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# QSAR study in terms of conceptual density functional theory based descriptors in predicting toxicity of nitrobenzenes towards *Tetrahymena pyriformis*

Sandip Kumar Rajak

Department of Chemistry, Dumkal College, Basantapur, Murshidabad, 742 406, West Bengal, India
E-mail: sandip1ku@gmail.com

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Quantitative Structure -Activity Relationship (QSAR) models are enormously significant to understand the correlation of chemical structure with the biological activity and toxicity of chemicals. In the ongoing study reveals the prediction power of toxicity of 45 nitrobenzenes (NBs) entailing some conceptual density functional theory based reactivity descriptors namely electrophilicity index (ω), lowest unoccupied molecular orbital ($\varepsilon_{lumo}$) and molecular compressibility (β) along with the hydrophobicity index (logP). Multilinear Regression (MLR) method is adopted to develop the QSAR model. Stability of the present QSAR model is confirmed through the cross validation method and is potentially describe the 85% of the variance of the experimental toxicity.

**Keywords:** CDFT, Nitobenzenes, QSAR, Regression, Toxicity

The quantitative structure-activity relationship (QSAR) analysis is accompanied to derive empirical models that relate the activity of chemical compounds to their structure[1]. The basic assumption is that the chemical structure of a compound implicit determines its actions towards biological systems. The most essential scientific principle of developing a QSAR model includes: understanding the mechanism of interaction between compounds and biological system. The attainment of information about a dose range for the biological effect of a chemical compound can be useful in the experimental drug design and toxicity research, and also calculation of the activity of new chemical compounds. Further, QSAR modes is popular for saving both time and experimental resources for synthesizing and biological experiment of a great number of compounds and offer possibility of reduction of living thing use in research and toxicity testing. Various statistical methods namely regression analysis, partial least squares, classification trees, and neural networks[2] are used widely in developing QSAR.

Toxicity prediction is crucial subject of concern and a lot of studies have been done to elucidate its effects with the help of various quantum chemical atomic and molecular descriptors[3]. Toxicity arises as a consequence of stereochemical electronic interaction amongst the reactive site and toxicant. Toxicity being a basic observable fact requires understanding of its origin so as to be concerned of its effects. In vivo and in vitro methods are followed simultaneously or separately for the prediction of toxicity. In vitro methodology is mostly preferred over the other due to its less time consuming and its economical property. QSAR (quantitative structure-activity relationship) and QSPR (quantitative structure-property relationship) are two major methodologies for correlating biological activity with physicochemical properties through descriptors characteristic of molecular structure and /or properties[4-8]. QSAR/QSPR domain is being dominated by Density Functional Theory (DFT) in the recent years. Several Conceptual Density Functional Theory (CDFT)- based descriptors have been invoked widely to study the reactive site, to model biological properties, and in addition to predict experimental behaviours[9-14].

Acute toxicity in the domain of QSAR study have been reported in a large number in the literature[15]. Many authors[16-20] have introduced quantitative relationship between toxicity and hydrophobicity, wherein the hydrophobicities are measured by octanol-water partition coefficient ($\log P_{oct}$ values) or octanol-water distribution coefficient ($\log D_{oct}$ values) as descriptors.

Response-surface approach has been widely invoked for the development of mechanistically comprehensible QSAR modes for toxicity. The central idea of this approach is that the toxic action depends on the biouptake and bioavailability as well as on the electrophilic reactivity of the toxicant at an active site. $\log P_{oct}$ or $\log D_{oct}$ have been introduced as

a descriptor for encoding biouptake and bioavailability and energy of lowest unoccupied molecular orbital ($E_{LUMO}$) as descriptor for encoding the electrophilc reactivity. This scientific knowledge has been applied to different species, including the bacterium Vibrio fischei[21], the protozoan Tetrahymena pyriformis[22-23], the yeast *Saccharomyces cerevisiae*[24], the mould *Aspergillus nidulans*[25], the algae *Scenedesmus obliquus*[26] and *Chlorella vulgais*[25], the plant *Cucumis sativus*[27-28], and mice[25].

