Journal of Molecular Graphics and Modelling 61 (2015) 89–101

Contents lists available at ScienceDirect

Journal of Molecular Graphics and Modelling

journal homepage: www.elsevier.com/locate/JMGM

Exploring the role of quantum chemical descriptors in modeling acute toxicity of diverse chemicals to *Daphnia magna*

Reenu, Vikas *

Quantum Chemistry Group, Department of Chemistry & Centre of Advanced Studies in Chemistry, Panjab University, Chandigrah 160014, India

ARTICLE INFO

Article history:
Received 7 April 2015
Received in revised form 4 June 2015
Accepted 20 June 2015
Available online 24 June 2015

Keywords:
Quantitative structure–activity relationships
Aquatic toxicology
Computational toxicology
Environmental toxicology
Organic contaminants

ABSTRACT

Various quantum-mechanically computed molecular and thermodynamic descriptors along with physico-chemical, electrostatic and topological descriptors are compared while developing quantitative structure–activity relationships (QSARs) for the acute toxicity of 252 diverse organic chemicals towards *Daphnia magna*. QSAR models based on the quantum-chemical descriptors, computed with routinely employed advanced semi-empirical and *ab-initio* methods, along with the electron-correlation contribution (CORR) of the descriptors, are analyzed for the external predictivity of the acute toxicity. The models with reliable internal stability and external predictivity are found to be based on the HOMO energy along with the physico-chemical, electrostatic and topological descriptors. Besides this, the total energy and electron-correlation energy are also observed as highly reliable descriptors, suggesting that the intra-molecular interactions between the electrons play an important role in the origin of the acute toxicity, which is in fact an unexplored phenomenon. The models based on quantum-chemical descriptors such as chemical hardness, absolute electronegativity, standard Gibbs free energy and enthalpy are also observed to be reliable. A comparison of the robust models based on the quantum-chemical descriptors computed with various quantum-mechanical methods suggests that the advanced semi-empirical methods such as PM7 can be more reliable than the *ab-initio* methods which are computationally more expensive.

1. Introduction

Daphnia magna, a type of water-flea, is a widely used laboratory animal for the testing of ecotoxicity, and it has been a subject for modeling the toxic effects of diverse chemicals through quantitative structure–activity relationships (QSARs) [1–4]. The toxicity in water leads to the demise of daphnids, and this perturbs the food chain because daphnids serve as food for many aquatic organisms. In fact, chemicals which are toxic to *D. magna* can, directly or indirectly, cause toxicological effects at all the trophic levels. Therefore, the thirst for the externally predictive QSAR models for the acute toxicity of diverse chemicals towards the *D. magna* had been continued since many years [5–8]. In the literature [4,9–12], the toxic effects of various hazardous chemicals towards *D. magna*, have been modeled mainly through the physico-chemical descriptors like octanol/water partition coefficient (log *P*) representing the hydrophobicity, besides several topological and quantum-chemical descriptors particularly the energy of highest occupied molecular orbital (HOMO) [9].

It should be noted that the present work assesses the QSAR models based on regression to make quantitative prediction for the toxicity of diverse chemicals towards *D. magna*. However, there have been equally important advanced and sophisticated QSAR approaches based on the classification method [13] which can effectively predict whether a chemical is biologically active or inactive. Recently [14–21], such classification based QSAR models have been reported for predicting the toxicity, of large and heterogeneous datasets of compounds, against many organisms, besides assessing multiple toxicological profiles under diverse experimental conditions. For example, Tenorio-Borroto et al. [14–16], had proposed multi-target quantitative structure–activity/property relationships (mt-QSAR/QSPR) models along with the flow cytometry analysis for the prediction of cytotoxicity and immunotoxicity, which can effectively models the drug-target interactions and effects of organic compounds over the cellular and molecular targets of immune system. Moreover, such techniques can be important for the high throughput screening of drugs to elucidate the drug discovery processes. Besides this, a topological and structure based approach commonly referred as TOPS-MODE approach [17] has also gained popularity to develop the mt-QSARs for the identification of compounds as a drug, pesticide, herbicide *etc.*

* Corresponding author.
E-mail addresses: qlabspu@pu.ac.in, qlabspu@yahoo.com (Vikas).

http://dx.doi.org/10.1016/j.jmgm.2015.06.009
1093-3263/

Recently, this approach has been applied for developing the mt-QSAR for tyrosine kinase inhibitors [18].

In fact, an increasing interest of research groups towards the development of toxicity models has added significant tools to the field of computational modeling. In a recent study, Kleandrova et al. [19] has reviewed significant advancements in the QSAR modeling for the prediction of acute toxicity, and has also introduced a multitasking toxicity model. Besides this, Furuhama et al. [20] has proposed quantitative structure–activity–activity relationships (QSAAR) for modeling the species-specific acute aquatic toxicity of aromatic amine and phenols, whereas Speck-Planche et al. [21] had predicted multiple ecotoxicological effects of agrochemical fungicides through multi-species QSAR models. Moreover, QSAR approaches based on molecular docking and simulation techniques have also been quite promising [22,23].

