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QSAR Study on Narcotic Mechanism of Action and Toxicity: a Molecular Connectivity Approach to *Vibrio fischeri* Toxicity Testing

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Abstract—Quantitative structure–activity relationships (QSARs) have been established based on narcotic mechanism of action and toxicity data to *Vibrio fischeri* using molecular connectivity indices. The results obtained suggest that both, the degree of branching and electronic characteristic of the compounds have dominant role in the exhibition of toxicity. The information obtained in the present study will be useful in designing more potent compounds.

Introduction

The toxic substances control Act (TSCA) provided the Environmental Protection Agency's (EPA) Office of Pollution Prevention and Toxicities (OPPT) with the authority to require development of adequate data for assessing the risk to human health and the natural environment from industrial chemicals identified as having risk potential.[1,2] Within OPPT, the Environmental Effects Branch (EEB) has provided the expert scientific and theoretical evaluation of the environmental/ecological hazard of industrial chemicals, and has differentiated the type and adequacy of data needed to identify and assess their possible adverse effects. This approach ultimately required the active development of structure–activity relationship technology (SAR/QSAR) for establishing ecotoxicity from chemical structure, hazard 'assessment factors' for estimating chemical concentrations of concern, and risks by contrasting the ecotoxicity and exposure data.

The development and use of structure–activity relationships (SARs) and quantitative SAR (QSAR) area of interest in OPPT/EEB. This SAR/QSAR have become an important development became essential because estimation of ecotoxicity have to be provided in a very short time-frame for the risk assessments required for the thousands of new industrial chemicals that are submitted by industries to OPPT for evaluation.

The OPPT aquatic toxicity QSARs used for estimating the acute toxicity of industrial chemicals to fish, daphnia, and algae have generally been proven to be quite reliable. The validation of these SAR/QSAR study is an ongoing effort and confine to expand.

Environmental QSAR studies are very important from the view point of chemical risk assessment, now. The QSAR have provided a valuable approach in research on toxicity of organic chemicals to aquatic organism.[3] Partition coefficient dependent QSAR was greatly used for predicting the toxicity of non-polar narcotics for the guppy (*Basecilia reticulata*), the fathead minnow (*Pimephales promelas*) and eitiats *Tetrahymena pyriformix*.

We have chosen first-order valence-connectivity index[4] ($^1\chi^v$) to model *Vibrio fischeri* toxicity of diversified compounds (Table 1). The choice of $^1\chi^v$ is due to its wide spread successful applications in QSARs.[4–13] Our earlier research[9,12,13] has indicated that coupling $^1\chi^v$ with equalized electronegativity (χ_{eq}) improved the quality of proposed QSAR models. Consequently, χ_{eq} was chosen another parameter for modelling the toxicity, where $^1\chi^v$ is a numerical descriptor of molecules, size, shape, symmetry and heterogencity of a molecule, while χ_{eq} accounts for the electronegativity effect of the substituents. In addition to $^1\chi^v$ and χ_{eq}, we have also used indicator parameters. The selected models were

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subjected to multiple regression[14–16] that calculated correlation matrix, analysis of variance, adjusted R^2 (R^2_A) F, model standard error of estimation, model probability intercept, and parameter coefficients, observed values, predicted values, and residuals. The results are discussed below.

In this work, toxicities (pEC_{50}) of 39 chemicals to *Vibrio fischeri* were adopted by us from the literature.[3] We have investigated QSARs of these chemicals and showed that simple QSAR models with topological indices and indicator variables based on the degree of branching and the substructure features of them gave good estimates of toxicity. The primary aim was to investigate how size, branching, hetero-atom, and the electro-negativities of the substituents affect the toxicity. As is discussed below we observed that molecular connectivity and equalized electro-negativity approach is the most suitable for such studies. Thus, first-order valence connectivity index ($^1\chi^v$) and equalized electronegativity (χ_{eq}) are used in the present investigation.

Results and Discussion

It is commonly believed that structurally similar molecules have a comparable range of property and biological activity, or vice-versa. Molecular similarity is characterized by the numerical values of topological index and by regression analysis of topological indices that provide numerical information regarding a molecular structure (more precisely by hydrogen depleted molecular structure called molecular graph). Molecular property/activity is a function of its intrinsic structure, as well as its interaction with neighboring molecules. The topological index used ($^1\chi^v$), like other topological indices, characterize adjacency and neighboring relations in the molecule.

