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Electrophilicity as a possible descriptor for toxicity prediction

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Abstract—Electrophilicity is one of the cardinal chemical reactivity descriptors successfully employed in various molecular reactivity studies within a structure–activity relationship parlance. The applications of this quantity in the modeling of toxicological properties have inspired us to perform a more exhaustive study in order to test and/or to validate the application of electrophilicity in assessing its chemical and toxicological potential. For this reason the toxicity of a large data set of molecules comprising 252 aliphatic compounds on the *Tetrahymena pyriformis* is studied. A quantitative structure–activity relationship analysis enabled us to model toxicity in terms of global and local electrophilicities, which provide a reasonably good prediction of aliphatic toxicity. It is heartening to note that the global and local electrophilicity values together can explain the toxicity of a large variety of aliphatic compounds nicely without resorting to any other descriptor or other microscopic/macroscopic physicochemical properties as is the situation in all other QSAR studies.

1. Introduction

Electrophilicity index (ω) is defined within a density functional theory (DFT)[1] framework, by Parr et al.[2] as a measure of energy lowering due to maximal electron flow between a donor and an acceptor. They defined electrophilicity index (ω) as follows:

$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

where $\mu \approx -(I + A)/2$ and $\eta \approx (I - A)/2$ are the electronic chemical potential and the chemical hardness of the ground state of atoms or molecules, respectively, approximated in terms of the vertical ionization potential (I) and electron affinity (A). The earlier works of Maynard and Covell[3] have formed the basis for the electrophilicity index, which provided the direct relationship between the rates of reaction and the ability to identify the function or capacity of an electrophile and the electrophilic power of the inhibitors. This new reactivity index measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment. The electrophilicity is a descriptor of reactivity that allows a quantitative classification of the global electrophilic nature of a molecule within a relative scale. The importance of this new reactivity quantity has been recently demonstrated in understanding the toxicity of various pollutants in terms of their reactivity and site selectivity. The usefulness of electrophilicity index in unraveling the toxicity of polychlorinated biphenyls and benzidine has been analyzed.[4,5] It was found that electrophilicity is sufficient to describe the toxicity of those molecules. It has been believed that the interaction between a toxin and a biosystem essentially occurs through a charge transfer process supplemented by the π-stacking. Hence the importance of global and local electrophilicities as well as the conformational flexibility of the toxins in understanding the toxicity of these molecules is felt.[4,5]

Subsequently, attempts have been made to probe the usefulness of electrophilicity and other global quantities in the QSAR parlance. The ability of electrophilicity to predict the biological activity of testosterone derivatives with activity described in terms of various biological activity parameters and of the estrogen derivatives by relative binding affinity (RBA) values has also been probed.[6] It is observed[6] that the electrophilicity index is suitable in effectively describing the biological activity.

Recently, the generalized concept of philicity has been proposed by Chattaraj et al.[7] It contains almost all

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information about hitherto known different global and local reactivity and selectivity descriptors, in addition to the information regarding electrophilic/nucleophilic power of a given atomic site in a molecule. It is possible to define a local quantity called philicity associated with a site k in a molecule with the help of the corresponding condensed-to-atom variants of the Fukui function (FF), f_k^α, as[7]

$$\omega_k^\alpha = \omega f_k^\alpha \tag{2}$$

where α represents local philic quantities describing nucleophilic (+), electrophilic (−) and radical (0) attacks. In Eq. 2 the condensed Fukui functions are calculated as follows:

$$f_k^+ = q_k(N+1) - q_k(N) \quad \text{for nucleophilic attack} \tag{3a}$$

$$f_k^- = q_k(N) - q_k(N-1) \quad \text{for electrophilic attack} \tag{3b}$$

$$f_k^0 = [q_k(N+1) - q_k(N-1)]/2 \quad \text{for radical attack} \tag{3c}$$

where q_k is the electronic population of atom k in a molecule.

In the light of the generalized philicity concept, a group philicity (ω_g) has also been defined.[8] Usefulness of the unified philicity concept and the group philicity (ω_g) to predict the intermolecular reactivity trends in various carbonyl compounds vis-a-vis other known local descriptors has been investigated.[8]

Computer simulation techniques have gained significance in bridging the gap between the experimental and theoretical evidences. Modeling macroscopic processes in the realistic environment is one of the most challenging problems in theoretical and computational chemistry. Recently, QSAR has gained importance in the field of pharmacological sciences.[9,10] The QSAR methodologies save resources and expedite the process of development of new molecules and drugs. Success of QSAR not only rests on the development of new drug molecules but also in exploring the toxicological and ecotoxicological characteristics of molecules.[11–16] Quantitative structure–toxicity relationships (QSTRs) are predictive tools for a preliminary evaluation of the hazards of chemical compounds by using computer aided models. Use of quantum chemical descriptors in the development of QSAR has received attention due to their reliability and versatility of prediction.[1,17–19] Specifically, toxicity of various chemical compounds and associated biochemical processes have been related to their molecular structures. In this context, the SAR based on electrophilicity is shown to be promising. The purpose of the present study is to estimate the predictive potential of the electrophilicity for modeling the toxicity of aliphatic chemical compounds on *Tetrahymena pyriformis*.

T. pyriformis is one of the generally used ciliated protozoa for laboratory research.[20–22] In this ciliate species, diverse endpoints can be used to originate the cytotoxic effects and xenobiotics. Experimental determination of toxicological and biochemical endpoints as well as the human health endpoints is a difficult task. Hence, QSAR modeling of the toxicity of aliphatic compounds on the *T. pyriformis* is of vital importance in investigating its toxicity in terms of its inhibitory growth concentration, using the predictive power of electrophilicity and local philicity indices.

