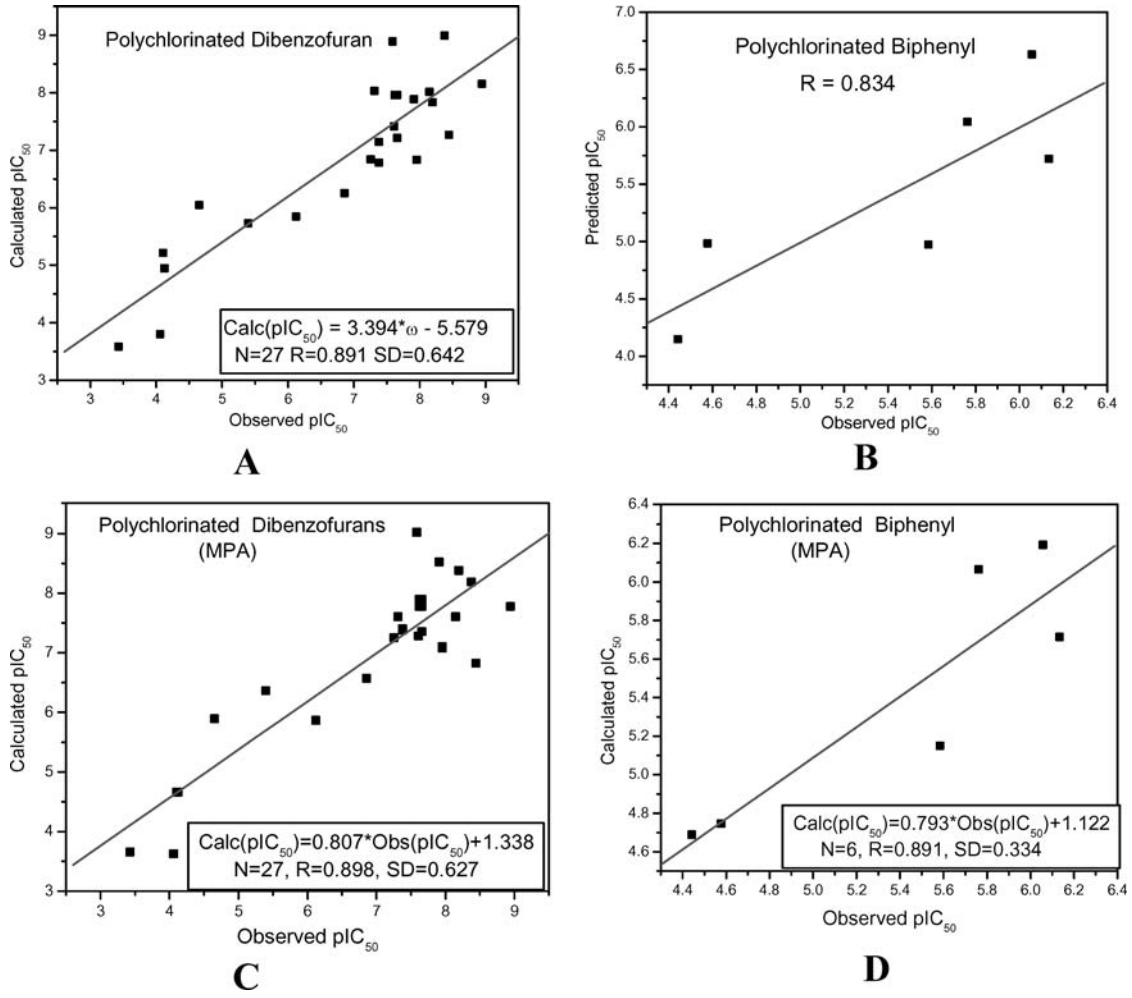


Figure 3. (A) Calculated versus observed values of biological activity (pIC_{50}) for training set of PCDFs, (B) Predicted versus observed values of biological activity (pIC_{50}) for test set of PCBs in gas phase. Calculated versus observed biological activity (pIC_{50}) values using MPA derived Δ_{ij}^{ω} between guanine and (C) PCDFs and (D) PCBs.

nucleophilicity ($\omega_{\max}^{-}$) at the nitrogen (N) site in a molecule is considered as an independent variable because there is no global nucleophilicity index.

The gas phase data (Table 9) of the training set of aliphatic amines are used for the linear regression analysis (Table 8). The observed along with calculated $\log(IGC_{50}^{-1})$ values are presented in Table 9. The NPA derived $\omega_{\max}^{-}$ values are capable of providing a correlation (R) of 0.936.