Consequent to above degeneracy may exist in property, activity, and derived topological indices. This is found to be so in present case also (Table 1). Furthermore, because of the narrow range of substituent variations the derived activity/property/molecular descriptors also vary in a small range.

Table 1. Name of the compounds, their toxicities (pEC_{50}),[3] and their molecular descriptors (χ_{eq}, $^1\chi^v$, Ip_1, Ip_2, Ip_3, Ip_4, Ip_5)

Compd Ip_5 no.	Name of compd	pEC_{50}	χ_{eq}	$^1\chi^v$	Ip_1	Ip_2	Ip_3	Ip_4	Ip_5
1	4-Chloro-benzylchloride	5.01	2.8688	2.6322	0	0	1	0	0
2	4-Chloro-benzaldehide	4.15	2.4179	2.5150	0	0	1	0	0
3	3-Chloro-benzaldehide	4.00	2.4179	2.5137	0	0	1	0	0
4	3,4-Dichloro-benzaldehide	4.68	2.4820	2.6390	0	0	0	1	0
5	3,4-Dichloro-benzonitrile	4.22	2.6322	2.5098	0	0	0	1	0
6	4-Chloro-benzonitrile	4.20	2.5966	1.7751	0	0	1	0	0
7	4-Chloro-benzylcynide	4.73	2.6110	2.4820	0	0	1	0	0
8	2-Chloro-benzylcynide	4.26	2.6119	2.2390	0	0	1	0	0
9	2,4,6-Trichloro aniline	4.51	2.4853	2.5104	1	0	0	0	1
10	2,6-Dichloro aniline	4.16	2.4225	2.4106	1	0	0	1	0
11	2,4-Dichloro aniline	4.09	2.4225	2.4040	1	0	0	1	0
12	3,4-Dichloro aniline	4.20	2.4225	2.1540	1	0	0	1	0
13	3-Chloro,4-fluoro aniline	3.28	2.3972	2.4047	1	0	0	1	0
14	4-Chloro,4-fluoro aniline	3.57	2.3630	2.2980	1	0	0	1	0
15	4-Bromo,4-fluoro aniline	3.92	2.3541	2.2980	1	0	0	1	0
16	2-Chloro, 4-nitro aniline	3.99	2.5196	2.8030	1	0	0	1	0
17	2,4-Dinitro aniline	4.16	2.6004	3.2030	1	0	0	1	0
18	4-Nitro aniline	3.70	2.4638	2.6970	1	0	1	0	0
19	3-Nitro aniline	3.77	2.4638	2.6970	1	0	1	0	0
20	Diphenylamine	4.88	2.3141	4.3213	0	0	0	0	0
21	Aniline	3.28	2.3079	2.1990	1	0	0	0	0
22	Pentachloro phenol	5.69	2.6931	1.9470	0	1	0	0	1
23	2,4-Dichloro phenol	4.45	2.4757	2.0880	0	1	0	1	0
24	4-Chloro phenol	4.48	2.4082	2.2320	0	1	1	0	0
25	4-Nitro phenol	4.05	2.4082	2.2390	0	1	1	0	0
26	2-Methyl phenol	3.75	2.5125	2.6320	0	1	1	0	0
27	Recorcinol	3.00	2.3208	2.5509	0	1	1	0	0
28	Phenol	3.64	2.3474	3.5430	0	1	0	0	0
29	Hexachloro ethane	5.52	2.8571	1.1310	0	0	0	0	1
30	1,2-Dichloro ethane	2.43	2.3760	0.5340	0	0	0	1	0
31	Tetrachloro ethane	3.94	2.8129	1.0060	0	0	0	0	1
32	Dichloro methane	1.96	2.4777	0.5346	0	0	0	1	0
33	1-Octanol	4.90	2.2395	4.0230	0	0	0	0	0
34	Cyclohexanone	2.95	2.2802	3.6150	0	0	0	0	0
35	Acetone	0.90	2.3027	1.2041	0	0	0	0	0
36	Cyclohexane	3.16	2.2183	3.0000	0	0	0	0	0
37	Hexane	3.27	2.2060	2.9140	0	0	0	0	0
38	Diethyl ether	1.68	2.2569	1.5773	0	0	0	0	0
39	Tetrahydrofuran	1.90	2.2831	2.0773	0	0	0	0	0