2. Computational details

Six different groups of aliphatic compounds such as alcohols (saturated, unsaturated, α-acetylenic, amino, diol and halogenated), esters (mono and di), acids (carboxylic and halogenated), aldehydes, ketones and amines are chosen with their toxicity values in terms of 50% inhibitory growth concentration (IGC_{50}^{-1}) against the ciliate *T. pyriformis*. All the geometries are optimized at the Hartree–Fock level with the 6-311G** basis set using the *Gaussian03* package.[23] Electrophilicity and the local philicity values are calculated using the standard working equations. For calculation of $(N+1)$ or $(N-1)$ electronic system, the same optimized structure of N electronic system has been used. The ω_m^+ value has been calculated on the carbon (C) site with maximum f^+ value and the ω_m^- values are calculated on the oxygen (O) or nitrogen (N) site with maximum f^- value. The condensed Fukui function values f^+ and f^- are calculated using both the MPA[24] and NPA[25] population analysis schemes. By comparing the electronegativity values of the aliphatic compounds with the corresponding values of NA/DNA bases/base pairs, electron accepting/donating nature of the selected group of aliphatic compounds were determined. Two parameter QSARs are performed[26] using least square error estimation method[27] to predict the toxicity values.

3. Results and discussion

The structure–toxicity modeling of the selected 252 aliphatic compounds with the ciliate *T. pyriformis* ($\log(IGC_{50}^{-1})$) using DFT based descriptors namely, electrophilicity and local philicity as predictors is presented in this study. Both the MPA[24] and NPA[25] schemes show almost similar correlations between the experimental and predicted toxicity values and only NPA results are reported due to their slightly better performance in most cases. The regression modeling is obtained with the experimental toxicity data ($\log(IGC_{50}^{-1})$) of the compounds taken as dependent variable and the DFT based descriptors namely, electrophilicity and local philicity (ω_m^+/ω_m^-) as independent variables. Initially the analysis has been carried out by dividing the set of 252 aliphatic compounds into six groups viz., alcohols, acids, esters, aldehydes, ketones and amines. Then combining all these groups, an overall estimation has also been studied. Analysis has been carried out with the idea that each of these compounds is thought of exhibiting toxicity through an electrophilic (nucleophilic) mechanism.

To simplify the analysis selected compounds are classified based on their electron donating/accepting nature by comparing their electronegativity values with those of the nucleic acid bases (adenine, thymine, guanine, cytosine and uracil)/selected DNA base pairs (GCWC and ATH).[4] Each groups are identified as electron acceptor/donor according to the tendency of the major members in the respective group. Nine groups are found to be electron acceptors (saturated alcohols, diols and halogenated alcohols, mono and diesters, carboxylic and halogenated acids, aldehydes and ketones) and four groups were found to be electron donors (unsaturated, α-acetylenic and amino alcohols and amines). We therefore calculated ω_m^+ for the systems belonging to the electron acceptor group and ω_m^- for the members of the electron donor group to get a correlation. Among the biosystems (simulated by NA bases/DNA base pairs) uracil and guanine are the most and the least electronegative compounds, respectively, and are in general exceptions (uracil is the acceptor when other bases are donors and guanine is the donor when other bases are acceptors) in the situations when all bases/base pairs do not show the identical behaviour towards electron flow to/from the aliphatic toxins. It may be noted that this simulation by NA bases/DNA base pairs may not be always sacrosanct, which, however, is used here only to assign the direction of the electron flow between the toxin and the biosystem.

3.1. Aliphatic alcohol

Aliphatic alcohols can be classified under the following categories viz., saturated, unsaturated, α-acetylenic, amino, diol and halogenated alcohol. The regression models of the above systems for the NPA scheme are reported in Table 1. Some of the α-acetylenic alcohols behave as electron acceptors when interact with NA bases/DNA base pairs.

All the experimental and predicted $\log(IGC_{50}{}^{-1})$ values of saturated alcohols are presented in Table 2. The correlation coefficient (r^2) among the observed and predicted $\log(IGC_{50}{}^{-1})$ ranges from 0.751 to 0.929 for all the six aliphatic alcohol groups.

A correlation plot between the experimental and predicted $\log(IGC_{50}{}^{-1})$ values for the complete set of selected 109 aliphatic alcohols (Fig. 1) with r^2 value 0.831 shows the effectiveness of choosing electrophilicity and local philicity together as predictors of toxicity.

3.2. Aliphatic acid

Regression models along with coefficients of determination as 0.788 and 0.785, respectively, of the selected carboxylic and halogenated acids are presented in Table 1. The experimental and predicted $\log(IGC_{50}{}^{-1})$ values for carboxylic and halogenated acids are given in Table 2.

A combined analysis involving the complete set of selected 39 aliphatic acids considered in this study shows that ω and local philicity are capable of explaining maximum variation in data (78.7%) with a low SD of 0.187 (Fig. 2). Hence ω and local philicity (ω_m^+) seem to be good predictors of the toxicity of aliphatic acids.

3.3. Aliphatic ester

Aliphatic esters consisting of mono- and di-esters along with their regression models and coefficients of determination are given in Table 1. The experimental and the predicted $\log(IGC_{50}{}^{-1})$ values for both the mono- and di-esters are provided in Table 2. Some of the diesters act as electron donors when interacted with NA bases/DNA base pairs.