To improve the statistical fit of the model, additional indicator variables and other parameters have been added with the response surface approach[29,30].

It is well established that toxicity is a outcome of electronic interaction among the atom/ molecules of the reactive site and the toxicant. In present study, CDFT based descriptor, that is Compressibility is used in addition to the other descriptors as compressibility plays a vital role in understanding various interactions including toxic interactions[31] as like as molecular polarizability which is a promising descriptor to study chemicl -biological interactions[32].

The expression of chemical toxicity is a combination of penetration into, or through, biological membranes and the interaction of the toxicant with the site of action. This principle is modeled mathematically as the following standard QSAR[33].

log (toxicity)$^{-1}$=A (log of penetration) +B (log of interaction)

Penetration to the site of action is generally represented by hydrophobicity, most often quantified by the 1-octanol/water partition coefficient (log P)[33]. Interaction of the chemical with the active site is more complicated and describes electronic and /or steric properties.

The purpose of the present work is to study the predictive potential of compressibility for modeling the toxicity of NBs on *Tetrahymena pyriformis* along withthe other well-known CDFT-based reactivity descriptors like electrophilicity index (ω), energy of lowest unoccupied molecular orbital ($\varepsilon_{LUMO}$) to examine the structure activity relationship for 45 NBs.

## Theoretical Background

There is a paradigm shift in the realm of conceptual chemistry due to the density functional underpinning of Parr et al[34-37]. The useful qualitative entities like hardness, electronegativity and electrophilicity index which were abstract semiotic representations are now considered as theoretical quantities of cognitive representations. According to DFT, given the electron density function ρ(r) of a chemical system and the ground state energy and everything can be determined. The chemical potential, μ of that system in equilibrium has been defined as the derivative of the energy functional E (ρ) with respect to the electron density at fixed molecular geometry.

The chemical potential, μ, is given by[38]

$$\mu = -\chi = [\delta E(\rho) / \delta \rho]_v \quad \ldots(1)$$

where v is the external potential acting on an electron due to the presence of nucleus.

The differential definition more appropriate to atomic system is on the basis that for a system of N electrons with ground state energy E [N,v],

$$\mu = -\chi = [\partial E / \partial N]_v \quad \ldots(2)$$

The absolute hardness is defined[39] as

$$\eta = \tfrac{1}{2} [\partial \mu / \partial N]_v = \tfrac{1}{2} [(\partial^2 E / \partial N^2)]_v \quad \ldots(3)$$

The ansatz for hardness is mathematically difficult because the numerical method is required to be invoked to solve it[40]. However, Parr and Pearson[39], invoking finite difference approximation, suggested an approximate formula for the evaluation of hardness and electronegativity as

$$\eta = \tfrac{1}{2} (I - A) \quad \ldots(4)$$

$$\chi = \tfrac{1}{2} (I + A) \quad \ldots(5)$$

where, I is the ionization energy and A is the electron affinity of the chemical species.

Pearson[41] proceeded further to evaluate 'I' and 'A' in terms of orbital energies of the highest occupied molecular orbital, HOMO and the lowest unoccupied molecular orbital, LUMO by connecting it with Hartree - Fock SCF theory and invoking Koopmans' theorem the hardness and electronegativity are reformulated as

$$\eta = \tfrac{1}{2} (-\varepsilon_{HOMO} + \varepsilon_{LUMO}) \quad \ldots(6)$$

and $\chi = -\mu = -\tfrac{1}{2} (\varepsilon_{LUMO} + \varepsilon_{HOMO}) \quad \ldots(7)$

where $I = -\varepsilon_{HOMO}$, and $A = -\varepsilon_{LUMO}$.