pEC_{50}, toxicity; χ_{eq}, equalized electronegativity; $^1\chi^v$, first-order valence connectivity; Ip_1, unity when $-NH_2$ group is present otherwise zero; Ip_2, unity when –OH group is present otherwise zero; Ip_3, unity for mono substitution otherwise zero; Ip_4, unity for di-substitution otherwise zero; Ip_5, unity for polychloro substitution (tri or more) otherwise zero.

A complete set of molecular descriptors, namely: χ_{eq}, $^1\chi^v$ and five indicator parameters for the set of 39 molecules are recorded in Table 1. By the use of multiple regression analyses,[14–16] the toxicity (pEC_{50}) values were screened against the possible two-, three-, four- and so on variable combinations of χ_{eq}, $^1\chi^v$, Ip_1, Ip_2, Ip_3, Ip_4, Ip_5 which were selected as the best set correlating with the activity (pEC_{50}) value. All such statistically significant combinations are summarized in Table 3, while the correlation matrix is given in Table 2. The regression parameters and the quality of each of the statistically significant models are presented in Table 4.

A perusal of the correlation matrix (Table 2) shows that χ_{eq}, $^1\chi^v$, and Ip_5 are the better parameters for modelling pEC_{50} in multiparametric correlations. Also that, none of the molecular descriptors correlate singly with the toxicity (pEC_{50}). This means that no mono-parametric models are possible for modelling the toxicity (pEC_{50}) of the compounds under present investigation. Out of the five indicator parameters, only Ip_3 and Ip_4 exhibit significant collinearity.

An inspection of Tables 3 and 4 shows that the only bi-parametric model which was found statistically significant was the combination of $^1\chi^v$ and χ_{eq}. This model is shown below:

$$pEC_{50} = 0.7450\ (\pm 0.1355)^1\chi^v + 4.5945\ (\pm 0.6565)\chi_{eq} - 9.2306$$
$$n = 39,\ \mathrm{Se} = 0.6077,\ R = 0.7927,\ R_A^2 = 0.6283,$$
$$F = 30.429,\ Q = 1.2454 \quad (1)$$

The positive signs associated with both $^1\chi^v$ and χ_{eq} in eq 1 indicates their positive role in the exhibition of activity (pEC_{50}). A large coefficient of χ_{eq}, term indicates dominant role of electronegativity in the exhibition of pEC_5.

Two tri-parametric models were possible (Table 4) and the one involving $^1\chi^v$, χ_{eq} and Ip_5 gave better results. This model was found as under:

$$pEC_{50} = 0.7882\ (\pm 0.1329)\ ^1\chi^v + 3.9313\ (\pm 0.7254)\chi_{eq} + 0.7354\ (\pm 0.3901)Ip_5 - 7.7818$$
$$n = 39,\ \mathrm{Se} = 0.6337,\ R = 0.8140,\ R_A^2 = 0.6626,$$
$$F = 20.910,\ Q = 1.3240 \quad (2)$$

This means that addition of Ip_5 to eq 1 resulted into better quality tri-parametric model (eq 2) so that the R-value increased from 0.7927 to 0.8140. However, it

Table 2. Correlation matrix for the parameters given in Table 1

	pEC_{50}	χ_{eq}	$^1\chi^v$	Ip_1	Ip_2	Ip_3	Ip_4	Ip_5
pEC_{50}	1.0000	0.5622	0.3501	0.0530	0.1612	0.1763	−0.0139	0.3740
χ_{eq}		1.0000	−0.3192	−0.0708	−0.0009	0.1574	0.0869	0.5357
$^1\chi^v$			1.0000	0.1121	0.0522	0.0388	−0.1738	−0.3087
Ip_1				1.0000	−0.3118	−0.0356	0.3229	−0.0423
Ip_2					1.0000	0.2071	−0.1447	0.0621
Ip_3						1.0000	−0.4690	−0.2530
Ip_4							1.0000	−0.2119
Ip_5								1.0000