Experimental and predicted $\log(IGC_{50}{}^{-1})$ values of the complete set of selected 51 aliphatic esters plotted in Figure 3 gives a coefficient of determination 0.766. This provides the fact that global and local philicity can be used together as better predictors of toxicity.

Table 1. Regression models, coefficient of determinations and the standard deviations for the different groups of the aliphatic compounds

Aliphatic compounds	Regression model	r^2	SD
Aliphatic alcohols			
Amino alcohols	$\log(IGC_{50}^{-1}) = -0.4016 * \omega - 2.1948 * \omega_m^- - 1.5179$	0.929	0.139
α-Acetylenic alcohols	$\log(IGC_{50}^{-1}) = -60.8818 * \omega - 15.0335 * \omega_m^- + 36.15186$	0.768	0.454
Diols	$\log(IGC_{50}^{-1}) = -35.9319 * \omega - 14.7924 * \omega_m^+ + 30.7237$	0.809	0.486
Halogenated alcohols	$\log(IGC_{50}^{-1}) = -11.8389 * \omega - 0.0875 * \omega_m^+ + 10.7962$	0.763	0.415
Saturated alcohols	$\log(IGC_{50}^{-1}) = -27.2555 * \omega - 6.1169 * \omega_m^+ + 23.8691$	0.778	0.607
Unsaturated alcohols	$\log(IGC_{50}^{-1}) = -10.3735 * \omega - 3.2555 * \omega_m^- + 4.4651$	0.751	0.321
Aliphatic acids			
Carboxylic acids	$\log(IGC_{50}^{-1}) = -7.3980 * \omega - 2.3302 * \omega_m^+ + 7.0966$	0.788	0.180
Halogenated acids	$\log(IGC_{50}^{-1}) = 2.0081 * \omega + 1.5738 * \omega_m^+ - 2.1139$	0.785	0.223
Aliphatic esters			
Monoesters	$\log(IGC_{50}^{-1}) = -28.6178 * \omega - 0.2133 * \omega_m^+ + 26.4532$	0.763	0.458
Diesters	$\log(IGC_{50}^{-1}) = -10.9817 * \omega + 1.1645 * \omega_m^+ + 7.0714$	0.745	0.465
Aldehydes	$\log(IGC_{50}^{-1}) = -4.9428 * \omega + 4.4641 * \omega_m^+ + 3.8681$	0.803	0.248
Ketones	$\log(IGC_{50}^{-1}) = -42.4946 * \omega - 0.3212 * \omega_m^+ + 34.2450$	0.778	0.612
Amines	$\log(IGC_{50}^{-1}) = -1.6894 * \omega - 2.3265 * \omega_m^- - 0.6727$	0.791	0.188

Table 2. Experimental and calculated values of $\log(IGC_{50}^{-1})$ for the complete set of aliphatic compounds with *Tetrahymena pyriformis*