In this case the QSAR equation becomes:

$$pIC_{50} = 2.2137\ (0.2076)*\omega_{N\,\max}^{-} - 1.6895\ (+0.0822)$$
$$N = 18,\ SE = 0.1493,\ R = 0.9363,\ R_{\text{adj}}^{2} = 0.8689$$

t-tests reveal again the significance of the constant and the coefficient of $\omega_{N\,\max}^{-}$. The F-ratio was found to be 113.7066, a high value compared to $F\ (0.01; 1; 17) = 8.4$. Q^2 leaving out 5 points was found to be 0.8243, a high value. The probability that the correlation is merely a chance correlation is 0.18×10^{-5}, indicating that a random distribution of the points is very unlikely to yield the computed correlation coefficient.

This QSAR model is used to predict the pIC_{50} values of molecules in the test set of amino alcohols. Figure 4B shows the correlation obtained between the experimental activities and the ones predicted for the test set using the above QSAR equation.

Here R looks good, but the equation is $y = 0.0094x - 1.6427$, which is too far from $y = x$. Looking at the distribution of the points, it looks more or less like just two "spots". The high Q squared reported above indicates good internal validation, but it is well-known that internal cross validation can only decisively point out if a model has bad predictive capacities. A high Q^2 does not automatically infer high predicitive capacity for an external test set. May be more than one descriptor is needed for donor type toxins especially with more than one active sites and/or there is a possibility that two reaction mechanisms play a role. It