Table 3. Statistically significant models proposed for modelling toxicities (log $1/EC_{50}$)

Model no.	Models	Se	R_A^2	R	F	Q
1	pEC_{50} = 0.7450 (±0.1355) $^1\chi^v$ + 4.5945 (±0.6565)χ_{eq} − 9.2306	0.6077	0.6283	0.7927	30.429	1.246
2	pEC_{50} = 0.7354 (±0.1344) $^1\chi^v$ + 4.5904 (±0.6502)χ_{eq} + 0.3436(±0.6502)Ip_2 − 9.2350	0.6152	0.6456	0.8035	21.250	1.275
3	pEC_{50} = 0.7882 (±0.1329) $^1\chi^v$ + 3.9313 (±0.7254)χ_{eq} + 0.7354 (±0.3901)Ip_5 − 7.7818	0.6337	0.6626	0.8140	22.910	1.324
4	pEC_{50} = 0.7773 (±0.1324) $^1\chi^v$ + 3.9542 (±0.7214)χ_{eq} + 0.3046 (±0.2562)Ip_2 + 6.6931 (±0.3892)Ip_5 − 7.7818	0.6379	0.6760	0.8222	17.738	1.345
5	pEC_{50} = 0.7836 (±0.1320) $^1\chi^v$ + 3.5952 (±0.7713)χ_{eq} + 0.2753 (±0.2258)Ip_3 + 0.9391 (±0.4219)Ip_5 − 7.0664	0.6387	0.6767	0.8226	17.793	1.347
6	pEC_{50} = 0.8867 (±0.1248) $^1\chi^v$ + 2.2796 (±0.8331)χ_{eq} + 0.8881 (±0.2940)Ip_3 + 0.8880 (±0.3061)Ip_4 + 1.9269 (±0.5119)Ip_5 − 4.6563	0.7075	0.7424	0.8616	19.022	1.557

was found that in the improved model (eq 2) Se was also increased from 0.6071 to 0.6337. Furthermore, the quality factor Q[15,16] ($Q = R/\mathrm{Se}$) increased from 1.2454 to 1.3240. This means that R or Se alone are not fit for deciding the quality of the model, instead we have to judge the quality by simultaneous use of R and Se; preferably in the form of quality factor, Q.[15,16]

It is interesting to record that R^2_A values take into account of the adjustment of R^2. Therefore, if a variable is added that does not contribute its fair share, the R^2_A value will actually decline. We observed that by the addition of Ip_5 to the model (1) (eq 1) R^2_A is increased from 0.6283 to 0.6626 indicating that Ip_5 had a fair contribution in the proposed model (2) (eq 2). Recall that Ip_5 is used for polychloro substitution. Therefore, increased quality of the model expressed by eq 2 is a consequence of polychlorination. Its coefficient indicates that its influence is parallel to the influence due to $^1\chi^v$ in this model. The role of $^1\chi^v$ and χ_{eq} based on their respective coefficients is similar to that of the model expressed by eq 1.

Successive combination of molecular descriptors resulted into two tetra-parametric models. The quality data indicates that they have similar potential for modelling the activity (pEC_{50}). Both these tetraparametric models are found better than the triparametric model discussed earlier.

Table 4. Comparison of pEC_{50} obsd versus estimated using model (6)

Compd	pEC_{50} (nm)	Estimated pEC_{50}	Residue
1	5.01	5.11	−0.10
2	4.15	3.97	0.18
3	4.00	3.97	0.05
4	4.68	4.23	0.45
5	4.22	4.46	−0.24
6	4.20	3.73	0.47
7	4.73	4.39	0.34
8	4.26	4.17	0.09
9	4.51	5.16	−0.65
10	4.16	3.89	0.27
11	4.09	3.89	0.20
12	4.20	3.66	0.54
13	3.28	3.83	−0.55
14	3.57	3.66	−0.09
15	3.92	3.64	0.28
16	3.99	4.46	−0.47
17	4.16	5.00	−0.84
18	3.70	4.24	−0.54
19	3.77	4.24	−0.47
20	4.88	4.45	0.43
21	3.28	2.56	0.72
22	5.69	5.14	0.55
23	4.45	3.73	0.72
24	4.48	3.70	0.78
25	4.05	3.71	0.34
26	3.75	4.29	−0.54
27	3.00	3.78	−0.78
28	3.64	3.84	−0.20
29	5.52	4.79	0.73
30	2.43	2.12	0.31
31	3.94	4.58	−0.64
32	1.96	2.35	−0.39
33	4.90	4.02	0.88
34	2.95	3.75	−0.80
35	0.90	1.66	−0.70
36	3.16	3.06	0.10
37	3.27	2.96	0.31
38	1.68	1.89	−0.21
39	1.90	2.39	−0.49