In the present study, QSAR models are proposed and analyzed for predicting the acute toxicity of diverse hazardous chemicals towards the *D. magna*. The models are mainly developed using the physico-chemical, electrostatic and topological descriptors along with the quantum-chemical molecular and thermodynamic descriptors computed using advanced semi-empirical methods like PM7 [24], and *ab-initio* methods such as the Hartree–Fock (HF) [25,26] and the density functional theory (DFT) [26,27]. Notably, the quantum-chemical descriptors formulated through the electron-correlation contribution (CORR) [28–33] are also employed to see the role of instantaneous electron–electron interactions in the modeling of the acute toxicity at the level of electron-dynamics. In our recent studies, the electron-correlation contribution of a quantum-chemical descriptor was observed to be highly significant while modeling the externally predictive QSAR models for the biological activities [28,29,32] and physico-chemical properties [30,31,33] of different chemicals. For example, the contribution of electron-correlation to the total energy of a molecule, energy of the HOMO, and to the electrophilicity are found to be highly significant while modeling the mutagenic activity of nitrated-PAHs [28,29,32] Besides this, the correlation energy is also observed as a robust descriptor while developing single-parameter based externally predictive quantitative structure–property relationship (QSPR) models for the super cooled vapor pressure of polychlorinated-naphthalenes [30], and also for the aqueous solubility, subcooled liquid vapor pressure, *n*-octanol/water and *n*-octanol/air partition coefficients of the polychlorinated-dibenzo-*p*-dioxins (PCDDs) and -dibenzo-furans (PCDFs) [31] and polychlorinated naphthalenes [33].

In our recent work [32], we had also analyzed the performance of various exchange-correlation functionals of the DFT while developing externally predictive QSARs for the mutagenicity of nitrated-PAHs. In this study, it was observed that the quantum-mechanical exchange interactions can be quite critical along with the electron-correlation in modeling the mutagenicity, however, the incorporation of electron-correlation is found to be highly significant in the QSAR models in order to have low errors in the external prediction. However, modeling toxicity of a data set constituting diverse chemicals is difficult since it involves multiple mechanisms [34]. Therefore, modeling of the toxicity with quantum-chemical descriptors and their electron-correlation contribution may pave new insights into the mechanisms of toxicity besides the existing knowledge from the models based on the topological descriptors and physico-chemical properties which are though known to be quite useful while developing QSAR models since partition coefficients can be quite crucial factor in the determination of a chemical's absorption through the cellular membranes.

Fig. 1 depicts the chemicals under investigation in the present study, which are also listed in Supporting information Table S1. These chemicals are comprised of a wide range of organic functionalities such as linear hydrocarbons, benzene, substituted benzenes, chemicals with —OH, —NO_2, —NH_2, —C═O, —C═S, R—O—R' functional groups, ring system of C, H atoms, with and without hetero atoms such as N, O, S *etc.*, chemicals containing Cl atom(s) and chemicals having P atom *etc.* Most of these chemicals are present as major pollutants in the environment, and are frequently used as pesticides. Many of these chemicals, particularly those having functionalities like —OH, —NO_2, —NH_2 *etc.*, are capable of extensive biotransformation. Moreover, their metabolite or degradation product(s) are also hazardous in nature. Further, some of the chemicals included in the present study namely, the halogen substituted hydrocarbons, amines, phenols are associated with skin, liver and kidney diseases [35–37], chemicals like alcohols are central nervous system depressants and are responsible for neurological disorders [38]. Carcinogenity is well known hazard of most of these chemicals, mainly due to the benzene derivatives such as nitrobenzenes, poly-aromatic- and heteroaromatic hydrocarbons [35,39]. The dangerous effects of these chemicals raise the need for modeling the toxicity associated with them, to regulate the use of such chemicals by industries and organizations for the purpose of risk assessment.

This paper is organized as follows: Section 2 provides the detailed theoretical strategy employed for the computation of various quantum-chemical descriptors utilized in this work and for the estimation of their electron-correlation contribution. This is followed by Section 3 on materials and methods, which provide information on the chemical data set and toxicity under investigation, and on the development and statistical validation of the QSAR models. The developed models are further analyzed in Section 4 on results and discussion where the internal and external predictivity of the present models is explored and compared with the robust models available in the literature [9]. Finally, the last section makes few concluding remarks.

2. Theoretical and computational details

In the present study, a number of quantum-chemical molecular descriptors are employed such as the total electronic energy of molecule (E), energies of the highest occupied and lowest unoccupied molecular orbital (E_{HOMO} and E_{LUMO}), absolute electronegativity (χ), chemical hardness (η), electrophilicity index (ω), and dipole moment (d) [28–30]. Besides these, the widely accepted thermodynamic descriptors, namely, standard Gibbs free energy (G) and enthalpy (H) computed using the quantum-mechanical methods are also employed for the model development. Since these descriptors account for most of the electronic properties associated with the chemical structure [40], therefore, when the toxicity of a chemical results mainly due to the covalent interactions of it with the cellular target at the atomic level, these descriptors are expected to be influential for the ADME (absorption, distribution, metabolism and excretion) properties of a chemical [41]. In such a scenario, the energies of frontier orbitals (E_{HOMO} and E_{LUMO}) and Gibbs free-energy of a chemical could prove to be reliable descriptors as they can account for the charge transfer interactions between a chemical and cellular target.

The energy of the HOMO/LUMO represents the chemical's ability of accepting or donating electrons, whereas the Gibbs free-energy represents the capacity of a chemical to do work during a chemical transformation. Similarly, the total energy of a chemical can be a measure of its covalent and non-covalent interaction with the target. Furthermore, the electron density based descriptors such as absolute electronegativity, chemical hardness and electrophilicity index could also be advantageous for the same purpose [42]. The chemical hardness, which in fact is representative of the energy-gap between HOMO and LUMO, is an indicator for the stability. A chemical with large HOMO–LUMO energy-gap is likely to be less active