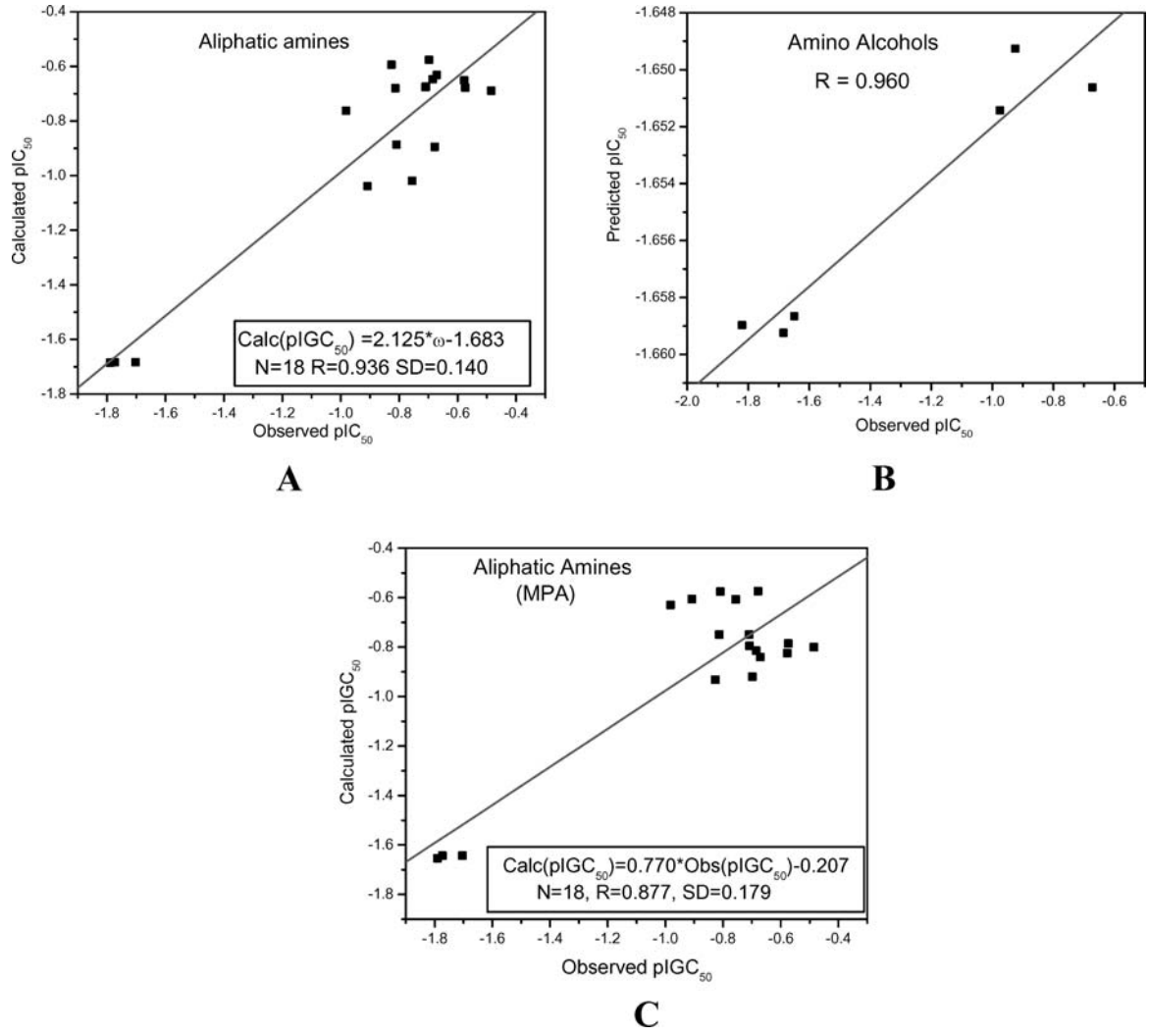


Figure 4. (A) Calculated versus observed values of the activity ($pIGC_{50}$) for training set of aliphatic amines and (B) Predicted versus observed values of biological activity ($pIGC_{50}$) for test set of Amino alcohols in gas phase using NPA method. Calculated versus observed biological activity ($pIGC_{50}$) values using MPA derived Δ_{ij}^{ω} between (C) uracil and aliphatic amines.

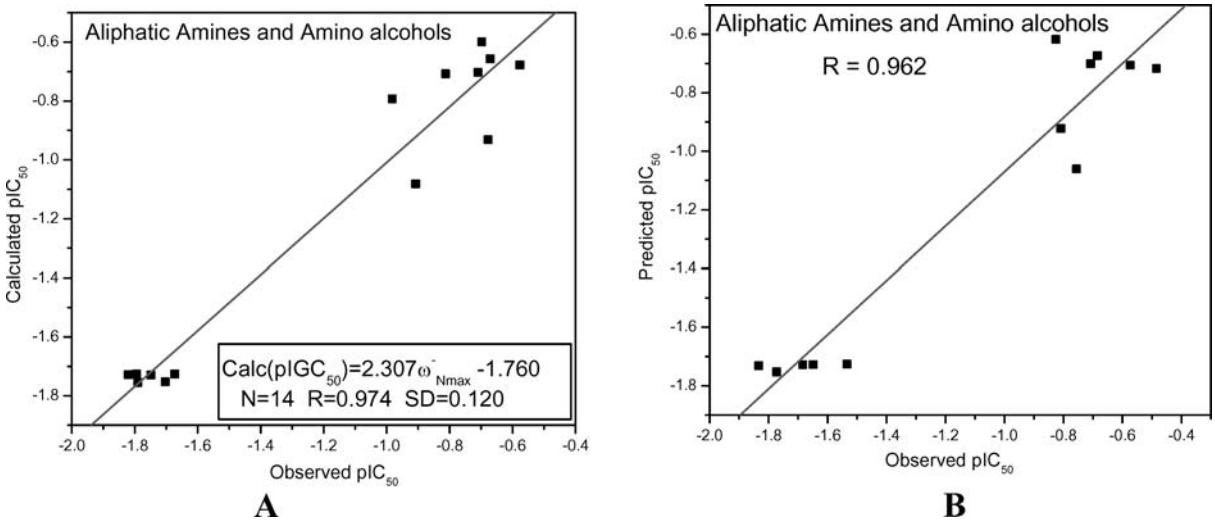


Figure 5. (A) Calculated versus observed activity ($pIGC_{50}$)) values of the training set of aliphatic amines and amino alcohols and (B) Predicted versus observed activity (log ($pIGC_{50}$) values for the test set of aliphatic amines and amino alcohols in gas phase using NPA method.

Table 10. Experimental and predicted biological activity (pIC_{50}) in gas phase for the test set of amino alcohols.

No.	Molecules	ω	$\omega^-_{N\,max}$ (NPA)	Observed $pIGC_{50}$	Calculated $pIGC_{50}$
1	2-(methylamino)ethanol	0.5611	0.0138	−1.8202	−1.6590
2	4-amino-1-butanol	0.6562	0.0172	−0.9752	−1.6514
3	2-(ethylamino)ethanol	0.5658	0.0139	−1.6491	−1.6587
4	2-Propylaminoethanol	0.5548	0.0137	−1.6842	−1.6592
5	DL-2-amino-1-pentanol	0.6623	0.0176	−0.6718	−1.6506
6	3-amino-2, 2-dimethyl-1-propanol	0.6792	0.0182	−0.9246	−1.6493

Table 11a. Experimental and calculated biological activity (pIC_{50}) in gas phase for the training set of aliphatic amines and amino alcohols.