Parr et al[42] defined another global parameter, the electrophilicity index (ω), as a measure of the decrease in energy due to the maximal transfer of electrons from a donor to an acceptor system and is given as

$$\omega = (\mu)^2 / (2\eta) \quad \ldots(8)$$

Atomic compressibility[31] is defined (β) as a property of electronic distribution. Thus, the study has been carried out with the concept that very selected compound display toxicity due to modification in its volume or size (compressibility) due to electrophilic (nucleophilic) attack. Higher compressibility signifies increased attractive interactions between atoms and molecules consequently pulling the atoms and molecules together. In, general, an increase in compressibility increases closeness of electrons in an atom/ molecule, perhaps contributing in exhibiting atomic/ molecular character more significantly, for instance, toxic behavior.

On extending this concept to molecular systems, Scientist defined group compressibility (Gβ) as a summation of compressibility of each atom present in a molecule[43]. Atomic compressibility (β) is represented mathematically[31] as

$$\beta=(12\pi^2\varepsilon_0/e^2)r^2/\omega \quad \ldots(9)$$

where e is the unit charge of an electron, r is the absolute radius of an atom, ω is the electropilicity index of the atom and $\varepsilon_0$ is the vacuum permittivity and group compressibility (Gβ) as represented as

$$G\beta = \sum\beta_i \quad \ldots(10)$$

where $\beta_i$ signify the atomic compressibility of the $i^{th}$ atom in a molecule with N atoms.

## Method of computation

A total of 45 Nitro-benzenes with other substituents have studied in the present work. The outline of the structure is shown in Fig. 1.

The experimental toxicity data log ($1/IGC_{50}$) of the 45 NBs is listed in the table[44]

Computational study is performed within DFT (Density Functional Theory) framework and descriptors have been calculated using conceptual density functional theory. All the modeling and structural optimization of compounds have been performed using Gaussian 09 software package[45]. For optimization purpose, B3LYP with basis set 6-31G(d) has been adopted.

Atomic compressibility value for each atom taken from reference[31], to compute the molecular compressibility with the help of equation (10).

The value for the hydrophobicity term i.e logP (logarithum of octanol/water partition coefficient) is taken from reference[46].

Structural -toxicity models are developed using the multilinear regression using the statistical software

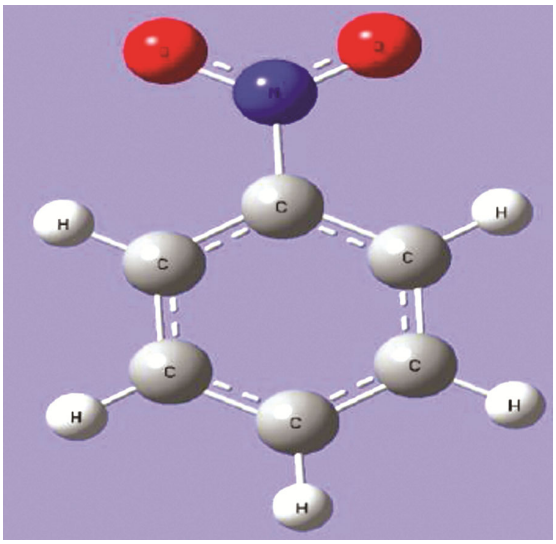


Figure 1 — Outline of the structure of nitrobenzenes (NBs)

Minitab[47]. log($I/IGC_{50}$) values are used as the dependent variable and logP, $\varepsilon_{lumo}$, ω and β, as the independent variables. Goodness-of-fit for the proposed model is accomplished by assessing the coefficient of determination ($R^2$), $R^2$-adjusted, the standard error (S) and the number of sample size is also noted. The robustness of the model illustrates the stability of its parameters by performing validation of the model using leave-1/3-of set-out validation.

## Results and Discussion

Several linear QSAR models involving one, two, three and four descriptors are established and strongest multi-linear correlations are identified by regression analysis of the Minitab program[45].