No.	Molecule	$\log(IGC_{50}^{-1})$	
		Expt[a]	Calcd[b]
Alcohols: amino alcohols			
1	2-(Methylamino)ethanol	−1.8202	−1.7173
2	4-Amino-1-butanol	−0.9752	−0.7542
3	2-(Ethylamino)ethanol	−1.6491	−1.7228
4	2-Propylaminoethanol	−1.6842	−1.7190
5	DL-2-Amino-1-pentanol	−0.6718	−0.7349
6	3-Amino-2,2-dimethyl-1-propanol	−0.9246	−0.7051
7	6-Amino-1-hexanol	−0.9580	−0.7667
8	DL-2-Amino-1-hexanol	−0.5848	−0.7344
9	DL-2-Amino-3-methyl-1-butanol	−0.5852	−0.7683
10	2-Amino-3,3-dimethyl-butanol	−0.7178	−0.7582
11	2-Amino-3-methyl-1-pentanol	−0.6594	−0.7704
12	2-Amino-4-methyl-pentanol	−0.6191	−0.7456
13	2-(*tert*-Butylamino)ethanol	−1.6730	−1.7296
14	Diethanolamine	−1.7941	−1.7271
15	1,3-Diamino-2-hydroxy-propane	−1.4275	−1.3486
16	*N*-Methyldiethanol amine	−1.8338	−1.7093
17	3-(Methylamino)-1,2-propanediol	−1.5341	−1.7294
18	Triethanolamine	−1.7488	−1.7197
α-Acetylenic alcohols			
1	3-Butyn-2-ol	−0.4024	−0.8605
2	1-Pentyn-3-ol	−1.1776	−0.8974
3	2-Pentyn-1-ol	−0.5724	−0.2757
4	2-Penten-4-yn-1-ol	−0.5549	−0.6276
5	1-Hexyn-3-ol	0.6574	−0.0108
6	1-Heptyn-3-ol	−0.2650	0.1742
7	4-Heptyn-3-ol	−0.0336	−0.0762
8	2-Octyn-1-ol	0.1944	0.3618
9	2-Nonyn-1-ol	0.6486	1.0400
10	2-Decyn-1-ol	0.9855	1.1035
11	2-Tridecyn-1-ol	2.3665	1.4479
12	4-Methyl-1-pentyn-3-ol	−0.0267	−0.0108
13	4-Methyl-1-heptyn-3-ol	0.7426	1.1939
Diols			
1	(±)-1,2-Butanediol	−2.0482	−1.7370
2	(±)-1,3-Butanediol	−2.3013	−2.8507
3	1,4-Butanediol	−2.2365	−1.3755
4	1,2-Pentanediol	−1.6269	−1.3986
5	1,5-Pentanediol	−1.9344	−1.4975
6	2-Methyl-2,4-pentanediol	−1.9531	−2.4013
7	(±)-1,2-Hexanediol	−1.2669	−1.2254
8	1,6-Hexanediol	−1.4946	−1.6112
9	1,2-Decanediol	0.7640	0.3895
10	1,10-Decanediol	0.2240	−0.1663
Halogenated alcohols			
1	2-Bromoethanol	−0.8457	−0.3538
2	2-Chloroethanol	−1.4174	−1.5343
3	1-Chloro-2-propanol	−1.4920	−1.2446
4	3-Chloro-1-propanol	−1.3992	−1.1622
5	4-Chloro-1-butanol	−0.7594	−0.5329
6	3-Chloro-2,2-dimethyl-1-propanol	−0.7822	−0.8568
7	6-Chloro-1-hexanol	−0.2726	−0.3530
8	8-Chloro-1-octanol	0.4878	−0.1879
9	6-Bromo-1-hexanol	0.0074	0.5721
10	8-Bromo-1-octanol	1.0424	0.6629
11	2,3-Dibromopropanol	−0.4861	−0.9264
Saturated alcohols			
1	Methyl alcohol	−2.6656	−1.6737
2	Ethyl alcohol	−1.9912	−1.1817
3	1-Propanol	−1.7464	−0.6668
4	2-Propanol	−1.8819	−2.0221
5	1-Butanol	−1.4306	−0.5057
6	(±)-2-Butanol	−1.5420	−1.3589
7	2-Methyl-1-propanol	−1.3724	−0.5559
8	2-Pentanol	−1.1596	−0.8549
9	3-Pentanol	−1.2437	−0.5792
10	3-Methyl-2-butanol	−0.9959	−0.5801
11	*tert*-Amylalcohol	−1.1729	−1.7071
12	2-Methyl-1-butanol	−0.9528	−0.8265
13	3-Methyl-1-butanol	−1.0359	−1.2548
14	2,2-Dimethyl-1-propanol	−0.8702	−1.4445
15	2-Methyl-2-propanol	−1.7911	−2.2465
16	1-Hexanol	−0.3789	−0.5329
17	3,3-Dimethyl-1-butanol	−0.7368	−1.7219
18	4-Methyl-1-pentanol	−0.6372	−1.4506
19	1-Heptanol	0.1050	−0.5543
20	2,4-Dimethyl-3-pentanol	−0.7052	−0.9954
21	1-Octanol	0.5827	−0.0246
22	2-Octanol	0.0011	−0.1232
23	3-Octanol	0.0309	0.4817
24	1-Nonanol	0.8551	0.5361
25	2-Nonanol	0.6183	0.2630
26	3-Ethyl-2,2-dimethyl-3-pentanol	−0.1691	0.6559
27	1-Decanol	1.3354	0.9988
28	(±)-4-Decanol	0.8499	1.5184
29	3,7-Dimethyl-3-octanol	0.3404	0.2420
30	1-Undecanol	1.9547	1.3736
31	1-Dodecanol	2.1612	1.6379
32	1-Tridecanol	2.4497	1.9591
Unsaturated alcohols			
1	2-Methyl-3-buten-2-ol	−1.3889	−1.1341
2	4-Pentyn-1-ol	−1.4204	−1.5841
3	2-Methyl-3-butyn-2-ol	−1.3114	−1.4998
4	*trans*-3-Hexen-1-ol	−0.7772	−0.4616
5	*cis*-3-Hexen-1-ol	−0.8091	−0.7768
6	5-Hexyn-1-ol	−1.2948	−1.1331
7	3-Methyl-1-pentyn-3-ol	−1.3226	−1.6055
8	4-Hexen-1-ol	−0.7540	−0.4819
9	5-Hexen-1-ol	−0.8411	−0.4857
10	4-Pentyn-2-ol	−1.6324	−1.3337
11	5-Hexyn-3-ol	−1.4043	−1.3286
12	3-Heptyn-1-ol	−0.3231	−0.3513
13	4-Heptyn-2-ol	−0.6160	−0.3635
14	3-Octyn-1-ol	0.0170	−0.3007
15	3-Nonyn-1-ol	0.3401	−0.2685
16	2-Propen-1-ol	−1.9178	−1.3668
17	2-Buten-1-ol	−1.4719	−1.1700
18	(±)-3-Buten-2-ol	−1.0529	−1.1584
19	*cis*-2-Buten-1,4-diol	−2.1495	−2.2131
20	*cis*-2-Penten-1-ol	−1.1052	−1.5419
21	3-Penten-2-ol	−1.4010	−1.4567
22	*trans*-2-Hexen-1-ol	−0.4718	−0.3238
23	1-Hexen-3-ol	−0.8113	−0.6063
24	*cis*-2-Hexen-1-ol	−0.7767	−1.0832
25	*trans*-2-Octen-1-ol	0.3654	−0.3020
Acids: carboxylic acids			
1	Propanoic acid	−0.5123	−0.3425
2	Butyric acid	−0.5720	−0.4506
3	Valeric acid	−0.2674	−0.2910
4	Hexanoic acid	−0.2083	−0.2092
5	Heptanoic acid	−0.1126	−0.0960
6	Octanoic acid	0.0807	0.0429
7	Nonanoic acid	0.3509	0.2028
8	Decanoic acid	0.5063	0.3512
9	Undecanoic acid	0.8983	0.4813