No.	Molecule	ω	$\omega^-_{N\,max}$ (NPA)	Obs $pIGC_{50}$	Calc. $pIGC_{50}$
1	2-Methoxyethylamine	0.659	0.002	−1.790	−1.755
2	3-Ethoxypropylamine	0.660	0.003	−1.703	−1.753
3	triethanolamine	0.560	0.013	−1.7488	−1.73
4	2-(methylamino)ethanol	0.561	0.0138	−1.8202	−1.728
5	2-(tert.butylamino)ethano	0.586	0.0145	−1.673	−1.726
6	diethanolamine	0.588	0.0146	−1.7941	−1.726
7	N,N–Dimethylethylamine	0.477	0.294	−0.908	−1.081
8	N–Methylbutylamine	0.542	0.359	−0.678	−0.931
9	N–Methylpropargylamine	0.636	0.419	−0.982	−0.793
10	1–Ethylpropylamine	0.631	0.456	−0.813	−0.707
11	(+/−)-1, 2–Dimethylpropylamine	0.637	0.458	−0.710	−0.703
12	Isoamylamine	0.651	0.469	−0.577	−0.677
13	(+/−)-sec-Butylamine	0.663	0.478	−0.671	−0.657
14	tert-Amylamine	0.700	0.503	−0.698	−0.599

Table 11b. Experimental and predicted biological activity (pIC_{50}) in gas phase for the test set of aliphatic amines and amino alcohols.

No.	Molecule	ω	$\omega^-_{N\,max}$ (NPA)	Obs $pIGC_{50}$	Calc. $pIGC_{50}$
1	3-Methoxypropylamine	0.661	0.003	−1.773	−1.7527
2	N-methyldiethanol amine	0.531	0.0122	−1.8338	−1.7315
3	2-Propylaminoethanol	0.555	0.0137	−1.6842	−1.728
4	2-(ethylamino)ethanol	0.566	0.0139	−1.6491	−1.7276
5	3-(methylamino)–1, 2–propanediol	0.594	0.0145	−1.5341	−1.7262
6	N,N–Diethylmethylamine	0.489	0.303	−0.756	−1.0605
7	N–Methylpropylamine	0.546	0.363	−0.809	−0.922
8	Amylamine	0.622	0.452	−0.485	−0.7167
9	Butylamine	0.634	0.457	−0.574	−0.7051
10	Propylamine	0.636	0.459	−0.708	−0.7005
11	1–Methylbutylamine	0.655	0.471	−0.685	−0.6728
12	Propargylamine	0.690	0.495	−0.826	−0.6175

deserves a careful scrutiny. The correlation between Δ^{ω}_{ij} of amines and uracil (Figure 4C) and the related pIC_{50} values is reasonably well. Toxicity is inversely related to Δ^{ω}_{ij}, as expected.

For further cross-validation [53] we have amalgamated the training and test sets and generated new sets (Table 11 and Figure 5). As usual the correlation is very good. For a training set (Table 11a and Figure 5a) we have the QSAR equation as $Y = 2.3074 * X - 1.7596$ (both parameters are relevant as dictated by the t-test), $N = 14$ (point number 8 is a possible outlier), $R = 0.9743$, $R^2_{adj} = 0.9451$, $SE = 0.1229$, $Q^2 = 0.9329$, $F = 224.5973$. This QSAR equation is then applied on the test set (Table 11b, Figure 5b) resulting in $R = 0.9620$ for $N = 12$. A 2-descriptor correlation analysis is currently underway in our laboratory.

Conclusions

Experimental biological activities (pIC_{50}) of different polyaromatic hydrocarbons (PAH) namely polychlorinated dibenzofurans (PCDF) and polychlorinated biphenyls (PCB) are correlated with their corresponding activity (pIC_{50}values) calculated/ predicted using the electrophilicity index through regression analysis in gas phase. Also in the case of aliphatic amines and amino alcohols local philicity (ω^-_{max}) is shown to be capable of explaining the activity (log (IGC^{-1}_{50})) in an elegant manner albeit with slight cross-validation problem. The PAHs behave as electron acceptors during their interactions with biosystems, while the aliphatic amines act as electron donors. A reasonably good correlation has been obtained for all the systems showing the significance of the selected conceptual DFT based descriptors in the prediction of toxicity with similar trends originating from the NPA scheme. Reasonably good correlation of the amount of charge transfer with toxicity implies that the charge transfer plays a crucial role in the observed toxic behavior of PAHs and amines. Reasonably well correlations are obtained between Δ^{ω}_{ij} and pIC_{50} values for both electron donor and acceptor type toxins.

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