Four -parameter QSAR models:

$$\log(IGC^{-1}{}_{50}) = - 3.11 + 0.318 \log P + 0.0661 \beta + 3.31 \omega - 23.4 \varepsilon_{lumo} \quad \ldots(11)$$

N= 45 S = 0.268781 R-Sq = 85.1% R-Sq(adj) = 83.6%

The calculated quantum chemical descriptors, namely electrophilicity index (ω), $\varepsilon_{LUMO}$, compressibility (β) and the estimated partition co-efficient logP are given in Table 1

A significant improvement of the quality of QSAR model is obtained with a combination of the four parameters, namely partition coefficient logP, electrophilicity index(ω), LUMO energy ($\varepsilon_{lumo}$) and compressibility (β). Figure 2 shows the linear correlation between the observed and predicted toxicity values obtained using the four parameter QSAR model.

Table 1 — Descriptor values and predicted toxicity of nitrobenzene derivatives by Eq.11

| S. No | Compound | $\varepsilon_{LUMO}$(au) | ω (au) | β(au) | log P | Observed toxicity log($IGC^{-1}_{50}$) | Predicted toxicity | Residual |
|---|---|---|---|---|---|---|---|---|
| 1 | 2,6-Dimethylnitrobenzene | -0.08672 | 0.173449 | 2.995 | 2.87 | 0.3 | 0.603992949 | 0.303993 |
| 2 | 2,3-Dimethylnitrobenzene | -0.07445 | 0.150546 | 2.995 | 2.87 | 0.56 | 0.241068108 | -0.31893 |
| 3 | 2-Methyl-3-chloronitrobenzene | -0.08719 | 0.174427 | 2.571 | 3.1 | 0.68 | 0.663342446 | -0.01666 |
| 4 | 2-Methylnitrobenzene | -0.07747 | 0.156527 | 2.235 | 2.41 | 0.05 | 0.135016984 | 0.085017 |
| 5 | 2-Chloronitrobenzene | -0.08694 | 0.173913 | 2.081 | 2.34 | 0.68 | 0.38172225 | -0.29828 |
| 6 | 2-Methyl-5-chloronitrobenzene | -0.08827 | 0.17654 | 2.571 | 3.1 | 0.82 | 0.695609106 | -0.12439 |
| 7 | 2,4,5-Trichloronitrobenzene | -0.10982 | 0.224193 | 2.081 | 3.49 | 1.53 | 1.449239404 | -0.08076 |
| 8 | 2,5-Dichloronitrobenzene | -0.10356 | 0.209766 | 2.147 | 2.95 | 1.13 | 1.08764776 | -0.04235 |
| 9 | 6-Chloro-1,3-dinitrobenzene | -0.11718 | 0.242234 | 1.816 | 2.06 | 1.98 | 1.208925518 | -0.77107 |
| 10 | Nitrobenzene | -0.08179 | 0.16491 | 2.015 | 1.95 | 0.14 | 0.103029698 | -0.03697 |
| 11 | 3-Methylnitrobenzene | -0.08651 | 0.173102 | 2.235 | 2.41 | 0.05 | 0.401413805 | 0.351414 |
| 12 | 1,3-Dinitrobenzene | -0.11382 | 0.229118 | 1.75 | 1.62 | 0.89 | 0.942604161 | 0.052604 |
| 13 | 3,4-Dichloronitrobenzene | -0.10659 | 0.215379 | 2.147 | 3.16 | 1.16 | 1.243908203 | 0.083908 |
| 14 | 4-Methylnitrobenzene | -0.08381 | 0.168142 | 2.235 | 2.41 | 0.17 | 0.321817331 | 0.151817 |
| 15 | 1,4-Dinitrobenzene | -0.12698 | 0.26173 | 1.75 | 1.37 | 1.3 | 1.278991766 | -0.02101 |
| 16 | 4-Chloronitrobenzene | -0.09816 | 0.196654 | 2.081 | 2.6 | 0.43 | 0.8022227 | 0.372223 |
| 17 | 2,3,5,6-Tetrachloronitrobenzene | -0.11334 | 0.236069 | 2.454 | 3.73 | 1.82 | 1.671893361 | -0.14811 |
| 18 | 6-Methyl-1,3-dinitrobenzene | -0.10724 | 0.215088 | 2.24 | 2.08 | 0.87 | 0.920862213 | 0.050862 |