Table 2 (*continued*)

No.	Molecule	log(IGC_{50}^{-1})	
		Expt[a]	Calcd[b]
10	*iso*-Butyric acid	−0.3334	−0.0946
11	Isovalerianic acid	−0.3415	−0.4321
12	Trimethylacetic acid	−0.2543	−0.0674
13	3-Methylvaleric acid	−0.2331	−0.1521
14	4-Methylvaleric acid	−0.2724	−0.3793
15	2-Ethylbutyric acid	−0.1523	−0.1926
16	2-Propylpentanoic acid	0.0258	0.1539
17	2-Ethylhexanoic acid	0.0756	−0.0096
18	Succinic acid	−0.9395	−0.7453
19	Glutaric acid	−0.6387	−0.8671
20	Adipic acid	−0.6060	−0.5832
21	Pimelic acid	−0.5845	−0.5955
22	3,3-Dimethylglutaric acid	−0.6643	−0.7883
23	Suberic acid	−0.5116	−0.3289
24	Sebacic acid	−0.2676	−0.0413
25	1,10-Decanedicarboxylic acid	−0.0863	0.2054
26	Crotonic acid	−0.5448	−0.4081
27	*trans*-2-Pentenoic acid	−0.2774	−0.5791
28	*trans*-2-Hexenoic acid	−0.1279	−0.3541
Halogenated acids			
1	4-Bromobutyric acid	−0.7711	−0.5735
2	5-Bromovaleric acid	−0.6929	−0.6451
3	4-Chlorobutyric acid	−0.6773	−0.5687
4	3-Chloropropionic acid	−0.3321	−0.4323
5	5-Chlorovaleric acid	−0.2857	−0.6587
6	2-Bromobutyric acid	0.1221	0.2666
7	2-Bromoisobutyric acid	−0.5845	−0.5362
8	2-Bromoisovaleric acid	−0.5492	−0.4173
9	2-Bromovaleric acid	−0.0423	0.2453
10	2-Bromooctanoic acid	0.4907	0.2205
11	2-Bromohexanoic acid	0.4547	0.2318
Esters: monoesters			
1	Ethyl acetate	−1.2968	−0.5152
2	Propyl acetate	−1.2382	−0.9200
3	Isopropyl acetate	−1.5900	−1.2128
4	Butyl acetate	−0.4864	−0.6416
5	Amyl acetate	0.1625	−0.4805
6	Hexyl acetate	−0.0087	−0.2493
7	Octyl acetate	1.0570	0.3560
8	Decyl acetate	1.8794	1.2533
9	Ethyl propionate	−0.9450	−0.5793
10	Butyl propionate	0.1704	−0.3985
11	Isobutyl propionate	−0.6935	−1.3757
12	Propyl propionate	−0.8148	−0.7486
13	*tert*-Butyl propionate	−0.4095	−0.1357
14	Ethyl butyrate	−0.4903	−0.7031
15	Ethyl isobutyrate	−1.2709	−0.4733
16	Ethyl valerate	−0.3580	−0.3025
17	Propyl butyrate	−0.4138	−0.6957
18	Butyl butyrate	0.5157	−0.3811
19	Propyl valerate	0.0094	−0.4021
20	Amyl propionate	−0.0431	−0.2208
21	Ethyl hexanoate	0.0637	−0.0207
22	Methyl butyrate	−1.2463	−0.7942
23	Methyl valerate	−0.8448	−0.3994
24	Methyl hexanoate	−0.5611	−0.0889
25	Methyl heptanoate	0.1039	0.2382
26	Methyl octanoate	0.5358	0.6119
27	Methyl nonanoate	1.0419	1.0659
28	Methyl decanoate	1.3778	1.5173
29	Methyl undecanoate	1.4248	1.9437
30	Methyl formate	−1.4982	−1.4819
31	*tert*-Butyl formate	−1.3719	−1.0045

Table 2 (*continued*)