Further attempts of the combinations of molecular descriptors for obtaining still better models resulted into a pentaparametric model in which $^1\chi^v$, χ_{eq}, Ip_3, Ip_4, Ip_5 are involved (Table 3). Based on regression parameters this pentaparametric model is found to be the best for modelling pEC_{50}. However, it has the highest Se value compound to the models discussed herein. At the same time the Q value for this model is also highest ($Q = 1.557$). This supports combined effort of Se and R for modelling the activity.

It is worth recording that for the models 3–5 (Table 3), Q values more or less are the same, indicating their (models 3–5) similar potential in the exhibition of the activity.

It is interesting to record that R^2_A is particularly important, in the selection of appropriate models, as it takes into account the relationship between sample size and number of variables. R^2 may appear artificially high if the number of variables is high compared to sample size. R^2_A will decrease if the added variable does not reduce the unexplained variation enough to outset the loss of degree of freedom. Even with unusual numbers of dummy parameters the R^2_A values range between 0.6283 in the present study and 0.7424. For models 1–5, R^2_A is centered around 0.67. For model 6 (Table 3) R^2_A is highest. This confirms our earlier findings based on Se and R.

In all the proposed models the parameters involved have positive coefficients indicating their positive contribution in proposing the models. $^1\chi^v$ distinguishes the degree of unsaturation and the presence of hetero-atoms. Therefore, its positive contribution indicates that unsaturation and presence of hetero-atoms contributes strongly to the toxicity effects of the compounds used in the present study.

The positive coefficient of χ_{eq} shows that electronegativity of the substituent groups on the compounds under present study play an important role in governing toxicity. This lead us to conclude that fatality of the compounds can be minimized by the substitution of less electronegative groups. These results, therefore, may be of assistance in designing more potent analogues.

We tried still higher parametric models but none gave better and statistically significant results than the pentaparametric model discussed above.

The standard deviations of the regression coefficients for $^1\chi^v$ and χ_{eq} for models 1 to 5 (Table 3) suggest that no dummy parameters involved in these models contributed to the regression that is meaningful. It seems that indicator parameters used have only improved the apparent result of the analysis. Furthermore, none of

the proposed model contain Ip_1. This indicates that the presence of the $-NH_2$ group is not essential criterion for the exhibition of toxicity (pEC_{50}).

The results of the present investigation support the hypothesis that narcosis occurs as a result of toxicant acting at sites of interaction within membranes producing 'swelling' and thus interfering with its normal structural function. The work suggest that $^1\chi^v$ and χ_{eq} are good parameters to correlate with the toxicities of non-polar narcotic compounds, especially for fish and invertebrate toxicity. Our results also shows that bulk parameters may play an important role in toxicity to aquatic organism especially for organisms with lower lipid content, namely *V. fischeri*.

In order to confirm our results we have estimated pEC_{50} using the respective models and compared them with the observed values of pEC_{50} such a comparison is shown in Table 4. The predictable correlation coefficient (0.753) confirm our finding that the model (6) (Table 3) is the most appropriate model.

Conclusions

The aforementioned results and discussion lead us to the following conclusion:

i. Narcotic mechanism of action and toxicity can be explained and modelled by using $^1\chi^v$ and χ_{eq}.
ii. Robust QSAR models are developed for narcotic mechanism of action and toxicity;
iii. Potential difference in metabolism, accumulation, and clearance kinetics can be modelled topologically using $^1\chi^v$ and χ_{eq}, which is a separate issue; research in this direction is going on and will be published elsewhere.
iv. Positive sign associated with the parameters, namely $^1\chi^v$ and χ_{eq}, suggests that degree of saturation, presence of hetero-atoms, and electronegativity of the substituents play dominant role in governing toxicity (pEC_{50}).