| 19 | 3-Chloronitrobenzene | -0.0998 | 0.200436 | 2.081 | 2.64 | 0.73 | 0.86583791 | 0.135838 |
| 20 | 1,2-Dinitrobenzene | -0.10647 | 0.373047 | 1.75 | 1.84 | 1.25 | 1.316979587 | 0.06698 |
| 21 | 2-Bromonitrobenzene | -0.09387 | 0.190466 | 1.065 | 2.52 | 0.75 | 0.588756769 | -0.16124 |
| 22 | 3-Bromonitrobenzene | -0.09913 | 0.199511 | 1.065 | 2.52 | 1.03 | 0.741781541 | -0.28822 |
| 23 | 4-Bromonitrobenzene | -0.09789 | 0.196454 | 1.065 | 2.55 | 0.38 | 0.712183948 | 0.332184 |
| 24 | 2,4,6-Trimethylnitrobenzene | -0.08191 | 0.163948 | 2.605 | 3.33 | 0.86 | 0.580491684 | -0.27951 |
| 25 | 5-Methyl-1,2-dinitrobenzene | -0.10223 | 0.348662 | 2.24 | 2.3 | 1.52 | 1.31571646 | -0.20428 |
| 26 | 2,4-Dichloronitrobenzene | -0.10169 | 0.205448 | 2.147 | 3 | 0.99 | 1.045496163 | 0.055496 |
| 27 | 3,5-Dichloronitrobenzene | -0.10949 | 0.222328 | 2.147 | 3.34 | 1.13 | 1.392008534 | 0.262009 |
| 28 | 2,3,4,5-Tetrachloronitrobenzene | -0.11568 | 0.239098 | 2.279 | 3.94 | 1.78 | 1.791887824 | 0.011888 |
| 29 | 2,3-Dichloronitrobenzene | -0.10202 | 0.206657 | 2.147 | 2.9 | 1.07 | 1.025420726 | -0.04458 |
| 30 | 2,5-Dibromonitrobenzene | -0.10324 | 0.212776 | 3.475 | 3.12 | 1.37 | 1.231961958 | -0.13804 |
| 31 | 1,2-Dichloro-4,5 -dinitrobenzene | -0.12284 | 0.477847 | 1.882 | 3.2 | 2.21 | 2.488128523 | 0.278129 |
| 32 | 3-Methyl-4-bromonitrobenzene | -0.09478 | 0.189942 | 1.555 | 3.01 | 1.16 | 0.796525166 | -0.36347 |
| 33 | 2,3,4-Trichloronitrobenzene | -0.10822 | 0.220949 | 2.081 | 3.44 | 1.51 | 1.385163842 | -0.12484 |
| 34 | 2,4,6-Trichloro-1,3-dinitrobenzene | -0.12309 | 0.269736 | 1.948 | 3.41 | 1.43 | 1.876273533 | 0.446274 |
| 35 | 4,6-Dichloro-1,2-dinitrobenzene | -0.12206 | 0.4749 | 1.882 | 3.08 | 2.42 | 2.421962518 | 0.001963 |
| 36 | 3,5-Dinitrobenzylalcohol | -0.11037 | 0.222851 | 2.203 | 0.43 | 0.53 | 0.492654222 | -0.03735 |
| 37 | 3,4-Dinitrobenzylalcohol | -0.1032 | 0.354222 | 2.203 | 0.65 | 1.09 | 0.829672482 | -0.26033 |
| 38 | 2,3,5,6-Tetrachloro-1,4-dinitrobenzene | -0.14066 | 0.322619 | 2.454 | 2.92 | 2.74 | 2.340082588 | -0.39992 |
| 39 | 4-Fluoronitrobenzene | -0.08513 | 0.171119 | 1.697 | 1.8 | 0.25 | 0.133018411 | -0.11698 |
| 40 | 4-Fluoro-2-nitrotoluene | -0.086 | 0.172036 | 1.897 | 2.26 | 0.25 | 0.315909965 | 0.06591 |
| 41 | 1-Fluoro-2-nitrobenzene | -0.08431 | 0.169296 | 1.737 | 1.69 | 0.23 | 0.075459884 | -0.15454 |
| 42 | 1-Fluoro-3-nitrobenzene | -0.09023 | 0.180471 | 1.737 | 1.9 | 0.2 | 0.317758254 | 0.117758 |
| 43 | 4-Nitrobenzaldehyde | -0.10872 | 0.220357 | 2.248 | 1.56 | 0.2 | 0.808101368 | 0.608101 |
| 44 | 3-Nitrobenzaldehyde | -0.0966 | 0.193354 | 2.248 | 1.75 | 0.14 | 0.495534978 | 0.355535 |
| 45 | 3-Nitroacetophenon | -0.09211 | 0.184343 | 2.468 | 1.49 | 0.32 | 0.292505258 | -0.02749 |