No.	Molecule	log(IGC_{50}^{-1})	
		Expt[a]	Calcd[b]
Diesters			
1	Diethyl malonate	−0.9975	−0.4631
2	Diethyl sebacate	1.3536	1.1454
3	Diethyl suberate	0.7018	0.9150
4	Diethyl succinate	−0.8511	−0.3722
5	Dimethyl malonate	−1.2869	−0.8668
6	Dibutyl adipate	0.7918	1.0219
7	Dimethyl succinate	−1.0573	−0.5710
8	Diethyl adipate	−0.1265	0.6076
9	Dimethyl brassylate	1.6536	1.2830
10	Dimethyl sebacate	1.0106	0.9200
11	Dimethyl suberate	0.2962	0.6515
12	Diethyl pimelate	0.4069	0.8580
13	Dibutyl suberate	1.6556	1.0521
14	Diethyl butylmalonate	0.5566	−0.2594
15	Diethyl ethylmalonate	−0.2422	−0.3905
16	Diethyl 3-oxopimelate	−0.3778	−0.7245
17	Diethyl 4-oxopimelate	−0.6378	−0.9771
18	Diethyl methylmalonate	−0.5114	−0.4832
19	Diethyl propylmalonate	0.1341	−0.3053
20	Dibutyl succinate	0.5123	−0.0567
Aldehydes			
1	Propionaldehyde	−0.4855	−0.3058
2	Butyraldehyde	−0.3805	−0.2300
3	Isobutyraldehyde	−0.4328	−0.5224
4	Valeraldehyde	−0.0223	−0.1850
5	2-Methyl-butyraldehyde	−0.3107	−0.1531
6	Hexylaldehyde	−0.1731	−0.0915
7	2-Methylvaleraldehyde	−0.4745	−0.0877
8	2-Ethylbutyraldehyde	−0.0544	−0.1345
9	3,3-Dimethylbutyraldehyde	−0.3744	−0.4395
10	Heptaldehyde	−0.0019	−0.1373
11	2-Ethylhexanal	0.1608	−0.0573
12	*trans*-4-Decen-1-al	1.2076	0.7113
13	*cis*-7-Decen-1-al	0.9485	1.2395
Ketones			
1	Acetone	−2.2036	−2.7767
2	2-Butanone	−1.7457	−2.0777
3	2-Pentanone	−1.2224	−0.5067
4	3-Pentanone	−1.4561	−1.1185
5	4-Methyl-2-pentanone	−1.2085	−1.1000
6	2-Heptanone	−0.4872	0.3444
7	5-Methyl-2-hexanone	−0.6459	0.0096
8	4-Heptanone	−0.669	−0.2243
9	2-Octanone	−0.1455	0.4579
10	2-Nonanone	0.6598	0.5499
11	2-Decanone	0.5822	0.6125
12	3-Decanone	0.6265	0.2541
13	2-Undecanone	1.5346	0.6553
14	2-Dodecanone	1.6696	0.6919
15	7-Tridecanone	1.5214	1.0383
Amines			
1	Propylamine	−0.7075	−0.6791
2	Butylamine	−0.5735	−0.6801
3	*N*-Methylpropylamine	−0.8087	−0.7492
4	Amylamine	−0.4848	−0.6722
5	*N*-Methylbutylamine	−0.6784	−0.7521
6	Hexylamine	−0.2197	−0.6725
7	Isopropylamine	−0.8635	−0.6764
8	Isobutylamine	−0.2616	−0.6695
9	*N*,*N*-Dimethylethylamine	−0.9083	−0.7938
10	(±)-*sec*-Butylamine	−0.6708	−0.6815

(*continued on next page*)

Table 2 (*continued*)

No.	Molecule	log(IGC_{50}^{-1})	
		Expt[a]	Calcd[b]
11	Isoamylamine	−0.5774	−0.6811
12	1-Methylbutylamine	−0.6846	−0.6827
13	1-Ethylpropylamine	−0.8129	−0.6774
14	2-Methylbutylamine	−0.4774	−0.6819
15	*N*,*N*-Diethylmethylamine	−0.7559	−0.7949
16	*tert*-Butylamine	−0.8973	−0.6819
17	*tert*-Amylamine	−0.6978	−0.6841
18	(±)-1,2-Dimethylpropylamine	−0.7095	−0.6839
19	Propargylamine	−0.826	−0.6877
20	*N*-Methylpropargylamine	−0.9818	−0.7727
21	1-Dimethylamino-2-propyne	−1.1451	−0.8212
22	1,1-Dimethylpropargylamine	−0.9104	−0.6991
23	2-Methoxyethylamine	−1.7903	−1.7806
24	3-Methoxypropylamine	−1.7725	−1.7824
25	3-Ethoxypropylamine	−1.7027	−1.7802

[a] Experimental toxicity values obtained from Ref. 21.
[b] Calculated toxicity values.

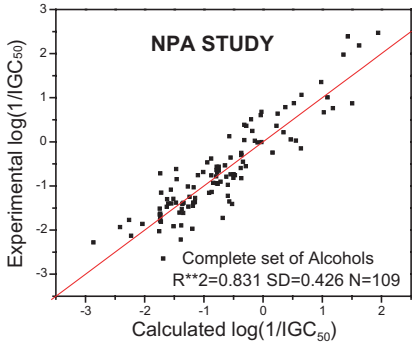

Figure 1. Experimental versus calculated log(IGC_{50}^{-1}) values of all aliphatic alcohols taken together.

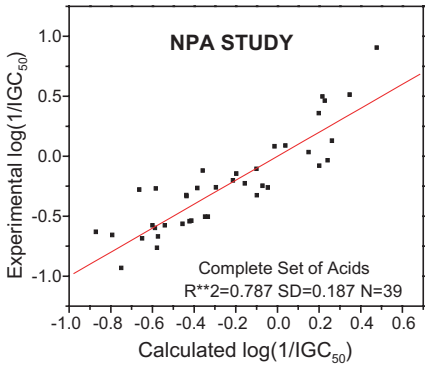

Figure 2. Experimental versus calculated log(IGC_{50}^{-1}) values of all aliphatic acids taken together.

3.4. Aliphatic aldehyde, ketone and amine

Regression models along with coefficients of determination and SD values of the selected aldehydes, ketones and amines are given in Table 1.

Aliphatic aldehydes are considered to exhibit their toxicity through the formation of schiff bases with amino groups, such as in the ε-amino derivatives of lysine that may be present in a biological membrane.[28,29] Experimental and predicted log(IGC_{50}^{-1}) values of all the selected 13 aliphatic aldehydes are listed in Table 2. Electrophilicity (ω) and NPA derived ω_m^+ provide a better correlation by explaining a wide variation in data (80.3%) with a low SD value of 0.248 (Fig. 4) in comparison with a previous study[32a] where the regression model of the toxicity is based on the optimization of correlation weights local invariants (OCWLI) of labelled hydrogen-filled graphs (LHFG).