Experimental

Test chemicals

Test chemical selection (Table 1) was based on the following criteria: all should be commercially available at a sufficient purity of testing (>95%), most should be listed as priority pollutants, all must show a recognizable mechanism of toxication. The compounds selected included chlorobenzenes, nitrobenzenes, anilines, phenols and others. These compounds were diluted with 3% NaCl solution for *V. fischeri* toxicity testing.

Biological activity

Toxicity to *V. fischeri* determined as EC_{50} $(nm)^3$ was converted into pEC_{50} nm and used in the present investigation.

Computational procedure: molecular modelling

The molecular connectivity indices. The connectivity index $\chi = \chi(G)$ of a graph G is defined by Randic[4–8] as:

$$\chi = \chi(G) = \sum_{ij} [d_i \ d_j]^{-0.5} \tag{3}$$

where d_i is the valence of a vertex i, equal to the number of bonds connected to the atom i, in G, representing the graph of a compound. Meaning of d_j is analogous.

In the case of hetero-systems the connectivity is given in terms of valence delta values δ_i^v and δ_j^v of atoms i and j and is denoted by χ^v. This version of the connectivity index is called the valence connectivity index and defined[5,7] as:

$$\chi^v = \chi^v(G) = \sum_{ij} \left[\delta_i^v \ \delta_j^v\right]^{-0.5} \tag{4}$$

where the sum is taken over all bonds i–j of the molecule. Valence delta values (δ_i^v) are given by

$$\delta_i^v = \frac{Z_i^v - H_i}{Z_i - Z_j - 1} \tag{5}$$

where Z_i is the atomic number of atom i, Z_i^v is the number of valence electron of the atom i and H_i is the number of hydrogen atoms attached to atom i.

Recall that nowadays the connectivity and the valence connectivity indices expressed by eqs 3 and 4 are termed as first-order connectivity and first-order valence connectivity index, respectively. Lower or higher order indices are also possible which are defined analogously.

Equalized electronegativity (χ_{eq}). Charge conservation equation leads to general expression for equalized electronegativity[9,10,17] (χ_{eq}) as shown below:

$$\chi_{eq} = N/\Sigma(V/\chi) \tag{6}$$

where, $N = \Sigma$, $V =$ total number of atoms in the species, V is the number of atoms of a particular element in the species and χ is the electronegativity of that element.

Now, the group negativity is defined as:

$$\chi_G = N_o/(V/\chi) \tag{7}$$

where, N_o is the number of atoms in the group formula.

Note that groups are fundamentally different from atoms in their ability to donate or withdraw charge. The important difference between atom and a group is that the groups have the ability to dissipate the charge over several atoms increasingly with increasing N_G. A group can be treated as 'pseudo-atoms' in electronegativity discussion because a polyatomic atom can be considered as a reservoir of enhance charge capacity potentially able or withdraw considerable amount of charge with only small variation in electronegativity.

Indicator parameters. These are dummy parameters sometimes used when some structural features are not governed by molecular descriptors. They assume only two values, one or zero, depending upon whether or not the concerned structural feature is present or absent in the set of molecules under study. In the present study, we have used five such dummy parameters (Ip_1, Ip_2, Ip_3, Ip_4, Ip_5). The parameters Ip_1 and Ip_2 are considered unity when $-NH_2$ and –OH groups are respectively present in the compounds. Similarly, Ip_3 and Ip_4 are taken as unity respectively for mono-, di- and poly-substitution. In absence of these characteristics the values of indicator parameters are considered to be zero.

Statistical analysis

All statistical analyses were performed by least-squares linear regression program, namely Regress-1 software supplied by Professor I. Lukovits, Hungarian Academy of Sciences, Budapest, Hungary. For each regressions, the following descriptive information is provided: number of observations used in the analyses (n), standard error of estimation (Se), correlation coefficient (R), adjustable R^2 (R^2_A), Fischer's criterion (F) and quality factor (Q).

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