**Cross-validation**

In order to check the reliability and stability of the QSAR model (Eq. 11), the leave -1/3-of -set -out validation is applied in the following way: the parent data points were divided three subsets namely A, B and C. In each of three combinations, two of the subset were combined into one and the correlation equation was determined with the same descriptors.

Table 2 — Cross-validation of the best QSAR model

| Training Set | N | $R^2$ | $R^2_{adj}$ | Test Set | N | $R^2$(Pred) | $R^2_{adj}$(Pred) |
|---|---|---|---|---|---|---|---|
| A+B | 31 | 0.88 | 0.86 | C | 14 | 0.76 | 0.73 |
| A+C | 30 | 0.81 | 0.78 | B | 15 | 0.89 | 0.88 |
| B+C | 29 | 0.88 | 0.85 | A | 16 | 0.84 | 0.82 |
| Average | | 0.86 | 0.83 | | | 0.83 | 0.81 |

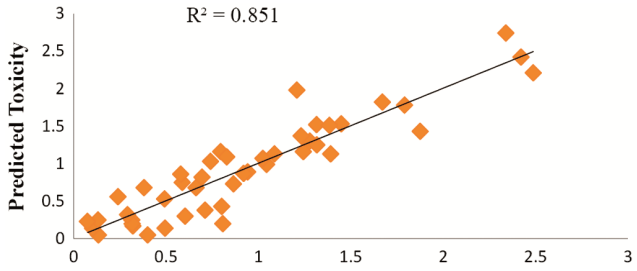


Figure 2 — Predicted vs observed toxicity using Eq.11

The obtained equation was used to predict data for the remaining subset. It turns out that the predicted $R^2$ values using subsets (A+B), (B+C) and (C+A) are close to that corresponding to the full training set (A+B+C) and the average values of $R^2$ and $R^2$(predicted ) given in the Table 2, are also close. So the data given in the Table 2 speaks in favour of the efficacy of the present model for estimating the toxicity of the nitrobenzenes for which experimental data are unavailable.

## Conclusion

A comprehensive QSAR analysis has been carried out for the 45 NBs using conceptual density functional theory based reactivity descriptors namely electrophilicity index (ω), lowest unoccupied molecular orbital ($\varepsilon_{lumo}$) and molecular compressibility (β) along with the hydrophobicity index (logP) to assess their toxic behaviour towards *T.pyriformis*. The high value of Coefficient of determination and robustness of the model establish the importance of these descriptors in the prediction of toxicity.

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