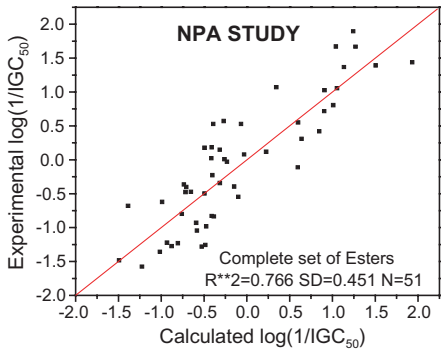

Figure 3. Experimental versus calculated log(IGC_{50}^{-1}) values of all aliphatic esters taken together.

The toxicity resulting from ketones undergoing Michael-type addition has been modeled previously by the use of hydrophobicity-based QSARs.[28–30] Table 2 lists the experimental and the predicted log(IGC_{50}^{-1}) values for the selected 15 ketones. The ω and ω_m^+, are capable of explaining 77.8% variation in data (Fig. 5).

The experimental and the predicted log(IGC_{50}^{-1}) values for the selected 25 aliphatic amines are presented in Table 2. It is seen that 79.1% variation in data is explained by ω and NPA derived ω_m^- values (Fig. 6).

Finally, the plots between the experimental and predicted log(IGC_{50}^{-1}) values of the complete set of selected 171 aliphatic compounds that are electron acceptors (Fig. 7a) and the remaining 81 that are electron donors (Fig. 7b) clearly show that the electrophilic-

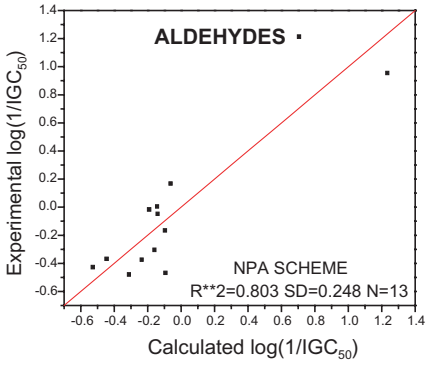

Figure 4. Experimental versus calculated log(IGC_{50}^{-1}) values of aldehydes.

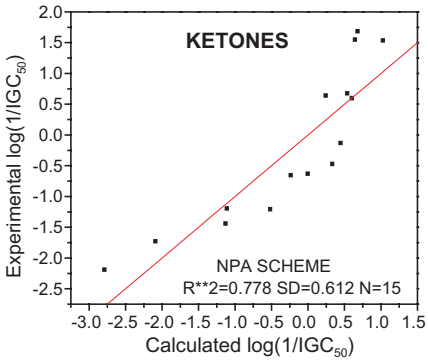

Figure 5. Experimental versus calculated $\log(IGC_{50}^{-1})$ values of ketones.

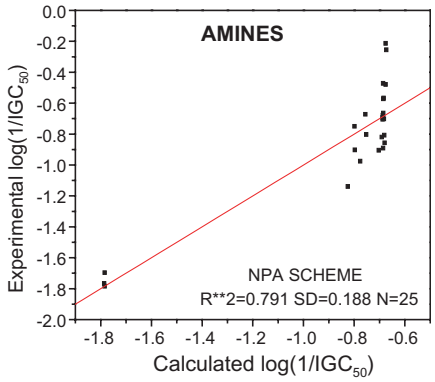

Figure 6. Experimental versus calculated $\log(IGC_{50}^{-1})$ values of amines.

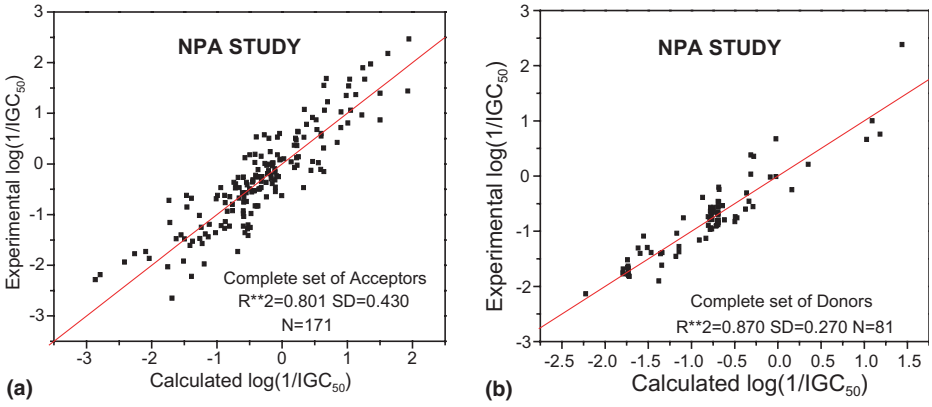

Figure 7. Experimental versus calculated $\log(IGC_{50}^{-1})$ values of all aliphatic compounds taken together: (a) electron acceptors, (b) electron donors.

ity (ω) and local philicity (ω_m^+ or ω_m^-) are capable of predicting the toxicity in a reasonable way. In the past the aliphatic toxicity to the *T. pyriformis* has been studied[31,32] in terms of a large number of descriptors (predictors) and/or with poor correlations. The present study provides a strong evidence of the ability of toxicity prediction by the global and local electrophilicities together. Further it is clear that for all the models developed in this study, the coefficients of determination are reasonably high. In addition the lower inter-correlation among the independent variables (predictors) highlights the importance of considering them as the better predictors of toxicity. The genesis of toxicity is supposed to be governed by the possible charge transfer between a toxin and a biosystem, which is reinforced by the presence of good correlation between toxicity and global and local electrophilicities.

4. Conclusions

Structure–activity analysis of the selected 252 aliphatic compounds on their toxicity in *T. pyriformis* using electrophilicity and local philicity as predictors has been performed in detail in this work and the results demonstrate that a reasonably good prediction of toxicity is obtained by the use of the selected descriptors. The significance of the toxicity prediction by these descriptors is established by the high values of the coefficients of determination and low correlation values among the selected descriptors. Above results clearly indicate the fact that electrophilicity along with corresponding local philicity can be effectively used as descriptors in the prediction of toxicity of diverse classes of aliphatic compounds.

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References and notes

1. Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, UK, 1989.
2. Parr, R. G.; Szentpaly, L. V.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922.
3. Maynard, A. T.; Covell, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 1047, and references therein.
4. Parthasarathi, R.; Padmanabhan, J.; Subramanian, V.; Maiti, B.; Chattaraj, P. K. *J. Phys. Chem. A* **2003**, *107*, 10346.

5. Parthasarathi, R.; Padmanabhan, J.; Subramanian, V.; Sarkar, U.; Maiti, B.; Chattaraj, P. K. *Internet Electron. J. Mol. Des.* **2003**, *2*, 798.
6. Parthasarathi, R.; Subramanian, V.; Roy, D. R.; Chattaraj, P. K. *Bioorg. Med. Chem.* **2004**, *12*, 5533.
7. Chattaraj, P. K.; Maiti, B.; Sarkar, U. *J. Phys. Chem. A* **2003**, *107*, 4973.
8. Parthasarathi, R.; Padmanabhan, J.; Elango, M.; Subramanian, V.; Chattaraj, P. K. *Chem. Phys. Lett.* **2004**, *394*, 225.
9. Smeyers, Y. G.; Bouniam, L.; Smeyers, N. J.; Ezzamarty, A.; Hernandez-Laguna, A.; Sainz-Diaz, C. I. *Eur. J. Med. Chem.* **1998**, *33*, 103.
10. Busse, W. D.; Ganellin, C. R.; Mitscher, L. A. *Eur. J. Med. Chem.* **1996**, *31*, 747.
11. Hansch, C.; Hoekman, D.; Leo, A.; Weininger, D.; Selassie, C. *Chem. Rev.* **2002**, *102*, 783.
12. Hansch, C.; Kurup, A.; Garg, R.; Gao, H. *Chem. Rev.* **2001**, *101*, 619.
13. Hansch, C.; Maloney, P. P.; Fujita, T.; Muir, R. M. *Nature* **1962**, *194*, 178.
14. Hansch, C.; Li, R. I.; Blaney, J. M.; Langridge, R. *J. Med. Chem.* **1982**, *25*, 777.
15. Leach, A. R.; Gillet, V. J. *An Introduction to Chemoinformatics*; Kluwer: Dordrecht, 2003.
16. Ormerod, A.; Willett, P.; Bawden, D. *Quant. Struct.-Act. Relat.* **1989**, *8*, 115.
17. Chermette, H. *J. Comp. Chem.* **1999**, *20*, 129.
18. Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.
19. Chattaraj, P. K.; Nath, S.; Maiti, B. Reactivity Descriptors. In *Computational Medicinal Chemistry for Drug Discovery*; Tollenaere, J., Bultinck, P., Winter, H. D., Langenaeker, W., Eds.; Marcel Dekker: New York, 2003, Chapter 11, pp 295–322.
20. Akers, K. S.; Sinks, G. D.; Schultz, T. W. *Environ. Toxicol. Pharmacol.* **1999**, *7*, 33.
21. Schultz, T. W. *Toxicol. Methods* **1997**, *7*, 289.
22. Dimitrov, S. D.; Mekenyan, O. G.; Sinks, G. D.; Schultz, T. W. *J. Mol. Struct. (Theochem)* **2003**, *622*, 63.
23. *Gaussian 03*, Revision B.03; Gaussian, Inc.: Pittsburgh, PA, 2003.
24. Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.
25. Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1998**, *88*, 899.
26. *MATLAB*; The Math Works, Inc.: Natick, USA, 1999.
27. Penrose, R. *Proc. Cambridge Phil. Soc.* **1955**, *51*, 406.
28. Karabunarliev, S.; Mekenyan, O. G.; Karcher, W.; Russom, C. L.; Bradbury, S. P. *Quant. Struct.-Act. Relat.* **1996**, *15*, 302.
29. Lipnick, R. L. *Sci. Total Environ.* **1991**, *109*, 131.
30. Gawley, R. E. *Synthesis* **1976**, *12*, 777.
31. Netzeva, T. I.; Schultz, T. W.; Aptula, A. O.; Cronin, M. T. D. *SAR QSAR Environ. Res.* **2003**, *14*, 265; Schultz, T. W.; Cronin, M. T. D.; Netzeva, T. I.; Aptula, A. O. *Chem. Res. Toxicol.* **2002**, *15*, 1602.
32. (a) Toropov, A. A.; Benfenati, E. *J. Mol. Struct. (Theochem)* **2004**, *679*, 225; (b) Castro, E. A.; Toropov, A. A.; Nesterova, A. I.; Nazarov, A. U. *J. Mol. Struct. (Theochem)* **2003**, *639*, 129.